Hydroxylamine-Mediated Arene C-H Amination and C-C Amination via Aza-Hock Rearrangement

Submitted to the
Combined Faculty of Natural Sciences and Mathematics
Heidelberg University, Germany
For the degree of
Doctor of Natural Sciences (Dr. rer. nat.)

Presented by
Tao Wang
from Henan, China

Oral examination: September 2021

Dissertation

Submitted to the
Combined Faculty of Natural Sciences and Mathematics
Heidelberg University, Germany
For the degree of
Doctor of Natural Sciences (Dr. rer. nat.)

Presented by
Tao Wang
from Henan, China

Oral examination: September 29th, 2021

Hydroxylamine-Mediated Arene C-H Amination and C-C Amination via Aza-Hock Rearrangement

Reviewer: Prof. Dr. A. Stephen K. Hashmi

Prof. Dr. Milan Kivala

Acknowledegments

It's not easy for me, "hang around" for two years after obtaining my master's degree, to pursue my doctorate, and the present work was finished in the last three years. It's my honor to work in a good atmosphere and enjoy the freedom in such a prime international group. It would be impossible to compose this thesis without your help, and let me express a "vote of thanks" to those making this accomplishment easier.

First and foremost, I am obliged to my supervisor, Prof. Dr. A. Stephen K. Hashmi, for offering me a platform to carry out my Ph.D. research at Heidelberg University. The words "not yes always, what do you think?" make me get rid of shyness on talking to you and other "foreign professors". It puts me in a panic, sometimes, but also pushes me to move forward and become better. With your help and investment in my future, I can confidently go anywhere in the world.

I'm grateful to Dr. Matthias Rudolph, for providing me wholehearted support on all kinds of research problems: giving me suggestions, teaching me writing skills, correcting my manuscripts.

I would like to thank Edina Hasagić, an intern under my guidance, for trusting me and helping me with the experiments of the first project for three months (Chapter 2).

I want to give credits to Prof. Dr. Andreas Dreuw and his Ph.D. student Marvin Hoffmann, putting much energy and enthusiasm on DFT calculations; Prof. Dr. Peter Comba and Dr. Marion Kerscher, helping me with EPR experiments; Prof. Günter Helmchen, holding weekly seminar and discussion on the mechanism of the first project. I also appreciate all workers from the Faculty of Chemistry for technical and analytical support (NMR, HRMS, X-ray, chemical store and glass work).

I owe thanks to Alexander Flatow in chemical supplies and equipment maintenance, Petra Krämer in analytical measurements (IR, UV/Vis spectra, GC, etc), and Christiane Eckert in administration and letter delivery.

To all my Chinese group members, you guys are incredible! Yangyang Yang, thank you for the wisdom offered. Yufeng Wu, thank you for the care given. Chao Hu, thank you for the instructions in daily life. Hongwei Shi, thank you for the daily details. Thanks a lot to my other Chinese colleague: Yu Xu, Zhongyi Zeng, Ximei Zhao, Xiaoji Si, Lumin Zhang, Xianhai Tian, Lina Song, Long Hu, Jun Li, Cheng Zhang, Chunyu Han, Zuozuo Wu, Huili Zhang, Yaowen Liu, Shan Zhang, Qiaoying Sun and Jian Yin, we have good memory here!

My thanks go to my German colleagues: Sina Witzel, giving suggestions on paper submitting and EPR studies; Philipp M. Stein, processing the data of kinetics and translating my English abstract into German; Fabian Stuck, carrying out the CV experiments; Elena Michel, providing me four compounds for the third project (Chapter 4). I also thank Marc Zimmer, Tapas Adak, Sara Tavakkolifard, Alejandro Cervantes Reyes, Daniel Eppel, Christoph Hendrich, Vanessa Vethacke, Kirsten Emler, Shaista Tahir, Alexandra Mackenroth, Robin Heckershoff, Jonas Wunsch, Martin Dietl, Simon Kohl, Michael Schukin, Rebeka Eshagh-Saatlo and Ketevan Museridze for lively socials.

I would like to express my sincere gratitude to my family for giving me the strength, understanding, allowance on studying in a foreign nation. Without your blessings, this achievement is out of imagination.

At last, I acknowledge my beloved nation-China and China Scholarship Council, which sponsor me studying and living in Germany.

List of Abbreviations

Ac	Acetyl
Ar	Aryl
ATR	Attenuated Total Refraction
BHT	Butylated hydroxytoluene
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
Bz	Benzoyl
Calcd.	Calculated
CDFT	Constrained Density-Functional Theory
CDI	Carbonyldiimidazole
CI	Configuration Interaction
CT	Charge Transfer
Cy	Cyclohexyl
CV	Cyclic voltammetry
DART	Direct analysis in real time
DCM	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	Diisopropyl azodicarboxylate
DMF	dimethyl formamide
DMPO	5,5-Dimethyl-1-pyrroline *N*-oxide
EDG	Electron donating group
EA	Ethyl acetate
EI	Electron ionization
EPR	Electron paramagnetic resonance
Eq.	Equivalent
ESI	Electrospray ionization
Et	Ethyl
EWG	Electron withdrawing group

GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
h	hour
HFIP	Hexafluoroisopropanol
HOSA	Hydroxylamine-*O*-sulfonic acid
HRMS	High resolution mass spectrometry
Hz	Hertz
i	iso
ICP	Inductively Coupled Plasma
Int	Intermediate
IR	Infrared
KIE	Kinetic Isotope Effect
LUMO	Lowest Unoccupied Molecular Orbital
m	*meta*
Me	Methyl
Mes	Mesityl
MHz	Megahertz
Min	Minutes
MP	Melting point
Ms	Mesyl
MS	Mass spectrometry
MSH	*O*-Mesitylenesulfonylhydroxylamine
m/z	mass per charge
NBS	*N*-bromo succinimide
NMR	Nuclear magnetic resonance
Ns	4-Nitrobenzenesulfonyl
o	*ortho*
OES	Optical Emission Spectrometry
p	*para*
PE	Petroleum ether

Ph	Phenyl
Pin	Pinacolato
Pr	Propyl
rt	room temperature
SET	Single Electron Transfer
t	*tert*
Tf	Triflate
TFA	Trifluoroacetic acid
TFE	Trifluoroethanol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethyl silyl
Ts	4-Toluenesulfonyl
UV	Ultraviolet
Vis	Visible
$\tilde{\nu}$	Wavenumber

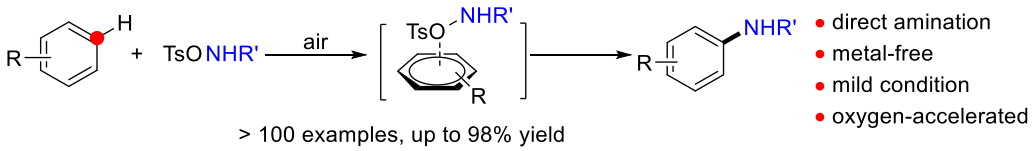
Publications

1. Chao Hu, **Tao Wang**, Matthias Rudolph, Thomas Oeser, Abdullah M. Asiri, A. Stephen K. Hashmi*, Gold(I)-Catalyzed Cycloisomerization of 3-Alkoxyl-1,6-diynes: A Facile Access to Bicyclo[2.2.1]hept-5-en-2-one, *Angew. Chem. Int. Ed.* **2020**, *59*, 8522-8526.
2. **Tao Wang**, Marvin Hoffmann, Andreas Dreuw, Edina Hasagić, Chao Hu, Philipp M. Stein, Sina Witzel, Hongwei Shi, Yangyang Yang, Matthias Rudolph, Fabian Stuck, Frank Rominger, Marion Kerscher, Peter Comba, and A. Stephen K. Hashmi*, A Metal-Free Direct Arene C-H Amination, *Adv. Synth. Catal.* **2021**, *363*, 2783-2795.
3. Chao Hu, Kaveh Farshadfar, Martin C. Dietl, Alejandro Cervantes-Reyes, **Tao Wang**, Tapas Adak, Matthias Rudolph, Frank Rominger, Jun Li, Alireza Ariafard*, and A. Stephen K. Hashmi*, Gold-Catalyzed [5,5]-Rearrangement, *ACS Catal.* **2021**, *11*, 6510-6518.
4. **Tao Wang**, Hongwei Shi, Chao Hu, Matthias Rudolph, and A. Stephen K. Hashmi*, Hydroxylamine-Mediated C-C Amination via an Aza-Hock Rearrangement, *Nat. Commun.* in revision.
5. **Tao Wang**, Zuozuo Wu, Elena Michel, Hongwei Shi, Matthias Rudolph, and A. Stephen K. Hashmi*, Anilines synthesis from alkylarenes, benzyl alcohol esters and styrenes via direct aza-Hock rearrangement mediated by hydroxylamines, in manuscript.

Abstract

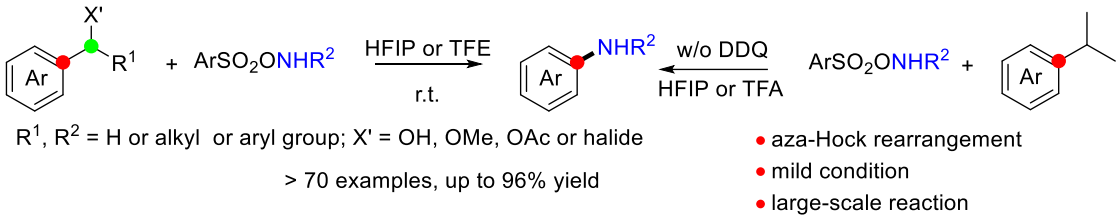
The thesis is focused on hydroxylamine-mediated direct arene C-H amination and C-C amination from benzyl alcohols, alkylarenes, styrenes and benzyl ethers/esters, which are used for the anilines synthesis. Additionally, this thesis consists of three parts.

In the first part (Chapter 2), a direct metal-free arene C-H amination mediated by hydroxylamines (TsONHBoc or TsONHR) was discovered, accidentally. Besides one literature reported with only three examples, this is the only report for an aniline synthesis via hydroxylamine derivatives under metal-free conditions. Primary anilines and secondary anilines are afforded under open flask conditions with this protocol, by using TsONHBoc or TsONHR, respectively. In contrast to metal-catalyzed processes, the reaction is triggered by an oxygen-accelerated SET (single electron transfer) from the aromatic systems to the electron-deficient hydroxylamine derivatives. The recombination of an arene radical cation and an aminyl radical, which are in close proximity, then affords the aminated products. The methodology can be applied for the amination of a variety of complex molecules, natural bioactive products and best-selling drugs. The operationally easy, broad functional group tolerance and scalability of this reaction in the absence of any metal make it appealing for both academy and industry.

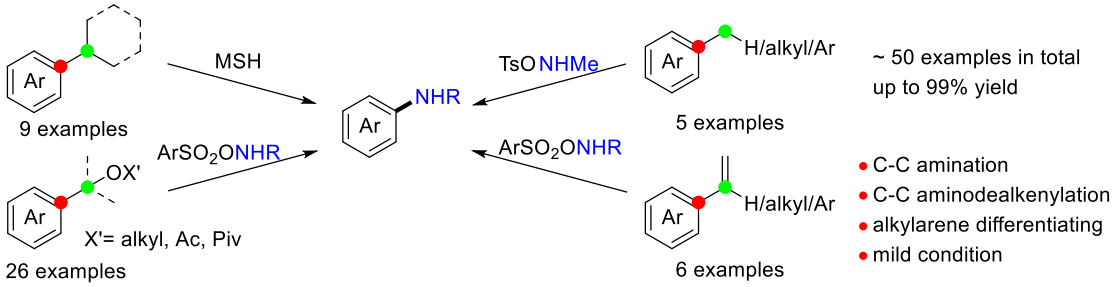


The second part (Chapter 3) describes an aza-Hock rearrangement of benzyl alcohols by using hydroxylamines ($ArSO_2ONHR$) as reagents under mild conditions, which makes primary anilines accessible from *O*-(2,4,6-trimethylbenzenesulfonyl)hydroxylamine (MSH) and secondary anilines available from other aminating reagents like TsONHR. Mechanistically we could prove that an aza-Hock rearrangement operates. Other benzyl cation precursors (eg. benzyl

ethers/esters/halides and alkylarenes) are also potent substrates for this strategy, expanding the synthetic utility. In addition, chemoselective C-C brominations and oxygenations are possible under similar conditions. Interestingly, despite some early evidence for such a reactivity pattern, until now the synthetic utility of this process is limited and our report might pave the way for further protocols based on such pattern in the future.



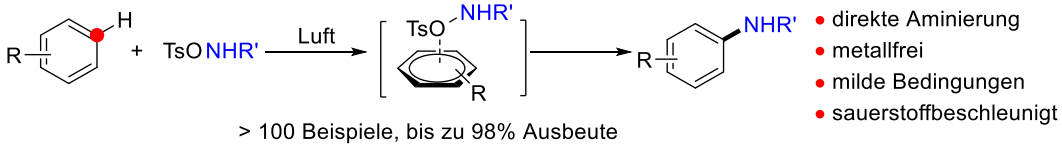
A modified aza-Hock rearrangement of benzyl cation precursors – alkylarenes, styrenes and benzyl ethers/esters – mediated by hydroxylamines, was investigated in the third part (Chapter 4). Notably, i-alkylarenes are differentiated by the aminating reagent MSH over *n*-alkylarenes, and *n*-alkylarenes are smoothly converted into anilines with TsONHMe. This rare phenomenon points out a way to distinguish different kinds of alkylarenes with such a pattern. Moreover, aminodealkenylation (C-C amination of styrenes) opens a gateway for employing styrenes in a plethora of known benzyl cation transformations, which should serve as a valuable tool for anilines synthesis, adding to the growing catalogue of C-C functionalization.



Zusammenfassung

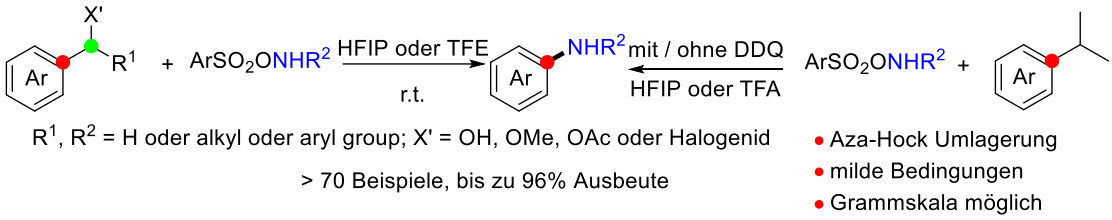
In der vorliegenden Arbeit wurde sich der Hydroxylamin-vermittelte direkte Aren-C-H-Aminierung und C-C-Aminierung aus Benzylalkoholen, Alkylarenen, Styrolen und Benzylethern/Estern, die für die Anilinsynthese Verwendung finden gewidmet. Die Arbeit gliedert sich in die folgenden drei Teile:

Im ersten Teil (Kapitel 2) wurde unverhoffter Weise eine durch Hydroxylamine (TsONHBoc oder TsONHR) vermittelte direkte metallfreie C-H-Aminierung von Arenen entdeckt. In der Literatur lässt sich hierzu lediglich eine Veröffentlichung mit drei Beispielen zur Anilinsynthese über Hydroxylaminderivate unter metallfreien Bedingungen finden. Primäre und sekundäre Aniline werden mit diesem Protokoll unter *„open flask conditions“*, also ohne Anwendung von Schutzgastechniken, unter Verwendung von TsONHBoc bzw. TsONHR dargestellt. Im Gegensatz zu metallkatalysierten Prozessen wird die Reaktion durch einen sauerstoffbeschleunigten SET *(„single electron transfer“)* von gegebenen aromatischen Systemen hin zu den elektronenarmen Hydroxylamin-Derivaten ausgelöst. Die Rekombination eines Arenradikalkations und eines Aminylradikals, die sich in unmittelbarer Nähe befinden, liefert daraufhin die aminierten Produkte. Die hier präsentierte Methodik kann für die Aminierung einer Vielzahl komplexer Moleküle, natürlicher bioaktiver Produkte und meistverkaufter Medikamente angewendet werden. Zudem steigern die einfache Handhabung, die hohe Toleranz gegenüber funktionellen Gruppen, die mögliche Skalierbarkeit sowie die Abwesenheit von Metallen die Attraktivität der vorgestellten Synthese sowohl für die akademische Forschung als auch für die Industrie.

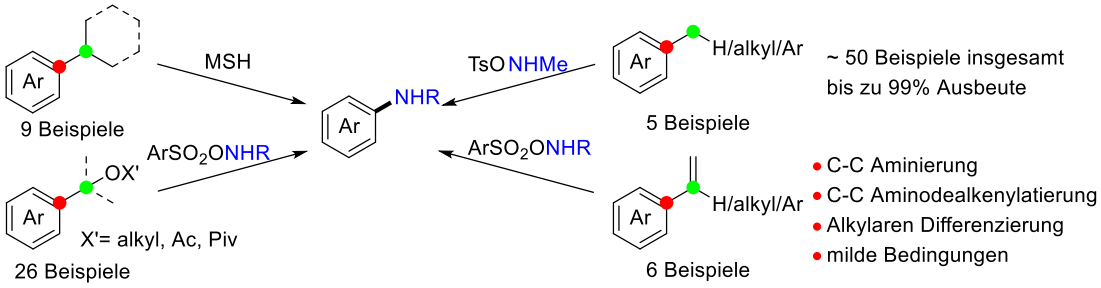


Der zweite Teil (Kapitel 3) beschreibt eine Aza-Hock-Umlagerung von Benzylalkoholen unter Verwendung von Hydroxylaminen ($ArSO_2ONHR$) als Reagenzien unter milden Bedingungen. Dies ermöglicht den einfachen Zugang

primärer Aniline aus *O*-(2,4,6-Trimethylbenzolsulfonyl)hydroxylamin (MSH) und den sekundärer Aniline, aus Aminierungsreagenzien wie TsONHR. Mechanistisch wurde das Ablaufen einer Aza-Hock-Umlagerung bewiesen. Weitere Benzylkationen-Vorstufen, wie z. B. Benzylether/Ester/Halogenide und Alkylarene, stellen ebenfalls geeignete Substrate für diese Strategie dar und erweitern somit den synthetischen Nutzen dieser. Darüber hinaus sind unter ähnlichen Bedingungen chemoselektive C-C-Bromierungen und Oxygenierungen möglich. Interessanterweise ist der synthetische Nutzen dieses Prozesses trotz einiger früher Beweise für ein solches Reaktivitätsmuster begrenzt, sodass unser Bericht den Weg für weitere Protokolle ebnen könnte, die auf einem derartigen Muster basieren.



Im dritten Teil (Kapitel 4) wurde eine durch Hydroxylamine vermittelte modifizierte Aza-Hock-Umlagerung von Benzylkation-Vorstufen – Alkylarene-, Styrol- und Benzylether/Ester – untersucht. Bemerkenswerterweise unterscheiden sich *i*-Alkylarene durch das Aminierungsreagenz MSH gegenüber *n*-Alkylarenen, welche mittels TsONHMe effizient in Aniline überführt. Dieses seltene Phänomen bietet die Möglichkeit, diverse Arten von Alkylarenen anhand eins solchen Musters zu unterscheiden. Darüber hinaus eröffnen sich anhand der Aminodealkenylierung (C-C-Aminierung von Styrolen) neue Wege für den Einsatz von Styrol-Derivaten in einer Vielzahl bekannter Benzylkationen-Transformationen, welche zugleich als wertvolles Werkzeug für Anilinsynthesen dienen könnten und damit den wachsenden Katalog der C-C-Funktionalisierung ergänzen.


Ar
MSH
9 Beispiele
OX'
Ar
ArSO2ONHR
X'= alkyl, Ac, Piv
26 Beispiele
Ar
NHR
TsO NHMe
ArSO2ONHR
Ar
H/alkyl/Ar
5 Beispiele
Ar
H/alkyl/Ar
6 Beispiele
~ 50 Beispiele insgesamt
bis zu 99% Ausbeute
C-C Aminierung
C-C Aminodealkenylatierung
Alkylaren Differenzierung
milde Bedingungen

Contents

Chapter 1 General Introduction

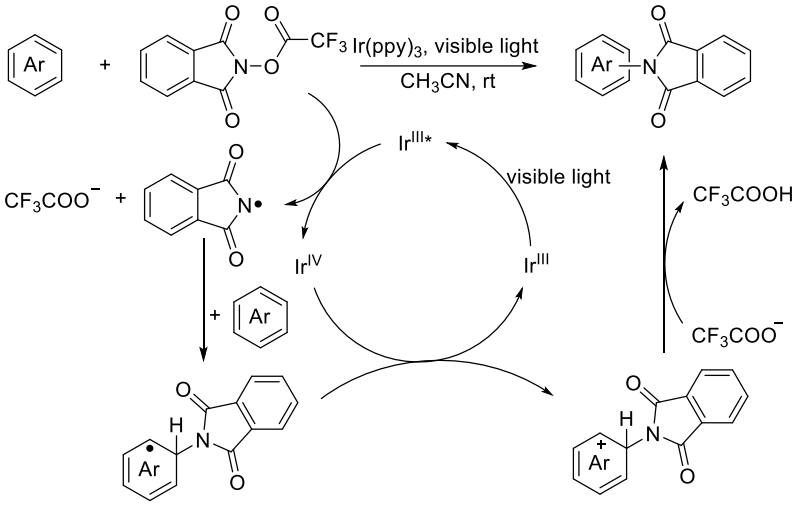
Anilines are of paramount importance to all aspects of chemical science (pharmaceuticals, agrochemicals, organic chemicals and natural bioactive products).[1] The past decades have witnessed a significant improvement of amination reactions of arenes. Such motifs are typically accessed by a nitration-reduction sequence or by transition metal-catalyzed cross-coupling reactions (Buchwald-Hartwig,[2] Ullmann[3] and Chan-Lam reaction[4]). In the case of the former conventional nitration-reduction, harsh conditions are needed and often poor site-selectivity is accompanied; in the case of the latter cross-couplings, pre-functionalized aryl (pseudo) halides are required and needed several steps to synthesize them. As such, methods for the direct amination of unfunctionalized arenes are highly desirable while far from being developed.[5] To address this drawback, modern methods for direct arene C-H amination via organometallic chemistry,[5-6] photochemistry[7] and electrochemistry[8] and arene C-C amination mediated by azides with/without iron catalysis[9] and hydroxylamine derivatives[10] are invented, which both represent rapid and reliable ways to construct C-N bonds from easily affordable chemical feedstocks. This chapter is focused on methodologies of C-H/C-C amination, and in addition, hydroxylamines-involved relevant reactions are therefore discussed here (regarding the power of hydroxylamines in amination reactions). So a brief overview of aminating protocols is summarized below: arene C-H amination, arene C-C amination and other reactions with hydroxylamines.

1.1 Arene C-H Amination

1.1.1 Photocatalytic Arene C-H Amination

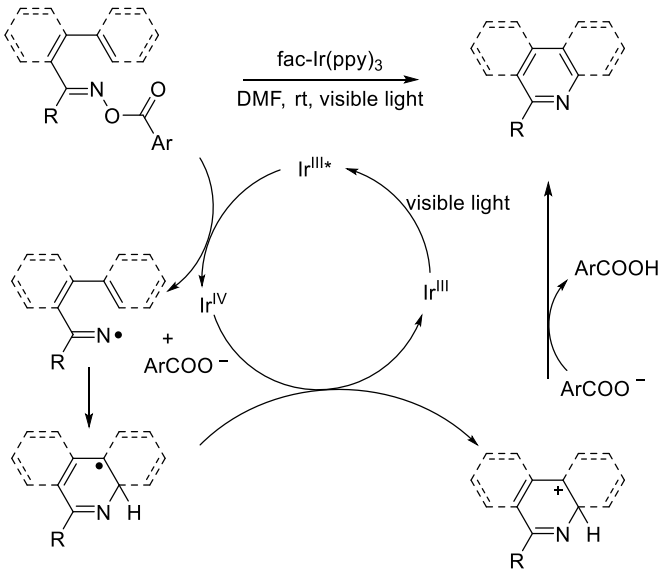
Photochemistry can serve as an alternative for the direct C-H amination of simple arenes,[7] but special apparatuses and expensive catalysts are necessary. For example, in 2014, Sanford[11] reported a new photocatalytic, $Ir(ppy)_3$-catalyzed method with *N*-acyloxyphthalimides for the C-H amination of arenes and heteroarenes (Scheme 1). In

the reaction, phthalimide nitrogen radical was generated from *N*-acyloxyphthalimide induced by iridium catalyst, followed by the addition of nitrogen radical to arene to afford aryl radical, then oxidized by Ir^{IV} to form the Wheland intermediate, which was irreversibly deprotonated to acquire the aminated product. However, the site-selectivity is a big challenge: *ortho*- vs *meta*- vs *para*-aminated product for all substrates.



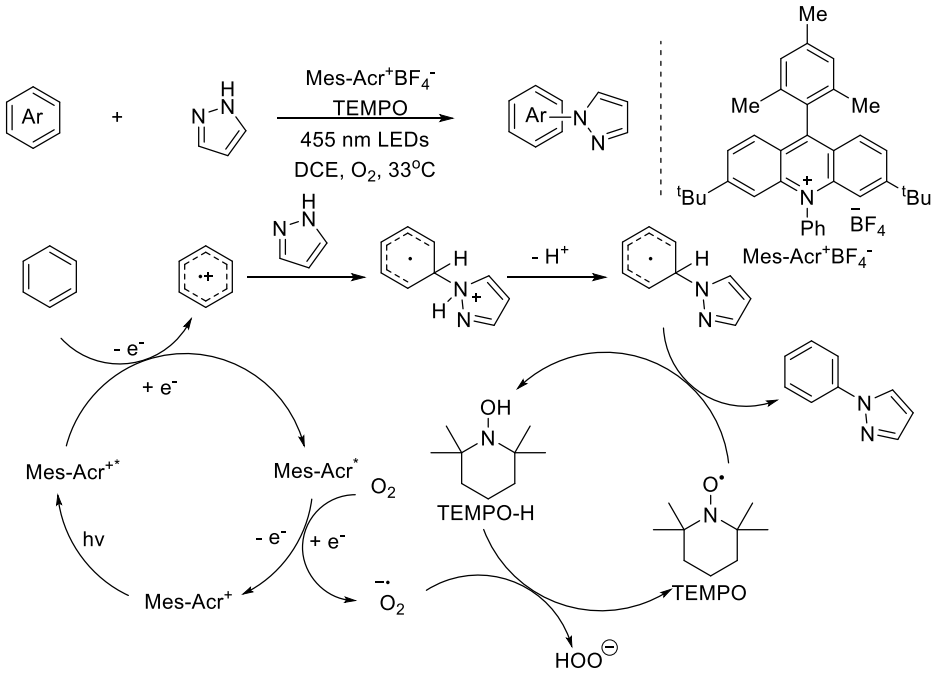
Scheme 1. Arene/heteroarene C-H amination with *N*-acyloxyphthalimide

Later, an intramolecular arene C-H amination via iminyl radical from *O*-acyl hydroxylamine promoted by visible light was reported by Zhang and Yu,[12] which developed a new approach to access to heteroarenes systems–pyridines, quinolines and phenanthridines (Scheme 2).



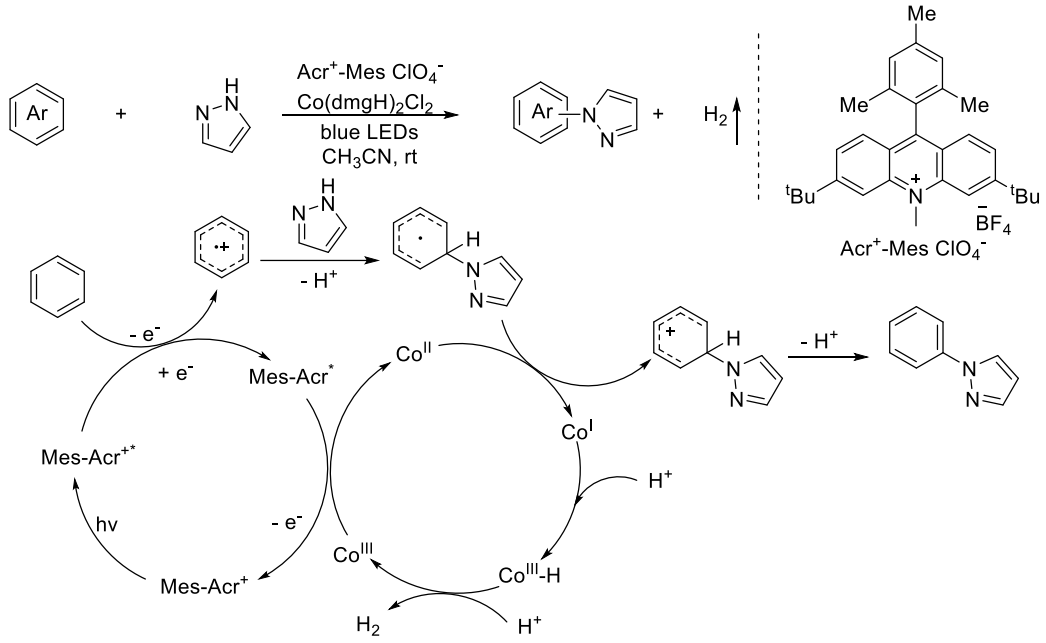
Scheme 2. 6-*endo-trig* Amination of iminyl radicals from oximes

In 2015, Nicewicz[13] developed an elegant C-H amination of simple arenes by an organic acridinium photoredox catalyst (Mes-Acr^{+}F$_4$B^{-}) with TEMPO as cocatalyst (Scheme 3). The reaction showed good selectivity; however, the substrate scope was limited to electron-rich arenes and aminating partners relied on pyrazoles or similarities (although not with restrictions on the use of amides and imides), and only 8 primary anilines were documented with ammonium carbamate ($NH_4^+H_2NCOO^-$) as an aminating reagent.



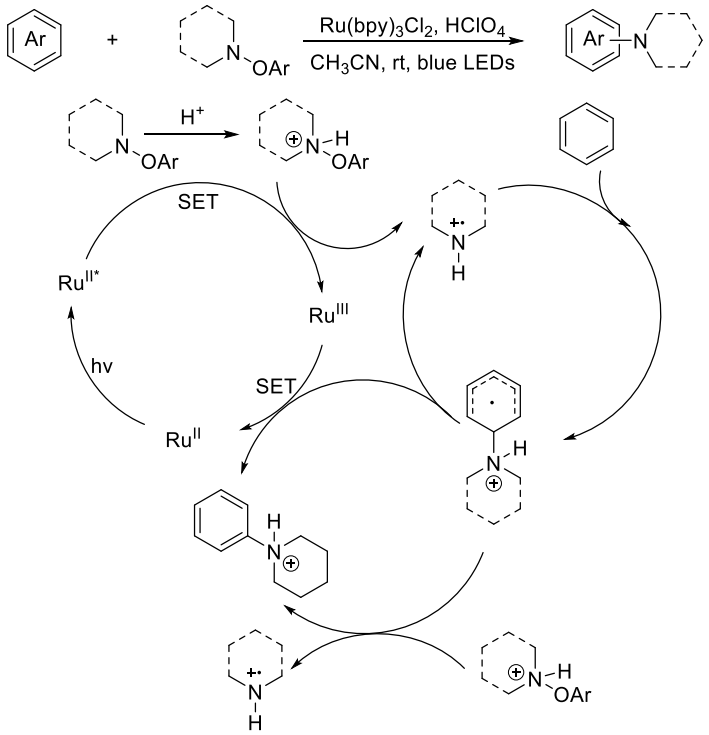
Scheme 3. Acridinium-catalyzed arene C-H amination

Subsequently, the method was improved by Lei and coworkers[14] by using heterocyclic azoles as nitrogen sources under oxidant-free conditions with good selectivity (Scheme 4). Not like Nicewicz's work,[13] cobalt was used instead of oxidants (TEMPO, O_2) in combination with H_2 evolution.



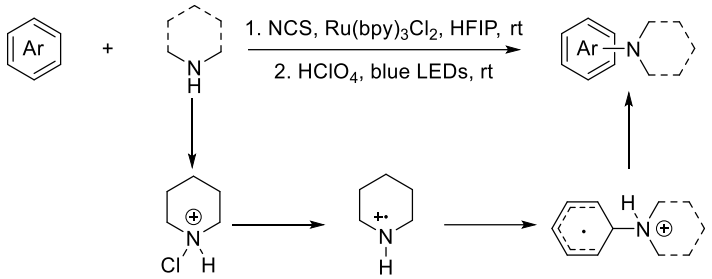
Scheme 4. Photochemical cobalt-catalyzed C-H amination between arenes and azoles

In 2017, the hydroxylamine derivatives ArONRR' as aminating reagents were developed by Leonori[15] in a $Ru(bpy_3)Cl_2$-catalyzed arene C-H amination (Scheme 5). With this strategy, amine partners were expanded to alkylamine (not limited to amides, imides and azoles), and late-stage functionalizations with such protocol were also successfully applied.



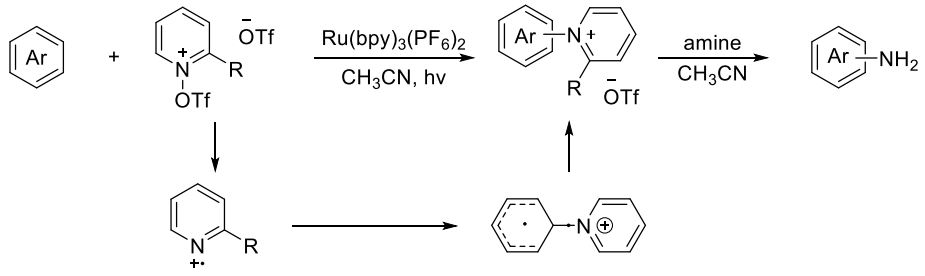
Scheme 5. $Ru(bpy)_3Cl_2$-catalyzed arene C-H amination via aminium radicals

Recently, the method was highlighted again by Leonori's group[16] with direct simple amines as the nitrogen source, in combination with $HClO_4$ as strong acid (used for inhibiting side-products chloroarenes) (Scheme 6). And this is a big step for arene C-H amination with simple alkylamines as nitrogen partners, which makes it appealing from a synthetic utility aspect.



Scheme 6. $Ru(bpy)_2Cl_2$-catalyzed regioselective arene C-H amination with alkyl amines

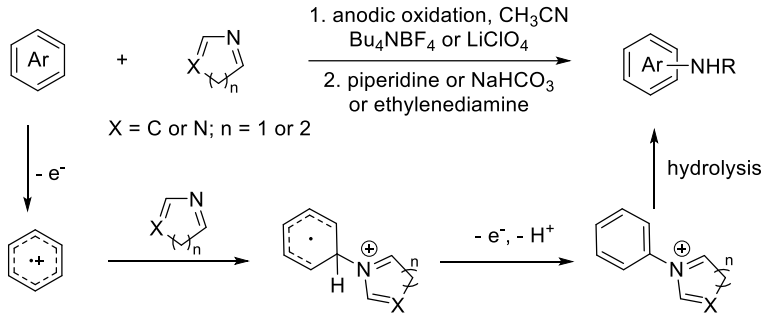
Togni and Carreira,[17] as well as Ritter[18] reported that *N*-OTf pyridine as pyridine radical cation could be used for the construction of C-N bonds in 2019 (Scheme 7). In this case, *meta*-aminated electron-poor arenes were also accessible as the early transition state of the addition of pyridine radical to arene was supposed to dominate the reaction, therefore it is an unsolved problem to afford one isomer of the desired anilines.



Scheme 7. $Ru(bpy)_3(PF_6)_2$-catalyzed arene C-H amination using pyridine radical cation

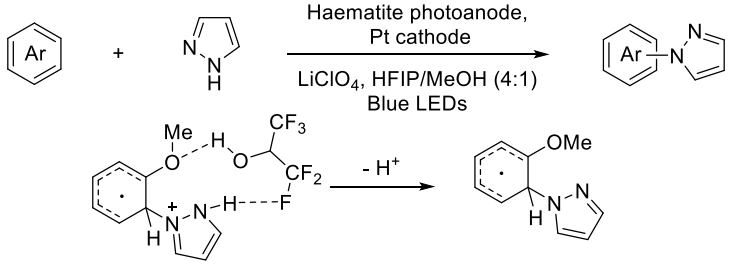
1.1.2 Electrochemical Arene C-H Amination

Another approach to achieve C-H amination, developed by Yoshida's group,[19] is based on electrochemical oxidation[7] – under the formation of aryl radical cations, nucleophilic addition of nitrogen partners, aryl aminium generation after loss 1 e^- and 1 H^+, aryl amine production after hydrolysis (Scheme 8). In addition, strategies based on electrochemistry need special apparatuses and harsh conditions. In this way, a high potential is needed to oxidize the arenes and only imidazole or similarities were used as nitrogen partners.



Scheme 8. Electrochemical oxidation arene C-H amination with heteroarenes

In 2019, Hu and coworkers[20] developed a photoelectrocatalytic arene amination showing an unusual *ortho*-selectivity, but the scope was limited to electron-rich arenes (Scheme 9). The unusual *ortho*-selectivity was attributed to the formation of hydrogen bonding between the anisole radical intermediate and the solvent HFIP.

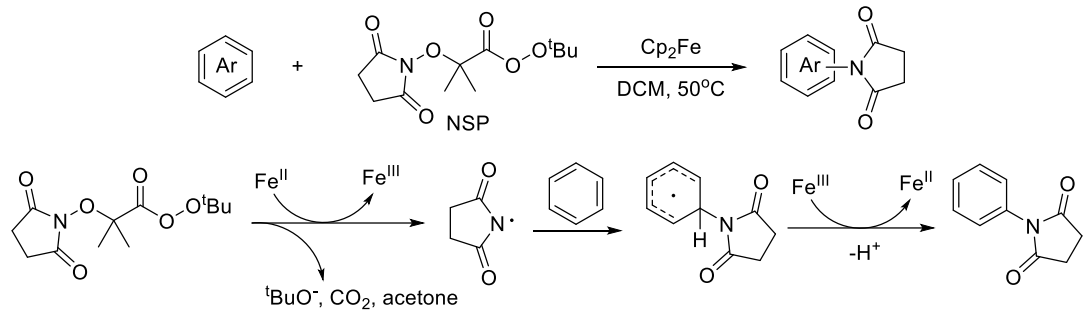


Scheme 9. Photoelectrocatalytic *ortho*-selective arene C-H amination

1.1.3 Transition Metal-Catalyzed Arene C-H Amination

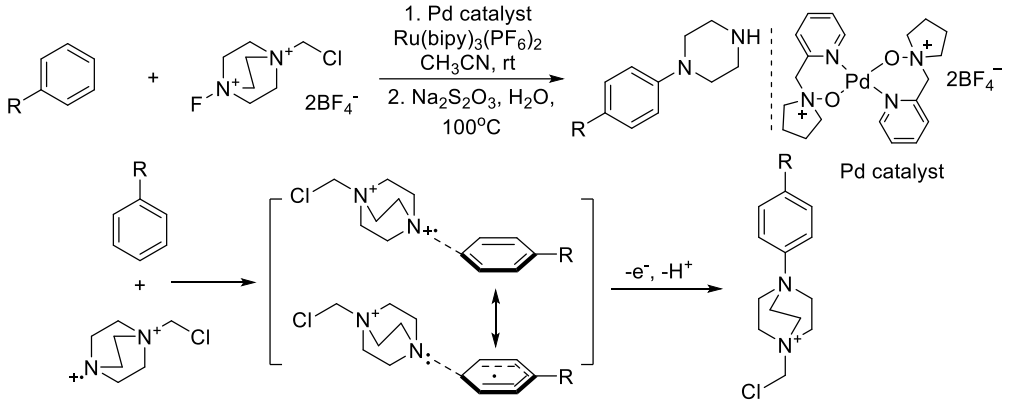
Furthermore, a powerful route to arylamines is the transition metal-catalyzed direct arene C-H amination without a directing group.[6, 21] For example, Baran[22] developed

a ferrocene-catalyzed arene C-H amination with NSP (*N*-succinimidyl perester) as a reagent in 2014 (Scheme 10). Instead of light irradiation in combination with iridium catalyst (Sanford's work[11]), Cp_2Fe alone could also generate aminyl radical from NSP, which added to arene to form aryl radical, then loss of one electron and proton to yield the aminated product. In analogy to Sanford's work,[11] selectivity is also a challenge.



Scheme 10. Cp_2Fe-catalyzed arene C-H amination with *N*-succinimidyl perester

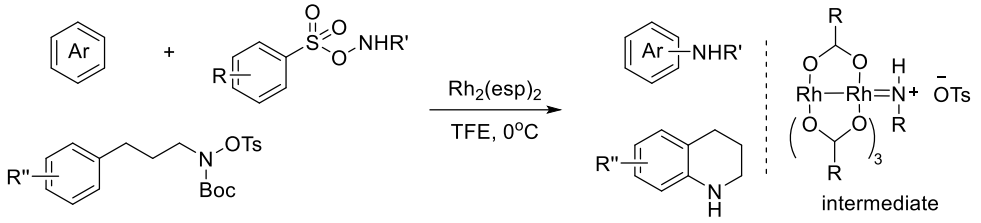
In 2016, Ritter and coworkers[23] proposed a charge-transfer transition state between the arene substrates and an aminium radical (derived from Selectfluor) in a double transition metal-catalyzed process as the key step to afford *para*-selective aminated products with high selectivity (Scheme 11). The perfect selectivity was attributed to the high electron affinity of the $TEDA^{2+\bullet}$ radical, which can be explained by Fukui indices.



Scheme 11. *para*-Selective C-H amination enabled by charge-transfer-directed radical substitution

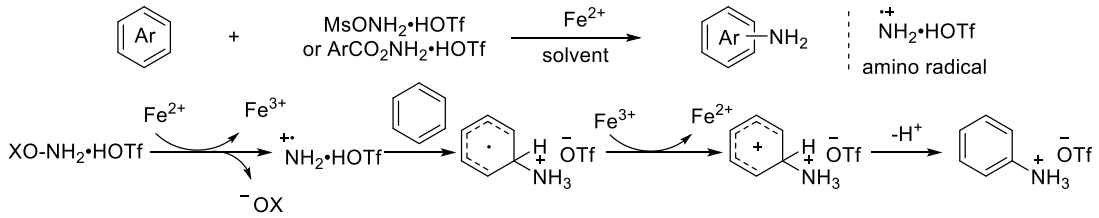
In 2016, Falck[24] invented a rhodium-catalyzed directed arene C-H amination with hydroxylamine under mild conditions, delivering arylamines and tetrahydroquinolines in good yields (Scheme 12). This is the first time hydroxylamines were used for metal-

catalyzed arene C-H amination, and rhodium imine was responsible for the conversion according to DFT calculations. However, only electron-rich substrates were tolerated, and primary aniline was shown for one example.



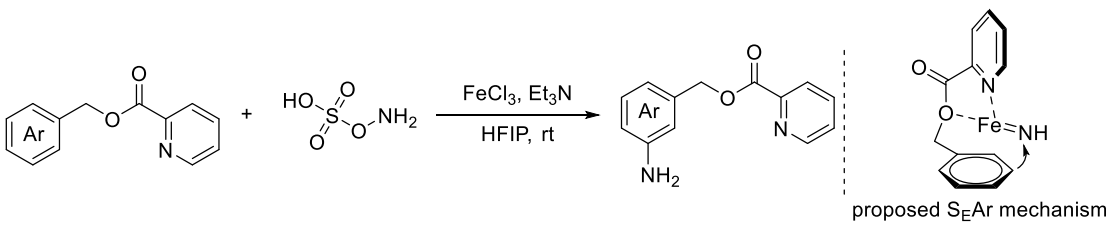
Scheme 12. $Rh_2(esp)_2$-catalyzed arene C-H amination with hydroxylamine

Later, a direct arene C-H amination was successful by using hydroxylamine derivatives ($MsONH_2$•HOTf, $ArCO_2NH_2$•HOTf) in combination with iron by Morandi,[25] Ning[26] and Ritter.[27] (Scheme 13). An amino radical initiated by an iron catalyst was proved in the reaction. Electron-deficient arenes could be aminated with $MsONH_2$•HOTf in HFIP. Additionally, Ritter first testified that $MsONH_2$•HOTf could achieve an arene C-H amination under metal-free conditions, but with the restriction that only electron-deficient arenes (three examples) could be applied.



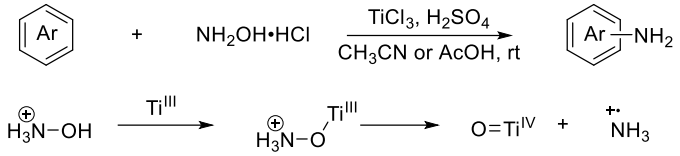
Scheme 13. Iron-catalyzed arene C-H amination with hydroxylamine triflate salt

Recently, in an iron-catalyzed process, *meta*-C-H aminated products were achieved with HOSA and picolinates as directing group by Falck[28]; in which picolinate-directed, iron-nitrenoid electrophilic aromatic substitution (S_EAr) was proved by relevant experiments (Scheme 14).



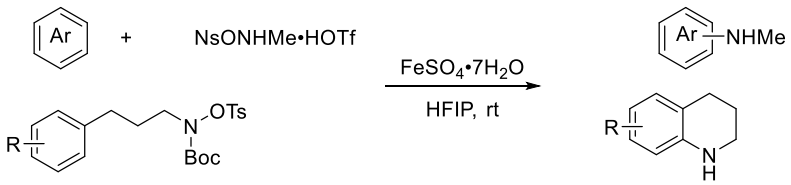
Scheme 14. $FeCl_3$-catalyzed arene *meta*-C-H amination with HOSA

And a titanium-catalyzed arene C-H amination with NH_2OH•HCl was disclosed by Sanford,[29] which underwent an aminyl radical pathway (Scheme 15). But stoichiometric titanium (2 eq.) and a large amount of sulfuric acid (10 eq.) were needed to finish the transformation.



Scheme 15. $TiCl_3$-catalyzed arene C-H amination with NH_2OH•HCl

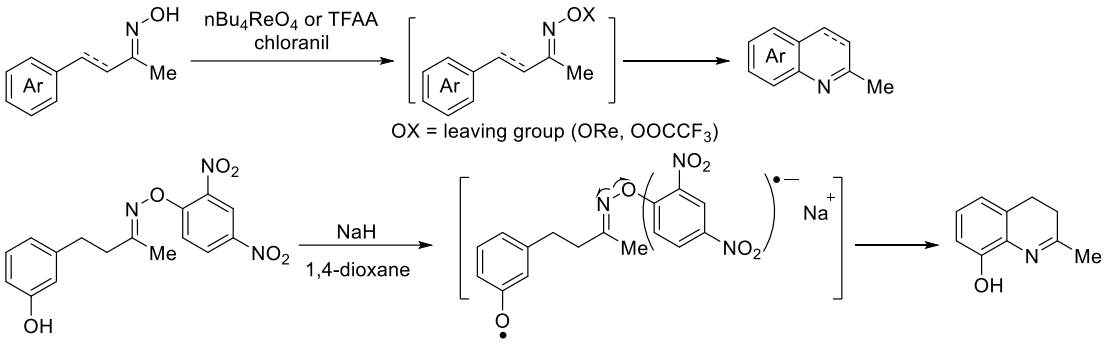
During our manuscript of the first project transferred to different journals, Morandi[30] published an iron-promoted aromatic C−H amination with NsONHMe•HOTf (Scheme 16). In this case, strong electron-deficient arenes (benzoate, nitrobenzene, etc.) were not included.



Scheme 16. $FeSO_4$-catalyzed arene C-H amination with hydroxylamine derivatives

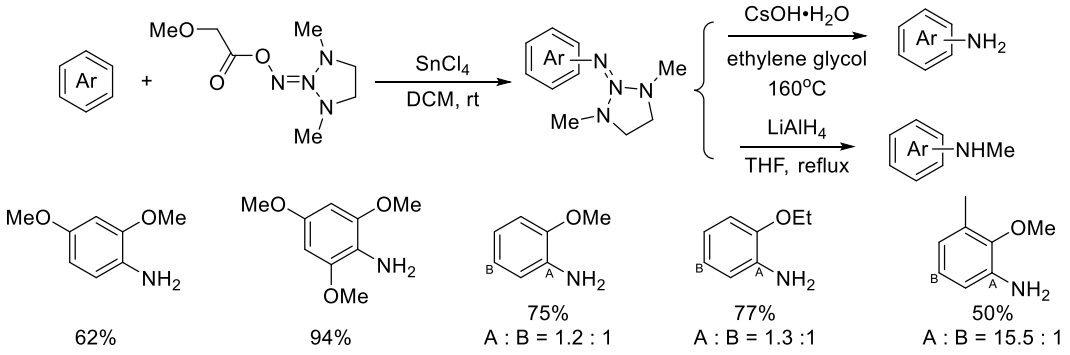
1.1.4 Metal-free Arene C-H Amination

For these above protocols, metals are needed, which leads to economic pressure in the purification step (removal of the metal contamination), especially in the pharmaceutical industry. Thus, metal-free arene C-H amination is a practical, economical alternative for this conversion. For example, intramolecular arene C-H aminations of oximes or derivatives with normal reagents (TFAA or NaH) were reported by Narasaka (Scheme 17). For the upper equation in Scheme 17, an S_N2-type amination mechanism was proposed,[31] and for the down equation in Scheme 17, radical cyclization of oximes was hypothesized.[32]



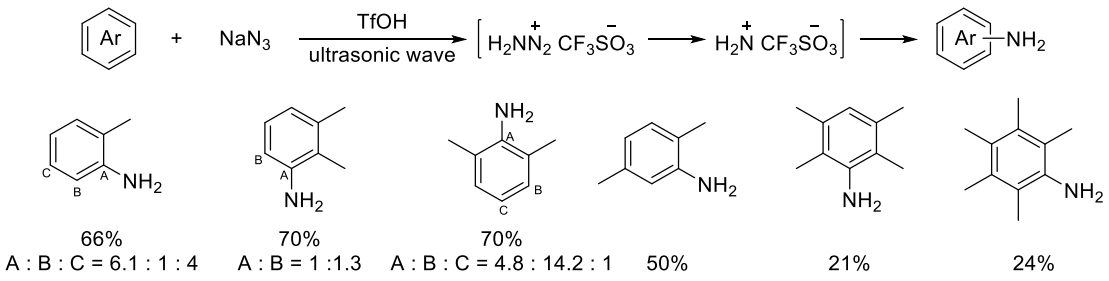
Scheme 17. Intramolecular S_N2-type/radical amination of oximes

For the above two cases, only intramolecular aryl ketoximes C-H aminations were feasible. But in 2003, Narasaka[33] successfully reported nucleophilic addition of arenes with *N*, *N*-dimethyl-2-imidazolidinone *O*-methoxyacetyloxime, followed by hydrolysis with CsOH or reduction with $LiAlH_4$, delivering arylamines as the products, but only five examples of anisoles were documented (Scheme 18).



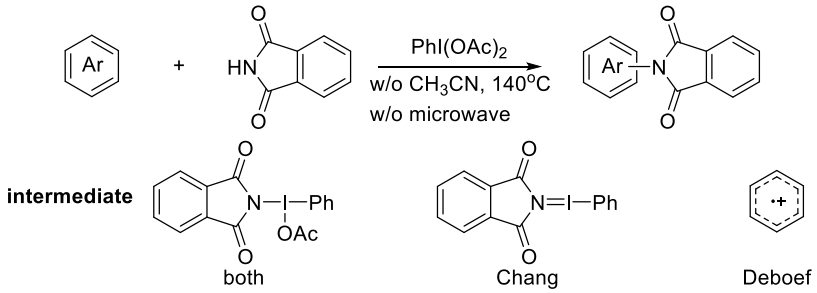
Scheme 18. Arene C-H amination with *N*, *N*-dimethyl-2-imidazolidinone *O*-methoxyacetyloxime

Later, Shubin[34] presented a metal-free electrophilic amination of arenes with nitrenium ion (from triflic acid and NaN_3), but only 6 examples of alkylarenes were demonstrated (Scheme 19).



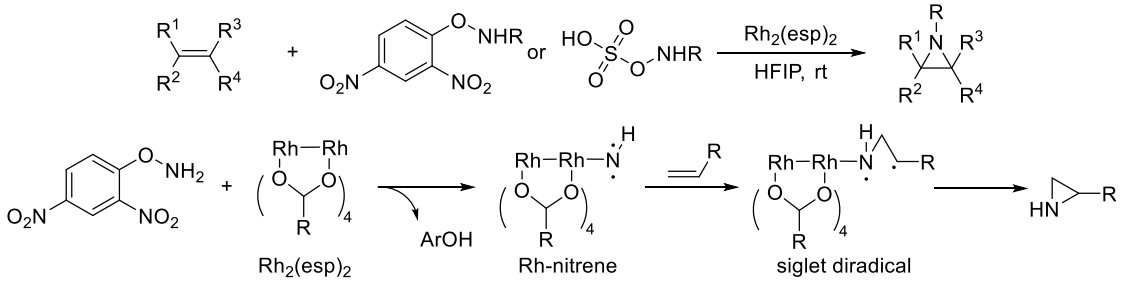
Scheme 19. Electrophilic amination of alkylarene with NaN_3

Besides, the groups of Chang[35] and Deboef[36] employed $PhI(OAc)_2$ as the oxidant in combination with amides as the nitrogen source to afford aryl amides, but harsh conditions were needed, the substrate scope was limited and the selectivity was moderate (Scheme 20). Interestingly, both groups proposed an "N-I" intermediate; in addition, Chang believed that iodine nitrene was also involved in the reaction, but aryl radical cation (one-electron transfer from arene to $PhI(OAc)_2$), thought by Deboef, was responsible for such conversion.



Scheme 20. $PhI(OAc)_2$-mediated arene C-H amination with phthalimide

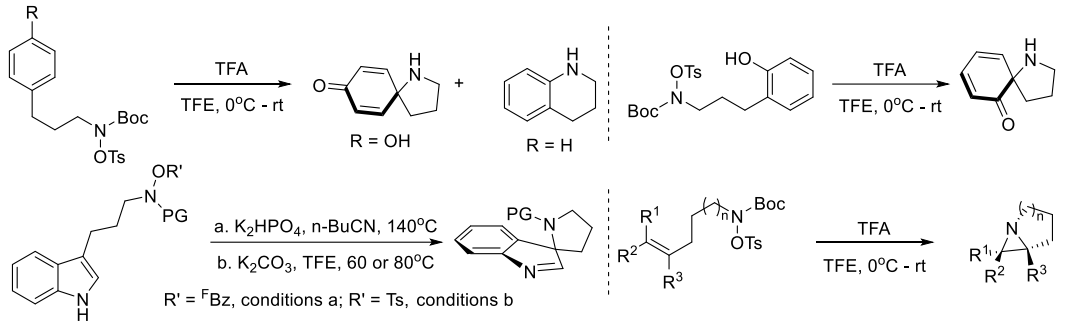
Besides, regardless of the arylamine synthesis, simple hydroxylamine or its derivatives are also used for the construction of aliphatic C-N bonds. For example, commercially available HOSA (hydroxylamine-*O*-sulfonic acid) and DPH (*O*-(2,4-dinitrophenyl)hydroxylamine) were used for aziridinations of olefins with rhodium as the catalyst, which was reported by Kürti and Falck (Scheme 21).[37] A rhodium nitrene was proved for this transformation by DFT calculation.



Scheme 21. $Rh_2(esp)_2$-catalyzed aziridination between olefin and hydroxylamine

Besides, several publications on intramolecular arene C-H amination under metal-free

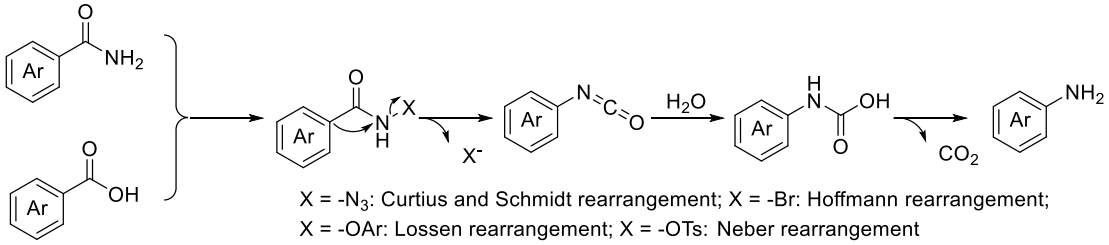
conditions with aryl or indolyl hydroxylamine derivatives were achieved by Bower,[38] affording the products of the dearomatization of arenes and indoles (Scheme 22). For aryl hydroxylamines substrates, an SEAr-like mechanism was proposed; for alkenyl hydroxylamines, a concerted aza-Prilezhaev-type mechanism was calculated by DFT.[39]



Scheme 22. Intramolecular dearomatization via arene C-H amination with aryl/indolyl hydroxylamine

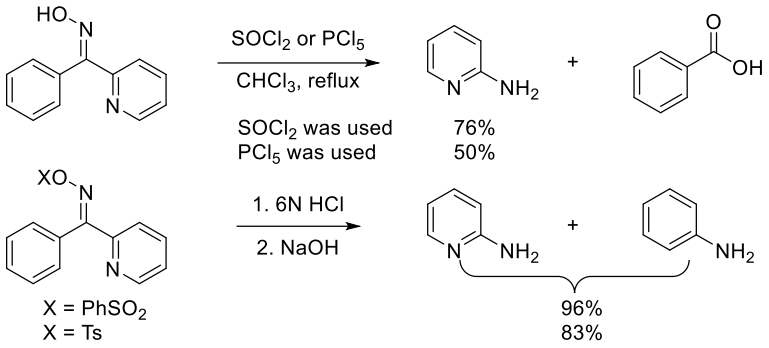
1.2 Arene C-C Amination

However, specific site-selectivity is a significant challenge for C-H amination protocols — *ortho*- versus *para*-selectivity for electron-rich substrates; *ortho*- versus *meta*- versus *para*-selectivity for electron-deficient substrates. Alternatively, direct C-C amination is a method to address the site-selectivity problem. Many examples for transition metal-catalyzed functionalizations via decarboxylative aminations[40] as well as metal-free reactions (Lossen,[41] Hoffmann,[42] Curtius,[43] Schmidt[44] and Neber rearrangements,[45] Scheme 23) of carboxylic acids and their derivatives exist, but several synthetic steps are needed. Only a few publications report on direct access to anilines under metal-free conditions in a one-step approach.



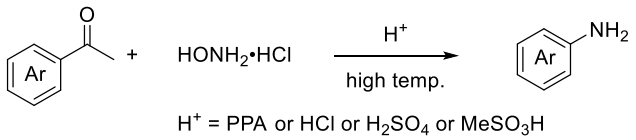
Scheme 23. the Mechanism of Curtius, Schmidt, Hoffmann, Lossen and Neber rearrangements

The Beckmann rearrangement[46] is a classical way to synthesize anilines from ketoximes or surrogates. A pioneering work reported by Walter[47] relied on a similar strategy, starting from 2-benzoylpyridine ketoxime or its *O*-*p*-toluenesulfonate, followed by a Beckmann rearrangement and hydrolysis to provide 2-amino pyridine or anilines, but only two examples were presented: aniline could be accessible as the byproduct when acid as a solvent was used (Scheme 24).



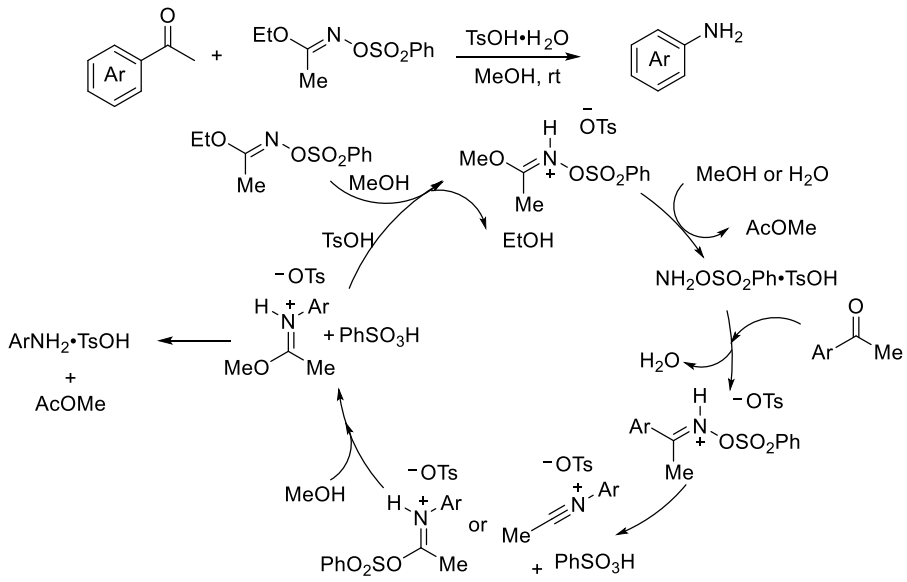
Scheme 24. Beckmann rearrangement of the oximes of 2-benzoylpridines

A recent patent[10a] described the preparation of anilines using the Beckmann rearrangement of aryl ketoximes, which still needed strong acid (PPA, H_2SO_4, $MeSO_3H$, or HCl) and high temperature (>100ºC) to facilitate the transformation (Scheme 25).



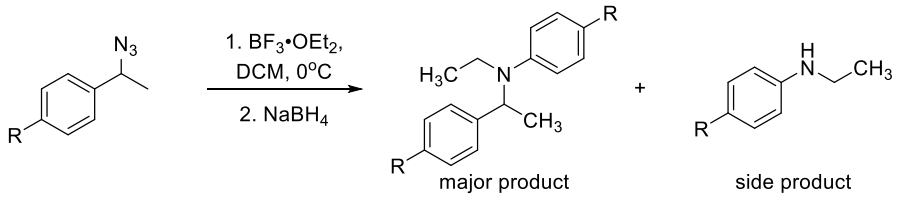
Scheme 25. Direct deacylative amination of ketones with NH_2OH•HCl

Later this method was improved by Uchida, [10b] who realized the direct deacylative amination of acyl arenes with ketoxime benzenesulfonate, affording anilines through a cascade reaction under mild conditions (Scheme 26). However, via this Beckmann methodology only primary anilines are accessible.



Scheme 26. Direct deacylative amination of acyl arenes with ketoxime benzenesulfonate

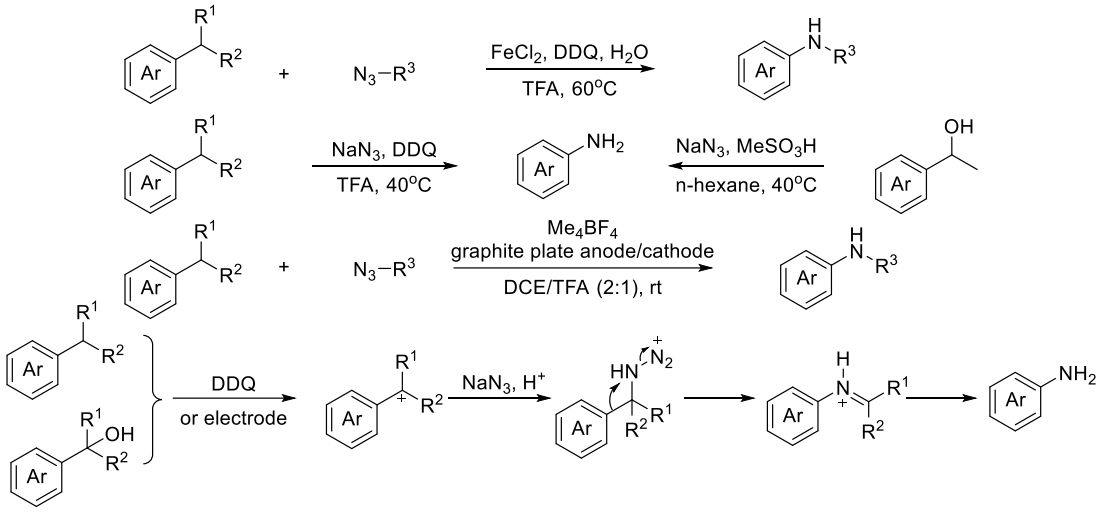
Still, metal-free direct dealkylative aminations remain an underexplored area, especially for the difficult C(sp^2)–C(sp^3) bond cleavage (bond dissociation energy: C(sp^2)–C(sp^3) 98–100 kcal/mol).[48] One other way to address this problem is the Schmidt rearrangement of α-azido ethylbenzene intermediates. An initial intramolecular C-C amination was possible when starting from benzylic azides in the presence of Lewis acids (CF_3SO_3H or $EtAlCl_2$) as the catalyst, secondary amines were observed as side-products (Scheme 27).[49]



Scheme 27. Lewis acid-mediated Schmidt rearrangement of benzylic azides

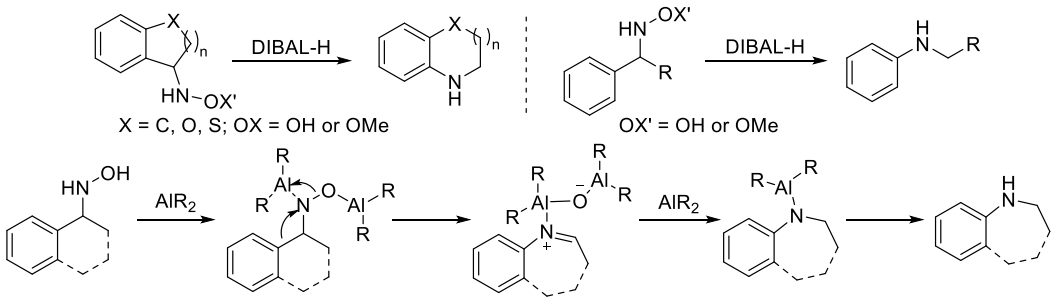
Later the Ning group[9, 50] demonstrated that alkylarenes or secondary benzyl alcohols were feasible to undergo C-C aminations with DDQ as oxidant and NaN_3 or alkyl azides as the aminating reagents (Scheme 28). At first, the transformation was achieved in combination with $FeCl_2$, and moderate yields were afforded without an iron catalyst;

later the technique was developed with NaN_3 and DDQ in the absence of iron. Further later, this technique was developed further by the same group,[51] replacing common oxidants by electrochemistry. However, highly toxic and explosive sodium azides or alkyl azides are essentially needed for this Schmidt-like transformation, thus safety precautions should be taken when undertaking such reactions. Besides, different kinds of alkylarenes (such as *n*-alkylarenes, *i*-alkylarenes) can not be distinguished with this protocol.



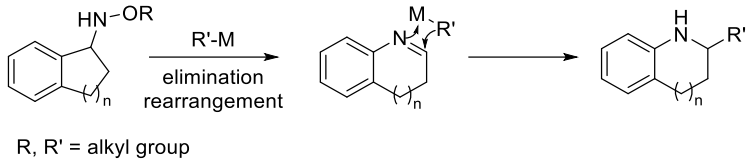
Scheme 28. Arene dealkylative amination with azides

Moreover, intramolecular arene C-C amination with hydroxylamines mediated by Lewis acid can be tracked. Swain,[52] Tokuyama[53] and Naito[54] described DIBAL-H-mediated intramolecular rearrangement of hydroxylamine respectively, delivering the ring-enlargement products; however, all examples were limited to intramolecular reactions (Scheme 29).



Scheme 29. DIBAL-H-mediated intramolecular rearrangement of arylhydroxylamine

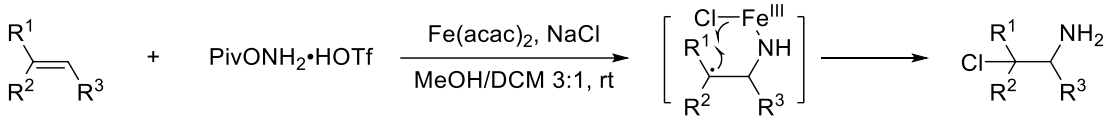
Subsequently, the above strategy was improved by Naito[55] and Miyata,[56] who reported domino elimination/rearrangement/addition reaction of *N*-alkoxy(arylmethyl)amines with alkyl metal reagents, giving α-alkyl-substituted tetrahydroquinoline similarities (Scheme 30).



Scheme 30. Domino reaction of hydroxylamine with organic metal reagents

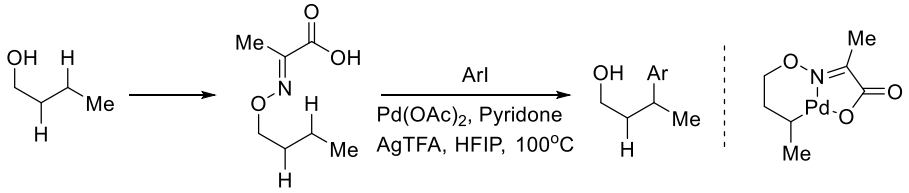
1.3 Other Reactions with Hydroxylamines

In addition to the power of hydroxylamine in amination reactions, several classical examples with hydroxylamine substructures in different types of reactions in recent years are presented below. In 2018, efficient access to primary anilines by an iron-catalyzed aminochlorination of alkenes was reported by Morandi[57] (Scheme 31). This is the first time to directly access 2-chloroalkyamines via a radical pathway, and in combination with anti-Markovnikov regioselectivity with respect to the amino group.



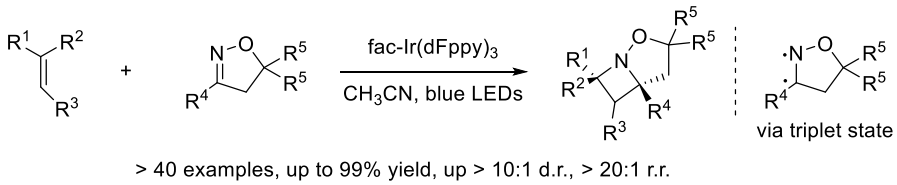
Scheme 31. $Fe(acac)_2$-catalyzed aminochlorination of alkenes

A hydroxylamine sequence can also be used as directing group in palladium-catalyzed C-H functionalization. Yu[58] noted that a distal γ-Csp^3–H activation rather than a proximate β-Csp^3–H activation takes place with pyruvic acid oxime ether as directing group directed by a less strained six-membered cyclopalladation intermediate, which reversed the conventional site-selectivity in Csp^3–H activation (Scheme 32).



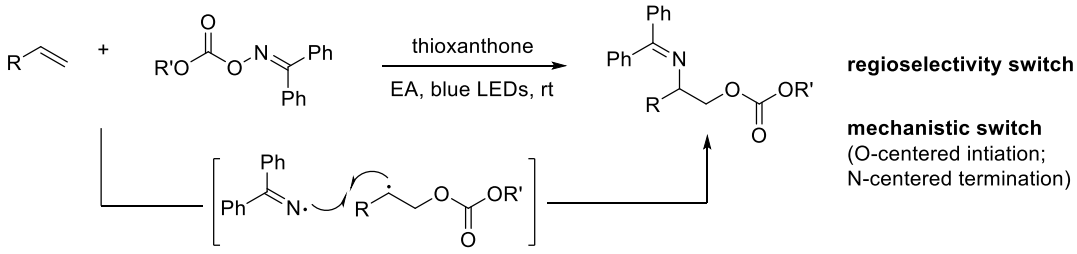
Scheme 32. Pd(OAc)$_2$-catalyzed γ-Csp^3–H functionalization

Hydroxylamine derivatives can also be used in photo-mediated [2+2] reactions. In 2020, Schindler[59] reported an unprecedented visible-light-mediated intermediated intermolecular aza-Paternò–Büchi reaction for the synthesis of azetidines (Scheme 33). The key intermediate was the long-lived diradical of the isoxazoline in the triplet state.



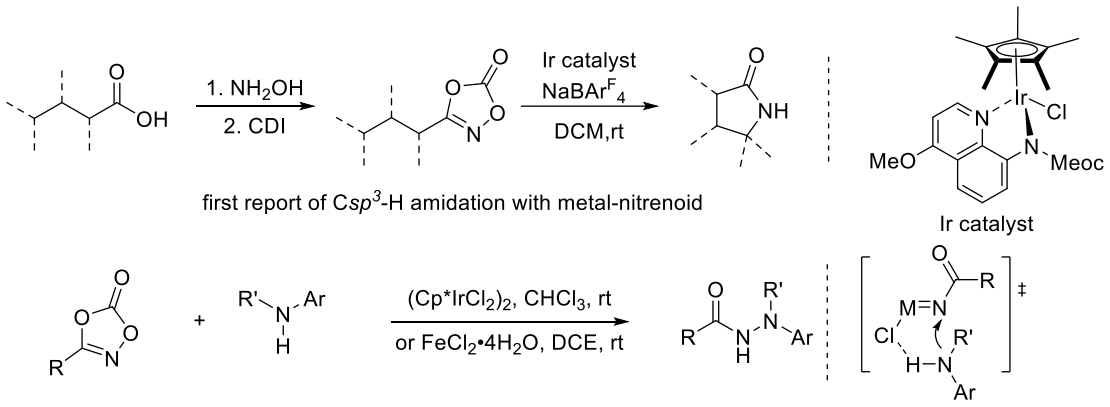
Scheme 33. Photo-mediated intermolecular aza-Paternò–Büchi reaction

In 2021, an oxyimination of unactivated alkenes with bifunctional oxime carbonate was reported by Glorius,[60] which showed different regioselectivity (2-amino-1-alcohol *versus* 1-amino-2-alcohol) and mechanism (oxygen radical initiated, then iminyl radical terminated) (Scheme 34).



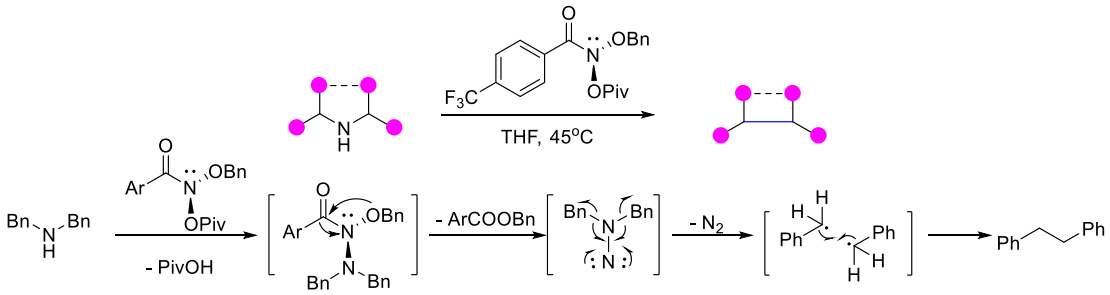
Scheme 34. Photo-mediated oxyimination of alkenes

Dioxazolone, a hydroxylamine derivative, was frequently used as a nitrene precursor by Chang. In 2018, Chang published the first Csp^3-H amidation with an iridium-nitrenoid, and Curtius-type side products were inhibited with the special iridium catalyst (Scheme 35, up).[61] Later, hydrazides were acquired by the intermolecular N-N coupling with the aid of iridium or iron via the same strategy (Scheme 35, down).[62]



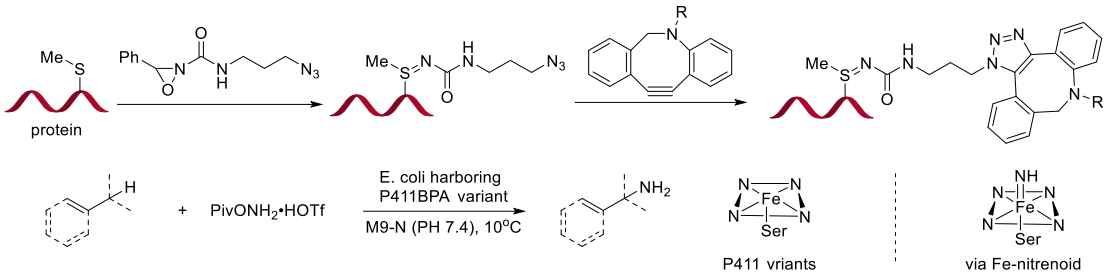
Scheme 35. Metal-nitrene mediated Csp^3-H amidation and N-N coupling reaction

Very recently, a skeletal editing through direct nitrogen deletion of secondary amines enabled by *N*-pivaloyloxy-*N*-alkoxyamides was reported by Levin.[63] He proved that molecular nitrogen was formed, then short-lived diradicals rapidly generated the new carbon-carbon bond (Scheme 36).



Scheme 36. Direct nitrogen deletion of secondary amines

Besides, hydroxylamine could also be used in biology. Toste and Chang[64] disclosed the chemoselective reaction of the native methionine side chains in proteins with oxaziridines to form sulfimidates which was an excellent example of hydroxylamines applied in biology (Scheme 37, up). Later, Arnold[65] reported benzylic and allylic Csp^3-H amination with PivONH$_2$•HOTf catalyzed by enzyme P411 variants (Scheme 37, down).



Scheme 37. Hydroxylamines used in biological sulfimidation and amination

1.4 Objectives

Despite the significant advances, a direct C-N bond formation, particularly a method that enables a direct C-H amination of arenes under benign conditions, is still of high importance. In principle, metal-free processes are preferred, especially in the pharmaceutical industry. As a consequence, safe and easy-to-handle protocols are still needed for direct C-H and C-C aminations under metal-free conditions. Hydroxylamines are often used for photocatalytic/transition metal-catalyzed arene C-H amination or olefin aziridination, and intramolecular aminations were also achieved. The special utility of hydroxylamines in aminations suggests that hydroxylamine derivatives might be powerful aminating reagents for intermolecular reactions. Thus, hydroxylamines were investigated by us to facilitate intermolecular arene C-H/C-C amination under metal-free conditions in an appropriate solvent. In addition, we attempted to afford the site-selective aminated product from different kinds of substrates.

1.5 References

[1] a) U. Scholz, B. Schlummer, in *Science of Synthesis: Houben–Weyl methods of molecular transformations, Vol. 31b*, 1st Edition ed. (Eds.: C. A. Ramsden, D. Bellus), Georg Thieme Verlag, Stuttgart, **2007**, pp. 1565-1678; b) A. Ricci, *Amino Group Chemistry: From Synthesis to the Life Sciences*, Wiley-VCH, **2008**; c) N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Educ.* **2010**, *87*, 1348-1349;

d) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257-10274; e) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546-576; f) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383-394.

[2] a) J. F. Hartwig, *Acc. Chem. Res.* **1998**, *31*, 852-860; b) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564-12649.

[3] a) F. Ullmann, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382-2384; b) I. Goldberg, *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691-1692; c) C. Sambiagio, S. P. Marsden, A. J. Blacker, P. C. McGowan, *Chem. Soc. Rev.* **2014**, *43*, 3525-3550.

[4] a) D. M. T. Chan, K. L. Monaco, R.-P. Wang, M. P. Winters, *Tetrahedron Lett.* **1998**, *39*, 2933-2936; b) D. A. Evans, J. L. Katz, T. R. West, *Tetrahedron Lett.* **1998**, *39*, 2937-2940.

[5] J. Jiao, K. Murakami, K. Itami, *ACS Catal.* **2016**, *6*, 610-633.

[6] Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247-9301.

[7] Y. Zhao, W. Xia, *Chem. Soc. Rev.* **2018**, *47*, 2591-2608.

[8] M. D. Karkas, *Chem. Soc. Rev.* **2018**, *47*, 5786-5865.

[9] C. Qin, T. Shen, C. Tang, N. Jiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6971-6975.

[10] a) F. Chen, **2018**; b) K. Hyodo, G. Hasegawa, H. Maki, K. Uchida, *Org. Lett.* **2019**, *21*, 2818-2822.

[11] L. J. Allen, P. J. Cabrera, M. Lee, M. S. Sanford, *J. Am. Chem. Soc.* **2014**, *136*, 5607-5610.

[12] a) H. Jiang, X. An, K. Tong, T. Zheng, Y. Zhang, S. Yu, *Angew. Chem. Int. Ed.* **2015**, *54*, 4055-4059; b) X. D. An, S. Yu, *Org. Lett.* **2015**, *17*, 2692-2695.

[13] N. A. Romero, K. A. Margrey, N. E. Tay, D. A. Nicewicz, *Science* **2015**, *349*, 1326-1330.

[14] L. Niu, H. Yi, S. Wang, T. Liu, J. Liu, A. Lei, *Nat. Commun.* **2017**, *8*, 14226.

[15] T. D. Svejstrup, A. Ruffoni, F. Julia, V. M. Aubert, D. Leonori, *Angew. Chem. Int. Ed.* **2017**, *56*, 14948-14952.

[16] A. Ruffoni, F. Julia, T. D. Svejstrup, A. J. McMillan, J. J. Douglas, D. Leonori, *Nat. Chem.* **2019**, *11*, 426-433.

[17] S. L. Rossler, B. J. Jelier, P. F. Tripet, A. Shemet, G. Jeschke, A. Togni, E. M. Carreira, *Angew. Chem. Int. Ed.* **2019**, *58*, 526-531.

[18] W. S. Ham, J. Hillenbrand, J. Jacq, C. Genicot, T. Ritter, *Angew. Chem. Int. Ed.* **2019**, *58*, 532-536.

[19] a) T. Morofuji, A. Shimizu, J. Yoshida, *J. Am. Chem. Soc.* **2013**, *135*, 5000-5003; b) T. Morofuji, A. Shimizu, J. Yoshida, *J. Am. Chem. Soc.* **2014**, *136*, 4496-4499; c) T. Morofuji, A. Shimizu, J. Yoshida, *Chem.-Eur. J.* **2015**, *21*, 3211-3214; d) T. Morofuji, A. Shimizu, J. Yoshida, *J. Am. Chem. Soc.* **2015**, *137*, 9816-9819.

[20] L. Zhang, L. Liardet, J. Luo, D. Ren, M. Gratzel, X. Hu, *Nat. Catal.* **2019**, *2*, 266-373.

[21] a) F. Minisci, *Synthesis* **2002**, *1973*, 1-24; b) M. L. Louillat, F. W. Patureau, *Chem. Soc. Rev.* **2014**, *43*, 901-910.

[22] K. Foo, E. Sella, I. Thome, M. D. Eastgate, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 5279-5282.

[23] G. B. Boursalian, W. S. Ham, A. R. Mazzotti, T. Ritter, *Nat. Chem.* **2016**, *8*, 810-815.

[24] M. P. Paudyal, A. M. Adebesin, S. R. Burt, D. H. Ess, Z. Ma, L. Kürti, J. R. Falck, *Science* **2016**, *353*, 1144-1147.

[25] L. Legnani, G. Prina Cerai, B. Morandi, *ACS Catal.* **2016**, *6*, 8162-8165.

[26] J. Liu, K. Wu, T. Shen, Y. Liang, M. Zou, Y. Zhu, X. Li, X. Li, N. Jiao, *Chem.-Eur. J.* **2017**, *23*, 563-567.

[27] E. M. D'Amato, J. Borgel, T. Ritter, *Chem. Sci.* **2019**, *10*, 2424-2428.

[28] R. R. Anugu, S. Munnuri, J. R. Falck, *J. Am. Chem. Soc.* **2020**, *142*, 5266-5271.

[29] Y. Y. See, M. S. Sanford, *Org. Lett.* **2020**, *22*, 2931-2934.

[30] E. Falk, V. C. M. Gasser, B. Morandi, *Org. Lett.* **2021**, *23*, 1422-1426.

[31] S. Mori, K. Uchiyama, Y. Hayashi, K. Narasaka, E. Nakamura, *Chem. Lett.* **1998**, *27*, 111-112.

[32] a) K. Uchiyama, A. Ono, Y. Hayashi, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2945-2955; b) K. Uchiyama, Y. Hayashi, K. Narasaka, *Synlett* **1997**, *1997*, 445-446.

[33] N. Baldovini, M. Kitamura, K. Narasaka, *Chem. Lett.* **2003**, *32*, 548-549.

[34] G. I. Borodkin, I. R. Elanov, V. G. Shubin, *Russ. J. Organ. Chem.* **2009**, *45*, 934-935.

[35] H. J. Kim, J. Kim, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 16382-16385.

[36] A. A. Kantak, S. Potavathri, R. A. Barham, K. M. Romano, B. DeBoef, *J. Am. Chem. Soc.* **2011**, *133*, 19960-19965.

[37] a) J. L. Jat, M. P. Paudyal, H. Gao, Q. L. Xu, M. Yousufuddin, D. Devarajan, D. H. Ess, L. Kürti, J. R. Falck, *Science* **2014**, *343*, 61-65; b) Z. Ma, Z. Zhou, L. Kürti, *Angew. Chem. Int. Ed.* **2017**, *56*, 9886-9890.

[38] a) J. J. Farndon, X. Ma, J. F. Bower, *J. Am. Chem. Soc.* **2017**, *139*, 14005-14008; b) X. Ma, J. J. Farndon, T. A. Young, N. Fey, J. F. Bower, *Angew. Chem. Int. Ed.* **2017**, *56*, 14531-14535.

[39] J. J. Farndon, T. A. Young, J. F. Bower, *J. Am. Chem. Soc.* **2018**, *140*, 17846-17850.

[40] S. Arshadi, S. Ebrahimiasl, A. Hosseinian, A. Monfared, E. Vessally, *RSC Adv.* **2019**, *9*, 8964-8976.

[41] a) W. Lossen, *Ann. Chem. Pharm.* **1872**, *161*, 347-362; b) H. L. Yale, *Chem. Rev.* **1943**, *33*, 209-256.

[42] A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2725-2736.

[43] T. Curtius, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3023-3033.

[44] H. Wolff, in *Organic Reactions*, **2011**, pp. 307-336.

[45] R. G. Wallace, J. M. Barker, M. L. Wood, *Synthesis* **1990**, *1990*, 1143-1144.

[46] a) E. Beckmann, *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 988-993; b) R. E. Gawley, in *Organic Reactions*, **1988**, pp. 1-75.

[47] E. H. Huntress, H. C. Walter, *J. Am. Chem. Soc.* **1948**, *70*, 3702-3707.

[48] a) D. F. McMillen, D. M. Golden, *Annu. Rev. Phys. Chem.* **1982**, *33*, 493-532; b) J. J. Brocks, H.-D. Beckhaus, A. L. J. Beckwith, C. Rüchardt, *J. Org. Chem.* **1998**, *63*, 1935-1943.

[49] A. Murali, M. Puppala, B. Varghese, S. Baskaran, *Eur. J. Org. Chem.* **2011**, 5297-

5302.

[50] J. Liu, X. Qiu, X. Huang, X. Luo, C. Zhang, J. Wei, J. Pan, Y. Liang, Y. Zhu, Q. Qin, S. Song, N. Jiao, *Nat. Chem.* **2019**, *11*, 71-77.

[51] Y. Adeli, K. Huang, Y. Liang, Y. Jiang, J. Liu, S. Song, C.-C. Zeng, N. Jiao, *ACS Catal.* **2019**, *9*, 2063-2067.

[52] S. E. Booth, P. R. Jenkins, C. J. Swain, *J. Chem. Soc., Chem. Commun.* **1993**.

[53] H. Tokuyama, H. Cho, K. Sugimoto, Y. Iwama, N. Mitsuhashi, K. Okano, *Heterocycles* **2011**, *82*.

[54] O. Miyata, T. Koizumi, H. Asai, R. Iba, T. Naito, *Tetrahedron* **2004**, *60*, 3893-3914.

[55] T. Naito, O. Miyata, T. Ishikawa, M. Ueda, *Synlett* **2006**, *2006*, 2219-2222.

[56] M. Ueda, S. Kawai, M. Hayashi, T. Naito, O. Miyata, *J. Org. Chem.* **2010**, *75*, 914-921.

[57] L. Legnani, G. Prina-Cerai, T. Delcaillau, S. Willems, B. Morandi, *Science* **2018**, *362*, 434-439.

[58] G. Xia, J. Weng, L. Liu, P. Verma, Z. Li, J. Q. Yu, *Nat. Chem.* **2019**, *11*, 571-577.

[59] M. R. Becker, E. R. Wearing, C. S. Schindler, *Nat. Chem.* **2020**, *12*, 898-905.

[60] T. Patra, M. Das, C. G. Daniliuc, F. Glorius, *Nat. Catal.* **2021**, *4*, 54-61.

[61] S. Y. Hong, Y. Park, Y. Hwang, Y. B. Kim, M. H. Baik, S. Chang, *Science* **2018**, *359*, 1016-1021.

[62] H. Wang, H. Jung, F. Song, S. Zhu, Z. Bai, D. Chen, G. He, S. Chang, G. Chen, *Nat. Chem.* **2021**, *13*, 378-385.

[63] S. H. Kennedy, B. D. Dherange, K. J. Berger, M. D. Levin, *Nature* **2021**, *593*, 223-227.

[64] S. Lin, X. Yang, S. Jia, A. M. Weeks, M. Hornsby, P. S. Lee, R. V. Nichiporuk, A. T. Iavarone, J. A. Wells, F. D. Toste, C. J. Chang, *Science* **2017**, *355*, 597-602.

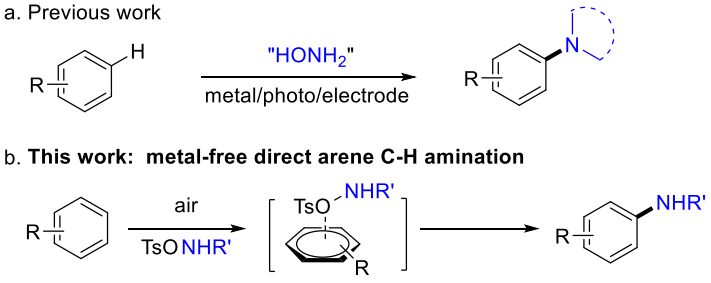
[65] Z. J. Jia, S. Gao, F. H. Arnold, *J. Am. Chem. Soc.* **2020**, *142*, 10279-10283.

Chapter 2 A Metal-free Arene C-H amination

2.1 Introduction

Anilines, key units in chemistry, are widely applied in pharmaceuticals, agrochemicals, organic materials, and natural bioactive products.[1] Until now, a variety of methods are developed for anilines synthesis: traditional nitration-reduction, transition metal-catalyzed coupling reactions and metal/photo/electro-mediated direct arene C-H aminations. Among these, arene C-H aminations are superior to access to anilines, as harsh reaction conditions and aryl pseudo halides are not required. However, special apparatus and expensive transition metals/photosensitizers hamper the utility of those C-H aminations. Accordingly, methods for direct amination under mild conditions without any expensive catalysts are highly desirable while far from being developed.

In all published literature, simple hydroxylamine or its derivatives are often used for the construction of C-N bonds. The representative examples were illustrated below (Scheme 1a): in 2016, Falck[2] invented a rhodium-catalyzed directed arene C-H amination with TsONHMe under mild conditions; Later, a direct arene C-H amination was successful by using hydroxylamine derivatives ($MsONH_2$•HOTf, RCO_2NH_2•HOTf, NsONHMe•HOTf, NH_2OH•HCl) in combination with iron or titanium as the catalyst by Morandi,[3] Ning,[4] Ritter[5] and Sanford;[6] Recently, in an iron-catalyzed process, *meta*-C-H aminated products were achieved with hydroxylamine-*O*-sulfonic acid (HOSA) by Falck;[7] Additionally, Ritter[5] first testified that $MsONH_2$•HOTf could achieve an arene C-H amination under metal-free conditions, providing three examples, which suggests the possibility of hydroxylamine in a metal-free arene C-H amination.



Scheme 1. Methods for the synthesis of arylamines

Based on the above-mentioned protocols, we envisioned that the hydroxylamine derivative in an appropriate solvent would enable a metal-free direct arene C-H amination. Especially, fluorinated solvents (HFIP and TFE), showing strong power in arene C-H amination, might be a good choice in this metal-free amination. Herein, we report that charge transfer in the transition state and radical recombination can lead to *para*-selective amination products without metal and under mild conditions in good yields (especially for electron-rich substrates, Scheme 1b).

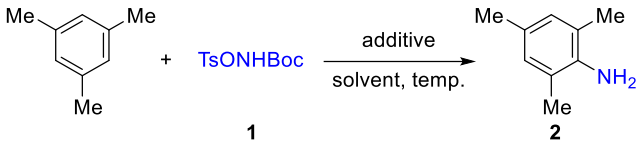
2.2 Results and Discussion

2.2.1 Optimization of the Reaction Condition towards Primary Anilines

Initially, we conducted arene C-H amination in combination with TsONHBoc **1**, inspired by the work of Falck,[2] He[8] and Ritter[9] (Falck: rhodium-catalyzed arene C-H amination with hydroxylamine derivatives; He: gold nitrene initiated arene C-H amination; Ritter: direct arene C-H oxygenation with peroxide MsOOMs). TsONHBoc, bearing a weak N-O bond as MsOOMs does, was deemed to be a potential aminating reagent for the anilines synthesis. Initial investigation of mesitylene, **1** and $AuCl_3$ as a catalyst in TFE at room temperature, provided 2,4,6-trimethylaniline **2** in 41% yield (entry 2). The optimization of aniline synthesis was illustrated in Table 1. The choice of solvent is crucial: no fluorinated DCM failed in the transformation; fluorinated alcohols TFE afforded anilines in moderate yields and more polar, non-nucleophilic HFIP exhibited better performance than TFE, giving 67% yield (entries 1 – 3). Surprisingly, $AuCl_3$ is not essential for the reaction, an even better yield was acquired without gold catalyst (entries 2, 3). Moreover, the concentration of reaction affected the yield: high yield was afforded with a high concentration (entries 4 – 6); 2 equivalents of **1** gave better yield (entries 6, 8). Room temperature performed better than an elevated temperature (entries 6, 7). The relevant aminating reagent, MsONHBoc, generated a comparable yield (entries 8, 9). 0.2 mol/L of mesitylene in combination with TsONHMe (**1**, 0.4 mmol) in 1mL HFIP at room temperature turned out the

optimized condition, delivering isolated 81% yield. A control experiment of **1** alone in HFIP indicated that the Boc group was removed in the acidic HFIP within 3 h (see Experimental Section).

Table 1. Optimization of the C-H amination between mesitylene with TsONHBoc



1 **2**

Entry	Solvent	Additive	Yield[a]
1	DCM (0.1M, r.t.)	$AuCl_3$	0
2	TFE (0.1M, r.t.)	$AuCl_3$	41%
3	TFE (0.1M, r.t.)	None	45%
4	HFIP (0.1M, r.t.)	None	67%
5	HFIP (0.2M, r.t.)	None	70%
6	HFIP (0.4M, r.t.)	None	76%
7	HFIP (0.4M, 50°C)	None	70%
8[b]	**HFIP (0.4M, r.t.)**	**None**	**81% (81%[c])**
9[d]	HFIP (0.4M, r.t.)	None	74%

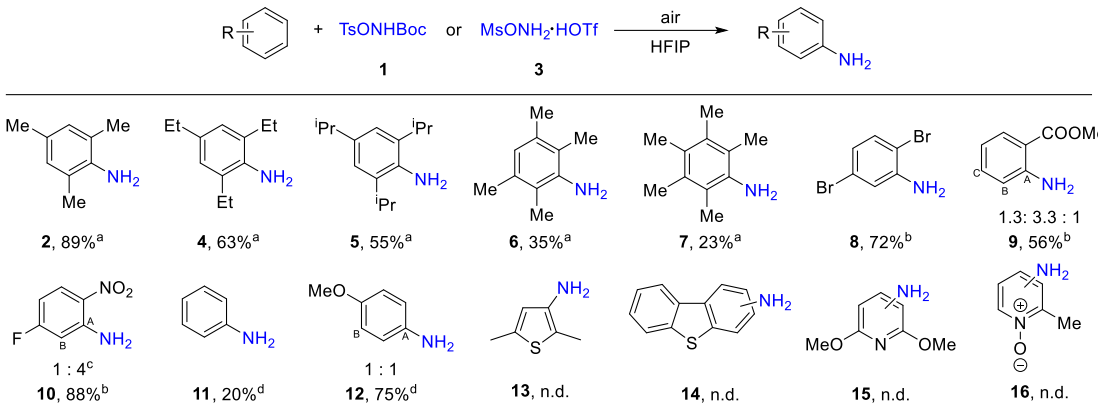
Reaction conditions: mesitylene (0.2 mmol), **1** (0.3 mmol), $AuCl_3$ (0.01 mmol), HFIP (0.5 mL), 36 h. [a]NMR yield (1,3,5-trimethoxybenzene as internal standard). [b] **1** (0.4 mmol) instead of **1** (0.3 mmol). [c]isolated yield. [d] MsONHBoc (0.4 mmol) instead of **1**.

2.2.2 Scope and Limitation with Respect to Primary Anilines

With optimized conditions in hand, we explored the arene scope with **1** as the aminating reagent (Table 2). Trisubstituted benzenes were feasible in the reaction, providing anilines in moderate to good yields (**2**, **4**, **5**), but polysubstituted benzenes showed less efficiency in the reaction as the relevant anilines (**6**, **7**) are sensitive towards oxidants. Unsymmetric benzenes, anisoles and electron-deficient arenes C-H amination were not implemented with **1**; however, $MsONH_2$•HOTf (**3**), a more powerful aminating reagent, could successfully convert electron-deficient arenes into anilines in good yields at high temperatures (**8** – **10**), but also showed poor performance on an electron-neutral substrate and no anilines detected from electron-rich anisoles. That's is consistent with Ritter's report.[5] Later this problem was solved by Falck's methodology[2] ($Rh(esp)_2$-catalyzed arene C-H amination with *in situ* generated MSH in TFE). With this strategy,

anisole **12** could be aminated in 75% yield with **1** instead of Boc-MSH in HFIP (the *in situ* generated MSH could not completely convert anisole into aniline), but benzene **11** gave poor yield in such protocol. Heteroarenes with S or N atoms (**13** – **16**) could not proceed with C-H amination, as aminating reagents could aminate on heteroatoms first instead of carbons on arenes cores.

Table 2. Substrate scope with respect to the arenes for the synthesis of primary aryl amines



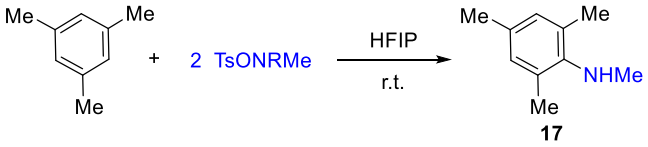
Reaction conditions: [a]arene (0.2 mmol), **1** (0.4 mmol), HFIP (0.5 mL), r.t., 36 h – 10 d, isolated yield, Isomeric ratio (A: B: C) determined by isolated isomers; [b]arene (0.2 mmol), **3** (0.4 mmol), 60°C or 80°C, 12 h – 36 h, isolated yield; [c]isomeric ratio (A: B) determined by NMR; [d]arene (0.2 mmol), $Rh_2(esp)_2$ (0.004 mmol), **1** (0.4 mmol), HFIP (0.5 mL), r.t. 12 h, isomeric ratio (A: B: C) determined by isolated isomers.

2.2.3 Optimization of the Reaction Condition towards Secondary Anilines

The success of arene C-H amination towards primary anilines promoted us to investigate the synthesis of secondary anilines with such protocol. As depicted in Table 3, the first try of mesitylene, *in situ*-generated TsONHMe **18** in the presence of TFA in HFIP afforded *N*,2,4,6-tetramethylaniline **17** in 50% yield (entry 1). But prepared aminating reagent **18** gave a better yield (entry 2). The additive also had an effect on the reaction: $TsOH•H_2O$ slightly decreased the yield, while K_2CO_3 almost totally inhibited the reaction (entries 3, 4). Other reaction parameters were also investigated: a comparable yield was obtained when the reaction was conducted in the dark or under an oxygen atmosphere (entries 5, 7); but the yield decreased significantly (by 9%) when

the reaction was performed under nitrogen atmosphere (entry 6), which means oxygen indeed plays an important role in the reaction. MsONHMe as an alternative aminating reagent could also facilitate the reaction, albeit in a lower yield (76%). 0.2 mmol/L mesitylene with TsONHMe (**18**, 0.4 mmol) in 0.5 mL HFIP at room temperature turned out to be optimal for the synthesis of aniline **17**. All reactions were conducted in new vials, and trace metals are not involved in the arene C-H amination from the ICP experiments (TsONHMe: < 1ppm for Fe, Cu, and Pd, Rh, Ru below the detection limit; HFIP: Fe, Cu, Pd, Rh, Ru below the detection limit). Despite mesitylene's weak benzylic C-H bonds, which are prone to benzylic C-H aminations, only an aromatic Csp^2-H amination was observed in excellent chemoselectivity. No double aminations were observed in our system.

Table 3. Optimization of the C-H amination between mesitylene and TsONHMe



17

Entry	R	Additive	Yield[a]
1	Boc	2 eqs TFA	50%
2	**H**	**None**	**83% (83%)[b]**
3	H	1 eq TsOH•H_2O	76%
4	H	1 eq K_2CO_3	Trace
5[c]	H	None	80%
6[d]	H	None	74%
7[e]	H	None	81%
8[f]	H	None	76%

Reaction conditions: mesitylene (0.2 mmol), aminating reagent (0.4 mmol), HFIP (0.5 mL), 36 h; [a]NMR yield (1,3,5-trimethoxybenzene as internal standard); [b]isolated yield; [c]in the dark; [d]under argon atmosphere; [e]under oxygen atmosphere; [f]MsONHMe (0.4 mmol) instead of **18**.

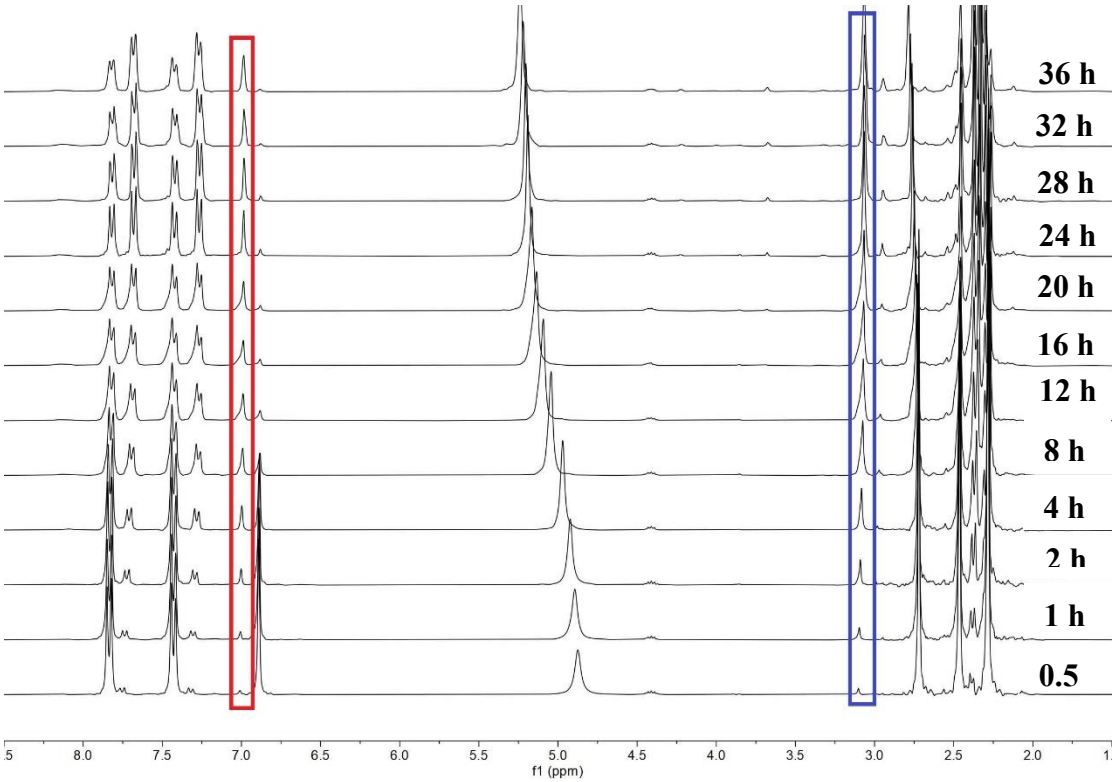


Figure 1. Overlay of ^{1}H NMR samples (d_2-HFIP) taken during the reaction
Aniline **17** signals for aromatic-H highlighted in red, signals for MeNH group in blue.

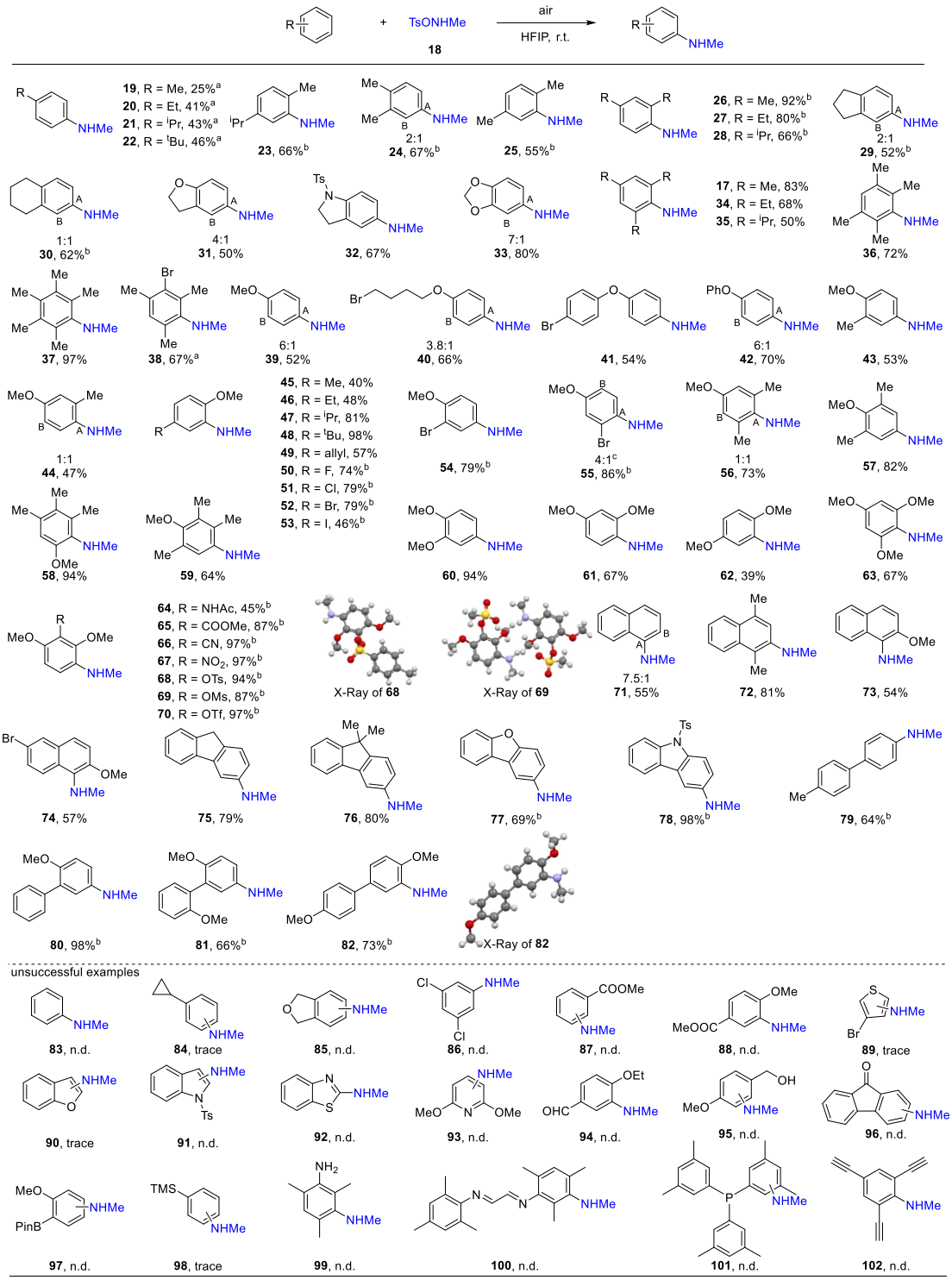
2.2.4 Scope and Limitation with Respect to Secondary Anilines

Next, we explored the scope with respect to the arenes in combination with **18**. As illustrated in Table 4, *para*-substituted anilines were the only isomer from mono-alkylsubstitued benzenes (**19** – **21**), albeit in low to moderate yields and long reaction time. Dialkyl-substituted benzenes (**23** – **28**) went smoothly with **18**, delivering anilines in good to excellent yields as well as good selectivity (except for *o*-xylene, *ortho*-C-H amination took as side reaction; other arenes gave only one isomer of anilines). Indan (**29**) and tetralin (**30**) worked as well, but poor selectivity in line with *o*-xylene. Heterocycles (**31** – **33**) were viable in the amination process, and noteworthy, only one aniline was isolated from 1-tosylindoline **32**. Trialkylsubstituted and polyalkylsubstituted benzenes (**17**, **34** – **38**) were good examples in the transformation, providing anilines in high yields. Besides, anisoles were also testified in our reaction. The successful synthesis of *para*-isomer of anilines from (4-bromobutoxy)benzene (**40**) was needed to point out, as it turned out to be unstable above 35°C. Exclusively the

para-isomer aniline was isolated from 1-bromo-4-phenoxybenzene (**41**), albeit in moderate yield, in contrast to diphenylether (**42**). Unexpectedly, 2-methylanisole afforded only 4-methoxy-*N*,3-dimethylaniline (**43**), compared to 3-methylanisole (**44**). The yields were increased with the steric hindrance of 4-substituted anisoles (**45** – **48**) growing as self-coupling of the amination products was inhibited (see discussion below). 1-Allyl-4-methoxybenzene (**49**), with an olefin which possibly is sensitive to aziridination with **18**, was converted smoothly in moderate yield (no other products were isolated).

Aryl halides would successfully facilitate this conversion with 4 equivalents of **18**, and the desired anilines are precursors for further manipulation as halogens are kept intact (**50** – **55**). Poly-substituted anisoles (**56** – **59**) were exposed to **18**, giving anilines in good yields and, except for **56**, in good selectivity. Different from *o*-xylene, 1,2-dimethoxybenzene (**60**) only produced one isomer in excellent yield; while 1,3-dimethoxybenzene (**61**) and 1,4-dimethoxybenzene (**62**) delivered similar results compared to *p*-xylene and *m*-xylene, respectively. Electron-rich 1,3,5-trimethoxybenzene (**63**) was also aminated in good yield. Fortunately, high to excellent yields, except for **64**, were obtained even if strong electron-withdrawing groups (-COOMe, -NHAc, -NO_2, -OTs, -OMs and -OTf) were introduced on 1,3-dimethoxybenzene derivatives (**64** – **70**), as two methoxyl group are essential to regulate the electronic properties. Naphthalenes (**71** – **74**), fluorenes (**75**, **76**) and heteroarenes (**77**, **78**) were also amenable to install a methylamine group on arene cores. Biphenyl substrates (**79** – **82**) were also implemented in the amination, delivering good to excellent yields, especially for 4-methyl-1,1'-biphenyl (**79**), which afforded the sole isomer. Electronically neutral and electron-deficient arenes (**83** – **88**) were also tested but could not provide the desired anilines; electron-rich/electron-deficient heteroarenes (**89** – **93**) failed in the amination; aldehyde, alcohol, ketone, boronic ester, silane, aniline, imine, phosphine and alkyne (**94** – **102**) were not tolerated in the reaction.

Table 4. Scope of arenes for the synthesis of secondary aryl amines

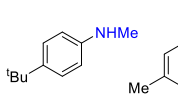
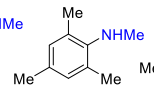
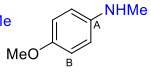
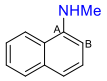
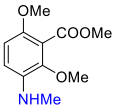
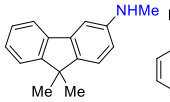
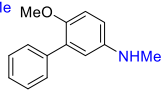


Reaction conditions: arene (0.2 mmol), **18** (0.4 mmol), HFIP (0.5 mL), r.t., 36 h, isolated yields; isomeric ratio (A: B) determined by isolated isomers; [a]**18** (0.8 mmol) was used, 10 d; [b]**18** (0.8 mmol) was used, 3 d, [c]isomeric ratio (A: B) determined by NMR.

Compared to Falck's work[2] (Rhodium-catalyzed arene C-H amination with TsONHMe), our protocol shows a broader substrate scope, albeit needing prolonged

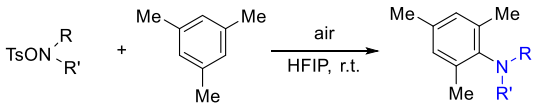
reaction time, especially mono-substituted arenes (**19** – **21**), heteroarenes (**31** – **33**, **77**, **78**) and biphenyls are exclusively mentioned in this study (Table 5).

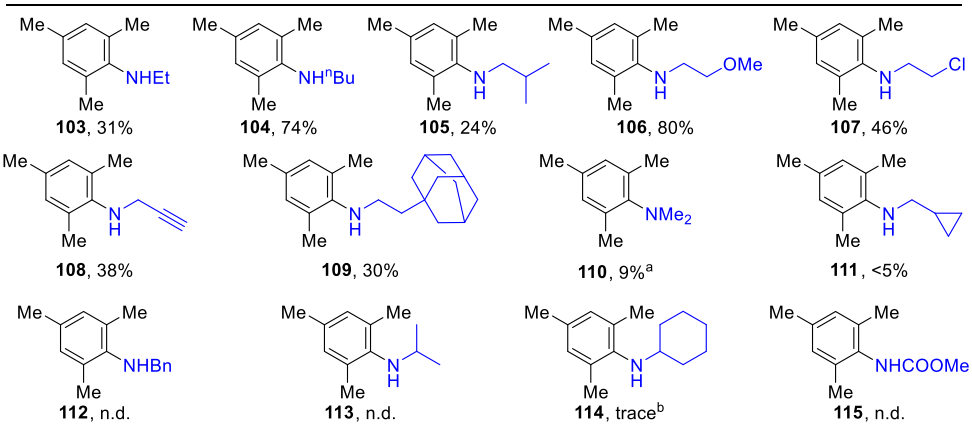
Table 5. Comparison to another aminating method

							
Our method TsONHMe, HFIP	46%, 10 d	83%, 36 h	52%, 6:1, 36 h	55%, 7.5:1, 36 h	87%, 3 d	80%, 36 h	98%, 3 d
Falck's work TsONHMe, $Rh_2(esp)_2$ *Science*, **2016**, 353, 1144	not reported	75%, 0.5 h (TFE)	69%, 16:1, 0.33h (TFE/AcOH)	72%, 4:1, 0.5 h (TFE/MeOH)	61%, 2.5 h TFE	not reported	not reported

To demonstrate the variety of the amination reagents, over 10 hydroxylamines were prepared and converted under the conditions of our protocol (Table 6). The yields were increased with electron-rich aminating reagents (**103** – **107**), but sensitive **103** and branched reagent **105** gave low yields. Remarkably, propargyl amine **108** was still installed in 35% yield, and sterically hindered reagent **109** was successfully converted, too. Tertiary aniline or cyclopropyl amine was isolated in low yield from reagents **110**, **111**, respectively. Aminating reagents (**112** – **115**) with benzyl, isopropyl, cyclohexyl or carbamate groups, failed in the reaction.

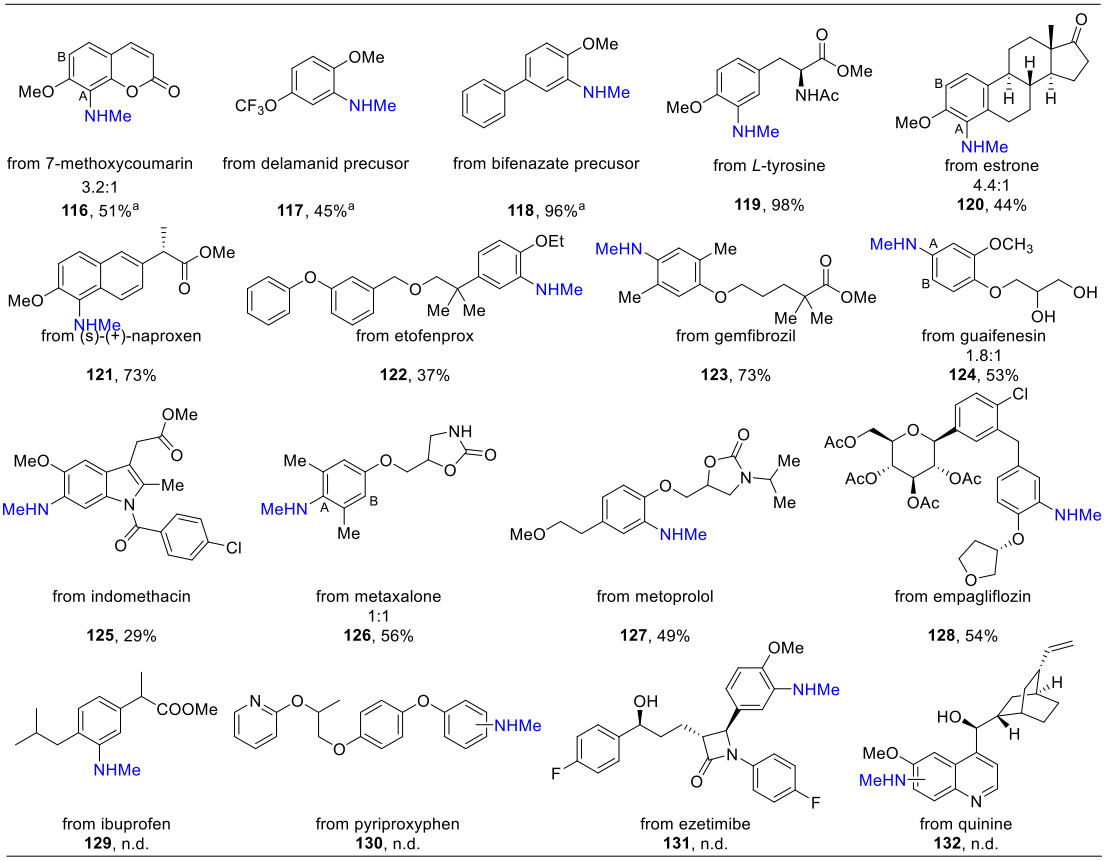
Table 6. Evaluation of the amine partners





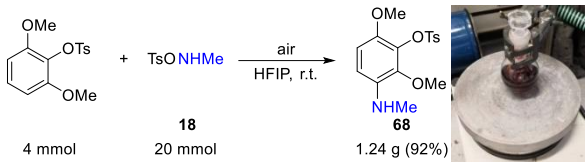
Reaction conditions: arene (0.2 mmol), aminating reagents (0.8 mmol), HFIP (0.5 mL), r.t., 3 d, isolated yields. [a]aminating reagent (0.4 mmol), 36 h; [b]$CyNHOSO_2OH$ (0.4 mmol) was used.

Table 7. Application in late-stage functionalization and related reactions



Reaction conditions: arene (0.2 mmol), **18** (0.4 mmol), HFIP (0.5 mL), r.t., 36 h – 5 d, isolated yields, isomeric distribution (A : B) determined by isolated isomers; [a]**18** (0.8 mmol) were used.

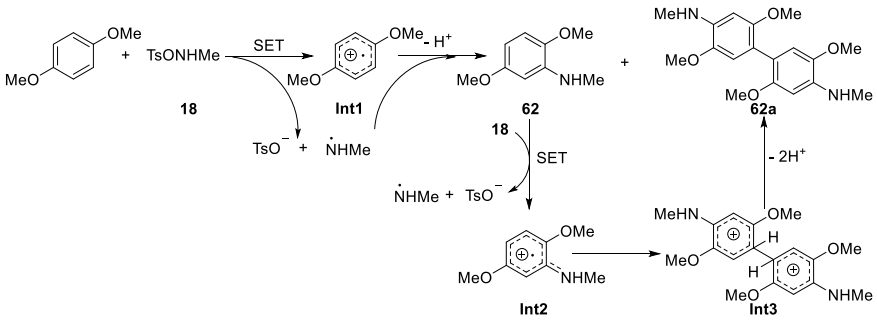
To evaluate the robustness of our protocol, respective drugs and natural bioactive molecules were subjected to late-stage functionalization (Table 7). Coumarin (**116**) and drug precursors (**117** for delamanid, **118** for bifenazate) delivered anilines in moderate to excellent yields. In addition, natural products (*L*-tyrosine **119** and estrone **120**) were also amenable to the arene C-H amination. A variety of pharmaceuticals (naproxen, etofenprox, gemfibrozil, guaifenesin, indomethacin and metaxalone, **121** – **126**) delivered the desired anilines in low to good yields. Metoprolol (**127**, a top 150 best seller in 2019) and empaglifiozin (**128**, a top 50 best seller in 2018) underwent this functionalization smoothly. However, other drugs (electron-neutral or electron-poor or with heteroatoms, **129** – **132**) failed in the reaction. Besides, a large-scale reaction was successfully carried out almost without any loss compared to the small-scale when 2,6-dimethoxyphenyl 4-methylbenzenesulfonate was used as the substrate (Scheme 2).



Scheme 2. Large-scale reaction

2.2.5 Mechanistic Studies

Based on the obtained anilines distribution, an SE_{Ar} seems impossible as only one isomer of anilines from monosubstituted arenes (**19** – **22**) are not indicative of SE_{Ar} regioselectivity. In general, electron-rich arenes afford better yields than electron-deficient arenes, in line with a nitrogen-centered pathway. Moreover, *para*-selectivity is shown by most arenes in the reaction, strongly differing from Sanford's work[10] who reported a poor selectivity of neutral nitrogen radical adding to related or equal arenes. All this suggests not a neutral nitrogen radical but rather an electrophilic nitrogen radical (aminyl or aminium radical) or arene radical cation might be the key intermediate in the reaction. More support for a radical pathway can also be obtained from the self-coupling aniline **62a** (can not be explained by simple aromatic substitution, scheme 3). Plausibly, **62a** was generated via radical cation **Int2** dimerization, which can be derived from the electron-rich aniline **62** to the electron-deficient aminating reagent **18** via an SET process. Besides, a charge transfer between 1,4-dimethoxy benzene and reagent **18** could be involved from the fact that the reaction became yellow from colorless (**18** was decomposed, aniline was formed gradually after the addition of **18** in the d_2-HFIP solution of mesitylene, see experiment part).



Scheme 3. Self-coupling of aniline

In order to get more proof, a series of mechanistic experiments was conducted. The observed bathochromic shifts (absorption band around 400 – 700 nm) in UV/Vis spectra (Figure 2a) upon addition of **18** to 4-*tert*-butylanisole and 1,4-dimethoxybenzene, are in line with Oka's report[11] on the 4-*tert*-butylanisole radical cation (**Int4**) and the 1,4-dimethoxybenzene radical cation (**Int1**). Time-dependent UV/Vis spectra of 1,4-dimethoxybenzene and **18** in HFIP showed Int1 was detected at an early stage, then **Int2** dominated the spectra after a short period and overlapped the signal of **Int1** (Figure 2b). It was verified by the fact that the same bathochromic shifts (450 – 500 nm) were visible between UV1 (1,4-dimethoxybenzene, **18** in HFIP under air) after 50 min and UV2 (**62**, **18** in HFIP under air) after 2 min. The detection of these intermediate species **Int1**, **Int2** and **Int4** strongly support the formation of arene radical cations in our system.

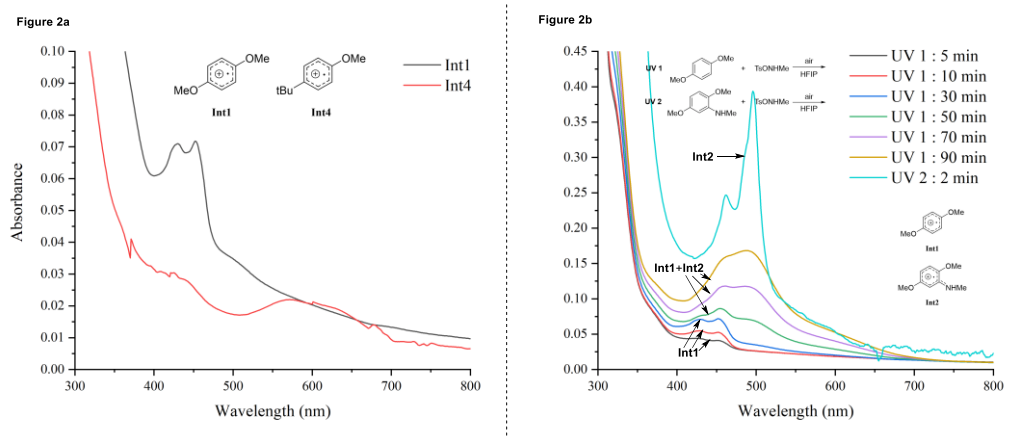


Figure 2. UV/Vis bands of TsONHMe with different arenes

Figure 2a. UV/Vis bands of **Int1** (spectrum measured in UV1 at 10 min under air) and **Int4** (spectrum measured in UV3 (4-*tert*-butylanisole and **18** in HFIP under air) at 3 min under air), Figure 2b. time-dependent UV/Vis bands of UV1 (**18** with 1,4-dimethoxybenzene in HFIP under air) and **Int2** (spectrum measured in UV2 after 2 min under air).

EPR spectra of various samples (Figure 3) were recorded to get more information on the reaction mechanism, specifically the radicals involved (see Scheme 3). Interestingly, the reaction of both 1,4-dimethoxybenzene and **62** with aminating reagent **18** yielded the same product (Figures 3a and 3b), i.e. **Int1** decayed rapidly and cannot be trapped and observed under our experimental conditions. The low stability of **Int1** is in line

with the results from UV/Vis spectra. Our attempts to trap an aminyl radical under argon in presence of DMPO as a radical trapping reagent[12] failed. However, the instability of **Int1** in the reaction mixture is further supported by the spectrum of **Int1** as produced according to Sieiro's report[13] and the corresponding spectrum was shown in Figure 3c. That is, the high decay rate of **Int1** under the reaction conditions is due to the radical recombination involving the aminyl radical. With optimized conditions, fine-structure on each of the eleven transitions was resolved, indicating that there is a very small coupling to the six OMe hydrogen atoms just as in **Int1** (Figure 3c). The observed eleven transitions in the spectra (Figures 3a – 3c) assigned to **Int2**, therefore must be due to the aniline N and H atoms, the three aromatic H atoms and the $NHCH_3$ group. The splitting pattern and intensity distribution suggested that the hyperfine coupling to all H atoms is approx. identical with an approx. double as large coupling to N. The coupling that was well resolved on some of the lines in Figure 3d indicated that the radical couples to the four phenyl H atoms, and the much smaller additional splitting is due to the H atoms of the two OMe groups. The general pattern with an 11 line spectrum and the observed intensity distribution was interpreted as being the result of two isomers of the *para*-dimethoxy radical.[15] The only radical in our proposed mechanism in Scheme 3, following the decay of **Int1** is **Int2**.

Radical trapping experiments were also done to gain more support (Scheme 4): the reaction was almost totally inhibited when a radical scavenger (TEMPO or BHT) was used, confirming that radical species are involved in the reaction. The postulated aminyl radical, formed after the SET process via mesolysis, was efficiently trapped by BHT (aniline **133**, which might be also formed by Bower's concerted mechanism[15]). This provides evidence for the generation of an aminyl radical in our reaction system. The same yield was isolated as BHT was aminated by **18** even without mesitylene, suggesting BHT is a better donor than mesitylene.

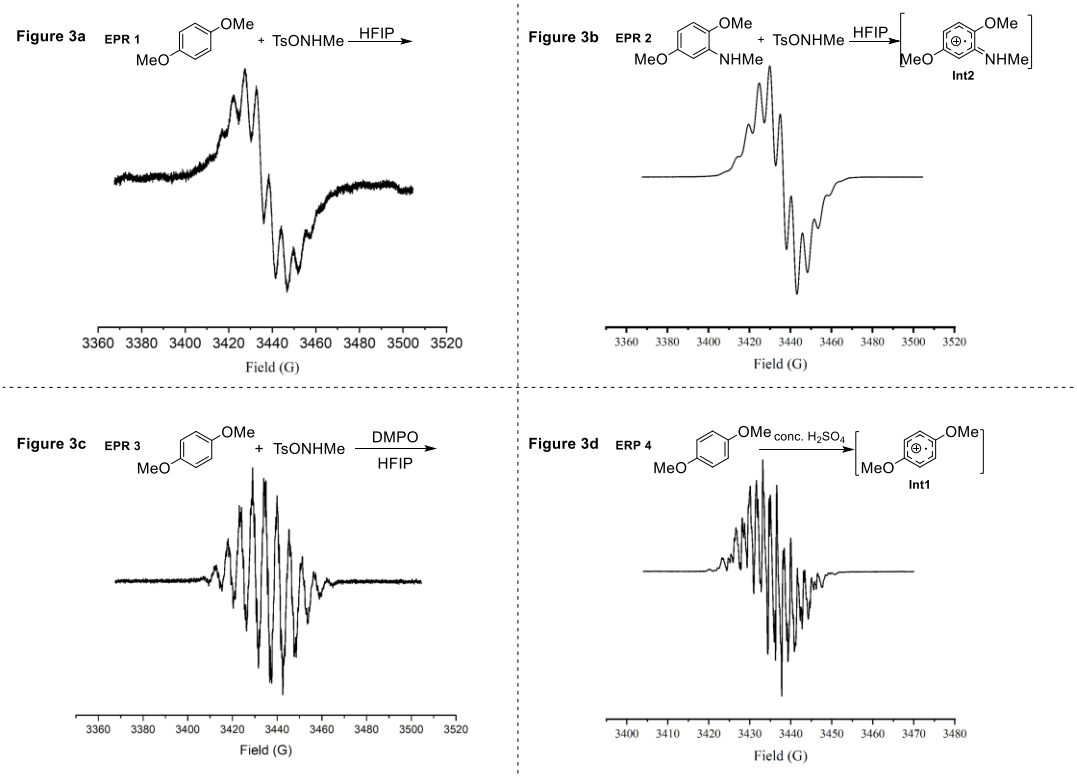
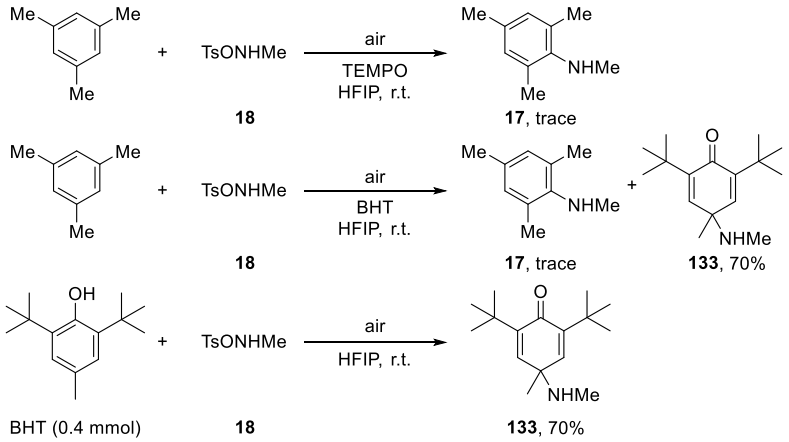


Figure 3. EPR spectra of different radicals

Figure 3a. EPR spectrum: **18** with 1,4-dimethoxybenzene in HFIP; Figure 3b. EPR spectrum: **18** with 2,5-dimethoxy-*N*-methylaniline **62** in HFIP; Figure 3c. EPR spectrum: **18** with 1,4-dimethoxybenzene and DMPO in HFIP; Figure 3d. EPR spectrum: 1,4-dimethoxybenzene in 96% conc.H_2SO_4.



Scheme 4. Radical trapping experiment

Consequently, we hypothesize that a single electron transfer (SET) is initiating the direct metal-free arene C-H amination reaction. To evaluate the possibility of an SET process, the cyclic voltammetry study of aminating reagent **18** was done (see

experimental part; for potentials of arene substrates, see Nicewicz's work[16]): **18** showed a reduction wave at -1.06 V (CH_3CN, vs. Ag), confirming that it can serve as an SET oxidant for electron-rich arenes. Hence, the formation of an initial radical anion ($1e^-$ was transferred from arenes to **18**) is a reasonable process, which then in a fast reaction delivers the aminyl radical via mesolysis, a process reported for these types of nitrogen radicals by Macmillan[17] and Gaunt.[18]

Theoretical Calculations

As already mentioned, oxygen plays an important role in our reaction. This is manifested by the observation that, in contrast to the experiments under open flask conditions discussed above, under an argon atmosphere almost no bathochromic shifts were detected if 4-*tert*-butylanisole or 1,4-dimethoxybenzene were added to **18** (see experiments). This verifies, that oxygen accelerates the SET process (formation of radical cations) in our reaction system, a yet unreported phenomenon in the field of amination chemistry with or without metals.

To further shed light on this observation, geometry optimizations for a hypothetical "sandwich-like" complex, consisting of TsONHMe, 1,4-dimethoxybenze and molecular oxygen, were conducted. The two energetically lowest configurations found (Figure 4), which differ in less than 0.5 kcal/mol, were used for the further analysis of the electron-transfer step (see experiments).

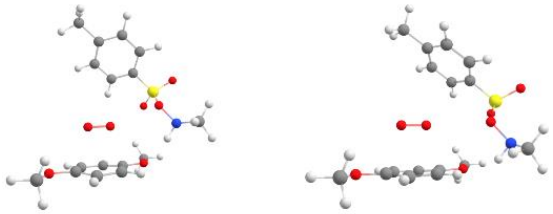


Figure 4. TsONHMe-oxygen-1,4-dimethoxybenzene "sandwich-like" complex

For both structures respectively, a configuration interaction (CI) hamiltonian (in an orthogonal basis) was constructed based on states generated through constrained

density-functional theory (CDFT). By using a two-state model (i->f) for the electron transfer between 1,4-dimethoxybenzene, **18** and the resulting off-diagonal element H_{if}, the magnitude coupling element is paramount for the rate of electron transfer process[19] (Figure 5). Within Marcus' theory, the rate of an electron transfer process is quadratically dependent on the aforementioned coupling element. By taking into account a third state for the upper analyzed "Sandwich-like" complexes by, explicitly involving oxygen via an oxygen mediated bridging state v, a more than threefold increase in the magnitude of the coupling element H_{if} (for both of the considered conformers) resulted and, directly correlated to this, the efficiency of the electron transfer process increased. In line with the experimental observations, this theoretically verifies that the bridging state, available through the presence of oxygen, has an accelerating effect on the electron transfer step between arene substrates and the aminating reagent **18**. A related involvement of an oxygen-mediated bridging state for a triplet excitation energy transfer process was reported by Valkunas group.[20] This theory is also in line with GC kinetic results: at the early stage, under dioxygen the reaction is faster than under dinitrogen atmosphere, and under air (open flask) faster than under dinitrogen; the final yields according to GC are essentially the same (Figure 6).

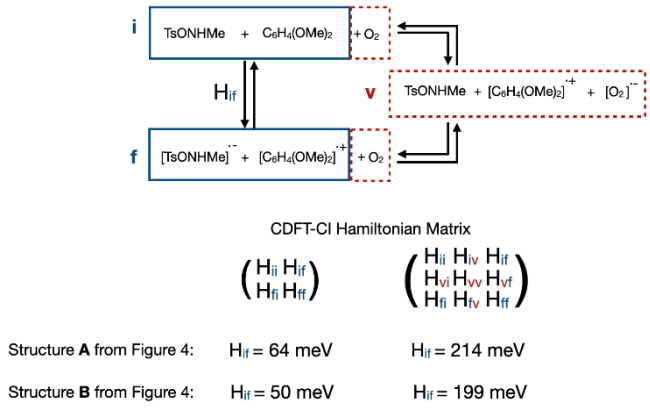


Figure 5. CDFI-CI Hamiltonian matrices

Resulting CDFT-CI Hamiltonian matrices (PBE50/pcseg-1) and the resulting electron transfer coupling element H_{if} resulting from the two-state (left) and three-state model (right).

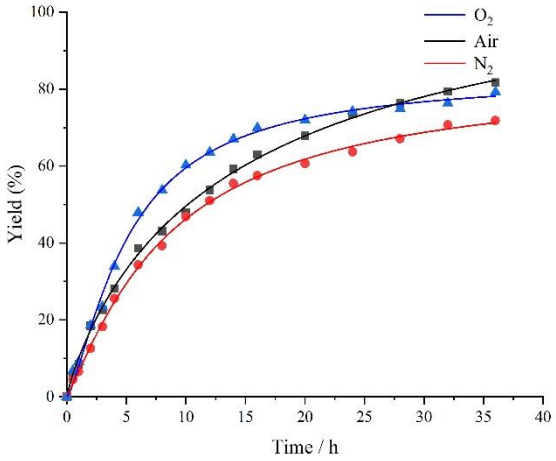
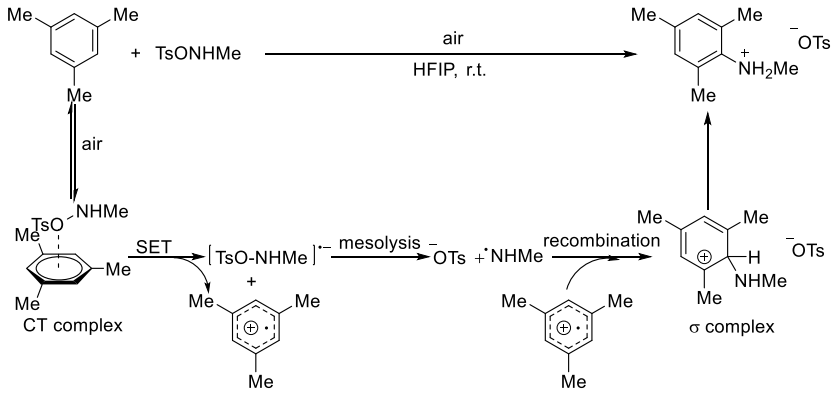


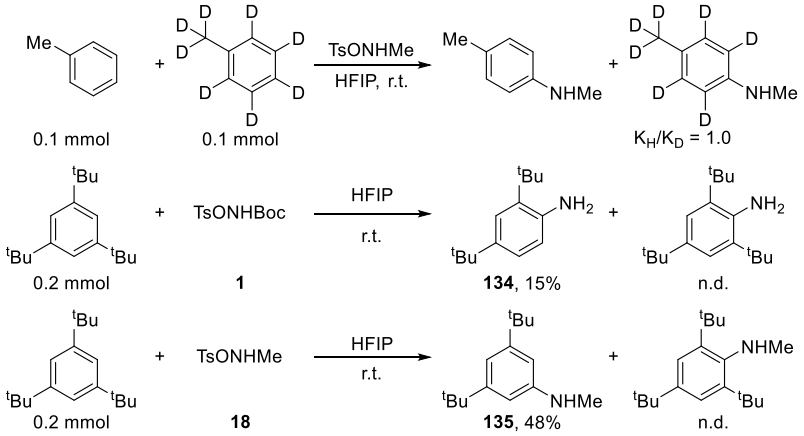
Figure 6. Time/conversion profiles of the reaction under either dioxygen, air or nitrogen. Reaction conditions: mesitylene (0.2 mmol), **18** (0.4 mmol) and nitrobenzene (0.2 mmol; as internal standard) in 0.5 mL HFIP under O_2 or air or N_2 at r.t.

In conclusion, an outer-sphere SET pathway is proposed: a charge-transfer complex (CT complex, arene-TsONHMe) is formed first, and then an oxygen-accelerated SET (electron transfer from arene to **18**) generates an arene radical cation (stabilized by HFIP) and hydroxylamine radical anion. The following mesolysis of the radical anion bearing weak N-O bond then affords aminyl radical (or ammonium radical, protonated by HFIP or tosylic acid generated *in situ*, not shown in Scheme 4). The recombination of arene radical cation and aminyl (or aminium) radical (both species are in close proximity due to the charge transfer event) provides a Wheland complex ((σ-complex), a common intermediate for SE_{Ar} reactions in polar solvents. Finally, this is irreversibly deprotonated to form the protonated aniline.



Scheme 4. Proposed reaction mechanism of C-N bond formation

To gain additional mechanistic insight a KIE experiment with one equimolar mixture of toluene and d_8-toluene was conducted (Scheme 5). The ratio of K_H/K_D is 1:1, indicating that C-H cleavage is not the rate-determining step. Besides, for 1,3,5-tri-*tert*-butylbenzene, instead of substitution of a proton, one *tert*-butyl group was eliminated either **1** or **18** used in the reaction; especially for **18**, C-C amination rather than C-H amination occurred (Scheme 5).



Scheme 5. Kinetic isotope effect and control experiments

The good yield and selectivity of the arene C-H amination are attributed to the unique properties of HFIP[21]: high polarity, weak nucleophilicity, stabilizing arene radical cations, strong hydrogen-donor/acceptor and thus lowering the LUMO of hydroxylamines via hydrogen-bond interactions. Besides, self-coupling side products of anilines are inhibited by the steric hindrance on substrates. Multiple methylamine groups are avoided to introduce on the arene core, as overamination is suppressed (except for **62**) by the formation of protonated anilines in the reaction. Moreover, *para*-selectivity is more favored, especially *para*-isomers are the only products when mono-substituted alkylbenzenes were used, which can be explained by Fukui Indices or the stability of the intermediate arene radical cation. The aminyl (aminium) radical reactivity is distinct from Hofmann–Löffler–Freytag reaction that easily abstracts H atom from Csp^3. Instead, arenes with Csp^2-H functionalization are favored; and no side products are formed based on carbon radicals.

2.3 Conclusion

A direct metal-free arene C-H amination under mild conditions in moderate to excellent yields was developed. In contrast to metal-catalyzed processes, the reaction is triggered by an oxygen-accelerated SET from arene substrates to electron-deficient hydroxylamine derivatives. The recombination of an arene radical cation and an aminyl radical, which are in close proximity, then after proton elimination affords the aniline products. The methodology can be applied for the amination of a variety of complex molecules, natural bioactive products and best-selling drugs. The operationally easy, broad functional group tolerance and scalability of this reaction make it appealing for the academy and industry. Especially noteworthy is the absence of any metal, which makes this process especially attractive for the use in late-stage processes of medicinal chemistry and drug synthesis.

2.4 Experimental Section

2.4.1 General Materials and Methods

Chemicals were purchased from commercial suppliers (Sigma-Aldrich, Alfa Aesar and TCI) and used as delivered. Dry solvents were dispensed from solvent purification system MB SPS-800. HFIP was used directly without further purification. Deuterated solvents were bought from Euriso-Top. Unless otherwise stated, all reactions and manipulations were carried out under ambient atmosphere in new reaction vials or flasks.

NMR Spectra were recorded on a Bruker Avance-III-300, Bruker Avance-III-400, Bruker Avance-III-500, Bruker Avance-III-600. Chemical shifts are reported in ppm with the solvent resonance as the internal standard. For ^{1}H NMR: $CDCl_3$, 7.26; $(CD_3)_2SO$, 2.50; CD_3OD, 3.31; D_2-HFIP, 4.41. For ^{13}C NMR: $CDCl_3$, 77.16; $(CD_3)_2SO$, 39.52; CD_3OD, 49.00. Data is reported as follows: s = singlet, d = doublet, t = triplet, q =quartet, m = multiplet, brs = broad singlet, dd =doublet of doublets, td =triplet of

doublets; coupling constants in Hz; integration.

Mass spectra (MS and HRMS) were determined in the chemistry department of the University Heidelberg under the direction of Dr. J. Gross. EI+ -spectra were measured on a JOEL JMS-700 spectrometer. For ESI+ -spectra a Bruker ApexQu FT-ICR-MS spectrometer was applied.

Gas Chromatography / Mass Spectrometry (GC/MS) spectra were measured on two different hardware systems: 1. HP 5972 Mass Selective Detector, coupled with a HP 5890 SERIES II plus gas chromatography. 2. Agilent 5975C Mass Selective Detector, coupled with an Agilent 7890A gas chromatography. In both cases, as a capillary column, an OPTIMA 5 cross-linked Methyl Silicone column (30 m x 0.32 mm, 0.25 μm) was employed and helium was used as the carrier gas.

UV/Vis spectra were recorded at room temperature on Jasco UV/VIS V-670 spectrophotometer and 1 x 3 cm quartz cuvette. The measurements were done in HFIP.

EPR spectra were carried out at room temperature using a Bruker ELEXSYS E580 CW EPR spectrometer. The measurements were done in HFIP or conc. H_2SO_4.

Infrared Spectroscopy (IR) was processed on an FT-IR Bruker (IF528), IR Perkin Elmer (283) or FT-IR Bruker Vector 22. The solvent or matrix is denoted in brackets. For the most significant bands the wave number ν (cm^{-1}) is given.

Melting points were measured in open glass capillaries in a Büchi melting point apparatus (according to Dr. Tottoli) and were not corrected.

X-ray crystal structure analyses were measured at the chemistry department of the University of Heidelberg under the direction of Dr. F. Rominger on a Bruker Smart CCD or Bruker APEX-II CCD instrument using Mo-Kα-radiation. Diffraction intensities were corrected for Lorentz and polarization effects. An empirical absorption correction was applied using SADABS based on the Laue symmetry of reciprocal space. Hydrogen atoms were either isotropically refined or calculated. The structures were solved and refined by Dr. F. Rominger using the SHELXTL software package.

ICP-OES measurements were carried out using a Agilent 720 ICP-OES with charge coupled devices (CCD) simultaneous detection systems. Plasma torch alignment was performed by using a Mn solution (5 ug/g) at emission line 257.61 nm.

Cyclic voltammetry was performed on a VersaSTAT3-200 potentiostat (Princeton Applied Research). And it was carried out using a glassy carbon working electrode, a platinum/titanium wire auxiliary electrode, a silver wire pseudo-reference electrode, a 0.1 M NBu_4PF_6 solution in N_2 degassed dry acetonitrile.

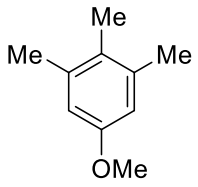
Gas Chromatography (GC) was processed on HP 58090 SERIES II with a HP 1 column. Nitrogen was used as the carrier gas.

Flash Column Chromatography was accomplished using Silica gel 60 (0.04 – 0.063 mm / 230 – 400 mesh ASTM) purchased from Macherey-Nagel.

Analytical / Preparative thin-layer chromatography (TLC) was carried out on pre-coated aluminum sheets provided by Macherey-Nagel ALUGRAM® Xtra SIL G/UV254. Components were visualized by treatment with aqueous $KMnO_4$ solution or by irradiation under UV light (254 nm).

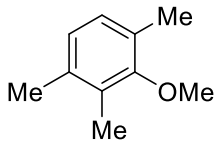
2.4.2 Preparation of Aminating Reagents and Substrates

5-Methoxy-1,2,3-trimethylbenzene was prepared according to a published procedure; spectral data were in agreement with literature values[22]



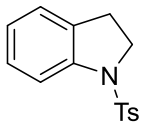
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (s, 2H), 3.78 (s, 3H), 2.28 (s, 6H), 2.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.96, 137.49, 127.05, 113.00, 55.13, 20.81, 14.52.

2-Methoxy-1,3,4-trimethylbenzene was prepared according to a published procedure; spectral data were in agreement with literature values[23]



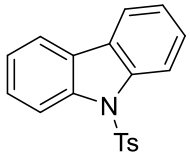
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, J = 7.6 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 3.71 (s, 3H), 2.28 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.75, 135.82, 129.42, 127.99, 127.80, 125.14, 59.79, 19.83, 15.98, 12.18.

1-Tosylindoline was prepared according to a published procedure; spectral data were in agreement with literature values[24]



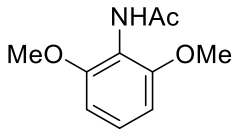
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.61 (m, 3H), 7.25 – 7.14 (m, 3H), 7.07 (d, *J* = 7.3 Hz, 1H), 6.97 (td, *J* = 7.4, 0.8 Hz, 1H), 3.91 (t, *J* = 8.4 Hz, 2H), 2.88 (t, *J* = 8.4 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.99, 141.98, 134.02, 131.72, 129.61, 127.67, 127.29, 125.06, 123.67, 114.99, 49.90, 27.85, 21.50.

9-Tosyl-9*H*-carbazole was prepared according to a published procedure; spectral data were in agreement with literature values[25]



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J = 8.4 Hz, 2H), 7.90 (dd, J = 7.7, 0.9 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.49 (td, J = 7.7, 0.9 Hz, 2H), 7.36 (td, J = 7.7, 0.9 Hz, 2H), 7.09 (d, J = 7.7 Hz, 2H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.82, 138.38, 134.99, 129.61, 127.35, 126.45, 126.36, 123.85, 119.96, 115.14, 21.45.

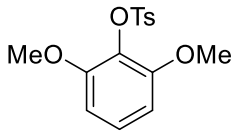
***N*-(2,6-Dimethoxyphenyl)acetamide** was prepared according to a published procedure; spectral data were in agreement with literature values[26]



^{1}H NMR (500 MHz, DMSO-d6) δ 8.83 (s, 1H), 7.19 (t, J = 8.4 Hz, 1H), 6.66 (d, J = 8.4 Hz, 2H), 3.72 (s, 6H), 1.95 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 167.96, 155.97, 127.45, 114.89, 104.33, 55.66, 22.76.

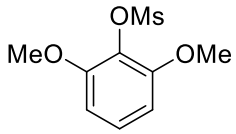
2,6-Dimethoxyphenyl 4-methylbenzenesulfonate was prepared according to a

published procedure; spectral data were in agreement with literature values[27]



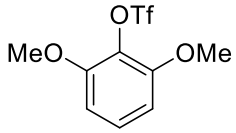
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.13 (t, *J* = 8.5 Hz, 1H), 6.55 (d, *J* = 8.5 Hz, 2H), 3.67 (s, 6H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.51, 144.38, 134.98, 129.09, 128.35, 128.26, 127.31, 104.91, 55.90, 21.60.

2,6-Dimethoxyphenyl methanesulfonate was prepared according to a published procedure; spectral data were in agreement with literature values[27]



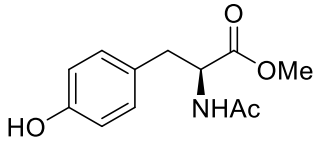
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, *J* = 8.5 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 2H), 3.88 (s, 6H), 3.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.31, 128.24, 127.41, 105.00, 56.22, 39.79.

2,6-Dimethoxyphenyl trifluoromethanesulfonate was prepared according to a published procedure; spectral data were in agreement with literature values[28]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (t, *J* = 8.5 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 2H), 3.88 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.57, 128.50, 128.07, 118.67 (q, *J* = 320.5 Hz), 104.89, 56.24. ^{19}F NMR (283 MHz, $CDCl_3$) δ -73.73.

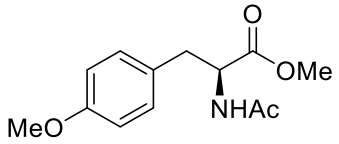
Methyl acetyl-*L*-tyrosinate spectral data were in agreement with literature values[29]



To a suspension of *L*-tyrosine methyl ester hydrochloride (695 mg, 3 mmol) in 15 mL DCM was added Et_3N (319 mg, 3.15 mmol) at 0°C. After 5 min, acetic anhydride (322 mg, 3.15 mmol) was added to the followed mixture at 0°C, then the reaction was warmed up to room temperature and stirred overnight. The reaction was washed with 15 mL sat. brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residual mixture was purified by silica gel chromatography with PE/EA (1:1) as eluting solvent to afford the methyl acetyl-*L*-tyrosinate as a colorless solid (571 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.5 Hz, 2H), 6.18 (d, *J* = 8.0 Hz, 1H), 4.85 (dt, *J* = 8.0, 5.6 Hz, 1H), 3.73 (s, 3H), 3.07 (dd, *J* = 14.1, 5.6 Hz, 1H), 2.95 (dd, *J* = 14.1, 5.6 Hz, 1H), 1.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.31, 170.51, 155.59, 130.19, 126.82, 115.57, 53.39, 52.42, 37.12, 22.94.

Methyl (*S*)-2-acetamido-3-(4-methoxyphenyl)propanoate spectral data were in agreement with literature values[29]

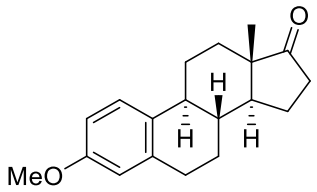


To a suspension of methyl acetyl-*L*-tyrosinate (356 mg, 1.5mmol) and K_2CO_3 (415 mg, 3 mmol) in 4 mL DMF was added CH_3I (426 mg, 3 mmol) at room temperature and the reaction was stirred overnight. Then the reaction was diluted with 10 mL EA and washed with sat. brine (10 mL × 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual mixture was purified by silica gel chromatography with PE/EA (1:1) as eluting solvent to afford the methyl (*S*)-2-acetamido-3-(4-methoxyphenyl)propanoate as a colorless solid (341 mg, 91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.95 (d, *J* = 6.9 Hz, 1H), 4.83 (dt, *J* = 7.8, 5.7 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.14 – 2.96 (m, 2H), 1.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.15, 169.55, 158.68, 130.18, 127.70, 113.96, 55.16, 53.21, 52.25, 36.94, 23.08.

(8*R*,9*S*,13*S*,14*S*)-3-Methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*

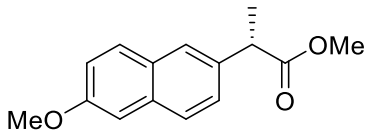
cyclopenta[*a*] phenanthren-17-one spectral data were in agreement with literature values[30]



To a solution of KOH (224 mg, 4 mmol) in DMSO (2 mL) was added estrone (270 mg, 1 mmol) and MeI (230 mg, 2 mmol) at room temperature. The reaction was stirred at room temperature overnight and a colorless solid was formed. Then the solid was filtered and washed with water to afford (8*R*,9*S*,13*S*,14*S*)-3-Methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H* cyclopenta[*a*]phenanthren-17-one as a colorless solid (245 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.6 Hz, 1H), 6.73 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.65 (d, *J* = 2.7 Hz, 1H), 3.78 (s, 3H), 2.91 (dd, *J* = 9.5, 4.8 Hz, 2H), 2.51 (dd, *J* = 18.3, 8.3 Hz, 1H), 2.44 – 1.90 (m, 6H), 1.71 – 1.35 (m, 6H), 0.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.87, 157.57, 137.71, 132.00, 126.30, 113.86, 111.54, 55.17, 50.39, 47.98, 43.95, 38.35, 35.84, 31.56, 29.64, 26.52, 25.90, 21.56, 13.82.

Methyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate spectral data were in agreement with literature values[31]

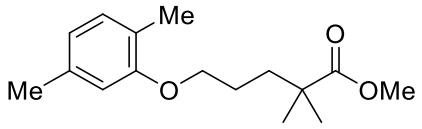


To 10 mL MeOH in a round bottom flask was added (s)-(+)-Naproxen chloride (496 mg, 0.2 mmol) at room temperature, then it was stirred at room temperature for 2 h. The reaction was concentrated in vacuo, and the residual mixture was purified by silica gel chromatography with PE/EA (10:1) as eluting solvent to afford methyl(*S*)-2-(6-methoxynaphthalen-2-yl)propanoate as a colorless solid (463 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.69 (s, 1H), 7.67 (d, *J* = 1.5 Hz, 1H), 7.41 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.17 – 7.10 (m, 2H), 3.91 (s, 3H), 3.87 (q, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 1.59 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.11,

157.62, 135.65, 133.67, 129.24, 128.90, 127.15, 126.15, 125.90, 118.96, 105.57, 55.27, 52.00, 45.31, 18.56.

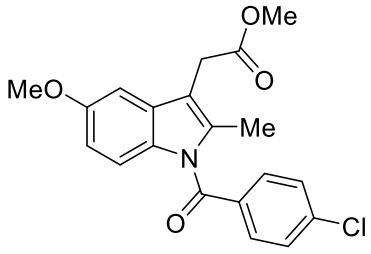
Methyl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate spectral data were in agreement with literature values[32]



To a suspension of methyl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (gemfibrozil, 300 mg, 1.2 mmol) and K_2CO_3 (216 mg, 1.56 mmol) in 3 mL DMF was added CH_3I (276 mg, 2.4 mmol) at room temperature and the reaction was stirred overnight. Then the reaction was diluted with 10 mL EA and washed with sat. brine (10 mL × 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual mixture was purified by silica gel chromatography with PE/EA (30:1) as eluting solvent to afford the methyl 5-(2,5-dimethyl phenoxy)-2,2-dimethyl pentanoate as a colorless liquid (298 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 7.4 Hz, 1H), 6.66 (d, *J* = 7.4 Hz, 1H), 6.61 (s, 1H), 3.94 – 3.91(m, 2H), 3.67 (s, 3H), 2.31 (s, 3H), 2.18 (s, 3H), 1.74 – 1.71 (m, 4H), 1.23 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.30, 156.92, 136.41, 130.26, 123.56, 120.65, 111.92, 67.86, 51.69, 42.08, 37.09, 25.17, 25.16, 21.37, 15.71.

Methyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate spectral data were in agreement with literature values[33]

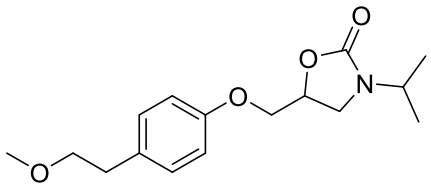


To a suspension of 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid (indomethacin, 1.00 g, 2.8 mmol) thionylchloride (1.16 g, 9.8 mmol) was added

dropwise over 2 min at room temperature, leading to a clear solution. After 10 min, a colorless solid started to form, and the stirrer was turned off. The mixture was allowed to stand at room temperature for 30 min, then the colorless solid was collected by filtration. The solid was washed with 20 mL MeOH, and dried in vacuo to afford methyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate as a colorless solid (601 mg, 58%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.67 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 3.67 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.29, 168.26, 156.06, 139.24, 135.94, 133.91, 131.15, 130.81, 130.63, 129.09, 114.92, 112.49, 111.59, 101.34, 55.70, 52.11, 30.11, 13.28.

3-Isopropyl-5-((4-(2-methoxyethyl)phenoxy)methyl)oxazolidin-2-one



To a suspension of metoprolol tartrate (685 mg, 2 mmol) and CDI (486 mg, 3 mmol) in anhydrous THF (10 mL) was added Et_3N (404 mg, 4 mmol) at room temperature. Then the reaction was heated up to 50°C and stirred at the same temperature for 24 h. The reaction mixture was diluted with EA (10 mL) and filtered through celite. The filtrate was concentrated in vacuo, and the residual mixture was purified by silica gel chromatography with PE/EA (1:1) to afford the 3-isopropyl-5-((4-(2-methoxyethyl) phenoxy)methyl)oxazolidin-2-one as a colorless solid (414 mg, 71%).

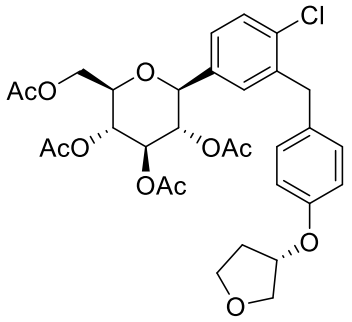
Mp: 83°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.79 (td, *J* = 8.6, 5.6 Hz, 1H), 4.27 – 3.96 (m, 3H), 3.64 (t, *J* = 8.6 Hz, 1H), 3.56 (t, *J* = 7.0 Hz, 2H), 3.47 (dd, *J* = 8.6, 5.6 Hz, 1H), 3.34 (s, 3H), 2.82 (t, *J* = 7.0 Hz, 2H), 1.19 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.71, 156.61, 132.05, 129.86, 114.43, 73.68, 70.76, 68.24, 58.60, 44.76, 41.86, 35.23, 19.73, 19.66.

IR (ATR): ṽ = 2977, 2935, 2898, 2870, 2820, 1735, 1612, 1514, 1480, 1444, 1393, 1372, 1311, 1249, 1206, 1181, 1119, 1057, 941, 879, 838, 761, 710, 620 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 293.16216, found 293.16387.

(2*R*,3*R*,4*R*,5*S*,6*S*)-2-(Acetoxymethyl)-6-(4-chloro-3-(4-(((*S*)-tetrahydrofuran-2-yl)oxy)benzyl) phenyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate



To a suspension of (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-(((S)-tetrahydrofuran-3-yl)oxy)benzyl) phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (empagliflozin, 316 mg, 0.7 mmol), K_2CO_3 (193 mg, 1.4 mmol) in 10 mL 1,4-dioxane was added acetic anhydride (714 mg, 7 mmol) under ambient atmosphere. Then the reaction was stirred at 60°C for 24 h. The reaction mixture was diluted with 20 mL EA, washed with 20 mL sat. brine, and the organic layer was concentrated in vacuo. The residual mixture was purified by silica gel chromatography with PE/EA (1:1) as eluting solvent to afford (2*R*,3*R*,4*R*,5*S*,6*S*)-2-(acetoxymethyl)-6-(4-chloro-3-(4-(((*S*)-tetrahydrofuran-2-yl)oxy)benzyl) phenyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate as a colorless solid (266 mg, 61%).

Mp: 155°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.2 Hz, 1H), 7.18 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 5.28 (t, J = 9.6 Hz, 1H), 5.19 (t, J = 9.6 Hz, 1H), 5.04 (t, J = 9.6 Hz, 1H), 4.88 (ddd, *J* = 7.8, 5.7, 2.4 Hz, 1H), 4.31 (d, *J* = 9.6 Hz, 1H), 4.26 (dd, *J* = 12.4, 4.8 Hz, 1H), 4.19 – 4.10 (m, 1H), 4.08 – 3.84 (m, 6H), 3.79 (ddd, *J* = 9.6, 4.8, 2.4 Hz, 1H), 2.23 – 2.10 (m, 2H), 2.07 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.67, 170.31, 169.46, 168.71, 155.94, 138.89, 135.14, 134.60, 131.56, 129.89, 129.81,

129.77, 126.09, 115.38, 79.47, 77.26, 76.13, 74.09, 73.10, 72.52, 68.48, 67.17, 62.27, 38.24, 32.99, 20.73, 20.60, 20.27.

IR (ATR): $\tilde{\nu}$ = 2872, 1741, 1614, 1580, 1509, 1478, 1438, 1369, 1217, 1174, 1144, 1146, 1094, 1034, 973, 909, 815, 788, 703, 639, 614 cm^{-1}

HRMS (ESI+) m/z: $[M+1]^+$ calcd 619.1941, found 619.1943; $[M+Na]^+$ calcd 641.1760, found 641.1759.

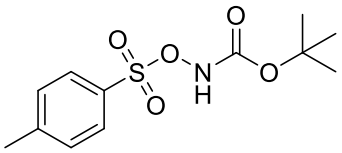
General Procedure for the Mitsunobu Reaction – GP1

To a solution of PPh_3 (1.0 eq) in dry THF was added DIAD (1.0 eq) at 0°C under nitrogen atmosphere. A colorless solid was formed after 10min. After 30 min, a solution of alcohol (1.0 eq) in THF and TsONHBoc (1.0 eq) in THF were added to the mixture successively. Then the reaction was stirred at 0°C for another 1h, and then at room temperature overnight. The reaction was concentrated in vacuo and purified by silica gel chromatography with PE/EA to afford the desired product.

General Procedure for the removal of the Boc Group – GP2

To a solution of *N*-Boc-*N*-alkyl-*O*-tosyl hydroxylamine (1.0 eq) in DCM was added TFA (20.0 eq) at 0°C, then it was stirred at 0°C for 3h. The reaction was basified with sat. $NaHCO_3$ solution at 0°C and then extracted with DCM. The combined organic phases were washed with sat. brine and concentrated in vacuo. The residual mixture was purified by silica gel chromatography with PE/EA to afford the desired product or directly used for the next step without further purification (for unstable aminating reagents).

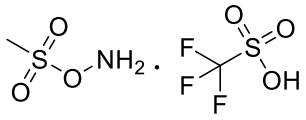
***tert*-Butyl (tosyloxy)carbamate (1)** was prepared according to a published procedure; spectral data were in agreement with literature values[4]



^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2H), 7.67 (s, 1H), 7.36 (d, J = 8.4

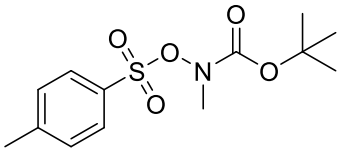
Hz, 2H), 2.45 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.08, 145.90, 130.58, 129.65, 129.60, 83.84, 27.69, 21.71.

$MsONH_2$•HOTf (3) was prepared according to a published procedure; spectral data were in agreement with literature values[3a]



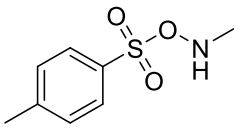
^{1}H NMR (300 MHz, DMSO) δ 2.46 (s, 3H), 4.36 (br, 3H). ^{13}C NMR (75 MHz, DMSO) δ 120.79 (q, J = 322.2 Hz), 39.60. ^{19}F NMR (283 MHz, DMSO) δ -77.74.

***tert*-Butyl methyl(tosyloxy)carbamate (S17)** was prepared according to a published procedure; spectral data were in agreement with literature values[34].



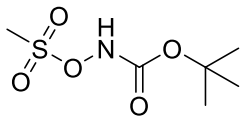
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 3.24 (s, 3H), 2.45 (s, 3H), 1.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.07, 145.67, 131.22, 129.71, 129.52, 83.29, 40.15, 27.57, 21.68.

***N*-Methyl-*O*-tosylhydroxylamine (16)** was prepared according to a published procedure; spectral data were in agreement with literature values[34]



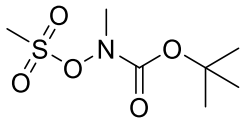
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 5.85 (s, 1H), 2.74 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.93, 132.26, 129.50, 128.94, 40.10, 21.65.

***tert*-Butyl ((methylsulfonyl)oxy)carbamate** was prepared according to a published procedure; spectral data were in agreement with literature values[5].



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 3.17 (s, 3H), 1.52 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.55, 84.75, 36.34, 27.97.

tert-Butyl methyl((methylsulfonyl)oxy)carbamate



To a solution of *N*-methyl hydroxylamine hydrochloride (2.51 g, 30 mmol) in THF/ H_2O (1:1, 20 mL) was added K_2CO_3 (2.07 g, 15 mmol) at 0ºC. Then a solution of di-*tert*-butyl dicarbonate (6.55 g, 30 mmol) in 10 mL THF was added dropwise to the followed mixture and stirring for 2 h at 0°C and then 3 h at room temperature. The reaction was reduced in vacuo and the residue dissolved in 20 mL DCM, washed with water (3 x 10 mL), 20 mL sat. brine and dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford *N*-Boc-*N*-methyl hydroxylamine (3.82 g) as a pale orange oil which was directly used for the next step without further purification.

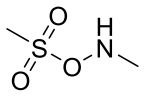
To a solution of *N*-Boc-*N*-methyl hydroxylamine (1.47 g, 10 mmol) in 20 mL dichloromethane was added triethylamine (1.53 mL, 11 mmol) and methanesulfonyl chloride (1.26 g, 11 mmol) at 0ºC. The reaction mixture was allowed to warm to room temperature and stirring for 18 h. The reaction was washed with 20 mL 1.0 M HCl, 20 mL sat. brine and dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA 10:1 as eluting solvent to afford *tert*-butyl methyl((methylsulfonyl)oxy)carbamate as a colorless oil (1.58 g, 40% for two steps).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32 (s, 3H), 3.14 (s, 3H), 1.52 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.08, 84.30, 40.57, 36.63, 28.00.

IR (EXTRACT): $\tilde{\nu}$ = 2981.87, 2942.15, 2295.41, 1729.09, 1459.80, 1412.77, 1368.75, 1324.41, 1258.24, 1182.59, 1148.05, 1107.38, 967.83, 846.25, 811.90, 773.80, 714.71, 650.52 cm^{-1}

HRMS (EI+) m/z: $[M+H]^+$ calcd 226.0744, found 226.0757.

_N_-methyl-_O_-(methylsulfonyl)hydroxylamine



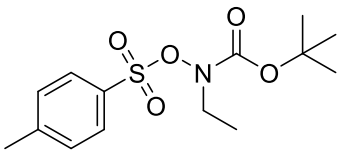
To an solution of *tert*-butyl methyl((methylsulfonyl)oxy)carbamate (450 mg, 2 mmol) in 3 mL DCM was added trifluoroacetic acid (3.0 ml, 40 mmol) at 0ºC. The reaction was stirring for 3 h at 0 °C and then it's poured into 10 mL ice water and extracted with DCM (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel chromatograph to afford *N*-methyl-*O*-(methylsulfonyl)hydroxylamine as a pale yellow oil (152 mg, 61%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (s, 1H), 3.09 (s, 3H), 2.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.43, 34.98.

IR (EXTRACT): ṽ = 3290.89, 3024.58, 2976.02, 2942.26, 1630.82, 1473.67, 1437.47, 1343.12, 1214.22, 1168.40, 1040.91, 1006.95, 964.06, 799.96, 724.95 cm^{-1}

HRMS (ES+) m/z: $[M]^+$ calcd 125.0141, found 125.0133.

***tert*-butyl ethyl(tosyloxy)carbamate**



Following **GP1**, TsONHBoc (862 mg, 3 mmol), ethanol (138mg, 3 mmol), PPh_3 (787 mg, 3 mmol), and DIAD (607 mg, 3 mmol) in 25 mL dry THF solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl ethyl(tosyloxy)carbamate as a colorless solid (744 mg, 79%).

MP: 78ºC

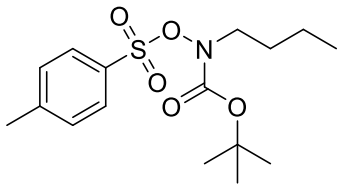
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 2H), 3.66 (br, 2H), 2.45 (s, 3H), 1.22 (s, 9H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$)

δ 155.49, 145.59, 131.24, 129.69, 129.47, 83.18, 48.16, 27.58, 21.68, 10.66.

IR (EXTRACT): ṽ = 2985.48, 2974.09, 2934.12, 1933.83, 1715.98, 1596.76, 1455.23, 1370.66, 1341.05, 1284.53, 1257.84, 1192.63, 1173.44, 1153.55, 1121.83, 1082.73, 1041.28, 1002.80, 949.57, 840.46, 820.44, 749.54, 704.69, 668.95, 636.55 cm^{-1}

HRMS (DART+) m/z: $[M+18]^+$ calcd 333.1479, found 333.1475.

***tert*-Butyl butyl(tosyloxy)carbamate (S22)** spectral data were in agreement with literature values[2]

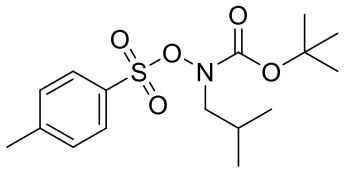


Following **GP1**, TsONHBoc (1.44 g, 5 mmol), *n*-butanol (370 mg, 5 mmol), PPh_3 (1,31 g, 5 mmol), and DIAD (1.01 g, 5 mmol) in 25 mL dry THF solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded *tert*-butyl butyl(tosyloxy)carbamate **S22** as a colorless solid (1.60 g, 93%).

MP: 59°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 3.60 (br, 2H), 2.45 (s, 3H), 1.66 – 1.52 (m, 2H), 1.32 – 1.22 m, 2H), 1.22 (s, 9H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.52, 145.59, 131.32, 129.68, 129.48, 83.03, 52.67, 27.82, 27.58, 21.67, 19.73, 13.68.

***tert*-Butyl isobutyl(tosyloxy)carbamate**



Following **GP1**, TsONHBoc (862 mg, 3 mmol), 2-methylpropan-1-ol (168 mg, 3 mmol), PPh_3 (787 mg, 3 mmol), and DIAD (607 mg, 3 mmol) in 25 mL dry THF

solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl *tert*-butyl isobutyl(tosyloxy)carbamate as a colorless solid (868 mg, 84%).

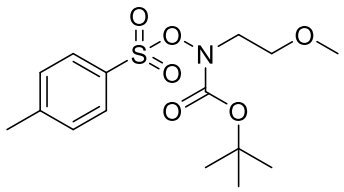
MP: 48°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 3.50 (d, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 2.17 (dt, *J* = 13.8, 6.8 Hz, 1H), 1.22 (s, 9H), 0.88 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.42, 145.64, 131.35, 129.68, 129.51, 82.84, 59.22, 27.57, 25.99, 21.67, 19.92.

IR (EXTRACT): $\tilde{\nu}$ = 2961.14, 2928.04, 2873.95, 1715.77, 1595.51, 1473.02, 1450.28, 1377.26, 1359.90, 1330.86, 1256.15, 1192.76, 1181.30, 1157.35, 1091.40, 1018.06, 847.92, 815.04, 747.36, 667.02, 655.78 cm^{-1}

HRMS (DART+) m/z: $[M+18]^+$ calcd 361.1792, found 361.1794.

tert-Butyl (2-methoxyethyl)(tosyloxy)carbamate



Following **GP1**, TsONHBoc (862 mg, 3 mmol), 2-methoxyethan-1-ol (228 mg, 3 mmol), PPh_3 (787 mg, 3 mmol), and DIAD (607 mg, 3 mmol) in 15 mL dry THF solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl(2-methoxyethyl) (tosyloxy)carbamate as a colorless solid (920 mg, 89%).

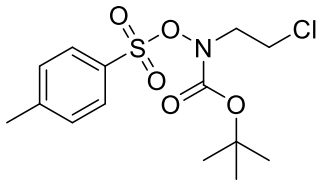
MP: 64°C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 3.63 (br, 4H), 3.29 (s, 3H), 2.44 (s, 3H), 1.20 (s, 9H).^{13}C NMR (125 MHz, $CDCl_3$) δ 155.74, 145.66, 131.00, 129.71, 129.46, 83.02, 67.18, 58.71, 51.73, 27.43, 21.66.

IR (ATR): $\tilde{\nu}$ = 2982, 2936, 2900, 1719, 1598, 1451, 1373, 1310, 1294, 1256, 1183, 1159, 1118, 1018, 959, 862, 847, 819, 752, 670 cm^{-1}

HRMS (ESI+) m/z: $[M+Na]^+$ calcd 368.1138, found 368.1142.

***tert*-Butyl (2-chloroethyl)(tosyloxy)carbamate**



Following **GP1**, TsONHBoc (862 mg, 3 mmol), 2-chloroethan-1-ol (241 mg, 3 mmol), PPh_3 (787 mg, 3 mmol), and DIAD (607 mg, 3 mmol) in 15 mL dry THF solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl(2-chloroethyl)(tosyloxy) carbamate as a colorless solid (855 mg, 82%).

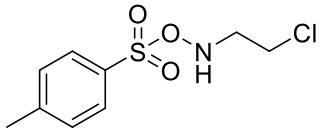
Mp: 104ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 3.99 (t, *J* = 6.5 Hz, 2H), 3.73 (t, *J* = 6.5 Hz, 2H), 2.46 (s, 3H), 1.21 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.81, 146.01, 130.80, 129.78, 129.62, 83.78, 53.46, 39.01, 27.50, 21.70.

IR (ATR): ṽ = 2983, 2946, 1720, 1599, 1450, 1439, 1370, 1292, 1259, 1180, 1162, 1093, 1070, 1063, 985, 901, 845, 820, 773,743, 704, 669 cm^{-1}

HRMS (ESI+) m/z: $[M+Na]^+$ calcd 372.0643, found 372.0645.

***N*-(2-chloroethyl)-*O*-tosylhydroxylamine**



Following **GP2**, *tert*-butyl(2-chloroethyl)(tosyloxy) carbamate (500 mg, 1.4 mmol), TFA (2.1 mL, 28 mmol) in 2 mL DCM solution were stirred at 0ºC for 3h. Purification by silica gel chromatography with PE/EA (8:1) as eluting solvent afforded *N*-(2-chloroethyl)-*O*-tosylhydroxylamine as a colorless solid (317 mg, 89%).

Mp: 71ºC

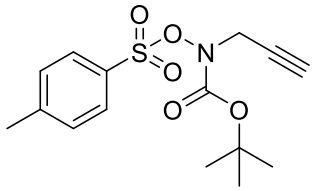
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 5.72 (s, 1H), 3.65 (t, *J* = 5.4 Hz, 2H), 3.26 (t, *J* = 5.4 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (125

MHz, $CDCl_3$) δ 145.26, 131.82, 129.60, 129.06, 53.83, 40.92, 21.69.

IR (ATR): ṽ = 3263, 1595, 1493, 1468, 1426, 1380, 1348, 1307, 1188, 1170, 1123, 1094, 1078, 998, 927, 860, 817, 785, 706, 656 cm^{-1}

HRMS (ESI+) m/z: $[M]^+$calcd 249.02346, found 249.02209.

tert-Butyl prop-2-yn-1-yl(tosyloxy)carbamate



Following **GP1**, TsONHBoc (862 mg, 3 mmol), prop-2-yn-1-ol (168 mg, 3 mmol), PPh_3 (787 mg, 3 mmol), and DIAD (607 mg, 3 mmol) in 25 mL dry THF solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl prop-2-yn-1-yl(tosyloxy)carbamate as a colorless solid (826 mg, 85%).

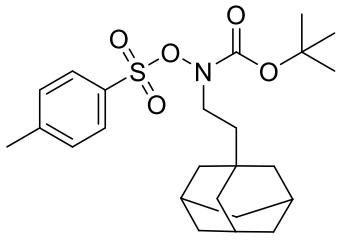
MP: 70°C

^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 4.30 (br, 2H), 2.45 (s, 3H), 2.25 (t, J = 2.4 Hz, 1H), 1.26 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ 154.92, 145.85, 131.02, 129.72, 129.56, 84.33, 76.30, 73.16, 42.88, 27.55, 21.68.

IR (EXTRACT): ṽ = 3274.81, 3003.97, 2985.44, 2924.90, 2121.66, 1727.15, 1596.60, 1459.05, 1422.39, 1380.06, 1341.38, 1322.49, 1258.97, 1192.66, 1179.03, 1149.61, 1092.99, 1048.76, 1017.40, 922.90, 838.51, 816.64, 753.62, 664.36, 648.13, 629.51 cm^{-1}

HRMS (DART+) m/z: $[M+18]^+$ calcd 343.1316, found 343.1322.

tert-Butyl (2-(adamantan-1-yl)ethyl)(tosyloxy)carbamate (S26)



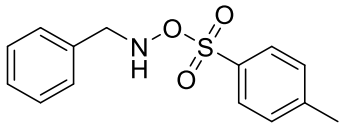
Following **GP1**, TsONHBoc (574 mg, 2 mmol), 2-(adamantan-1-yl)ethan-1-ol (360 mg, 2 mmol), PPh_3 (524 mg, 2 mmol), and DIAD (404 mg, 2 mmol) in 25 mL dry THF solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl (2-(adamantan-1-yl)ethyl)(tosyloxy)carbamate **S26** as a colorless oil (866 mg, 96%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 3.60 (br, 2H), 2.44 (s, 3H), 1.95 – 1.89 (m, 2H), 1.72 – 1.54 (m, 6H), 1.45 (d, *J* = 2.8 Hz, 6H), 1.23 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.49, 145.54, 131.35, 129.67, 129.44, 83.03, 48.53, 42.07, 39.02, 36.98, 31.41, 28.49, 27.62, 21.65.

IR (EXTRACT): $\tilde{\nu}$ = 2901.61, 2846.37, 1716.54, 1596.16, 1452.71, 1372.90, 1352.91, 1315.94, 1291.56, 1276.08, 1255.18, 1189.83, 1174.54, 1158.19, 1118.21, 1093.54, 1071.68, 1032.59, 992.03, 845.89, 813.92, 766.09, 743.11, 703.74, 665.28, 648.29cm^{-1}

HRMS (DART+) m/z: $[M+18]^+$ calcd 467.2574, found 467.2571.

_N_-Benzyl-_O_-tosylhydroxylamine



To a mixture of 60% NaH (120 mg, 3 mmol) in 5 mL DCM was added *N*-Benzylhydroxylamine hydrochloride (239 mg, 1.5 mmol) in small portions at 0ºC, and it was stirred at 0ºC for 10min. Then TsCl (286 mg, 1.5 mmol) was added to the mixture after it was cooled down to -20ºC, and the reaction was stirred for 1h at -20ºC. The reaction was quenched with 2 mL H_2O, extracted with DCM (5 mL × 3). The combined organic phases were washed with 10 mL sat. brine, and concentrated in vacuo. The residual mixture was purified by silica gel chromatography with PE/EA (8:1) to afford *N*-benzyl-*O*-tosylhydroxylamine as a colorless solid (66 mg, 16%).

Mp: 151ºC

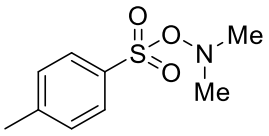
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.27 (m, 5H), 5.91 (s, 1H), 4.06 (s, 2H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ

145.09, 134.61, 129.75, 129.73, 129.68, 129.19, 128.51, 128.07, 56.71, 21.70.

IR (ATR): $\tilde{\nu}$ = 3395, 3065, 3039, 2920, 2854, 1738, 1595, 1493, 1455, 1365, 1335, 1325, 1306, 1294, 1254, 1213, 1183, 1165, 1088, 1050, 1017, 887, 832, 813, 769, 723, 697, 654 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 277.07672, found 277.07728.

***N*, *N*-dimethyl-*O*-tosylhydroxylamine**



To a solution of *N*,*N*-dimethylhydroxylamine hydrochloride (292 mg, 3 mmol) and Et_3N (0.9 mL, 6.6 mmol) in 25 mL DCM was added TsCl (600 mg, 1.05 mmol) in 3 mL DCM solution dropwise at 0°C. A colorless solid was formed after 20 min, and the reaction was stirred at 0°C for 1h. The reaction mixture was filtered to remove the solid, concentrated in vacuo. The residual mixture was purified by silica gel chromatography with PE/EA (10:1) to afford *N*,*N*-dimethyl-*O*-tosylhydroxylamine as a colorless solid (177 mg, 27%).

Mp: 79°C

^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 2.63 (s, 6H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.79, 132.51, 129.41, 128.93, 48.91, 21.65.

IR (ATR): $\tilde{\nu}$ = 3098, 3063, 3007, 2970, 2909, 2874, 2819, 1942, 1738, 1668, 1597, 1495, 1466, 1443, 1399, 1354, 1298, 1213, 1182, 1161, 1122, 1096, 1042, 1018, 993, 918, 829, 815, 794, 774, 705, 660 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 215.06107, found 215.06092.

2.4.3 Substrate Scope

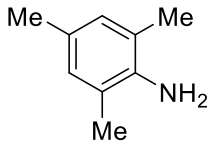
General Procedure for the Amination Reaction (for Primary Amine Products and Secondary Amine Products) – GP 3

To a stirred solution of the aminating reagent (0.4 mmol) in 0.5 mL HFIP solution was added the arene (0.2 mmol) under ambient atmosphere at room temperature, unless otherwise stated. The reaction was stirred at room temperature for 36 h to 10 days (monitored by GCMS or TLC). Then the reaction was diluted with 1mL DCM and basified with 1mL saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with DCM (3 mL × 3), and the combined organic layers were washed with sat. brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by preparative thin-layer chromatography or silica gel chromatography with PE/EA or DCM/MeOH to afford the desired product.

General Procedure for the Amination Reaction (for Secondary Amine Products) – GP 4

To a stirring solution of TsONHMe or other aminating reagents (0.8 mmol) in 0.5 mL HFIP solution was added the arene (0.2 mmol) under ambient atmosphere at room temperature, unless otherwise stated. The reaction was stirred at room temperature for 36 h to 10 days (monitored by GCMS or TLC). Then the reaction was diluted with 1mL DCM and basified with 1 mL saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with DCM (3 mL × 3), and the combined organic layers were washed with sat. brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by preparative thin-layer chromatography or silica gel chromatography with PE/EA or DCM/MeOH to afford the desired product.

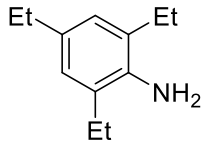
2,4,6-Trimethylaniline (2) spectral data were in agreement with literature values[2]



Following **GP 3**, mesitylene (24 mg, 0.2 mmol), TsONHBoc (86 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded methyl 2,4,6-trimethylaniline **2** as a yellow oil (24 mg, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 2H), 3.45 (br, 2H), 2.21 (s, 3H), 2.16 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.10, 128.81, 127.14, 121.84, 20.33, 17.55.

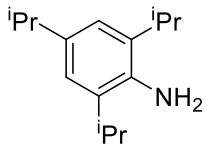
2,4,6-Triethylaniline (4) spectral data were in agreement with literature values[35]



Following **GP 3**, 1,3,5-triethylbenzene (32 mg, 0.2 mmol), TsONHBoc (86 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded methyl 2,4,6-triethylaniline **4** as a yellow oil (22 mg, 63%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 2H), 3.53 (br, 2H), 2.61 – 2.48 (m, 6H), 1.33 – 1.15 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.20, 134.09, 127.87, 125.50, 28.21, 24.41, 16.06, 13.17.

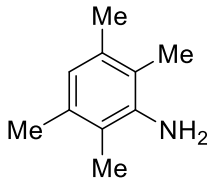
2,4,6-Triisopropylaniline (5) spectral data were in agreement with literature values[36]



Following **GP 3**, 1,3,5-triisopropylbenzene (41 mg, 0.2 mmol), TsONHBoc (86 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded methyl 2,4,6-triisopropylaniline **5** as a yellow oil (24 mg, 55%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 2H), 3.60 (br, 2H), 3.03 – 2.87 (m, 2H), 2.85 – 2.75 (m, 1H), 1.29 (d, J = 6.8 Hz, 12H), 1.25 (d, J = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.71, 138.03, 132.41, 120.69, 33.81, 28.07, 24.36, 22.51.

2,3,5,6-Tetramethylaniline (6)



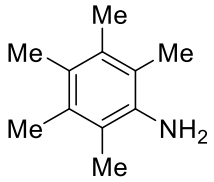
Following **GP 3**, 1,2,4,5-tetramethylbenzene (27 mg, 0.2 mmol), TsONHBoc (86 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 10 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded methyl 2,3,5,6-tetramethylaniline **6** as a yellow solid (11 mg, 35%).

Mp: 66°C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (s, 1H), 3.66 (br, 2H), 2.27 (s, 6H), 2.12 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.54, 133.56, 122.00, 117.90, 20.17, 12.91.

2,3,4,5,6-Pentamethylaniline (7)



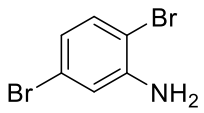
Following **GP 3**, 1,2,3,4,5-pentamethylbenzene (30 mg, 0.2 mmol), TsONHBoc (86 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 10 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded methyl 2,3,4,5,6-pentamethyl aniline **7** as a yellow solid (8 mg, 23%).

Mp: 149°C

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (br, 2H), 2.26 (s, 6H), 2.23 (s, 3H), 2.17 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.24, 132.24, 125.01, 118.13, 16.62, 16.38, 13.74.

2,5-Dibromoaniline (8) spectral data were in agreement with literature values[5]

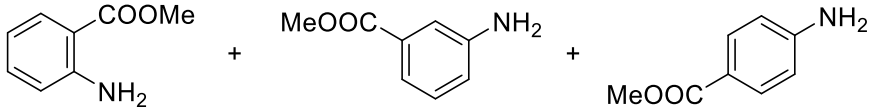


Following **GP 3**, 1,4-dibromobenzene (47 mg, 0.2 mmol), $MsONH_2$•HOTf (104 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred overnight at 60°C. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 2,5-dibromoaniline

8 as a yellow solid (36 mg, 72%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 2.2 Hz, 1H), 6.73 (dd, *J* = 8.4, 2.2 Hz, 1H), 4.13 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.26, 133.59, 122.13, 121.72, 118.09, 107.72.

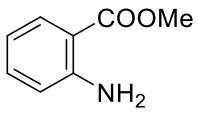
Methyl 2-aminobenzoate (9a), methyl 3-aminobenzoate (9b) and methyl 4-aminobenzoate (9c)



9a **9b** **9c**

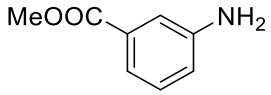
Following **GP 3**, methyl benzoate (27 mg, 0.2 mmol), $MsONH_2$•HOTf (104 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred overnight at 60°C. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded methyl 2-aminobenzoate **9a** as a yellow oil (4 mg, 13%), methyl 3-aminobenzoate **9b** as a yellow solid (10 mg, 33%) and methyl 4-aminobenzoate **9c** as a yellow solid (3 mg, 10%).

Methyl 2-aminobenzoate (9a) spectral data were in agreement with literature values[37]



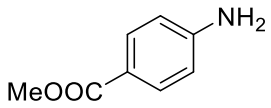
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.26 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 6.75 – 6.57 (m, 2H), 5.71 (br, 2H), 3.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.56, 150.41, 134.05, 131.20, 116.64, 116.25, 110.76, 51.47.

Methyl 3-aminobenzoate (9b) spectral data were in agreement with literature values[38]



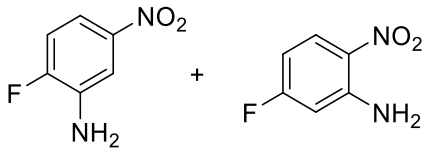
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.35 (t, *J* = 2.2 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 6.85 (ddd, *J* = 7.9, 2.2, 1.2 Hz, 1H), 3.89 (s, 3H), 3.70 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.25, 146.45, 131.11, 129.23, 119.68, 119.35, 115.73, 52.00.

Methyl 4-aminobenzoate (9c) spectral data were in agreement with literature values[39]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 8.7 Hz, 2H), 4.05 (br, 2H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.14, 150.78, 131.58, 119.75, 113.78, 51.58.

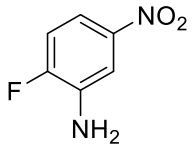
2-Fluoro-5-nitroaniline (10a) and 5-fluoro-2-nitroaniline (10b)



10a **10b**

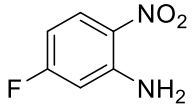
Following **GP 3**, 1-fluoro-4-nitrobenzene (28 mg, 0.2 mmol), $MsONH_2$•HOTf (104 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 40 h at 80°C. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 2-fluoro-5-nitroaniline **10a** and 5-fluoro-2-nitroaniline **10b** as the yellow solid (28 mg combined, 88%, the ratio of 2-fluoro-5-nitroaniline **10a** : 5-fluoro-2-nitroaniline **10b** = 4 : 1 from NMR).

2-Fluoro-5-nitroaniline (10a) spectral data were in agreement with literature values[40]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.8, 2.8 Hz, 1H), 7.58 (ddd, *J* = 8.8, 4.2, 2.8 Hz, 1H), 7.07 (dd, *J* = 10.2, 8.8 Hz, 1H), 4.08 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.64 (d, *J* = 250.1 Hz), 144.66, 135.52 (d, *J* = 14.5 Hz), 115.46 (d, *J* = 21.5 Hz), 114.01 (d, *J* = 8.3 Hz), 111.40 (d, *J* = 6.0 Hz). ^{19}F NMR (283 MHz, $CDCl_3$) δ -125.31.

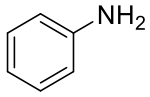
5-Fluoro-2-nitroaniline (10b) spectral data were in agreement with literature values[41]



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 9.6, 5.9 Hz, 1H), 6.48 (dd, *J* = 10.3, 2.5 Hz, 1H), 6.43 (ddd, *J* = 9.6, 7.5, 2.5 Hz, 1H), 6.23 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.87 (d, *J* = 256.3 Hz), 147.28, 146.73 (d, *J* = 13.5 Hz), 129.31 (d, *J* = 12.1 Hz),

105.69 (d, J = 24.6 Hz), 103.65 (d, J = 26.0 Hz). ^{19}F NMR (283 MHz, $CDCl_3$) δ -101.50.

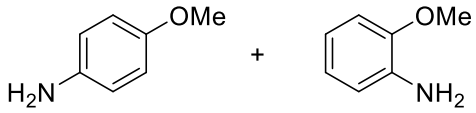
Aniline (11) spectral data were in agreement with literature values[42]



To a stirred solution of the TsONHBoc (115 mg, 0.4 mmol) and $Rh_2(esp)_2$ (3.0 mg, 0.004 mmol) in 0.5 mL HFIP was added benzene (16mg, 0.2 mmol) under ambient atmosphere at room temperature,. The reaction was stirred for 12 h at room temperature. Then the reaction was diluted with 1mL DCM and basified with 1mL saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with DCM (3 mL × 3), and the combined organic layers were washed with sat. brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by preparative thin-layer chromatography or silica gel chromatography with PE/EA (5:1) to afford aniline **11** as a yellow oil (4 mg, 22%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 – 7.14 (m, 2H), 6.81 – 6.74 (m, 1H), 6.75 – 6.66 (m, 2H), 3.57 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.29, 129.26, 118.55, 115.09.

4-methoxyaniline (12a) and 2-methoxyaniline (12b)

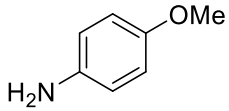


12a **12b**

To a stirred solution of the TsONHBoc (115 mg, 0.4 mmol) and $Rh_2(esp)_2$ (3.0 mg, 0.004 mmol) in 0.5 mL HFIP was added anisole (22mg, 0.2 mmol) under ambient atmosphere at room temperature. The reaction was stirred for 12 h at room temperature. Then the reaction was diluted with 1mL DCM and basified with 1mL saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with DCM (3 mL × 3), and the combined organic layers were washed with sat. brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by preparative thin-layer chromatography or silica gel chromatography with PE/EA (4:1) to afford 4-methoxyaniline **12a** as a brown oil (9 mg, 37%) and 2-methoxyaniline

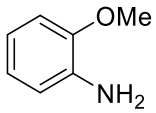
12b as a brown oil (9 mg, 37%).

4-methoxyaniline (12a) spectral data were in agreement with literature values[43]



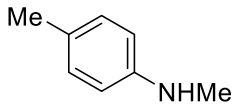
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, J = 8.8 Hz, 2H), 6.65 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H), 3.42 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.78, 139.88, 116.39, 114.77, 55.70

2-methoxyaniline (12b) spectral data were in agreement with literature values[44]



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 – 6.77 (m, 2H), 6.76 – 6.71 (m, 2H), 3.85 (s, 3H), 3.80 (br, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.29, 136.09, 121.03, 118.46, 114.99, 110.37, 55.39.

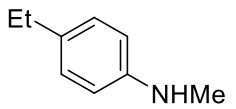
***N*,4-Dimethylaniline (19)** spectral data were in agreement with literature values[45]



Following **GP 4**, toluene (18 mg, 0.2 mmol), TsONHMe (162 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 10 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded *N*,4-dimethylaniline **19** as a yellow oil (6 mg, 25%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.2 Hz, 2H), 6.57 (d, *J* = 8.2 Hz, 2H), 3.34 (br, 1H), 2.83 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.94, 129.67, 126.65, 112.74, 31.19, 20.35.

4-Ethyl-*N*-methylaniline (20) spectral data were in agreement with literature values[46]

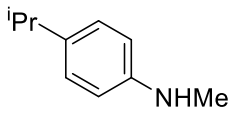


Following **GP 4**, ethylbenzene (21 mg, 0.2 mmol), TsONHMe (162 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 10 days at room temperature. Purification by

silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 4-ethyl-*N*-methylaniline **20** as a yellow oil (11 mg, 41%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.5 Hz, 2H), 6.60 (d, *J* = 8.5 Hz, 2H), 3.57 (br, 1H), 2.84 (s, 3H), 2.57 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.10, 133.37, 128.50, 112.75, 31.16, 27.91, 15.96.

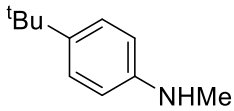
4-Isopropyl-*N*-methylaniline (21) spectral data were in agreement with literature values[47]



Following **GP 4**, cumene (24 mg, 0.2 mmol), TsONHMe (162 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 10 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 4-isopropyl-*N*-methylaniline **21** as a yellow oil (13 mg, 41%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.4 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 2H), 3.36 (br, 1H), 2.90 – 2.79 (m, 1H), 2.84 (s, 3H), 1.25 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.38, 137.80, 127.02, 112.49, 33.14, 30.99, 24.23.

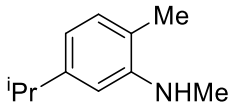
4-(*Tert*-butyl)-*N*-methylaniline (22) spectral data were in agreement with literature values[46]



Following **GP 4**, *tert*-butylbenzene (27 mg, 0.2 mmol), TsONHMe (162 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 10 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 4-(*tert*-butyl)-*N*-methylaniline **22** as a yellow oil (15 mg, 46%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.60 (d, *J* = 8.7 Hz, 2H), 2.84 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.00, 140.06, 125.94, 112.21, 33.81, 31.54, 30.95.

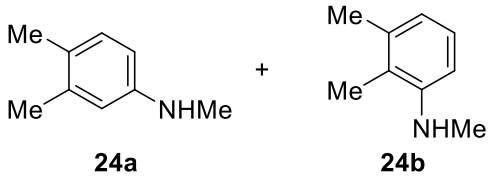
5-Isopropyl-*N*,2-dimethylaniline (23)



Following **GP 4**, *p*-cymene (27 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 5-isopropyl-*N*,2-dimethylaniline **23** as a yellow oil (21 mg, 66%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, *J* = 7.6 Hz, 1H), 6.57 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.50 (d, *J* = 1.4 Hz, 1H), 2.92 (s, 3H), 2.91 – 2.80 (m, 1H), 2.11 (s, 3H), 1.27 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.11, 147.06, 129.81, 119.40, 114.58, 107.58, 34.27, 30.80, 24.16, 16.96.

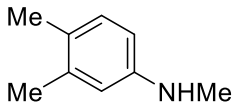
***N*,3,4-Trimethylaniline (24a) and *N*,2,3-trimethylaniline (24b)**



24a **24b**

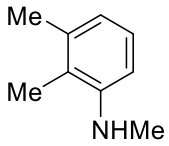
Following **GP 4**, o-xylene (21 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by preparative thin-layer chromatography with PE/EA (20:1) as eluting solvent afforded *N*,3,4-trimethylaniline **24a** as a yellow oil (12 mg) and *N*,2,3-trimethylaniline **24b** as a yellow oil (6 mg) (18 mg total, 67% combined yield).

***N*,3,4-Trimethylaniline (24a)** spectral data were in agreement with literature values[48]



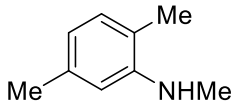
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, *J* = 8.0 Hz, 1H), 6.43 (d, *J* = 2.4 Hz, 1H), 6.40 (dd, *J* = 8.0, 2.4 Hz, 1H), 3.36 (br, 1H), 2.83 (s, 3H), 2.23 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.55, 137.19, 130.20, 125.27, 114.32, 109.93, 31.09, 19.99, 18.63.

***N*,2,3-Trimethylaniline (24b)** spectral data were in agreement with literature values[49]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (t, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 2.89 (s, 3H), 2.29 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.21, 136.33, 126.21, 120.21, 119.25, 107.37, 31.10, 20.60, 12.37.

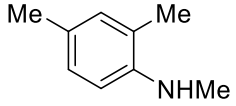
***N*,2,5-Trimethylaniline (25)** spectral data were in agreement with literature values[50]



Following **GP 4**, *p*-xylene (21 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded *N*,2,5-trimethylaniline **25** as a yellow oil (15 mg, 55%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (d, *J* = 7.4 Hz, 1H), 6.50 (d, *J* = 7.4 Hz, 1H), 6.45 (s, 1H), 2.90 (s, 3H), 2.33 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.06, 136.77, 129.73, 118.91, 117.43, 110.10, 30.78, 21.52, 16.90.

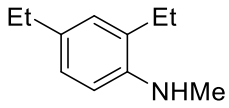
***N*,2,4-Trimethylaniline (26)** spectral data were in agreement with literature values[51]



Following **GP 4**, *m*-xylene (21 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded *N*,2,4-trimethylaniline **26** as a yellow oil (25 mg, 92%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, *J* = 7.8 Hz, 1H), 6.91 (s, 1H), 6.55 (d, *J* = 7.8 Hz, 1H), 2.89 (s, 3H), 2.26 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.98, 130.79, 127.34, 126.01, 122.08, 109.37, 31.05, 20.30, 17.31.

2,4-Diethyl-*N*-methylaniline (27)



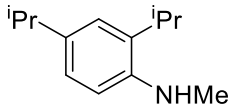
Following **GP 4**, 1,3-diethylbenzene (27 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 2,4-diethyl-*N*-methylaniline **27** as a yellow oil (26 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 3.47 (br, 1H), 2.90 (s, 3H), 2.59 (q, *J* = 7.5 Hz, 2H), 2.50 (q, *J* = 7.5 Hz, 2H), 1.28 (t, *J* = 7.5 Hz, 3H), 1.24 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.62, 132.81, 127.72, 127.47, 125.99, 109.68, 31.09, 28.04, 23.82, 16.06, 12.96.

IR (Reflexion): ṽ = 3436, 2964, 2930, 2874, 2810, 1851, 1814, 1769, 1727, 1615, 1584, 1521, 1454, 1416, 1373, 1307, 1267, 1217, 1171, 1156, 1125, 1061, 961, 887, 812, 723, 623 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 163.13555, found 163.13511.

2,4-Diisopropyl-*N*-methylaniline (28)



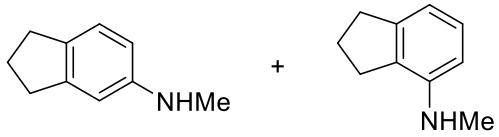
Following **GP 4**, 1,3-diisopropylbenzene (32 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 2,4-diethyl-*N*-methylaniline **28** as a yellow oil (25 mg, 66%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 – 7.03(m, 2H), 6.69 – 6.59 (m, 1H), 3.56 (br, 1H), 2.90 (s, 3H), 2.96 – 2.80 (m, 2H), 1.30 – 1.24 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.98, 137.57, 132.21, 124.09, 123.16, 109.94, 33.44, 31.22, 27.20, 24.33, 22.39.

IR (Reflexion): ṽ = 3412, 2958, 2926, 2869, 2812, 1737, 1613, 1510, 1458, 1418, 1380, 1360, 1309, 1262, 1217, 1186, 1172, 1146, 1087, 1043, 927, 889, 811, 750, 634 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 191.16685, found 191.16767.

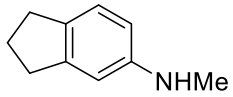
***N*-Methyl-2,3-dihydro-1*H*-inden-5-amine (29a) and *N*-methyl-2,3-dihydro-1*H*-inden-4-amine (29b)**



29a **29b**

Following **GP 4**, 2,3-dihydro-1*H*-indene (24 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by preparative thin-layer chromatography with PE/EA (20:1) as eluting solvent afforded *N*-methyl-2,3-dihydro-1*H*-inden-5-amine **29a** as a yellow liquid (10 mg) and *N*-methyl-2,3-dihydro-1*H*-inden-4-amine **29b** as a yellow oil (5 mg) (15 mg total, 52% combined yield).

***N*-Methyl-2,3-dihydro-1*H*-inden-5-amine (29a)**

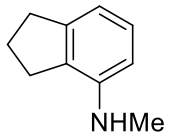


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.0 Hz, 1H), 6.55 (d, *J* = 2.2 Hz, 1H), 6.45 (dd, *J* = 8.0, 2.2 Hz, 1H), 2.91 – 2.74 (m, 4H), 2.83 (s, 3H), 2.13 – 1.99 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.21, 145.38, 133.03, 124.68, 110.94, 108.62, 33.13, 31.90, 31.28, 25.71.

IR (Relexion): ṽ = 3406, 3012, 2945, 2888, 2843, 2808, 1853, 1618, 1585, 1507, 1443, 1413, 1335, 1295, 1258, 1213, 1157, 1124, 1091, 1052, 841, 806, 747, 699, 627 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 147.10425, found 147.10379.

***N*-Methyl-2,3-dihydro-1*H*-inden-4-amine (29b)**



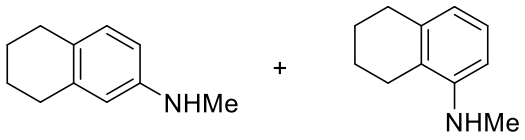
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (t, *J* = 7.7 Hz, 1H), 6.67 (d, *J* = 7.7 Hz, 1H), 6.45 (d, *J* = 7.7 Hz, 1H), 2.96 – 2.87 (m, 2H), 2.89 (s, 3H), 2.68 (m, 2H), 2.18 – 2.02 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.47, 144.70, 128.19, 127.68, 113.57, 106.94, 33.34, 30.77, 29.31, 24.59.

IR (Reflexion): ṽ = 3419, 3040, 2948, 2841, 2811, 1892, 1593, 1503, 1475, 1440, 1338,

1311, 1161, 1125, 1085, 1058, 1000, 945, 762, 709, 637cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 147.10425, found 147.10365.

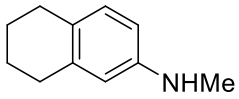
_N_-Methyl-5,6,7,8-tetrahydronaphthalen-1-amine (30a) and _N_-methyl-5,6,7,8-tetrahydronaphthalen-2-amine (30b)



30a **30b**

Following **GP 4**, 1,2,3,4-tetrahydronaphthalene (26 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by preparative thin-layer chromatography with PE/EA (20:1) as eluting solvent afforded *N*-methyl-5,6,7,8-tetrahydronaphthalen-2-amine **30a** as a yellow oil (10 mg) and *N*-methyl-5,6,7,8-tetrahydronaphthalen-1-amine **30b** as a yellow liquid (10 mg) (20 mg total, 62% combined yield).

_N_-Methyl-5,6,7,8-tetrahydronaphthalen-2-amine (30a)



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, *J* = 8.2 Hz, 1H), 6.44 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 3.34 (br, 1H), 2.82 (s, 3H), 2.75 – 2.62(m, 4H), 1.85 – 1.68 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.20, 137.75, 129.72, 126.12, 112.50, 110.92, 31.10, 29.71, 28.50, 23.65, 23.40.

IR (Reflexion): ṽ = 3405, 2926, 2855, 2836, 2660, 1877, 1839, 1617, 1581, 1514, 1470, 1447, 1407, 11352, 1332, 1321, 1306, 1262, 1234, 1204, 1171, 1156, 1117, 1069, 1057, 988, 941, 903, 847, 822, 799, 699 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 161.11990, found 161.12049.

_N_-Methyl-5,6,7,8-tetrahydronaphthalen-1-amine (30b)

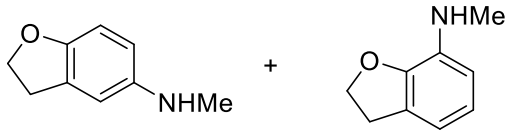
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (t, *J* = 7.8 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 6.47

(d, *J* = 7.8 Hz, 1H), 3.57 (br, 1H), 2.90 (s, 3H), 2.76 (t, *J* = 6.2 Hz, 2H), 2.40 (t, *J* = 6.2 Hz, 2H), 1.92 – 1.83 (m, 2H), 1.81 – 1.73 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.89, 137.41, 126.09, 121.04, 118.17, 106.40, 30.87, 30.04, 23.70, 23.12, 22.70.

IR (Reflexion): ṽ = 3433, 3071, 3035, 2926, 2857, 2834, 2813, 1800, 1590, 1509, 1472, 1439, 1338, 1313, 1285, 1249, 1167, 1151, 1106, 1081, 1060, 1005, 966, 882, 859, 830, 763, 711 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 161.11990, found 161.12102.

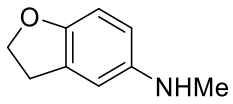
_N_-Methyl-2,3-dihydrobenzofuran-5-amine (31a) and _N_-methyl-2,3-dihydrobenzofuran-7-amine (31b)



31a **31b**

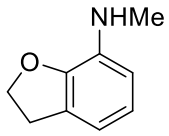
Following **GP 3**, 2,3-dihydrobenzofuran (24 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by preparative thin-layer chromatography with PE/EA (10:1) as eluting solvent afforded *N*-methyl-2,3-dihydrobenzofuran-5-amine **31a** as a yellow oil (12 mg) and *N*-methyl-2,3-dihydrobenzofuran-7-amine **31b** as a brown oil (3 mg) (15 mg total, 50% combined yield).

_N_-Methyl-2,3-dihydrobenzofuran-5-amine (31a) spectral data were in agreement with literature values[52]



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 1.9 Hz, 1H), 6.41 (dd, *J* = 8.4, 1.9 Hz, 1H), 4.49 (t, *J* = 8.6 Hz, 2H), 3.15 (t, *J* = 8.6 Hz, 2H), 2.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.57, 143.83, 127.77, 112.09, 110.07, 109.37, 70.89, 32.00, 30.41.

_N_-Methyl-2,3-dihydrobenzofuran-7-amine (31b)

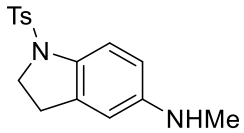


^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (t, *J* = 7.6 Hz, 1H), 6.61 (d, *J* = 7.6, 1H), 6.48 (d, *J* = 7.6 Hz, 1H), 4.56 (t, *J* = 8.7 Hz, 2H), 3.21 (t, *J* = 8.7 Hz, 2H), 2.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.10, 134.56, 125.28, 121.31, 113.21, 109.15, 71.16, 30.62, 30.54.

IR (Reflexion): ṽ = 3397, 3026, 2955, 2918, 2889, 2854, 2803, 1823, 1604, 1492, 1444, 1358, 1336, 1310, 1219, 1152, 1099, 1052, 984, 944, 847, 802, 706 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 149.08352, found 149.08312.

_N_-Methyl-1-tosylindolin-5-amine (32)



Following **GP 3**, 1-tosylindoline (55 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by preparative thin-layer chromatography with PE/EA (4:1) as eluting solvent afforded *N*-methyl-1-tosylindolin-5-amine **32** as a yellow oil (40 mg, 67%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.50 (d, *J* = 8.3 Hz, 1H), 6.38 (s, 1H), 3.86 (t, *J* = 8.1 Hz, 2H), 2.79 (s, 3H), 2.65 (t, *J* = 8.1 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.10, 143.64, 133.96, 129.46, 127.36, 117.23, 112.18, 109.31, 50.26, 31.45, 28.39, 21.48.

IR (Reflexion): ṽ = 3416, 3029, 2954, 2923, 2809, 2255, 1615, 1597, 1491, 1448, 1347, 1305, 1286, 1240, 1184, 1163, 1090, 1053, 972, 912, 813, 731, 708, 691, 662, 612 cm^{-1}

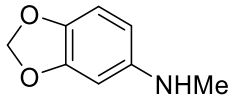
HRMS (EI+) m/z: $[M]^+$ calcd 302.10835, found 302.10730.

_N_-Methylbenzo[*d*][1,3]dioxol-5-amine (33a) and _N_-methylbenzo[*d*][1,3]dioxol-4-amine (33b)

33a **33b**

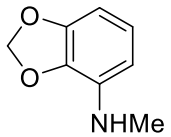
Following **GP 3**, benzo[*d*][1,3]dioxole (25 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by preparative thin-layer chromatography with PE/EA (5:1) as eluting solvent afforded *N*-methylbenzo[*d*][1,3]dioxol-5-amine **33a** as a yellow oil (21 mg) and *N*-methylbenzo[*d*][1,3]dioxol-4-amine **33b** as a yellow oil (3 mg) (24 mg total, 80% combined yield).

***N*-Methylbenzo[*d*][1,3]dioxol-5-amine (33a)** spectral data were in agreement with literature values[45]



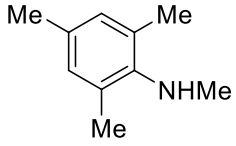
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (d, *J* = 8.3 Hz, 1H), 6.25 (d, *J* = 2.3 Hz, 1H), 6.04 (dd, *J* = 8.3, 2.3 Hz, 1H), 5.85 (s, 2H), 3.38 (br, 1H), 2.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.36, 145.24, 139.55, 108.60, 103.80, 100.55, 95.59, 31.64.

***N*-Methylbenzo[*d*][1,3]dioxol-4-amine (33b)** spectral data were in agreement with literature values[53]



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (t, *J* = 8.2 Hz, 1H), 6.33 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.29 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.90 (s, 2H), 2.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.06, 134.10, 133.75, 122.39, 105.77, 100.51, 99.00, 30.69.

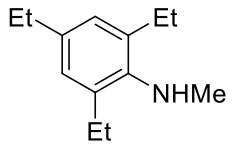
***N*,2,4,6-Tetramethylaniline (17)** spectral data were in agreement with literature values[2]



Following **GP 3**, mesitylene (27 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*,2,4,6-tetramethylaniline **17** as a yellow oil (25 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 2H), 2.74 (s, 3H), 2.27 (s, 6H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.84, 131.32, 129.52, 129.43, 35.58, 20.52, 18.12.

2,4,6-Triethyl-*N*-methylaniline (34)



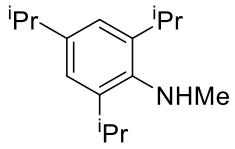
Following **GP 3**, 1,3,5-triethylbenzene (32mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 2,4,6-triethyl-*N*-methylaniline **34** as a yellow oil (26 mg, 68%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (s, 2H), 2.75 (s, 3H), 2.66 (q, J = 7.6 Hz, 4H), 2.58 (q, J = 7.6 Hz, 2H), 1.30 – 1.20 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.96, 138.38, 136.31, 126.17, 37.19, 28.32, 24.34, 15.62, 15.02.

IR (Reflexion): $\tilde{\nu}$ = 3390, 2964, 2932, 2872, 2798, 1758, 1681, 1588, 1475, 1417, 1374, 1319, 1280, 1221, 1139, 1071, 1028, 873, 740, 696 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 191.16685, found 191.16769.

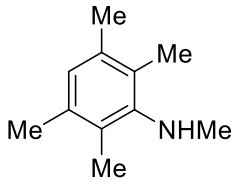
2,4,6-Triisopropyl-*N*-methylaniline (35)



Following **GP 3**, 1,3,5-triisopropylbenzene (41 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 2,4,6-triisopropyl-*N*-methylaniline **35** as a yellow oil (23 mg, 50%).

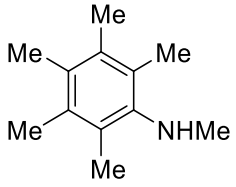
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 2H), 3.29 (hept, *J* = 7.0 Hz, 2H), 2.87 (hept, *J* = 7.0 Hz, 1H), 2.73 (s, 3H), 1.27 (d, *J* = 7.0 Hz, 12H), 1.26 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.71, 142.28, 142.03, 121.48, 38.57, 33.93, 27.74, 24.31, 24.12.
IR (Reflexion): ṽ = 3390, 2961, 2869, 2796, 1763, 1728, 1682, 1606, 1584, 1471, 1417, 1382, 1362, 1310, 1280, 1246, 1217, 1180, 1123, 1069, 1024, 941, 876, 820, 751, 703, 648, 609 cm^{-1}
HRMS (EI+) m/z: $[M]^+$ calcd 233.21380, found 233.21425.

N,2,3,5,6-Pentamethylaniline (36)



Following **GP 3**, 1,2,4,5-tetramethylbenzene (27mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*,2,3,5,6-pentamethylaniline **36** as a yellow solid (23 mg, 72%).
Mp: 49ºC
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (s, 1H), 3.00 (br, 1H), 2.72 (s, 3H), 2.25 (s, 6H), 2.22 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.26, 134.25, 126.32, 126.18, 35.96, 20.30, 13.85.
IR (ATR): ṽ = 3347, 3012, 2948, 2919, 2863, 2798, 1724, 1679, 1611, 1564, 1495, 1464, 1446, 1422, 1395, 1301, 1261, 1225, 1179, 1153, 1126, 1107, 1006, 894, 860, 775, 744, 680, 640, 614 cm^{-1}
HRMS (EI+) m/z: $[M]^+$ calcd 163.13555, found 163.13537.

***N*,2,3,4,5,6-Hexamethylaniline (37)**



Following **GP 3**, 1,2,3,4,5-pentamethylbenzene (30 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*,2,3,4,5,6-hexamethylaniline **37** as a yellow solid (34 mg, 97%).

Mp: 51°C

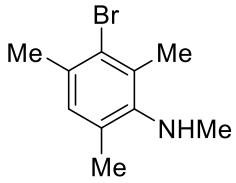
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (br, 1H), 2.70 (s, 3H), 2.29 (s, 6H), 2.25 (s, 6H), 2.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.72, 133.01, 129.78, 126.80, 36.32, 16.79, 16.51, 14.63.

IR (ATR): $\tilde{\nu}$ = 3378, 3304, 2923, 2791, 1656, 1572, 1460, 1406, 1376, 1308, 1255, 1127, 1109, 1065, 1014, 963, 902, 838, 756, 718, 668, 636, 621, 610 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 177.15120, found 177.15147.

3-Bromo-*N*,2,4,6-tetramethylaniline (38)

Following **GP 4**, 2-bromo-1,3,5-trimethylbenzene (40 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 10 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 3-bromo-*N*,2,4,6–tetramethyl aniline **38** as a yellow oil (30 mg, 67%).

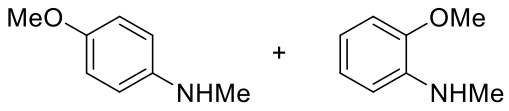


^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 2.71 (s, 3H), 2.42 (s, 3H), 2.33 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.29, 131.96, 130.52, 129.97, 128.60, 125.97, 35.79, 23.47, 18.89, 17.78.

IR (Reflexion): $\tilde{\nu}$ = 3385, 2950, 2922, 2857, 2795, 1795, 1679, 1594, 1469, 1406, 1377, 1306, 1260, 1188, 1143, 1025, 972, 863 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 227.03041, found 227.03070.

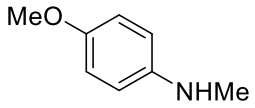
4-Methoxy-*N*-methylaniline (39a) and 2-methoxy-*N*-methylaniline (39b)



39a **39b**

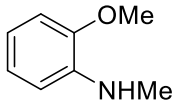
Following **GP 3**, anisole (22 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by preparative thin-layer chromatography with PE/EA (20:1) as eluting solvent afforded 4-methoxy-*N*-methylaniline **39a** as a yellow liquid (12 mg) and 2-methoxy-*N*-methylaniline **39b** as a yellow oil (2 mg) (14 mg total, 52% combined yield).

4-methoxy-*N*-methylaniline (39a) spectral data were in agreement with literature values[2]



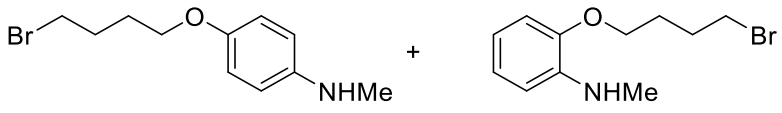
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 3H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.09, 143.62, 114.89, 113.66, 55.83, 31.62.

2-Methoxy-*N*-methylaniline (39b) spectral data were in agreement with literature values[2]



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (td, J = 7.6, 1.5 Hz, 1H), 6.79 (dd, J = 7.6, 1.5 Hz, 1H), 6.69 (td, J = 7.6, 1.5 Hz, 1H), 6.63 (dd, J = 7.6, 1.5 Hz, 1H), 4.24 (br, 1H), 3.86 (s, 3H), 2.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.88, 139.30, 121.31, 116.30, 109.34, 109.22, 55.36, 30.35.

4-(4-Bromobutoxy)-*N*-methylaniline (40a) and 2-(4-bromobutoxy)-*N*-methyl aniline (40b)

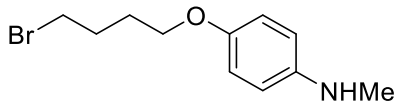


40a **40b**

Following **GP 3**, (4-bromobutoxy)benzene (46 mg, 0.2 mmol), TsONHMe (81 mg, 0.4

mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by preparative thin-layer chromatography with PE/EA (20:1) as eluting solvent afforded 4-(4-bromobutoxy)-*N*-methyl aniline **40a** as a brown oil (27 mg, not stable above 35°C, the solvent was evaporated at 0°C in vacuo) and 2-(4-bromobutoxy)-*N*-methylaniline **40b** as a brown oil (7 mg) (34 mg total, 67% combined yield).

4-(4-Bromobutoxy)-*N*-methylaniline (40a)

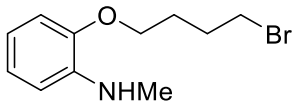


^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (d, *J* = 7.6 Hz, 2H), 6.59 (d, *J* = 7.6 Hz, 2H), 3.93 (br, 2H), 3.48 (t, *J* = 6.4 Hz, 2H), 2.81 (s, 3H), 2.09 – 2.02(m, 2H), 2.00 – 1.83 (m,2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.52, 143.15, 115.68, 113.99, 67.54, 33.59, 31.82, 29.47, 27.99.

IR (Reflexion): ṽ = 3431, 2954, 2875, 2634, 2574, 2471, 1602, 1510, 1471, 1395, 1307, 1254, 1180, 1117, 1033, 969, 941, 836, 733, 640 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 257.04098, found 257.04118.

2-(4-Bromobutoxy)-*N*-methylaniline (40b)

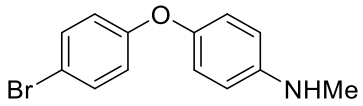


^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (td, *J* = 7.6, 1.4 Hz, 1H), 6.75 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.67 – 6.57 (m, 2H), 4.03 (t, *J* = 5.9 Hz, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 2.87 (s, 3H), 2.19 – 1.85 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.97, 139.39, 121.44, 116.24, 110.09, 109.42, 67.05, 33.49, 30.36, 29.58, 27.91.

IR (ATR): ṽ = 3394, 2925, 2594, 1736, 1609, 1503, 1466, 1401, 1292, 1261, 1216, 1164, 1105, 1043, 1009, 965, 866, 761, 627, 612 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 257.04098, found 257.04132.

4-(4-Bromophenoxy)-*N*-methylaniline (41)



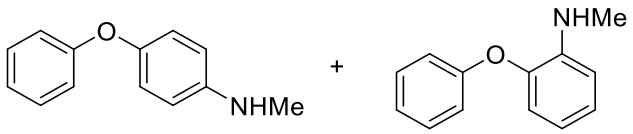
Following **GP 3**, 1-bromo-4-phenoxybenzene (50 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 4-(4-bromophenoxy)-*N*-methylaniline **41** as a yellow oil (30 mg, 54%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 8.8 Hz, 2H), 2.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.39, 147.14, 146.16, 132.33, 121.23, 118.68, 114.10, 113.44, 31.21.

IR (ATR): $\tilde{\nu}$ = 3416, 2981, 2919, 2882, 2811, 1611, 1582, 1510, 1480, 1399, 1316, 1281, 1234, 1164, 1098, 1068, 1006, 871, 822, 753, 684, 653, 617 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 277.00968, found 277.00901.

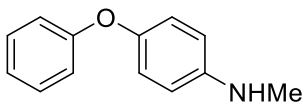
_N_-Methyl-4-phenoxyaniline (42a) and _N_-methyl-2-phenoxyaniline (42b)



42a **42b**

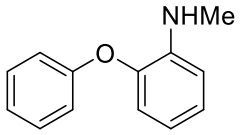
Following **GP 3**, oxydibenzene (34 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 2 days at room temperature. Purification by preparative thin-layer chromatography with PE/EA (20:1) as eluting solvent afforded *N*-methyl-4-phenoxyaniline **42a** as a yellow oil (24 mg) and *N*-methyl-2-phenoxyaniline **42b** as a brown oil (4 mg) (28 mg total, 70% combined yield).

_N_-Methyl-4-phenoxyaniline (42a) spectral data were in agreement with literature values[54]



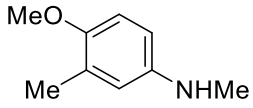
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (t, *J* = 8.9 Hz, 2H), 6.97 (t, *J* = 8.9 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 4H), 6.57 (d, *J* = 8.9 Hz, 2H), 3.21 (br, 1H), 2.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.14, 147.55, 145.95, 129.45, 121.85, 121.22, 117.01, 113.35, 31.22.

***N*-Methyl-2-phenoxyaniline (42b)** spectral data were in agreement with literature values[55]



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8.0 Hz, 2H), 7.08 (t, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.66 (t, *J* = 7.8 Hz, 1H), 2.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.52, 142.79, 141.56, 129.66, 125.04, 122.60, 119.21, 117.15, 116.57, 110.91, 30.32.

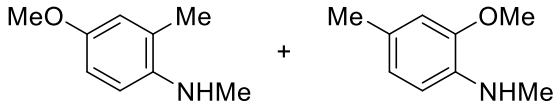
4-Methoxy-*N*,3-dimethylaniline (43) spectral data were in agreement with literature values[52]



Following **GP 3**, 1-methoxy-2-methylbenzene (24 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 4-methoxy-*N*,3-dimethylaniline **43** as a yellow oil (16 mg, 53%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (d, *J* = 8.5 Hz, 1H), 6.49 (d, *J* = 2.8 Hz, 1H), 6.44 (dd, *J* = 8.5, 2.8 Hz, 1H), 3.77 (s, 3H), 2.80 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.43, 143.42, 127.64, 116.10, 111.81, 110.01, 56.15, 31.62, 16.34.

4-Methoxy-*N*,2-dimethylaniline (44a) and 2-methoxy-*N*,4-dimethylaniline (44b)

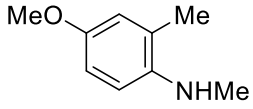


44a **44b**

Following **GP 3**, 1-methoxy-3-methylbenzene (24 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by preparative thin-layer chromatography with PE/EA (20:1) as eluting solvent afforded 4-methoxy-*N*,2-dimethylaniline **44a** as a yellow oil (7 mg) and 2-

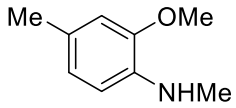
methoxy-*N*,4-dimethylaniline **44b** as a brown oil (7 mg) (14 mg total, 47% combined yield).

4-Methoxy-*N*,2-dimethylaniline (44a) spectral data were in agreement with literature values[56]



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 – 6.69 (m, 2H), 6.56 (d, *J* = 8.4 Hz, 1H), 3.75 (s, 3H), 2.86 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.70, 141.59, 123.82, 117.00, 111.58, 110.23, 55.84, 31.50, 17.62.

2-Methoxy-*N*,4-dimethylaniline (44b)

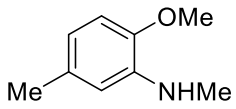


^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 7.9, 0.9 Hz, 1H), 6.60 (d, *J* = 0.9 Hz, 1H), 6.51 (d, *J* = 7.9 Hz, 1H), 3.83 (s, 3H), 2.84 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.94, 137.05, 125.89, 121.24, 110.53, 109.50, 55.37, 30.70, 20.89.

IR (Reflexion): $\tilde{\nu}$ = 3422, 2932, 2831, 1606, 1512, 1468, 1415, 1378, 1287, 1229, 1167, 1151, 1107, 1063, 1041, 996, 924, 863, 798, 715 cm^{-1}.

HRMS (EI+) m/z: $[M]^+$ calcd 151.09917, found 151.09847.

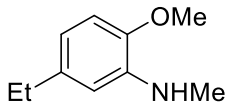
2-Methoxy-*N*,5-dimethylaniline (45) spectral data were in agreement with literature values[57]



Following **GP 3**, 1-methoxy-4-methylbenzene (24 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 2-methoxy-*N*,5-dimethylaniline **45** as a yellow oil (12 mg, 40%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (d, *J* = 7.9 Hz, 1H), 6.47 (dd, *J* = 7.9, 1.9, 1H), 6.43 (d, *J* = 1.9 Hz, 1H), 4.17 (br, 1H), 3.82 (s, 3H), 2.86 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.94, 139.15, 130.71, 116.30, 110.44, 109.27, 55.59, 30.37, 21.14.

5-Ethyl-2-methoxy-*N*-methylaniline (46)



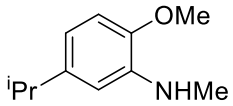
Following **GP 3**, 1-ethyl-4-methoxybenzene (27 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 5-ethyl-2-methoxy-*N*-methylaniline **46** as a yellow oil (16 mg, 48%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (d, *J* = 8.0 Hz, 1H), 6.51 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.47 (d, *J* = 2.0 Hz, 1H), 4.21 (br, 1H), 3.83 (s, 3H), 2.88 (s, 3H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.07, 139.18, 137.31, 114.99, 109.29, 109.20, 55.52, 30.38, 28.65, 15.95.

IR (Reflexion): $\tilde{\nu}$ = 3433, 2962, 2932, 2832, 2805, 1600, 1524, 1479, 1451, 1431, 1415, 1351, 1318, 1294, 1265, 1224, 1167, 1128, 1058, 1031, 909, 845, 799, 765, 700, 633 cm^{-1}.

HRMS (EI+) m/z: $[M]^+$ calcd 165.11482, found 165.11449.

5-Isopropyl-2-methoxy-*N*-methylaniline (47)



Following **GP 3**, 1-isopropyl-4-methoxybenzene (30 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 5-isopropyl-2-methoxy-*N*-methylaniline **47** as a yellow oil (31 mg, 81%).

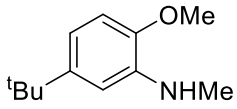
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (d, *J* = 8.1 Hz, 1H), 6.55 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 4.21 (br, 1H), 3.83 (s, 3H), 2.89 (s, 3H), 2.88 – 2.78 (m, 1H), 1.26 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.10, 141.97, 139.11, 113.42, 109.08, 107.92, 55.47, 33.88, 30.39, 24.26.

IR (Reflexion): $\tilde{\nu}$ = 3437, 2958, 2832, 2806, 1600, 1524, 1479, 1458, 1431, 1414, 1381, 1361, 1311, 1296, 1280, 1257, 1224, 1196, 1175, 1164, 1123, 1059, 1031, 936, 847,

797, 769, 690, 645 cm^{-1}.

HRMS (EI+) m/z: $[M]^+$ calcd 179.13047, found 179.13045.

5-(*tert*-Butyl)-2-methoxy-*N*-methylaniline (48)



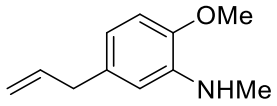
Following **GP 3**, 1-(*tert*-butyl)-4-methoxybenzene (33 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 5-(*tert*-butyl)-2-methoxy-*N*-methylaniline **48** as a yellow oil (39 mg, 98%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 – 6.86 (m, 2H), 6.66 (s, 1H), 4.21 (br, 1H), 3.83 (s, 3H), 2.89 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.86, 144.16, 138.72, 112.63, 108.67, 107.10, 55.43, 34.31, 31.59, 30.44.

IR (Reflexion): $\tilde{\nu}$ = 3438, 3072, 2958, 2902, 2868, 2833, 2802, 1598, 1527, 1479, 1461, 1408, 1361, 1335, 1302, 1263, 1224, 1204, 1167, 1133, 1106, 1032, 918, 848, 795, 772, 649 cm^{-1}.

HRMS (EI+) m/z: $[M]^+$ calcd 193.14612, found 193.14703.

5-Allyl-2-methoxy-*N*-methylaniline (49)



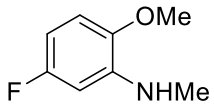
Following **GP 3**, 1-allyl-4-methoxybenzene (30 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 5-allyl-2-methoxy-*N*-methylaniline **49** as a yellow oil (20 mg, 57%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (d, *J* = 8.0 Hz, 1H), 6.49 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.43 (d, *J* = 2.0 Hz, 1H), 5.99 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1H), 5.20 – 4.94 (m, 2H), 4.21 (br, 1H), 3.83 (s, 3H), 3.33 (d, *J* = 6.7 Hz, 2H), 2.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.38, 139.28, 138.22, 132.99, 115.84, 115.06, 109.78, 109.20, 55.52, 40.09, 30.34.

IR (Reflexion): $\tilde{\nu}$ = 3434, 3075, 2999, 2975, 2936, 2899, 2832, 2805, 1638, 1601, 1524, 1479, 1450, 1431, 1415, 1350, 1261, 1225, 1166, 1126, 1032, 995, 959, 911, 845, 797, 766, 645 cm^{-1}.

HRMS (EI+) m/z: $[M]^+$ calcd 177.11482, found 177.11459.

5-Fluoro-2-methoxy-*N*-methylaniline (50)



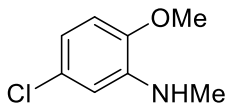
Following **GP 4**, 1-fluoro-4-methoxybenzene (25 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 5 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 5-fluoro-2-methoxy-*N*-methylaniline **50** as a yellow oil (23 mg, 74%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (dd, *J* = 9.3, 5.0 Hz, 1H), 6.37 – 6.20 (m, 2H), 4.36 (br, 1H), 3.81 (s, 3H), 2.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.54 (d, *J* = 235.4 Hz), 142.90 (d, *J* = 1.9 Hz), 140.61 (d, *J* = 11.1 Hz), 109.34 (d, *J* = 10.2 Hz), 100.46 (d, *J* = 23.1 Hz), 97.00 (d, *J* = 28.2 Hz), 55.89, 30.10. ^{19}F NMR (283 MHz, $CDCl_3$) δ -122.09.

IR (Reflexion): $\tilde{\nu}$ = 3439, 2938, 2906, 2854, 2835, 2807, 1621, 1523, 1480, 1453, 1430, 1416, 1355, 1283, 1256, 1216, 1182, 1167, 1109, 1030, 958, 823, 782, 709 cm^{-1}.

HRMS (EI+) m/z: $[M]^+$ calcd 155.07295, found 155.07336.

5-Chloro-2-methoxy-*N*-methylaniline (51)



Following **GP 4**, 1-chloro-4-methoxybenzene (28 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 2 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 5-chloro-2-methoxy-*N*-methylaniline **51** as a yellow oil (27 mg, 79%).

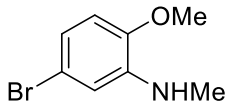
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 – 6.56 (m, 2H), 6.52 (d, *J* = 2.1 Hz, 1H), 4.31 (br, 1H), 3.82 (s, 3H), 2.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.40, 140.33, 126.53,

115.17, 109.75, 109.12, 55.62, 30.09.

IR (Reflexion): $\tilde{\nu}$ = 3434, 3079, 2937, 2837, 1601, 1519, 1463, 1429, 1405, 1340, 1278, 1257, 1220, 1179, 1159, 1120, 1091, 1028, 884, 830, 787, 642 cm^{-1}.

HRMS (EI+) m/z: $[M]^+$ calcd 171.04454, found 171.04461.

5-Bromo-2-methoxy-*N*-methylaniline (52)



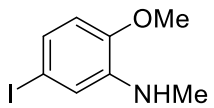
Following **GP 4**, 1-bromo-4-methoxybenzene (37 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 5-bromo-2-methoxy-*N*-methylaniline **52** as a yellow oil (34 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.65 (d, *J* = 2.3 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 4.28 (br, 1H), 3.81 (s, 3H), 2.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.91, 140.63, 118.26, 114.07, 111.88, 110.32, 55.60, 30.10.

IR (ATR): $\tilde{\nu}$ = 3422, 3078, 3002, 2989, 2958, 2933, 2887, 2837, 1808, 1736, 1598, 1512, 1477, 1459, 1449, 1429, 1402, 1341, 1277, 1256, 1220, 1177, 1159, 1121, 1026, 862, 822, 789, 767, 623 cm^{-1}.

HRMS (EI+) m/z: $[M]^+$ calcd 214.99403, found 214.99307.

5-Iodo-2-methoxy-*N*-methylaniline (53)



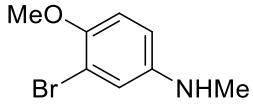
Following **GP 4**, 1-iodo-4-methoxybenzene (47 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 7 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 5-iodo-2-methoxy-*N*-methylaniline **53** as a yellow oil (24 mg, 46%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.81 (d, *J* = 2.1 Hz, 1H), 6.47 (d, *J* = 8.3 Hz, 1H), 4.26 (br, 1H), 3.80 (s, 3H), 2.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.71, 140.79, 124.72, 117.53, 110.97, 84.25, 55.46, 30.10.

IR (Reflexion): $\tilde{\nu}$ = 3427, 3073, 2998, 2954, 2933, 2834, 2812, 2591, 1986, 1799, 1594, 1518, 1476, 1458, 1428, 1398, 1335, 1282, 1256, 1223, 1178, 1162, 1121, 1069, 1027, 901, 879, 832, 786, 687, 668, 613 cm^{-1}.

HRMS (EI+) m/z: $[M]^+$ calcd 262.98016, found 262.97959.

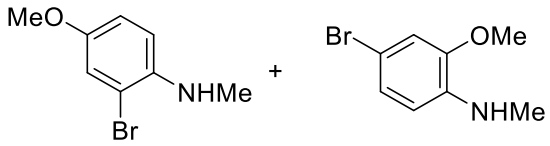
3-Bromo-4-methoxy-*N*-methylaniline (54) spectral data were in agreement with literature values[2]



Following **GP 4**, 1-bromo-2-methoxybenzene (37 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 4 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 3-bromo-4-methoxy-*N*-methylaniline **54** as a yellow oil (34 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, *J* = 2.8 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.53 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.81 (s, 3H), 2.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.20, 144.57, 117.29, 114.07, 112.73, 112.34, 57.15, 31.29.

2-Bromo-4-methoxy-*N*-methylaniline (55a) and 4-bromo-2-methoxy-*N*-methyl aniline (55b)

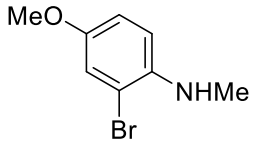


55a **55b**

Following **GP 4**, 1-bromo-3-methoxybenzene (37 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. The two isomers can not be separated preparative thin-layer chromatography or silica gel chromatography (the ratio of 2-bromo-4-methoxy-*N*-methylaniline **55a** : 4-bromo-2-methoxy-*N*-methyl aniline **55b** = 4:1 as the yellow oil from NMR, 37 mg total, 86% combined yield, the two isomers are separated by further derivation).

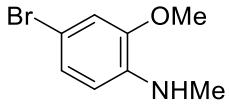
2-Bromo-4-methoxy-*N*-methylaniline (55a) spectral data were in agreement with

literature values[58]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, *J* = 2.8 Hz, 1H), 6.83 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.59 (d, *J* = 8.9 Hz, 1H), 4.01 (br, 1H), 3.74 (s, 3H), 2.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.54, 140.65, 118.37, 114.51, 112.56, 111.41, 56.06, 30.24.

4-Bromo-2-methoxy-*N*-methylaniline (55b)

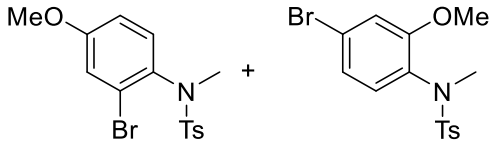


^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.83 (d, *J* = 2.1 Hz, 1H), 6.43 (d, *J* = 8.4 Hz, 1H), 4.01 (br, 1H), 3.82 (s, 3H), 2.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.40, 138.48, 123.83, 110.06, 109.74, 107.56, 56.06, 30.24.

IR (Reflexion): $\tilde{\nu}$ = 3417, 2924, 2853, 1737, 1688, 1673, 1650, 1641, 1588, 1573, 1512, 1493, 1461, 1396, 1345, 1280, 1260, 1239, 1154, 1121, 1088, 1061, 1027, 965, 889, 834, 814, 713, 698, 661, 614cm^{-1} (for two isomers).

HRMS (EI+) m/z: $[M]^+$ calcd 214.99403, found 214.99324 (for two isomers).

***N*-(2-bromo-4-methoxyphenyl)-*N*,4-dimethylbenzenesulfonamide (55aa) and *N*-(4-bromo-2-methoxyphenyl)-*N*,4-dimethylbenzenesulfonamide (55ba)**

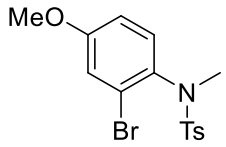


55aa **55ba**

To a solution of 2-bromo-4-methoxy-N-methylaniline and 4-bromo-2-methoxy-*N*-methylaniline (71 mg, 0.33 mmol) in 3 mL DCM was added Et_3N (40 mg, 0.4 mmol) at room temperature. Then TsCl was added to the followed mixture, and the reaction was stirred at room temperature overnight. Then the reaction was diluted with 5 mL DCM, washed with sat. brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residual mixture was purified by preparative thin-layer chromatography with PE/EA (8:1) as eluting solvent to afford *N*-

(2-bromo-4-methoxyphenyl)-*N*,4-dimethylbenzenesulfonamide **55aa** as a colorless solid (22 mg) and *N*-(4-bromo-2-methoxyphenyl)-*N*,4-dimethylbenzene sulfonamide **55ba** as a yellow oil (19 mg) (41 mg total, 34% combined yield).

***N*-(2-Bromo-4-methoxyphenyl)-*N*,4-dimethylbenzenesulfonamide (55aa)**



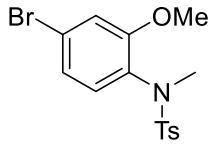
Mp: 93°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 2.9 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 6.77 (dd, *J* = 8.8, 2.9 Hz, 1H), 3.79 (s, 3H), 3.15 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.62, 143.49, 136.06, 132.79, 130.70, 129.48, 127.89, 125.38, 118.73, 113.96, 55.70, 38.49, 21.55.

IR (ATR): $\tilde{\nu}$ = 3062, 2970, 2928, 2842, 1920, 1883, 1738, 1597, 1562, 1491, 1457, 1439, 1419, 1404, 1382, 1340, 1284, 1263, 1219, 1195, 1158, 1084, 1028, 891, 872, 836, 812, 721, 708, 681, 638, 607cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 369.00288, found 369.00200.

***N*-(4-Bromo-2-methoxyphenyl)-*N*,4-dimethylbenzenesulfonamide (55ba)**



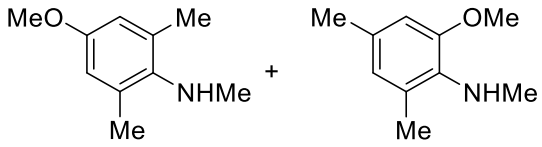
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.05 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.92 (d, *J* = 2.1 Hz, 1H), 3.41 (s, 3H), 3.15 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.94, 143.00, 136.30, 132.75, 129.09, 128.41, 127.59, 123.83, 122.72, 115.43, 55.26, 37.68, 21.47.

IR (ATR): $\tilde{\nu}$ = 3012, 2970, 2939, 1926, 1738, 1590, 1491, 1458, 1441, 1395, 1343, 1303, 1288, 1258, 1240, 1158, 1125, 1085, 1061, 1030, 953, 888, 828, 732, 713, 699, 658, 613cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 369.00288, found 369.00193.

4-Methoxy-*N*,2,6-trimethylaniline (56a) and 2-methoxy-*N*,4,6-trimethylaniline

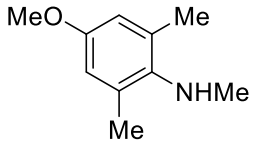
(56b)



56a **56b**

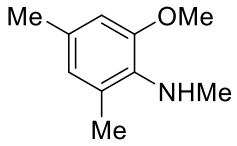
Following **GP 3**, 1-methoxy-3,5-dimethylbenzene (27 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by preparative thin-layer chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*,2,6-trimethylaniline **56a** as a brown oil (12 mg) and 2-methoxy-*N*,4,6-trimethylaniline **56b** as a yellow oil (12 mg) (24 mg total, 73% combined yield).

4-Methoxy-*N*,2,6-trimethylaniline (56a) spectral data were in agreement with literature values[59]



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (s, 2H), 3.75 (s, 3H), 2.92 (br, 1H), 2.70 (s, 3H), 2.29 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.84, 140.47, 131.73, 113.90, 55.30, 35.83, 18.25.

2-Methoxy-*N*,4,6-trimethylaniline (56b)

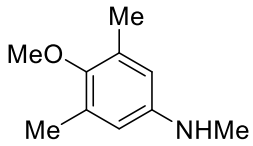


^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (s, 1H), 6.54 (s, 1H), 3.82 (s, 3H), 3.57 (br, 1H), 2.76 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.12, 135.86, 130.84, 129.51, 123.93, 109.37, 55.68, 35.58, 21.06, 18.17.

IR (Reflexion): $\tilde{\nu}$ = 3378, 2951, 2864, 2800, 1684, 1593, 1496, 1462, 1411, 1323, 1276, 1232, 1188, 1148, 1091, 1032, 999, 920, 830, 750 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 165.11482, found 165.11472.

4-Methoxy-*N*,3,5-trimethylaniline (57)



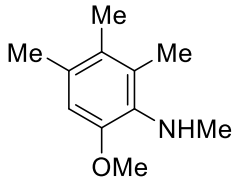
Following **GP 3**, 1-methoxy-3,5-dimethylbenzene (27 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*,3,5-trimethyl aniline **57** as a yellow oil (27 mg, 82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (s, 2H), 3.66 (s, 3H), 2.79 (s, 3H), 2.24 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.85, 145.38, 131.31, 112.52, 59.99, 31.24, 16.23.

IR (Reflexion): $\tilde{\nu}$ = 3398, 2977, 2932, 2821, 1609, 1489, 1420, 1374, 1343, 1224, 1188, 1164, 1084, 1011, 835, 754 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 165.11482, found 165.11370.

6-Methoxy-*N*,2,3,4-tetramethylaniline (58)



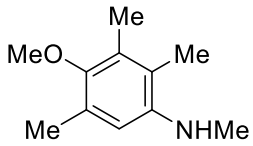
Following **GP 3**, 5-methoxy-1,2,3-trimethylbenzene (30 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 6-methoxy-*N*,2,3,4-tetramethyl aniline **58** as a yellow oil (34 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (s, 1H), 3.80 (s, 3H), 3.06 (br, 1H), 2.70 (s, 3H), 2.25 (s, 6H), 2.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.38, 136.33, 129.92, 129.71, 127.94, 110.14, 55.83, 36.35, 20.67, 15.43, 14.87.

IR (Reflexion): $\tilde{\nu}$ = 3372, 2940, 2864, 2795, 2729, 1682, 1600, 1491, 1463, 1417, 1403, 1324, 1272, 1238, 1190, 1155, 1114, 1081, 1034, 1010, 974, 926, 835, 769, 749, 682, 620 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 179.13407, found 179.12953.

4-Methoxy-*N*,2,3,5-tetramethylaniline (59)



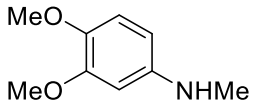
Following **GP 3**, 2-methoxy-1,3,4-trimethylbenzene (30 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*,2,3,5-tetramethyl aniline **59** as a yellow oil (23 mg, 64%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (s, 1H), 3.65 (s, 3H), 2.87 (s, 3H), 2.29 (s, 3H), 2.23 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.70, 143.32, 129.40, 128.01, 119.30, 109.63, 60.25, 31.35, 16.29, 12.79, 12.73.

IR (ATR): $\tilde{\nu}$ = 3428, 2979, 2933, 2823, 1680, 1631, 1604, 1590, 1505, 1473, 1404, 1337, 1238, 1222, 1161, 1089, 1033, 1002, 920, 834, 684 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 179.13407, found 179.13100.

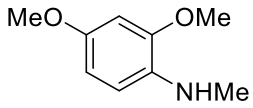
3,4-Dimethoxy-*N*-methylaniline (60) spectral data were in agreement with literature values[2]



Following **GP 3**, 1,2-dimethoxybenzene (27 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 3,4-dimethoxy-*N*-methylaniline **60** as a brown oil (31 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.5 Hz, 1H), 6.24 (d, *J* = 2.6 Hz, 1H), 6.15 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.01, 144.34, 141.48, 113.33, 102.99, 98.53, 56.73, 55.67, 31.44.

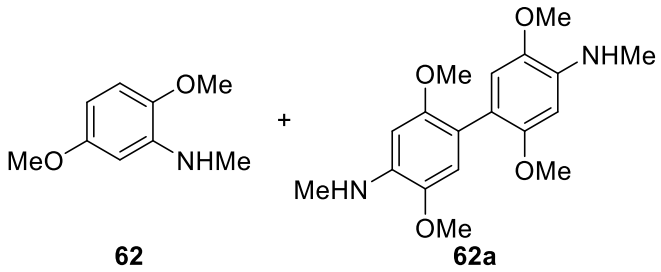
2,4-Dimethoxy-*N*-methylaniline (61) spectral data were in agreement with literature values[2]



Following **GP 3**, 1,3-dimethoxybenzene (27 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 2,4-dimethoxy-*N*-methylaniline **61** as a brown oil (22 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (d, *J* = 8.3 Hz, 1H), 6.46 (d, *J* = 2.3 Hz, 1H), 6.45 (dd, *J* = 8.3, 2.3 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 2.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.82, 147.95, 133.83, 109.50, 103.78, 99.10, 55.80, 55.39, 31.03.

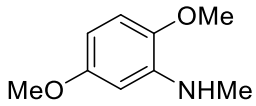
2,5-Dimethoxy-*N*-methylaniline (62) and 2,2',5,5'-tetramethoxy-N^4,$N^{4'}$-dimethyl-[1,1'-biphenyl]-4,4'-diamine (62a)



62 **62a**

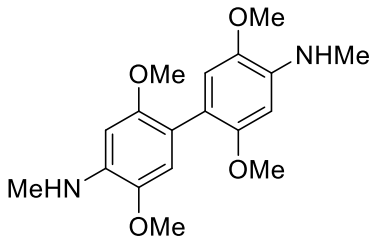
Following **GP 3**, 1,4-dimethoxybenzene (27 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 2,5-dimethoxy-*N*-methylaniline **62** as a brown oil (13 mg, 39%) and 2,2',5,5'-tetramethoxy-N^4,$N^{4'}$-dimethyl-[1,1'-biphenyl]-4,4'-diamine **62a** as a yellow solid (16 mg, 48%).

2,5-Dimethoxy-*N*-methylaniline (62) spectral data were in agreement with literature values[60]



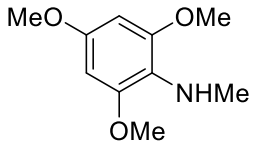
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (d, *J* = 8.5 Hz, 1H), 6.21 (d, *J* = 2.9 Hz, 1H), 6.15 (dd, *J* = 8.5, 2.9 Hz, 1H), 4.26 (br, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 2.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.94, 141.58, 140.47, 109.74, 98.39, 97.59, 55.99, 55.49, 30.19.

2,2',5,5'-Tetramethoxy-N^4,$N^{4'}$-dimethyl-[1,1'-biphenyl]-4,4'-diamine (62a) spectral data were in agreement with literature values[61]



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73 (s, 2H), 6.32 (s, 2H), 4.30 (s, 2H), 3.80 (s, 6H), 3.75 (s, 6H), 2.91 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.97, 140.80, 139.09, 114.84, 113.50, 95.99, 56.84, 56.04, 30.48.

2,4,6-Trimethoxy-*N*-methylaniline (63)



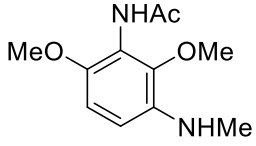
Following **GP 3**, 1,3,5-trimethoxybenzene (34 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 2,4,6-trimethoxy-*N*-methylaniline **63** as a brown oil (26 mg, 67%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (s, 2H), 3.89 (br, 1H), 3.81 (s, 6H), 3.76 (s, 3H), 2.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.81, 152.20, 122.26, 91.41, 55.81, 55.50, 35.24.

IR (Reflexion): $\tilde{\nu}$ = 3381, 2996, 2954, 2837, 2799, 1679, 1603, 1505, 1457, 1415, 1338, 1301, 1223, 1203, 1186, 1154, 1108, 1062, 1038, 947, 921, 810, 726, 660, 624 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 197.10464, found 197.10450.

***N*-(2,6-Dimethoxy-3-(methylamino)phenyl)acetamide (64)**



Following **GP 4**, *N*-(2,6-dimethoxyphenyl)acetamide (39 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (2:1) as eluting solvent afforded

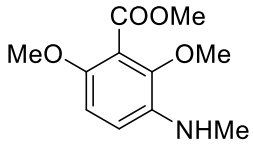
methyl *N*-(2,6-dimethoxy-3-(methylamino)phenyl)acetamide **64** as a yellow oil (20 mg, 45%).

^{1}H NMR (500 MHz, MeOD) δ 6.70 (d, J = 8.8 Hz, 1H), 6.59 (d, J = 8.8 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.77 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (125 MHz, MeOD) δ 172.82, 149.01, 145.87, 138.94, 120.54, 110.82, 108.82, 60.36, 56.77, 31.35, 22.60.

IR (Reflexion): $\tilde{\nu}$ = 3380, 3268, 2991, 2937, 2903, 2833, 2815, 2400, 1664, 1503, 1444, 1333, 1273, 1232, 1202, 1160, 1092, 1010, 908, 793 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 224.1155, found 224.1162.

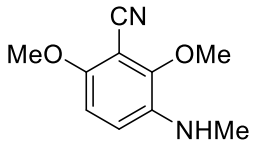
Methyl 2,6-dimethoxy-3-(methylamino)benzoate (65) spectral data were in agreement with literature values[2]



Following **GP 4**, methyl 2,6-dimethoxybenzoate (39 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded methyl 2,6-dimethoxy-3-(methylamino)benzoate **65** as a yellow solid (39 mg, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 – 6.58 (m, 2H), 3.92 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.00, 148.11, 144.56, 137.11, 118.21, 111.85, 107.83, 60.90, 56.62, 52.39, 30.95.

2,6-Dimethoxy-3-(methylamino)benzonitrile (66)



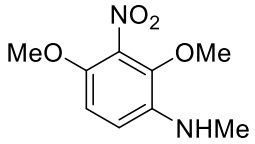
Following **GP 4**, 2,6-dimethoxybenzonitrile (33 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 2,6-dimethoxy-3-(methylamino)benzonitrile **66** as a yellow oil (39 mg, 97%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (d, *J* = 8.9 Hz, 1H), 6.60 (d, *J* = 8.9 Hz, 1H), 3.98 (s, 3H), 3.83 (s, 3H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.91, 149.90, 136.72, 115.03, 114.35, 106.69, 95.66, 60.98, 56.38, 30.70.

IR (Reflexion): $\tilde{\nu}$ = 3407, 2939, 2840, 2818, 2228, 1585, 1507, 1458, 1404, 1337, 1278, 1228, 1191, 1155, 1090, 1005, 942, 890, 803 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 192.08933, found 192.08806.

2,4-Dimethoxy-*N*-methyl-3-nitroaniline (67)



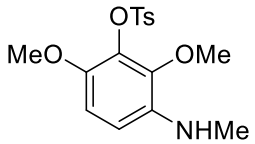
Following **GP 4**, 1,3-dimethoxy-2-nitrobenzene (37 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 5 days at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 2,4-dimethoxy-*N*-methyl-3-nitroaniline **67** as a yellow oil (41 mg, 97%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (d, *J* = 9.0 Hz, 1H), 6.64 (d, *J* = 9.0 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 2.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.43, 139.00, 137.46, 111.73, 108.89, 61.35, 57.10, 30.82.

IR (Reflexion): $\tilde{\nu}$ = 3420, 2942, 2903, 2841, 2821, 1817, 1612, 1584, 1509, 1455, 1374, 1336, 1271, 1216, 1172, 1136, 1091, 999, 938, 899, 799, 644 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 212.07916, found 212.07984.

2,6-Dimethoxy-3-(methylamino)phenyl 4-methylbenzenesulfonate (68)



Following **GP 4**, 2,6-dimethoxyphenyl 4-methylbenzenesulfonate (62 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 2,6-dimethoxy-3-(methylamino)phenyl 4-methylbenzenesulfonate **68**

as a colorless solid (64 mg, 94%).

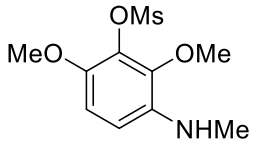
Mp: 114°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 6.58 (d, *J* = 8.9 Hz, 1H), 6.44 (d, *J* = 8.9 Hz, 1H), 3.67 (s, 3H), 3.55 (s, 3H), 2.80 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.55, 144.45, 141.23, 137.94, 134.73, 132.99, 129.18, 128.35, 108.17, 107.97, 60.13, 56.35, 30.82, 21.64.

IR (ATR): $\tilde{\nu}$ = 3404, 2990, 2932, 2901, 2873, 2836, 2811, 1914, 1737, 1597, 1518, 1486, 1463, 1417, 1361, 1307, 1281, 1219, 1196, 1175, 1152, 1092, 1013, 968, 908, 808, 786, 723, 684, 665 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 337.09784, found 337.09701.

2,6-Dimethoxy-3-(methylamino)phenyl methanesulfonate (69)



Following **GP 4**, 2,6-dimethoxyphenyl methanesulfonate (46 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (2:1) as eluting solvent afforded 2,6-dimethoxy-3-(methylamino) phenyl methanesulfonate **69** as a colorless solid (45 mg, 87%).

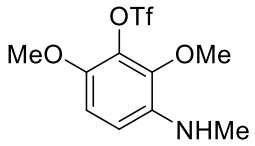
Mp: 118°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (d, *J* = 9.0 Hz, 1H), 6.47 (d, *J* = 9.0 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.30 (s, 3H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.14, 141.02, 138.10, 133.04, 108.53, 108.12, 60.37, 56.71, 39.54, 30.79.

IR (ATR): $\tilde{\nu}$ = 3380, 3039, 3009, 2980, 2941, 2896, 2878, 2842, 2814, 1824, 1620, 1515, 1459, 1415, 1358, 1277, 1220, 1172, 1148, 1089, 1007, 967, 902, 801, 769, 723, 675, 647 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 261.06654, found 261.06720.

2,6-Dimethoxy-3-(methylamino)phenyl trifluoromethanesulfonate (70)



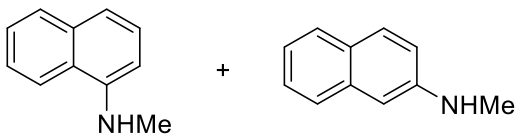
Following **GP 4**, 2,6-dimethoxyphenyl trifluoromethanesulfonate (57 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 2,6-dimethoxy-3-(methylamino) phenyl trifluoromethanesulfonate **70** as a yellow oil (61 mg, 97%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (d, *J* = 9.0 Hz, 1H), 6.46 (d, *J* = 9.0 Hz, 1H), 3.75 (s, 6H), 2.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.30, 140.02, 137.98, 132.94, 118.65 (q, *J* = 318.47 Hz), 109.10, 108.75, 60.49, 56.75, 30.75.^{19}F NMR (283 MHz, $CDCl_3$) δ -73.83.

IR (ATR): $\tilde{\nu}$ = 3424, 3015, 2973, 2944, 2910, 2842, 1515, 1477, 1453, 1417, 1278, 1246, 1215, 1198, 1135, 1087, 1002, 961, 906, 827, 803, 765, 731, 690, 612 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 315.03714, found 315.03751.

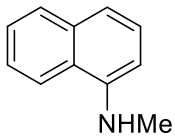
_N_-Methylnaphthalen-1-amine (71a) and _N_-methylnaphthalen-2-amine (71b)



71a **71b**

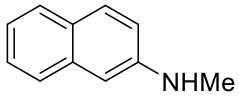
Following **GP 3**, naphthalene (26 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by preparative thin-layer chromatography with PE/EA (10:1) as eluting solvent afforded *N*-methylnaphthalen-1-amine **71a** as a brown oil (15 mg) and *N*-methylnaphthalen-2-amine **71b** as a brown oil (2 mg) (17 mg total, 55% combined yield).

***N*-Methylnaphthalen-1-amine (71a)** spectral data were in agreement with literature values[2]



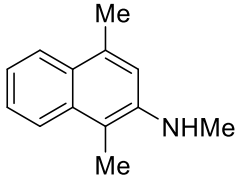
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.76 (m, 2H), 7.48 – 7.40 (m, 2H), 7.38(t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 3.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.47, 134.21, 128.63, 126.64, 125.67, 124.66, 123.44, 119.76, 117.32, 103.81, 31.01.

***N*-Methylnaphthalen-2-amine (71b)** spectral data were in agreement with literature values[62]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 3H), 7.46 – 7.33 (m, 1H), 7.25 – 7.18 (m, 1H), 6.89 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.82 (d, *J* = 2.3 Hz, 1H), 3.74 (br, 1H), 2.95 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.94, 135.26, 128.77, 127.61, 127.46, 126.27, 125.90, 121.86, 117.85, 103.75, 30.73.

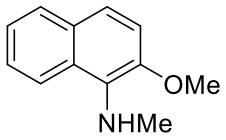
***N*,1,4-Trimethylnaphthalen-2-amine (72)** spectral data were in agreement with literature values[2]



Following **GP 3**, 1,4-dimethylnaphthalene (31 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*,1,4-trimethylnaphthalen-2-amine **72** as a yellow solid (30 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.6 Hz, 2H), 7.46 (ddd, *J* = 8.6, 6.7, 1.1 Hz, 1H), 7.28 (ddd, *J* = 8.6, 6.7, 1.1 Hz, 1H), 7.00 (s, 1H), 3.04 (s, 3H), 2.71 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.82, 133.48, 133.17, 126.61, 125.72, 124.60, 122.75, 121.16, 114.33, 110.34, 31.46, 19.80, 11.11.

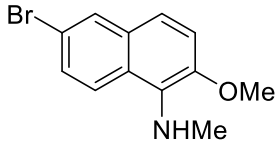
2-Methoxy-*N*-methylnaphthalen-1-amine (73) spectral data were in agreement with literature values[2]



Following **GP 3**, 2-methoxynaphthalene (32 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 2-methoxy-*N*-methylnaphthalen-1-amine **73** as a brown oil (20 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.06 (m, 1H), 7.80 – 7.75 (m, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.45 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.34 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.26 (d, *J* = 8.9 Hz, 1H), 3.96 (s, 3H), 2.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.45, 134.01, 129.97, 128.28, 128.20, 125.23, 123.54, 122.82, 122.45, 113.57, 56.88, 37.10.

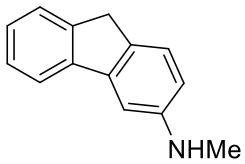
6-Bromo-2-methoxy-*N*-methylnaphthalen-1-amine (74) spectral data were in agreement with literature values[2]



Following **GP 3**, 2-bromo-6-methoxynaphthalene (47 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 5 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 6-bromo-2-methoxy-*N*-methylnaphthalen-1-amine **74** as a brown oil (30 mg, 57%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 9.1 Hz, 1H), 7.91 (d, *J* = 2.0 Hz, 1H), 7.48 (dd, *J* = 9.1, 2.0 Hz, 1H), 7.39 (d, *J* = 9.0 Hz, 1H), 7.24 (d, *J* = 9.0 Hz, 1H), 3.94 (s, 3H), 2.95 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.66, 134.17, 130.96, 130.08, 128.40, 126.54, 124.83, 121.50, 117.36, 114.27, 56.73, 37.18.

***N*-Methyl-9*H*-fluoren-3-amine (75)**



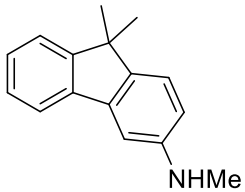
Following **GP 3**, 9*H*-fluorene (33 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 2 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-methyl-9*H*-fluoren-3-amine **75** as a yellow oil (31 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.4 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.19 (t, *J* = 7.4, 1H), 6.82 (d, *J* = 1.7 Hz, 1H), 6.66 (dd, *J* = 8.2, 1.7 Hz, 1H), 3.84 (s, 2H), 2.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.77, 145.14, 142.35, 142.13, 131.82, 126.56, 124.72, 124.64, 120.55, 118.36, 111.66, 108.76, 36.90, 31.04.

IR (ATR): ṽ = 3413, 3362, 3039, 3012, 2972, 2892, 2810, 1617, 1585, 1514, 1459, 1398, 1350, 1318, 1286, 1274, 1261, 1224, 1198, 1180, 1156, 1118, 1094, 1064, 1020, 949, 842, 813, 764, 731cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 195.10425, found 195.10311.

_N_,9,9-Trimethyl-9_H_-fluoren-3-amine (76)



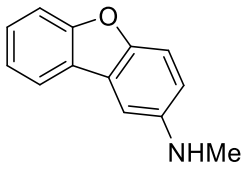
Following **GP 3**, 9,9-dimethyl-9*H*-fluorene (39 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*,9,9-trimethyl-9*H*-fluoren-3-amine **76** as a yellow oil (35 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.4 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.28 (td, *J* = 7.4, 1.0 Hz, 1H), 7.19 (td, *J* = 7.4, 1.0 Hz, 1H), 6.68 (d, *J* = 2.2 Hz, 1H), 6.60 (dd, *J* = 8.2, 2.2 Hz, 1H), 2.92 (s, 3H), 1.46 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.46, 152.70, 149.20, 139.87, 129.13, 126.79, 125.21, 122.24, 120.83, 118.49, 111.42, 106.53, 46.60, 31.05, 27.41.

IR (Reflexion): $\tilde{\nu}$ = 3417, 3059, 3039, 3010, 2958, 2922, 2861, 2812, 1941, 1902, 1868, 1615, 1581, 1505, 1463, 1412, 1380, 1353, 1320, 1298, 1274, 1217, 1157, 1131, 1078, 1021, 937, 849, 815, 776, 758, 735, 682 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 223.13555, found 223.13664.

_N_-Methyldibenzo[b,d]furan-2-amine (77)



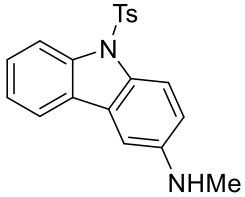
Following **GP 4**, dibenzo[*b*,*d*]furan (34 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-methyldibenzo[*b*,*d*]furan-2-amine **77** as a yellow oil (27 mg, 69%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.41 (td, *J* = 7.8, 1.2Hz, 1H), 7.39 (d, *J* = 8.8, 1H), 7.30 (td, *J* = 7.8, 1.2 Hz, 1H), 7.16 (d, *J* = 2.4 Hz, 1H), 6.80 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.47 (br, 1H), 2.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.70, 149.95, 145.19, 126.76, 124.81, 124.53, 122.14, 120.49, 114.39, 111.94, 111.58, 102.52, 31.95.

IR (ATR): $\tilde{\nu}$ = 3407, 3057, 2915, 2810, 2362, 1737, 1633, 1604, 1510, 1485, 1450, 1318, 1279, 1238, 1184, 1116, 1056, 1018, 936, 840, 800, 749, 683, 617 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 197.08352, found 197.08359.

_N_-Methyl-9-tosyl-9*H*-carbazol-3-amine (78)



Following **GP 4**, 9-tosyl-9*H*-carbazole (64 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded *N*-methyl-

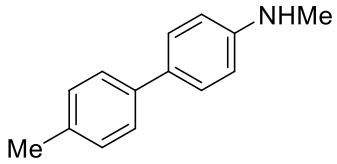
9-tosyl-9*H*-carbazol-3-amine **78** as a yellow oil (69 mg, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.8 Hz, 1H), 8.12 (d, *J* = 8.9 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 2.2 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.83 (dd, *J* = 8.9, 2.2 Hz, 1H), 2.91 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.81, 144.50, 138.97, 134.64, 131.31, 129.45, 127.74, 127.10, 126.84, 126.41, 123.68, 119.85, 116.25, 115.46, 114.70, 101.93, 31.62, 21.43.

IR (ATR): ṽ = 3428, 2924, 2808, 1738, 1621, 1599, 1494, 1447, 1365, 1306, 1229, 1202, 1187, 1171, 1152, 111, 1090, 1031, 1018, 974, 909, 810, 767, 748, 732, 705, 687, 659, 632 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 350.10835, found 350.10738.

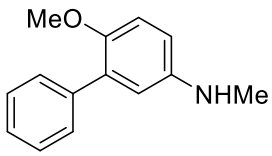
***N*,4'-Dimethyl-[1,1'-biphenyl]-4-amine (79)** spectral data were in agreement with literature values[63]



Following **GP 4**, 4-methyl-1,1'-biphenyl (34 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 5 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*,4'-dimethyl-[1,1'-biphenyl]-4-amine **79** as a yellow solid (25 mg, 64%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 4H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.70 (d, *J* = 8.4 Hz, 2H), 2.89 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.38, 138.43, 135.64, 130.32, 129.33, 127.70, 126.15, 112.76, 30.86, 20.99.

6-Methoxy-*N*-methyl-[1,1'-biphenyl]-3-amine (80)



Following **GP 4**, 2-methoxy-1,1'-biphenyl (37 mg, 0.2 mmol), TsONHMe (162 mg, 0.8

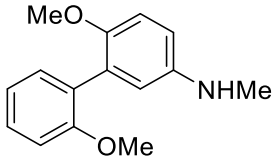
mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 6-methoxy-*N*-methyl-[1,1'-biphenyl]-3-amine **80** as a yellow oil (42 mg, 98%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.3 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.65 (d, *J* = 2.9 Hz, 1H), 6.61 (dd, *J* = 8.5, 2.9 Hz, 1H), 3.73 (s, 3H), 2.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.06, 143.78, 138.90, 131.77, 129.41, 127.90, 126.82, 115.68, 113.54, 112.12, 56.60, 31.54.

IR (ATR): ṽ = 3407, 3054, 3024, 2932, 2899, 2832, 2809, 1952, 1884, 1812, 1665, 1615, 1601, 1573, 1509, 1463, 1443, 1397, 1327, 1297, 1262, 1236, 1179, 1158, 1131, 1066, 1045, 1028, 915, 865, 804, 771, 742, 699, 623, 611 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 213.11482, found 213.11398.

2',6-Dimethoxy-*N*-methyl-[1,1'-biphenyl]-3-amine (81)



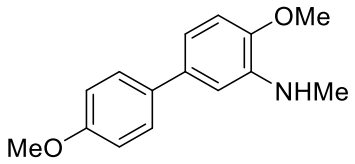
Following **GP 3**, 2,2'-dimethoxy-1,1'-biphenyl (43 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 2',6-dimethoxy-*N*-methyl-[1,1'-biphenyl]-3-amine **81** as a yellow oil (32 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (ddd, *J* = 8.2, 7.5, 1.8 Hz, 1H), 7.26 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.03 – 6.97 (m, 2H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.62 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.58 (d, *J* = 2.9 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 2.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.01, 149.80, 143.35, 131.33, 128.96, 128.47, 128.24, 120.30, 116.39, 113.29, 112.25, 111.06, 56.79, 55.68, 31.55.

IR (ATR): ṽ = 3405, 2933, 2833, 2244, 1739, 1615, 1599, 1580, 1491, 1462, 1434, 1397, 1326, 1232, 1179, 1160, 1115, 1053, 1028, 910, 865, 803, 754, 732, 629 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 243.12538, found 243.12593.

4,4'-Dimethoxy-*N*-methyl-[1,1'-biphenyl]-3-amine (82)



Following **GP 3**, 4,4'-dimethoxy-1,1'-biphenyl (43 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 4,4'-dimethoxy-*N*-methyl-[1,1'-biphenyl]-3-amine **82** as a colorless solid (35 mg, 73%).

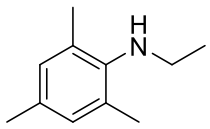
Mp: 89°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.83 – 6.78 (m, 3H), 4.31 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 2.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.56, 146.19, 139.38, 134.60, 134.29, 127.88, 114.60, 113.97, 109.40, 108.07, 55.55, 55.30, 30.40.

IR (ATR): $\tilde{\nu}$ = 3424, 3073, 3002, 2963, 2939, 2836, 2034, 1894, 1823, 1600, 1537, 1505, 1449, 1400, 1339, 1301, 1278, 1240, 1216, 1180, 1162, 1134, 1116, 1044, 1018, 886, 831, 793, 772, 720, 640 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 243.12538, found 243.12627.

_N_-ethyl-2,4,6-trimethylaniline (103)



Following **GP 2**, *tert*-butyl ethyl(tosyloxy)carbamate (252 mg, 0.8 mmol), TFA (1.82g, 16 mmol) in 1 mL DCM solution to give crude *N*-ethyl-*O*-tosylhydroxylamine, which was directly used for the next step without further purification.

Following **GP 4**, mesitylene (24 mg, 0.2 mmol), crude *N*-ethyl-*O*-tosylhydroxylamine (0.8 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-ethyl-2,4,6-trimethylaniline **103** as a yellow oil (10 mg, 31%).

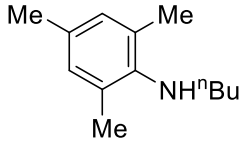
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 2H), 2.98 (q, *J* = 7.2 Hz, 2H), 2.39 (br, 1H), 2.26 (s, 6H), 2.23 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.64,

131.10, 129.58, 129.34, 43.28, 20.52, 18.31, 16.22.

IR (EXTRACT): $\tilde{\nu}$ = 3371.99, 2967.20, 2923.43, 2859.15, 2729.43, 2672.83, 1734.45, 1658.15, 1486.02, 1449.40, 1375.56, 1344.76, 1303.88, 1232.52, 1140.03, 1030.99, 853.42, 733.47, 695.99 cm^{-1}

HRMS (EI+) m/z: [M-15]+ calcd 148.1126, found 148.1317

***N*-Butyl-2,4,6-trimethylaniline (104)** spectral data were in agreement with literature values[2]



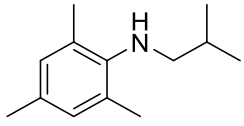
Following **GP 2**, *tert*-butyl butyl(tosyloxy)carbamate (252 mg, 0.8 mmol), TFA (1.82g, 16 mmol) in 1 mL DCM solution to give crude *N*-butyl-*O*-tosylhydroxylamine, which was directly used for the next step without further purification.

Following **GP 4**, mesitylene (24 mg, 0.2 mmol), crude *N*-butyl-*O*-tosylhydroxylamine (0.8 mmol) in 0.5 mL HFIP solution were stirred for 4 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-butyl-2,4,6-trimethylaniline **104** as a yellow oil (28 mg, 74%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 2H), 2.93 (t, *J* = 7.2 Hz, 2H), 2.80 (br, 1H), 2.26 (s, 6H), 2.23 (s, 3H), 1.65 – 1.50 (m, 2H), 1.49 – 1.34 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.79, 131.02, 129.46, 129.38, 48.69, 33.24, 20.48, 20.35, 18.28, 13.95.

***N*-isobutyl-2,4,6-trimethylaniline (105)**



Following **GP 2**, *tert*-butyl isobutyl(tosyloxy)carbamate (274 mg, 0.8 mmol), TFA (1.82g, 16 mmol) in 1 mL DCM solution to give crude *N*-isobutyl-*O*-tosylhydroxylamine, which was directly used for the next step without further purification.

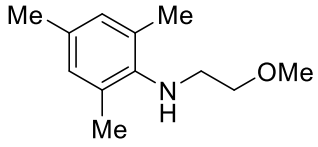
Following **GP 4**, mesitylene (24 mg, 0.2 mmol), crude *N*-isobutyl-*O*-tosylhydroxylamine (0.8 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-isobutyl-2,4,6-trimethylaniline **105** as a yellow oil (9 mg, 24%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (s, 2H), 2.73 (d, J = 6.6 Hz, 2H), 2.26 (s, 6H), 2.22 (s, 3H), 1.83 (sept, J = 6.6 Hz, 1H), 1.01 (d, J = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.84, 130.96, 129.44, 129.41, 56.73, 29.51, 20.55, 20.52, 18.28.

IR (EXTRACT): ṽ = 2956.03, 2923.13, 2869.73, 2819.42, 1735.14, 1485.65, 1384.80, 1371.95, 1303.42, 1229.74, 1148.28, 1058.44, 1029.04, 853.14, 733.50 cm^{-1}

HRMS (EI+) m/z: [M$^+$ calcd 191.1669, found 191.1855

***N*-(2-Methoxyethyl)-2,4,6-trimethylaniline (106)**



Following **GP 2**, *tert*-butyl (2-methoxyethyl)(tosyloxy)carbamate (274 mg, 0.8 mmol), TFA (1.82g, 16 mmol) in 1 mL DCM solution to give crude *N*-(2-methoxyethyl)-*O*-tosylhydroxylamine, which was directly used for the next step without further purification.

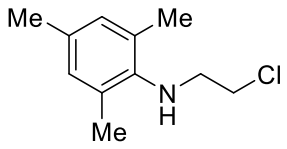
Following **GP 4**, mesitylene (24 mg, 0.2 mmol), crude *N*-(2-methoxyethyl)-*O*-tosylhydroxylamine (0.8 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded *N*-(2-methoxyethyl)-2,4,6- trimethylaniline **106** as a yellow oil (31 mg, 80%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 2H), 3.49 (t, J = 5.0 Hz, 2H), 3.40 (s, 3H), 3.12 (t, J = 5.0 Hz, 2H), 2.27 (s, 6H), 2.23 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.94, 131.28, 129.79, 129.35, 71.86, 58.67, 48.11, 20.52, 18.15.

IR (Reflexion): ṽ = 3379, 2922, 2891, 2730, 1733, 1682, 1596, 1487, 1455, 1376, 1349, 1305, 1234, 1190, 1156, 1122, 1095, 1033, 1012, 959, 937, 853, 741, 695 cm^{-1}

HRMS (EI+) m/z: [M]$^+$ calcd 193.14612, found 193.14520.

_N_-(2-Chloroethyl)-2,4,6-trimethylaniline (107)



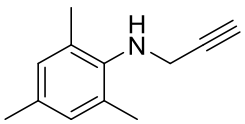
Following **GP 4**, mesitylene (24 mg, 0.2 mmol), *N*-(2-chloroethyl)-*O*-tosylhydroxylamine (200 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 4 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-(2-chloroethyl)-2,4,6-trimethylaniline **107** as a yellow oil (18 mg, 46 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 2H), 3.68 (t, J = 5.6 Hz, 2H), 3.30 (t, J = 5.6 Hz, 2H), 2.29 (s, 6H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.73, 131.97, 130.05, 129.55, 49.87, 45.04, 20.52, 18.28.

IR (ATR): $\tilde{\nu}$ = 3380, 2998, 2946, 2920, 2856, 2731, 2688, 1730, 1684, 1656, 1610, 1485, 1445, 1376, 1291, 1233, 1205, 1180, 1154, 1111, 1099, 1071, 1031, 978, 957, 928, 901, 879, 854, 789, 735, 688, 667 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 197.09658, found 197.09710.

2,4,6-trimethyl-*N*-(prop-2-yn-1-yl)aniline (108)



Following **GP 2**, *tert*-butyl prop-2-yn-1-yl(tosyloxy)carbamate (260 mg, 0.8 mmol), TFA (1.82g, 16 mmol) in 1 mL DCM solution to give crude *N*-(prop-2-yn-1-yl)-*O*-tosylhydroxylamine, which was directly used for the next step without further purification.

Following **GP 4**, mesitylene (24 mg, 0.2 mmol), crude *N*-(prop-2-yn-1-yl)-*O*-tosylhydroxylamine (0.8 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 2,4,6-trimethyl-*N*-(prop-2-yn-1-yl)aniline **108** as a yellow solid (13 mg, 38%).

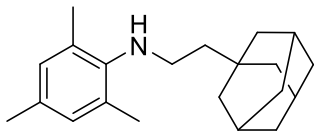
MP: 49°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 2H), 3.74 (d, *J* = 2.4 Hz, 2H), 3.25 (br, 1H), 2.30 (s, 6H), 2.24 (s, 3H), 2.20 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.93, 132.24, 130.32, 129.44, 82.24, 71.42, 37.58, 20.59, 18.25.

IR (EXTRACT): $\tilde{\nu}$ = 3372.80, 3261.96, 3244.87, 2944.30, 2934.54, 2105.85, 1731.09, 1608.66, 1485.55, 1445.49, 1370.68, 1341.04, 1307.17, 1222.91, 1158.06, 1072.05, 1032.11, 983.08, 928.17, 911.25, 858.25, 768.22, 747.20, 700.32, 676.93, 658.69, 608.61 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 173.1199, found 173.1368

_N_-(2-(adamantan-1-yl)ethyl)-2,4,6-trimethylaniline (109)



Following **GP 2**, *tert*-butyl (2-(adamantan-1-yl)ethyl)(tosyloxy)carbamate (360 mg, 0.8 mmol), TFA (1.82g, 16 mmol) in 1 mL DCM solution to give crude *N*-(2-(adamantan-1-yl)ethyl)-*O*-tosylhydroxylamine, which was directly used for the next step without further purification.

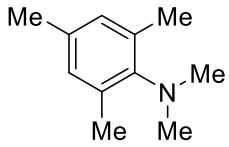
Following **GP 4**, mesitylene (24 mg, 0.2 mmol), *N*-(2-(adamantan-1-yl)ethyl)-*O*-tosylhydroxylamine (0.8 mmol), in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-ethyl-2,4,6-trimethylaniline **109** as a yellow oil (18 mg, 30%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (s, 2H), 2.97 – 2.89 (m, 2H), 2.25 (s, 6H), 2.22 (s, 3H), 1.96 – 1.91 (m, 3H), 1.75 – 1.56 (m, 6H), 1.51 (d, *J* = 2.8 Hz, 6H), 1.41 – 1.32 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.07, 130.95, 129.37, 45.66, 43.59, 42.61, 37.13, 31.95, 28.65, 20.52, 18.43.

IR (EXTRACT): $\tilde{\nu}$ = 2903.17, 2845.95, 2672.53, 2656.99, 1731.83, 1682.05, 1484.69, 1448.89, 1373.19, 1279.82, 1228.69, 1192.21, 1155.06, 1098.99, 1028.03, 891.82, 852.55, 686.58 cm^{-1}

HRMS (EI+) m/z: [M]+ calcd 297.2452, found 297.3071

***N*,*N*,2,4,6-Pentamethylaniline (110)** spectral data were in agreement with literature values[64]

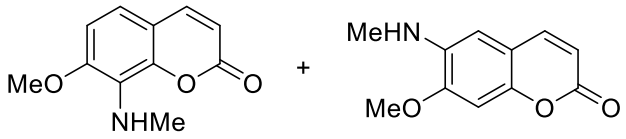


Following **GP 3**, mesitylene (24 mg, 0.2 mmol), *N*,*N*-dimethyl-*O*-tosylhydroxylamine (86 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (40:1) as eluting solvent afforded *N*,*N*,2,4,6-pentamethylaniline **110** as a yellow oil (3 mg, 9 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 2H), 2.82 (s, 6H), 2.29 (s, 6H), 2.27 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.06, 136.94, 134.14, 129.42, 42.55, 20.65, 18.98.

2.3 Late-Stage C-H Aminations

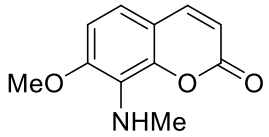
7-Methoxy-8-(methylamino)-2*H*-chromen-2-one (116a) and 7-methoxy-6-(methylamino)-2*H*- chromen-2-one (116b)



116a **116b**

Following **GP 4**, 7-methoxy-2*H*-chromen-2-one (7–methoxycoumarin, 35 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 5 days at room temperature. Purification by preparative thin-layer chromatography with PE/EA (4:1) as eluting solvent afforded 7-methoxy-8-(methylamino)-2*H*-chromen-2-one **116a** as a yellow solid (16mg) and 7-methoxy-6-(methylamino)-2*H*-chromen-2-one **116b** as a colorless solid (5mg) (21 mg total, 51% combined yield).

7-Methoxy-8-(methylamino)-2*H*-chromen-2-one (116a)



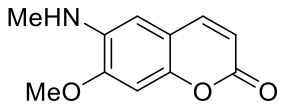
Mp: 76ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 9.5 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.22 (d, *J* = 9.5 Hz, 1H), 3.92 (s, 3H), 3.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.94, 151.98, 144.37, 144.25, 127.49, 118.01, 113.60, 112.96, 107.55, 56.16, 34.17.

IR (ATR): ṽ = 3386, 3057, 3021, 2971, 2942, 2924, 2842, 2819, 1713, 1612, 1568, 1507, 1483, 1464, 1445, 1424, 1409, 1280, 1214, 1162, 1134, 1095, 1073, 978, 845, 825, 784, 763, 708, 675, 615 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 205.07334, found 205.07256.

7-Methoxy-6-(methylamino)-2*H*-chromen-2-one (116b)



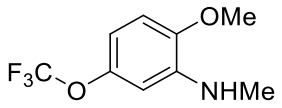
Mp: 143ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 9.3 Hz, 1H), 6.85 – 6.78 (m, 2H), 6.30 (s, 1H), 4.69 (br, 1H), 3.83 (s, 3H), 2.87 (d, *J* = 5.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.85, 158.24, 149.01, 132.27, 125.65, 115.10, 112.44, 105.33, 100.73, 55.61, 29.90.

IR (ATR): ṽ = 3443, 2956, 2924, 2853, 2813, 1701, 1631, 1577, 1504, 1489, 1455, 1424, 1359, 1349, 1270, 1248, 1186, 1163, 1117, 1025, 969, 936, 862, 841, 824, 801, 770, 694, 617 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 205.07334, found 205.07271.

2-Methoxy-*N*-methyl-5-(trifluoromethoxy)aniline (117)



Following **GP 4**, 1-methoxy-4-(trifluoromethoxy)benzene (38 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 2-methoxy-*N*-methyl-5-(trifluoromethoxy)aniline **117** as a yellow oil (20 mg, 45%).

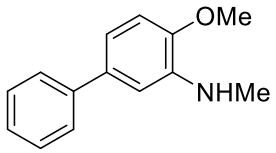
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (d, *J* = 8.6 Hz, 1H), 6.48 (ddd, *J* = 8.6, 2.4, 1.0 Hz,

1H), 6.40 (d, *J* = 2.4 Hz, 1H), 4.31 (br, 1H), 3.84 (s, 3H), 2.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.14, 143.99, 140.29, 124.92 (q, *J* = 203.1 Hz), 108.82, 107.45, 102.48, 55.69, 30.05. ^{19}F NMR (283 MHz, $CDCl_3$) δ -58.01.

IR (Reflexion): ṽ = 3447, 2941, 2911, 2856, 2839, 2811, 1615, 1529, 1482, 1454, 1432, 1417, 1357, 1250, 1213, 1159, 1117, 1069, 1031, 979, 878, 837, 793, 762, 687cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 221.06467, found 221.06484.

4-Methoxy-*N*-methyl-[1,1'-biphenyl]-3-amine (118)



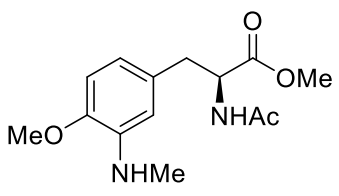
Following **GP 4**, 4-methoxy-1,1'-biphenyl (37 mg, 0.2 mmol), TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 4-methoxy-*N*-methyl-[1,1'-biphenyl]-3-amine **118** as a yellow oil (41 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.4, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.65 (d, *J* = 2.6 Hz, 1H), 6.61 (dd, *J* = 8.6 Hz, 2.6Hz, 1H), 3.72 (s, 3H), 2.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.11, 143.78, 138.92, 131.82, 129.42, 127.91, 126.83, 115.71, 113.60, 112.16, 56.63, 31.57.

IR (ATR): ṽ = 3585, 3405, 3052, 3023, 2933, 2898, 2831, 2809, 1739, 1615, 1573, 1491, 1463, 1442, 1396, 1327, 1297, 1262, 1233, 1179, 1158, 1130, 1066, 1044, 1027, 915, 864, 803, 771, 742, 699, 665, 624, 610 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 213.11482, found 213.11574.

Methyl (*S*)-2-acetamido-3-(4-methoxy-3-(methylamino)phenyl)propanoate (119)



Following **GP 3**, methyl (*S*)-2-acetamido-3-(4-methoxyphenyl)propanoate (50 mg, 0.2

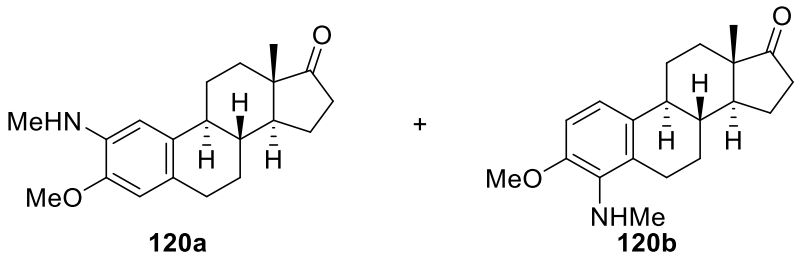
mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 5 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded methyl (*S*)-2-acetamido-3- (4-methoxy-3-(methylamino)phenyl)propanoate **119** as a yellow oil (55 mg, 98%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (d, *J* = 8.0 Hz, 1H), 6.36 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.28 (d, *J* = 2.0 Hz, 1H), 5.94 (d, *J* = 7.6 Hz, 1H), 4.82 (dt, *J* = 7.6, 5.6 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.03 (d, *J* = 5.6 Hz, 2H), 2.82 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.31, 169.60, 146.08, 139.23, 128.41, 116.76, 110.10, 109.10, 55.40, 53.23, 52.18, 37.48, 30.30, 23.12.

IR (ATR): ṽ = 3419, 3293, 2951, 2851, 2242, 1741, 1657, 1602, 1523, 1435, 1373, 1262, 1227, 1168, 1130, 1028, 912, 852, 789, 732, 685, 666, 645, 610 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 280.14176, found 280.14158.

(*8R*,9*S*,13*S*,14*S*)-3-Methoxy-13-methyl-2-(methylamino)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (120a) and (8*R*,9*S*,13*S*,14*S*)-3-methoxy-13-methyl-4- (methylamino)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (120b)

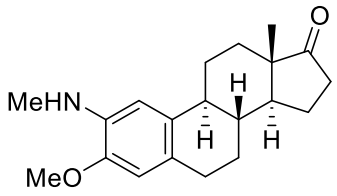


120a **120b**

Following **GP 3**, (8*R*,9*S*,13*S*,14*S*)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*- cyclopenta[*a*]phenanthren-17-one (57 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by preparative thin-layer chromatography with PE/EA (10:1) as eluting solvent afforded (8*R*,9*S*,13*S*,14*S*)-3-methoxy-13-methyl-2-(methylamino)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one **120a** as a yellow solid (22 mg) and (8*R*,9*S*,13*S*,14*S*)-3-methoxy-13-methyl-4-(methylamino)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one **120b** as a

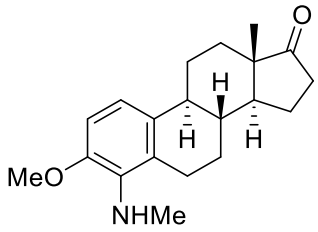
yellow solid (5 mg) (27 mg, 44% combined yield).

(8*R*,9*S*,13*S*,14*S*)-3-Methoxy-13-methyl-2-(methylamino)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (120a) spectral data were in agreement with literature values[2]



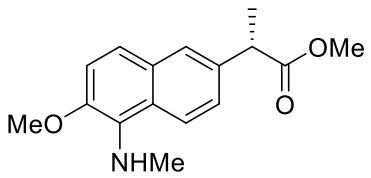
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (s, 1H), 6.50 (s, 1H), 3.81 (s, 3H), 2.86 (s, 3H), 2.93 – 2.66 (m, 2H), 2.50 (dd, *J* = 18.3, 8.1 Hz, 1H), 2.45 – 1.89 (m, 6H), 1.70 – 1.35 (m, 6H), 0.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.13, 145.42, 137.22, 131.76, 124.05, 109.99, 106.74, 55.45, 50.44, 48.05, 44.38, 38.57, 35.89, 31.69, 30.69, 29.11, 26.84, 26.14, 21.56, 13.87.

(8*R*,9*S*,13*S*,14*S*)-3-Methoxy-13-methyl-4-(methylamino)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (120b) spectral data were in agreement with literature values[2]



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, *J* = 8.5 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 1H), 3.83 (s, 3H), 2.92 (ddd, *J* = 16.7, 5.8, 1.9 Hz, 1H), 2.80 (s, 3H), 2.50 (dd, *J* = 18.6, 8.6 Hz, 1H), 2.42 – 2.33 (m, 1H), 2.27 (td, *J* = 10.7, 4.3 Hz, 1H), 2.20 – 2.01 (m, 3H), 2.01 – 1.89 (m, 1H), 1.70 – 1.37 (m, 7H), 0.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.91, 149.48, 137.19, 133.14, 129.01, 118.88, 108.53, 55.79, 50.53, 47.98, 44.58, 37.92, 35.90, 35.27, 31.69, 26.41, 26.17, 25.65, 21.58, 13.86.

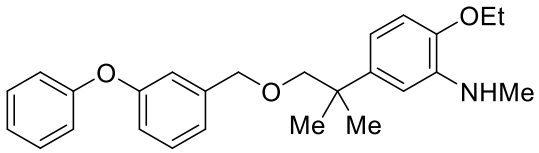
Methyl (*S*)-2-(6-methoxy-5-(methylamino)naphthalen-2-yl)propanoate (121) spectral data were in agreement with literature values[2]



Following **GP 3**, methyl(*S*)-2-(6-methoxynaphthalen-2-yl) propanoate (49 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 5 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded methyl (*S*)-2-(6-methoxy-5- (methylamino)naphthalen-2-yl)propanoate **121** as a yellow oil (43 mg, 73 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.8 Hz, 1H), 7.65 (d, *J* = 1.9 Hz, 1H), 7.45 (d, *J* = 8.9 Hz, 1H), 7.39 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.24 (d, *J* = 8.9 Hz, 1H), 3.94 (s, 3H), 3.86 (q, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 2.96 (s, 3H), 1.58 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.12, 147.41, 135.55, 134.03, 129.96, 127.28, 126.41, 125.09, 123.40, 122.26, 113.85, 56.89, 52.01, 45.26, 37.12, 18.47.

2-Ethoxy-*N*-methyl-5-(2-methyl-1-((3-phenoxybenzyl)oxy)propan-2-yl)aniline(122)



Following **GP 3**, 1-((2-(4-ethoxyphenyl)-2-methylpropoxy)methyl)-3-phenoxybenzen (etofenprox, 75 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by preparative thin-layer chromatography with PE/EA (15:1) as eluting solvent afforded 2-ethoxy-*N*-methyl-5-(2-methyl-1-((3-phenoxybenzyl)oxy)propan-2-yl)aniline **122** as a yellow oil (30 mg, 37%).

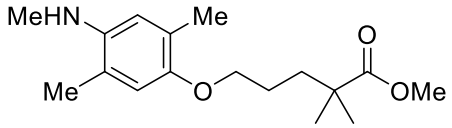
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H), 7.31 – 7.24 (m, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.06 – 7.00 (m, 3H), 6.98 (s, 1H), 6.91 (dd, *J* = 8.0, 2.1 Hz, 1H), 6.72 – 6.61 (m, 3H), 4.47 (s, 2H), 4.03 (q, *J* = 7.0 Hz, 2H), 3.45 (s, 2H), 2.86 (s, 3H), 1.41 (t, *J* = 7.0 Hz, 3H), 1.34 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.28, 157.22, 144.48, 141.17, 140.34, 138.83, 129.67, 129.46, 123.16, 122.03, 118.90, 117.63, 117.61, 113.61,

109.65, 107.69, 80.54, 72.77, 63.66, 38.81, 30.40, 26.15, 15.03.

IR (Reflexion): ṽ = 3436, 3066, 3039, 2975, 2917, 2875, 2849, 2803, 2241, 1792, 1698, 1584, 1525, 1487, 1444, 1410, 1391, 1360, 1304, 1255, 1215, 1164, 1135, 1104, 1046, 959, 931, 908, 848, 789, 731, 691, 649 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 405.22985, found 405.23112.

Methyl 5-(2,5-dimethyl-4-(methylamino)phenoxy)-2,2-dimethylpentanoate (123)



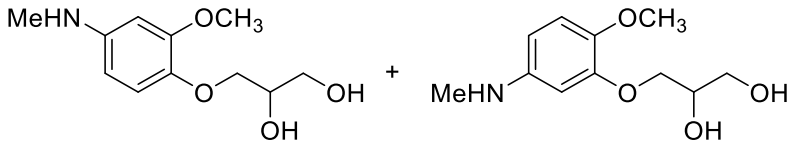
Following **GP 3**, methyl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (gemfibrozil methyl ester, 53 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded methyl 5-(2,5-dimethyl-4-(methylamino)phenoxy)-2,2-dimethylpentanoate **123** as a yellow oil (43 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (s, 1H), 6.44 (s, 1H), 3.86 – 3.81 (m, 2H), 3.66 (s, 3H), 2.85 (s, 3H), 2.21 (s, 3H), 2.10 (s, 3H), 1.71 – 1.69 (m, 4H), 1.21 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.34, 148.98, 141.25, 125.32, 120.17, 115.76, 112.61, 69.62, 51.66, 42.07, 37.13, 31.50, 25.40, 25.13, 17.26, 16.03.

IR (ATR): ṽ = 3427, 3029, 2950, 2928, 2871, 2812, 1730, 1620, 1519, 1471, 1404, 1389, 1321, 1220, 1198, 1146, 1057, 990, 855, 774, 655 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 293.19855, found 293.19836.

3-(2-Methoxy-4-(methylamino)phenoxy)propane-1,2-diol (124a) and 3-(2-methoxy-5- (methylamino)phenoxy)propane-1,2-diol (124b)

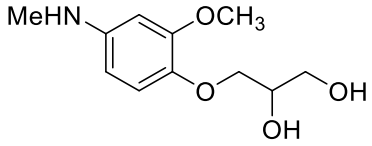


124a **124b**

Following **GP 3**, 3-(2-methoxyphenoxy)propane-1,2-diol (guaifenesin, 40 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 3 days

at room temperature. Purification by preparative thin-layer chromatography with DCM/MeOH (1:1) as eluting solvent afforded 3-(2-methoxy-4-(methylamino)phenoxy)propane-1,2-diol **124a** as a brown oil(14 mg) and 3-(2-methoxy-5-(methylamino) phenoxy)propane-1,2-diol **124b** as a brown oil (8 mg) (22 mg, 53% combined yield)

3-(2-Methoxy-4-(methylamino)phenoxy)propane-1,2-diol (124a)

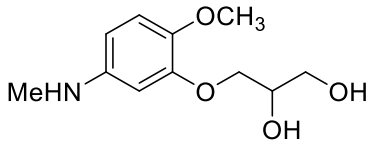


^{1}H NMR (500 MHz, MeOD) δ 6.80 (d, *J* = 8.6 Hz, 1H), 6.37 (d, *J* = 2.6 Hz, 1H), 6.21 (dd, *J* = 8.6, 2.6 Hz, 1H), 4.03 (dd, *J* = 8.9, 3.8 Hz, 1H), 3.99 – 3.91 (m, 2H), 3.75 (s, 3H), 3.72 – 3.62 (m, 2H), 2.72 (s, 3H). ^{13}C NMR (125 MHz, MeOD) δ 150.79, 146.66, 142.97, 115.96, 105.74, 101.93, 71.78, 71.59, 64.24, 57.86, 31.67.

IR (ATR): ṽ = 3422, 3321, 2926, 2863, 2538, 2470, 1735, 1617, 1589, 1515, 1459, 1446, 1301, 1243, 1178, 1162, 1133, 1107, 1033, 1017, 938, 862, 830, 819, 794, 777, 683, 626 cm^{-1}

HRMS (ESI+) m/z: $[2M+Na]^{+}$ calcd 477.2207, found 477.2231.

3-(2-Methoxy-5-(methylamino)phenoxy)propane-1,2-diol (124b)

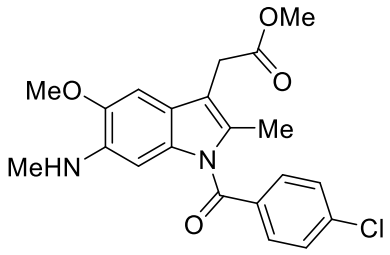


^{1}H NMR (500 MHz, MeOD) δ 6.82 (d, *J* = 8.6 Hz, 1H), 6.35 (d, *J* = 2.6 Hz, 1H), 6.17 (dd, *J* = 8.6, 2.6 Hz, 1H), 4.00 – 3.90 (m, 2H), 3.88 – 3.83 (m, 1H), 3.80 (s, 3H), 3.71 – 3.59 (m, 2H), 2.73 (s, 3H). ^{13}C NMR (125 MHz, MeOD) δ 152.18, 147.22, 141.73, 118.30, 105.26, 100.31, 73.59, 71.94, 64.41, 56.27, 31.62.

IR (ATR): ṽ = 3345, 2979, 2957, 2943, 2925, 2874, 2799, 2539, 2479, 2363, 1736, 1614, 1591, 1513, 1457, 1427, 1408, 1309, 1237, 1214, 1184, 1154, 1131, 1104, 1045, 1028, 949, 919, 871, 857, 824, 796, 684, 631 cm^{-1}

HRMS (ESI+) m/z: $[M+H]^{+}$ calcd 228.1230, found 228.1238; $[2M+Na]^{+}$ calcd 477.2207, found 477.2237.

Methyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-6-(methylamino)-1*H*-indol-3-yl) acetate (125)



Following **GP 3**, methyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl) acetate(74 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 2 days at room temperature. Purification by thin-layer chromatography with PE/EA (4:1) as eluting solvent afforded methyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-6-(methylamino)-1*H*-indol-3-yl) acetate **125** as a yellow oil (23 mg, 29%).

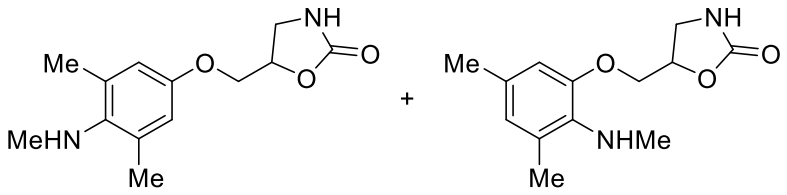
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 6.82 (s, 1H), 6.32 (s, 1H), 3.89 (s, 3H), 3.69 (s, 3H), 3.62 (s, 2H), 2.61 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.56, 168.65, 144.90, 138.72, 137.15, 134.49, 131.55, 131.06, 130.86, 128.92, 119.36, 112.77, 98.58, 96.08, 55.82, 52.03, 30.42, 30.28, 13.36.

IR (ATR): ṽ = 3438, 2951, 2928, 1736, 1677, 1622, 1588, 1501, 1476, 1435, 1399, 1383, 1363, 1317, 1225, 1166, 1088, 1073, 1035, 1015, 991, 967, 911, 841, 753, 732, 688, 650, 627 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 400.11844, found 400.11788.

5-((3,5-Dimethyl-4-(methylamino)phenoxy)methyl)oxazolidin-2-one (126a) and 5-((3,5-dimethyl-2-(methylamino)phenoxy)methyl)oxazolidin-2-one (126b)

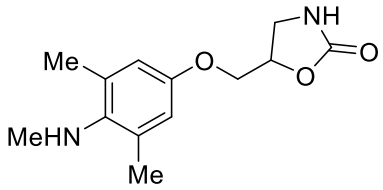


126a **126b**

Following **GP 3**, 5-((3,5-dimethylphenoxy)methyl)oxazolidin-2-one (metaxalone, 44 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for

36h at room temperature. Purification by preparative thin-layer chromatography with DCM/MeOH (20:1) as eluting solvent afforded 5-((3,5-dimethyl-4-(methylamino)phenoxy)methyl)oxazolidin-2-one **126a** as a yellow liquid (14 mg) and 5-((3,5-dimethyl-2-(methylamino) phenoxy)methyl)oxazolidin-2-one **126b** as a yellow liquid (14 mg) (28 mg total, 56% combined yield).

5-((3,5-Dimethyl-4-(methylamino)phenoxy)methyl)oxazolidin-2-one (126a)

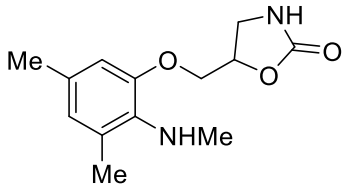


^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (s, 2H), 5.76 (s, 1H), 4.98 – 4.82 (m, 1H), 4.14 – 3.97 (m, 2H), 3.74 (t, *J* = 8.7 Hz, 1H), 3.67 – 3.49 (m, 1H), 2.69 (s, 3H), 2.27 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.47, 153.28, 141.32, 131.73, 114.81, 74.25, 68.27, 42.74, 35.74, 18.29.

IR (ATR): ṽ = 3243, 3153, 2912, 2875, 2796, 1738, 1601, 1487, 1446, 1314, 1231, 1161, 1128, 1084, 1063, 1004, 962, 937, 879, 863, 769, 718 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 250.13119, found 250.13221.

5-((3,5-Dimethyl-2-(methylamino)phenoxy)methyl)oxazolidin-2-one (126b)



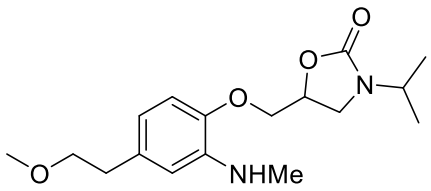
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (s, 1H), 6.52 (s, 1H), 5.95 (s, 1H), 5.02 – 4.92 (m, 1H), 4.19 – 4.07 (m, 2H), 3.78 (t, *J* = 8.8 Hz, 1H), 3.67 – 3.52 (m, 1H), 3.03 (br, 1H), 2.76 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.52, 149.44, 136.09, 130.87, 129.83, 125.15, 111.08, 74.26, 69.20, 42.62, 35.58, 20.92, 18.20.

IR (ATR): ṽ = 3399, 3247, 3152, 2964, 2920, 2876, 2807, 1734, 1589, 1500, 1447, 1419, 1317, 1293, 1237, 1166, 1086, 1008, 964, 880, 828, 765, 705, 621 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 250.13119, found 250.13188.

3-Isopropyl-5-((4-(2-methoxyethyl)-2-(methylamino)phenoxy)methyl)oxazolidin-

2-one (127)



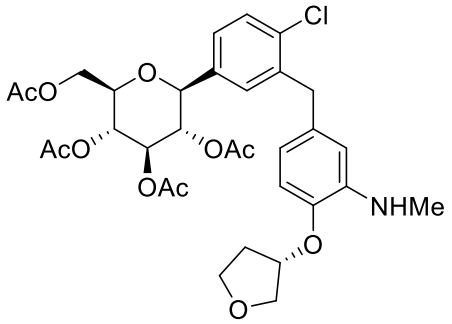
Following **GP 3**, 3-isopropyl-5-((4-(2-methoxyethyl)phenoxy)methyl)oxazolidin-2-one (59 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 5 days at room temperature. Purification by silica gel chromatography with PE/EA (1:1) as eluting solvent afforded 3-isopropyl-5-((4-(2-methoxyethyl)-2-(methylamino) phenoxy)methyl)oxazolidin-2-one **127** as a yellow oil (30 mg, 49%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (d, *J* = 7.7 Hz, 1H), 6.51 – 6.47 (m, 2H), 4.82 (qd, *J* = 8.8, 4.6 Hz, 1H), 4.18 – 4.08 (m, 1H), 4.10 (d, *J* = 4.6 Hz, 2H), 3.64 (t, *J* = 8.8 Hz, 1H), 3.58 (t, *J* = 7.2 Hz, 2H), 3.43 (dd, *J* = 8.6, 4.6 Hz, 1H), 3.35 (s, 3H), 2.84 (s, 3H), 2.80 (t, *J* = 7.2 Hz, 2H), 1.20 (d, *J* = 4.2 Hz, 3H), 1.18 (d, *J* = 4.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.76, 143.82, 139.40, 133.16, 116.28, 111.12, 110.64, 73.95, 70.95, 69.16, 58.60, 44.83, 41.76, 36.00, 30.34, 19.71, 19.68.

IR (ATR): ṽ = 3433, 2956, 2926, 2856, 2730, 1743, 1601, 1524, 1458, 1435, 1369, 1261, 1220, 1173, 1113, 1045, 789, 762, 640 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 322.18871, found 322.18885.

(2*R*,3*R*,4*R*,5*S*,6*S*)-2-(Acetoxymethyl)-6-(4-chloro-3-(3-(methylamino)-4-(((*S*)-tetrahydrofuran-2-yl)oxy)benzyl)phenyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (128)



Following **GP 3**, (2*R*,3*R*,4*R*,5*S*,6*S*)-2-(acetoxymethyl)-6-(4-chloro-3-(4-(((*S*)-tetrahydrofuran-2-yl)oxy)benzyl)phenyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate

(124 mg, 0.2 mmol), TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 5 days at room temperature. Purification by silica gel chromatography with PE/EA (1:1) as eluting solvent afforded (2*R*,3*R*,4*R*,5*S*,6*S*)-2-(acetoxymethyl)-6-(4-chloro-3-(3-(methylamino)-4-(((*S*)-tetrahydrofuran-2-yl)oxy)benzyl)phenyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **128** as a yellow solid (70 mg, 54%).

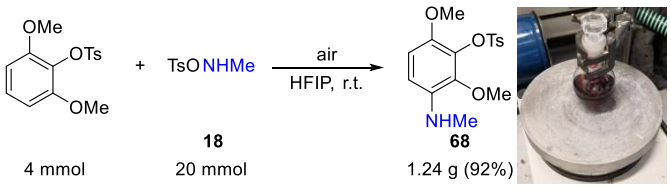
Mp: 127°C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.3 Hz, 1H), 7.17 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.07 (d, *J* = 2.1 Hz, 1H), 6.59 (d, *J* = 8.1 Hz, 1H), 6.42 (d, *J* = 1.8 Hz, 1H), 6.36 (dd, *J* = 8.1, 1.8 Hz, 1H), 5.27 (t, *J* = 9.6 Hz, 1H), 5.19 (t, *J* = 9.6 Hz, 1H), 5.03 (t, *J* = 9.6 Hz, 1H), 4.90 (ddd, *J* = 7.7, 5.6, 2.4 Hz, 1H), 4.30 (d, *J* = 9.6 Hz, 1H), 4.25 (dd, *J* = 12.4, 4.8 Hz, 1H), 4.13 (dd, *J* = 12.4, 2.2 Hz, 1H), 4.05 – 3.85 (m, 6H), 3.78 (ddd, *J* = 9.8, 4.8, 2.3 Hz, 1H), 2.81 (s, 3H), 2.22 – 2.10 (m, 2H), 2.06 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.67, 170.31, 169.46, 168.73, 143.04, 140.00, 139.19, 135.05, 134.55, 132.58, 129.80, 129.68, 125.75, 116.25, 111.46, 110.54, 79.49, 77.86, 76.11, 74.13, 73.22, 72.54, 68.52, 67.20, 62.32, 38.82, 33.03, 30.26, 20.71, 20.59, 20.22.

IR (ATR): $\tilde{\nu}$ = 3429, 2948, 2874, 1745, 1601, 1523, 1478, 1434, 1417, 1368, 1216, 1107, 1035, 972, 909, 824, 794, 731, 646 cm^{-1}

HRMS (EI+) m/z: $[M+H]^+$ calcd 648.2206, found 648.2205; $[M+Na]^+$ calcd 670.2026, found 670.2028.

2.4.4 Large-Scale Reaction



Scheme S1. Large-scale reaction

To a stirred solution of **18** (3.23g, 16 mmol) in 10 mL HFIP solution was added 2,6-

dimethoxyphenyl 4-methylbenzenesulfonate (1.23 g, 4 mmol) under ambient atmosphere at room temperature. The reaction was stirred for 36 h at room temperature (monitored by TLC). Then the reaction was diluted with 10 mL DCM and basified with 20mL saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with DCM (30 mL × 3), and the combined organic layers were washed with sat. brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA (5:1) as eluting solvent to afford 2,6-dimethoxy-3-(methylamino)phenyl 4-methylbenzenesulfonate **68** as a pale colorless solid (1.24 g, 92%).

2.4.5 Time-Dependent NMR

Decomposition of TsONHBoc in HFIP: TsONHBoc (15 mg, 0.05 mmol) in 0.5 mL $CDCl_3$ or d_2-HFIP under an ambient atmosphere at room temperature was monitored by ^1H NMR

TsONHBoc was quite stable in $CDCl_3$, however, it's gradually decomposed in 3 h in acidic d_2-HFIP as the Boc group was removed in d_2-HFIP ("traceless", as CO_2 and isobutene are formed).

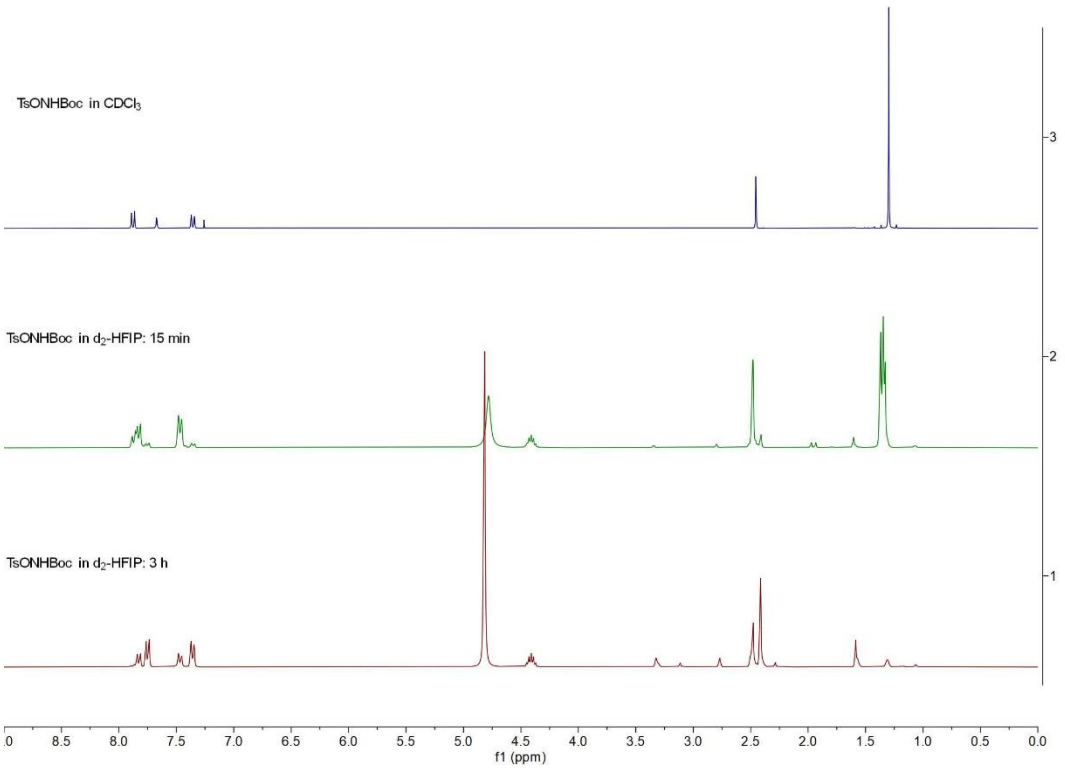


Figure S2. ^{1}H NMR spectra of TsONHBoc in $CDCl_3$ or d_2-HFIP

To a solution of TsONHMe (81 mg, 0.4 mmol) in 0.5 mL d_2-HFIP solution was added mesitylene (24 mg, 0.2 mmol) under ambient atmosphere at room temperature. And the reaction was monitored by ^{1}H NMR.

TsONHMe is stable in d_2-HFIP for several hours, however, it decomposed after the addition of mesitylene (for mesitylene, the aromatic-H could be deuterated in d_2-HFIP). This underlines that a π-complex and an electron charge transfer are involved, which in turn caused the decomposition of TsONHMe

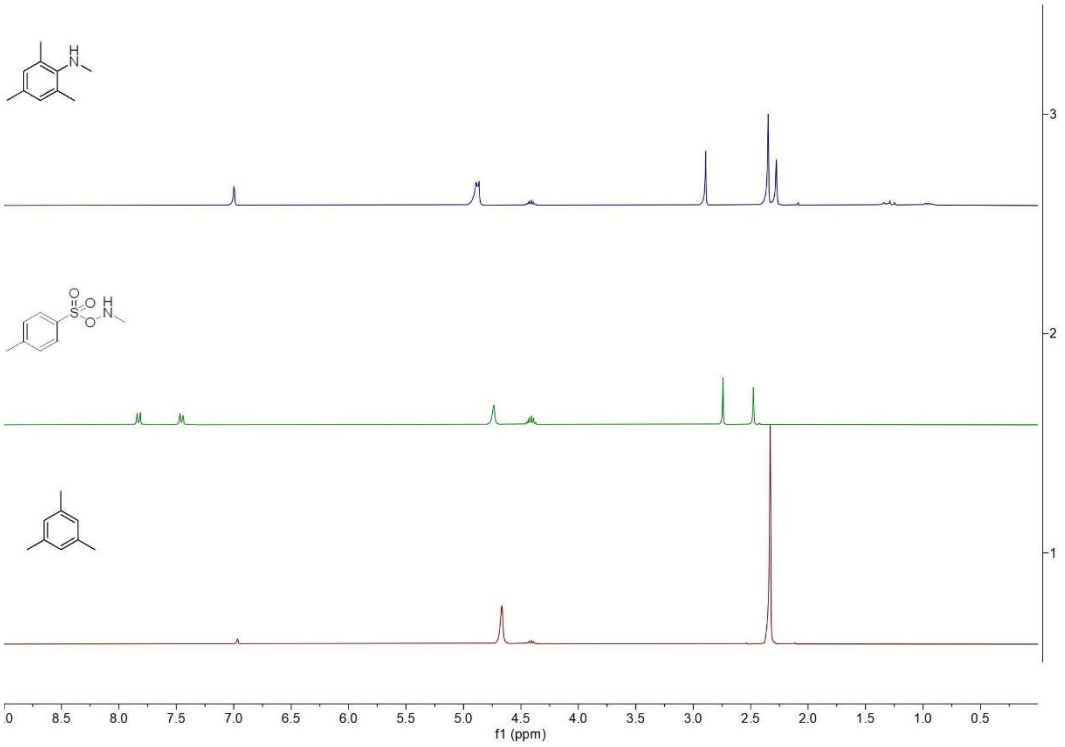


Figure S3. ^{1}H NMR spectra of mesitylene, TsONHMe and *N*,2,4,6-tetramethylaniline in d_2-HFIP

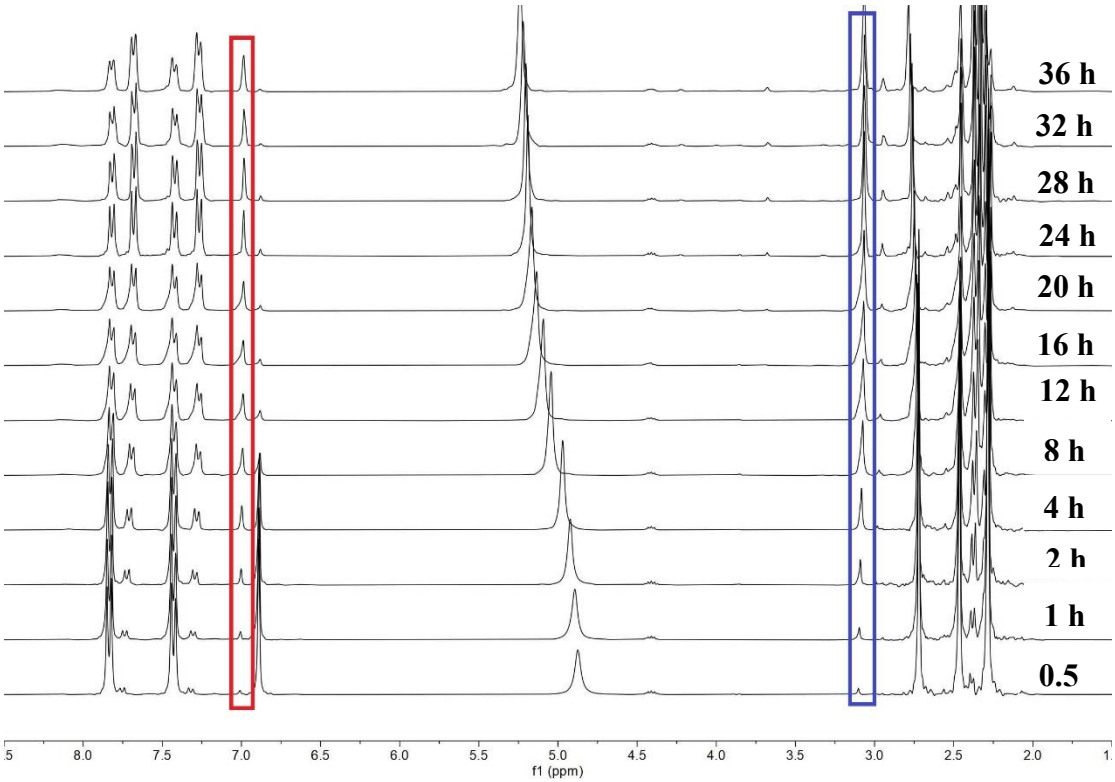


Figure S7. Overlay of ^{1}H NMR samples (d_2-HFIP) taken during the reaction

Product signals for aromatic-H highlighted in red, signals for MeNH group in blue.

2.4.6 ICP-OES Experiments

Reagents and standards All solutions were prepared with high-purity water of 18.2 MΩ cm resistivity obtained from a Milli-Q-system. Reagents used for the sample digestion were nitric acid (65%, P.A. quality). Polytetrafluoroethylene (PTFE) vessels (metal-free) were used to hold aqueous samples.

Preparation of samples:

1> 2.5 mL 65% HNO_3 was added to 200 mg TsONHBoc in a PTFE vessel, then it's diluted up to 10 mL with Milli-Q water.

2> 2.5 mL 65% HNO_3 was added to 200 mg TsONHMe in a PTFE vessel, then it's diluted up to 10 mL with Milli-Q water.

3> 2.5 mL 65% HNO_3 was added to 200 uL HFIP in a PTFE vessel, then it's diluted up to 10 mL with Milli-Q water.

Table S1. Elemental concentrations in original compounds or solvent (ug/g or ug/mL)

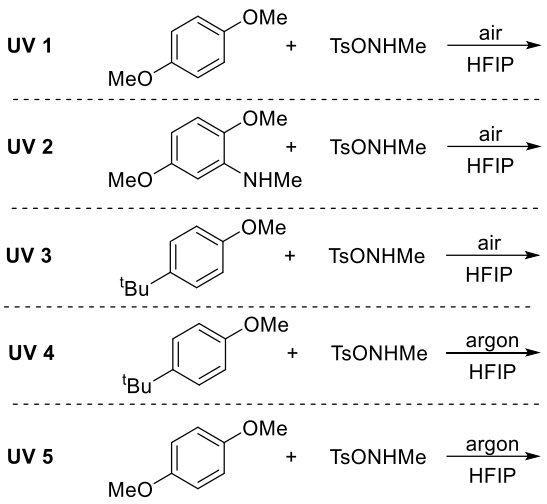
	Cu	Fe	Pd	Rh	Ru
TsONHBoc	< 0.25	4.41	< 0.25	< 0.25	< 0.25
TsONHMe	0.48	0.30	< 0.25	< 0.25	< 0.25
HFIP	< 0.25	< 0.25	< 0.25	< 0.25	< 0.25

Procedure detection limit: 0.25 ug/g, 0.25 ug/mL

ICP measurements verified a metal-free amination with TsONHMe in HFIP. No metal traces (< 1ppm for Fe, Cu and Pd, Rh, Ru below the detection limit) in TsONHMe, no metal traces (4.41 ppm for Fe, and Cu, Pd, Rh, Ru below the detection limit) in TsONHBoc, and no metal traces (Fe, Cu, Pd, Rh, Ru below the detection limit) in HFIP were detected.

2.4.7 UV/Vis Spectroscopy

To a solution of TsONHMe (24 mg, 0.12 mmol, 2.0 equiv) in 1.5 mL HFIP solution in a 3 mL quartz cuvette was added the arene (0.06 mmol, 1.0 equiv) in 1.5 mL HFIP solution at room temperature under aerobic condition or in a glovebox, and then it was closed with a Teflon-lined cap and shaken for 10 seconds. The UV/Vis absorption spectra of the reaction mixture were measured on Jasco UV/VIS V-670 spectrophotometer (for UV1, UV2 and UV3, the delay time between the preparation of samples and acquisition of UV spectrums is around 1 min; for UV4 and UV 5, 3 min of delay time).



Scheme S2. Different reactions for UV/Vis

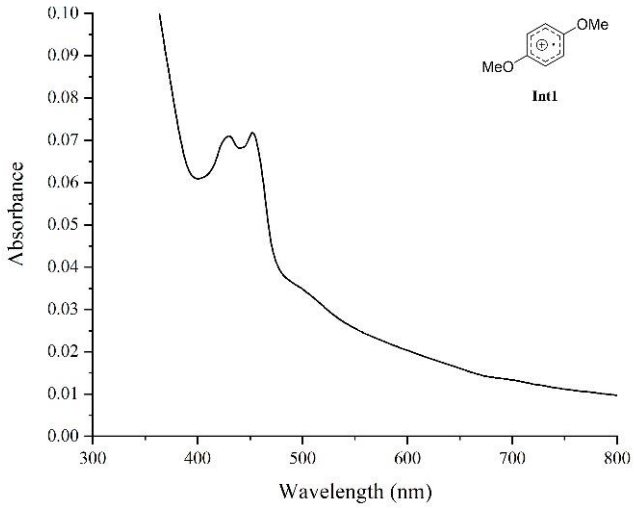


Figure S8. UV/Vis absorption spectrum of UV 1 (1,4-dimethoxybenzene and TsONHMe in HFIP solution under aerobic condition; spectrum picked up from UV 1 at 5 min)

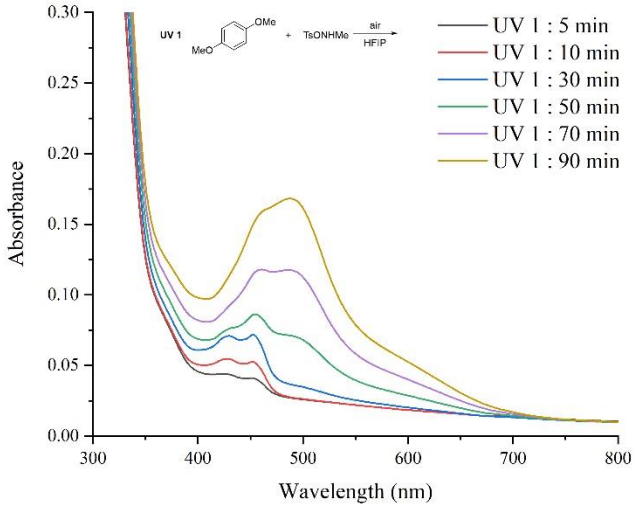


Figure S9. Time-dependent UV/Vis absorption spectra of UV 1 (1,4-dimethoxybenzene and TsONHMe in HFIP solution under air condition)

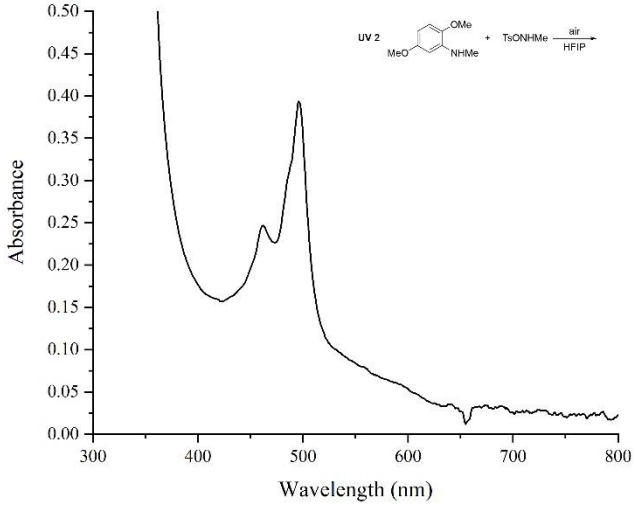


Figure S10. UV/Vis absorption spectrum of UV 2 (2,5-dimethoxy-*N*-methylaniline and TsONHMe in HFIP solution under aerobic conditions; spectrum picked up from UV 2 at 2min)

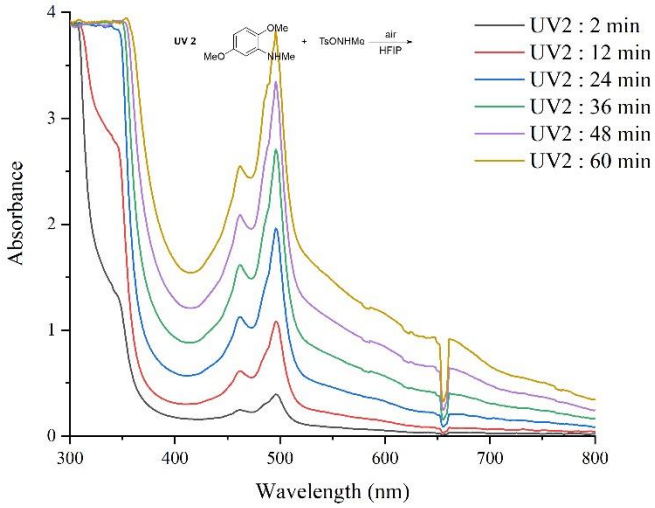


Figure S11. Time-dependent UV/Vis absorption spectra of UV 2 (2,5-dimethoxy-*N*-methylaniline and TsONHMe in HFIP solution under air condition)

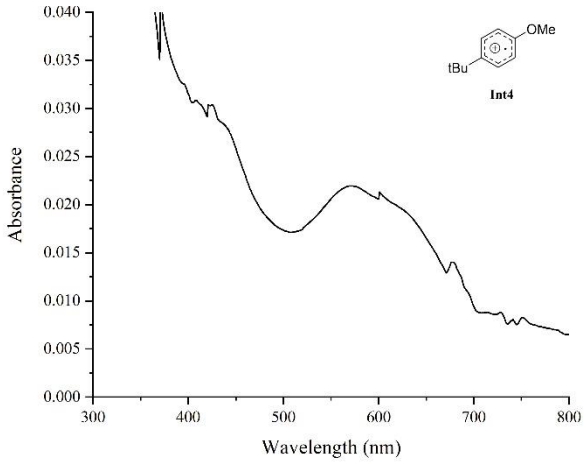


Figure S12. UV/Vis absorption spectrum of UV 3 (4-*tert*-butylanisole and TsONHMe in HFIP under air condition; spectrum picked up from UV 3 at 3 min)

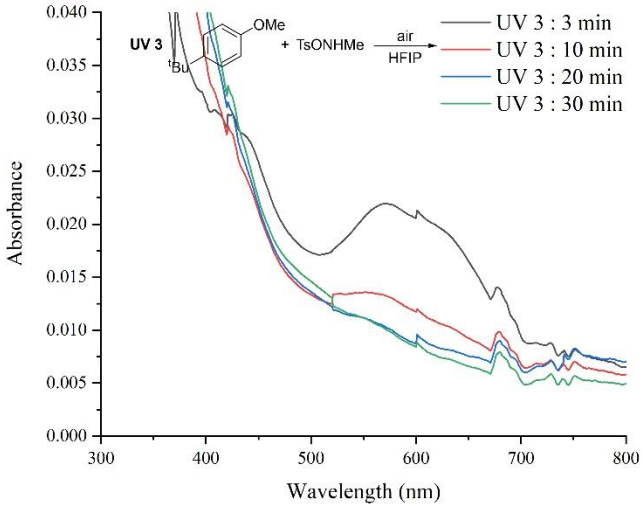


Figure S13. Time-dependent UV/Vis absorption spectra of UV 3 (4-*tert*-butylanisole and TsONHMe in HFIP solution under air condition)

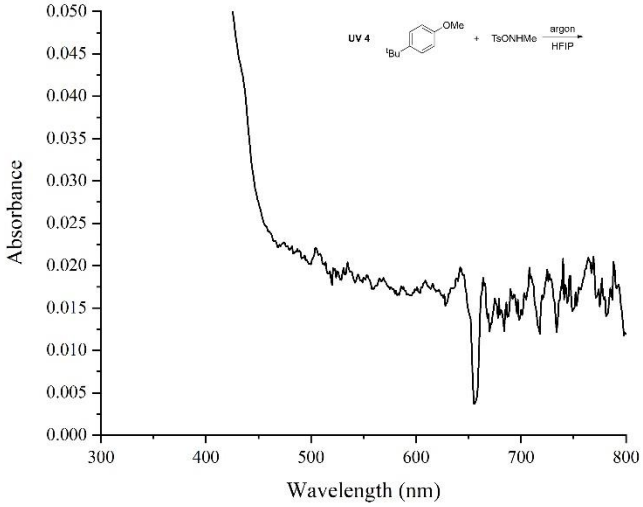


Figure S14. UV/Vis absorption spectrum of UV 4 (4-*tert*-butylanisole and TsONHMe in HFIP solution under argon atmosphere)

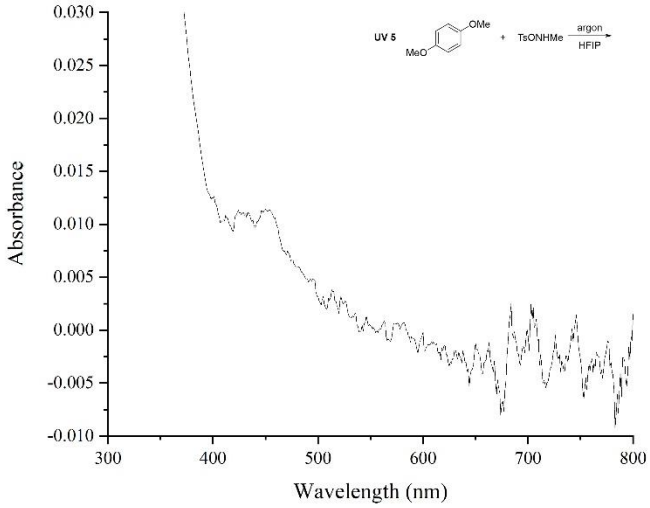


Figure S15. UV/Vis absorption spectrum of UV 5 (1,4-dimethoxybenzene and TsONHMe in HFIP solution under argon atmosphere)

The spectra of UV 1 and UV 3 showed bathochromic shifts (absorption band among 400–700 nm), which confirm that the radical cations **Int1** and **Int4** are involved in our reaction. The same bathochromic shifts (450–500 nm) in the UV 1 spectra after 50min are visible as shown in UV 2, which suggests that **Int2** is involved in the reaction (1,4-dimethoxybenzene and TsONHMe in HFIP solution). The comparison of the measurements under either inert or aerobic conditions (UV 1 vs UV 5; UV 3 vs UV 4) shows that only under aerobic atmosphere significant amounts of the radical cation can be detected in the UV spectra. Thus one can conclude, that oxygen can accelerate the formation of the radical cation in our reaction.

2.4.8 EPR Studies

All EPR samples were prepared and handled under argon atmosphere at room temperature.

Sample1: TsONHMe (34 mg, 0.16 mmol) was added to 1,4-dimethoxybenzene (11 mg, 0.08 mmol) in 0.2 mL HFIP solution under argon atmosphere, then it was stirred for 30 min and the mixture gradually turned brown.

Sample 2: TsONHMe (34 mg, 0.16 mmol) was added to 2,5-dimethoxy-*N*-

methylaniline (13 mg, 0.08 mmol) in 0.2 mL HFIP solution under argon atmosphere, then it was stirred for 30min and the mixture gradually turned brown.

Sample 3: TsONHMe (34 mg, 0.16 mmol) was added to 1,4-dimethoxybenzene (11 mg, 0.08 mmol) and DMPO (18 mg, 0.16 mmol) in 0.2 mL HFIP solution under argon atmosphere, then it was stirred for 10 min and the mixture gradually turned yellow.

Sample 4: 1,4-dimethoxybenzene (11 mg, 0.08 mmol) in 0.2 mL 97% conc. H_2SO_4 solution was stirred for 30 min under argon atmosphere, and the mixture gradually turned yellow.

All four samples were analyzed by EPR spectroscopy (Figure S16 - S19). Parameters for EPR-spectra acquisition: modulation frequency = 100.00 KHz, modulation amplitude = 2.0 G, temperature = 23°C, EPR tube: A glass capillary was filled with the sample and placed inside a 4 mm EPR-tube.

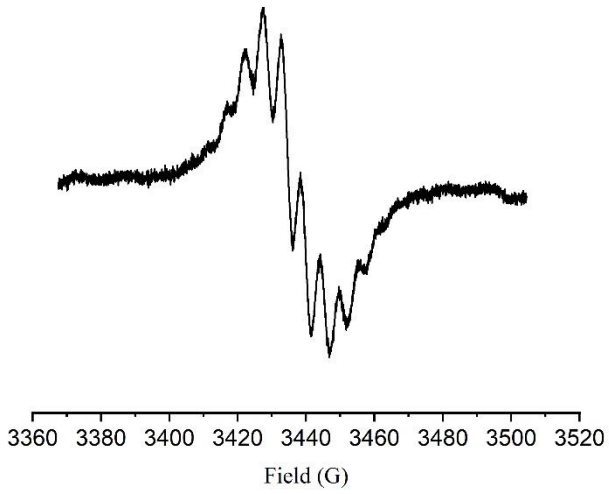


Figure S16. EPR spectrum of sample 1: ν = 9.638679 GHz, MP = 6.308 mW, RG = 65 dB

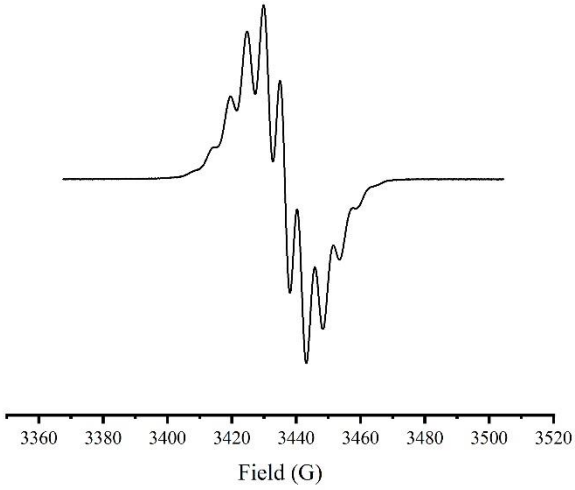


Figure S17. EPR spectrum of sample 2: ν = 9.637432 GHz, MP = 0.02512 mW, RG = 60 dB

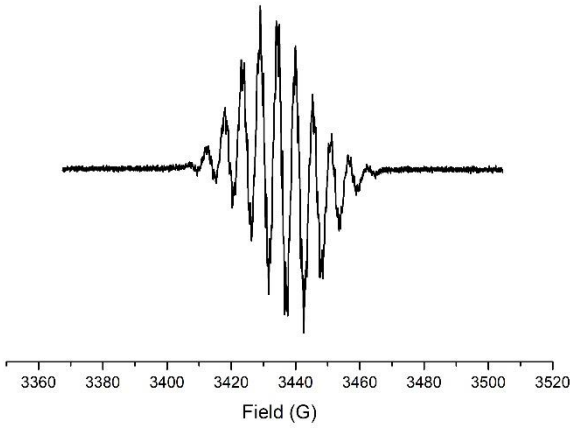


Figure S18 EPR spectrum of sample 3: ν = 9.635575 GHz, MP = 6.301mW, RG = 64 dB

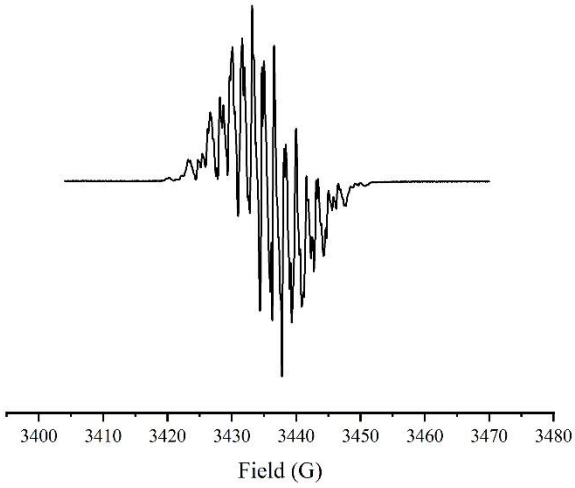


Figure S19. EPR spectrum of sample 4: ν = 9.636954 GHz, MP = 6.301 mW, RG = 60 dB

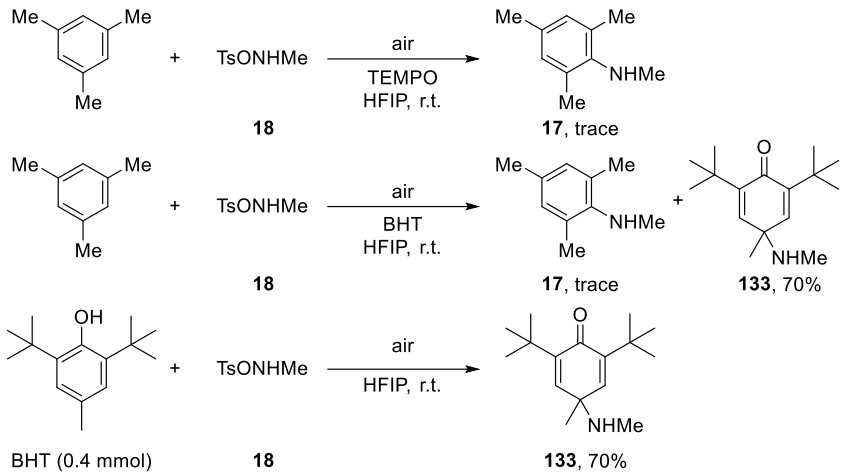
2.4.9 Radical Trapping Experiments

To a stirred solution of TsONHMe (115 mg, 0.4 mmol) in 0.5 mL HFIP solution 1,3,5-trimethylbenzene (24 mg, 0.2 mmol) was added or not added under ambient atmosphere at room temperature, then TEMPO (63 mg, 0.4 mmol) or BHT (88 mg, 0.4 mmol) was added to the mixture. The reaction was stirred at room temperature for 36h (monitored by GCMS or TLC).

For the TEMPO reaction, traces of *N*,2,4,6-tetramethylaniline were detected.

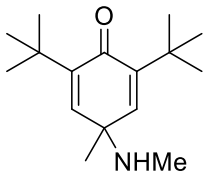
For the BHT reaction, traces of *N*,2,4,6-tetramethylaniline were detected, but 2,6-di-*tert*-butyl-4-methyl-4-(methylamino)cyclohexa-2,5-dien-1-one **133** was isolated as a yellow oil (70 mg, 70%); **133** was also acquired with the same yield as above even mesitylene was excluded.

The results show that a radical pathway and a nitrogen-centered radical (NHMe radical) are involved in the reaction, and BHT is a good donor than mesitylene.



Scheme S3. Radical trapping experiments

2,6-di-*tert*-Butyl-4-methyl-4-(methylamino)cyclohexa-2,5-dien-1-one (133)



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37 (s, 2H), 2.18 (s, 3H), 2.03 (s, 1H), 1.29 (s, 3H), 1.23 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.32, 148.05, 144.57, 54.32, 34.79, 30.38, 29.62, 27.58

IR (ATR): ṽ = 3335, 2961, 2951, 2867, 2792, 1657, 1627, 1485, 1460, 1387, 1363, 1335, 1246, 1200, 1164, 1133, 1066, 1019, 930, 913, 881, 819, 801, 742, 646 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 249.20872, found 249.20844.

2.4.10 Cyclic Voltammetry

Cyclic voltammetry was conducted on an EmStat (PalmSens) potentiostat using a 3-electrode cell configuration. Measurements were performed in dry acetonitrile with tetrabutylammonium hexafluorophosphate (0.1 M) as the electrolyte, and the cyclic voltammograms were collected using a glassy carbon working electrode, a platinum wire counter electrode, and an Ag reference at a scan rate of 0.1 V s^{-1}. All the solutions were degassed by bubbling N_2 prior to measurements. With these parameters, all compounds listed in Table S3 exhibited irreversible reduction waves.

Table S2. Electrochemical potentials for N-O compounds

Substrate	**Ep (V vs. Ag)**
TsONHBoc	-0.74 V
TsONHMe	-1.06 V

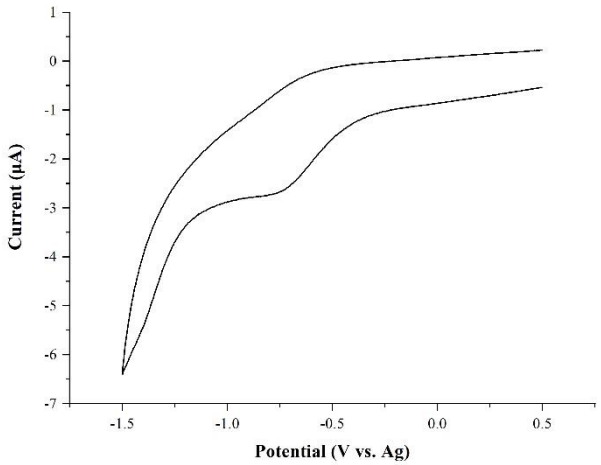


Figure S20. Cyclic voltammetry of **TsONHBoc**

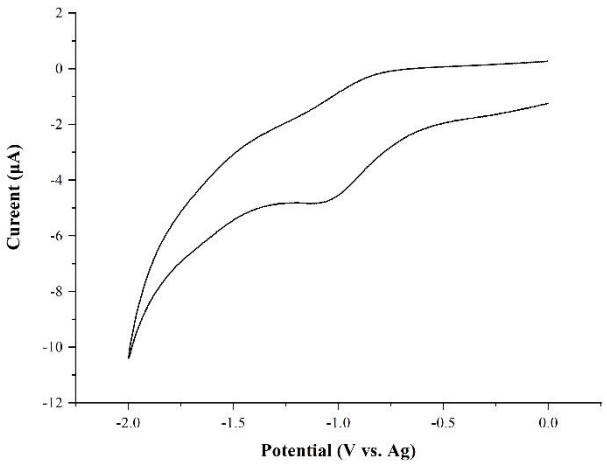
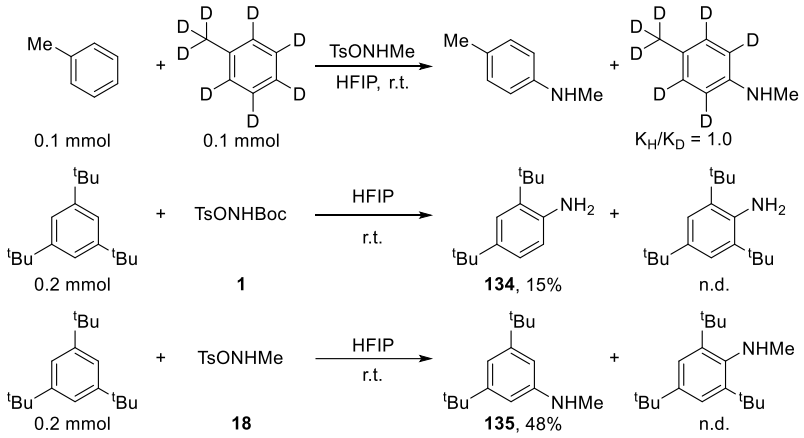


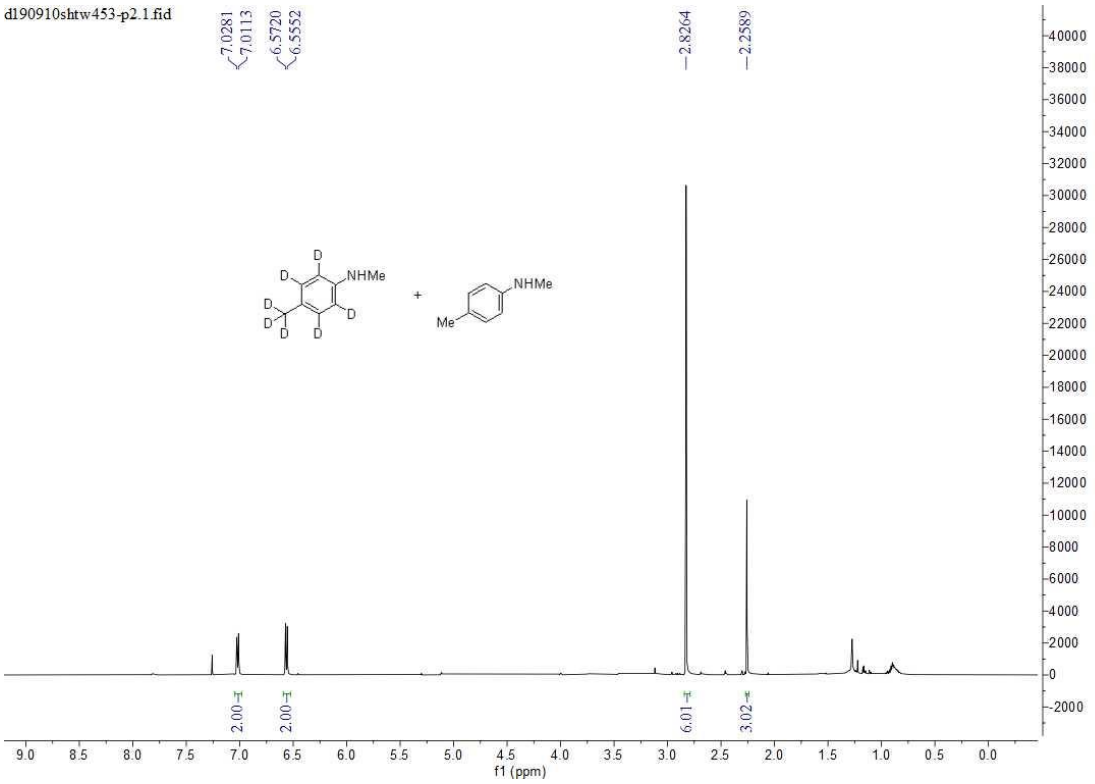
Figure S21. Cyclic voltammetry of **TsONHMe**

2.4.11 KIE and Control Experiments



Scheme S4. Kinetic isotope effect and control experiments

To a stirred solution of TsONHMe (162 mg, 0.8 mmol) in 0.5 mL HFIP solution was added toluene (9 mg, 0.1 mmol) and d_8-toluene (8 mg, 0.1 mmol) under ambient atmosphere at room temperature. The reaction was stirred at room temperature for 10 days. Then the reaction was diluted with 1mL DCM and basified with 1mL saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with DCM (3 mL × 3), and the combined organic layers were washed with sat. brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by preparative thin-layer chromatography to afford the isomer as a yellow oil (8 mg, 32%).



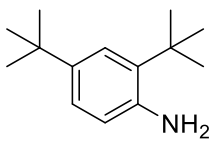
To a stirring solution of TsONHBoc (115 mg, 0.4 mmol) or TsONHMe (81 mg, 0.4 mmol) in 0.5 mL HFIP solution was added 1,3,5-tri-*tert*-butylbenzene (49 mg, 0.2 mmol) under ambient atmosphere at room temperature. The reaction was stirred at room temperature for 1 month or 36 h, respectively.

For the TsONHBoc reaction, only removal of *tert*-butyl group and formation of product 2,4-di-*tert*-butylaniline **134** (6 mg, 15%) as a yellow oil was isolated.

For TsONHMe reaction, only the C-C aminated product was observed and formation of product 3,5-di-*tert*-butyl-*N*-methylaniline **135** as a yellow oil (21 mg, 48%), no C-H aminated product was formed.

Those two experiments show that *tert*-butyl group is more easier to be removed than the proton, especially for 1,3,5-tri-*tert*-butylbenzene as the substrate.

2,4-Di-*tert*-butylaniline (134) spectral data were in agreement with literature values[65]



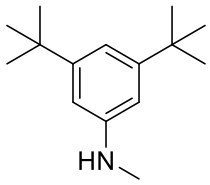
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 2.3 Hz, 1H), 7.08 (dd, *J* = 8.2, 2.3 Hz, 1H),

6.62 (d, *J* = 8.2 Hz, 1H), 3.65 (br, 2H), 1.45 (s, 9H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.94, 141.13, 133.25, 123.60, 123.53, 117.54, 34.55, 34.13, 31.60, 29.69.

IR (Reflexion): $\tilde{\nu}$ = 3484, 3379, 2962, 2906, 2870, 1869, 1771, 1620, 1529, 1504, 1481, 1465, 1407, 1363, 1292, 1278, 1245, 1200, 1163, 1129, 1103, 1019, 905, 888, 819, 639 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 205.18250, found 205.18303.

3,5-Di-*tert*-butyl-*N*-methylaniline (135) spectral data were in agreement with literature values[66]



H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.52 (d, *J* = 1.5 Hz, 2H), 2.88 (s, 3H), 1.34 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.66, 148.67, 112.14, 107.13, 34.82, 31.45, 30.97.

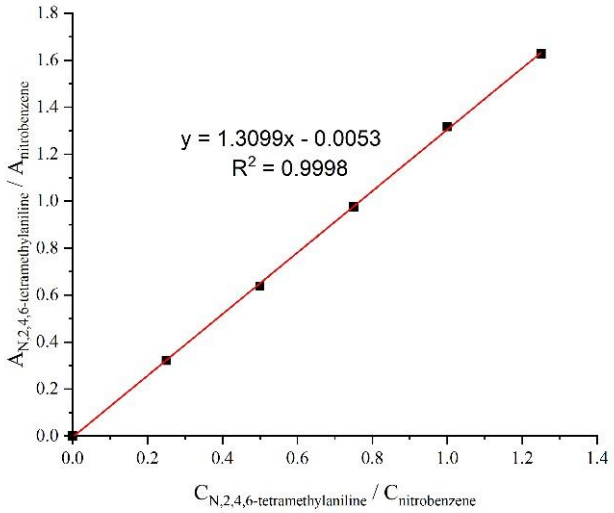
IR (Reflexion): $\tilde{\nu}$ = 3410, 3079, 2965, 2903, 2867, 2806, 1675, 1602, 1514, 1477, 1453, 1422, 1392, 1362, 1334, 1312, 1247, 1205, 1164, 1129, 1088, 1026, 996, 924, 899, 845, 708 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 219.21815, found 219.21805.

2.4.12 GC Analysis

Standard curve plot and RF

The *N*,2,4,6-tetramethylaniline (analyte) and internal standard (IS) nitrobenzene (20.6 uL, 0.2 mmol) were dissolved in 2.0 mL MeOH in various stoichiometric ratios (nitrobenzene / *N*,2,4,6-tetramethylaniline: 1 : 1.25, 1 : 1, 1 : 0.75, 1 : 0.5, 1 : 0.25, 1 : 0). The solutions were analyzed by gas chromatography.



$$RF = \frac{Area_{IS} \times C_{analyte}}{Area_{analyte} \times C_{Is}} = \frac{1}{1.3099} = 0.7634$$

Figure S22. Standard curve plot

To a stirred solution of the TsONHMe (80.5 mg, 0.4 mmol) in 0.5 mL HFIP solution was added the mesitylene (24.0 mg, 0.2 mmol) and internal standard (IS) nitrobenzene (24.6 mg, 0.2 mmol) under ambient atmosphere or N_2 atmosphere or O_2 atmosphere at room temperature. The samples of the reaction mixture were taken in time intervals adjust to the reaction rate, and they were analyzed by gas chromatography.

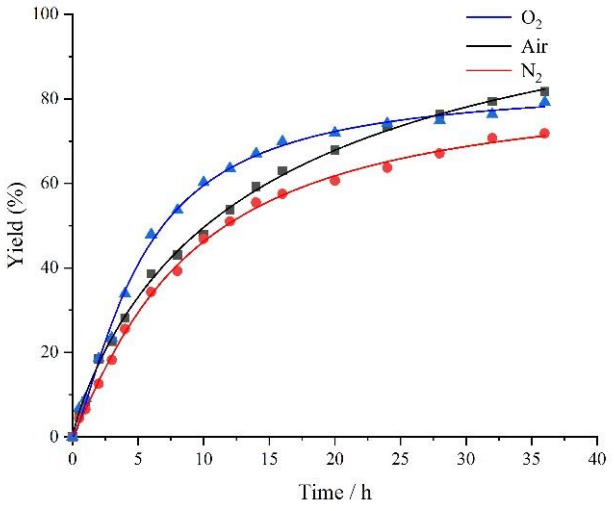


Figure S23. Reaction under air, N_2 and O_2 condition

2.4.13 Computational Details

Geometry optimization of the complexes were conducted on the PBE0-D3/aug-pc-1 level of theory using the TeraChem[67] software package. Configuration interaction constrained density functional theory calculations were performed within the Q-Chem software package[68] on the PBE50/pcseg-1 level of theory. In all calculations a conductor-like polarizable continuum model (dielectric constant of 16.7) was used in order to implicitly simulate the influence of the solvent (HFIP).

CI-CDFT Hamiltonians (in atomic units)

Structure a)

	i	f
i	-1599.87650	-0.00236
f	-0.00236	-1599.71772

	i	v	f
i	-1599.86642	0.03622	-0.00786
v	0.03622	-1599.76989	0.00369
f	-0.00786	0.00369	-1599.71983

Structure b)

	i	f

i	-1,599.87438	-0.00183
f	-0.00183	-1,599.71701

	i	v	f
i	-1,599.86341	-0.03796	-0.00730
v	-0.03796	-1,599.76913	-0.00501
f	-0.00730	-0.00501	-1,599.71731

Optimized structures

Structure a)

C	1.5435998505	2.3891791719	-2.1006212400
C	2.5171695418	2.5517402180	-1.1325944200
C	2.3833143155	1.9690206241	0.1337697210
C	1.2425095766	1.2173501663	0.4091510414
C	0.2575857636	1.0324427285	-0.5512849868
C	0.4213685914	1.6244561479	-1.7934302061
H	1.6535781315	2.8453228606	-3.0802593526
H	3.4012108579	3.1427359650	-1.3599814152
C	3.4545017156	2.1588465377	1.1674417467
H	1.1236720154	0.7593213769	1.3878180212
H	-0.6236717980	0.4353340041	-0.3414206075
S	-0.8130952846	1.3652822480	-3.0249155270
O	0.0855480504	0.3898969898	-4.0011360219
H	3.5899704278	3.2228764882	1.3926990999
H	4.4152283140	1.7793642487	0.8010190021

H	3.2076668042	1.6368709019	2.0958069138
O	-1.1145645040	2.5985554672	-3.7609785016
O	-1.9332810522	0.6027373298	-2.4668282639
N	-0.7138034324	-0.0238691616	-5.1303484732
H	-0.7358723384	-1.0348396278	-4.9953364210
C	0.0399495162	0.3116946118	-6.3274382228
H	0.0580243538	1.3966376035	-6.4574846427
H	-0.4949899318	-0.1389842789	-7.1694433295
H	1.0667612147	-0.0767916702	-6.3017388101
C	1.7002891898	-2.8616258451	-3.9479423041
C	2.9284681225	-3.3636842093	-3.5966929580
C	3.0515897199	-4.0647266103	-2.3875918648
C	1.8990261281	-4.3883288001	-1.6401239005
C	0.6593522804	-3.9500750826	-2.0327075672
C	0.5621695460	-3.1129694138	-3.1531738655
H	1.5805294458	-2.2567454447	-4.8417758141
H	3.7936972214	-3.1474845205	-4.2120469486
O	4.2078793968	-4.5502475602	-1.9034610433
H	2.0211214186	-4.9868967540	-0.7422972420
H	-0.2129849384	-4.1967603668	-1.4392340317
O	-0.5913616604	-2.5908046131	-3.6077033753
C	-1.7779605420	-2.7651516496	-2.8315083294
H	-2.0523613487	-3.8236960151	-2.7826570903
H	-2.5536239477	-2.2010071525	-3.3485174684
H	-1.6372294092	-2.3603736950	-1.8247293181
C	5.4138839261	-4.2772717889	-2.6159343272
H	6.2125158696	-4.7375131994	-2.0338003135
H	5.5816524651	-3.1973455094	-2.6901305162
H	5.3809658041	-4.7216576833	-3.6163979712
O	2.6653505549	-1.9581482863	-1.2724768643

O	1.6766516519	-1.4227225001	-1.8104807115

Structure b)

C	0.4951491626	2.8800247500	-0.0736043067
C	1.6503425315	3.3552475859	0.5235600101
C	2.5150535339	2.4956294222	1.2090013911
C	2.1968250386	1.1381571677	1.2799141456
C	1.0465337346	0.6404316264	0.6876174743
C	0.2099996907	1.5220113426	0.0175838450
H	-0.1774466653	3.5503637020	-0.5998471564
H	1.8866739031	4.4145881655	0.4585643950
C	3.7473911224	3.0314098911	1.8764743976
H	2.8623391219	0.4575708698	1.8047492923
H	0.8028202790	-0.4150629100	0.7366404208
S	-1.2451659325	0.8977574043	-0.7548936444
O	-0.6125945938	0.6940592162	-2.2639414120
H	3.4943612233	3.4585254311	2.8549331792
H	4.2039383932	3.8272854001	1.2797115278
H	4.4863511952	2.2411844894	2.0373581137
O	-2.2866272318	1.9285348175	-0.8246516493
O	-1.6012501830	-0.4150668675	-0.2082912478
N	-1.6267629058	0.1692844471	-3.1472630270
H	-1.2350342237	-0.7377794854	-3.4043634496
C	-1.6767480283	1.0500532338	-4.3024746711
H	-2.1180373273	2.0080211438	-4.0162510274
H	-2.3269399106	0.5638097472	-5.0369329995
H	-0.6875693924	1.2154749148	-4.7490363714
C	1.4424539508	-2.5950317714	-3.9176525774
C	2.7810793945	-2.8847005380	-3.8374637373

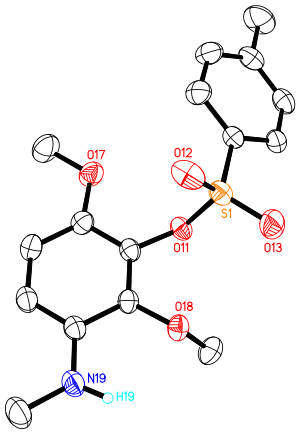
C	3.2508953375	-3.5903194426	-2.7194211081
C	2.3350332562	-4.1453695522	-1.7978936624
C	0.9870129035	-3.9256860719	-1.9252168523
C	0.5397214395	-3.0700978778	-2.9416250778
H	1.0480345266	-1.9889122211	-4.7281042802
H	3.4624173107	-2.4983494772	-4.5859340464
O	4.5433042861	-3.8732816761	-2.4867840103
H	2.7292907260	-4.7437260568	-0.9819243377
H	0.2997287745	-4.3433920679	-1.1994803864
O	-0.7496755881	-2.7292049766	-3.1316811251
C	-1.7216101170	-3.1787288560	-2.1821898451
H	-1.7736038475	-4.2716390373	-2.1782640476
H	-2.6722078785	-2.7641378962	-2.5171435665
H	-1.4832822275	-2.7983527953	-1.1852001503
C	5.5243815202	-3.3739039369	-3.3955241407
H	6.4863108267	-3.7056128546	-3.0040999704
H	5.4939455319	-2.2795741033	-3.4321905109
H	5.3686134615	-3.7879733506	-4.3973572676
O	2.7251510767	-1.6473118062	-1.4155524644
O	1.5804790047	-1.2736648965	-1.7453132227

2.4.14 X-Ray Crystallographic Analysis

2,6-dimethoxy-3-(methylamino)phenyl 4-methylbenzenesulfonate (**68**) (CCDC 1958321)

colorless crystal (brick), dimensions 0.122 x 0.113 x 0.070 mm^3, crystal system monoclinic, space group C2/c, Z=8, a=22.5901(7) Å, b=9.5502(3) Å, c=19.0900(9) Å, alpha=90 deg, beta=126.1418(8) deg, gamma=90 deg, V=3325.9(2) $Å^3$, rho=1.348 g/cm^3, T=200(2) K, $Theta_{max}$= 31.452 deg, radiation MoK , lambda=0.71073 Å, 0.5 deg omega-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 3.73 and a completeness of 93.1% to a resolution of

0.68 Å, 20918 reflections measured, 5130 unique (R(int)=0.0430), 3431 observed (I > 2 (I)), intensities were corrected for Lorentz and polarization effects, an empirical scaling and absorption correction was applied using SADABS[69] based on the Laue symmetry of the reciprocal space, mu=0.22mm^{-1}, T_{min}=0.90, T_{max}=0.96, structure solved with SHELXT-2014 (Sheldrick 2014)[70] and refined against F^2 with a Full-matrix least-squares algorithm using the SHELXL-2018/3 (Sheldrick, 2018) software[71], 216 parameters refined, hydrogen atoms were treated using appropriate riding models, except H19 at N19, which was refined isotropically, goodness of fit 0.77 for observed reflections, final residual values R1(F)=0.047, wR(F^2)=0.147 for observed reflections, residual electron density -0.36 to 0.39 eÅ^{-3}.

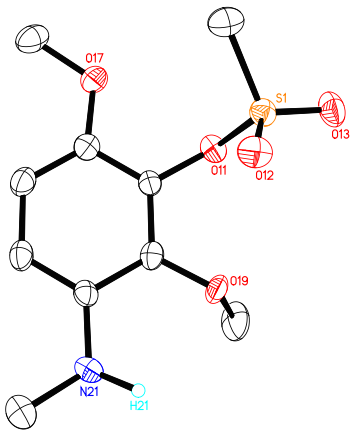


Empirical formula	$C_{16}H_{19}NO_5S$
Formula weight	337.38
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	C2/c
Z 8	
Unit cell dimensions	a = 22.5901(7) Å =90 deg.
b =	9.5502(3) Å = 126.1418(8) deg.
c =	19.0900(9) Å =90 deg.
Volume	3325.9(2) Å^3

Density (calculated)	1.35 g/cm^3
Absorption coefficient	0.22 mm^{-1}
Crystal shape	brick
Crystal size	0.122 x 0.113 x 0.070 mm^3
Crystal colour	colorless
Theta range for data collection	2.2 to 31.5 deg.
Index ranges	-33 h 31, -13 k 13, -27 l 28
Reflections collected	20918
Independent reflections	5130 (R(int) = 0.0430)
Observed reflections	3431 (I > 2 (I))
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.96 and 0.90
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5130 / 0 / 216
Goodness-of-fit on F^2	0.77
Final R indices (I>2sigma(I))	R1 = 0.047, wR2 = 0.147
Largest diff. peak and hole	0.39 and -0.36 eÅ^{-3}

2,6-dimethoxy-3-(methylamino)phenyl methanesulfonate (**69**) (CCDC 1958322) colorless crystal (plank), dimensions 0.065 x 0.060 x 0.047 mm^3, crystal system monoclinic, space group P2$_1$, Z=4, a=7.9499(7) Å, b=16.7242(13) Å, c=9.2361(7) Å, alpha=90 deg, beta=97.566(2) deg, gamma=90 deg, V=1217.30(17) Å^3, rho=1.426 g/cm^3, T=200(2) K, Theta$_{max}$= 26.137 deg, radiation MoK , lambda=0.71073 Å, 0.5 deg omega-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 6.04and a completeness of 99.8% to a resolution of 0.81 Å, 15210 reflections measured, 4822 unique (R(int)=0.0782), 3679 observed (I > 2 (I)), intensities were corrected for Lorentz and polarization effects, an empirical scaling and absorption correction was applied using SADABS[69] based on the Laue symmetry of the reciprocal space, mu=0.28mm^{-1}, T$_{min}$=0.78, T$_{max}$=0.96, structure solved with SHELXT-2014 (Sheldrick 2014)[70] and refined against F^2 with a Full-

matrix least-squares algorithm using the SHELXL-2018/3 (Sheldrick, 2018) software[71], 323 parameters refined, hydrogen atoms were treated using appropriate riding models, except H21 at N21, which were refined isotropically, Flack absolute structure parameter 0.12(8), goodness of fit 1.05 for observed reflections, final residual values R1(F)=0.069, wR(F^2)=0.167 for observed reflections, residual electron density -0.44 to 1.57 eÅ^{-3}



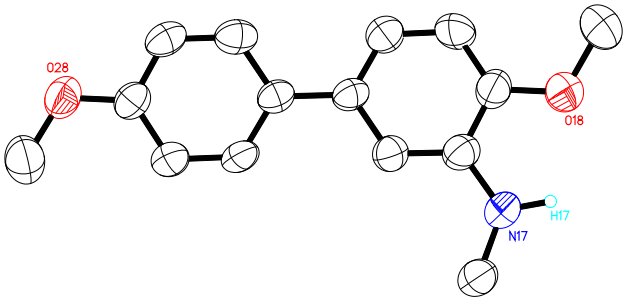
Empirical formula	$C_{10}H_{15}NO_5S$	
Formula weight	261.29	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	$P2_1$	
Z 4		
Unit cell dimensions	a = 7.9499(7) Å	=90 deg.
b =	16.7242(13) Å	=97.566(2) deg.
c =	9.2361(7) Å	=90 deg.
Volume	1217.30(17) Å^3	
Density (calculated)	1.43 g/cm^3	
Absorption coefficient	0.28 mm^{-1}	
Crystal shape	plank	
Crystal size	0.065 x 0.060 x 0.047 mm^3	

Crystal colour	colorless
Theta range for data collection	2.5 to 26.1 deg.
Index ranges	-9 h 9, -20 k 20, -11 l 11
Reflections collected	15210
Independent reflections	4822 (R(int) = 0.0782)
Observed reflections	3679 (I > 2 (I))
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.96 and 0.78
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4822 / 1 / 323
Goodness-of-fit on F^2	1.05
Final R indices (I>2sigma(I))	R1 = 0.069, wR2 = 0.167
Absolute structure parameter	0.12(8)
Largest diff. peak and hole	1.57 and -0.44 e$Å^{-3}$

4,4'-dimethoxy-*N*-methyl-[1,1'-biphenyl]-3-amine (**82**) (CCDC 1958323)

colorless crystal (brick), dimensions 0.153 x 0.044 x 0.042 mm^3, crystal system orthorhombic, space group $P2_12_12_1$, Z=4, a=6.9628(10) Å, b=8.4066(12) Å, c=21.812(3) Å, alpha=90 deg, beta=90 deg, gamma=90 deg, V=1276.7(3) $Å^3$, rho=1.266 g/cm^3, T=200(2) K, $Theta_{max}$= 21.738 deg, radiation MoK , lambda=0.71073 Å, 0.5 deg omega-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 6.95and a completeness of 100.0% to a resolution of 0.96 Å, 6422 reflections measured, 1512 unique (R(int)=0.0615), 982 observed (I > 2 (I)), intensities were corrected for Lorentz and polarization effects, an empirical scaling and absorption correction was applied using SADABS[69] based on the Laue symmetry of the reciprocal space, mu=0.08mm^{-1}, T_{min}=0.90, T_{max}=0.96, structure solved with SHELXT-2014 (Sheldrick 2014)[70] and refined against F^2 with a Full-matrix least-squares algorithm using the SHELXL-2018/3 (Sheldrick, 2018) software[71], 170 parameters refined, hydrogen atoms were treated using appropriate riding models, except H17 at N17, which was refined isotropically, Flack absolute structure parameter

0.6(10), goodness of fit 1.01 for observed reflections, final residual values R1(F)=0.047, wR(F^2)=0.092 for observed reflections, residual electron density -0.15 to 0.11 eÅ^{-3}.



Empirical formula	$C_{15}H_{17}NO_2$
Formula weight	243.29
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Z 4	
Unit cell dimensions	a = 6.9628(10) Å =90 deg.
b =	8.4066(12) Å =90 deg.
c =	21.812(3) Å =90 deg.
Volume	1276.7(3) Å^3
Density (calculated)	1.27 g/cm^3
Absorption coefficient	0.08 mm^{-1}
Crystal shape	brick
Crystal size	0.153 x 0.044 x 0.042 mm^3
Crystal colour	colorless
Theta range for data collection	1.9 to 21.7 deg.
Index ranges	-7 h 7, -8 k 8, -22 l 22
Reflections collected	6422
Independent reflections	1512 (R(int) = 0.0615)
Observed reflections	982 (I > 2 (I))

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.96 and 0.90
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1512 / 0 / 170
Goodness-of-fit on F^2	1.01
Final R indices (I>2sigma(I))	R1 = 0.047, wR2 = 0.092
Absolute structure parameter	0.6(10)
Largest diff. peak and hole	0.11 and -0.15 $eÅ^{-3}$

2.5 References

[1] a) U. Scholz, B. Schlummer, in *Science of Synthesis: Houben–Weyl methods of molecular transformations, Vol. 31b*, 1st Edition ed. (Eds.: C. A. Ramsden, D. Bellus), Georg Thieme Verlag, Stuttgart, **2007**, pp. 1565-1678; b) A. Ricci, *Amino Group Chemistry: From Synthesis to the Life Sciences*, Wiley-VCH, **2008**; c) N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Educ.* **2010**, *87*, 1348-1349; d) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257-10274; e) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546-576; f) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383-394.

[2] M. P. Paudyal, A. M. Adebesin, S. R. Burt, D. H. Ess, Z. Ma, L. Kürti, J. R. Falck, *Science* **2016**, *353*, 1144-1147.

[3] a) L. Legnani, G. Prina Cerai, B. Morandi, *ACS Catal.* **2016**, *6*, 8162-8165; b) E. Falk, V. C. M. Gasser, B. Morandi, *Org. Lett.* **2021**, *23*, 1422-1426.

[4] J. Liu, K. Wu, T. Shen, Y. Liang, M. Zou, Y. Zhu, X. Li, X. Li, N. Jiao, *Chem.-Eur. J.* **2017**, *23*, 563-567.

[5] E. M. D'Amato, J. Borgel, T. Ritter, *Chem. Sci.* **2019**, *10*, 2424-2428.

[6] Y. Y. See, M. S. Sanford, *Org. Lett.* **2020**, *22*, 2931-2934.

[7] R. R. Anugu, S. Munnuri, J. R. Falck, *J. Am. Chem. Soc.* **2020**, *142*, 5266-5271.

[8] Z. Li, D. A. Capretto, R. O. Rahaman, C. He, *J. Am. Chem. Soc.* **2007**, *129*, 12058-

12059.

[9] J. Borgel, L. Tanwar, F. Berger, T. Ritter, *J. Am. Chem. Soc.* **2018**, *140*, 16026-16031.

[10] L. J. Allen, P. J. Cabrera, M. Lee, M. S. Sanford, *J. Am. Chem. Soc.* **2014**, *136*, 5607-5610.

[11] Y. Kita, H. Tohma, K. Hatanaka, T. Takada, S. Fujita, S. Mitoh, H. Sakurai, S. Oka, *J. Am. Chem. Soc.* **1994**, *116*, 3684-3691.

[12] J. Li, Z. Zhang, L. Wu, W. Zhang, P. Chen, Z. Lin, G. Liu, *Nature* **2019**, *574*, 516-521.

[13] C. Sieiro, P. Calle, N. Lorenzo, *J. Mol. Struct.-Theochem* **1998**, *433*, 329-338.

[14] A. Zweig, W. G. Hodgson, W. H. Jura, *J. Am. Chem. Soc.* **1964**, *86*, 4124-4129.

[15] J. J. Farndon, X. Ma, J. F. Bower, *J. Am. Chem. Soc.* **2017**, *139*, 14005-14008.

[16] D. Nicewicz, H. Roth, N. Romero, *Synlett* **2015**, *27*, 714-723.

[17] G. Cecere, C. M. König, J. L. Alleva, D. W. MacMillan, *J. Am. Chem. Soc.* **2013**, *135*, 11521-11524.

[18] M. Nappi, M. J. Gaunt, *Organometallics* **2018**, *38*, 143-148.

[19] Q. Wu, T. Van Voorhis, *J. Chem. Phys.* **2006**, *125*, 164105.

[20] E. G. Petrov, B. Robert, S. H. Lin, L. Valkunas, *Biophys. J.* **2015**, *109*, 1735-1745.

[21] a) I. Colomer, A. E. R. Chamberlain, M. B. Haughey, T. J. Donohoe, *Nat. Rev. Chem.* **2017**, *1*, 0088; b) L. Eberson, M. P. Hartshorn, O. Persson, F. Radner, *Chem. Commun.* **1996**, 2105 - 2112; c) X. D. An, J. Xiao, *Chem. Rec.* **2020**, *20*, 142-161.

[22] E. Baciocchi, A. Dalla Cort, L. Eberson, L. Mandolini, C. Rol, *J. Org. Chem.* **1986**, *51*, 4544-4548.

[23] W. G. Lee, A. H. Chan, K. A. Spasov, K. S. Anderson, W. L. Jorgensen, *ACS Med. Chem. Lett.* **2016**, *7*, 1156-1160.

[24] S. Ortgies, A. Breder, *Org. Lett.* **2015**, *17*, 2748-2751.

[25] B. Urones, R. Gomez Arrayas, J. C. Carretero, *Org. Lett.* **2013**, *15*, 1120-1123.

[26] J. K. Augustine, R. Kumar, A. Bombrun, A. B. Mandal, *Tetrahedron Lett.* **2011**, *52*, 1074-1077.

[27] X. Lei, A. Jalla, M. Abou Shama, J. Stafford, B. Cao, *Synthesis* **2015**, *47*, 2578-2585.

[28] W. M. Seganish, P. DeShong, *J. Org. Chem.* **2004**, *69*, 1137-1143.

[29] M. H. Beyzavi, D. Mandal, M. G. Strebl, C. N. Neumann, E. M. D'Amato, J. Chen, J. M. Hooker, T. Ritter, *ACS Cent. Sci.* **2017**, *3*, 944-948.

[30] Q. Guo, X. Ren, Z. Lu, *Org. Lett.* **2019**, *21*, 880-884.

[31] B. S. Bodnar, P. F. Vogt, *J. Org. Chem.* **2009**, *74*, 2598-2600.

[32] L. Y. Liu, K. S. Yeung, J. Q. Yu, *Chem.-Eur. J.* **2019**, *25*, 2199-2202.

[33] F. Berger, M. B. Plutschack, J. Riegger, W. Yu, S. Speicher, M. Ho, N. Frank, T. Ritter, *Nature* **2019**, *567*, 223-228.

[34] O. R. John, N. M. Killeen, D. A. Knowles, S. C. Yau, M. C. Bagley, N. C. Tomkinson, *Org. Lett.* **2007**, *9*, 4009-4012.

[35] S. Saha, J. N. Moorthy, *J. Org. Chem.* **2011**, *76*, 396-402.

[36] C. Hering-Junghans, A. Schulz, M. Thomas, A. Villinger, *Dalton Trans.* **2016**, *45*, 6053-6059.

[37] R. Nisal, P. J. G, C. Shanbhag, J. Kalia, *Org. Biomol. Chem.* **2018**, *16*, 4304-4310.

[38] T. Mandal, S. Jana, J. Dash, *Eur. J. Org. Chem.* **2017**, *2017*, 4972-4983.

[39] G. E. Martinez, J. W. Nugent, A. R. Fout, *Organometallics* **2018**, *37*, 2941-2944.

[40] G. Theodoridis, M. C. Manfredi, J. D. Krebs, *Tetrahedron Lett.* **1990**, *31*, 6141-6144.

[41] J.-B. Baek, F. W. Harris, *Macromolecules* **2005**, *38*, 297-306.

[42] P. L. Reddy, M. Tripathi, R. Arundhathi, D. S. Rawat, *Chem.-Asian J.* **2017**, *12*, 785-791.

[43] W. Li, J. Artz, C. Broicher, K. Junge, H. Hartmann, A. Besmehn, R. Palkovits, M. Beller, *Catal. Sci. Technol.* **2019**, *9*, 157-162.

[44] N. Arai, N. Onodera, A. Dekita, J. Hori, T. Ohkuma, *Tetrahedron Lett.* **2015**, *56*, 3913-3915.

[45] A. Lator, S. Gaillard, A. Poater, J.-L. Renaud, *Org. Lett.* **2018**, *20*, 5985-5990.

[46] M. Huang, Y. Li, Y. Li, J. Liu, S. Shu, Y. Liu, Z. Ke, *Chem. Commun.* **2019**, *55*, 6213-6216.

[47] L. Jiang, F. Guo, Y. Wang, J. Jiang, Y. Duan, Z. Hou, *Asian J. Org. Chem.* **2019**, *8*, 2046-2049.

[48] N. Sakai, M. Sasaki, Y. Ogiwara, *Chem. Commun.* **2015**, *51*, 11638-11641.

[49] S. Roscales, A. G. Csákÿ, *ACS Omega* **2019**, *4*, 13943-13953.

[50] J. Neumann, S. Elangovan, A. Spannenberg, K. Junge, M. Beller, *Chem.-Eur. J.* **2017**, *23*, 5410-5413.

[51] A. Itai, S. Muto, R. Tokuyama, H. Fukasawa, T. Yanase, *WO 2009038064 A1* **2009**.

[52] W. Xiang, S. Choudhary, E. Hamel, S. L. Mooberry, A. Gangjee, *Bioorg. Med. Chem.* **2018**, *26*, 2437-2451.

[53] A. Maiti, P. V. N. Reddy, M. Sturdy, L. Marler, S. D. Pegan, A. D. Mesecar, J. M. Pezzuto, M. Cushman, *J. Med. Chem.* **2009**, *52*, 1873-1884.

[54] L. Wang, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2019**, *58*, 5417-5421.

[55] B. Paul, S. Shee, K. Chakrabarti, S. Kundu, *ChemSusChem* **2017**, *10*, 2370-2374.

[56] B. Redko, A. Albeck, G. Gellerman, *New J. Chem.* **2012**, *36*, 2188-2191.

[57] T. Gao, P. Sun, *J. Org. Chem.* **2014**, *79*, 9888-9893.

[58] Y. Tokimizu, S. Oishi, N. Fujii, H. Ohno, *Angew. Chem. Int. Ed.* **2015**, *54*, 7862-7866.

[59] J. Z. Chan, Y. Chang, M. Wasa, *Org. Lett.* **2019**, *21*, 984-988.

[60] A. Gangjee, O. A. Namjoshi, S. Raghavan, S. F. Queener, R. L. Kisliuk, V. Cody, *J. Med. Chem.* **2013**, *56*, 4422-4441.

[61] J. Pan, J. Li, R. Huang, X. Zhang, H. Shen, Y. Xiong, X. Zhu, *Tetrahedron* **2015**, *71*, 5341-5346.

[62] R. A. Green, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2015**, *54*, 3768-3772.

[63] A. Ohwada, S. Nara, T. Sakamoto, Y. Kikugawa, *J. Chem. Soc., Perkin Trans. 1* **2001**, 3064-3068.

[64] T. Senthamarai, K. Murugesan, K. Natte, N. V. Kalevaru, H. Neumann, P. C. J. Kamer, R. V. Jagadeesh, *ChemCatChem* **2018**, *10*, 1235-1240.

[65] S. Herold, S. Möhle, M. Zirbes, F. Richter, H. Nefzger, S. R. Waldvogel, *Eur. J. Org. Chem.* **2016**, *2016*, 1274-1278.

[66] S. B. Herzon, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 6690-6691.

[67] a) I. S. Ufimtsev, T. J. Martinez, *J. Chem. Theory Comput.* **2009**, *5*, 2619-2628; b) A. V. Titov, I. S. Ufimtsev, N. Luehr, T. J. Martinez, *J. Chem. Theory Comput.* **2013**, *9*, 213-221.

[68] Y. Shao, Z. Gan, E. Epifanovsky, A. T. B. Gilbert, M. Wormit, J. Kussmann, A. W. Lange, A. Behn, J. Deng, X. Feng, D. Ghosh, M. Goldey, P. R. Horn, L. D. Jacobson, I. Kaliman, R. Z. Khaliullin, T. Kuś, A. Landau, J. Liu, E. I. Proynov, Y. M. Rhee, R. M. Richard, M. A. Rohrdanz, R. P. Steele, E. J. Sundstrom, H. L. Woodcock, P. M. Zimmerman, D. Zuev, B. Albrecht, E. Alguire, B. Austin, G. J. O. Beran, Y. A. Bernard, E. Berquist, K. Brandhorst, K. B. Bravaya, S. T. Brown, D. Casanova, C.-M. Chang, Y. Chen, S. H. Chien, K. D. Closser, D. L. Crittenden, M. Diedenhofen, R. A. DiStasio, H. Do, A. D. Dutoi, R. G. Edgar, S. Fatehi, L. Fusti-Molnar, A. Ghysels, A. Golubeva-Zadorozhnaya, J. Gomes, M. W. D. Hanson-Heine, P. H. P. Harbach, A. W. Hauser, E. G. Hohenstein, Z. C. Holden, T.-C. Jagau, H. Ji, B. Kaduk, K. Khistyaev, J. Kim, J. Kim, R. A. King, P. Klunzinger, D. Kosenkov, T. Kowalczyk, C. M. Krauter, K. U. Lao, A. D. Laurent, K. V. Lawler, S. V. Levchenko, C. Y. Lin, F. Liu, E. Livshits, R. C. Lochan, A. Luenser, P. Manohar, S. F. Manzer, S.-P. Mao, N. Mardirossian, A. V. Marenich, S. A. Maurer, N. J. Mayhall, E. Neuscamman, C. M. Oana, R. Olivares-Amaya, D. P. O'Neill, J. A. Parkhill, T. M. Perrine, R. Peverati, A. Prociuk, D. R. Rehn, E. Rosta, N. J. Russ, S. M. Sharada, S. Sharma, D. W. Small, A. Sodt, et al., *Mol. Phys.* **2014**, *113*, 184-215.

[69] L. Krause, R. Herbst-Irmer, G. M. Sheldrick, D. Stalke, *J. Appl. Cryst.* **2015**, *48*, 3-10.

[70] G. M. Sheldrick, *Acta Cryst.* **2015**, *A71*, 3-8.

[71] G. M. Sheldrick, *Acta Cryst.* **2015**, *C71*, 3-8.

Chapter 3 Hydroxylamine-Mediated C-C amination via Aza-Hock Rearrangement

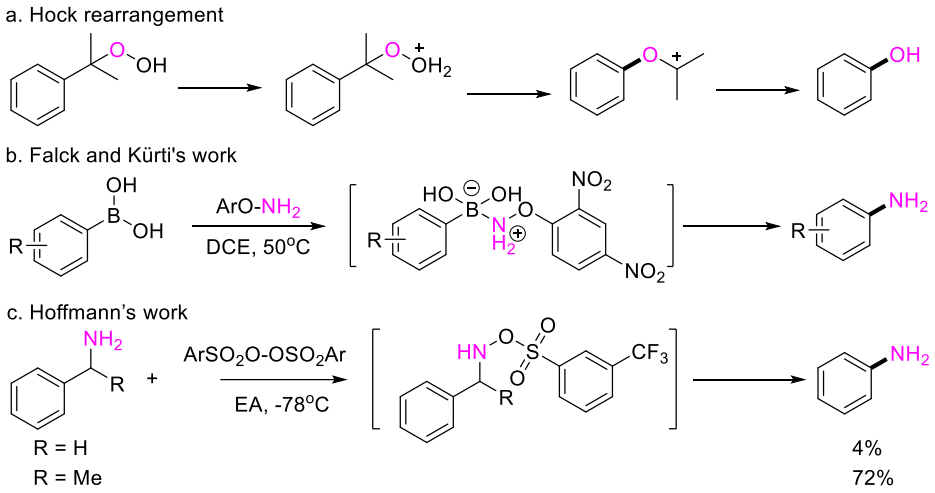
3.1 Introduction

Anilines are of paramount importance to all aspects of chemical science (pharmaceuticals, agrochemicals, organic chemicals and natural bioactive products). Such motifs are typically accessed by a nitration-reduction sequence or transition metal-catalyzed cross-coupling reactions and direct arene C-H aminations via organometallic chemistry, photochemistry and electrochemistry. However, specific site-selectivity is a significant challenge for most of the mentioned protocols.

Alternatively, direct C-C amination is a method to address the site-selectivity problem, such as transition metal-catalyzed decarboxylative aminations as well as metal-free reactions (Lossen, Hoffmann, Curtius, Schmidt and Neber rearrangements) from carboxylic acids and their derivatives, but several synthetic steps are needed. Only a few publications report on direct access to anilines under metal-free conditions in a one-step approach: one is the Beckmann rearrangement of ketoximes or surrogates, representative examples see Walter[1] and Uchida's work;[2] one other way is the Schmidt rearrangement of α-azido ethylbenzene intermediates, typical works see the reports of Ning group,[3] who noted that alkylarenes or secondary benzyl alcohols were feasible to undergo C-C aminations with DDQ/electricity as oxidant and NaN_3 or alkyl azides as the aminating reagents. This is especially remarkable as this paves the way for these types of aminations starting from alcohol or alkyl arene substrates. However, highly toxic and potentially explosive azides are essentially needed for this Schmidt-like transformation, thus safety precautions should be taken when undertaking such reactions.

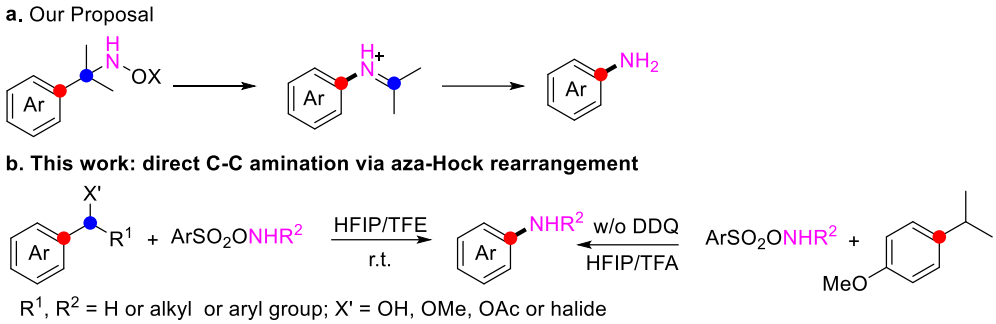
As a consequence, safe and easy-to-handle protocols are still needed for direct C-C aminations. Our approach was influenced by the synthesis of phenols via the Hock rearrangement, which is the key step for the industrial phenol synthesis (named

Cumene-Phenol process or Hock process, Scheme 1a). In the Hock rearrangement, cumene hydroperoxide, as a key intermediate, is transformed into phenol in acidic solvent after rearrangement and hydrolysis. A related migration of an aryl group in this case onto a nitrogen atom was realized by Falck and Kürti,[4] who used reactive $ArB(OH)_2NH_2OX$ intermediates bearing a weak N-O single bond as a pathway to primary anilines (Scheme 1b). The key intermediates were generated by the nucleophilic attack of hydroxylamine derivatives onto arylboronic acids. Hoffmann[5] reported that *N*-alkyl-*O*-(arylsulfonyl)hydroxylamines undergo cationic carbon-to-nitrogen rearrangements to form imines, which upon hydrolysis generate anilines (two examples, Scheme 1c).



Scheme 1. Hock rearrangement and related carbon-to-nitrogen rearrangements

Inspired by this technique, we hypothesized that cumene hydroxylamine derivatives, owning to the weak N-O bond (similar to the O-O bond in cumene hydroperoxide), are susceptible to a Hock-type rearrangement in an acidic solvent, yielding anilines as products (so-called aza-Hock rearrangement, Scheme **2**). Here we present a mild, general and scalable, chemoselective method for C-C aminations. It has a broad scope, including secondary benzyl alcohols, simple alkylarenes in combination with arylsulfonyl hydroxylamines ($ArSO_2ONHR$) as aminating reagents, delivering primary or secondary anilines in good to excellent yields (>70 examples, Scheme **1c**).



Scheme 2. Reaction design for C-C amination

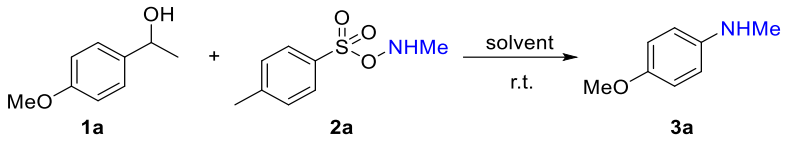
3.2 Results and Discussion

3.2.1 Optimization of the Reaction Condition towards Secondary Anilines

The powerful aminating ability of hydroxylamines derivatives enforces them frequently used for arene X-H aminations (X = C, O, N, S, P),[6] providing alternative ways to introduce amino groups on a variety of chemical motifs. However, C-C amination, especially for arene C-C, is seldom connected to hydroxylamine. Very recently, we[7] reported a direct metal-free arene C-H amination with hydroxylamine derivatives ($ArSO_2ONHR$) in HFIP. All this provoked the possibility of direct arene dealkylative amination in combination with hydroxylamines. 2-Phenylethanol, known as an electrophile in HFIP or TFE, could react with nucleophilic TsONHMe to generate the reactive Hock-type intermediate *in situ* bearing a weak N-O bond, which might undergo an aza-Hock rearrangement, following by hydrolysis of an intermediate iminium ion to afford aniline. As depicted in Table 1, the initial experiment with 1-(4-methoxyphenyl)ethan-1-ol **1a** and TsONHMe **2a** afforded aniline **3a** in a good yield (entry 6). The aminating reagent **2a** (0.22 mmol) in combination with 0.2 mol/L **1a** was proved as the optimal reaction condition with a 74% isolated yield. The reaction is highly dependent on solvent: nonfluorinated solvent (DCM, CH_3CN and MeOH) could not give any product, but fluorinated alcohols worked well and HFIP was superior to TFE (entries 1 – 5). More aminating reagents and higher concentrations might slightly decrease the yield (entries 5 – 7, and entries 6, 8, 9). A nitrogen atmosphere or under dark conditions did not affect the yield (entries 10, 11) and the addition of acid (triflic

acid or tosylic acid) suppressed the reaction as water elimination from alcohol was competitive to the C-C amination (entries 12, 13).

Table 1. Optimization of the C-C amination towards secondary anilines



Entry	Solvent	Yield[a]
1[b]	DCM (0.4 M)	trace
2[b]	CH_3CN (0.4 M)	trace
3[b]	MeOH (0.4 M)	trace
4[b]	TFE (0.4 M)	60%
5[b]	HFIP (0.4 M)	72%
6	HFIP (0.4 M)	75%
7[c]	HFIP (0.4 M)	77%
8	**HFIP (0.2 M)**	**78% (74%[d])**
9	HFIP (0.1 M)	81%
10[e]	HFIP (0.2 M)	78%
11[f]	HFIP (0.2 M)	78%
12[g]	HFIP (0.2 M)	16%
13[h]	HFIP (0.2 M)	60%

Reaction conditions: alcohol (0.2 mmol), **2a** (0.22 mmol), solvent (1 mL), r.t. 12 h; [a]NMR yield (1,3,5-trimethoxybenzene as internal standard); [b]**2a** (0.20 mmol) was used; [c]**2a** (0.24 mmol) was used; [d]isolated yield; [e]under nitrogen atmosphere; [f]under dark condition; [g]$TsOH•H_2O$ (0.22 mmol) as additive [h]TFA (0.22 mmol) as additive.

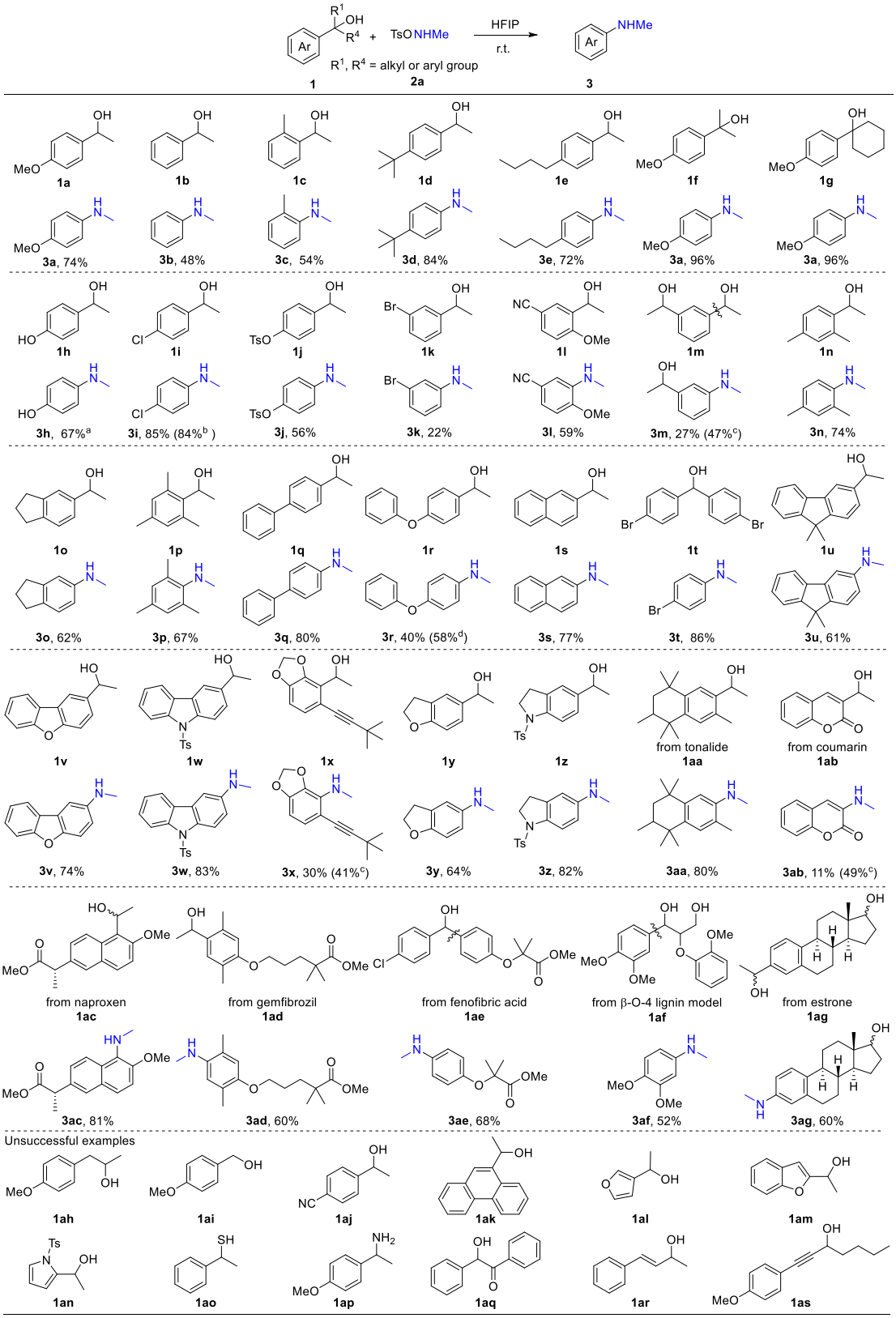
3.2.2 Scope and Limitation with Respect to Secondary Anilines

All secondary or tertiary benzyl alcohols in this C-C amination were transformed into anilines with excellent chemoselectivity and exemplified in Table 2. Higher yields were acquired with electron-donating groups on arene cores for commercially available secondary benzyl alcohols (**1a** – **1e**). Tertiary alcohols (**1f** – **1g**) proceeded smoothly

with the protocol, affording excellent yields. Noteworthy, the electron-rich 4-(methylamino)phenol **3h**, sensitive to oxidants, was successfully acquired with the related aminating regent MsONHMe **2b**. Electron-withdrawing groups (Br, Cl, OTs) on alcohols (**1i** – **1k**) were also tolerated in our reaction. In the case of the strong electron-withdrawing group (CN, **1l**), an additional MeO group was crucial to regulate the electronic properties. Aniline **3m** was the sole isomer when bifunctional alcohol **1m** was implemented in the reaction, which was attributed to the intermediate iminium salt for aniline **3m** before workup (see discussion). Di- or tri-substituted alcohols (**1n** – **1p**) were also compatible with our protocol and especially hindered alcohol **1p** was also amenable in the conversion. Biphenyl and diphenyl ether skeletons were tolerated as well as naphthalene and fluorene substructures (**3q** – **3s**, **3u**). It is worth pointing out aniline **3t** with an aldehyde in 70% isolated yield (key byproduct for the mechanism, see discussion below) was acquired when diphenyl methanol **1t** was implemented in the strategy. Moreover, heteroarenes and heterocycles (**1v** – **1z**) were viable for the C-C amination, even the triple bond of **3x** was kept intact.

To evaluate the robustness of our protocol, natural bioactive molecules, drugs and chemical waste were subjected to late-stage functionalization. Fragrances (tonalide **1aa**, coumarin **1ab**) were exposed to reagent **2a**, giving anilines in moderate to good yields; however, for coumarin, a higher concentration of **2a** was essential to accomplish the C-C amination and inhibit the formation of coumarin ether as a side-product (see experiment). Drugs (naproxen **1ac**, gemfibrozil **1ad** and fenofibric acid **1ae**) were feasible with this strategy, providing anilines in good yields; and again, the aldehyde as a byproduct was also characterized in the case of the reaction of **1ae** with **2a** (see experiment). Bio-renewable lignin **1af** was tested in the dealkylative amination, delivering aniline in good yield, which opens a window for the synthesis of valuable anilines from agricultural byproducts. Besides, the C-C bond of benzyl alcohols on the natural product (estrone, **1ag**) was selectively cleaved by aminating regent **2a**, leaving the aliphatic alcohol untouched. The robustness and practicality of this protocol were testified by the large-scale preparation of **3i** in almost the same efficiency. Moreover, unsuccessful examples were also shown in Table 2: 1-(4-methoxyphenyl)propan-2-ol

Table 2. Alcohol scope for the synthesis of secondary anilines

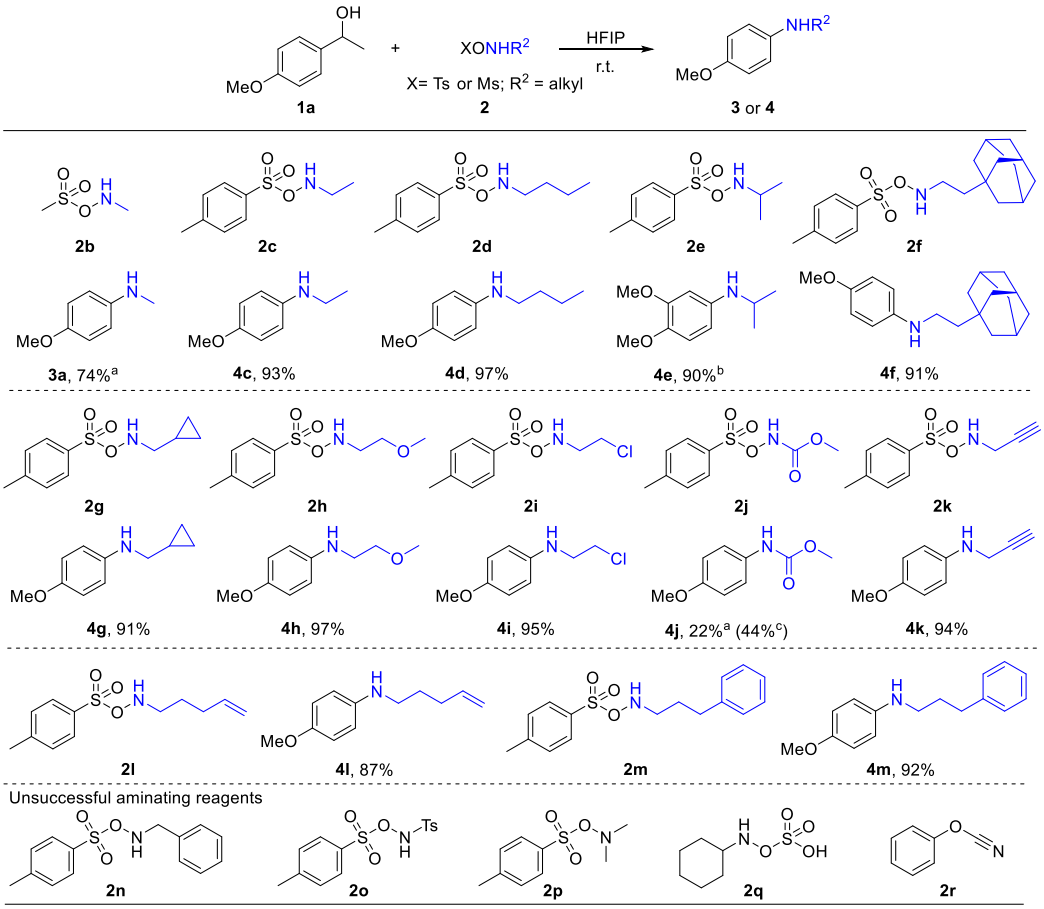


Reaction conditions: alcohol (0.2 mmol), **2a** (0.22 mmol), HFIP (1.0 mL), 12 h, r.t.; [a]MsONHMe **2b** (0.22 mmol) instead of **2a**; [b]**1i** (4 mmol), **2a** (4.4 mmol), HFIP (20 mL); [c]**2a** (0.44 mmol), HFIP (0.5 mL); [d]**2a (**0.26 mmol) was used.

1ah gave the C-H amination rather than the C-C amination product, while (4-methoxyphenyl)methanol **1ai** did not react with **2a**. Electron-rich/poor alcohols (**1aj** – **1ak**) could not facilitate this conversion under the standard reaction condition as well as heteroarenes (**1al** – **1an**). The thiol **1ao** and amine **1ap** were not tolerated in this reaction. Other alcohols (with carbonyl, C=C or C≡C bond, **1ar**, **1as**) failed this conversion. Interestingly, styrenes were tested for the C-C amination, delivering unexpected results (see experiment): α-alkyl-substituted styrenes (α-methyl styrene and 1-(1-cyclopropylvinyl)-4-methoxybenzene) were converted to anilines in low to moderate yield rather than normal aziridination or polymerization.

Next, twelve different aminating reagents (**2b** or $ArSO_2ONHR$, the latter accessed via Mitsunobu reactions) were therefore prepared to evaluate the possibility of introducing different *N*-substitutes with this protocol. As shown in Table 3, a variety of *N*-alkyl substituted anilines (**3a**, **4c** – **4i**) were afforded from hydroxylamine in excellent yields, even for sensitive (**2c**, **2d**) and sterically hindered (**2e**, **2f**) aminating reagents. An alkyl chloride of aniline **4i** was left untouched, allowing further manipulation. A carbamate group was smoothly introduced on arene core (**4j**), and a propargyl amine unit was successfully installed on anisole (**4k**). Noteworthy, the intermolecular C-C aminations (**4l**, **4m**) dominated the reaction, and no side products (intramolecular aziridination[8] or arene C-H amination[9]) were detected despite aminating reagent **2l** and **2m** could undergo aziridination or arene C-H amination respectively, in HFIP or TFE. Benzyl or cyclohexyl group could not be introduced with this strategy with very sensitive reagent **2n** or sterically crowded reagent **2q**. The electron-deficient regent **2o** could not be converted; a tertiary aniline was not accessible with **2p** as aminating regent. Besides, a remote cyano-introducing reagent **2r** was used under these conditions, but delivering no 4-methoxybenzonitrile.

Table 3. Hydroxylamine scope for the synthesis of secondary anilines



Reaction conditions: alcohol (0.2 mmol), aminating reagents (0.3 mmol), HFIP (1 mL), r.t., 12 h; [a]**2b** (0.22 mmol) instead of **2a**; [b]1-(3,4-dimethoxyphenyl)ethan-1-ol (**1at**, 0.2 mmol) instead of **1a**; [c]TFE (1mL) instead of HFIP.

3.2.3 Optimization of the Reaction Condition towards Primary Anilines

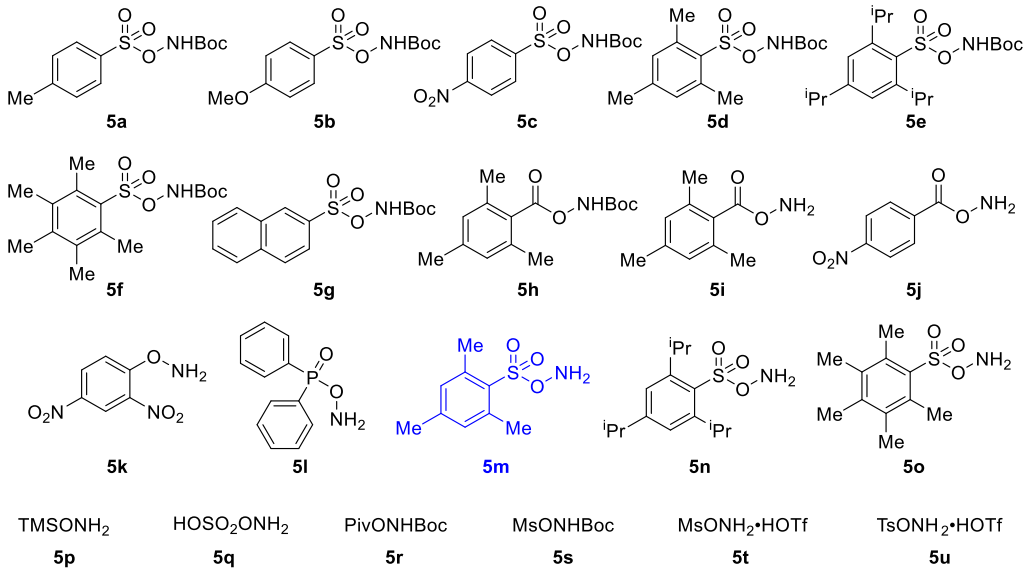


Figure 1. Hydroxylamine derivatives used for the synthesis of primary anilines

Table 4. Optimization of the C-C amination towards primary anilines

1a **5** **6a**

Entry	Reagent	Solvent	Yield[a]
1	**5a**	HFIP	28%
2	**5b**	HFIP	39%
3	**5c**	HFIP	20%
4	**5d**	HFIP	48%
5	**5e**	HFIP	50%
6	**5f**	HFIP	44%
7	**5g**	HFIP	48%
8	**5h**	HFIP	trace
9	**5i**	HFIP	trace
10	**5j**	HFIP	10%
11	**5k**	HFIP	n.d.
12	**5l**	HFIP	16%
13	**5m**	HFIP	59%
14	**5n**	HFIP	41%
15	**5o**	HFIP	33%
16	**5p**	HFIP	n.d.
17	**5q**	HFIP	17%
18	**5r**	HFIP	n.d.
19	**5s**	HFIP	44%
20	**5t**	HFIP	48%
21	**5u**	HFIP	36%
22	**5m**	TFE	63%
23	**5m** (1.3 eq)	TFE	72%
24	**5m (1.5 eq)**	**TFE**	**84% (79%[b])**

25	**5m** (1.5 eq)	TFE (0.4 M)	72%

Reaction conditions: alcohol (0.2 mmol), aminating reagent (0.22 mmol), solvent (1 mL), r.t., 12 h; [a]NMR yield (1,3,5-trimethoxybenzene as internal standard); [b]isolated yield.

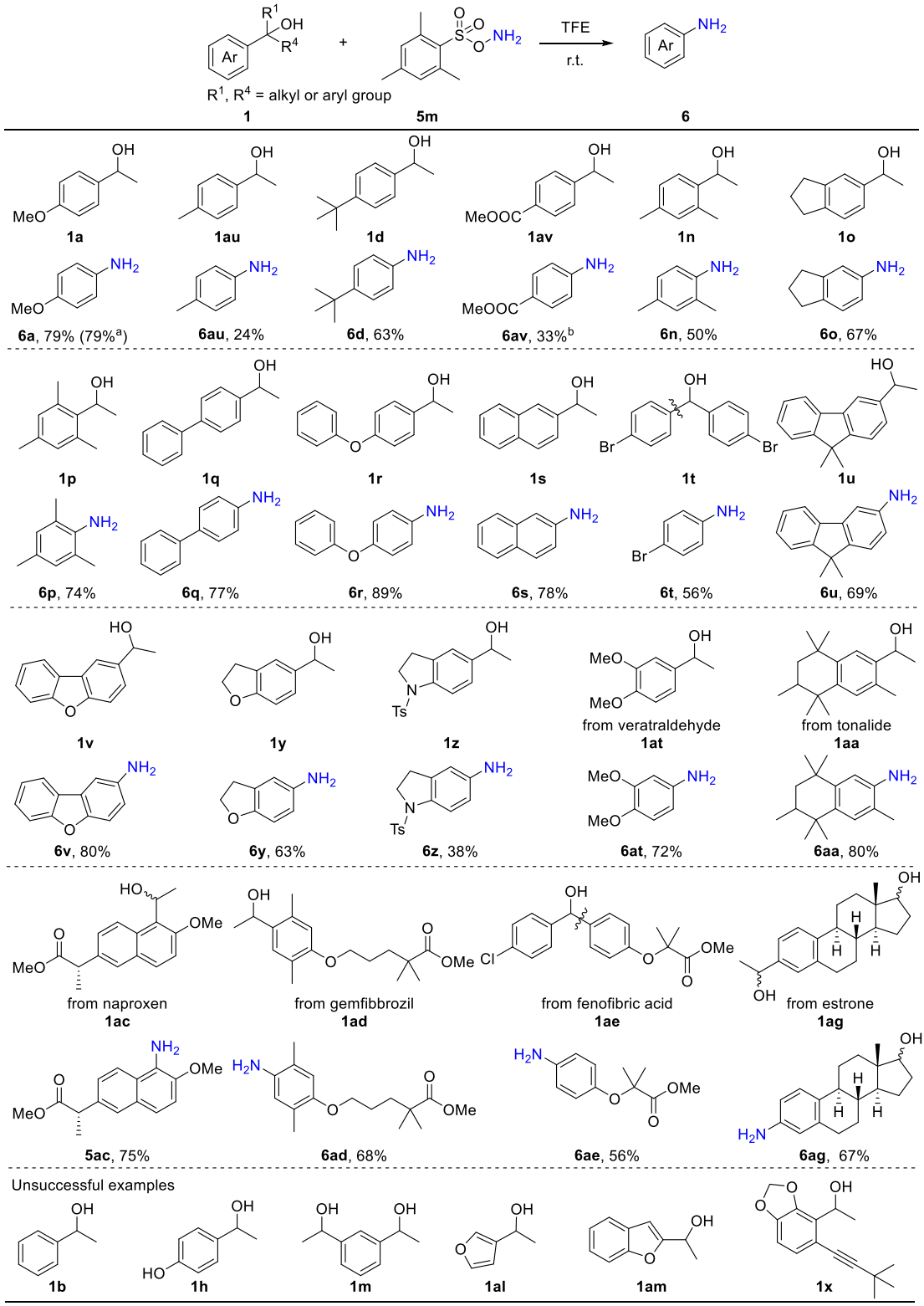
Next, the more challenging primary anilines synthesis was addressed via the C-C amination protocol. The optimization of the direct conversion to primary aniline from benzyl alcohol with over 20 aminating regents is summarized in Table 4. *N*-Boc sulfonyl hydroxylamines (**5a** – **5g**, **5s**) provided the aniline **6a** in moderate yields (entries 1 – 7, 19); and among all these reagents, the sterically hindered **5e** preformed best, delivering a moderate yield (50%). However, *O*-benzoyl or pivaloyl hydroxylamines (**5h** – **5j**, **5r**) only led to minor or trace products (entries 8 – 10, 18). Besides, other commercial reagents with a free amino group (like (2,4-dinitrophenyl)hydroxylamine DNPHA, **5k** in entry 11 and *O*-(diphenylphosphinyl)hydroxylamine, **5l** in entry1 12) were less effective in this transformation. But *O*-arylsulfonyl hydroxylamines with free amino group afforded comparable yields to their corresponding *N*-Boc derivatives (entries 4 and 13, entries 5 and 14, entries 6 and 15). It is noteworthy that *O*-mesitylenesulfonylhydroxylamine (MSH, **5m**) turned out to be superior for the C-C amination in a 59% yield (entry 13, MSH could be stored at -20ºC for one month with only a little decomposition, see experiment). The less acidic TFE appeared to be a better solvent than HFIP (5% higher yield), attributed to alcohol elimination as a side pathway to the C-C amination (entries 13, 22). Overall, 0.3 mmol **5m** in combination with 0.2 mol/L alcohol in TFE turned out to be the best condition for the primary aniline synthesis (79% isolated yield, entry 24). Furthermore, the often used commercially available hydroxylamine-*O*-sulfonic acid (HOSA, **5q**) delivered a low yield and $TMSONH_2$ **5p** was ineffective (entries 16, 17). Hydroxylamine triflate salts (**5t**, **5u**) only achieved moderate yields, which was attributed to the formation of free triflic acid which can decompose the alcohols (entries 20, 21).

3.2.4 Scope and Limitation with Respect to Primary Aniline

With optimized conditions in hand, we then explored the alcohol scope of this strategy. In a series of benzyl alcohols, with electron density increasing on the arene cores, anilines were delivered from low to good yields (**6a**, **6d**, **6au**). The alcohol with a strong electron-withdrawing group (-COOMe) could be smoothly transformed into aniline with the aid of $FeSO_4$[10] and a related powerful aminating reagent **5u**. Di- or tri-substituted alcohols (**1n** – **1p**) were amenable for C-C amination under our conditions, including sterically hindered substrate **1p**. Besides, biphenyl, naphthalene, diphenyl ether and fluorene substructures (**6q** – **6s**, **16u**) were feasible in this dealkylative amination. And diphenyl methanol (**1t**) was cleaved by reagent **5m**, affording aniline **6t**. Heteroarenes (**6v** – **6z**) were also effective transformation partners with our protocol. The further application of this strategy for late-stage functionalization of drugs and natural products was investigated next. The fragrances (veratraldehyde **1at**, tonalide **1aa**), drug leads (naproxen **1ac**, gemfibrozil **1ad** and fenofibric acid **1ae**) and a natural bioactive molecule (estrone **1ag**) were viable in the C-C amination. The scalability of the reaction was made evident by the preparation of aniline **6a** on a 4 mmol scale. Other unsuccessful examples were also summarized: electron-neutral **1b** or bifunctional alcohol **1m** was ineffective in this reaction; electron-rich alcohols (**1h**, **1al**, **1am**, **1x**) could not be converted into anilines.

Then further applications are demonstrated in Figure 2. 2-Phenyl anilines (**7**, **8**), commodity Buchwald ligand precursors (G2 – G4), were acquired in just one step with our direct C-C amination strategy. The formal total synthesis of Lidocaine[11] (from **9**) and Chlorambucil[12] (from **10**) could be obtained in short sequences. Ether and ester of benzyl alcohol (**11**, **12**, alternative precursors for benzylic cations) were effective substrates for the synthesis of anilines. Tertiary aniline **13** was accessible by a sequence of C-C amination of **2a** followed by a subsequent reduction with $NaBH_3CN$ in one pot. This strongly supports the intermediate imine generation in the reaction, but also further contributes to the synthetic potential of the protocol. Moreover, C-C oxygenations and brominations were also affordable with a similar strategy: a phenol **14** synthesis was

Table 5. Alcohol scope for the synthesis of primary anilines



Reaction conditions: alcohol (0.2 mmol), **4m** (0.3 mmol), TFE (1 mL), r.t., 12 h; [a]**1a** (4 mmol), **4m** (6 mmol), TFE (20 mL); [b]$TsONH_2$•HOTf **4u** (0.22 mmol) instead of **4m**, $FeSO_4$•$7H_2O$ (0.01 mmol) as additive.

viable when hydrogen peroxide was used and a bromobenzene **15** was feasible if NBS was applied with UV light.

3.2.5 Further Application

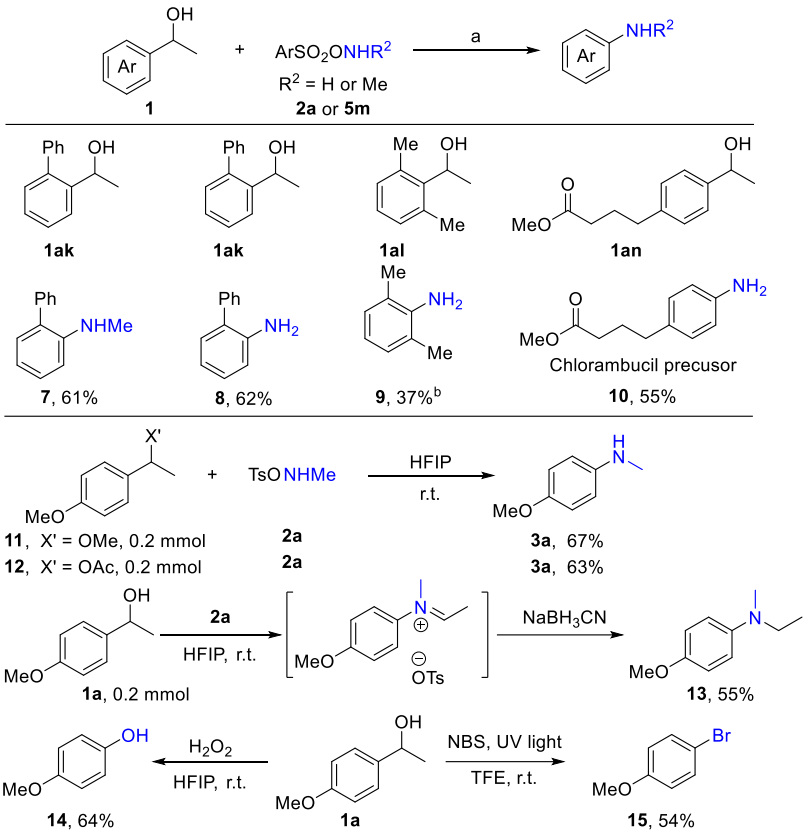


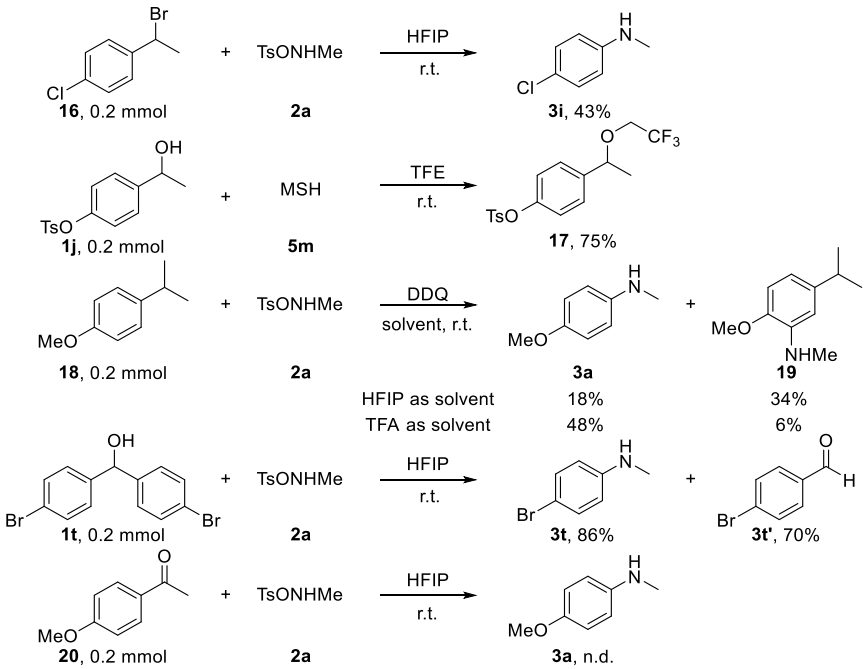
Figure 2. Further applications with our protocol

Reaction conditions: [a]alcohol (0.2 mmol), **2a** (0.22 mmol) or **4m** (0.3 mmol), HFIP (1mL) or TFE (1mL), 12 h, r.t.; [b]1-(2,6-dimethylphenyl)ethan-1-ol (1 mmol), **4m** (1.5 mmol), TFE (5 mL), 12 h, r.t.

3.2.6 Mechanistic Studies

Concerning the mechanism, a radical pathway was initially considered related to our previous work, however, all attempts to trap or detect radicals failed (see experiment). Thus, further mechanistic studies were conducted to get more proof. Aniline **3i** was obtained from benzyl bromide **16** by our protocol, which gives strong evidence that a benzyl cation is the key intermediate of the reaction (the generation of such a cation from benzyl alcohol/halide in HFIP is a well-known process[13]). Furthermore, the ether

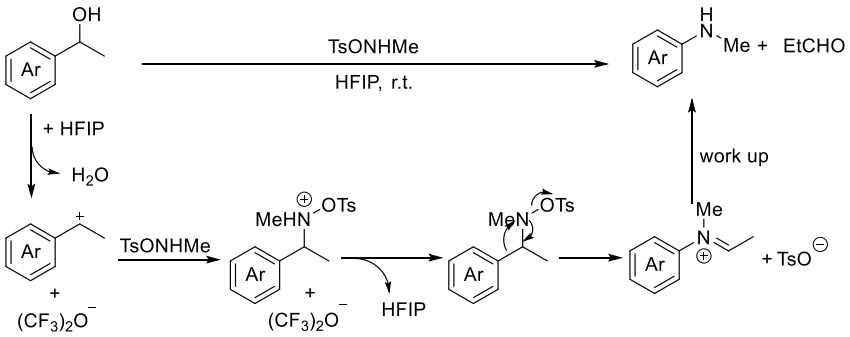
17 was undoubtedly obtained from electron-deficient alcohol **1j** and a direct dealkylative amination was accomplished from 4-isopropyl anisole **18** with Ning's strategy.[3b] All this supports unambitiously benzyl cation involved in the reaction. Besides, 4-bromobenzaldehyde was isolated as a byproduct when diphenyl methanol **1t** was subjected to the reaction, giving certain support for imine hydrolysis. Tertiary aniline **13** formation also confirmed the formation of intermediate imine. Moreover, a Beckmann rearrangement could be excluded for this protocol, as no aniline was detected when ketone **20** was treated with **2a**. Accordingly, an aza-Hock rearrangement in four steps is proposed by us: formation of a benzyl cation via benzyl alcohol solvolysis by HFIP; generation of a reactive *O*-(1-phenylethyl)hydroxylamine, which gives access to an iminium tosylate salt after aryl migration; and finally the irreversible hydrolysis of the imine to deliver the desired aniline after simple workup (Scheme 3).



Scheme 2. Mechanistic studies

The hydrolysis of iminium in the reaction only in the workup with $NaHCO_3$ (not in situ with the 1 equivalent of neutral water formed in the reaction – compare also the selective formation of **13** in Figure 2, which is based on the same effect), explains the selective cleave of one C-C bond instead of two C-C bonds in substrates with two

reactive benzylic alcohol groups (**1m** selectively forms **3m**); the iminium group in the intermediate iminium tosylate electronically de-activates the arene ring, the second benzylic alcohol does not react anymore.



Scheme 3. Proposed mechanism of the C-C amination

3.3 Conclusion

We report a mid, operationally simple and perfect chemoselective C-C amination of benzylic alcohols with arylsulfonyl hydroxylamines ($ArSO_2ONHR$) to anilines, which is not only for the academy but also industry. As depicted above, other benzyl alcohol surrogates further expand the synthetic utility. In addition, chemoselective C-C brominations and oxygenations are possible under similar conditions. Mechanistically, an aza-Hock rearrangement was proved for the reaction. Interestingly, despite some early evidence for such a reactivity pattern, until known the synthetic utility of this process was limited and our report might pave the way for further protocols based on this pattern in the future.

3.4 Experimental Section

3.4.1 General Materials and Methods

Chemicals were purchased from commercial suppliers (Sigma-Aldrich, Alfa Aesar and TCI) and used as delivered. Dry solvents were dispensed from solvent purification system MB SPS-800. HFIP was used directly without further purification. Deuterated solvents were bought from Euriso-Top. Unless otherwise stated, all reactions and

manipulations were carried out under ambient atmosphere in new reaction vials or flasks.

NMR Spectra were recorded on a Bruker Avance-III-300, Bruker Avance-III-400, Bruker Avance-III-500, Bruker Avance-III-600. Chemical shifts are reported in ppm with the solvent resonance as the internal standard. For ^{1}H NMR: $CDCl_3$, 7.26; $(CD_3)_2SO$, 2.50. For ^{13}C NMR: $CDCl_3$, 77.16; $(CD_3)_2SO$, 39.52. Data is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentalet, hept = heptalet, m = multiplet, br = broad singlet, dd =doublet of doublets, td =triplet of doublets; coupling constants in Hz; integration.

Mass spectra (MS and HRMS) were determined in the chemistry department of the University Heidelberg under the direction of Dr. J. Gross. EI+ -spectra were measured on a JOEL JMS-700 spectrometer. For ESI+ -spectra a Bruker ApexQu FT-ICR-MS spectrometer was applied.

Infrared Spectroscopy (IR) was processed on an FT-IR Bruker (IF528), IR Perkin Elmer (283) or FT-IR Bruker Vector 22. The solvent or matrix is denoted in brackets. For the most significant bands the wave number ν (cm^{-1}) is given.

Melting points were measured in open glass capillaries in a Büchi melting point apparatus (according to Dr. Tottoli) and were not corrected.

Flash Column Chromatography was accomplished using Silica gel 60 (0.04 – 0.063 mm / 230 – 400 mesh ASTM) purchased from Macherey-Nagel.

Analytical / Preparative thin-layer chromatography (TLC) was carried out on pre-coated aluminum sheets provided by Macherey-Nagel ALUGRAM® Xtra SIL G/UV254. Components were visualized by treatment with aqueous $KMnO_4$ solution or by irradiation under UV light (254 nm).

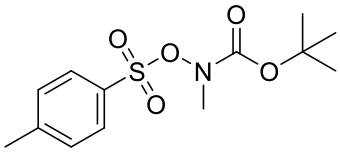
3.4.2 Preparation of Aminating Reagents and Substrates

General Procedure for Aminating Reagent Synthesis – GP1

To a solution of *tert*-butyl hydroxycarbamate, sulfonyl chloride or acetyl chloride in THF or Et_2O or DCM was slowly added Et_3N at 0°C, then the reaction was warmed up to room temperature and stirred overnight or 24 h (monitored by TLC). During the

process, colorless precipitation was developed. After the reaction was completed, it's filtrated to remove colorless precipitation, diluted with EA or DCM, washed with 1N HCl aq., sat. brine, dried over anhydrous Na_2SO_4, filtrated, concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA to afford the desired product.

***tert*-Butyl methyl(tosyloxy)carbamate (TsONBocMe)** spectral data were in agreement with literature values[7]



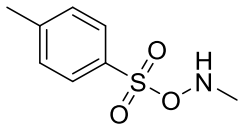
To a solution of *N*-methyl hydroxylamine hydrochloride (10.02 g, 120 mmol) in THF/ H_2O (1:1, 60 mL) was added K_2CO_3 (8.29g, 60 mmol) at 0ºC. Then a solution of di-*tert*-butyl dicarbonate (26.19 g, 120 mmol) in 40 mL THF was added dropwise to the above mixture, and the reaction was stirred for 2 h at 0°C and 3 h at room temperature. The reaction was concentrated in vacuo and the residue was dissolved in 100 mL DCM, washed with water (3 x 40 mL), 40 mL sat. brine and dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo to afford crude *N*-Boc-*N*-methyl hydroxylamine (16.56 g) as a pale orange oil which was directly used for the next step without further purification.

To a solution of crude *N*-Boc-*N*-methyl hydroxylamine (16.56 g, 112 mmol) in 250 mL DCM was added Et_3N (16.4 mL, 118 mmol) and TsCl (21.87 g, 115 mmol) at 0ºC. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction was washed with 100 mL 1.0 M HCl, 100 mL sat. brine and dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The residue was recrystallized with PE (60ºC – 80ºC) to afford TsONBocMe as a colorless solid (20.40 g, 56% for two steps) and the residue was concentrated to afford crude TsONBocMe (12.60 g, it still contained some TsCl, which was separated in the following step)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 3.24 (s, 3H), 2.45 (s, 3H), 1.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.07, 145.67, 131.22,

129.71, 129.52, 83.29, 40.15, 27.57, 21.68.

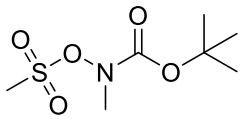
***N*-Methyl-*O*-tosylhydroxylamine (TsONHMe, 2a)** spectral data were in agreement with literature values[7]



To a solution of TsONBocMe (3.01 g, 10 mmol) in 15 mL DCM was added trifluoroacetic acid (15 ml, 200 mmol) at 0ºC. The reaction was stirred for 3 h at 0 °C and then it's poured into 30 mL ice water and extracted with DCM (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA (5:1) as eluting solvent to afford TsONHMe **2a** as a colorless solid (1.96 g, 98%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 5.85 (s, 1H), 2.74 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.93, 132.26, 129.50, 128.94, 40.10, 21.65.

***tert*-Butyl methyl((methylsulfonyl)oxy)carbamate (MsONBocMe)** spectral data were in agreement with literature values[7]



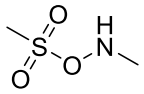
To a solution of *N*-methyl hydroxylamine hydrochloride (2.51 g, 30 mmol) in THF/ H_2O (1:1, 20 mL) was added K_2CO_3 (2.07 g, 15 mmol) at 0ºC. Then a solution of di-*tert*-butyl dicarbonate (6.55 g, 30 mmol) in 10 mL THF was added dropwise to the above mixture and stirred for 2 h at 0°C and then 3 h at room temperature. The reaction was concentrated in vacuo and the residue was dissolved in 20 mL DCM, washed with water (3 x 10 mL), 20 mL sat. brine and dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo to afford crude *N*-Boc-*N*-methyl hydroxylamine (3.82 g) as a pale orange oil which was directly used for the next step without further purification.

To a solution of *N*-Boc-*N*-methyl hydroxylamine (1.47 g, 10 mmol) in 20 mL DCM

was added Et_3N (1.53 mL, 11 mmol) and MsCl (1.26 g, 11 mmol) at 0ºC. The reaction mixture was warmed up to room temperature and stirred for 18 h. The reaction was washed with 20 mL 1.0 M HCl, 20 mL sat. brine and dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA (10:1) as eluting solvent to afford MsONBocMe as a colorless oil (1.58 g, 40% for two steps).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32 (s, 3H), 3.14 (s, 3H), 1.52 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.08, 84.30, 40.57, 36.63, 28.00.

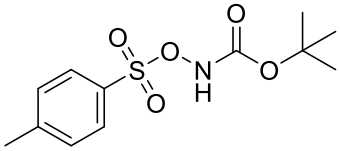
***N*-Methyl-*O*-(methylsulfonyl)hydroxylamine (MsONHMe, 2b)** spectral data were in agreement with literature values[7]



To a solution of MsONBocMe (450 mg, 2 mmol) in 3 mL DCM was added trifluoroacetic acid (3.0 ml, 40 mmol) at 0ºC. The reaction was stirred for 3 h at 0°C and then it's poured into 10 mL ice water and extracted with DCM (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA (5:1) as eluting solvent to afford MsONHMe **2b** as a pale yellow oil (152 mg, 61%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (s, 1H), 3.09 (s, 3H), 2.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.43, 34.98.

***tert*-Butyl (tosyloxy)carbamate (TsONHBoc, 5a)** spectral data were in agreement with literature values[7]

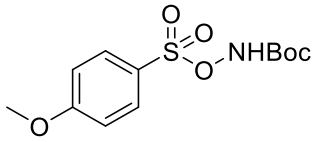


Following **GP 1**, *tert*-butyl hydroxycarbamate (13.98 g, 105 mmol), TsCl (19.06 g, 100 mmol), Et_3N (10.63 g, 105 mmol) in 250 mL THF solution were stirred for 4 h at room temperature. Purification with cyclohexane afforded TsONHBoc **5a** as a colorless solid

(24.55 g, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.67 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 2.45 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.08, 145.90, 130.58, 129.65, 129.60, 83.84, 27.69, 21.71.

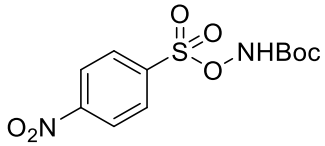
tert-Butyl (((4-methoxyphenyl)sulfonyl)oxy)carbamate (5b)



Following **GP1**, 4-methoxybenzenesulfonyl chloride (620 mg, 3 mmol), *tert*-butyl hydroxycarbamate (399 mg, 3 mmol) and Et_3N (438 uL, 3.15 mmol) in 10 mL THF solution were stirred for 4 h at 0°C. Purification by silica gel chromatography with PE/EA 5:1 as eluting solvent afforded *tert*-butyl (((4-methoxyphenyl)sulfonyl)oxy)carbamate **5b** as a colorless solid (780 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.9 Hz, 2H), 7.68 (s, 1H), 7.04 (d, *J* = 8.9 Hz, 2H), 3.91 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.59, 154.12, 131.94, 124.71, 114.23, 83.80, 55.78, 27.74.

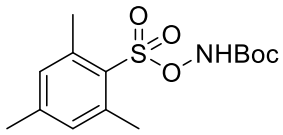
tert-Butyl (((4-nitrophenyl)sulfonyl)oxy)carbamate (5c)



Following **GP1**, 4-nitrobenzenesulfonyl chloride (2.21 g, 10 mmol), *tert*-butyl hydroxycarbamate (1.33 g, 10 mmol) and Et_3N (1.53 mL, 11 mmol) in 80 mL Et_2O solution were stirred for 6 h at 0°C. Purification with 30 mL hexane afforded *tert*-butyl (((4-nitrophenyl)sulfonyl)oxy)carbamate **5c** as a colorless solid (2.86 g, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.9 Hz, 2H), 8.22 (d, *J* = 8.9 Hz, 2H), 7.78 (s, 1H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.68, 151.26, 139.35, 131.06, 124.01, 84.78, 27.74.

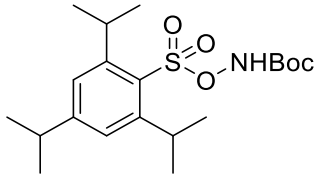
***tert*-Butyl ((mesitylsulfonyl)oxy)carbamate (5d)** spectral data were in agreement with literature values[14]



Following **GP1**, 2,4,6-trimethylbenzenesulfonyl chloride (10.94 g, 50 mmol), *tert*-butyl hydroxycarbamate (6.66 g, 50 mmol) and Et_3N (7.64 mL, 55 mmol) in 150 mL *tert*-butyl methyl ether solution were stirred overnight at room temperature. Purification with 50 mL hexane afforded *tert*-butyl ((mesitylsulfonyl)oxy)carbamate **5d** as a colorless solid (13.05 g, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 6.99 (s, 2H), 2.67 (s, 6H), 2.32 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.14, 144.38, 141.92, 131.62, 128.51, 83.79, 27.70, 23.09, 21.08.

***tert*-Butyl (((2,4,6-triisopropylphenyl)sulfonyl)oxy)carbamate (5e)**



Following **GP1**, 2,4,6-triisopropylbenzenesulfonyl chloride (3.03 g, 10 mmol), *tert*-butyl hydroxycarbamate (1.40 g, 10.5 mmol) and Et_3N (1.46 mL, 10.5 mmol) in 50 mL THF solution were stirred overnight at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded *tert*-butyl (((2,4,6-triisopropylphenyl)sulfonyl)oxy)carbamate **5e** as a colorless solid (3.28 g, 82%).

Mp: 87°C

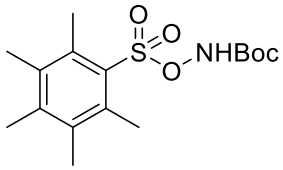
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.20 (s, 2H), 4.12 (hept, J = 6.8 Hz, 2H), 2.92 (hept, J = 6.8 Hz, 1H), 1.40 (s, 9H), 1.29 (s, 6H), 1.26 (s, 9H), 1.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.68, 154.19, 152.34, 127.70, 123.90, 83.70, 34.30, 30.05, 27.88, 24.73, 23.47.

IR (EXTRACT): $\tilde{\nu}$ = 3219.13, 3127.94, 2962.11, 2873.81, 1697.68, 1598.27, 1565.16, 1461.19, 1425.33, 1381.81, 1368.59, 1352.88, 1320.96, 1259.76, 1185.53, 1158.30,

1108.07, 1072.81, 1037.40, 1008.33, 937.05, 885.56, 846.67, 801.44, 740.54, 719.22, 660.49, 633.73 cm^{-1}

HRMS (DART+) m/z: $[M+18]^+$ calcd 417.2418, found 417.2419.

tert-Butyl (((2,3,4,5,6-pentamethylphenyl)sulfonyl)oxy)carbamate (5f)



Following **GP1**, 2,3,4,5,6-pentamethylbenzenesulfonyl chloride (1.23 g, 5 mmol), *tert*-butyl hydroxycarbamate (699 mg, 5.25 mmol) and Et_3N (0.73 mL, 5.25 mmol) in 20 mL THF solution were stirred overnight at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded *tert*-butyl (((2,3,4,5,6-pentamethylphenyl)sulfonyl)oxy)carbamate **5f** as a colorless solid (1.40 g, 81%).

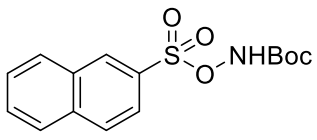
Mp: 102°C

^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 2.61 (s, 6H), 2.30 (s, 3H), 2.25 (s, 6H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.40, 141.74, 136.75, 134.93, 130.90, 83.70, 27.75, 19.16, 17.99, 17.06.

IR (ATR): $\tilde{\nu}$ = 3488, 3333, 3264, 2986, 2919, 1738, 1643, 1554, 1452, 1408, 1377, 1335, 1317, 1202, 1163, 1047, 1005, 940, 855, 823, 778, 746, 684, 634cm^{-1}

HRMS (ESI+) m/z: $[M+Na]^+$ calcd 366.1346, found 366.1345; $[2M+Na]^+$ calcd 709.2799, found 709.2804.

tert-Butyl ((naphthalen-2-ylsulfonyl)oxy)carbamate (5g)

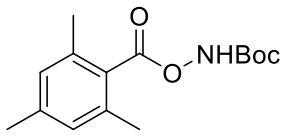


Following **GP1**, naphthalene-2-sulfonyl chloride (1.13 g, 5 mmol), *tert*-butyl hydroxycarbamate (699 mg, 5.25 mmol) and Et_3N (0.73 mL, 5.25 mmol) in 20 mL THF solution were stirred overnight at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl ((naphthalen-

2-ylsulfonyl)oxy)carbamate **5g** as a colorless solid (1.37 g, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.25 – 7.86 (m, 4H), 7.82 – 7.48 (m, 3H), 1.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.08, 135.69, 131.88, 131.79, 130.42, 129.79, 129.49, 129.22, 127.93, 127.81, 123.71, 83.94, 27.56.

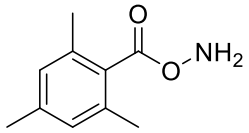
***tert*-Butyl ((2,4,6-trimethylbenzoyl)oxy)carbamate (5h)**



Following **GP1**, 2,4,6-trimethylbenzoyl chloride (1.82 g, 10 mmol), *tert*-butyl hydroxycarbamate (1.40 g, 10.5 mmol) and Et_3N (1.46 mL, 10.5 mmol) in 50 mL DCM solution were stirred for 18 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl ((2,4,6-trimethylbenzoyl)oxy)carbamate **5h** as a colorless solid (2.47 g, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.88 (s, 2H), 2.37 (s, 6H), 2.29 (s, 3H), 1.53 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.22, 155.53, 140.74, 136.70, 128.63, 126.68, 83.30, 28.08, 21.19, 19.96.

***O*-(2,4,6-Trimethylbenzoyl)hydroxylamine (5i)**

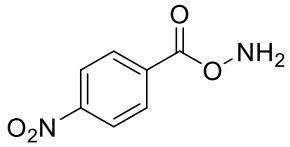


To a solution of *tert*-butyl ((2,4,6-trimethylbenzoyl)oxy)carbamate (**5h**, 1.40 g, 5 mmol) in 7.4 mL DCM was added TFA (7.4 mL, 100 mmol) at 0°C, and the reaction was stirred at 0°C for 3 h. The reaction mixture was quenched with 15 mL H_2O, extracted with DCM (30 mL × 3), and the combined organic layers were concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA (5:1) as eluting solvent to afford *O*-(2,4,6-trimethylbenzoyl)hydroxylamine **5i** as an off-white solid (864 mg, 96%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (s, 2H), 6.31 (br, 2H), 2.22 (s, 9H).^{13}C NMR (75

MHz, $CDCl_3$) δ 170.76, 140.20, 135.90, 128.48, 21.15, 19.76.

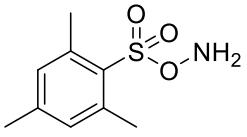
***O*-(4-Nitrobenzoyl)hydroxylamine (5j)** spectral data were in agreement with literature values[15]



To a solution of *tert*-butyl hydroxycarbamate (1.34 g, 10.1 mmol), Et_3N (1.53 mL, 11 mmol) in 15 mL DCM was dropwise added 4-nitrobenzoyl chloride (1.85 g, 10 mmol) at 0°C, then the reaction was stirred at 0°C for 5 min and then warmed up to room temperature. The reaction was quenched with 5 mL H_2O, washed with aqueous 8 mL 4% K_2HPO_4 aq., 10 mL sat. brine., dried over Na_2SO_4. Then methanesulfonic acid (1.44 g, 15 mmol) was added to the above DCM phase, and stirred at room temperature for 20 h. The mixture was treated with 15 mL 20% K_2HPO_4 aq. at room temperature for 10 min. Then 15 mL THF was added to the above mixture. The organic layer was separated, washed with 30 mL sat. brine and dried over Na_2SO_4, filtrated, concentrated in vacuo. 15 mL Heptane was slowly added to the residue for crystallization. The solid was collected by filtration, washed with THF-heptane (1:2, 6 mL), and dried in vacuo to afford *O*-(4-nitrobenzoyl)hydroxylamine **5j** as a yellow solid (1.35 g, 74%)

^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 8.9 Hz, 2H), 8.19 (d, J = 8.9 Hz, 2H), 6.74 (br, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.48, 150.71, 133.30, 130.53, 123.72.

***O*-Mesitylenesulfonylhydroxylamine (MSH, 5m)** spectral data were in agreement with literature values[16]



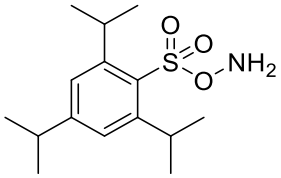
To 70 mL TFA in a flask was added *tert*-butyl ((mesitylsulfonyl)oxy)carbamate (**5d**, 9.46 g, 30 mmol), and then the reaction was stirred for 3 h at 0°C. Then it's poured into 150 mL ice-water and stirred for 30 min, during this time, a colorless precipitate was developed, filtrated to afford the crude product. The crude product was dissolved in 80

mL Et_2O at 0°C, then 150 mL cold PE was added to the above mixture, crystallized for 30 min, filtrated, dried under vacuum to afford *O*-mesitylenesulfonylhydroxylamine **5m** as a colorless solid (4.80 g, 74%).

^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2H), 4.35 (br, 2H), 2.66 (s, 6H), 2.35 (s, 3H).

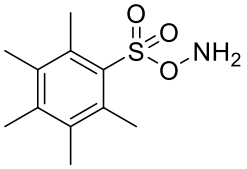
^{13}C NMR (100 MHz, $CDCl_3$) δ 143.76, 140.95, 131.68, 129.11, 22.67, 21.03.

***O*-((2,4,6-Triisopropylphenyl)sulfonyl)hydroxylamine (5n)**



To a solution of *tert*-butyl (((2,4,6-triisopropylphenyl)sulfonyl)oxy)carbamate (**5e**, 2.00 g, 5 mmol) in 8 mL 1,4-dioxane was added 70% $HClO_4$ (8.1 mL, 100 mmol) at 0°C, and stirred for 3 h at 0°C. Then it's poured into 30 mL ice-water and stirred for 30 min, during this time, colorless precipitate was developed, filtrated to afford the crude *O*-((2,4,6-triisopropylphenyl)sulfonyl)hydroxylamine **5n** (1.41 g, 95%), which was directly used for the next step without further purification.

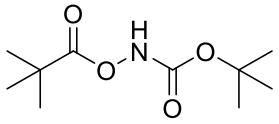
***O*-((2,3,4,5,6-Pentamethylphenyl)sulfonyl)hydroxylamine (5o)**



To a solution of *tert*-butyl (((2,3,4,5,6-pentamethylphenyl)sulfonyl)oxy)carbamate (**5f**, 654 mg 2 mmol) in 5 mL DCM was added TFA (2.97 mL, 40 mmol) at 0°C, and stirred for 3 h at 0°C. Then it's poured into 20 mL ice-water and stirred for 30 min, during this time, a colorless precipitate was developed, filtrated to afford the crude *O*-((2,3,4,5,6-pentamethylphenyl)sulfonyl)hydroxylamine **5o** (378 mg, 78%), which was directly used for the next step without further purification.

***tert*-Butyl (pivaloyloxy)carbamate (PivONHBoc, 5r)** spectral data were in agreement

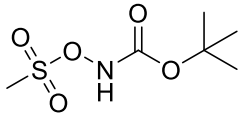
with literature values[17]



To a solution of *tert*-butyl hydroxycarbamate (2.66 g, 20 mmol) in 50 mL $CHCl_3$ was added Piv_2O (4.87 mL, 24 mmol) at room temperature, then the reaction was refluxed overnight. The reaction was cooled down to room temperature, washed with 50 mL sat.$NaHCO_3$ aq., 50 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA 20:1 as eluting solvent to afford PivONHBoc **5r** asa a colorless solid (1.96 g, 45%)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (s, 1H), 1.48 (s, 9H), 1.29 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.78, 155.65, 83.06, 38.15, 28.02, 26.94.

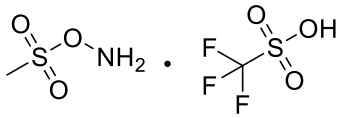
***tert*-Butyl ((methylsulfonyl)oxy)carbamate (MsONHBoc, 5s)** spectral data were in agreement with literature values[7]



Following **GP1**, MsCl (4.06 mL, 52.5 mmol), *tert*-butyl hydroxycarbamate (6.66 g, 50 mmol) and Et_3N (7.3 mL, 52.5 mmol) in 150 mL Et_2O solution were stirred at 0°C for 12 h. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded MsONHBoc **5s** as a colorless solid (9.46 g, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 3.17 (s, 3H), 1.52 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.55, 84.75, 36.34, 27.97.

$MsONH_2$•HOTf (5t) spectral data were in agreement with literature values[7]

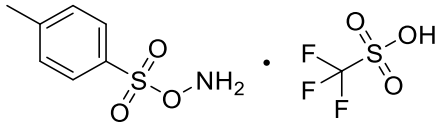


To a solution of MsONHBoc **5s** (1.06 g, 5 mmol) in 15 mL Et_2O was slowly added HOTf (463 uL, 5.25 mmol) at 0°C, then the reaction was stirred for 1 h at room

temperature. 15 mL pentane was added to the reaction, and it's stirred for 15 min, filtrated, washed with Et_2O, dried under vacuum to afford $MsONH_2$•HOTf **5t** as a colorless solid (1.19 g, 91%)

^1H NMR (300 MHz, DMSO) δ 2.46 (s, 3H), 4.36 (br, 3H). ^{13}C NMR (75 MHz, DMSO) δ 120.79 (q, J = 322.2 Hz), 39.60. ^{19}F NMR (283 MHz, DMSO) δ -77.74.

$TsONH_2$•HOTf (5u) spectral data were in agreement with literature values[18]



To a solution of TsONHBoc (**5a**, 862 mg, 3 mmol) in 8 mL Et_2O was slowly added HOTf (278 uL, 3.15 mmol) at 0°C, then the reaction was stirred for 1 h at room temperature. 8 mL pentane was added to the reaction, and it's stirred for 15 min, filtrated, washed with Et_2O, dried under vacuum to afford $TsONH_2$•HOTf **5u** as a colorless solid (952 mg, 94%)

^1H NMR (400 MHz, DMSO) δ 7.51 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 4.37 (br, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 144.54, 138.65, 128.45, 125.59, 120.77 (q, J = 320.1 Hz), 20.87. ^{19}F NMR (283 MHz, DMSO) δ -77.74.

General Procedure for the Mitsunobu Reaction – GP2

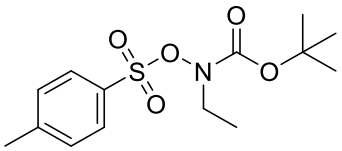
To a solution of PPh_3 (1.0 eq) in dry THF was added DIAD (1.0 eq) at 0°C under nitrogen atmosphere. A colorless solid was formed after 10 min, and the it's stirred for 30 min at 0°C. Then the solution of alcohol (1.0 eq) in THF and TsONHBoc (1.0 eq) in THF were added to the above mixture successively. Then the reaction was stirred at 0°C for another 1 h, and then at room temperature overnight (monitored by TLC). The reaction was concentrated in vacuo and purified by silica gel chromatography with PE/EA to afford the desired product.

General Procedure for the Removal of the Boc Group – GP3

To a solution of *N*-Boc-*N*-alkyl-*O*-tosyl hydroxylamine (1.0 eq) in DCM was added

TFA (20.0 eq) at 0ºC, then it was stirred at 0ºC for 3 h (monitored by TLC). The reaction was quenched with cold water at 0ºC and then extracted with DCM. The combined organic layers were washed with sat. brine and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA to afford the desired product or directly used for the next step without further purification.

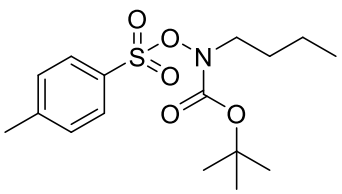
***tert*-Butyl ethyl(tosyloxy)carbamate** spectral data were in agreement with literature values[7]



Following **GP2**, TsONHBoc (862 mg, 3 mmol), ethanol (138 mg, 3 mmol), PPh_3 (787 mg, 3 mmol), and DIAD (607 mg, 3 mmol) in 25 mL dry THF solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl ethyl(tosyloxy)carbamate as a colorless solid (744 mg, 79%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 3.66 (br, 2H), 2.45 (s, 3H), 1.22 (s, 9H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.49, 145.59, 131.24, 129.69, 129.47, 83.18, 48.16, 27.58, 21.68, 10.66.

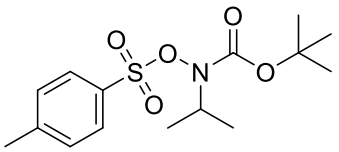
***tert*-Butyl butyl(tosyloxy)carbamate** spectral data were in agreement with literature values[7]



Following **GP2**, TsONHBoc (1.44 g, 5 mmol), *n*-butanol (370 mg, 5 mmol), PPh_3 (1,31 g, 5 mmol), and DIAD (1.01 g, 5 mmol) in 35 mL dry THF solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded *tert*-butyl butyl(tosyloxy)carbamate as a colorless solid (1.60 g, 93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 3.60 (br, 2H), 2.45 (s, 3H), 1.66 – 1.52 (m, 2H), 1.32 – 1.22 (m, 2H), 1.22 (s, 9H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.52, 145.59, 131.32, 129.68, 129.48, 83.03, 52.67, 27.82, 27.58, 21.67, 19.73, 13.68.

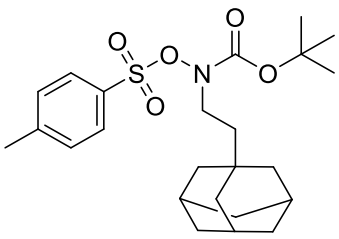
***tert*-Butyl isopropyl(tosyloxy)carbamate** spectral data were in agreement with literature values[19]



Following **GP2**, TsONHBoc (1.14 g, 4 mmol), propan-2-ol (240 mg, 4 mmol), PPh_3 (1048 mg, 4 mmol), and DIAD (808 mg, 4 mmol) in 35 mL dry THF solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl isopropyl(tosyloxy)carbamate as a colorless solid (1.04 g, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 4.13 (hept, *J* = 6.7 Hz, 1H), 2.44 (s, 3H), 1.28 (s, 9H), 1.18 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.36, 145.41, 131.87, 129.59, 129.43, 83.28, 56.57, 27.64, 21.65, 19.10.

***tert*-Butyl (2-(adamantan-1-yl)ethyl)(tosyloxy)carbamate** spectral data were in agreement with literature values[7]

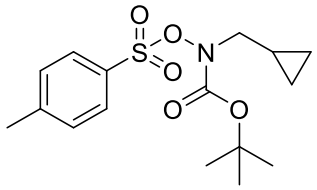


Following **GP2**, TsONHBoc (574 mg, 2 mmol), 2-(adamantan-1-yl)ethan-1-ol (360 mg, 2 mmol), PPh_3 (524 mg, 2 mmol), and DIAD (404 mg, 2 mmol) in 25 mL dry THF solution was stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl (2-

(adamantan-1-yl)ethyl)(tosyloxy)carbamate as a colorless oil (866 mg, 96%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 3.60 (br, 2H), 2.44 (s, 3H), 1.95 – 1.89 (m, 2H), 1.72 – 1.54 (m, 6H), 1.45 (d, *J* = 2.8 Hz, 6H), 1.23 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.49, 145.54, 131.35, 129.67, 129.44, 83.03, 48.53, 42.07, 39.02, 36.98, 31.41, 28.49, 27.62, 21.65.

***tert*-Butyl (cyclopropylmethyl)(tosyloxy)carbamate**



Following **GP2**, TsONHBoc (862 mg, 3 mmol), cyclopropylmethanol (216 mg, 3 mmol), PPh_3 (787 mg, 3 mmol), and DIAD (607 mg, 3 mmol) in 25 mL dry THF solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl (cyclopropylmethyl)(tosyloxy)carbamate as a colorless solid (762 mg, 74%).

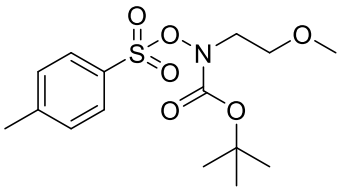
Mp: 63^{o}C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz,2H), 7.34 (d, *J* = 8.3 Hz, 2H), 3.50 (s, 2H), 2.45 (s, 3H), 1.23 (s, 9H), 1.18 – 1.06 (m, 1H), 0.50 (d, *J* = 7.8 Hz, 2H), 0.27 (d, *J* = 4.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.71, 145.55, 131.32, 129.69, 129.46, 83.10, 57.60, 27.57, 21.67, 8.02, 3.35.

IR (EXTRACT): $\tilde{\nu}$ = 3095.86, 3015.89, 2982.25, 2936.40, 1934.02, 1713.53, 1595.72, 1429.96, 1374.16, 1346.05, 1321.57, 1273.12, 1256.10, 1193.96, 1159.30, 1092.35, 1028.94, 975.88, 930.21, 892.77, 846.69, 815.70, 747.20, 704.21, 666.31, 651.02, 632.52 cm^{-1}

HRMS (ESI+) m/z: $[M+Na]^+$ calcd 364.1189, found 364.1190; $[2M+Na]^+$ calcd 705.2486, found 705.2492.

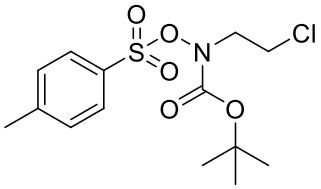
***tert*-Butyl (2-methoxyethyl)(tosyloxy)carbamate** spectral data were in agreement with literature values[7]



Following **GP2**, TsONHBoc (862 mg, 3 mmol), 2-methoxyethan-1-ol (228 mg, 3 mmol), PPh_3 (787 mg, 3 mmol), and DIAD (607 mg, 3 mmol) in 25 mL dry THF solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl(2-methoxyethyl) (tosyloxy)carbamate as a colorless solid (920 mg, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 3.63 (br, 4H), 3.29 (s, 3H), 2.44 (s, 3H), 1.20 (s, 9H).^{13}C NMR (125 MHz, $CDCl_3$) δ 155.74, 145.66, 131.00, 129.71, 129.46, 83.02, 67.18, 58.71, 51.73, 27.43, 21.66.

***tert*-Butyl (2-chloroethyl)(tosyloxy)carbamate** spectral data were in agreement with literature values[7]



Following **GP2**, TsONHBoc (862 mg, 3 mmol), 2-chloroethan-1-ol (241 mg, 3 mmol), PPh_3 (787 mg, 3 mmol), and DIAD (607 mg, 3 mmol) in 25 mL dry THF solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl(2-chloroethyl)(tosyloxy) carbamate as a colorless solid (855 mg, 82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 3.99 (t, *J* = 6.5 Hz, 2H), 3.73 (t, *J* = 6.5 Hz, 2H), 2.46 (s, 3H), 1.21 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.81, 146.01, 130.80, 129.78, 129.62, 83.78, 53.46, 39.01, 27.50, 21.70.

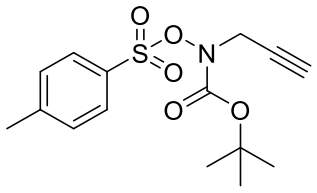
Methyl (tosyloxy)carbamate (2j)

To a solution of hydroxylamine hydrochloride (6.95 g, 100 mmol) in 80 mL 1.5 M NaOH aq. was slowly added methyl chloroformate (1.5 mL, 20 mmol) at 0ºC. Then the reaction was warmed up to room temperature, and stirred for 4 h. The reaction mixture was adjusted to PH 4.5 with 6 M HCl aq., extracted with Et_2O (100 mL × 3), and the combined organic layers were washed with 100 mL sat. brine, dried over Na_2SO_4, concentrated in vacuo to afford the crude methyl hydroxycarbamate as a colorless oil (600 mg).

To a solution of crude methyl hydroxycarbamate (600 mg, 6.59 mmol) and TsCl (1256 mg, 6.59 mmol) in 30 mL Et_2O was slowly added Et_3N (0.96 mL, 6.59 mmol) at 0°C. The reaction mixture was warmed up to room temperature and stirred overnight. The reaction mixture was washed with 30 mL H_2O, 30 mL sat. brine, dried over Na_2SO_4, concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA (3:1) as eluting solvent afforded methyl (tosyloxy)carbamate **2j** as a colorless solid (1.32 g, 27% for two steps).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 3.64 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.97, 146.19, 130.28, 129.73, 129.53, 53.66, 21.77.

***tert*-Butyl prop-2-yn-1-yl(tosyloxy)carbamate** spectral data were in agreement with literature values[7]

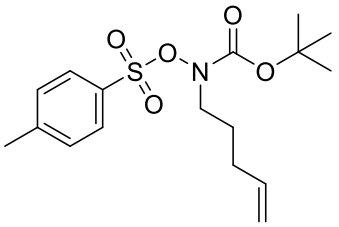


Following **GP2**, TsONHBoc (862 mg, 3 mmol), prop-2-yn-1-ol (168 mg, 3 mmol), PPh_3 (787 mg, 3 mmol), and DIAD (607 mg, 3 mmol) in 25 mL dry THF solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl prop-2-yn-1-yl(tosyloxy)carbamate

as a colorless solid (826 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 4.30 (br, 2H), 2.45 (s, 3H), 2.25 (t, *J* = 2.4 Hz, 1H), 1.26 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ 154.92, 145.85, 131.02, 129.72, 129.56, 84.33, 76.30, 73.16, 42.88, 27.55, 21.68.

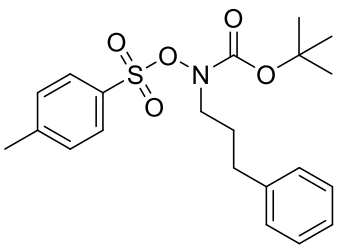
***tert*-Butyl pent-4-en-1-yl(tosyloxy)carbamate** spectral data were in agreement with literature values[20]



Following **GP2**, TsONHBoc (574 mg, 2 mmol), pent-4-en-1-ol (172 mg, 2 mmol), PPh_3 (524 mg, 2 mmol), and DIAD (404 mg, 2 mmol) in 15 mL dry THF solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl pent-4-en-1-yl(tosyloxy)carbamate as a colorless solid (576 mg, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 5.76 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.08 – 4.92 (m, 2H), 3.62 (br, 2H), 2.45 (s, 3H), 2.03 (q, *J* = 7.8 Hz, 2H), 1.72 (p, *J* = 7.8 Hz, 2H), 1.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.42, 145.64, 137.29, 131.27, 129.69, 129.49, 115.27, 83.15, 52.44, 30.58, 27.59, 24.89, 21.67.

***tert*-Butyl (3-phenylpropyl)(tosyloxy)carbamate** spectral data were in agreement with literature values[21]

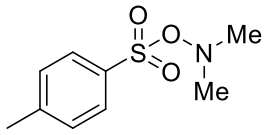


Following **GP2**, TsONHBoc (574 mg, 2 mmol), 3-phenylpropan-1-ol (272 mg, 2 mmol),

PPh_3 (524 mg, 2 mmol), and DIAD (404 mg, 2 mmol) in 15 mL dry THF solution were stirred at room temperature overnight. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *tert*-butyl (3-phenylpropyl)(tosyloxy)carbamate as a colorless solid (800 mg, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.30 – 7.25 (m, 2H), 7.23 – 7.13 (m, 3H), 3.64 (br, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.45 (s, 3H), 1.97 (p, *J* = 7.8Hz, 2H), 1.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.46, 145.66, 141.09, 131.26, 129.68, 129.52, 128.42, 128.30, 126.00, 83.23, 52.64, 32.82, 27.61, 27.42, 21.69.

***N*,*N*-Dimethyl-*O*-tosylhydroxylamine** spectral data were in agreement with literature values[7]



To a solution of *N*,*N*-dimethylhydroxylamine hydrochloride (878 mg, 9 mmol) and Et_3N (2.75 mL, 19.8 mmol) in 100 mL DCM was dropwise added TsCl (1.89 g, 9.9 mmol) in 10 mL DCM solution at 0°C. A colorless precipitate was formed after 20 min, and the reaction was stirred at 0°C for 2 h. The reaction mixture was filtrated, and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA (10:1) to afford *N*,*N*-dimethyl-*O*-tosylhydroxylamine as a colorless solid (702 mg, 36%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 2.63 (s, 6H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.79, 132.51, 129.41, 128.93, 48.91, 21.65.

General Procedure for Alcohols Synthesis

GP4a. To a mixture of ketone (1 eq.) in MeOH or THF/H_2O (5:1) solution was portionwise added $NaBH_4$ (1.2 – 2.0 eq.) at 0°C, then the reaction mixture was stirred for 3 h at 0°C. The reaction was quenched with 1N HCl aq., extracted with EA, and the

combined organic layers were washed with sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA to afford the desired alcohol.

GP4b. To a solution of $AlCl_3$ (2.0 – 3.0 eq.) in DCE or DCM was added acetyl chloride (2.0 – 3.0 eq.) at 0°C, and the mixture was stirred for 10 min at 0°C. Then the arene (1.0 eq) was added to the above mixture at 0°C, stirred for 3 h. The reaction was quenched with sat. NH_4Cl aq. at 0°C, extracted with DCM, and the combined organic layers were washed with sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo to afford the crude ketone.

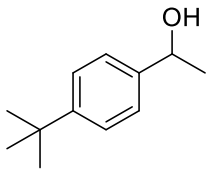
To a solution of the above crude ketone in MeOH or THF/H_2O (5:1) was portionwise added $NaBH_4$ (2.0 eq) at 0°C, and stirred for 3 h at 0°C. The reaction was quenched with 1N HCl aq., extracted with EA, and the combined organic layers were washed with sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA to afford the desired alcohol.

GP4c. To a solution of ketone in THF was portionwise added $LiAlH_4$ (x mg) at 0°C, then the reaction was refluxed for some time. The reaction was cooled down to 0°C, then H_2O (x mg) was added to the above mixture, stirred for 10 min, followed by 15% NaOH (x mg), stirred for 10 min, finally H_2O (3x mg) was added, and stirred for 2 h at 0°C. The colorless precipitate was developed during this process, and it's filtrated with celite, and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA to afford the desired alcohol.

GP4d. To a solution of ketone (1.0 eq) in THF was slowly added Grignard reagent (1.5 – 2.0 eq.) at 0°C, then the reaction was stirred overnight at room temperature. The reaction was quenched with sat. NH_4Cl aq., extracted with EA, and the combined organic layers were washed with sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography

with PE/EA to afford the desired alcohol.

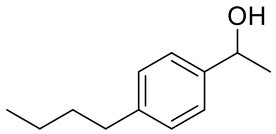
1-(4-(*tert*-Butyl)phenyl)ethan-1-ol (1d) spectral data were in agreement with literature values[22]



Following **GP4a**, 1-(4-(*tert*-butyl)phenyl)ethan-1-one (881 mg, 5 mmol), $NaBH_4$ (227 mg, 6 mmol) in 10 mL MeOH solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 1-(4-(*tert*-butyl)phenyl)ethan-1-ol **1d** as a colorless solid (873 mg, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 4.88 (q, *J* = 6.5 Hz, 1H), 1.82 (br, 1H), 1.51 (d, *J* = 6.5 Hz, 3H), 1.33 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.44, 142.76, 125.39, 125.14, 70.17, 34.48, 31.34, 24.89.

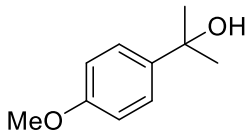
1-(4-Butylphenyl)ethan-1-ol (1e) spectral data were in agreement with literature values[22]



Following **GP4a**, 1-(4-butylphenyl)ethan-1-one (881 mg, 5 mmol), $NaBH_4$ (227 mg, 6 mmol) in 10 mL MeOH solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 1-(4-butylphenyl)ethan-1-ol **1e** as a colorless liquid (873 mg, 98%).

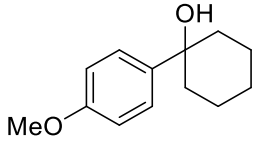
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 4.87 (q, *J* = 6.4 Hz, 1H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.77 (br, 1H), 1.67 – 1.54 (m, 2H), 1.49 (d, *J* = 6.4 Hz, 3H), 1.36 (dq, *J* = 14.5, 7.3 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.01, 142.18, 128.49, 125.32, 70.24, 35.27, 33.63, 24.97, 22.33, 13.91.

2-(4-Methoxyphenyl)propan-2-ol (1f) spectral data were in agreement with literature values[23]



Following **GP4d**, 1-(4-methoxyphenyl)ethan-1-one (751 mg, 5 mmol), 3.0 M CH_3MgBr (2.0 mL, 6 mmol) in 10 mL Et_2O solution were stirred overnight at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 2-(4-methoxyphenyl)propan-2-ol **1f** as a colorless oil (471 mg, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.8 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 1. (br, 1H), 1.57 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.30, 141.34, 125.58, 113.46, 72.16, 55.24, 31.75.

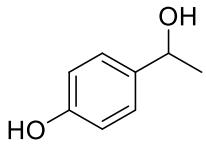
1-(4-Methoxyphenyl)cyclohexan-1-ol (1g) spectral data were in agreement with literature values[24]



Following **GP4d**, cyclohexanone (490 mg, 5 mmol), 0.5 M (4-methoxyphenyl)magnesium bromide (12.0 mL, 6 mmol) in 8 mL DCM solution were stirred for 3 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 1-(4-methoxyphenyl)cyclohexan-1-ol **1g** as a colorless oil (414 mg, 40%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 1.86 – 1.52 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.28, 141.59, 125.78, 113.46, 72.72, 55.22, 38.90, 25.50, 22.26.

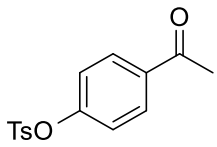
4-(1-Hydroxyethyl)phenol (1h) spectral data were in agreement with literature values[25]



Following **GP4d**, 4-hydroxybenzaldehyde (733 mg, 6 mmol), 3.0 M CH_3MgBr (6.0 mL, 18 mmol) in 20 mL THF solution were stirred overnight at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-(1-hydroxyethyl)phenol **1h** as a yellow solid (389 mg, 47%).

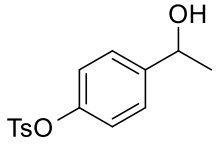
^{1}H NMR (300 MHz, DMSO) δ 9.16 (s, 1H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 8.5 Hz, 2H), 4.91 (d, *J* = 4.0 Hz, 1H), 4.60 (qd, *J* = 6.4, 4.0 Hz, 1H), 1.27 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, DMSO) δ 155.95, 137.67, 126.41, 114.63, 67.76, 25.93.

4-Acetylphenyl 4-methylbenzenesulfonate was prepared according to a published procedure; spectral data were in agreement with literature values[26]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 2.57 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.60, 152.96, 145.74, 135.67, 132.11, 130.01, 129.89, 128.44, 122.47, 26.57, 21.70.

4-(1-Hydroxyethyl)phenyl 4-methylbenzenesulfonate (1j)



Following **GP4a**, 4-acetylphenyl 4-methylbenzenesulfonate (871 mg, 3 mmol), $NaBH_4$ (227 mg, 6 mmol) in 15 mL MeOH solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-(1-hydroxyethyl)phenyl 4-methylbenzenesulfonate **1j** as a colorless liquid (843 mg, 96%).

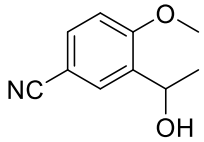
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 6.8 Hz, 2H), 7.28 (d, *J* = 6.8 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 4.86 (q, *J* = 6.4 Hz, 1H), 2.45 (s, 3H), 1.89

(br, 1H), 1.45 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.69, 145.32, 144.68, 132.43, 129.73, 128.46, 126.59, 122.32, 69.62, 25.27, 21.68.

IR (EXTRACT): ṽ = 3549.68, 3388.69, 3065.92, 2971.44, 2946.75, 2927.26, 2866.93, 1909.46, 1596.63, 1501.03, 1453.96, 1369.39, 1292.22, 1196.71, 1174.85, 1153.67, 1108.85, 1090.67, 1016.28, 933.09, 863.24, 845.68, 814.47, 777.20, 741.31, 706.49, 682.31, 657.97cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 292.0764, found 292.0749.

3-(1-Hydroxyethyl)-4-methoxybenzonitrile (1l)



To a solution of 3-acetyl-4-hydroxybenzonitrile (483 mg, 3 mmol) in 10 mL acetone was added K_2CO_3 (1.24 g, 9 mmol), then the reaction mixture was stirred for 1h at room temperature. Then CH_3I (554 mg, 3.9 mmol) was added to the above mixture, and stirred for 24 h at room temperature. The reaction was diluted with 10 mL EA, washed with 20 mL H_2O, 20 mL sat. brine, dried over Na_2SO_4, and concentrated in vacuo to afford crude 3-acetyl-4-methoxybenzonitrile, which was directly used for the next step without further purification.

Following **GP4a**, crude 3-acetyl-4-methoxybenzonitrile, $NaBH_4$ (227 mg, 6 mmol) in 15 mL MeOH solution were stirred for 3 h at 0ºC. Purification by silica gel chromatography with PE/EA (2:1) as eluting solvent afforded 3-(1-hydroxyethyl)-4-methoxybenzonitrile **1l** as a colorless solid (483 mg, 91%).

Mp: 95ºC

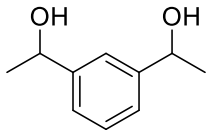
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 2.1 Hz, 1H), 7.55 (dd, J = 8.6, 2.1 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 5.11 (q, J = 6.4 Hz, 1H), 3.91 (s, 3H), 2.42 (br, 1H), 1.46 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.42, 135.33, 132.96, 129.86, 119.27, 110.76, 104.06, 64.98, 55.68, 23.01.

IR (EXTRACT): ṽ = 3234.74, 2977.50, 2929.08, 2849.15, 2223.54, 1602.48, 1493.21, 1456.64, 1439.44, 1369.01, 1347.42, 1320.92, 1294.92, 1258.01, 1188.21, 1161.28,

1134.83, 1072.76, 1018.51, 929.25, 911.05, 877.54, 830.79, 819.30, 766.65, 680.80, 614.10 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 177.0784, found 177.0774.

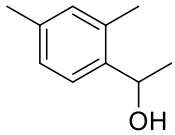
1,1'-(1,3-Phenylene)bis(ethan-1-ol) (1m) spectral data were in agreement with literature values[27]



Following **GP4a**, 1,1'-(1,3-phenylene)bis(ethan-1-one) (487 mg, 3 mmol), $NaBH_4$ (227 mg, 6 mmol) in 10 mL MeOH solution were stirred for 3 h at 0ºC. Purification by silica gel chromatography with PE/EA (2:1) as eluting solvent afforded 1,1'-(1,3-phenylene)bis(ethan-1-ol) **1m** as a colorless liquid (396 mg, 80%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 1H), 7.33 – 7.29 (m, 1H), 7.26 – 7.22 (m, 2H), 4.86 (q, *J* = 6.4 Hz, 2H), 2.27 (br, 2H), 1.47 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.08, 146.06, 128.58, 124.50, 124.47, 122.41, 122.35, 70.31, 70.29, 25.12, 25.10.

1-(2,4-Dimethylphenyl)ethan-1-ol (1n) spectral data were in agreement with literature values[28]

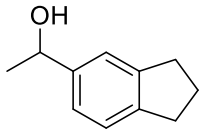


Following **GP4a**, 1-(2,4-dimethylphenyl)ethan-1-one (741 mg, 5 mmol), $NaBH_4$ (227 mg, 6 mmol) in 15 mL MeOH solution were stirred for 3 h at 0ºC. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 1-(2,4-dimethylphenyl)ethan-1-ol **1n** as a colorless liquid (746 mg, 99%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 6.97 (s, 1H), 5.10 (q, *J* = 6.4 Hz, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 1.73 (br, 1H), 1.47 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.85, 136.74, 134.16, 131.15, 126.96,

124.47, 66.69, 23.92, 20.90, 18.80.

1-(2,3-Dihydro-1*H*-inden-5-yl)ethan-1-ol (1o)



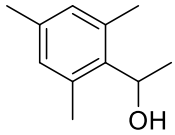
Following **GP4a**, 1-(2,3-dihydro-1*H*-inden-5-yl)ethan-1-one (800 mg, 5 mmol), $NaBH_4$ (227 mg, 6 mmol) in 10 mL MeOH solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 1-(2,3-dihydro-1*H*-inden-5-yl)ethan-1-ol **1o** as a colorless liquid (640 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 4.88 (q, *J* = 6.4 Hz, 1H), 2.91 (td, *J* = 7.4, 3.6 Hz, 4H), 2.09 (p, *J* = 7.4 Hz, 2H), 1.84 (br, 1H), 1.50 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.58, 143.86, 143.57, 124.30, 123.37, 121.39, 70.53, 32.78, 32.52, 25.50, 25.15.

IR (EXTRACT): $\tilde{\nu}$ = 3348.20, 3006.72, 2966.29, 2888.90, 2866.10, 2843.17, 1889.66, 1764.66, 1613.50, 1581.67, 1490.88, 1438.72, 1367.50, 1338.47, 1293.16, 1262.40, 1232.27, 1193.14, 1141.37, 1072.03, 1009.50, 926.37, 876.04, 821.24, 780.34, 709.84 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 162.1039 found 162.1034.

1-Mesitylethan-1-ol (1p) spectral data were in agreement with literature values[29]

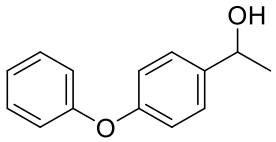


Following **GP4c**, 1-mesitylethan-1-one (811 mg, 5 mmol), $LiAlH_4$ (949 mg, 25 mmol) in 20 mL THF solution were refluxed for 24 h. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 1-mesitylethan-1-ol **1p** as a colorless solid (820 mg, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 2H), 5.37 (q, *J* = 6.7 Hz, 1H), 2.42 (s, 6H), 2.25 (s, 3H), 1.64 (br, 1H), 1.53 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.63,

136.40, 135.62, 130.11, 67.46, 21.57, 20.66, 20.48.

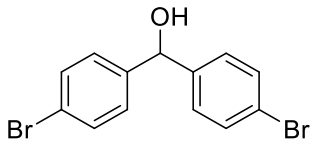
1-(4-Phenoxyphenyl)ethan-1-ol (1r) spectral data were in agreement with literature values[30]



Following **GP4a**, 1-(4-phenoxyphenyl)ethan-1-one (636 mg, 3 mmol), $NaBH_4$ (227 mg, 6 mmol) in 10 mL MeOH solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 1-(4-phenoxyphenyl)ethan-1-ol **1r** as a colorless liquid (640 mg, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 4H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.03 – 6.97 (m, 4H), 4.90 (q, *J* = 6.4 Hz, 1H), 1.76 (br, 1H), 1.51 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.23, 156.54, 140.63, 129.71, 126.85, 123.22, 118.83, 118.81, 69.92, 25.13.

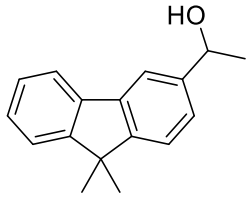
Bis(4-bromophenyl)methanol (1t) spectral data were in agreement with literature values[31]



Following **GP4a**, bis(4-bromophenyl)methanone (850 mg, 2.5 mmol), $NaBH_4$ (113 mg, 3 mmol) in 10 mL MeOH solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded bis(4-bromophenyl)methanol **1t** as a colorless liquid (848 mg, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 4H), 7.22 (d, *J* = 8.4 Hz, 4H), 5.75 (d, *J* = 2.9 Hz, 1H), 2.28 (d, *J* = 2.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.24, 131.70, 128.17, 121.74, 75.02.

1-(9,9-Dimethyl-9*H*-fluoren-3-yl)ethan-1-ol (1u)



Following **GP4b**, 9,9-dimethyl-9*H*-fluorene (388 mg, 2.0 mmol), acetyl chloride (427 uL, 6 mmol) and $AlCl_3$ (800 mg, 6 mmol) in 15 mL DCM solution were stirred for 3 h at 0°C. Simple workup afforded the crude 1-(9,9-dimethyl-9*H*-fluoren-3-yl)ethan-1-one, which was directly used for the next step without further purification.

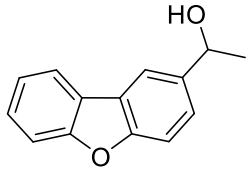
The crude 1-(9,9-dimethyl-9*H*-fluoren-3-yl)ethan-1-one, $NaBH_4$ (91 mg, 2.4 mmol) in 5 mL MeOH solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 1-(9,9-dimethyl-9*H*-fluoren-3-yl)ethan-1-ol **1u** as a colorless oil (424 mg, 89%)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.67 (m, 2H), 7.47 (d, *J* = 1.6 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.38 – 7.28 (m, 3H), 4.99 (q, *J* = 6.4 Hz, 1H), 1.83 (br, 1H), 1.57 (d, *J* = 6.4 Hz, 3H), 1.50 (s, 3H), 1.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.98, 153.76, 145.05, 138.88, 138.66, 127.14, 126.92, 124.34, 122.56, 119.91, 119.60, 70.76, 46.83, 27.16, 25.29.

IR (EXTRACT): ṽ = 3 3549.99, 3354.08, 3060.32, 3012.58, 2965.31, 2922.97, 2861.86, 1946.52, 1906.70, 1801.68, 1669.91, 1606.81, 1471.43, 1447.71, 1421.77, 1360.84, 1326.72, 1298.20, 1274.00, 1216.90, 1181.89, 1156.02, 1137.28, 1119.02, 1071.31, 1012.72, 938.15, 905.87, 832.06, 783.77, 758.76, 738.34, 707.60 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 238.1355, found 238.1350.

1-(Dibenzo[*b*,*d*]furan-2-yl)ethan-1-ol (1v) spectral data were in agreement with literature values[32]



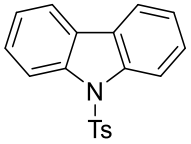
Following **GP4b**, dibenzo[*b*,*d*]furan (1.00 g, 6.0 mmol), acetyl chloride (498 uL, 6.6 mmol) and $AlCl_3$ (880 mg, 6.6 mmol) in 15 mL $CHCl_3$ solution were stirred for 4 h at

room temperature. Simple workup afforded the crude 1-(dibenzo[*b*,*d*]furan-2-yl)ethan-1-one, which was directly used for the next step without further purification.

The crude 1-(dibenzo[*b*,*d*]furan-2-yl)ethan-1-one, $NaBH_4$ (272 mg, 7.2 mmol) in 20 mL MeOH solution were stirred for 3 h at 0ºC. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 1-(dibenzo[*b*,*d*]furan-2-yl)ethan-1-ol **1v** as a colorless solid (406 mg, 32%)

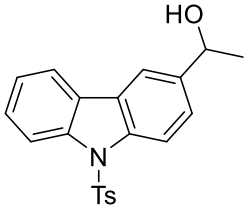
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.8 Hz, 1H), 7.95 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.50 – 7.42 (m, 2H), 7.35 (td, *J* = 7.6, 1.0 Hz, 1H), 5.07 (q, *J* = 6.4 Hz, 1H), 2.00 (br, 1H), 1.59 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.57, 155.58, 140.55, 127.18, 124.76, 124.27, 124.14, 122.70, 120.62, 117.43, 111.68, 111.48, 70.50, 25.64.

9-Tosyl-9*H*-carbazole was prepared according to a published procedure; spectral data were in agreement with literature values[7]



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J = 8.4 Hz, 2H), 7.90 (dd, J = 7.7, 0.9 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.49 (td, J = 7.7, 0.9 Hz, 2H), 7.36 (td, J = 7.7, 0.9 Hz, 2H), 7.08 (d, J = 7.7 Hz, 2H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.82, 138.38, 134.99, 129.61, 127.35, 126.45, 126.36, 123.85, 119.96, 115.14, 21.45.

1-(9-Tosyl-9*H*-carbazol-3-yl)ethan-1-ol (1w)



Following **GP4b**, 9-tosyl-9*H*-carbazole (321 mg, 1.0 mmol), acetyl chloride (90 uL, 1.2 mmol) and $AlCl_3$ (160 mg, 1.2 mmol) in 5 mL DCE solution were stirred for 4 h at 0ºC. Simple workup afforded the crude 1-(9-tosyl-9*H*-carbazol-3-yl)ethan-1-one,

which was directly used for the next step without further purification.

The crude 1-(9-tosyl-9*H*-carbazol-3-yl)ethan-1-one, $NaBH_4$ (113 mg, 3 mmol) in 6 mL THF/H_2O (5:1) solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (2:1) as eluting solvent afforded 1-(9-tosyl-9*H*-carbazol-3-yl)ethan-1-ol **1w** as a colorless solid (147 mg, 40%)

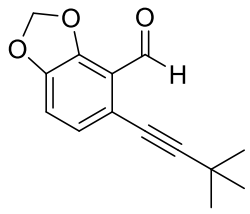
Mp: 59°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.4 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 1.7 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.51 – 7.44 (m, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 2H), 5.05 (q, *J* = 6.5 Hz, 1H), 2.25 (s, 3H), 2.04 (br, 1H), 1.57 (d, *J* = 6.5 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 144.84, 141.64, 138.67, 137.68, 134.93, 129.63, 127.40, 126.47, 126.45, 126.28, 124.99, 123.87, 119.98, 116.72, 115.10, 115.04, 70.29, 25.50, 21.46.

IR (EXTRACT): ṽ = 3546.22, 2972.78, 2926.28, 2872.96, 1911.69, 1798.83, 1711.58, 1597.97, 1484.33, 1444.30, 1366.10, 1305.90, 1227.75, 1207.33, 1170.69, 1154.28, 1117.55, 1089.33, 1032.29, 1020.23, 976.74, 898.56, 812.07, 771.31, 748.48, 703.29, 685.72, 659.77, 628.82 cm^{-1}

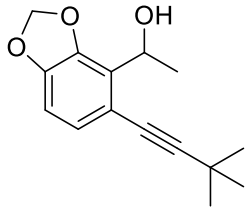
HRMS (EI+) m/z: $[M]^+$ calcd 365.1080, found 365.1062.

5-(3,3-Dimethylbut-1-yn-1-yl)benzo[*d*][1,3]dioxole-4-carbaldehyde was prepared according to a published procedure; spectral data were in agreement with literature values[33]



^{1}H NMR (300 MHz, $CDCl_3$) δ 10.42 (s, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.13 (s, 2H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.72, 148.29, 147.46, 126.90, 119.76, 119.26, 112.70, 103.67, 102.95, 74.72, 30.80, 28.21.

1-(5-(3,3-Dimethylbut-1-yn-1-yl)benzo[*d*][1,3]dioxol-4-yl)ethan-1-ol (1x)



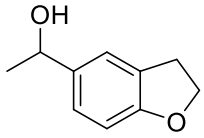
Following **GP4d**, 5-(3,3-dimethylbut-1-yn-1-yl)benzo[*d*][1,3]dioxole-4-carbaldehyde (322 mg, 1.4 mmol), 3.0 M CH_3MgBr (0.84 mL, 2.52 mmol) in 10 mL THF solution were stirred overnight at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 1-(5-(3,3-dimethylbut-1-yn-1-yl)benzo[*d*][1,3]dioxol-4-yl)ethan-1-ol **1x** as a yellow oil (342 mg, 100%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.11 – 5.87 (m, 2H), 5.20 (dq, *J* = 9.1, 6.7 Hz, 1H), 2.88 (d, *J* = 9.1 Hz, 1H), 1.58 (d, *J* = 6.7 Hz, 3H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.32, 144.15, 128.40, 126.67, 114.57, 107.13, 101.71, 101.25, 76.68, 67.00, 30.91, 28.11, 23.01.

IR (EXTRACT): ṽ = 3548.28, 3441.36, 2969.22, 2927.99, 2898.62, 2868.30, 2781.11, 1627.50, 1596.48, 1500.44, 1469.49, 1392.01, 1362.69, 1322.35, 1243.04, 1215.05, 1200.55, 1098.19, 1035.12, 990.45, 959.73, 931.32, 881.05, 865.82, 807.07, 775.27, 743.82, 640.13 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 246.1251, found 246.1240.

1-(2,3-Dihydrobenzofuran-5-yl)ethan-1-ol (1y)



Following **GP4a**, 1-(2,3-dihydrobenzofuran-5-yl)ethan-1-one (800 mg, 5 mmol), $NaBH_4$ (378 mg, 10 mmol) in 10 mL MeOH solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 1-(2,3-dihydrobenzofuran-5-yl)ethan-1-ol **1y** as a colorless oil (640 mg, 78%).

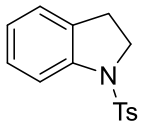
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 1.9 Hz, 1H), 7.09 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 4.83 (q, *J* = 6.4 Hz, 1H), 4.56 (t, *J* = 8.6 Hz, 2H), 3.20 (t, *J* = 8.6 Hz, 2H), 1.83 (br, 1H), 1.47 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ

159.50, 138.04, 127.20, 125.38, 122.17, 108.95, 71.29, 70.24, 29.68, 25.09.

IR (EXTRACT): $\tilde{\nu}$ = 3270.02, 2968.76, 2894.62, 1612.88, 1490.11, 1434.95, 1410.68, 1367.91, 1347.25, 1320.98, 1304.89, 1288.00, 1231.04, 1134.72, 1103.48, 1070.58, 1011.37, 981.30, 945.46, 920.98, 896.57, 880.11, 825.91, 791.07, 733.33, 672.21, 607.21 cm^{-1}

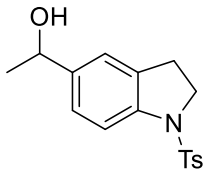
HRMS (EI+) m/z: $[M]^+$ calcd 164.0832, found 164.0821.

1-Tosylindoline was prepared according to a published procedure; spectral data were in agreement with literature values[7]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.61 (m, 3H), 7.25 – 7.14 (m, 3H), 7.07 (d, *J* = 7.3 Hz, 1H), 6.96 (td, *J* = 7.4, 0.8 Hz, 1H), 3.91 (t, *J* = 8.4 Hz, 2H), 2.88 (t, *J* = 8.4 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.99, 141.98, 134.02, 131.72, 129.61, 127.67, 127.29, 125.06, 123.67, 114.99, 49.90, 27.85, 21.50.

1-(1-Tosylindolin-5-yl)ethan-1-ol (1z)



Following **GP4b**, 1-tosylindoline (273 mg, 1.0 mmol), acetyl chloride (90 uL, 1.2 mmol) and $AlCl_3$ (160 mg, 1.2 mmol) in 5 mL DCE solution were stirred for 4 h at 0°C. Simple workup afforded the crude 1-(1-tosylindolin-5-yl)ethan-1-one, which was directly used for the next step without further purification.

The crude 1-(1-tosylindolin-5-yl)ethan-1-one, $NaBH_4$ (113 mg, 3 mmol) in 6 mL THF/H_2O (5:1) solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (2:1) as eluting solvent afforded 1-(1-tosylindolin-5-yl)ethan-1-ol **1z** as a yellow oil (305 mg, 96%)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.22

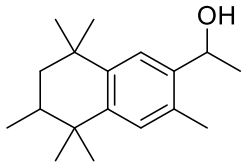
(d, *J* = 8.2 Hz, 2H), 7.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.11 (d, *J* = 1.8 Hz, 1H), 4.82 (q, *J* = 6.4 Hz, 1H), 3.90 (t, *J* = 8.4 Hz, 2H), 2.88 (t, *J* = 8.4 Hz, 2H), 2.37 (s, 3H), 1.83 (br, 1H), 1.44 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.02, 141.33, 141.31, 133.93, 132.03, 129.64, 127.30, 125.07, 122.24, 114.63, 69.97, 50.07, 27.81, 25.14, 21.50.

IR (EXTRACT): ṽ = 3539.14, 3064.62, 2971.59, 2924.92, 2873.82, 1920.31, 1709.98, 1612.42, 1597.09, 1485.19, 1443.45, 1399.44, 1357.43, 1305.26, 1293.56, 1248.09, 1185.15, 1169.60, 1110.01, 1092.48, 1017.42, 974.79, 923.69, 893.01, 831.20, 815.81, 735.55, 707.42, 663.26, 614.71cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 317.1080, found 317.1059.

1-(3,5,5,6,8,8-Hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethan-1-ol (1aa)

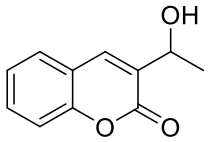
spectral data were in agreement with literature values[34]



Following **GP4a**, 1-(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethan-1-one (517 mg, 2 mmol), $NaBH_4$ (151 mg, 4 mmol) in 6 mL THF/MeOH (5:1) solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 1-(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethan-1-ol **1aa** as a colorless oil (520 mg, 100%).

major + minor diastereoisomers ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 2.6 Hz, 1H), 7.12 (s, 1H), 5.08 (qd, *J* = 6.4, 2.6 Hz, 1H), 2.32 (s, 3H), 1.87 (dqd, *J* = 13.2, 6.6, 2.6 Hz, 1H), 1.70 (br, 1H), 1.64 (t, *J* = 13.2 Hz, 1H), 1.49 (dd, *J* = 6.4, 4.8 Hz, 3H), 1.37 (td,*J* = 13.2, 2.2 Hz, 1H), 1.33 (d, *J* = 3.9 Hz, 4H), 1.31 (s, 3H), 1.27 (d, *J* = 2.2 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.92, 142.76, 142.70, 140.90, 140.84, 131.46, 128.87, 128.80, 122.48, 122.38, 67.04, 43.77, 37.40, 34.60, 34.53, 34.23, 32.45, 32.37, 32.09, 32.06, 28.69, 28.44, 24.97, 24.92, 23.83, 23.72, 18.70, 16.81.

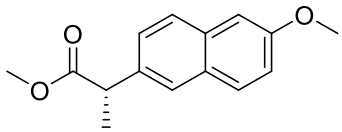
3-(1-Hydroxyethyl)-2*H*-chromen-2-one (1ab) spectral data were in agreement with literature values[35]



To a mixture of 3-acetyl-2*H*-chromen-2-one (564 mg, 3mmol), $CeCl_3$ (739 mg, 3 mmol) in 10 mL THF was added $NaBH_4$ (113 mg, 3 mmol) at 0°C, and the reaction was stirred at 0°C for 4 h. The mixture was filtrated, concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA (3:1) as eluting solvent to afford 3-(1-hydroxyethyl)-2*H*-chromen-2-one **1ab** as a colorless liquid (285 mg, 50%)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.49 – 7.42 (m, 2H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.24 – 7.18 (m, 1H), 4.87 (q, *J* = 6.5 Hz, 1H), 3.01 (br, 1H), 1.50 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.20, 153.03, 137.24, 132.01, 131.29, 127.93, 124.57, 119.09, 116.46, 66.05, 21.85.

Methyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate spectral data were in agreement with literature values[7]

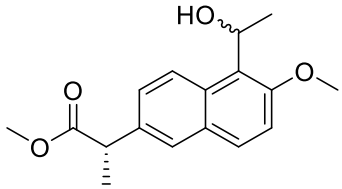


To 10 mL MeOH in a round bottom flask was added (*s*)-(+)-naproxen chloride (496 mg, 0.2 mmol) at room temperature, then it was stirred at room temperature for 2 h. The reaction was concentrated in vacuo, and the residue was purified by silica gel chromatography with PE/EA (10:1) as eluting solvent to afford methyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate as a colorless solid (463 mg, 95%)**.**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.69 (s, 1H), 7.67 (d, *J* = 1.5 Hz, 1H), 7.41 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.17 – 7.10 (m, 2H), 3.91 (s, 3H), 3.85 (q, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 1.59 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.11, 157.62, 135.65, 133.67, 129.24, 128.90, 127.15, 126.15, 125.90, 118.96, 105.57, 55.27,

52.00, 45.31, 18.56.

Methyl (2*S*)-2-(5-(1-hydroxyethyl)-6-methoxynaphthalen-2-yl)propanoate (1ac)



Following **GP4b**, methyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate (244 mg, 1.0 mmol), acetyl chloride (0.21 mL, 3.0 mmol) and $AlCl_3$ (400 mg, 3 mmol) in 5 mL DCE solution were stirred for 4 h at 0ºC. Simple workup afforded the crude methyl (*S*)-2-(5-acetyl-6-methoxynaphthalen-2-yl)propanoate, which was directly used for the next step without further purification.

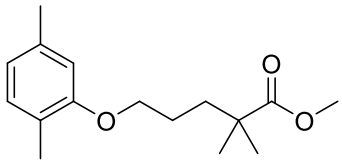
The crude methyl (*S*)-2-(5-acetyl-6-methoxynaphthalen-2-yl)propanoate, $NaBH_4$ (90 mg, 2.4 mmol) in 6 mL THF/MeOH (5:1) solution was stirred for 3 h at 0ºC. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded methyl (2*S*)-2-(5-(1-hydroxyethyl)-6-methoxynaphthalen-2-yl)propanoate **1ac** as a yellow oil (181 mg, 63% for two steps)

major + minor diastereoisomers ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.1 Hz, 1H), 7.75 (d, *J* = 9.1 Hz, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.44 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.28 (d, *J* = 9.0 Hz, 1H), 5.77– 5.66 (m, 1H), 4.00 (s, 3H), 3.90 (br, 1H), 3.86 (q, *J* = 7.1 Hz, 1H), 3.67 (s, 3H), 1.65 (d, *J* = 6.8 Hz, 3H), 1.58 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.98, 154.22, 135.62, 135.60, 130.37, 129.37, 128.93, 126.73, 126.67, 126.52, 126.44, 125.56, 123.40, 123.38, 113.64, 66.04, 56.36, 52.04, 45.12, 45.10, 23.76, 18.45, 18.39.

IR (EXTRACT): ṽ = 3528.45, 3440.74, 2975.41, 2950.34, 2841.16, 1733.51, 1627.72, 1598.87, 1504.27, 1480.40, 1454.76, 1373.64, 1329.36, 1247.76, 1197.33, 1163.68, 1116.15, 1075.68, 1023.81, 995.91, 972.81, 921.29, 886.81, 830.13, 804.67, 761.08, 692.56, 662.89, 613.05 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 288.1356, found 288.1347.

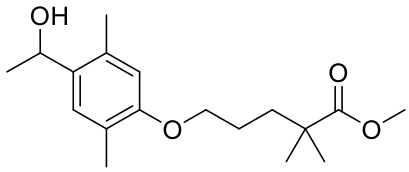
Methyl 5-(2,5-dimethyl phenoxy)-2,2-dimethyl pentanoate spectral data were in agreement with literature values[7]



To a suspension of methyl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (gemfibrozil, 300 mg, 1.2 mmol) and K_2CO_3 (216 mg, 1.56 mmol) in 3 mL DMF was added CH_3I (276 mg, 2.4 mmol) at room temperature and the reaction was stirred overnight. Then the reaction was diluted with 10 mL EA and washed with sat. brine (10 mL × 3). The organic layer was dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA (30:1) as eluting solvent to afford the methyl 5-(2,5-dimethyl phenoxy)-2,2-dimethyl pentanoate as a colorless liquid (298 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 7.4 Hz, 1H), 6.66 (d, *J* = 7.4 Hz, 1H), 6.61 (s, 1H), 3.94 – 3.91(m, 2H), 3.67 (s, 3H), 2.31 (s, 3H), 2.18 (s, 3H), 1.74 – 1.71 (m, 4H), 1.23 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.30, 156.92, 136.41, 130.26, 123.56, 120.65, 111.92, 67.86, 51.69, 42.08, 37.09, 25.17, 25.16, 21.37, 15.71.

Methyl 5-(4-(1-hydroxyethyl)-2,5-dimethylphenoxy)-2,2-dimethylpentanoate (1ad) spectral data were in agreement with literature values[3b]



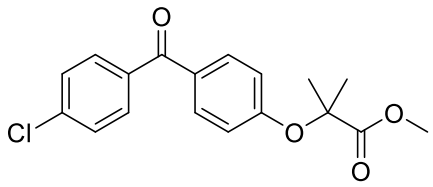
Following **GP4b**, methyl 5-(2,5-dimethyl phenoxy)-2,2-dimethyl pentanoate (205 mg, 0.78 mmol), acetyl chloride (0.17 mL, 2.4 mmol) and $AlCl_3$ (320 mg, 2.4 mmol) in 5 mL DCE solution were stirred for 4 h at 0°C. Simple workup afforded the crude methyl 5-(4-acetyl-2,5-dimethylphenoxy)-2,2-dimethylpentanoate, which was directly used for the next step without further purification.

The crude methyl 5-(4-acetyl-2,5-dimethylphenoxy)-2,2-dimethylpentanoate, $NaBH_4$ (72 mg, 1.9 mmol) in 5 mL MeOH solution were stirred for 3 h at 0°C. Purification by

silica gel chromatography with PE/EA (10:1) as eluting solvent afforded methyl 5-(4-(1-hydroxyethyl)-2,5-dimethylphenoxy)-2,2-dimethylpentanoate **1ad** as a colorless oil (200 mg, 83%)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (s, 1H), 6.55 (s, 1H), 5.06 (q, *J* = 6.4 Hz, 1H), 4.05 – 3.80 (m, 2H), 3.66 (s, 3H), 2.30 (s, 3H), 2.20 (s, 3H), 1.95 – 1.66 (m, 4H), 1.65 (br, 1H), 1.44 (d, *J* = 6.4 Hz, 3H), 1.22 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.29, 155.99, 135.17, 132.69, 126.98, 124.42, 113.01, 68.05, 66.49, 51.70, 42.07, 37.06, 25.16, 25.14, 23.99, 18.84, 15.80.

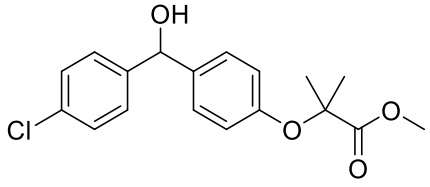
Methyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate



To a solution of 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoic acid (956 mg, 3 mmol) in 30 mL MeOH was dropwise added $SOCl_2$ (1.09 mL, 15 mmol) at 0ºC, then the reaction was warmed up to room temperature and stirred overnight. The reaction was concentrated in vacuo, and the residue was purified by silica gel chromatography with PE/EA (10:1) as eluting solvent to afford methyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate as a colorless solid (990 mg, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.9 Hz, 2H), 7.70 (s, d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 3.77 (s, 3H), 1.67 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.19, 174.20, 159.55, 138.38, 136.34, 132.02, 131.15, 130.48, 128.53, 117.30, 79.35, 52.68, 25.39.

Methyl 2-(4-((4-chlorophenyl)(hydroxy)methyl)phenoxy)-2-methylpropanoate (1ae)



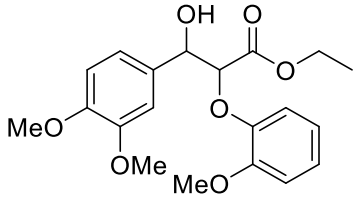
Following **GP4a**, methyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate (665 mg, 2.0 mmol), $NaBH_4$ (151 mg, 4.0 mmol) in 10 mL MeOH solution were stirred for 3 h at 0ºC. Purification by silica gel chromatography with PE/EA (8:1) as eluting solvent afforded methyl 2-(4-((4-chlorophenyl)(hydroxy)methyl)phenoxy)-2-methylpropanoate **1ae** as a colorless liquid (666 mg, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 4H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 5.75 (s, 1H), 3.75 (s, 3H), 2.25 (br, 1H), 1.58 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.72, 154.98, 142.23, 137.14, 133.16, 128.52, 127.79, 127.62, 119.00, 79.09, 75.10, 52.50, 25.33, 25.31.

IR (EXTRACT): ṽ = 3505.56, 2993.62, 2950.71, 2874.03, 1904.78, 1736.44, 1608.44, 1583.70, 1507.48, 1489.22, 1466.18, 1436.05, 1404.33, 1383.97, 1365.82, 1289.67, 1239.64, 1175.95, 1145.83, 1089.37, 1038.61, 1013.31, 962.72, 891.23, 828.76, 800.92, 775.01, 735.29, 686.17, 619.33 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 334.0966, found 334.0951.

Ethyl 3-(3,4-dimethoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propanoate spectral data were in agreement with literature values[36]

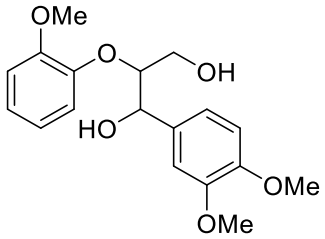


To a shrank flask with 15 mL THF was slowly added 2 M LDA (8.25 mL, 16.5 mmol) at -78ºC under N_2 atmosphere, then it's stirred for 15 min at -78ºC. Then ethyl 2-(2-methoxyphenoxy)acetate (3.15 g, 15 mmol) in 30 mL THF solution was dropwise added to the above mixture at -78ºC, then the mixture was stirred for 10 min at -78ºC. A solution of 3,4-dimethoxybenzaldehyde (2.49 g, 15 mmol) in 30 mL THF solution was dropwise added to the above mixture at -78ºC and the reaction was stirred for 2 h. The reaction was warmed up to room temperature, and quenched with 20 mL H_2O, extracted with EA (80 mL × 3), then the combined organic layers were washed with 100 mL 1N HCl aq., 100 mL sat. brine, concentrated in vacuo. the residue was purified

by silica gel chromatography with PE/EA (2:1) as eluting solvent to afford ethyl 3-(3,4-dimethoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propanoate as a colorless solid (3.70 g, 66%).

major + minor diastereoisomers ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 6.66 (m, 7H), 5.14 and 5.06 (d, *J* = 5.0 Hz and d, *J* = 7.1 Hz, 1H), 4.74 and 4.49 (d, *J* = 5.0 Hz and d, *J* = 7.1 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 1H), 4.11 – 3.99 (m, 1H), 3.90 – 3.82 (m, 9H), 1.15 and 1.07 (t, *J* = 7.1 Hz and t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.38, 169.31, 150.59, 150.39, 149.12, 148.97, 148.81, 148.75, 147.34, 147.26, 131.74, 130.61, 123.89, 121.08, 121.04, 119.62, 119.31, 118.89, 118.28, 112.32, 112.29, 110.79, 110.76, 110.21, 110.08, 85.51, 83.89, 74.84, 73.81, 61.18, 61.16, 55.88, 55.86, 55.83, 55.79, 14.03, 13.89.

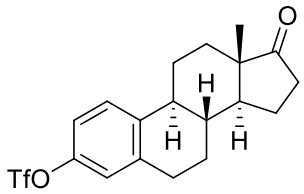
1-(3,4-Dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol (1af) spectral data were in agreement with literature values[37]



Following **GP4c**, ethyl 3-(3,4-dimethoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propanoate (1.88 g, 5 mmol), $LiAlH_4$ (474 mg, 12.5 mmol) in 40 mL THF solution were refluxed for 2 h. Purification by silica gel chromatography with PE/EA (1:1) as eluting solvent afforded 1-(3,4-dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol **1af** as a colorless oil (1.65 g, 99%).

major + minor diastereoisomers ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 – 6.76 (m, 7H), 5.00 – 4.99 (m, 1H), 4.20 – 4.07 (m, 1H), 3.95 – 3.90 (m, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.72 – 3.44 (m, 1H), 2.60 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.59, 151.30, 149.08, 149.02, 148.90, 148.46, 147.58, 146.88, 132.45, 132.09, 124.25, 124.20, 121.67, 121.61, 121.04, 121.00, 119.60, 118.38, 112.16, 111.01, 109.89, 109.20, 89.47, 87.39, 73.90, 72.67, 61.02, 60.73, 55.88, 55.86.

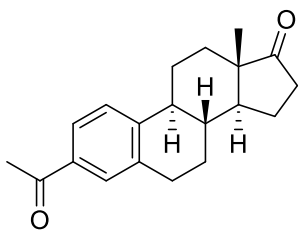
(8*R*,9*S*,13*S*,14*S*)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl trifluoromethanesulfonate spectral data were in agreement with literature values[38]



To a solution of estrone (1.0 g, 3.7 mmol), pyridine (0.6 mL, 7.4 mmol) in 20 mL DCM was dropwise added Tf_2O (0.75 mL, 4.4 mmol) at 0°C, and the reaction was stirred at 0°C for 2 h. The reaction was quenched with 20 mL H_2O, extracted with DCM (20 mL × 3), and the combined organic layers were washed with 30 mL sat. brine, dried over Na_2SO_4, concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA (10:1) as eluting solvent to afford (8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl trifluoromethanesulfonate as a colorless solid (1.48 g, 99%)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.6 Hz, 1H), 7.03 (dd, *J* = 8.6, 2.8 Hz, 2H), 6.99 (d, *J* = 2.8 Hz, 1H), 2.94 (dd, *J* = 8.9, 4.3 Hz, 3H), 2.52 (dd, *J* = 18.3, 8.4 Hz, 1H), 2.45 – 2.25 (m, 2H), 2.22 – 1.94 (m, 4H), 1.77 – 1.36 (m, 6H), 0.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.36, 147.56, 140.25, 139.27, 127.16, 121.20, 118.72 (q, *J* = 320.7 Hz), 118.27, 50.35, 47.82, 44.06, 37.72, 35.76, 31.45, 29.35, 26.05, 25.65, 21.53, 13.76. ^{19}F NMR (283 MHz, $CDCl_3$) δ -72.96.

(8*R*,9*S*,13*S*,14*S*)-3-Acetyl-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one spectral data were in agreement with literature values[39]

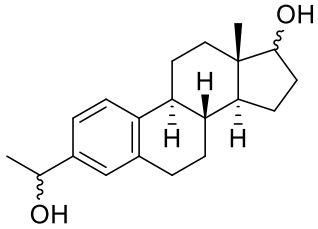


To a mixture of (8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-

decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl trifluoromethanesulfonate (603 mg, 1.5 mmol), 1-(vinyloxy)butane (775 uL, 6 mmol), $Pd(OAc)_2$ (33.6 mg, 0.15 mmol), dppp (68 mg, 0.165 mmol) in 5 mL anhydrous DMF was added Et_3N (417 uL, 3 mmol) under N_2 atmosphere at room temperature. Then the reaction was warmed up to 80°C, and stirred overnight. The reaction was cooled down to room temperature, and was quenched with 5 mL 2 M HCl aq., and stirred for 30 min. The mixture was filtrated with celite, extracted with EA (10 mL × 3), and the combined organic layers were washed with sat. brine (20 mL × 3), dried over Na_2SO_4, concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA (5:1) as eluting solvent to afford (8*R*,9*S*,13*S*,14*S*)-3-acetyl-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one as a colorless solid (381 mg, 86%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.69 (d, *J* = 1.9 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 2.96 (td, *J* = 6.9, 2.1 Hz, 2H), 2.57 (s, 3H), 2.55 – 2.47 (m, 1H), 2.47 – 2.28 (m, 2H), 2.22 – 1.90 (m, 4H), 1.73 – 1.40 (m, 6H), 0.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.40, 198.03, 145.42, 136.88, 134.86, 128.88, 125.80, 125.53, 50.51, 47.83, 44.68, 37.81, 35.75, 31.51, 29.26, 26.50, 26.25, 25.54, 21.54, 13.76.

(8*R*,9*S*,13*S*,14*S*)-3-(1-Hydroxyethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (1ag)



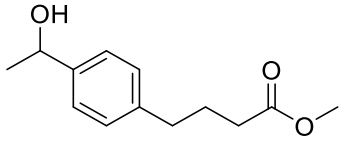
Following **GP4a**, (8*R*,9*S*,13*S*,14*S*)-3-acetyl-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (296 mg, 1 mmol), $NaBH_4$ (91 mg, 2.5 mmol) in 6 mL THF/H_2O (5:1) solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (3:1) as eluting solvent afforded (8*R*,9*S*,13*S*,14*S*)-3-(1-hydroxyethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol **1ag** as a colorless solid (287 mg, 96%).

Mp: 145°C

major + minor diastereoisomers ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 8.1 Hz, 1H), 7.11 (s, 1H), 4.84 (q, *J* = 6.4 Hz, 1H), 3.73 (t, *J* = 8.5 Hz, 1H), 3.07 – 2.80 (m, 2H), 2.42 – 2.33 (m, 1H), 2.28 – 2.20 (m, 1H), 2.18 – 2.07 (m, 1H), 2.01 – 1.86 (m, 2H), 1.77 – 1.67 (m, 1H), 1.65 (br, 1H), 1.59 – 1.51 (m, 1H), 1.49 (d, *J* = 6.4 Hz, 3H), 1.48 – 1.16 (m, 6H), 0.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.06, 139.65, 136.89, 126.00, 125.98, 125.53, 122.73, 122.71, 81.85, 70.20, 70.15, 50.15, 44.35, 43.21, 38.63, 36.72, 30.56, 29.60, 29.57, 27.19, 26.12, 24.93, 24.91, 23.11, 11.01. IR (EXTRACT): $\tilde{\nu}$ = 3737.20, 3372.69, 2909.71, 2868.41, 2848.07, 2359.45, 1498.42, 1449.09, 1380.65, 1360.21, 1339.26, 1318.94, 1264.01, 1245.62, 1214.74, 1157.16, 1136.04, 1090.30, 1076.40, 1055.61, 1021.23, 1010.44, 962.98, 920.10, 897.04, 862.57, 849.70, 818.22, 784.07, 718.17, 655.01, 609.07 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 300.2084, found 300.2085.

Methyl 4-(4-(1-hydroxyethyl)phenyl)butanoate (1an)



Following **GP4b**, methyl 4-phenylbutanoate (1.07 g, 10 mmol), acetyl chloride (0.91 mL, 12 mmol) and $AlCl_3$ (2.40 g, 18 mmol) in 30 mL DCM solution were stirred for overnight. Simple workup afforded the crude methyl 4-(4-acetylphenyl)butanoate, which was directly used for the next step without further purification.

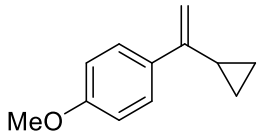
The crude methyl 4-(4-acetylphenyl)butanoate, $NaBH_4$ (454 mg, 12 mmol) in 20 mL MeOH solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded methyl 4-(4-(1-hydroxyethyl)phenyl)butanoate **1an** as a yellow oil (977 mg, 73% for two steps)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 4.87 (q, *J* = 6.5 Hz, 1H), 3.66 (s, 3H), 2.63 (t, *J* = 7.4 Hz, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.00 – 1.91 (m, 2H), 1.89 (br, 1H), 1.48 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.91, 143.50, 140.59, 128.56, 125.46, 70.17, 51.48, 34.72, 33.33, 26.43, 25.04.

IR (EXTRACT): $\tilde{\nu}$ = 3428.39, 2969.88, 2951.67, 2929.75, 2865.67, 1908.64, 1736.36, 1613.57, 1513.29, 1437.33, 1367.18, 1249.09, 1200.71, 1176.70, 1146.26, 1116.45, 1088.69, 1006.20, 897.20, 839.75, 818.32, 706.69 cm^{-1}

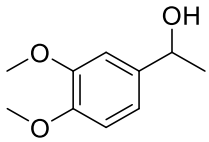
HRMS (EI+) m/z: $[M]^+$ calcd 222.1251, found 222.1241.

1-(1-Cyclopropylvinyl)-4-methoxybenzene was prepared according to a published procedure; spectral data were in agreement with literature values[40]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.20 (d, *J* = 1.1 Hz, 1H), 4.86 (t, *J* = 1.2 Hz, 1H), 3.82 (s, 3H), 1.68 – 1.57 (m, 1H), 1.00 – 0.75 (m, 2H), 0.63 – 0.49 (m, 2H).

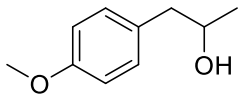
1-(3,4-Dimethoxyphenyl)ethan-1-ol (1at) spectral data were in agreement with literature values[37]



Following **GP4d**, 3,4-dimethoxybenzaldehyde (831 mg, 5.0 mmol), 3.0 M CH_3MgBr (2.0 mL, 6 mmol) in 10 mL THF solution were stirred overnight at room temperature. Purification by silica gel chromatography with PE/EA (3:1) as eluting solvent afforded 1-(3,4-dimethoxyphenyl)ethan-1-ol **1at** as a yellow oil (835 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J* = 2.0 Hz, 1H), 6.88 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 4.84 (q, *J* = 6.4 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 1.87 (br, 1H), 1.48 (d, *J* = 6.4 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 149.07, 148.37, 138.56, 117.50, 111.03, 108.69, 70.17, 55.92, 55.82, 25.04.

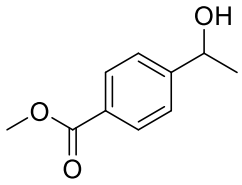
1-(4-Methoxyphenyl)propan-2-ol (1ah) spectral data were in agreement with literature values[41]



Following **GP4a**, 1-(4-methoxyphenyl)propan-2-one (821 mg, 5 mmol), $NaBH_4$ (227 mg, 6 mmol) in 10 mL MeOH solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 1-(4-methoxyphenyl)propan-2-ol **1ah** as a colorless oil (820 mg, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.05 – 3.89 (m, 1H), 3.79 (s, 3H), 2.80 – 2.46 (m, 2H), 1.61 (br, 1H), 1.23 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.27, 130.44, 130.30, 113.95, 68.90, 55.22, 44.81, 22.65.

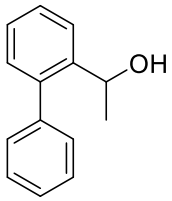
Methyl 4-(1-hydroxyethyl)benzoate (1av) spectral data were in agreement with literature values[42]



Following **GP4a**, methyl 4-acetylbenzoate (534 mg, 3 mmol), $NaBH_4$ (227 mg, 6 mmol) in 15 mL MeOH solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (3:1) as eluting solvent afforded methyl 4-(1-hydroxyethyl)benzoate **1av** as a colorless liquid (843 mg, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 4.94 (q, *J* = 6.5 Hz, 1H), 3.90 (s, 3H), 2.13 (br, 1H), 1.49 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.96, 150.94, 129.82, 129.17, 125.26, 69.93, 52.04, 25.25.

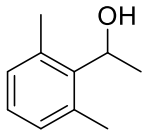
1-([1,1'-Biphenyl]-2-yl)ethan-1-ol (1ak) spectral data were in agreement with literature values[43]



Following **GP4d**, [1,1'-biphenyl]-2-carbaldehyde (547 mg, 3 mmol), 3.0 M CH_3MgBr (1.5 mL, 4.5 mmol) in 15 mL THF solution were stirred overnight at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 1-([1,1'-biphenyl]-2-yl)ethan-1-ol **1ak** as a yellow oil (511 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.46 – 7.36 (m, 4H), 7.36 – 7.29 (m, 3H), 7.22 (dd, *J* = 7.6, 1.4 Hz, 1H), 4.99 (q, *J* = 6.4 Hz, 1H), 1.73 (br, 1H), 1.42 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.05, 140.90, 140.32, 129.93, 129.25, 128.14, 127.96, 127.10, 127.08, 125.32, 66.44, 24.87.

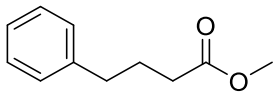
1-(2,6-Dimethylphenyl)ethan-1-ol (1al) spectral data were in agreement with literature values[44]



Following **GP4c**, 1-mesitylethan-1-one (593 mg, 4 mmol), $LiAlH_4$ (759 mg, 20 mmol) in 20 mL THF solution were refluxed for 36 h. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 1-(2,6-dimethylphenyl)ethan-1-ol **1al** as a colorless solid (586 mg, 98%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 – 6.96 (m, 3H), 5.39 (q, *J* = 6.8 Hz, 1H), 2.46 (s, 6H), 1.78 (br, 1H), 1.54 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.52, 135.66, 129.38, 126.91, 67.64, 21.43, 20.60.

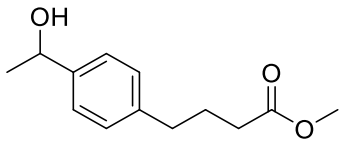
Methyl 4-phenylbutanoate spectral data were in agreement with literature values[45]



To a solution of 4-phenylbutanoic acid (1.64 g, 10 mmol) in 50 mL MeOH was dropwise added $SOCl_2$ (3.63 mL, 50 mmol) at 0°C, and then the reaction was stirred overnight at room temperature. The reaction was concentrated in vacuo, and the residue was purified by silica gel chromatography with PE/EA (10:1) as eluting solvent to afford methyl 4-phenylbutanoate as a colorless liquid (1.68 g, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 7.24 – 7.13 (m, 3H), 3.67 (s, 3H), 2.65 (t, *J* = 7.4 Hz, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 2.06 – 1.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.91, 141.34, 128.46, 128.36, 125.96, 51.47, 35.10, 33.37, 26.45.

Methyl 4-(4-(1-hydroxyethyl)phenyl)butanoate (1an)



Following **GP4b**, methyl 4-phenylbutanoate (1.07 g, 10 mmol), acetyl chloride (0.91 mL, 12 mmol) and $AlCl_3$ (2.40 g, 18 mmol) in 30 mL DCM solution were stirred for overnight. Simple workup afforded the crude methyl 4-(4-acetylphenyl)butanoate, which was directly used for the next step without further purification.

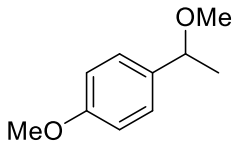
The crude methyl 4-(4-acetylphenyl)butanoate, $NaBH_4$ (454 mg, 12 mmol) in 20 mL MeOH solution were stirred for 3 h at 0°C. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded methyl 4-(4-(1-hydroxyethyl)phenyl)butanoate **1an** as a yellow oil (977 mg, 73% for two steps)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 4.87 (q, *J* = 6.5 Hz, 1H), 3.66 (s, 3H), 2.63 (t, *J* = 7.4 Hz, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.00 – 1.91 (m, 2H), 1.89 (br, 1H), 1.48 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.91, 143.50, 140.59, 128.56, 125.46, 70.17, 51.48, 34.72, 33.33, 26.43, 25.04.

IR (EXTRACT): $\tilde{\nu}$ = 3428.39, 2969.88, 2951.67, 2929.75, 2865.67, 1908.64, 1736.36, 1613.57, 1513.29, 1437.33, 1367.18, 1249.09, 1200.71, 1176.70, 1146.26, 1116.45, 1088.69, 1006.20, 897.20, 839.75, 818.32, 706.69 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 222.1251, found 222.1241.

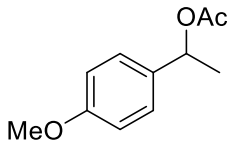
1-Methoxy-4-(1-methoxyethyl)benzene (11) spectral data were in agreement with literature values[46]



To a mixture of 1-(4-methoxyphenyl)ethan-1-ol (609 mg, 4.0 mmol) in 10 mL THF was slowly added 60% NaH (208 mg, 5.2 mmol) at 0ºC, and the mixture was stirred for 30min 0ºC. Then CH_3I (373 uL, 6.0 mmol) was added to the above mixture at 0ºC, and the reaction was warmed up to room temperature and stirred overnight. The reaction was quenched with 2 mL H_2O, extracted with EA (10 mL × 3), and the combined organic layers were washed with 20 mL sat. brine, dried over Na_2SO_4, filtrated and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA (20:1) as eluting solvent to afford the 1-methoxy-4-(1-methoxyethyl)benzene **11** as a colorless liquid (538 mg, 81%).

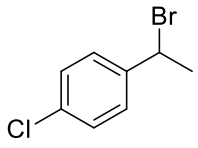
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.25 (q, *J* = 6.4 Hz, 1H), 3.81 (s, 3H), 3.20 (s, 3H), 1.42 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.98, 135.50, 127.39, 113.76, 79.09, 56.17, 55.23, 23.74.

1-(4-Methoxyphenyl)ethyl acetate (12) was prepared according to a published procedure; spectral data were in agreement with literature values[47]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.85 (q, *J* = 6.6 Hz, 1H), 3.80 (s, 3H), 2.05 (s, 3H), 1.52 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.36, 159.26, 133.73, 127.58, 113.81, 71.98, 55.25, 21.92, 21.38.

1-(1-Bromoethyl)-4-chlorobenzene (16) spectral data were in agreement with literature values[48]



To a solution of 1-(4-chlorophenyl)ethan-1-ol (470 mg, 3 mmol) in 10 mL DCM was slowly added PBr_3 (1.22 g, 4.5 mmol) at 0ºC, then it's warmed up to room temperature and stirred for 2 h. The reaction was quenched with 5 mL ice/water, extracted with

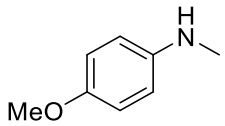
DCM (10 mL × 3), and the combined organic layers were washed with 20 mL sat. $NaHCO_3$ aq., 20 mL sat. brine, dried over Na_2SO_4, filtrated and concentrated in vacuo to afford 1-(1-bromoethyl)-4-chlorobenzene **16** as a colorless liquid (618 mg, 94%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 5.17 (q, *J* = 6.9 Hz, 1H), 2.03 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.75, 134.01, 128.84, 128.17, 48.18, 26.72.

3.4.3 Substrate Scope with Respect to Secondary Anilines

General Procedure for the Synthesis of Secondary Anilines – GP5

To a solution of the alcohol (0.2 mmol) in 1.0 mL HFIP was added aminating reagent (0.22 mmol) at room temperature under ambient atmosphere, unless otherwise stated. The reaction was stirred at room temperature for 12 h (monitored by GCMS or TLC). The reaction was diluted with 1 mL DCM and basified with 1 mL saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with DCM (3 mL × 3), and the combined organic layers were washed with 5 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA to afford the desired product.

4-Methoxy-*N*-methylaniline (3a) spectral data were in agreement with literature values[7]



Following **GP5**, 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-methylaniline **3a** as a yellow oil (20 mg, 74%).

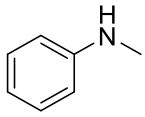
Following **GP5**, 2-(4-methoxyphenyl)propan-2-ol (**1f**, 33 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting

solvent afforded 4-methoxy-*N*-methylaniline **3a** as a yellow oil (25 mg, 96%).

Following **GP5**, 1-(4-methoxyphenyl)cyclohexan-1-ol (**1g**, 41 mg, 0.2 mmol), TsONHMe (**2a**, 52 mg, 0.26 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-methylaniline **3a** as a yellow oil (26 mg, 96%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 3.76 (s, 3H), 3.31 (br, 1H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.06, 143.68, 114.89, 113.61, 55.83, 55.81, 31.57.

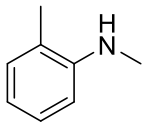
***N*-Methylaniline (3b)** spectral data were in agreement with literature values[49]



Following **GP5**, 1-phenylethan-1-ol (**1b**, 24 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-methylaniline **3b** as a yellow oil (10 mg, 48%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.14 (m, 2H), 6.78 – 6.66 (m, 1H), 6.63 (d, *J* = 8.7 Hz, 1H), 3.73 (br, 1H), 2.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.32, 129.18, 117.24, 112.40, 30.71.

***N*,2-Dimethylaniline (3c)** spectral data were in agreement with literature values[49]

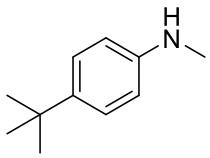


Following **GP5**, 1-(*o*-tolyl)ethan-1-ol (**1c**, 27 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded *N*,2-dimethylaniline **3c** as a yellow oil (13 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (td, *J* = 7.8, 1.4 Hz, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 6.68 (td, *J* = 7.4, 1.4 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 1H), 2.91 (s, 3H), 2.14 (s, 3H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ 147.22, 129.89, 127.17, 121.88, 116.85, 109.13, 30.75, 17.34.

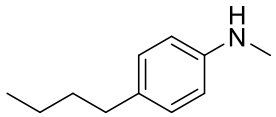
4-(*tert*-Butyl)-*N*-methylaniline (3d) spectral data were in agreement with literature values[7]



Following **GP5**, 1-(4-(*tert*-butyl)phenyl)ethan-1-ol (**1d**, 36 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 4-(*tert*-butyl)-*N*-methylaniline **3d** as a yellow oil (27 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2H), 6.60 (d, J = 8.7 Hz, 2H), 3.60 (br, 1H), 2.84 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.03, 140.06, 125.95, 112.20, 33.81, 31.54, 30.95.

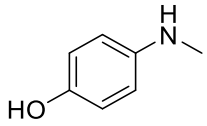
4-Butyl-*N*-methylaniline (3e) spectral data were in agreement with literature values[50]



Following **GP5**, 1-(4-butylphenyl)ethan-1-ol (**1e**, 36 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-butyl-*N*-methylaniline **3e** as a yellow oil (23 mg, 72%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 8.4 Hz, 2H), 6.58 (d, J = 8.4 Hz, 2H), 3.42 (br, 1H), 2.84 (s, 3H), 2.53 (t, J = 7.7 Hz, 2H), 1.71 – 1.49 (m, 2H), 1.43 – 1.27 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.27, 131.73, 129.04, 112.48, 34.69, 34.02, 31.01, 22.31, 13.96.

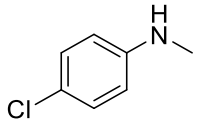
4-(Methylamino)phenol (3h) spectral data were in agreement with literature values[51]



Following **GP5**, 4-(1-hydroxyethyl)phenol (**1h**, 28 mg, 0.2 mmol), MsONHMe (**2b**, 28 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (3:1) as eluting solvent afforded 4-(methylamino)phenol **3h** as a yellow solid (16 mg, 59%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (d, *J* = 8.8 Hz, 2H), 6.55 (d, *J* = 8.8 Hz, 2H), 4.08 (br, 2H), 2.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.88, 143.39, 116.18, 114.11, 31.78.

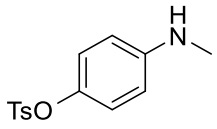
4-Chloro-*N*-methylaniline (3i) spectral data were in agreement with literature values[49]



Following **GP5**, 1-(4-chlorophenyl)ethan-1-ol (**1i**, 31 mg, 0.2 mmol), TsONHMe (44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-chloro-*N*-methylaniline **3i** as a yellow oil (24 mg, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.8 Hz, 2H), 6.57 (d, *J* = 8.8 Hz, 2H), 4.02 (br, 1H), 2.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.29, 129.04, 122.40, 113.88, 31.10.

4-(Methylamino)phenyl 4-methylbenzenesulfonate (3j)



Following **GP5**, 4-(1-hydroxyethyl)phenyl 4-methylbenzenesulfonate (**1j**, 58 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as

eluting solvent afforded 4-(methylamino)phenyl 4-methylbenzenesulfonate **3j** as a yellow solid (31 mg, 56%).

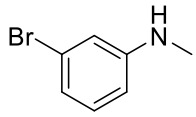
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 6.76 (d, *J* = 9.0 Hz, 2H), 6.43 (d, *J* = 9.0 Hz, 2H), 2.78 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.00, 144.95, 140.73, 132.55, 129.57, 128.57, 123.10, 112.39, 30.76, 21.66.

Mp: 88°C

IR (EXTRACT): ṽ = 3417.69, 2980.75, 2928.84, 2891.13, 2816.28, 1918.00, 1873.06, 1733.02, 1598.57, 1514.78, 1447.15, 1432.45, 1402.46, 1339.36, 1295.28, 1267.66, 1194.65, 1174.66, 1145.70, 1117.86, 1091.37, 1061.96, 1004.16, 852.41, 826.57, 807.28, 727.94, 705.43, 679.75, 633.95 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 277.0767, found 277.0759.

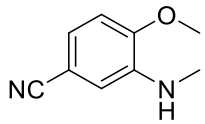
3-Bromo-*N*-methylaniline (3k) spectral data were in agreement with literature values[52]



Following **GP5**, 1-(3-bromophenyl)ethan-1-ol (**1k**, 40 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 3-bromo-*N*-methylaniline **3k** as a yellow oil (8 mg, 22%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (t, *J* = 8.1 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.73 (t, *J* = 2.1 Hz, 1H), 6.51 (dd, *J* = 8.1, 2.1 Hz, 1H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.52, 130.38, 123.28, 119.90, 114.76, 111.22, 30.49.

4-Methoxy-3-(methylamino)benzonitrile (3l)



Following **GP5**, 3-(1-hydroxyethyl)-4-methoxybenzonitrile (**1l**, 35 mg, 0.2 mmol),

TsONHMe (**2a**, 89 mg, 0.44 mmol) in 0.5 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-methoxy-3-(methylamino)benzonitrile **3l** as a colorless solid (19 mg, 59%).

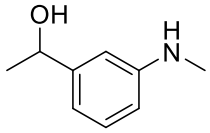
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 4.43 (br, 1H), 3.88 (s, 3H), 2.85 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.90, 139.64, 121.53, 120.22, 110.82, 108.78, 104.31, 55.57, 29.88.

Mp: 68ºC

IR (EXTRACT): ṽ = 3422.41, 3026.82, 2996.21, 2915.97, 2847.20, 2798.57, 2220.87, 1819.25, 1592.66, 1521.00, 1479.62, 1458.53, 1445.40, 1431.88, 1407.66, 1350.01, 1290.54, 1266.49, 1233.89, 1164.24, 1121.96, 1019.51, 936.31, 837.27, 799.49, 768.86, 684.28, 622.08 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 162.0788, found 162.0773.

1-(3-(Methylamino)phenyl)ethan-1-ol (3m)



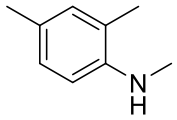
Following **GP5**, 1,1'-(1,3-phenylene)bis(ethan-1-ol) (**1m**, 33 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (2:1) as eluting solvent afforded 1-(3-(methylamino)phenyl)ethan-1-ol **3m** as a yellow solid (8 mg, 27%).

Following **GP5**, 1,1'-(1,3-phenylene)bis(ethan-1-ol) (**1m**, 33 mg, 0.2 mmol), TsONHMe (**2a**, 89 mg, 0.44 mmol) in 0.5 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (2:1) as eluting solvent afforded 1-(3-(methylamino)phenyl)ethan-1-ol **3m** as a yellow solid (14 mg, 47%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.64 (t, *J* = 1.9 Hz, 1H), 6.53 (dd, *J* = 7.8, 1.9 Hz, 1H), 4.82 (q, *J* = 6.4 Hz, 1H), 2.85 (s, 3H),

2.62 (br, 2H), 1.48 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.53, 147.08, 129.34, 114.31, 111.56, 109.27, 70.63, 30.75, 24.99.

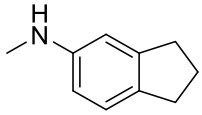
***N*,2,4-Trimethylaniline (3n)** spectral data were in agreement with literature values[7]



Following **GP5**, 1-(2,4-dimethylphenyl)ethan-1-ol (**1n**, 30 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded *N*,2,4-trimethylaniline **3n** as a yellow oil (20 mg, 74%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (dd, J = 8.0, 2.1 Hz, 1H), 6.91 (d, J = 2.1 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 3.51 (br, 1H), 2.90 (s, 3H), 2.26 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.77, 130.83, 127.35, 126.24, 122.22, 109.60, 31.16, 20.30, 17.30.

***N*-Methyl-2,3-dihydro-1*H*-inden-5-amine (3o)** spectral data were in agreement with literature values[7]

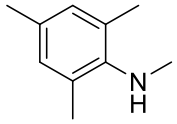


Following **GP5**, 1-(2,3-dihydro-1*H*-inden-5-yl)ethan-1-ol (**1o**, 32 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-methyl-2,3-dihydro-1*H*-inden-5-amine **3o** as a yellow oil (18 mg, 62%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 2.3 Hz, 1H), 6.45 (dd, J = 8.0, 2.3 Hz, 1H), 3.39 (br, 1H), 2.86 (t, J = 7.3 Hz, 2H), 2.84 (s, 3H), 2.83 (t, J = 7.3 Hz, 2H), 2.06 (p, J = 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.23, 145.36, 132.98, 124.66, 110.91, 108.58, 33.12, 31.89, 31.25, 25.70.

***N*,2,4,6-Tetramethylaniline (3p)** spectral data were in agreement with literature

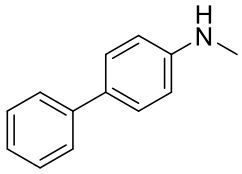
values[7]



Following **GP5**, 1-mesitylethan-1-ol (**1p**, 33 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*,2,4,6-tetramethylaniline **3p** as a yellow oil (20 mg, 67%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 2H), 2.82 (br, 1H), 2.75 (s, 3H), 2.28 (s, 6H), 2.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.80, 131.31, 129.50, 129.42, 35.56, 20.50, 18.11.

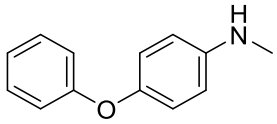
***N*-Methyl-[1,1'-biphenyl]-4-amine (3q)** spectral data were in agreement with literature values[53]



Following **GP5**, 1-([1,1'-biphenyl]-4-yl)ethan-1-ol (**1q**, 40 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-methyl-[1,1'-biphenyl]-4-amine **3q** as a yellow oil (29 mg, 80%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 2H), 7.48 (d, J = 7.9 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.28 (t, J = 7.9 Hz, 1H), 6.70 (d, J = 7.9 Hz, 2H), 3.81 (br, 1H), 2.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.71, 141.27, 130.09, 128.61, 127.87, 126.26, 125.98, 112.61, 30.73.

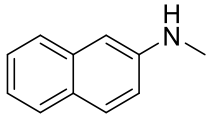
***N*-Methyl-4-phenoxyaniline (3r)** spectral data were in agreement with literature values[7]



Following **GP5**, 1-(4-phenoxyphenyl)ethan-1-ol (**1r**, 43 mg, 0.2 mmol), TsONHMe (**2a**, 52 mg, 0.26 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-methyl-4-phenoxyaniline **3r** as a yellow oil (23 mg, 58%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.04 – 6.96 (m, 1H), 6.93 (d, *J* = 8.8 Hz, 4H), 6.61 (d, *J* = 8.8 Hz, 2H), 3.60 (br, 1H), 2.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.15, 147.52, 146.00, 129.46, 121.85, 121.24, 117.01, 113.31, 31.20.

***N*-Methylnaphthalen-2-amine (3s)** spectral data were in agreement with literature values[7]



Following **GP5**, 1-(naphthalen-2-yl)ethan-1-ol (**1s**, 35 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-methylnaphthalen-2-amine **3s** as a yellow solid (24 mg, 77%).

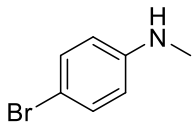
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.59 (m, 3H), 7.38 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.21 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 6.89 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 3.73 (br, 1H), 2.95 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.95, 135.26, 128.78, 127.61, 127.45, 126.27, 125.90, 121.86, 117.85, 103.73, 30.73.

4-Bromo-*N*-methylaniline (3t) and 4-bromobenzaldehyde (3t')

Following **GP5**, bis(4-bromophenyl)methanol (**1t**, 68 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature.

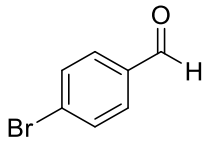
Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded 4-bromo-*N*-methylaniline **3t** as a yellow oil (32 mg, 86%) and 4-bromobenzaldehyde **3t'** as a colorless solid (26 mg, 70%).

4-Bromo-*N*-methylaniline (3t) spectral data were in agreement with literature values[50]



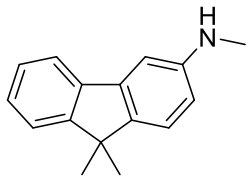
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 8.8 Hz, 2H), 3.60 (br, 1H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.24, 131.83, 113.90, 108.76, 30.67.

4-Bromobenzaldehyde (3t') spectral data were in agreement with literature values[54]



^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.03, 135.07, 132.43, 130.95, 129.77.

***N*,9,9-Trimethyl-9*H*-fluoren-3-amine (3u)** spectral data were in agreement with literature values[7]

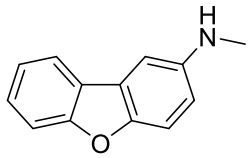


Following **GP5**, 1-(9,9-dimethyl-9*H*-fluoren-3-yl)ethan-1-ol (**1u**, 48 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*,9,9-trimethyl-9*H*-fluoren-3-amine **3u** as a yellow oil (28 mg, 61%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.4 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.30 (td, *J* = 7.4, 1.2 Hz, 2H), 7.21 (td, *J* = 7.4, 1.2 Hz, 1H), 6.68

(d, J = 2.2 Hz, 1H), 6.61 (dd, J = 8.2, 2.2 Hz, 1H), 2.92 (s, 3H), 1.48 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.43, 152.67, 149.25, 139.86, 129.01, 126.78, 125.17, 122.22, 120.81, 118.46, 111.32, 106.44, 46.58, 30.98, 27.39.

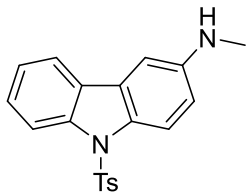
***N*-Methyldibenzo[*b,d*]furan-2-amine (3v)** spectral data were in agreement with literature values[7]



Following **GP5**, 1-(dibenzo[*b,d*]furan-2-yl)ethan-1-ol (**1v**, 42 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-methyldibenzo[*b,d*]furan-2-amine **3v** as a yellow solid (29 mg, 74%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.42 (td, J = 7.6, 1.2 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.30 (td, J = 7.6, 1.2 Hz, 1H), 7.13 (d, J = 2.5 Hz, 1H), 6.78 (dd, J = 8.7, 2.5 Hz, 1H), 3.47 (br, 1H), 2.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.68, 149.73, 145.64, 126.70, 124.77, 124.58, 122.10, 120.46, 114.13, 111.89, 111.56, 102.06, 31.68.

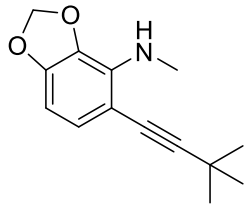
***N*-Methyl-9-tosyl-9*H*-carbazol-3-amine (3w)** spectral data were in agreement with literature values[7]



Following **GP5**, 1-(9-tosyl-9*H*-carbazol-3-yl)ethan-1-ol (**1w**, 73 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (2:1) as eluting solvent afforded *N*-methyl-9-tosyl-9*H*-carbazol-3-amine **3w** as a yellow solid (58 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.9 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.43 (ddd, *J* = 8.4, 7.6, 1.2 Hz, 1H), 7.30 (td, *J* = 7.6, 1.2 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.78 (dd, *J* = 8.9, 2.4 Hz, 1H), 2.91 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.62, 144.43, 139.01, 134.73, 130.94, 129.43, 127.77, 127.01, 126.98, 126.43, 123.65, 119.80, 116.26, 115.51, 114.30, 101.18, 31.21, 21.43.

5-(3,3-Dimethylbut-1-yn-1-yl)-*N*-methylbenzo[*d*][1,3]dioxol-4-amine (3x)



Following **GP5**, 1-(5-(3,3-dimethylbut-1-yn-1-yl)benzo[*d*][1,3]dioxol-4-yl)ethan-1-ol (**1x**, 49 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 5-(3,3-dimethylbut-1-yn-1-yl)-*N*-methylbenzo[*d*][1,3]dioxol-4-amine **3x** as a yellow oil (14 mg, 30%).

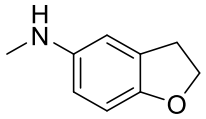
Following **GP5**, 1-(5-(3,3-dimethylbut-1-yn-1-yl)benzo[*d*][1,3]dioxol-4-yl)ethan-1-ol (**1x**, 49 mg, 0.2 mmol), TsONHMe (**2a**, 88 mg, 0.44 mmol) in 0.5 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 5-(3,3-dimethylbut-1-yn-1-yl)-*N*-methylbenzo[*d*][1,3]dioxol-4-amine **3x** as a yellow oil (19 mg, 41%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.0 Hz, 1H), 6.22 (d, *J* = 8.0 Hz, 1H), 5.86 (s, 2H), 4.13 (br, 1H), 3.09 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.36, 135.03, 133.34, 126.14, 104.88, 102.54, 100.26, 98.75, 75.19, 32.67, 31.26, 28.23.

IR (EXTRACT): ṽ = 3397.69, 2967.84, 2926.91, 2897.97, 2867.42, 2817.03, 2774.18, 1733.52, 1631.59, 1600.89, 1511.74, 1478.85, 1435.66, 1392.62, 1361.76, 1329.25, 1291.98, 1267.19, 1242.04, 1221.32, 1171.84, 1128.64, 1092.82, 1052.82, 994.17, 937.04, 868.52, 784.30, 736.79, 688.25, 652.88, 624.22 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 231.1254, found 231.1236.

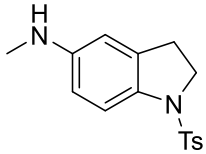
***N*-Methyl-2,3-dihydrobenzofuran-5-amine (3y)** spectral data were in agreement with literature values[7]



Following **GP5**, 1-(2,3-dihydrobenzofuran-5-yl)ethan-1-ol (**1y**, 33 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-methyl-2,3-dihydrobenzofuran-5-amine **3y** as a yellow oil (19 mg, 64%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (d, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 2.5 Hz, 1H), 6.41 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.50 (t, *J* = 8.5 Hz, 2H), 3.15 (t, *J* = 8.5 Hz, 2H), 2.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.45, 143.84, 127.71, 111.96, 109.96, 109.30, 70.83, 31.91, 30.36.

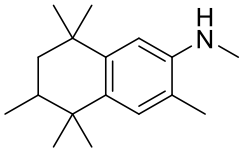
***N*-Methyl-1-tosylindolin-5-amine (3z)** spectral data were in agreement with literature values[7]



Following **GP5**, 1-(1-tosylindolin-5-yl)ethan-1-ol (**1z**, 64 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (2:1) as eluting solvent afforded *N*-methyl-1-tosylindolin-5-amine **3z** as a yellow solid (49 mg, 82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.46 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.33 (d, *J* = 2.6 Hz, 1H), 3.86 (t, *J* = 8.2 Hz, 2H), 3.60 (br, 1H), 2.78 (s, 3H), 2.64 (t, *J* = 8.2 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.83, 143.59, 134.02, 133.99, 132.82, 129.44, 127.37, 117.35, 111.66, 108.75, 50.27, 31.11, 28.44, 21.48.

***N*,3,5,5,6,8,8-Heptamethyl-5,6,7,8-tetrahydronaphthalen-2-amine (3aa)**



Following **GP5**, 1-(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethan-1-ol (**1aa**, 52 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded methyl *N*,3,5,5,6,8,8-heptamethyl-5,6,7,8-tetrahydronaphthalen-2-amine **3aa** as a yellow solid (39 mg, 80%).

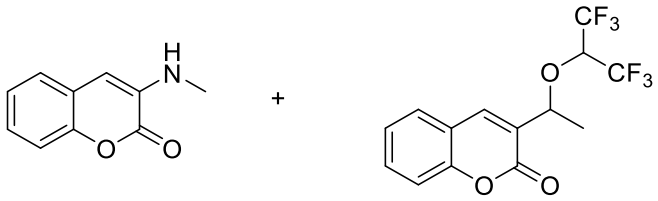
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.53 (s, 1H), 3.29 (br, 1H), 2.91 (s, 3H) ,2.13 (s, 3H), 1.94 – 1.81 (m, 1H), 1.66 (t, *J* = 13.1 Hz, 1H), 1.39 – 1.36 (m, 1H), 1.33 (s, 3H), 1.31 (s, 6H), 1.06 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.77, 143.28, 134.53, 128.48, 120.27, 106.56, 44.01, 36.83, 34.73, 34.32, 32.32, 32.19, 30.90, 28.82, 24.99, 17.20, 16.85.

Mp: 54ºC

IR (EXTRACT): ῦ = 3420.82, 3023.66, 2962.92, 2930.04, 2906.60, 2806.59, 1734.64, 1618.78, 1571.82, 1527.33, 1512.74, 1469.80, 1433.17, 1396.26, 1360.13, 1340.96, 1325.36, 1298.38, 1267.67, 1241.50, 1174.41, 1140.82, 1113.79, 1080.38, 1031.90, 1004.83, 883.60, 849.74, 732.07, 671.78, 644.33 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 245.2138, found 245.2113.

3-(Methylamino)-2*H*-chromen-2-one (3ab) and 3-(1-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)ethyl)-2*H*-chromen-2-one (3ab')

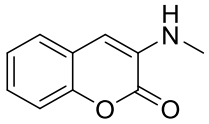


Following **GP5**, 3-(1-hydroxyethyl)-2*H*-chromen-2-one (**1ab**, 38 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 3-(methylamino)-2*H*-chromen-2-one **3ab** as a yellow solid (4

mg, 11%) and 3-(1-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)ethyl)-2*H*-chromen-2-one **3ab'** as a colorless solid (33 mg, 49%).

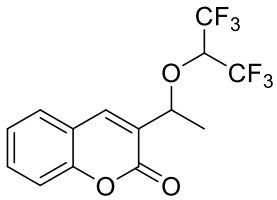
Following **GP5**, 3-(1-hydroxyethyl)-2*H*-chromen-2-one (**1ab**, 38 mg, 0.2 mmol), TsONHMe (**2a**, 88 mg, 0.44 mmol) in 0.5 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 3-(methylamino)-2*H*-chromen-2-one **3ab** as a yellow solid (17 mg, 49%) and 3-(1-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)ethyl)-2*H*-chromen-2-one **3ab'** as a colorless solid (14 mg, 21%)

3-(Methylamino)-2*H*-chromen-2-one (3ab)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 1H), 7.29 – 7.23 (m, 1H), 7.23 – 7.16 (m, 2H), 6.30 (s, 1H), 4.91 (br, 1H), 2.91 (d, *J* = 4.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.58, 147.86, 134.11, 125.56, 124.94, 124.60, 121.81, 116.04, 104.29, 29.75.

3-(1-((1,1,1,3,3,3-Hexafluoropropan-2-yl)oxy)ethyl)-2*H*-chromen-2-one (3ab')



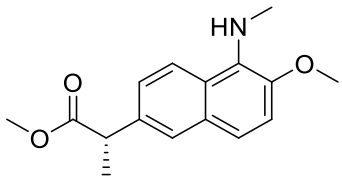
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.58 – 7.52 (m, 2H), 7.38 – 7.28 (m, 2H), 5.05 (q, *J* = 6.4 Hz, 1H), 4.40 (hept, *J* = 5.9 Hz, 1H), 1.59 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.54, 153.29, 138.88, 131.97, 128.61, 128.27, 124.74, 121.55 (qq, *J* = 282.6, 2.7 Hz), 121.22 (qq, *J* = 282.6, 2.7 Hz), 118.81, 116.61, 76.65, 75.30 (hept, *J* = 32.5 Hz), 20.58. ^{19}F NMR (283 MHz, $CDCl_3$) δ -73.80 (dm, *J* = 42.3 Hz).

Mp: 92°C

IR (EXTRACT): $\tilde{\nu}$ = 2993.76, 2932.75, 1691.86, 1634.80, 1607.92, 1575.31, 1453.10, 1410.03, 1387.45, 1375.41, 1293.72, 1262.54, 1226.71, 1181.39, 1141.94, 1116.94, 1103.11, 1033.70, 1002.66, 951.35, 932.42, 913.63, 891.61, 863.02, 846.28, 783.22, 754.76, 734.88, 692.92, 678.36, 610.98 cm^{-1}

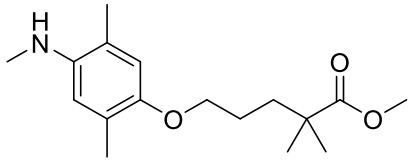
HRMS (EI+) m/z: $[M]^+$ calcd 340.0529, found 340.0496.

Methyl (*S*)-2-(6-methoxy-5-(methylamino)naphthalen-2-yl)propanoate (3ac) spectral data were in agreement with literature values[7]



Following **GP5**, methyl (2*S*)-2-(5-(1-hydroxyethyl)-6-methoxynaphthalen-2-yl)propanoate (**1ac**, 58 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (3:1) as eluting solvent afforded methyl (*S*)-2-(6-methoxy-5-(methylamino)naphthalen-2-yl)propanoate **3ac** as a brown oil (44 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.9 Hz, 1H), 7.65 (d, *J* = 1.9 Hz, 1H), 7.46 (d, *J* = 8.9 Hz, 1H), 7.40 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.24 (d, *J* = 8.9 Hz, 1H), 3.94 (s, 3H), 3.86 (q, *J* = 7.1 Hz, 1H), 3.67 (s, 3H), 3.60 (br, 1H), 2.97 (s, 3H), 1.58 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.11, 147.41, 135.55, 133.92, 129.94, 127.25, 126.40, 125.10, 123.38, 122.30, 113.83, 56.86, 52.00, 45.25, 37.10, 18.46.

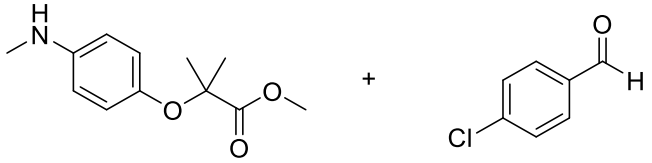
Methyl 5-(2,5-dimethyl-4-(methylamino)phenoxy)-2,2-dimethylpentanoate (3ad) spectral data were in agreement with literature values[7]



Following **GP5**, methyl 5-(4-(1-hydroxyethyl)-2,5-dimethylphenoxy)-2,2-dimethylpentanoate (**1ad**, 61 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (3:1) as eluting solvent afforded methyl 5-(2,5-dimethyl-4-(methylamino)phenoxy)-2,2-dimethylpentanoate **3ad** as a brown oil (35 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (s, 1H), 6.44 (s, 1H), 3.95 – 3.80 (m, 2H), 3.67 (s, 3H), 2.99 (br, 1H), 2.86 (s, 3H), 2.22 (s, 3H), 2.10 (s, 3H), 1.72 – 1.68 (m, 4H), 1.22 (s,

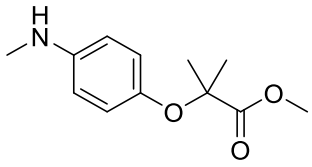
6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.32, 148.92, 141.25, 125.30, 120.15, 115.73, 112.56, 69.61, 51.65, 42.06, 37.13, 31.48, 25.40, 25.13, 17.26, 16.03.

Methyl 2-methyl-2-(4-(methylamino)phenoxy)propanoate (3ae) and 4-chlorobenzaldehyde (3ae')



Following **GP5**, methyl 2-(4-((4-chlorophenyl)(hydroxy)methyl)phenoxy)-2-methylpropanoate (**1ae**, 67 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded methyl 2-methyl-2-(4-(methylamino)phenoxy)propanoate **3ae** as a yellow oil (30 mg, 68%) and 4-chlorobenzaldehyde **3ae'** as a colorless solid (15 mg, 54%)

Methyl 2-methyl-2-(4-(methylamino)phenoxy)propanoate (3ae)

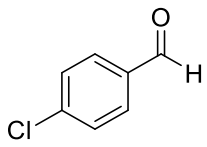


^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.9 Hz, 2H), 6.49 (d, *J* = 8.9 Hz, 2H), 3.77 (s, 3H), 2.79 (s, 3H), 1.51 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.94, 146.50, 145.40, 122.27, 112.78, 79.78, 52.25, 31.17, 25.20.

IR (EXTRACT): ṽ = 3409.11, 2989.74, 2949.52, 2882.14, 2810.77, 1735.25, 1612.61, 1512.88, 1465.85, 1434.38, 1381.95, 1364.61, 1284.40, 1224.36, 1191.66, 1170.62, 1136.29, 1062.18, 1008.85, 949.63, 884.76, 827.13, 770.26, 748.92, 643.54 cm^{-1}

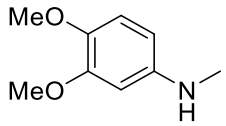
HRMS (EI+) m/z: $[M]^+$ calcd 223.1203, found 223.1196

4-Chlorobenzaldehyde (3ae') spectral data were in agreement with literature values[55]



^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.83, 140.95, 134.71, 130.89, 129.44.

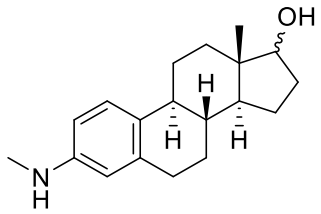
3,4-Dimethoxy-*N*-methylaniline (3af) spectral data were in agreement with literature values[7]



Following **GP5**, 1-(3,4-dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol (**1af**, 67 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 3,4-dimethoxy-*N*-methylaniline **3af** as a yellow oil (17 mg, 52%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.5 Hz, 1H), 6.24 (d, *J* = 2.6 Hz, 1H), 6.15 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.01, 144.34, 141.48, 113.33, 102.99, 98.53, 56.73, 55.67, 31.44.

(8*R*,9*S*,13*S*,14*S*)-3-(1-Hydroxyethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (3ag)



Following **GP5**, (8*R*,9*S*,13*S*,14*S*)-13-methyl-3-(methylamino)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (**1ag**, 60 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (3:1) as eluting solvent afforded (8*R*,9*S*,13*S*,14*S*)-3-(1-hydroxyethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol **3ag** as a colorless solid (34 mg, 60%).

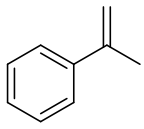
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.4, 1H), 6.47 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.37 (d, *J* = 2.6 Hz, 1H), 3.73 (t, *J* = 8.4 Hz, 1H), 2.91 – 2.74 (m, 2H), 2.82 (s, 3H), 2.33 – 2.26(m, 1H), 2.22 – 2.07 (m, 2H), 1.99 – 1.81 (m, 2H), 1.74 – 1.65 (m, 1H), 1.57 – 1.13 (m, 7H), 0.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.25, 137.46, 129.49, 126.08, 112.56, 110.65, 81.94, 50.03, 43.93, 43.28, 39.06, 36.73, 30.98, 30.58, 29.82, 27.37, 26.34, 23.10, 11.04.

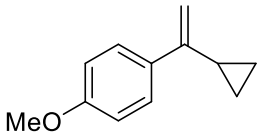
Mp: 162^{o}C

IR (EXTRACT): ῦ = 3401.43, 3285.92, 2917.03, 2862.89, 2239.99, 1734.63, 1664.84, 1611.43, 1500.77, 1469.52, 1446.43, 1431.77, 1381.48, 1352.27, 1332.17, 1304.77, 1289.12, 1263.39, 1203.61, 1169.58, 1135.81, 1075.51, 1057.02, 1029.35, 1009.82, 980.35, 961.53, 949.20, 908.49, 869.00, 812.24, 776.68, 730.61, 710.21, 648.24, 610.08 cm^{-1}

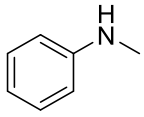
HRMS (EI+) m/z: $[M]^+$ calcd 285.2087, found 285.2080.

Styrenes for C-C amination



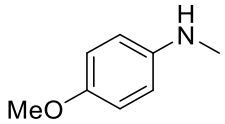


***N*-methylaniline (3b)**



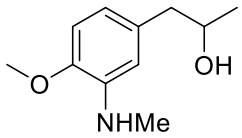
Following **GP5**, a-methyl styrene (23 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 0.5 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (20:1) as eluting solvent afforded *N*-methylaniline **3b** as a yellow oil (5 mg, 24%).

4-Methoxy-*N*-methylaniline (3a)



Following **GP5**, 1-(1-cyclopropylvinyl)-4-methoxybenzene (35 mg, 0.2 mmol), TsONHMe (**2a**, 81 mg, 0.4 mmol) in 0.5 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-methylaniline **3a** as a yellow oil (15 mg, 56%).

1-(4-Methoxy-3-(methylamino)phenyl)propan-2-ol (1ah)



Following **GP5**, 1-(4-methoxyphenyl)propan-2-ol (**1ah**, 33 mg, 0.2 mmol), TsONHMe (**2a**, 80 mg, 0.4 mmol) in 1 mL HFIP solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (2:1) as eluting solvent afforded 1-(4-methoxy-3-(methylamino)phenyl)propan-2-ol as a yellow oil (23 mg, 59%).

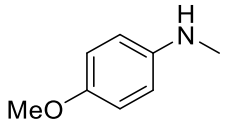
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (d, *J* = .0 Hz, 1H), 6.50 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.43 (d, *J* = 2.0 Hz, 1H), 4.17 – 3.89 (m, 1H), 3.82 (s, 3H), 2.86 (s, 3H), 2.74 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.56 (dd, *J* = 13.5, 8.4 Hz, 1H), 1.25 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.68, 139.40, 131.20, 116.70, 110.25, 109.25, 68.86, 55.46, 45.64, 30.30, 22.58.

IR (EXTRACT): ṽ = 3397.69, 2967.84, 2926.91, 2897.97, 2867.42, 2817.03, 2774.18, 1733.52, 1631.59, 1600.89, 1511.74, 1478.85, 1435.66, 1392.62, 1361.76, 1329.25, 1291.98, 1267.19, 1242.04, 1221.32, 1171.84, 1128.64, 1092.82, 1052.82, 994.17, 937.04, 868.52, 784.30, 736.79, 688.25, 652.88, 624.22 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 195.1254, found 195.1259.

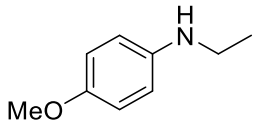
Hydroxylamine Substrate for Secondary Anilines

4-Methoxy-*N*-methylaniline (3a)



Following **GP5**, 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol), *N*-methyl-*O*-(methylsulfonyl)hydroxylamine (**2b**, 28 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-methylaniline **3a** as a yellow oil (20 mg, 74%).

***N*-Ethyl-4-methoxyaniline (4c)** spectral data were in agreement with literature values[56]

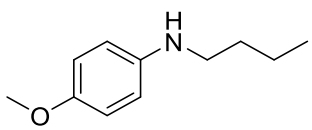


Following **GP3**, *tert*-butyl ethyl(tosyloxy)carbamate (95 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-ethyl-*O*-tosylhydroxylamine **2c** which was directly used for next step without further purification.

Following **GP5**, 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol), crude *N*-ethyl-*O*-tosylhydroxylamine (**2c**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-ethyl-4-methoxyaniline **4c** as a yellow oil (52 mg, 91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (d, J = 8.9 Hz, 2H), 6.59 (d, J = 8.9 Hz, 2H), 3.75 (s, 3H), 3.22 (br, 1H), 3.12 (q, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.05, 142.71, 114.86, 114.10, 55.79, 39.43, 14.95.

***N*-Butyl-4-methoxyaniline (4d)** spectral data were in agreement with literature values[57]



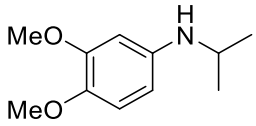
Following **GP3**, *tert*-butyl butyl(tosyloxy)carbamate (103 mg, 0.3 mmol), TFA (0.45

mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-butyl-*O*-tosylhydroxylamine **2d**, which was directly used for the next step without further purification.

Following **GP5**, 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol), crude *N*-butyl-*O*-tosylhydroxylamine (**2d**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-butyl-4-methoxyaniline as a yellow oil (**4d**, 35 mg, 97%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (d, *J* = 8.9 Hz, 2H), 6.59 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 3H), 3.18 (br, 1H), 3.07 (t, *J* = 7.2 Hz, 2H), 1.69 – 1.51 (m, 2H), 1.50 – 1.34 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.96, 142.81, 114.88, 114.02, 55.81, 44.70, 31.76, 20.29, 13.90.

***N*-Isopropyl-3,4-dimethoxyaniline (4e)** spectral data were in agreement with literature values[58]

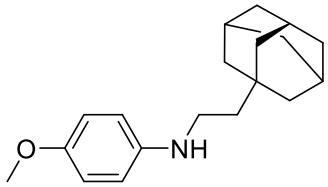


Following **GP3**, *tert*-butyl isopropyl(tosyloxy)carbamate (135 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-isopropyl-*O*-tosylhydroxylamine **2e**, which was directly used for the next step without further purification.

Following **GP5**, 1-(3,4-dimethoxyphenyl)ethan-1-ol (**1at**, 36 mg, 0.2 mmol), crude *N*-isopropyl-*O*-tosylhydroxylamine (**2e**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (4:1) as eluting solvent afforded *N*-isopropyl-3,4-dimethoxyaniline **4e** as a brown oil (35 mg, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (d, *J* = 8.5 Hz, 1H), 6.23 (d, *J* = 2.6 Hz, 1H), 6.14 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.55 (hept, *J* = 6.2 Hz, 1H), 3.16 (br, 1H), 1.19 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.00, 142.38, 141.31, 113.30, 104.36, 99.56, 56.68, 55.66, 45.06, 23.04.

***N*-(2-(Adamantan-1-yl)ethyl)-4-methoxyaniline (4f)** spectral data were in agreement with literature values[59]

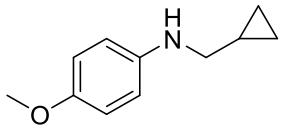


Following **GP3**, *tert*-butyl (2-(adamantan-1-yl)ethyl)(tosyloxy)carbamate (135 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(2-(adamantan-1-yl)ethyl)-*O*-tosylhydroxylamine **2f**, which was directly used for the next step without further purification.

Following **GP5**, 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol), crude *N*-(2-(adamantan-1-yl)ethyl)-*O*-tosylhydroxylamine (**2f**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-(2-(adamantan-1-yl)ethyl)-4-methoxyaniline **4f** as a yellow oil (52 mg, 91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (d, *J* = 9.0 Hz, 2H), 6.58 (d, *J* = 9.0 Hz, 2H), 3.75 (s, 3H), 3.24 – 2.93 (m, 2H), 1.99 – 1.95 (m, 3H), 1.75 – 1.61 (m, 6H), 1.56 (d, *J* = 2.9 Hz, 6H), 1.41 – 1.35 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.91, 142.88, 114.83, 114.01, 55.80, 44.14, 42.58, 39.53, 37.08, 31.96, 28.61.

***N*-(Cyclopropylmethyl)-4-methoxyaniline (4g)** spectral data were in agreement with literature values[60]



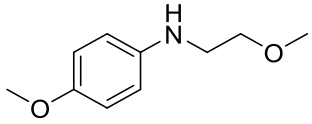
Following **GP3**, *tert*-butyl (cyclopropylmethyl)(tosyloxy)carbamate (102 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(cyclopropylmethyl)-*O*-tosylhydroxylamine **2g**, which was directly used for the next step without further purification.

Following **GP5**, 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol), crude *N*-

(cyclopropylmethyl)-*O*-tosylhydroxylamine (**2g**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-(cyclopropylmethyl)-4-methoxyaniline **4g** as a yellow oil (32 mg, 91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 3H), 3.19 (br, 1H), 2.92 (d, *J* = 6.9 Hz, 2H), 1.19 – 1.03 (m, 1H), 0.67 – 0.48 (m, 2H), 0.26 – 0.20 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.09, 142.76, 114.87, 114.16, 55.80, 50.14, 10.97, 3.38.

4-Methoxy-*N*-(2-methoxyethyl)aniline (4h)

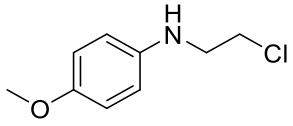


Following **GP3**, *tert*-butyl (2-methoxyethyl)(tosyloxy)carbamate (102 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(2-methoxyethyl)-*O*-tosylhydroxylamine **2h**, which was directly used for the next step without further purification.

Following **GP5**, 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol), crude *N*-(2-methoxyethyl)-*O*-tosylhydroxylamine (**2h**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-(2-methoxyethyl)aniline **4h** as a yellow oil (35 mg, 97%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (d, *J* = 8.9 Hz, 2H), 6.61 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 3H), 3.60 (d, *J* = 5.2 Hz, 2H), 3.39 (s, 3H), 3.24 (d, *J* = 5.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.28, 142.41, 114.82, 114.49, 71.10, 58.72, 55.75, 44.53.

***N*-(2-Chloroethyl)-4-methoxyaniline (4i)**



Following **GP3**, *tert*-butyl (2-chloroethyl)(tosyloxy)carbamate (105 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(2-chloroethyl)-*O*-tosylhydroxylamine **2i**, which was directly used for the next step without further purification.

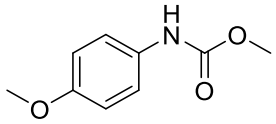
Following **GP5**, 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol), crude *N*-(2-chloroethyl)-*O*-tosylhydroxylamine (**2i**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-(2-chloroethyl)-4-methoxyaniline **4i** as a ayellow oil (35 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, *J* = 8.9 Hz, 2H), 6.64 (d, *J* = 8.9 Hz, 2H), 3. (s, 3H), 3.70 (t, *J* = 5.9 Hz, 2H), 3.46 (t, *J* = 5.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.88, 140.87, 115.02, 115.00, 55.74, 46.65, 43.53.

IR (EXTRACT): ṽ = 3385.95, 2997.65, 2956.31, 2830.63, 1617.85, 1513.23, 1461.62, 1441.78, 1363.94, 1296.58, 1272.20, 1238.62, 1179.26, 1149.10, 1121.67, 1032.35, 944.48, 820.76, 731.99, 661.53 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 185.0602, found 185.0581.

Methyl (4-methoxyphenyl)carbamate (4j) spectral data were in agreement with literature values[61]



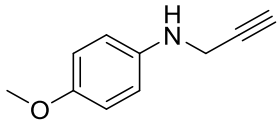
Following **GP5**, 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol), methyl (tosyloxy)carbamate (**2j**, 54 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (3:1) as eluting solvent afforded methyl (4-methoxyphenyl)carbamate **4j** as a colorless solid (8 mg, 22%).

Following **GP5**, 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol), methyl (tosyloxy)carbamate (**2j**, 54 mg, 0.22 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (3:1)

as eluting solvent afforded methyl (4-methoxyphenyl)carbamate **4j** as a colorless solid (16 mg, 44%).

^{1}H NMR (300 MHz, DMSO) δ 9.41 (br, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 3.70 (s, 3H), 3.63 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 154.75, 154.15, 132.17, 119.82, 113.94, 55.15, 51.46.

4-Methoxy-*N*-(prop-2-yn-1-yl)aniline (4k) spectral data were in agreement with literature values[62]

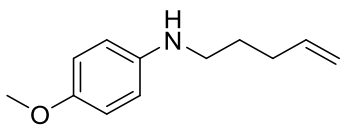


Following **GP3**, *tert*-butyl prop-2-yn-1-yl(tosyloxy)carbamate (98 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(prop-2-yn-1-yl)-*O*-tosylhydroxylamine **2k**, which was directly used for the next step without further purification.

Following **GP5**, 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol), crude *N*-(prop-2-yn-1-yl)-*O*-tosylhydroxylamine (**2k**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-methoxy-*N*-(prop-2-yn-1-yl)aniline **4k** as a yellow oil (30 mg, 94%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (d, *J* = 8.9 Hz, 2H), 6.68 (d, *J* = 8.9 Hz, 2H), 3.90 (d, *J* = 2.4 Hz, 2H), 3.76 (s, 3H), 3.65 (br, 1H), 2.21 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.90, 140.83, 115.05, 114.73, 81.30, 71.18, 55.65, 34.51.

4-Methoxy-*N*-(pent-4-en-1-yl)aniline (4l) spectral data were in agreement with literature values[63]



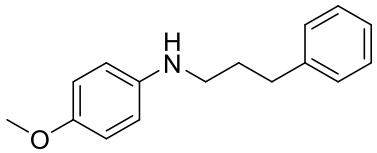
Following **GP3**, *tert*-butyl pent-4-en-1-yl(tosyloxy)carbamate (107 mg, 0.3 mmol),

TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(pent-4-en-1-yl)-*O*-tosylhydroxylamine **2l**, which was directly used for the next step without further purification.

Following **GP5**, 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol), crude *N*-(pent-4-en-1-yl)-*O*-tosylhydroxylamine (**2l**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-(pent-4-en-1-yl)aniline **4l** as a brown oil (33 mg, 87%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (d, *J* = 9.1 Hz, 2H), 6.59 (d, *J* = 9.1 Hz, 2H), 5.85 (ddt, *J* = 17.0, 10.0, 6.4 Hz, 1H), 5.06 (dq, *J* = 17.0, 1.9 Hz, 1H), 5.00 (dd, *J* = 10.0, 1.9 Hz, 1H), 3.75 (s, 3H), 3.10 (t, *J* = 7.2 Hz, 2H), 2.17 (q, *J* = 6.4 Hz, 2H), 1.71 (p, *J* = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.95, 142.63, 138.09, 114.99, 114.85, 114.02, 55.79, 44.39, 31.31, 28.70.

4-Methoxy-*N*-(3-phenylpropyl)aniline (4m) spectral data were in agreement with literature values[64]



Following **GP3**, *tert*-butyl (3-phenylpropyl)(tosyloxy)carbamate (122 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(3-phenylpropyl)-*O*-tosylhydroxylamine **2m**, which was directly used for the next step without further purification.

Following **GP5**, 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol), crude *N*-(3-phenylpropyl)-*O*-tosylhydroxylamine (**2m**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-(3-phenylpropyl)aniline **4m** as a yellow oil (44 mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.26 – 7.19 (m, 3H), 6.79 (d, *J* = 9.1 Hz, 2H), 6.57 (d, *J* = 9.1 Hz, 2H), 3.76 (s, 3H), 3.12 (t, *J* = 7.3 Hz, 2H), 2.75 (t, *J* =

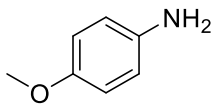
7.3 Hz, 2H), 1.95 (p, *J* = 7.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.97, 142.58, 141.70, 128.38, 128.36, 125.88, 114.83, 114.04, 55.77, 44.40, 33.40, 31.15.

3.4.4 Substrate Scope with Respect to Primary Anilines

General Procedure for the Synthesis of Primary Anilines – GP6

To a solution of the alcohol (0.2 mmol) in 1.0 mL TFE was added MSH (0.3 mmol) under ambient atmosphere at room temperature, unless otherwise stated. The reaction was stirred at room temperature for 12 h (monitored by GCMS or TLC). Then the reaction was diluted with 1mL DCM and basified with 1mL saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with DCM (3 mL × 3), and the combined organic layers were washed with 5 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA to afford the desired product.

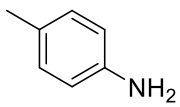
4-Methoxyaniline (6a) spectral data were in agreement with literature values[7]



Following **GP6**, 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-methoxyaniline **6a** as a brown solid (19 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 3.75 (s, 3H), 3.42 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.78, 139.88, 116.39, 114.77, 55.70.

***p*-Toluidine (6au)** spectral data were in agreement with literature values[3b]

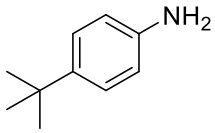


Following **GP6**, 1-(*p*-tolyl)ethan-1-ol (**1ai**, 27 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3

mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *p*-toluidine **6au** as a brown oil (5 mg, 24%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.1 Hz, 2H), 6.62 (d, *J* = 8.1 Hz, 2H), 3.53 (br, 2H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.79, 129.71, 127.72, 115.21, 20.40.

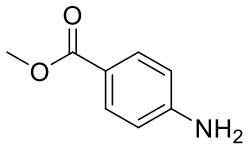
4-(*tert*-Butyl)aniline (6d) spectral data were in agreement with literature values[65]



Following **GP6**, 1-(4-(*tert*-butyl)phenyl)ethan-1-ol (**1d**, 36 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-(*tert*-butyl)aniline as a yellow oil (**6d**, 19 mg, 63%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 2H), 6.66 (d, *J* = 8.6 Hz, 2H), 3.48 (br, 2H), 1.29 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.75, 141.40, 126.02, 114.90, 33.88, 31.50.

Methyl 4-aminobenzoate (6av) spectral data were in agreement with literature values[7]



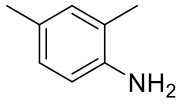
Following **GP6**, methyl 4-(1-hydroxyethyl)benzoate (**1av**, 36 mg, 0.2 mmol), $TsONH_2$•HOTf (**5u**, 74 mg, 0.22 mmol) and $FeSO_4$•$7H_2O$ (2.8 mg, 0.01mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (4:1) as eluting solvent afforded methyl 4-aminobenzoate **6av** as a colorless solid (10 mg, 33%).

MP: 100^{o}C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 8.7 Hz, 2H), 4.05

(br, 2H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.14, 150.78, 131.58, 119.75, 113.78, 51.58.

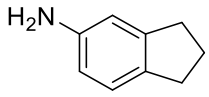
2,4-Dimethylaniline (6n) spectral data were in agreement with literature values[66]



Following **GP6**, 1-(2,4-dimethylphenyl)ethan-1-ol (**1n**, 30 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 2,4-dimethylaniline **6n** as a brown oil (12 mg, 50%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.86 (d, J = 7.8 Hz, 1H), 6.60 (d, J = 7.8 Hz, 1H), 3.43 (br, 2H), 2.24 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.94, 131.09, 127.82, 127.29, 122.42, 115.07, 20.38, 17.28.

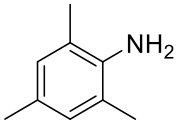
2,3-Dihydro-1*H*-inden-5-amine (6o) spectral data were in agreement with literature values[67]



Following **GP6**, 1-(2,3-dihydro-1*H*-inden-5-yl)ethan-1-ol (**1o**, 32 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 2,3-dihydro-1*H*-inden-5-amine **6o** as a yellow solid (18 mg, 67%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, J = 7.8 Hz, 1H), 6.61 (d, J = 2.1 Hz, 1H), 6.51 (dd, J = 7.8, 2.1 Hz, 1H), 3.51 (br, 2H), 2.84 (t, J = 7.2 Hz, 2H), 2.81 (t, J = 7.2 Hz, 2H), 2.05 (p, J = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.47, 144.74, 134.22, 124.71, 113.25, 111.45, 32.95, 31.91, 25.64.

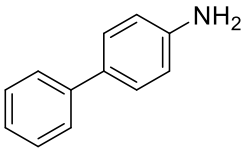
2,4,6-Trimethylaniline (6p) spectral data were in agreement with literature values[7]



Following **GP6**, 1-mesitylethan-1-ol (**1p**, 33 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 2,4,6-trimethylaniline **6p** as a brown oil (20 mg, 74%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 2H), 3.40 (br, 2H), 2.24 (s, 3H), 2.18 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.05, 128.80, 127.12, 121.83, 20.31, 17.53.

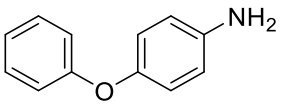
[1,1'-Biphenyl]-4-amine (6q) spectral data were in agreement with literature values[3b]



Following **GP6**, 1-([1,1'-biphenyl]-4-yl)ethan-1-ol (**1q**, 40 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded [1,1'-biphenyl]-4-amine **6q** as a yellow solid (26 mg, 77%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, J = 8.3, 1.3 Hz, 2H), 7.49 – 7.37 (m, 4H), 7.28 (t, J = 7.3 Hz, 1H), 6.77 (d, J = 8.5 Hz, 2H), 3.73 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.80, 141.12, 131.54, 128.62, 127.97, 126.36, 126.21, 115.35.

4-Phenoxyaniline (6r) spectral data were in agreement with literature values[65]

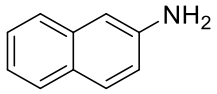


Following **GP6**, 1-(4-phenoxyphenyl)ethan-1-ol (**1r**, 43 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-phenoxyaniline **6r** as a yellow solid (33 mg, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dd, J = 8.6, 7.3 Hz, 2H), 7.01 (tt, J = 7.3, 1.2 Hz,

1H), 6.94 (dd, *J* = 8.6, 1.2 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.68 (d, *J* = 8.7 Hz, 2H), 3.59 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.87, 148.57, 142.65, 129.48, 122.03, 121.09, 117.19, 116.21.

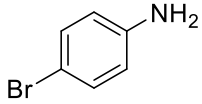
Naphthalen-2-amine (6s) spectral data were in agreement with literature values[65]



Following **GP6**, 1-(naphthalen-2-yl)ethan-1-ol (**1s**, 34 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded naphthalen-2-amine **6s** as a yellow solid (22 mg, 78%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.39 (ddd, *J* = 8.2, 6.7, 1.2 Hz, 1H), 7.25 (ddd, *J* = 8.2, 6.7, 1.2 Hz, 1H), 6.99 (d, *J* = 2.3 Hz, 1H), 6.95 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.83 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.06, 134.87, 129.16, 127.93, 127.67, 126.30, 125.75, 122.42, 118.19, 108.54.

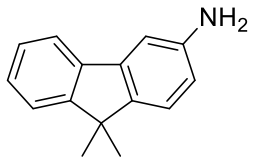
4-Bromoaniline (6t) spectral data were in agreement with literature values[3b]



Following **GP6**, bis(4-bromophenyl)methanol (**1t**, 68 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-bromoaniline **6t** as a yellow solid (19 mg, 56%).

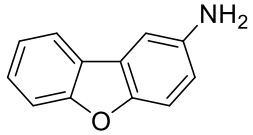
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.56 (d, *J* = 8.7 Hz, 2H), 3.66 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.39, 131.98, 116.67, 110.17.

9,9-Dimethyl-9*H*-fluoren-3-amine (6u)



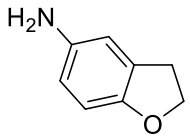
Following **GP6**, 1-(9,9-dimethyl-9*H*-fluoren-3-yl)ethan-1-ol (**1u**, 48 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 9,9-dimethyl-9*H*-fluoren-3-amine **6u** as a yellow solid (29 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.30 (td, *J* = 7.4, 1.3 Hz, 1H), 7.22 (td, *J* = 7.4, 1.3 Hz, 1H), 6.77 (d, *J* = 2.1 Hz, 1H), 6.67 (dd, *J* = 8.0, 2.1 Hz, 1H), 3.76 (br, 2H), 1.46 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 155.48, 152.73, 146.11, 139.61, 130.24, 126.80, 125.50, 122.28, 120.83, 118.63, 113.95, 109.46, 46.55, 27.28.

Dibenzo[*b*,*d*]furan-2-amine (6v) spectral data were in agreement with literature values[65]



Following **GP6**, 1-(dibenzo[*b*,*d*]furan-2-yl)ethan-1-ol (**1v**, 42 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded dibenzo[*b*,*d*]furan-2-amine **6v** as a yellow solid (29 mg, 80%).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.42 (td, *J* = 8.3, 1.2 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.29 (td, *J* = 7.4, 1.2 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.4 Hz, 1H), 3.59 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.73, 150.33, 142.01, 126.89, 124.84, 124.28, 122.19, 120.51, 115.72, 111.89, 111.59, 105.94.

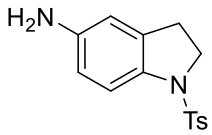
2,3-Dihydrobenzofuran-5-amine (6y) spectral data were in agreement with literature values[65]



Following **GP6**, 1-(2,3-dihydrobenzofuran-5-yl)ethan-1-ol (**1y**, 32 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (3:1) as eluting solvent afforded 2,3-dihydrobenzofuran-5-amine **6y** as a yellow solid (17 mg, 63%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (d, *J* = 8.3 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 6.46 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.49 (t, *J* = 8.6 Hz, 2H), 3.30 (br, 2H), 3.12 (t, *J* = 8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.14, 139.81, 127.76, 114.60, 112.68, 109.26, 70.86, 30.18.

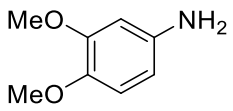
1-Tosylindolin-5-amine (6z) spectral data were in agreement with literature values[68]



Following **GP6**, 1-(1-tosylindolin-5-yl)ethan-1-ol (**1z**, 64 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (2:1) as eluting solvent afforded1-tosylindolin-5-amine **6z** as a brown solid (22 mg, 38%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.53 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.41 (d, *J* = 2.5 Hz, 1H), 3.86 (t, *J* = 8.2 Hz, 2H), 3.54 (br, 2H), 2.63 (t, *J* = 8.2 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.69, 143.43, 134.01, 133.93, 133.91, 129.47, 127.37, 117.22, 114.26, 111.84, 50.23, 28.25, 21.49.

3,4-Dimethoxyaniline (6at) spectral data were in agreement with literature values[3b]

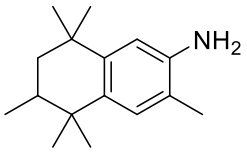


Following **GP6**, 1-(3,4-dimethoxyphenyl)ethan-1-ol (**1at**, 36 mg, 0.2 mmol), MSH (**5m**,

84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (2:1) as eluting solvent afforded 3,4-dimethoxyaniline **6at** as a brown solid (22 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, *J* = 8.4 Hz, 1H), 6.30 (d, *J* = 2.6 Hz, 1H), 6.22 (dd, *J* = 8.4, 2.6 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.40 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.88, 142.17, 140.64, 113.17, 106.36, 100.74, 56.60, 55.67.

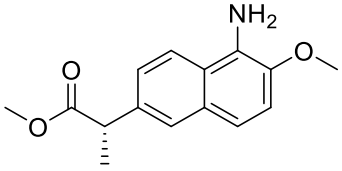
3,5,5,6,8,8-Hexamethyl-5,6,7,8-tetrahydronaphthalen-2-amine (6aa)



Following **GP6**, 1-(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethan-1-ol (**1aa**, 52 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-amine **6aa** as a yellow solid (37 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (s, 1H), 6.61 (s, 1H), 3.44 (br, 2H), 2.15 (s, 3H), 1.85 (dqd, *J* = 13.2, 6.7, 2.5 Hz, 1H), 1.62 (t, *J* = 13.2 Hz, 1H), 1.32 (dd, *J* = 13.2, 2.5 Hz, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.24 (s, 3H), 1.04 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.45, 141.96, 136.55, 128.86, 120.63, 112.47, 43.83, 36.91, 34.71, 33.98, 32.37, 32.09, 28.83, 25.07, 17.22, 16.84.

Methyl (*S*)-2-(5-amino-6-methoxynaphthalen-2-yl)propanoate (6ac) spectral data were in agreement with literature values[18]

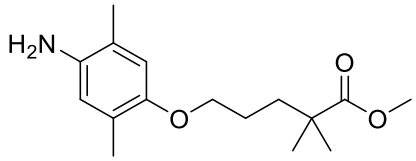


Following **GP6**, methyl (2*S*)-2-(5-(1-hydroxyethyl)-6-methoxynaphthalen-2-yl)propanoate (**1ac**, 58 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel

chromatography with PE/EA (3:1) as eluting solvent afforded methyl (*S*)-2-(5-amino-6-methoxynaphthalen-2-yl)propanoate **6ac** as a brown oil (39 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.43 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.34 (d, *J* = 8.9 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 4.27 (br, 2H), 4.01 (s, 3H), 3.91 (q, *J* = 7.1 Hz, 1H), 3.72 (s, 3H), 1.63 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.11, 142.56, 135.54, 129.56, 129.43, 126.53, 124.78, 123.02, 120.87, 118.27, 113.87, 56.71, 52.01, 45.27, 18.44.

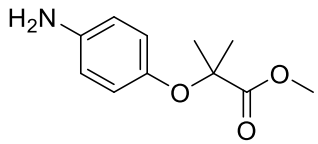
5-(4-Amino-2,5-dimethylphenoxy)-2,2-dimethylpentanoate (6ad) spectral data were in agreement with literature values[3b]



Following **GP6**, methyl 5-(4-(1-hydroxyethyl)-2,5-dimethylphenoxy)-2,2-dimethylpentanoate (**1ad**, 62 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (3:1) as eluting solvent afforded methyl 5-(4-amino-2,5-dimethylphenoxy)-2,2-dimethylpentanoate **6ad** as a brown oil (38 mg, 68%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (s, 1H), 6.50 (s, 1H), 3.87 – 3.75 (m, 2H), 3.66 (s, 3H), 3.29 (br, 2H), 2.14 (s, 3H), 2.13 (s, 3H), 1.77 – 1.57 (m, 4H), 1.21 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.33, 150.15, 137.64, 125.39, 120.39, 118.05, 114.90, 69.17, 51.67, 42.07, 37.12, 25.33, 25.14, 17.34, 15.67.

Methyl 2-(4-aminophenoxy)-2-methylpropanoate (6ae)



Following **GP6**, methyl 2-(4-((4-chlorophenyl)(hydroxy)methyl)phenoxy)-2-methylpropanoate (**1ae**, 67 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel

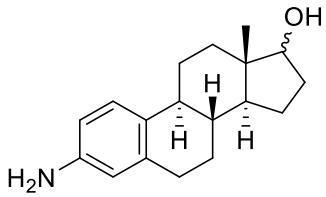
chromatography with PE/EA (3:1) as eluting solvent afforded methyl 2-(4-aminophenoxy)-2-methylpropanoate **6ae** as a brown oil (23 mg, 56%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 3.76 (s, 3H), 3.50 (br, 2H), 1.50 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.90, 147.36, 141.97, 122.04, 115.69, 79.68, 52.30, 25.17.

IR (REFLEXION): ṽ = 3446, 3369, 3225, 3036, 2991, 2952, 2850, 1875, 1740, 1627, 1512, 1465, 1436, 1383, 1365, 1284, 1224, 1172, 1146, 1011, 963, 885, 831, 773, 751, 646 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 209.1046, found 209.1047.

(8*R*,9*S*,13*S*,14*S*)-3-Amino-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (6ag)

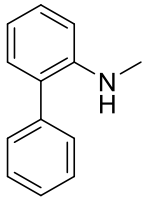


Following **GP6**, (8*R*,9*S*,13*S*,14*S*)-3-(1-hydroxyethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (**1ag**, 60 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (2:1) as eluting solvent afforded (8*R*,9*S*,13*S*,14*S*)-3-amino-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol **6ag** as a colorless solid (36 mg, 67%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.3 Hz, 1H), 6.52 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.45 (d, *J* = 2.6 Hz, 1H), 3.73 (t, *J* = 8.5 Hz, 1H), 2.95 – 2.62 (m, 2H), 2.32 – 2.26 (m, 1H), 2.20 – 2.05 (m, 2H), 1.93 (dt, *J* = 12.6, 3.4 Hz, 1H), 1.87 – 1.80 (m, 1H), 1.73 – 1.63 (m, 1H), 1.58 – 1.24 (m, 6H), 1.22 – 1.15 (m, 1H), 0.77 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.91, 137.60, 130.70, 126.18, 115.40, 112.97, 81.89, 49.95, 43.88, 43.22, 38.91, 36.66, 30.53, 29.58, 27.25, 26.27, 23.07, 11.03.

3.4.5 Further Application

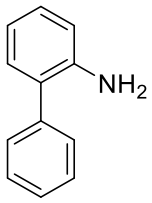
***N*-Methyl-[1,1'-biphenyl]-2-amine (7)** spectral data were in agreement with literature values[69]



Following **GP5**, 1-([1,1'-biphenyl]-2-yl)ethan-1-ol (**1ak**, 40 mg, 0.2 mmol), TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-methyl-[1,1'-biphenyl]-2-amine **7** as a yellow oil (22 mg, 61%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.42 (m, 4H), 7.40 – 7.34 (m, 1H), 7.30 (td, *J* = 8.0, 1.7 Hz, 1H), 7.12 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.80 (td, *J* = 7.4, 1.7 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 3.99 (br, 1H), 2.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.14, 139.48, 129.99, 129.38, 128.82, 128.73, 127.54, 127.14, 116.76, 109.75, 30.73.

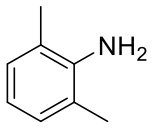
[1,1'-Biphenyl]-2-amine (8) spectral data were in agreement with literature values[70]



Following **GP6**, 1-([1,1'-biphenyl]-2-yl)ethan-1-ol (**1ak**, 40 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded [1,1'-biphenyl]-2-amine **8** as a yellow solid (21 mg, 62%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.41 (m, 4H), 7.44 – 7.30 (m, 1H), 7.23 – 7.07 (m, 2H), 6.85 (td, *J* = 7.6, 1.2 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 3.77 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.45, 139.49, 130.41, 129.05, 128.76, 128.45, 127.60, 127.11, 118.60, 115.56.

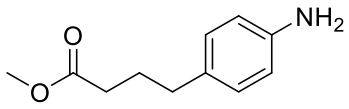
2,6-Dimethylaniline (9) spectral data were in agreement with literature values[11]



Following **GP6**, 1-(2,6-dimethylphenyl)ethan-1-ol (**1al**, 150 mg, 1 mmol), MSH (**5m**, 419 mg, 1.5 mmol) in 5.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 2,6-dimethylaniline **9** as a yellow oil (45 mg, 37%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, *J* = 7.4 Hz, 2H), 6.67 (t, *J* = 7.4 Hz, 1H), 3.50 (br, 2H), 2.21 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.66, 128.19, 121.64, 117.94, 17.55.

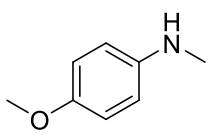
Methyl 4-(4-aminophenyl)butanoate (10) spectral data were in agreement with literature values[71]



Following **GP6**, methyl 4-(4-(1-hydroxyethyl)phenyl)butanoate (**1an**, 44 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1.0 mL TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (4:1) as eluting solvent afforded methyl 4-(4-aminophenyl)butanoate **10** as a yellow solid (21 mg, 55%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (d, *J* = 8.3 Hz, 2H), 6.62 (d, *J* = 8.3 Hz, 2H), 3.66 (s, 3H), 3.55 (br, 2H), 2.54 (t, *J* = 7.5 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.90 (p, *J* = 7.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.06, 144.36, 131.34, 129.21, 115.20, 51.41, 34.20, 33.32, 26.74.

4-methoxy-*N*-methylaniline (3a)

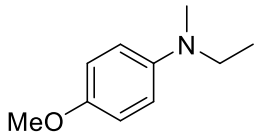


Following **GP5**, 1-methoxy-4-(1-methoxyethyl)benzene (**11**, 33 mg, 0.2 mmol) and

TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1 mL HFIP were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-methylaniline **3a** as a yellow oil (18 mg, 67%).

Following **GP5**, 1-(4-methoxyphenyl)ethyl acetate (**12**, 39 mg, 0.2 mmol) and TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1 mL HFIP were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-methylaniline **3a** as a yellow oil (17 mg, 63%).

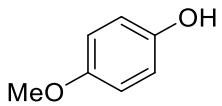
***N*-ethyl-4-methoxy-*N*-methylaniline (13)** spectral data were in agreement with literature values[72]



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, *J* = 9.1 Hz, 2H), 6.73 (d, *J* = 9.1 Hz, 2H), 3.77 (s, 3H), 3.31 (q, *J* = 7.1 Hz, 2H), 2.84 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.68, 144.23, 115.00, 114.71, 55.75, 47.99, 38.26, 11.03.

To a solution of 1-(4-methoxyphenyl)ethan-1-ol (**2a**, 30 mg, 0.2 mmol) in 1.0 mL HFIP was added TsONHMe (**2a**, 44 mg, 0.22 mmol) at room temperature, and the reaction was stirred for 12 h at room temperature. Then $NaBH_3CN$ (64 mmol, 1.0 mmol) was added to the above reaction mixture and the reaction was stirred for 3 h at room temperature. The reaction was quenched with 1mL saturated $NaHCO_3$ aq., extracted with DCM (3 mL × 3), and the combined organic layers were washed with 5 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA (10:1) as eluting solvent to afford *N*-ethyl-4-methoxy-*N*-methylaniline **13** as a yellow oil (18 mg, 55%)

4-Methoxyphenol (14) spectral data were in agreement with literature values[73]

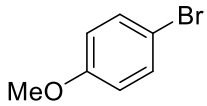


To a solution of 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol) in 1.0 mL HFIP

was added 35% H_2O_2 (29 mg, 0.3 mmol) at room temperature, and the reaction was stirred for 12 h at room temperature. Then the reaction was diluted with 1mL DCM and basified with 1mL saturated $NaHCO_3$ aq., extracted with DCM (3 mL × 3), and the combined organic layers were washed with 5 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA (10:1) as eluting solvent to afford 4-methoxyphenol **14** as a yellow solid (16 mg, 64%)

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 – 6.74 (m, 4H), 4.95 (br, 1H), 3.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.68, 149.48, 116.04, 114.86, 55.80.

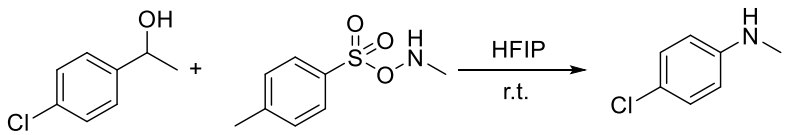
1-Bromo-4-methoxybenzene (15) spectral data were in agreement with literature values[74]



To a solution of 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol) in 1.0 mL TFE was added NBS (35 mg, 0.2 mmol) under nitrogen atmosphere. Then the reaction was stirred under UV light for 12 h at room temperature. The reaction was concentrated in vacuo, and the residue was purified by silica gel chromatography with PE/EA (20:1) as eluting solvent to afford 1-bromo-4-methoxybenzene **15** as a colorless liquid (20 mg, 54%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.68, 132.22, 115.71, 112.80, 55.42.

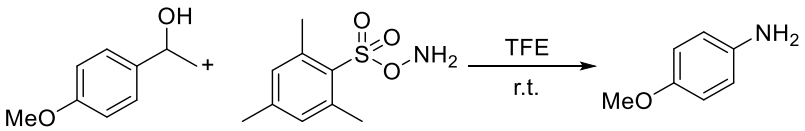
3.4.6 Large-Scale Reaction



1i, 4 mmol **2a**, 4.4 mmol **3i**, 84%

Following **GP5**, 1-(4-chlorophenyl)ethan-1-ol (**1i**, 626 mg, 4 mmol), TsONHMe (**2a**,

885 mg, 4.4 mmol) in 20 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-chloro-*N*-methylaniline **3i** as a yellow oil (478 mg, 84%).



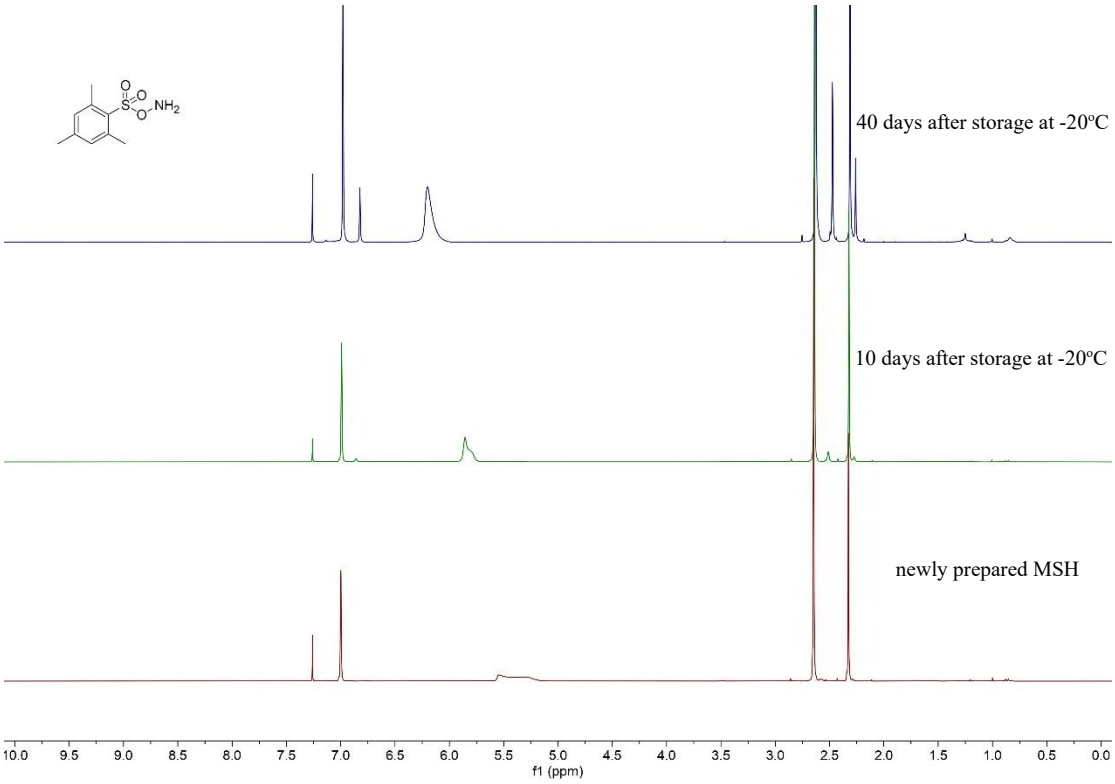
1a, 4 mmol **5m**, 6 mmol **6a**, 79%

Following **GP6**, 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 608 mg, 4 mmol), MSH (**5m**, 1676 mg, 6 mmol) in 20 mL TFE solution were stirred for 12 h. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-methoxyaniline **6a** as a brown solid (388 mg, 79%).

3.4.7 Evaluation of MSH Storage Time

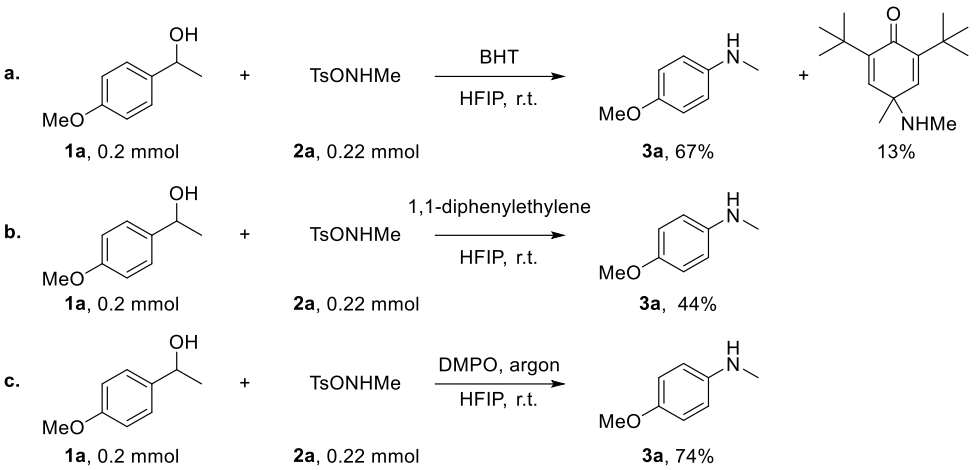
New prepared MSH (*O*-(mesitylsulfonyl)hydroxylamine) was stored at -20ºC, and NMR was used to measure how MSH was decomposed at different time. From the figure below, we can see: new prepared MSH was 100% pure; around 5% decomposition after 10 days storage at -20ºC; but around 20% decomposition after 40 days storage at -20ºC.

Besides, A competitive reaction was done to check the efficiency of MSH, which was stored at -20ºC after 40 days: MSH (**5m**, 1.67 g) reacted with 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 608 mg), delivering 4-methoxylaniline (**6a**, 388 mg, 79%), almost without any weight loss compared to small-scale reaction. (details see **Large-Scale Reaction** above), i.e. MSH, stored for 40 days at -20ºC, doesn't have any negative effect on the yield.



3.4.8 Control Experiments

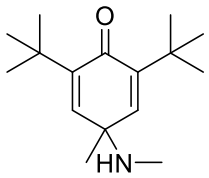
The yield was decreased when BHT or 1,1-diphenylethylene as an additive in the standard reaction (1-(4-methoxyphenyl)ethan-1-ol **1a**, and TsONHMe **2a** in HFIP), which, however, doesn't support a radical pathway involved in the reaction. And this can be explained: simple BHT could also react with TsONHMe via stepwise or concerted pathway,[7] affording the same adduct 2,6-di-*tert*-butyl-4-methyl-4-(methylamino)cyclohexa-2,5-dien-1-one as in the below (reaction **a**, scheme 1); ethylene might be not compatible with TsONHMe.[75] That's the reason of BHT or 1,1-diphenylethylene inhibiting the reaction. More proof from reaction **c** in Scheme 1: no radical was involved in the reaction (no signal was detected on EPR), and same yield was acquired even with the DMPO as an additive compared to the standard reaction.



Scheme 1. Control Experiments

a. To a solution of 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol) and BHT (48 mg, 0.2 mmol) in 1 mL HFIP was slowly added TsONHMe (**2a**, 44 mg, 0.22 mmol), and the reaction was stirred for 12 h at room temperature. The reaction was quenched with 1 mL sat. $NaHCO_3$, extracted with DCM (3 × 3 mL), and the combined organic layers were washed with 5 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-methylaniline (**3a**, 18 mg, 67%) as a yellow oil and 2,6-di-*tert*-butyl-4-methyl-4-(methylamino)cyclohexa-2,5-dien-1-one (7 mg, 13 %) as a yellow solid.

2,6-Di-*tert*-butyl-4-methyl-4-(methylamino)cyclohexa-2,5-dien-1-one spectral data were in agreement with literature values[7]



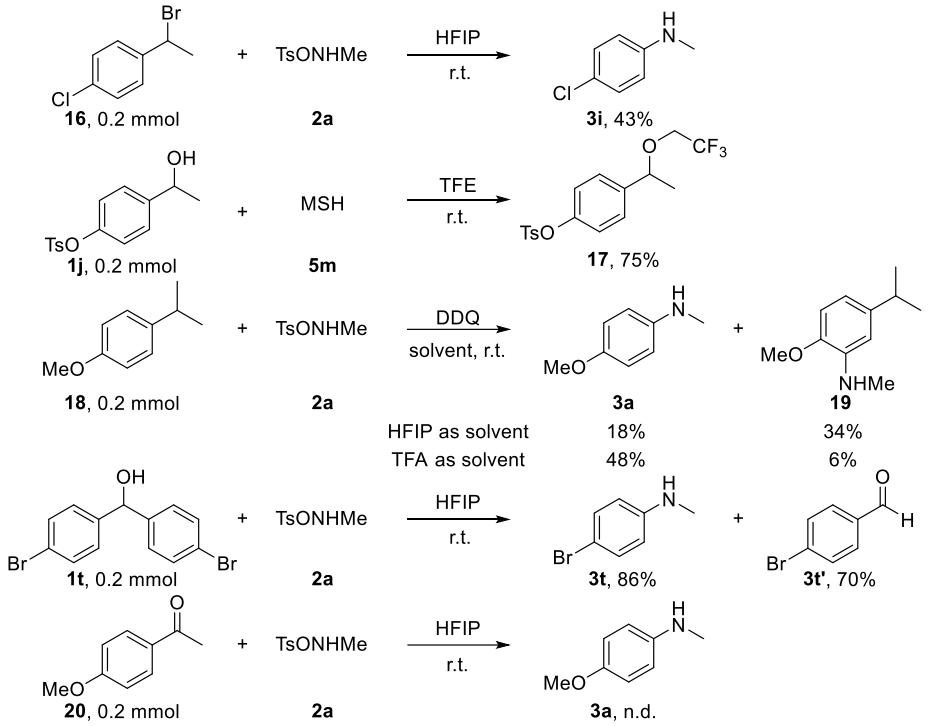
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37 (s, 2H), 2.18 (s, 3H), 2.03 (s, 1H), 1.29 (s, 3H), 1.23 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.32, 148.05, 144.57, 54.32, 34.79, 30.38, 29.62, 27.58.

b. To a solution of 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol) and 1,1-diphenylethylene (40 mg, 0.2 mmol) in 1 mL HFIP was slowly added TsONHMe (**2a**,

44 mg, 0.22 mmol), and the reaction was stirred for 12 h at room temperature. The reaction was quenched with 1 mL sat. $NaHCO_3$, extracted with DCM (3 × 3 mL), and the combined organic layers were washed with 5 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-methylaniline (**3a**, 12 mg, 44%) as a yellow oil.

c. To a solution of 1-(4-methoxyphenyl)ethan-1-ol (**1a**, 30 mg, 0.2 mmol) and DMPO (44 mg, 0.2 mmol) in 1 mL HFIP was slowly added TsONHMe (**2a**, 44 mg, 0.22 mmol), and the reaction was stirred for 12 h under argon atmosphere at room temperature. The reaction was quenched with 1 mL sat. $NaHCO_3$, extracted with DCM (3 × 3 mL), and the combined organic layers were washed with 5 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-methylaniline as a yellow oil (**3a**, 20 mg, 74%). And DMPO was also detected with GC-MS (m/z 113.1). No radicals were detected by EPR machine when the same reaction was prepared under argon atmosphere at room temperature and sent to EPR measurement.

3.4.9 Mechanistic Studies

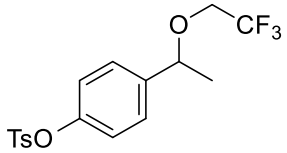


Scheme 2. Mechanistic Studies

a. Following **GP5**, 1-(1-bromoethyl)-4-chlorobenzene (**16**, 44 mg, 0.2 mmol) and TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1 mL HFIP were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-chloro-*N*-methylaniline **3i** as a yellow oil (12 mg, 43%)

b. Following **GP6**, 4-(1-hydroxyethyl)phenyl 4-methylbenzenesulfonate (**1j**, 59 mg, 0.2 mmol), MSH (**5m**, 84 mg, 0.3 mmol) in 1 mL TFE solution were stirred for 12 h. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-(1-(2,2,2-trifluoroethoxy)ethyl)phenyl 4-methylbenzenesulfonate **17** as a colorless oil (56 mg, 75%).

4-(1-(2,2,2-Trifluoroethoxy)ethyl)phenyl 4-methylbenzenesulfonate (17)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 4.54 (q, *J* = 6.5 Hz, 1H), 3.62 (q, *J* = 8.7

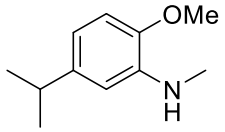
Hz, 2H), 2.45 (s, 3H), 1.45 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.20, 145.46, 140.84, 132.43, 129.76, 128.43, 127.39, 123.90 (q, J = 278.7 Hz), 122.64, 78.73, 65.83 (q, J = 34.2 Hz), 23.59, 21.66. ^{19}F NMR (283 MHz, $CDCl_3$) δ -74.17.

IR (EXTRACT): $\tilde{\nu}$ = 3069.15, 2981.11, 2932.91, 2106.42, 1914.34, 1731.83, 1598.22, 1502.87, 1434.99, 1372.87, 1275.81, 1197.92, 1152.36, 1130.84, 1091.38, 1016.90, 964.54, 862.22, 814.53, 779.09, 741.92, 707.89, 684.29, 657.77, 608.58 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 374.0794, found 374.0790.

c. To a solution of 1-isopropyl-4-methoxybenzene (**18**, 30 mg, 0.2 mmol) in 1 mL HFIP or TFA was slowly added DDQ (50 mg, 0.22 mmol) and TsONHMe (**2a**, 44 mg, 0.22 mmol), and the reaction was stirred for 12 h at room temperature. The reaction was quenched with 1 mL sat. $NaHCO_3$, extracted with DCM (3 × 3 mL), and the combined organic layers were washed with 5 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded desired products: HFIP as the solvent: 4-methoxy-*N*-methylaniline **3a** as a yellow oil (5 mg, 18%) and 5-isopropyl-2-methoxy-*N*-methylaniline **19** as a yellow oil (12 mg, 34%); TFA as the solvent : 4-methoxy-*N*-methylaniline **3a** as a yellow oil (13 mg, 48%) and 5-isopropyl-2-methoxy-*N*-methylaniline **19** as a yellow oil (2 mg, 6%).

5-Isopropyl-2-methoxy-*N*-methylaniline (19) spectral data were in agreement with literature values[7]



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (d, J = 8.1 Hz, 1H), 6.55 (dd, J = 8.1, 2.0 Hz, 1H), 6.50 (d, J = 2.0 Hz, 1H), 4.21 (s, 1H), 3.83 (s, 3H), 2.89 (s, 3H), 2.88 – 2.78 (m, 1H), 1.26 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.10, 141.97, 139.11, 113.42, 109.08, 107.92, 55.47, 33.88, 30.39, 24.26.

d. See **Substrate Scope for Secondary Anilines**

e. Following **GP5**, 1-(4-methoxyphenyl)ethan-1-one (**20**, 30 mg, 0.2 mmol) and TsONHMe (**2a**, 44 mg, 0.22 mmol) in 1 mL HFIP were stirred for 12 h at room temperature. The reaction mixture was detected with GC-MS: 4-methoxy-*N*-methylaniline **3a** was formed

3.5 References

[1] E. H. Huntress, H. C. Walter, *J. Am. Chem. Soc.* **1948**, *70*, 3702-3707.

[2] K. Hyodo, G. Hasegawa, H. Maki, K. Uchida, *Org. Lett.* **2019**, *21*, 2818-2822.

[3] a) C. Qin, T. Shen, C. Tang, N. Jiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6971-6975; b) J. Liu, X. Qiu, X. Huang, X. Luo, C. Zhang, J. Wei, J. Pan, Y. Liang, Y. Zhu, Q. Qin, S. Song, N. Jiao, *Nat. Chem.* **2019**, *11*, 71-77; c) Y. Adeli, K. Huang, Y. Liang, Y. Jiang, J. Liu, S. Song, C.-C. Zeng, N. Jiao, *ACS Catal.* **2019**, *9*, 2063-2067.

[4] C. Zhu, G. Li, D. H. Ess, J. R. Falck, L. Kürti, *J. Am. Chem. Soc.* **2012**, *134*, 18253-18256.

[5] R. V. Hoffman, A. Kumar, *J. Org. Chem.* **2002**, *50*, 1859-1863.

[6] a) Y. Tamura, J. Minamikawa, M. Ikeda, *Synthesis* **1977**, *1977*, 1-17; b) R. Sun, M. Lu, L. Chen, Q. Li, H. Song, F. Bi, R. Huang, Q. Wang, *J. Agric. Food Chem.* **2008**, *56*, 11376-11391; c) S. Sabir, G. Kumar, J. L. Jat, *Org. Biomol. Chem.* **2018**, *16*, 3314-3327.

[7] T. Wang, M. Hoffmann, A. Dreuw, E. Hasagić, C. Hu, P. M. Stein, S. Witzel, H. Shi, Y. Yang, M. Rudolph, F. Stuck, F. Rominger, M. Kerscher, P. Comba, A. S. K. Hashmi, *Adv. Synth. Catal.* **2021**, *363*, 2783-2795.

[8] J. J. Farndon, T. A. Young, J. F. Bower, *J. Am. Chem. Soc.* **2018**, *140*, 17846-17850.

[9] J. J. Farndon, X. Ma, J. F. Bower, *J. Am. Chem. Soc.* **2017**, *139*, 14005-14008.

[10] E. M. D'Amato, J. Borgel, T. Ritter, *Chem. Sci.* **2019**, *10*, 2424-2428.

[11] U. D. S, F. Julia, A. Luridiana, J. J. Douglas, D. Leonori, *Nature* **2020**, *584*, 75-

81.

[12] X. Gao, J. Li, M. Wang, S. Xu, W. Liu, L. Zang, Z. Li, H. Hua, J. Xu, D. Li, *Eur. J. Med. Chem.* **2018**, *146*, 588-598.

[13] a) P. Trillo, A. Baeza, C. Najera, *J. Org. Chem.* **2012**, *77*, 7344-7354; b) F. Z. Zhang, Y. Tian, G. X. Li, J. Qu, *J. Org. Chem.* **2015**, *80*, 1107-1115; c) I. Colomer, A. E. R. Chamberlain, M. B. Haughey, T. J. Donohoe, *Nat. Rev. Chem.* **2017**, *1*, 0088; d) X. D. An, J. Xiao, *Chem. Rec.* **2020**, *20*, 142-161.

[14] Masruri, A. C. Willis, M. D. McLeod, *J. Org. Chem.* **2012**, *77*, 8480-8491.

[15] Z. Shi, S. Kiau, P. Lobben, J. Hynes, H. Wu, L. Parlanti, R. Discordia, W. W. Doubleday, K. Leftheris, A. J. Dyckman, S. T. Wrobleski, K. Dambalas, S. Tummala, S. Leung, E. Lo, *Org. Process Res. Dev.* **2012**, *16*, 1618-1625.

[16] A. Kitowski, E. Jimenez-Moreno, M. Salvado, J. Mestre, S. Castillon, G. Jimenez-Oses, O. Boutureira, G. J. L. Bernardes, *Org. Lett.* **2017**, *19*, 5490-5493.

[17] S. Makai, E. Falk, B. Morandi, *J. Am. Chem. Soc.* **2020**, *142*, 21548-21555.

[18] J. Liu, K. Wu, T. Shen, Y. Liang, M. Zou, Y. Zhu, X. Li, X. Li, N. Jiao, *Chem.-Eur. J.* **2017**, *23*, 563-567.

[19] Y. Tamura, H. Ikeda, I. Morita, H. Tsubouchi, M. Ikeda, *Chem Pharm Bull* **1982**, *30*, 1221-1224.

[20] J. J. Farndon, X. Ma, J. F. Bower, *J. Am. Chem. Soc.* **2017**, *139*, 14005-14008.

[21] M. P. Paudyal, A. M. Adebesin, S. R. Burt, D. H. Ess, Z. Ma, L. Kürti, J. R. Falck, *Science* **2016**, *353*, 1144-1147.

[22] R. Luo, L. Ouyang, N. Luo, Y. Zhong, J.-T. Liu, *Synthesis* **2020**, *52*, 3439-3445.

[23] Y. Yamashita, H. Suzuki, I. Sato, T. Hirata, S. Kobayashi, *Angew. Chem. Int. Ed.* **2018**, *57*, 6896-6900.

[24] J. Xiang, M. Shang, Y. Kawamata, H. Lundberg, S. H. Reisberg, M. Chen, P. Mykhailiuk, G. Beutner, M. R. Collins, A. Davies, M. Del Bel, G. M. Gallego, J. E. Spangler, J. Starr, S. Yang, D. G. Blackmond, P. S. Baran, *Nature* **2019**, *573*, 398-402.

[25] T. Mandal, S. Jana, J. Dash, *Eur. J. Org. Chem.* **2017**, *2017*, 4972-4983.

[26] J. Duczynski, A. N. Sobolev, S. A. Moggach, R. Dorta, S. G. Stewart,

Organometallics **2019**, *39*, 105-115.

[27] P. Qu, M. Kuepfert, S. Jockusch, M. Weck, *ACS Catal.* **2019**, *9*, 2701-2706.

[28] X. Dong, A. Weickgenannt, M. Oestreich, *Nat. Commun.* **2017**, *8*, 15547.

[29] T. Hashimoto, T. Ishimaru, K. Shiota, Y. Yamaguchi, *Chem. Commun.* **2020**, *56*, 11701-11704.

[30] K. Polidano, B. G. Reed-Berendt, A. Basset, A. J. A. Watson, J. M. J. Williams, L. C. Morrill, *Org. Lett.* **2017**, *19*, 6716-6719.

[31] M. Padmanaban, A. T. Biju, F. Glorius, *Org. Lett.* **2011**, *13*, 98-101.

[32] S. R. Patpi, L. Pulipati, P. Yogeeswari, D. Sriram, N. Jain, B. Sridhar, R. Murthy, T. Anjana Devi, S. V. Kalivendi, S. Kantevari, *J. Med. Chem.* **2012**, *55*, 3911-3922.

[33] A. S. Hashmi, I. Braun, P. Nosel, J. Schadlich, M. Wieteck, M. Rudolph, F. Rominger, *Angew. Chem. Int. Ed.* **2012**, *51*, 4456-4460.

[34] D. Berthier, A. Herrmann, N. Paret, L. Ouali, WO 2013/079435A l, **2013**.

[35] S.-L. Zhou, L.-N. Guo, X.-H. Duan, *Eur. J. Org. Chem.* **2014**, *2014*, 8094-8100.

[36] J. Bomon, E. Van Den Broeck, M. Bal, Y. Liao, S. Sergeyev, V. Van Speybroeck, B. F. Sels, B. U. W. Maes, *Angew. Chem. Int. Ed.* **2020**, *59*, 3063-3068.

[37] L. E. Hofmann, D. Hofmann, L. Prusko, L. M. Altmann, M. R. Heinrich, *Adv. Synth. Catal.* **2020**, *362*, 1485-1489.

[38] M. Tang, S. Han, S. Huang, S. Huang, L. G. Xie, *Org. Lett.* **2020**, *22*, 9729-9734.

[39] Y. Xia, J. Wang, G. Dong, *J. Am. Chem. Soc.* **2018**, *140*, 5347-5351.

[40] L. Liu, W. Lee, M. Yuan, C. Acha, M. B. Geherty, B. Williams, O. Gutierrez, *Chem. Sci.* **2020**, *11*, 3146-3151.

[41] W. Liu, T. Leischner, W. Li, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2020**, *59*, 11321-11324.

[42] R. K. Sahoo, M. Mahato, A. Jana, S. Nembenna, *J. Org. Chem.* **2020**, *85*, 11200-11210.

[43] D. L. Clive, S. Kang, *J. Org. Chem.* **2001**, *66*, 6083-6091.

[44] K. Lafleur, J. Dong, D. Huang, A. Caflisch, C. Nevado, *J. Med. Chem.* **2013**, *56*, 84-96.

[45] X. G. Liu, C. J. Zhou, E. Lin, X. L. Han, S. S. Zhang, Q. Li, H. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 13096-13100.

[46] T. Tokumaru, K. Nakata, *Tetrahedron Lett.* **2015**, *56*, 2336-2339.

[47] C. Zhang, G. Zhang, S. Luo, C. Wang, H. Li, *Org. Biomol. Chem.* **2018**, *16*, 8467-8471.

[48] C. Li, Y. Zhang, Q. Sun, T. Gu, H. Peng, W. Tang, *J. Am. Chem. Soc.* **2016**, *138*, 10774-10777.

[49] E. Falk, V. C. M. Gasser, B. Morandi, *Org. Lett.* **2021**, *23*, 1422-1426.

[50] V. Botla, C. Barreddi, R. V. Daggupati, C. Malapaka, *J. Chem. Sci.* **2016**, *128*, 1469-1473.

[51] V. Blanco, D. A. Leigh, V. Marcos, J. A. Morales-Serna, A. L. Nussbaumer, *J. Am. Chem. Soc.* **2014**, *136*, 4905-4908.

[52] S. Zhang, J. J. Ibrahim, Y. Yang, *Org. Chem. Front.* **2019**, *6*, 2726-2731.

[53] H. Seo, A.-C. Bédard, W. P. Chen, R. W. Hicklin, A. Alabugin, T. F. Jamison, *Tetrahedron* **2018**, *74*, 3124-3128.

[54] H. Tan, S. A. Wang, Z. Yan, J. Liu, J. Wei, S. Song, N. Jiao, *Angew. Chem. Int. Ed.* **2021**, *60*, 2140-2144.

[55] H. Aman, Y. C. Chen, J. W. Tu, C. C. Chang, G. J. Chuang, *ChemistrySelect* **2020**, *5*, 15015-15019.

[56] D. Sang, H. Yue, Z. Zhao, P. Yang, J. Tian, *J. Org. Chem.* **2020**, *85*, 6429-6440.

[57] X. Ge, M. Ge, X. Chen, C. Qian, X. Liu, S. Zhou, *Mol. Catal.* **2020**, *484*, 110726.

[58] V. H. Hoang, V. T. H. Ngo, M. Cui, N. V. Manh, P. T. Tran, J. Ann, H. J. Ha, H. Kim, K. Choi, Y. H. Kim, H. Chang, S. J. Y. Macalino, J. Lee, S. Choi, J. Lee, *J. Med. Chem.* **2019**, *62*, 8011-8027.

[59] S. P. Panchenko, A. S. Abel, A. D. Averin, O. A. Maloshitskaya, E. N. Savelyev, B. S. Orlinson, I. A. Novakov, I. P. Beletskaya, *Russ. J. Organ. Chem.* **2017**, *53*, 1497-1504.

[60] Y. Wei, C. Zhao, Q. Xuan, Q. Song, *Org. Chem. Front.* **2017**, *4*, 2291-2295.

[61] Q. Zhang, H.-Y. Yuan, X.-T. Lin, N. Fukaya, T. Fujitani, K. Sato, J.-C. Choi, *Green Chem.* **2020**, *22*, 4231-4239.

[62] C. H. Chou, B. Rajagopal, C. F. Liang, K. L. Chen, D. Y. Jin, H. Y. Chen, H. C. Tu, Y. Y. Shen, P. C. Lin, *Chem.-Eur. J.* **2018**, *24*, 1112-1120.

[63] T. J. Brown, M. Cumbes, L. J. Diorazio, G. J. Clarkson, M. Wills, *J. Org. Chem.* **2017**, *82*, 10489-10503.

[64] P. T. K. Arachchige, H. Lee, C. S. Yi, *J. Org. Chem.* **2018**, *83*, 4932-4947.

[65] H. Gao, Z. Zhou, D. H. Kwon, J. Coombs, S. Jones, N. E. Behnke, D. H. Ess, L. Kürti, *Nat. Chem.* **2017**, *9*, 681-688.

[66] Y. Y. See, M. S. Sanford, *Org. Lett.* **2020**, *22*, 2931-2934.

[67] Z. Qiu, L. Lv, J. Li, C. C. Li, C. J. Li, *Chem. Sci.* **2019**, *10*, 4775-4781.

[68] M. C. Henry, H. M. Senn, A. Sutherland, *J. Org. Chem.* **2019**, *84*, 346-364.

[69] R. A. Green, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2015**, *54*, 3768-3772.

[70] A. A. De la Fuente-Olvera, O. R. Suárez-Castillo, D. Mendoza-Espinosa, *Eur. J. Inorg. Chem.* **2019**, *2019*, 4879-4886.

[71] C. A. Mosley, S. J. Myers, E. E. Murray, R. Santangelo, Y. A. Tahirovic, N. Kurtkaya, P. Mullasseril, H. Yuan, P. Lyuboslavsky, P. Le, L. J. Wilson, M. Yepes, R. Dingledine, S. F. Traynelis, D. C. Liotta, *Bioorg. Med. Chem.* **2009**, *17*, 6463-6480.

[72] Y. Wei, Q. Xuan, Y. Zhou, Q. Song, *Org. Chem. Front.* **2018**, *5*, 3510-3514.

[73] N. Llopis, A. Baeza, *J. Org. Chem.* **2020**, *85*, 6159-6164.

[74] D. Phuc Tran, A. Nomoto, S. Mita, C.-p. Dong, S. Kodama, T. Mizuno, A. Ogawa, *Tetrahedron Lett.* **2020**, *61*, 151959.

[75] Q.-Q. Cheng, Z. Zhou, H. Jiang, J. H. Siitonen, D. H. Ess, X. Zhang, L. Kürti, *Nat. Catal.* **2020**, *3*, 386-392.

Chapter 4 Anilines Synthesis from Alkylarenes, Benzyl Ethers/Esters and Styrenes via Aza-Hock Rearrangement Mediated by Hydroxylamines

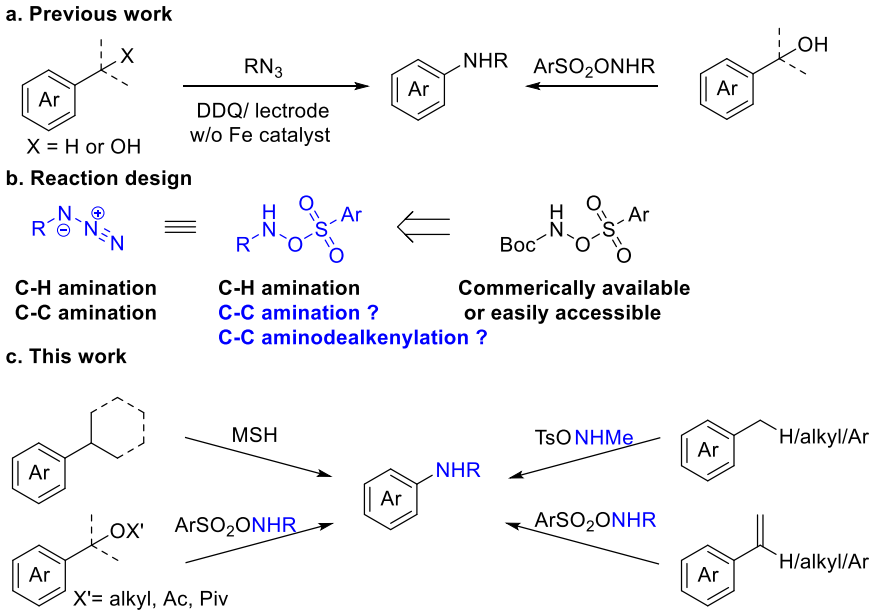
4.1 Introduction

Anilines, as fundamental motifs in chemistry, have revolutionized the field of pharmacy, agriculture, and organic materials. A common idea in anilines synthesis is the assembly of "N" onto the arene cores from simple arenes or aryl pseudohalides, which undergoes through the well-established conventional nitration-reduction, cross-coupling reactions or metal/photo/electro-catalyzed arene C-H aminations. The approaches above are adopted universally; nonetheless, essentially harsh reaction conditions and the need for prepared aryl halides (or surrogates) as well as site-selectivity problems by starting from arenes still make the synthesis of special anilines a challenge. Accordingly, other strategies of affording anilines under mild conditions and excellent chemoselectivity would be particularly attractive.

The C-C amination is an alternative to address such problems: indeed, a variety of classical reactions-especially in the chemistry textbook-facilitates such conversions successfully, making anilines accessible from carboxylic acids (such as Lossen, Hoffmann, Curtius, Schmidt and Neber rearrangements). A variation of this transformation is the Beckmann rearrangement of a ketone in conjunction with simple hydroxylamine[1] and a modified Schmidt rearrangement/aza-Hock rearrangement of benzyl alcohols,[2] providing another way for anilines synthesis. However, ketones and benzyl alcohols are therefore needed to be prepared. The most intriguing work on aniline synthesis was reported by Ning's group: alkylarenes were amenable to undergo a Schmidt-type rearrangement accompanied by azides and DDQ/electricity as oxidants. [2-3] Nonetheless, hazardous and potentially explosive azides can not be avoided in the protocol. Given the profuse number of anilines in all aspects of chemical science, the development of a save surrogate for organic azides would be extremely useful and

complementary.

We envisaged that arylsulfonyl hydroxylamines ($ArSO_2ONHR$) might behave similarly as organic azides–instead of the exclusion of 1 molecule of N_2 for azides a loss of 1 molecule of $ArSO_2O^-$ in these reactions seems reasonable. Therefore these reagents were considered to be viable for arene C-H[4]/C-C aminations as well. Accordingly, we hypothesized that hydroxylamines, $ArSO_2ONHR$, could enable a direct modified aza-Hock rearrangement of alkylarenes under mild conditions to deliver anilines as products. Here, we report that alkylarenes, styrenes, benzyl alcohols ethers and esters are amenable in arene C-C amination with $ArSO_2ONHR$ via aza-Hock rearrangement. It needs to point out that alkylarenes can be differentiated with different aminating reagents: i-alkylarenes are selectively cleaved by *O*-(mesitylsulfonyl)hydroxylamine (MSH) while *n*-alkylarenes are cleaved by *N*-methyl-*O*-tosylhydroxylamine (TsONHMe), and C-C amination of styrenes (break aryl Csp^2-alkenyl Csp^2, form anilines) rather than harness of C=C bond[5] is underdeveloped before. The reactions are shown here involve the cleavage of aryl Csp^2-alkenyl Csp^2 bonds, followed by the formation of a new C-N bond, which is referred to as aminodealkenylation, coined with a nod to hydrodealkenylation[6] that is exemplified in the transformation of prop-1-en-2-ylcycloalkane to cycloalkane.



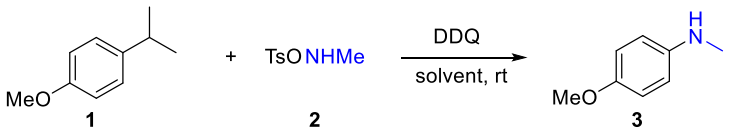
Scheme 1. Previous work and reaction design for this work

4.2 Results and Discussion

4.2.1 Optimization of the Reaction Condition

Our approach was based on our previous work, which testified that benzyl cations are the key intermediate of an aza-Hock rearrangement in C-C aminations. Also 4-isopropylanisole was smoothly transformed into aniline with TsONHMe **2**. After refining the reaction parameters promoting aza-Hock rearrangement of 4-isopropylanisole, we found that the reaction was highly dependent on the solvent: strong acidic TFA afforded aniline in 74% yield while other solvents (HFIP, AcOH and $MeSO_3H$) performed poor in the reaction–less or no aniline was produced, which might be attributed to the stability of the benzyl cations in TFA. And 1.5 equivalent of **2** yielded more aniline than 1.1 equivalent. A subsequent experiment showed that MSH proceeded smoothly in the C-C amination with 4-isopropylanisole as substrate, delivering primary aniline as the product. So alkylarene (0.2 mmol/L), aminating reagents (TsONHMe **2** or MSH **4**, 0.3 mmol) and DDQ (0.22 mmol) in 1 mL TFA was the optimal conditions for this alkylarene C-C amination.

Table 1. Optimization of C-C amination between 4-isopropylanisole and TsONHMe



Entry	Solvent	Yield[a]
1[b]	HFIP	18%
2[b]	TFA	48%
3	**TFA**	**74%**
4	AcOH	28%
5	$MeSO_3H$	n.d.

Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), DDQ (0.22 mmol), solvent (1 mL), r.t., 12 h; [a]isolated yield; [b]**2** (0.22 mmol) was used.

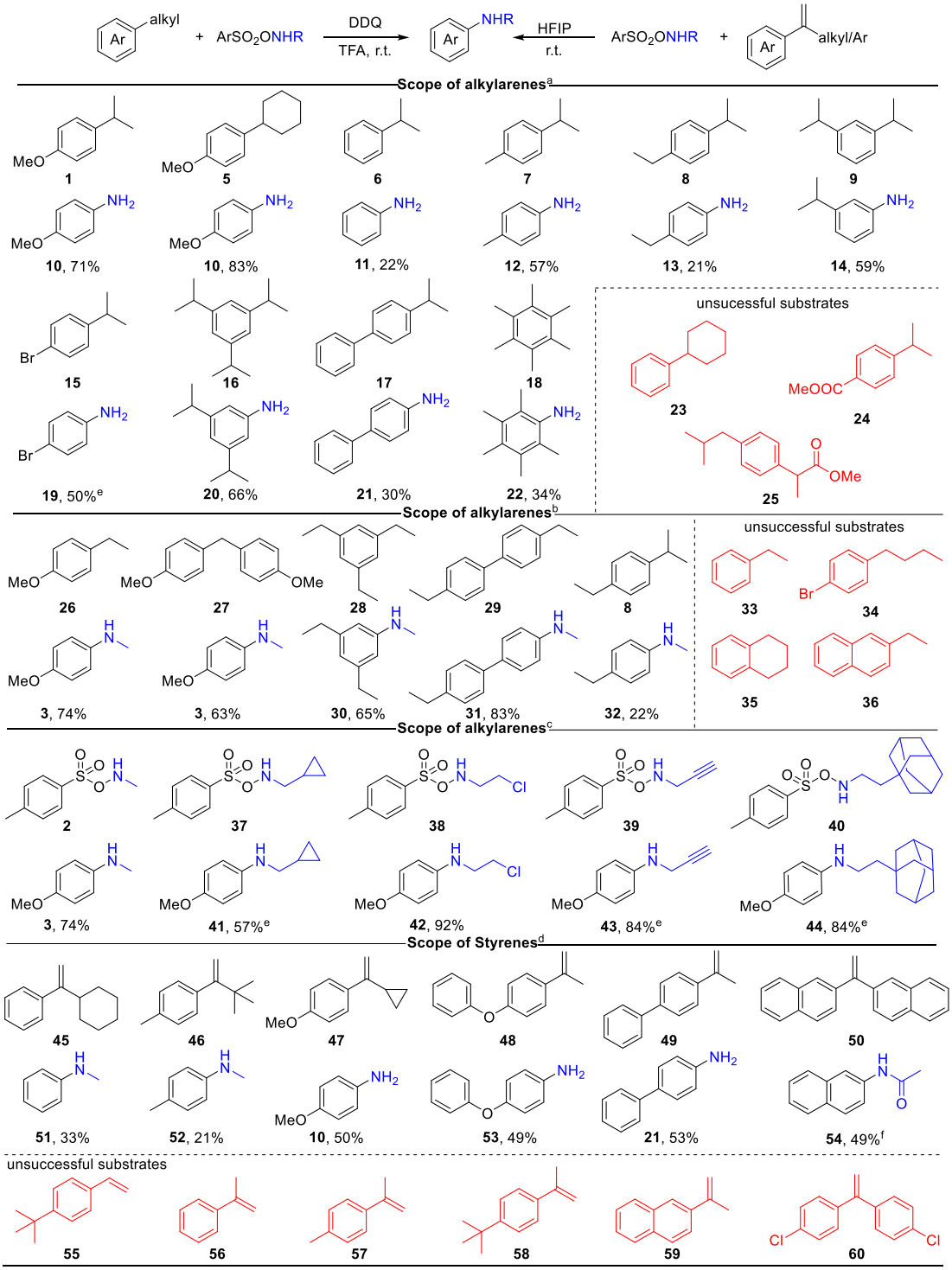
4.2.2 Scope and Limitation with Respect to Alkylarenes and Styrenes

Under the optimized conditions, we then explored the alkylarene substrate scope for the C-C amination. As depicted in Table 2, a range of electronically differentiated i-alkylarenes was amenable in this protocol, with the merge of MSH as the aminating reagent. The yields of anilines were increasing with increasing electron density on the arene cores (**1**, **5** – **7**), except for 4-ethylcumene **8**, which delivered 4-ethylaniline **13** as the only product (trace 4-isopropylaniline detected by GC-MS), albeit in low yield. This suggests that i-alkyl groups are superior to be cleaved even in the presence of *n*-alkyl groups on the alkylarenes. Besides, 4-bromoaniline **19** was also accessible from the electron-deficient 4-bromocumene **15**. Only one isopropyl group of **9** and **16** was cleaved, leaving the other/others intact. 4-isoproylbiphenyl **17** and hexamethylbenzene **18** underwent such C-C aminations successfully, but in low yields. But cyclohexylbenzene **23** and electron-deficient alkylarene **24**, **25** were not compatible in this reaction. However, 4-ethylanisole **26**, as an *n*-alkylarene, was not able to convert into the aniline with MSH, and other aminating reagents ($MsONH_2$•HOTf, $TsONH_2$•HOTf, HOSA, (2,4-dinitrophenyl)hydroxylamine and *O*-(diphenylphosphinyl)hydroxylamine) also failed in this transformation. Unexpectedly, TsONHMe **2**, *N*-alkyl-arylsulfonylhydroxylamine, was feasible in this transformation with **26**, delivering 4-methoxy-*N*-methylaniline **3** in good yield. Facile conversion of biphenyl methane **27** into aniline **3** was accompanied by an aldehyde as a side-product (the ratio of aniline/aldehyde was 1 : 1.5), which highlights the aza-Hock pathway in the reaction. Triethylbenzene **29** and biphenyl **30** are also good examples under standard conditions, generating a single isomer of anilines in good yield. As anticipated, in analogy to aniline **13** from **8**, the ethyl group rather than the isopropyl group in **8** was fragmented with **2**, delivering the sole aniline **32**. This unprecedented method of different hydroxylamines differentiating alkylarenes (mainly on *n*-alkylarene and i-alkylarene) is rarely noticed, which opens a window for research on distinguishing different alkylarenes. Several unsuccessful examples were also presented here: trace C-C amination from ethylbenzene **33** was detected, and the major product was arene C-H

amination product; an electron-poor alkylarene **34** was not tolerated; an "N"-inserted aniline was detected from tetrahydronaphthalene **35**, but it was not isolated due to low yield. Naphthalene **36** did not work in this system as it is sensitive to DDQ. With respect to structural variations, several aminating reagents (**2**, **37** – **40**) were straightforwardly prepared and they turned out to be feasible in this C-C amination, which exhibited the possibility of increasing aniline diversity direct from alkylarenes.

Furthermore, this strategy was also applicable to styrenes, which directly forged styrenes into anilines. This rare phenomenon was seldomly reported before (except our previous work with two examples), as C=C bonds of styrenes are often harnessed, i.e. C=C functionalization rather than dealkenylation. α-alkyl styrenes were viable in the special aminodealkenylation, affording anilines in low to moderated yields. Styrene **51** and **52** performed poorly in the reaction while an electron-rich arene core in styrenes (**47** – **49**) delivered anilines in moderate yields. 2,2'-(ethene-1,1-diyl)dinaphthalene **50** could facilitate the transformation, affording aniline and a ketone (it was not easy to separate those two compounds due to intermolecular hydrogen bond formation), which needed to be separated by via simple derivation of the aniline with acetyl chloride. More substrates were prepared to testify the system: normal styrenes (eg. 4-*tert*-butylstyrene **55**) polymerized in the reaction, and less hindered α-methyl styrenes (**56** – **59**) gave less of the desired anilines (< 10%) as these also turned to decompose when they were subjected to the aminating reagents. Electron-poor diphenyl ethylene **60** could not be converted into aniline

Table 2. alkylarene and styrene scope towards the anilines synthesis

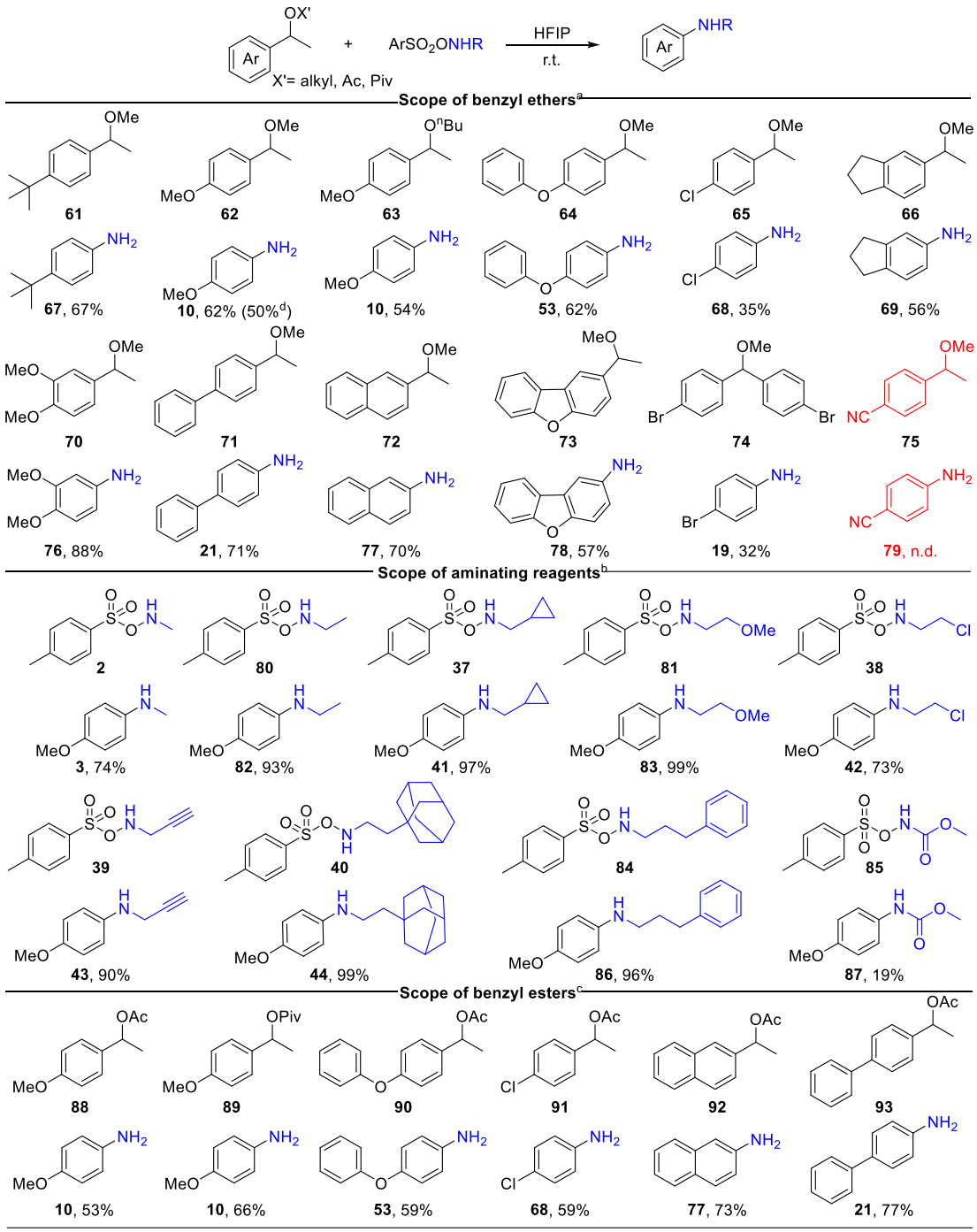


Reaction conditions: alkyarene (0.2 mmol), aminating reagent (0.3 mmol), DDQ (0.22 mmol), TFA (1 mL), r.t., 12 h; [a]**4** (0.3 mmol) was used; [b]**2** (0.3 mmol) was used; [c]TsONHR (0.3 mmol) and **1** (0.2 mmol) were used. [d]styrene (0.2 mmol), **4** (0.3 mmol) or **2** (0.22 mmol), HFIP (1 mL), r.t., 6 h; [e]2 days [f]1> condition d, 2> AcCl (0.4 mmol), Et_3N (0.4 mmol), DCM (3 mL), r.t., 6 h.

4.2.3 Scope and Limitation with Respect to Benzyl Ethers/Esters

To amplify the synthetic utility of this C-C amination protocol, we extended it to other benzyl cation precursors substrates–benzyl ethers and esters. In principle, any substrate that generates a benzyl cation in TFE/HFIP should be compatible with our reactions. As drawn in Table 3, the electron-donating groups on the arene cores of ethers (**61** – **64**) promoted the reaction efficiency, but the electron-withdrawing group in **65** decreased the reaction yield. In contrast to aniline **10** from **62**, long-chained ether **63** demonstrated a comparable yield. Disubstituted benzyl ethers (**66** and **70**) delivered moderate to good yields. Other substructures (biphenyl **71**, naphthalene **72**, dibenzo[*b*,*d*]furan **73**) were also amenable in this transformation. The electron-poor ethers (**74**, **75**) afforded less or no aniline. Then a series of hydroxylamines were evaluated under the standard conditions, delivering anilines with good to excellent yields. Noteworthy, propargyl amine **43** and alkyl chloride **42** were accessible with this protocol, which can be further manipulated; arene C-C amination dominated the reaction when aminating reagent **84** was subjected to the reaction, even though **84** could undergo arene C-H amination in HFIP. But for electron-deficient aniline, only a low yield was obtained from reagent **85**. Moreover, to showcase the viability of such a protocol, several benzyl esters (**88** – **93**) were testified which enabled access to anilines in good yield. The benzyl alcohol pivalate **89** gave a better yield than the corresponding acetate **88**. Both electron-rich **90** and electron-poor benzyl ester **91** could work in the reaction. Other motifs (naphthalene **92** and biphenyl **93**) could generate anilines in good yields.

Table 3. benzyl ether/ester scope towards the anilines synthesis



Reaction conditions: benzyl ether/benzyl ester (0.2 mmol), aminating reagent (0.3 mmol), HFIP (1 mL), r.t., 12 h; [a]**4** (0.3 mmol) was used; [b]TsONHR (0.3 mmol) and **62** (0.2 mmol) were used, [c]MSH (0.3 mmol) was used; [d]TFE (1 mL) was used; [e]**2** (0.22 mmol) was used.

4.3 Conclusion

We have developed an aza-Hock rearrangement of benzyl cation precursors–alkylarene,

styrene, benzyl ethers and esters mediated by hydroxylamines in mild conditions. Notably, i-alkylarenes can be differentiated with MSH from *n*-alkylarenes, and *n*-alkylarenes are successfully transformed into anilines with TsONHMe. Moreover, aminodealkenylation (C-C amination of styrenes) opens a gateway for employing styrenes in a plethora of known benzyl cation transformations. This powerful protocol should serve as a valuable tool for aniline synthesis, adding to the growing catalogue of C-C functionalization.

4.4 Experimental Section

4.4.1 General Materials and Methods

Chemicals were purchased from commercial suppliers (Sigma-Aldrich, Alfa Aesar and TCI) and used as delivered. Dry solvents were dispensed from solvent purification system MB SPS-800. HFIP was used directly without further purification. Deuterated solvents were bought from Euriso-Top. Unless otherwise stated, all reactions and manipulations were carried out under ambient atmosphere in new reaction vials or flasks.

NMR Spectra were recorded on a Bruker Avance-III-300, Bruker Avance-III-400, Bruker Avance-III-500, Bruker Avance-III-600. Chemical shifts are reported in ppm with the solvent resonance as the internal standard. For ^{1}H NMR: $CDCl_3$, 7.26. For ^{13}C NMR: $CDCl_3$, 77.16. Data is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentalet, hept = heptalet, m = multiplet, br = broad singlet, dd =doublet of doublets, td =triplet of doublets; coupling constants in Hz; integration.

Mass spectra (MS and HRMS) were determined in the chemistry department of the University Heidelberg under the direction of Dr. J. Gross. EI+ -spectra were measured on a JOEL JMS-700 spectrometer. For ESI+ -spectra a Bruker ApexQu FT-ICR-MS spectrometer was applied.

Infrared Spectroscopy (IR) was processed on an FT-IR Bruker (IF528), IR Perkin Elmer (283) or FT-IR Bruker Vector 22. The solvent or matrix is denoted in brackets. For the most significant bands the wave number ν (cm^{-1}) is given.

Melting points were measured in open glass capillaries in a Büchi melting point apparatus (according to Dr. Tottoli) and were not corrected.

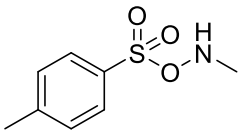
Flash Column Chromatography was accomplished using Silica gel 60 (0.04 – 0.063 mm / 230 – 400 mesh ASTM) purchased from Macherey-Nagel.

Analytical / Preparative thin-layer chromatography (TLC) was carried out on pre-coated aluminum sheets provided by Macherey-Nagel ALUGRAM® Xtra SIL G/UV254. Components were visualized by treatment with aqueous $KMnO_4$ solution or by irradiation under UV light (254 nm).

4.4.2 Preparation of Aminating Reagents and Substrates

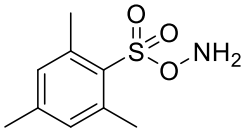
Aminating reagents were synthesized according to literature; styrenes were synthesized from Wittig reaction, benzyl ethers were synthesized from Williamson ether synthesis; benzyl esters were synthesized from alcoholysis of acyl chlorides and acid anhydrides.

***N*-Methyl-*O*-tosylhydroxylamine (TsONHMe, 2)** was prepared according to a published literature procedure; spectral data were in agreement with literature values[4]



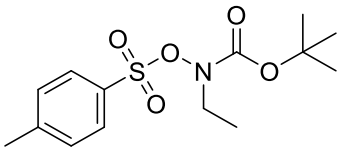
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 5.85 (s, 1H), 2.74 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.93, 132.26, 129.50, 128.94, 40.10, 21.65.

***O*-Mesitylenesulfonylhydroxylamine (MSH, 4)** was prepared according to a published literature procedure; spectral data were in agreement with literature values[7]



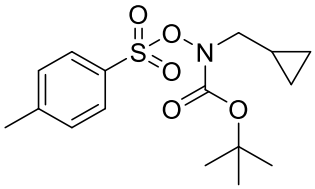
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2H), 4.35 (br, 2H), 2.66 (s, 6H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.76, 140.95, 131.68, 129.11, 22.67, 21.03.

***tert*-Butyl ethyl(tosyloxy)carbamate** was prepared according to a published literature procedure; spectral data were in agreement with literature values[4]



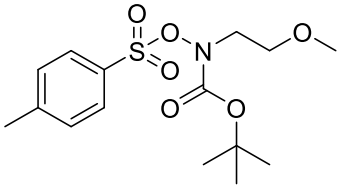
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 2H), 3.66 (br, 2H), 2.45 (s, 3H), 1.22 (s, 9H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.49, 145.59, 131.24, 129.69, 129.47, 83.18, 48.16, 27.58, 21.68, 10.66.

***tert*-Butyl (cyclopropylmethyl)(tosyloxy)carbamate**



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz,2H), 7.34 (d, *J* = 8.3 Hz, 2H), 3.50 (s, 2H), 2.45 (s, 3H), 1.23 (s, 9H), 1.18 – 1.06 (m, 1H), 0.50 (d, *J* = 7.8 Hz, 2H), 0.27 (d, *J* = 4.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.71, 145.55, 131.32, 129.69, 129.46, 83.10, 57.60, 27.57, 21.67, 8.02, 3.35.

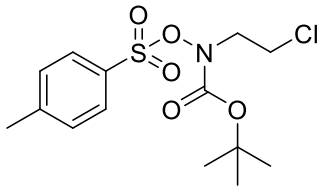
***tert*-Butyl (2-methoxyethyl)(tosyloxy)carbamate** was prepared according to a published literature procedure; spectral data were in agreement with literature values[4]



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 3.63 (br, 4H), 3.29 (s, 3H), 2.44 (s, 3H), 1.20 (s, 9H).^{13}C NMR (125 MHz, $CDCl_3$) δ 155.74, 145.66, 131.00, 129.71, 129.46, 83.02, 67.18, 58.71, 51.73, 27.43, 21.66.

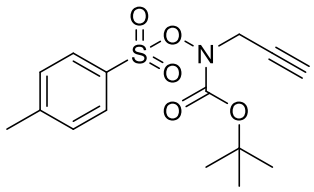
***tert*-Butyl (2-chloroethyl)(tosyloxy)carbamate** was prepared according to a published

literature procedure; spectral data were in agreement with literature values[4]



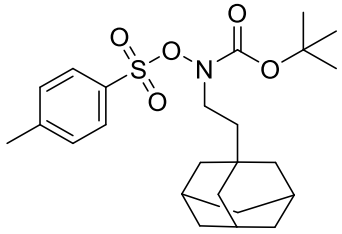
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 3.99 (t, *J* = 6.5 Hz, 2H), 3.73 (t, *J* = 6.5 Hz, 2H), 2.46 (s, 3H), 1.21 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.81, 146.01, 130.80, 129.78, 129.62, 83.78, 53.46, 39.01, 27.50, 21.70.

***tert*-Butyl prop-2-yn-1-yl(tosyloxy)carbamate** was prepared according to a published literature procedure; spectral data were in agreement with literature values[4]



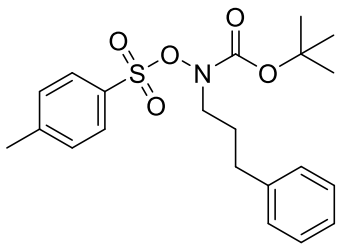
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 4.30 (br, 2H), 2.45 (s, 3H), 2.25 (t, *J* = 2.4 Hz, 1H), 1.26 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ 154.92, 145.85, 131.02, 129.72, 129.56, 84.33, 76.30, 73.16, 42.88, 27.55, 21.68.

***tert*-Butyl (2-(adamantan-1-yl)ethyl)(tosyloxy)carbamate** was prepared according to a published literature procedure; spectral data were in agreement with literature values[4]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 3.60 (br, 2H), 2.44 (s, 3H), 1.95 – 1.89 (m, 2H), 1.72 – 1.54 (m, 6H), 1.45 (d, *J* = 2.8 Hz, 6H), 1.23 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.49, 145.54, 131.35, 129.67, 129.44, 83.03, 48.53, 42.07, 39.02, 36.98, 31.41, 28.49, 27.62, 21.65.

***tert*-Butyl (3-phenylpropyl)(tosyloxy)carbamate** was prepared according to a published literature procedure; spectral data were in agreement with literature values[8]

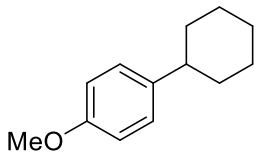


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.30 – 7.25 (m, 2H), 7.23 – 7.13 (m, 3H), 3.64 (br, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.45 (s, 3H), 1.97 (p, *J* = 7.8Hz, 2H), 1.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.46, 145.66, 141.09, 131.26, 129.68, 129.52, 128.42, 128.30, 126.00, 83.23, 52.64, 32.82, 27.61, 27.42, 21.69.

Methyl (tosyloxy)carbamate (85) was prepared according to a published literature procedure; spectral data were in agreement with literature values[8]

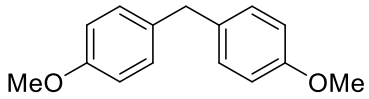
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 3.64 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.97, 146.19, 130.28, 129.73, 129.53, 53.66, 21.77.

1-Cyclohexyl-4-methoxybenzene (5) was prepared according to a published literature procedure; spectral data were in agreement with literature values[9]



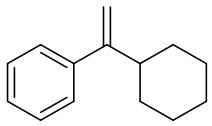
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 2.51 – 2.40 (m, 1H), 1.91 – 1.79 (m, 4H), 1.77 – 1.69 (m, 1H), 1.52 – 1.17 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.66, 140.39, 127.62, 113.66, 55.24, 43.70, 34.73, 26.97, 26.19.

bis(4-Methoxyphenyl)methane (27) was prepared according to a published literature procedure; spectral data were in agreement with literature values[10]



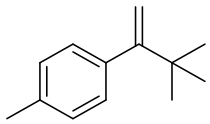
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.7 Hz, 4H), 6.83 (d, *J* = 8.7 Hz, 4H), 3.88 (s, 2H), 3.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.92, 133.72, 129.72, 113.85, 55.24, 40.10.

(1-Cyclohexylvinyl)benzene (45) was prepared according to Wittig reaction procedure; spectral data were in agreement with literature values[11]



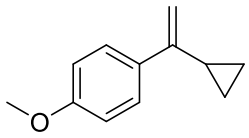
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.15 (m, 5H), 5.14 (s, 1H), 5.02 (s, 1H), 2.67 – 2.30 (m, 1H), 2.02 – 1.62 (m, 5H), 1.48 – 0.99 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.02, 142.98, 128.09, 126.96, 126.62, 110.30, 42.58, 32.70, 26.82, 26.43.

1-(3,3-Dimethylbut-1-en-2-yl)-4-methylbenzene (46) was prepared according to Wittig reaction procedure; spectral data were in agreement with literature values[12]



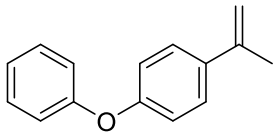
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.3 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 5.15 (d, *J* = 1.8 Hz, 1H), 4.75 (d, *J* = 1.8 Hz, 1H), 2.35 (s, 3H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.79, 140.55, 135.72, 128.88, 127.95, 111.39, 36.10, 29.67, 21.06.

1-(1-Cyclopropylvinyl)-4-methoxybenzene (47) was prepared according to Wittig reaction procedure; spectral data were in agreement with literature values[13]



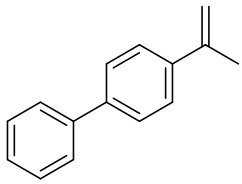
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.21 (s, 1H), 4.86 (s, 1H), 3.83 (s, 3H), 1.65 – 1.60 (m, 1H), 0.92 – 0.78 (m, 2H), 0.68 – 0.53 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.10, 148.53, 134.12, 127.14, 113.45, 107.41, 55.26, 15.64, 6.51.

1-Phenoxy-4-(prop-1-en-2-yl)benzene (48) was prepared according to Wittig reaction procedure



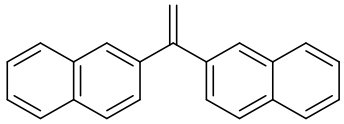
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.8 Hz, 2H), 7.38 – 7.30 (m, 2H), 7.16 – 7.08 (m, 1H), 7.06 – 7.01 (m, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.34 (s, 1H), 5.06 (s, 1H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.22, 156.68, 142.47, 136.32, 129.73, 126.84, 123.26, 118.88, 118.50, 111.68, 21.87.

4-(Prop-1-en-2-yl)-1,1'-biphenyl (49) was prepared according to Wittig reaction procedure; spectral data were in agreement with literature values[14]



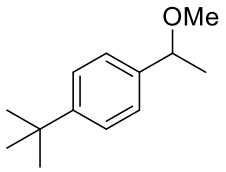
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.54 (m, 6H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 5.46 (s, 1H), 5.14 (s, 1H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.76, 140.76, 140.19, 140.11, 128.76, 127.25, 126.97, 126.91, 125.89, 112.45, 21.78.

2,2'-(Ethene-1,1-diyl)dinaphthalene (50) was prepared according to Wittig reaction procedure; spectral data were in agreement with literature values[15]



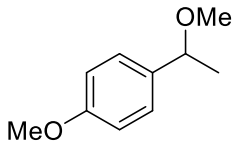
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 – 7.76 (m, 8H), 7.63 – 7.42 (m, 6H), 5.70 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.03, 138.92, 133.31, 133.00, 128.21, 127.76, 127.61, 127.42, 126.47, 126.19, 126.06, 115.33.

1-(*tert*-Butyl)-4-(1-methoxyethyl)benzene (61) was prepared according to Williamson ether synthesis



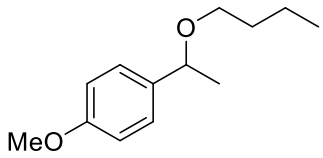
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 4.28 (q, *J* = 6.4 Hz, 1H), 3.23 (s, 3H), 1.44 (d, *J* = 6.4 Hz, 3H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.30, 140.35, 125.88, 125.26, 79.35, 56.39, 34.48, 31.38, 23.68.

1-Methoxy-4-(1-methoxyethyl)benzene (62) was prepared according to Williamson ether synthesis; spectral data were in agreement with literature values[16]



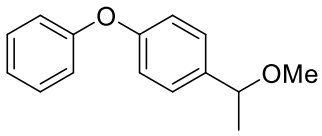
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.25 (q, *J* = 6.4 Hz, 1H), 3.81 (s, 3H), 3.20 (s, 3H), 1.42 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.98, 135.50, 127.39, 113.76, 79.09, 56.17, 55.23, 23.74.

1-(1-Butoxyethyl)-4-methoxybenzene (63) was prepared according to a published literature; spectral data were in agreement with literature values[16]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H),4.33 (q, J = 6.5 Hz, 1H), 3.81 (s, 3H), 3.27 (t, J = 6.6 Hz, 2H), 1.59 – 1.47 (m, 2H), 1.41 (d, J = 6.5 Hz, 2H), 1.39 – 1.22 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H).

1-(1-Methoxyethyl)-4-phenoxybenzene (64)



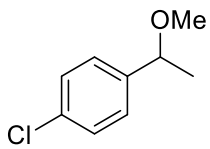
To a solution of 1-(4-phenoxyphenyl)ethan-1-ol (214 mg, 1 mmol) in 5 mL THF was added 40% NaH (48 mg, 1.2 mmol) at 0°C, then the mixture was stirred for 30 min at 0°C, followed by added CH_3I (124 uL, 2 mmol) at 0°C. The reaction was warmed up to room temperature, and stirred overnight at room temperature. Then the reaction was quenched with 5 mL sat. NH_4Cl aq., extracted with EA (10 mL × 3), the combined organic layer was washed with 20 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA (10 : 1) to afford the 1-(1-methoxyethyl)-4-phenoxybenzene as a colorless liquid (196 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 2H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.14 – 7.07 (m, 1H), 7.05 – 6.96 (m, 4H), 4.29 (q, *J* = 6.4 Hz, 1H), 3.24 (s, 3H), 1.44 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.22, 156.56, 138.28, 129.71, 127.58, 123.21, 118.86, 118.73, 79.08, 56.34, 23.73.

IR (Reflexion) ṽ = 3063, 3039, 2976, 2929, 2877, 2819, 1590, 1505, 1489, 1371, 1346, 1280, 1240, 1165, 1103, 1083, 1061, 1014, 995, 872, 840, 757, 692 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 228.1145, found 228.1117.

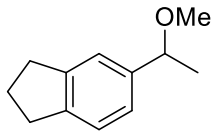
1-Chloro-4-(1-methoxyethyl)benzene (65) was prepared according to Williamson ether synthesis; spectral data were in agreement with literature values[18]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 4.27

(q, J = 6.4 Hz, 1H), 3.22 (s, 3H), 1.41 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.07, 133.06, 128.60, 127.54, 78.95, 56.45, 23.79.

5-(1-Methoxyethyl)-2,3-dihydro-1*H*-indene (66)



To a solution of 1-(2,3-dihydro-1*H*-inden-5-yl)ethan-1-ol (310 mg, 1.9 mmol) in 20 mL THF was added 40% NaH (228 mg, 3.8 mmol) at 0°C, then the mixture was stirred for 30 min at 0°C, followed by added CH_3I (236 uL, 3.8 mmol) at 0°C. The reaction was warmed up to room temperature, and stirred for 16 h at room temperature. Then the reaction was quenched with 20 mL sat. NH_4Cl aq., extracted with EA (20 mL × 3), the combined organic layer was washed with 30 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA (10 : 1) to afford the 5-(1-methoxyethyl)-2,3-dihydro-1*H*-indene as a colorless liquid (201 mg, 60%).

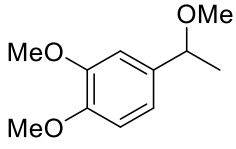
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 2H), 7.08 (dd, J = 7.7, 1.7 Hz, 1H), 4.28 (q, J = 6.4 Hz, 1H), 3.23 (s, 3H), 2.91 (td, J = 7.5, 3.2 Hz, 4H), 2.09 (p, J = 7.5 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.48, 143.50, 141.41, 124.20, 124.18, 122.12, 79.71, 56.34, 32.78, 32.55, 25.47, 24.00.

IR (Reflexion) $\tilde{\nu}$ = 2973, 2932, 2892, 2845, 2817, 1681, 1613, 1581, 1489, 1439, 1369, 1343, 1317, 1257, 1234, 1203, 1139, 1112, 1082, 1058, 994, 896, 871, 848, 821, 711, 618 cm^{-1}

HRMS (EI+) m/z: $[M-15]^+$ calcd 161.0966, found 161.0945.

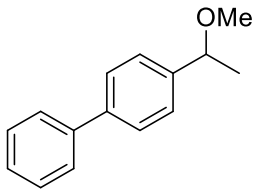
1,2-Dimethoxy-4-(1-methoxyethyl)benzene (70) was prepared according to Williamson ether synthesis



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 – 6.82(m, 3H), 4.24 (q, J = 6.4 Hz, 1H), 3.89 (s,

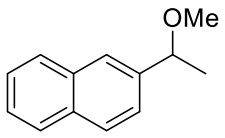
3H), 3.87 (s, 3H), 3.21 (s, 3H), 1.43 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.17, 148.36, 136.09, 118.65, 110.83, 108.85, 79.37, 56.25, 55.88, 55.83, 23.81.

4-(1-Methoxyethyl)-1,1'-biphenyl (71) was prepared according to Williamson ether synthesis; spectral data were in agreement with literature values[19]



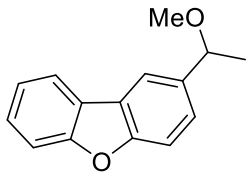
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.56 (m, 4H), 7.51 – 7.30 (m, 5H), 4.36 (q, J = 6.4 Hz, 1H), 3.28 (s, 3H), 1.49 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.56, 140.92, 140.42, 128.73, 127.19, 127.06, 126.62, 79.36, 56.49, 23.82.

2-(1-Methoxyethyl)naphthalene (72) was prepared according to Williamson ether synthesis; spectral data were in agreement with literature values[16]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.81 (m, 3H), 7.74 (d, J = 1.6 Hz, 1H), 7.53 – 7.43 (m, 3H), 4.47 (q, J = 6.4 Hz, 1H), 3.27 (s, 3H), 1.52 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.92, 133.28, 133.04, 128.35, 127.81, 127.69, 126.06, 125.71, 125.13, 124.11, 79.75, 56.51, 23.83.

2-(1-Methoxyethyl)dibenzo[*b*,*d*]furan (73)



To a solution of 1-(dibenzo[*b*,*d*]furan-2-yl)ethan-1-ol (149 mg, 0.7 mmol) in 3 mL THF was added 40% NaH (34 mg, 0.84 mmol) at 0°C, then the mixture was stirred for 30 min at 0°C, followed by added CH_3I (87 uL, 1.4 mmol) at 0°C. The reaction was

warmed up to room temperature, and stirred for 16 h at room temperature. Then the reaction was quenched with 3 mL sat. NH_4Cl aq., extracted with EA (7 mL × 3), the combined organic layer was washed with 10 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA (10 : 1) to afford the 2-(1-methoxyethyl)dibenzo[*b*,*d*]furan as a colorless liquid (146 mg, 92%).

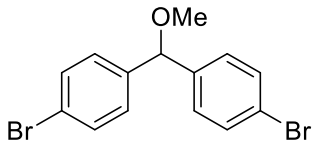
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (ddd, *J* = 7.6, 1.2, 0.7 Hz, 1H), 7.91 (d, *J* = 1.8 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.49 – 7.43 (m, 1H), 7.41 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.35 (td, *J* = 7.6, 1.2 Hz, 1H), 4.47 (q, *J* = 6.5 Hz, 1H), 3.27 (s, 3H), 1.53 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.55, 155.68, 138.18, 127.15, 125.45, 124.30, 124.15, 122.68, 120.64, 118.23, 111.67, 111.49, 79.69, 56.44, 24.31.

IR (Reflexion) ṽ = 3050, 2975, 2928, 2873, 2819, 1602, 1479, 1449, 1371, 1332, 1293, 1262, 1243, 1194, 1149, 1110, 1084, 1059, 1022, 996, 931, 887, 842, 816, 768, 748, 661, 634 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 226.0988, found 226.0987.

4,4'-(Methoxymethylene)bis(bromobenzene) (74)

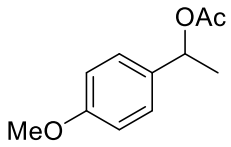


To a solution of bis(4-bromophenyl)methanol (342 mg, 1 mmol) in 5 mL THF was added 60% NaH (48 mg, 1.2 mmol) at 0°C, and then stirred for 30 min, followed by the addition of iodomethane (124 uL, 2 mmol). The reaction was warmed up to room temperature, and stirred overnight. The reaction was quenched with 5 mL sat. NH_4Cl aq., extracted with EA (10 mL × 3), the combined organic layer was washed with 20 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA (20 : 1) to afford the 4,4'-(methoxymethylene)bis(bromobenzene) as a colorless solid (347 mg, 97%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 4H), 7.19 (d, *J* = 8.4 Hz, 4H), 5.15 (s, 1H), 3.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.63, 131.62, 128.53, 121.62,

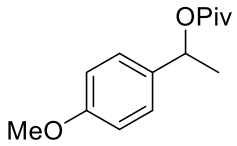
84.02, 56.99.

1-(4-Methoxyphenyl)ethyl acetate (88) was prepared according to a published procedure; spectral data were in agreement with literature values[20]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.85 (q, *J* = 6.6 Hz, 1H), 3.80 (s, 3H), 2.05 (s, 3H), 1.52 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.36, 159.26, 133.73, 127.58, 113.81, 71.98, 55.25, 21.92, 21.38.

1-(4-Methoxyphenyl)ethyl pivalate (89)



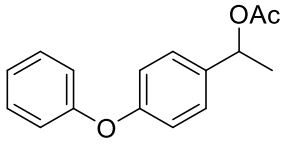
To a solution of 1-(4-methoxyphenyl)ethan-1-ol (761 mg, 5 mmol), DAMP (61 mg, 0.5 mmol), pivaloyl chloride (800 uL, 1.5 mmol) in 20 mL DCM solution was added Et_3N (1.04 mL, 7.5 mmol) at 0ºC, then the reaction mixture was warmed up to room temperature and stirred overnight. Then the reaction was quenched with 20 mL sat. NH_4Cl aq., extracted with DCM (20 mL × 3), the combined organic layer was washed with 30 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA (20 : 1) to afford 1-(4-methoxyphenyl)ethyl pivalate as a colorless liquid (350 mg, 30%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.81 (q, *J* = 6.6 Hz, 1H), 3.80 (s, 3H), 1.50 (d, *J* = 6.6 Hz, 3H), 1.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.68, 159.06, 134.25, 127.20, 113.77, 71.61, 55.23, 38.67, 27.08, 22.18.

IR (Reflexion) ṽ = 2977, 2935, 2908, 2872, 2837, 1810, 1729, 1614, 1586, 1516, 1480, 1460, 1396, 1368, 1282, 1250, 1210, 1165, 1098, 1062, 1036, 1001, 939, 909, 868, 832, 771, 721, 639 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 236.1407, found 236.1391.

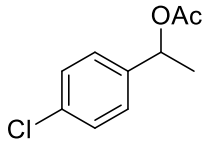
1-(4-phenoxyphenyl)ethyl acetate (90)



To a solution of 1-(4-phenoxyphenyl)ethan-1-ol (857 mg, 4 mmol), DAMP (49 mg, 0.4 mmol), acetic anhydride (563 uL, 6 mmol) in 20 mL DCM solution was added Et_3N (834 uL, 6 mmol) at 0°C, then the reaction mixture was warmed up to room temperature and stirred overnight. Then the reaction was quenched with 20 mL sat. NH_4Cl aq., extracted with DCM (20 mL × 3), the combined organic layer was washed with 30 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA (10 : 1) to afford 1-(4-phenoxyphenyl)ethyl acetate as a colorless liquid (850 mg, 83%).

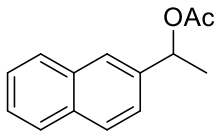
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.02 (dd, *J* = 8.6, 1.2 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 5.88 (q, *J* = 6.6 Hz, 1H), 2.07 (s, 3H), 1.54 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.32, 156.97, 136.36, 129.74, 127.69, 123.39, 119.04, 118.60, 71.85, 22.07, 21.36.

1-(4-chlorophenyl)ethyl acetate (91) was prepared according to a published procedure; spectral data were in agreement with literature values[21]



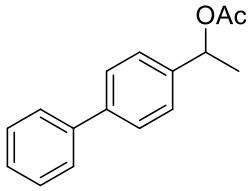
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 4H), 5.84 (q, *J* = 6.6 Hz, 1H), 2.07 (s, 3H), 1.51 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.19, 140.19, 133.60, 128.65, 127.50, 71.57, 22.12, 21.26.

1-(Naphthalen-2-yl)ethyl acetate (92) was prepared according to a published procedure; spectral data were in agreement with literature values[22]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.80 (m, 4H), 7.55 – 7.41 (m, 3H), 6.05 (q, *J* = 6.6 Hz, 1H), 2.10 (s, 3H), 1.63 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.34, 138.99, 133.17, 133.01, 128.34, 128.01, 127.64, 126.21, 126.04, 125.00, 124.08, 72.41, 22.16, 21.37.

1-([1,1'-Biphenyl]-4-yl)ethyl acetate (93)



To a solution of 1-([1,1'-biphenyl]-4-yl)ethan-1-ol (397 mg, 2 mmol), acetic chloride (284 uL, 4 mmol) in 15 mL DCM solution was added Et_3N (834 uL, 6 mmol) at 0ºC, then the reaction mixture was warmed up to room temperature and stirred overnight. Then the reaction was quenched with 20 mL sat. NH_4Cl aq., extracted with DCM (15 mL × 3), the combined organic layer was washed with 30 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA (10 : 1) to afford 1-([1,1'-Biphenyl]-4-yl)ethyl acetate as a colorless liquid (200 mg, 42%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.1 Hz, 4H), 7.48 – 7.40 (m, 4H), 7.38 – 7.31 (m, 1H), 5.93 (q, *J* = 6.6 Hz, 1H), 2.10 (s, 3H), 1.58 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.36, 140.88, 140.76, 140.65, 128.76, 127.34, 127.28, 127.12, 126.57, 72.09, 22.14, 21.38.

IR (Reflexion) $\tilde{\nu}$ = 3056, 3030, 2981, 2933, 1730, 1600, 1486, 1450, 1409, 1370, 1306, 1235, 1061, 1023, 1007, 942, 835, 764, 732, 696 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 240.1145, found 240.1145.

General Procedure for the Synthesis of Anilines – GP 1 (for alkylarenes)

To a solution of the alkylarene (0.2 mmol) in 1.0 mL TFA was added aminating reagent

(0.3 mmol) and DDQ (50 mg, 0.22 mmol) at room temperature under ambient atmosphere, and the reaction was stirred at room temperature for 12 h (monitored by GCMS or TLC) unless otherwise stated. The reaction was diluted with 1 mL DCM and basified with 1 mL saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with DCM (3 mL × 3), and the combined organic layers were washed with 5 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA to afford the desired aniline.

General Procedure for the Synthesis of Anilines – GP 2 (for styrenes, benzyl ethers and esters)

To a solution of the styrenes/benzyl ethers/benzyl esters (0.2 mmol) in 1.0 mL HFIP was added aminating reagent (0.3 mmol) at room temperature under ambient atmosphere, and the reaction was stirred at room temperature for 6 h or 12 h (monitored by GCMS or TLC) unless otherwise stated. The reaction was diluted with 1 mL DCM and basified with 1 mL saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with DCM (3 mL × 3), and the combined organic layers were washed with 5 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA to afford the desired aniline.

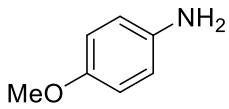
General Procedure for the Removal of the Boc Group – GP 3

To a solution of *N*-Boc-*N*-alkyl-*O*-tosyl hydroxylamine (1.0 eq) in DCM was added TFA (20.0 eq) at 0°C, then it was stirred at 0°C for 3 h (monitored by TLC). The reaction was quenched with cold water at 0°C and then extracted with DCM. The combined organic layers were washed with sat. brine and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EA to afford the desired product or directly used for the next step without further purification.

4.4.3 Substrate Scope with Respect to Alkylarenes and Styrenes

Alkylarene Scope

4-Methoxyaniline (10) spectral data were in agreement with literature values[4]

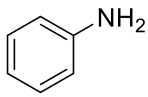


Following **GP 1**, 4-isopropylanisole (**1**, 30 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-methoxyaniline **10** as a yellow oil (17 mg, 71%).

Following **GP 1**, 1-cyclohexyl-4-methoxybenzene (**5**, 38 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-methoxyaniline **10** as a yellow oil (20 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 3.75 (s, 3H), 3.42 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.78, 139.88, 116.39, 114.77, 55.70.

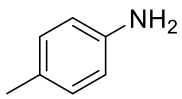
Aniline (11) spectral data were in agreement with literature values[4]



Following **GP 1**, cumene (**6**, 24 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded aniline **11** as a yellow oil (4 mg, 32%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 – 7.14 (m, 2H), 6.81 – 6.74 (m, 1H), 6.75 – 6.66 (m, 2H), 3.57 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.29, 129.26, 118.55, 115.09.

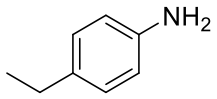
***p*-Toluidine (12)** spectral data were in agreement with literature values[4]



Following **GP 1**, *p*-cymene (**7**, 24 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded *p*-toluidine **12** as a yellow solid (12 mg, 57%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.1 Hz, 2H), 6.62 (d, *J* = 8.1 Hz, 2H), 3.53 (br, 2H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.79, 129.71, 127.72, 115.21, 20.40.

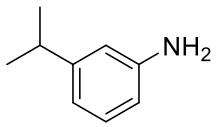
4-Ethylaniline (13) spectral data were in agreement with literature values[4]



Following **GP 1**, 4-ethylcumene (**8**, 29 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-ethylaniline **13** as a yellow oil (5 mg, 21%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.3 Hz, 2H), 6.64 (d, *J* = 8.3 Hz, 2H), 3.54 (br, 2H), 2.56 (q, *J* = 7.6 Hz, 2H), 1.20 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.02, 134.43, 128.55, 115.24, 27.94, 15.91.

3-Isopropylaniline (14)

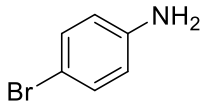


Following **GP 1**, 1,3-diisopropylbenzene (**9**, 32 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 3-isopropylaniline **14** as a yellow oil (16 mg, 59%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (t, *J* = 7.7 Hz, 2H), 6.66 (d, *J* = 7.7 Hz, 1H), 6.58 (t, *J* = 2.2 Hz, 2H), 6.53 (dd, *J* = 7.7, 2.2 Hz, 1H), 3.57 (br, 2H), 2.82 (hept, *J* = 6.8 Hz, 1H), 1.24 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.22, 146.30, 129.16,

116.85, 113.31, 112.67, 34.05, 23.89.

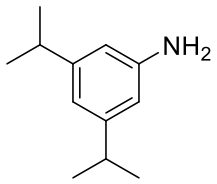
4-Bromoaniline (15) spectral data were in agreement with literature values[2]



Following **GP 1**, 4-bromocumene (**19**, 40 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 36 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-bromoaniline **15** as a brown solid (17 mg, 50%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.56 (d, *J* = 8.7 Hz, 2H), 3.66 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.39, 131.98, 116.67, 110.17.

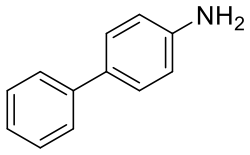
3,5-Diisopropylaniline (20) spectral data were in agreement with literature values[23]



Following **GP 1**, 1,3,5-triisopropylbenzene (**16**, 41 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 3,5-diisopropylaniline **20** as a yellow oil (23 mg, 66%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (d, *J* = 1.6 Hz, 1H), 6.42 (d, *J* = 1.6 Hz, 2H), 3.57 (br, 2H), 2.80 (hept, *J* = 6.9 Hz, 2H), 1.23 (d, *J* = 6.9 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.09, 146.13, 115.54, 110.88, 34.12, 23.95.

[1,1'-Biphenyl]-4-amine (21) spectral data were in agreement with literature values[2]

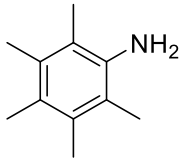


Following **GP 1**, 4-phenylcumene (**17**, 39 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room

temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded [1,1'-biphenyl]-4-amine **21** as a yellow solid (10 mg, 30%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.49 – 7.37 (m, 4H), 7.28 (t, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 2H), 3.73 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.80, 141.12, 131.54, 128.62, 127.97, 126.36, 126.21, 115.35.

2,3,4,5,6-Pentamethylaniline (22) spectral data were in agreement with literature values[4]



Following **GP 1**, hexamethylbenzene (**18**, 32 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 2,3,4,5,6-pentamethylaniline **22** as a brown solid (11 mg, 34%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (s, 2H), 2.26 (s, 6H), 2.23 (s, 3H), 2.17 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.24, 132.24, 125.01, 118.13, 16.62, 16.38, 13.74.

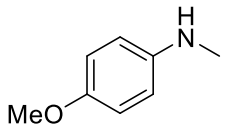
4-Methoxy-*N*-methylaniline (3) and 4-methoxybenzaldehyde

Following **GP 1**, 4-ethylanisole (**26**, 27 mg, 0.2 mmol), TsONHMe (**2**, 60 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-methoxy-*N*-methylaniline **3** as a yellow oil (20 mg, 74%).

Following **GP 1**, bis(4-methoxyphenyl)methane (**27**, 45 mg, 0.2 mmol), TsONHMe (**2**, 60 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-methoxy-*N*-methylaniline **3** as a yellow oil (17 mg,

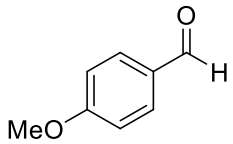
63%) and 4-methoxybenzaldehyde (25 mg, 93%).

4-Methoxy-*N*-methylaniline (3) spectral data were in agreement with literature values[4]



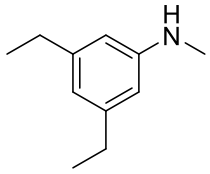
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 3.76 (s, 3H), 3.31 (br, 1H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.06, 143.68, 114.89, 113.61, 55.83, 55.81, 31.57.

4-Methoxybenzaldehyde spectral data were in agreement with literature values[24]



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.75, 164.60, 131.94, 129.97, 114.29, 55.54.

3,5-Diethyl-*N*-methylaniline (30)



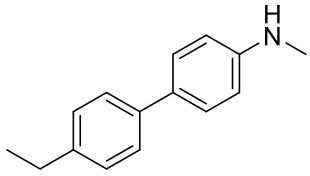
Following **GP 1**, 1,3,5-triethylbenzene (**28**, 32 mg, 0.2 mmol), TsONHMe (**2**, 60 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 3,5-diethyl-*N*-methylaniline **30** as a yellow oil (21 mg, 65%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (s, 1H), 6.32 (s, 2H), 3.42 (br 1H), 2.85 (s, 3H), 2.59 (q, *J* = 7.6 Hz, 4H), 1.25 (t, *J* = 7.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.50, 145.33, 116.86, 109.52, 30.84, 29.01, 15.55.

IR (Reflexion) $\tilde{\nu}$ = 3408, 2963, 2930, 2872, 2809, 1604, 1514, 1462, 1350, 1299, 1188, 1065, 992, 914, 839, 701 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 163.1355, found 163.1345.

4'-Ethyl-*N*-methyl-[1,1'-biphenyl]-4-amine (31)



Following **GP 1**, 4,4'-diethylbiphenyl (**29**, 42 mg, 0.2 mmol), TsONHMe (**2**, 60 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4'-ethyl-*N*-methyl-[1,1'-biphenyl]-4-amine **31** as a yellow solid (35 mg, 83%).

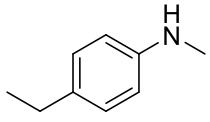
MP. 32°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.44(m, 4H), 7.25 (d, *J* = 8.1 Hz, 2H), 6.69 (d, *J* = 8.6 Hz, 2H), 3.76 (br, 1H), 2.88 (s, 3H), 2.69 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.51, 142.03, 138.72, 130.20, 128.13, 127.73, 126.21, 112.63, 30.76, 28.43, 15.61.

IR (ATR) $\tilde{\nu}$ = 3416, 3022, 2962, 2929, 2871, 2812, 1612, 1533, 1503, 1452, 1321, 1302, 1276, 1256, 1183, 1156, 1124, 1063, 962, 817, 717, 638 cm^{-1}

HRMS (EI+) m/z: $[M]^+$ calcd 211.1355, found 211.1342.

4-Ethyl-*N*-methylaniline (32) spectral data were in agreement with literature values[4]

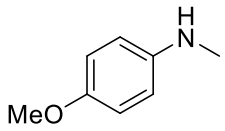


Following **GP 1**, 4-ethylcumene (**8**, 29 mg, 0.2 mmol), TsONHMe (**2**, 60 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-ethyl-*N*-methylaniline **32** as a yellow oil (6 mg, 22%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.5 Hz, 2H), 6.60 (d, *J* = 8.5 Hz, 2H), 3.57 (s, 1H), 2.84 (s, 3H), 2.57 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.10, 133.37, 128.50, 112.75, 31.16, 27.91, 15.96.

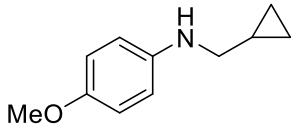
Aminating Reagents Scope

4-Methoxy-*N*-methylaniline (3)



Following **GP 1**, 4-isopropylanisole (**1**, 30 mg, 0.2 mmol), TsONHMe (**2**, 60 mg, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-methoxy-*N*-methylaniline **3** as a yellow oil (20 mg, 74%).

***N*-(Cyclopropylmethyl)-4-methoxyaniline (41)** spectral data were in agreement with literature values[25]

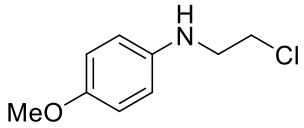


Following **GP 3**, *tert*-butyl (cyclopropylmethyl)(tosyloxy)carbamate (102 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(cyclopropylmethyl)-*O*-tosylhydroxylamine **37**, which was directly used for the next step without further purification.

Following **GP 1**, 4-isopropylanisole (**1**, 30 mg, 0.2 mmol), crude *N*-(cyclopropylmethyl)-*O*-tosylhydroxylamine (**37**, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 2 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-(cyclopropylmethyl)-4-methoxyaniline **41** as a yellow oil (20 mg, 57%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 3H), 3.19 (br, 1H), 2.92 (d, *J* = 6.9 Hz, 2H), 1.19 – 1.03 (m, 1H), 0.67 – 0.48 (m, 2H), 0.26 – 0.20 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.09, 142.76, 114.87, 114.16, 55.80, 50.14, 10.97, 3.38.

***N*-(2-Chloroethyl)-4-methoxyaniline (42)**

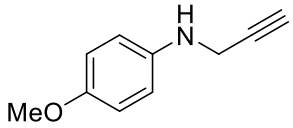


Following **GP 3**, *tert*-butyl (2-chloroethyl)(tosyloxy)carbamate (105 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(2-chloroethyl)-*O*-tosylhydroxylamine **38**, which was directly used for the next step without further purification.

Following **GP 1**, 4-isopropylanisole (**1**, 30 mg, 0.2 mmol), crude *N*-(2-chloroethyl)-*O*-tosylhydroxylamine (**38**, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-(2-chloroethyl)-4-methoxyaniline **42** as a yellow oil (34 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, *J* = 8.9 Hz, 2H), 6.64 (d, *J* = 8.9 Hz, 2H), 3. (s, 3H), 3.70 (t, *J* = 5.9 Hz, 2H), 3.46 (t, *J* = 5.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.88, 140.87, 115.02, 115.00, 55.74, 46.65, 43.53.

4-Methoxy-*N*-(prop-2-yn-1-yl)aniline (43) spectral data were in agreement with literature values[26]



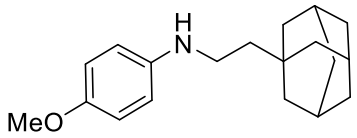
Following **GP 3**, *tert*-butyl prop-2-yn-1-yl(tosyloxy)carbamate (98 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(prop-2-yn-1-yl)-*O*-tosylhydroxylamine **39**, which was directly used for the next step without further purification.

Following **GP 1**, 4-isopropylanisole (**1**, 30 mg, 0.2 mmol), crude *N*-(prop-2-yn-1-yl)-*O*-tosylhydroxylamine (**39**, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-(prop-2-

yn-1-yl)aniline **43** as a yellow solid (27 mg, 84%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (d, *J* = 8.9 Hz, 2H), 6.68 (d, *J* = 8.9 Hz, 2H), 3.90 (d, *J* = 2.4 Hz, 2H), 3.76 (s, 3H), 3.65 (br, 1H), 2.21 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.90, 140.83, 115.05, 114.73, 81.30, 71.18, 55.65, 34.51.

***N*-(2-(Adamantan-1-yl)ethyl)-4-methoxyaniline (44)** spectral data were in agreement with literature values[27]



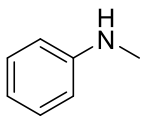
Following **GP 3**, *tert*-butyl (2-(adamantan-1-yl)ethyl)(tosyloxy)carbamate (135 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(2-(adamantan-1-yl)ethyl)-*O*-tosylhydroxylamine **40**, which was directly used for the next step without further purification.

Following **GP 1**, 4-isopropylanisole (**1**, 30 mg, 0.2 mmol) crude *N*-(2-(adamantan-1-yl)ethyl)-*O*-tosylhydroxylamine (**40**, 0.3 mmol) and DDQ (50 mg, 0.22 mmol) in 1.0 mL TFA solution were stirred for 3 days at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-(2-(adamantan-1-yl)ethyl)-4-methoxyaniline **44** as a yellow solid (56 mg, 99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (d, *J* = 9.0 Hz, 2H), 6.58 (d, *J* = 9.0 Hz, 2H), 3.75 (s, 3H), 3.24 – 2.93 (m, 2H), 1.99 – 1.95 (m, 3H), 1.75 – 1.61 (m, 6H), 1.56 (d, *J* = 2.9 Hz, 6H), 1.41 – 1.35 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.91, 142.88, 114.83, 114.01, 55.80, 44.14, 42.58, 39.53, 37.08, 31.96, 28.61.

Styrenes scope

***N*-Methylaniline (51)** spectral data were in agreement with literature values[28]

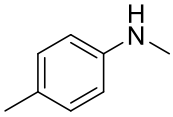


Following **GP 2**, (1-cyclohexylvinyl)benzene (**45**, 37 mg, 0.2 mmol) and TsONHMe (**2**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature.

Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-methylaniline **51** as a yellow oil (7 mg, 33%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.14 (m, 2H), 6.78 – 6.66 (m, 1H), 6.63 (d, *J* = 8.7 Hz, 1H), 3.73 (br, 1H), 2.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.32, 129.18, 117.24, 112.40, 30.71.

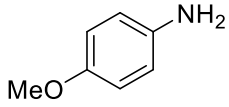
***N*,4-Dimethylaniline (52)** spectral data were in agreement with literature values[4]



Following **GP 2**, 1-(3,3-dimethylbut-1-en-2-yl)-4-methylbenzene (**46**, 35 mg, 0.2 mmol) and TsONHMe (**2**, 44 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*,4-dimethylaniline **52** as a yellow oil (5 mg, 21%).

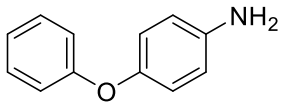
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.2 Hz, 2H), 6.57 (d, *J* = 8.2 Hz, 2H), 3.34 (s, 1H), 2.83 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.94, 129.67, 126.65, 112.74, 31.19, 20.35.

4-Methoxyaniline (10)



Following **GP 2**, 1-(1-cyclopropylvinyl)-4-methoxybenzene (**47**, 35 mg, 0.2 mmol) and MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-methoxyaniline **10** as a brown oil (12 mg, 50%).

4-Phenoxyaniline (53) spectral data were in agreement with literature values[29]

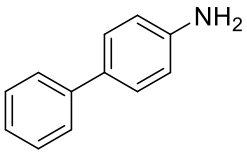


Following **GP 2**, 1-phenoxy-4-(prop-1-en-2-yl)benzene (**48**, 42 mg, 0.2 mmol) and MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room

temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-phenoxyaniline **53** as a brown oil (18 mg, 49%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 8.6, 7.3 Hz, 2H), 7.01 (tt, *J* = 7.3, 1.2 Hz, 1H), 6.94 (dd, *J* = 8.6, 1.2 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.68 (d, *J* = 8.7 Hz, 2H), 3.59 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.87, 148.57, 142.65, 129.48, 122.03, 121.09, 117.19, 116.21.

[1,1'-Biphenyl]-4-amine (21)



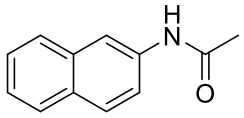
Following **GP 2**, 4-(prop-1-en-2-yl)-1,1'-biphenyl (**49**, 38 mg, 0.2 mmol) and MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded [1,1'-biphenyl]-4-amine **21** as a yellow solid (18 mg, 53%).

***N*-(Naphthalen-2-yl)acetamide (54) and 1-(naphthalen-2-yl)ethan-1-one**

Following **GP 2**, 1-phenoxy-4-(prop-1-en-2-yl)benzene (**50**, 42 mg, 0.2 mmol) and MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. The reaction was diluted with 1 mL DCM and basified with 1 mL saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with DCM (3 mL × 3), and the combined organic layers were washed with 5 mL sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The residue was dissolved in 5 mL DCM, then AcCl (28 uL, 0.4 mmol) and Et_3N (55.6 uL, 0.4 mmol) were added to the above reaction at 0^{o}C, then the reaction was warmed up to room temperature and stirred for 6 h at room temperature. The reaction was quenched with 5 mL NH_4Cl aq., extracted with DCM (5 mL × 3), the combined organic layers were washed with 20 mL

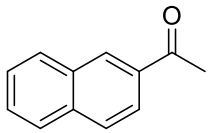
sat. brine, dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EA to afford the desired *N*-(naphthalen-2-yl)acetamide **54** as a pale yellow solid (18mg, 49%) and 1-(naphthalen-2-yl)ethan-1-one as a colorless solid (27 mg, 79%).

***N*-(Naphthalen-2-yl)acetamide (54)** spectral data were in agreement with literature values[30]



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 2.2 Hz, 1H), 7.91 – 7.61 (m, 3H), 7.53 – 7.34 (m, 4H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.82, 135.40, 133.83, 130.69, 128.73, 127.67, 127.56, 126.49, 125.04, 120.00, 116.82, 24.62.

1-(Naphthalen-2-yl)ethan-1-one spectral data were in agreement with literature values[31]

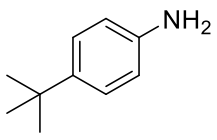


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 0.8 Hz, 1H), 8.03 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.96 (dd, *J* = 8.0, 0.8 Hz, 0H), 7.92 – 7.84 (m, 2H), 7.63 – 7.53 (m, 2H), 2.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.05, 135.58, 134.51, 132.51, 130.15, 129.53, 128.44, 128.39, 127.76, 126.75, 123.88, 26.62.

4.4.4 Substrate Scope with Respect to Benzyl Ethers/Esters

Benzyl Ether Scope

4-(*tert*-Butyl)aniline (67) spectral data were in agreement with literature values[29]

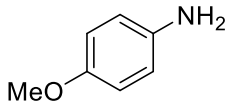


Following **GP 2**, 1-(tert-butyl)-4-(1-methoxyethyl)benzene (**61**, 38 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting

solvent afforded 4-(*tert*-butyl)aniline **67** as a yellow oil (20 mg, 67%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 2H), 6.66 (d, *J* = 8.6 Hz, 2H), 3.48 (br, 2H), 1.29 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.75, 141.40, 126.02, 114.90, 33.88, 31.50.

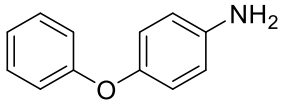
4-Methoxyaniline (10)



Following **GP 2**, 1-methoxy-4-(1-methoxyethyl)benzene (**62**, 33 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP or TFE solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-methoxyaniline **10** as a yellow oil (HFIP as the solvent: 15 mg, 62%; TFE as the solvent: 12 mg, 50%).

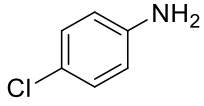
Following **GP 2**, 1-(1-butoxyethyl)-4-methoxybenzene (**63**, 42 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-methoxyaniline **10** as a yellow oil (13 mg, 54%).

4-Phenoxyaniline (53)



Following **GP 2**, 1-(1-methoxyethyl)-4-phenoxybenzene (**64**, 45 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-phenoxyaniline **53** as a yellow solid (23 mg, 62%).

4-Chloroaniline (68) spectral data were in agreement with literature values[29]

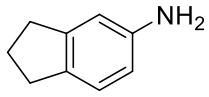


Following **GP 2**, 1-chloro-4-(1-methoxyethyl)benzene (**65**, 34 mg, 0.2 mmol), MSH (**4**,

64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-chloroaniline **68** as a yellow solid (12 mg, 35%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.7 Hz, 2H), 6.60 (d, *J* = 8.7 Hz, 2H), 3.65 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.92, 129.08, 123.11, 116.19.

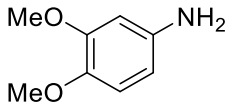
2,3-Dihydro-1*H*-inden-5-amine (69) spectral data were in agreement with literature values[32]



Following **GP 2**, 5-(1-methoxyethyl)-2,3-dihydro-1*H*-indene (**66**, 35 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 2,3-dihydro-1*H*-inden-5-amine **69** as a yellow solid (15 mg, 56%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 2.1 Hz, 1H), 6.51 (dd, *J* = 7.8, 2.1 Hz, 1H), 3.51 (br, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.05 (p, *J* = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.47, 144.74, 134.22, 124.71, 113.25, 111.45, 32.95, 31.91, 25.64.

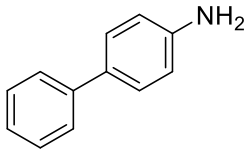
3,4-Dimethoxyaniline (76) spectral data were in agreement with literature values[2]



Following **GP 2**, 1,2-dimethoxy-4-(1-methoxyethyl)benzene (**70**, 39 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 3,4-dimethoxyaniline **76** as a yellow oil (27 mg, 88%).

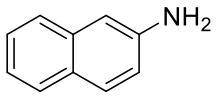
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, *J* = 8.4 Hz, 1H), 6.30 (d, *J* = 2.6 Hz, 1H), 6.22 (dd, *J* = 8.4, 2.6 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.40 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.88, 142.17, 140.64, 113.17, 106.36, 100.74, 56.60, 55.67.

[1,1'-Biphenyl]-4-amine (21)



Following **GP 2**, 4-(1-methoxyethyl)-1,1'-biphenyl (**71**, 42 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded [1,1'-Biphenyl]-4-amine **21** as a yellow solid (24 mg, 71%).

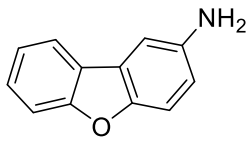
Naphthalen-2-amine (77) spectral data were in agreement with literature values[29]



Following **GP 2**, 2-(1-methoxyethyl)naphthalene (**72**, 37 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded naphthalen-2-amine **77** as a yellow solid (20 mg, 70%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.39 (ddd, *J* = 8.2, 6.7, 1.2 Hz, 1H), 7.25 (ddd, *J* = 8.2, 6.7, 1.2 Hz, 1H), 6.99 (d, *J* = 2.3 Hz, 1H), 6.95 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.83 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.06, 134.87, 129.16, 127.93, 127.67, 126.30, 125.75, 122.42, 118.19, 108.54.

Dibenzo[*b*,*d*]furan-2-amine (78) spectral data were in agreement with literature values[29]

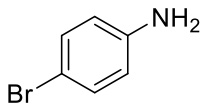


Following **GP 2**, 2-(1-methoxyethyl)dibenzo[*b*,*d*]furan (**73**, 35 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded

4-methoxyaniline **78** as a yellow solid (21 mg, 57%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.42 (td, *J* = 8.3, 1.2 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.29 (td, *J* = 7.4, 1.2 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.4 Hz, 1H), 3.59 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.73, 150.33, 142.01, 126.89, 124.84, 124.28, 122.19, 120.51, 115.72, 111.89, 111.59, 105.94.

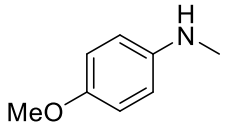
4-Bromoaniline (19)



Following **GP 2**, 4,4'-(methoxymethylene)bis(bromobenzene) (**74**, 71 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-bromoaniline **19** as a yellow solid (11 mg, 32%).

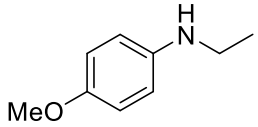
Aminating reagents scope

4-Methoxy-*N*-methylaniline (3)



Following **GP 2**, 1-methoxy-4-(1-methoxyethyl)benzene (**62**, 33 mg, 0.2 mmol), TsONHMe (**2**, 60 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-methoxy-*N*-methylaniline **3** as a yellow oil (20 mg, 74%).

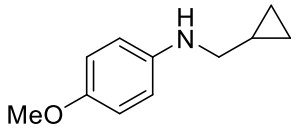
***N*-Ethyl-4-methoxyaniline (82)** spectral data were in agreement with literature values[33]



Following **GP 3**, *tert*-butyl ethyl(tosyloxy)carbamate (95 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-ethyl-*O*-tosylhydroxylamine **80** which was directly used for the next step without further purification.

Following **GP 2**, 1-methoxy-4-(1-methoxyethyl)benzene (**62**, 33 mg, 0.2 mmol), crude *N*-ethyl-*O*-tosylhydroxylamine (**80**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded *N*-ethyl-4-methoxyaniline **82** as a yellow oil (28 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (d, *J* = 8.9 Hz, 2H), 6.59 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 3H), 3.22 (br, 1H), 3.12 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.05, 142.71, 114.86, 114.10, 55.79, 39.43, 14.95.

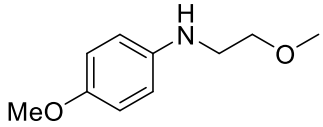
_N_-(Cyclopropylmethyl)-4-methoxyaniline (41)



Following **GP 3**, *tert*-butyl (cyclopropylmethyl)(tosyloxy)carbamate (102 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(cyclopropylmethyl)-*O*-tosylhydroxylamine **37**, which was directly used for the next step without further purification.

Following **GP 2**, 1-methoxy-4-(1-methoxyethyl)benzene (**62**, 33 mg, 0.2 mmol), crude *N*-(cyclopropylmethyl)-*O*-tosylhydroxylamine (**37**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-(cyclopropylmethyl)-4-methoxyaniline **41** as a yellow oil (34 mg, 97%).

4-Methoxy-_N_-(2-methoxyethyl)aniline (83)

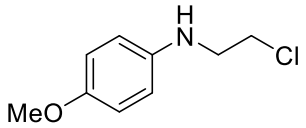


Following **GP 3**, *tert*-butyl (2-methoxyethyl)(tosyloxy)carbamate (102 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(2-methoxyethyl)-*O*-tosylhydroxylamine **81**, which was directly used for the next step without further purification.

Following **GP 2**, 1-methoxy-4-(1-methoxyethyl)benzene (**62**, 33 mg, 0.2 mmol), crude *N*-(2-methoxyethyl)-*O*-tosylhydroxylamine (**81**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-(2-methoxyethyl)aniline **83** as a yellow oil (36 mg, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (d, *J* = 8.9 Hz, 2H), 6.61 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 3H), 3.60 (d, *J* = 5.2 Hz, 2H), 3.39 (s, 3H), 3.24 (d, *J* = 5.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.28, 142.41, 114.82, 114.49, 71.10, 58.72, 55.75, 44.53.

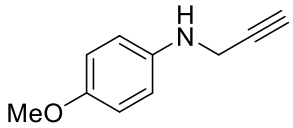
_N_-(2-Chloroethyl)-4-methoxyaniline (42)



Following **GP 3**, *tert*-butyl (2-chloroethyl)(tosyloxy)carbamate (105 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(2-chloroethyl)-*O*-tosylhydroxylamine **38**, which was directly used for the next step without further purification.

Following **GP 2**, 1-methoxy-4-(1-methoxyethyl)benzene (**62**, 33 mg, 0.2 mmol), crude *N*-(2-chloroethyl)-*O*-tosylhydroxylamine (**38**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-(2-chloroethyl)-4-methoxyaniline **42** as a yellow oil (27 mg, 73%).

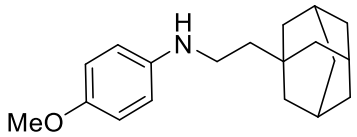
4-Methoxy-_N_-(prop-2-yn-1-yl)aniline (43)



Following **GP 3**, *tert*-butyl prop-2-yn-1-yl(tosyloxy)carbamate (98 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(prop-2-yn-1-yl)-*O*-tosylhydroxylamine **39**, which was directly used for the next step without further purification.

Following **GP 2**, 1-methoxy-4-(1-methoxyethyl)benzene (**62**, 33 mg, 0.2 mmol), crude *N*-(prop-2-yn-1-yl)-*O*-tosylhydroxylamine (**39**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-(prop-2-yn-1-yl)aniline **43** as a yellow solid (29 mg, 90%).

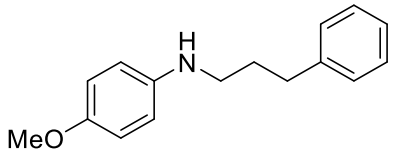
_N_-(2-(Adamantan-1-yl)ethyl)-4-methoxyaniline (44)



Following **GP 3**, *tert*-butyl (2-(adamantan-1-yl)ethyl)(tosyloxy)carbamate (135 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(2-(adamantan-1-yl)ethyl)-*O*-tosylhydroxylamine **40**, which was directly used for the next step without further purification.

Following **GP 2**, 1-methoxy-4-(1-methoxyethyl)benzene (**62**, 33 mg, 0.2 mmol), crude *N*-(2-(adamantan-1-yl)ethyl)-*O*-tosylhydroxylamine (**40**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded *N*-(2-(adamantan-1-yl)ethyl)-4-methoxyaniline **44** as a yellow solid (56 mg, 99%).

4-Methoxy-*N*-(3-phenylpropyl)aniline (86) spectral data were in agreement with literature values[34]

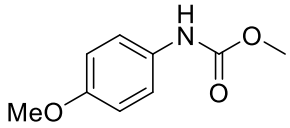


Following **GP 3**, *tert*-butyl (3-phenylpropyl)(tosyloxy)carbamate (122 mg, 0.3 mmol), TFA (0.45 mL, 6 mmol) in 0.5 mL DCM solution were to give crude *N*-(3-phenylpropyl)-*O*-tosylhydroxylamine **84**, which was directly used for the next step without further purification.

Following **GP 2**, 1-methoxy-4-(1-methoxyethyl)benzene (**62**, 33 mg, 0.2 mmol), crude *N*-(3-phenylpropyl)-*O*-tosylhydroxylamine (**84**, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (10:1) as eluting solvent afforded 4-methoxy-*N*-(3-phenylpropyl)aniline **86** as a yellow solid (46 mg, 96%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.26 – 7.19 (m, 3H), 6.79 (d, *J* = 9.1 Hz, 2H), 6.57 (d, *J* = 9.1 Hz, 2H), 3.76 (s, 3H), 3.12 (t, *J* = 7.3 Hz, 2H), 2.75 (t, *J* = 7.3 Hz, 2H), 1.95 (p, *J* = 7.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.97, 142.58, 141.70, 128.38, 128.36, 125.88, 114.83, 114.04, 55.77, 44.40, 33.40, 31.15.

Methyl (4-methoxyphenyl)carbamate (87) spectral data were in agreement with literature values[35]

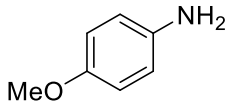


Following **GP 2**, 1-methoxy-4-(1-methoxyethyl)benzene (**62**, 33 mg, 0.2 mmol), methyl (tosyloxy)carbamate (**85**, 54 mg, 0.22 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded methyl (4-methoxyphenyl)carbamate **87** as a yellow solid (7 mg, 19%).

^{1}H NMR (300 MHz, DMSO) δ 9.41 (br, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 3.70 (s, 3H), 3.63 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 154.75, 154.15, 132.17, 119.82, 113.94, 55.15, 51.46.

Benzyl acetate scope

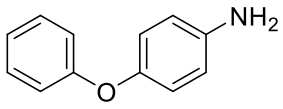
4-Methoxyaniline (10)



Following **GP 2**, 1-(4-methoxyphenyl)ethyl acetate (**88**, 39 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-methoxyaniline **10** as a yellow oil (13 mg, 54%).

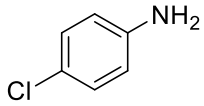
Following **GP 2**, 1-(4-methoxyphenyl)ethyl pivalate (**89**, 47 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-methoxyaniline **10** as a yellow oil (16 mg, 66%).

4-phenoxyaniline (53)



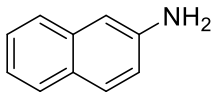
Following **GP 2**, 1-(4-phenoxyphenyl)ethyl acetate (**90**, 51 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-phenoxyaniline **53** as a yellow oil (22 mg, 59%).

4-chloroaniline (68)



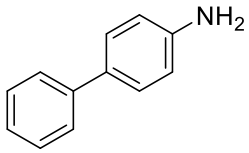
Following **GP 2**, 1-(4-chlorophenyl)ethyl acetate (**91**, 40 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded 4-chloroaniline **68** as a yellow oil (15 mg, 59%).

Naphthalen-2-amine (77)



Following **GP 2**, 1-(naphthalen-2-yl)ethyl acetate (**92**, 43 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded naphthalen-2-amine **77** as a yellow solid (21 mg, 73%).

[1,1'-Biphenyl]-4-amine (21)



Following **GP 2**, 1-([1,1'-biphenyl]-4-yl)ethyl acetate (**93**, 48 mg, 0.2 mmol), MSH (**4**, 64 mg, 0.3 mmol) in 1.0 mL HFIP solution were stirred for 12 h at room temperature. Purification by silica gel chromatography with PE/EA (5:1) as eluting solvent afforded [1,1'-Biphenyl]-4-amine **21** as a yellow solid (26 mg, 77%).

4.5 References

[1] a) F. Chen, **2018**; b) K. Hyodo, G. Hasegawa, H. Maki, K. Uchida, *Org. Lett.* **2019**, *21*, 2818-2822.

[2] J. Liu, X. Qiu, X. Huang, X. Luo, C. Zhang, J. Wei, J. Pan, Y. Liang, Y. Zhu, Q. Qin, S. Song, N. Jiao, *Nat. Chem.* **2019**, *11*, 71-77.

[3] a) C. Qin, T. Shen, C. Tang, N. Jiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6971-6975; b) Y. Adeli, K. Huang, Y. Liang, Y. Jiang, J. Liu, S. Song, C.-C. Zeng, N. Jiao, *ACS Catal.* **2019**, *9*, 2063-2067.

[4] T. Wang, M. Hoffmann, A. Dreuw, E. Hasagić, C. Hu, P. M. Stein, S. Witzel, H. Shi, Y. Yang, M. Rudolph, F. Stuck, F. Rominger, M. Kerscher, P. Comba, A. S. K. Hashmi, *Adv. Synth. Catal.* **2021**, *363*, 2783-2795.

[5] L. Legnani, G. Prina-Cerai, T. Delcaillau, S. Willems, B. Morandi, *Science* **2018**,

362, 434-439.

[6] A. J. Smaligo, M. Swain, J. C. Quintana, M. F. Tan, D. A. Kim, O. Kwon, *Science* **2019**, *364*, 681-685.

[7] A. Kitowski, E. Jimenez-Moreno, M. Salvado, J. Mestre, S. Castillon, G. Jimenez-Oses, O. Boutureira, G. J. L. Bernardes, *Org. Lett.* **2017**, *19*, 5490-5493.

[8] M. P. Paudyal, A. M. Adebesin, S. R. Burt, D. H. Ess, Z. Ma, L. Kürti, J. R. Falck, *Science* **2016**, *353*, 1144-1147.

[9] S. K. Ghorai, M. Jin, T. Hatakeyama, M. Nakamura, *Org. Lett.* **2012**, *14*, 1066-1069.

[10] L. Bering, K. Jeyakumar, A. P. Antonchick, *Org. Lett.* **2018**, *20*, 3911-3914.

[11] C. Chatalova-Sazepin, Q. Wang, G. M. Sammis, J. Zhu, *Angew. Chem. Int. Ed.* **2015**, *54*, 5443-5446.

[12] O. Cusso, X. Ribas, J. Lloret-Fillol, M. Costas, *Angew. Chem. Int. Ed.* **2015**, *54*, 2729-2733.

[13] L. Liu, W. Lee, M. Yuan, C. Acha, M. B. Geherty, B. Williams, O. Gutierrez, *Chem. Sci.* **2020**, *11*, 3146-3151.

[14] A. L. Hansen, J. P. Ebran, T. M. Gogsig, T. Skrydstrup, *J. Org. Chem.* **2007**, *72*, 6464-6472.

[15] X. Shen, P. Liu, Y. Liu, B. Dai, *Tetrahedron* **2017**, *73*, 6558-6563.

[16] T. Tokumaru, K. Nakata, *Tetrahedron Lett.* **2015**, *56*, 2336-2339.

[17] J.-L. Yu, H. Wang, K.-F. Zou, J.-R. Zhang, X. Gao, D.-W. Zhang, Z.-T. Li, *Tetrahedron* **2013**, *69*, 310-315.

[18] F. Ke, Z. Li, H. Xiang, X. Zhou, *Tetrahedron Lett.* **2011**, *52*, 318-320.

[19] H. Hu, S.-J. Chen, M. Mandal, S. M. Pratik, J. A. Buss, S. W. Krska, C. J. Cramer, S. S. Stahl, *Nat. Catal.* **2020**, *3*, 358-367.

[20] C. Zhang, G. Zhang, S. Luo, C. Wang, H. Li, *Org. Biomol. Chem.* **2018**, *16*, 8467-8471.

[21] D. A. Powell, G. Pelletier, *Tetrahedron Lett.* **2008**, *49*, 2495-2498.

[22] P. Toy, S. Ma, *Synlett* **2016**, *27*, 1207-1210.

[23] A. V. Malkov, M. Figlus, S. Stoncius, P. Kocovsky, *J. Org. Chem.* **2007**, *72*, 1315-

1325.

[24] M. Wissing, M. Niehues, B. J. Ravoo, A. Studer, *Adv. Synth. Catal.* **2020**, *362*, 2245-2253.

[25] Y. Wei, C. Zhao, Q. Xuan, Q. Song, *Org. Chem. Front.* **2017**, *4*, 2291-2295.

[26] C. H. Chou, B. Rajagopal, C. F. Liang, K. L. Chen, D. Y. Jin, H. Y. Chen, H. C. Tu, Y. Y. Shen, P. C. Lin, *Chem.-Eur. J.* **2018**, *24*, 1112-1120.

[27] S. P. Panchenko, A. S. Abel, A. D. Averin, O. A. Maloshitskaya, E. N. Savelyev, B. S. Orlinson, I. A. Novakov, I. P. Beletskaya, *Russ. J. Organ. Chem.* **2017**, *53*, 1497-1504.

[28] E. Falk, V. C. M. Gasser, B. Morandi, *Org. Lett.* **2021**, *23*, 1422-1426.

[29] H. Gao, Z. Zhou, D. H. Kwon, J. Coombs, S. Jones, N. E. Behnke, D. H. Ess, L. Kürti, *Nat. Chem.* **2017**, *9*, 681-688.

[30] J. Xu, Y. Gao, Z. Li, J. Liu, T. Guo, L. Zhang, H. Wang, Z. Zhang, K. Guo, *Eur. J. Org. Chem.* **2020**, *2020*, 311-315.

[31] W. Hu, L. Shan, F. Ma, Y. Zhang, Y. Yang, D. Wang, *Inorg. Chem. Commun.* **2019**, *109*.

[32] Z. Qiu, L. Lv, J. Li, C. C. Li, C. J. Li, *Chem. Sci.* **2019**, *10*, 4775-4781.

[33] D. Sang, H. Yue, Z. Zhao, P. Yang, J. Tian, *J. Org. Chem.* **2020**, *85*, 6429-6440.

[34] P. T. K. Arachchige, H. Lee, C. S. Yi, *J. Org. Chem.* **2018**, *83*, 4932-4947.

[35] Q. Zhang, H.-Y. Yuan, X.-T. Lin, N. Fukaya, T. Fujitani, K. Sato, J.-C. Choi, *Green Chem.* **2020**, *22*, 4231-4239.

Eidesstattliche Versicherung gemäß § 8 der Promotionsordnung für die Naturwissenschaftlich-Mathematische Gesamtfakultät der Universität Heidelberg

1. Bei der eingereichten Dissertation zu dem Thema
Hydroxylamine-Mediated Arene C-H Amination and C-C Amination via Aza-Hock Rearrangement
handelt es sich um meine eigenständig erbrachte Leistung.

2. Ich habe nur die angegebenen Quellen und Hilfsmittel benutzt und mich keiner unzulässigen Hilfe Dritter bedient. Insbesondere habe ich wörtlich oder sinngemäß aus anderen Werken übernommene Inhalte als solche kenntlich gemacht.

3. Die Arbeit oder Teile davon habe ich wie folgt/bislang nicht[1)] an einer Hochschule des In-oder Auslands als Bestandteil einer Prüfungs- oder Qualifikationsleistung vorgelegt
Titel der Arbeit:
Hochschule und Jahr:
Art der Prüfungs- oder Qualifikationsleistung:

4. Die Richtigkeit der vorstehenden Erklärungen bestätige ich.

5. Die Bedeutung der eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unrichtigen oder unvollständigen eidesstattlichen Versicherung sind mir bekannt.

Ich versichere an Eides statt, dass ich nach bestem Wissen die reine Wahrheit erklärt und nichts verschwiegen habe.

_____ _____

Ort und Datum Unterschrift

[1)] Nicht Zutreffendes streichen. Bei Bejahung sind anzugeben: der Titel der andernorts vorgelegten Arbeit, die Hochschule, das Jahr der Vorlage und die Art der Prüfungs- oder Qualifikationsleistung