INAUGURAL - DISSERTATION

zur
Erlangung der Doktorwürde
Der Naturwissenschaftlich-Mathematischen-gesamtfakultät
der
Ruprecht-Karls-Universität
Heidelberg

vorgelegt von
M. Sc. Oana G. Schramm
Aus Barlad, Rumänien

Tag der Disputation:
21.07.06

Multi-component Heterocycle Syntheses Based upon Sonogashira Coupling-Isomerization

Gutachter: Prof. Dr. Thomas J. J. Müller

Prof. Dr. Sven Doye

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbständig und ohne unerlaubte Hilfsmittel durchgeführt habe.

Heidelberg, im Mai 2006

Acknowledgements

First and foremost, I would like to thank my advisor, Prof. Dr. Thomas J. J. Müller, for his excellent guidance, patience and continuous support. Throughout my doctoral work he encouraged me to develop independent thinking and research skills.

I am very grateful to Mrs. Dr. Christa Krämer, Mr. Dr. Alexei Karpov, and Mr. Dr. Alexandru Rotaru for helpful discussions and valuable advices.

I am truly thankful to Mrs. Karin Memminger, Mrs. Nadine Körber, and Mr. Benjamin Willy for their useful suggestions and comments during the preparation of this manuscript.

I extend many thanks to all my colleagues for their support and special working atmosphere.

I also thank to Mrs. Anette Loos and Mrs. Birgit Thaler for their efforts during the research practice.

I am indebted to Mrs. Tanja Coelho, Mrs. Margaret Fischer, Mr. David Haseloff, Mr. Dr. Julien Furrer and Mr. Dr. Schilling for NMR spectra, Mrs. Petra Krämer for UV/Vis and IR spectra, Mrs. Bianka Flock, Mrs. Angelika Seith, Mr. Norbert Nieth, and Mr. Dr. Jürgen Gross for mass spectra, Mrs. Vetter, and Mr. Liebscher for carrying out of elemental analyses, Mr. Dr. Thomas Oeser and Mr. Dr. Romminger for supplying with X-Ray structures.

I am deeply grateful to my parents Florica and Ioan Dediu, and my brother Ionut Dediu who have always encouraged and supported me.

I would like also to thank my husband, Berthold, for being by my side and encouraging me during my Ph.D. work.

Last, but far from least, I would like to thank all my friends for their kind support.

Parts of this thesis have already been published or submitted for publication:

Publications

1. "The Coupling-Isomerization Approach to Enimines and the First Sequential Three-Component Access to 2-Ethoxy Pyridines", **Oana G. Dediu**, Nasser A. M. Yehia, and Thomas J. J. Müller, *Z. Naturforsch*. **2004**, *59b*, 443–450.

2. "Coupling-Isomerization-Enamine Addition-Cyclocondensation Sequences: A Multicomponent Approach to Substituted and Annelated Pyridines", **Oana G. Dediu**, Nasser A. M. Yehia, Thomas Oeser, Kurt Polborn, and Thomas J. J. Müller, *Eur. J. Org. Chem.* **2005**, 1834–1848.

3. "Coupling-Isomerization-*N*,*S*-Ketene Acetal-Addition Sequences – A Three-Component Approach to Highly Fluorescent Pyrrolo[2,3-b]pyridines, [1,8]Naphthyridines, and Pyrido[2,3-b]azepines", **Oana G. Schramm neé Dediu**, Thomas Oeser, Thomas J. J. Müller, *J. Org. Chem.* **2006**, *71*(9), 3494–3500.

4. "Microwave-Accelerated Coupling-Isomerisation-Enamine Addition-Aldol Condensation Sequences to 1-Acetyl-2-amino-cyclohexa-1,3-dienes", **Oana G. Schramm neé Dediu**, Thomas J. J. Müller *Synlett.* **2006**, *accepted*.

Additionally, parts of this thesis were presented in form of oral contribution or posters:

Oral Contribution

"Microwave Deviating Effects in Consecutive One-Pot Syntheses based on Coupling-Isomerisation Reaction (CIR)", 14-23 Oktober 2005, New Methodology and Techniques in Organic Chemistry: Sustainable Development in a Secure Environment (**NeMeTOC**), NATO Workshop, Certosa di Pontigniano (Siena), Italy.

Posters

1. "Novel [3+2+1] and [3+3] One-Pot Syntheses of Highly substituted Pyridines and Dihydropyridines", Heidelberg Forum of Molecular Catalysis, Heidelberg, Germany, **2003**, abstracts.

2. "Novel Three-Component One-Pot Syntheses of Tetrahydro [1,8] Naphthyridines and Azepines Based upon CIR", Vortragstagung der Liebig-Vereinigung für Organische Chemie (ORCHEM), Bad Nauheim, Germany, **2004**, abstracts.

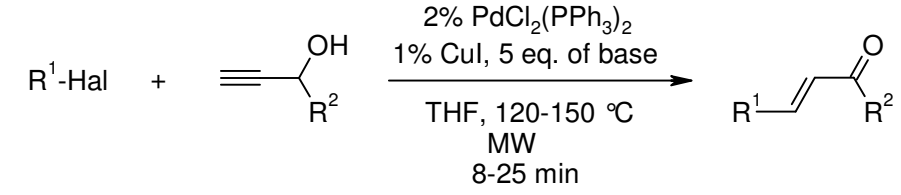
3. "Microwave-Assisted Coupling-Isomerization-Enamine MCR-Syntheses – Effects in Consecutive One-Pot Reactions", Heidelberg Forum of Molecular Catalysis, Heidelberg, Germany, **2005**, abstracts.

Abbreviations

Ar	aryl
^{n}Bu	*n*-butyl
Boc	*tert*-butoxycarbonyl
COSY	correlated spectroscopy
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
ddd	doublet of doublets of doublets
DMF	*N*,*N*-dimethylforamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
eq	equivalent
EDG	electron-donating group
EWG	electron-withdrawing group
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
Hz	hertz
LUMO	lowest unoccupied molecular orbital
m	multiplet
NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
s	singlet
t	triplet
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
THF	tetrahydrofuran
TLC	thin-layer chromatography

1 Summary

The optimization studies of coupling-isomerization reactions (CIR) of electron poor (hetero)aryl halides with propargyl alcohols using microwave heating allowed the synthesis of chalcones in only 8-25 minutes in high yields, using reduced amounts of base (Scheme 1).

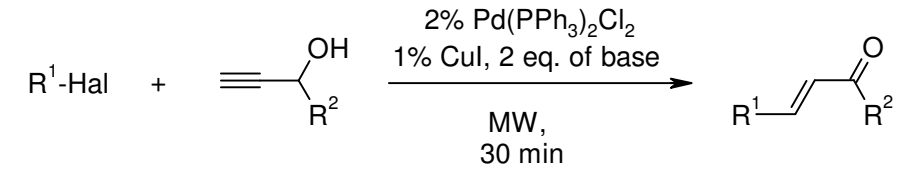


1 **2** **4**

R^1 = EWG-π- R^2 = Aryl, Alkyl 62 - 96 %

Scheme 1 Microwave accelerated CIR of electron withdrawing (hetero)aryl halides with propargyl alcohols.

Moreover the microwave-assisted coupling-isomerization reaction (MACIR) was successfully extended to electron rich aryl halides that commonly did not undergo CIR when conventional literature conditions were used (Scheme 2).



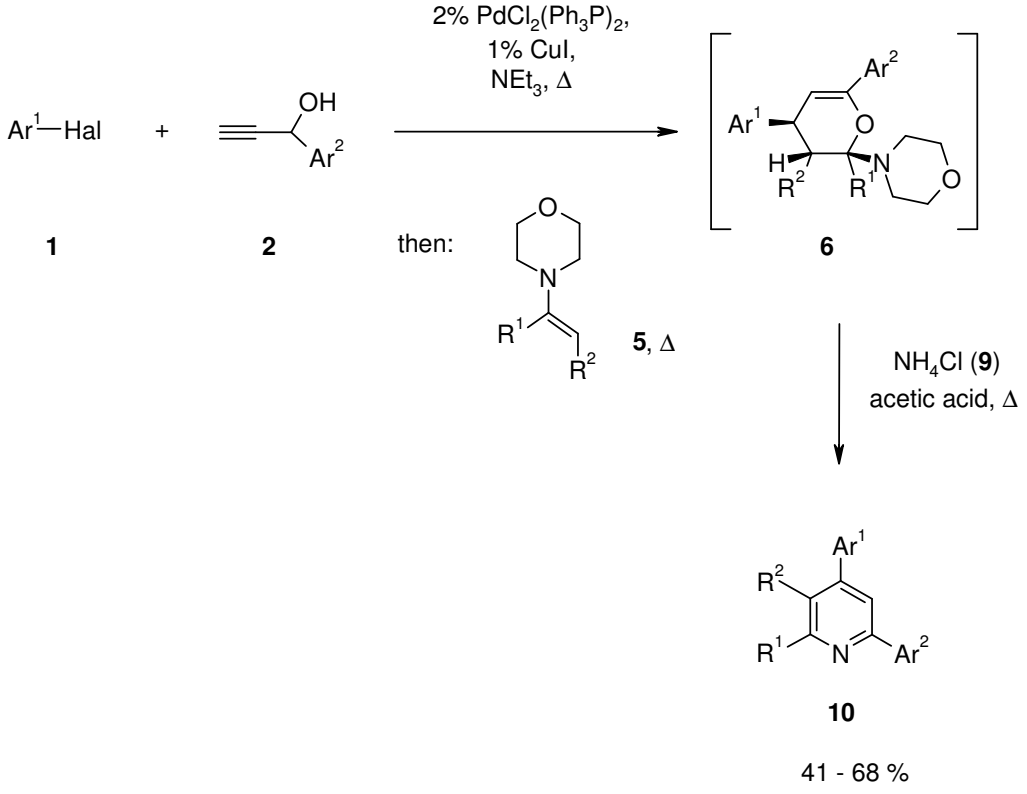
1 **2** **4**

R^1 = EDG-π- R^2 = Aryl 70 - 92 %

Scheme 2 Microwave assisted CIR of electron donating aryl halides with propargyl alcohols.

These transformations required the use of stronger bases like DBU (pK_B ~ 1.1). However, only 2 equivalents were sufficient for the completion of CIR for a large variety of substrates.

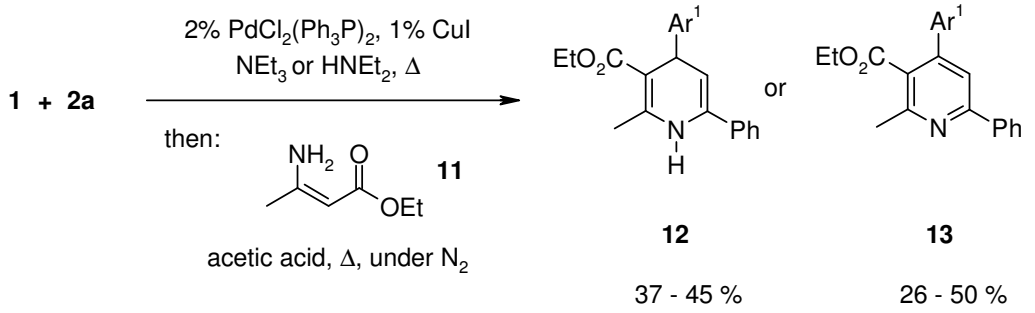
The versatility of 1,3-di(hetero)aryl enones as 3-carbon building blocks was exploited in one-pot polysubstituted pyridine **10** synthesis starting from readily available aryl halides **1** and propargyl alcohols **2**, using a CIR-enamine addition-cyclocondensation sequence (Scheme 3).



Scheme 3 One-pot four-component synthesis of pyridine derivatives **10**.

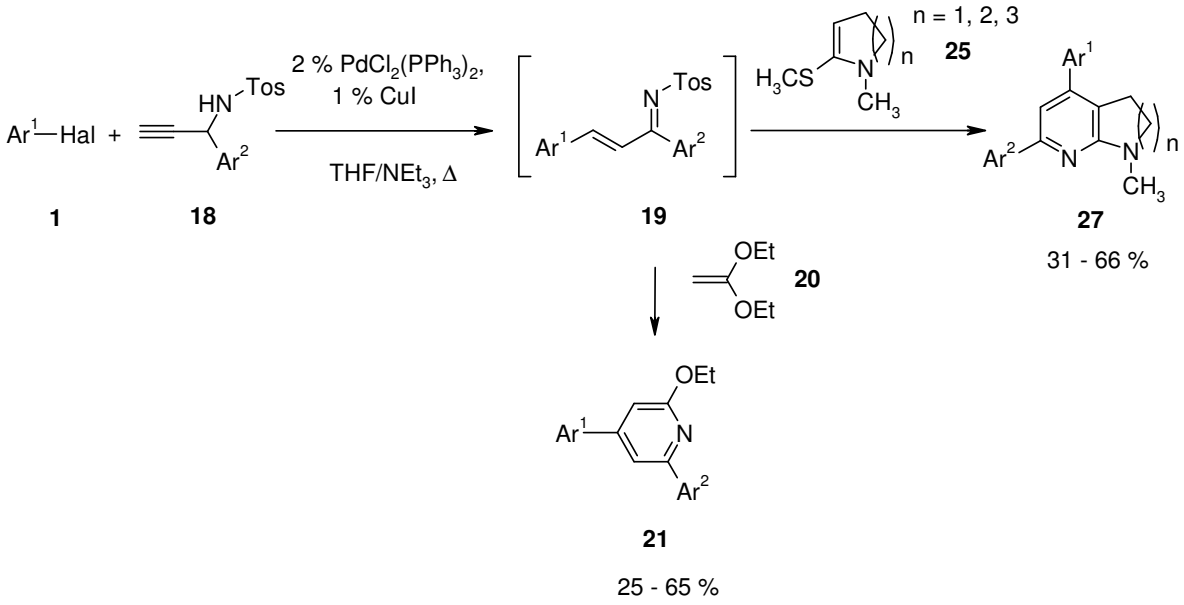
The mechanism of the enamine addition to chalcone is supported by the isolation of the Diels-Alder cycloadduct **6**. The formation of the intermediate **6** was in agreement with molecular modeling studies.

Following the same CIR-enamine addition-cyclocondensation sequence and using appropriate enaminones **11**, different dihydropyridines **12** and pyridine derivatives **13** could be synthesized in moderate yields (Scheme 4).



Scheme 4 One-pot three-component synthesis of dihydropyridines **12** and pyridines **13**.

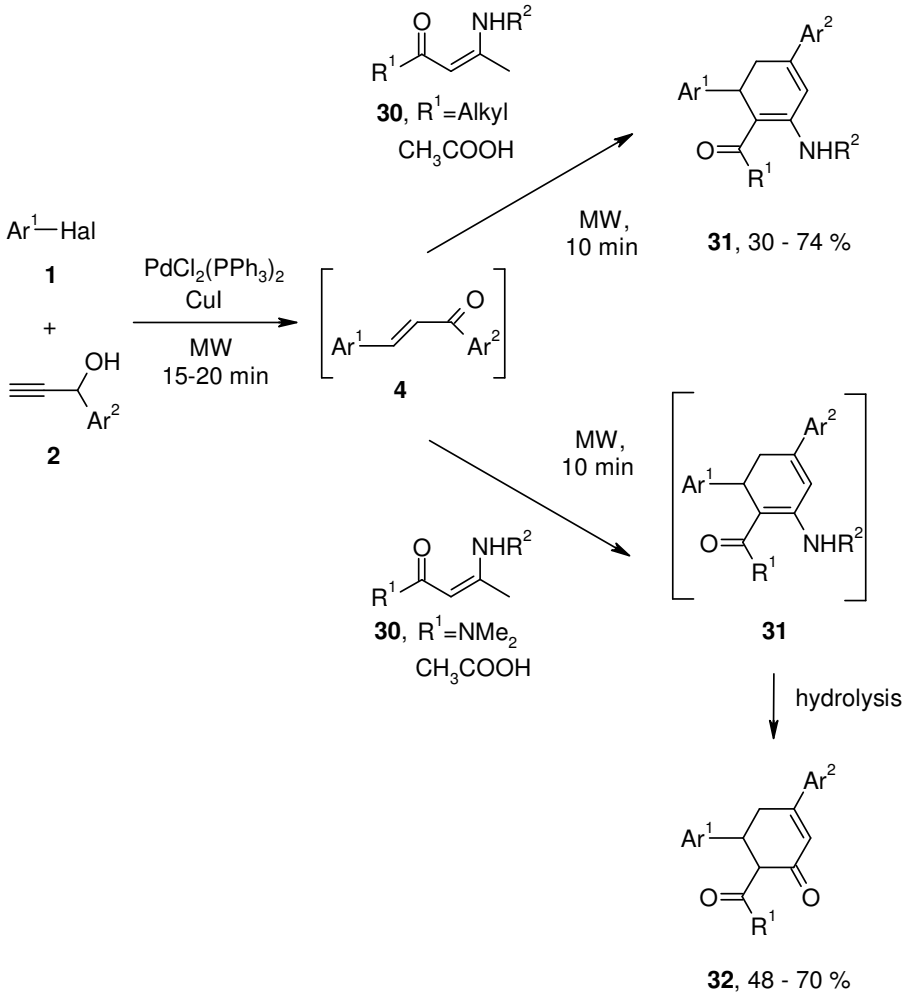
Similar to chalcones, the 1,3-di(hetero)aryl enimines were used as key intermediates in one-pot pyridine derivatives synthesis, in this case as 2-carbon-1-nitrogen synthons. The enimines underwent inverse Diels-Alder reactions with electron demand when reacted with electron rich ketene diethyl acetal or with even more electron rich *N*,*S* cyclic ketene acetals (Scheme 5).



Scheme 5 One-pot three-component synthesis of pyridines **21** and **27.**

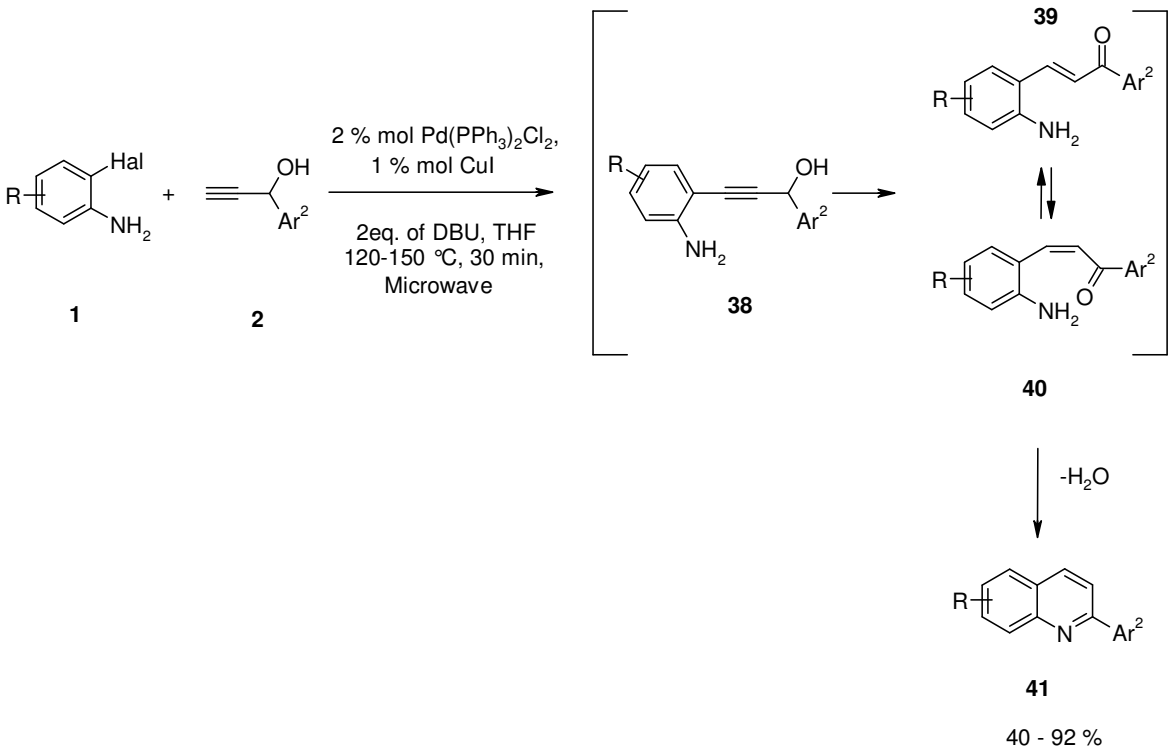
Whereas multicomponent syntheses with β-enamino crotonates under conductive heating led to the formation of pyridines and dihydropyridines in low to moderate yields, by a CIR-enamine addition-cyclocondensation sequence, the microwave assisted multicomponent

syntheses gave rise to the unexpected formation of cyclohexadienes **31** or cyclohexenones **32**, in good yields. These products can be interpreted as the results of a MACIR-enamine addition-aldol condensation sequence (Scheme 6).



Scheme 6 One-pot MW-assisted multicomponent synthesis of cyclohexadienes **31** and cycohexanones **32**.

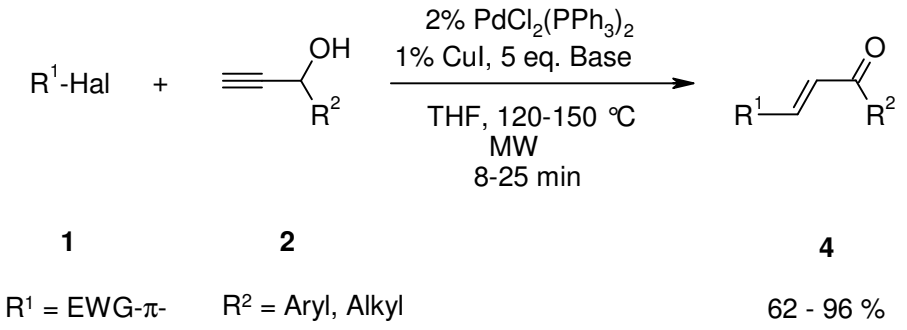
A direct application of MACIR allowed the one-pot synthesis of quinoline derivatives **41**, in good to excellent yields (40 – 92 %). Based upon this methodology, naturally occuring chimanine alkaloids were synthesized starting from the readily available *o*-amino aryl halides **1** and propargyl alcohols **2**, in 30 minutes (Scheme 7).



Scheme 7 One-pot microwave-assisted quinoline **41** synthesis.

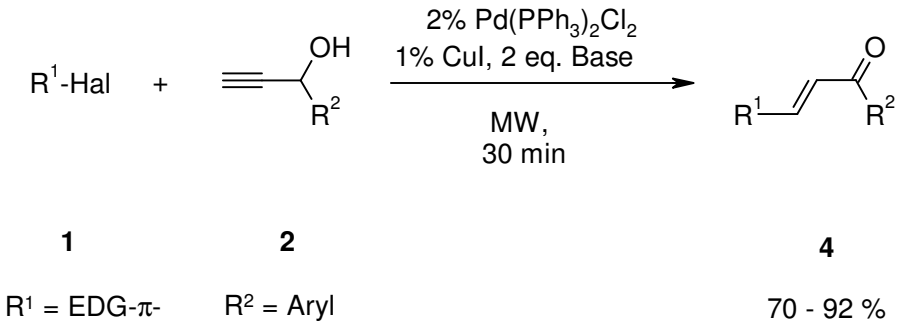
2 Zusammenfassung

Die Studien zur Optimierung der Kupplung–Isomerisierungs–Reaktion (KIR) von elektronenarmen (Hetero)Arylhalogeniden **1** mit Propargylalkoholen **2** unter Mikrowellenbestrahlung führten zu Chalkonsynthesen mit sehr kurzen Reaktionszeiten. Zudem konnte der Verbrauch an Base reduziert werden (Schema 1).



Schema 1 MUKIR von elektronenarmen Arylhalogeniden mit Propargylalkoholen zu Chalkonen **4**.

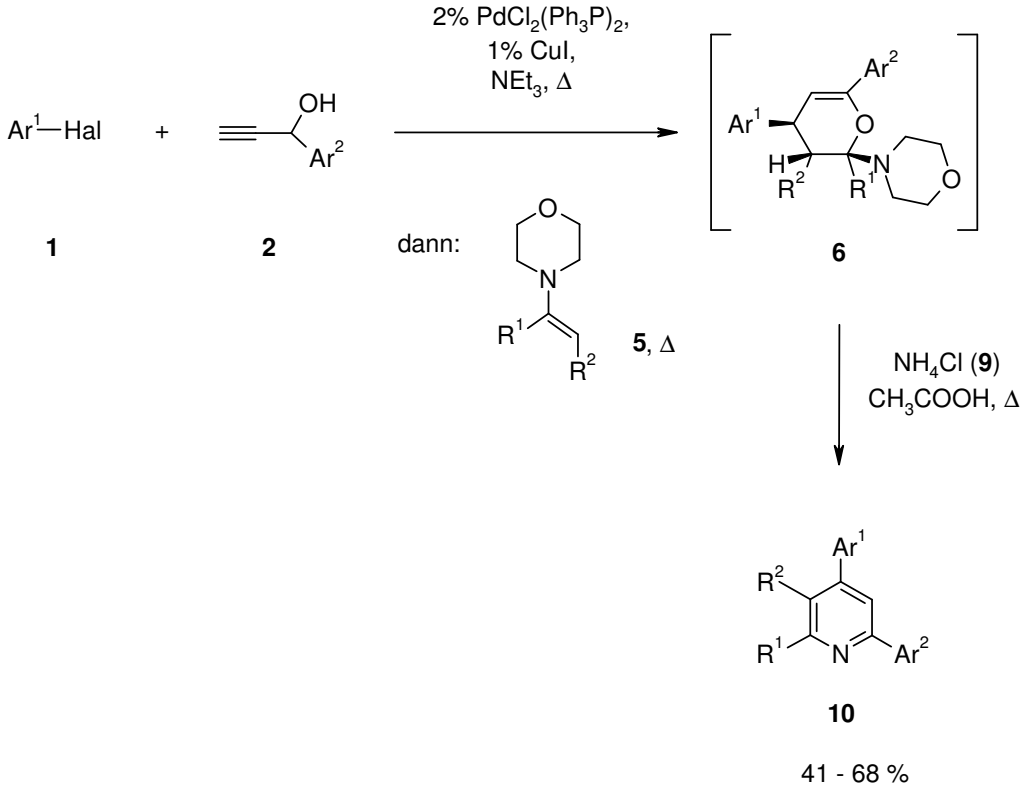
Des weiteren konnte die mikrowellenunterstützte Kupplung–Isomerisierungs-Reaktion (MUKIR) bei leicht abgewandelten Reaktionsbedingungen erfolgreich auf elektronenreiche Arylhalogenide ausgeweitet werden.



Schema 2 MUKIR von elektronereichen Arylhalogeniden mit Propargylalkoholen zu Chalkonen **4**.

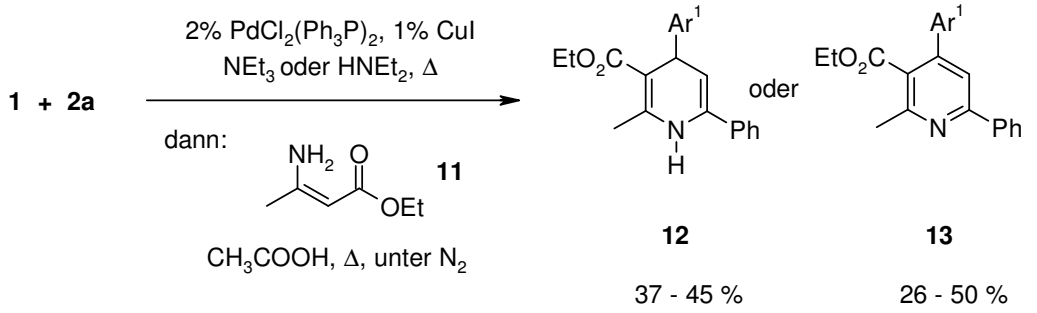
Bei diesen Transformationen kamen stärkere Basen wie zum Beispiel DBU zum Einsatz. Hierdurch konnte aber auch die für die Reaktion benötigte Basenmenge in den meisten Fällen auf zwei Äquivalente abgesenkt werden.

1,3-Di(hetero)arylenonen sind als C3-Bausteine für Ein-Topf-Reaktion zur Darstellung von Pyridinen **10** ausgezeichnet geeignet. Ausgangsverbindungen stellten wiederum die verfügbaren Arylhalogenide **1** und die Propargylalkohole **2** dar (Schema 3).



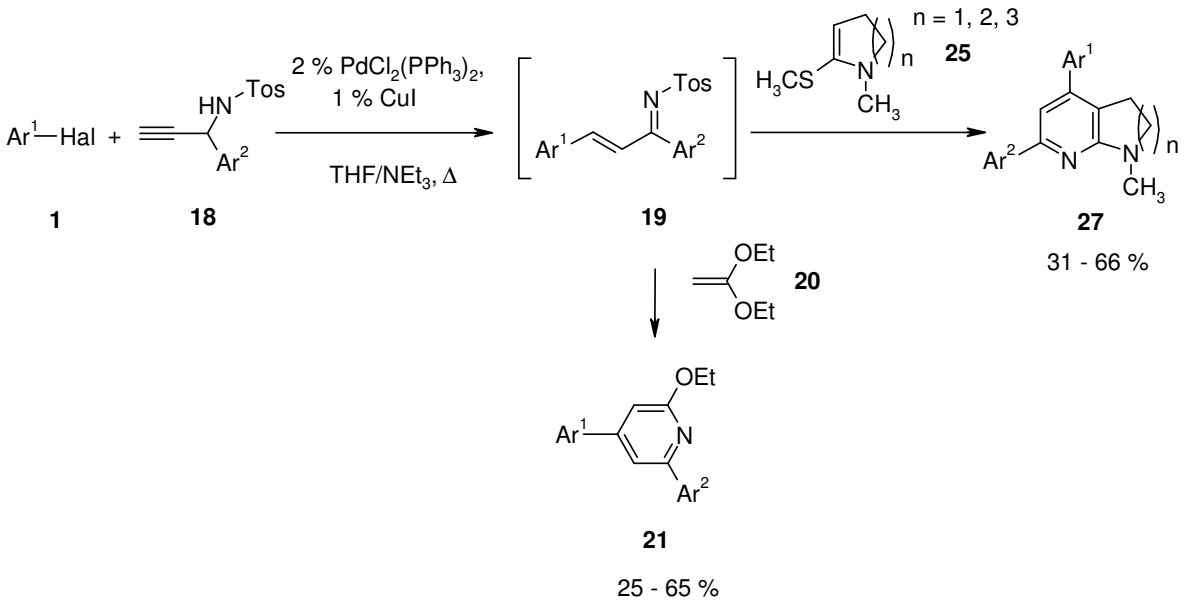
Schema 3 Ein-Topf-Vier-Komponenten-Synthese von Pyridinen **10**.

Aufgrund der Isolierung des Diels-Alder-Cycloadduktes **6** konnte der mechanistische Verlauf der Enaminaddition gestützt werden. Die Bildung dieses Intermediates stimmt mit den berechneten Strukturvorhersagen überein. Bei Nutzung geeigneter Enaminone **11** konnten unter Befolgung der gleichen Reaktionswege verschiedene Dihydropyridine **12** und Pyridinderivative **13** synthetisiert werden (Schema 4).



Schema 4 Ein-Topf-Drei-Komponenten-Synthese von Dihydropyridinen **12** und Pyridinen **13**.

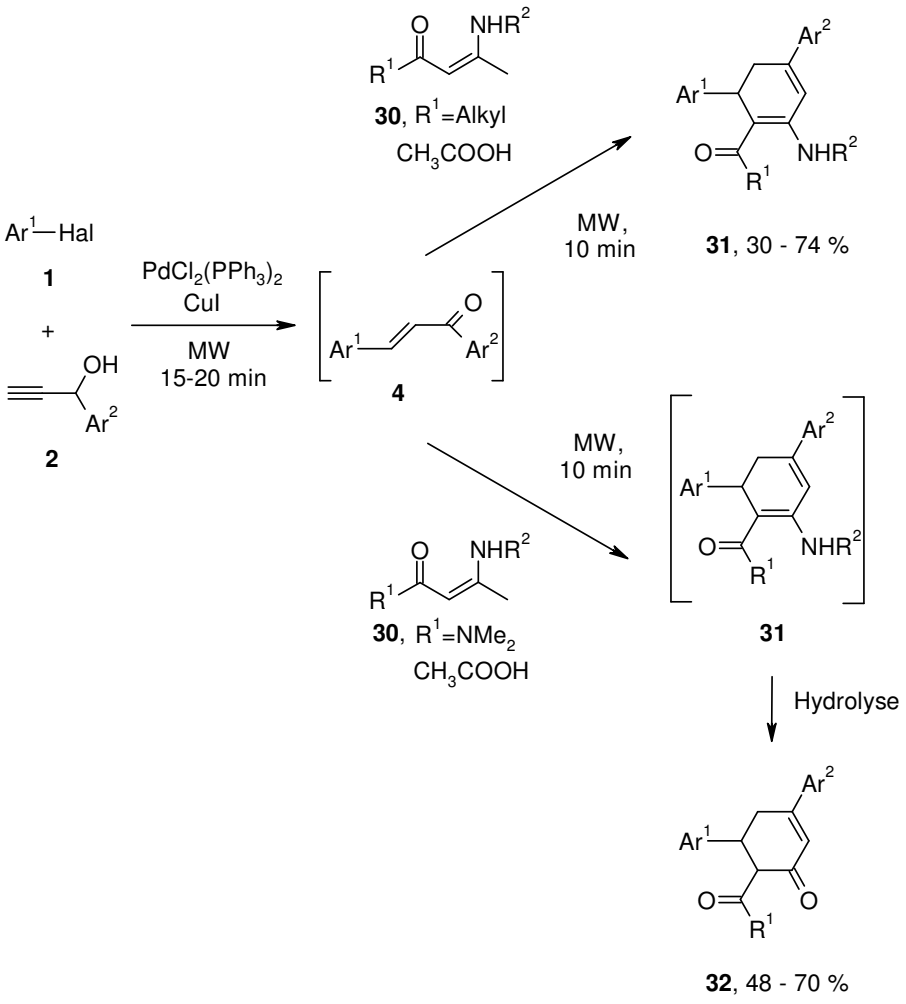
Analog den Chalkonen **4** wurden die 1,3-Di(hetero)arylenimine **19** als Schlüsselintermediate – in diesem Fall als C2N-Synthone – für eine Ein-Topf-Pyridinsynthese genutzt. Die Enimine **19** durchlaufen bei der Reaktion mit elektronenreichen Ketendiethylacetalen **20** oder noch nucleophileren cyclischen *N*,*S*-Ketenacetalen **25** Diels-Alder Reaktionen mit inversem Elektronenbedarf (Schema 5).



Schema 5 Ein-Topf-Drei-Komponenten-Synthese der Pyridine **21** and **27**.

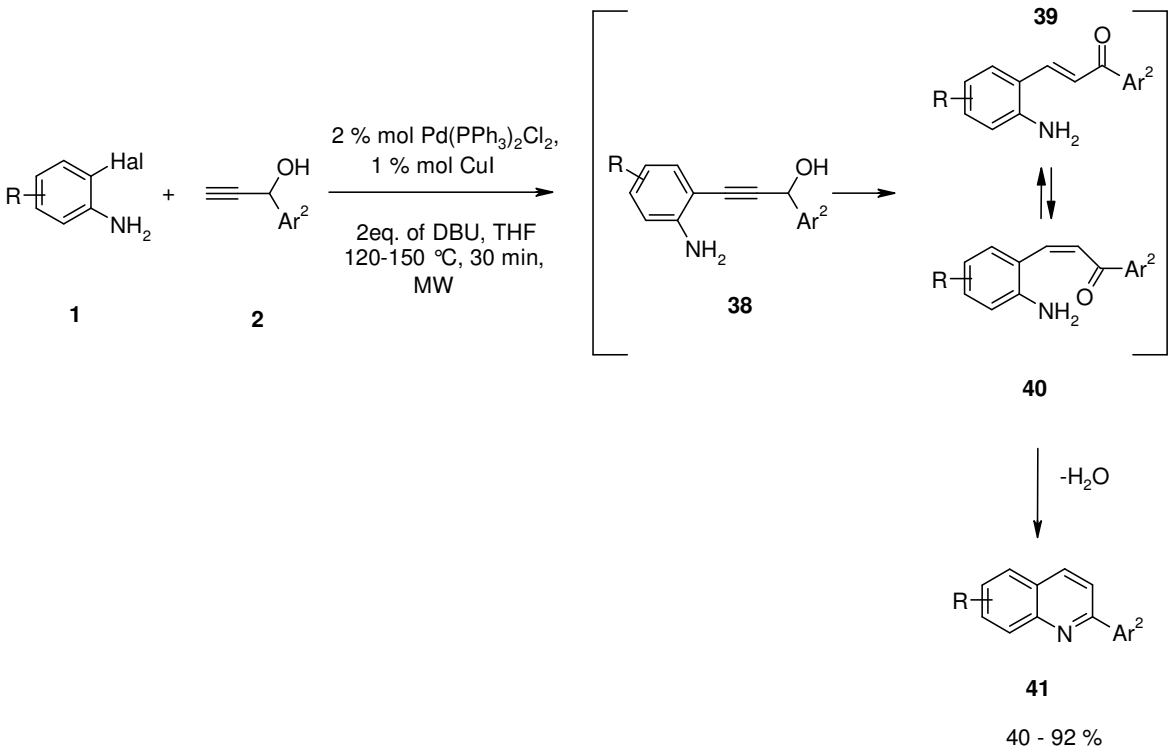
Während bei konventionellem Erhitzen die Multikomponentensynthese mit β-Enaminocrotonaten **30** zur Bildung von Pyridinen und Dihydropyridinen in niedrigen oder moderaten Ausbeute führt, kommt es beim Erhitzen durch Mikrowellen zur unerwarteten Bildung von Cyclohexadienen **31** oder Cyclohexenonen **32** mit guten Ausbeuten. Diese

Produkte können als Ergebnis einer MUKIR-Enamin-Additions-Aldolkondensations-Sequenz interpretiert werden (Schema 6).



Schema 6: Mikrowellenunterstützte Mehrkomponentensynthese von Cyclohexadienen **31** und Cycohexanonen **32**.

Einen direkten Anwendungsbezug der MACIR ermöglicht die Ein-Topf-Synthese von Chinolinderivaten **41** anhand der Reaktion von *o*-Aminoarylhalogeniden **1** mit Propargyl-alkoholen **2**. Basierend auf dieser Methode wurden die in der Natur vorkommenden Chimanine Alkaloiden in guten bis exzellenten Ausbeuten dargestellt (Schema 7).



Schema 7 Mikrowellenunterstützte Ein-Topf-Chinolinsynthese.

3 Introduction

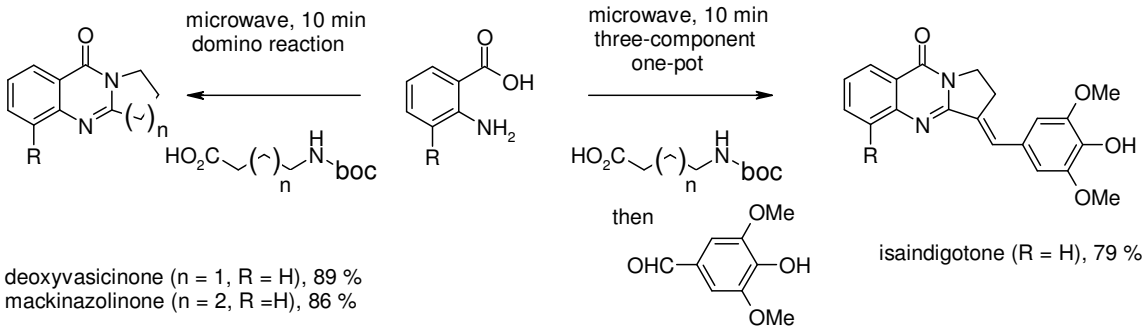
One-pot multicomponent processes address very fundamental principles of synthetic efficiency and reaction design, and therefore have gained a considerable and steadily increasing academic, economic, and ecological interest.[1,2] They are diversity oriented syntheses[3] that can be often developed into combinatorial and solid-phase strategies,[2d,4] promising manifold opportunities for generating novel structures of pharmaceuticals, catalysts, and even novel molecule based materials.

The combination of one-pot multicomponent reactions and microwave irradiation might be one of the most straightforward steps in the development of multicomponent processes since the microwave heating is able to speed up reactions, reduce side reactions, increase yields and improve reproducibility. For instance, the formation of heterocycles, well-known constituents of many natural and biologically active compounds, by cyclocondensation reactions is typically a well-suited process for microwave acceleration. Many of these condensation reactions require high temperatures and conventional reaction conditions very often involve heating the reactants in an oil or sand bath for many hours or even days.

Similarly, the rate of the transition metal-catalyzed carbon-carbon and carbon-heteroatom bond-forming reactions that typically need hours or days to reach completion with conventional conductive heating under reflux conditions, can be enhanced significantly by employing microwave heating under sealed vessel conditions. The use of metal catalysts in conjunction with microwaves may have great advantages since the inverted temperature gradients under microwave conditions may lead to an increased lifetime of the catalyst and the elimination of wall effects.

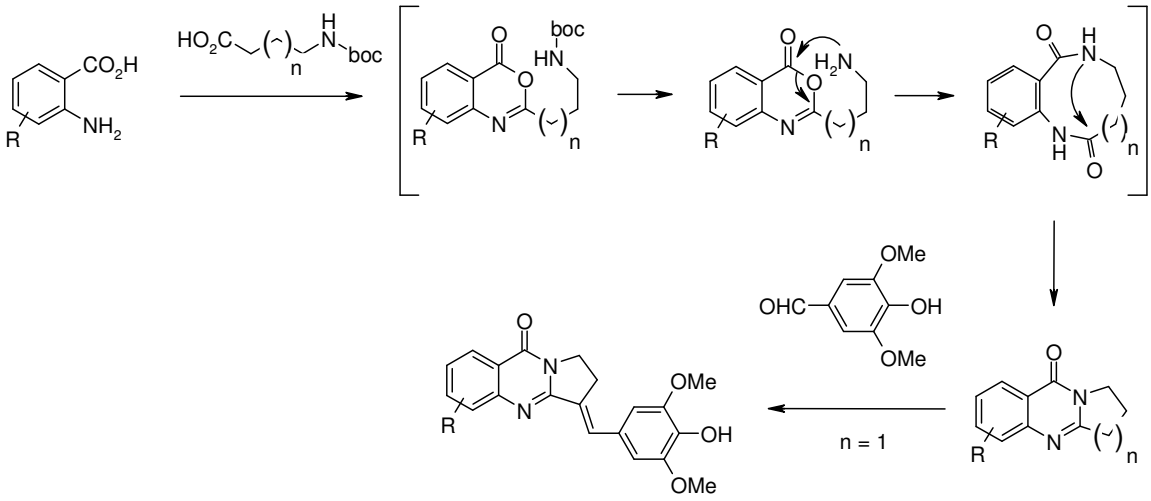
Numerous reports on microwave-assisted transition metal-catalyzed reactions and one-pot multicomponent reactions have been published, therefore, only a few recent examples were selected for detailed description.

Liu et al.[5] reported a microwave-assisted one-pot total synthesis of several quinazolinone alkaloids as deoxyvasicinone, mackinazolinone, isaindigotone and their derivatives that exhibit anti-inflammatory, antimicrobial and antidepressant activities (Scheme 8).



Scheme 8 One-pot total synthesis of quinazolinone alkaloids promoted by microwave irradiation.

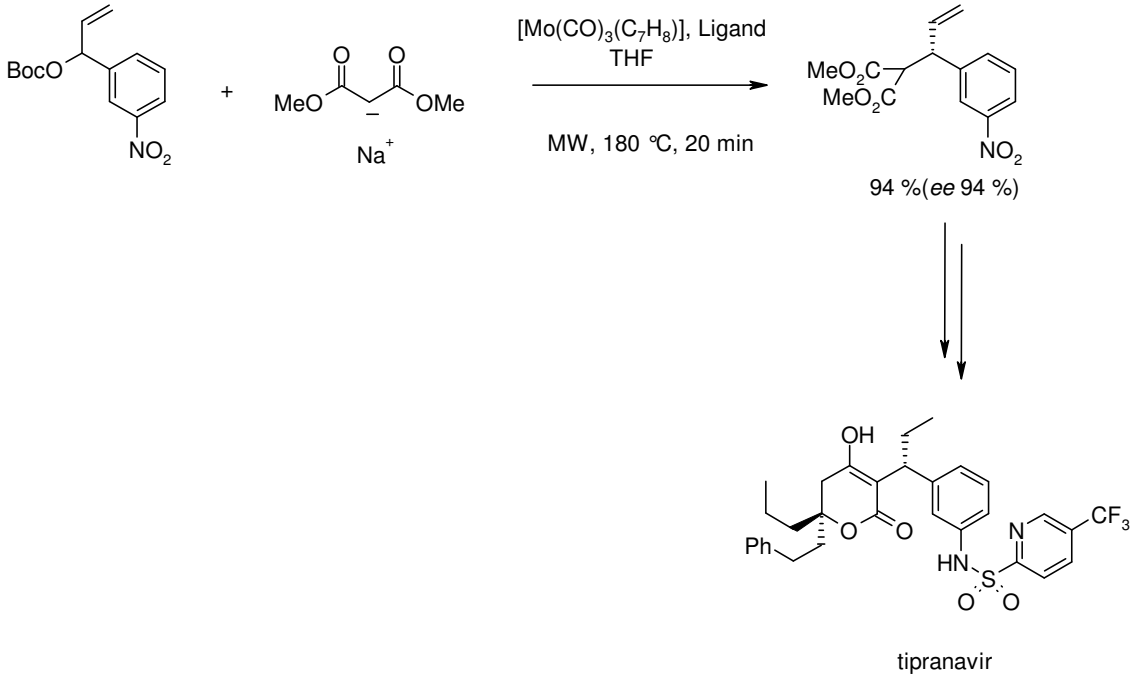
A plausible mechanism for the formation of the quinazolinone core involves a transannular cyclization of the intermediate cyclic diamide (Scheme 9). The cyclic diamide may be prepared via ring expansion of the intermediate benzoxazinone, which could be accessed *in situ* from boc-protected benzoxazinone, which in turn should be generated *in situ* from the readily available anthranilic acid and boc-protected amino acids. In addition, the isaindigotone could be synthesized through a condensation reaction of quinazolinone with the appropriate aldehyde via a three-component one-pot reaction process.



Scheme 9 Mechanistic rationale of the quinazolinone derivatives synthesis.

Microwave synthesis has been frequently criticized because of the typically high reaction temperatures that invariably would lead to reduced selectivities. This is perhaps the reason why comparatively few enantioselective processes driven by microwave heating have been reported in the literature. In 2000 the research groups of Moberg, Hallberg, and Larhed reported on microwave-mediated palladium-[6] and molybdenum-catalyzed[7] asymmetric allylic alkylation reactions involving neutral carbon, nitrogen, and oxygen nucleophiles. Both processes were carried out under non-inert conditions and yielded the desired products in high chemical yield and with typical *ee* values of over 98 %.

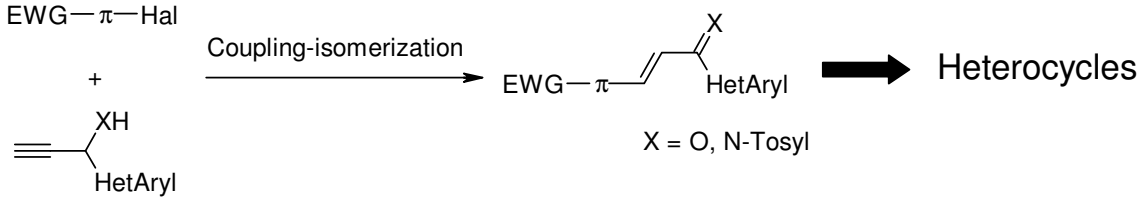
More recently, Trost and Andersen have applied this concept in their approach to the orally bioavailable HIV inhibitor tipranavir[8] (Scheme 10). Synthesis of the key chiral intermediate was achieved by asymmetric allylic alkylation starting from a carbonate derivative. A 94 % yield of the product was achieved by employing 10 mol% of the molybdenum precatalyst and 15 mol% of a chiral ligand with 2.0 equivalents of sodium dimethylmalonate as the additive. The reaction was carried out by sealed-vessel microwave heating at 180 °C for 20 minutes. Thermal heating under reflux conditions (67 °C) required 24 h and produced the same chemical yield of the key intermediate, though higher enantiomeric purity (96 % *ee*) could be reached



Scheme 10 MW-assisted molybdenum-catalyzed asymmetric allylic alkylation in the total synthesis of the HIV inhibitor tipranavir.

Thus, the microwave irradiation has proven its significant benefit and general applicability in organic synthesis.

A challenging and unexplored concept that combines synergetically the advantages of the metal-catalyzed reactions with multicomponent process and microwave technique can be envisioned. Thus, the implementation of the Sonogashira coupling-isomerization as a mild and efficient route to chalcones or enimines into microwave-assisted multicomponent methodologies for the synthesis of biologically active heterocycles and new scaffolds represents an interesting and challenging goal. (Scheme 11).



Scheme 11 General concept.

Therefore, the goals of this thesis were:

1) The optimization of the reaction parameters for an efficient, rapid and general coupling-isomerization reaction of electron poor as well as electron rich (hetero)aryl halides with propargyl alcohols,
2) To perform coupling-isomerization reactions of aryl halides with propargyl alcohols or propargyl amines and transform the intermediate chalcones or enimines directly without isolation in a one-pot fashion into biologically active pyridines, tetrahydroquinolines, naphthyridines, quinolines,
3) To investigate the microwave effects on multicomponent synthesis versus conventional heated multicomponent synthesis, and
4) To extend this general coupling-isomerization reaction to the synthesis of selected natural products.

4 General Part – Results and Discussion

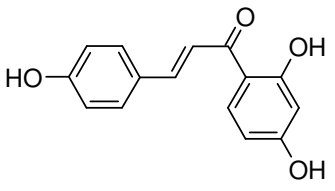
4.1 Chalcones – Natural and Synthetic Compounds, Versatile Synthons for Cycloaddition Reactions

4.1.1 Chalcones – Literature Review

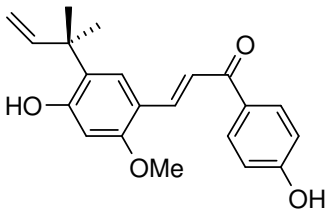
Flavonoids, a group of ~ 5000 naturally occurring compounds, have long been known to function as defence compounds in protecting the seeds and the roots of plants from insects, bacteria, fungi and alien plants.[9] 1,3-diaryl-2-propen-1-ones, constitute a class of naturally occurring and synthetic compounds belonging to the flavonoid family. They are often referred as "chalcones", the term being first coined by Kostanecki[10] who did pioneering work in the synthesis of natural colouring compounds.

Chalcones possess a broad spectrum of biological activity. Not many structural templates can claim association with such a diverse range of pharmacological activities, among which cyctotoxicity,[11] antitumour,[12] anti-inflammatory,[13] antiplasmodial,[14] antioxidant[15] properties are widely cited. Dimmock and coworkers gave an insightful review of the biological properties of chalcones in 1999.[16]

Two naturally occurring chalcones, Isoliquiritigenin and Licochalcone A (Fig. 1) extracted from licorice plant (*glycyrrhiza glabra*), one of the oldest known botanicals in Chinese medicine, may account for many of its beneficial activities (anti-inflammation, antiulcer, antiallergy, and anticarcinogenesis).[17]



isoliquiritigenin



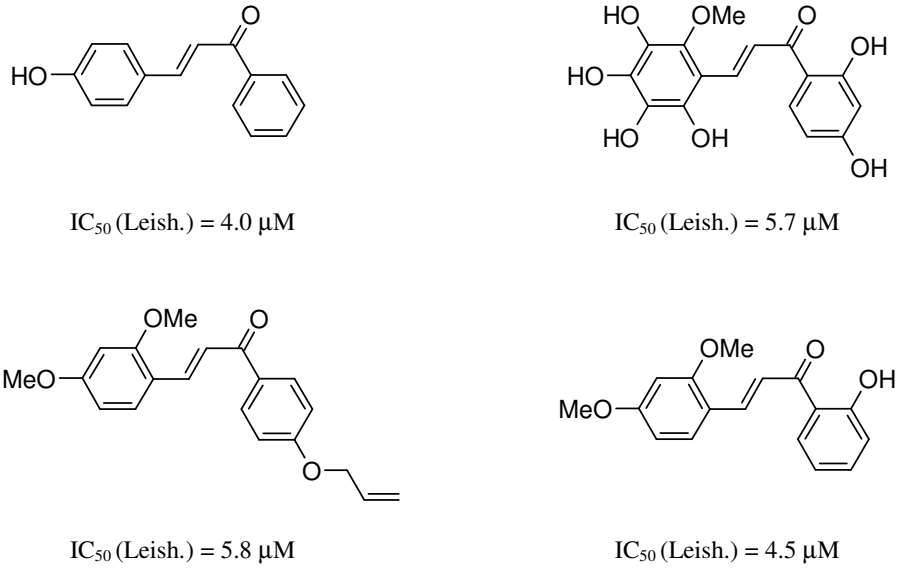
licochalcone A

IC_{50} (Leish.) = 4.0 μM

IC_{50} (Tuberc.) = 5-10 μM

Fig. 1 Naturally occurring chalcones extracted from Chinese licorice.

Additionally, Zhai et al.[18] have found that Licochalcone A alters the ultrastructure of the parasite mitochondria and inhibits their function, having a strong antileishmanial activity. Similarly to Licochalcone A, other synthetic oxygenated chalcones exhibit a strong antileishmanial activity both *in vitro* and *in vivo* (Fig. 2).



IC_{50} (Leish.) = 4.0 μM

IC_{50} (Leish.) = 5.7 μM

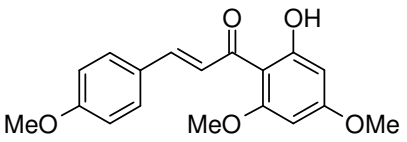
IC_{50} (Leish.) = 5.8 μM

IC_{50} (Leish.) = 4.5 μM

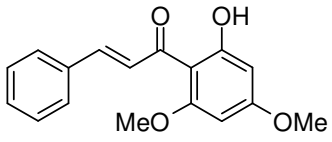
Fig. 2 Synthetic oxygenated chalcones with antileishmanial activity.

Leishmaniasis is a major and increasing health problem, particularly in Africa, Asia and Latin America. In Europe, the disease is endemic in many southern countries, and imported leishmaniasis is a growing problem, and the emergence of AIDS-related leishmaniasis has added a new dimension to the problem.

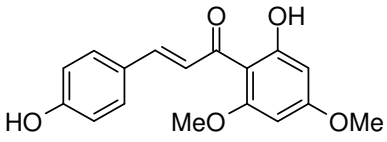
Recently, Simoneau et al.[19] have identified the flavokawains (Fig. 3), from kawa extracts that have been commonly used by South Pacific Islanders for thousands of years, as anticarcinogen agents and apoptosis inducers.



flavokawain A



flavokawain B

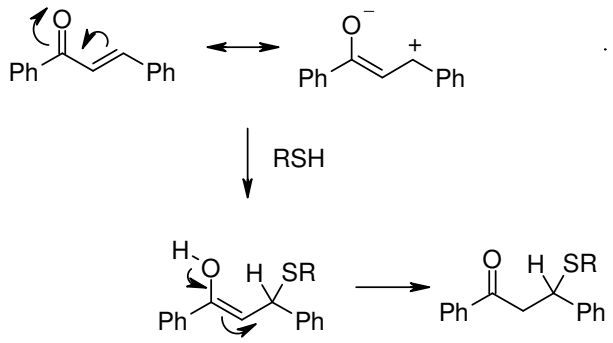


flavokawain C

Fig. 3 Flavokains, naturally occurring chalcones extracted from Kawa.

Apoptosis is considered as a physiological process to extinguish DNA-damaged cells with minimal damage to surrounding normal cells or tissue. Novel apoptosis inducers, therefore, would provide more effective therapy and prevention against cancer.

Comprehensive accounts of the effects of structure on activity are given by Liu and Dhar.[11,12] Generally, due to the α,β-unsaturated ketone moiety, chalcones have a preferential reactivity toward soft nucleophiles as thiols, rather than hard nucleophiles like amino and hydroxy groups[19] (Scheme 12). Therefore, chalcones are less likely to interact with nucleic acids and then avoid the problems of mutagenicity and carcinogenity associated with certain alkylating agents in cancer chemotherapy.[16] In addition, chalcones which are typical Michael acceptors, can bind to particular receptors and lead to the induction of phase II enzymes against carcinogens.[20]



Scheme 12 Reaction of a representative chalcone (Michael acceptor) and a nucleophilic thiol (RSH).

For antimitotic activity, the presence of methoxy substituents, α-methylation of enone moiety and the presence of 2' oxygenated substituents are favourable features. Conformational restraint of the chalcone template generally leads to a decrease in cytotoxic activity. Chemoprotection by chalcones may be a consequence of their antioxidant properties, mediated via inhibition or induction of metabolic enzymes, by anti-invasive effect or a reduction in nitric oxide production. Hydroxy and prenyl substituents are generally associated with antioxidant properties.[21]

4.1.2 Chalcone Synthesis – Literature Review

Chalcones are the first isolable compounds of the flavonoid biosynthesis in plants, but do not necessarily accumulate to any appreciable degree unless the enzyme chalcone isomerase, which catalyses the cyclization of chalcone to flavone, is absent.[22] Chalcones are readily synthesized in the laboratory and in the literature there are numerous references to structural modifications of the chalcone template. Some examples are introducing different substituents on the phenyl rings A and B, (Fig. 4) replacing the phenyl rings with heterocyclic and polyaromatic rings, and cyclization of the chalcone gives rise to the formation of conformationally restricted analogues.

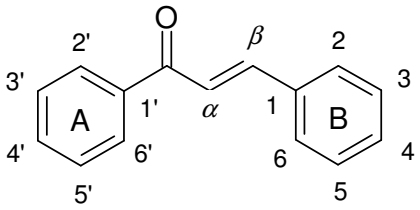
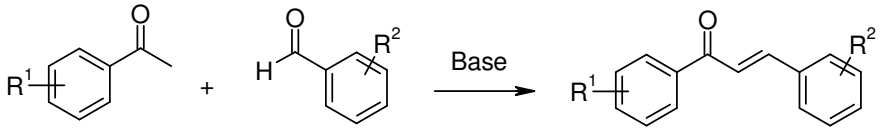


Fig. 4 Substituting sites on chalcone template.

Most synthetic methods are based on the base-catalysed Claisen-Schmidt condensation of aldehydes and appropriate acetophenones in polar solvents (Scheme 13).



Scheme 13 Synthesis of chalcones by base-catalyzed Claisen-Schmidt condensation of ketones and aldehydes.

The method is versatile and convenient, although yields may be variable, ranging from 5 % to 90 %. Many investigators have sought to improve yields using alternative catalysts, other than the widely employed alkaline bases like NaOH and KOH. Among different catalysts used were sodium phosphate doped with sodium nitrate[23] and hydrated aluminium-magnesium hydroxides.[24]

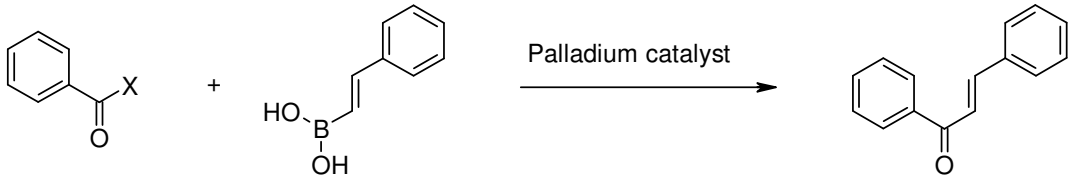
In an effort to encourage "green chemistry", some solvent-free Claisen-Schmidt methods have been developed. Fringuelli et al. used a polymer-supported TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) catalyst, obtaining good results, although the same reactions performed under solvent-free conditions by using non-supported base (TBD) gave closely comparable results both in terms of the reaction time and isolated yields.[25]

Ultrasound and microwave-assisted methods reduced reaction times and facilitated work-up for the synthesis of chalcones.[26] Claisen-Schmidt condensation in the presence of pulverised KOH or KF supported alumina, under ultrasound gave good yields under milder conditions and at shorter reaction times.[27]

The utility of microwave-assisted synthesis was investigated for 2'-hydroxy chalcones that are generally impeded by cyclization to flavonones. Unfortunately, protecting the 2' hydroxy group for minimising the cyclization reaction is not a viable option due to the *ortho* position of the group. Stoyanov and coworkers[28] noted that microwave irradiation of the reactants in 20 % KOH/ethanol in a closed pressure vial gave excellent yields of 2'-hydroxy chalcones with no trace of side products. When the reaction was repeated in an oil bath at the same temperature (~ 130 °C) identical yields were obtained. Thus, a high temperature and short heating time are important conditions for ensuring good yields of 2'-hydroxy chalcones.

Despite its versatility and generality, the aldol condensation is not a suitable method for multistep-synthesis due to the required drastic conditions such as strong alkaline base, or strong Lewis acids that are not compatible with further transformations of chalcones.

New methodologies for synthesis of chalcones have also been described in the literature. A general method, based on the Suzuki reaction, between benzoyl chloride and styrylboronic acid gave chalcones in nearly quantitative yields[29] (Scheme 14). This reaction is not affected by substituents (electron-donating, electron withdrawing) on the acid chloride or styrylboronic acid.

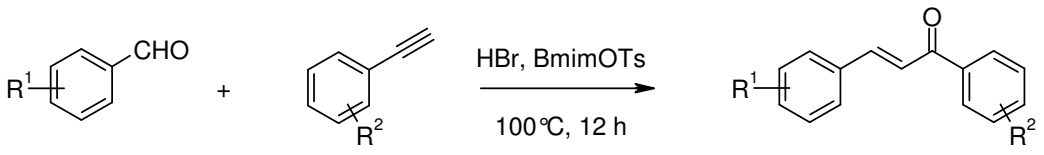


benzoyl chloride (X=Cl) styrylboronic acid

Scheme 14 Chalcone synthesis by Suzuki coupling between activated benzoic acids and styrylboronic acids.

On the other hand, coupling cinnamoyl chloride and phenylboronic acid in presence of palladium catalyst gave a complex mixture of products.

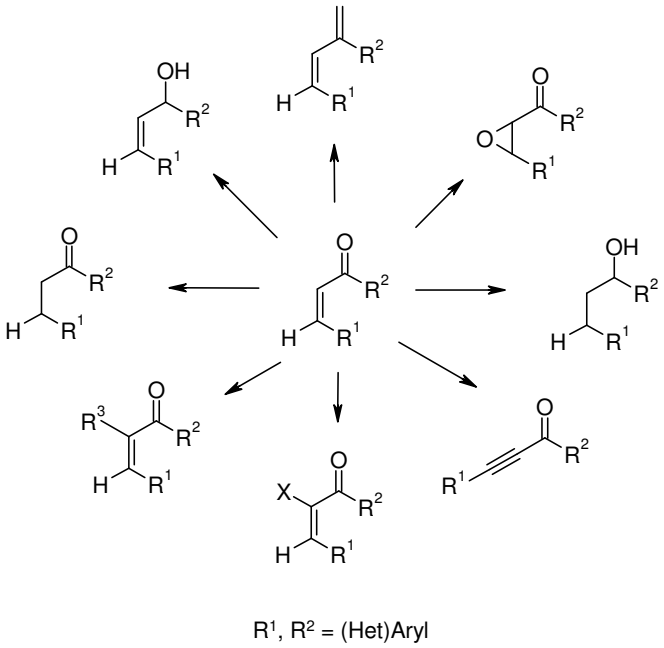
Xu et al[30] have examined the acid-catalysed coupling reaction of aromatic alkynes with aldehydes in ionic liquids (Scheme 15). They found out that aromatic aldehydes with electron-donating and electron-withdrawing groups including those bearing an alkoxy, chloro, bromo or nitro substituents were able to undergo the corresponding coupling reaction and displayed high conversion to chalcones, although with aliphatic alkynes, as starting material, no reaction occurred even after prolonged reaction times.



Scheme 15 Chalcone synthesis via ionic-liquid-promoted coupling of alkynes with aldehydes.

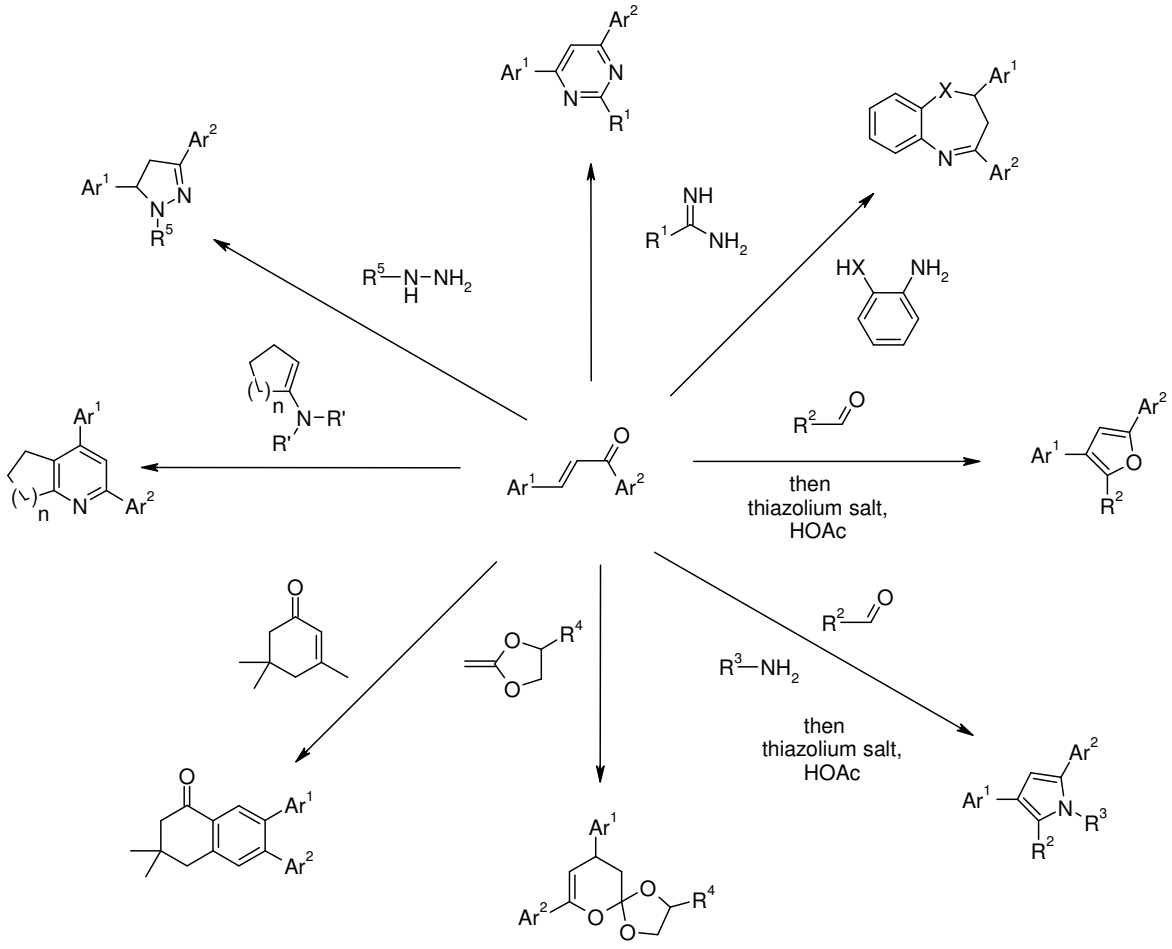
4.1.3 Reactions of Chalcones

The α,β-unsaturated ketone moiety is an extremely common feature of many organic compounds. As such, it serves as a very useful site for syntheses and transformations. Numerous reactions have been extensively developed over the years: e.g., Michael additions; β-cuprate additions; α-alkylations or arylations by reductive trapping or oxidative couplings; carbonyl refunctionalizations by addition, oxidation, reduction, and alkylidenations and α-oxidations by halogen-dehalogenation (Scheme 16).



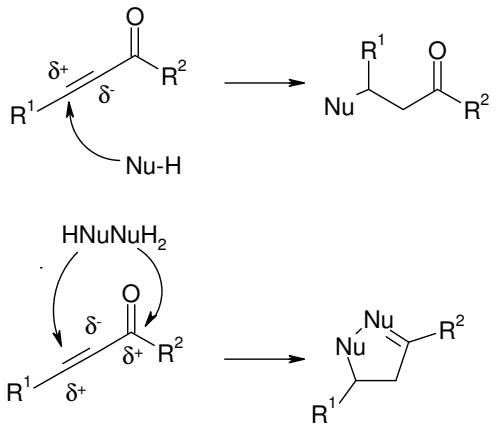
Scheme 16 Chalcone transformation reactions.

Besides the refunctionalization reactions of the "ene" and "one" functionalities, chalcones have proven to be useful synthons for the preparation of various heterocycles such as, pyridine,[31] pyrimidine,[32] furans,[33d] pyrroles, pyrazolines, [34] spiroadducts,[35] α-tetralones,[36] pyrindines, tetrahydroquinolines[33f] and heterazepines,[33b,c] (Scheme 17). Furthermore, the chalcones potency as building blocks was successfully exploited in various one-pot multicomponent heterocycle syntheses.[33]



Scheme 17 Heterocycle syntheses using chalcone as building block.

Since chalcones possess two electrophilic centers, the reactions with nucleophiles (Michael addition) and binucleophiles (cyclocondensation) are the most important transformations for heterocycle synthesis (Scheme 18).



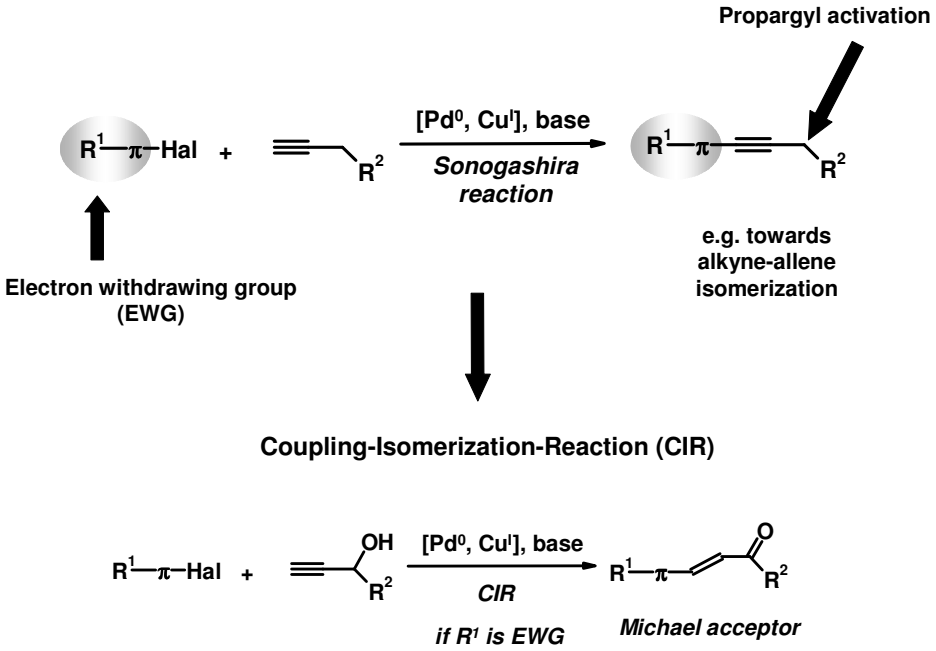
Scheme 18 The electrophilic centers of chalcone.

Although not so numerous, some transformations involving the nucleophilic center of chalcone have also been reported, such as tandem Michael addition-Robbinson reactions with the formation carbocyclic rings.[37]

4.1.4 Synthesis of Chalcones via Sonogashira Coupling-Isomerization Reaction

Transition metal mediated croos-couplings have proven to be powerful reactions for mild, highly efficient carbon-carbon bond formations. Among these processes, the bimetallic, catalytic Sonogashira coupling has turned out to be a versatile and mild alkyne-to-alkyne transformation, i.e. a powerful tool for transforming a terminal alkyne into an internal one as a consequence of a sp-sp^2-CC-bond forming reaction.[38] Besides mild reaction conditions, an excellent compatibility with fragile functional groups dispenses with tedious protection-deprotection operations, and since hydrogen halide (scavenged by weak bases such as amines) is formed as the sole by-product, the Sonogashira coupling displays a high degree of atom economy.

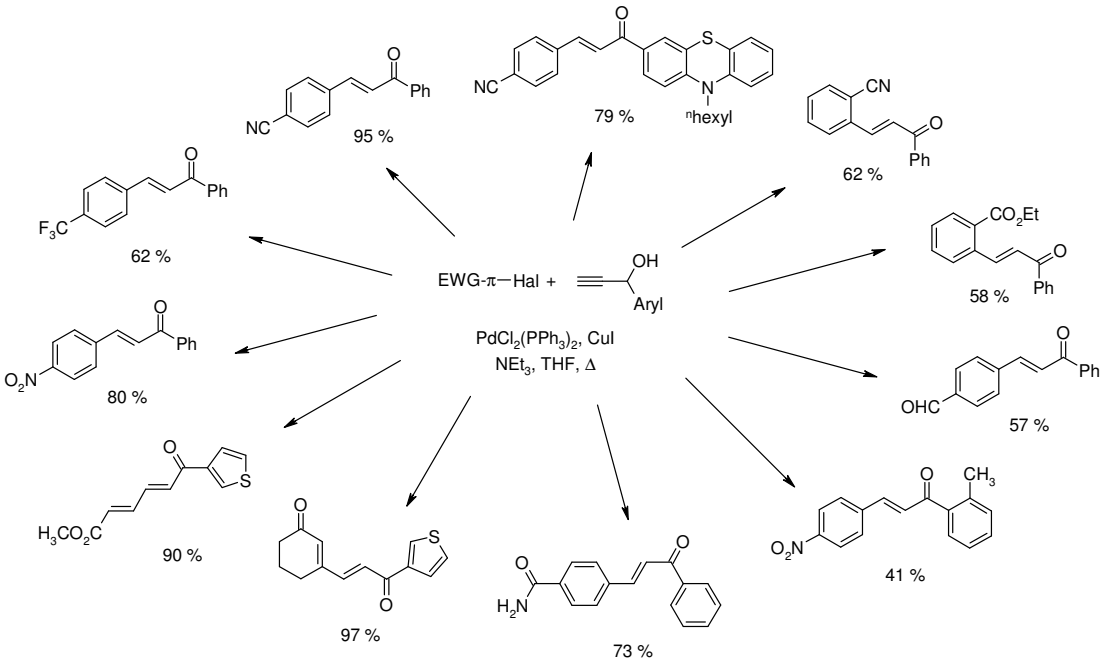
Our group has recently discovered and developed an unusual mode of alkyne activation by a detouring outcome of the Sonogashira coupling, i.e. a coupling-isomerization reaction.[39]



Scheme 19 The coupling-isomerization-reaction as a peculiar mode of alkyne activation by cross-coupling.

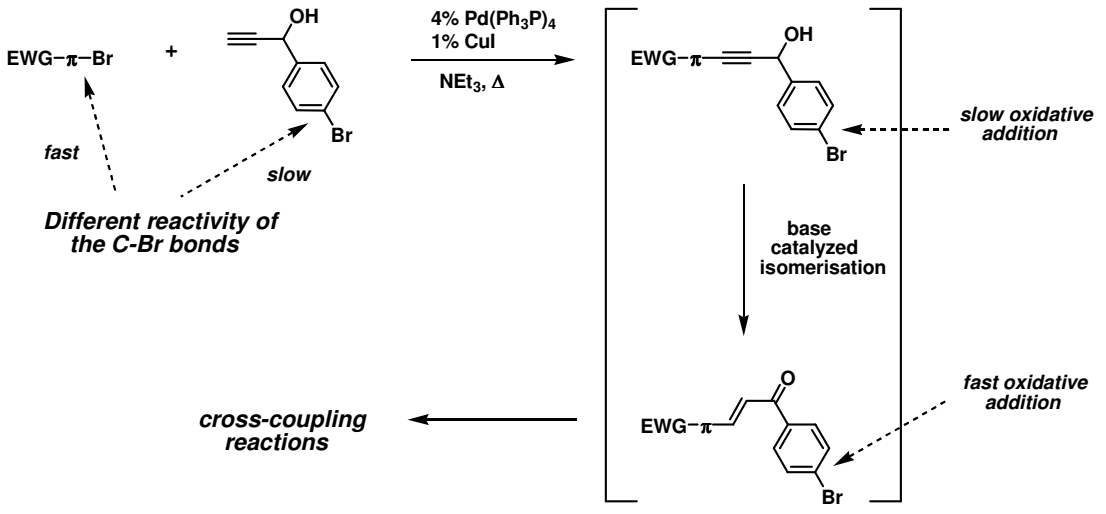
Conceptually, the cross-coupling reaction of an electron deficient halide with a terminal alkyne not only activates the newly formed internal triple bond towards Michael-type additions but also at the propargyl position, e.g. towards an alkyne-allene isomerization (Scheme 19).

In particular, the Sonogashira coupling of electron poor halides with 1-(hetero)aryl propargyl alcohols furnishes chalcones in good to excellent yields (Scheme 20).



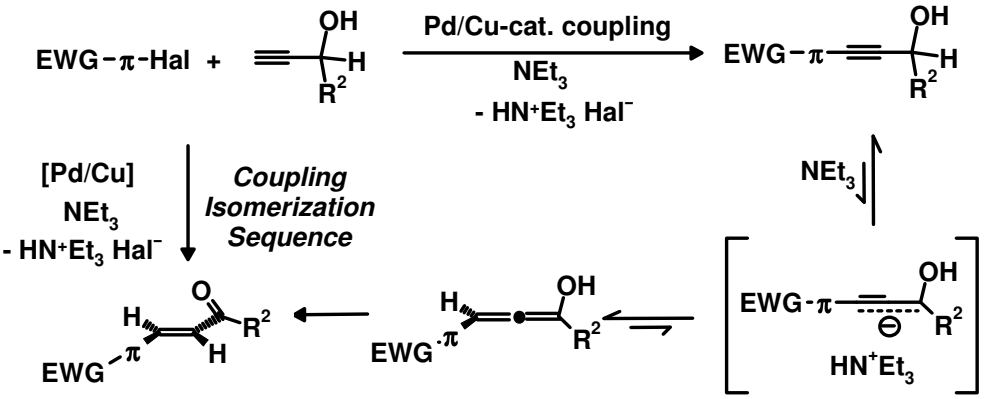
Scheme 20 Chalcones synthesized by CIR.

The mild conditions of CIR allow to apply chalcones as *in-situ* generated Michael acceptors in multicomponent syntheses of a large variety of heterocycles in one-pot fashion (Scheme 17). Besides exploiting the Michael reactivity for the multicomponent reactions (MCR) heterocyclizations, the synergism between palladium-copper catalyst system and the generated electron-deficiency at the α-(hetero)aryl substituent became the key to conceive and further devise sequential Pd-catalyzed reactions such as additional Sonogashira, Heck, Suzuki, or coupling isomerization[40] (Scheme 21).



Scheme 21 Exploiting gradual reactivity differences for coupling-isomerization sequence.

Although the Sonogashira coupling-isomerization has found many applications, CIR lacks generality. The substitution pattern of π-system halide is limited to electron deficient halides and aromatic propargylic alcohols are generally preferred over the alkyl-propargylic alcohols. Another drawback of CIR is the required large excess of base, both for the coupling and for the isomerization step (Scheme 22).



Scheme 22 Mechanistic rationale of CIR.

The large excess of base does not necessarily favours the compability of CIR with the multistep methodologies, especially in the case of the acid catalyzed subsequent steps. Trying to overcome these main drawbacks a new microwave–assisted CIR was conceived.

4.1.5 Microwave Assisted Coupling–Isomerization Reaction (MACIR) – Towards a General CIR

4.1.5.1 Literature Overview on Microwave Acceleration of Transition Metal Catalysis

The number of publications on microwave assisted organic synthesis has been increasing exponentially since the first report on the use of microwave heating to accelerate organic chemical transformations by the groups of Gedye, Giguere and Majetich in 1986.[41] Microwave heating is not only able to reduce reaction times from hours to minutes, but it is also known to reduce side reactions, increase yields, and improve reproducibility. Therefore, many academic and industrial research groups are already using microwave as a forefront technology. Also a large number of review articles[42] and several monographs[43] provide an extensive coverage of the subject.

Homogenous transition metal-catalyzed reactions have attracted considerable interest in microwave assisted organic synthesis, representing one of the most important and best studied reaction types in this field.[44] Transition metal catalyzed carbon-carbon and carbon-heteroatom bond-forming reactions typically need hours or days to reach completion by conventional heating under reflux conditions.

The use of metal catalysis in conjunction with dielectric microwave heating may have significant advantages over traditional conductive heating methods, since the inverted temperature gradients under microwave conditions may lead to an increased lifetime of the catalyst through elimination of wall effects[45] (Fig. 5), together with a controlled heating at "molecular level".[46] The microwave irradiation raises the temperature of the whole reaction volume simultaneously (bulk heating) whereas in the oil-heated tube, the reaction mixture in contact with the vessel wall is heated first.

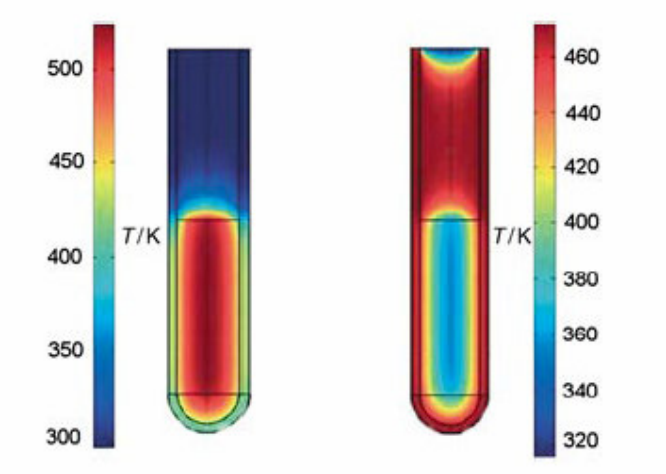
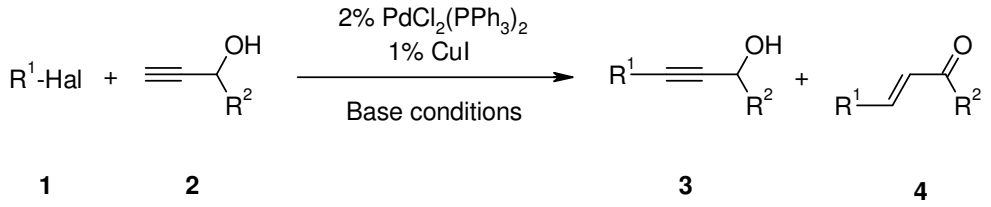


Fig. 5 Inverted temperature gradients in microwave versus oil-bath heating: difference in the temperature profiles (finite element modelling) after 1 min of microwave irradiation (left) and treatment in oil bath (right).

Sonogashira reaction enjoys remarkable popularity as a reliable and general method for the preparation of unsymmetrical alkynes. Numerous elegant synthetic transformations based on C-C bond forming Sonogashira reactions have been developed both in classical organic synthesis and natural product chemistry.[47] General protocols for microwave–assisted Sonogashira reactions under controlled conditions were first reported in 2001 by Erdelyi and Gogoll.[48] Typical reaction conditions for the coupling of aryl iodides, bromides, chlorides and triflates involve DMF as solvent, diethyl amine as the base in large excess, $PdCl_2(PPh_3)_2$ (2-5 mol %) and CuI (5 mol %) as catalysts.

Although there are many reports on MW-assisted Sonogashira reaction in the literature, MW-assisted Sonogashira coupling-isomerization reaction (MACIR) (Scheme 23) has not been reported to date.



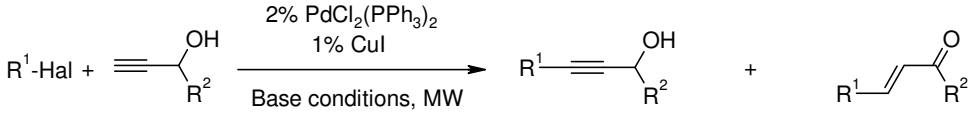
Scheme 23 Sonogashira coupling-isomerization reaction.

4.1.5.2 The General MACIR

Attempts to optimize Sonogashira coupling-isomerization under microwave irradiation would have to address some of CIR limitations observed under conventional heating conditions:

- the limited choice of the reaction medium,
- large excess of base,
- long reaction times, 16-24 h,
- the demand for a reactive arene derivative.

First optimisation studies of Sonogashira coupling-isomerization under microwave irradiation were focused on reducing the reaction time (under conventional condition, reaction times are over 16 h) and the amount of base in order to enhance the enones reactivity as dienes, i.e. under Lewis acid catalyzed Diels-Alder reaction conditions. Therefore, different electron poor aryl-halides **1** and propargyl alcohols **2** were subjected to CIR (Scheme 24) screening various parameters such as, base, temperature, reaction time, concentration of the substrate and solvent.



1 **2** **3** **4**

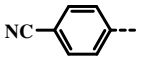
3a, R^1 = *p*-NCC_6H_4-, R^2 = Ph
3e, R^1 = *p*-$EtO_2CC_6H_4$-, R^2 =Ph
3k, R^1 = *p*-NCC_6H_4-, R^2 = Me
3l, R^1 = Ph, R^2 = Ph,
3m, R^1 = *p*-$H_3CC_6H_4$-, R^2 = Ph
3n, R^1 = *p*- $MeOC_6H_4$-, R^2 = Ph
3o, R^1 = *m*-$H_2NC_6H_4$-, R^2 = Ph

4a, R^1 = *p*-NCC_6H_4-, R^2 = Ph
4b, R^1 = 2-pyrimidyl, R^2 = Ph
4c, R^1 = 2-pyridyl, R^2 = Ph
4d, R^1 = *p*-$F_3CC_6H_4$-, R^2 = Ph
4e, R^1 = *p*-$EtO_2CC_6H_4$-, R^2 = Ph
4f, R^1 = *p*-$O_2NC_6H_4$-, R^2 = Ph
4g, R^1 = *p*-$H_2NO_2SC_6H_4$-, R^2 = Ph
4h, R^1 = *p*-NCC_6H_4-, R^2 = 2-thienyl
4i, R^1 = *p*-NCC_6H_4-, R^2 = 3-thienyl
4j, R1= *p*-NCC_6H_4-, R^2 = *n*-propyl
4l, R^1 = Ph, R^2 = Ph
4m, R^1 = *p*-$H_3CC_6H_4$-, R^2 = Ph
4n, R^1 = *p*-$MeOC_6H_4$-, R^2 = Ph
4o, R^1 = *m*-$H_2NC_6H_4$-, R^2 = Ph

Scheme 24 MACIR of (hetero)aryl halides **1** with propargylic alcohols **2**.

The amount of base was varied between 1.05 – 10 eq., the optimum being achieved for 5 equivalents of NEt_3 and THF as a solvent, with a conversion of 100% and 84% yield of the desired chalcone **4a** (entry 15, Table 1). Obviously, acetonitrile and dimethylformamide are not suitable solvents for CIR. Side-reactions such as Michael additions, Diels-Alder reactions may occur, and consequently the yields are lower, i.e. 67 % using acetonitrile (entry 10), and 73 % for dimethylformamide (entry 12, Table 1).

Table 1 Optimization MACIR experiments for the reaction of **1a** (R^1 = *p*-NCC_6H_4-) and **2a** (R^2 = Ph) using NEt_3 as a base.

R^1 =  **R^2 =** 

No.	Equivalents of NEt3	Solvent	Solvent [mL]	Ratio Solvent/Base [mL]	Time [min]	Temp. [°C]	Yield, **4a** [%]
1	3.0	CH_3CN	2.0	6.67 : 1	60	120	63
2	3.0	CH_3CN	2.0	6.67 : 1	100	120	61
3	3.0	CH_3CN	0.7	2.33 : 1	60	120	61
4	5.0	CH_3CN	3.0	5.00 : 1	60	120	66
5	5.0	CH_3CN	2.0	3.33 : 1	60	150	52
6	5.0	CH_3CN	2.0	3.33 : 1	20	150	58
7	5.0	CH_3CN	1.3	2.17 : 1	60	150	44
8	5.0	CH_3CN	2.0	3.33 : 1	20	120	50
9	5.0	CH_3CN	2.0	3.33 : 1	40	120	52
10	**10.0**	**CH_3CN**	**3.0**	**2.14 : 1**	**60**	**120**	**67**
11	10.0	CH_3CN	3.0	2.14 : 1	60	180	54
12	**10.0**	**DMF**	**0.5**	**0.64 : 1**	**20**	**120**	**73**
13	10.0	DMF	0.5	0.64 : 1	10	120	70
14	2.5	THF	1.0	4.89 : 1	30	150	62
15	**5.0**	**THF**	**1.0**	**2.44 : 1**	**30**	**150**	**84**
16	6.0	THF	1.0	2.04 : 1	30	150	76
17	7.0	THF	1.0	1.75 : 1	30	150	80
18	10.0	THF	1.0	1.22 : 1	30	150	52
19	10.0	THF	2.0	2.44 : 1	30	150	84
20	5.0	THF	2.0	4.89 : 1	30	150	72
21	5.0	THF	0.5	1.22 : 1	30	150	56

Within the optimization scope, the reaction temperature was varied between 100 and 180 °C, with an optimal reaction enhancement at 150 °C. At higher temperatures fast decomposition of the palladium catalyst together with the product decomposition were observed (entry 11).

Using triphenylphosphane as additive, the yields of the desired chalcones were improved by over 10 %, entry 4 and 9 (Table 2). The role of this additive is not well established. It might increase the catalyst's solubility or the catalyst's stability at higher temperatures[49] and it also facilitates the reduction of Pd^{2+} to Pd^{0}.

Table 2 Optimization MACIR experiments for the reaction of **1a** (R^1 = *p*-NCC_6H_4-) and **2a** (R^2 = Ph) using PPh_3 as additive.

No.	Solvent/ Additive	Solvent [ml]/ Additive [eq]	Ratio Solvent/ Base [molar]	Ratio Solvent/ Base [mL]	Time [min]	Temp. [°C]	Yield, **4a** [%]
1	THF/PPh_3	1.0/0.2	2.44 : 1	1.67 : 1	45	150	79
2	THF/PPh_3	1.0/0.2	2.44 : 1	1.67 : 1	30	150	88
3	THF/PPh_3	1.0/0.2	2.44 : 1	1.67 : 1	20	150	92
4	**THF/PPh_3**	**1.0/0.2**	**2.44 : 1**	**1.67 : 1**	**15**	**150**	**96**
5	THF/PPh_3	1.0/0.2	3.06 : 1	2.00 : 1	15	150	73
6	DMF/PPh_3	1.0/0.2	2.58 : 1	1.67 : 1	60	150	79
7	DMF/PPh_3	1.0/0.2	2.56 : 1	1.67 : 1	20	150	78
8	DMF/PPh_3	1.0/0.2	2.58 : 1	1.67 : 1	10	150	87
9	**DMF/PPh_3**	**1.0/0.2**	**2.58 : 1**	**1.67 : 1**	**5**	**150**	**87**
10	DMF/PPh_3	1.0/0.2	2.58 : 1	1.67 : 1	10	120	76
11	DMF/PPh_3	0.5/0.2	0.64 : 1	0.36 : 1	10	120	84

The reaction time was varied between 5 to 100 minutes. Surprisingly, the reaction showed full completion after 5 min using DMF as solvent, 0.2 eq of PPh_3 and 5 eq of NEt_3, yield 87 % (entry 9). Longer reaction times did not improve the yields (entries 6-8), and they might lead to side reactions together with product decomposition.

Using THF as solvent, the yield of the desired chalcone was almost quantitative, but the reaction needed longer time, 15 minutes (entry 4). Similarly, longer reaction times did not

improve the yields. Optimal concersion was achieved after 15 min, whereas prolonging the reaction time to 20-35 min the yield significantly decreased (Fig. 6).

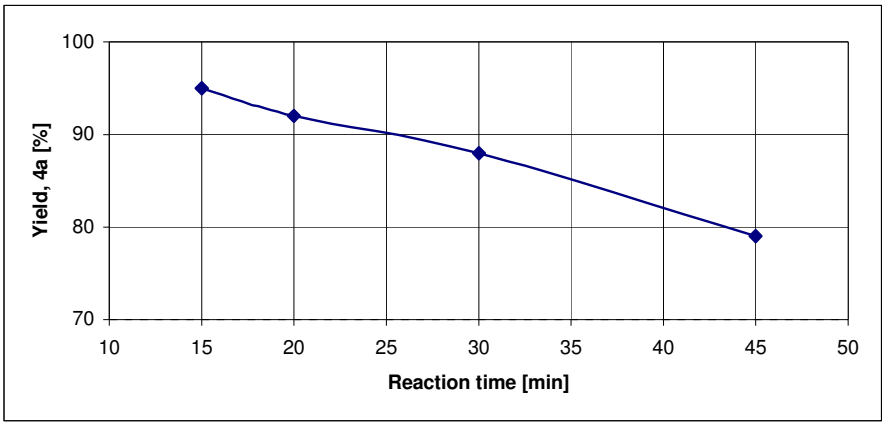


Fig. 6 Reaction time - yield dependence for MACIR using THF as solvent

Reaction rates strongly depend on the substrate concentrations. Optimal rates were found for 0.25 *M*. At higher concentrations, the probability of explosions increases as Pd and Cu catalysts are very strong microwave absorbers and higher concentration of the catalysts might be critical.

The optimal results were found for 5 eq of triethylamine, less amounts of base gave lower yields of the chalcone **4a** (entry 14, Table 1 and entry 5, Table 2). In order to decrease the amount of base, alternative stronger bases, for instance DBU (pK_b ~1.1), were tested. The chalcone **4a** (85%) was obtained in 5 minutes using only 1.05 eq of DBU, entry 1 (Table 3). Neither longer reaction time, entry 2, nor higher temperature, entry 4 (Table 3) improved the product formation.

Table 3 Optimization MACIR experiments for the reaction of **1a** (R^1 = *p*-NCC_6H_4-) and **2a** (R^2 = Ph) using DBU as base, in presence of PPh_3, in THF.

No.	base	[eq]	Solvent [mL]/ Additive [eq]	Solvent [mL]/ Base [mL]	Time [min]	Temp. [°C]	Yield, **4a** [%]
1	**DBU**	**1.05**	**1.0/0.2**	**10 : 1**	**5**	**150**	**85**
2	DBU	1.05	1.0/0.2	10 : 1	10	150	82
3	DBU	1.05	1.0/0.2	10 : 1	2.5	150	65
4	DBU	1.05	1.0/0.2	10 : 1	5	160	73
5	DBU	1.05	1.5/0.2	15 : 1	5	120	70

MACIR method was optimized for a large variety of electron poor aryl halides **1** with 1-phenylprop-2-yn-1-ol **2** (Table 4─Table 6).

Table 4 Temperature and time optimization for the reaction of **1b** (R^1 =2-pyrimidyl) and **2a** (R^2 = Ph) using NEt_3 as base, in the presence of PPh_3, in THF.

R¹ =  **R² =** 

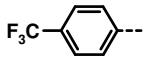
No.	Equivalents of base	Solvent [mL]	Time [min]	Temp. [°C]	Yield, **4b** [%]
1	5.0	1.0	10	150	70
2	5.0	1.0	15	150	80
3	5.0	1.0	20	150	69
4	5.0	1.0	15	170	25
5	**5.0**	**1.0**	**15**	**120**	**84**
6	5.0	1.0	15	100	52

Table 5 Optimization experiments for the reaction of **1c** (R^1 = 2-pyridyl) and **2a** (R^2 =Ph) using NEt_3 as base, in the presence of PPh_3, in THF.

R¹ =  **R² =** 

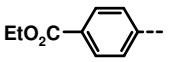
No.	Equivalents of base	Solvent [mL]	Time [min]	Temp. [°C]	Yield, **4c** [%]
1	**5.0**	**1.0**	**15**	**150**	**78**
2	5.0	1.0	15	150	76

Table 6 Optimization experiments for the reaction of **1d** (R^1 = *p*-$F_3CC_6H_4$-) and **2a** (R^2 =Ph) using NEt_3 as base, in the presence of PPh_3, in THF.

R¹ =  **R² =** 

No.	Equivalents of base	Solvent [mL]	Time [min]	Temp. [°C]	Yield, **4d** [%]
1	5.0	1.0	15	150	53
2	5.0	1.0	25	150	47
3	**5.0**	**1.0**	**15**	**170**	**65**

Table 7 Optimization experiments for the reaction of **1e** (R^1 = *p*-$EtO_2CC_6H_4$-) and **2a** (R^2 = Ph) using NEt_3 as base, in the presence of PPh_3, in THF.

R^1 =  **R^2 =** 

No.	Equivalents of base	Solvent [mL]	Time [min]	Temp. [°C]	Yield, **4e** [%]
1	5.0	1.0	15	150	not complete
2	5.0	1.0	20	150	49
3	**5.0**	**1.0**	**30**	**150**	**62**
4	5.0	1.0	45	150	61

For the chalcone formation high temperatures and short reaction times are generally more favourable. Good to excellent yields (57–96 %) were obtained in 8–30 minutes (Table 8). Various substituents, such as sulfonamide, 2 or 3-thienyl substituents, well-known motifs in pharmacophor molecules, were inserted into the chalcone template (entries 8–10, Table 8).

Aryl acetylenes are generally more reactive than alkyl acetylenes, due to the increasing acidity of the acetylenic hydrogen.[48] In order to increase the MACIR rate for the alkyl propargyl alcohols, aryl iodides were used instead of corresponding less reactive aryl bromides. However, MACIR using 1-hexyn-3-ol (**2d**) and *p*-iodobenzonitrile (**1h**) furnished the corresponding chalcone **4j** in a moderate yield, 62 % (entry 11). In the case of 1-butyn-3-ol (**2e**) available as 0.5 M aqueous solution, the only isolated product was the unisomerized alkyne **3k** (entry 13). The exclusive formation of **3k** might be explained by the higher stability of the alcohol in an aqueous solution.

Table 8 MACIR for different electron poor aryl halides **1** and propargyl alcohols **2**.

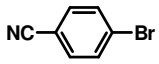
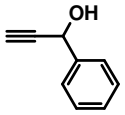
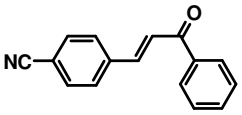
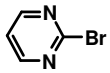
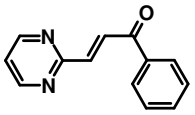
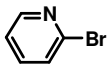
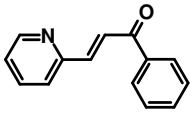
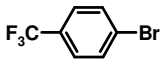
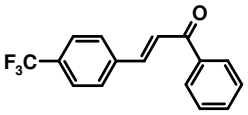
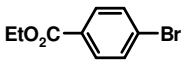
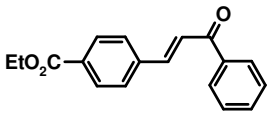
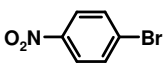
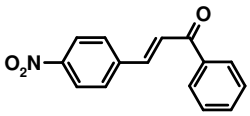
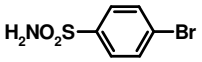
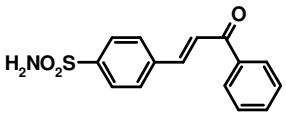
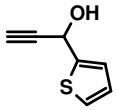
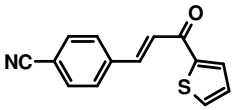
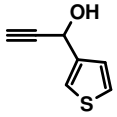
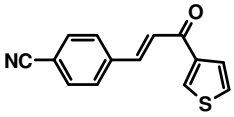
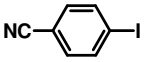
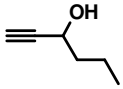
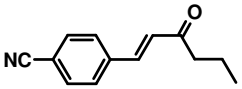
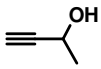
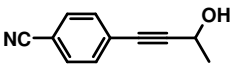
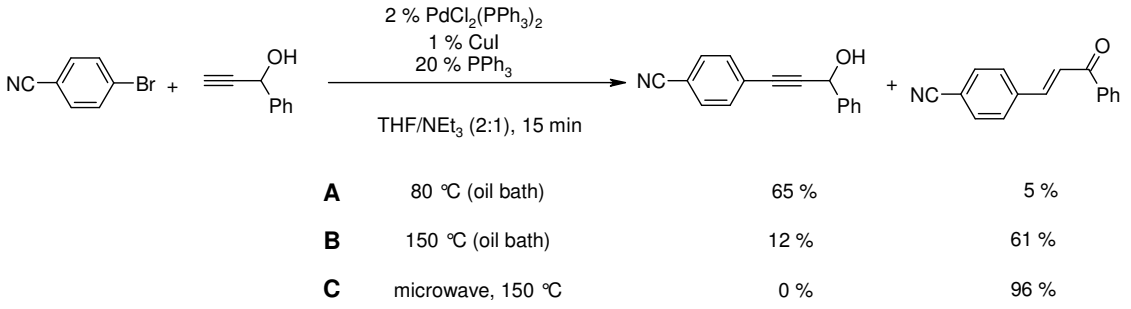
No.	Aryl-hal, **1**	Propargyl alcohol, **2**	Product	Base	Yield, Conventional cond. (~80 °C, 16-24h)	Yield, MW irra-diation (conditions)
1	 **1a**	 **2a**	 **4a**	NEt_3	95 %	**96 %** (150 °C, 15 min., 5 eq. of base)
2	**1a**	**2a**	**4a**	DBU	80 %	**85 %** (150 °C, 15 min., 5 eq. of base)
3	 **1b**	**2a**	 **4b**	NEt_3	91 %	**84 %** (120 °C, 15 min., 5 eq base)
4	 **1c**	**2a**	 **4c**	NEt_3	79 %	**78 %** (150 °C, 15 min, 5 eq. of base)
5	 **1d**	**2a**	 **4d**	NEt_3	75 %	**65 %** (170 °C, 15 min., 5 eq. of base)
6	 **1e**	**2a**	 **4e**	NEt_3	59%	**62 %** (150 °C, 30 min., 5 eq. of base)
7	 **1f**	**2a**	 **4f**	NEt_3	82%	**63 %**

Table 8 *continued*

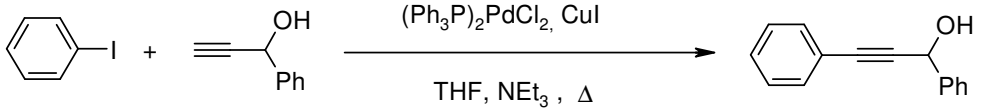
8	 **1g**	**2a**	 **4g**	NEt_3	31%	**62 %**
9	**1a**	 **2b**	 **4h**	NEt_3	-	**87 %**
10	**1a**	 **2c**	 **4i**	NEt_3	-	**70 %**
11	 **1h**	 **2d**	 **4j**	DBU	-	**62 %**
12	**1h**	 **2e**	 **3k**	DBU	-	**92 %**

The remarkably short reaction times for microwave-assisted CIR achieved through these optimization studies raised the question of whether the reaction might have been affected by any kind of special rate enhancing microwave effect. Such non-thermal effects were discussed for a long time in the literature.[50] Therefore, the coupling-isomerization reactions were carried out at exactly similar conditions using both conventional conductive and dielectric heating. The chosen model was the CIR of *p*-bromobenzonitrile (**1a**) with 1-phenylprop-2-yn-1-ol (**2a**), which furnished excellent results under microwave irradiation, entry 1 (Table 8). As expected, the conventional CIR (method B, Scheme 25) furnished lower yields of the desired chalcone, with over 30 %. The significant difference of the isolated yields can be reduced to the entirely thermal microwave effect[51] as a consequence of more efficient heating, so called "molecular heating".



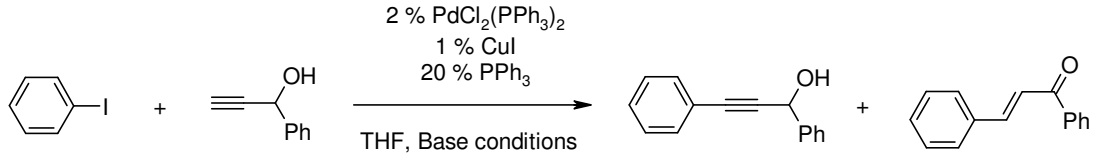
Scheme 25 Evidence experiments for MW effects.

In order to scout the scope and the generality of MACIR procedure, also electron rich aryl halides, substrates that commonly do not participate in the CIR fashion were examined. All reports on CIR sustained the necessity for strong acceptor halides, the main limiting condition for the propargyl alcohol-enone isomerization. Thus CIR of electron neutral aryl halides stopped after Sonogashira coupling without further isomerization (Scheme 26).



Scheme 26 CIR Experiments of an electron neutral aryl halide.

As the isomerization is a base-catalyzed process, different type of bases of various pK_b were tested (Table 9) to find out the optimal conditions for the CIR of electron rich aryl halides. The MACIR of iodobenzene **1i** and 1-phenylprop-2-yn-1-ol **2a** (Scheme 27) was chosen as model reaction.



1i **2a** **3l** **4l**

Scheme 27 MACIR experiments of iodobenzene **1i** with 1-phenylprop-2-yn-1-ol **2a**.

Table 9 MACIR experiments using different type of bases.

Entry	Base Solvent THF (1.5 mL)	Conditions	Coupling Product (**3m**)	Chalcone (**4l**)
1	NEt_3 (5 eq) pK_b ~ 3.35	microwave, 100 °C, 30 min	0 %	35 %
2	NEt_3 (5 eq)	microwave, 120 °C, 20 min	30 %	0 %
3	piperidine (5 eq) pK_b ~ 3.2	microwave, 100 °C, 30 min	80 %	0 %
4	piperidine (5 eq)	microwave, 150 °C, 30 min	9 %	0%
5	DBU (1.05 eq) pK_b ~ 1.1	microwave, 100 °C, 60 min	70 %	8 %
6	**DBU (2 eq)**	**microwave, 100 °C, 30 min**	**0 %**	**92 %**
7	DBU	100 °C (oil bath), 30 min	0 %	71 %

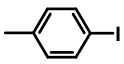
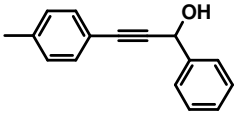
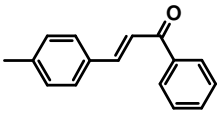
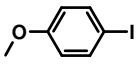
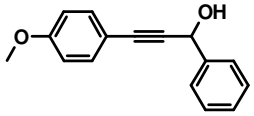
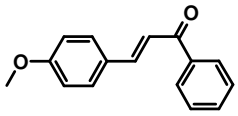
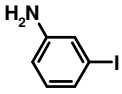
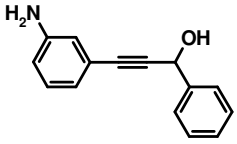
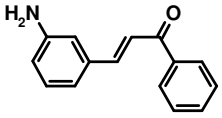
Using triethylamine (pK_b ~3.35) the isolated yields were poor both for the coupling product **3l** and the coupling-isomerization product **4l** (entry 1 and 2). In case of piperidine (pK_b ~3.2), a slightly stronger base than triethylamine, the coupling product **3l** is formed at

100 °C in higher yields (80 %, entry 3). At higher temperature, the chalcone can undergo either a conjugate addition or a Mannich reaction and consequently only 9 % of the coupling product **3l** and 0 % of the chalcone **4l** were obtained, entry 4 (Table 9). Using only 1.05 eq. DBU, as much stronger organic base (pK_b ~1.1), the reaction furnished 70 % of **3l** and 8 % of chalcone **4l** (entry 5). This promising result encouraged me to investigate the CIR using higher amount of DBU. As expected, higher yields were obtained using 2 eq. of DBU, the coupling product was completely isomerized to the corresponding chalcone **4l** (30 min, at 100 °C, 92 %, entry 6). For the same parameters, but under conventional heating condition, the reaction furnished only 71 % of chalcone **4l** (entry 7). The large difference of the isolated yields, over 20 %, can be accounted for microwave effects, since all other parameters had the same values in both cases.

The conditions for the productive CIR of *p*-iodobenzene under microwave irradiation were applied to further substrates. The electron rich *p*-iodotoluene and the even more electron rich *p*-iodoanisol and 3-iodoaniline were successfully subjected to MACIR, although to complete the isomerization, slightly higher temperatures were needed, 120 °C (entries 2, 5, 8, Table 10).

In summary, a new, general, rapid and efficient microwave-assisted Sonogashira coupling-isomerization reaction (MACIR) was developed. It was applied to the coupling of various electron poor and electron rich (hetero)aryl halides, with propargyl-aryl(alkyl) alcohols using a reduced amount of base (1.05–5 eq). Good to excellent yields (52–96 %) were obtained within a few minutes (8–30 min.). The generality and the efficiency of this method were also proven by new CIR examples of electron rich aryl halides that gave excellent results (73–92 %), as compared to conventional literature conditions, when no product formation was detected.

Table 10 MACIR experiments with electron rich electron aryl halides.

Entry	Aryl halide (**1**)	Base	Conditions (Solvent THF, 1.5 mL)	Coupling Product (**3**)	Chalcone (**4**)
1	 **1j**	DBU (2 eq)	microwave, 100 °C, 30 min	 **3m**, 46 %	 **4m**, 46 %
2	**1j**	**DBU (2 eq)**	**microwave, 120 °C, 20 min**	**3m, 0 %**	**4m, 92 %**
3	**1j**	DBU (2 eq)	microwave 100 °C, 30 min	**3m**, 0 %	**4m**, 70 %
4	 **1k**	DBU (2 eq)	microwave, 100 °C, 30 min	 **3n**, 44 %	 **4n**, 46 %
5	**1k**	**DBU (2 eq)**	**microwave, 120 °C, 30 min**	**3n, 0 %**	**4n, 85 %**
6	**1k**	**DBU (2 eq)**	Conventional heating, 120°C, 30 min.	**3n**, 0 %	**4n**, 60%
7	 **1l**	DBU (2 eq)	microwave, 100 °C, 60 min	 **3o**, 40 %	 **4o**, 44 %
8	**1l**	**DBU (2 eq)**	**Microwave, 120 °C, 30 min**	**3o, 0 %**	**4o, 73 %**

Spectroscopic Data

Most characteristically in ^{1}H NMR, and as an indication for the successful CIR, are the resonances of the (*E*)-olefinic protons of the chalcones. They appear as doublets, in the range of δ 7.05–7.92, with large trans coupling constants J = 15.5–18.9 Hz. In some cases, (**4a** and **4e**) variable mixtures of *Z*/*E*-configurated chalcones (up to 1:4) could be observed, wherein the lower coupling constants, J = 12.5–12.8 Hz, were assigned to the *Z*-configurated chalcones. Due to the electron withdrawal effect of the ring B (Fig. 4) in the chalcones **4a–j** or the electron donating effect of the ring B in the chalcones **4l–o**, the signals of the olefinic protons are accordingly shifted to lower fields (up to δ 7.92 in the case of chalcone **4f**) or to higher fields respectively (up to δ 7.05 in the case of chalcone **4n**). However, the conjugation through the chalcone shifts the signals of the olefinic protons from the usual values to lower field. The aromatic protons display typical chemical shifts in the range of δ 6.70–8.77. The lowest field, δ 8.77, was found for the pyrimidine protons of chalcone **4b**, and the most upfield shift for the protons *ortho* positioned to the methoxy group of chalcone **4n**, δ 6.70. The signals of the ethoxy protons of chalcone **4e** are detected as a triplet at δ 1.41 and a quartet at δ 4.39 with a coupling constant of 6.9 Hz.

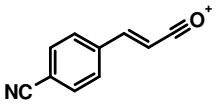
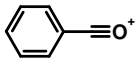
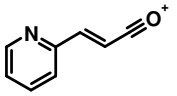
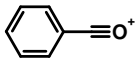
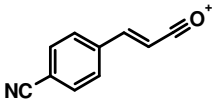
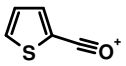
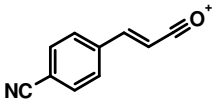
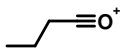
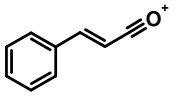
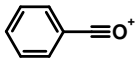
^{13}C NMR resonances appear for α,β-unsaturated ketones between δ 188.4 and 190.7, where the signals at lower field, δ 190.7, are for **4m** and **4o**. The carbon nucleus of the ester group in **4e** resonates, as expected, at higher field, δ 165.7.

The carbon nuclei of the nitrile groups for **4a**, **4h**, **4i** and **4j** resonate in the range of δ 118.3−122.1. The other signals for the aromatic carbon nuclei are detected between δ 112.9−166.3.

The mass spectra of all the obtained compounds display the molecular peaks. The fragmentation mode leads to the loss of the NH_2, CH_3, OCH_3 and OC_2H_5 groups for the chalcones **4e**, **4g**, **4m**, **4n** and **4o** respectively.

For all chalcones, α-fragmentation at the carbonyl group, a characteristic feature of ketones, could be examined. The C-C bonds are lightly to break on both sites leading to the typical fragments (Table 11).

Table 11 The Fragmentation of selected chalcones **4** (EI, 70 eV)

Compound	Fragment	*m/z* (%)	Fragment	*m/z* (%)
4a		156 (33)		105 (38)
4c		132 (42)		105 (8)
4h		156 (40)		111 (100)
4j		156 (39)		71 (11)
4l		131 (45)		105 (28)

The α-fragments lose the CO group (M^+ - 28) leading to the corresponding peaks of significantly lower intensity, however still detectable.

The stretching vibrations of carbonyl groups for α,β-unsaturated ketones **4** give rise to a strong and distinctive IR absorbtion in the range of 1675–1656 cm^{-1}. Another characteristic band at 2223–2230 cm^{-1} can be assigned to the nitrile groups, even if the vibration is slightly downshifted due to the conjugation with the aromatic ring.

In addition, the absorptions of highly polarized double bonds in the IR spectra of α,β-unsaturated ketones, **4** are detected at 1589–1568 cm^{-1}.

Moreover, the structure of **4b** is unambiguously supported by an X-ray analysis (Fig. 7). The chalcone structure is almost planar, with a dihedral angle of 16.39 ° between the aromatic rings. The dihedral angle of the α,β-unsaturated ketone moiety is 5.19 °.

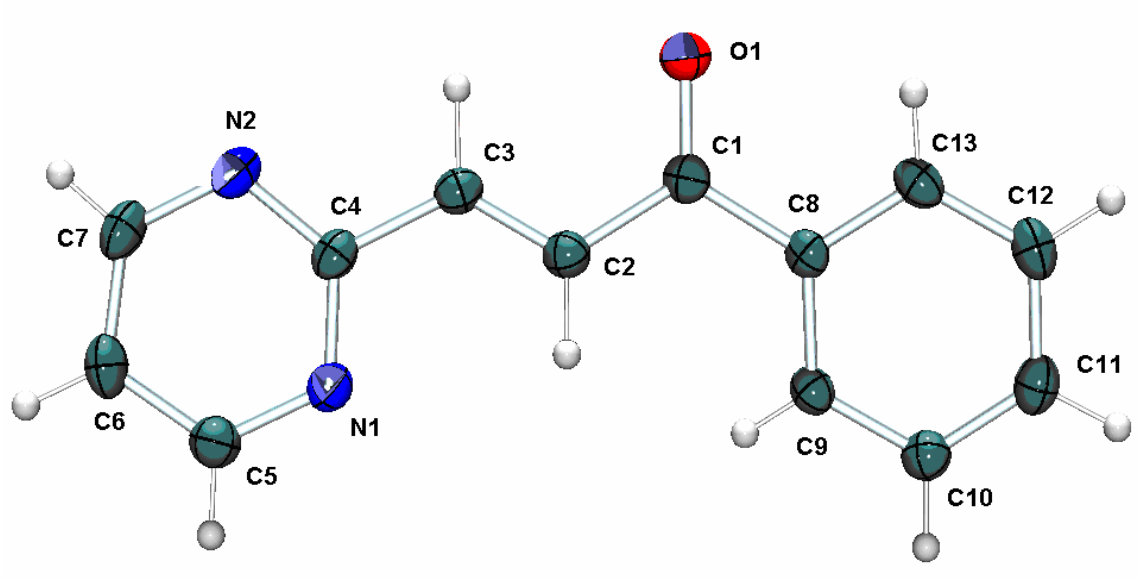


Fig. 7 ORTEP plot of compound **4b**.

4.2 [3+2+1] Pyridine Derivatives Synthesis Based upon CIR

4.2.1 Pyridines – Literature Review

Among six membered aromatic heterocycles the pyridyl core[52] adopts a central role. In nature, pyridine is the constituting structural unit in the coenzyme vitamin B_6 family (pyridoxal, pyridoxol, pyridoxamine) and an important subunit in numerous alkaloids[53] (Fig. 8).

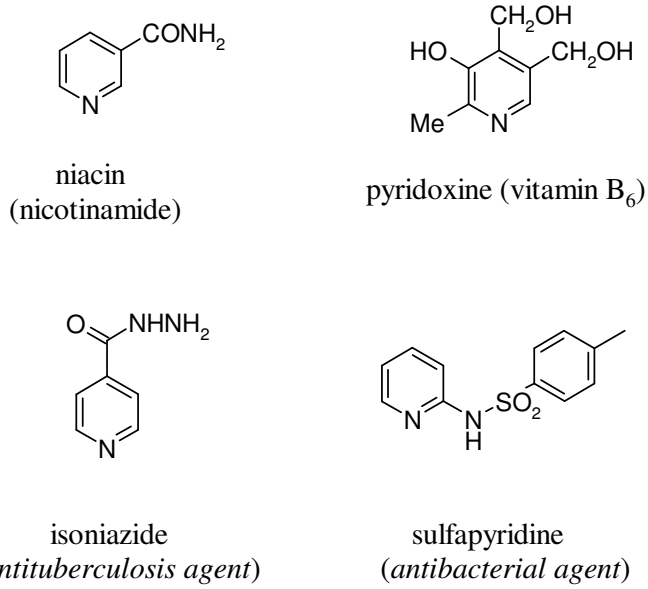
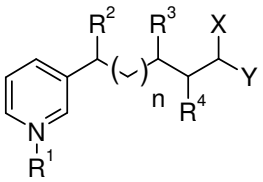


Fig. 8 Naturally occurring pyridine derivatives.

Many relatively simple 3-alkylpyridines alkaloids extracted from marine organisms have already been used or tested for their biological activity. For example, the antileukemic and antineoplastic theonelladins C and D were isolated from Okinawan marine sponge *theonella swinhoei*.[54] The antileukemic niphatesines C and D and the cytotoxic and antimicrobial niphatesine G have been obtained from the Okinawan marine sponge *niphates* sp.[55] The cytotoxic ikimines A-C have been isolated from a Micronesian sponge.[56] The antimicrobial xestamine C comes from a Caribbean sponge *xestospongia wiedenmayeri*, whilethe antimicrobial xestamines D-H have been extracted from a Bahamian sponge *calyx podatypa*[57] (Fig. 9).



	R^1	R^2	R^3	R^4	*n*	X, Y
theonelladin C	-	H	H	H	9	H, NH_2
theonelladin D	-	H	H	H	9	H, NHMe
niphatesine C	-	H	H	Me	8	H, NH_2
niphatesine D	-	H	Me	H	8	H, NH_2
niphatesine G	-	H	H	Me	9	=NOMe
ikimine A	-	H	H	Me	8	=NOMe
ikimine B	-	H	Me	H	8	=NOMe
ikimine C	-	H	H	H	9	H, NHOMe
xestamine C	-	Me	H	H	10	H, NMe(Ome)
xestamine D	-	H	H	H	10	H, NMe(Ome)
xestamine E	-	H	H	H	11	H, NMe(Ome)
xestamine G	Me^+	H	H	H	10	H, NMe(Ome)
xestamine H	Me^+	H	H	H	11	H, NMe(Ome)

Fig. 9 Some naturally occuring pyridine alkaloids

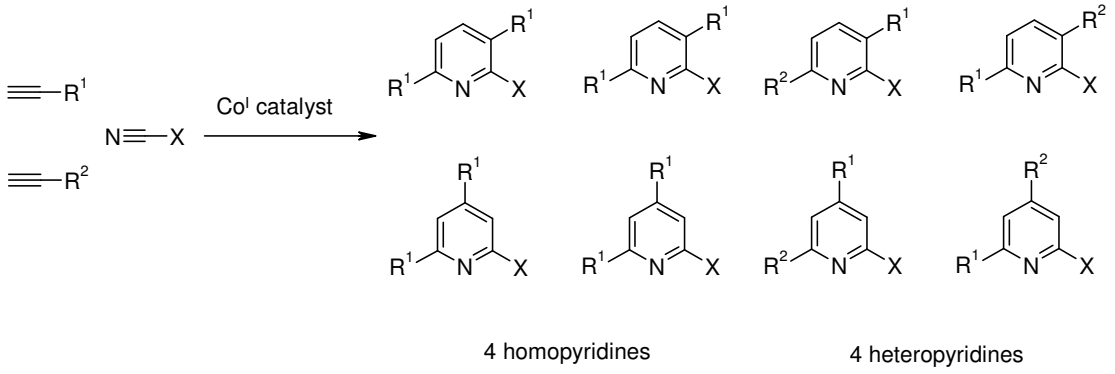
In pharmaceutical chemistry, also highly substituted[58] and annealed[59] pyridines, like 6,7-dihydro-*5H*-[1]pyrindines and 5,6,7,8-tetrahydroquinolines, have recently gained considerable interest as antiarteriosclerotics since they efficiently inhibit HMG-CoA reductase and cholesterol transport proteins. Besides, the classes of pyrindine, tetrahydroquinoline and naphthyridine derivatives additionally display antimycobacterial,[60] fungicidal and bactericidal,[61] antiulcer,[62] antivertigo,[63] antiviral,[64] and anti-inflammatory activities.[65]

The pyridines also find broad applications as versatile building blocks in the syntheses of natural products and as ligands in supramolecular coordination chemistry. In the past few decades luminescent metal complexes based on polypyridine ligands, have already been used in various fields such as solar energy conversion,[66] information storage,[67] photocleavage of DNA,[68] and oxygen sensors[69] due to to their long-lived metal-to-ligand charge-transfer (MLCT) excited states.

Although many methods have been reported for the synthesis of the pyridine heterocyles, due to their great importance, the development of novel and efficient synthetic methods remains an active research area.

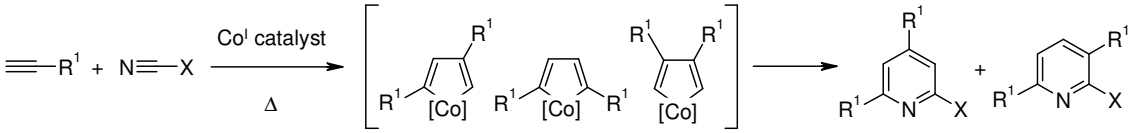
A literature overview reveals the large number of preparation approaches proposed for ring-pyridine construction that include (a) [5+1] type ring annulations from a nitrogen derivative and a five-carbon fragment, usually a 1,5-diketone,[70] (b) [2+2+2] type reactions of substituted acetylenes and nitriles, (c) [3+3] cyclizations of chalcones and iminophosphoranes,[71] Bohlmann-Rathtz pyridine synthesis from β-amino-crotonates and alkynones and cyclocondensation of 1,3-diketones with enaminones,[72] (d) [4+2] reactions of unsaturated imines with enolates and intramolecular 6π-electrocyclization of aza-unsaturated compounds,[73] (e) [3+2+1] reaction of α-benzotriazolyl ketones with α,β-unsaturated ketones,[74] (f) [2+2+1+1] Hantzsch dihydropyridine synthesis followed by subsequent oxidation. Besides the condensation and cycloaddition approaches, there are exceptions, such as ring expansion from 5-membered rings, but these methods are generally low-yielding and narrow in applicability.

A straightforward protocol is the transition metal mediated cycloaddition of alkynes and nitriles, method (b). Although a variety of stoichiometric methods have been described,[75] catalytic systems are restricted to Fe, Rh, Co, Ni and Ru complexes.[76] Both Fe and Rh systems need elevated temperatures and afford more arene byproducts than the desired pyridine.[77] Cobalt catalyzed methods are versatile, but suffer from a main drawback: except for symmetrical alkynes or reaction yielding fused pyridines, regioisomers are produced (Scheme 28).



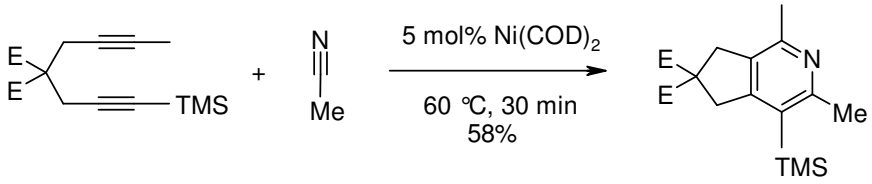
Scheme 28 Two different terminal alkynes react with one nitrile to afford eight different pyridines.

For symmetrical alkynes, the substitution pattern is limited to either the 2,4,6- or the 2,5,6-trisubstituted pyridines[78] (Scheme 29).



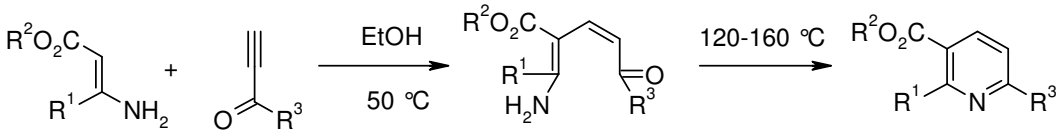
Scheme 29 Addition of a nitrile to three possible cobaltacyclopentadienes furnishing only 2,4,6- and 2,5,6-pyridine isomers.

In general, milder conditions are employed with Ru catalysts. Nevertheless, substrates are currently limited to activated nitriles (e.g., cyanides).[79] Complete regioselectivity was observed using a Ni catalyst for both intramolecular (Scheme 30) and intermolecular reactions,[76c] although the substitution pattern is also limited.



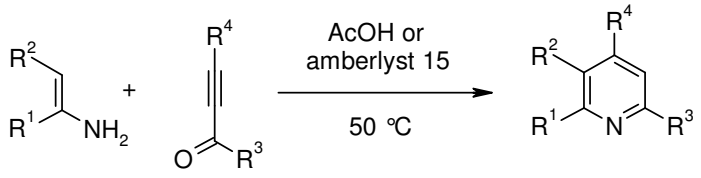
Scheme 30 Nickel catalyzed cycloaddition of alkynes and nitrile.

Among [3+3] approaches (method c) one of the most important is Bohlmann-Rahtz synthesis (Scheme 31).



Scheme 31 Bohlmann-Rahtz synthesis

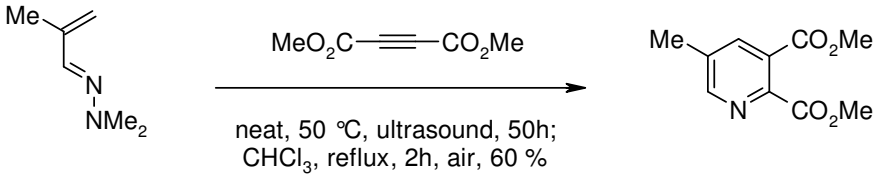
Elevated temperatures in the dehydration step can be avoided by performing the condensation under acidic conditions (Scheme 32). However, poor yields were obtained for aromatic substituents, R^4.[80]



Scheme 32 Improved conditions for Bohlmann-Rahtz pyridine synthesis.

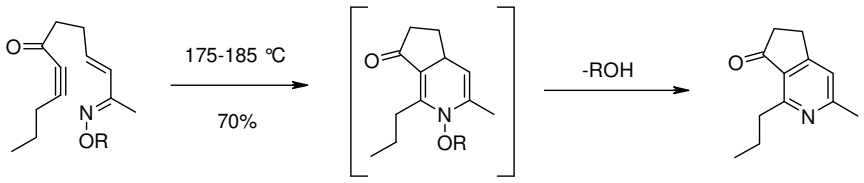
The Bohlmann-Rahtz procedure served as key step in the synthesis of the thiopeptide promothiocin A, an antibiotic,[81] and for dimethyl sulfocinamate, an important synthon for sulfomycin antibiotics.[82]

The most straightforward [4+2] cycloaddtion approach to pyridines (method d) involves a Diels-Alder reaction of 1-azadienes with alkene or alkyne followed by subsequent oxidation. However, this route is rarely used, as the Diels-Alder reaction is disfavoured on electronic, conformational and thermodynamic grounds. A method modification consists in the introduction of an electron donating group on nitrogen, which is subsequently eliminated (Scheme 33).



Scheme 33 Diels-Alder reaction of 1-azadiene.

This methodology was used by Boger in his approach to the rubrolone aglycon, an alkaloid isolated from *streptomyces enchinoruber*, by an intramolcular hetero-Diels-Alder cycloaddition[83] (Scheme 34).



Scheme 34 Key-step in rubrolone synthesis.

Due to the intransigence of 1-azadienes [4+2] cycloadditions, the use of a variety of heterocyclic azadiene in an inverse demand Diels-Alder reaction, followed by either the extrusion of a part of the resulting bicycle in a retro-[4+2] reaction or the scission of the resulting bridge, has become a favoured method for constructing pyridine rings.[84] Despite of the use of a large excess of electron rich dienophile, the yields are moderate.

Using [3+2+1] type of reaction (method e) Katritzky et al. have recently reported the reaction of α,β-unsaturated ketones and α-benzotriazolyl ketones that furnish the 2,4,6 trisubstituted pyridines in quite good yields, but the synthesis of α-benzotriazolyl ketones decreases the overall yields of this procedure.[85]

The most important [2+2+1+1] approach (method f) is the classical Hantzsch multicomponent dihydropyridine synthesis followed by oxidation. This route suffers of several limitations with respect of substitution patterns. The products incorporate acyl or carbonyl groups in the 3 and 5-positions.

Among the numerous synthetic approaches to highly substituted pyridines, the novel multicomponent strategies, comparable to the powerful, classical Hantzsch dihydropyridine synthesis,[86] remain particularly challenging.

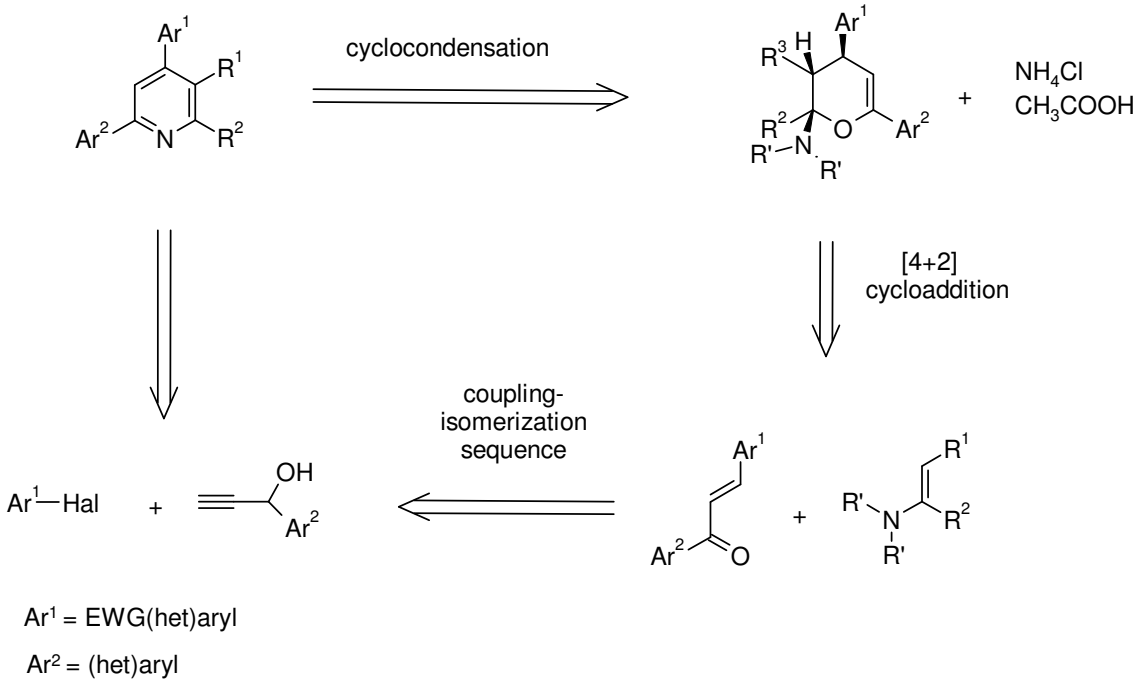
4.2.2 One-Pot Four-Component CIR-Enamine Addition-Cyclocondensation Pyridine Synthesis

Facile accesses to unsymmetrical pyridines by cocondensation of Michael acceptors with enols, enamines or stabilized ylids and ammonia[87] represent an intriguing starting point for the development of a novel multicomponent reaction, in particular, with respect to the generation of combinatorial libraries. From this point of view, a four-component reaction is most attractive, as it allows, by individual variations of the components, to generate large diversity of products.

In previous chapters it was shown that CIR is the most elegant and atom-economic way of transforming aryl halides into chalcones, highly reactive Michael acceptors, that readily react with all kinds of mono- and bidentate nucleophiles. Therefore, chalcones have directly been subjected, in a one-pot fashion, to the reaction with enamines and ammonium chloride providing access to substituted and annelated pyridines.

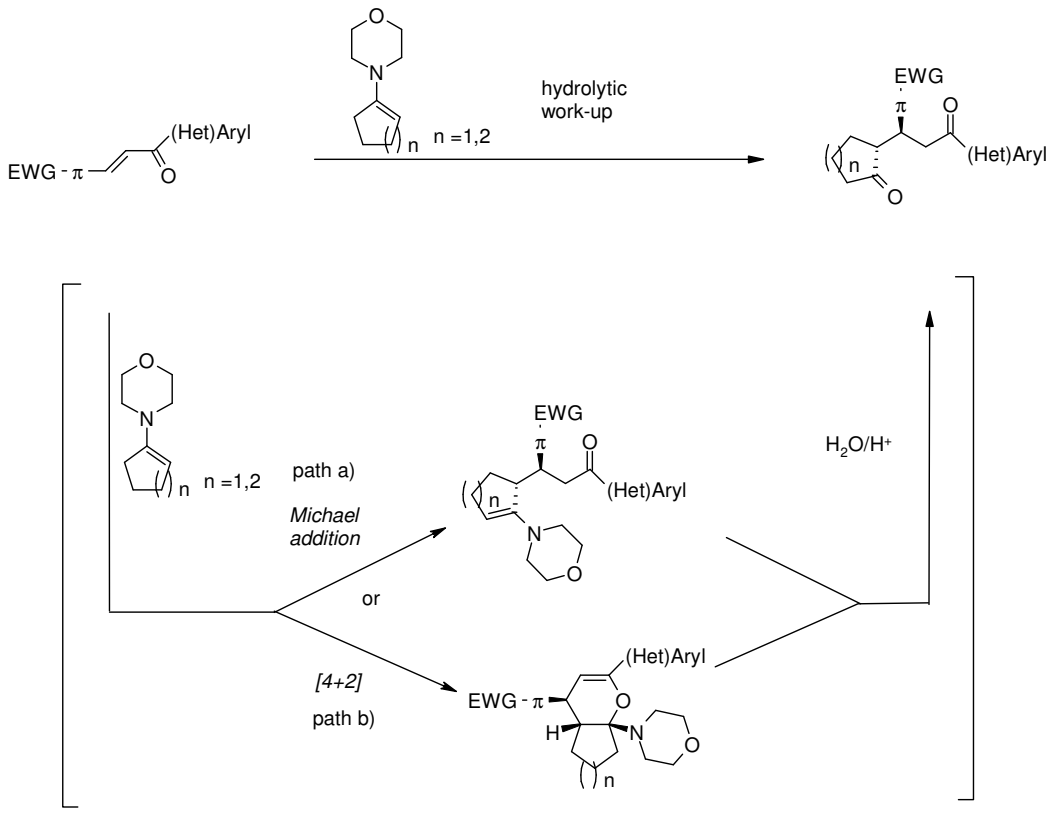
Hence, a novel four-component pyridine synthesis based upon a CIR, followed by a consecutive enamine cycloaddition and a concluding cyclocondensation with ammonium

chloride was developed. The retrosynthetic scheme for the pyridine synthesis via a coupling-isomerization sequence provides aryl bromides, propargyl alcohols and ammonium chloride as readily available starting materials (Scheme 35).



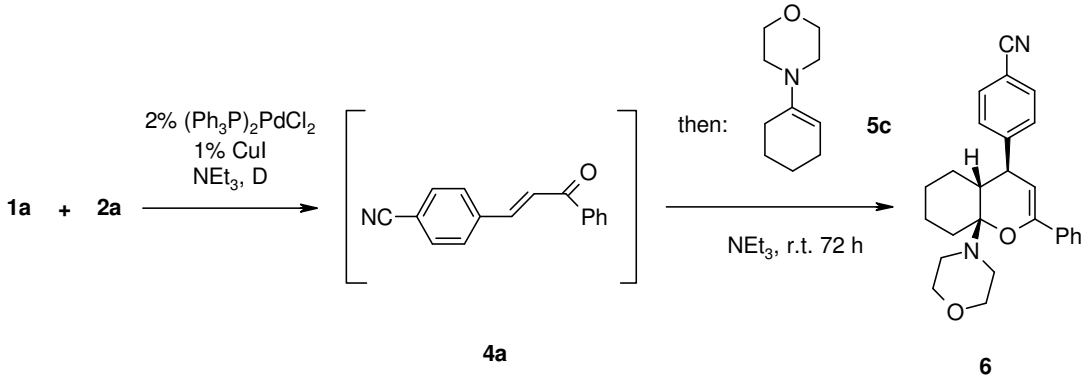
Scheme 35 Retrosynthetic concept of consecutive one-pot four-component pyridine synthesis.

Product analysis suggests that the intermediate is either a keto enamine or a cycloadduct, as a consequence of a Michael addition or a Diels-Alder reaction with inverse electron demand[88] between an enamine and a chalcone. The aqueous work-up of the intermediate does not help in the structure elucidation of the intermediate, since the hydrolysis product in both cases is a 1,5-diketone (Scheme 36).



Scheme 36 Hydrolitic formation of 1,5-diketones.

Therefore, in order to elucidate the reaction pathway, according to Katritzky,[89] after CIR of **1a** and **2a** furnishing the chalcone **4a**, and after subsequent addition of enamine **5c** followed by reaction at room temperature for 72 h, suitable single crystals of the cycloadduct **6** were isolated by careful crystallization of the crude product from petroleum ether (Scheme 37, Fig. 10).



Scheme 37 Coupling-isomerization-cycloaddition sequence.

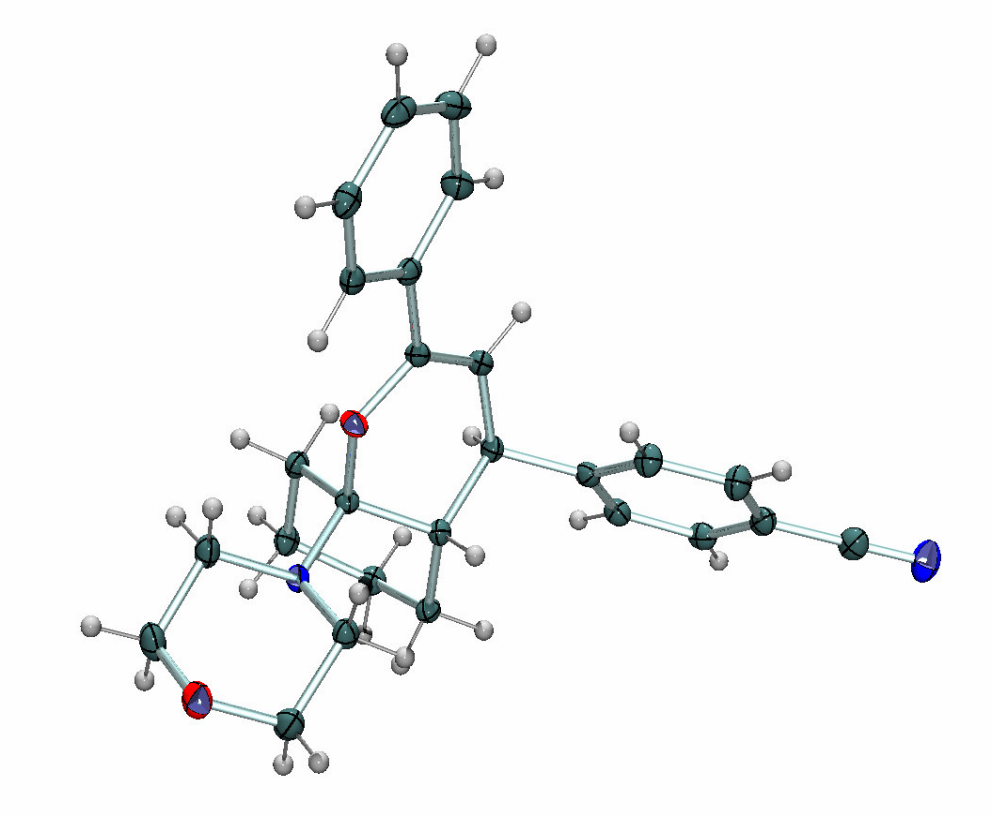


Fig. 10 ORTEP plot of cycloadduct **6**

The proton NMR spectrum of the isolated product shows the appearance of a signal at δ 5.25 and unambiguously indicates the formation of a vinyl ether that can be attributed to a cycloadduct. Formally, the formation of the *endo*-product **6** is the result of a concerted or stepwise [4+2] cycloaddition. The intermediacy of **6** in the CI-enamine addition reaction is also in full agreement with the observed stereochemistry in the diketone, which can be considered to be the hydrolysis product of the cyclic aminal **6**.

Molecular modeling of alternative reaction pathways (Fig. 11), i.e. concerted and stepwise [4+2] cycloaddition and ene reaction, respectively, was performed on the PM3 level of theory,[90] both in gas phase and water.[91] The results of the computations reveal that, although the heat of formation of the ene product, i.e. the enamino ketone **7**, is thermodynamically slightly favoured over the cycloadduct **6**, under kinetic control a stepwise [4+2] cycloaddition occurs most likely. In particular, in polar solvents the formation of the dipolar iminium enolate **8** as an intermediate in the rate determining step most likely concludes to the 1,6-dipolar cyclization of the zwitter ion **8** to give the experimentally observed reaction product **6**.

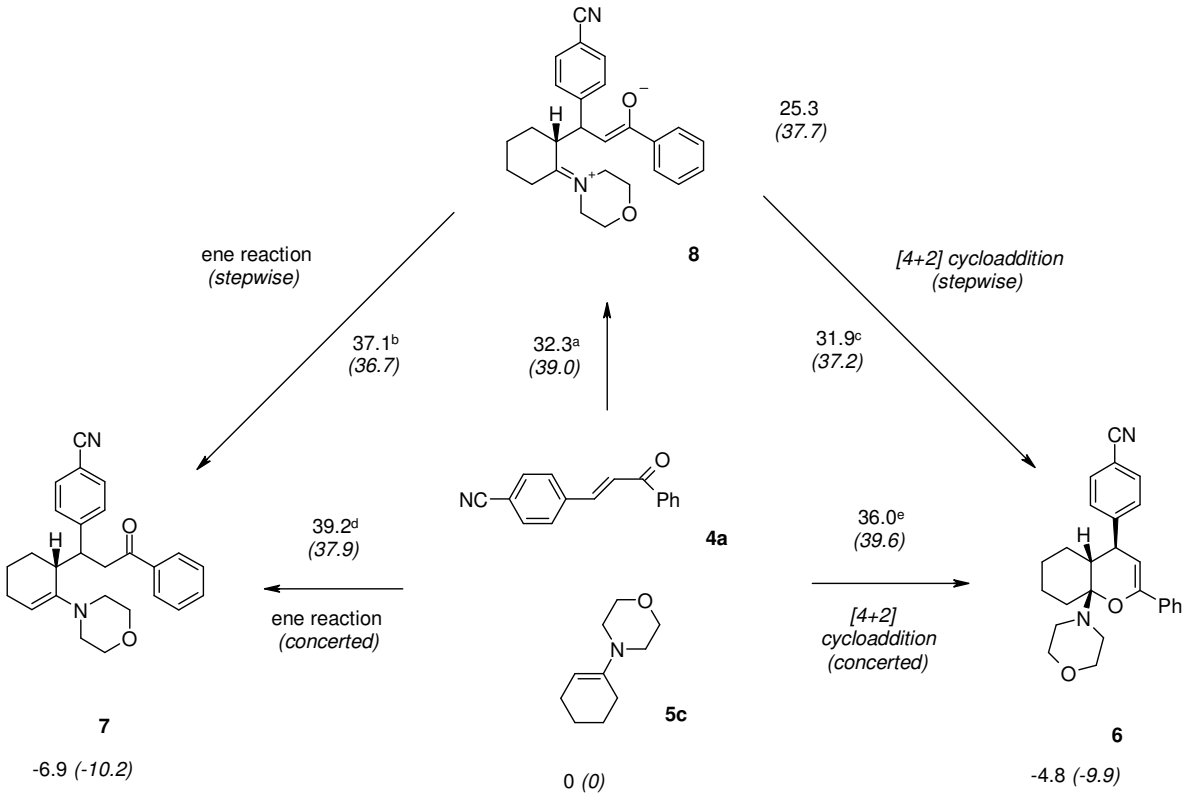
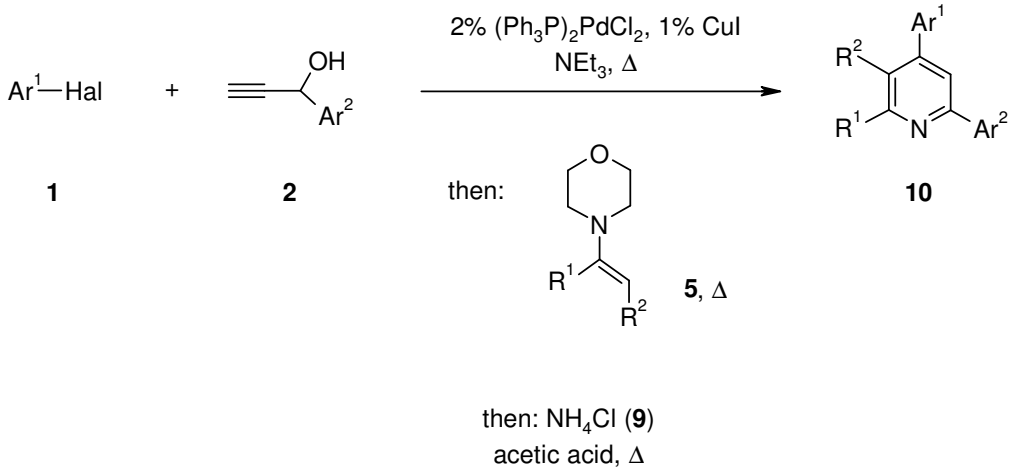


Fig. 11 Calculated PM3 energies [kcalmol^{-1}] of the addition of an enamine to a chalcone in solution and in the gas phase (in parentheses). Imaginary frequencies that verify transition states: [a]i473.2 cm^{-1}, [b]i735.1 cm^{-1}, [c]i100.9 cm^{-1}, [d]i947.2 cm^{-1}, [e]i487.4 cm^{-1}.

After the coupling-isomerization reaction and the subsequent enamine cycloaddition, the final step of this new one-pot four-component reaction begins with the protonation of the cycloadduct with acetic acid to give a reactive electrophilic iminium ion that now initiates the concluding cyclocondensation step with ammonium chloride or benzyl amine.

Thus, applying electron poor (hetero)aryl halides **1** and aryl propynols **2** to the conditions of the CIR, and after complete conversion to the corresponding chalcones, adding (hetero)cyclic and a cyclic morpholino enamines **5** to the reaction mixture and, finally, adding ammonium chloride **9** in the presence of acetic acid tetrahydro-[1,6]naphthyridines **10a-d**, pyrindines **10e-h**, tetrahydroquinolines **10i-k**, tri(hetero)aryl pyridines **10l-o** were formed in moderate to good yields as colourless crystals (Scheme 38, Table 12).



1 **2** **10**

Scheme 38 Four-component synthesis of annealed and substituted pyridines **10** based upon a CIR-enamine addition-cyclocondensation sequence.

Conformationally fixed enamines like *N*-morpholino cyclopentene, cyclohexene or tetrahydropyridine, or enamines of acetophenone derivatives smoothly react in the enamine addition step, and finally lead to the formation of annealed or substituted pyridines (Table 12). Acyclic disubstituted enamines rather give a mixture of products and were, therefore, not considered for further investigation.

Table 12 One-pot synthesis of annealed and substituted pyridines **10**.

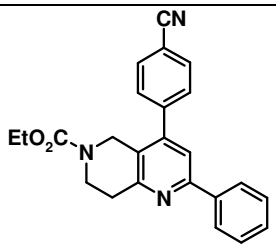
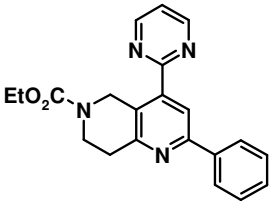
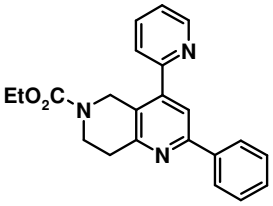
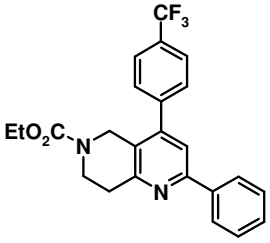
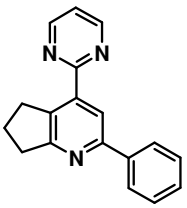
Entry	Aryl halide **1**	Propargyl alcohol **2**	Enamine **5**	Pyridines **10** (Yield)
1[a,b]	Ar^1 = *p*-C_6H_4CN (**1a**)	Ar^2 = Ph (**2a**)	R^1, R^2 = $(CH_2)_2N(CO_2Et)CH_2$, (**5a**)	 **10a** (61 %)
2[a,b]	Ar^1 = 2-pyrimidyl (**1b**)	**2a**	**5a**	 **10b** (57 %)
3[a,b]	Ar^1 = 2-pyridyl (**1c**)	**2a**	**5a**	 **10c** (41 %)
4[a,b]	Ar^1 = *p*-$C_6H_4CF_3$ (**1d**)	**2a**	**5a**	 **10d** (58 %)
5[b,c]	**1b**	**2a**	R^1, R^2 =$(CH_2)_3$ (**5b**)	 **10e** (59 %)

Table 12 *continued*

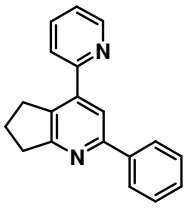
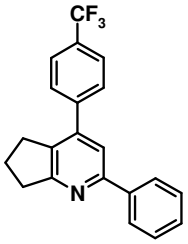
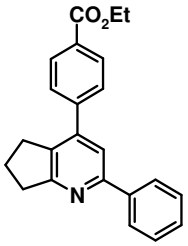
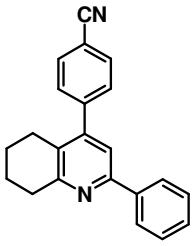
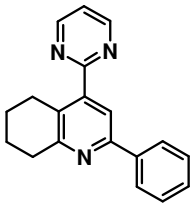
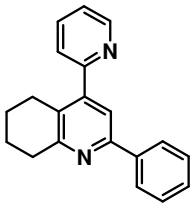
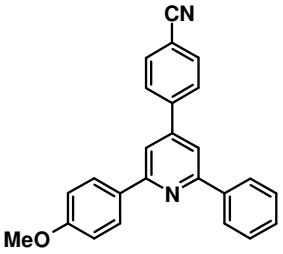
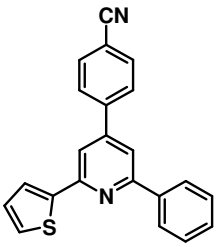
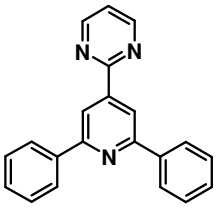
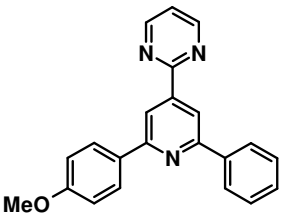
6[b,c]	**1c**	**2a**	**5b**	 **10f** (62 %)
7[c,d]	**1d**	**2a**	**5b**	 **10g** (54 %)
8[b,c]	Ar^1 = *p*-$C_6H_4CO_2Et$ (**1e**)	**2a**	**5b**	 **10h** (42 %)
9[a]	**1a**	**2a**	$R^1,R^2 = (CH_2)_4$ (**5c**)	 **10i** (70 %)
10[b,c]	**1b**	**2a**	**5c**	 **10j** (50 %)

Table 12 *continued*

11[c,d]	**1c**	**2a**	**5c**	 **10k** (64 %)
12[a,b]	**1a**	**2a**	R^1 = *p*-C_6H_4OMe, R^2 = H (**5d**)	 **10l** (54 %)
13[a,b]	**1a**	**2a**	R^1 = 2-thienyl, R^2 = H (**5e**)	 **10m** (46 %)
14[b,c]	**1b**	**2a**	R^1 = Ph, R^2 = H (**5f**)	 **10n** (68 %)
15[a,b]	**1b**	**2a**	**5d**	 **10o** (39 %)

[a]Reaction time of the CIR 16 h. [b]In NEt_3. [c]Reaction time of the CIR 12 h. [d]In $HNEt_2$.

Spectroscopic Data

The structure of the pyridine derivatives **10** is unambiguously supported by the expected appearance of the characteristic proton and carbon resonances and multiplicities. In particular, in the ^{1}H NMR spectra of **10** the diagnostic singlets for the pyridine methine signals, appearing between δ 7.5 and 8.5, are applied for the assignments of the *ortho* phenyl or phenylene doublets by 2D NOESY spectra, indicating clear cross-peaks as a consequence of spatial proximity. Likewise, the structure of naphthyridines **10a–d** can be established by thorough inspection of 2D NOESY correlations between the methylene groups in the saturated ring appearing as singlets at δ 4.5–4.9 and the proximal methine resonances steming from the electron poor (hetero)aryl substituent. The signals for the ethyl protons for **10a–d** are detected as a multiplet in the range of δ 1.18–1.26, with an intensity of 3 protons and a quartet in the range of δ 4.05–4.12, with coupling constants of *J* 7.0–7.1 Hz.

Characteristically for the dihydropyrindines **10e–h** are the downfieldshifted signals of the methylene protons that appear as triplets in the range of δ 3.01–3.38, with coupling constants of *J* 7.3–7.8 Hz. Similarly, the methylene protons of the tetrahydronaphthyridines **10i–k**, are detected as triplets, in the range of δ 2.59–3.11, with coupling constants of 6.4–6.6 Hz.

The mass spectra of all obtained compounds show the molecular peaks. The usual fragmentation mode for all pyridine derivatives leads to the loss of phenyl fragments. For **10a–d** the loss of ethyl and carboethoxy groups were detected.

The vibrations of CN group in **10a**, **10i** and **10l** were identified at 2224–2227 cm^{-1} in the IR spectra.

Furthermore, the structures of pyrindines, tetrahydroquinolines, and naphthyridines **10** were corroborated by X-ray crystal structure analyses of compounds **10a**, **10f**, **10g**, **10j**, **10k** and **10n** (Fig. 12–Fig. 17).

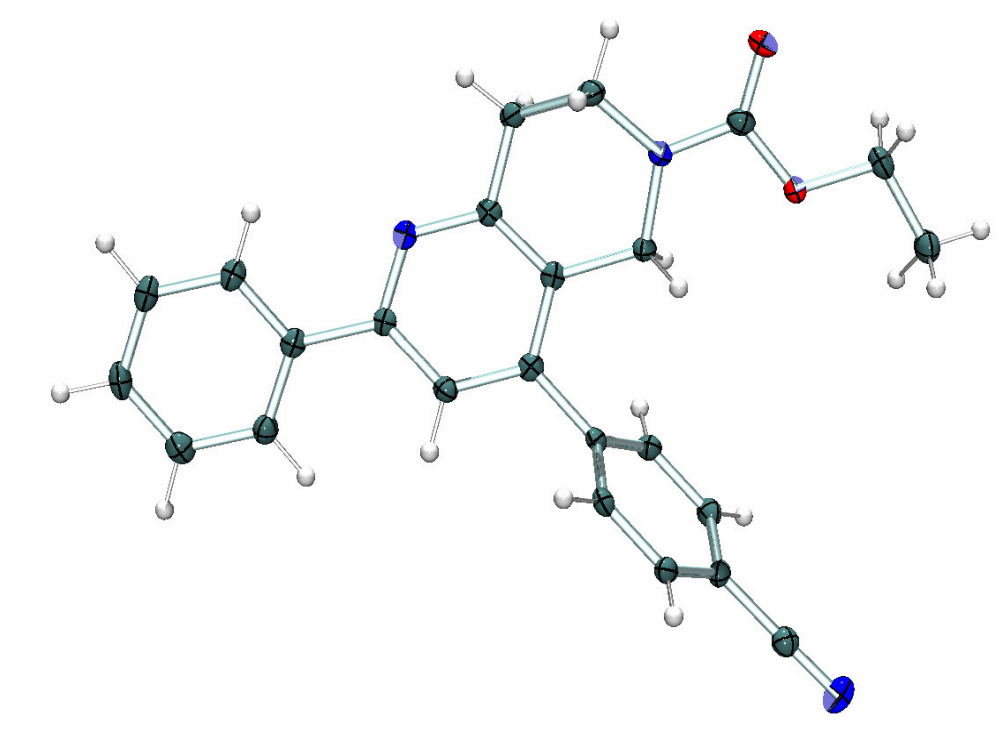


Fig. 12 ORTEP plot of compound **10a**.

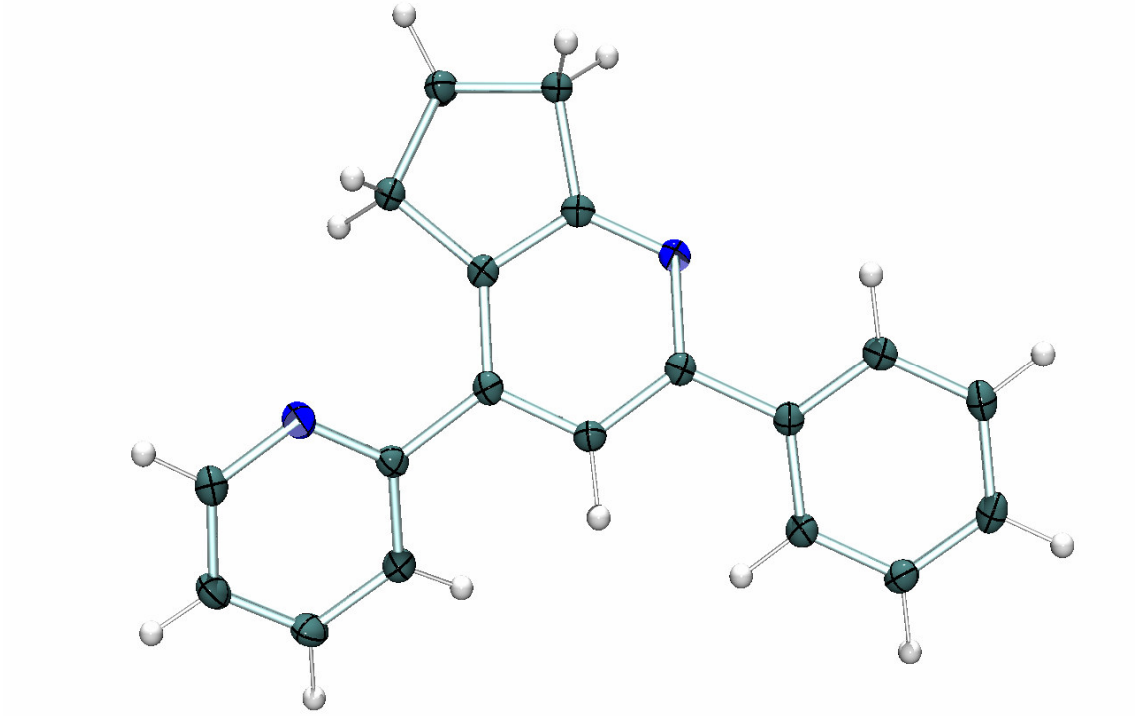


Fig. 13 ORTEP plot of compound **10f**.

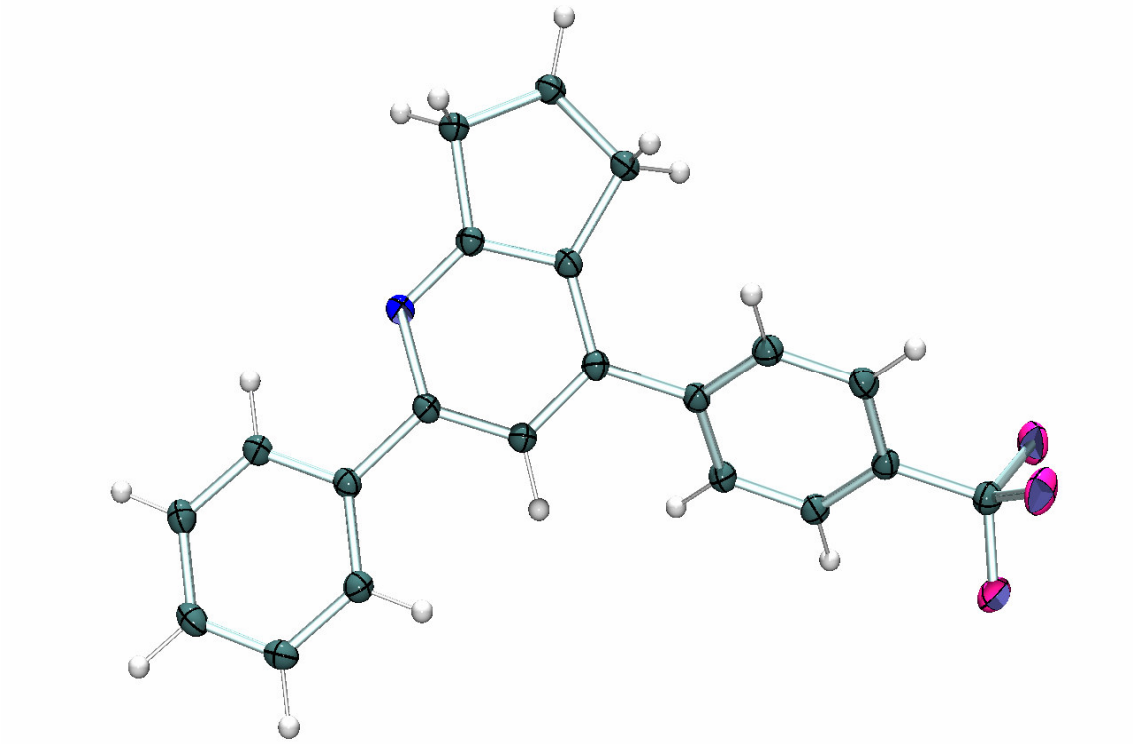


Fig. 14 ORTEP plot of compound **10g**.

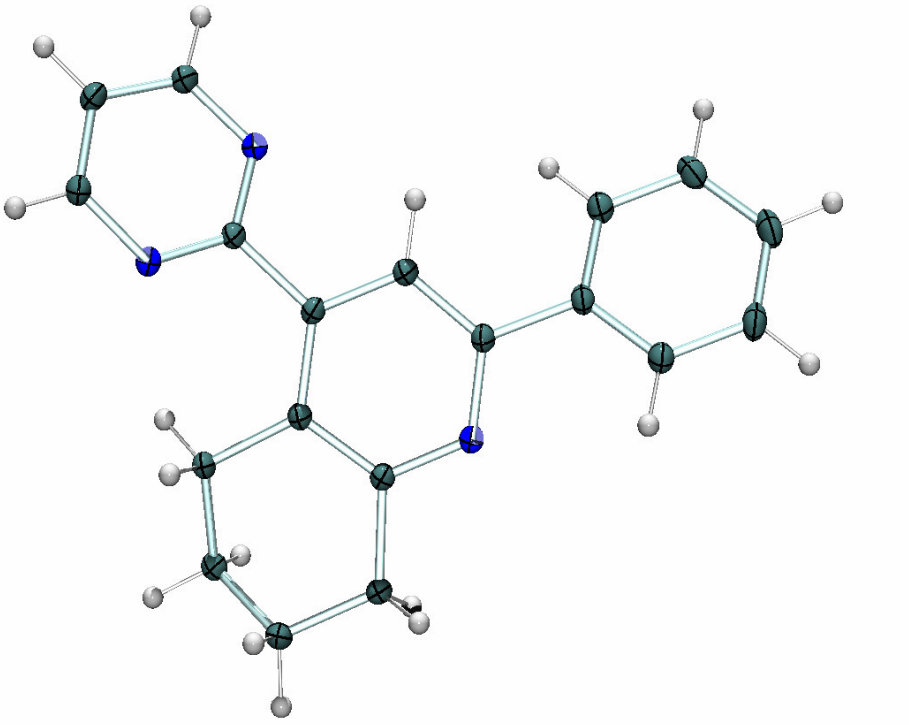


Fig. 15 ORTEP plot of compound **10j**.

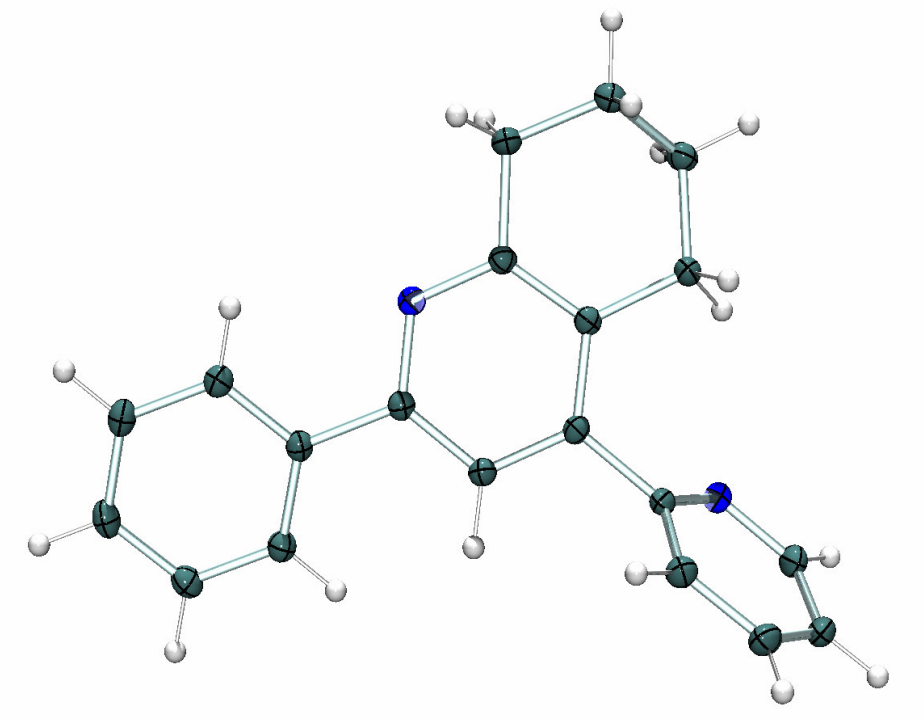


Fig. 16 ORTEP plot of compound **10k**.

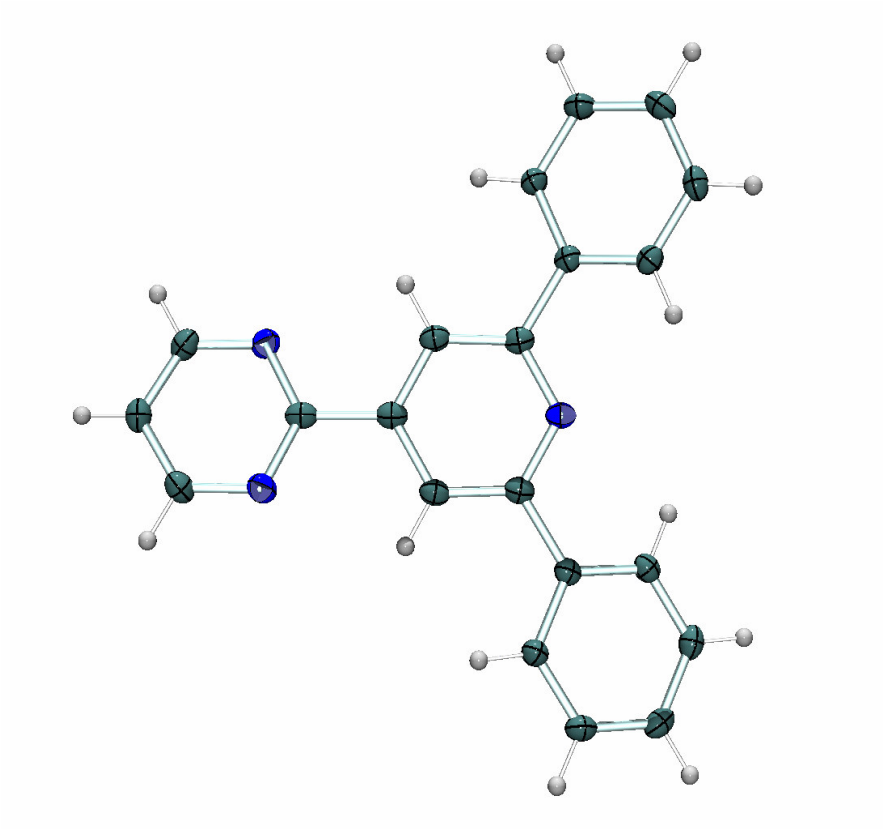


Fig. 17 ORTEP plot of compound **10n**.

4.3 [3+3] Dihydropyridine and Pyridine Syntheses Based upon CIR

4.3.1 Dihydropyridines – Literature Review

First mentioned by Hantzsch[92] almost one century ago, dialkyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates (1,4-DHP) have now been recognized as vital drugs in the treatment of angina and hypertension. Some of them (amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, Fig. 18) have been commercialized and it has been proven that their therapeutic success is related to their efficacy to bind to calcium channels, and consequently to decrease the passage of the transmembrane calcium current, associated in smooth muscle with a long lasting relaxation and in cardiac muscles with a reduction of contractility throughout the heart.[93]

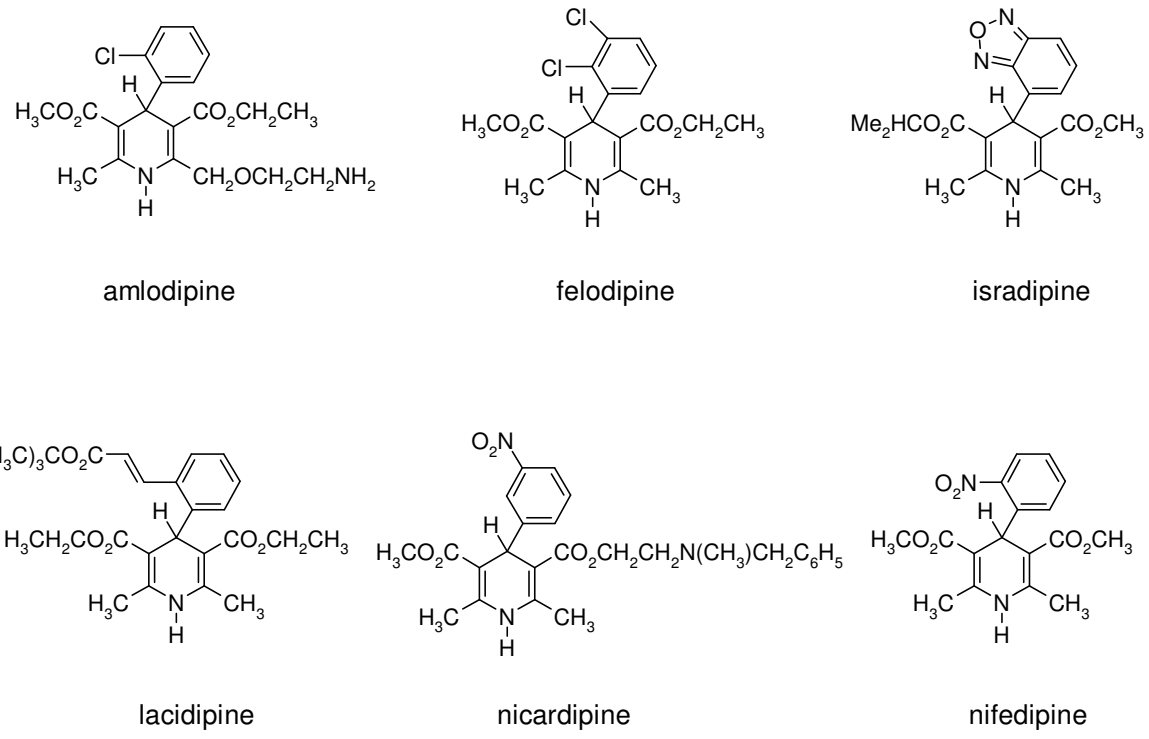
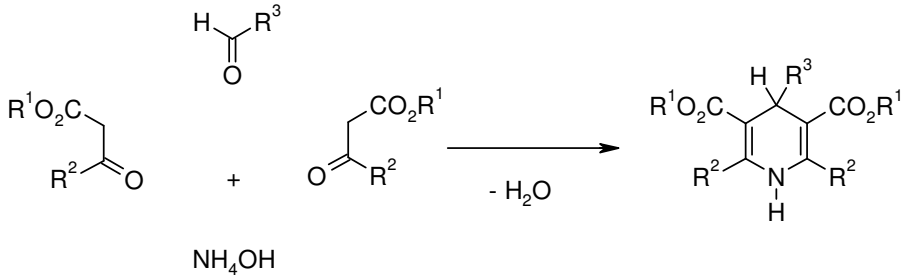


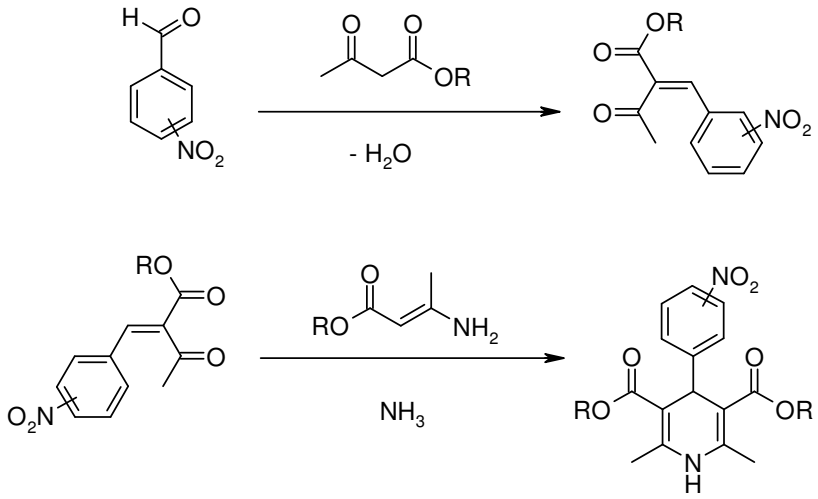
Fig. 18 Calcium channel blocker pyridines.

The usefulness of the calcium antagonists has led to the development of novel synthetic strategies[94] to improve the classical Hantzsch dihydropyridine synthesis, (Scheme 39) and microwave activation stands among the alternative routes proposed the past decade.[95]



Scheme 39 Hantzsch Synthesis.

Recently, Santander et al.[96] reported a modified Hantzsch 1,4-dihydropyridines synthesis, starting with the condensation of nitrobenzaldehyde with α,β-ketoesters and subsequent cyclocondensation with alkyl 3-amino crotonates (Scheme 40).



Scheme 40 Modified Hantzsch dihydropyridine synthesis.

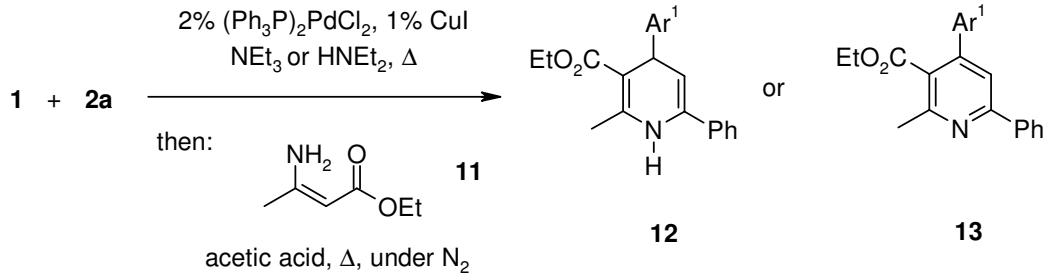
Aromatization of 1,4-DHP has also attracted considerable attention in recent years as Böcker[97] has demonstrated that metabolism of those drugs involves a cytochrome P-450 catalyzed oxidation in the liver. The so-obtained pyridines are devoid of the pharmacological activity of the parent heterocycles and are further transformed by additional chemical modifications. Due to the biological importance of the oxidation step of 1,4-DHP, the reaction

has been the subject of a large number of studies and a plethora of reagents has been utilized to mimic the *in vivo* transformation.[98]

Jacobson et al.[99] showed that both the dihydropyridine and the corresponding pyridine derivatives are good antagonist for A_3 adenosine receptor and, therefore, potential antiinflamatory, antihismatic and antiischemic agents. They also found defined common pharmacophore elements for pyridine and dihydropyridine structures, e.g., ester group and 6-phenyl group using molecular modelling based on the steric and electrostatic alignment (SEAL) method. Moreover, a relationship between affinity and hydrophobicity was examined for the pyridines.

4.3.2 One-Pot Three-Component CIR-Enamine Addition-Cyclocondensation Dihydropyridine and Pyridine Syntheses

The great importance of 1,4-dihydropyridines and their corresponding pyridine derivatives prompted us to develop a new one-pot, three-components synthesis, using coupling-isomerization, enamine addition, cyclocondensation sequence, in one-pot fashion. Thus, upon performing the CIR with the aryl halides **1** and the propargyl alcohol **2a** followed by the addition of ethyl 3-amino crotonate **11** as a suitable enamine in the presence of acetic acid and under nitrogen, in a few cases the expected dihydropyridines **12** could be isolated (Scheme 41).

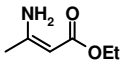
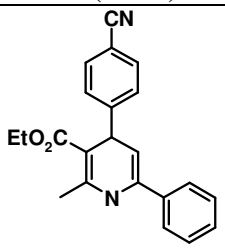
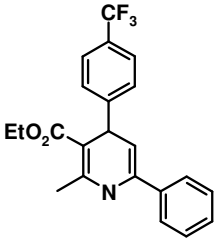
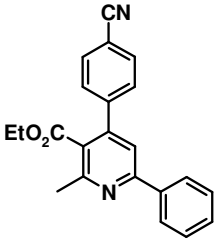
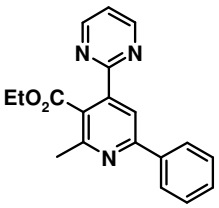
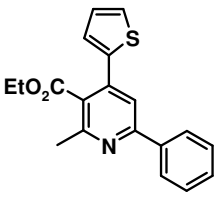
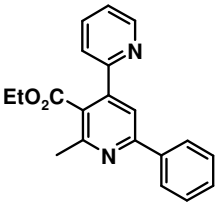


12a: Ar^1 = *p*-C_6H_4CN (45 %)
12b: Ar^1 = *p*-$C_6H_4CF_3$ (37 %)

13a: Ar^1 = *p*-C_6H_4CN (40 %)[a]
13b: Ar^1 = 2-pyrimidyl (50 %)
13c: Ar^1 = 2-thiazolyl (26 %)
13d: Ar^1 = 2-pyridyl (26 %)

Scheme 41 Three-component synthesis of functionalized dihydropyridines **12** and pyridines **13** based upon a CIR-enamine addition-cyclocondensation sequence.

Table 13 One-pot synthesis of dihydropyridines **13** and pyridines **14**.

Entry	Aryl halide **1**	Propargyl alcohol **2**	Enamine **11**	Dihydropyridines **12** / Pyridines **13** (Yield)
1[a]	Ar^1 = *p*-C_6H_4CN (**1a**)	Ar^2 = Ph (**2a**)	 **11**	 **12a** (45 %)
2[a]	Ar^1 = *p*-$C_6H_4CF_3$ (**1c**)	**2a**	**11**	 **12b** (37 %)
3[b]	Ar^1 = *p*-C_6H_4CN (**1a**)	**2a**	**11**	 **13a** (40 %)
4[a]	Ar1 = 2-pyrimidyl (**1b**)	**2a**	**11**	 **13b** (50 %)
5[a]	Ar1 = 2-thiazolyl (**1a**)	**2a**	**11**	 **13c** (26 %)
6[a]	Ar1 = 2-pyridyl (**1c**)	**2a**	**11**	 **13d** (26 %)

[a]All reaction steps were performed under nitrogen. [b]After CIR the reaction was performed under air.

However, either under aerobic (compound **13a**) or anaerobic conditions in most cases the aromatization readily furnishes the ethyl nicotinoate derivatives **13** in moderate yields.

Again, in this three-component pyridine synthesis as before in the four-component sequence, the oxidative aromatization of the actual dihydropyridine intermediate readily occurs under the reaction conditions assisted by the presence of the palladium and copper species that obviously catalyze this final step in the sequence. A moderate substituent effect in this dehydrogenating aromatization can be attributed to the fact that only for slightly weaker acceptors such as cyano and trifluoromethyl groups give rise to the isolation of the dihydropyridine intermediate. Although, the three-component pyridine synthesis opens an entry to further functionalized pyridines such as ethyl nicotinoate derivatives **13**, the yields of the four-component sequence are consistently higher.

Spectroscopic data

The formation of the dihydropyridines **12** and pyridines **13** is unequivocally supported by the appearance of the characteristic methine proton resonances in the ^{1}H NMR spectra as multiplets at δ 5.0 for dihydropyridines **12** and as singlets between δ 7.5 and 8.5 for ethyl nicotinoate derivatives **13**. The ethyl proton resonances for all dihydropyridines **12** and pyridines **13**, are detected as triplets in the range of δ 1.01–1.27 with a coupling constant of *J* 7.0 Hz, and quintets in the range of δ 3.86–4.36 with a coupling constant of *J* 7.0 Hz. The methyl protons of all dihydropyridine and pyridine derivatives resonate in the range of δ 2.3–2.90, as singlets.

The mass spectra of all obtained compounds show the molecular peaks. The usual fragmentation mode for all dihydropyridines and pyridines leads to the loss of ethyl and carboxyethyl fragments.

Besides the mass spectrometric, IR spectroscopic, and combustion analytical data are in agreement with the suggested molecular structure of the dihydropyridines **12** and ethyl nicotinoate derivatives **13**. Additionally, the structures of the nicotinoates **13** were corroborated by X-ray crystal structure analyses of compounds **13a**, **13b**, and **13c** (Fig. 19–Fig. 21).

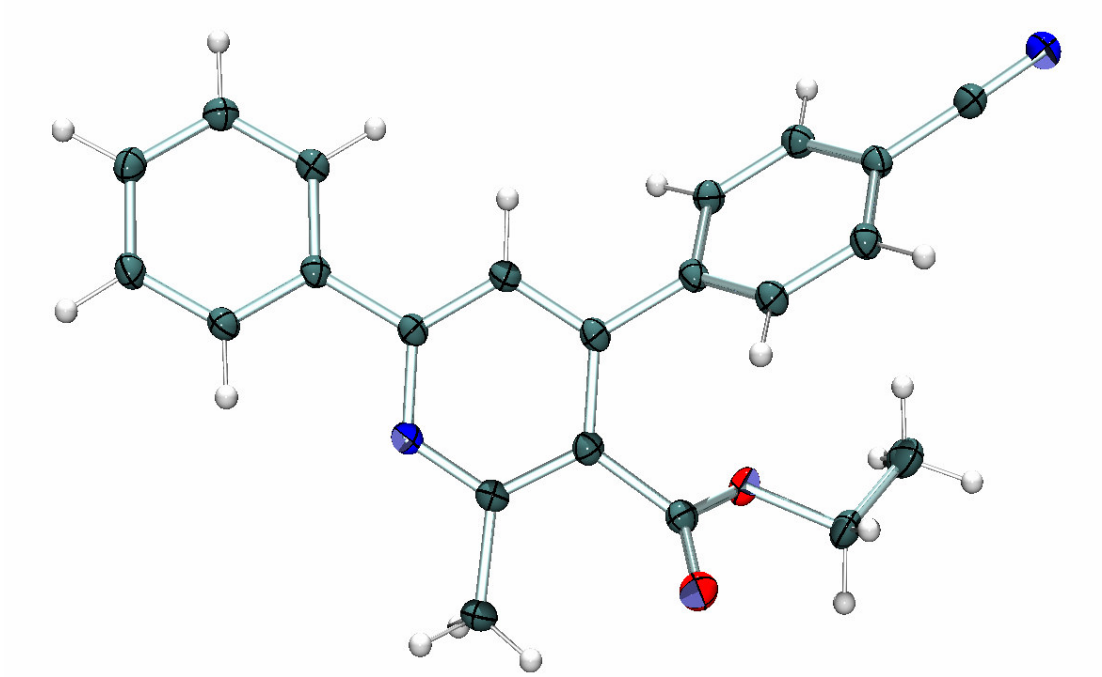


Fig. 19 ORTEP plot of compound **13a**.

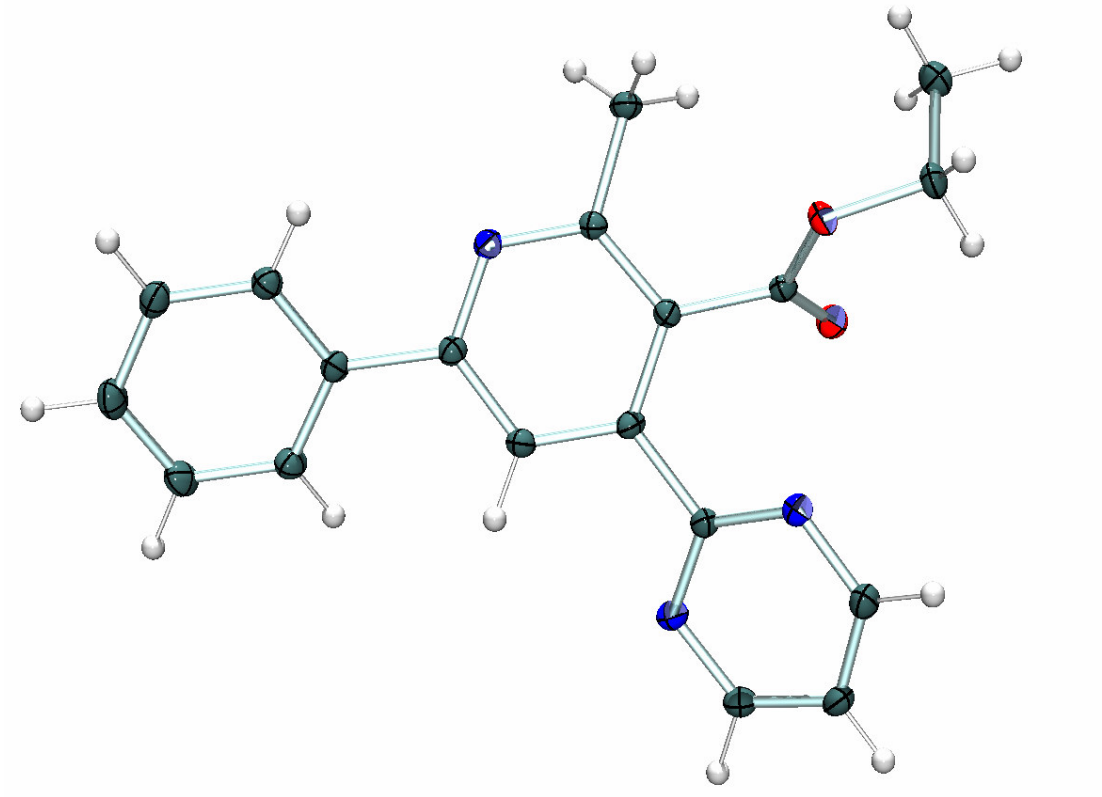


Fig. 20 ORTEP plot of compound **13b**.

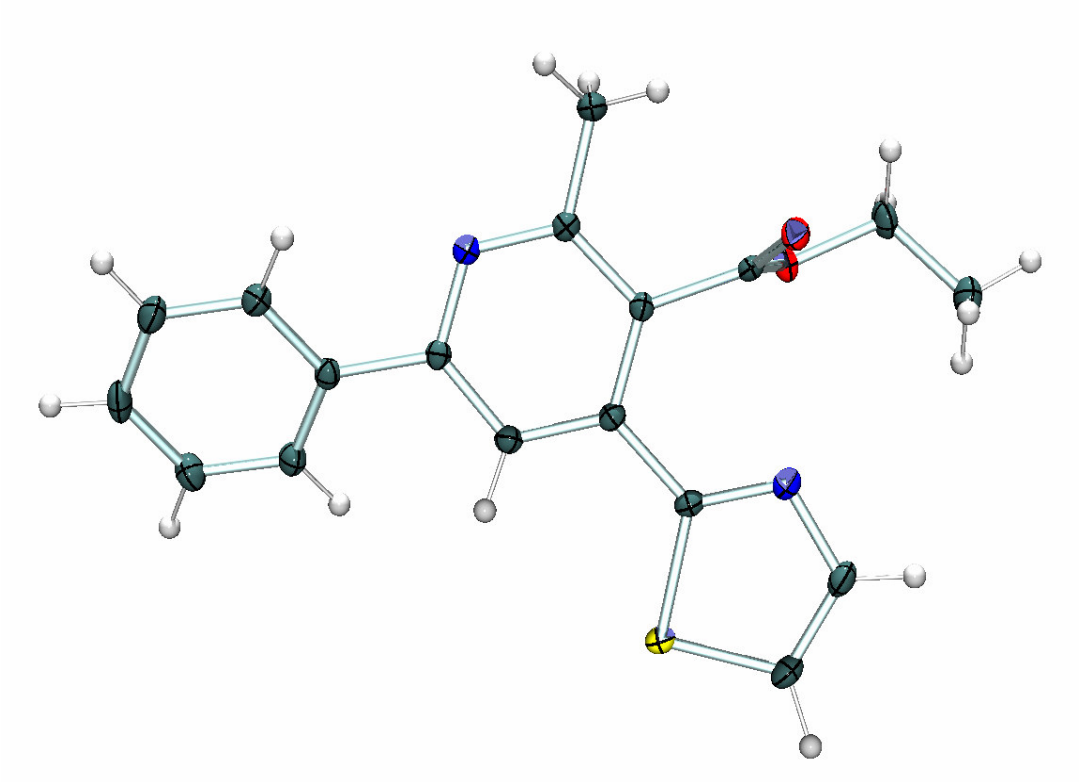
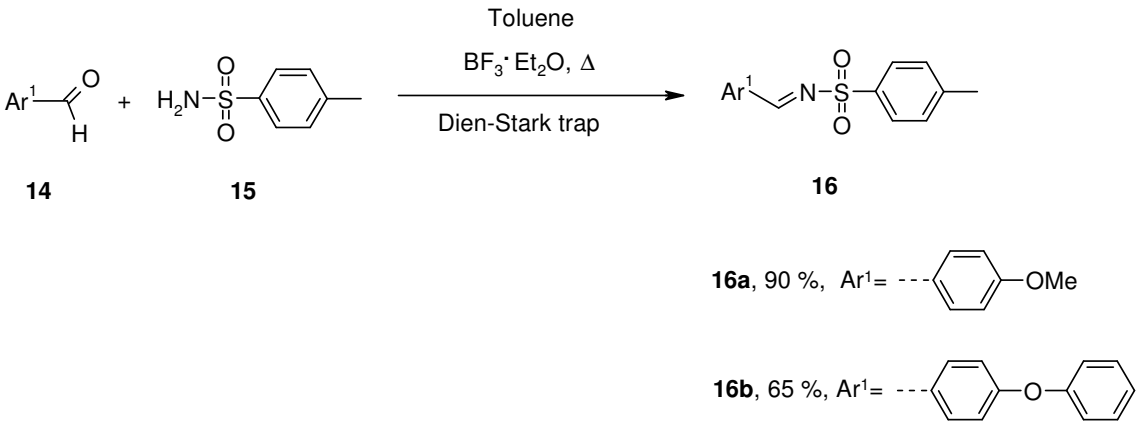


Fig. 21 ORTEP plot of compound **13c**.

4.4 [4+2] 2-Ethoxy Pyridine Synthesis Based upon CIR

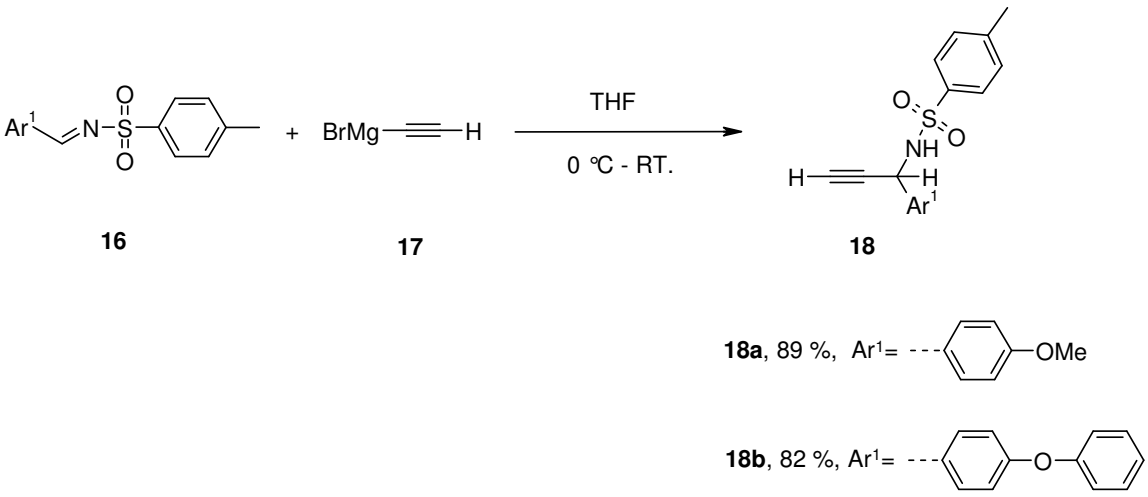
4.4.1 Synthesis of *N*-Propargyl Tosyl Amides

The azomethine **16** were synthesized according to the standard literature procedure,[100] from the corresponding aromatic aldehydes, **14**, and tosylamine, **17** (Scheme 42). The acid catalyzed reaction is performed in toluene using the Dean-Stark water-trap.



Scheme 42 Synthesis of azomethine **16**.

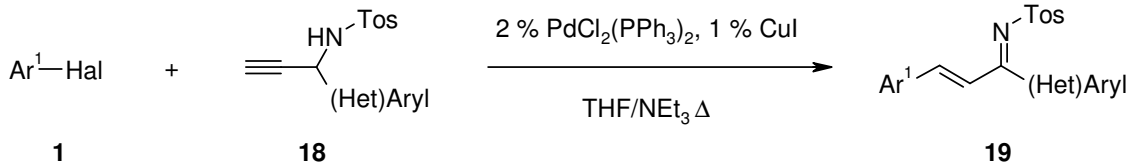
The azomethines **16** were reacted with ethynylmagmesium bromide, **17**, according to Brandsma,[101] to furnish the desired propargyl tosylamine **18** in excellent yields (Scheme 43).



Scheme 43 Synthesis of *N*-propargyl tosyl amide **18**.

4.4.2 Enimine Synthesis Based upon CIR

Recently we have reported an extension of the CIR to *N*-propargyl tosyl amide substrates that opens a new and efficient access to *N*-tosyl-enimines (Scheme 44). [102]



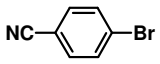
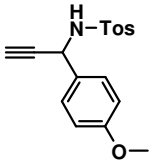
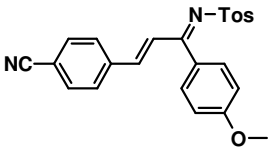
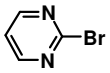
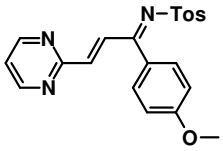
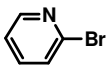
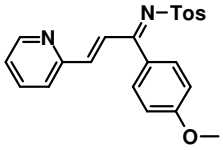
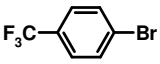
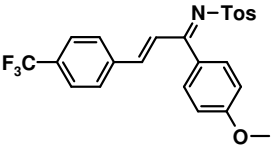
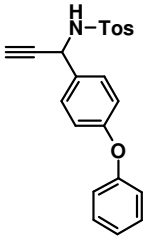
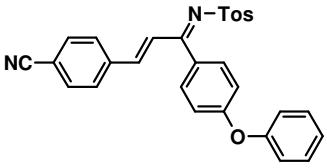
1 **18** **19**

Scheme 44 CIR access to *N*-tosyl enimines **19** from propargyl *N*-tosyl amides **18**.

Although the electron deficient 1-azadienes do not easily participate in [4+2] cycloadditions, *N*-tosyl-enimines are more suitable for Diels-Alder reactions with inverse electron demand due to the tosyl group with an excellent leaving group propensity. Therefore, their increased reactivity towards cycloadditions, with the formation of new heterocycle derivatives, motivated us to synthesize a series of new *N*-tosyl-enimines with a diversified substitution pattern.

Thus, electron deficient aromatic and heteroaromatic halides **1** and *N*-[1-(hetero)aryl-prop-2-ynyl] tosyl amides **18** were submitted to the reaction conditions of the CIR in a boiling mixture of triethylamine and THF to give after trituration of the crude products in ethanol the *N*-tosyl enimines **19a-e** in excellent yields (Table 14). However, it should be mentioned that, due to the hydrolytic sensitivity of enamine functionality, column chromatography often led to the isolation of the corresponding chalcones. Therefore, purification of the crude enimines is most efficiently achieved by recristallization from ethanol, or ethyl acetate/hexane mixtures.

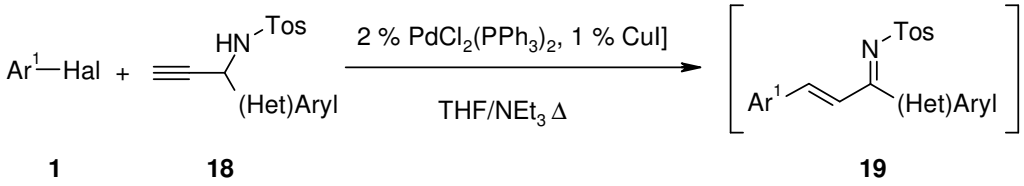
Table 14 CIR synthesis of enimines **19a–e**.

No.	(Hetero)Aryl[1]-Hal, **1**	N-Propargyl tosyl amide, **19**	*N*-tosyl enimines **20**	Yield
1	 **1a**	 **18a**	 **19a**	96 %
2	 **1b**	**18a**	 **19b**	~100 %
3	 **1c**	**18a**	 **19c**	~100 %
4	 **1d**	**18a**	 **19d**	~ 100 %
5	**1a**	 **18b**	 **19e**	94 %

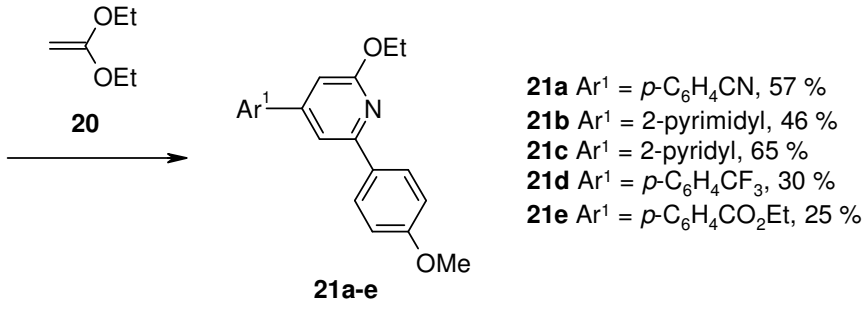
4.4.3 One-Pot Three-Component CIR-Ketene Acetal-Cycloaddition Syntheses of 2-Ethoxy Pyridines

The aza Diels-Alder reaction has become an important synthetic route to pyridines and several recent reviews discuss the scope and limitation of this versatile methodology.[103]

The electron rich 1-azabutadienes are well known to undergo facile HOMO-diene controlled [4+2] cycloadditions,[104] but the 4π-participation of the electron deficient 1-azadiene is reported[105] to suffer from low conversion, competitive [2+2] addition, and low reactivity due to an unfavorable s-*cis*/s-*trans* equilibrium, tautomerism of γ-alkyl substituted 1-azadienes to enamines precluding [4+2] addition and instability of endocyclic enamine products. In the last decade some successful methods have been proposed for the 4π-participation of electron deficient 1-azabutadienes in LUMO-diene controlled hetero-Diels-Alder reactions, among these the use of *N*-sulfonyl[84b-d] substituents is particularly notable, although the aromatization of the corresponding cycloadducts, does not take place unless strong bases or oxidation agents are added. Nevertheless the electron-poor 1-aza-dienes, despite their potential as heterodienes in Diels-Alder reactions, have received much less attention.



1 **18** **19**



Scheme 45 Three-component synthesis of 2-ethoxy pyridines **21**.

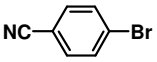
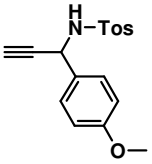
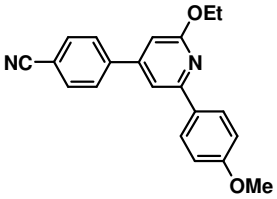
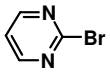
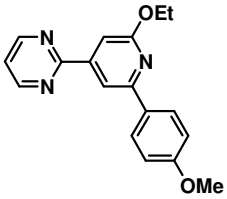
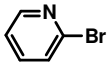
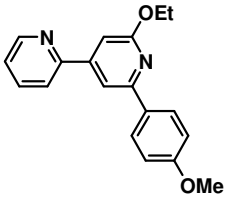
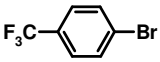
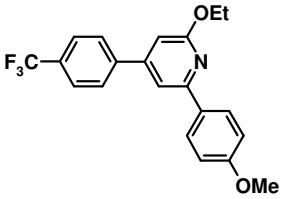
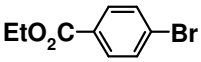
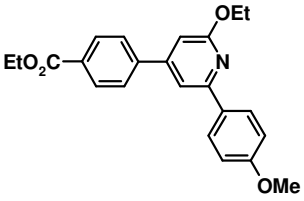
As shown previously, the *N*-tosyl enimines (**19**), readily available by CIR of (hetero)aryl halides (**1**) with N-propargyl tosyl amides (**18**), offer the advantage compared to other electron deficient 1-azadienes, of a good leaving group that facilitates their participation to the [4+2] cycloadditions. These properties were exploited in one-pot multcomponent pyridine syntheses based upon CIR-ketene acetal-cycloaddition sequence (Scheme 45, Table 15).

Thus, after performing the CIR with the aryl halides **1** and the *N*-propargyl tosyl amides **18** the electron rich diethyl ketene acetal **20** was added to the reaction mixture. After reaction times of 24-48 h, the 2-ethoxy pyridines **21** were isolated in moderate to good yields as colorless to yellow crystals or as light yellow oil.

Mechanistically, the formation of 2-ethoxypyridines **21** can be rationalized by either a concerted or stepwise [4+2] cycloaddition of the transient *N*-tosyl enimine **19** to furnish a tetrahydropyridine intermediate. However, the excellent leaving group propensity of the *N*-tosyl group could lead to a base induced elimination giving rise to a dihydropyridine that rapidly eliminates ethanol with concomitant aromatization, thereby, concluding the formation of the aromatic pyridine core.

In conclusion, we have demonstrated that the CIR can successfully be extended to the synthesis of *N*-tosyl enimines starting from propargyl *N*-tosyl amides. These electron deficient heterodienes are perfectly suited as reaction partners in Diels-Alder reactions with inverse electron demand. Therefore, we designed a one-pot three-component synthesis of 2-ethoxy pyridines by CIR-cyclocondensation sequence. This novel consecutive pyridine synthesis not only enhances molecular and structural diversity in a combinatorial sense and potentially in solid phase applications, but also allows a rapid construction of complex multicore heterocyclic arrays.

Table 15 Three-component synthesis of 2-ethoxy pyridine synthesis **21**.

No.	(Hetero)Aryl[1]-Hal, 1	*N*-Propargyl tosyl amide, **18**	2-Ethoxy pyridine, **22**	Yield
1	 **1a**	 **18a**	 **21a**	57 %
2	 **1b**	**18a**	 **21b**	46 %
3	 **1c**	**18a**	 **21c**	65 %
4	 **1d**	**18a**	 **21d**	30 %
5	 **1e**	**18a**	 **21e**	25 %

Spectroscopic data

The structure of the 2-ethoxy-6-(*p*-anisyl)pyridines **21** is unambiguously supported by the expected appearance of the characteristic proton and carbon resonances and multiplicities. In particular, in the ^{1}H-NMR spectra of **21** the diagnostic triplets for the ethoxy methyl proton signals at δ 1.35−1.46 (*J* 7.1 Hz) and the quartets for the ethoxy methylene protons at δ4.39−4.53 (*J* 7.1 Hz) are applied for the assignments of the 3-methine doublets of the newly formed pyridyl core at δ 6.73−7.05 (*J* 1.3 Hz) by NOESY spectra, indicating clear cross-peaks as a consequence of spatial proximity (Fig. 22).

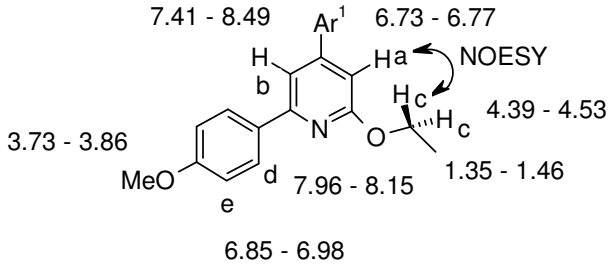


Fig. 22 Assignment of the chemical shifts in ^{1}H NMR for pyridine **21**.

The signals of the methoxy protons are detected as singlets, in the range of δ3.73–3.86.

Additionally, the mass spectrometric, IR spectroscopic, and combustion analytical data are in full agreement with the suggested molecular structure of the 2-ethoxy pyridines **21**. The mass spectra of all obtained compounds show the molecular peaks. The usual fragmentation mode for all pyridines leads to the loss of ethyl, methyl and carboxymethyl fragments. Furthermore, the structure of **21** is corroborated by an X-ray crystal structure analysis of compound **21e** (Fig. 23).

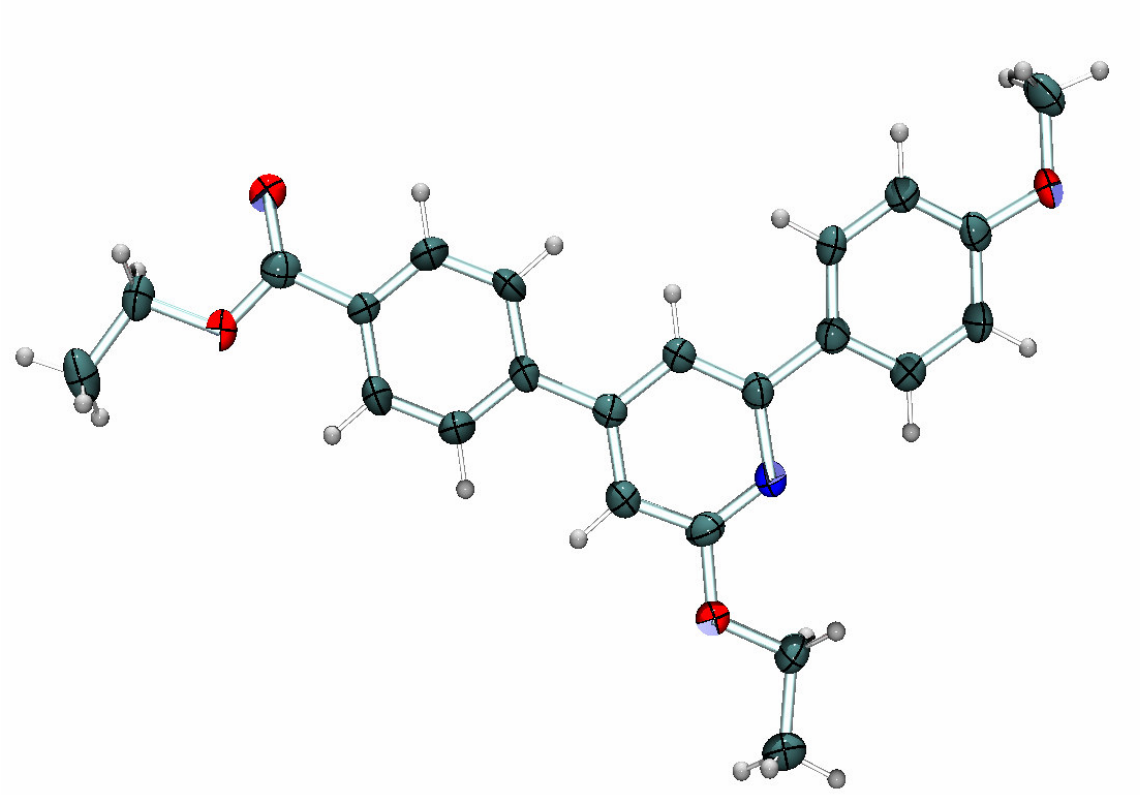


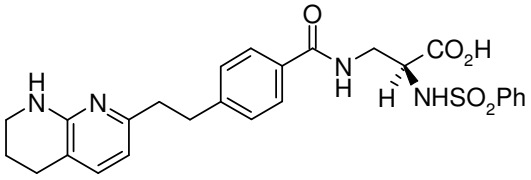
Fig. 23 ORTEP plot of compound **21e**.

4.5 [4+2] Synthesis of Annelated 2-Amino Pyridines Based upon CIR

4.5.1 Annelated 2-Amino Pyridines – Literature Review

Annelated 2-amino pyridines where the amino group is an *endo* constituent of the annelated saturated ring are pharmaceutically intriguing structures. In particular, pyrrolo[2,3-*b*]pyridines or 7-azaindolines,[106] [1,8]naphthyridines,[107] and pyrido[2,3-b]azepines,[108] have received considerable interest as a consequence of their broad pharmacological activities among which anti-inflammatory, antibacterial, antitumour, cardiotonic and anticonvulsivant properties.

Recently, Hartman et al.,[107e] have identified the 5,6,7,8-tetrahydro[1,8]naphthyridine (THN) moiety as a lipofilic, moderately basic *N*-terminus that provides molecules with excellent potency and selectivity for the integrin receptor $\alpha_v\beta_3$, therefore good antiosteoporosis agents (Fig. 24).

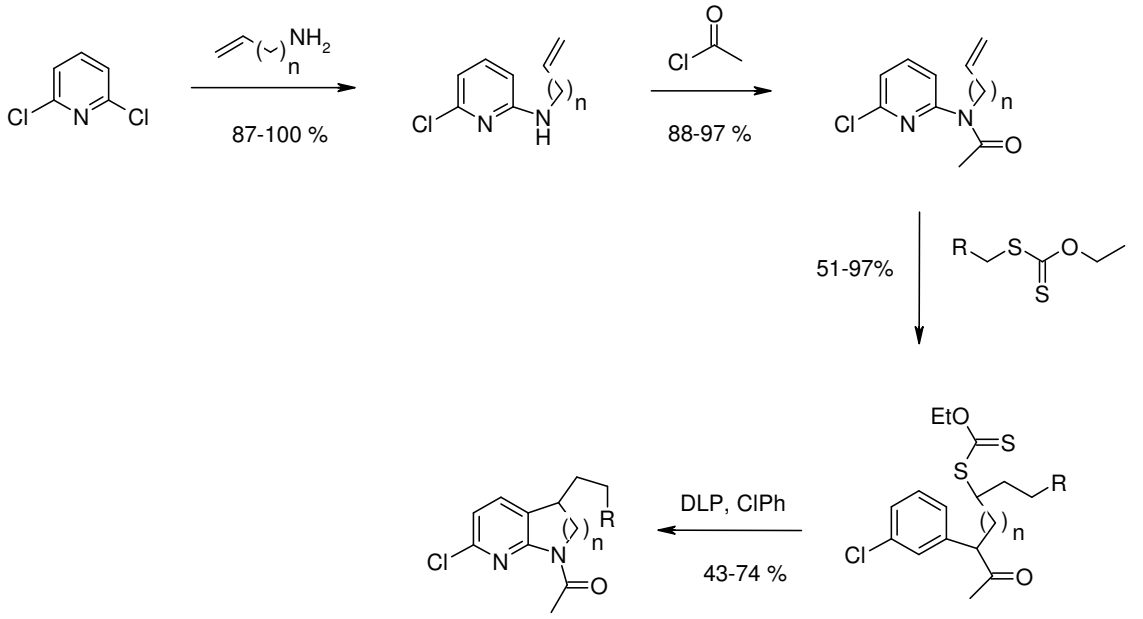


IC_{50} 3 nM
(inhibition of rat osteoclast-mediated
bone resorption in vivo)

Fig. 24 THN-derivative - inhibitor of bone resorption.

For a convenient access to new potential biologically active 2-amino annelated pyridines, it is essential that reliable, flexible and general synthetic methods to be readily available. However, the various synthetic routes towards these compounds are limited with respect to yields and scope.

As a recent example, Zard et al.,[109] reported a synthetic route involving a tin free-radical-mediated cyclization onto the pyridine ring as the key step (Scheme 46).

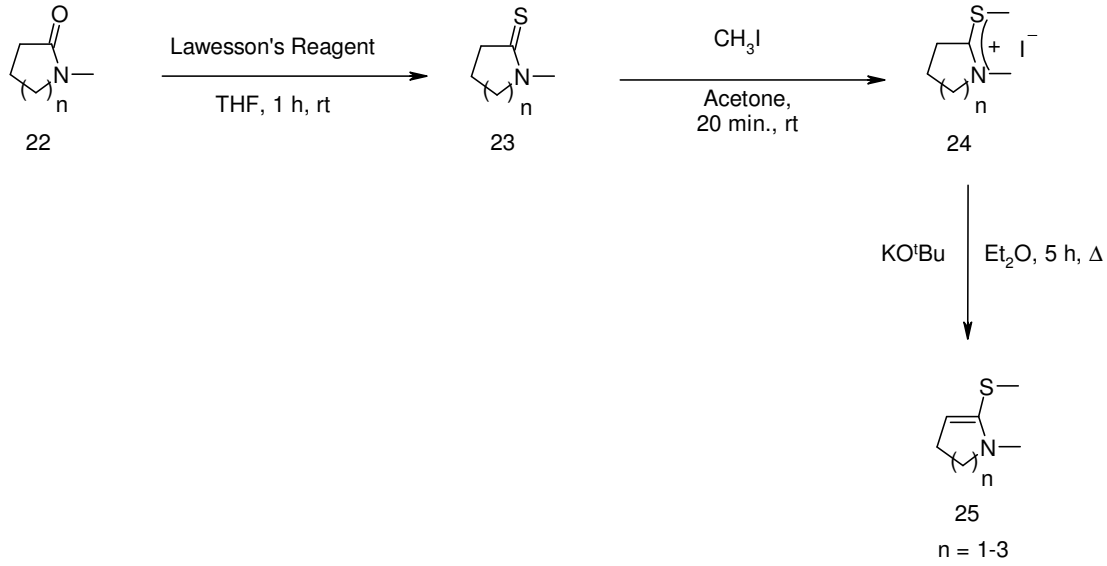


Scheme 46 Free radical mediated synthesis of 7-azaindolines and tetrahydro[1,8]naphthyridines.

Despite its flexibility towards 5 to 7-membered annelated ring (n = 1–3), the method furnished the desired compounds only in poor overall yields (15–57 %).

4.5.2 Synthesis of Ketene *N*,*S*-Acetals as Electron Rich Dienophiles for [4+2] Cycloadditions

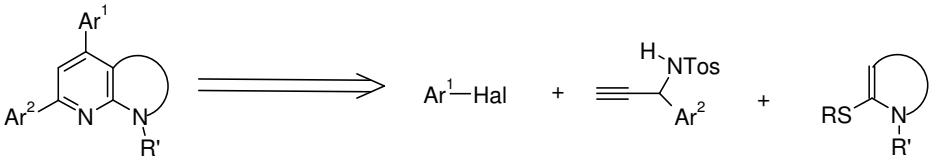
Ketene *N*,*S*-acetals are widely used as electron rich dienophiles[110] for [4+2] cycloaddition reactions. They were synthesized in a three step sequence starting from the corresponding cyclic amides **22**, according to Thomsen et al.[111] By thionation with Lawesson´s reagent the amides **22** were converted into the the thiocarbonyl compounds **23** in excellent yields (85–95 %). After methylation with methyl iodide and recrystallizsation from acetone *S*-alkylated iodide salts **24** (75–90 %) were treated with potassium *tert*.-butoxide to furnish the *N*,*S*-ketene acetals **25** in moderate overall yields (35–65 %, Scheme 47).



Scheme 47 Three-steps synthesis of ketene *N*,*S*-acetals.

4.5.3 One-Pot Three-Component CIR-Ketene Acetals-Cycloaddition Synthesis of Pyrrolo[2,3-*b*]pyridines, [1,8]Naphthyridines and Pyrido[2,3-*b*]azepines

Based upon our experience in diversity oriented heterocycle syntheses in a consecutive one-pot fashion and preliminary studies on CIR-cycloaddition sequences,[112] the retrosynthetic analysis of 5-, 6-, and 7-membered annelated amino pyridines based upon the CI-approach (Scheme 48) suggests enimines as key intermediates. Since *N*,*S*-ketene acetals are fairly electron rich dienophiles for [4+2] cycloadditions with inverse electron demand a facile three-component CI-cycloaddition-aromatization synthesis of annelated 2-amino pyridines can be easily envisioned.

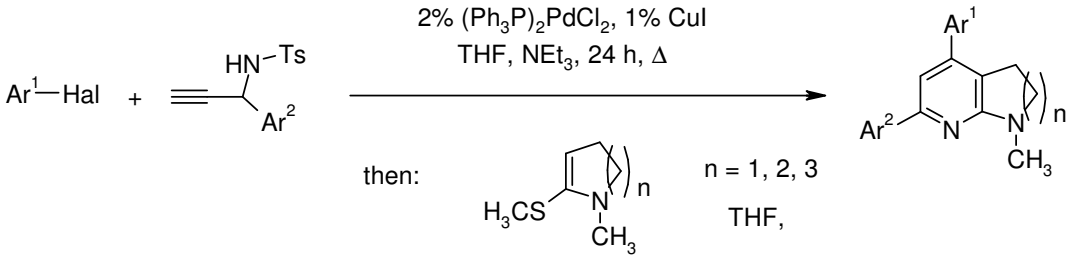


Ar^1 = EWG(het)aryl

Ar^2 = (het)aryl

Scheme 48 Retrosynthetic concept of a consecutive one-pot three-component annelated 2-amino pyridine synthesis.

Thus, we submitted *p*-bromo benzonitrile (**1a**), 2-bromo pyrimidine (**1b**), or 2-bromo pyridine (**1c**) and *N*-[1-aryl-prop-2-ynyl] tosyl amides **18**, and after some reaction time cyclic *N*,*S*-ketene acetals **25** to the reaction conditions of the CIR in boiling mixture of THF and triethylamine. After aqueous workup the annelated 2-aminopyridines **27** were obtained in 31-66 % yield as light yellow crystalline solids (**27a-e**, **26g-i**) or brown oils (**27f**, **27i**) (Scheme 49, Table 16).



1 **18** **25** **27** (31-66 %)

Scheme 49 One-pot synthesis of annelated 2-amino pyridines **27**.

Table 16 One-pot synthesis of annelated 2-amino pyridines **27**.

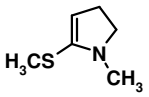
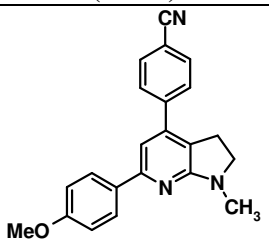
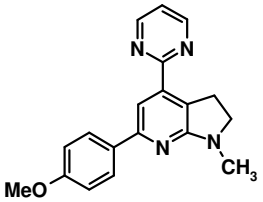
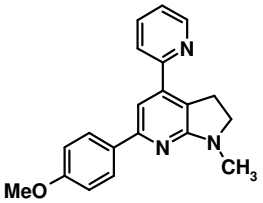
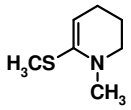
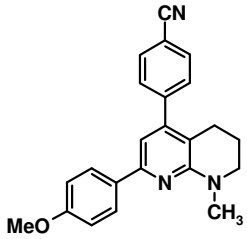
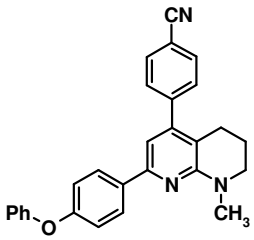
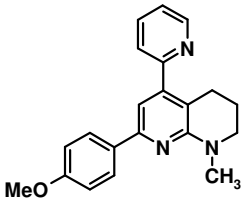
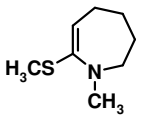
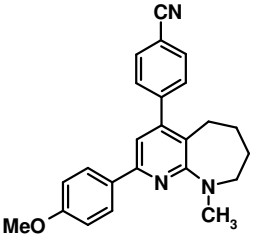
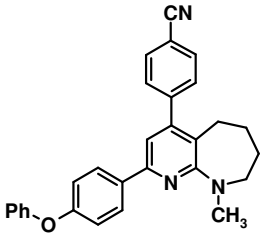
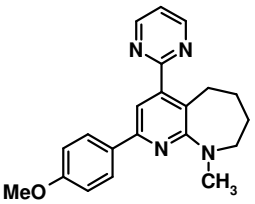
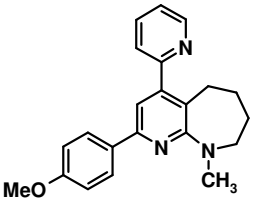
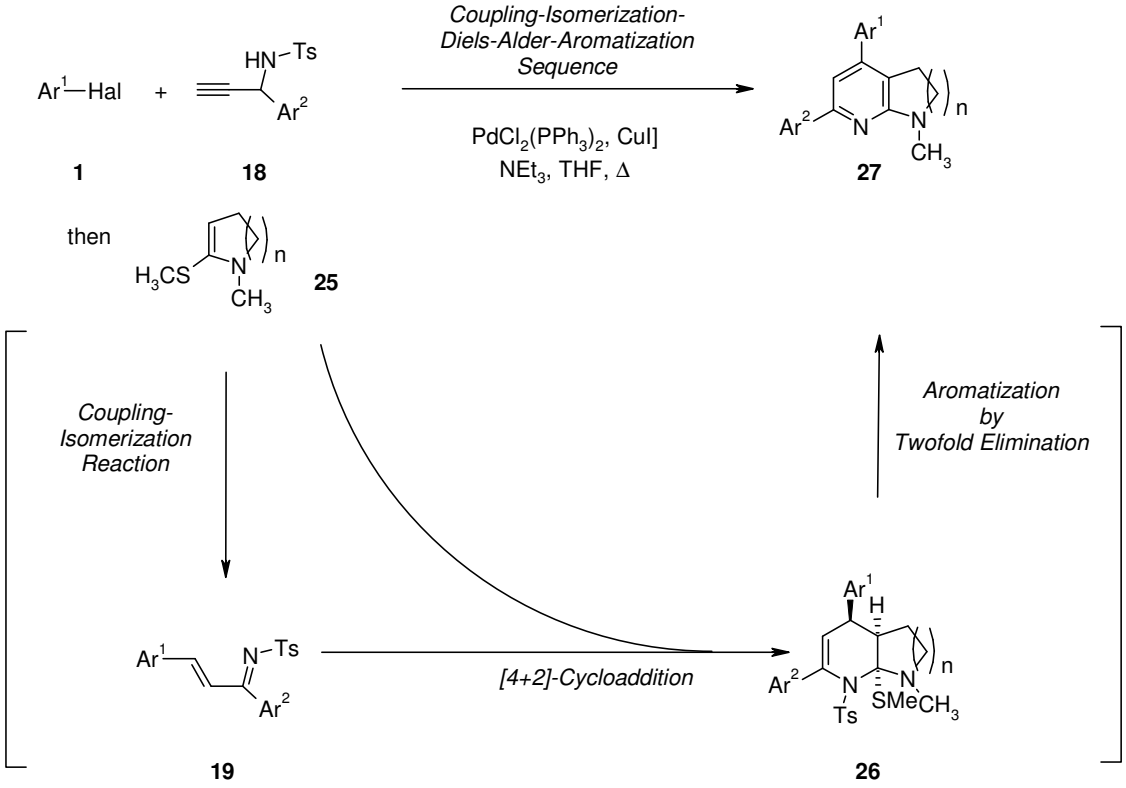
Entry	Aryl halide **1**	Propargyl *N*-tosyl amine **18**	*N*,*S*-ketene acetal **25**	2-Amino pyridines **27** (Yield)
1	Ar^1 = *p*-C_6H_4CN (**1a**)	Ar^2 = *p*-C_6H_4OMe (**19a**)	 (**25a**)	 **27a** (64 %)
2	Ar^1 = 2-pyrimidyl (**1b**)	**18a**	**25a**	 **27b** (66 %)
3	Ar^1 = 2-pyridyl (**1c**)	**18a**	**25a**	 **27c** (49 %)
4	**1a**	**18a**	 (**25b**)	 **27d** (31 %)
5	**1a**	Ar^2 = *p*-C_6H_4OPh (**18b**)	**25b**	 **27e** (43 %)

Table 16 *continued*

6	**1c**	**18a**	**25b**	 **27f** (48 %)
7	**1a**	**18a**	 (**25c**)	 **27g** (52 %)
8	**1a**	**18b**	**25c**	 **27h** (43 %)
9	**1b**	**18a**	**25c**	 **27i** (56 %)
10	**1c**	**18a**	**25c**	 **27j** (52 %)

The tentative mechanism of this one-pot sequence can be described as follows (Scheme 50). After the CIR of the electron-deficient (hetero)aryl halide **1** and the propargyl tosyl amides **18** furnishing an enimine **19** the added *N*,*S*-ketene acetal **25** readily undergoes a [4+2]

cycloadditions with inverse electron demand with **19** to give the annelated tetrahydropyridine **26** as the expected cycloadduct. However, under the reaction conditions the twofold base-assisted elimination of tolylsulfinate and methyl mercaptane from **26** furnishes upon aromatization the annelated pyridine **27**.



Scheme 50 Mechanistic rationale of the CIR-Diels-Alder-aromatization sequence.

In conclusion, the mild reaction conditions of the CI sequence of electron poor (hetero)aryl halides with 1-aryl propargyl *N*-tosyl amines giving rise to enimines, can be extended to a one-pot three-component synthesis of annelated 2-amino pyridines, such as pyrrolo[2,3-*b*]pyridines, [1,8]naphthyridines, and pyrido[2,3-b]azepines, applying a cycloaddition with *N*,*S*-ketene acetals and subsequent aromatization. This methodology combines modern catalytic cross-coupling processes with pericyclic reactions and, therefore, opens new one-pot synthetic strategies as a consequence of mild reaction conditions and functional group compatibility.

Moreover all annelated 2-amino pyridines display pronounced blue or green fluorescence (see spectral data) that can be controlled by reversible protonation in weakly acidic media for pyrido[2,3-b]azepines. Therefore, the fluorescence dyes, synthesized in a

modular diversity oriented fashion are ideal candidates for fluorescence labels for studying p*H* dependent and p*H* alternating cellular processes.

Spectroscopic data

The structures of the annulation products **27** were unambiguously assigned by ^{1}H, ^{13}C, COSY, and NOESY NMR experiments. Most characteristically, in the ^{1}H NMR spectra of **27** the appearance of the methine singlets at δ 6.87–7.81 can be clearly attributed to the formation of pentasubstituted pyridyl core unit. In addition, the signals of *N*-methyl protons are found as singlets at δ 3.02–3.22.

The mass spectra of all compounds show the molecular peaks. The usual fragmentation mode for all pyridine derivatives leads to the loss of methyl fragment.

Furthermore, the mass spectrometric and IR spectroscopic data are in full agreement with structural assignments.

All annelated 2-amino pyridines **27** absorb in the UV between 338 and 392 nm (Table 17). As a consequence of steric interactions between the annelated ring and the acceptor substituents in the position 4 of the central pyridine ring the latter are twisted out of coplanarity with increasing conformational bias of the annulated moiety. Hence, the longest wavelength maxima are found for the pyrrolo[2,3-*b*]pyridines **27a**–**c**. Furthermore, these longest wave length π–π^* transitions, also reflecting the S_0–S_1 excitation, display dominant charge transfer character with a significant mutual HOMO-LUMO overlap in a conformationally flexible 4-acceptor pyridyl framework. This is also nicely supported by calculations on the DFT level of theory (B3LYP G-31** density functional)[113] performed on the 2-pyrimidyl substituted pyrrolo[2,3-*b*]pyrimidine **27b** (Fig. 26) and the pyrido[2,3-*b*]azepine **27i** (Fig. 27). The increase of steric bias upon enlarging the annelated five membered to a seven membered ring affects the orbital overlap and correlates with the absorption energy. Therefore, in all series the absorption maxima are bathochromically shifted upon increasing the acceptor strength of the substituent at position 4 of the pyridine moiety from 2-pyridyl over *p*-cyanophenyl to 2-pyrimidyl.

Table 17 Selected UV/Vis and fluorescence properties (recorded in dichloromethane) of annelated 2-amino pyridines **27**.

Compound	Absorption $\lambda_{max,abs}$ [nm],(ε)	Emission $\lambda_{max,em}$ [nm]	Quantum yield Φ_f [%]	$\Delta\nu$ [cm^{-1}][a]	Fluorescence color
27a	**372** (3200) 310 (4400) 258 (21900)	**469**	32	5600	green
27b	**392** (6500) 284 (12900) 252 (40700)	**468** 516 sh	63	4200	green
27c	**360** (15900) 276 (41700) 248 (47900)	**466** 512 sh	53	6300	green
27d	**362** (5900) 306 (5900) 258 (31600)	**438** 512 sh	12	4800	blue
27e	**364** (6600) 312 (5200) 258 (38000)	**444** 518 sh	17	5000	blue
27f	**358** (6200) 256 (20400)	**445** 513 sh	25	5500	blue
27g	**338** (3500) 260 (18200)	**501**	24	9600	blue
27h	**340** (6600) 258 (38900)	**495**	34	9200	blue
27i	**348** (5500) 280 (14800) 254 (23400)	**511**	15	9200	green
27j	**338**	**478**	26	8700	blue

[a] $\Delta\tilde{\nu} = 1/\lambda_{max,\,abs} - 1/\lambda_{max,\,em}$ [cm^{-1}].

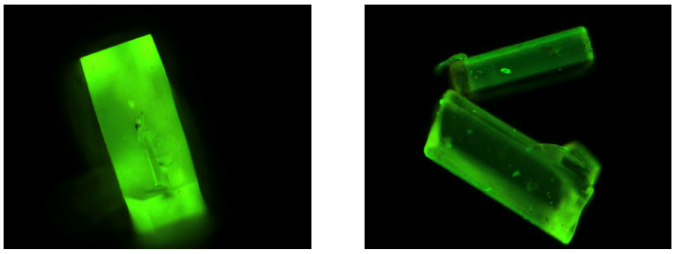


Fig. 25 Solid-state fluorescence of single crystals of **27a** (left) and **27b** (right).

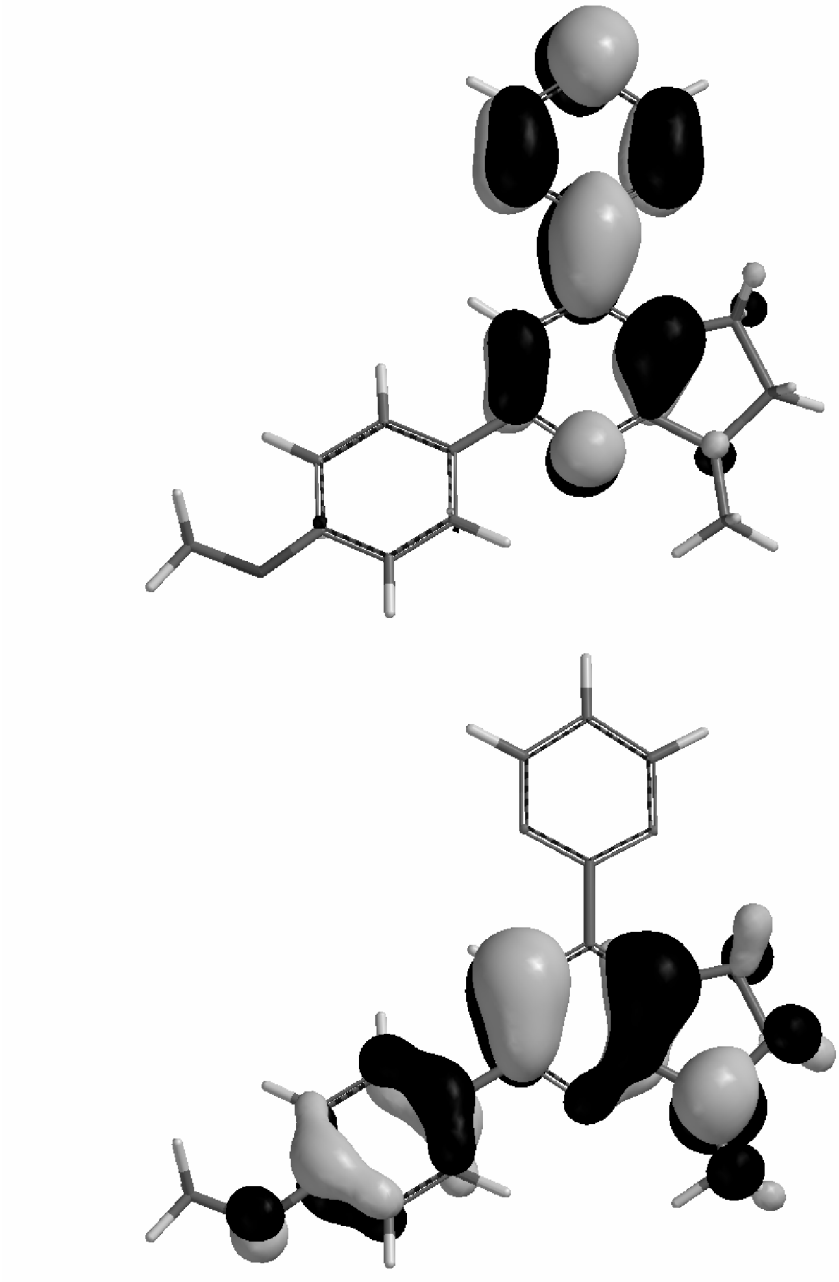


Fig. 26 LUMO (top) and HOMO (bottom) of the pyrrolo[2,3-*b*]pyrimidine **27b**.

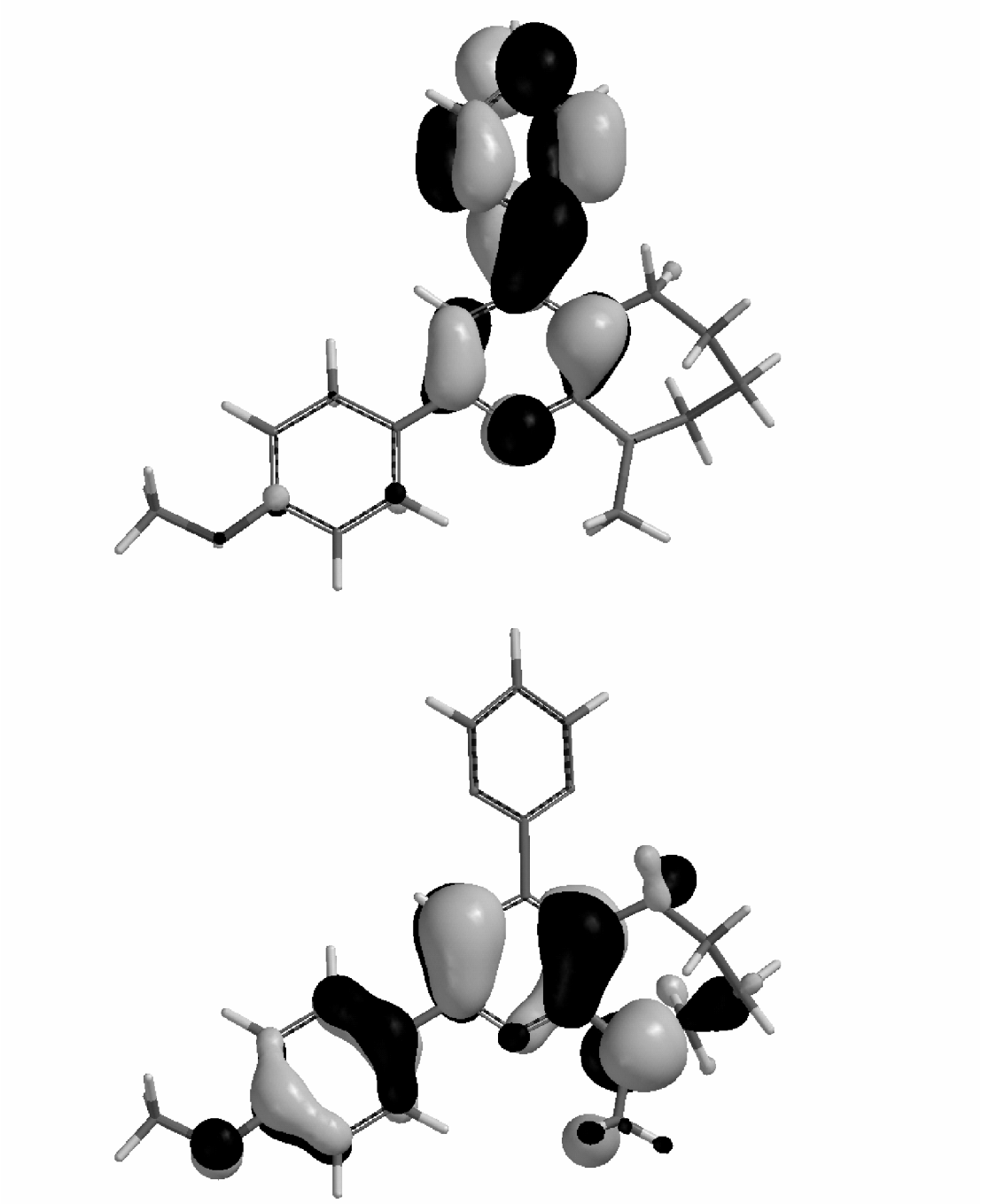


Fig. 27 LUMO (top) and HOMO (bottom) of the pyrido[2,3-b]azepine **27i**.

Furthermore, all annelated 2-amino pyridines **27** emit blue (**27d–h**, **27j**) or green light (**27a–c**, **27i**) upon excitation at the corresponding absorption wavelengths (Table 17). The Stokes shifts are rather pronounced and lie between 4200 and 9600 cm^{-1}. For all representatives the quantum yields Φ_f were determined.[114] Pyrrolo[2,3-*b*]pyridines (**27a–c**) fluoresce with significantly higher quantum yields (Φ_f = 32–63 %) than [1,8]naphthyridines

(**27d–f**, Φ_f = 12–25 %), and pyrido[2,3-*b*]azepines (**27g–j**, Φ_f = 15–34 %). The longest wavelength emission maxima, however, are found in the series of pyrido[2,3-*b*]azepines. As pointed out before for the absorption properties the emission behavior is as well affected by steric biases that control the efficiency of the spontaneous emission. Therefore, the charge transfer character of the HOMO-LUMO transition responsible for the electronic absorption spectra is well reflected in the torsion dependent emission efficiency from the excited S_1 state.[115]

The presence of a basic pyridyl nitrogen in the annelated 2-amino pyridines **27** invites to scrutinize the p*H*-dependence of the absorption and emission properties (Table 3). A discrete halochromicity can be detected for the 2-pyrimidyl substituted pyrrolo[2,3-*b*]pyridine **27b** and the pyrido[2,3-b]azepine **27i**, where bathochromic shifts of the longest wave length absorption maxima are found by lowering the p*H* from p*H* 9 (**27b**: 384 nm, **27i**: 372 nm) to p*H* 1 (**27b**: 392 nm) or p*H* 4 (**27i**: 380 nm). This decrease of the HOMO-LUMO gap upon protonation is also reproduced in DFT calculations (B3LYP G-31** density functional)[113] on **27b**, **27b-H$^+$**, **28i**, and **27i-H$^+$**. For the couple **27b/27b-H$^+$** the HOMO-LUMO gap reduces slightly upon protonation (**27b**: $\Delta_{HOMO\text{-}LUMO}$ 3.35 eV; **27b-H$^+$**: $\Delta_{HOMO\text{-}LUMO}$ 3.29 eV) whereas the decrease of the HOMO-LUMO gap is larger for the couple **27i/27i-H$^+$** (**27i**: $\Delta_{HOMO\text{-}LUMO}$ 3.50 eV; **27i-H$^+$**: $\Delta_{HOMO\text{-}LUMO}$ 3.38 eV). However, the emission behavior is even more affected from protonation than the absorption properties. The emission spectra of the 2-pyrimidyl substituted pyrrolo[2,3-*b*]pyridine **27b** (Fig. 28) and the pyrido[2,3-*b*]azepine **27i** (Fig. 29) display a quite different behavior upon altering the p*H*. Whereas for the pyrrolo[2,3-*b*]pyridine **27b** the emission maximum only shifts slightly upon protonation (478 nm at p*H* 9; 482 nm at p*H* 1), for the pyrido[2,3-*b*]azepine **27i** a significant bathochromic shift from 478 nm at p*H* 9 to 512 nm at p*H* 4 is observed. In the latter case protonation of the pyridyl nitrogen is obviously occurring at higher pK_a as a consequence of an increase in basicity. Again, the steric bias causes a twist out of coplanarity of the 2-pyridyl substituent (*vide supra*) and, hence, exerts a diminished electron withdrawing effect. The appearance of the fluorescence spectra of **27b** and **27i** with shoulders at longer wavelengths indicates that dual fluorescence of these donor-acceptor substituted pyridines is obviously responsible for the variable p*H*-sensitivity. In the former system the 2-pyrimidyl substituent is already coplanar with the pyridine in the ground state and the geometrical changes upon protonation are only minimal, whereas in the latter fluorophore the S_0–S_1 excitation from the pyridyl core to the pyrimidine occurs with dominant charge transfer character to an excited state that is coplanar and has to relax to a twisted state again. All this makes the

pyrido[2,3-*b*]azepine **27i** a p*H*-sensitive fluorescence sensor that can be operative in neutral and weakly acidic media.

Table 18 Selected UV/Vis and fluorescence properties (recorded in 0.1 *M* acetate buffered DMSO solution, *T* = 298 K) and calculated HOMO and LUMO energies of pyrrolo[2,3-*b*]pyridines **27b** and pyrido[2,3-*b*]azepine **27i**.

Compound	Absorption $\lambda_{max,abs}$ [nm] (ε)	Emission $\lambda_{max,em}$ [nm]	$\Delta\nu$ [cm^{-1}][a]	HOMO [eV]	LUMO [eV]	$\Delta_{HOMO-LUMO}$ [eV]
4c	**384** (2700)[b] 250 (8600)	**478**[b]	5100	-4.889	-1.544	3.345
4c-H$^+$	**392** (10900)[c] 280 (15100)	**482**[c]	4800	-8.563	-5.269	3.294
4j	**372** (9500)[b] 298 (11800) 268 (12300)	**478**[b]	6000	-4.911	-1.409	3.502
4j-H$^+$	**380** (6300)[d] 282 (7600)	**512**[d]	6800	-8.605	-5.224	3.381

[a] $\Delta\tilde{\nu} = 1/\lambda_{max,\,abs} - 1/\lambda_{max,\,em}$ [cm^{-1}]. [b] At p*H* 9. [c] At p*H* 1. [d] At p*H* 4.

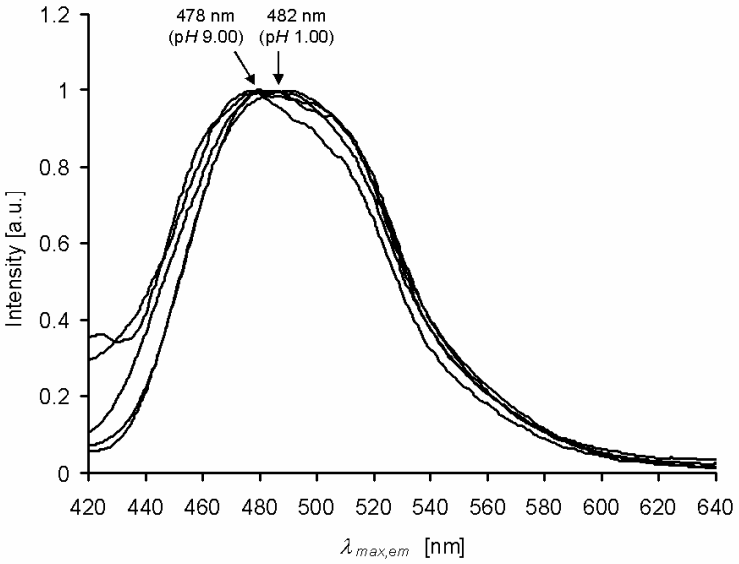


Fig. 28 Emission maxima $\lambda_{max,em}$ [nm] (arbitrary units) of **28b** at p*H* 1.00, 2.00, 3.00, 4.00 and 9.00 (recorded in 0.1 *M* acetate buffered DMSO solution, *T* = 298 K, $\lambda_{max,\,excitation}$ = 340 nm).

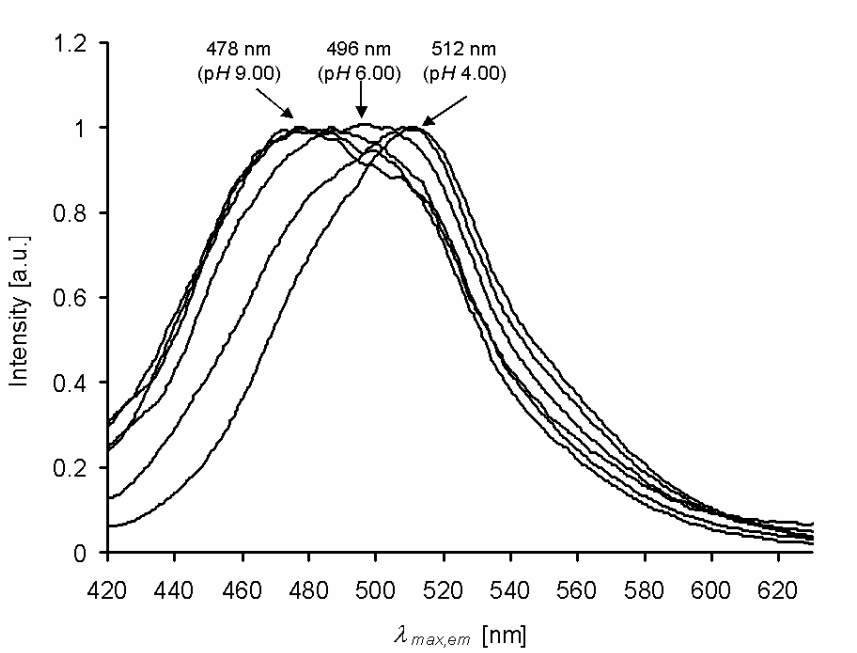


Fig. 29 Emission maxima $\lambda_{max,em}$ [nm] (arbitrary units) of **28i** at p*H* 4.00, 5.00, 6.00, 7.00, 8.00 and 9.00 (recorded in 0.1 *M* acetate buffered DMSO solution, T = 298 K, $\lambda_{max,\ excitation}$ = 340 nm).

Finally, the structure of **27** was unambiguously supported by X-ray crystal structure analyses of compounds **27a**, **27b**, **27e**, **27h**, and **27j** (Fig. 30–Fig. 34). Depending on the conformational bias of the annelated ring the steric interactions force the acceptor substituted (hetero)aryl ring to twist out of coplanarity with the pyridyl core. The interplanar angle of *p*-cyano phenyl ring and the central pyridine moiety increases from the pyrrolo[2,3-*b*]pyridine **27a** (42.4°) over the pyrido[2,3-*b*]azepine **27h** (64.6°) to the [1,8]naphthyridine **27e** (88.8°). However, 2-pyrimidyl substituents as shown in the crystal structure analysis of **27c** (5.5°) impose the least steric bias.

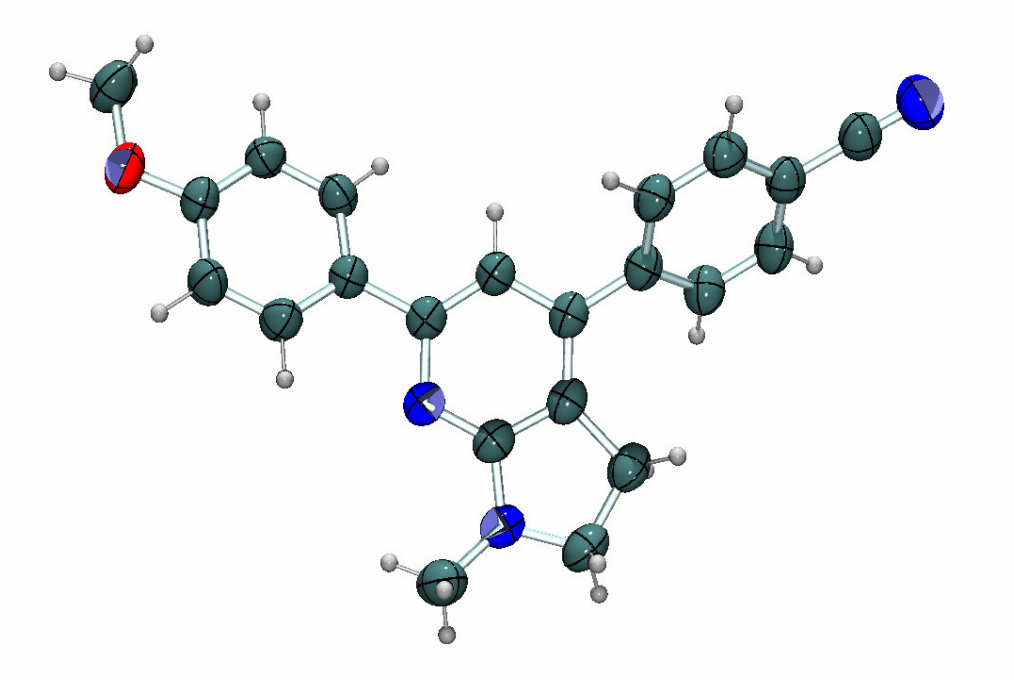


Fig. 30 ORTEP plot of compound **27a**.

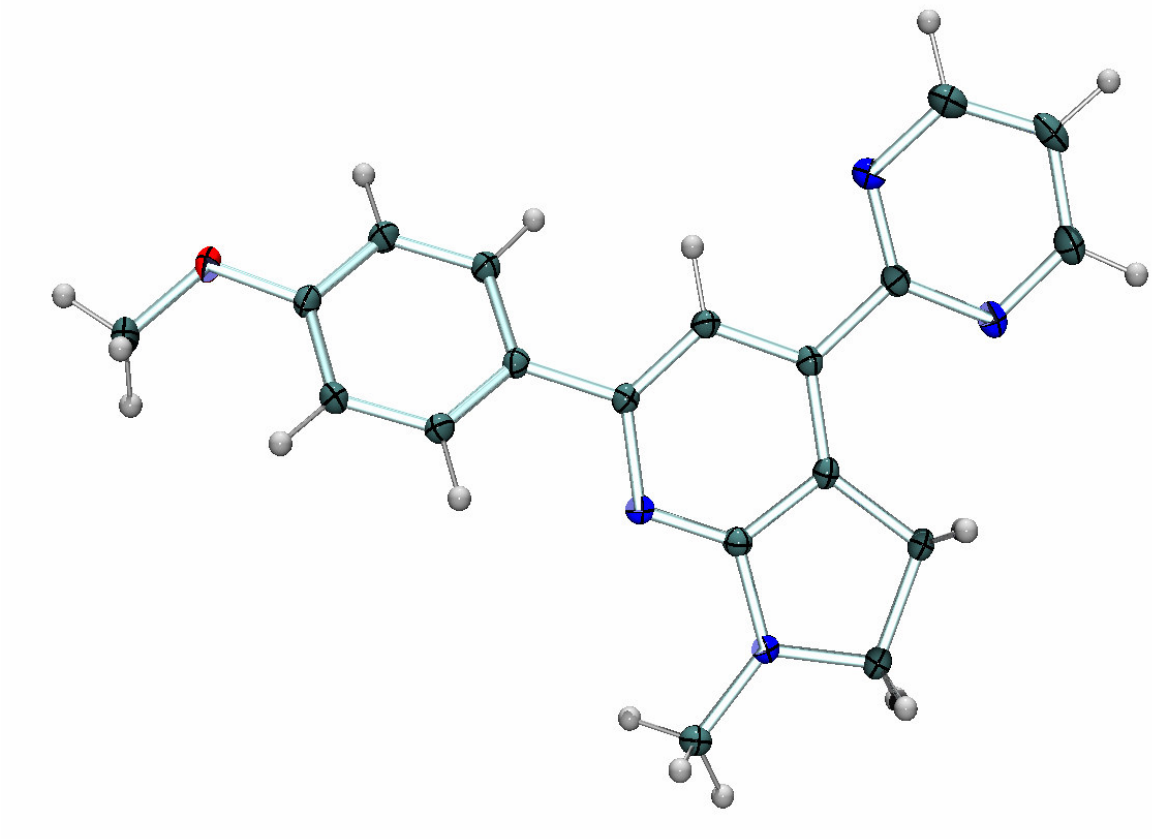


Fig. 31 ORTEP plot of compound **27b**.

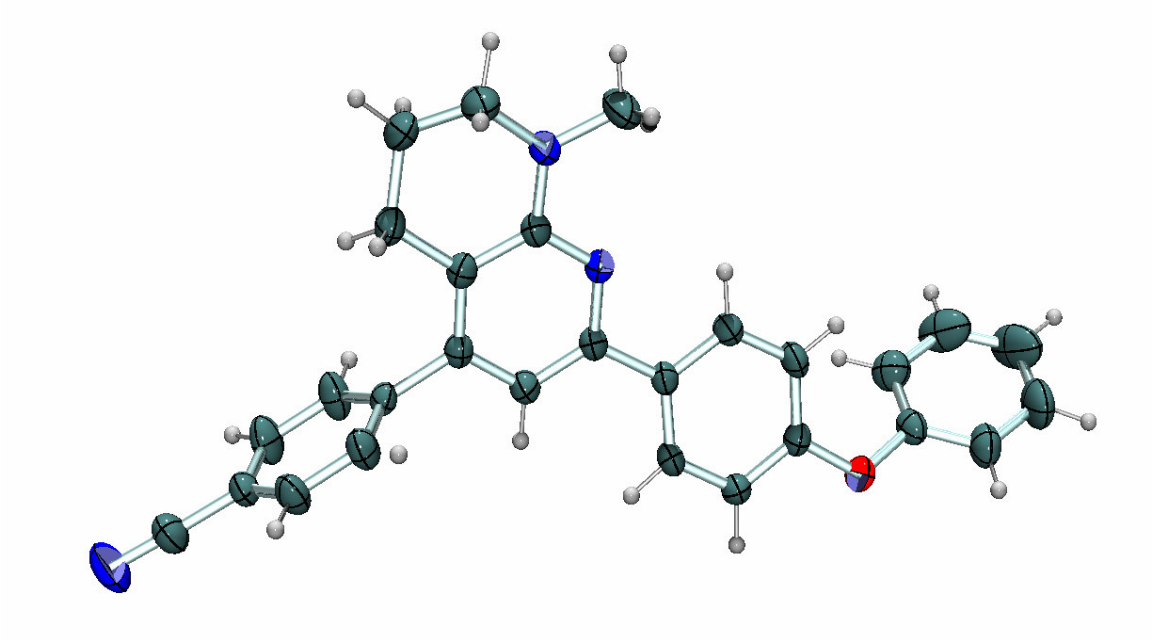


Fig. 32 ORTEP plot of compound **27e**.

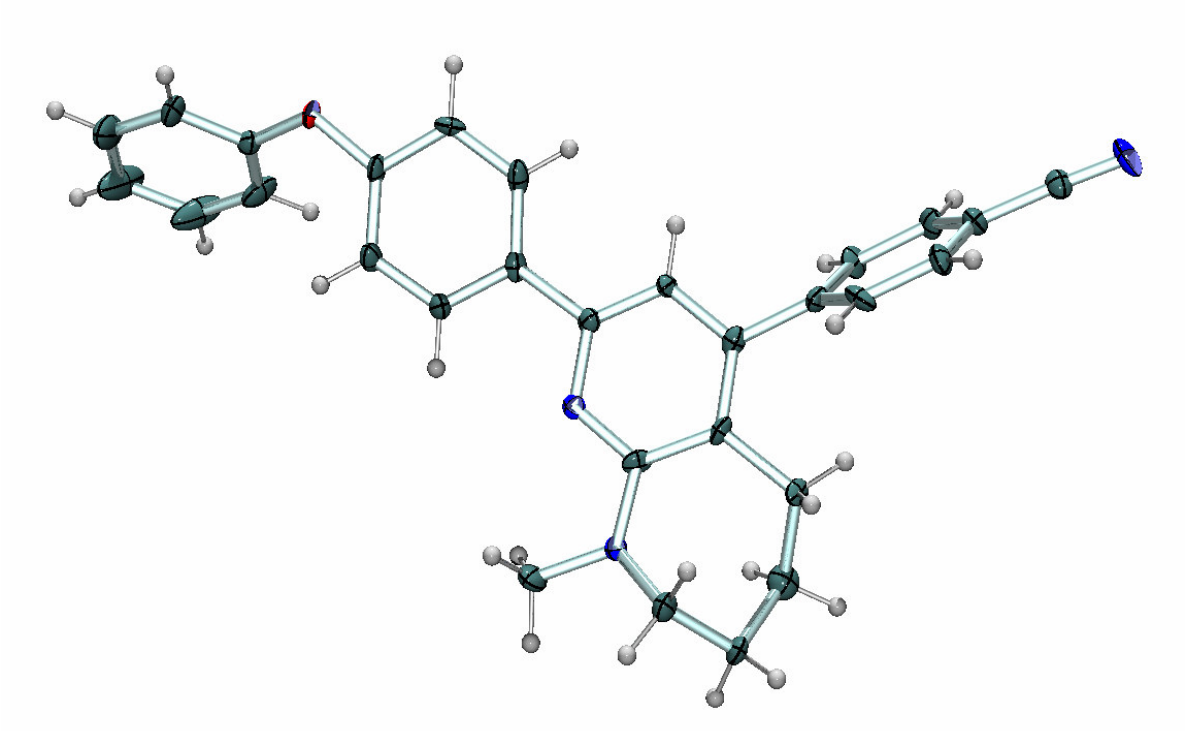


Fig. 33 ORTEP plot of compound **27h**.

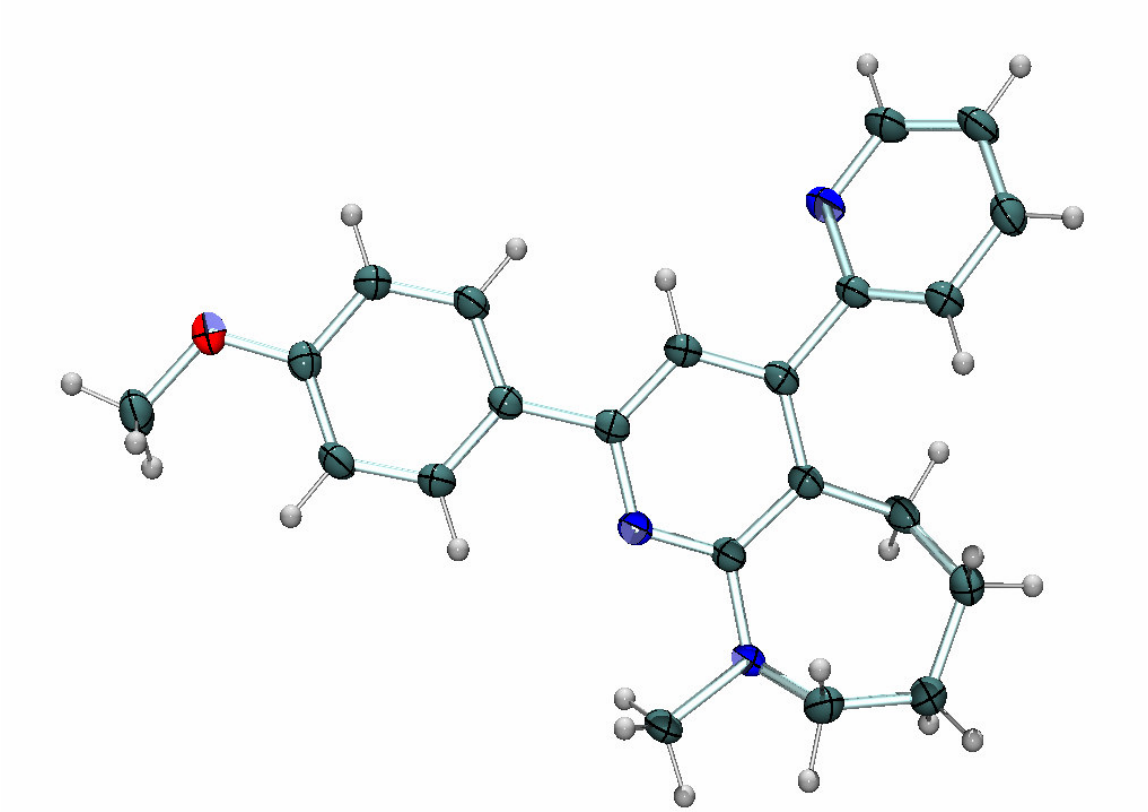


Fig. 34 ORTEP plot of compound **27j**.

4.6 One-Pot Microwave-Assisted Multicomponent Synthesis of Cyclohexadienes and Cyclohexenone Derivatives Based upon CIR

In previous chapters it was shown that Sonogashira coupling-ismerizations offer the most elegant and atom-economic way of transforming electron poor arylhalides into chalcones. Moreover, microwave-assisted CIR, not only reduces reaction times, but also inserts electron donating arylhalides as reactive halides in CIR, now completing the generality of the CIR.

The excellent results obtained for the microwave-assisted CIR, encouraged me to investigate the microwave effect on the CIR-enamine addition-cyclocondensation multicomponent reactions, where conventional procedures furnished only moderate yields.

4.6.1 Synthesis of *β*-Enaminones

β-Enaminones are interesting building-blocks due to their ability to function as both ambident nucleophiles and electrophiles.[116] Typical electrophilic positions are C-3 (alkylamino methylene group) and C-1 (the carbonyl group). Secondly, *β*-enaminones exhibit enamine character towards electrophiles, with a nucleophilic position at C-2 (Fig. 35).

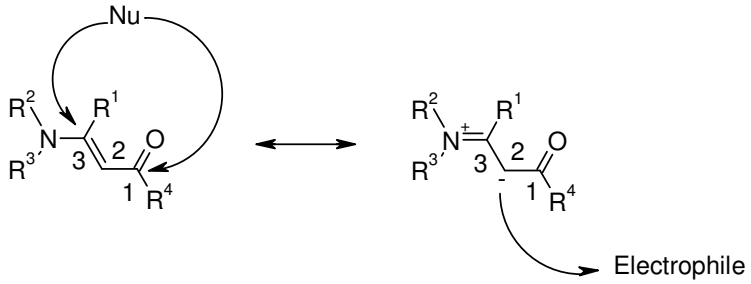
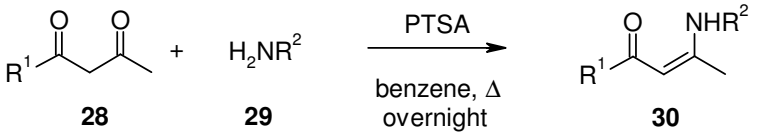


Fig. 35 Reactivity of *β*-enaminones.

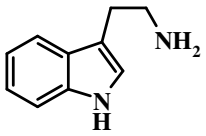
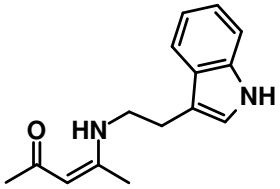
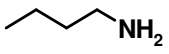
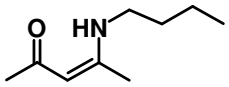
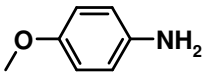
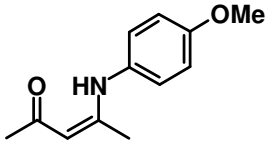
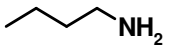
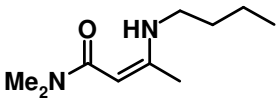
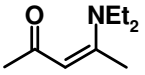
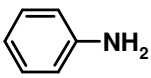
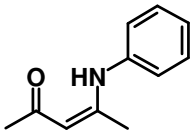
The *β*-enaminones **30** can be easily synthesized by a condensation reaction between 1,3-dicarbonylic compounds **28** and substituted amines **29**, under acidic conditions, in boiling benzene, using Dean-Stark trap[117] (Scheme 51).



Scheme 51 Synthesis of β-enaminones **30**.

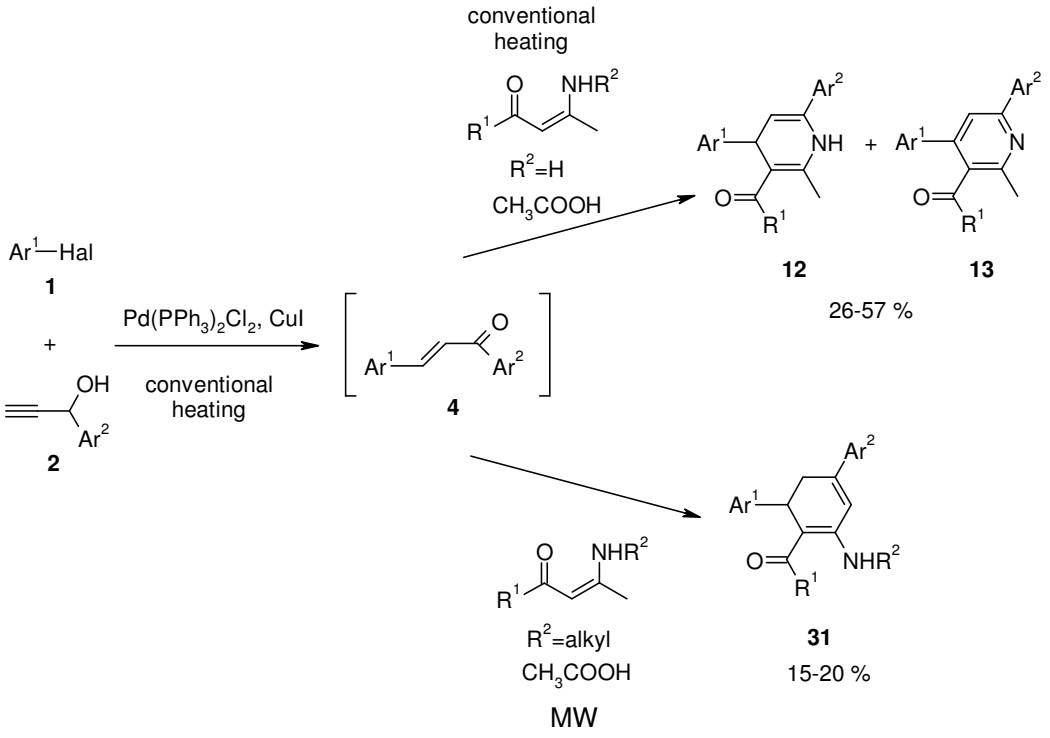
The condensation reaction can be applied for a large variety of substrates, furnishing β-enaminones in excellent yields (70-98 %, Table 19).

Table 19 Synthesis of β-enaminones **30**.

R^1	Amine	Enamine **30,** Yield (%)
-- CH_3		 **30a** (70)
-- CH_3		 **30b** (98)
-- CH_3		 **30c** (80)
-- NMe_2		 **30d** (92)
-- CH_3	$HNEt_2$	 **30e** (74)
-- CH_3		 **30f** (98)

4.6.2 One-Pot Synthesis of Cyclohexadienes and Cyclohexenones

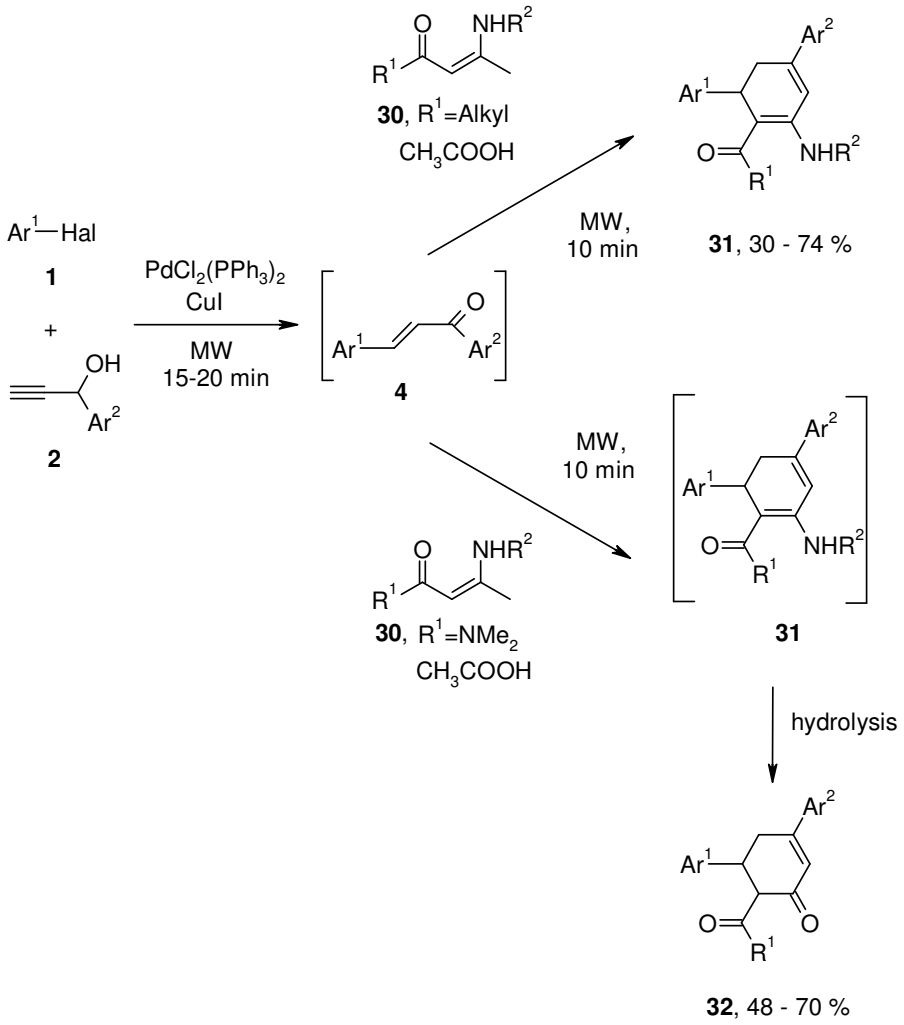
In previous chapters it has already been shown that β-enaminones, as the source of nitrogen in a [3+3] cycloaddition reaction with chalcones, gave rise to the formation of dihydropyridines that oxidised to the corresponding pyridines, in moderate overall yields. Following the same mechanistic rationale, the *N*-substituted enaminones, in a [3+3] cyclocondensation fashion, would inhibit the subsequent oxidation step and open a new entry to the asymmetrical dihydropyridines. But, similarly to literature reports on Hantzsch synthesis, where the use of primary amine as a source of nitrogen led to the low yields or no reaction,[118] all attempts of the conventional thermal cyclocondensations of chalcones with *N*-substituted enaminones gave poor yields of a mixture of products: the dihydropyridines and the unexpected cyclohexadienes (Scheme 52).



Scheme 52 Thermal conditions CIR-enamine addition-cyclocondesation multicomponent synthesis.

As microwave heating not only reduces the reaction times from hours to minutes, facilitating as well, the optimization studies, but also minimizes the side reactions, increases yields and improves reproducibility, I decided to apply this procedure on CIR-enamine-addition-cyclocondensation multicomponent reactions.

Thus, upon performing MACIR with aryl halides **1** and the propargylic alcohols **2** and subsequent addition of enaminones **30**, in presence of acetic acid, in one-pot fashion, various intramolecular aldol-type products could be isolated, as cyclohexadienes **31** and cyclohexenones **32** (Scheme 53, Table 20). The effect of microwave irradiation allowed these compounds to be formed within a few minutes, in high yields (45-74%) via a one-pot CIR-enamine addition-condensation reaction.



Scheme 53 Microwave assisted CIR-enamine addition-cyclocondensation multicomponent synthesis.

Table 20 MW-assisted multicomponent synthesis of cyclohexadiene **31**.

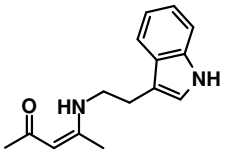
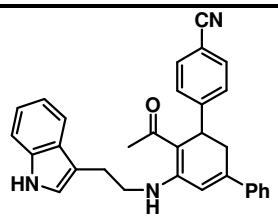
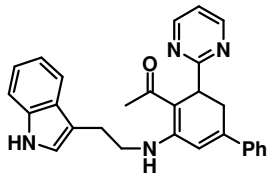
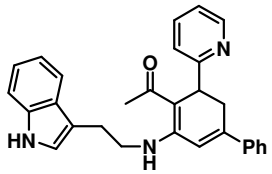
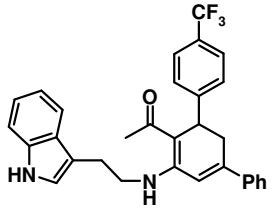
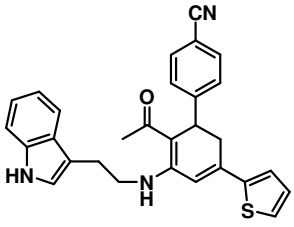
Entry	Aryl halide **1**	Propargyl alcohol **2**	Enamine **30**	Cyclohexadiene **31** (Yield)
1	Ar^1 = *p*-C_6H_4CN (**1a**)	Ar^2 = -C_6H_5 (**2a**)	 (**30a**)	 **31a** (68 %)
2	Ar^1 = 2-pyrimidyl (**1b**)	**2a**	**30a**	 **31b** (74 %)
3	Ar^1 = 2-pyridyl (**1c**)	**2a**	**30a**	 **31c** (70 %)
4	Ar^1 = *p*-$C_6H_4CF_3$ (**1d**)	**2a**	**30a**	 **31d** (47 %)
5	**1a**	Ar^2 = 2-thienyl (**2b**)	**30a**	 **31e** (54 %)

Table 20 *continued*

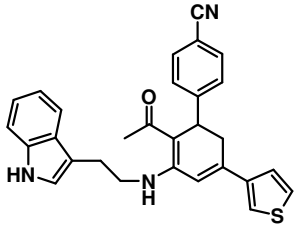
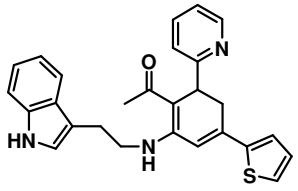
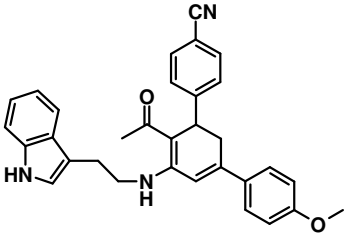
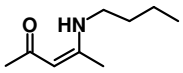
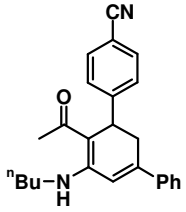
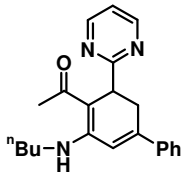
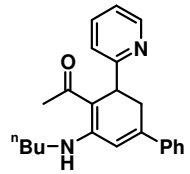
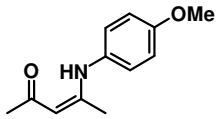
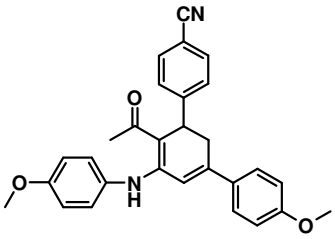
6	**1a**	Ar^2 = 3-thienyl (**2c**)	**30a**	 **31f** (64 %)
7	**1c**	**2b**	**30a**	 **31g** (60 %)
7	**1a**	Ar^2 = *p*-C_6H_4OMe (**2f**)	**30a**	 **31h** (68 %)
8	**1a**	**2a**	 (**30b**)	 **31i** (54 %)
9	**1b**	**2a**	**30b**	 **31j** (52)

Table 20 *continued*

10	**1c**	**2a**	**30b**	 **31k** (52 %)
11	**1a**	**2a**	 (**30c**)	 **31l** (30 %)

The use of microwaves was successfully extended to the Sonogashira coupling-isomerization (CIR) and was found to be very effective for the new multicomponent syntheses of cyclohexadienes and cyclohexenones.

The enamine cycloaddition to the chalcone and the subsequent acidic catalysed ring opening and intramolecular aldol-condensation reaction take place in one step, in 10-20 minutes at 150° C, under microwave irradiation.

Acidic conditions are crucial for the ring opening reaction, since no product formation was observed in the absence of acid.

Although, the aldol-condensation reaction is also a base-catalyzed reaction no product formation was detected using different base catalysts (KO^iPr, KOH, Na_2CO_3, Table 21).

The investigation on the process optimization showed that the amount of enamine is also important for product formation. The optimal amount was found for an excess of 3:1 enamine:chalcone (Table 21).

Table 21 Optimization experiments for the synthesis of cyclohexadiene **31a**.

Enamine [eq]	CH_3COOH [ml]	Reaction Time [min]	Yield [%]
1.1	0.5	20	40
2	0.5	20	52
2	2	20	40
2	0	20	0
3	0.75	20	60
3	0.75	10	68

The nature of *N*-substituents, R^2, on the enamines, plays an important role. The *N*-alkyl-substituted enaminones undergo more readily the addition reactions than the corresponding *N*-aryl-substituted enaminones. A plausible explanation is the decrease of the enamine reactivity towards addition with the loss of nucleophilicity by the conjugation with the aromatic ring. Accordingly, using the enamine **30f**, (Table 19) no product formation was observed. This drawback is avoided by the insertion of a donor substituent on the aromatic substituent of the enaminone, as for the enamine **30c**, although the yield of the coresponding cyclohexadiene is rather poor, 30 %, entry 11 (Table 20).

The substituent R^1 of the enamines influences the stability of the product (**7**) towards hydrolysis, so a higher electronic withdrawing effect of the carbonyl group on the enamine, increases the stability of cyclohexadiene (**31**). Decreasing the electron withdrawal effect of the carbonyl group, as in the case of the amide group, the corresponding cyclohexadiene (**31**) is more susceptible towards hydrolysis (Scheme 53).

Thus, submitting the (hetero)aryl halides **1** and propargylic alcohols **2** to the microwave-conditions of the Sonogashira coupling-isomerization and subsequent amide-enamine addition under acidic conditions, and after aqueous work up, the cyclohexenones **32** were obtained in few minutes, 25-35 minutes, in good to excellent yields (Table 22).

Table 22 MW-assisted synthesis of cyclohexanones **32**.

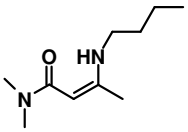
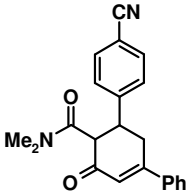
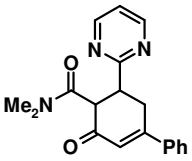
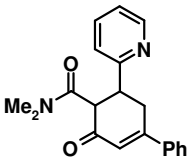
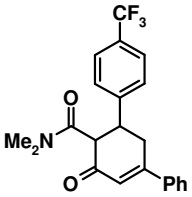
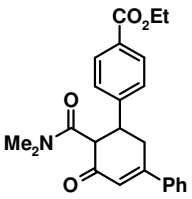
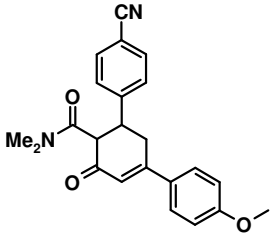
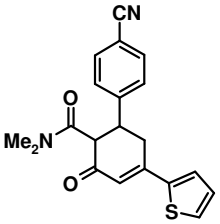
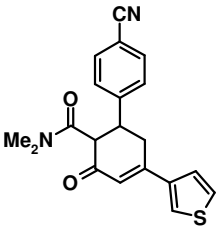
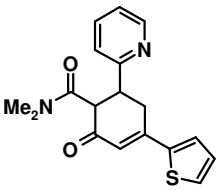
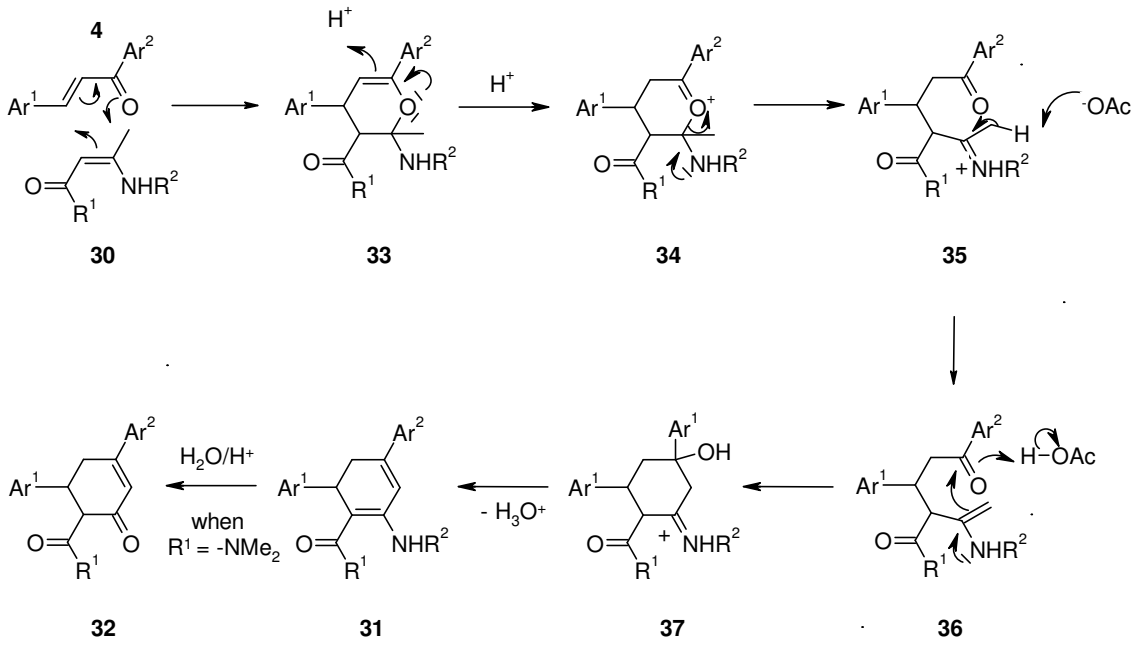
Entry	Aryl halide **1**	Propargyl alcohol **2**	Enamine **30**	Cyclohexenones **32** (Yield)
1	Ar^1 = *p*-C_6H_4CN (**1a**)	Ar^2 = -C_6H_5 (**2a**)	 (**30d**)	 **32a** (66 %)
2	Ar^1 = 2-pyrimidyl (**1b**)	**2a**	**30d**	 **32b** (68 %)
3	Ar^1 = 2-pyridyl (**1c**)	**2a**	**30d**	 **32c** (48 %)
4	Ar^1 = *p*-$C_6H_4CF_3$ (**1d**)	**2a**	**30d**	 **32d** (70 %)
5	Ar^1 = *p*-$C_6H_4CO_2Et$ (**1e**)	**2a**	**30d**	 **32e** (48 %)

Table 22 *continued*

6	**1a**	Ar^2 = *p*-C_6H_4OMe (**2f**)	**30d**	 **32f** (58 %)
7	**1a**	Ar^2 = 2-thienyl (**2b**)	**30d**	 **32g** (66 %)
8	**1a**	Ar^2 = 3-thienyl (**2c**)	**30d**	 **32h** (62 %)
9	**1c**	**2b**	**30d**	 **32i** (62 %)

Mechanistically, the formation of the cyclohexadienes **31** and cyclohexanones **32** presumes the formation of the [4+2] cycloadducts **33** which in acidic conditions open to the iminium ions **35** that now readilly undergo an acid catalyzed aldol condensation.

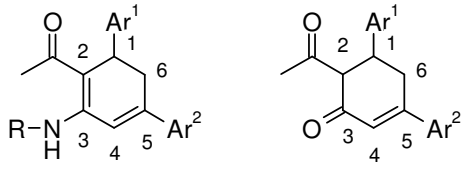


Scheme 54 Mechanistic rationale for CIR-enamine addition-aldol condensation sequence.

The cyclohexanones **32** are formed upon an *in situ* hydrolisys of the enamine moiety that is facilitated by the acidic reaction conditions (Scheme 54).

Spectroscopic data

The structures of cyclohexadiene **31** and cyclohexanone **32** were unambiguously assigned by ^{1}H, ^{13}C, COSY, HMBC and NOESY NMR experiments. Characteristically, in the ^{1}H NMR spectra of **31** and **32** is the appearance of the olefinic proton resonances as dublets, at δ 6.31–6.89, with coupling constants of ^{4}J = 1.9–2.8 Hz. The long range coupling between the 4-H olefinic protons and the 6-H methylenic protons can be unambiguously assigned from the cross-peak in the COSY NMR spectra (Fig. 36). Cross-peaks were also detected between the olefinic 4-H protons and the *ortho*-phenyl or heteroaryl (-Ar^2) protons by 2D NOESY experiments.



31 **32**

Fig. 36 The numeration of cyclohexadiene **31** and cyclohexenone **32**.

The NH enamine protons for **31a–l** were detected as triplets in the range of δ 11.7–11.85, with coupling constants of 4.8–6.0 Hz and an intensity of one proton. These downfieldshifted NH resonances suggest a six-membered intramolecular hydrogen bonding. The sufficiently slow proton exchanges in DMSO-D_6, at room temperature, allowed the detection of the vicinal couplings ^3J between CH-NH protons.

Broad singlets at low field between δ 8.86 and 10.92, were assigned to the NH protons of the indol moiety for **31a–h**.

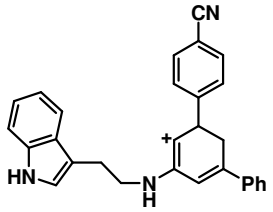
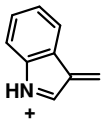
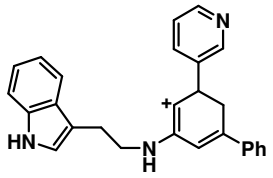
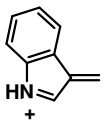
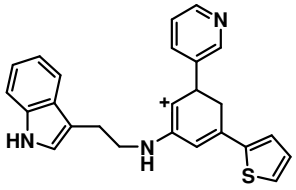
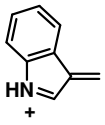
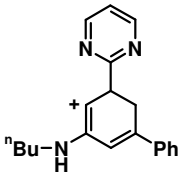
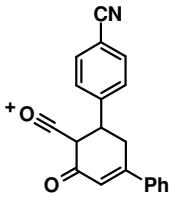
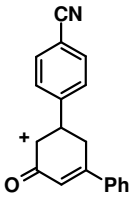
The 1-H methine protons resonances for **31a–f**,**g** and **31j–l** were found in the range of δ 4.13-4.32 as doublets, with coupling contants between J 5.25-8.0 Hz. For **31g**,**i** they were identified as doublets of doublets with coupling constants of 6.5, 7.75 Hz (axial-axial coupling) and 1.25 and 1.75 Hz as a consequence of equatorial-equatorial or axial-equatorial coupling.

The resonances of the methylenic protons 6-H are more complex, due to the additional geminal coupling. Thus, for **31i**,**j** one of the methylenic proton signal appears as doublet of doublet at δ 2.98 (^2J = 16.8 Hz, ^3J = 2.0 Hz) and δ 3.51 (^2J = 16.8, ^3J = 1.8 Hz) respectively, and the other one as doblet of doublets of doublets at δ 3.17 (J = 16.8 Hz, J = 7.8 Hz, J = 2.5 Hz) and at δ 3.02 (J = 16.8 Hz, J = 7.6, J = 2.9 Hz) respectively. For the cyclohexadiene **31a–h** and **31j–l** the resonances of the 6-methylenic protons are detected as a set of doublets of doublets of doublets in the range of δ 2.52–3.14. The *n*-butyl protons for the cyclohexadienes **31i–k** were identified as sets of signals, triplets at δ 0.90–0.91 with a coupling constant between J 7.25–7.3 Hz, and three multiplets in the range of δ 1.31–1.52, 1.52–1.69 and 3.31–3.58.

Characteristically for the cyclohexenones **32a–i** are the protons of the two *N*-methyl groups that resonate in the ^{1}H NMR in the range of δ 2.66–2.75 and δ 2.81–3.14 as singlets.

Additionally, the mass spectrometric, IR spectroscopic, and combustion analytical data are in full agreement with the suggested molecular structure of the cyclohexadienes **31** and cyclohexenones **32**. The mass spectra of all obtained compounds show the molecular peaks. The usual fragmentation mode for the cyclohexadiene **31** leads to the loss of acetyl groups and for the cyclohexenones **32** to the loss of *N*,*N*-dimethyl amido fragments (**Table 23**).

Table 23 Fragmentation of selected cyclohexadienes **31** and cyclohexenones **32**.

Com-pound	Fragment	*m/z* (%)	Fragment	*m/z* (%)	Fragment	*m/z* (%)
31a		414 (12)		130 (100)		43 (18)
31c		390 (70)		130 (20)		43 (19)
31g		396 (65)		130 (100)		43 (25)
31j		304 (100)		43 (26)		
32a		300 (7)		272 (100)		72 (23)

Furthermore, the structure of **31 and 32** are corroborated by an X-ray crystal structure analysis of compound **31a,g** and **32b**,**d**,**g** (Fig. 37–Fig. 41).

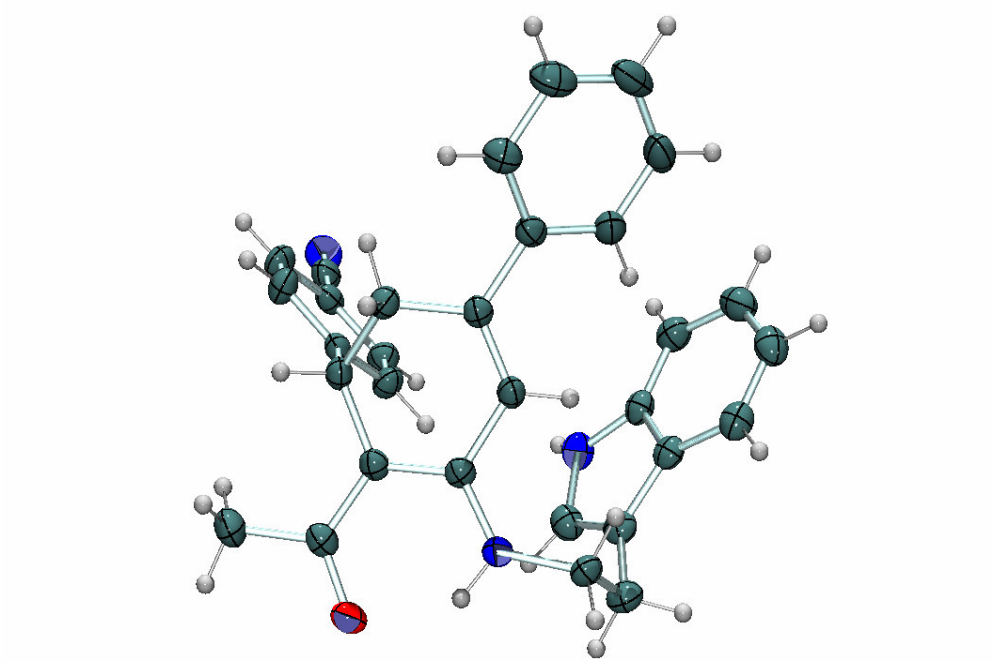


Fig. 37 ORTEP plot of compound **31a**.

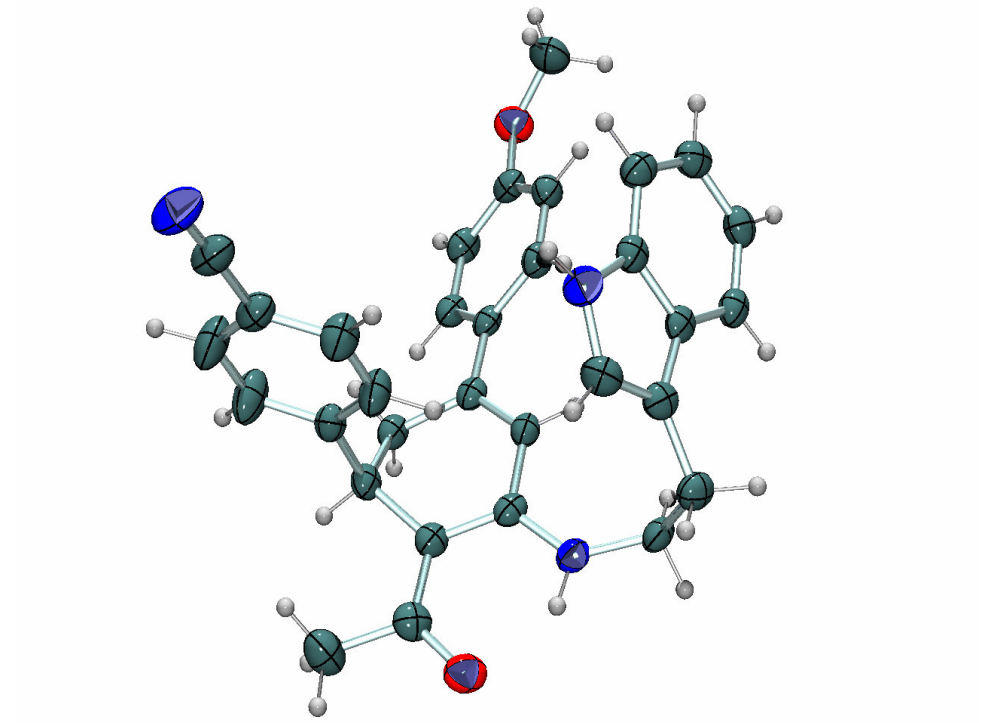


Fig. 38 ORTEP plot of compound **31g**.

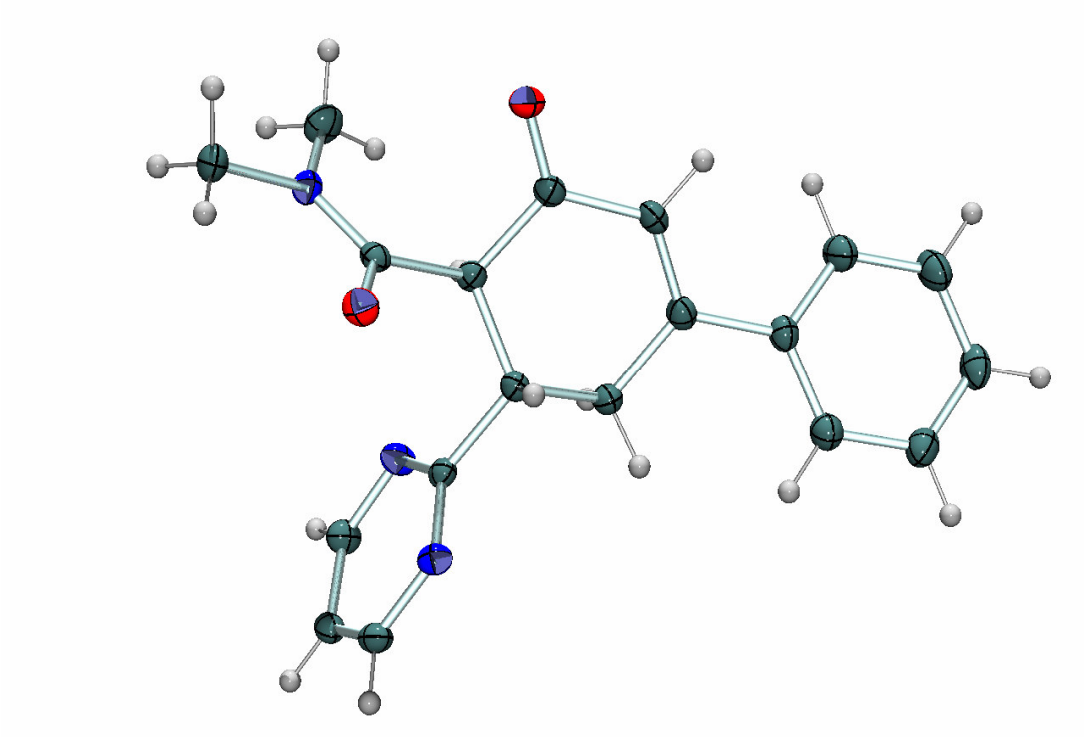


Fig. 39 ORTEP plot of compound **32b**.

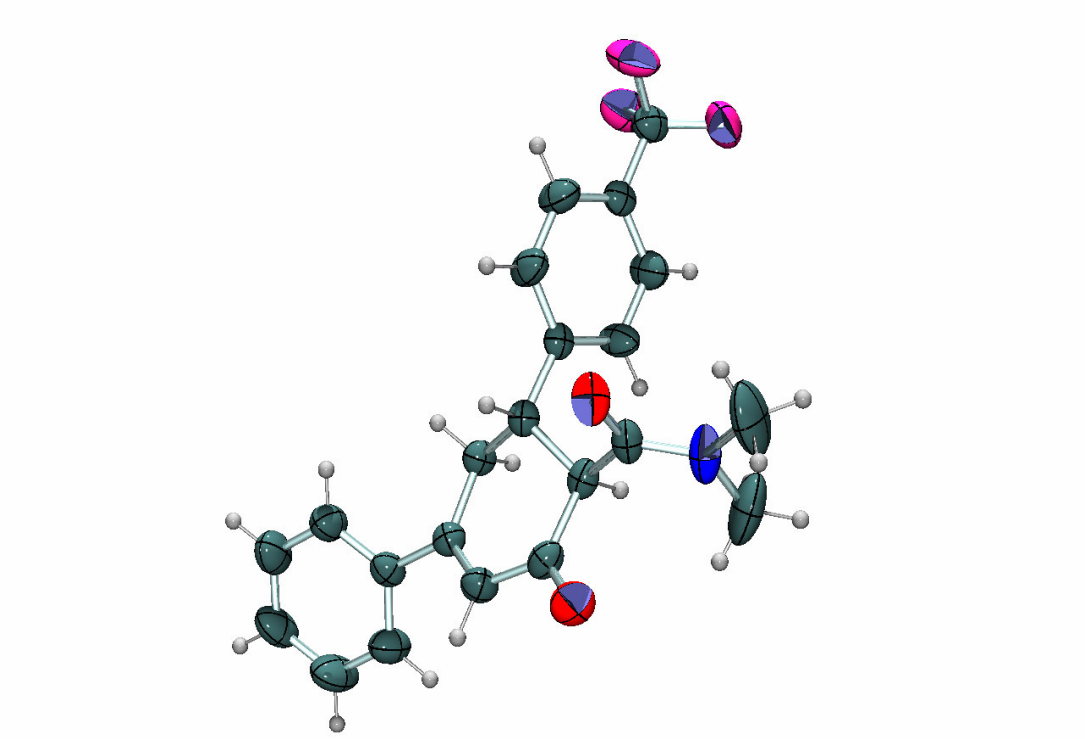


Fig. 40 ORTEP plot of compound **32d**.

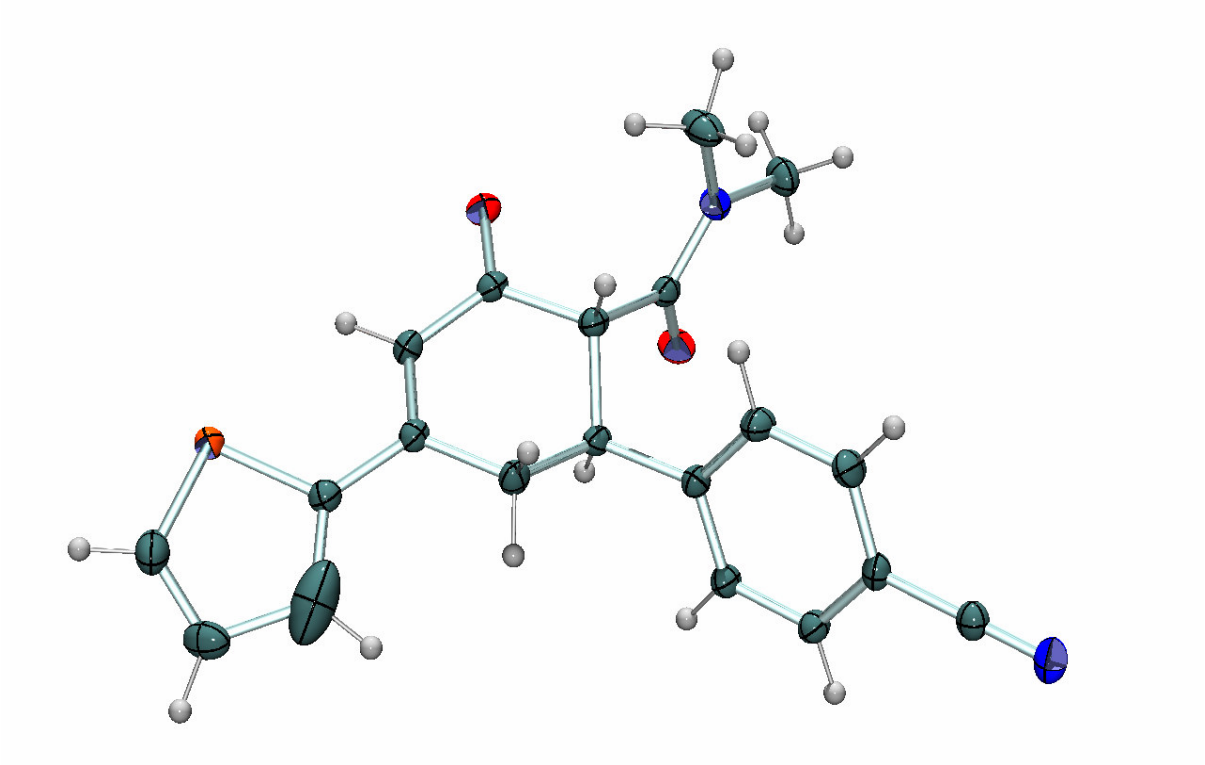


Fig. 41 ORTEP plot of compound **32g**.

4.7 One-Pot Microwave–Assisted Quinoline Synthesis Based upon MACIR

4.7.1 Quinolines – Literature review

Quinoline derivatives represent a major class of heterocycles, and a number of preparations have been known since the late 1800s. The quinoline ring system occurs in various natural products, especially in alkaloids. The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties. In 1820, quinine (Fig. 42) was isolated as the active ingredient from the bark of Cinchona trees and successively replaced the crude bark for the treatment of malaria. Despite its relatively low efficacy and tolerability, quinine still plays an important role in the treatment of multiresistant malaria.[119] Malaria is one of the most devastating infectious diseases in the world, afflicting 200-500 milion people and killing 1-2 milion annually.[120] The worldwide increase in drug-resistance to many of the affordable chemotherapies, such as chloroquine, has created a demand for the development of new malaria treatments, among them, mefloquine, quinacrine and other quinoline compounds.[121]

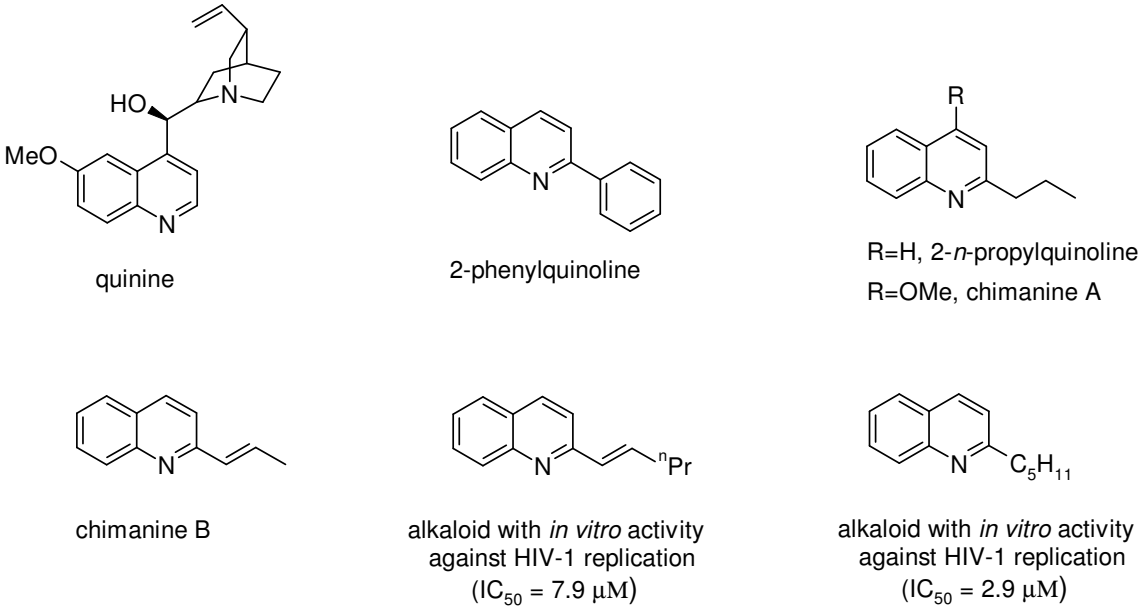


Fig. 42 Naturally occuring quinolines.

Chimanine alkaloids, simple quinolines, isolated from the bark of *galipea longiflora* trees of the rutaceae family,[122] are effective against the parasitic diseases such as

leishmaniasis and trypanosomiasis. The leishmaniases[123] constitute a diverse group of diseases that varies from simple cutaneous leishmaniasis to visceral leishmaniasis (VL), a very fatal disease if left untreated. VL, also known as "kala-azar" is a severe disease and epidepimcs are generally devastating. More recently, VL has also gained attention as an opportunistic infection in AIDS. Owing to the fact that overlapping geographical distribution of leishmaniasis and HIV/AIDS is increasing, *Leishmania*-HIV co-infection has been regarded as an emerging infectious disease.

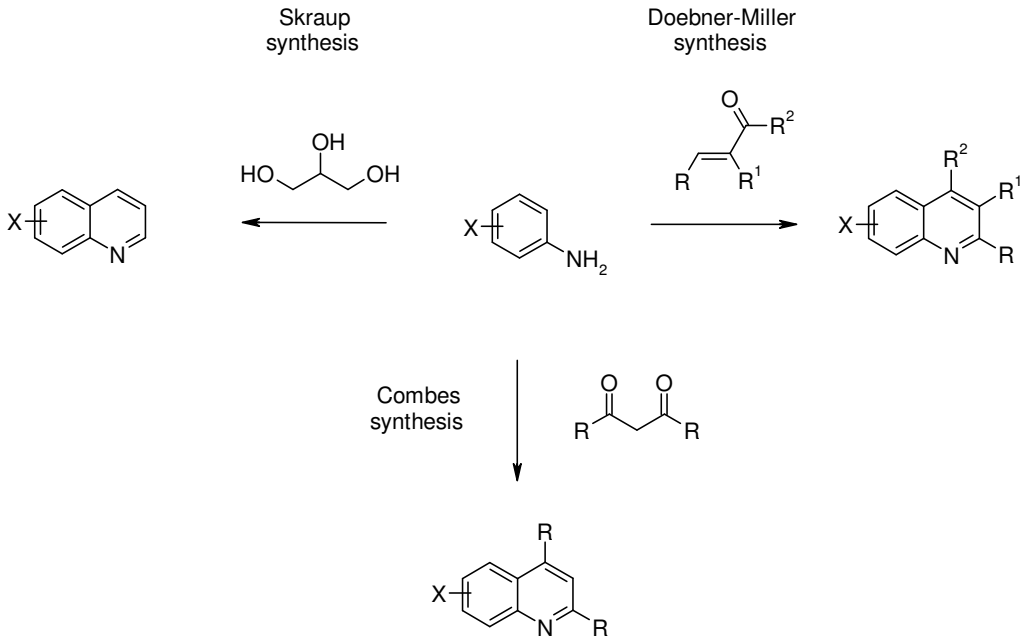
Figadere et al.[124] synthesized a serie of 2-substituted quinolines similar with chimanine alkaloids that present *in vitro* activity against the causal agents of cutaneous leishmaniasis, visceral leishmaniasis, African trypanosomiasis and Caga's disease. Furthermore, several quinolines also demonstrated *in vitro* activity against HIV-1 replication (Fig. 42).

Thus, substituted quinolines have found attractive applications as pharmaceuticals (antimalarials, antibacterials, protein kinase inhibitors) NADH models, and agrochemicals, in coordination chemistry as ligands[125] as well as being general synthetic blocks.[126]

Although numerous elegant syntheses have been developed for quinolines, because of their great importance, it is still challenging to explore new and efficient synthetic routes for this class of compounds, particularly those with wide general applicability.

Among the various routes available for the synthesis of quinoline derivatives, particularly interesting seems the approach employing aromatic primary amines as the nucleophilic nitrogen donating component as C-C-N unit and electrophilic three-carbon unit, usually carbonyl compounds, referring to Skraup, Doebner-von Miller, Combes and Conrad-Limpach syntheses [127] (Scheme 55).

The classical Skraup and Doebner von Miller synthesis are very similar, the former involves heating anilines with acrolein, generated *in situ* from glycerol and strong acid, whereas the latter method is based on generating a substituted acrolein, both methods also requiring an oxidant. The Combes method involves heating anilines with acetylacetone (Scheme 55).



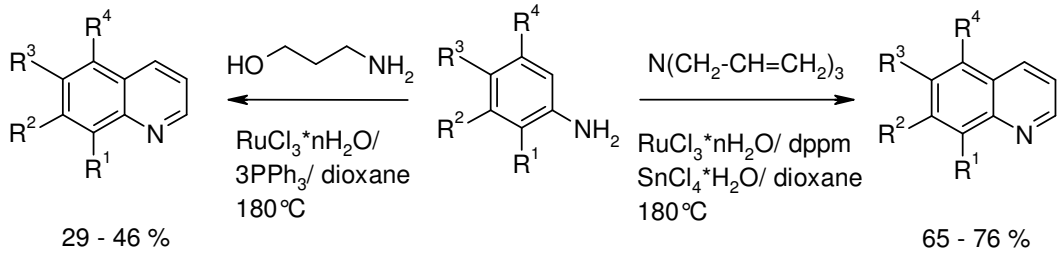
Scheme 55 Approaches involving aromatic primary amine as C-C-N unit.

In spite of their generality, versatility and simplicity, these syntheses have considerable drawbacks, such as harsh reaction conditions and highly acidic medium, which makes them tedious to isolate the product from the crude mixture. Moreover, reactions of *meta*- or 3,4-disubstituted anilines normally give a mixture of regioisomers, which are also difficult to separate. In case of Combes synthesis, the use of unsymmetrical 1,3-diketones complicates separation process.

Another way of preparing quinoline derivatives uses *ortho*-substituted anilines (C-C-C-N unit) and two carbon unit, usually carbonyl compounds containing a reactive α- methylene group. Aniline derivatives substituted at the 2-position and *o*-substituted nitrobenzenes are frequently employed as starting materials. The Friedländer synthesis of quinolines from *o*-aminobenzaldehydes is a staple reaction of organic synthesis. Although it does not require a catalyst, the Friedländer synthesis can be acid- or base-catalyzed. The uncatalyzed Friedländer synthesis requires more drastic reaction conditions, with temperatures in the range 150-220 °C. Hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid, and polyphosphoric acid were widely employed as catalysts. A complicating factor in this reaction is the relative instability of the *ortho*-amino aldehyde, which can readily undergo self-condensation reactions. The Pfitzinger reaction, the Niemantowski reaction and the Borsche synthesis[128] are helpful in reducing problems due to *o*-aminobenzaldehyde instability.

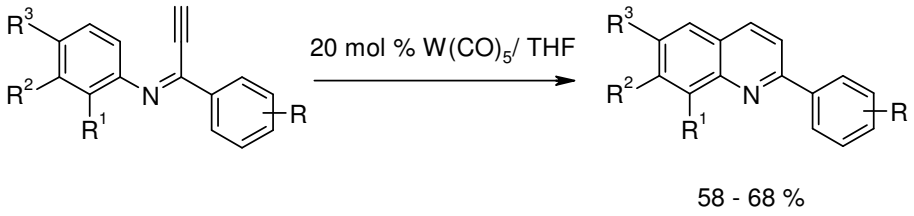
Due to these synthetic problems, there is still a need for developing mild, regioselective and practical syntheses for these heterocycles.

Therefore, new metal-catalyzed coupling cyclizations or acid catalyzed cycloadditions of appropriate precursors come to compete with classical syntheses in efficacy and rapidity of the quinoline construction. The formation of quinoline skeletons has been attempted by remarkable catalytic action of transition metal catalysts such as palladium, rhodium, ruthenium, cobalt and iron complexes.[129] It was suggested that metal-catalyzed heteroannulation proceeds *via* amine exchange reaction between anilines and alkylamines, allyl alcohols or 1,3-diols. For instance, anilines react with 3-amino-1-propanol in dioxane at 180 °C in the presence of catalytic amounts of $RuCl_3$ in H_2O/PPh_3 and $SnCl_2 \cdot 2H_2O$ together with hydrogen acceptor (acetone, nitrobenzene or hex-1-ene) to afford the corresponding quinolines in moderate yields (29-46%).[130] The use of triallylamine and ruthenium (III) chloride and bis(diphenylphosphino) methane allowed to obtain the 3-ethyl-3-methylquinoline derivatives in high yields[131] (Scheme 56). The quinoline yield was not decisively affected by the electronic nature and the position of the substituent on aniline.



Scheme 56 Ruthenium-catalyzed quinoline synthesis.

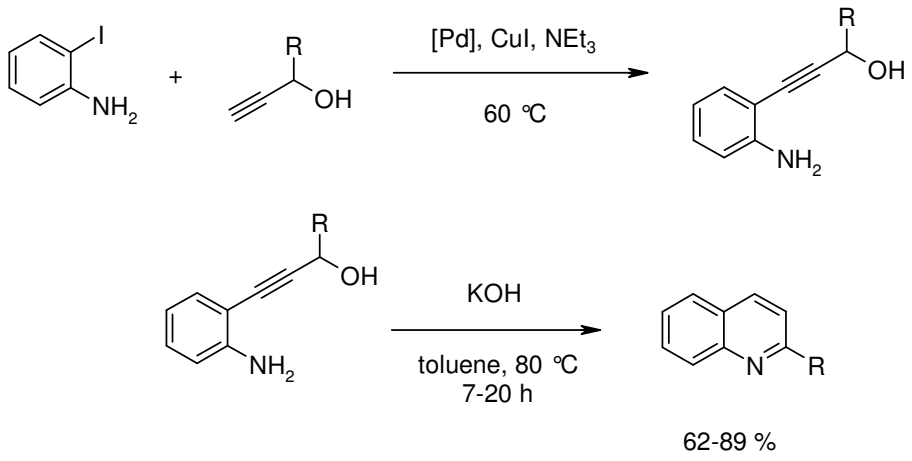
Akiyama and co-workers[132] described a novel quinoline synthesis that proceeds *via* catalytically tungsten vinylidene complexes - $W(CO)_5(THF)$. Alkynyl imines underwent [4+2] electrocyclization in the presence of 20 mol % catalyst to give 2-arylquinolines in good yields (Scheme 57).



Scheme 57 Tungsten-catalyzed quinoline synthesis

The elevated temperature for the ruthenium-catalyzed quinoline synthesis and the starting material that are not readily available, in case of the cobalt-[133] and tungsten-catalyzed reactions, [134] do not make these methods versatile and attracting procedures.

An interesting access to 2-substituted quinolines, recently reported by Shim et al.,[135] makes use of a base-mediated consecutive isomerization and cyclization sequence of 3-(2-aminophenyl)-1-arylprop-2-yn-1-ols that are easily available by Sonogashira coupling of iodoaniline with propargyl alcohols (Scheme 58).

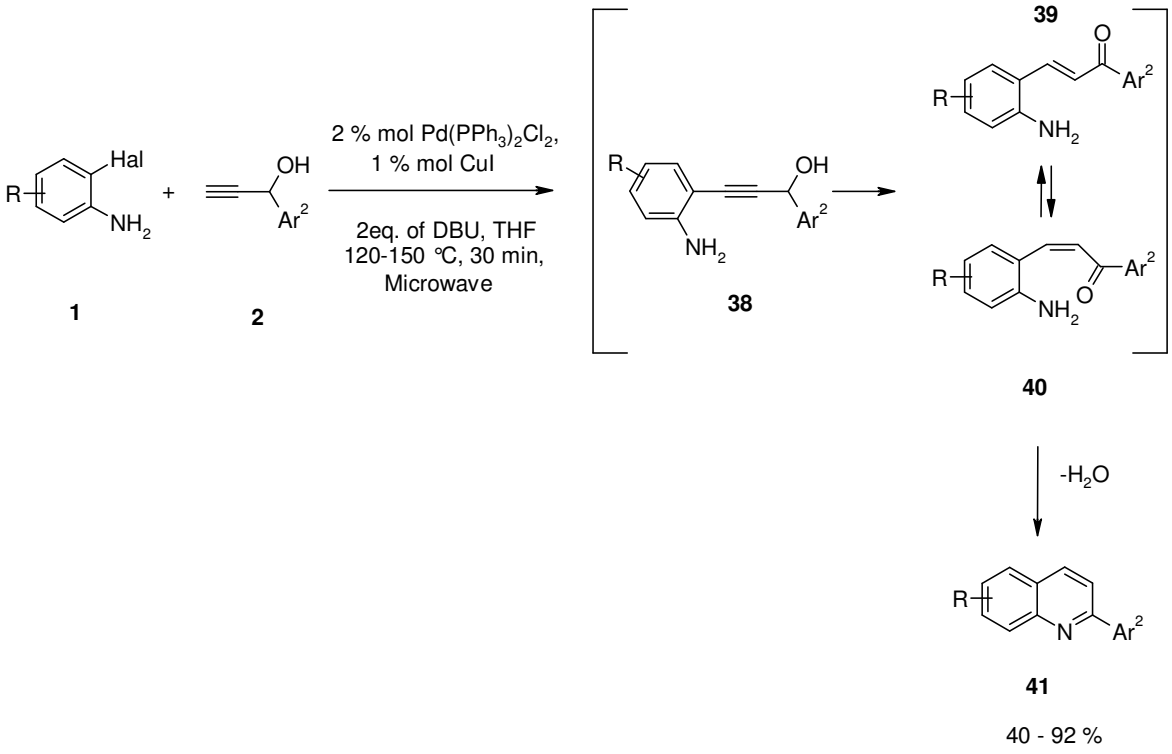


Scheme 58 Quinoline synthesis by isomerization-cyclocondensation of 3-(2-aminophenyl)-1-arylprop-2-yn-1-ols.

Remarkable for this approach is that the electron rich coupling compounds do not undergo isomerization to the corresponding enones even after prolonged reaction time or elevated temperature (180 °C). Stronger anorganic bases, such as KOH, were required that the isomerization took place by refluxing in ethanol for several hours (7-20 h).

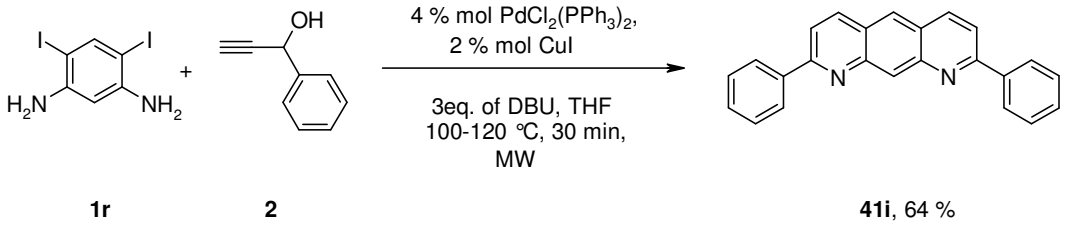
4.7.2 Quinoline Synthesis Based upon MACIR

Microwave irradiation facilites the electron rich aryl halides to undergo successfully coupling-isomerization reactions. *Para*- and *meta*- donating groups, as methoxy as well as amino groups substituents at the aromatic ring are well tolerated in the MACIR conditions. Aryl halides with an amino group in *ortho* position would be even more nucleophilic. Generally, *ortho* positions are not favored due to the steric hindrance, but in this case, the CIR product would be an unsaturated 1-amino 5-carbonyl compound that under base conditions of the MACIR could easily undergo an intramolecular condensation reaction with the formation of a new 6-membered ring. Indeed, subjecting *o*-amino (hetero)aryl halides **1** and propargyl alcohols **2** to the MACIR conditions, after 30 minutes reaction time, I was able to isolate the corresponding quinoline derivatives **41** in good to excellent yields (57-92 %, Scheme 59, Table 24).



Scheme 59 Quinoline Synthesis Based upon MACIR.

Furthermore starting with the disubstituted 1,5-diamino 2,4-diiodobenzene **1r**, the twofold coupling-isomerization reaction followed by intramolecular condensation furnished the expected pyrido-quinoline derivative **41i** (Scheme 60).



Scheme 60 Synthesis of pyrido-quinoline derivative **41i** *via* twofold MACIR

The coupling-isomerization reaction and the intramolecular condensation take place in one step, without the isolation of the intermediates **38** and **39**. Performing the reaction at lower temperature, 120 °C the alkyne **38** could be isolated as the main product, entry 6 (Table 24).

Mechanistically, the formation of the quinoline core presumes a (*Z*)-(*E*) isomerization that might readily occur under the MACIR conditions, followed by an intramolecular condensation. The isomerization may be favorized by the intramolecular hydrogen bond formation.

In conclusion, a new efficient one-pot quinoline and related heterocycles synthesis was developed as a direct application of the MACIR of the *o*-amino (hetero)aryl halides with propargyl aclcohols. Moreover, this new method allowed the synthesis of the naturally occurring quinolines, as 2-phenylquinoline, **41a**, and chimanine B, **41f**, within 30 minutes, in good to excellent yields (40-81 %). (Table 24) These quinolines have already been tested as antileishmanial agents, presenting good in vitro activity (IC_{50} = 12-100 μM). Further investigations for the new 2-quinolines as potential antileishmanial agents are in progress.

Table 24 MACIR of *o*-amino (hetero)aryl halides **1** with propargyl alcohols **2**.

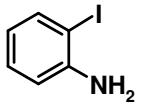
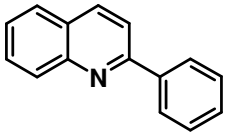
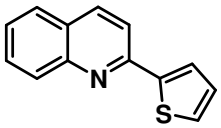
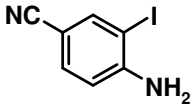
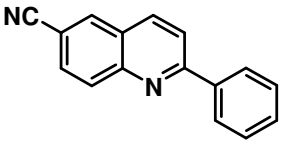
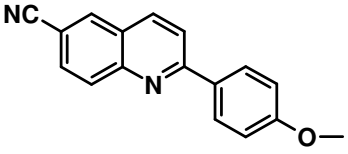
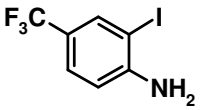
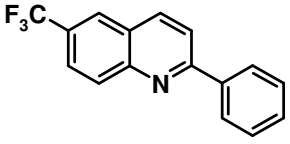
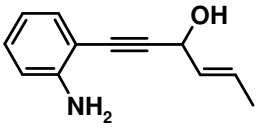
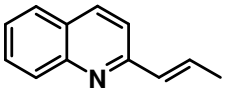
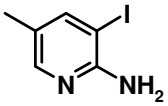
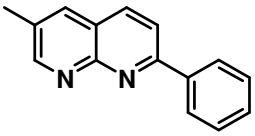
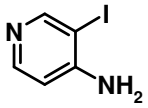
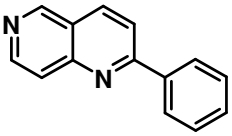
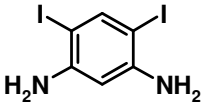
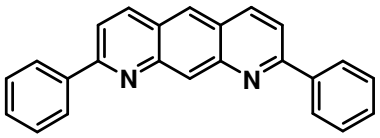
Entry	Aryl halide **1**	Propargyl alcohol **2**	Product **38** or **41** (Yield)
1[a]	 (**1m**)	Ar^2 = -C_6H_5 (**2a**)	 **41a** (81 %)
2[a]	**1m**	Ar^2 = 2-thienyl (**2b**)	 **41b** (80 %)
3[a]	 (**1n**)	**2a**	 **41c** (70 %)
4[a]	**1n**	Ar^2 = -C_6H_4OMe (**2f**)	 **41d** (57 %)
5[a]	 (**1o**)	**2a**	 **41e** (92 %)

Table 24 *continued*

6[a]	**1m**	**2g**	 **38a** (44 %)
7[b]	**1m**	**2g**	 **41f** (40 %)
8[b]	 (**1p**)	**2a**	 **41g** (79 %)
9[b]	 (**1q**)	**2a**	 **41h** (78 %)
10[a]	 (**1r**)	**2a**	 **41i** (64 %)

[a]Reaction temperature 120 °C.[b]Reaction temperature 150 °C.

Spectroscopic data

The structure of the quinoline derivatives **41a–f**,**i** and naphthyridines **41g**,**h** is unambiguously supported by the expected appearance of the characteristic proton and carbon resonances and multiplicities. In particular, in the ^{1}H NMR spectra of **41** the doublets for the 3-, 4- methine signals, appear between δ 7.89 and 8.27, with coupling constants J = 8.0–8.3 Hz. Additionally, the assignments of 3-positioned methine protons are supported by 2D NOESY spectra that indicate clear cross-peaks as a consequence of spatial proximity with *ortho*-phenyl, phenylene, or 3-thienyl protons (-Ar^2, Fig. 43).

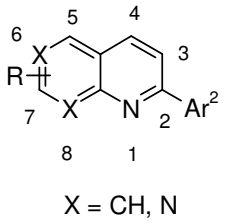


Fig. 43 The numeration of the quinolines and naphthyridines **41**.

The thienyl protons for **41b** are identified as a triplet at δ 7.16 with a coupling constant of J = 4.0 Hz, a doublet at δ 7.61 with a coupling constant of J = 5.0 Hz, and a multiplet at 7.69, each of them with an intensity of one proton. The signals of the methyl protons for **41d** and **41g** are detected as singlets at δ 3.89 and 2.54 respectively, with an intensity of three protons. The resonances of the methyl protons for **38** and **41f** appear as a doublet at δ 1.69 with a coupling constant of J = 6.3 Hz, and at δ 2.1 with a coupling constant of J = 6.9 Hz respectively. The broad singlets in ^{1}H NMR spectrum of compound **38**, appear at δ 2.64 and 4.06 respectively. They clearly support the non-cyclic structure of the alkyn-ol derivative. The characteristic α-cleavage detected in the mass spectrum of **38** also confirms the alcohol structure. The most downshifted signal in ^{1}H NMR spectrum of compound **41f**, was assigned to the proton positioned *ortho* with respect of the pyridine cores that resonate at δ 8.77 as singlet with an intensity of one proton.

The mass spectra of all obtained compounds show the molecular peaks. The usual fragmentation mode for the 2-substituted quinoline and naphthyridine derivatives leads to the loss of phenyl and thienyl fragments. For **41d,g** the loss of methyl group was detected. For **41c**, the cyanohydric acid was identified as a fragment in the mass spectrum.

The nitrile vibration was detected in the IR spectrum of compound **41c** at 2224–2227 cm^{-1}.

Furthermore, the structure of quinolines was corroborated by X-ray crystal structure analysis of compound **41c**.

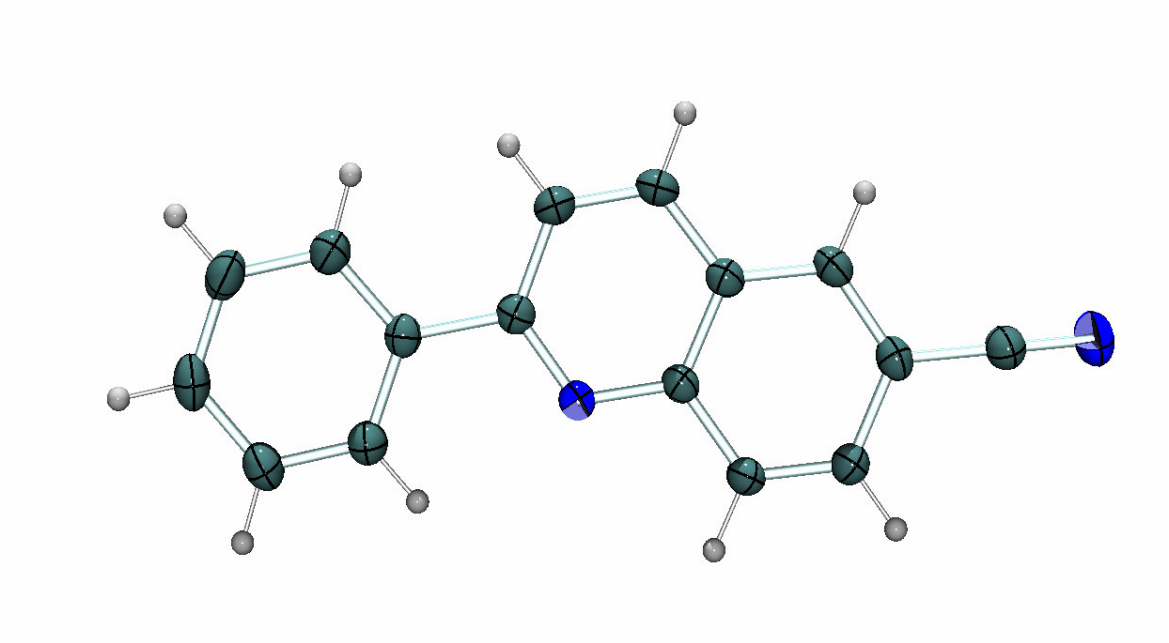


Fig. 44 ORTEP plot of compound **41c**.

5 Conclusions and Outlook

It was shown that the major goals in methodological studies on coupling–isomerization reaction, as the reduction of reaction times of the rate limiting isomerization step and reduction of the amount of base could be achieved by the use of the microwave assisted CIR (MACIR). Furthermore, the microwave-assisted coupling–isomerization reaction was successfully extended to electron rich aryl halides that commonly do not undergo CIR under conventional conditions. As a direct application of MACIR of electron rich aryl halides, a novel one-pot synthesis of quinoline derivatives was developed via MACIR of *o*-amino aryl halides with propargyl alcohols. Based upon this methodology, chimanine alkaloids were synthesized in 30 minutes, 40-81%. New rapid and efficient syntheses of the pyrido-quinoline derivatives as multidentate ligands can be envisioned by use of this methodology.

Also the microwave effects on multicomponent synthesis were investigated. Thus, while conventional heated muticomponent processes furnished pyridines or dihydropyridines as main reaction products by a CIR-enamine addition cyclocondensation sequence, in 48-72 h, the same reaction components under microwave irradiation underwent a CIR-enamine addition-intra-aldol condensation sequence, with the formation of the cyclohexadienes or cyclohexanones as main reaction products, within 25-35 minutes.

The potential of MACIR-enamine addition-intra-aldol condensation sequence is not limited to the reactions described in this thesis. The microwave assisted three component syntheses might be further developed to new four-component processes. For example, the cyclohexadienes can be subjected to subsequent Lewis acid catalyzed Diels-Alder or Pictet-Spengler reactions in one-pot fashion. Similarly, the keto-cyclohexadiene can be used in 1,3-cycloaddition reactions for the synthesis of new annelated heterocycles.

The mechanism of enamine addition to the chalcones under conventional heating conditions was elucidated by the isolation of the Diels-Alder cycloadduct **6**. This result was also confirmed by the molecular modeling investigations.

It was discovered that the enimines, as products of CIR of aryl halides with propargyl amines, could be used as electron poor heterodienes in a Diels-Alder reaction with inverse electron demand, furnishing pyridine derivatives, among them, interesting fluorescent 2-amino annelated pyridines with high florescence quantum yields of 12–63 %.

6 Experimental Part

6.1 General Considerations

All reactions involving palladium-copper catalysis were performed in degassed oxygen free solvents under a nitrogen atmosphere using Schlenk and syringe techniques. Halogen compounds **1**, $(Ph_3P)_2PdCl_2$, and CuI were purchased reagent grade from ACROS, Aldrich, Fluka or Merck and used without further purification. Triethylamine and THF were dried and distilled according to standard procedures.[103] All reactions involving microwave irradiation were conducted under nitrogen in heavy-walled glass Smith process vials sealed with aluminum crimp caps fitted with a silicon septum. The inner diameter of the vial filled to the height of 2 cm was 1.3 cm. The microwave heating was performed in a Smith Synthesizer single-mode microwave cavity producing continuous irradiation at 2450 MHz (Personal Chemistry AB, Uppsala, Sweden). Reaction mixtures were stirred with a magnetic stir bar during the irradiation. The temperature, pressure and irradiation power were monitored during the course of the reaction. The average pressure during the reaction was 3-4 bar. After completed irradiation, the reaction tube was cooled with highpressure air until the temperature had fallen below 39 °C (ca. 2 min). – Column chromatography: silica gel 60 (Merck, Darmstadt), mesh 70–230. TLC: silica gel plates (60 F_{254} Merck, Darmstadt). Melting points (uncorrected values): Büchi Melting Point B-540. – ^1H and ^{13}C NMR spectra: Bruker ARX 300, Varian VXR 400S $CDCl_3$, C_2D_6O and $[D_6]$DMSO. The assignments of quaternary C CH, CH_2 and CH_3 have been made by using DEPT spectra. – IR: Perkin Elmer Lambda 3. – UV/vis: Perkin Elmer Models Lambda 16. – Fluorescence: Perkin Elmer LS-55. – MS: Finnigan MAT 90 and MAT 95 Q. – Elemental analysis were carried out in the Microanalytical Laboratories of the Organisch-Chemisches Institut, Ruprecht-Karls-Universität Heidelberg.

6.2 General Procedure for the Coupling Reactions/Coupling-Isomerization Reactions of Aryl halides 1 with Propargylyl Alcohols 2

A magnetically stirred solution of 1.00 mmol of halogen compound **1**, 1.05 mmols of propargyl alcohol **2**, 20 mg (0.02 mmols) of $(PPh_3)_2PdCl_2$, and 2 mg (0.01 mmols) of CuI in 2-5 eq. of degassed base and 1.5 mL of THF under nitrogen was stirred under nitrogen in a heavy-walled SmithCreator process vial at the microwave generated temperature and for the

time indicated, (for experimental details see Table 25) in the microwave cavity. After cooling to room temp. the reaction mixture was poured to 40 mL of ethyl acetate and 40 mL of water were added and stirring was continued for 5 to 10 min. The aqueous layer was extracted with ethyl acetate (4 × 15 mL) and the combined organic phases were dried over magnesium sulfate. After filtration the solvents were removed *in vacuo* and the residue was chromatographed on silica gel (hexane/ethyl acetate 4:1 or 1:1) and crystallized from ethanol or pentane/chloroform (1:1) to give the analytically pure alkyne **3** and chalcone **4**, respectively.

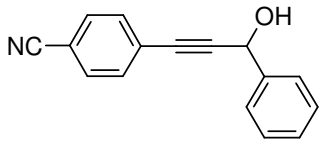
Table 25 Experimental details of the coupling/coupling-Isomerization reactions

Entry	Aryl halide **1**	Propargyl alcohol **2**	Base	Tempe-rature [°C]	t [min]	Product (Yield, %)
1	182 mg (1.00 mmol) of **1a**	139 mg (1.05 mmols) of **2a**	505 mg (5.0 mmols) of NEt_3	120	8	79 mg (34 %) of **3a**
2	225 mg (1.00 mmol) of **1d**	139 mg (1.05 mmols) of **2a**	505 mg (5.0 mmols) of NEt_3	120	10	80 mg (29 %) of **3d**
3	229 mg (1.00 mmol) of **1e**	139 mg (1.05 mmols) of **2a**	505 mg (5.0 mmols) of NEt_3	120	10	69 mg (25 %) of **3e**
4	182 mg (1.00 mmol) of **1a**	74 mg (1.05 mmols) of **2e**	608 mg (4.0 mmols) of DBU	120	10	157 mg (92 %) of **3k**
5	204 mg (1.00 mmol) of **1i**	139 mg (1.05 mmols) of **2a**	153 mg (1.05 mmols) of DBU	100	60	145 mg (70 %) of **3l**
6	234 mg (1.00 mmol) of **1k**	139 mg (1.05 mmols) of **2a**	304 mg (2.0 mmols) of DBU	100	30	109 mg (46 %) of **3n**
7	182 mg (1.00 mmol) of **1a**	139 mg (1.05 mmols) of **2a**	505 mg (5.0 mmols) of NEt_3	150	15	224 mg (96 %) of **4a**
8	159 mg (1.00 mmol) of **1b**	139 mg (1.05 mmols) of **2a**	505 mg (5.0 mmols) of NEt_3	120	15	176 mg (84 %) of **4b**
9	158 mg (1.00 mmol) of **1c**	139 mg (1.05 mmols) of **2a**	505 mg (5.0 mmols) of NEt_3	150	15	163 mg (78 %) of **4c**
10	225 mg (1.00 mmol) of **1d**	139 mg (1.05 mmols) of **2a**	505 mg (5.0 mmols) of NEt_3	170	15	180 mg (65 %) of **4d**

Table 25 *continued*

11	229 mg (1.00 mmol) of **1e**	139 mg (1.05 mmols) of **2a**	505 mg (5.0 mmols) of NEt_3	150	30	173 mg (62 %) of **4e**
12	202 mg (1.00 mmol) of **1a**	139 mg (1.05 mmols) of **2a**	505 mg (5.0 mmols) of NEt_3	150	15	160 mg (63 %) of **4f**
13	236 mg (1.00 mmol) of **1g**	139 mg (1.05 mmols) of **2a**	505 mg (5.0 mmols) of NEt_3	150	15	178 mg (62 %) of **4g**
14	182 mg (1.00 mmol) of **1a**	145 mg (1.05 mmols) of **2b**	505 mg (5.0 mmols) of NEt_3	175	10	208 mg (87 %) of **4h**
15	182 mg (1.00 mmol) of **1a**	145 mg (1.05 mmols) of **2c**	505 mg (5.0 mmols) of NEt_3	175	10	224 mg (96 %) of **4i**
16	182 mg (1.00 mmol) of **1a**	103 mg (1.05 mmols) of **2d**	153 mg (1.05 mmols) of DBU	200	10	123 mg (62 %) of **4j**
17	204 mg (1.00 mmol) of **1i**	139 mg (1.05 mmols) of **2a**	304 mg (2.0 mmols) of DBU	100	30	191 mg (92 %) of **4l**
18	218 mg (1.00 mmol) of **1j**	139 mg (1.05 mmols) of **2a**	304 mg (2.0 mmols) of DBU	120	30	204 mg (92 %) of **4m**
19	234 mg (1.00 mmol) of **1k**	139 mg (1.05 mmols) of **2a**	304 mg (2.0 mmols) of DBU	120	30	202 mg (85 %) of **4n**
20	219 mg (1.00 mmol) of **1l**	139 mg (1.05 mmols) of **2a**	304 mg (2.0 mmols) of DBU	120	30	162 mg (73 %) of **4o**

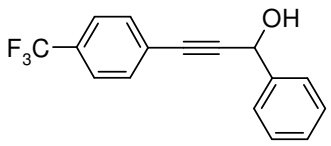
4-(3-Hydroxy-3-phenyl-prop-1-ynyl)-benzonitrile (3a)[136]



According to the GP after chromatography on silica gel (hexane/ethyl acetate 4:1), 79 mg (34 %) of **3a** were isolated as a red-brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.67 (d, J = 5.8, 1 H), 5.70 (d, J = 5.5 Hz, 1 H), 7.30–7.46 (m, 3 H), 7.41–7.59 (m, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 64.9 (CH), 84.7 ($C_{quat.}$), 93.2 ($C_{quat.}$), 111.9 ($C_{quat.}$), 118.3 ($C_{quat.}$), 126.6 (CH), 127.3 ($C_{quat.}$), 128.6 (CH), 128.8 (CH), 132.0 (CH), 132.2 (CH), 140.0 (CH). EI MS (70 eV), *m/z* (%): 233 (M^+, 71), 232 (M^+- H, 100), 204 (48), 156 (M^+- C_6H_5, 4), 77 ($C_6H_5^+$, 57). IR (KBr):

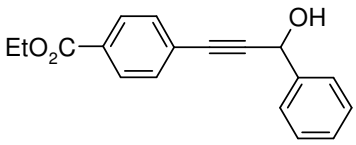
$\tilde{\nu}$ 3431, 3061, 3032, 2226, 2203, 1639, 1602, 1499, 1453, 1387, 1287, 1176, 1012, 959, 835, 765, 699 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 250 nm (14700), 262 (25300), 274 (25300).

1-Phenyl-3-(4-trifluormethyl-phenyl)-prop-2-yn-1-ol (3d)



According to the GP after chromatography on silica gel (hexane/ethyl acetate 4:1), 80 mg (29 %) of **3e** were isolated as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.00–2.23 (m, 1 H), 5.70 (s, 1 H), 7.36–7.44 (m, 3 H), 7.57–7.62 (m, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 65.0 (CH), 91.1 ($C_{quat.}$), 125.2 ($C_{quat.}$), 126.7 (CH), 128.6 (CH), 128.8 (CH), 132.0 (CH), 140.2 ($C_{quat.}$). EI MS (70 eV), *m/z* (%): 276 (M^+, 100), 259 (M^+- OH, 26), 207 (M^+- CF_3, 43), 170 105 ($C_7H_5O^+$, 16), 77 ($C_6H_5^+$, 47). IR (film): $\tilde{\nu}$ 1615, 1405, 1324, 1168, 1126, 1106, 1068, 1018, 1002, 964, 843, 762, 749, 717, 698, 598 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 210 nm (17500), 248 (21400), 258 (18600).

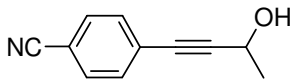
Ethyl 4-(3-hydroxy-3-phenylprop-1-ynyl)benzoate (3e)



According to the GP after chromatography on silica gel (hexane/ethyl acetate 4:1), 69 mg (25 %) of **3e** were isolated as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38 (t, *J* = 7.1 Hz, 3 H), 3.63 (s 1 H), 4.37 (q, J = 7.1 Hz, 2 H), 5.70 (s, 1 H), 7.35–7.44 (m, 3 H), 7.50–7.52 (d, *J* = 8.4 Hz, 2 H), 7.59–7.71 (m, 2 H), 7.97–8.00 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.3 (CH_3), 61.2 (CH_2), 65.1 (CH), 85.8 ($C_{quat.}$), 91.6 ($C_{quat.}$), 126.7 (CH), 127.0 ($C_{quat.}$), 127.9 (CH), 128.4 (CH), 128.6 (CH), 128.7 (CH), 129.4 (CH), 131.4 (CH), 140.3 ($C_{quat.}$), 166.0 ($C_{quat.}$). EI MS (70 eV), *m/z* (%): 280 (M^+, 100), 251 (M^+- C_2H_5, 25), 207 (M^+- $CO_2C_2H_5$, 54), 105 ($C_7H_5O^+$, 11), 77 ($C_6H_5^+$, 8). IR (film): $\tilde{\nu}$ 3428, 3065, 2931, 1713, 1602,

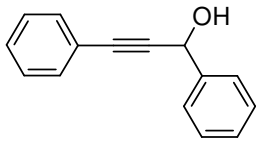
1275, 1107, 770, 725, 696, 596, 565, 542, cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 254 nm (9700), 266 (10500), 376 (9300).

4-(3-hydroxybut-1-ynyl)benzonitrile (3k)



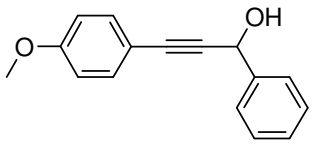
According to the GP after chromatography on silica gel (hexane/ethyl acetate 4:1), 158 mg (92 %) of **3k** were isolated as a light brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.48 (d, J = 4.75 Hz, 3 H), 2.5 (s, 3 H), 4.67 (q, J = 5.5 Hz, 1 H), 7.39 (d, J = 7.0 Hz, 2 H), 7.49 (d, J = 7.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.0 (CH_3), 58.6 (CH), 82.2 ($C_{quat.}$), 95.5 ($C_{quat.}$), 111.5 ($C_{quat.}$), 118.3 ($C_{quat.}$), 128.4 ($C_{quat.}$), 131.9 (CH), 132.1 (CH). EI MS (70 eV), *m/z* (%): 171.07 (M^+, 20), 156 (M^+- CH_3, 100), 128 (M^+- CH_3, - CO, 25). HRMS calcd. for $C_{11}H_9NO$: 171.0684; found 171.0672.

1, 3-Diphenylprop-2-yn-1-ol (3l)[137]



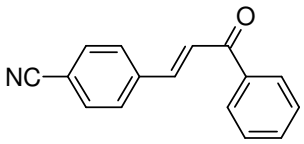
According to the GP after chromatography on silica gel (hexane/ethyl acetate 4:1), 145 mg (70 %) of **3l** were isolated as a yellow oil. ^{1}H NMR (C_3D_6O, 300 MHz), δ 5.18 (d, J = 5 Hz, 1 H), 5.71 (d, J = 5 Hz, 1 H), 7.29–7.47 (m, 8 H), 7.62 (d, J = 6.3 Hz, 1 H). ^{13}C NMR (C_3D_6O, 100 MHz), δ 63.9 (CH), 84.8 ($C_{quat.}$), 90.5 ($C_{quat.}$), 122.9 (CH), 126.6 (CH), 127.7 (CH), 128.0 (CH), 128.3 (CH), 128.5 (CH), 131.4 (CH), 142.1 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 208.0 (M^+, 100), 191 (M^+ - OH, 25), 77 ($C_6H_5^+$, 35).

3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-ol (3n)[138]



According to the GP after chromatography on silica gel (hexane/ethyl acetate 4:1), 110 mg (46 %) of **3n** were isolated as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.62 (s, 1 H), 3.68 (s, 3 H), 5.56 (s, 1 H), 6.71 (d, J = 8.5 Hz, 2 H), 7.14–7.31 (m, 5 H), 7.49 (d, J = 6.8 Hz, 2 H). ^{13}C NMR (C_3D_6O, 100 MHz), δ 55.2 (CH_3), 65.0 (CH), 86.4 ($C_{quat.}$), 87.4 ($C_{quat.}$), 113.9 (CH), 114.5 ($C_{quat.}$), 126.7 (CH), 128.4 (CH), 128.7 (CH), 132.1 (CH), 140.8 ($C_{quat.}$), 159.7 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 238.0 (M^+, 100), 221 (M^+ - OH, 30), ($C_6H_5^+$, 40).

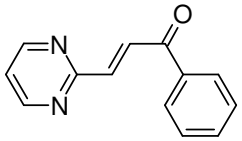
(*E*)-3-(4-Cyanophenyl)-1-phenylprop-2-en-1-one (4a)[139]



According to the GP after chromatography on silica gel (hexane/ethylacetate 4:1) and recrystallization from ethanol 224 mg (96 %) of **4a** were isolated as light yellow crystals. M.p.159–160 °C (lit. 156–157 °C).[139] ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.46–7.53 (m, 2 H), 7.56–7.64 (m, 1 H), 7.59 (d, J = 15.8 Hz, 1 H), 7.67–7.73 (m, 4 H), 7.76 (d, J = 15.8 Hz, 1 H), 8.00-8.04 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 113.5 ($C_{quat.}$), 118.3 ($C_{quat.}$), 125.1 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 132.6 (CH), 133.2 (CH), 137.6 ($C_{quat.}$), 139.2 ($C_{quat.}$), 142.0 (CH), 189.7 ($C_{quat.}$). EI MS (70 eV), *m/z* (%): 233 (M^+, 100), 232 (M^+- H, 86), 205 (13), 204 (37), 190 (12), 156 (M^+- C_6H_5, 33), 128 (M^+- C_6H_5 - CO, 20), 105 ($C_7H_5O^+$, 38), 77 ($C_6H_5^+$, 29). IR (KBr): $\tilde{\nu}$ 2222, 1664, 1605, 1578, 1412, 1336, 1311, 1223, 1017, 988, 833, 779, 727, 697, 689, 650, 549 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 302 nm (27249). Anal. calcd. for $C_{16}H_{11}N0$ (233.3): C 82.38, H 4.75, N 6.00; found: C 82.40, H 4.85, N 5.84.

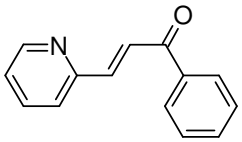
(*E*)/(*Z*)-configurated chalcones were obtained in different ratios from 4:1 up to pure (*E*)-chalcone. Characteristic for (*Z*)-chalcone: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.01 (d, J = 12.8 Hz, 1 H), 6.82 (d, J = 12.8 Hz, 1 H). Characteristic for (*E*)-chalcone: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.59 (d, J = 15.8 Hz, 1 H), 7.76 (d, J = 15.8 Hz, 1 H).

(*E*)-1-Phenyl-3-pyrimidinprop-2-en-1-one (4b)



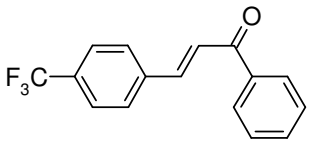
According to the GP after chromatography on silica gel (hexane/ethylacetate 3:1) 176 mg (84 %) of **4b** were isolated as a light-brown solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.22 (d, J = 2.94 Hz, 1 H), 7.23–7.59 (m, 3 H), 7.72 (d, J = 9.3 Hz, 1 H), 8.05–8.047 (m, 2 H), 8.25 (d, J = 9.27 Hz, 1 H), 8.77 (d, J = 2.91 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ120.2 (CH), 128.7 (CH), 128.8 (CH), 130.5 (CH), 133.3 (CH), 137.4 ($C_{quat.}$), 142.2 (CH), 157.3 (CH), 163.3 ($C_{quat.}$), 190.4 ($C_{quat.}$). EI MS (70 eV), *m/z* (%): 210 (M^+, 50), 181 (100), 133 (M^+- C_6H_5, 15), 105 (M^+- $C_7H_5O^+$, 43), 77 ($C_6H_5^+$, 56). IR (KBr): $\tilde{\nu}$ 1680, 1620, 1596, 1564, 1443, 1422, 1371, 1328, 1297, 1223, 1183, 1011, 809, 757, 727, 695, 635, 607, 523 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 254 nm (13667), 278 (13000). Anal. calcd. for $C_{13}H_{10}N_2O$ (210.2): C 74.27, H 4.79, N 13.32; found: C 74.01, H 4.82, N 12.98.

(*E*)-1-Phenyl-3-pyridinprop-2-en-1-one (4c)



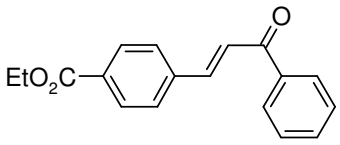
According to the GP after chromatography on silica gel (hexane/ethylacetate 3:1) 163 mg (78 %) of **4c** were isolated as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.06–7.10 (m, 1 H), 7.27–7.42 (m, 5 H), 7.51 (dd, J = 1.8 Hz, J = 7.7 Hz, 1 H), 7.58 (d, J = 15.8 Hz, 1 H), 7.88–7.91 (m, 2 H), 7.92 (d, J = 15.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ124.3 (CH), 125.2 (CH), 125.4 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 133.0 (CH), 136.8 (CH), 137.7 ($C_{quat.}$), 142.7 (CH), 150.0 (CH), 153.1 ($C_{quat.}$), 190.3 ($C_{quat.}$). EI MS (70 eV), *m/z* (%): 209 (M^+, 100), 180 (M^+- H - CO, 12), 149, 132 (M^+- C_6H_5, 42), 105 ($C_7H_5O^+$, 8), 104 (M^+- C_6H_5 - O, 22), 77 ($C_6H_5^+$, 12). IR (KBr): $\tilde{\nu}$ 3056, 2927, 1722, 1665, 1613, 1594, 1578, 1563, 1446, 1430, 1329, 1317, 1299, 1289, 1216, 1150, 1014, 991, 972, 759, 691, 593 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 276 nm (11800), 304 (16100).

(*E*)-3-(4-Trifluormethylphenyl)-1-phenylprop-2-en-1-one (4d)[140]



According to the GP after chromatography on silica gel (hexane/ethylacetate 5:1) and recrystalization from ethanol, 180 mg (65 %) of **4d** were isolated as light-yellow crystals. M.p.128–29 °C (lit. 116–118 °C).[140] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.49–7.65 (m, 4 H), 7.66–7.77 (m, 4 H), 7.82 (d, J = 18.9 Hz, 1 H), 8.02–8.05 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 123.8 (q, J = 272.3 Hz, $C_{quat.}$), 124.3 (CH), 125.9 (q, J = 3.8 Hz, CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 131.9 (q, J = 32.6 Hz, $C_{quat.}$), 133.1 (CH), 137.8 ($C_{quat.}$), 138.3 (q, J = 1.4 Hz, $C_{quat.}$), 142.7 (q, J = 0.6 Hz, CH), 190.0 ($C_{quat.}$). EI MS (70 eV), *m/z* (%): 276 (M^+), 257, 207, 199 (M^+- C_6H_5), 179, 171 (M^+- C_6H_5 - CO), 151, 105 ($C_7H_5O^+$), 77 ($C_6H_5^+$). IR (film): $\tilde{\nu}$ 3063, 2928, 1664, 1637, 1611, 1578, 1448, 1416, 1319, 1170, 1113, 1018, 984, 838, 779, 738, 697 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 294 nm (16522). Anal. calcd. for $C_{16}H_{11}F_30$ (276.3): C 69.56, H 4.01; found: C 69.43, H 4.10.

(*E*)-Ethyl 4-(3-oxo-3-phenylprop-1-enyl)benzoate (4e)[141]

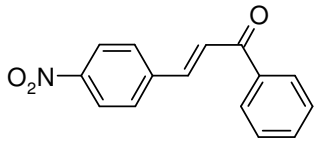


According to the GP after chromatography on silica gel (hexane/ethylacetate 5:1) 173 mg (62 %) of **4e** were isolated as brown powder. M.p. 82 °C (lit. 83–84 °C).[141] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (t, J = 6.9 Hz, 3 H), 4.39 (q, J = 6.9 Hz, 2 H), 7.49-7.62 (m, 4 H), 7.68-7.71 (m, 2 H), 7.81 (d, J = 15.5 Hz, 1 H), 8.01-8.09 (m, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (CH_3), 61.0 (CH_2), 123.9 (CH), 128.0 (CH), 128.4 (CH), 128.5 (CH), 129.9 (CH), 131.7 ($C_{quat.}$), 132.8 (CH), 137.7 ($C_{quat.}$), 138.8 ($C_{quat.}$), 143.1 (CH), 165.7 ($C_{quat.}$), 190.0 ($C_{quat.}$). EI MS (70 eV), *m/z* (%): 280 (M^+), 279 (M^+- H), 251 (M^+- C_2H_5, 14), 207 (M^+- $C_2H_5CO_2$, 11), 105 ($C_7H_5O^+$), 77 ($C_6H_5^+$). IR (film): $\tilde{\nu}$ 1713, 1684, 1669, 1639, 1608, 1447, 1367, 1319,

1280, 1219, 1180, 1124, 1105, 1018, 849, 756, 692, 681, 618 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 248 nm (14400), 310 (14600).

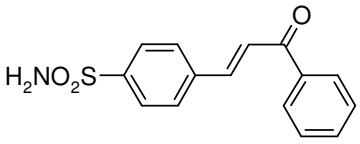
(*E*)/(*Z*)-configurated chalcones were obtained in different ratios from 5:1 up to pure (*E*)-chalcone. Characteristic signals for (*Z*)-chalcone: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.05 (d, *J* = 12.5 Hz, 1 H). Characteristic signals for (*E*)-chalcone: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50 (d, *J* = 15.5 Hz, 1 H), 7.81 (d, *J* = 15.5 Hz, 1 H).

(*E*)-3-(4-Nitrophenyl)-1-phenylprop-2-en-1-one (4f)[142]



According to the GP after chromatography on silica gel (hexane/ethylacetate 3:1) 160 mg (63 %) of **4f** were isolated as a yellow solid. M.p. 163–164 °C (lit. 164 °C).[142] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.49–7.55 (m, 2 H), 7.59–7.64 (m, 1 H), 7.64 (d, *J* = 15.7 Hz, 1 H), 7.78 (d, *J* = 8.7 Hz, 2 H), 7.81 (d, *J* = 15.6 Hz, 1 H), 8.01–8.04 (m, 2 H), 8.26 (d, *J* = 8.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 124.2 (CH), 125.7 (CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 133.3 (CH), 137.5 ($C_{quat.}$), 141.0 ($C_{quat.}$), 141.5 (CH), 148.6 ($C_{quat.}$), 189.6 ($C_{quat.}$). EI MS (70 eV), *m/z* (%): 253 (M^+, 67), 252 (M^+- H, 15), 176 (M^+- C_6H_5, 18), 105 ($C_7H_5O^+$, 61), 77 ($C_6H_5^+$, 100). IR (KBr): $\tilde{\nu}$ 1659, 1609, 1598, 1517, 1340, 1320, 1220, 1016, 983, 845, 784, 746, 705, 687, 658, 622, 539 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 316 nm (25600).

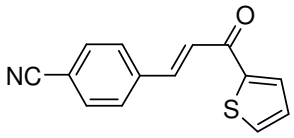
(*E*)-4-(3-Oxo-3-phenyl-propenyl)-benzolsulfonamide (4g)



According to the GP after chromatography on silica gel (hexane/ethylacetate 1:1) and recrystallization from ethanol, 178 mg (62 %) of **4g** were isolated as a yellow solid. M.p. 182 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.68 (s, 2 H), 7.54–7.66 (m, 5 H), 7.81 (d, *J* = 15.7 Hz, 1 H), 7.94–8.04 (m, 4 H), 8.17 (d, *J* = 15.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 125.3 (CH), 127.4 (CH), 128.7 (CH), 129.2 (CH), 129.4 (CH), 129.5 (CH), 129.6 (CH),

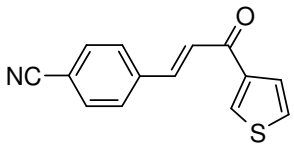
129.8 (CH), 132.7 ($C_{quat.}$), 133.9 (CH), 138.8 ($C_{quat.}$), 139.4 ($C_{quat.}$), 142.8 (CH), 146.2 ($C_{quat.}$), 189.8 ($C_{quat.}$). EI MS (70 eV), *m/z* (%): 287 (M^+), 286 (M^+- H), 271, 210 (M^+ - $C_6H_5^+$), 105 ($C_7H_5O^+$), 77 ($C_6H_5^+$). IR (KBr): $\tilde{\nu}$ 1657, 1605, 1569, 1407, 1337, 1287, 1221, 1182, 1165, 1096, 1017, 979, 827, 778, 724, 698, 646, 576, 544 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 272 nm (11000), 300 (18900). Anal. calcd. for $C_{15}H_{13}NO_3S$ (287.3): C 62.70, H 4.56, N 4.87, S 11.16; found: C 62.39, H 4.62, N 4.86, S 11.03.

(*E*)-4-(3-Oxo-3-(thiophen-2-yl)prop-1-enyl)benzonitrile (4h)[143]



According to the GP after chromatography on silica gel (hexane/ethylacetate 1:1) 208 mg (87 %) of **4h** were isolated as a light brown powder. M.p. 187 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ7.19 (dd, *J* = 3.6 Hz, *J* = 4.8 Hz, 1 H), 7.45 (d, *J* = 15.6 Hz, 1 H), 7.71–7.73 (m, 5 H), 7.78 (d, *J* = 15.3 Hz, 1 H), 7.87 (dd, *J* = 0.9 Hz, *J* = 3.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ113.5 ($C_{quat.}$), 118.3 ($C_{quat.}$), 124.7 (CH), 128.4 (CH), 128.7 (CH), 132.3 (CH), 132.7 (CH), 134.6 (CH), 139.0 ($C_{quat.}$), 141.4 ($C_{quat.}$), 145.0 (CH), 181.3 ($C_{quat.}$). EI MS (70 eV), *m/z* (%): 239 (M^+, 85), 156 (M^+ - C_4H_3S, 40), 111 ($C_5H_3OS^+$, 100). IR (KBr): $\tilde{\nu}$ 3436 cm^{-1}, 2226, 1651, 1597, 1559, 1513, 1413, 1355, 1331, 1302, 1241, 1227, 1179, 1087, 1065, 975, 862, 827, 740, 549. UV/Vis (CH_2Cl_2): λ_{max} (ε) 300 nm (25400), 318 (32900).

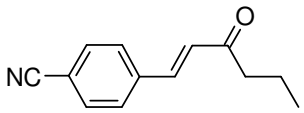
(*E*)-4-(3-Oxo-3-(thiophen-3-yl)prop-1-enyl)benzonitrile (4i)



According to the GP after chromatography on silica gel (hexane/ethylacetate 1:1) 167 mg (70 %) of **4i** were isolated as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38 (dd, *J* = 3.0 Hz, *J* = 6.0 Hz, 1 H), 7.45 (d, *J* = 15.6 Hz, 1 H), 7.66 (dd, *J* = 1.5 Hz, *J* = 5.1 Hz, 1 H), 7.70–7.72 (m, 4 H), 7.74 (d, *J* = 15.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ113.4 ($C_{quat.}$),

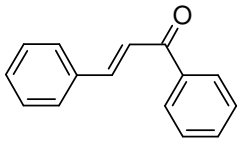
118.3 ($C_{quat.}$), 125.7 (CH), 126.8 (CH), 127.3 (CH), 128.5 (CH), 128.6 (CH), 132.6 (CH), 132.7 (CH), 139.1 ($C_{quat.}$), 141.4 ($C_{quat.}$), 141.3 (CH), 142.6 ($C_{quat.}$), 183.0 ($C_{quat.}$). EI MS (70 eV), *m/z* (%): 239 (M^+, 85), 111 ($C_5H_3OS^+$, 100). HRMS calcd. for $C_{14}H_9NOS$: 239.0405; found 239.0415.

(*E*)-4-(3-oxohex-1-enyl)benzonitrile (4j)



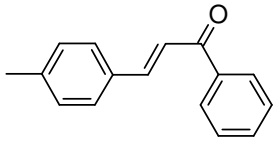
According to the GP after chromatography on silica gel (hexane/ethylacetate 1:1) and recrystallization from ethanol, 123 mg (62 %) of **4j** were isolated as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.94 (t, *J* = 7.2 Hz, 3 H), 1.61–1.76 (m, 2 H), 2.62 (t, *J* = 7.5 Hz, 2 H), 6.74 (d, *J* = 16.2 Hz, 1 H), 7.45 (d, *J* = 16.2 Hz, 1 H), 7.57–7.65 (m, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.7 (CH_3), 17.5 (CH_2), 43.2 (CH_2), 113.3 ($C_{quat.}$), 118.3 ($C_{quat.}$), 128.4 (CH), 128.5 (CH), 131.9 (CH), 132.5 (CH), 138.9 ($C_{quat.}$), 139.5 (CH), 199.7 ($C_{quat.}$). EI MS (70 eV), *m/z* (%): 199 (M^+, 20), 156 (M^+ - C_3H_7, 100), 128 (M^+ - C_3H_7CO, 60), 71 (C_3H_7CO, 11). HRMS calcd. for $C_{13}H_{13}NO$: 199.0997; found 199.1000.

(*E*)-Chalcone (4l)[144]



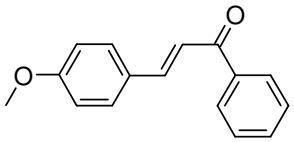
According to the GP after chromatography on silica gel (hexane/ethyl acetate 4:1), 191 mg (92 %) of **4m** were isolated as light yellow crystals. M.p. 58 °C (lit. 57–59 °C).[145] ^{1}H NMR (C_3D_6O, 300 MHz), δ 7.44–7.46 (m, 3 H), 7.53–7.58 (m, 2 H), 7.62–7.66 (m, 2 H), 7.77–7.90 (m, 4 H), 8.14–8.17 (m, 2 H). ^{13}C NMR (C_3D_6O, 100 MHz), δ 122.0 (CH), 128.4 (CH), 128.6 (CH), 128.64 (CH), 128.8 (CH), 128.9 (CH), 132.8 (CH), 135.1 ($C_{quat.}$), 138.2 ($C_{quat.}$), 144.0 (CH), 189.1 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 208.0 (M^+, 70), 131 (M^+ - C_6H_5, 45), 105 (M^+ - C_9H_7O, 28), 77 ($C_6H_5^+$, 100).

(*E*)-1-Phenyl-3-p-tolylprop-2-en-1-one (4m)[146]



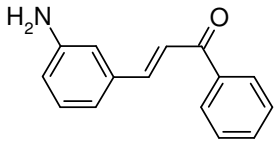
According to the GP after chromatography on silica gel (hexane/ethyl acetate 4:1), 204 mg (92 %) of **4m** were isolated as yellow crystals. M.p. 75 °C (lit. 73–75°C).[147] ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.4 (s, 3 H), 7.22 (d, J = 8.1 Hz, 2 H), 7.47–7.59 (m, 6 H), 7.78 (d, J = 15.3 Hz, 1 H), 8.00–8.03 (m, 2 H). ^{13}C NMR (C_3D_6O, 100 MHz), δ 21.5 (CH_3), 121.2 (CH), 128.5 (CH), 128.6 (CH), 129.0 (CH), 129.7 (CH), 132.2 ($C_{quat.}$), 132.7 (CH), 138.4 ($C_{quat.}$), 141.1 ($C_{quat.}$), 145.0 (CH), 190.7 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 222.1 (M^+, 80), 207.05 (M^+ - CH_3, 100), 179.06 (M^+ - CH_3CO, 20), 77 ($C_6H_5^+$, 25). IR (KBr), $\tilde{\nu}$ 3442 cm^{-1}, 3347, 1659, 1626, 1598, 1582, 1494, 1448, 1342, 1311, 1284, 1216, 1179, 1033, 1019, 983, 772, 708, 689, 584. UV/vis (CH_2Cl_2), λ_{max} (ε) 264 nm (7000), 320 (20500).

(*E*)-3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one (4n)[148]



According to the GP after chromatography on silica gel (hexane/ethyl acetate 4:1), 202 mg (85 %) of **4n** were isolated as yellow crystals. M.p. 75 °C (lit. 76-77 °C).[149] ^{1}H NMR ($CDCl_3$, 300 MHz), δ 3.62 (s, 3 H), 6.70 (d, J = 8.0 Hz, 2 H), 7.05–7.40 (m, 6 H), 7.55 (d, J = 15.5 Hz, 1 H), 7.78 (d, J = 9.0 Hz, 2 H). ^{13}C NMR (C_3D_6O, 100 MHz), δ 55.4 (CH_3), 114.5 (CH), 119.8 (CH), 127.6 ($C_{quat.}$), 128.4 (CH), 128.6 (CH), 130.3 (CH), 132.6 (CH), 138.5 ($C_{quat.}$), 144.7 (CH), 161.7 ($C_{quat.}$), 190.5 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 238.1 (M^+, 100), 223 (M^+ - CH_3, 18), 207 (M^+ - CH_3O, 15), 77 ($C_6H_5^+$, 19). HRMS calcd. for $C_{16}H_{14}O_2$: 238.0993; found 238.0981.

(*E*)-3-(3-Aminophenyl)-1-phenylprop-2-en-1-one (4o)[150]



According to the GP after chromatography on silica gel (hexane/ethyl acetate 1:1), 162 mg (73 %) of **4o** were isolated as yellow crystals. M.p. 163 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ3.8 (s, 2 H), 6.75 (dd, *J* = 8.0 Hz, *J* = 2.0 Hz, 1 H), 6.97 (s, 1 H), 7.06 (d, *J* = 8.3 Hz, 1 H), 7.20–7.29 (m, 1 H), 7.47–7.64 (m, 4 H), 7.72 (d, *J* = 15.8 Hz, 1 H), 8.03 (d, *J* = 7.0 Hz, 2 H). ^{13}C NMR (C_3D_6O, 100 MHz), δ 114.5 (CH), 117.4 (CH), 119.0 (CH), 122.0 (CH), 128.5 (CH), 128.6 (CH), 1129.9 (CH), 132.7 (CH), 135.9 ($C_{quat.}$), 138.3 ($C_{quat.}$), 145.2 (CH), 146.9 ($C_{quat.}$), 190.7 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 223.08 (M^+, 100), 207.06 (M^+ - NH_2, 35), 146.04 (M^+ - C_6H_5, 18), 77 ($C_6H_5^+$, 18). IR (KBr), $\tilde{\nu}$ 3442, 3347, 1659, 1626, 1598, 1582, 1494, 1448, 1342, 1311, 1284, 1216, 1179, 1033, 1019, 983, 772, 708, 689, 584 cm^{-1}. UV/vis (CH_2Cl_2), λ_{max} (ε) 266 nm (16300), 308 (18800).

6.3 General Procedure for the Coupling-Isomerization-Enamine-Addition-Amino-Cyclocondensation Sequence to Pyridines 10

A magnetically stirred solution of 1.0-2.0 mmols of **1**, 1.05-2.8 mmols of propargyl alcohol **2**, 28 mg (0.04 mmols) of $Pd(PPh_3)_2Cl_2$, and 4 mg (0.02 mmols) of CuI in 4 mL of a degassed mixture of triethylamine and THF (3 : 1) or in 4 mL of triethylamine or diethylamine under nitrogen was heated to reflux temperature for 12-16 h. After cooling to room temperature 2.5–7 mmols of enamine **5** in 1 mL of triethylamine were added and the reaction mixture was heated to reflux temperature for 16 h. After cooling to room temperature (4-8 mmols) of ammonium chloride (**9**) and 5 mL of acetic acid were added and the mixture was heated to reflux temperature for the time indicated. After cooling to room temperature, 40 mL of an aqueous solution of K_2CO_3 and 40 mL of ethylacetate were added. The aqueous layer was extracted several times with ethylacetate (4 x 20 mL). The combined organic phases were dried with magnesium sulfate and the solvents were removed *in vacuo* and the residue was chromatographed on silica gel (hexane/ethylacetate or n-heptane/ethylacetate 2:1) and/or

recrystallized from ethanol to give the analytically pure tetrahydronaphthyridines, dihydropyrindines and tetrahydroquinolines **10**.

Table 26 Experimental details for one-pot synthesis of pyridine derivatives **10**

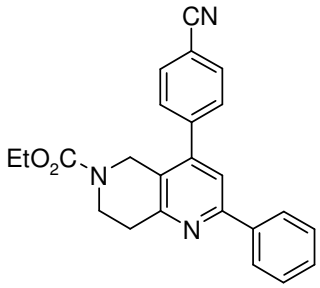
Entry	Aryl halide **1**	Propargyl alcohol **2**	Enamine **5**	Amine **9**	t (h)	Pyridines **10** (Yield, %)
1[a,b]	182 mg (1.00 mmol) of **1a**	139 mg (1.05 mmols) of **2a**	300 mg (1.25 mmols) of **5a**	214 mg (4.00 mmols) of **9**	24	234 mg (61 %) of **10a**
2[a,b]	160 mg (1.00 mmol) of **1b**	139 mg (1.05 mmols) of **2a**	300 mg (1.25 mmols) of **5a**	214 mg (4.00 mmols) of **9**	24	206 mg (57 %) of **10b**
3[a,b]	159 mg (1.00 mmol) of **1c**	139 mg (1.05 mmols) of **2a**	300 mg (1.25 mmols) of **5a**	214 mg (4.00 mmols) of **9**	24	148 mg (41 %) of **10c**
4[a,b]	225 mg (1.00 mmol) of **1d**	139 mg (1.05 mmols) of **2a**	300 mg (1.25 mmols) of **5a**	214 mg (4.00 mmols) of **9**	24	248 mg (58 %) of **10d**
5[b,c]	322 mg (2.03 mmols) of **1b**	278 mg (2.10 mmols) of **2a**	404 mg (2.64 mmols) of **5b**	428 mg (8.00 mmols) of **9**	48	330 mg (59 %) of **10e**
6[b,c]	320 mg (2.03 mmols) of **1c**	278 mg (2.10 mmols) of **2a**	404 mg (2.64 mmols) of **5b**	428 mg (8.00 mmols) of **9**	36	344 mg (62 %) of **10f**
7[c,d]	455 mg (2.02 mmols) of **1d**	278 mg (2.10 mmols) of **2a**	404 mg (2.64 mmols) of **5b**	428 mg (8.00 mmols) of **9**	48	368 mg (54 %) of **10g**
8[b,c]	465 mg (2.03 mmols) of **1e**	278 mg (2.10 mmols) of **2a**	404 mg (2.64 mmols) of **5b**	428 mg (8.00 mmols) of **9**	36	296 mg (42 %) of **10h**

Table 26 *continued*

9[a]	364 mg (2.00 mmols) of **1a**	280 mg (2.10 mmols) of **2a**	460 mg (2.84 mmols) of **5c**	428 mg (8.00 mmols) of **9**	14	432 mg (70 %) of **10i**
10[b,c]	322 mg (2.03 mmols) of **1b**	278 mg (2.10 mmols) of **2a**	427 mg (2.55 mmols) of **5c**	428 mg (8.00 mmols) of **9**	48	290 mg (50 %) of **10j**
11[c,d]	320 mg (2.03 mmols) of **1c**	278 mg (2.10 mmols) of **2a**	427 mg (2.55 mmols) of **5c**	428 mg (8.00 mmols) of **9**	48	372 mg (64 %) of **10k**
12[a,b]	182 mg (1.00 mmol) of **1a**	139 mg (1.05 mmols) of **2a**	275 mg (1.25 mmols) of **5d**	214 mg (4.00 mmols) of **9**	24	177 mg (54 %) of **10l**
13[a,b]	159 mg (0.87 mmols) of **1a**	139 mg (1.05 mmols) of **2a**	245 mg (1.25 mmols) of **5e**	214 mg (4.00 mmols) of **9**	24	136 mg (46 %) of **10m**
14[b,c]	161 mg (1.01 mmols) of **1b**	139 mg (1.05 mmols) of **2a**	427 mg (2.26 mmols) of **5f**	214 mg (4.00 mmols) of **9**	48	211 mg (68 %) of **10n**
15[a,b]	160 mg (1.00 mmol) of **1b**	139 mg (1.05 mmols) of **2a**	275 mg (1.25 mmols) of **5d**	214 mg (4.00 mmols) of **10a**	24	132 mg (39 %) of **10o**

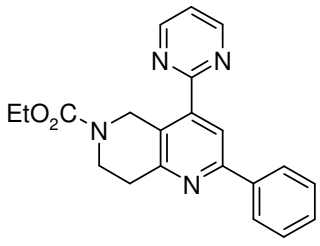
[a]Reaction time of the CIR 16 h. [b]In NEt_3. [c]Reaction time of the CIR 12 h. [d]In $HNEt_2$.

4-(4-Cyano-phenyl)-2-phenyl-7,8-dihydro-5H-[1,6]naphthyridine-6-carboxylic acid ethyl ester (10a)



According to the GP after work up, chromatography on silica gel (hexane/ethyl acetate, 4:1) and recrystallization from ethanol, 234 mg (61 %) of **10a** were isolated as light yellow crystals. M.p. 189 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.20–1.31 (m, 3 H), 3.19 (t, J = 6.0 Hz, 2 H), 3.83 (t, J = 6.1 Hz, 2 H), 4.10 (q, J = 7.1 Hz, 2 H), 4.48 (s, 2 H), 7.38–7.49 (m, 6 H), 7.77 (d, J = 8.2 Hz, 2 H), 7.96 (dd, J = 1.5, 8.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 14.7 (CH_3), 32.6 (CH_2), 41.4 (CH_2), 43.6 (CH_2), 61.7 (CH_2), 112.5 ($C_{quat.}$), 118.3 ($C_{quat.}$), 119.0 (CH), 126.9 (CH), 128.8 (CH), 129.2 (CH), 129.2 (CH), 132.6 (CH), 138.6 ($C_{quat.}$), 142.8 ($C_{quat.}$), 155.5 ($C_{quat.}$), 155.7 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 383 (M^+, 18), 354 (M^+ - CH_2CH_3, 100), 310 (M^+ - $CO_2CH_2CH_3$, 55). IR (KBr), $\tilde{\nu}$ 2984 cm^{-1}, 2225, 1698, 1591, 1545, 1482, 1468, 1418, 1386, 1329, 1270, 1240, 1190, 1135, 1103, 1024, 846, 781, 697. UV/vis (CH_2Cl_2), λ_{max} (ε) 254 nm (47900), 300 (12900). Anal. calcd. for $C_{22}H_{14}N_2S$ (383.4): C 75.18, H 5.52, N 10.96; found C 74.91, H 5.53, N 10.83.

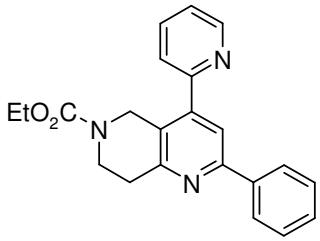
2-Phenyl-4-pyrimidin-2-yl-7,8-dihydro-5H-[1,6]naphthyridine-6-carboxylic acid ethyl ester (10b)



According to the GP after work up, chromatography on silica gel (hexane/ethyl acetate, 4:1) and recrystallization from ethanol, 206 mg (57 %) of **10b** were isolated as yellow crystals.

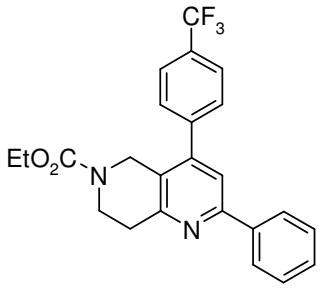
M.p. 163 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.18–1.23 (m, 3 H), 3.13 (t, J = 6.0 Hz, 2 H), 3.78 (t, J = 6.1 Hz, 2 H), 4.05 (q, J = 7.1 Hz, 2 H), 5.00 (s, 2 H), 7.23 (t, J = 4.9 Hz, 1 H), 7.29–7.41 (m, 3 H), 7.73 (d, J = 8.1 Hz, 2 H), 7.96 (dt, J = 1.5, 6.9 Hz, 2 H), 8.16 (s, 1 H), 8.80 (d, J = 4.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 14.7 (CH_3), 33.0 (CH_2), 41.1 (CH_2), 44.6 (CH_2), 61.4 (CH_2), 119.4 (CH_2), 119.8 (CH), 125.7 (CH), 126.9 (CH), 128.6 (CH), 128.8 (CH), 138.9 ($C_{quat.}$), 155.5 ($C_{quat.}$), 155.5 ($C_{quat.}$), 157.1 (CH), 164.7 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 360 (M^+, 92), 287 (M^+ - $CO_2CH_2CH_3$, 100), 260 (M^+, 58). IR (KBr), $\tilde{\nu}$ 2984 cm^{-1}, 2939, 1685, 1589, 1542, 1468, 1437, 1415, 1385, 1306, 1287, 1274, 1169, 1105, 818, 782, 739, 704. UV/vis (CH_2Cl_2), λ_{max} (ε) 250 nm (30900), 288 (6000), 312 (8100). Anal. calcd. for $C_{21}H_{20}N_4O_2$ (360.4): C 69.98, H 5.59, N 15.55; found C 69.52, H 5.56, N 15.22.

2-Phenyl-4-pyridin-2-yl-7,8-dihydro-5H-[1,6]naphthyridine-6-carboxylic acid ethyl ester (10c)



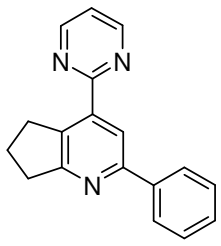
According to the GP after work up, chromatography on silica gel (hexane/ethyl acetate, 4:1), 148 mg (41 %) of **10c** were isolated as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.20–1.26 (m, 3 H), 3.13 (t, J = 6.0 Hz, 2 H), 3.85 (t, J = 6.1 Hz, 2 H), 4.12 (q, J = 7.0 Hz, 2 H), 4.82 (s, 2 H), 7.42–7.51 (m, 4 H), 7.76 (dd, J = 1.0, 8.0 Hz, 1 H), 7.85 (s, 1 H), 7.97 (dt, J = 1.8, 8.0 Hz, 1 H), 8.16–8.20 (m, 2 H), 8.74–8.76 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 14.9 (CH_3), 33.4 (CH_2), 42.0 (CH_2), 44.7 (CH_2), 61.7 (CH_2), 119.2 (CH_2), 124.1 (CH), 124.9 (CH), 127.5 (CH), 129.4 (CH), 129.7 (CH), 138.0 (CH), 139.8 ($C_{quat.}$), 147.5 ($C_{quat.}$), 151.4 (CH), 156.3 ($C_{quat.}$), 157.8 ($C_{quat.}$). IR (KBr), $\tilde{\nu}$ 2980 cm^{-1}, 1696, 1583, 1547, 1430, 1384, 1332, 1271, 1239, 1203, 1172, 1144, 1107, 1048, 1024, 794, 774, 748, 696. UV/vis (CH_2Cl_2), λ_{max} (ε) 254 nm (19100), 300 (9100), 366 (900). HRMS calcd. for $C_{22}H_{21}N_3O_2$: 359.1634; found 359.1645.

2-Phenyl-4-(4-trifluoromethyl-phenyl)-7,8-dihydro-5H-[1,6]naphthyridine-6-carboxylic acid ethyl ester (10d)



According to the GP after work up, chromatography on silica gel (hexane/ethyl acetate, 4:1) and recrystallization from ethanol, 248 mg (58 %) of **10d** were isolated as yellow crystals. M.p. 126 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.22–1.25 (m, 3 H), 3.19 (t, J = 6.1 Hz, 2 H), 3.84 (t, J = 6.1 Hz, 2 H), 4.11 (q, J = 7.1 Hz, 2 H), 4.51 (s, 2 H), 7.38–7.49 (m, 6 H), 7.73 (d, J = 8.1 Hz, 2 H), 7.96–7.99 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 14.7 (CH_3), 32.6 (CH_2), 41.4 (CH_2), 43.6 (CH_2), 61.6 (CH_2), 119.3 ($CH_.$), 119.0 (CH), 125.7 (CH), 125.8 (CH), 125.8 (CH), 126.9 (CH), 128.7 (CH), 130.4 (CH), 130.9 (CH), 138.8 ($C_{quat.}$), 141.7 ($C_{quat.}$), 155.5 ($C_{quat.}$), 155.5 ($C_{quat.}$), 155.7 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 426 (M^+, 10), 397 (M^+ - CH_2CH_3, 100), 353 (M^+ - $CO_2CH_2CH_3$, 30). IR (KBr), $\tilde{\nu}$ 2984 cm^{-1}, 1698, 1592, 1548, 1469, 1431, 1387, 1326, 1284, 1270, 1243, 1198, 1169, 1129, 1108, 1065, 1019, 847, 778, 696. UV/vis (CH_2Cl_2), λ_{max} (ε) 250 nm (22400), 288 (10000), 298 (9500). Anal. calcd. for $C_{24}H_{21}N_2O_2$ (426.4): C 67.60, H 4.96, N 6.57; found C 67.30, H 5.19, N 6.81.

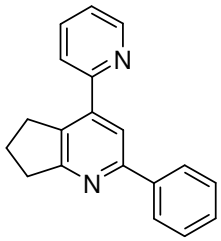
2-Phenyl-4-pyrimidin-2-yl-6,7-dihydro-5H-[1]pyrindine (10e)



According to the GP after chromatography on silica gel (hexane/ethylacetate, 4:1) and recrystallization from ethanol 330 mg (59 %) of **10e** were isolated as light brown crystals. M.p. 120 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.09-2.20 (m, 2 H), 3.11 (t, J = 7.8 Hz, 2 H),

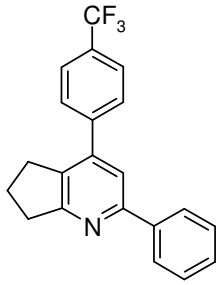
3.38 (t, J = 7.5 Hz, 2 H), 7.16 (t, J = 4.8 Hz, 1 H), 7.25–7.47 (m, 3 H), 8.02–8.06 (m, 2 H), 8.37 (s, 1 H), 8.79 (d, J = 4.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 22.9 (CH_2), 32.0 (CH_2), 34.1 (CH_2), 117.6 (CH), 119.3 (CH), 126.9 (CH), 127.1 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 133.9 ($C_{quat.}$), 139.5 ($C_{quat.}$), 141.5 ($C_{quat.}$), 156.1 ($C_{quat.}$), 156.7 (CH), 156.8 (CH), 164.4 ($C_{quat.}$), 167.6 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 273 (M^+, 100), 245 (M^+ - C_2H_4, 5), 194 (M^+ - C_5H_5N 8). IR (KBr), $\tilde{\nu}$ = 3063 cm^{-1}, 3040, 2961, 1592, 1569, 1548, 1457, 1424, 1375, 1261, 1232, 1186, 1176, 1075, 818, 773, 696, 628. UV/vis (CH_2Cl_2), λ_{max} (ε) 250 nm (30900), 290 (5100), 342 (6600). Anal. calcd. for $C_{18}H_{15}N_3$ (273.3): C 79.10, H 5.53, N 15.37; found C 78.66, H 5.53, N 14.55.

2-Phenyl-4-pyridin-2-yl-6,7-dihydro-5H-[1]pyrindine (10f)



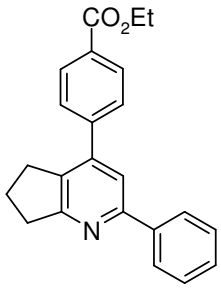
According to the GP after chromatography on silica gel (hexane/ethylacetate, 4:1) and recrystallization from ethanol 344 mg (62 %) of **10f** were isolated as light brown crystals. M.p. 93 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.06–2.17 (m, 2 H), 3.10–3.17 (m, 4 H), 7.22–7.44 (m, 4 H), 7.45–7.69 (m, 1 H), 7.70 (dt, J = 1.8, 7.7 Hz, 1 H), 7.87 (s, 1 H), 8.00–8.03 (m, 2 H), 8.70–8.72 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 23.2 (CH_2), 30.9 (CH_2), 34.3 (CH_2), 117.3(CH), 122.7 (CH), 122.8 (CH), 126.8 (CH), 128.3 (CH), 128.4 (CH), 133.2 (C_{quat}), 136.3 (CH), 139.6 (C_{quat}), 143.8 (C_{quat}), 149.5 (CH), 156.24 (C_{quat}), 156.28 (C_{quat}), 167.0 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 272.1 (M^+, 100), 217.1 (M^+ - C_3H_6N 10), 167.1 (M^+ - C_5H_6N 12). IR (KBr), $\tilde{\nu}$ 3060 cm^{-1}, 2957, 2927, 1587, 1577, 1556, 1476, 1458, 1434, 1423, 1376, 1231, 992, 879, 793, 778, 748, 733, 696. UV/vis (CH_2Cl_2), λ_{max} (ε) 248 nm (24000), 266 (21900), 310 (8300). Anal. calcd. for $C_{19}H_{16}N_2$ (272.4): C 83.79, H 5.90, N 10.29; found C 83.31, H 6.10, N 10.06.

2-Phenyl-4-(4-trifluoromethyl-phenyl)-6,7-dihydro-5H-[1]pyrindine (10g)



According to the GP after chromatography on silica gel (hexane/ethylacetate, 4:1) and recrystallization from ethanol, 368 mg (54 %) of **10g** were isolated as light-brown crystals. M.p. 115–118 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.12–2.22 (m, 2 H), 3.01 (t, J = 7.3 Hz, 2 H), 3.17 (t, J = 7.6 Hz, 2 H), 7.37–7.5 (m, 3 H), 7.50 (s, 1 H), 7.62–7.76 (m, 4 H), 7.97–7.99 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 23.5 (CH_2), 30.4 (CH_2), 34.6 (CH_2), 118.0 (CH), 122.2 (CH), 125.6 (CH), 125.5 (CH), 125.6 (CH), 125.8 ($C_{quat.}$), 133.2 ($C_{quat.}$), 139.3 ($C_{quat.}$), 142.5 ($C_{quat.}$), 144.7 ($C_{quat.}$), 156.6 ($C_{quat.}$), 166.9 ($C_{quat.}$). MS (70eV, EI): *m/z* (%): 339 (M^+, 65), 338 (M^+ - H, 100), 320 (M^+ - F, 7), 270 (M^+, - F, - HF, 7). IR (KBr), $\tilde{\nu}$ = 3058 cm^{-1}, 2993,2974, 2954, 2885, 2836, 1619, 1592, 1576, 1560, 1438, 1425, 1412, 1373, 1324, 1160, 1134, 1126, 1109, 1065, 1016, 846, 776, 695. UV/vis (CH_2Cl_2), λ_{max} (ε) 254 nm (30900), 306 (8700). Anal. calcd. for $C_{21}H_{16}F_3N$ (339.4): C 74.33, H 4.75, N 4.13; found C 74.08, H 4.45, N 4.25.

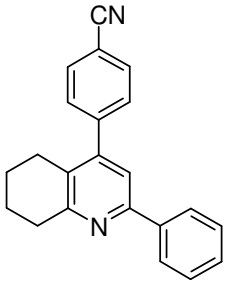
4-(2-Phenyl-6,7-dihydro-5H-[1]pyrindin-4-yl)-benzoic acid ethyl ester (10h)



According to the GP after chromatography on silica gel (hexane/ethylacetate, 4:1) and recrystallization from ethanol 296 mg (42 %) of **10h** were isolated as light yellow crystals. M.p. 95–96 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.42 (t, J = 7.1 Hz, 3 H), 2.15 (m, 2 H), 3.03

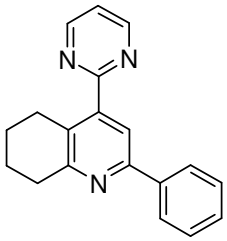
(t, *J* = 7.3 Hz, 2 H), 3.16 (t, *J* = 7.6 Hz, 2 H) 4.4 (q, *J* = 7.1 Hz, 2 H), 7.32–7.48 (m, 3 H), 7.51 (s, 1 H), 7.56 (dt, *J* = 1.8, 8.6 Hz, 2 H), 7.96–7.98 (m, 2 H), 8.13 (d, *J* = 8.3 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 14.3 (CH_3), 23.5 (CH_2), 30.5 (CH_2), 34.7 (CH_2), 61.1 (CH_2), 117.9 (CH), 127.0 (CH), 128.1 (CH), 128.6 (CH), 128.7 (CH), 129.8 (CH), 130.2 ($C_{quat.}$), 133.1 ($C_{quat.}$), 139.5 ($C_{quat.}$), 143.3 ($C_{quat.}$), 144.9 ($C_{quat.}$), 156.5 ($C_{quat.}$), 166.2 ($C_{quat.}$), 166.8 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 343 (M^+, 100), 342 (M^+ - H, 70), 314 (M^+ - C_2H_5, 38). IR (KBr), $\tilde{\nu}$ 2975 cm^{-1}, 1715, 1610, 1591, 1577, 1554, 1458, 1440, 1424, 1367, 1311, 1274, 1182, 1106, 1021, 859, 776, 708, 698. UV/vis (CH_2Cl_2), λ_{max} (ε) 262 nm (34700), 308 (7800). Anal. calcd. for $C_{23}H_{21}NO_2$ (343.4): C 80.44, H 6.16, N 4.08; found C 80.11, H 6.19, N 4.08.

4-(2-Phenyl-5,6,7,8-tetrahydroquinolin-4-yl)-benzonitrile (10i)



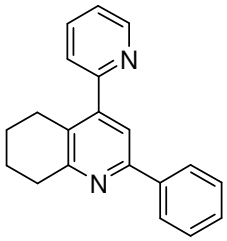
According to the GP after chromatography on silica gel (cyclohexane/ethylacetate 1:1) and recrystallization from ethanol 432 mg (70 %) of analytically pure **10i** were isolated as colorless crystals. M.p. 194–195 °C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.77 (m, *J* = 7.0 Hz, 2 H), 1.95 (m, *J* = 6.0 Hz, 2 H), 2.59 (t, *J* = 6.4 Hz, 2 H), 3.10 (t, *J* = 6.6 Hz, 2 H), 7.26 (s, 1 H), 7.34–7.50 (m, 5 H), 7.75 (dd, *J* = 8.6 Hz, *J* = 2.0 Hz, 2 H), 7.96 (dd, *J* = 8.0 Hz, *J* = 1.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 22.8 (CH_2), 22.9 (CH_2), 27.1 (CH_2), 33.2 (CH_2), 111.7 ($C_{quat.}$), 118.3 ($CH_{.}$), 118.5 ($C_{quat.}$), 126.8 ($CH_{.}$), 127.8 ($C_{quat.}$), 128.7 (CH), 128.7 (CH), 129.4 (CH), 132.2 ($CH_{.}$), 139.2 ($C_{quat.}$), 144.5 ($C_{quat.}$), 148.2 ($C_{quat.}$), 154.6 ($C_{quat.}$), 158.1 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 310 (M^+, 92), 309 (M^+ - H, 100). IR (KBr), $\tilde{\nu}$ 2934 cm^{-1}, 2224 (C≡N), 1590, 1537, 1442, 1433, 1381, 901, 843, 774, 691, 590. Anal. calcd. for $C_{22}H_{18}N_2$ (310.4): C 85.13, H 5.85, N 9.02; found C 84.80, H 5.87, N 8.94.

2-Phenyl-4-pyrimidin-2-yl-5,6,7,8-tetrahydro-quinoline (10j)



According to the GP after chromatography on silica gel (hexane/ethylacetate, 4:1) and recrystallization from ethanol 290 mg (50 %) of **10j** were isolated as light brown crystals. M.p. 120 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.33–1.82 (m, 2 H), 1.90–2.16 (m, 2 H), 2.94 (t, J = 6.4 Hz, 2 H), 3.11 (t, J =6.4 Hz, 2 H), 7.26 (t, J = 4.8 Hz, 1 H), 7.32-7.46 (m, 3 H), 7.84 (s, 1 H), 7.98–8.02 (m, 2 H), 8.85 (d, J 4.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 22.6 (CH_2), 22.7 (CH_2), 26.7 (CH_2), 33.3 (CH_2), 118.8 (CH), 119.3 (CH), 126.7 (CH), 128.3 (CH), 128.9 (CH), 129.1 ($C_{quat.}$), 139.3 ($C_{quat.}$), 145.8 ($C_{quat.}$), 154.3 ($C_{quat.}$), 156.8 (CH), 158.2 ($C_{quat.}$), 166.1 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 287 (M^+, 100), 272 (M^+ - CH_3, 32), 259 (M^+ - C_2H_4, 12). IR (KBr), $\tilde{\nu}$ 3050 cm^{-1}, 2939, 2915, 2878, 2857, 1592, 1564, 1543, 1456, 1440, 1419, 1378, 1228, 845, 831, 771, 736, 694, 633. UV/vis (CH_2Cl_2), λ_{max} (ε) 250 nm (26300), 286 (7100), 308 (7600). Anal. calcd. for $C_{19}H_{17}N_3$ (287.4): C 79.41, H 5.96, N 14.62; found C 79.15, H 5.93, N 14.49.

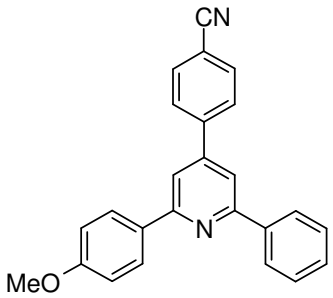
2-Phenyl-4-pyridin-2-yl-5,6,7,8-tetrahydro-quinoline (10k)



According to the GP after chromatography on silica gel (hexane/ethylacetate, 4:1) and recrystallization from ethanol 372 mg (64 %) of **10k** were isolated as red-brown crystals. M.p. 95–96 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.73–1.81 (m, 2 H), 1.90–2.03 (m, 2 H), 2.74 (t, J = 6.36 Hz, 2 H), 3.07 (t, J = 6.45 Hz, 2 H), 7.29–7.46 (m, 5 H), 7.52 (s, 1 H), 7.76 (dt, J =

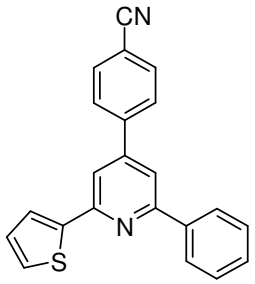
1.8, 7.7 Hz, 1 H), 7.95–7.99 (m, 2 H), 8.71–8.73 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ22.7 (CH_2), 22.8 (CH_2), 22.6 (CH_2), 33.2 (CH_2), 118.5 (CH), 122.4 (CH), 123.6 (CH), 126.7 (CH), 128.3 (CH), 128.4 (CH), 136.6 (CH), 139.4 ($C_{quat.}$), 148.2 ($C_{quat.}$), 149.2 (CH), 154.3 ($C_{quat.}$), 157.9 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 287 (M^+ + 1, 28), 286 (M^+ - C_2H_4, 68), 77 ($C_6H_5^+$, 100). IR (KBr), $\tilde{\nu}$ 2936 cm^{-1}, 2858, 1630, 1583, 1567, 1544, 1473, 1455, 1444, 1429, 1383, 793, 776, 753, 695, 657, 602, 584, 549. UV/vis (CH_2Cl_2), λ_{max} (ε) 240 nm (19500), 258 (21400), 300 (9300). Anal. calcd. for $C_{20}H_{18}N_2$ (286.4): C 83.88, H 6.34, N 9.78; found C 83.76, H 6.30, N 9.80.

4-[2-(4-Methoxy-phenyl)-6-phenyl-pyridin-4-yl]-benzonitrile (10l)



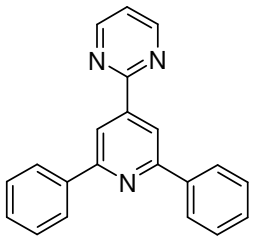
According to the GP after chromatography on silica gel (hexane/ethyl acetate, 4:1) and recrystallization from ethanol 177 mg (54 %) of **10l** were isolated as colorless crystals. M.p. 134–135 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 3.88 (s, 3 H), 7.02 (d, J = 8.9 Hz, 2 H), 7.45–7.54 (m, 3 H), 7.75–7.79 (m, 6 H), 8.13–8.19 (m, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ55.4 (OCH_3), 112.5 ($C_{quat.}$), 114.1 (CH), 116.0 (CH), 116.1 (CH), 118.5 ($C_{quat.}$), 127.0 (CH), 127.9 (CH), 128.4 (CH), 128.7 (CH), 129.3 (CH), 131.6 ($C_{quat.}$), 132.8 (CH), 139.1 ($C_{quat.}$), 143.6 ($C_{quat.}$), 148.0 ($C_{quat.}$), 157.4 ($C_{quat.}$), 157.7 ($C_{quat.}$), 160.8 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 362 (M^+, 100), 347 (M^+ - CH_3, 20). IR (KBr), $\tilde{\nu}$ 2922 cm^{-1}, 2227, 1599, 1580, 1566, 1542, 1513, 1432, 1417, 1391, 1249, 1178, 1209, 831, 776, 694, 586, 547, 516. UV/vis (CH_2Cl_2), λ_{max} (ε) 250 nm (36300), 282 (28200), 332 (5900). Anal. calcd. for $C_{25}H_{18}N_2O$ (326.4): C 82.85, H 5.01, N 7.73; found C 82.61, H 5.01, N 7.71.

4-(2-Phenyl-6-thiophen-2-yl-pyridin-4-yl)-benzonitrile (10m)



According to the GP after chromatography on silica gel (hexane/ethyl acetate, 4:1) and recrystallization from ethanol 136 mg (46 %) of **10m** were isolated as yellow crystals. M.p. 192 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.14–7.16 (m, 1 H), 7.33–7.54 (m, 4 H), 7.71–7.74 (m, 3 H), 7.80–7.81 (m, 4 H), 8.14–8.17 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 112.6 ($C_{quat.}$), 114.8 (CH), 116.3 (CH), 118.2 ($C_{quat.}$), 126.8 (CH), 127.7 (CH), 127.9 (CH), 127.9 (CH), 128.6 (CH), 129.3 (CH), 132.7 (CH), 138.3 ($C_{quat.}$), 143.1 ($C_{quat.}$), 144.7 ($C_{quat.}$), 148.0 ($C_{quat.}$), 152.9 ($C_{quat.}$), 157.5 ($C_{quat.}$). MS (70eV, EI): *m/z* (%): 338 (M^+, 100), 305 (M^+ - HS, 8). IR (KBr), $\tilde{\nu}$ 2227 cm^{-1}, 1597, 1581, 1569, 1544, 1508, 1497, 1437, 1419, 1389, 1236, 832, 775, 732, 695, 634. UV/vis (CH_2Cl_2), λ_{max} (ε) 268 nm (55000), 290 (31600), 336 (11000). Anal. calcd. for $C_{22}H_{14}N_2S$ (338.4): C 78.08, H 4.17, N 8.28; found C 77.66, H 4.23, N 8.28.

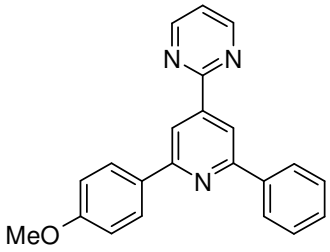
2-(2,6-Diphenyl-pyridin-4-yl)-pyrimidine (10n)



According to the GP after chromatography on silica gel (hexane/ethylacetate, 1:1) and recrystallization from ethanol, 211 mg (68 %) of **10n** were isolated as light-brown crystals. M.p. 224 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.32 (t, J = 4.8 Hz, 1 H), 7.42–7.56 (m, 6 H), 8.29–8.32 (m, 4 H), 8.75 (s, 2H), 8.90 (d, J = 4.89, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 116.9 (CH), 120.3 (CH), 127.0 (CH), 128.5 (CH), 128.9 (CH), 129.1 (CH), 139.2 ($C_{quat.}$), 146.2

($C_{quat.}$), 157.2 (CH), 157.5 ($C_{quat.}$), 163.0 ($C_{quat.}$). MS (70eV, EI): *m/z* (%): 309 (M^+, 68), 77 ($C_6H_5^+$, 100). IR (KBr), $\tilde{\nu}$ 3038 cm^{-1}, 1602, 1580, 1565, 1549, 1462, 1449, 1424, 1399, 1233, 896, 811, 772, 732, 691, 669, 640, 629, 618. UV/vis (CH_2Cl_2), λ_{max} (ε) 248 nm (79400), 270 (38000), 332 (11200). Anal. calcd. for $C_{21}H_{15}N_3$ (309.4): C 81.53, H 4.89, N 13.58; found C 81.30, H 4.84, N 13.23.

2-[2-(4-Methoxy-phenyl)-6-phenyl-pyridin-4-yl]-pyrimidine (10o)



According to the GP after work up, chromatography on silica gel (hexane/ethyl acetate, 1:1) and recrystallization from ethanol, 132 mg (39 %) of **10o** were isolated as yellow crystals. M.p. 144 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 3.87 (s, 3 H), 7.02 (dt, *J* = 1.5, 5.3 Hz, 2H), 7.29 (t, *J* = 2.9 Hz, 1 H), 7.43–7.52 (m, 3 H), 8.24–8.28 (m, 4 H), 8.52 (s, 1 H), 8.53 (s, 1 H), 8.87 (d, *J* = 2.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 55.3 (OCH_3), 114.0 (CH), 116.3 (CH), 116.3 (CH), 120.5 (CH), 127.1 (CH), 128.4 (CH), 128.6 (CH), 129.0 (CH), 132.0 ($C_{quat.}$), 139.5 ($C_{quat.}$), 146.3 ($C_{quat.}$), 157.3 ($C_{quat.}$), 157.4 ($C_{quat.}$), 157.4 ($C_{quat.}$), 160.6 ($C_{quat.}$), 163.2 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 339 (M^+, 100), 324 (M^+ - CH_3, 20), 296 (M^+, 18). IR (KBr), $\tilde{\nu}$ 3043 cm^{-1}, 2831, 1606, 1580, 1566, 1547, 1515, 1457, 1434, 1419, 1400, 1305, 1251, 1232, 1176, 1031, 835, 807, 773, 696, 640. UV/vis (CH_2Cl_2), λ_{max} (ε) 282 (20900), 344 (8300). Anal. calcd. for $C_{20}H_{17}N_3O$ (339.4): C 77.88, H 5.01, N 12.39; found C 77.66, H 5.08, N 12.27.

6.4 General Procedure for the One-Pot Coupling-Isomerization-Enamino Ester-Cyclocondensation Synthesis of Dihydropyrines 12 and Pyridines 13

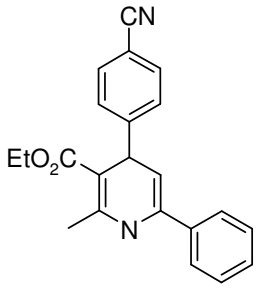
A magnetically stirred solution of 1.0 mmol of halogen compound **1**, 1.05 mmols of propargyl alcohol **2a**, 0.02 mmols of $Pd(PPh_3)Cl_2$, and 0.01 mmols of CuI in 4 mL of degassed triethylamine or diethylamine under nitrogen was heated to reflux temperature for 12 h (for experimental details see Table 7). After cooling at room temperature solution of 2.0 mmols of ethyl 3-amino crotonate (**11**) in 1 mL of triethylamine or diethylamine and 2 mL of acetic acid were added and the reaction mixture was heated to reflux temperature for 24 h. After cooling to room temperature 40 mL of ethyl acetate and 40 mL of water were added and stirring was continued for 5 to 10 min. The aqueous layer was extracted with ethyl acetate (4 × 15 mL) and the combined organic phase was dried with magnesium sulfate. After filtration the solvents were removed *in vacuo* and the residue was chromatographed on silica gel (hexane/ethyl acetate 4:1 or 1:1) and recrystallized from ethanol or pentane/chloroform (1:1) to give the analytically pure dihydropyridine (**12**) and pyridine derivatives (**13**).

Table 27 Experimental Details for the One-Pot Three-Component Synthesis of Dihydropyridines **12** and Pyridines **13.**

Entry	Aryl halide **1**	1-Phenyl propargyl alcohol (**2a**)	Ethyl 3-aminocrotonate (**11**)	Dihydropyridine **12** / Pyridines **13** (Yield)
1[a]	182 mg (1.00 mmol) of **1a**	139 mg (1.05 mmols)	263 mg (2.00 mmols)	155 mg (45 %) of **12a**
2[b]	561 mg (2.00 mmols) of **1f**	278 mg (2.10 mmols)	526 mg (4.00 mmols)	268 mg (37 %) of **12b**
3[a]	182 mg (1.00 mmol) of **1a**	139 mg (1.05 mmols)	263 mg (2.00 mmols)	137 mg (40 %) of **13a**
4[a]	161 mg (1.00 mmol) of **1e**	139 mg (1.05 mmols)	263 mg (2.00 mmols)	154 mg (50 %) of **13b**
5[c]	140 mg (1.00 mmol) of **1b**	139 mg (1.05 mmols)	263 mg (2.00 mmols)	85 mg (26 %) of **13c**
6[b]	320 mg (2.00 mmol) of **1d**	139 mg (1.05 mmols)	263 mg (2.00 mmols)	83 mg (26 %) of **13d**

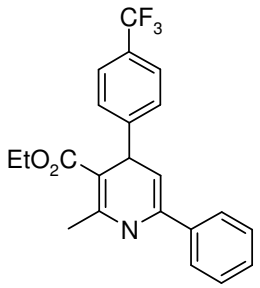
[a]In NEt_3. [b]In $HNEt_2$. [c]In NEt_3/THF (1:1).

Ethyl 4-(4-cyanophenyl)-2-methyl-6-phenyl-1,4-dihydropyridine-3-carboxylate (12a)



According to the GP after chromatography on silica gel (hexane/ethylacetate, 4:1) 155 mg (45 %) of **12a** were isolated as yellow crystals. ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.01 (t, J = 7 Hz, 3 H), 2.34 (s, 3 H), 3.89–3.98 (m, 2 H), 4.66 (d, J = 5.5 Hz, 1 H), 5.00 (dd, J = 2, 5.3 Hz, 1 H), 5.78 (s, 1 H), 7.18–7.35 (m, 7 H), 7.45–7.48 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 14.5 (CH_3), 19.7 (CH_3), 41.6 (CH), 59.5 (CH_2), 97.5 ($C_{quat.}$), 103.9 (CH), 110.1 ($C_{quat.}$), 119.7 ($C_{quat.}$), 126.3 (CH), 127.1 (CH), 129.2 (CH), 132.9 (CH), 133.2 (CH), 136.2 ($C_{quat.}$), 136.6 ($C_{quat.}$), 150.2 ($C_{quat.}$), 151.3 ($C_{quat.}$), 155.5 ($C_{quat.}$), 168.3 ($C_{quat.}$). MS (70eV, EI): *m/z* (%): 344.2 (M^+, 15), 315.1 (M^+ - C_2H_5, 36), 271.2 (M^+ - $CO_2C_2H_5$, 20), 242.2 (M^+ - C_7H_4N, 100).

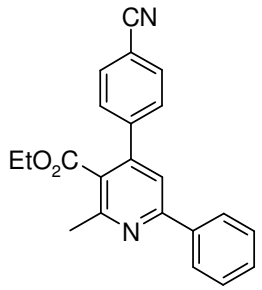
Ethyl 2-methyl-6-phenyl-4-(4-(trifluoromethyl)phenyl)-1,4-dihydropyridine-3-carboxylate (12b)



According to the GP after chromatography on silica gel (hexane/ethylacetate, 5:1) 268 mg (37 %) of **12b** were isolated as yellow crystals. ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.01 (t, J = 7 Hz, 3 H), 2.30 (s, 3 H), 3.86–3.94 (m, 2 H), 4.64 (d, J = 5.25 Hz, 1 H), 5.00 (dd, J = 1.75,

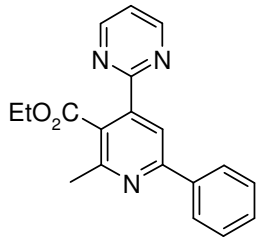
5.25 Hz, 1 H), 5.65 (s, 1 H), 7.20–7.33 (m, 7 H), 7.40 (d, J = 8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 14.1 (CH_3), 20.6 (CH_3), 41.0 (CH), 59.3 (CH_2), 98.4 ($C_{quat.}$), 104.1 (CH), 125.1 (CH), 128.3 (CH), 128.7 (CH), 134.9 ($C_{quat.}$), 147.4 ($C_{quat.}$), 152.7 ($C_{quat.}$), 168.0 ($C_{quat.}$). MS (70eV, EI): *m/z* (%): 387.1 (M^+, 15), 358.1 (M^+ - C_2H_5, 18), 314.1 (M^+ - $CO_2C_2H_5$, 25), 242.1 (M^+ - $C_7H_4F_3$, 100). HRMS calcd. for ($C_{22}H_{20}F_3NO_2$): 387.1446; found 387.1453.

4-(4-Cyano-phenyl)-2-methyl-6-phenyl-nicotinic acid ethyl ester (13a)



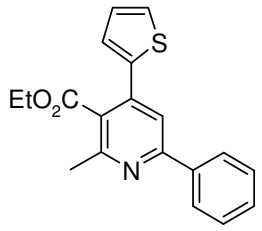
According to the GP after chromatography on silica gel (hexane/ethylacetate, 4:1) and recrystallization from ethanol, 137 mg (40 %) of **13a** were isolated as light-brown crystals. M.p. 131 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.01 (t, J = 7.1 Hz, 3 H), 2.73 (s, 1 H), 4.09 (q, J = 7.2 Hz, 2 H), 7.43–7.53 (m, 6 H), 7.72–7.75 (m, 2 H), 8.00–8.03 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 13.7 (CH_3), 23.2 (CH_3), 61.5 (CH_2), 112.4 ($C_{quat.}$), 117.9 (CH), 118.3 ($C_{quat.}$), 126.1 ($C_{quat.}$), 127.1 (CH), 128.7 (CH), 128.8 (CH), 129.6 (CH), 132.1 (CH), 132.2 (CH), 138.2 ($C_{quat.}$), 143.6 ($C_{quat.}$), 147.1 ($C_{quat.}$), 156.3 ($C_{quat.}$), 157.7 ($C_{quat.}$), 168.1 ($C_{quat.}$). MS (70eV, EI): *m/z* (%): 342 (M^+, 100), 313 (M^+ - C_2H_5, 60), 297 (M^+ - C_2H_5O, 76). IR (KBr), $\tilde{\nu}$ 3060 cm^{-1}, 2993, 2229, 1722, 1588, 1567, 1540, 1500, 1380, 1361, 1280, 1265, 1243, 1184, 1148, 1097, 1078, 850, 772, 695, 587. UV/vis (CH_2Cl_2), λ_{max} (ε) 256 (35500), 298 (12000). Anal. calcd. for $C_{22}H_{18}N_2O_2$ (342.4): C 77.17, H 5.30, N 8.18; found C 76.84, H 5.33, N 8.12.

2-Methyl-6-phenyl-4-pyrimidin-2-yl-nicotinic acid ethyl ester (13b)



According to the GP after chromatography on silica gel (hexane/ethylacetate, 1:1) and recrystallization from ethanol, 154 mg (50 %) of **13b** were isolated as light-brown crystals. M.p. 115–118 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.27–1.35 (m, 3 H), 2.77 (s, 3 H), 4.36 (q, J = 7.2 Hz, 2 H), 7.28 (t, J = 4.9 Hz, 1 H), 7.44–7.53 (m, 3 H), 8.13–8.15 (m, 2 H), 8.49 (s, 1 H), 8.83 (d, J = 4.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 13.9 (CH_3), 22.8 (CH_3), 61.2 (CH_2), 117.3 (CH), 120.2 (CH), 126.5 ($C_{quat.}$), 127.0 (CH), 127.1 (CH), 128.6 (CH), 129.3 (CH), 138.5 ($C_{quat.}$), 143.8 ($C_{quat.}$), 156.1 ($C_{quat.}$), 156.9 (CH), 157.6 ($C_{quat.}$), 162.9($C_{quat.}$), 169.3 ($C_{quat.}$). MS (70eV, EI): *m/z* (%): 319 (M^+, 93), 274 (M^+ - C_2H_5O, 100), 246 (M^+ - $C_3H_5O_2$, 36). IR (KBr), $\tilde{\nu}$ 2975 cm^{-1}, 1715, 1585, 1565, 1550, 1457, 1424, 1386, 1369, 1274, 1175, 1158, 1110, 1075, 1010, 837, 813, 760, 696. UV/vis (CH_2Cl_2), λ_{max} (ε) 250 nm (28200), 314 (10200). Anal. calcd. for $C_{19}H_{17}N_3O_2$ (319.4): C 71.46, H 5.37, N 13.16; found C 71.28, H 5.35, N 13.08.

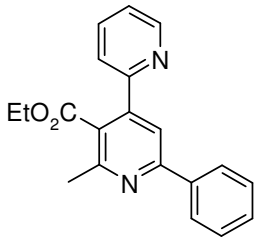
Etyl 2-methyl-6-phenyl-4-(thiazol-2-yl)nicotinate (13c)



According to the GP after chromatography on silica gel (hexane/ethylacetate, 5:1) 85 mg (26 %) of **14c** were isolated as yellow crystals. ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.30 (t, J = 7 Hz, 3 H), 2.90 (s, 3 H), 4.36 (q, J = 7 Hz 2 H), 7.4 (d, J = 3.25 Hz, 1 H), 7.47–7.51 (m, 3 H), 7.88 (s, 1 H), 7.94 (d, J = 3.25 Hz, 1 H), 8.03–8.06 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz),

δ 14.1 (CH_3), 22.9 (CH_3), 62.1 (CH_2), 117.2 (CH), 122.6 (CH), 123.1 (CH), 126.1 ($C_{quat.}$), 127.9 (CH), 129.6 (CH), 130.5 (CH), 138.8 ($C_{quat.}$), 139.9 ($C_{quat.}$), 144.9 (CH), 156.8 ($C_{quat.}$), 158.2 ($C_{quat.}$), 164.4 ($C_{quat.}$), 168.7 ($C_{quat.}$). MS (70eV, EI): *m/z* (%) = 324.0 (M^+, 38), 295.0 (M^+ - C_2H_5, 10), 279.1 (M^+ - C_2H_5O, 36).387.1446.

2'-Methyl-6'-phenyl-1'-4'-dihydro-[2,4']bipyridinyl-3'-carboxilyc acid ethyl ester (13d)



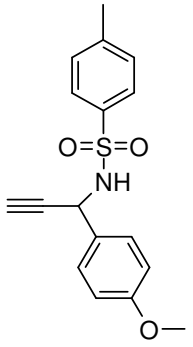
According to the GP after chromatography on silica gel (hexane/ethylacetate, 1:1) and recrystallization from ethanol, 83 mg (26 %) of **13d** were isolated as a brown oil. ^{1}H NMR ($CDCl_3$, 3000 MHz), δ 1.03 (t, *J* = 7 Hz, 3 H), 2.68 (s, 3 H), 4.12 (q, *J* = 7 Hz, 2 H), 7.23–7.28 (m, 1 H), 7.35–7.45 (m, 3 H), 7.57 (d, *J* = 8 Hz, 1 H), 7.70–7.77 (m, 2 H), 7.96-8.00 (m, 2 H), 8.59-8.61 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 13.7 (CH_3), 23.1 (CH_3), 61.2 (CH_2), 117.3 (CH), 122.3 (CH), 122.3 (CH), 123.3 (CH), 127.4 (C_{quat}), 128.7 (CH), 136.8 (CH), 138.7 (C_{quat}), 147.0 (C_{quat}), 149.3 (CH), 156.0 (C_{quat}), 156.5 (C_{quat}), 157.6 (C_{quat}), 169.0 (C_{quat}). IR (KBr), $\tilde{\nu}$ 3060 cm^{-1}, 2980, 2930, 2902, 2860, 1952, 1728, 1585, 1549, 1474, 1434, 1383, 1364, 1344, 1269, 1183, 1153, 1106, 1028, 994, 859, 797, 768, 695. UV/vis (CH_2Cl_2), λ_{max} (ε): 252 nm (19500), 304 (9300). HRMS calcd. for $C_{20}H_{18}N_2O_2$: 318.1368; found 318.1367.

6.5 General Procedure for *N*-[1-(Hetero)aryl-prop-2-ynyl] tosyl Amides 18

To 1.3 equiv. of a 0.5 *M* solution of ethynyl magnesium bromide in THF at 0 °C (ice-water) 1.0 eq. of a solution of the corresponding azomethine **16** in THF (1.25 mmols/mL) was added dropwise within 15 min. After stirring of the suspension for 15 min at 0 °C the reaction mixture was stirred for 1 h at room temperature. After the reaction was complete according to TLC monitoring 120 mL of a saturated aqueous solution of NH_4Cl was added to the reaction mixture and the aqueous phase was extracted three times with diethylether (3×100 mL). The

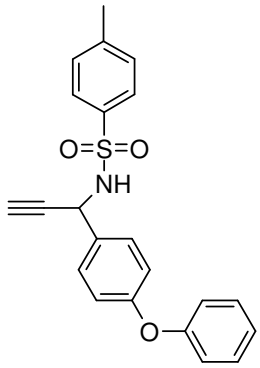
combined organic layers were dried with anhydrous magnesium sulfate and after evaporation sufficiently pure (according to ^{1}H NMR spectra) *N*-[1-(hetero)aryl-prop-2-ynyl] tosyl amide **18** was isolated such that it could be recrystallized from ethanol in case of impurities.

_N_-[1-(4-Methoxyphenyl)-prop-2-ynyl]-4-methyl-benzenesulfonamide (18a)



According to the GP from the reaction of 10.1 g (34.5 mmols) of *N*-(4-methoxybenzylidene)-4-methyl-benzenesulfonamide (**16a**) and 102 ml (52 mmols) of a 0.5 *M* solution of ethynyl magnesium bromide in 45 ml of THF, 7.3 g (89 %) of **18a** were obtained as colorless crystals. M.p. 124.5–125.5 °C. ^{1}H NMR (300 MHz, CDCl3): δ2.29 (d, *J* = 2.3 Hz, 1 H), 2.41 (s, 3 H), 3.76 (s, 3 H), 5.17 (d, *J* = 8.6 Hz, 1 H), 5.23 (dd, *J* = 2.2, 8.6 Hz, 1 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.7 Hz, 2 H), 7.73 (d, *J* = 8.3 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ21.5 (CH_3), 48.4 (CH), 55.2 (CH_3), 74.5 (CH), 80.6 ($C_{quat.}$), 113.9 (CH), 127.4 (CH), 128.4 (CH), 129.1 ($C_{quat.}$), 129.4 (CH), 137.3 ($C_{quat.}$), 143.4 ($C_{quat.}$), 159.6 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 315 (M^+, 2), 159 (M^+ - $C_7H_7SO_2$ - H, 100), 145 (M^+ - $C_7H_7SO_2$ - NH, 45), 91 (C_7H_7, 13).

4-Methyl-N-(1-(4-phenoxyphenyl)prop-2-ynyl)benzenesulfonamide (18b)

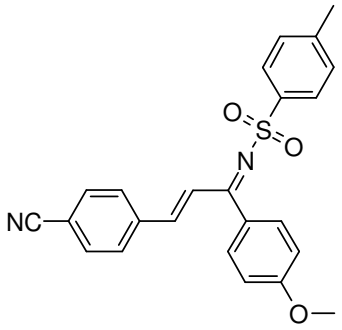


According to the GP from the reaction of 12.1 g (34.5 mmols) of *N*-(4-phenoxybenzylidene)-4-methylbenzenesulfonamide (**16b**) and 102 ml (52 mmols) of a 0.5 *M* solution of ethynyl magnesium bromide in 45 ml of THF, 10.7 g (82 %) of **18b** were obtained as colorless crystals. M.p. 96–97 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.31 (d, J = 0.7 Hz, 1 H), 2.41 (s, 3H, CH_3), 5.27 (s, 2 H, NH, CH), 6.90 (d, J = 8.7 Hz, 2 H), 6.97(dd, J = 8.7 Hz, J = 0.8 Hz, 2 H), 7.11 (t, J = 7.4 Hz, 1 H), 7.26 (d, J = 8.1 Hz, 2 H), 7.31 (dd, J = 8.0, J = 0.8 Hz, 2 H), 7.35–7.40 (m, 2 H), 7.75 (d, J = 8.3 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.49 (CH_3), 48.38 (CH), 74.68 (CH), 80.41 ($C_{quat.}$), 118.57 (CH), 119.06 (CH), 123.57 (CH), 127.38 (CH), 128.69 (CH), 129.43 (CH), 129.76 (CH), 131.61 ($C_{quat.}$), 137.23 ($C_{quat.}$), 143.52 ($C_{quat.}$), 156,63 ($C_{quat.}$), 157.48 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 377 (M^+, 2), 222 (M^+ - $C_7H_7SO_2$, 80), 207 (M^+ - $C_7H_7SO_2$ -NH, 28), 155 ($C_7H_7SO_2$, 7), 91 (C_7H_7, 44).

6.6 General Procedure for the Enimine 19 Synthesis

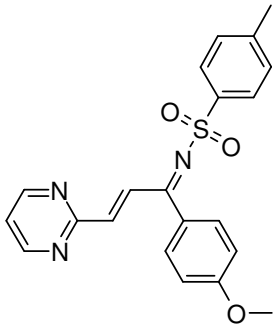
A magnetically stirred solution of 1.0 mmol of (het)arylhalide **1**, 1.05 mmols of propargyl *N*-tosyl amine **18**, 14 mg (0.02 mmols) of $Pd(PPh_3)Cl_2$, and 2 mg (0.01 mmols) of CuI in 4 mL of degassed triethylamine and 5 mL of THF under nitrogen was heated to reflux temperature for 24 – 48 h. After cooling to room temperature 30 mL of diethyl ether was added to the reaction mixture. After filtration the solvents were removed *in vacuo* and the residue was washed with ethanol to give the enimines **19**. Further purification could be achieved by recrystallization from ethanol or trituration with ethanol.

***N*-[3-(4-Cyanophenyl)-1-(4-methoxyphenyl)-allylidene]-4-methyl-benzenesulfonamide (19a)**



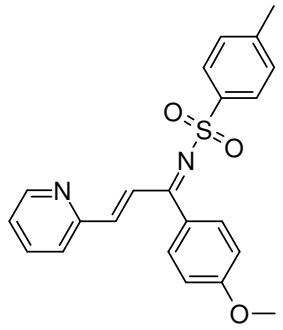
According to the GP the reaction of 182 mg (1.00 mmol) of 4-bromobenzonitrile (**1a**) and 331 mg (1.05 mmols) of **18a** furnished, after recrystallization from ethanol, 375 mg (90 %) of **19a** as light yellow crystals. M.p. 129–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3 H), 3.87 (s, 3 H), 6.94 (d, *J* = 8.8 Hz, 2 H), 7.04 (d, *J* = 16.3 Hz, 1 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 7.71 (d, *J* = 8.6 Hz, 2 H), 7.72 (d, *J* = 8.7 Hz, 2 H), 7.90 (d, *J* = 8.3 Hz, 2 H), 8.03 (d, *J* = 16.1 Hz, 1 H), 8.24 (d, *J* = 8.7 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 (CH_3), 55.5 (CH_3), 114.0 (CH), 124.1 (CH), 127.1 (CH), 128.8 (CH), 129.4 (CH), 130.9 ($C_{quat.}$), 132.5 (CH), 138.5 ($C_{quat.}$), 140.8 ($C_{quat.}$), 142.4 (CH), 143.6 ($C_{quat.}$), 148.5 ($C_{quat.}$), 163.7 ($C_{quat.}$), 175.2 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 416 (M^+ +2H, 2), 261 (M^+ - $C_7H_7SO_2$, 100), 247 (M^+ - $C_7H_7SO_2$ - NH, 12), 155 ($C_7H_7SO_2$, 6), 91 (C_7H_7, 20).

***N*-[1-(4-Methoxy-phenyl)-3-pyrimidin-2-yl-allylidene]-4-methyl-benzenesulfonamide (19b)**



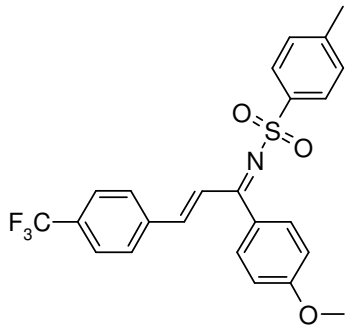
^{1}H NMR (250 MHz, $CDCl_3$), mixture of two isomers (*trans/cis* = 1:1): δ 2.21 (s, 3 H, Tol*Me*), 3.71 (s, 3 H, O*Me*), 6.78–6.88 (m, 3 H), 7.01–7.23 (m, 4 H), 7.57–7.69 (m, 2 H), 7.78 (d, *J* = 6.0 Hz, 1 H), 7.73 (dt, *J* = 2.0, 7.0 Hz, *J* = 2 Hz, 1 H), 8.64–8.67 (m, 2 H).

_N_-[1-(4-Methoxyphenyl)-3-(pyridin-2-yl)-allylidene]-4-methyl-benzenesulfonamide (19c)



^{1}H NMR (250 MHz, $CDCl_3$), mixture of two isomers (*trans/cis* = 7:1): δ 2.29 (s, 3 H, Tol*Me*), 3.73 (s, 3 H, O*Me*), 6.80–6.88 (m, 2 H), 6.87 (d, *J* =16.0 Hz, 1 H), 7.07 – 7.20 (m, 4 H), 7.40 (d, *J* =7.6 Hz, 1 H), 7.58–7.68 (m, 6 H), 7.76–7.79 (m, 3 H), 7.80 (dt, *J* = 1.7, 8.4 Hz, 1 H), 7.98–8.19 (m, 1H), 8.55 (d, *J* = 4.8 Hz, 1 H). HRMS calcd. for $C_{22}H_{20}N_2O_3S$: 392.1195; found: 392.1206.

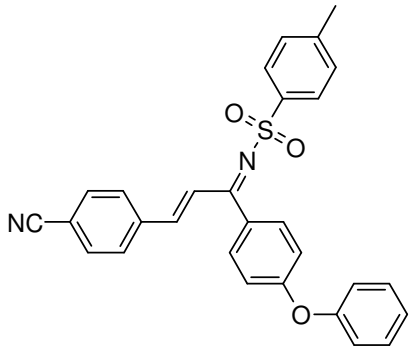
_N_-[1-(4-Methoxyphenyl)-3-(4-trifluoromethylphenyl)-allylidene]-4-methyl benzenesulfonamide (19d)



^{1}H NMR (250 MHz, $CDCl_3$), mixture of two isomers (*trans/cis* = 4 : 1): δ 2.24 (s, 3 H), 3.69 (s, 3 H), 6.76–6.84 (m, 1 H), 6.87 (d, *J* = 16.2 Hz, 1 H), 7.03–7.22 (m, 2 H), 7.47–7.67 (m,

6 H), 7.76–7.79 (m, 2 H), 7.87–7.93 (m, 2 H). HRMS calcd. for $C_{24}H_{20}F_3N_2O_3S$: 459.1116; found: 459.1128.

_N_-[3-(4-Cyanophenyl)-1-(4-phenoxyphenyl)-allylidene]-4-methyl-benzenesulfonamide (19e)



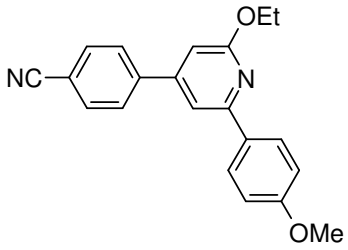
According to the GP the reaction of 182 mg (1.00 mmol) of 4-bromobenzonitrile (**1a**) and 396 mg (1.05 mmols) of **18b** furnished, after recrystallization from ethanol, 450 mg (94 %) of **19e** as light yellow crystals. M. p. 137.5–138.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3 H), 6.99 (d, J = 8.6 Hz, 2 H), 7.03 (d, J = 16.2 Hz, 1 H), 7.07 (d, J = 8.0 Hz, 2 H), 7.18–7.25 (m, 1 H), 7.32 (d, J = 8.2 Hz, 2 H), 7.37–7.42 (m, 2 H), 7.64–7.71 (m, 6 H), 7.91 (d, J = 8.2 Hz, 2 H), 8.02 (d, J = 9.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 (CH_3), 117.3 (CH), 118.3 ($C_{quat.}$), 120.2 (CH), 124.8 (CH), 126.2 ($C_{quat.}$), 127.1 (CH), 128.7 (CH), 129.5 (CH), 130.1 (CH), 130.1 ($C_{quat.}$), 132.4 (CH), 132.6 (CH), 138.4 ($C_{quat.}$), 138.8 ($C_{quat.}$), 143.6 (CH), 155.2 ($C_{quat.}$), 162.1 ($C_{quat.}$), 175.2 ($C_{quat.}$). MS (70 eV, EI); *m/z* (%): 478 (M^+, 1), 323 (M^+ - $C_7H_7SO_2$, 100), 231 ($C_7H_8^+$, 25), 155 ($C_7H_7SO_2$, 3), 91 (C_7H_7, 8).

6.7 General Procedure for the One-Pot Synthesis of 2-Ethoxy-6-*p*-anisylpyridines 21

A magnetically stirred solution of 1.00 mmol of (het)arylhalide **1**, 1.05 mmols of propargyl *N*-tosyl amine **18**, 14 mg (0.02 mmols) of $Pd(PPh_3)Cl_2$, and 2 mg (0.01 mmols) of CuI in 4 mL of degassed triethylamine and 5 mL of THF or toluene under nitrogen was heated to reflux temperature for 24–48 h. After cooling to room temperature a solution of 4 mmols of diethyl ketene acetal in 5 mL of THF or acetonitrile were added and the reaction mixture was heated to reflux temperature for 24–48 h. After cooling to room temperature 40 mL of ethyl

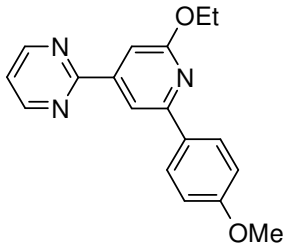
acetate and 40 mL of water were added and stirring was continued for 5 to 10 min. The aqueous layer was extracted with ethyl acetate (4×15 mL) and the combined organic phases were dried with magnesium sulfate. After evaporation of the solvents *in vacuo* the residue was chromatographed on silica gel (hexane/ethyl acetate 4:1 or 1:1) and recrystallized from ethanol or pentane/chloroform (1:1) to give the analytically pure pyridine derivatives **21**.

4-[2-Ethoxy-6-(4-methoxyphenyl)-pyridin-4-yl]-benzonitrile (21a)



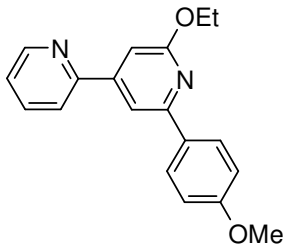
According to the GP the reaction of 182 mg (1.00 mmol) of 4-bromobenzonitrile (**1a**), 331 mg (1.05 mmols) of **18a**, and 470 mg (4.00 mmols) of diethyl ketene acetal in acetonitrile furnished, after chromatography on silica gel (hexane/ethyl acetate, 4:1) and recrystallization from ethanol, 188 mg (57 %) of **21a** as yellow crystals. M.p. 97–98 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.46 (t, *J* = 7.3 Hz, 3 H), 3.86 (s, 3 H), 4.53 (q, *J* = 7.1 Hz, 2 H), 6.77 (d, *J* = 1.1 Hz, 1 H), 6.98 (d, *J* = 8.9 Hz, 2 H), 7.41 (d, *J* = 1.1 Hz, 1 H), 7.70–7.76 (m, 4 H), 8.02 (d, *J* = 8.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.7 (CH_3), 55.4 (CH_3, OMe), 61.9 (CH_2, OCH_2CH_3), 106.5 (CH), 110.4 (CH), 112.5 ($C_{quat.}$), 114.1 (CH), 118.6 ($C_{quat.}$), 127.8 (CH), 128.1 (CH), 131.4 ($C_{quat.}$), 132.7 (CH), 143.5 ($C_{quat.}$), 149.9 ($C_{quat.}$), 155.5 ($C_{quat.}$), 160.7 ($C_{quat.}$), 164.2 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 330.1 (M^+, 43), 315 (M^+ - CH_3, 100), 302 (M^+ - C_2H_4, 30). IR (KBr): $\tilde{\nu}$ 3065, 2973, 2227 (C≡N), 1602, 1545, 1515, 1425, 1380, 1342, 1296, 1260, 1260, 1176, 1037, 830, 586, 516 cm^{-1}. Anal. calcd. for $C_{21}H_{18}N_2O_2$ (330.4): C 76.34, H 5.49, N 8.48; found C 76.25, H 5.47, N 8.39.

2-[2-Ethoxy-6-(4-methoxyphenyl)-pyridin-4-yl]-pyrimidine (21b)



According to the GP the reaction of 160 mg (1.00 mmol) of 2-bromopyrimidine (**1b**), 331 mg (1.05 mmols) of **18a**, and 470 mg (4.00 mmols) of diethyl ketene acetal in toluene furnished, after chromatography on silica gel (hexane/ethyl acetate, 1:1) and recrystallization from ethanol, 141 mg (46 %) of **21b** as colorless crystals. M.p. 120.9 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27–1.35 (m, 3 H, CH_3), 3.77 (s, 3 H), 4.36 (q, J = 7.2 Hz, 2 H), 7.28 (t, J = 4.9 Hz, 1 H), 7.44–7.53 (m, 3 H), 8.13–8.15 (m, 2 H), 8.49 (s, 1 H), 8.83 (d, J = 4.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.8 (CH_3), 55.4 (CH_3, OMe), 61.9 (CH_2, OCH_2CH_3), 107.2 (CH), 110.6 (CH), 113.9 (CH), 128.2 (CH), 131.8 ($C_{quat.}$), 155.2 ($C_{quat.}$), 157.3 ($C_{quat.}$), 160.4 ($C_{quat.}$), 164.5 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 307 (M^+, 57), 291 (M^+ - CH_3, 100), 279 (M^+ - C_2H_4, 34). UV/vis (CH_2Cl_2): λ_{max} (ε) 272 nm (4.62), 322 (4.00). IR (KBr): $\tilde{\nu}$ 2979, 1715, 1605, 1549, 1516, 1427, 1342, 1278, 1253, 1241, 1208, 1183, 1105, 834, 774 cm^{-1}. Anal. calcd. for $C_{18}H_{17}N_3O_2$ (307.4): C 70.34, H 5.58, N 13.67; found C 70.12, H 5.50, N 13.66.

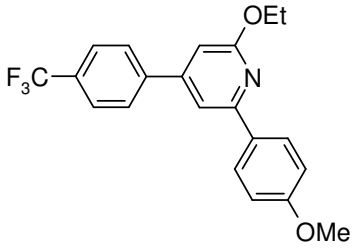
2'-Ethoxy-6'-(4-methoxyphenyl)-[2,4']bipyridinyl (21c)



According to the GP the reaction of 158 mg (1.00 mmol) of 2-bromo pyridine (**1c**), 331 mg (1.05 mmols) of **18a**, and 470 mg (4.00 mmols) of diethyl ketene acetal in toluene furnished, after chromatography on silica gel (hexane/ethyl acetate, 1:1) and recrystallization from ethanol, 199 mg (65 %) of **21c** as yellow crystals. M.p. 98.5 °C. ^{1}H NMR (CDCl3, 300 MHz): δ 1.38 (t, J = 7.3, 3 H, CH_3), 3.73 (s, 3 H, OMe), 4.39 (q, J = 7.0 Hz, 2 H), 6.85–6.91 (m,

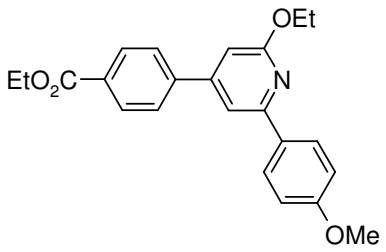
2 H), 7.05 (d, *J* = 1.3 Hz, 1 H), 7.15–7.23 (m, 1 H), 7.64–7.67 (m, 2 H), 7.83 (d, *J* = 1.3 Hz, 1 H), 7.96–8.02 (m, 2 H), 8.6 (dt, *J* = 1.3, 4.5 Hz, 1 H). ^{13}CNMR ($CDCl_3$, 75 MHz): δ14.8 (CH_3), 55.3 (CH_3, OMe), 61.7 (CH_2, OCH_2CH_3), 106.0 (CH), 110.1 (CH), 113.9 (CH), 121.1 (CH), 123.6 (CH), 128.2 (CH), 131.1 ($C_{quat.}$), 137.1 (CH), 149.8 (CH), 155.2 ($C_{quat.}$), 155.3 ($C_{quat.}$), 160.4 ($C_{quat.}$), 164.3 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 306.2 (M^+, 90), 291 (M^+ - CH_3, 100), 278 (M^+ - C_2H_4, 30), 247 (M^+ - CH_3, - C_2H_5O, 12). UV/vis (CH_2Cl_2): λ_{max} (ε) 254 nm (4.25), 264 (4.39), 290 (4.12), 328 (4.03). IR (KBr): $\tilde{\nu}$ 2970, 2935, 2895, 1611, 1588, 1577, 1555, 1516, 1473, 1432, 1416, 1383, 1343, 1297, 1255, 1215, 1205, 1178, 1040, 833, 785 cm^{-1}. Anal. calcd. for $C_{19}H_{18}N_2O_2$ (306.4): C 74.49, H 5.92, N 9.14; found C 73.96, H 5.91, N 8.93.

2-Ethoxy-6-(4-methoxyphenyl)-4-(4-trifluoromethylphenyl)-pyridine (21d)



According to the GP the reaction of 272 mg (1.00 mmol) of 4-iodobenzotrifluoride (**1d**), 331 mg (1.05 mmols) of **18a**, and 470 mg (4.00 mmols) of diethyl ketene acetal in toluene furnished, after chromatography on silica gel (hexane/ethyl acetate, 1:1) and recrystallization from ethanol, 111 mg (30 %) of **21d** as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ1.37 (t, *J* = 7.0 Hz, 3 H, CH_3), 3.8 (s, 3 H, OMe), 4.43 (q, *J* = 7.0 Hz, 2 H), 6.74 (d, *J* = 1.3 Hz, 1 H), 6.91–6.96 (m, 2 H), 7.40 (d, *J* = 1.3 Hz, 1 H) 7.63–7.71 (m, 4 H), 7.94–8.00 (m, 2 H). ^{13}CNMR ($CDCl_3$, 75 MHz): δ14.72 (CH_3), 55.36 (CH_3, OMe), 61.78 (CH_2, OCH_2CH_3), 106.6 (CH), 110.6 (CH), 114.0 (CH), 125.86 (CH), 125.91 (CH), 127.4 (CH), 128.1 (CH), 131.6 (CH), 150.4 ($C_{quat.}$), 155.3 ($C_{quat.}$), 160.5 ($C_{quat.}$), 164.2 ($C_{quat.}$). UV/vis (CH_2Cl_2): λ_{max} (ε) 260 nm (4.40), 290 (4.00), 296 (3.98), 322 (4.05), 348 (3.36). IR (KBr): $\tilde{\nu}$ 2981, 2932, 1607, 1551, 1515, 1428, 1381, 1342, 1326, 1252, 1207, 1177, 1127, 1068, 1036, 1017, 830 cm^{-1}. HRMS calcd. for $C_{21}H_{18}F_3NO_2$: 373.1281; found 373.1303.

4-[2-Ethoxy-6-(4-methoxyphenyl)-pyridin-4-yl]-benzoic acid ethyl ester (21e)



According to the GP the reaction of 229 mg (1.00 mmols) of ethyl 4-bromobenzoate (**1e**), 331 mg (1.05 mmols) of **18a**, and 470 mg (4.00 mmols) of diethyl ketene acetal in toluene furnished, after chromatography on silica gel (hexane/ethyl acetate, 5:1) and recrystallization from ethanol, 94 mg (25 %) of **21e** as colorless crystals. M.p. 96 °C. ^{1}H NMR (CDCl3, 300 MHz): δ1.30 (t, *J* = 7 Hz, 3 H, CH3), 1.34 (t, *J* = 7 Hz, 3 H, CH3), 3.76 (s, 3 H, OMe), 4.27 (q, *J* = 7 Hz, 2 H), 4.40 (q, *J* = 7 Hz, 2 H), 6.73 (d, *J* = 1.25 Hz, 1 H), 6.87–6.93 (m, 2 H), 7.37 (d, *J* = 1.0 Hz, 1 H), 7.59–7.62 (m, 2 H), 7.91–7.97 (m, 2 H), 8.01–8.07 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ14.3 (CH_3), 14.7 (CH_3), 55.3 (CH_3, OMe), 61.07 (CH_2, OCH_2CH_3), 61.67 (CH_2, OCH_2CH_3), 106.5 (CH), 110.5 (CH), 114.0 (CH), 125.9 (CH), 128.0 (CH), 130.1 (CH), 130.6 ($C_{quat.}$), 131.6 ($C_{quat.}$), 143.2 ($C_{quat.}$), 150.7 ($C_{quat.}$), 155.1 ($C_{quat.}$), 160.5 ($C_{quat.}$), 164.1 ($C_{quat.}$), 166.2 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 377 (M^+, 72), 362 (M^+ - CH_3, 100), 348.9 (M^+ - C_2H_4, 42). UV/vis (CH_2Cl_2): λ_{max} (ε) 272 (4.62), 322 (4.00). IR (KBr): $\tilde{\nu}$ 2979, 1715, 1605, 1549, 1516, 1427, 1342, 1278, 1253, 1241, 1208, 1183, 1105, 834, 774, 587 cm^{-1}. Anal. calcd. for $C_{23}H_{23}NO_4$ (377.4): C 73.19, H 6.14, N 3.71; found C 73.18, H 6.09, N 3.82.

6.8 General Procedure for the Coupling-Isomerization-Cycloaddition Sequence to Annelated 2-Amino Pyridines 27

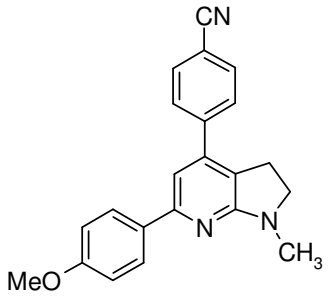
A magnetically stirred solution of 1.00 mmol of halogen compound 1, 1.05 mmols of propargyl tosyl amide 18, 20 mg (0.02 mmols) of $(PPh_3)_2PdCl_2$, and 2 mg (0.01 mmols) of CuI in 3.5 mL of degassed triethylamine and 5 mL THF under nitrogen was heated to reflux temperature for 24 h (for experimental details, see Table 28). After cooling to room temperature a solution of 5 mmols of *N*,*S*-ketene acetals 25 in 1 mL of THF were added and the reaction mixture was heated to reflux temperature for 12 h. After cooling to room temperature 40 mL of ethyl acetate and 40 mL of water were added and stirring was

continued for 5 to 10 min. The aqueous layer was extracted with ethyl acetate (4 × 15 mL) and the combined organic phases were dried with magnesium sulfate. After filtration the solvents were removed *in vacuo* and the residue was chromatographed on silica gel (hexane/ethyl acetate 4:1 or 1:1) and recrystallized from ethanol or pentane/chloroform (1:1) to give the analytically pure annelated 2-amino pyridine derivatives 27.

Table 28 Experimental details for the synthesis of annelated 2-amino pyridines **27**.

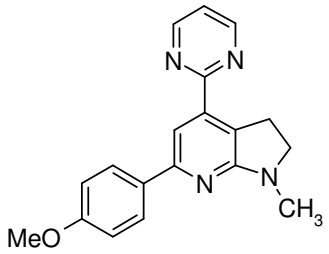
Aryl halide **1**	Propargyl *N*-tosyl amine **18**	*N*,*S*-ketene acetal **25**	Annelated 2-amino pyridines **27** (yield)
182 mg (1.00 mmol) of **1a**	331 mg (1.05 mmols) of **18a**	650 mg (5.00 mmols) of **25a**	219 mg (64 %) of **27a**
159 mg (1.00 mmol) of **1b**	331 mg (1.05 mmols) of **18a**	650 mg (5.00 mmols) of **25a**	210 mg (66 %) of **27b**
158 mg (1.00 mmol) of **1c**	331 mg (1.05 mmols) of **18a**	650 mg (5.00 mmols) of **25a**	156 mg (49 %) of **27c**
182 mg (1.00 mmol) of **1a**	331 mg (1.05 mmols) of **18a**	720 mg (5.00 mmols) of **25** (2 h)	111 mg (31 %) of **27d**
182 mg (1.00 mmol) of **1a**	400 mg (1.05 mmols) of **18b**	720 mg (5.00 mmols) of **25b**	180 mg (43 %) of **27e**
158 mg (1.00 mmol) of **1c**	331 mg (1.05 mmols) of **18a**	720 mg (5.00 mmols) of **25b**	160 mg (48 %) of **27f**
182 mg (1.00 mmol) of **1a**	331 mg (1.05 mmols) of **18a**	790 mg (5.00 mmols) of **25c**	192 mg (52 %) of **27g**
182 mg (1.00 mmol) of **1a**	400 mg (1.05 mmols) of **18b**	790 mg (5.00 mmols) of **25c**	186 mg (43 %) of **27h**
159 mg (1.00 mmol) of **1b**	331 mg (1.05 mmols) of **18a**	790 mg (5.00 mmols) of **25c**	194 mg (56 %) of **27i**
158 mg (1.00 mmol) of **1c**	331 mg (1.05 mmols) of **18a**	790 mg (5.00 mmols) of **25c**	180 mg (52 %) of **27j**

4-[6-(4-Methoxy-phenyl)-1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridin-4-yl]-benzonitrile (27a)



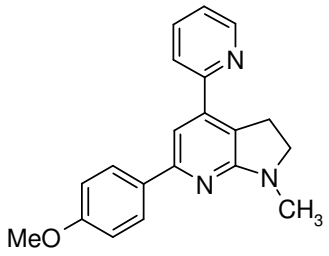
According to the GP after chromatography on silica gel (hexane/acetone, 5:1) and recrystallization from diethylether 219 mg (64 %) of **27a** were isolated as yellow crystals. M.p. 162 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.03 (t, J = 8.1 Hz, 2 H), 3.05 (s, 3 H), 3.5 (t, J = 8.1 Hz, 2 H), 3.84 (s, 3 H), 6.87 (s, 1 H), 6.94 (d, J = 8.9 Hz, 2 H), 7.57 (d, J = 8.5 Hz, 2 H), 7.71 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.7 (CH_2), 32.8 (CH_3), 52.2 (CH_2), 55.3 (CH_3), 107.6 (CH), 111.5 ($C_{quat.}$), 118.2 ($C_{quat.}$), 118.6 ($C_{quat.}$), 127.8 (CH), 128.5 (CH), 132.3 (CH), 132.4 (CH), 142.2 ($C_{quat.}$), 142.8 ($C_{quat.}$), 154.9 ($C_{quat.}$), 160.0 ($C_{quat.}$), 164.3 ($C_{quat.}$). EI MS (70 eV): *m/z* (%): 341.1 (M^+, 100), 313.1 (M^+ - CH_3, 8), 250.2 (M^+ - CO, - OH, 15). IR (KBr): $\tilde{\nu}$ 2228 cm^{-1} (C≡N), 1606, 1583, 1553, 1510, 1465, 1438, 1405, 1366, 1332, 1299, 1242, 1182, 1032, 853, 824, 576, 548, 513. UV/vis (CH_2Cl_2): λ_{max} (ε) 258 nm (21900), 310 (4400), 372 (3200). Anal. calcd. for $C_{22}H_{19}N_3O$ (341.4): C 77.40, H 5.61, N 12.31; found C 76.43, H 5.63, N 12.32.

6-(4-Methoxy-phenyl)-1-methyl-4-pyrimidin-2-yl-2,3-1*H*-pyrrolo[2,3-b]pyrimidine (27b)



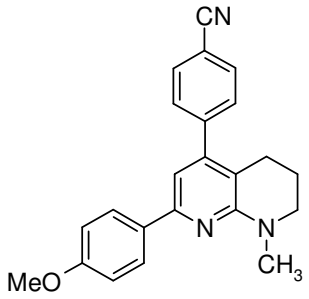
According to the GP after chromatography on silica gel (hexane/acetone, 2.5:1) and recrystallization from diethylether 210 mg (66 %) of **27b** were isolated as yellow crystals. M.p. 190 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.02 (s, 3 H), 3.44–3.57 (m, 4 H), 3.85 (s, 3 H), 6.99 (d, J = 9.0 Hz, 2 H), 7.20 (t, 1 H), 7.43 (t, J = 4.8 Hz, 1 H), 7.91 (s, 1 H), 8.07 (d, J = 8.9 Hz, 2 H), 8.93 (d, J = 5.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.7 (CH_2), 32.9 (CH_3), 53.8 (CH_2), 55.6 (CH_3), 107.1 (CH), 114.6 (CH), 120.8 (CH), 122.7 ($C_{quat.}$), 128.4 (CH), 141.0 ($C_{quat.}$), 154.7 ($C_{quat.}$), 158.1 (CH), 160.9 ($C_{quat.}$), 161.0 ($C_{quat.}$), 165.8 ($C_{quat.}$). EI MS (70 eV): *m/z* (%) = 318.2 (M^+, 100), 303.2 (M^+ - CH_3, 7). IR (KBr): $\tilde{\nu}$ 3003 cm^{-1}, 2929, 2874, 2836, 1610, 1601, 1584, 1570, 1554, 1512, 1477, 1441, 1417, 1370, 1335, 1299, 1282, 1260, 1240, 1170, 1036, 807, 568. UV/vis (CH_2Cl_2): λ_{max} (ε) 252 (40700), 284 (12900), 392 (6500). Anal. calcd. for $C_{19}H_{18}N_4O$ (318.4): C 71.68, H 5.70, N 17.60; found: C 71.58, H 5.70, N 17.86.

6-(4-Methoxy-phenyl)-1-methyl-4-pyridin-2-yl-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridine (27c)



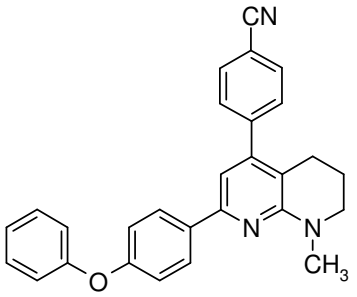
According to the GP after chromatography on silica gel (hexane/acetone, 4:1) and recrystallization from diethylether 156 mg (49 %) of **27c** were isolated as light yellow crystals. M.p. 191 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.01 (s, 3 H), 3.02–3.32 (m, 2 H), 3.49–3.55 (m, 2 H), 3.85 (s, 3 H), 6.98 (d, J = 8.9 Hz, 2 H), 7.36–7.41 (m, 1 H), 7.47 (s, 1 H), 7.90–7.92 (m, 2 H), 8.09 (d, J = 8.9 Hz, 2 H), 8.72–8.74 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.7 (CH_2), 33.0 (CH_3), 53.0 (CH_2), 55.9 (CH_3), 107.3 (CH), 114.5 (CH), 120.3 ($C_{quat.}$), 123.2 (CH), 123.7 (CH), 128.5 (CH), 133.7 ($C_{quat.}$), 137.5 (CH), 143.0 ($C_{quat.}$), 150.4 (CH), 157.5 ($C_{quat.}$), 161.0 ($C_{quat.}$), 165.8 ($C_{quat.}$). EI MS (70 eV), *m/z* (%): 317.1 (M^+, 92), 316.1 (M^+, - H, 100), 302.1 (M^+ - CH_3, 8), 287.1 (M^+ - CH_3, - CH_3, 5). IR (KBr): $\tilde{\nu}$ 2901 cm^{-1}, 1609, 1585, 1571, 1555, 1514, 1444, 1430, 1417, 1403, 1368, 1334, 1276, 1260, 1247, 1182, 1172, 811, 568. UV/vis (CH_2Cl_2): λ_{max} (ε) 248 (47900), 276 (41700), 360 (15900). $C_{20}H_{19}N_3O$ (317.4): calcd. C 75.69, H 6.03, N 13.24; found C 75.36, H 6.03, N 12.91.

4-[2-(4-Methoxy-phenyl)-8-methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-4-yl]-benzonitrile (27d)



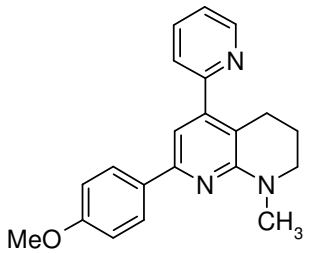
According to the GP after chromatography on silica gel (hexane/acetone, 4:1) and recrystallization from diethylether 111 mg (31 %) of **27d** were isolated as light yellow crystals. M.p. 202 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.88 (tt, J = 6.2 Hz, 2 H), 2.63 (t, J = 6.3 Hz, 2 H), 3.25 (s, 3 H), 3.45 (t, J = 5.7 Hz, 2 H), 3.83 (s, 3 H), 6.89 (s, 1 H), 6.96 (d, J = 8.9 Hz, 2 H), 7.60 (d, J = 8.2 Hz, 2 H), 7.86 (d, J = 8.2 Hz, 2 H), 8.04 (d, J = 8.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.1 (CH_2), 26.0 (CH_2), 36.9 (CH_3), 50.4 (CH_2), 55.5 (CH_3), 108.4 (CH), 112.0 ($C_{quat.}$), 113.0 ($C_{quat.}$), 114.3 (CH), 114.4 (CH), 128.3 (CH), 130.5 (CH), 132.5 (CH), 133.2 ($C_{quat.}$), 146.1 ($C_{quat.}$), 147.7 ($C_{quat.}$), 152.9 ($C_{quat.}$), 156.8 ($C_{quat.}$), 161.0 ($C_{quat.}$). EI MS (70 eV): *m/z* (%): 355.1 (M^+, 100), 340.1 (M^+ - CH_3, 18), 326.0 (M^+ - HCN, 54). IR (KBr): $\tilde{\nu}$ 2934 cm^{-1}, 2841, 2224, 1609, 1589, 1545, 1514, 1461, 1443, 1410, 1371, 1356, 1328, 1253, 1201, 1177, 1033, 1003, 828, 578. UV/vis (CH_2Cl_2): λ_{max} (ε) 258 (31600), 306 (5900), 362 (5900). Anal. calcd. for $C_{23}H_{21}N_3O$ (355.4): C 77.72, H 5.96, N 11.82; found C 77.42, H 5.93, N 11.72.

4-[2-(4-Phenoxy-phenyl)-8-methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-4-yl]-benzonitrile (27e)



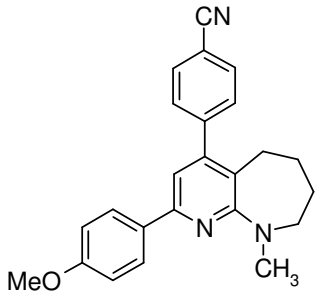
According to the GP after chromatography on silica gel (hexane/acetone, 4:1) and recrystallization from diethylether 180 mg (43 %) of **27e** were isolated as light yellow crystals. M.p. 219 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.87 (m, 2 H), 2.63 (t, J = 6.3 Hz, 2 H), 3.25 (s, 3 H), 3.45 (t, J = 5.8 Hz, 2 H), 6.95 (s, 1 H), 7.03–7.07 (m, 4 H), 7.18 (t, J = 7.5 Hz, 1 H), 7.41 (t, J = 7.7 Hz, 2 H), 7.62 (d, J = 8.5 Hz, 2 H), 7.87 (d, J = 8.5 Hz, 2 H), 8.12–8.15 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.0 (CH_2), 26.0 (CH_2), 36.9 (CH_3), 50.3 (CH_2), 108.8 (CH), 112.1 ($C_{quat.}$), 113.6 ($C_{quat.}$), 119.1 (CH), 119.7 (CH), 124.2 (CH), 128.7 (CH), 130.5 (CH), 130.7 (CH), 132.9 (CH), 135.9 ($C_{quat.}$), 146.0 ($C_{quat.}$), 147.7 ($C_{quat.}$), 152.4 ($C_{quat.}$), 156.9 ($C_{quat.}$), 157.9 ($C_{quat.}$), 158.5 ($C_{quat.}$). EI MS (70 eV): *m/z* (%): 416.9 (M^+, 100), 388 (M^+ – HCN, 20), 77.1 ($C_6H_5^+$, 8). IR (KBr): $\tilde{\nu}$ 3052 cm^{-1}, 2924, 2841, 2229, 1591, 1562, 1547, 1507, 1489, 1459, 1407, 1371, 1357, 1329, 1202, 1164, 873, 845, 829, 754, 692. UV/vis (CH_2Cl_2): λ_{max} (ε) 258 (38000), 312 (5200), 364 (6600). Anal. calcd. for $C_{28}H_{23}N_3O$ (417.5): C 80.55, H 5.55, N 10.06; found C 80.39, H 5.89, N 9.83.

4-[2-(4-Methoxy-phenyl)-8-methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-4-yl]pyridine (27f)



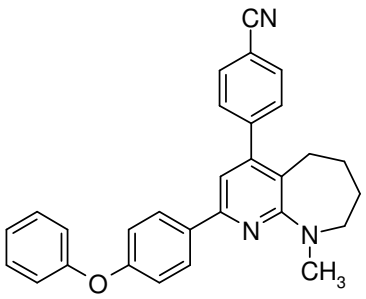
According to the GP after chromatography on silica gel (hexane/acetone, 3:1) 160 mg (48 %) of **27f** were isolated as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.88 (m, 2 H), 2.74 (t, J = 6.3 Hz, 2 H), 3.24 (s, 3 H), 3.45 (t, J = 5.7 Hz, 2 H), 3.82 (s, 3 H), 6.95 (d, J = 8.9 Hz, 2 H), 7.05 (s, 1 H), 7.35–7.37 (m, 1H), 7.51 (d, J = 7.8 Hz, 1 H), 7.84 (t, J = 7.9 Hz, 1 H), 8.05 (d, J = 8.9 Hz, 2 H), 8.66–8.68 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.3 (CH_2), 26.2 (CH_2), 37.1 (CH_3), 50.5 (CH_2), 55.5 (CH_3), 108.8 (CH), 113.9 ($C_{quat.}$), 113.0 ($C_{quat.}$), 114.5 (CH), 123.2 (CH), 124.7 (CH), 128.0 (CH), 128.3 (CH), 133.5 ($C_{quat.}$), 137.2 (CH), 148.0 ($C_{quat.}$), 150.0 (CH), 157.1 ($C_{quat.}$), 159.5 ($C_{quat.}$), 160.9 ($C_{quat.}$). IR (KBr): $\tilde{\nu}$ 2834 cm^{-1}, 1665, 1609, 1585, 1572, 1555, 1513, 1471, 1428, 1410, 1399, 1369, 1356, 1327, 1246, 1202, 1179, 1170, 1032, 831, 792. UV/vis (CH_2Cl_2): λ_{max} (ε) 256 (20400), 358 (6200). HRMS calcd. for $C_{21}H_{21}N_3O$: 331.1685; found 331.1679.

4-[2-(4-Methoxy-phenyl)-9-methyl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-b]azepin-4-yl]-benzonitrile (27g)



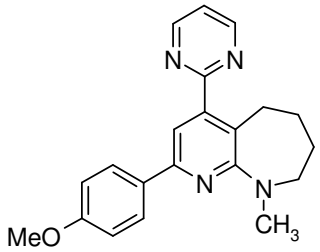
According to the GP after chromatography on silica gel (hexane/acetone, 4:1) and recrystallization from diethylether 192 mg (52 %) of **27g** were isolated as light yellow crystals. M.p. 142 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.66–1.73 (m, 2 H), 1.83–1.89 (m, 2 H), 2.16–2.57 (m, 2 H), 3.16 (s, 3 H), 3.26–3.30 (m, 2 H), 3.84 (s, 3 H), 6.93–6.96 (m, 1 H), 6.97 (d, J = 6.5 Hz, 2 H), 7.44 (d, J = 8.4 Hz, 2 H), 7.71 (d, J = 8.37 Hz, 2 H), 7.97 (d, J = 8.88 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.1 (CH_2), 27.8 (CH_2), 28.5 (CH_2), 40.8 (CH_3), 54.0 (CH_2), 55.31 (CH_3), 111.2 (CH), 111.4 ($C_{quat.}$), 113.9 (CH), 118.7 ($C_{quat.}$), 120.7 ($C_{quat.}$), 127.7 (CH), 129.7 (CH), 132.1 (CH), 146.0 ($C_{quat.}$), 149.0 ($C_{quat.}$), 151.6 ($C_{quat.}$), 160.1 ($C_{quat.}$), 162.2 ($C_{quat.}$). IR (KBr): $\tilde{\nu}$ 2932 cm^{-1}, 2228 (C≡N), 1636, 1608, 1586, 1573, 1561, 1541, 1514, 1439,1369, 1353, 1253, 1236, 1182, 1181, 831, 584, 562, 551. UV/vis (CH_2Cl_2): λ_{max} (ε) 260 (18200), 338 (3500). EI MS (70 eV): *m/z* (%): 369.2 (M^+, 100), 340.2 (M^+ – HCN, 41), 325.2 (M^+ - HCN - CH_3, 16). Anal. calcd. for $C_{24}H_{23}N_3O$ (369.5): C 78.02, H 6.27, N 11.37; found C 77.68, H 6.64, N 11.26.

4-[9-Methyl-2-(4-phenoxy-phenyl)-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-b]azepin-4-yl]-benzonitrile (27h)



According to the GP after chromatography on silica gel (hexane/acetone, 4:1) and recrystallization from diethylether 186 mg (43 %) of **27h** were isolated as light yellow crystals. M.p. 187 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.70–1.76 (m, 2 H), 1.83–1.88 (m, 2 H), 2.56–2.60 (m, 2 H), 3.13 (s, 3 H), 3.29–3.33 (m, 2 H), 7.03–7.07 (m, 4 H), 7.15 (t, J = 7.4 Hz, 1 H), 7.20 (s, 1 H), 7.37–7.40 (m, 2 H), 7.62 (d, J = 8.3 Hz, 2 H), 7.87 (d, J = 8.4 Hz, 2 H), 8.15 (d, J = 8.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.7 (CH_2), 28.6 (CH_2), 29.4 (CH_2), 41.0 (CH_3), 54.6 (CH_2), 112.2 (CH), 112.3 (CH), 119.2 (CH), 119.3 (CH), 120.0 (CH), 121.9 ($C_{quat.}$), 124.4 (CH), 128.9 (CH), 130.8 (CH), 133.0 (CH), 135.5 ($C_{quat.}$), 146.5 ($C_{quat.}$), 150.3 ($C_{quat.}$), 151.7 ($C_{quat.}$), 158.0 ($C_{quat.}$), 158.7 ($C_{quat.}$), 163.1 ($C_{quat.}$). EI MS (70 eV): *m/z* (%): 431.3 (M^+, 83), 416 ($M^+ - CH_3$, 17), 402.2 ($M^+ - C_2H_5$, 34), 77.1 ($C_6H_5^+$). IR (KBr): $\tilde{\nu}$ 3051 cm^{-1}, 2933, 2858, 2228, 1588, 1573, 1542, 1504, 1489, 1440, 1408, 1369, 1353, 1334, 1234, 1164, 970, 873, 836, 754, 692. UV/vis (CH_2Cl_2): λ_{max} (ε) 258 (38900), 340 (6600). Anal. calcd. for $C_{29}H_{25}N_3O$ (431.5): C 80.72, H 5.84, N 9.74; found C 80.39, H 5.89, N 9.83.

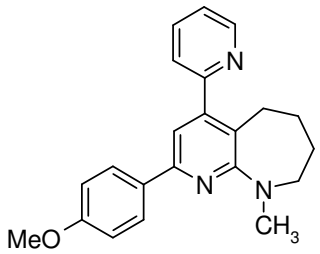
2-(4-Methoxy-phenyl)-9-methyl-4-pyrimidin-2-yl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-b]azepine (27i)



According to the GP after chromatography on silica gel (hexane/acetone, 4:1) and recrystallization from diethylether 194 mg (56 %) of **27i** were isolated as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.83–1.89 (m, 4 H), 2.73–2.77 (m, 2 H), 3.15 (s, 3 H), 3.27–3.30 (m, 2 H), 3.79 (s, 3 H), 6.92 (d, J = 8.9 Hz, 2 H), 7.17 (t, J = 4.9 Hz, 1 H), 7.47 (s, 1 H), 8.04 (d, J = 8.9 Hz, 2 H), 8.78 (d, J = 4.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.3 (CH_2), 27.3 (CH_2), 28.3 (CH_2), 40.4 (CH_3), 53.7 (CH_2), 55.1 (CH_3), 111.1 (CH), 113.6 (CH), 119.1 (CH), 121.9 ($C_{quat.}$), 127.6 (CH), 132.3 ($C_{quat.}$), 147.1 ($C_{quat.}$), 151.3 ($C_{quat.}$), 156.8 (CH), 159.7 ($C_{quat.}$), 162.0 ($C_{quat.}$), 167.1 ($C_{quat.}$). IR (KBr): $\tilde{\nu}$ 2932 cm^{-1}, 1608, 1589, 1566, 1547, 1513, 1492, 1443, 1418, 1368, 1350, 1333, 1296, 1247, 1191, 1179, 1032, 838, 813. UV/vis

(CH_2Cl_2): λ_{max} (ε) 254 (23400), 280 (14800), 348 (5500). HRMS calcd. for $C_{21}H_{22}N_4O$: 346.1794; found 346.1797.

2-(4-Methoxy-phenyl)-9-methyl-4-pyridin-2-yl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-b]azepine (27j)

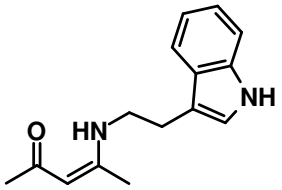


According to the GP after chromatography on silica gel (hexane/acetone, 4:1) and recrystallization from diethylether 180 mg (52 %) of **27j** were isolated as yellow crystals. M.p. 121 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.75–1.90 (m, 4 H), 2.63–2.85 (m, 2 H), 3.12 (s, 3 H), 3.27–3.30 (m, 2 H), 3.84 (s, 3 H), 6.98 (d, J = 9.0 Hz, 2 H), 7.31 (s, 1 H), 7.38–7.42 (m, 1 H), 7.55 (dt , J = 1.0 Hz, J = 6.8 Hz, 1 H), 7.87 (td, J = 7.5 Hz, J = 1.75 Hz, 2 H), 8.09 (d, J = 9.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.6 (CH_2), 28.7 (CH_2), 29.3 (CH_2), 30.1 (CH_2), 41.1 (CH_3), 54.9 (CH_2), 55.6 (CH_3), 112.0 (CH), 114.5 (CH), 122.1 ($C_{quat.}$), 123.2 (CH), 124.8 (CH), 128.3 (CH), 133.1 ($C_{quat.}$), 137.1 (CH), 150.1 (CH), 150.6 ($C_{quat.}$), 151.8 ($C_{quat.}$), 159.8 ($C_{quat.}$), 161.0 ($C_{quat.}$), 163.0 ($C_{quat.}$). EI MS (70 eV): *m/z* (%): 345.2 (M^+, 100), 330.1 ($M^+ - CH_3$, 20), 316.2 ($M^+ - C_2H_5$, 48), 302.2 ($M^+ - C_3H_7$, 22), 288.2 (M^+ - C_4H_9, 18). Anal. calcd. for $C_{22}H_{23}N_3O$ (345.4): C 76.49, H 6.71, N 12.16; found C 76.02, H 6.70, N 12.13.

6.9 General Procedure for Synthesis of Enamine 30

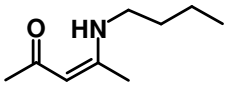
A mixture of 50 mmols of 1,3-diketone **28**, 50 mmols of amine **29**, and catalytical amount of *p*-toluenesulfonic acid (PTSA), in 100 mL dry benzene, were refluxed for 16 hours, using the water trap, under inert atmosphere (nitrogen). The reaction mixture was added to 20 mL of diethyl ether, and after filtration and solvent evaporation the pure enamine was isolated. In same cases, the enamines were purified by distillation at low pressure.

(*Z*)-4-(2-(1*H*-indol-3-yl)ethylamino)pent-3-en-2-one (30a)[151]



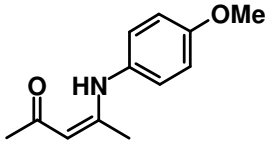
According to the GP, 170 mg (70 %) of **30a** were isolated. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.83 (s, 3 H), 1.99 (s, 3 H), 3.03 (t, *J* = 6.0 Hz, 2 H), 3.51 (q, *J* = 6.0 Hz 2 H), 4.93 (s, 1 H), 7.07–7.24 (m, 3 H), 7.31 (d, *J* = 9.0 Hz, 1 H), 7.54 (d, *J* = 9.0 Hz, 1 H), 8.75 (s, 1 H), 10.90 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 18.9 (CH_3), 26.0 (CH_2), 28.6 (CH_3), 43.4 (CH_2), 95.2 (CH), 111.5 (CH), 111.7 ($C_{quat.}$), 118.2 (CH), 119.1 (CH), 121.8 (CH), 123.0 (CH), 127.0 ($C_{quat.}$), 136.5 ($C_{quat.}$), 163.2 ($C_{quat.}$), 194.6 ($C_{quat.}$). HRMS calcd. for $C_{15}H_{18}N_2O$: 242.1419; found: 242.1427.

(*Z*)-4-(butylamino)pent-3-en-2-one (30b)[152]



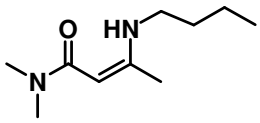
According to the GP, 152 mg (98 %) of **30b** were isolated. ^{1}H NMR ($CDCl_3$, 300 MHz), δ0.88 (t, *J* = 6.0 Hz, 2 H), 1.33–1.41 (m, 2 H), 1.49–1.56 (m, 2 H), 1.88 (s, 3 H), 1.96 (s, 3 H), 3.16 (q, *J* = 6.0 Hz 2 H), 4.91 (s, 1 H), 10.83 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ13.7 (CH_3), 18.7 (CH_3), 20.0 (CH_2), 28.7 (CH_3), 32.1 (CH_2), 42.7 (CH_2), 94.9 (CH), 163.1 ($C_{quat.}$), 194.6 ($C_{quat.}$). HRMS calcd. for $C_9H_{17}NO$: 155.1310; found: 155.1320.

(Z)-4-(4-methoxyphenylamino)pent-3-en-2-one (30c)[153]



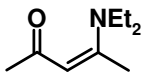
According to the GP, 205 mg (80 %) of **30c** were isolated. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.88 (s, 3 H), 2.06 (s, 3 H), 3.76 (s, 3 H), 5.13 (s, 1 H), 6.82 (d, J = 9.0 Hz, 2 H), 7.0 (d, J = 9.0 Hz, 2 H), 12.26 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 19.3 (CH_3), 29.1 (CH_3), 55.5 (CH_3), 96.8 (CH), 114.3 (CH), 126.7 (CH), 131.5 ($C_{quat.}$), 157.7 ($C_{quat.}$), 161.2 ($C_{quat.}$), 195.8 ($C_{quat.}$). HRMS calcd. for $C_{12}H_{15}NO_2$: 205.1103; found: 205.1110.

(Z)-3-(butylamino)-*N*,*N*-dimethylbut-2-enamide (30d)[154]



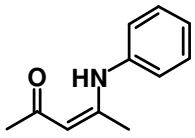
According to the GP, 169 mg (92 %) of **30d** were isolated. ^{1}H NMR ($CDCl_3$, 250 MHz), δ 1.34 (t, J = 7.3 Hz, 3 H), 1.37–1.53 (m, 4 H), 1.85 (s, 3 H), 2.86 (s, 6 H), 3.07 (q, J = 6.6 Hz, 2 H), 4.46 (s, 1 H). HRMS calcd. for $C_{10}H_{20}N_2O$: 184.1576; found 184.1582.

4-(Diethylamino)pent-3-en-2-one (30e)[155]



According to the GP, 115 mg (74 %) of **30e** were isolated. ^{1}H NMR ($CDCl_3$, 250 MHz), δ 1.14 (t, J = 7.14 Hz, 6 H), 2.05–2.07 (m, 3 H), 2.54 (s, 3 H), 3.25 (q, J = 7.14 Hz, 4 H), 5.08 (s, 1 H). HRMS calcd. for $C_9H_{17}NO$: 155.1310; found 155.1316.

(Z)-4-(Phenylamino)pentan-2-one (30f)[156]



According to the GP, 175 mg (98 %) of **30f** were isolated. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 0.88 (t, J = 6.0 Hz, 2 H), 1.33–1.41 (m, 2 H), 1.49–1.56 (m, 2 H), 1.88 (s, 3 H), 1.96 (s, 3 H), 3.16 (q, J = 6.0 Hz 2 H), 4.91 (s, 1 H), 10.83 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz),

δ 18.88 (CH_3), 26.0 (CH_2), 28.6 (CH_3), 43.4 (CH_2), 95.2 (CH), 111.5 (CH), 111.7 ($C_{quat.}$), 118.2 (CH), 119.1 (CH), 121.8 (CH), 123.0 (CH), 127.0 ($C_{quat.}$), 136.5 ($C_{quat.}$), 163.2 ($C_{quat.}$), 194.61 ($C_{quat.}$). HRMS calcd. for $C_{13}H_{13}NO$: 175.0997; found 175.1004.

6.10 General Procedure for the Coupling-Isomerization-Enamine Addition-Aldol-Condensation Multicomponent Synthesis of Cyclohexadienes 31 and Cyclohexenones 32

A magnetically stirred solution of 1.00 mmol of halogen compound **1**, 1.05 mmols of propargyl alcohol **2**, 20 mg (0.02 mmols) of $Pd(PPh_3)Cl_2$, and 2 mg (0.01 mmols) of CuI in ~0.5 mL (505 mg) of degassed triethylamine and 1.5 mL THF under nitrogen, in a sealed vessel was heated to 150 ºC, for 10-15 min, under microwave irradiation. After cooling to room temperature 3 mmols of enamine **30** and 0.75 mL of CH_3COOH were added and the reaction mixture was heated to 150 ºC, for another 10–15 min. After cooling to room temperature the reaction mixture was poured to 40 mL of ethyl acetate and 40 mL of water and stirring was continued for 5 to 10 min. The aqueous layer was extracted with ethyl acetate (4x15 mL) and the combined organic phases were dried over magnesium sulfate. After filtration the solvents were removed *in vacuo* and the residue was chromatographed on silica gel (hexane/ethyl acetate 4:1 or 1:1) and recrystallized from ethanol or pentane/chloroform (1:1) to give the analytically pure cyclohexadienes **30a–k**, or cyclohexanones **32a–i**.

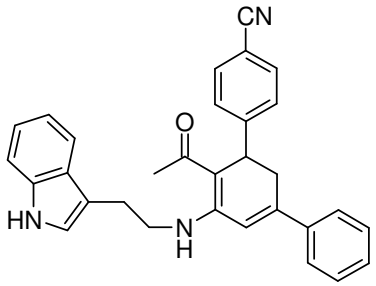
Table 29 Experimental details of the synthesis of cyclohexadienes **30** and cyclohexanones **32**.

Ar^1- Hal **1**	Propargyl-alcohol **2**	Enamine **4**	CH_3COOH	T_1 (min.)	T_2 (min.)	Yield
182 mg (1.00 mmol) of **1a**	139 mg (1.05 mmols) of **2a**	726 mg (3.00 mmols) of **4a**	0.75 mL	15	10	311 mg (68 %) of **31a**
159 mg (1.00 mmol) of **1b**	139 mg (1.05 mmols) of **2a**	726 mg (3.00 mmols) of **4a**	0.75 mL	15	10	321 mg (74 %) of **31b**
158 mg (1.00 mmol) of **1c**	139 mg (1.05 mmols) of **2a**	726 mg (3.00 mmols) of **4a**	0.75 mL	15	10	304 mg (70 %) of **31c**
272 mg (1.00 mmol) of **1d**	139 mg (1.05 mmols) of **2a**	339 mg (1,40 mmols) of **4a**	0.75 mL	20	20	235 mg (47 %) of **31d**
182 mg (1.00 mmol) of **1a**	145 mg (1.05 mmols) of **2b**	726 mg (3.00 mmols) of **4a**	0.75 mL	15	15	250 mg (54 %) of **31e**

Table 29 *continued*

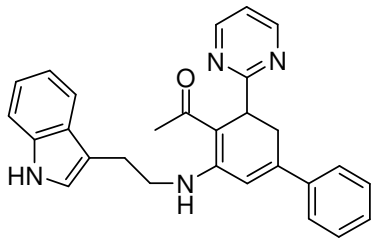
182 mg (1.00 mmol) of **1a**	145 mg (1.05 mmols) of **2c**	726 mg (3 mmols) of **4a**	0.75 mL	15	15	297 mg (61 %) of **31f**
158 mg (1.00 mmol) of **1c**	145 mg (1.05 mmols) of **2b**	726 mg (3 mmols) of **4a**	0.75 mL	15	15	264 mg (60 %) of **31g**
182 mg (1.00 mmol) of **1a**	170 mg (1.05 mmols) of **2f**	726 mg (3 mmols) of **4a**	0.75 mL	15	10	331 mg (68 %) of **31h**
182 mg (1.00 mmol) of **1a**	139 mg (1.05 mmols) of **2a**	310 mg (2 mmols) **4b**	0.5 mL	15	20	200 mg (54 %) of **31i**
159 mg (1.00 mmol) of **1b**	139 mg (1.05 mmols) of **2a**	465 mg (3 mmols) of **4b**	0.75 mL	15	10	180 mg (52 %) of **31j**
158 mg (1.00 mmol) of **1c**	139 mg (1.05 mmols) of **2a**	465 mg (3 mmols) of **4b**	0.75 mL	15	10	180 mg (52 %) of **31k**
182 mg (1.00 mmol) of **1a**	139 mg (1.05 mmols) of **2a**	615 mg (3 mmols) of **4c**	1.5 mL	15	10	126 mg (30 %) **31l**
182 mg (1.00 mmol) of **1a**	139 mg (1.05 mmols) of **2a**	576 mg (3 mmols) of **4d**	0.75 mL	15	10	227 mg (66 %) of **32a**
159 mg (1.00 mmol) of **1b**	139 mg (1.05 mmols) of **2a**	576 mg (3 mmols) of **4d**	0.75 mL	15	10	218 mg (68 %) **32b**
158 mg (1.00 mmol) of **1c**	139 mg (1.05 mmols) of **2a**	576 mg (3 mmols) of **4d**	0.75 mL	15	10	154 mg (48 %) **32c**
272 mg (1.00 mmol) of **1d**	139 mg (1.05 mmols) of **2a**	576 mg (3 mmols) of **4d**	0.75 mL	15	10	272 mg (70 %) of **32d**
229 mg (1.00 mmol) of **1e**	139 mg (1.05 mmols) of **2a**	576 mg (3 mmols) of **4d**	0.75 mL	15	10	186 mg (48 %) of **32e**
182 mg (1.00 mmol) of **1a**	170 mg (1.05 mmols) of **2f**	576 mg (3 mmols) of **4d**	0.75 mL	15	10	217 mg (58 %) of **32f**
182 mg (1.00 mmol) of **1a**	145 mg (1.05 mmols) of **2b**	576 mg (3 mmols) of **4d**	0.75 mL	15	10	227 mg (66 %) of **32g**
182 mg (1.00 mmol) of **1a**	145 mg (1.05 mmols) of **2c**	576 mg (3 mmols) of **4d**	0.75 mL	15	10	217 mg (62 %) of **32h**
158 mg (1.00 mmol) of **1c**	145 mg (1.05 mmols) of **2b**	576 mg (3 mmols) of **4d**	0.75 mL	15	10	201 mg (62 %) of **32i**

4-{2-Acetyl-3-[2-(1*H*-indol-3-yl)-ethylamino]-5-phenyl-cyclohexa-2,4-dienyl}-benzonitrile (31a)



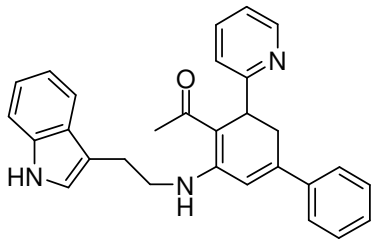
According to the GP after chromatography on silica gel (hexane/acetone 2:1) and recrystallization from acetone 311 mg (68 %) of **31a** were isolated as yellow crystals. M.p. 227 °C. ^{1}H NMR (DMSO-D_6, 300 MHz), δ 1.80 (s, 3 H), 2.75–2.81 (m, 1 H), 2.94–3.12 (m, 3 H), 3.68–3.89 (m, 2 H), 4.17 (d, *J* = 7.0 Hz, 1 H), 6.49 (d, *J* = 1.9 Hz, 1 H), 7.00–7.05 (m, 3 H), 7.14 (t, *J* = 7.4 Hz, 1 H), 7.21–7.29 (m, 4 H), 7.32 (d, *J* = 8.12 Hz, 2 H), 7.36 (d, *J* = 8.12 Hz, 1 H), 7.62 (d, *J* = 8.12 Hz, 1 H), 7.69 (d, *J* = 8.12 Hz, 2 H), 10.92 (s, 1 H), 11.72 (t, *J* = 6.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 26.6 (CH_2), 26.9 (CH_3), 34.8 (CH_2), 38.2 (CH), 42.4 (CH_2), 97.7 ($C_{quat.}$), 108.9 ($C_{quat.}$), 110.9 ($C_{quat.}$), 111.5 ($C_{quat.}$), 115.7 (CH), 118.2 ($C_{quat.}$), 118.5 (CH), 118.9 (CH), 121.0 (CH), 123.7 (CH), 125.5 (CH), 127.0 ($C_{quat.}$), 128.3 (CH), 128.5 (CH), 128.8 (CH), 132.0 (CH), 136.4 ($C_{quat.}$), 138.6 ($C_{quat.}$), 145.2 ($C_{quat.}$), 146.9 ($C_{quat.}$), 151.1 ($C_{quat.}$), 156.1 ($C_{quat.}$), 192.8 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 457.2 (M^+, 14), 414.2 (M^+ - CH_3CO, 12), 327.2 (M^+ - C_9H_8N, 44), 144.1 ($C_{10}H_{10}N$, 4), 130.1 ($C_9H_8N^+$, 100), 43 (CH_3CO^+, 18). IR (KBr), $\tilde{\nu}$ 3060 cm^{-1}, 2219, 1632, 1604, 1576, 1561, 1551, 1463, 1443, 1429, 1357, 1328, 1308, 1291, 1251, 1240, 1208, 768, 747, 696, 544. UV/vis (CH_2Cl_2), λ_{max} (ε) 282 nm (11200), 290 (10700), 404 (5300). Anal. calcd. for $C_{31}H_{27}N_3O$ (457): C 81.40, H 5.91, N 9.19; found: C 81.02, H 6.05, N 9.09.

1-(2-(2-(1*H*-Indol-3-yl)ethylamino)-4-phenyl-6-(pyrimidin-2-yl)cyclohexa-1,3-dienyl)ethanone (30b)



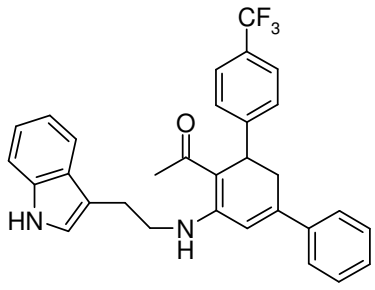
According to the GP after chromatography on silica gel (hexane/acetone 2:1) and recrystallization from acetone 321 mg (74 %) of **30b** were isolated as yellow crystals. Mp. 211 °C. ^{1}H NMR (DMSO-D_6, 300 MHz), δ 1.93 (s, 3 H), 2.52–3.05 (m, 4 H), 3.30–3.42 (m, 2 H), 4.17 (d, J = 7.14 Hz, 1 H), 6.54 (d, J = 2.5 Hz, 1 H), 6.92 (t, J = 4.95 Hz, 1 H), 7.06–7.08 (m, 1 H), 7.18–7.22 (m, 2 H), 7.23–7.34 (m, 4 H), 7.36–7.41 (m, 2 H), 7.59 (d, J = 7.77 Hz, 1 H), 8.44 (d, J = 4.74 Hz, 2 H), 10.85 (s, 1 H), 11.74 (t, J = 5.24 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 26.0 (CH_2), 27.4 (CH_3), 31.5 (CH_2), 41.4 (CH), 42.7 (CH_2), 99.1 ($C_{quat.}$), 111.0 (CH), 111.4 ($C_{quat.}$), 111.7 (CH), 118.3 (CH), 118.9 (CH), 121.0 (CH), 123.5 (CH), 126.0 (CH), 127.0 ($C_{quat.}$), 128.6 (CH), 128.8 (CH), 136.3 ($C_{quat.}$), 139.2 ($C_{quat.}$), 147.2 ($C_{quat.}$), 155.4 ($C_{quat.}$), 157.0 (CH), 172.2 ($C_{quat.}$), 193.6 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 434.2 (M^+, 18), 391.2 (M^+ - CH_3CO, 16), 304.1 (M^+ - C_9H_8N, 60), 130.1 ($C_9H_8N^+$, 100), 43 (CH_3CO^+, 22). IR (KBr), $\tilde{\nu}$ 3065 cm^{-1}, 1633, 1562, 1493, 1456, 1440, 1414, 1357, 1325, 1290, 1250, 1233, 1201, 762, 741, 696, 626, 560. UV/vis (CH_2Cl_2), λ_{max} (ε) 282 nm (11300), 290 (5000), 404 (3400). Anal. calcd. for $C_{28}H_{26}N_4O$ (434): C 77.39, H 6.03, N12.89; found: C 77.44, H 6.08, N 12.93.

1-(2-(2-(1*H*-Indol-3-yl)ethylamino)-4-phenyl-6-(pyridin-2-yl)cyclohexa-1,3-dienyl)ethanone (31c)



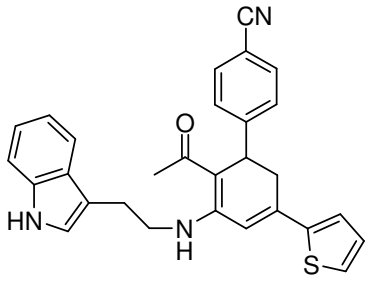
According to the GP after chromatography on silica gel (hexane/acetone 2:1), 304 mg (70 %) of **31c** were isolated as brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz), δ2.00 (s, 3 H), 2.58 (ddd, *J* = 16.84 Hz, *J* = 7.87 Hz, *J* = 2.7 Hz, 1 H), 3.00–3.04 (m, 2 H), 3.19 (dd, *J* = 16.84 Hz, *J* = 1.75 Hz 1 H), 3.56 (m, 2 H), 4.21 (d, *J* = 6.75 Hz, 1 H), 6.31 (d, *J* = 2.7 Hz, 1 H), 6.89–7.12 (m, 10 H), 7.18 (dd, *J* = 6.75 Hz, , *J* = 1.7 Hz, 1 H), 7.31 (td, *J* = 7.7 Hz, , *J* = 1.75 Hz, 1 H), 7.49 (d, *J* = 6.75 Hz 1 H), 8.38-8.40 (m, 1 H), 8.86 (s, 1 H), 11.75 (t, *J* = 5.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ26.5 (CH_2), 27.1 (CH_3), 33.8 (CH_2), 41.3 (CH_2), 99.4 (CH), 111.4 (CH), 112.0 ($C_{quat.}$), 115.5 (CH), 118.3 (CH), 119.2 (CH), 121.2 (CH), 121.5 (CH), 121.8 (CH), 123.0 (CH), 125.8 (CH), 127.1 ($C_{quat.}$), 128.4 (CH), 128.8 (CH), 136.5 ($C_{quat.}$), 139.4 ($C_{quat.}$), 148.1 ($C_{quat.}$), 149.1 (CH), 157.0 ($C_{quat.}$), 163.8 ($C_{quat.}$), 194.6 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 433.2 (M^+, 50), 390.2 (M^+ - CH_3CO, 70), 303.1 (M^+ - C_9H_8N, 100), 130.1 ($C_9H_8N^+$, 20), 43 (CH_3CO^+, 19). HRMS calcd. for $C_{29}H_{27}N_3O$: 433.2154; found 433.2155.

1-(2-(2-(1*H*-Indol-3-yl)ethylamino)-4-phenyl-6-(4-(trifluoromethyl)phenyl)cyclohexa-1,3-dienyl)ethanone (31d)



According to the GP after chromatography on silica gel (hexane/acetone 2:1) and recrystallization from acetone 235 mg (47 %) of **31d** were isolated as yellow crystals. M.p. 230 °C. ^{1}H NMR (DMSO-D_6, 300 MHz), δ 1.81 (s, 3 H), 2.79 (d, J = 15.75 Hz, 1 H), 2.94–3.14 (m, 3 H), 3.68–3.84 (m, 2 H), 4.18 (d, J = 7.75 Hz, 1 H), 6.55 (d, J = 2.5 Hz, 1 H), 6.90 (t, J = 6.9 Hz, 1 H), 7.09–7.39 (m, 10 H), 7.59–7.62 (m, 3 H), 10.93 (s, 1 H), 11.70 (t, J = 5.75 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 26.5 (CH_2), 26.9 (CH_3), 34.9 (CH_2), 37.9 (CH), 42.5 (CH_2), 98.0 ($C_{quat.}$), 110.9 ($C_{quat.}$), 111.4 (CH), 115.7 (CH), 118.2 (CH), 118.3 (CH), 121.0 (CH), 123.6 (CH), 124.9 (CH), 125.0 (CH), 125.5 (CH), 127.0 ($C_{quat.}$), 128.0 (CH), 128.5 (CH), 128.7 (CH), 136.3 ($C_{quat.}$), 138.7 ($C_{quat.}$), 145.2 ($C_{quat.}$), 149.9 ($C_{quat.}$), 155.9 ($C_{quat.}$), 192.9 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 500.1 (M^+, 18), 457.2 (M^+ - CH_3CO, 8), 370.1 (M^+ - C_9H_8N, 75), 130.1 ($C_9H_8N^+$, 100), 43 (CH_3CO^+, 20). IR (KBr), $\tilde{\nu}$ 3045 cm^{-1}, 1633, 1563, 1544, 1459, 1441, 1358, 1326, 1292, 1245, 1210, 1163, 1122, 1112, 1068, 767, 745, 695, 626, 534. UV/vis (CH_2Cl_2), λ_{max} (ε) 282 nm (16700), 290 (15600), 404 (8300). Anal. calcd. for $C_{31}H_{27}F_3N_2O$ (500): C 74.38, H 5.44, N 5.6; found : C 74.47, H 5.56, N 5.69.

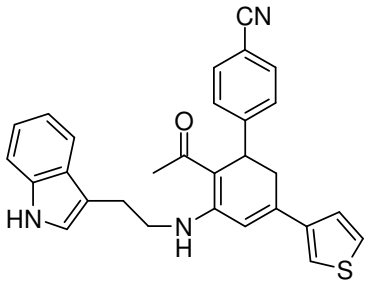
4-(3-(2-(1*H*-Indol-3-yl)ethylamino)-2-acetyl-5-(thiophen-2-yl)cyclohexa-2,4-dienyl)benzonitrile (31e)



According to the GP after chromatography on silica gel (hexane/acetone 2:1), 250 mg (54 %) of **31e** were isolated as brown oil. ^{1}H NMR (DMSO-D_6, 300 MHz), δ 1.78 (s, 3 H), 2.86–3.07 (m, 4 H), 3.66–3.85 (m, 2 H), 4.15 (d, J = 5.25 Hz, 1 H), 6.59 (s, 1 H), 6.99 (t, J = 6.0 Hz, 1 H), 7.07–7.12 (m, 2 H), 7.25–7.26 (m, 1 H), 7.30 (d, , J = 7.0 Hz, 2 H), 7.35 (s, 1 H), 7.44–7.46 (m, 1H), 7.55–7.56 (m, 1H), 7.61 (d, J = 6.25 Hz, 1 H), 7.67 (d, J = 7.0 Hz, 2 H), 10.88 (s, 1 H), 11.69 (t, J = 4.75 Hz, 1 H). ^{13}C NMR (DMSO-D_6, 100 MHz), δ 26.4 (CH_2), 26.8 (CH_3), 34.4 (CH_2), 38.0 (CH), 42.5 (CH_2), 97.8 ($C_{quat.}$), 108.8 (CH), 110.9 ($C_{quat.}$), 111.4 (CH), 114.0 ($C_{quat.}$), 118.3 (CH), 118.9 ($C_{quat.}$), 120.9 (CH), 123.5 (CH), 125.2 (CH), 126.9 (CH), 127.0 (CH), 132.0 (CH), 136.3 ($C_{quat.}$), 140.2 ($C_{quat.}$), 140.6 ($C_{quat.}$), 150.4 ($C_{quat.}$), 156.3

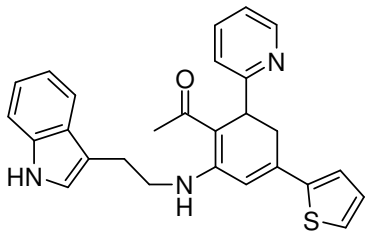
($C_{quat.}$), 192.4 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 463.4 (M^+, 100), 458.3 (M^+ - CH_3, 18), 420 (M^+ - CH_3CO, 22), 130.1 ($C_9H_8N^+$, 100), 43 (CH_3CO^+, 20). IR (KBr), $\tilde{\nu}$ 3425 cm^{-1}, 2230, 1628, 1604, 1559, 1458, 1427, 1354, 1320, 1280, 1245, 1209, 941, 785, 742, 668, 617, 547, 499, 462. UV/vis (CH_2Cl_2), λ_{max} (ε) 276 nm (15800), 284 (16800), 292 (17000), 406 (8800). Anal. calcd. for $C_{29}H_{25}N_3OS$ (463): C 75.13, H 5.44, N 9.06, S 6.92; found: C 75.38, H 5.36, N 8.85, S 6.88.

4-(3-(2-(1*H*-Indol-3-yl)ethylamino)-2-acetyl-5-(thiophen-3-yl)cyclohexa-2,4-dienyl)benzonitrile (31f)



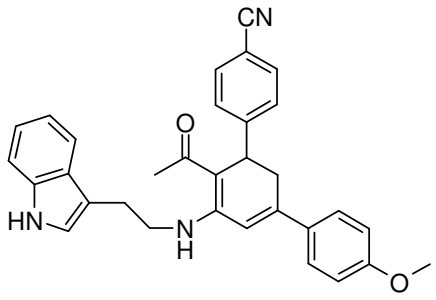
According to the GP after chromatography on silica gel (hexane/acetone 2:1), 296 mg (64 %) of **31f** were isolated as brown oil. ^{1}H NMR (DMSO-D_6, 300 MHz), δ 1.78 (s, 3 H), 2.86–2.92 (d, *J* = 15.75 Hz,1 H), 2.95–3.06 (m, 3 H), 3.65–3.80 (m, 2 H), 4.16 (d, *J* = 5.75 Hz, 1 H), 6.60 (s, 1 H), 6.98–7.03 (m, 2 H), 7.06 (t, *J* = 6.25 Hz, 1 H), 7.18–7.19 (m, 1 H), 7.25 (s, 1 H), 7.32–7.35 (m, 3 H), 7.55–7.56 (d, *J* = 4.0 Hz, 1 H), 7.60 (d, *J* = 6.5 Hz, 1 H), 7.67 (d, *J* = 6.25 Hz, 2 H), 10.88 (s, 1 H), 11.63 (t, *J* = 4.75 Hz, 1 H). ^{13}C NMR (DMSO-D_6, 100 MHz), δ 26.3 (CH_2), 26.8 (CH_3), 35.1 (CH_2), 38.1 (CH), 42.7 (CH_2), 98.0 ($C_{quat.}$), 108.9 ($C_{quat.}$), 110.9 ($C_{quat.}$), 11.4 (CH), 112.9 (CH), 118.2 (CH), 118.3 (CH), 118.8 ($C_{quat.}$), 128.1 (CH), 128.3 (CH), 128.4 (CH), 132.0 (CH), 136.3 ($C_{quat.}$), 139.0 ($C_{quat.}$), 142.7 ($C_{quat.}$), 150.8 ($C_{quat.}$), 155.8 ($C_{quat.}$), 192.5 ($C_{quat.}$).). MS (70 eV, EI): *m/z* (%): 464.4 (M^+ + H^+, 70), 463.4 (M^+, 60), 458.3 (M^+ - CH_3, 100), 420 (M^+ - CH_3CO, 27), 130.1 ($C_9H_8N^+$, 100), 43 (CH_3CO^+, 15). IR (KBr), $\tilde{\nu}$ 3423 cm^{-1}, 2920, 2227, 1623, 1559, 1500, 1458, 1423, 1384, 1352, 1325, 1284, 1244, 1209, 1152, 944, 847, 741, 707, 549. UV/vis (CH_2Cl_2), λ_{max} (ε) 282 nm (13000), 290 (11500), 326 (11700), 424 (8800). HRMS calcd. for $C_{29}H_{25}N_3OS$: 463.1745; found 463.1718.

1-(2-(2-(1*H*-Indol-3-yl)ethylamino)-6-(pyridin-2-yl)-4-(thiophen-2-yl)cyclohexa-1,3-dienyl)ethanone (31g)



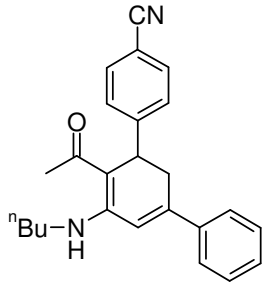
According to the GP after chromatography on silica gel (hexane/acetone 2:1) and recrystallization from acetone 264 mg (60 %) of **31g** were isolated as yellow oil. ^{1}H NMR (DMSO-D_6, 300 MHz), δ 1.90 (s, 3 H), 2.95 (dd, *J* = 2.25 Hz, *J* = 6.25 Hz, 1 H), 3.09–3.14 (m, 2 H), 3.37 (dd, *J* = 1.5 Hz, *J* = 13.5 Hz, 1 H), 3.72–3.85 (m, 2 H), 4.13 (dd, *J* = 1.25 Hz, *J* = 6.5 Hz, 1 H), 6.64 (d, *J* = 2.25 Hz, 1 H) 6.98–7.13 (m, 5 H), 7.15-7.16 (m, 1 H), 7.31 (d, *J* = 1.75 Hz, 1 H), 7.35 (d, *J* = 6.75 Hz, 1 H), 7.42 (dd, *J* = 1.0 Hz, *J* = 4.0 Hz, 1 H), 7.54 (td, *J* = 1.0 Hz, *J* = 6.25 Hz, 1 H), 7.66 (d, *J* = 6.75 Hz, 1 H), 8.47–8.49 (m, 1 H), 10.11 (s, 1 H), 11.85 (t, *J* = 4.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 27.2 (CH_3), 27.6 (CH_2), 34.4 (CH_2), 42.0 (CH), 44.1 (CH_2), 55.3 (CH_3), 112.2 (CH), 112.7 (C_{quat}), 119.1 (CH), 119.53 (CH), 121.8 (CH), 122.0 (CH), 124.1 (CH), 126.9 ($C_{quat.}$), 127.9 (CH), 128.4 (CH), 128.9 (CH), 137.7 (CH), 141.0 ($C_{quat.}$), 144.4 ($C_{quat.}$), 149.9 (C_{quat}), 156.9 ($C_{quat.}$), 164.9 (C_{quat}), 194.2 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 439.1 (M^+, 55), 396.1 (M^+ - CH_3CO, 65), 309.1 (M^+ - C_9H_8N, 100), 43 (CH_3CO^+, 25). IR (KBr), $\tilde{\nu}$ 3416 cm^{-1}, 3102, 3055, 2919, 1622, 1559, 1458, 1424, 1383, 1352, 1323, 1285, 1242, 1204, 1185, 1148, 943, 768, 741, 702. UV/vis (CH_2Cl_2), λ_{max} (ε) 272 nm (16200), 290 (13900), 326 (13100), 420 (10000). HRMS calcd. for $C_{27}H_{25}N_3OS$: 439.1718; found 439.1736.

4-(3-(2-(1*H*-Indol-3-yl)ethylamino)-2-acetyl-5-(4-methoxyphenyl)cyclohexa-2,4-dienyl)benzonitrile (31h)



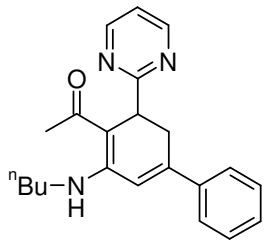
According to the GP after chromatography on silica gel (hexane/acetone 2:1) and recrystallization from acetone 331 mg (68 %) of **31h** were isolated as yellow crystals. M.p. 227 °C. ^{1}H NMR (DMSO-D_6, 300 MHz), δ 1.78 (s, 3 H), 2.75 (d, J = 16.75 Hz, 1 H), 2.89–3.11 (m, 3 H), 3.64–3.88 (m, 2 H), 3.72 (s, 3 H), 4.14 (d, J = 7.75 Hz, 1 H), 6.44 (s, 1 H) 6.77 (d, J = 9.0 Hz, 2 H), 6.99–7.07 (m, 3 H), 7.13 (t, J = 7.75 Hz, 1 H), 7.25–7.38 (m, 4 H), 7.61 (d, J = 7.75 Hz, 1 H), 7.67 (d, J = 7.75 Hz, 2 H), 10.89 (s, 1 H), 11.74 (t, J = 6.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 26.6 (CH_2), 26.9 (CH_3), 34.7 (CH_2), 38.3 (CH), 42.5 (CH_2), 55.3 (CH_3), 97.5 (C_{quat}) 108.9 ($C_{quat.}$), 110.9 ($C_{quat.}$), 111.0 ($C_{quat.}$), 111.5 (CH), 118.3 (CH), 118.5 (CH), 119.0 (C_{quat}), 121.1 (CH), 123.7 (CH), 127.2 (CH), 128.4 (CH), 130.9 ($C_{quat.}$), 132.6 (CH), 136.4 (C_{quat}), 145.0 ($C_{quat.}$), 151.3 (CH) 156.5 ($C_{quat.}$), 159.9 ($C_{quat.}$), 192.4($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 487.1 (M^+, 13), 444.1 (M^+ - CH_3CO, 10), 357.1 (M^+ - C_9H_8N, 80), 130.1 ($C_9H_8N^+$, 100), 43 (CH_3CO^+, 18). IR (KBr), $\tilde{\nu}$ 3406 cm^{-1}, 3050, 2227, 1629, 1604, 1559, 1512, 1458, 1357, 1331, 1295, 1257, 1232, 1210, 1180, 1030, 828, 745, 560. UV/vis (CH_2Cl_2), λ_{max} (ε) 284 nm (41100), 292 (42600), 312 (41100), 404 (40000), 312 (51800). Anal. calcd. for $C_{32}H_{29}N_3O_2$ (487): C 78.82, H 5.99, N 8.62; found: C 78.84, H 6.01, N 8.60.

4-(2-Acetyl-3-(butylamino)-5-phenylcyclohexa-2,4-dienyl)benzonitrile (31i)



According to the GP after chromatography on silica gel (hexane/acetone 2:1), 200 mg (54 %) of **31i** were isolated as brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 0.91 (t, J = 7.25 Hz, 3 H), 1.38–1.52 (m, 2 H), 1.60–1.69 (m, 2 H), 1.88 (s, 3 H), 2.98 (dd, J = 16.75 Hz, J = 2.0 Hz, 1 H), 3.17 (ddd, J = 16.75 Hz, J = 7.75 Hz, J = 2.5 Hz, 1 H), 3.47–3.58 (m, 2 H), 4.30 (dd, J = 7.75 Hz, J = 1.75 Hz, 1 H), 6.89 (d, J = 2.75 Hz, 1 H), 7.29–7.33 (m, 3 H), 7.41-7.45 (m, 2 H), 7.46 (d, J = 8.0 Hz, 2 H), 7.59 (d, J = 8.0 Hz, 2 H), 11.74 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 14.0 (CH_3), 20.6 (CH_2), 27.1 (CH), 33.1 (CH_2), 36.1 (CH_2), 39.7 (CH), 42.8 (CH_2), 99.0 ($C_{quat.}$), 110.5 ($C_{quat.}$), 116.7 (CH), 119.4 ($C_{quat.}$), 126.6 (CH), 129.1 (CH), 129.4 (CH), 129.6 (CH), 129.8 (CH), 132.7 (CH), 140.1 ($C_{quat.}$), 147.4 ($C_{quat.}$), 151.9 ($C_{quat.}$), 157.4 ($C_{quat.}$), 194.6 ($C_{quat.}$), 207.3 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 370.2 (M^+, 70), 327.2 (M^+ - CH_3CO, 100), 268.2 (M^+ - C_7H_4N, 50), 43 (CH_3CO^+, 28). IR (KBr), $\tilde{\nu}$ 2958 cm^{-1}, 2931, 2872, 2227, 1713, 1634, 1604, 1578, 1558, 1498, 1460, 1443, 1357, 1328, 1291, 1247, 1222, 830, 768, 696. UV/vis (CH_2Cl_2), λ_{max} (ε) 286 nm (14000), 402 (6200). HRMS calcd. for $C_{25}H_{26}N_2O$: 370.2045; found 370.2049.

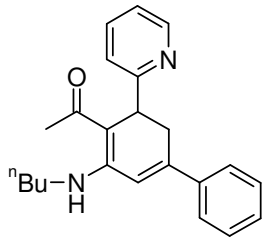
1-(2-(butylamino)-4-phenyl-6-(pyrimidin-2-yl)cyclohexa-1,3-dienyl)ethanone (31j)



According to the GP after chromatography on silica gel (hexane/acetone 2:1), 180 mg (52 %) of **31j** were isolated as brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 0.90 (t, J = 7.3 Hz, 3 H),

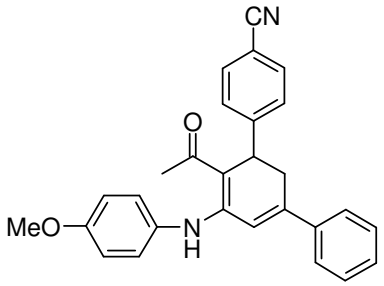
1.39–1.49 (m, 2 H), 1.57–1.67 (m, 2 H), 2.14 (s, 3 H), 3.02 (ddd, *J* = 16.8 Hz, *J* = 7.6 Hz, *J* = 2.85 Hz, 1 H), 3.32–3.40 (m, 2 H), 3.51 (dd, *J* = 16.8 Hz, *J* = 1.75 Hz, 1 H), 4.32 (d, *J* = 5.9 Hz, 1 H), 6.54 (d, *J* = 2.79 Hz, 1 H), 6.99 (t, *J* = 4.83 Hz, 1 H), 7.29-7.60 (m, 5 H), 8.57 (d, *J* = 4.83 Hz, 2 H), 11.75 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 13.6 (CH_3), 19.9 (CH_2), 27.2 (CH), 32.0 (CH_2), 32.3 (CH_2), 42.1 (CH), 42.3 (CH_2), 98.8 ($C_{quat.}$), 115.7 (CH), 117.8 (CH), 125.9 (CH), 126.1 (CH), 128.3 (CH), 128.5 (CH), 139.8 ($C_{quat.}$), 148.0 ($C_{quat.}$), 155.8 ($C_{quat.}$), 156.3 (CH), 172.6 ($C_{quat.}$), 194.5 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 347.2 (M^+, 45), 304.2 (M^+ - CH_3CO, 100), 268.1 (M^+ - $C_4H_3N_2$, 40), 43 (CH_3CO^+, 26). IR (KBr), $\tilde{\nu}$ 3034 cm^{-1}, 2958, 2930, 2872, 1792, 1634, 1562, 1466, 1416, 1295, 1164, 1129, 1079, 938, 762, 697. UV/vis (CH_2Cl_2), λ_{max} (ε) 250 nm (10100), 282 (13300), 402 (5100). HRMS calcd. for $C_{22}H_{25}N_3O$: 347.1998; found 347.1992.

1-(2-(Butylamino)-4-phenyl-6-(pyridin-2-yl)cyclohexa-1,3-dienyl)ethanone (31k)



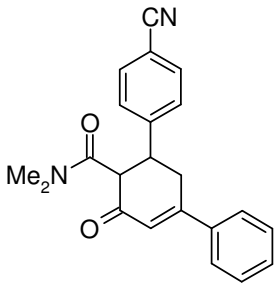
According to the GP after chromatography on silica gel (hexane/acetone 2:1), 180 mg (52 %) of **31k** were isolated as brown oil. ^{1}H NMR (DMSO-D_6, 300 MHz), δ 0.90 (t, *J* = 7.25 Hz, 3 H), 1.31–1.43 (m, 2 H), 1.52–1.64 (m, 2 H), 1.92 (s, 3 H), 3.02 (ddd, *J* = 16.75 Hz, *J* = 8.0 Hz, *J* = 2.75 Hz, 1 H), 3.31–3.36 (m, 2 H), 4.15 (d, *J* = 8.0 Hz, 1 H), 6.52 (d, *J* = 2.75 Hz, 1 H), 6.90–6.95 (m, 1 H), 7.04 (d, *J* = 7.75 Hz, 1 H), 7.18-7.28 (m, 5 H), 7.35 (td, *J* = 7.75 Hz, *J* = 1.75 Hz, 1 H), 8.42 (d, *J* = 4.75 Hz, 1 H), 11.70 (t, *J* = 5.25 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 13.8 (CH_3), 19.8 (CH_2), 26.8 (CH), 31.4 (CH_2), 33.6 (CH_2), 41.1 (CH), 42.3 (CH_2), 98.1 ($C_{quat.}$), 115.2 (CH), 120.9 (CH), 121.1 (CH), 125.8 (CH), 128.2 (CH), 128.4 (CH), 135.9 (CH), 148.2 ($C_{quat.}$), 148.8 (CH), 156.5 ($C_{quat.}$), 163.6 ($C_{quat.}$), 194.2 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 346.2 (M^+, 15), 303.2 (M^+ - CH_3CO, 100), 268.1 (M^+ - C_5H_4N, 40), 43 (CH_3CO^+, 22). IR (KBr), $\tilde{\nu}$ 3392 cm^{-1}, 3057, 2957, 2929, 2872, 1724, 1635, 1560, 1465, 1433, 1355, 1290, 1244, 1120, 964, 938, 763, 697, 542. UV/vis (CH_2Cl_2), λ_{max} (ε) 272 nm (13300), 402 (5000). HRMS calcd. for $C_{23}H_{26}N_2O$: 346.2045; found 346.2059.

4-(2-Acetyl-3-(4-methoxyphenylamino)-5-phenylcyclohexa-2,4-dienyl)benzonitrile (31l)



According to the GP after chromatography on silica gel (hexane/acetone 2:1), 126 mg (30 %) of **31l** were isolated as brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.02 (s, 3 H), 2.93 (d, J = 16.5 Hz, 1 H), 3.25–3.34 (m, 1 H), 3.81 (s, 3 H), 4.25 (d, J = 7.3 Hz, 1 H), 6.57 (d, J = 2.73 Hz, 1 H), 6.89 (dd, J = 6.81 Hz, J = 2.13 Hz, 2 H), 7.10 (d, J = 6.81 Hz, 2 H), 7.13–7.26 (m, 5 H), 7.35 (d, J = 8.25 Hz, 2 H), 7.51 (d, J = 8.25 Hz, 1 H), 12.60 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 27.4 (CH_3), 35.3 (CH_2), 39.3 (CH), 55.4 (CH_3), 100.5 ($C_{quat.}$), 110.3 ($C_{quat.}$), 114.3 (CH), 117.5 (CH), 118.8 ($C_{quat.}$), 125.6 (CH), 126.2 (CH), 127.5 (CH), 127.8 (CH), 128.3 (CH), 130.8 ($C_{quat.}$), 131.9 (CH), 139.0 ($C_{quat.}$), 145.2 ($C_{quat.}$), 149.9 ($C_{quat.}$), 154.2 ($C_{quat.}$), 157.5 ($C_{quat.}$), 195.8 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 420.1 (M^+, 70), 405.2 (M^+ - CH_3, 5), 377.2 (M^+ - CH_3CO, 60), 318.2 (M^+ - C_7H_4N, 18), 43 (CH_3CO^+, 17). IR (KBr), $\tilde{\nu}$ 2962 cm^{-1}, 2930, 2227, 1606, 1511, 1245, 1033, 824, 697. UV/vis (CH_2Cl_2), λ_{max} (ε) 270 nm (16500), 350 (5100), 386 (5000). HRMS calcd. for $C_{28}H_{24}N_2O_2$: 420.1838; found 420.1841.

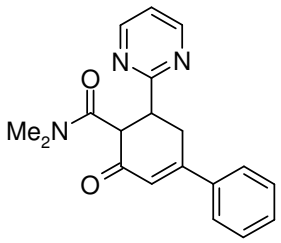
6-(4-Cyanophenyl)-*N*,*N*-dimethyl-2-oxo-4-phenylcyclohex-3-enecarboxamide (32a)



According to the GP after chromatography on silica gel (toluene/acetone 3:1) and recrystallization from acetone 227 mg (66 %) of **32a** were isolated as light yellow crystals. M.p. 164 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.79 (s, 3 H), 2.96 (s, 3 H), 2.99–3.01 (m, 2 H), 3.97 (ddd, J = 6.0 Hz, J = 12.0 Hz, J = 12.0 Hz, 1 H), 4.08 (d, J = 12.0 Hz, 1 H), 6.45 (s, 1 H),

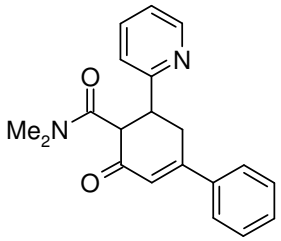
7.31–7.50 (m, 7 H), 7.53 (d, J = 8.16 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 35.3 (CH_2), 35.5 (CH_3), 37.4 (CH_3), 43.6 (CH), 54.7 (CH), 110.6 ($C_{quat.}$), 118.5 ($C_{quat.}$), 124.2 (CH), 125.5 (CH), 128.1 (CH), 128.7 (CH), 130.4 (CH), 132.7 (CH), 137.3 ($C_{quat.}$), 147.6 ($C_{quat.}$), 158.1 ($C_{quat.}$), 168.3 ($C_{quat.}$), 194.8 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 344.1 (M^+, 30), 300.1 (M^+ - $C_2H_6N^+$, 7), 272.1 (M^+ - C_2H_6NCO, 100), 244.1 (M^+ - C_2H_6NCO, - CO, 6), 72 ($C_2H_6NCO^+$, 23). IR (KBr), $\tilde{\nu}$ 3870 cm^{-1}, 3854, 3822, 3816, 3802, 3752, 3745, 3736, 3712, 3676, 3651, 3629, 3432, 3056, 2932, 2227, 1644, 1608, 1574, 1507, 1447, 1414, 1399, 1369, 1285, 1249, 1170, 1136, 1116, 1042, 1002, 970, 944, 914, 884, 864, 835, 762, 694, 609, 581, 509. UV/vis (CH_2Cl_2), λ_{max} (ε) 240 nm (20600), 288 (22600). Anal. calcd. for $C_{22}H_{20}N_2O_2$ (344): C 76.72, H 5.85, N 8.13; found : C 76.96, H 5.89, N 8.15.

***N*,*N*-Dimethyl-2-oxo-4-phenyl-6-(pyrimidin-2-yl)cyclohex-3-enecarboxamide (32b)**



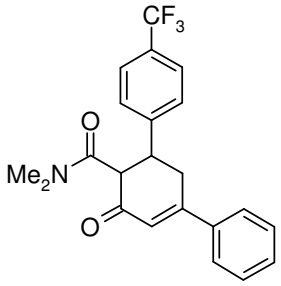
According to the GP after chromatography on silica gel (toluene/acetone 1:1) and recrystallization from acetone 218 mg (68 %) of **32b** were isolated as light brown crystals. M.p. 163 °C. ^{1}H NMR ($CDCl_3$, 250 MHz), δ 1.35–1.41 (m, 1 H), 2.71 (s, 3 H), 2.98 (s, 3 H), 3.14 (dd, J = 18.0 Hz, J = 4.5 Hz, 1 H), 4.09 (ddd, J = 4.5 Hz, J = 11.5 Hz, J = 11.8 Hz, 1 H), 4.29 (d, J = 11.8 Hz, 1 H), 6.29 (d, J = 2.0 Hz, 1 H), 7.41 (t, J = 2.0 Hz, 1 H), 7.23–7.46 (m, 5 H), 8.43 (d, J = 4.75 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 33.9 (CH_2), 35.6 (CH_3), 37.6 (CH_3), 46.0 (CH), 52.6 (CH), 119.0 (CH), 125.5 (CH), 124.5 (CH), 126.0 (CH), 128.4 (CH), 128.6 (CH), 130.1 (CH), 131.5 (CH), 131.9 (CH), 137.6 ($C_{quat.}$), 157.0 (CH), 157.9 ($C_{quat.}$), 169.5 ($C_{quat.}$), 170.3 ($C_{quat.}$), 195.1 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 321.2 (M^+, 5), 277.1 (M^+ - C_2H_6N, 100), 249.1 (M^+ - C_2H_6NCO, 9), 72 ($C_2H_6NCO^+$, 17). IR (KBr), $\tilde{\nu}$ 3342 cm^{-1}, 3052, 2930, 1645, 1569, 1563, 1494, 1493, 1423, 1396, 1369, 1265, 1120, 760, 721, 696, 542. UV/vis (CH_2Cl_2), λ_{max} (ε) 286 nm (30000). HRMS calcd. for $C_{19}H_{19}N_3O_2$: 321.1477; found: 321.1476.

_N_,_N_-Dimethyl-2-oxo-4-phenyl-6-(pyridin-2-yl)cyclohex-3-enecarboxamide (32c)



According to the GP after chromatography on silica gel (toluene/acetone 3:1) and recrystallization from acetone 154 mg (48 %) of **32c** were isolated as light brown crystals. M.p. 151 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.68 (s, 3 H), 2.87–3.18 (m, 5 H), 3.93 (ddd, J = 5.5 Hz, J = 12.0 Hz, J = 12.3 Hz, 1 H), 4.35 (d, J = 12.3 Hz, 1 H), 6.34 (d, J = 2.0 Hz, 1 H), 6.96–6.99 (m, 1 H), 7.10 (d, J = 7.25 Hz, 1 H), 7.22–7,24 (m, 2 H), 7.35–7.48 (m, 4 H), 8.36 (d, J = 4.75 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 34.6 (CH_2), 35.6 (CH_3), 37.6 (CH_3), 45.5 (CH), 53.9 (CH), 122.1 (CH), 123.8 (CH), 124.5 (CH), 126.1 (CH), 128.4 (CH), 130.2(CH), 136.8 (CH), 138.1 ($C_{quat.}$), 149.0 (CH), 158.3 ($C_{quat.}$), 161.0 ($C_{quat.}$), 169.5 ($C_{quat.}$), 195.5 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 320.2 (M^+, 18), 276.1 (M^+ - $N(CH_3)_2$, 42), 249.1 (M^+ - C_2H_6NCO, 100), 72 ($C_2H_6NCO^+$, 22). IR (KBr), $\tilde{\nu}$ 3440 cm^{-1}, 3055, 2931, 1645, 1591, 1571, 1496, 1473, 1439, 1398, 1352, 1292, 1163, 1141, 760, 691, 524. UV/vis (CH_2Cl_2), λ_{max} (ε) 264 nm (14100), 272 (16500), 288 (18900). Anal. calcd. for $C_{20}H_{20}N_2O_2$ (320): C 75.00, H 6.25, N 8.75; found: C 74.51, H 6.41, N 8.60.

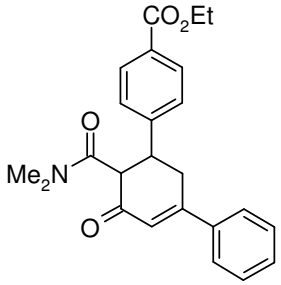
_N_,_N_-Dimethyl-2-oxo-4-phenyl-6-(4-(trifluoromethyl)phenyl)cyclohex-3-enecarboxamide (32d)



According to the GP after chromatography on silica gel (toluene/acetone 1:1) and recrystallization from acetone 218 mg (68 %) of **32d** were isolated as light brown crystals.

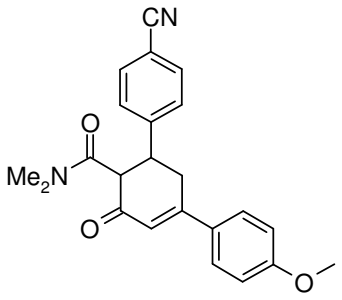
M.p. 177 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2,79 (s, 3 H), 2.90 (s, 3 H), 3.05–3.13 (dd, J = 17.5 Hz, J = 5.4 Hz, 2 H), 4.01–4.12 (m, 2 H), 6.59 (d, J = 2.0 Hz, 1 H), 7.29–7.65 (m, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 35.3 (CH_2), 35.5 (CH_3), 37.4 (CH_3), 43.2 (CH), 54.8 (CH), 124.4 (CH), 125.5 (CH), 126.0 (CH), 127.5 (CH), 130.3 (CH), 146.2 ($C_{quat.}$), 158.1 ($C_{quat.}$), 168.3 ($C_{quat.}$), 194.2 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 387.1 (M^+, 10), 315.1 (M^+ - $C_4H_{10}N$, 100), 72 ($C_2H_6NCO^+$, 9). IR (KBr), $\tilde{\nu}$ 3440 cm^{-1}, 3058, 2934, 1644, 1620, 1575, 1497, 1447, 1421, 1400, 1370, 1327, 1226, 1166, 1115, 1069, 1019, 837, 762, 694, 611, 520. UV/vis (CH_2Cl_2), λ_{max} (ε) 288 nm (18200). HRMS calcd. for $C_{22}H_{20}F_3NO_2$: 387.1446; found: 387.1439.

Ethyl 4-(6-(dimethylcarbamoyl)-5-oxo-3-phenylcyclohex-3-enyl)benzoate (32e)



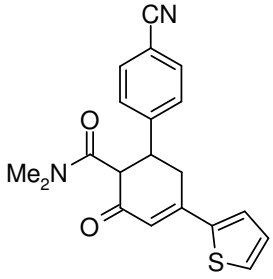
According to the GP after chromatography on silica gel (toluene/acetone 4:1) and recrystallization from acetone 186 mg (48 %) of **32e** were isolated as light brown oil. ^{1}H NMR ($CDCl_3$, 250 MHz), δ 1.18 (t, J = 7.25 Hz, 3 H), 2.66 (s, 3 H), 2.81 (s, 3 H), 2.85–2.98 (m, 2 H), 3.82–3.99 (m, 2 H), 4.14 (q, J = 7.25 Hz, 2 H), 6.35 (s, 1 H), 7.20–7.38 (m, 7 H), 7.82 (d, J = 8.5 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 14.1 (CH_3), 35.1 (CH_2), 35.5 (CH_3), 35.1 (CH_2), 35.5 (CH_3), 37.4 (CH_3), 43.4 (CH), 54.9 (CH), 60.7 (CH_2), 124.4 (CH), 126.0 (CH), 127.1 (CH), 128.7 (CH), 129.3 ($C_{quat.}$), 129.9 (CH), 130.3 (CH), 137.6 ($C_{quat.}$), 147.1 ($C_{quat.}$), 158.3 ($C_{quat.}$), 166.1 ($C_{quat.}$), 168.5 ($C_{quat.}$), 194.4 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%) : 391.2 (M^+, 11), 346.1 (M^+ - $C_2H_6N^+$, 6), 319.1 (M^+ - $C_2H_6NCO^+$, 100), 72 ($C_2H_6NCO^+$, 7). IR (KBr), $\tilde{\nu}$ 3325 cm^{-1}, 3059, 2958, 2933, 2246, 1714, 1643, 1611, 1575, 1447, 1366, 1279, 1183, 1106, 1021, 971, 774, 760, 732, 707. UV/vis (CH_2Cl_2), λ_{max} (ε) 240 nm (12700), 286 (12300), 382 (23600). HRMS calcd. for $C_{24}H_{25}NO_4$: 391.1783; found: 391.1760.

6-(4-Cyanophenyl)-4-(4-methoxyphenyl)-*N*,*N*-dimethyl-2-oxocyclohex-3-enecarboxamide (32f)



According to the GP after chromatography on silica gel (toluene/acetone 3:1), 217 mg (58 %) of **32f** were isolated as light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.75 (s, 3 H), 3.04 (s, 3 H), 3.06–3.09 (m, 2 H), 3.38 (s, 3 H), 3.92–4.02 (m, 1 H), 4.49 (d, J = 10.8 Hz, 1 H), 6.43 (s, 1 H), 7.00 (d, J = 7.75 Hz, 2 H), 7.63–7.72 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 35.3 (CH_3), 35.6 (CH_2), 37.5 (CH_3), 44.8 (CH), 55.4 (CH), 55.7 (CH_3), 111.2 ($C_{quat.}$), 115.0 (CH), 119.3 ($C_{quat.}$), 122.9 (CH), 128.8 (CH), 129.6 (CH), 130.6 ($C_{quat.}$), 132.9 (CH), 149.8 ($C_{quat.}$), 158.5 ($C_{quat.}$), 162.5 ($C_{quat.}$), 169.5 ($C_{quat.}$), 195.1 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 374.1 (M^+, 7), 302.1 (M^+ - $C_2H_6NCO^+$, 100), 72 ($C_2H_6NCO^+$, 11). IR (KBr), $\tilde{\nu}$ 3441 cm^{-1}, 2934, 2227, 1641, 1600, 1570, 1513, 1463, 1421, 1400, 1370, 1276, 1245, 1184, 1138, 1030, 827, 582, 569, 551. UV/vis (CH_2Cl_2), λ_{max} (ε) 318 nm (17100). HRMS calcd. for $C_{23}H_{22}N_2O_3$: 374.1630; found 374.1645.

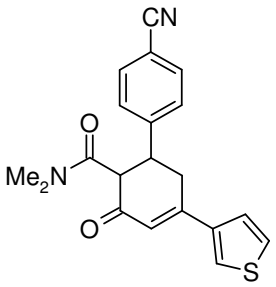
6-(4-Cyanophenyl)-*N*,*N*-dimethyl-2-oxo-4-(thiophen-2-yl)cyclohex-3-enecarboxamide (32g)



According to the GP after chromatography on silica gel (toluene/acetone 3:1) and recrystallization from acetone 231 mg (66 %) of **32g** were isolated as light yellow crystals.

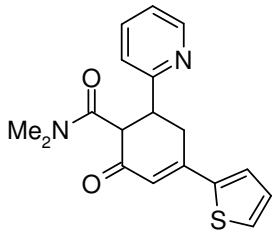
M.p. 176–177 °C. ^{1}H NMR (DMSO-D_6, 300 MHz), δ 2.67 (s, 3 H), 3.03 (s, 3 H), 3.10–3.15 (m, 1 H), 3.17 (dd, *J* = 6.0 Hz, *J* = 20.0 Hz, 1 H), 3.80 (ddd, *J* = 6.0 Hz, *J* = 14.4 Hz, *J* = 15.0 Hz, 1 H), 4.62 (d, *J* = 15.0 Hz 1 H), 6.43 (s, 1 H), 7.17 (t, *J* = 4.5 Hz, 1 H), 7.59 (d, *J* = 7.5 Hz , 2 H), 7.69 (d, *J* = 2.5 Hz , 1 H), 7.77–7.82 (m, 3 H). ^{13}C NMR (DMSO-D_6, 100 MHz), δ 34.87 (CH_2), 34.92 (CH_3), 37.1 (CH_3), 43.2 (CH), 53.7 (CH), 109.6 ($C_{quat.}$), 118.9 ($C_{quat.}$), 120.7 (CH), 128.8 (CH), 129.1 (CH), 129.5 (CH), 130.7 (CH), 132.4 (CH), 141.1 ($C_{quat.}$), 148.6 ($C_{quat.}$), 151.9 ($C_{quat.}$), 168.5 ($C_{quat.}$), 194.6 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 350.1 (M^+, 11), 278.1 (M^+ - $C_2H_6NCO^+$, 100), 72 ($C_2H_6NCO^+$, 18). IR (KBr), $\tilde{\nu}$ 3434 cm^{-1}, 2227, 1638, 1597, 1504, 1418, 1399, 1378, 1285, 1249, 1172, 1137, 828, 724, 610, 574, 554, 508, 474. UV/vis (CH_2Cl_2), λ_{max} (ε) 282 nm (7000), 326 (20000). Anal. calcd. for $C_{20}H_{18}N_2O_2S$ (350): C 68.55, H: 5.18, N 7.99, S 9.15; found: C 68.41, H 5.11, N 8.24, S 9.14.

6-(4-Cyanophenyl)-*N*,*N*-dimethyl-2-oxo-4-(thiophen-3-yl)cyclohex-3-enecarboxamide (32h)



According to the GP after chromatography on silica gel (toluene/acetone 3:1) and recrystallization from acetone 217 mg (62 %) of **32h** were isolated as light yellow oil. ^{1}H NMR (C_3H_6O-D_6, 300 MHz), δ 2.75 (s, 3 H), 3.04 (s, 3 H), 3.05–3.09 (m, 1 H), (dd, *J* = 6.0 Hz, *J* = 18.0 Hz, 1 H), 3.93 (ddd, *J* = 6.0 Hz, *J* = 12.0 Hz, *J* = 12.0 Hz, 1 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 6.50 (d, *J* = 2.0 Hz, 1 H), 7.56–7.61 (m, 2 H), 7.64 (d, *J* = 7.0 Hz, 2 H), 7.73 (d, *J* = 7.0 Hz, 2 H), 7.99 (m, 1 H). ^{13}C NMR (C_3H_6O-D_6, 100 MHz), δ 35.2 (CH_3), 35.6 (CH_2), 37.4 (CH_3), 44.5 (CH), 55.2 (CH), 111.2 ($C_{quat.}$), 119.3 ($C_{quat.}$), 123.3 (CH), 126.1 (CH), 127.3 (CH), 127.9 (CH), 129.6 (CH), 132.9 (CH), 140.7 ($C_{quat.}$), 149.7 ($C_{quat.}$), 153.2 ($C_{quat.}$), 169.3 ($C_{quat.}$), 195.4 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 350.1 (M^+, 38), 278.1 (M^+ - $C_2H_6NCO^+$, 100), 72 ($C_2H_6NCO^+$, 22). IR (KBr), $\tilde{\nu}$ 3439 cm^{-1}, 3854, 2226, 1641, 1607, 1506, 1416, 1399, 1285, 1248, 1175, 1140, 837, 791, 708, 634, 607, 579, 556, 503, 475. UV/vis (CH_2Cl_2), λ_{max} (ε) 300 nm (22900). HRMS calcd. for $C_{20}H_{18}N_2O_2S$: 350.1089; found 350.1095.

***N*,*N*-Dimethyl-2-oxo-6-(pyridin-2-yl)-4-(thiophen-2-yl)cyclohex-3-enecarboxamide (32i)**



According to the GP after chromatography on silica gel (toluene/acetone 3:1) 201 mg (62 %) of **32i** were isolated as brown oil. ^{1}H NMR (C_3D_6O, 300 MHz), δ 2.74 (s, 3 H), 3.05 (s, 3 H), 3.07–3.12 (m, 1 H), 3.16 (dd, *J* = 3.0 Hz, , *J* = 18.0 Hz, 1 H), 4.03 (ddd, *J* = 7.5 Hz, *J* = 7.5 Hz, *J* = 12.0 Hz, 1 H), 4.56 (d, *J* = 12.0 Hz, 1 H), 6.39 (d, *J* = 3.0 Hz, 1 H), 7.16–7.24 (m, 2 H), 7.34 (d, *J* = 7.0 Hz, 1 H), 7.61 (d, *J* = 3.0 Hz , 1 H), 7.67–7.75 (m, 2 H), 8.53 (d, *J* = 4.0 Hz , 1 H). ^{13}C NMR (C_3D_6O, 300 MHz), δ 34.7 (CH_2), 34.9 (CH_3), 37.2 (CH_3), 45.7 (CH), 54.0 (CH), 121.9 (CH), 122.5 (CH), 124.1 (CH), 129.0 (CH), 129.9 (CH), 137.0 (CH), 142.0 ($C_{quat.}$), 149.5 (CH), 151.6 ($C_{quat.}$), 161.5 ($C_{quat.}$), 164.5 ($C_{quat.}$), 195.5 ($C_{quat.}$). MS (70 eV, EI): *m/z* (%): 326.2 (M^+, 10), 254.1 (M^+ - $C_2H_6NCO^+$, 100), 72 ($C_2H_6NCO^+$, 33). IR (KBr), $\tilde{\nu}$ 3500 cm^{-1}, 2932, 1641, 1592, 1570, 1474, 1438, 1422, 1397, 1287, 1254, 1140, 826, 787, 750, 715, 609, 570, 547, 521, 473. UV/vis (CH_2Cl_2), λ_{max} (ε) 266 nm (8100), 270 (8100), 292 (18100). HRMS calcd. for $C_{18}H_{18}N_2O_2S$: 326.1089; found 326.1079.

6.11 General Procedure for the Coupling-Isomerization/Coupling of *o*-Amino Aryl Halides 1 with Propargylic Alcohols 2

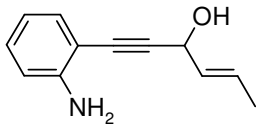
A magnetically stirred solution of 1.00 mmol of halogen compound **1**, 1.05 mmols of propargyl alcohols **2**, 20 mg (0.02 mmols) of $(PPh_3)_2PdCl_2$, and 2 mg (0.01 mmols) of CuI in 2 mmols of degassed DBU and 1.5 mL THF under nitrogen was stirred under nitrogen in a heavy-walled SmithCreator process vial at the temperature and time indicated, (for experimental details see Table 30) in the microwave cavity. After cooling to room temperature 40 mL of ethyl acetate and 40 mL of water were added and stirring was continued for 5 to 10 min. The aqueous layer was extracted with ethyl acetate (4 × 15 mL) and the combined organic phases were dried over magnesium sulfate. After filtration the solvents were removed *in vacuo* and the residue was chromatographed on silica gel

(hexane/ethyl acetate 4:1 or 1:1) and recrystallized from ethanol or pentane/chloroform (1:1) to give the analytically pure alkyne **38** and respectively the quinoline **41**.

Table 30 Experimental details of the synthesis of alkyne **38** and quinoline **40**.

Ar^1- Hal **1**	Propargyl-alcohol **2**	Temperature / Time	Yield
219 mg (1.00 mmol) of **1m**	101 mg (1.05 mmols) of **2g**	120 °C 30 min	83 mg (44 %) of **38**
219 mg (1.00 mmol) of **1m**	139 mg (1.05 mmols) of **2a**	120 °C 30 min	166 mg (81 %) of **41a**
219 mg (1.00 mmol) of **1m**	145 mg (1.05 mmols) of **2b**	120 °C 30 min	156 mg (74 %) of **41b**
244 mg (1.00 mmol) of **1n**	139 mg (1.05 mmols) of **2a**	120 °C 30 min	160 mg (70 %) of **41c**
244 mg (1.00 mmol) of **1n**	170 mg (1.05 mmols) of **2f**	120 °C 30 min	148 mg (57 %) of **41d**
287 mg (1.00 mmol) of **1o**	139 mg (1.05 mmols) of **2a**	120 °C 30 min	251 mg (92 %) of **41e**
219 mg (1.00 mmol) of **1m**	101 mg (1.05 mmols) of **2g**	150 °C 30 min	68 mg (40 %) of **41f**
234 mg (1.00 mmol) of **1p**	139 mg (1.05 mmols) of **2a**	150 °C 30 min	174 mg (79 %) of **41g**
220 mg (1.00 mmol) of **1q**	139 mg (1.05 mmols) of **2a**	150 °C 30 min	161 mg (78 %) of **41h**
360 mg (1.00 mmol) of **1r**	139 mg (1.05 mmols) of **2a**	150 °C 30 min	212 mg (64 %) of **41i**

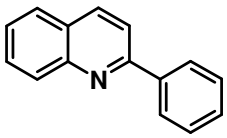
(*E*)-1-(2-Aminophenyl)hex-4-en-1-yn-3-ol (38)



According to the GP after chromatography on silica gel (hexane/ethyl acetate 5:1), 83 mg (44 %) of **38** were isolated as brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.69 (d, J = 6.3 Hz, 3 H),

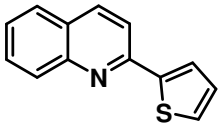
2.64 (s, 1 H), 4.06 (s, 2 H), 5.03 (d, *J* = 6.3 Hz, 1 H), 8.02 (dd, *J* = 6.0 Hz, *J* = 15.0 Hz, 1 H), 5.84–5.96 (m, 1 H), 6.6–6.65 (m, 2 H), 7.07 (t, *J* = 6.3 Hz, 1 H), 7.21 (d, *J* = 7.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 17.5 (CH_3), 63.4 (CH), 82.5 ($C_{quat.}$), 94.1 ($C_{quat.}$), 107.3 ($C_{quat.}$), 114.5 (CH), 117.9 (CH), 128.9 (CH), 129.8 (CH), 130.4 (CH), 132.3 (CH), 147.9 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 187.1 (M^+, 70), 168.1 (M^+ - H_3O^+, 100), 154 (M^+ - H_2O, - CH_3, 20), 144 (M^+ - C_2H_3O, 15), 117 (M^+ - C_4H_7O, 35). HRMS calcd. for $C_{12}H_{13}NO$): 187.0997; found 187.1000.

2-Phenylquinoline (41a)[157]



According to the GP after chromatography on silica gel (hexane/ethyl acetate 5:1), 166 mg (81 %) of **41a** were isolated as white crystals. M.p. 82 °C (lit. 82-83 °C).[157]
^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.47–7.58 (m, 4 H), 7.75 (t, *J* = 7.73 Hz, 1 H), 7.89 (d, *J* = 8.3 Hz, 1 H), 8.02 (d, *J* = 10.0 Hz, 1 H), 8.11 (d, *J* = 7.8 Hz, 1 H), 8.29–8.35 (m, 3 H). ^{13}C NMR (C_3D_6O, 100 MHz), δ 119.3 (CH), 127.1 (CH), 128.1 (CH), 128.5 (CH), 129.4 ($C_{quat.}$), 129.5 (CH), 130.2 (CH), 130.3 (CH), 130.4 (CH), 137.7 (CH), 140.1 ($C_{quat.}$), 149.0 ($C_{quat.}$), 157.3 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 205.1 (M^+, 100), 162.0 (M^+ - C_2H_5N, 12), 76 ($C_6H_4^+$, 7). (KBr), $\tilde{\nu}$ 3446 cm^{-1}, 3057, 1616, 1597, 1555, 1508, 1491, 1446, 1423, 1319, 1283, 1242, 1126, 1025, 831, 793, 773, 692, 677, 624, 551. UV/vis (CH_2Cl_2), λ_{max} (ε) 274 nm (57600), 308 (24400), 320 (28800), 334 (36100), 350 (35100). HRMS calcd. for $C_{15}H_{11}N$): calcd. 205.0891; found 205.0881.

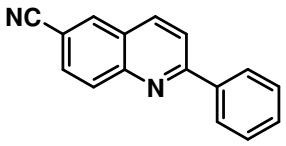
2-(Thiophen-2-yl)quinoline (41b)[158]



According to the GP after chromatography on silica gel (hexane/ethyl acetate 4:1), 156 mg (74 %) of **41b** were isolated as light-yellow crystals. M.p. 133 °C (lit. 131-133 °C).[158] ^{1}H

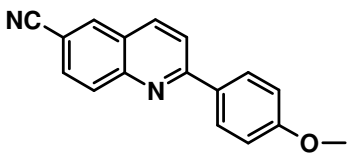
NMR ($CDCl_3$, 300 MHz), δ 7.16 (t, J = 4.0 Hz, 1 H), 7.48 (t, J = 6.8 Hz, 1 H), 7.61 (d, J = 5 Hz, 1 H), 7.69–7.76 (m, 1 H), 7.88–8.01 (m, 4 H), 8.27 (d, J = 8.0 Hz, 1 H). ^{13}C NMR (C_3D_6O, 100 MHz), δ 119.3 (CH), 127.1 (CH), 128.1 ($C_{quat.}$), 128.6 (CH), 129.6 (CH), 129.8 (CH), 130.2 (CH), 130.7 (CH), 137.6 (CH), 144.9 ($C_{quat.}$), 148.8 ($C_{quat.}$), 153.2 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 211 (M^+, 100), 178 (M^+ - HS, 10), 128 (M^+ - C_4H_3S, 10), 83.5 ($C_4H_4S^+$, 7). (KBr), $\tilde{\nu}$ 3441 cm^{-1}, 3101, 3060, 1614, 1595, 1554, 1500, 1427, 1317, 1242, 1228, 1122, 1057, 933, 858, 841, 826, 787, 759, 711, 619. UV/vis (CH_2Cl_2), λ_{max} (ε) 258 nm (14100). HRMS calcd. for ($C_{13}H_9NS$): 211.0455; found 211.0444.

2-Phenylquinoline-6-carbonitrile (41c)[159]



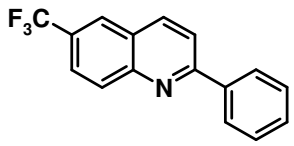
According to the GP after chromatography on silica gel (hexane/ethyl acetate 5:1), 160 mg (70 %) of **41c** were isolated as white crystals. M.p. 144 °C (lit. 142-143 °C).[159] ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.46–7.56 (m, 3 H), 7.79 (dd, J = 9.0 Hz, J = 3.0 Hz, 1 H), 7.93 (d, J = 9.0 Hz, 1 H), 8.14–8.22 (m, 5 H). ^{13}C NMR (C_3D_6O, 100 MHz), δ 109.7 ($C_{quat.}$), 118.8 ($C_{quat.}$), 120.4 (CH), 126.4 ($C_{quat.}$), 127.8 (CH), 129.0 (CH), 130.3 (CH), 130.4 (CH), 131.1 (CH), 133.7 (CH), 137.0 (CH), 138.5 ($C_{quat.}$), 149.2 ($C_{quat.}$), 160.0 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 230.1 (M^+, 100), 203.1 (M^+ - HCN, 9). (KBr), $\tilde{\nu}$ 3444 cm^{-1}, 2225, 1621, 1597, 1557, 1489, 1448, 1395, 1340, 1326, 1284, 898, 839, 786, 753, 687, 669, 594. UV/vis (CH_2Cl_2), λ_{max} (ε):262 nm (22400), 298 (11500), 328 (8100), 342 (6400). Anal calcd. for $C_{16}H_{10}N_2$ (230): C 83.46, H 4.38, N 12.17; found: C 83.40, H 4.44, N 12.10.

2-(4-Methoxyphenyl)quinoline-6-carbonitrile (41d)



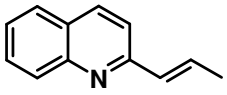
According to the GP after chromatography on silica gel (hexane/ethyl acetate 5:1), 148 mg (57 %) of **41d** were isolated as white crystals. M..p. 191 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 3.89 (s, 3 H), 7.04 (d, J = 9.0 Hz, 2 H), 7.81 (dd, J = 9.0 Hz, J = 1.5 Hz, 1 H), 7.93 (d, J = 8.4 Hz, 1H), 8.16 – 8.22 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 55.5 (CH_3), 109.2 ($C_{quat.}$), 114.4 (CH), 118.9 ($C_{quat.}$), 120.0 (CH), 126.2 ($C_{quat.}$), 129.2 (CH), 130.3 (CH), 130.9 (CH), 131.1 ($C_{quat.}$), 133.7 (CH), 136.8 (CH), 149.4 ($C_{quat.}$), 159.5 ($C_{quat.}$), 161.6 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 260.07 (M^+, 100), 245.05 (M^+ - CH_3, 20), 217.06 (M^+ - CH_3CO, 35). HRMS ($C_{17}H_{12}N_2O$): calcd. 260.0949; found 260.0930. (KBr), $\tilde{\nu}$ 3437 cm^{-1}, 3023, 2966, 2934, 2840, 2225, 1963, 1920, 1878, 1807, 1598, 1579, 1517, 1489, 1464, 1440, 1422, 1337, 1307, 1284, 1254, 1183, 1020, 906, 852, 835, 824, 592. UV/vis (CH_2Cl_2), λ_{max} (ε) 272 nm (18500), 310 (19900), 328 (8100), 320 (20500). Anal. calcd. for $C_{17}H_{12}N_2O$ (260): C 78.44, H 4.65, N 10.76, O: 6.15; found: C 78.10, H 4.67, N 10.66.

2-Phenyl-6-(trifluoromethyl)quinoline (41e)



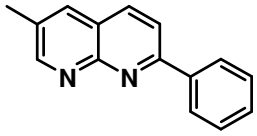
According to the GP after chromatography on silica gel (hexane/ethyl acetate 5:1), 251 mg (92 %) of **41e** were isolated as white crystals. M.p. 114 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.52–7.59 (m, 3 H), 7.95 (dd, J = 7.8 Hz, J = 1.5 Hz, 1 H), 8.19 (d, J = 7.8 Hz, 1 H), 8.25 (d, J = 7.5 Hz, 1H), 8.31–8.38 (m, 3 H), 8.54 (d, J = 8.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 120.8 (CH), 123.5 ($C_{quat.}$), 125.8 (CH), 126.9 (CH), 128.5 (CH), 129.4 (CH), 130.9 (CH), 131.8 (CH), 134.3 ($C_{quat.}$), 134.6 ($C_{quat.}$), 138.9 (CH), 139.5 ($C_{quat.}$), 150.1 ($C_{quat.}$), 159.8 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 273.1 (M^+, 100), 204.2 (M^+ - CF_3, 36), 126.6 (M^+ - CF_3, - C_6H_6, 12). HRMS ($C_{16}H_{10}F_3N$): calcd. 273.0765; found 273.0763. (KBr), $\tilde{\nu}$ 3434 cm^{-1}, 1630, 1603, 1474, 1449, 1355, 1332, 1304, 1281, 1244, 1199, 1166, 1122, 1065, 906, 894, 844, 763, 700, 692. UV/vis (CH_2Cl_2), λ_{max} (ε) 260 nm (74100), 286 (25300), 322 (18000), 336 (14500). Anal calcd. for $C_{16}H_{10}F_3N$ (273): C 70.33, H 3.66, N 5.13; found: C 70.58, H 3.80, N 5.10.

(E)-2-(Prop-1-enyl)quinoline (41f)[160]



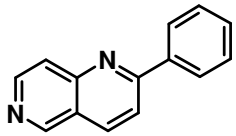
According to the GP after chromatography on silica gel (hexane/ethyl acetate 4:1), 68 mg (40 %) of **41f** were isolated as brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.1 (d, J = 6.9 Hz, 3 H), 6.72 (d, J = 619.5 Hz, 1 H), 6.83–6.87 (m, 1 H), 7.36–7.52 (m, 2 H), 7.66–7.78 (m, 2 H), 8.04–8.08 (m, 2 H). ^{13}C NMR (C_3D_6O, 100 MHz), δ 18.6 (CH_3), 118.7 (CH), 125.8 (CH), 127.1 ($C_{quat.}$), 127.4 (CH), 129.7 (CH), 129.5 (CH), 132.3 (CH), 132.7 (CH), 136.2 (CH), 156.4 ($C_{quat.}$), 173.2 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 169.1 (M^+, 80), 168.1 (M^+ - H, 100), 51 ($C_4H_3^+$, 10). HRMS calcd. for $C_{12}H_{11}N$: 169.0891; found 169.0887.

6-Methyl-2-phenyl-1,8-naphthyridine (41g)



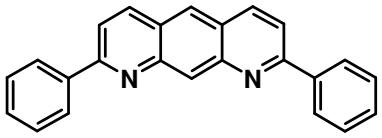
According to the GP after chromatography on silica gel (hexane/ethyl acetate 5:1), 174 mg (79 %) of **41g** were isolated as light yellow crystals. M.p. 142 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.54 (s, 3 H), 7.44–7.54 (m, 3 H), 7.91 (d, J = 1.5 Hz, 1 H), 7.94 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H), 8.28 (dd, J = 8.3 Hz, J = 1.5 Hz, 2 H), 8.96 (d, J = 2.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 18.6 (CH_3), 119.6 (CH), 121.3 ($C_{quat.}$), 127.8 (CH), 128.8 (CH), 129.9 (CH), 131.5 ($C_{quat.}$), 135.2 (CH), 137.1 (CH), 138.7 ($C_{quat.}$), 154.8 ($C_{quat.}$), 155.8 (CH), 159.3 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 220.1 (M^+, 100), 205.1 (M^+ - CH_3, 10), 77 ($C_6H_5^+$, 12). HRMS ($C_{15}H_{12}N_2$): calcd. 220.1000; found 220.1000. (KBr), $\tilde{\nu}$ 3420 cm^{-1}, 3027, 1604, 1581, 1546, 1503, 1481, 1458, 1434, 1321, 1278, 1140, 1025, 898, 814, 766, 739, 703, 678, 568. UV/vis (CH_2Cl_2), λ_{max} (ε) 256 nm (27200), 272 (11300), 332 (14000), 344 (11300). Anal. calcd. for $C_{15}H_{12}N_2$ (220): C 81.79, H 5.49, N 12.72; found: C 81.71, H 5.38, N 12.79.

2-Phenyl-1,6-naphthyridine (41h)[161]



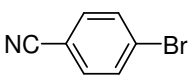
According to the GP after chromatography on silica gel (hexane/ethyl acetate 5:1), 161 mg (78 %) of **41h** were isolated as light yellow crystals. M.p. 98 °C (lit. 97-98 °C).[161] ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.24–7.49 (m, 3 H), 7.83–7.89 (m, 2 H), 8.07–8.10 (m, 2 H), 8.16 (d, J = 9.0 Hz, 1 H), 8.69 (s, 1 H), 9.16 (s, 1 H).^{13}C NMR ($CDCl_3$, 100 MHz), δ 120.3 (CH), 122.3 (CH), 127.9 (CH), 128.7 (CH), 130.3 (CH), 136.3 (CH), 138.6 ($C_{quat.}$), 147.2 (CH), 150.5 ($C_{quat.}$), 152.5 (CH), 161.4 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 206.1 (M^+, 100), 77 ($C_6H_5^+$, 8). (KBr), $\tilde{\nu}$ 3422 cm^{-1}, 3059, 1615, 1592, 1551, 1481, 1460, 1447, 1400, 1367, 1318, 1258, 1024, 945, 845, 760, 689, 639, 573, 554. UV/vis (CH_2Cl_2), λ_{max} (ε) 256 nm (12700). HRMS calcd. for $C_{14}H_{10}N_2$: 206.0844; found 206.0831.

Pyrido[3,2-g]quinoline, 2,8-diphenyl- (41i) [162]

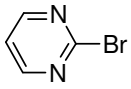


According to the GP after chromatography on silica gel (hexane/ethyl acetate 4:1), 212 mg (64 %) of **41i** were isolated as yellow crystals. M.p. 216 °C (lit. 217-218 °C).[162]
^{1}H NMR (C_3H_6O, 300 MHz), δ 7.40–7.52 (m, 6 H), 8.04 (d, J = 9.0 Hz, 2 H), 8.29–8.32 (m, 4 H), 8.50–8.53 (m, 3 H), 8.77 (s, 1 H). ^{13}C NMR (C_3D_6O, 100 MHz), δ 119.2 (CH), 125.9 ($C_{quat.}$), 126.3 (CH), 127.8 (CH), 128.4 (CH), 128.9 (CH), 129.0 (CH), 129.9 (CH), 134.2 (CH), 136.9 (CH), 139.4 ($C_{quat.}$), 147.3 ($C_{quat.}$), 158.6 ($C_{quat.}$). (70 eV, EI): *m/z* (%): 332.1 (M^+, 100), 305.1 (M^+ - HCN, 6), 77 ($C_6H_5^+$, 10). (KBr), $\tilde{\nu}$ 3442, 2226, 1621, 1574, 1545, 1490, 1466, 1453, 1430, 1338, 1307, 1253, 1205, 1181, 1020, 884, 818, 755, 695, 625, 595. UV/vis (CH_2Cl_2), λ_{max} (ε) 254 nm (34100), 290 (58100), 296 (57200), 376 (14800), 390 (15700). HRMS calcd. for $C_{24}H_{16}N_2$: 332.1313; found 332.1304.

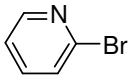
7 Molecule Contents



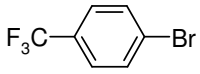
1a



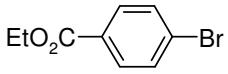
1b



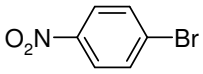
1c



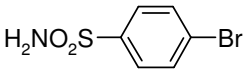
1d



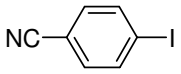
1e



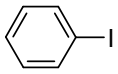
1f



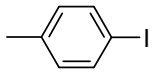
1g



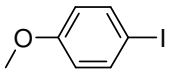
1h



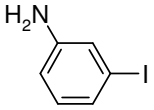
1i



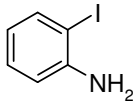
1j



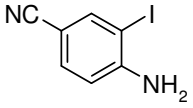
1k



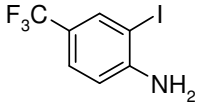
1l



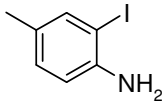
1m



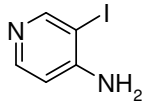
1n



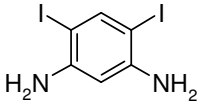
1o



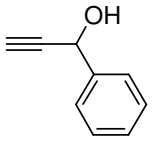
1p



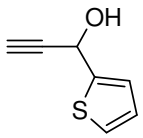
1q



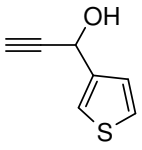
1r



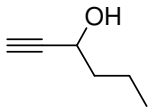
2a



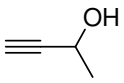
2b



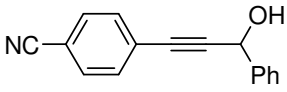
2c



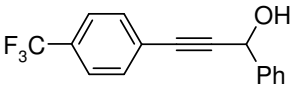
2d



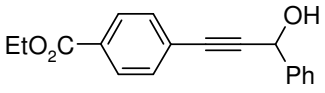
2e



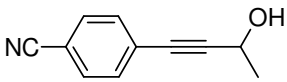
3a



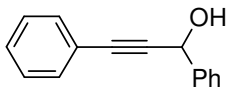
3d



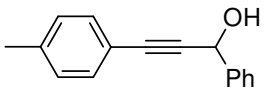
3e



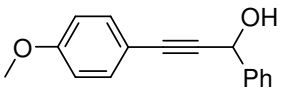
3k



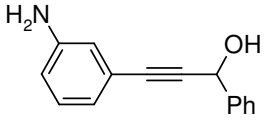
3l



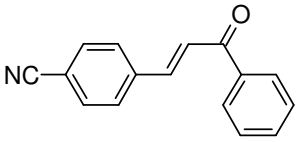
3m



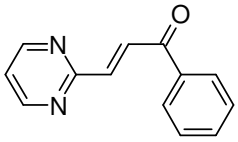
3n



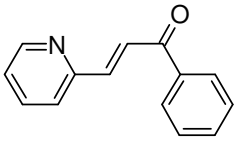
3o



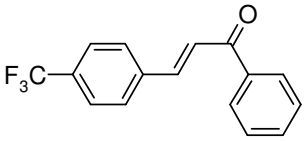
4a



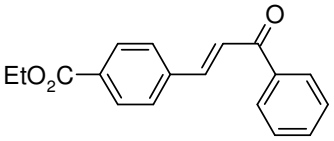
4b



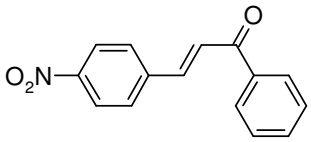
4c



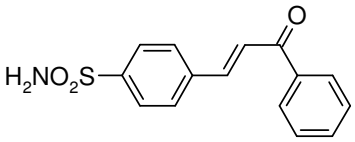
4d



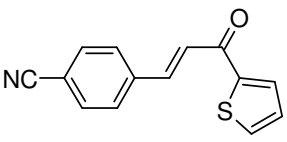
4e



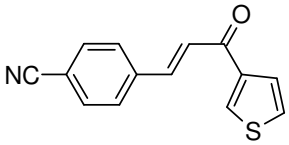
4f



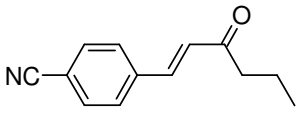
4g



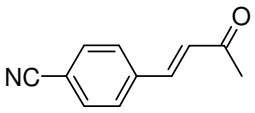
4h



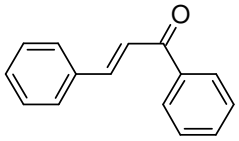
4i



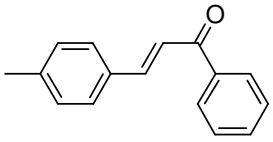
4j



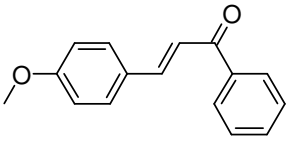
4k



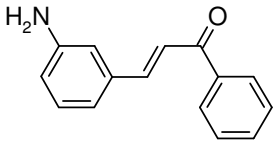
4l



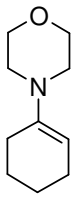
4m



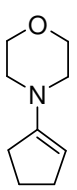
4n



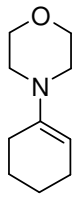
4o



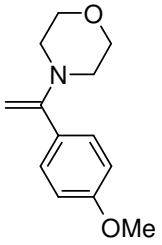
5a



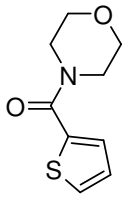
5b



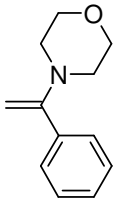
5c



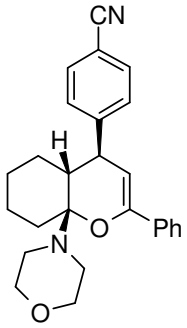
5d



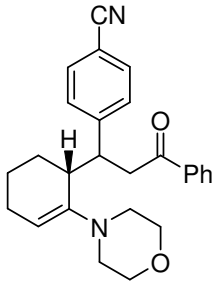
5e



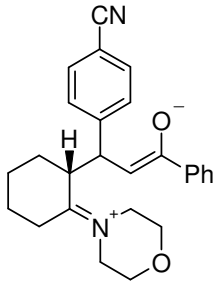
5f



6



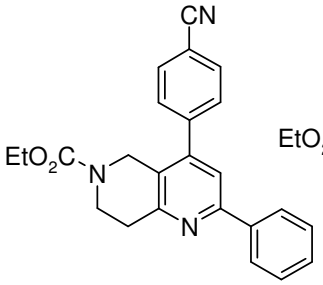
7



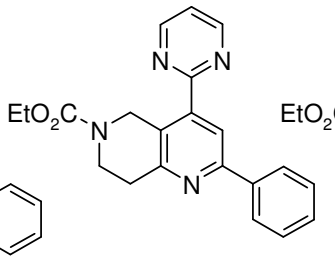
8

NH_4Cl

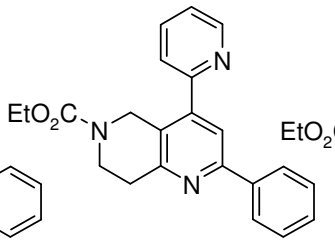
9



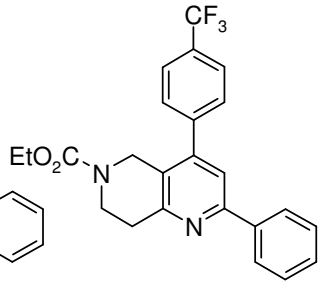
10a



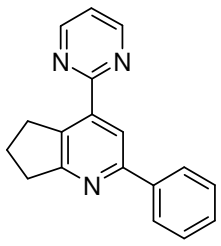
10b



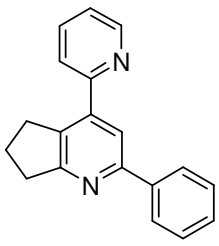
10c



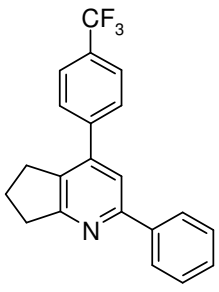
10d



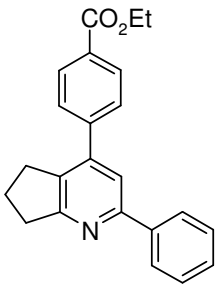
10e



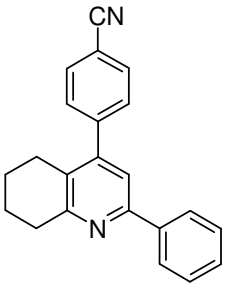
10f



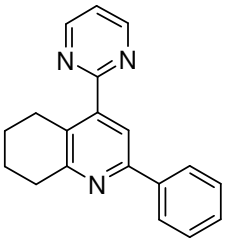
10g



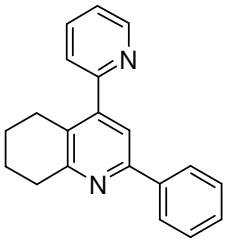
10h



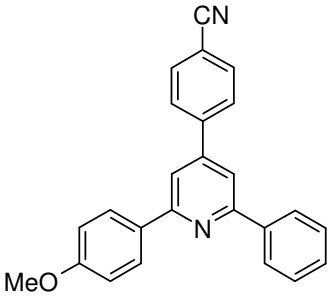
10i



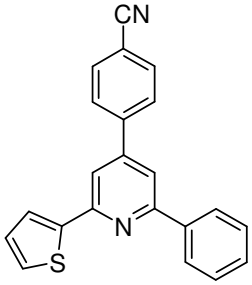
10j



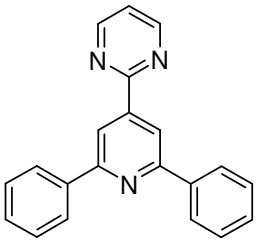
10k



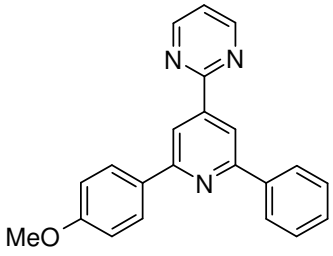
10l



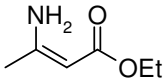
10m



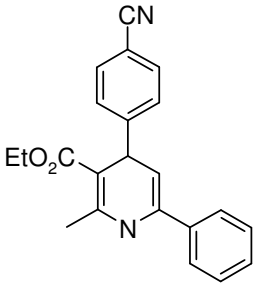
10n



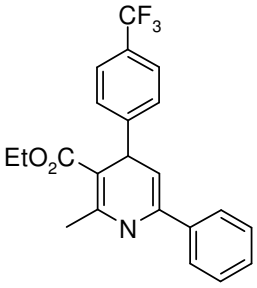
10o



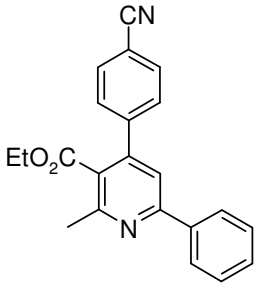
11



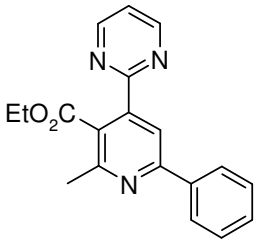
12a



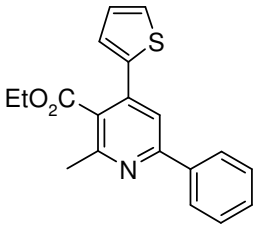
12b



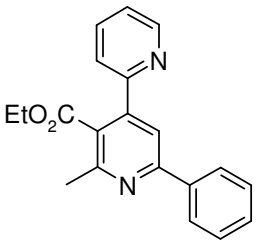
13a



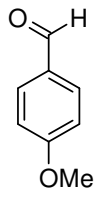
13b



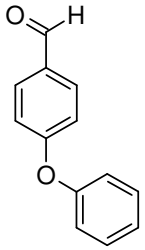
13c



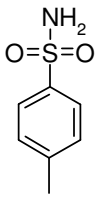
13d



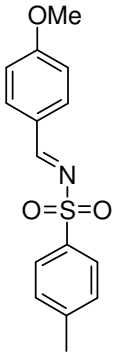
14a



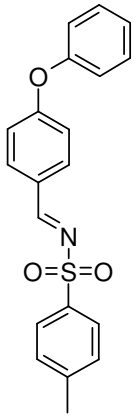
14b



15

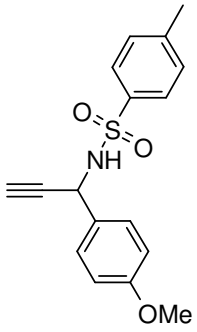


16a

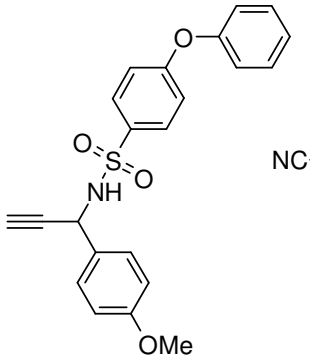


16b

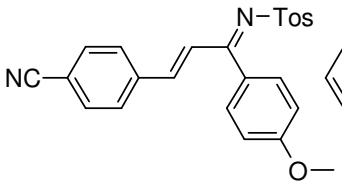
17



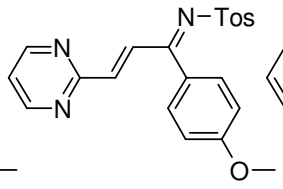
18a



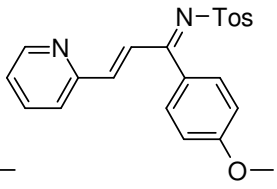
18b



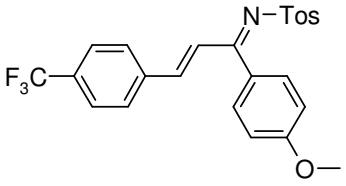
19a



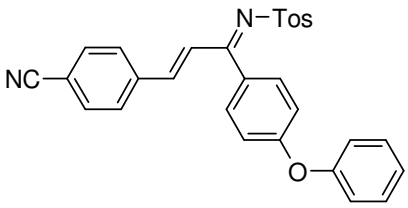
19b



19c

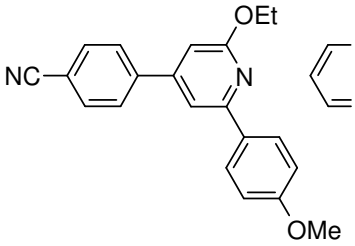


19d

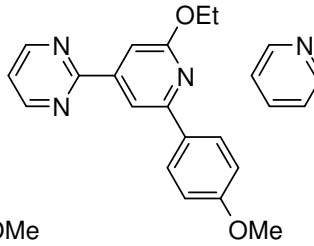


19e

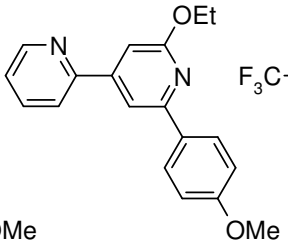
20



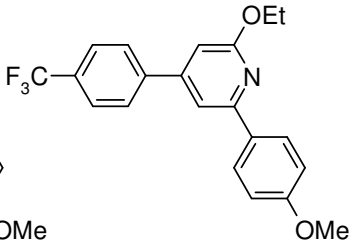
21a



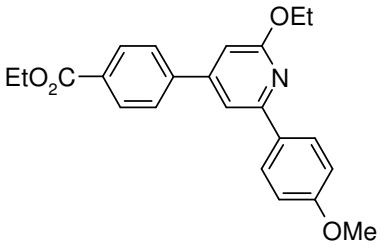
21b



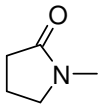
21c



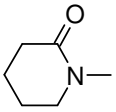
21d



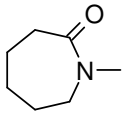
21e



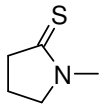
22a



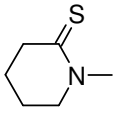
22b



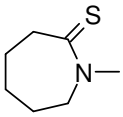
22c



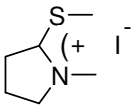
23a



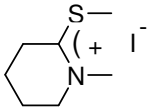
23b



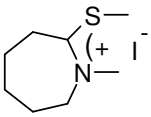
23c



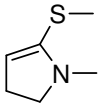
24a



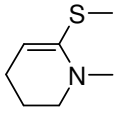
24b



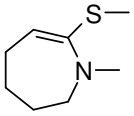
24c



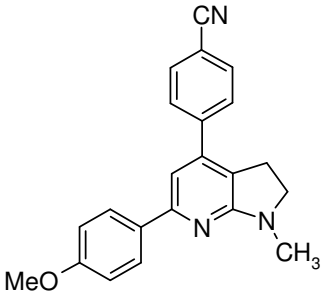
25a



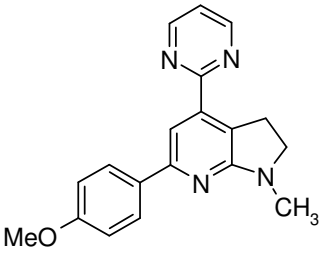
25b



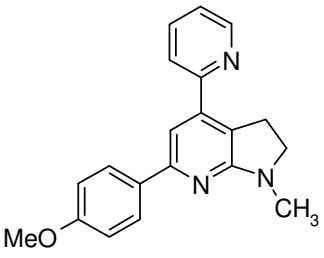
25c



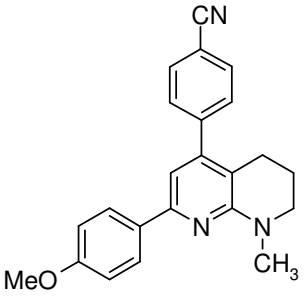
27a



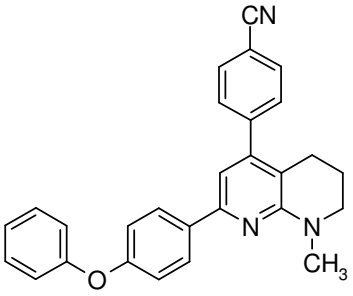
27b



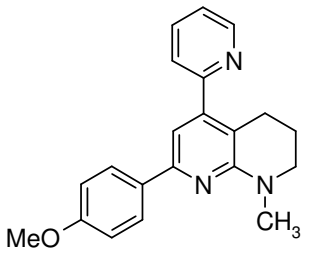
27c



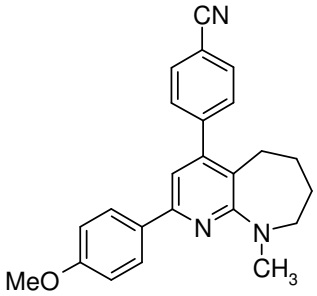
27d



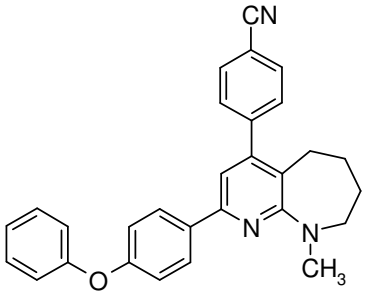
27e



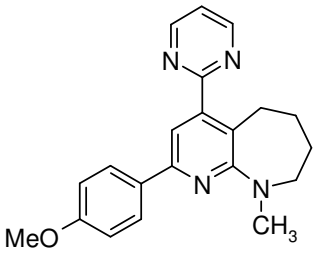
27f



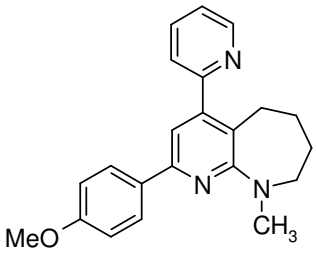
27g



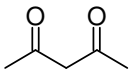
27h



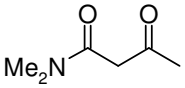
27i



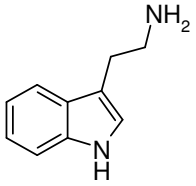
27j



28a

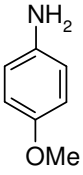


28b



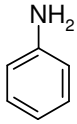
29a

29b

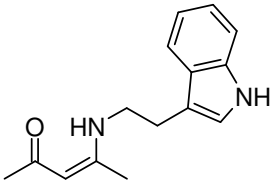


29c

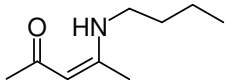
29d



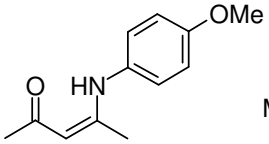
29e



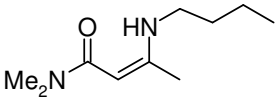
30a



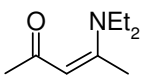
30b



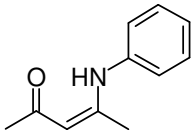
30c



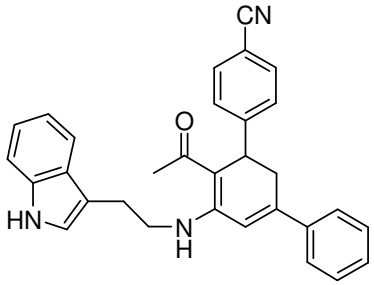
30d



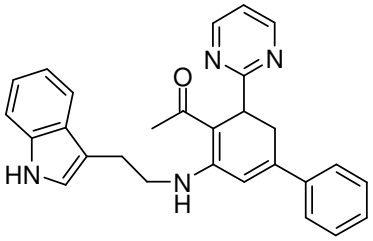
30e



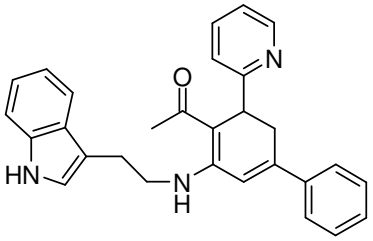
30f



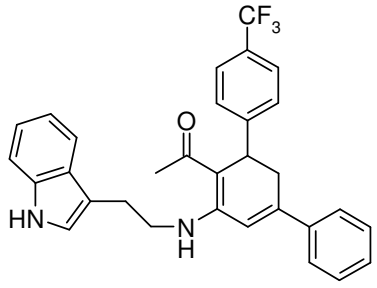
31a



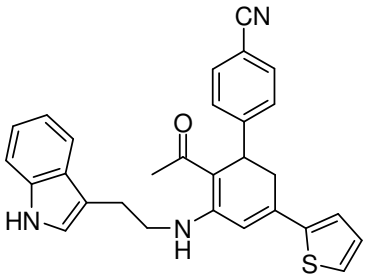
31b



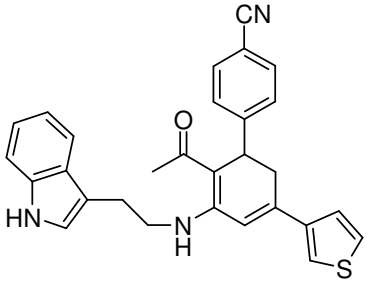
31c



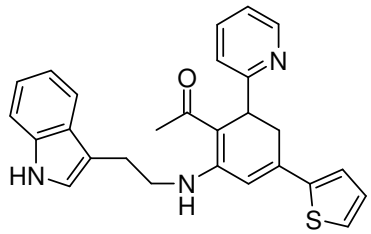
31d



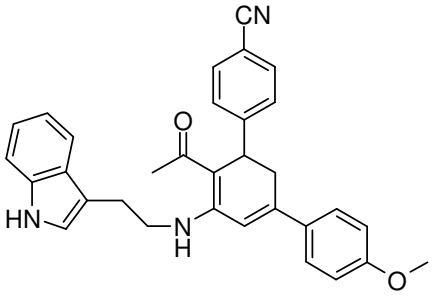
31e



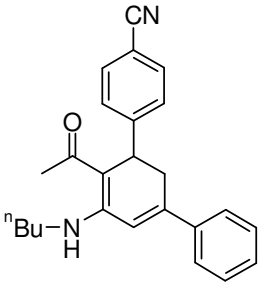
31f



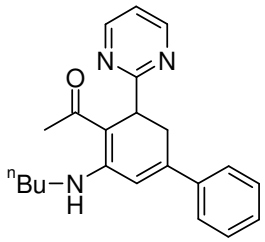
31g



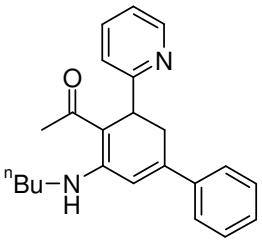
31h



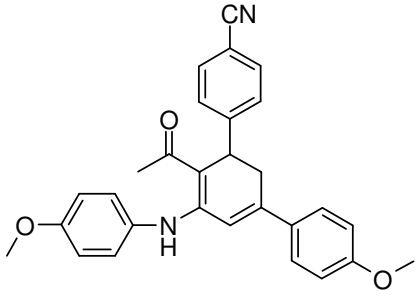
31i



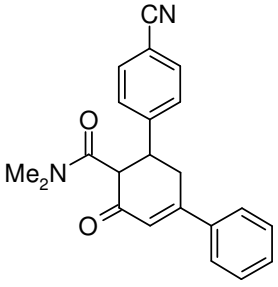
31j



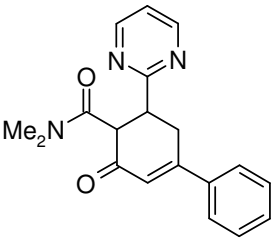
31k



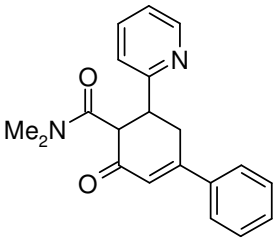
31l



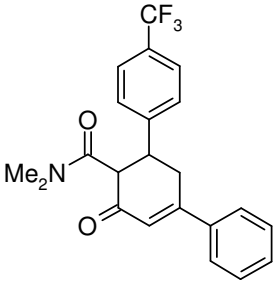
32a



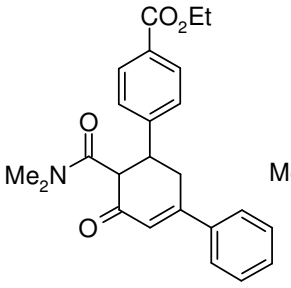
32b



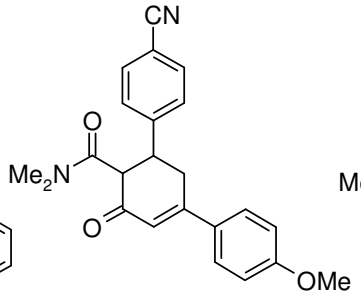
32c



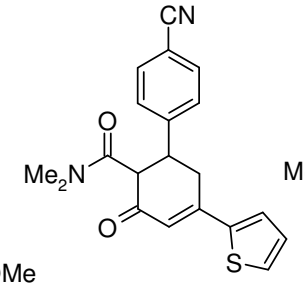
32d



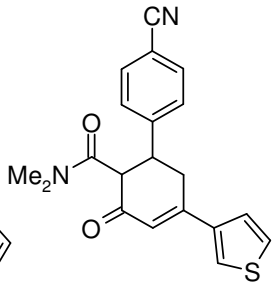
32e



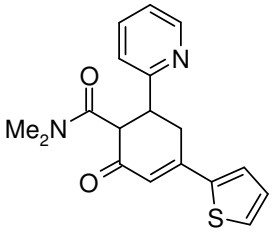
32f



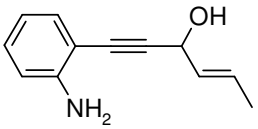
32g



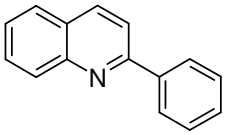
32h



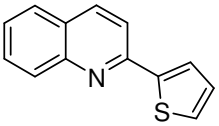
32i



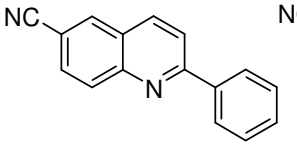
38



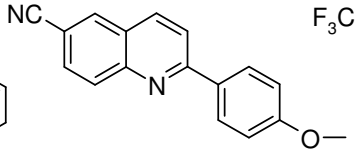
41a



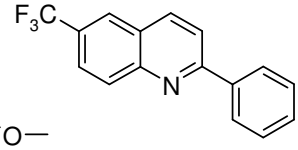
41b



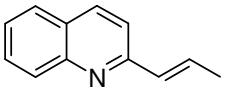
41c



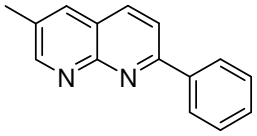
41d



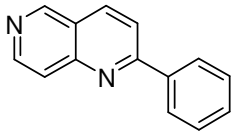
41e



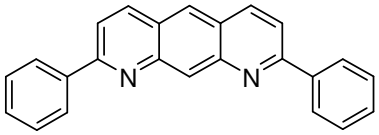
41f



41g



41h



41i

8 Crystal Data

Table 31 Data and Structure Refinement for (*E*)-1-Phenyl-3-pyrimidinprop-2-en-1-one, **4b**.

Empirical Formula	$C_{13}H_{10}N_2O$
Formula Weight	210.23
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorombic
Space group	Pna2 (1)
Unit cell dimensions	a = 22.813(5) Å $\alpha = 90$ °.
	b = 3.8386(9) Å $\beta = 90$ °.
	c = 11.683(4) Å $\gamma = 90$ °.
Volume	1023.1(4) $Å^3$
Z	4
Density (calculated)	1.36 g/cm^3
Absorption coefficient	0.089 mm^{-1}
Crystal size	0.34 x 0.32 x 0.23 mm
θ_{min} / θ_{max}	1.79 to 28.31 °.
Reflections collected	6859
Independent reflections	2450 [R(int) = 0.0391]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2450/ 0 /185
Goodness-of-fit on F^2	1.03
Final R indices ($I>2\sigma(I)$)	R_1 = 0.036 and R_2 = 0.096
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.27 and -0.21 eA^{-3}

Table 32 Data and Structure Refinement for 4-(8a-morpholino-2-phenyl-4a,5,6,7,8,8a-hexahydro-4H-chromen-4-yl)benzonitrile, **6**.

Empirical Formula	$C_{26}H_{28}N_2O_2$
Formula Weight	400.50
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 10.080(1) Å $\alpha = 90$ °.
	b = 11.664(1) Å $\beta = 103.976(2)$ °.
	c = 18.265(2) Å $\gamma = 90$ °.
Volume	2083.9(4) $Å^3$
Z	4
Density (calculated)	1.277 g/cm^3
Absorption coefficient	0.081 mm^{-1}
Crystal size	0.30 x 0.26 x 0.20 mm
θ_{min} / θ_{max}	2.7 to 28.28 °.
Reflections collected	20678
Independent reflections	5103 [R(int) = 0.0321]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5103/ 0 /383
Goodness-of-fit on F^2	1.05
Final R indices ($I>2\sigma(I)$)	$R_1 = 0.049$ and $R_2 = 0.114$
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.44 and -0.20 eA^{-3}

Table 33 Data and Structure Refinement for 4-(4-Cyano-phenyl)-2-phenyl-7,8-dihydro-5H-[1,6]naphthyridine-6-carboxylic acid ethyl ester, **10a**.

Empirical Formula	$C_{24}H_{21}N_3O_2$
Formula Weight	383.44
Temperature	373(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 12.194(2) Å $\alpha = 90$ °.
	b = 8.973(2) Å $\beta = 96.684(4)$ °.
	c = 17.515(3) Å $\gamma = 90$ °.
Volume	1903.5(6) $Å^3$
Z	4
Density (calculated)	1.338 g/cm^3
Absorption coefficient	0.087 mm^{-1}
Crystal size	0.26 x 0.23 x 0.12 mm
θ_{min} / θ_{max}	2.55 to 24.71 °.
Reflections collected	13721
Independent reflections	3236 [R(int) = 0.0612]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3236/ 0 /346
Goodness-of-fit on F^2	1.04
Final R indices ($I>2\sigma(I)$)	R_1 = 0.043 and R_2 = 0.086
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.20 and -0.19 eA^{-3}

Table 34 Data and Structure Refinement for 2-Phenyl-4-pyridin-2-yl-6,7-dihydro-5H-[1]pyrindine, **10f**.

Empirical Formula	$C_{19}H_{16}N_2$
Formula Weight	272.34
Temperature	100 K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 5.295(1) Å $\alpha = 90$ °. b = 9.989(2) Å $\beta = 90$ °. c = 25.956(6) Å $\gamma = 90$ °.
Volume	1372.8(5) $Å^3$
Z	4
Density (calculated)	1.32 g/cm^3
Absorption coefficient	0.078 mm^{-1}
Crystal size	0.42 x 0.15 x 0.12 mm
θ_{min} / θ_{max}	2.18 to 28.28 °.
Reflections collected	10186
Independent reflections	3389 [R(int) = 0.033]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3389/ 0 /254
Goodness-of-fit on F^2	1.05
Final R indices ($I>2\sigma(I)$)	$R_1 = 0.036$ and $R_2 = 0.092$
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.31 and -0.20 eA^{-3}

Table 35 Data and Structure Refinement for 2-Phenyl-4-(4-trifluoromethyl-phenyl)-6,7-dihydro-5H-[1]pyrindine, **10g**.

Empirical Formula	$C_{21}H_{16}F_3N$
Formula Weight	339.35
Temperature	100 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.3792(9) Å α = 112.508(2) °.
	b = 9.6624(9) Å β = 92.435(2) °.
	c = 9.7227(9) Å γ = 102.162(2) °.
Volume	788.3(1) $Å^3$
Z	2
Density (calculated)	1.43 g/cm^3
Absorption coefficient	0.11 mm^{-1}
Crystal size	0.30 x 0.26 x 0.19 mm
θ_{min} / θ_{max}	2.24 to 28.29 °.
Reflections collected	5866
Independent reflections	3857 [R(int) = 0.018]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3857/ 0 /290
Goodness-of-fit on F^2	1.07
Final R indices (I>2σ(I))	R_1 = 0.041 and R_2 = 0.110
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.37 and -0.32 eA^{-3}

Table 36 Data and Structure Refinement for 2-Phenyl-4-pyrimidin-2-yl-5,6,7,8-tetrahydro-quinoline, **10j**.

Empirical Formula	$C_{19}H_{17}N_3$
Formula Weight	287.36
Temperature	100 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.2677(8) Å α = 82.238(2) °.
	b = 9.452(1) Å β = 82.509(2) °.
	c = 10.920(1) Å γ = 75.802(2) °.
Volume	716.9(1) $Å^3$
Z	2
Density (calculated)	1.33 g/cm^3
Absorption coefficient	0.08 mm^{-1}
Crystal size	0.37 x 0.30 x 0.20 mm
θ_{min} / θ_{max}	2.77 to 28.33 °.
Reflections collected	5359
Independent reflections	3537 [R(int) = 0.036]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3537/ 0 /267
Goodness-of-fit on F^2	1.06
Final R indices (I>2σ(I))	R_1 = 0.041 and R_2 = 0.119
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.43 and -0.27 eA^{-3}

Table 37 Data and Structure Refinement for 2-Phenyl-4-pyridin-2-yl-5,6,7,8-tetrahydro-quinoline, **10k**.

Empirical Formula	$C_{20}H_{18}N_2$
Formula Weight	286.3
Temperature	100 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 20.269(2) Å α = 90 °.
	b = 9.4071(9) Å β = 107.228(2) °.
	c = 16.413(1) Å γ = 90 °.
Volume	2989.2(5) $Å^3$
Z	8
Density (calculated)	1.27 g/cm^3
Absorption coefficient	0.075 mm^{-1}
Crystal size	0.33 x 0.25 x 0.25 mm
θ_{min} / θ_{max}	2.58 to 28.32 °.
Reflections collected	10773
Independent reflections	3701 [R(int) = 0.023]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3701/ 0 /271
Goodness-of-fit on F^2	1.04
Final R indices ($I>2\sigma(I)$)	R_1 = 0.041 and R_2 = 0.110
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.39 and -0.21 eA^{-3}

Table 38 Data and Structure Refinement for 2-(2,6-Diphenyl-pyridin-4-yl)-pyrimidine, **10n**.

Empirical Formula	$C_{21}H_{15}N_3$
Formula Weight	309.36
Temperature	100 K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pbcn
Unit cell dimensions	a = 16.225(1) Å $\alpha = 90$ °.
	b = 11.3707(7) Å $\beta = 90$ °.
	c = 8.0467(5) Å $\gamma = 90$ °.
Volume	1484.5(2) $Å^3$
Z	4
Density (calculated)	1.38 g/cm^3
Absorption coefficient	0.083 mm^{-1}
Crystal size	0.25 x 0.20 x 0.14 mm
θ_{min} / θ_{max}	2.19 to 28.28 °.
Reflections collected	14072
Independent reflections	1852 [R(int) = 0.045]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1852/ 0 /141
Goodness-of-fit on F^2	1.05
Final R indices (I>2σ(I))	R_1 = 0.043 and R_2 = 0.119
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.39 and -0.36 eA^{-3}

Table 39 Data and Structure Refinement for 4-(4-Cyano-phenyl)-2-methyl-6-phenyl-nicotinic acid ethyl ester, **13a**.

Empirical Formula	$C_{22}H_{18}N_2O_2$
Formula Weight	342.38
Temperature	100 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 8.111(3) Å α = 100.097(7) °.
	b = 9.880(3) Å β = 96.569(7) °.
	c = 11.128(4) Å γ = 94.605(7) °.
Volume	874.9(5) $Å^3$
Z	2
Density (calculated)	1.30 g/cm^3
Absorption coefficient	0.084 mm^{-1}
Crystal size	0.28 x 0.23 x 0.15 mm
θ_{min} / θ_{max}	2.10 to 28.45 °.
Reflections collected	6550
Independent reflections	3823 [R(int) = 0.026]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3823/ 0 /307
Goodness-of-fit on F^2	1.04
Final R indices ($I>2\sigma(I)$)	R_1 = 0.041 and R_2 = 0.114
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.38 and -0.22 eA^{-3}

Table 40 Data and Structure Refinement for 2-Methyl-6-phenyl-4-pyrimidin-2-yl-nicotinic acid ethyl ester, **13b**.

Empirical Formula	$C_{19}H_{17}N_3O_2$
Formula Weight	319.36
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$Pca2_1$
Unit cell dimensions	a = 10.4549(8) Å $\alpha = 90$ °
	b = 19.132(1) Å $\beta = 90$ °
	c = 7.6580(6) Å $\gamma = 90$ °
Volume	1531.8(2) $Å^3$
Z	4
Density (calculated)	1.38 g/cm^3
Absorption coefficient	0.09 mm^{-1}
Crystal size	0.37 x 0.37 x 0.23 mm
θ_{min} / θ_{max}	2.13 to 28.35 °.
Reflections collected	10986
Independent reflections	3677 [R(int) = 0.030]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3677/ 0 /285
Goodness-of-fit on F^2	1.06
Final R indices ($I>2\sigma(I)$)	R_1 = 0.032 and wR_2 = 0.0875
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.36 and -0.26 eA^{-3}

Table 41 Data and Structure Refinement for Etyl 2-methyl-6-phenyl-4-(thiazol-2-yl)nicotinate, **13c**.

Empirical Formula	$C_{19}H_{16}N_2O_2S$
Formula Weight	324.39
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 10.776(3) Å $\alpha = 90$ °
	b = 7.141(2) Å $\beta = 92.832(5)$ °
	c = 20.236(3) Å $\gamma = 90$ °
Volume	1555.4(6) $Å^3$
Z	4
Density (calculated)	1.38 g/cm^3
Absorption coefficient	0.219 mm^{-1}
Crystal size	0.33 x 0.15 x 0.07 mm
θ_{min} / θ_{max}	2.7 to 28.32 °.
Reflections collected	11156
Independent reflections	3863 [R(int) = 0.028]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3863/ 0 /272
Goodness-of-fit on F^2	0.99
Final R indices ($I>2\sigma(I)$)	R_1 = 0.033 and wR_2 = 0.087
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.37 and -0.25 eA^{-3}

Table 42 Data and Structure Refinement for 4-[2-Ethoxy-6-(4-methoxyphenyl)-pyridin-4-yl]-benzoic acid ethyl ester, **21e**.

Empirical Formula	$C_{23}H_{23}NO_4$
Formula Weight	377.42
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Orthorombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 13.9831(4) Å $\alpha = 90$ °
	b = 23.5154(7) Å $\beta = 90$ °
	c = 23.8147(7) Å $\gamma = 90$ °
Volume	7830.74(5) $Å^3$
Z	16
Density (calculated)	1.28 g/cm^3
Absorption coefficient	0.09mm^{-1}
Crystal size	0.40 x 0.30 x 0.08 mm
θ_{min} / θ_{max}	1.7 to 22.0 °.
Reflections collected	51474
Independent reflections	9569 [R(int) = 0.0846]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	9569/ 0 /1009
Goodness-of-fit on F^2	1.06
Final R indices ($I>2\sigma(I)$)	R_1 = 0.048 and wR_2 = 0.098
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.18 and -0.20 eA^{-3}

Table 43 Data and Structure Refinement for 4-[6-(4-Methoxy-phenyl)-1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridin-4-yl]-benzonitrile, **27a**.

Empirical Formula	$C_{22}H_{19}N_3O$
Formula Weight	341.40
Temperature	571(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 11.4985(2) Å $\alpha = 90$ °.
	b = 8.2319(1) Å $\beta = 95.956(1)$ °.
	c = 19.1003(3) Å $\gamma = 90$ °.
Volume	1798.17(5) $Å^3$
Z	4
Density (calculated)	1.261 g/cm^3
Absorption coefficient	0.079 mm^{-1}
Crystal size	0.40 x 0.34 x 0.24 mm
θ_{min} / θ_{max}	2.14 to 23.26 °.
Reflections collected	12652
Independent reflections	2583 [R(int) = 0.0266]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2583/ 0 /311
Goodness-of-fit on F^2	1.07
Final R indices (I>2σ(I))	R_1 = 0.032 and R_2 = 0.081
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.10 and -0.13 eA^{-3}

Table 44 Data and Structure Refinement for 6-(4-Methoxy-phenyl)-1-methyl-4-pyrimidin-2-yl-2,3-1*H*-pyrrolo[2,3-b]pyrimidine, **27b**.

Empirical Formula	$C_{19}H_{18}N_4O$
Formula Weight	318.37
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.9223(4) Å $\alpha = 90$ °.
	b = 11.9648(7) Å $\beta = 90$ °.
	c = 18.529(1) Å $\gamma = 90$ °.
Volume	1534.6(2) $Å^3$
Z	4
Density (calculated)	1.378 g/cm^3
Absorption coefficient	0.089 mm^{-1}
Crystal size	0.25 x 0.15 x 0.14 mm
θ_{min} / θ_{max}	2.20 to 28.27 °.
Reflections collected	15822
Independent reflections	3805 [R(int) = 0.0251]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3805/ 0 /289
Goodness-of-fit on F^2	1.05
Final R indices (I>2σ(I))	$R_1 = 0.038$ and $R_2 = 0.100$
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.39 and -0.28 eA^{-3}

Table 45 Data and Structure Refinement for 4-[2-(4-Phenoxy-phenyl)-8-methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-4-yl]-benzonitrile, **27e**.

Empirical Formula	$C_{28}H_{23}N_3O$
Formula Weight	417.49
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 11.415(3) Å $\alpha = 90$ °.
	b = 10.313(3) Å $\beta = 93.896(7)$ °.
	c = 18.660(5) Å $\gamma = 90$ °.
Volume	2191.6(11) $Å^3$
Z	4
Density (calculated)	1.265 g/cm^3
Absorption coefficient	0.078 mm^{-1}
Crystal size	0.30 x 0.27 x 0.08 mm
θ_{min} / θ_{max}	2.19 to 21.97 °.
Reflections collected	12766
Independent reflections	2643 [R(int) = 0.0447]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2643/ 0 /381
Goodness-of-fit on F^2	1.02
Final R indices ($I>2\sigma(I)$)	R_1 = 0.039 and R_2 = 0.094
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.22 and -0.14 eA^{-3}

Table 46 Data and Structure Refinement for 4-[9-Methyl-2-(4-phenoxy-phenyl)-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-b]azepin-4-yl]-benzonitrile, **27h**.

Empirical Formula	$C_{29}H_{25}N_3O$
Formula Weight	431.52
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	Pc
Unit cell dimensions	a = 11.253(1) Å $\alpha = 90$ °.
	b = 39.851(6) Å $\beta = 94.469(3)$ °.
	c = 20.366(3) Å $\gamma = 90$ °.
Volume	9105(2) $Å^3$
Z	16
Density (calculated)	1.259 g/cm^3
Absorption coefficient	0.077 mm^{-1}
Crystal size	0.25 x 0.15 x 0.14 mm
θ_{min} / θ_{max}	1.43 to 28.39 °.
Reflections collected	95629
Independent reflections	44574 [R(int) = 0.0927]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	44574/ 2 /2385
Goodness-of-fit on F^2	0.98
Final R indices ($I>2\sigma(I)$)	R_1 = 0.073 and R_2 = 0.136
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.60 and -0.44 eA^{-3}

Table 47 Crystal Data and Structure Refinement for 2-(4-Methoxy-phenyl)-9-methyl-4-pyridin-2-yl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-b]azepine, **27j**.

Empirical Formula	$C_{22}H_{23}N_3O$
Formula Weight	345.43
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P 1
Unit cell dimensions	a = 8.9544(6) Å α = 66.502(2) °.
	b = 10.4943(7) Å β = 71.853(2) °.
	c = 11.4673(9) Å γ = 67.098(2) °.
Volume	894.61(11) $Å^3$
Z	2
Density (calculated)	1.282 g/cm^3
Absorption coefficient	0.080 mm^{-1}
Crystal size	0.34 x 0.32 x 0.22 mm
θ_{min} / θ_{max}	1.97 to 27.57 °.
Reflections collected	3467
Independent reflections	3236 [R(int) = 0.0297]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3246/ 0 /237
Goodness-of-fit on F^2	1.06
Final R indices (I>2σ(I))	R_1 = 0.040 and R_2 = 0.105
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.26 and -0.18 eA^{-3}

Table 48 Crystal Data and Structure Refinement for 4-{2-Acetyl-3-[2-(1*H*-indol-3-yl)-ethylamino]-5-phenyl-cyclohexa-2,4-dienyl}-benzonitrile, **31a**.

Empirical Formula	$C_{31}H_{27}N_3O$
Formula Weight	457.56
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.9084(3) Å α = 62.423(1) °.
	b = 11.65921(3) Å β = 70.337(1) °.
	c = 12.5576(4) Å γ = 75.469(1) °.
Volume	1203.02(6) $Å^3$
Z	2
Density (calculated)	1.263 g/cm^3
Absorption coefficient	0.077 mm^{-1}
Crystal size	0.40 x 0.38 x 0.16 mm
θ_{min} / θ_{max}	1.89 to 27.48 °.
Reflections collected	12574
Independent reflections	5473[R(int) = 0.0214]
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5473 0 /341
Goodness-of-fit on F^2	1.03
Final R indices (I>2σ(I))	R_1 = 0.038 and R_2 = 0.094
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.21 and -0.20 eA^{-3}

Table 49 Crystal Data and Structure Refinement for 1-(2-(2-(1*H*-Indol-3-yl)ethylamino)-6-(pyridin-2-yl)-4-(thiophen-2-yl)cyclohexa-1,3-dienyl)ethanone, **31g**.

Empirical Formula	$C_{35}H_{35}N_3O_3$
Formula Weight	545.66
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.8493(1) Å α = 104.226(1) °.
	b = 12.0664(2) Å β = 109.865(1) °.
	c = 14.0104(2) Å γ = 96.537(1) °.
Volume	1481.98(4) $Å^3$
Z	2
Density (calculated)	1.223 g/cm^3
Absorption coefficient	0.078 mm^{-1}
Crystal size	0.38 x 0.22 x 0.14 mm
θ_{min} / θ_{max}	1.62 to 24.71 °.
Reflections collected	12569
Independent reflections	5053 [R(int) = 0.0241]
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5053/ 0 /488
Goodness-of-fit on F^2	1.03
Final R indices (I>2σ(I))	R_1 = 0.038 and R_2 = 0.093
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.18 and -0.18 eA^{-3}

Table 50 Crystal Data and Structure Refinement for *N*,*N*-dimethyl-2-oxo-4-phenyl-6-(pyrimidin-2-yl)cyclohex-3-enecarboxamide, **32b**.

Empirical Formula	$C_{19}H_{19}N_3O_2$
Formula Weight	321.37
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 17.096(2) Å $\alpha = 90$ °.
	b = 12.0871(17) Å $\beta = 97.942(3)$ °.
	c = 7.9004(11) Å $\gamma = 90$ °.
Volume	1616.9(4) $Å^3$
Z	4
Density (calculated)	1.320 g/cm^3
Absorption coefficient	0.088 mm^{-1}
Crystal size	0.20 x 0.16 x 0.09 mm
θ_{min} / θ_{max}	1.20 to 28.31 °.
Reflections collected	16777
Independent reflections	4018 [R(int) = 0.0464]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4018/ 0 /293
Goodness-of-fit on F^2	1.01
Final R indices ($I>2\sigma(I)$)	$R_1 = 0.046$ and $R_2 = 0.105$
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.32 and -0.27 eA^{-3}

Table 51 Crystal Data and Structure Refinement for *N*,*N*-dimethyl-2-oxo-4-phenyl-6-(4-(trifluoromethyl)phenyl)cyclohex-3-enecarboxamide, **32d**.

Empirical Formula	$C_{22}H_{20}F_3NO_2$
Formula Weight	387.39
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.7411(1) Å α = 99.400(1) °.
	b = 13.6656(2) Å β = 103.720(1) °.
	c = 14.9311(3) Å γ = 106.400(1) °.
Volume	1979.14(5) $Å^3$
Z	4
Density (calculated)	1.300 g/cm^3
Absorption coefficient	0.102 mm^{-1}
Crystal size	0.40 x 0.24 x 0.20 mm
θ_{min} / θ_{max}	1.45 to 23.26 °.
Reflections collected	14698
Independent reflections	5674 [R(int) = 0.0246]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5674/ 0 /509
Goodness-of-fit on F^2	1.03
Final R indices (I>2σ(I))	R_1 = 0.043 and R_2 = 0.1.07
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.38 and -0.32 eA^{-3}

Table 52 Crystal Data and Structure Refinement for 6-(4-cyanophenyl)-*N*,*N*-dimethyl-2-oxo-4-(thiophen-2-yl)cyclohex-3-enecarboxamide, **32g**.

Empirical Formula	$C_{20}H_{18}N_2O_2S$
Formula Weight	350.42
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.925(2) Å α = 68.277(4) °.
	b = 10.178(2) Å β = 67.477(4) °.
	c = 10.300(2) Å γ = 68.712(4) °.
Volume	862.7(3) $Å^3$
Z	2
Density (calculated)	1.349 g/cm^3
Absorption coefficient	0.203 mm^{-1}
Crystal size	0.33 x 0.32 x 0.20 mm
θ_{min} / θ_{max}	2.22 to 28.30 °.
Reflections collected	9081
Independent reflections	4232 [R(int) = 0.0179]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4232/ 8 /313
Goodness-of-fit on F^2	1.02
Final R indices (I>2σ(I))	R_1 = 0.036 and R_2 = 0.099
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.35 and -0.25 eA^{-3}

Table 53 Crystal Data and Structure Refinement for 2-phenylquinoline-6-carbonitrile, **40c**.

Empirical Formula	$C_{16}H_{10}N_2$
Formula Weight	230.26
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 3.8902(2) Å α = 111.558(1) °.
	b = 11.7293(7) Å β = 92.791(1) °.
	c = 13.4790(8) Å γ = 90.013 °.
Volume	571.23(6) $Å^3$
Z	2
Density (calculated)	1.339 g/cm^3
Absorption coefficient	0.080 mm^{-1}
Crystal size	2.20 x 0.24 x 0.10 mm
θ_{min} / θ_{max}	1.63 to 27.48 °.
Reflections collected	5862
Independent reflections	2568 [R(int) = 0.0231]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2568/ 0 /203
Goodness-of-fit on F^2	1.03
Final R indices (I>2σ(I))	R_1 = 0.039 and R_2 = 0.109
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.20 and -0.23 eA^{-3}

9 References

[1] For a recent monography, see e. g. "*Multicomponent Reactions*", J. Zhu, H. Bienaymé, eds., Wiley-VCH, Weinheim, **2005**.

[2] For reviews, see e. g. a) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321–. b) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300–3344**;** *Angew. Chem. Int. Ed.* **2000**, 3168–3210. c) I. Ugi, A. Dömling, B. Werner, *J. Heterocycl. Chem.* **2000**, *37*, 647–658. d) L. Weber, K. Illgen, M. Almstetter, *Synlett* **1999**, 366–374. e) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.* **1996**, *29*, 123–131. f) I. Ugi, A. Dömling, W. Hörl, *Endeavour*, **1994**, *18*, 115–122. f) G. H. Posner, *Chem. Rev*. **1986**, *86*, 831–844.

[3] For reviews on diversity oriented syntheses, see e. g. a) S. L. Schreiber and M. D. Burke, *Angew. Chem.* **2004**, *116*, 48–60; *Angew. Chem. Int. Ed.* **2004**, *43*, 46–58. b) M. D. Burke, E. M. Berger, S. L. Schreiber, *Science* **2003**, *302*, 613–618. c) P. Arya, D. T. H. Chou, M. G. Baek, *Angew. Chem.* **2001**, *113*, 351–358; *Angew. Chem. Int. Ed.* **2001**, *40*, 339–346. d) M. J. Valler, D. Green, *Drug Discovery Today* **2000**, *5*, 286–290. e) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.

[4] S. Kobayashi, *Chem. Soc. Rev.* **1999**, *28*, 1–45.

[5] J.-F. Liu, P. Ye, K. Sprague, K. Sargent, D. Yohannes, C. M. Baldino, C. J. Wilson, S.-C. Ng, *Org. Lett.* **2005**, *7*, 3363–3366.

[6] a) N.-F. K. Kaiser, U. Bremberg, M. Larhed, C. Moberg, A. Hallberg, *J. Organomet. Chem.* **2000**, *603*, 2–5. b) U. Bremberg, S. Lutsenko, N.-F. K. Kaiser, M. Larhed, A. Hallberg, C. Moberg, *Synthesis* **2000**, 1004–1008.

[7] a) N.-F. K. Kaiser, U. Bremberg, M. Larhed, C. Moberg, A. Hallberg, *Angew. Chem.* **2000**, *112*, 3741–3744; *Angew. Chem. Int. Ed.* **2000**, *39*, 3596–3598 b) O. Belda, N.-F. Kaiser, U. Bremberg, M. Larhed, A. Hallberg, C. Moberg, *J. Org. Chem.* **2000**, *65*, 5868–5870 c) O. Belda, C. Moberg, *Synthesis*, **2002**, 1601–1606.

[8] B. M. Trost, N. G. Andersen, *J. Am. Chem. Soc.* **2002**, *124*, 14320–14321.

[9] C. S. Yang, J. M. Landau, M. T. Huang, H. L. Newmark, *Ann. Rev. Nutr.* **2001**, *21*, 381–406.

[10] St. V. Kostanecki, and J. Tambor, *Ber. Dtsch. Chem. Ges.* **1907**, *39*, 4022–4027.

[11] M. L. Go, X. L. Liu, *Cur. Med. Chem.* **2005**, *12*, 483–499.

[12] D. N. Dhar, *The chemistry of chalcones and related compounds*, Wiley-Interscience, New York, N.Y. **1981**.

[13] S. J. Won, C. T. Liu, L. T. Tsao, J. R. Weng, H. H. Ko, J. P. Wang, C. N. Lin, *Eur. J Med. Chem.* **2005**, *40*, 103–112.

[14] S. Frölich, C. Schubert, U. Bienzle, K. Jenett-Siems, *J. Antimicrob. Chemother.* **2005**, *55*, 883–887.

[15] G. Cioffi, L. M. Escobar, A. Braca, N. De Tommasi, *J. Nat. Prod.* **2003**, *66*, 1061−1064

[16] J. R. Dimmock, D. W. Elias, M. A. Beazely, N. M. Kandepu, *Curr. Med. Chem.* **1999**, *6***,** 1125–1149.

[17] B. R. Copp, *Nat. Prod. Rep.* **2003**, *20*, 535–557.

[18] L. Zhai, M. Chen, J. Blom, T. G. Theander, S. B. Christensen, A. Kharazmi, *J. Antimicrob. Chemother.* **1999**, *43*, 793–803.

[19] X. Zi, A. R. Simoneau, *Cancer Res.* **2005**, *65* (8), 3479–3486.

[20] A. T. Dinkova-Kostova, W. D. Holtzclaw, N. R. Cole, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 11908−11913.

[21] G. Cioffi, L. M. Escobar, A. Braca, N. De Tommasi, *J. Nat. Prod.* **2003**, *66*, 1061−1064.

[22] B. A. Bohm, *Introduction to Flavonoids*, Harwood Academic Publishers: Amsterdam, **1998**.

[23] S. Sebti, A. Solhi, R. Tahir, S. Boulaajaj, J. A. Mayoral, J. M. Fraile, A. Kossir, H. Oumimoun, *Tetrahedon Lett.* **2001**, *42*, 7953–7955.

[24] J. Lopez, R. Jacquot, F. Figueras, *Stud. Surf. Sci. Catal.* **2000**, *130*, 491–496.

[25] F. Fringuelli, F. Pizzo, C. Vittoriani, L. Vaccaio, *Chem. Commun.* **2004**, 2756–2757.

[26] E. Le Gall, F. Texier-Boullet, J. Hamelin, *Synth. Commun.* **1999**, *29*, 3651–3657.

[27] J. T. Li, W. Z. Yang, S. X. Wang, S. H. Li, T. S. Li, *Ultrason. Sonochem.* **2002**, *9*, 237–239.

[28] E. T. Stoyanov, Y. Champavier, A. Simon, J. P. Basly, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2685–2687.

[29] S. Eddarir, N. Cotelle, Y. Bakkour, C. Rolando, *Tetrahedron Lett.* **2003**, *44*, 5359–5363.

[30] L. W. Xu, L. Li, C. G. Xia, P. Q. Zhao, *Helv. Chem. Acta* **2004**, *87*, 3080–3084.

[31] M. Weiss, *J. Am. Chem. Soc.* **1952**, 74, 200–205.

[32] K. Funabiki, H. Nakamura, M. Matsui, K. Shibata, *Synlett.* **1999**, *6*, 756–758.

[33] a) T. J. J. Müller, R. Braun, M. Ansorge, *Org. Lett.* **2000**, *2*, 1967–1970. b) R. U. Braun, K. Zeitler, T. J. J. Müller, *Org. Lett.* **2000**, *2*, 4181–4184. c) R. U. Braun, T. J. J. Müller, *Tetrahedron* **2004**, *60*, 9463–9469. d) R. U. Braun, T. J. J. Müller, *Synthesis* **2004**, *14*, 2391–2406. e) R. U. Braun, K. Zeitler, T. J. J. Müller, *Org. Lett.* **2001**, *3*, 3297–3300. f) N. A. M. Yehia, K. Polborn, T. J. J. Müller, *Tetrahedron Lett.* **2002**, *43*, 6907–6910.

[34] M. P. Sammes, M. W. L. Chung, A. R. Katritzky, *J. Chem. Soc. Perkin Trans. 1* **1985**, 1773–1779.

[35] A. Diaz-Ortiz, E. Diez-Barra, A. de la Hoz, P. Prieto, A. Moreno, *J. Chem. Soc. Perkin Trans.1* **1994**, 3595–3598.

[36] B. Rissafi, A. El Louzi, A. Loupy, A. Petit, M. Soufiaoui, S. F. Tetouani, *Eur. J. Org. Chem.* **2002**, 2518–2523.

[37] a) B. Furth, *Bull. Soc. Chim. Fr.* **1967**, 650–657. b) J. Castells, E Dunach, F. Geijo, F. Lopez-Calahorra, M. Prats, O. Sanahuja, L. Villanova, *Tetrahedron Lett.* **1980**, *21*, 2291–2294.

[38]For lead reviews on Sonogashira couplings, see e.g. a) S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, *Synthesis* **1980**, 627–630. b) K. Sonogashira in *Metal catalyzed Cross-coupling Reactions*, Wiley-VCH, Weinheim, **1998**, 203–229. c) K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46–49. d) E.-I. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979–2018.

[39] T. J. J. Müller, M. Ansorge, D. Aktah, *Angew. Chem.* **2000**, *112*, 1323–1326; *Angew. Chem. Int. Ed.* **2000**, *39*, 1253–1256.

[40] R. U. Braun, T. J. J. Müller, *Mol. Diversity* **2003**, *6*, 251–259.

[41] a) R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge, J. Rousell, *Tetrahedron Lett.* **1986**, *27*, 279–282. b) R. J. Giguere, T. L. Bray, S. M. Duncan, G. Majetich, *Tetrahedron Lett.* **1986**, *27*, 4945–4958.

[42] a) C. O. Kappe, *Angew. Chem.* **2004**, 6408–6443; *Angew. Chem. Int. Ed.* **2004**, *43*, 6250–6284. b) M. Nüchter, B. Ondruschka, W. Bonrath, A.Gum, *Green Chem.* **2004**, *6*, 128–141. c) M. Nüchter, U. Müller, B. Ondruschka, A. Tied, W. Lautenschläger, *Chem. Eng. Technol.* **2003**, *26*, 1207–1216. d) A. de la Hoz, A. DWaz-Ortis, A. Moreno, F. Langa, *Eur. J. Org. Chem.* **2000**, 3659–3673. e) Y. Xu, Q.-X. Guo, *Heterocycles* **2004**, *63*, 903–974.

[43] a) *Microwaves in Organic Synthesis* (Ed.: A. Loupy), Wiley-VCH, Weinheim, **2002**. b) B. L. Hayes, *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing, Matthews

NC, **2002**. c) *Microwave-Assisted Organic Synthesis* (Eds.: P. LidstrUm, J. P.Tierney), Blackwell, Oxford, **2004**.

[44] a) M. Larhed, A. Hallberg, *J. Org. Chem.* **1996**, *61*, 9582–9584. b) K. S. A. Vallin, P. Emilsson, M. Larhed, A. Hallberg, *J. Org. Chem.* **2002**, *67*, 6243–6246. c) N. E. Leadbeater, M. Marco, *Angew. Chem.* **2003**, *115*, 1445–1447; *Angew. Chem. Int. Ed.* **2003**, *42*, 1407–1409. d) N. E. Leadbeater, M. Marco, *J. Org. Chem.* **2003**, *68*, 5660–5667. e) P. Walla, C. O. Kappe, *Chem. Commun.* **2004**, 564–565.

[45] a) K. Olofsson, S.-Y. Kim, M. Larhed,D. P. Curran, A. Hallberg, *J. Org. Chem*. **1999**, *64*, 4539–4541. b) A. G.Whittaker, D. M. P. Mingos, *J. Chem. Soc. Dalton Trans.* **2000**, 1521–1526.

[46] a) D. Bogdal, M. Lukasiewicz, J. Pielichowski, A. Miciak, S. Bednarz, *Tetrahedron* **2003**, *59*, 649–653. b) M. Lukasiewicz, D. Bogdal, J. Pielichowski, *Adv. Catal.* **2003**, *345*, 1269–1272.

[47] a) N. Cramer, S. Laschat, A. Baro, H. Schwalbe, C. Richter, *Angew. Chem.* **2004**, 831–833; *Angew. Chem. Int. Ed.* **2005**, *44* (5), 820–822. b) M. O. Duffey, A. LeTiran, J. P. Morken, *J. Am. Chem. Soc*. **2003**, *125* (6), 1458–1459 .

[48] M. Erdelyi, A. Gogoll, *J. Org. Chem.* **2001**, *66*, 4165–4169.

[49] S. Thorand, N. Krause, *J. Org. Chem.* **1998**, *63*, 8551–8553.

[50] a) K. C. Westaway, R. Gedye, *J. Microwave Power* **1995**, *30*, 219–230. b) F. Langa, P. de la Cruz, A. de la Hoz, A. Diaz-Ortiz, E. Diez-Barra, *Contemp. Org. Synth.* **1997**, *4*, 373–386. c) L. Perreux, A. Loupy, *Tetrahedron* **2001**, *57*, 9199–9223. d) N. Kuhnert, *Angew. Chem.* **2002**, *114*, 1943–1946; *Angew. Chem. Int. Ed.* **2002**, *41*, 1863–1866. e) C. R. Strauss, *Angew. Chem.* **2002**, *114*, 3741–3743; *Angew. Chem. Int. Ed.* **2002**, *41*, 3589–3590.

[51] D. A. Stuerga, P. Gaillard, *Tetrahedron* **1996**, *52* (15), 5505–5510.

[52] For excellent reviews, see e.g. a) *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky, C. W. Rees, A. J. Boulton, A. McKillop, eds.; Pergamon Press, Oxford, **1984**, *Vol. 2*. b) J. F. Toomey, R. Murugan in *Progress in Heterocyclic Chemistry*, H. Suschitzky, E. F. V. Scriven, eds.; Pergamon Press, Oxford, **1994**, *Vol. 6*.

[53] For reviews, see e.g. a) A. O. Plunkett, *Nat. Prod. Rep.* **1994**, *11*, 581–590. b) C. L. J. Wang, M. A. Wuonola, *Org. Prep. Proc. Int.* **1992**, *24*, 585–621. c) A. R. Pinder, *Nat. Prod. Rep.* **1992**, *9*, 491–504. d) A. Numata, T. Ibuka, in *The Alkaloids*, A. Brossi, ed.; Academic

Press, New York **1987**, *Vol. 31*. e) J. W. Daly, T. F. Spande in *Alkaloids. Chemical and Biological Perspectives*, S. W. Pelletier, ed.; Wiley, New York **1980**, *Vol. 4*, 1.

[54] a) J. Kobayashi, T. Murayama, Y. Ohizumi, *Tetrahedron Lett.* **1989**, *30*, 4833–4836. b) A. V. Rao, G. R. Reddy, B. V. Rao, *J. Org. Chem.* **1991**, *56*, 4545–4547.

[55] J. Kobayashi, T. Murayama, S.Kosuge, F. Kanda, M. Ishibashi, H. Kobayashi, Y. Ohizumi, T. Ohta, S. Nozoe, T. Sasaki, *J. Chem. Soc. Perkin Trans. 1* **1990**, 3301–3303.

[56] A. R. Carroll, P. J. Scheuer, *Tetrahedron* **1990**, *46*, 6637–6644.

[57] S. Sakemi, L. E. Totton, H. H. Sun, *J. Nat. Prod.* **1990**, *53*, 995–999.

[58] For computations, synthetic and pharmacological studies, see e.g. a) U. Cosentino, G. Moro, D. Pitea, S. Scolastico, R. Todeschini, C. Scolastico, *J. Comput.-Aided Mol. Des.* **1992**, *6*, 47–60. b) J. A. Robl, L. A. Duncan, J. Pluscec, D. S. Karanewsky, E. M. Gordon, C. P. Ciosek Jr., L. C. Rich, V. C. Dehmel, D. A. Slusarchyk, *J. Med. Chem.* **1991**, *34*, 2804–2815. c) B. D. Roth, T. M. A. Bocan, C. J. Blankley, A. W. Chucholowski, P. L. Creger, M. W. Creswell, E. Ferguson, R. S. Newton, P. O'Brien, *J. Med. Chem.* **1991**, *34*, 463–466. d) G. Beck, K. Kesseler, E. Baader, W. Bartmann, A. Bergmann, E. Granzer, H. Jendralla, B. von Kerekjarto, R. Krause, *J. Med. Chem.* **1990**, *33*, 52–60.

[59] See also a) G. Schmidt, J. Stoltefuss, M. Lögers, A. Brandes, C. Schmeck, K.-D. Bremm, H. Bischoff, D. Schmidt, *Ger. Offen.* **1999**, 42 pp. DE 19741399. b) J. Stoltefuss, M. Lögers, G. Schmidt, A. Brandes, C. Schmeck, K.-D. Bremm, H. Bischoff, D. Schmidt, *PCT Int. Appl.* **1999**, 107 pp. WO 9914215. c) H. W. Smith, *Eur. Pat. Appl.* **1985**, 35 pp. EP 161867.

[60] V. Klimesova, K. Churacek, J. Sova, Z. Odlerova, *Conf. Org. Chem. Adv. Org. Chem.* **1997**, 160–161.

[61] H. Knorr, H. Mildenberger, G. Salbeck, B. Sachse, P. Hartz, *Ger. Offen.* **1980**, 21 pp. DE 2918590.

[62] a) D. E. Beattie, R. Crossley, A. C. W. Curran, D. G. Hill, A. E. Lawrence, *J. Med. Chem.* **1977**, *20*, 718–721. b) D. E. Beattie, R. Crossley, A. C. W. Curran, G. T. Dixon, D. G. Hill, A. E. Lawrence, R. G. Shepherd, *J. Med. Chem.* **1977**, *20*, 714–718.

[63] A. Shiozawa, Y. Ichikawa, C. Komuro, M. Ishikawa, Y. Furuta, S. Kurashige, H. Miyazaki, H. Yamanaka, T. Sakamoto, *Chem. Pharm. Bull.* **1984**, *32*, 3981–3993.

[64] For inhibitors of HIV-1 integrase, see e. g. a) D. J. Hazuda, N. J. Anthony, R. P. Gomez, S. M. Jolly, J. S. Wai, L. Zhuang, T. E. Fisher, M. Embrey, J. P. Guare, M. S. Egbertson, J. P. Vacca, J. R. Huff, P. J. Felock, M. V. Witmer, K. A. Stillmock, R. Danovich, J. Grobler, M. D. Miller, A. S. Espeseth, L. Jin, I.-W. Chen, J. H. Lin, K. Kassahun, J. D. Ellis, B. K. Wong,

W. Xu, P. G. Pearson, W. A. Schleif, R. Cortese, E. Emini, V. Summa, M. K. Holloway, S. D. Young, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11233–11238. b) L. Zhuang, J. S. Wai, M. W. Embrey, T. E. Fisher, M. S. Egbertson, L. S. Payne, J. P. Guare, J. P. Vacca, D. J. Hazuda, P. J. Felock, A. L. Wolfe, K. A. Stillmock, M. V. Witmer, G. Moyer, W. A. Schleif, L. J. Gabryelski, Y. M. Leonard, J. J. Lynch, S. R. Michelson, S. D. Young, *J. Med. Chem.* **2003**, *46*, 453–456. c) For cytotoxic and antiviral activity, see e. g. H. I. El-Subbagh, S. M. Abu-Zaid, M. A. Mahran, F. A. Badria, A. M. Al-Obaid, *J. Med. Chem.* **2000**, *43*, 2915–2921.

[65] W. Calhoun, R. P. Carlson, R. Crossley, L. J. Datko, S. Dietrich, K. Heatherington, L. A. Marshall, P. J. Meade, A. Opalko, R. G. Shepherd, *J. Med. Chem.***1995**, *38*, 1473–1481.

[66] C. A. Bignozzi, J. R. Schoonover, F. Standola, *Prog. Inorg. Chem.* **1997**, *44*, 1–95.

[67] a) J. M. Lehn, *Supramolecular Chemistry*, VCH: Weilheim, **1995** b) J. P. Collin, P. Gavina, V. Heitz, J. P. Sauvage, *Eur. J. Inorg. Chem.* **1998**,1–14.

[68] A. Arounaguiry, B. G. Maiya, *Inorg. Chem.* **2000**, *39*, 4256–4272.

[69] G. Di Marco, M. Lanza, A. Mamo, I. Stefio, C. Di Pietro, G. Romeo, S. Campagna, *Anal. Chem.* **1998**, *70*, 5019–5023.

[70] G. Jones In *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky, C. W. Rees, Eds., Pergamon: New York, **1984**, *Vol.2*, Part. 2A, 395.

[71] M. Nitta, M. Ohnuma, Y. Iino, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1115–1118.

[72] K. Funabiki, A. Isomura, Y. Yamaguchi, W. Hashimoto, K. Matsunaga, K. Shibata, M. Matsui, *J. Chem. Soc. Perkin Trans. 1* **2001**, 2578–2582.

[73] K. Takanaka, S. Katsumura, *Org. Lett.* **2000**, *2*, 373–375.

[74] A. R. Katritzky, A. A. A. Abdel-Fattah, D. O. Tymoshenko, S. A. Essawy, *Synthesis* **1999**, *12*, 2114–2118.

[75] D. Suzuki, R. Tanaka, H. Urabe, F. Sato, *J. Am. Chem. Soc.* **2002**, *124*, 3518–3519.

[76] a) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127–2198. b) M. M. McCormick, H. A. Duong, G. Zuo, J. Louie, *J. Am. Chem. Soc.* **2005**, *127*, 5030–5031.

[77] F. Knoch, F. Kremer, U. Schmidt, U. Zenneck, P. L. Floch, F. Mathey, *Organometallics*, **1996**, *15*, 2713–2719.

[78] C. Bränli, T. R. Ward, *J. Comb. Chem.* **2000**, *2*, 42–47.

[79] Y. Yamamoto, R. Ogawa, K. Itoh, *J. Am. Chem. Soc.* **2001**, *123*, 6189–6190.

[80] M. C. Bagley, J. W. Dale, J. Bower, *Synlett.* **2001**, *7*, 1149–1151.

[81] M. C. Bagley, K. E. Bashford, C. L. Hesketh, C. J. Moody, *J. Am. Chem. Soc.* **2000**, *122*, 3301−3313.

[82] M. C. Bagley, K. Chapaneri, J. W. Dale, X. Xiong, J. Bower, *J. Org. Chem.* **2005**, *70*, 1389−1399.

[83] D. L. Boger, S. Ichikawa, H. Jiang, *J. Am. Chem. Soc.* **2000**, *122*, 12169−12173.

[84] a) F. Palacios, E. Herrean, G. Rubiales, J. M. Ezpelata, *J. Org. Chem.* **2002**, *67*, 2131−2135. b) B. S. J. Blagg, D. L. Boger, *Tetrahedron* **2002**, *58*, 6343−6349. c) D. L. Boger, O. Hütter, K. Mbyia, M. Zhang, *J. Am. Chem. Soc.* **1995**, *117*, 11839−11849. d) D. L. Boger, K. C. Cassidy, S. Nakahara, *J. Am. Chem. Soc.* **1993**, *115*, 10733−10741.

[85] A. R. Katritzky, A. A. A. Abdel-Fattah, D. O. Tymoshenko, S. A. Essawy, *Synthesis* **1999**,12, 2114−2118.

[86] a) T. L.Gilchrist, *Heterocyclenchemie*, VCH, Weinheim, New York, Basel, **1995**, Chpt. 5.2. b) T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles*, Wiley-VCH, Weinheim, **2003**, Chpt. 6.14.

[87] a) J. M. Robinson, L. W. Brent, C. Chau, K. A. Floyd, S. L. Gillham, T. L. McMahan, D. J. Magda, T. J. Motycka, M. J. Pack, A. L. Roberts, L. A. Seally, S. L. Simpson, R. R. Smith, K. N. Zalesny. *J. Org. Chem.* **1992**, *57*, 7352−7355. b) A. O. Abdelhamid, I. M. Abbas, A. M. Negm, *Egypt. J. Pharm. Sci.* **1989**, *30*, 61−64. c) C. Ruangsiyanand, H. J. Rimek, F. Zymalkowski, *Ber.Dtsch. Chem. Ges.* **1970**, *103*, 2403−2410.

[88] a) J. Sauer, H. Wiest, *Angew. Chem.* **1962**, *74*, 353−354; *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 268−269. b) J. Sauer, R. Sustmann, *Angew. Chem.* **1980**, *92*, 773−801; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779−787. c) D. L. Boger, M. Patel, in Prog. Heterocyclic Chem. (H. Suschitzky, E. F. V. Scriven, eds.), Pergamon Press, Oxford, **1989**, *Vol. 1*.

[89] A. R. Katritzky, A. M. El-Mowafy, G. Musumara, K. Sakizadeh, C. Sana-Ullah, S. M. M. El-Shafie, S. S. Thind, *J. Org. Chem.* **1981**, *46*, 3823−3830.

[90] *PC Spartan Pro*, Wavefunction Inc.: Irvine, CA, **2002**.

[91] Solvation model SM 5.4 (Cramer, Truhlar) as implemented in *PC Spartan Pro*, Wavefunction Inc.: Irvine, CA, **2002**.

[92] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **1881**,*14*, 1637−1638.

[93] a) B. Love, M. Goodman, K. Snader, R. Tedeschi, E. Macko, *J. Med. Chem.* **1974**, *17*, 956−965. b) F. Bossert, H. Meyer, E. Wehinger, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 762−769. c) B.G. Katzung in *Basic & Clinical Pharmacology* **1998,** Appleton & Lange, Stamford, CT (USA).

[94] a) M. F. Gordeev, D. V. Patel, E. M. Gordon, *J. Org. Chem.* **1996**, *61*, 924–928. b) J. G. Breitenbucher, G. Figliozzi, *Tetrahedron Lett.* **2000**, *41*, 4311–4315. c) J. J. Vanden Eynde, A. Mayence, *Intl. J. Med. Biol. Environ.* **2000**, *28*, 25–31.

[95] a) R. Alajarin, J. J. Vaquero, J. L. Garcia Navio, J. Alvarez-Builla, *Synlett.* **1992**, 297–298. b) R. Alajarin, P. Jordan, J. J. Vaquero, J. Alvarez-Builla, *Synthesis* **1995**, 389–391. c) L. Ohberg, J. Westman, *Synlett.* **2001**, 1296–1298. d) J. J. Vanden Eynde, A. Mayence, *Molecules* **2003**, *8*, 381–391.

[96] I. P.-G.Santander, L. J. Nunez-Vergara, J. A. Squella, P. A. Navarrete-Encina, *Synthesis* **2003**, *18*, 2781–2784.

[97] R. H. Böcker, F. P. Guengerich, *J. Med. Chem.* **1986**, *29*, 1596–1603.

[98] a) J. J. Vanden Eynde, F. Delfosse, A. Mayence, Y. Van Haverbeke, *Tetrahedron* **1995**, *51*, 6511–6516. b) R. S. Varma, D. Kumar, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1755–1757. c) N. Nakamichi, Y. Kawashita, M. Hayashi, *Org. Lett.* **2002**, *22*, 3955–3957.

[99] A.-H. Li, S. Moro, N. Melman, X-d. Ji, K. A. Jacobson, *J. Med. Chem.* **1998**, *41*, 3186–3201.

[100] *Organikum*, 21st ed.; H. G. O. Becker, R. Beckert, G. Domschke, E. Fanghänel, W. D. Habicher, P. Metz, D. Pavel, K. Schwetlick, Wiley-VCH, Weinheim, New York, Chichester, Brisbane, Singapore, Toronto, **2001**.

[101] L. Brandsma, *Preparative Acetylenic Chemistry*, 2nd Edition, Elsevier Amsterdam-Oxford-New York-Tokio, **1992**, 91–92.

[102] a) O. G. Dediu, N. A. M. Yehia, T. J. J. Müller, *Z. Naturforsch. B: Chem. Sci.* **2004**, *59b*, 443–450. b) N. A. M. Yehia, *Postodoctoral Progress Report*, **2001**.

[103] a) M. Behforouz, M. Ahmadian, *Tetrahedron* **2000**, *56*, 528–529. b) P. Buonora, J.-C Olsen, T. Oh, *Tetrahedron* **2001**, *57*, 6099–6138. c) S. Jayakumar, M. P. S. Ishar, M. P. Mahajan, *Tetrahedron* **2002**, *58*, 379–471.

[104] a) P. Nebois, H. Fillion, L. Benameur, B. Fenet, J.-L. Luche, *Tetrahedron* **1993**, *49*, 9767–9774. b) J. M. Perez, C. Avendano, J. C. Menendez, *Tetrahedron Lett.* **1997**, *38*, 4717–4720. c) A. Poumaroux, Z. Bouaziz, M. Domard, H. Fillion, *Heterocycles* **1997**, *45*, 585–596. d) M. M. Blanco, C. Avedano, J. C. Menendez, *Tetrahedron* **1996**, *52*, 5933–5944. e) M. M. Blanco, C. Avedano, J. C. Menendez, *Tetrahedron* **1999**, *55*, 12637–12646.

[105] D. L. Boger, *Tetrahedron* **1983**, *39*, 2869–2873.

[106] a) E. Desarbre, J.-Y. Mérour, *Tetrahedron Lett.* **1996**, *37*, 43–46. b) E. C. Taylor, J. L. Pont, *Tetrahedron Lett.* **1987**, *28*, 379–82. c) D. E. Beattie, R. Crossley, A. C. W. Curran, D. G. Hill, A. E. Lawrence, *J. Med. Chem.* **1977**, *20*, 718–21. d) M. M. Robison, B. L. Robison, F. P. Butler, *J. Am. Chem. Soc.* **1959**, *81*, 743–47. e) P. C. Ting, J.J. Kaminski, M. H. Sherlock, W. C. Tom, J. F. Lee, R. W. Bryant, A. S. Watnick, A. T. McPhail, *J. Med. Chem.* **1990**, *33*, 2697–2706.

[107] For a recent pharmaceutical use of this class of compounds, see e. g. a) J. H. Hutchinson, W. Halczenko, K. M. Brashear, M. J. Breslin, P. J. Coleman, L. T. Duong, C. Fernandez-Metzler, M. A. Gentile, J. E. Fisher, G. D. Hartman, J. R. Huff, D. B. Kimmel, C. T. Leu, R. S. Meissner, K. Merkle, R. Nagy, B. Pennypacker, J. J. Perkins, T. Prueksaritanont, G. A. Rodan, S. L. Varga, G. A. Wesolowski, A. E. Zartman, S. B. Rodan, M. E. Duggan, *J. Med. Chem.* **2003**, *46*, 4790–98. b) M. Badawneh, P. L. Ferrarini, V. Calderoni, C. Manera, E. Martinetti, C. Mori, G. Saccomanni, L. Testai, *Eur. J. Med. Chem.* **2001**, *36*, 925–34. c) K. Chen, S.-C. Kuo, M.-C. Hsieh, A. Mauger, C. M. Lin, E.Hamel, K.-H. Lee, *J. Med. Chem.* **1997**, *40*, 2266–2275. d) M. E. Duggan, L. T. Duong, J. E. Fisher, T. G. Hamill, W. F. Hoffman, J. R. Huff, N. C. Ihle, C.-T. Leu, R. M. Nagy, J. J. Perkins, S. B. Rodan, G. Wesolowski, D. B. Whitman, A. E. Zartman, G. A. Rodan, G. Hartman, *J. Med. Chem.* **2000**, *43*, 3736–3745.

[108] J. R. Kavali, B. V. Badami, *Il Farmaco* **2000**, 55, 406–409.

[109] E. Bacqué, M. El Qacemi, S. Z. Zard, *Org. Lett.* **2004**, *6*, 3671–3674.

[110] K. Müller, S. Sauer, *Tetrahedron Lett*. **1984**, *24*, 2541–2544.

[111] B. Yde, N. M. Yousif, U. Pedersen, I. Thomsen, S.-O. Lawesson, *Tetrahedron* **1984**, *40*, 2052–2055.

[112] D. M. D'Souza, F. Rominger, T. J. J. Müller, *Angew. Chem.* **2005**, *117,* 156–161; *Angew. Chem. Int. Ed.* **2005**, *44,* 153–158.

[113] As implemented in *PC Spartan Pro*, Wavefunction Inc.: Irvine, CA, **2002**.

[114] Determined with 7-diethylamino-4-methyl-chromen-2-one, coumarine 1, as a standard (Φf = 0.73), see G. Jones II, W. R. Jackson, C. Y. Choi, W. R. Bergmark, *J. Phys. Chem.* **1985**, *89*, 294–300.

[115] B. Valeur, *Molecular Fluorescence*, Wiley-VCH, Weinheim, **2002**.

[116] For the review on β-enaminones, see: a) J. V. Greenhill, *Chem. Soc. Rev.* **1977**, *6*, 277–294. b) J. P. Michael, C. B. De Koning, D. Gravestock, G. D. Hosken, A. S. Howard, C.

M. Jungmann, R. W. M. Krause, A. S. Parsons, S. C. Pelly, T. V. Stanbury, *Pure Appl. Chem.* **1999**, *71,* 979–988.

[117] a) H. Meyer, *Liebigs Ann. Chem.* **1981**, 1534–1544. b) G. Bobowski, J. Shavel, Jr., *J. Heterocycl. Chem.* **1985**, *22*, 1679–1688. c) D. Papapdopoulou, I. Papoutsis, S. Spyroudis, A. Varvoglis, *Tetrahedron Lett.* **1998**, *39*, 2865–2866.

[118] N. R. Natale, H. Hope, *J. Heterocycl. Chem.* **1986**, *23*, 711–713.

[119] J. Wiesner, R. Ortmann, H. Jomaa, M. Schlitzer, *Angew. Chem.* **2003**, *115*, 5432–5451; *Angew. Chem. Int. Ed.* **2003**, *43*, 5274–5293.

[120] M. H. Gilles, *Management of Severe Malaria: A Practical Handbook*, 2nd ed., World Health Organization: Geneva, **2000**.

[121] a) P. M. O'Neill, A. Mukhtar, P. A. Stocks, L. E. Randle, S. Hindley, Ward, S. A. R. C. Storr, J. F. Bickley, I. A. O'Neil, J. L. Maggs, R. H. Hughes, P.A. Winstanley, P. G.Bray, B. K. Park, *J. Med. Chem.* **2003**, *46*, 4933–4945. b) R. G. Ridley, W. Hofheinz, H. Matile, C. Jaquet, A. Dorn, R. Masciadri, S. Jolidon, W. F. Richter, A. Guenzi, M. A. Girometta, H. Urwyler, W. Huber, S. Thaithong, W. Peters, *Antimicrob. Agents Chemother.* **1996**, *40*, 1846–1854. c) P. A. Stocks, K. J. Raynes, P. G. Bray, B. K. Park, P. M. O'Neill, S. A. Ward, *J. Med. Chem.* **2002**, *45*, 4975–4983. d) R. Vlahov, St. Pavrushev, J. Vlahov, *Pure Appl. Chem.*, **1990**, *62*, 1303–1306. e) P. B. Madrid, J. Sherrill, A. P. Liou, J. L. Weisman, J. L. DeRisi, R. Kipling Guy, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1015–1018.

[122] a) A. Fournet, B. Vagneur, P. Richomme, J. Bruneton, *Can. J. Chem.* **1989**, *67*, 2116–2118. b) A. Fournet, R. Hocquemiller, F. Roblot, A.Cavé, P. Richomme, J. Bruneton, *J. Nat. Prod.* **1993**, *56*, 1547–52. c) A. Fournet, A.A. Barrios, V. Muñoz, R. Hocquemiller, A. Cavé, P. Richomme, J. Bruneton, *Antimicrob. Agents Chemother.* **1993**, *37*, 859–63.

[123] World Health Organization. Leishmaniasis and Leishmania/HIV co-Infection: http://www.who.int/emc-documents/surveillance/docs/whocdsisr2001.html/Leishmaniasis/ Leishmaniasis.htm.

[124] M. A. Fakhfakh, A. Fournet, E. Prina, J.-F. Mouscadet, X. Franck, R. Hocquemiller, B. Figadere, *Bioorg. Med. Chem.* **2003**, *11*, 5013–5023.

[125] a) P. J. Steel, *Coord. Chem. Rev.* **1990**, *106*, 227–265. b) S. Ernst, W. Kaim, *J. Am. Chem. Soc.* **1986**, *108*, 3578–3586. c) A. Mamo, S. Nicolleti, N. Cam Tat, *Molecules* **2002**, *7*, 618–627 d) H. Qaseer, *Croatica Chemica Acta* **2005**, *78*, 79–84.

[126] M. Balasubramanian, J. G. Keay, in *Comprehensive Hetrocyclic Chemistry II*, A. R. Katrizky, C. W. Rees, E. F. V. Scriven, Eds., Pergamon Press: Oxford, **1996**, Vol. *5*, Ch. 5.06, 245.

[127] R. H. F. Manske, M. Kukla, *Org. React.,* **1953**, *7*, 59–62.

[128] W. Borsche, W. Ried, *Ann.* **1943**, *554*, 269-290.

[129] For a review on recent progress in the synthesis of quinolines: V. V. Kouznetsov, L. Y. Mendez, C. M. Mendelez Gomez, *Curr. Org. Chem.* **2005**, *9*, 141–161.

[130] C. K. Cho, B. Ho Oh, S. C. Shim, *J. Heterocycl. Chem.* **1999**, *36*, 1175–1178.

[131] a) C. K. Cho, B. Ho Oh, S. C. Shim, *Tetrahedron Lett*. **1999**, *40*, 1499–1500. b) C. K. Cho, B. Ho Oh, S. C. Shim, D. H. Oh, *J. Heterocycl. Chem.* **2000**, *37*, 1315–1320. c) C. K. Cho, B. Ho Oh, J. S. Kim, T.-J. Kim, S. C. Shim, *Chem. Commun.* **2000**, 1885–1886.

[132] K. Sangu, K. Fuchibe, T. Akiyama, *Org. Lett.* **2004**, *6*, 353–355

[133] J. Jacob, W.D. Jones, *J. Org. Chem.* **2003**, *68*, 3563–3568.

[134] T. Akiyama, S. Nakashima, K. Yokota, K. Fuchibe, *Chem. Lett.* **2004**, *33*, 922–923.

[135] C. S. Cho, N. Y. Lee, T.-J. Kim, S. C. Shim, *J. Heterocycl. Chem.* **2004**, *41*, 409–411.

[136] R. Braun, *Dissertation* **2004**.

[137] A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron* **1985**, *41*, 5121–5131.

[138] M. P. R. Spee, J. Boersma, M. D. Meijir, M. Q. Martijn, G. van Koten, J. W. Geus, *J. Org. Chem.* **2001**, *66* (5), 1647–1656.

[139] G. Wagner, B. Voigt, D. Dänicke, T. Liebermann, *Pharmazie* **1976**, *31*, 528–532.

[140] G. Dannhardt, W. Kiefer, G. Krämer, S. Mährlein, U. Nowe, B. Fiebich, *Eur. J. Med. Chem.* **2000**, 499–510.

[141] I. S. MacLean, S. T. Widdows, *J. Chem. Soc.* **1914**, *105*, 2169–2175.

[142] I. Urasaki, Y. Ogata, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1285–1287.

[143] J. Kankare, J. Lukkari, P. Pasanen, K. Harmaa, C. Visy, *Macromol. Rapid Commun.* **1994**, *27* (15), 4327–4334.

[144] T. Nishio, Y. Omote, *Synthesis* **1980**, *5*, 392–394.

[145] J. V. Sinistierra, A. Garcia-Raso, J. A. Cabello, J. M. Marinas, *Synthesis* **1984**, *6*, 502–504.

[146] Y.-Q. Cao, Z. Dai, R. Zhang, B.-H. Chen, *Synth. Commun.* **2005**, *35* (8), 1045–1049.

[147] J. T. Gupton, J. Coury, M. Moebus, S. Fitzwater, *Synth. Commun.* **1986,** *16* (12), 1575–1586.

[148] Y. Ueno, L. D. S. Yadav, M. Okawara, *Chem. Lett.* **1983**, *6*, 831–834.

[149]Y. Kawamura, M. Maruyama, T. Tokuoka, *Synthesis* **2002**, *17*, 2490–2496.

[150] H. Kauffmann, H. Burckhardt, *Ber.* **1914**, *46*, 3808–3816.

[151] G. Bobowski, *J. Heterocycl. Chem.* **1983**, *20* (2), 267–272.

[152] R. S. Robinson, M. C. Dovey, D. Gravestock, *Tetrahedron Lett.* **2004**, *45* (36), 6787–6789.

[153] W. Walter, T. Fleck, *Liebigs Ann. Chem.* **1976**, *4*, 670–681.

[154] M. Nakamura, T. Fujimoto, K. Endo, E. Nakamura, *Org. Lett.* **2004**, *6* (26), 4837–4840.

[155] T. Cuvigny, H. Normant, *Bull. Soc. Chim. Fr.* **1960**, *3*, 515–521.

[156] B. Shao, S. Victory, V. I. Ilyin, R. R. Goehring, Q. Sun, D. Hogenkamp, D. D. Hodges, K. Islam, D. Sha, C. Thang, P. Nguyen, S. Robledo, G. Sakellaropoulos, R. B. Carter, L. P. Purdue Pharma, *J. Med. Chem.* **2004**, *47* (17), 4277–4285.

[157] S. C. Benson, J. L. Gross, J. K. Snyder, *J. Org. Chem.* **1990**, *55* (10), 3257–3269.

[158] G. T. Crisp, S. Papadopoulos, *Aust. J. Chem.* **1989**, *42* (2), 279–285.

[159] M. Ferles, P. Jancar, O. Kocian, *Collect. Czech. Chem. Commun.* **1979**, *44* (9), 2672–2676.

[160] M. Ishikura, I. Oda, M. Terashima, *Heterocycles* **1985**, *23* (9), 2375–2386.

[161] J. Takeuchi, Y. Hamada, *Chem. Pharm. Bull.* **1976**, *24* (8), 1813–1821.

[162] P. Ruggli, P. Hindermann, *Helv. Chim. Acta* **1937**, *20*, 272–282.