Sustainable Syntheses of Substituted Heterocycles through Ruthenium- and Palladium-Catalyzed Direct C–H Bond Functionalizations

Dissertation

zur Erlangung des mathematisch-naturwissenschaftlichen Doktorgrades

"Doctor rerum naturalium"

der Georg-August-Universität Göttingen

im Promotionsprogramm

Catalysis for Sustainable Synthesis

der Georg-August University School of Science (GAUSS)

vorgelegt von

Christoph Frank Kornhaaß

aus Rotenburg an der Fulda

Göttingen, 2014

Mitglieder des Betreuungsausschusses

Prof. Dr. L. Ackermann, Institut für Organische und Biomolekulare Chemie
Prof. Dr. U. Diederichsen, Institut für Organische und Biomolekulare Chemie
Prof. Dr. D. Stalke, Institut für Anorganische Chemie

Mitglieder der Prüfungskommission

Referent: Prof. Dr. L. Ackermann, Institut für Organische und Biomolekulare Chemie
Korreferent: Prof. Dr. U. Diederichsen, Institut für Organische und Biomolekulare Chemie

Weitere Mitglieder der Prüfungskommission:

Prof. Dr. D. Stalke, Institut für Anorganische Chemie
Prof. Dr. K. Koszinowski, Institut für Organische und Biomolekulare Chemie
Prof. Dr. H. Laatsch, Institut für Organische und Biomolekulare Chemie
Dr. A. Breder, Institut für Organische und Biomolekulare Chemie

Tag der mündlichen Prüfung: 20.06.2014

Vielen Dank ...

Als Erstes geht mein besonders aufrichtiger Dank an Herrn Prof. Dr. Lutz Ackermann dafür, dass er es mir ermöglicht hat meine Doktorarbeit in seiner Forschungsgruppe durchzuführen und mir die Möglichkeit gegeben hat einige interessante und höchst inspirative Aufgabenstellungen zu bearbeiten. Dabei konnte ich stets auf seine hervorragende fachliche und persönliche Unterstützung zählen, auch in Hinblick auf meinen zukünftigen Werdegang.

Auch bei den Korreferenten dieser Arbeit, den Herren Prof. Dr. Ulf Diederichsen und Prof. Dr. Dietmar Stalke, möchte ich mich herzlich für die Teilnahme an der Prüfungskommission bedanken, ebenso wie den Herren Prof. Dr. Konrad Koszinowski, Prof. Dr. Hartmut Laatsch und Dr. Alexander Breder.

Mein Dank für das sorgfältige und gewissenhafte Korrekturlesen dieser Arbeit geht insbesondere an Herrn Dr. Sergei I. Kozhushkov sowie an Herrn Dr. Suman De Sarkar, Karolina Graczyk, Svenja Warratz, Jie Li, Daniel Zell und Jonathan Hubrich.

Allen aktuellen und ehemaligen Mitgliedern der Forschungsgruppe von Prof. Ackermann danke ich für das freundliche und, gerade in interkultureller Hinsicht, einzigartige Arbeitsklima sowie für die vielen kleineren und größeren Gespräche zwischen den Experimenten (und natürlich auch für die ein oder andere außeruniversitäre Unternehmung). Allen voran danke ich hierbei natürlich Stefan Beußhausen, Gabi Keil-Knepel und Karsten Rauch für ihre unentbehrliche Hilfe bei kleineren (oder größeren) Problemen mit EDV, Verwaltung und der Laborausrüstung.

Für die erfolgreiche und gelungene Zusammenarbeit bei gemeinsamen Projekten bedanke ich mich bei Jie Li, Yingjun Zhu, Christian Kuper, Daniel Zell, Ana Cajaraville Leiro, Svenja Warratz sowie meinen beiden Bachelor-Studenten Kris Runge und Kathrin Dienst. Natürlich möchte ich mich auch bei den unzähligen Abteilungspraktikanten und dem gesamten Lab 302 bedanken.

Nicht unerwähnt bleiben sollte mein Dank an (inzwischen Dr.) Christian Maaß dafür, dass er so nett war, die in dieser Arbeit gezeigte Kristallstruktur, für mich zu messen (mit freundlicher Genehmigung durch Herrn Prof. Dr. Dietmar Stalke).

Ich möchte auch allen Mitarbeitern der analytischen Abteilungen des Instituts für die schnelle und gründliche Arbeit danken, besonders Herrn Reinhard Machinek und Herrn Dr. Holm Frauendorf, die immer zu Verfügung standen um mich bei NMR- und massespektrometrischen Untersuchungen zu beraten.

Auch den Organisatoren und Verantwortlichen des CaSuS-Promotionsprogramms danke ich dafür, dass sie mich mit einem Stipendium unterstützt haben. Dabei geht mein Dank auch an Dr. Hanna Steininger für die Hilfe bei organisatorischen Details.

Natürlich möchte ich mich auch ganz herzlich bei allen meinen Freunden, insbesondere der Clique um mein altes Semester, der ehemaligen Bauwagen-Truppe und meinen alten Abi-Kollegen, für die vielen einmaligen und unvergesslichen Erlebnisse und die nötige Zerstreuung abseits des universitären Alltags bedanken.

Ein ganz besonderer Dank geht an meine wunderbare Familie. Ich möchte meiner Mutter und meinem Vater danken, sie beide sind die besten Eltern die man sich wünschen kann. Auch meinen beiden Schwestern Elisa und Lara möchte ich herzlich danken, genauso wie meiner lieben Großmutter und meinem Großvater. Danken möchte ich auch meiner Tante Brigitte und natürlich Rainer. Sie alle haben mich während der letzten Jahre bedingungslos unterstützt und es mir erst ermöglicht, dass ich meinen Weg durch das Studium gehen konnte.

"Alle Hindernisse und Schwierigkeiten sind Stufen, auf denen wir in die Höhe steigen."

- Friedrich Nietzsche

Contents

Abbreviations

Ac	Acetyl
Ad	Adamantyl
Alk	Alkyl
AMLA	Ambiphilic metal-ligand activation
APT	Attached proton test
aq.	aqueous
Ar	Aryl
atm	Atmosphere
ATR	Attenuated total reflectance
bpy	2,2'-Bipyridine
Bn	Benzyl
Bu	Butyl
cat.	Catalytic
CMD	Concerted metalation-deprotonation
Cp*	1,2,3,4,5-Pentamethylcyclopentadienyl
Cp^t	1,3-Di(*tert*-butyl)cyclopentadienyl
Cy	Cyclohexyl
DavePhos	2-Dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl
DCE	1,2-Dichloroethane
DCIB	1,2-Dichloro-2-methylpropane
DG	Directing group
DMA	*N*,*N*-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DoM	Directed *ortho*-metalation
DPEPhos	(Oxydi-2,1-phenylene))bis(diphenylphosphine)
dppbz	1,2-Bis(diphenylphosphino)benzene
dppe	1,2-Bis(diphenylphosphino)ethane
ddpf	1,3-Bis(diphenylphosphino)ferrocene
dppp	1,1'-Bis(diphenylphosphino)propane
dtbpy	4,4'-Di-*tert*-butyl bipyridine
EI	Electron ionization

ESI	Electronspray ionization
Et	Ethyl
FTICR	Fourier transform ion cyclotron resonance
GC-MS	Gas chromatography-mass spectrometry
gem	Geminal
Hex	Hexyl
HiPrCl	1,3-Bis-(2,6-di-*iso*-propylphenyl)imidazolium chloride
HRMS	High resolution mass spectrometry
IES	Internal electrophilic substitution
i-Pr	*iso*-Propyl
IR	Infrared
JohnPhos	2-(Di-*tert*-butylphosphino)biphenyl
KIE	Kinetic isotopic effect
LDA	Lithium di-*iso*-propylamide
LED	Light-emitting diode
Mes	2,4,6-trimethylphenyl
Me	Methyl
m-	*meta*
mol.	Molecular
m.p.	Melting point
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect
NOESY	Nuclear overhauser enhancement and exchange spectroscopy
o-	*ortho*
p-cymene	4-*iso*-Propyltoluene
PEG	Polyethylene glycol
Pent	Pentyl
phen	Phenanthroline
Ph	Phenyl
Pin	Pinacol
Piv	Pivalyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
p-	*para*
RGB	Red-green-blue
SBM	σ-Bond metathesis
S_EAr	Electrophilic aromatic substitution
SPO	Secondary phosphine oxide
t-Am	*tert*-Amyl

TDS	Turnover-determining step
TFE	2,2,2-Trifluoroethanol
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofurane
TIPS	Tri-*iso*-propylsilyl
TLC	Thin layer chromatography
TM	Transition metal
TMS	Trimethylsilyl
TS	Transition state
UV	Utraviolet
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

1 Introduction

1.1 Transition Metal-Catalyzed Direct C−H Bond Functionalization

The selective construction of heterocyclic structural motifs is of key importance for many state of the art applications of synthetic organic chemistry. Heteroaromatic compounds with unique chemical and biological properties are used as pharmaceuticals, agrochemicals, materials (Figure 1.1).[1–5]

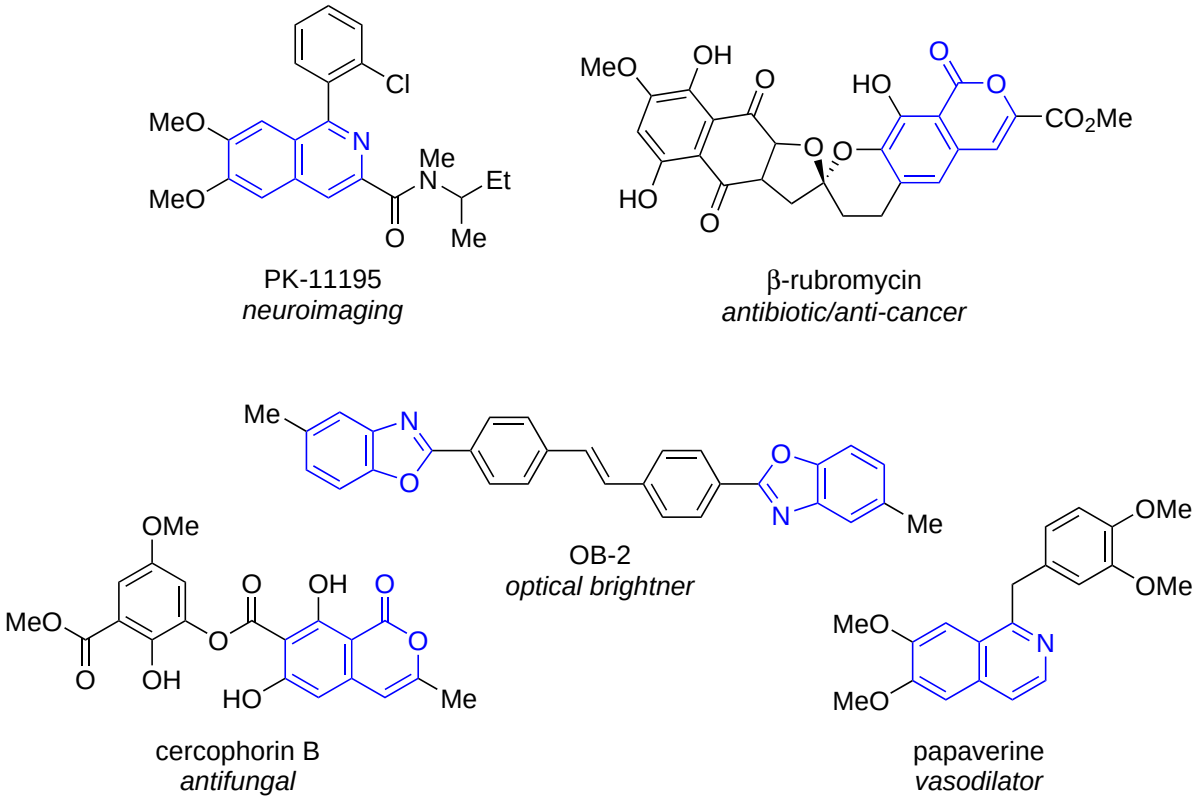
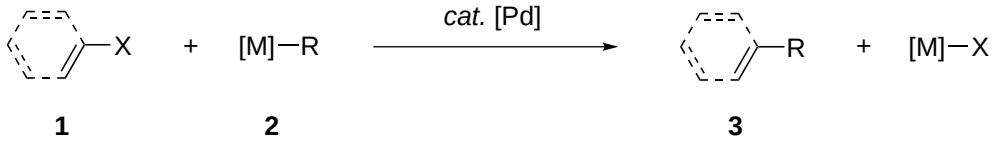


Figure 1.1: Naturally occuring and synthetic molecules with heterocyclic architectures.

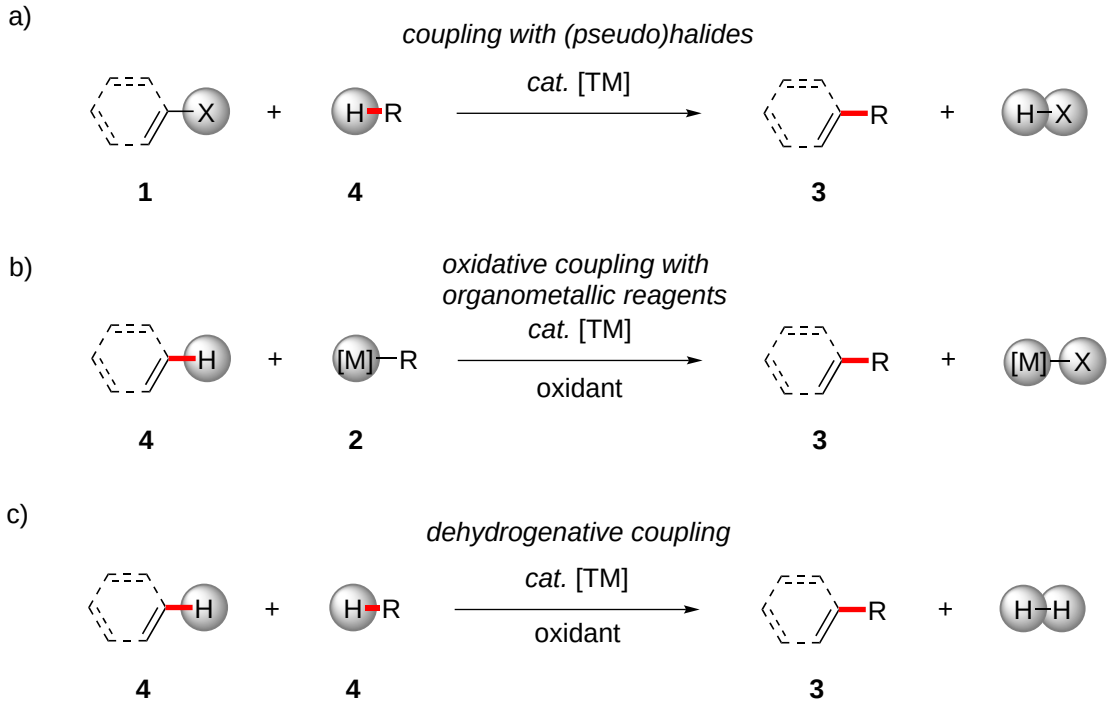
The preparation of such molecules on large scale is a challenging task and a perpetual driving force for the development of new synthetic methods. Especially the chemo- and site-selective formation of C−C bonds remains as an ongoing aspiration of synthetic organic chemistry. As a result considerable progress was made on transition metal-catalyzed C−C-coupling reactions during the past decades.[6–9] In this context it is important to mention that in 2010 the Nobel prize in chemistry was awarded to *R. F. Heck*, *E. Negishi* and *A. Suzuki* for their significant contributions to the development of palladium-catalyzed cross-coupling reactions.[10]

In these transformations, the palladium catalyst promotes the reaction between an aryl- or vinyl(pseudo)halide **1** and an organometallic reagent **2** to the cross-coupled product **3** (Scheme 1.1). Other metals are also known to catalyze these reactions, for example nickel and iron.[11, 12] Although these reactions are very efficient, they feature a significant disadvantage, namely that prefunctionalized stating materials are a prerequisite. These compounds most often need to be prepared in several steps starting from unfuctionalized molecules.



Scheme 1.1: Palladium-catalyzed cross-coupling reactions.

With respect of ecological and economical aspects of organic synthesis new concepts for more sustainable transition metal-catalyzed direct C−H bond functionalizations have been conceived.[13, 14] Direct C−H bond functionalizations have the advantage, that prefunctionalization of the starting materials is redundant, which is accompanied with a reduction of waste material. Scheme 1.2 displays three different strategies for transition metal-catalyzed direct C−H bond functionalizations.[15]

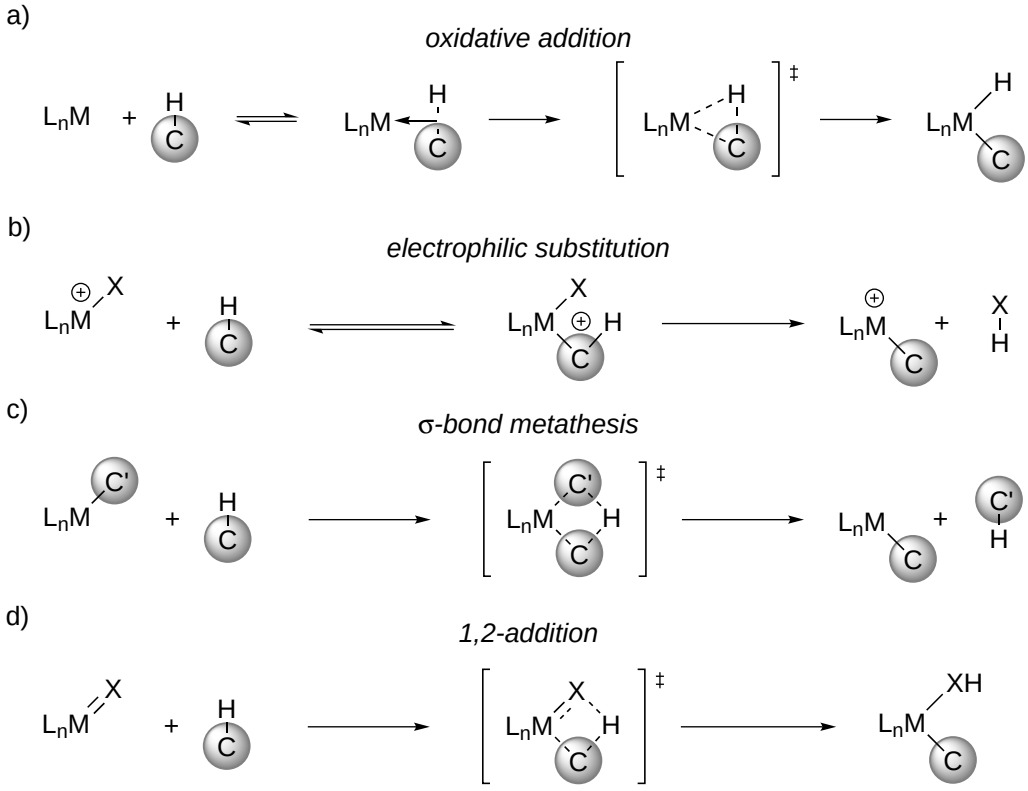


Scheme 1.2: Strategies for transition metal-catalyzed direct C−H bond functionalizations.

In analogy to traditional cross-coupling chemistry, Scheme 1.2 a shows the coupling between molecule **4** with an unactivated C−H bond and an aryl- or vinyl(pseudo)halide **1**. The reaction demonstrated in Scheme 1.2 b works inversely: C−H bond in an aryl- or vinyl-substrate is

activated and coupled with an organometallic reagent **2**. For these kind of reactions, however, the use of an oxidant is mandatory. The last example in Scheme 1.2 c describes the dehydrogenative coupling between molecules through activation of two C−H bonds and the formal generation of dihydrogen; an oxidant is also needed for this type of reactions.

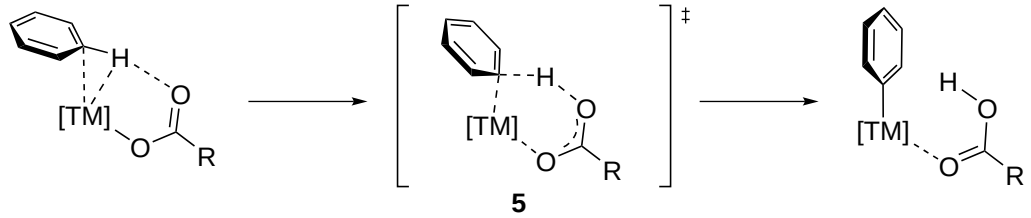
Although a number of transformations in which a C−H bond is functionalized with participation of a metal-activated ligand *via* a transition metal-induced radical-chain mechanism are known, *Shilov* classifies only specific types of reactions as "true C−H activation".[16] In these reactions, the metal is directly involved in the cleavage of the C−H bond and a M−C σ-bond is formed. Different mechanistic pathways, four of which are shown in Scheme 1.3 as the most generally accepted ones, can take place for this processes.[17–19]



Scheme 1.3: Different mechanisms for transition metal-catalyzed C−H activations.[19]

The first pathway shown in Scheme 1.3 a is the oxidative addition of a C−H bond to the metal center. This process can occur for electron-rich and low-valent late transition metals (Re, Fe, Ru, Os, Ir, Pt). If late- or post-transition metals are employed in high oxidation stages (Pd^{2+}, Pt^{2+}, Pt^{4+}, Hg^{2+}), the mechanism is frequently shifted towards an electrophilic substitution (Scheme 1.3 b). However, early group 3 and 4 transition metals as well as lanthanides cannot undergo oxidative addition; for these metals σ-bond metathesis (SBM) takes place (Scheme 1.3 c). C−H activation can also proceed *via* 1,2-addition to unsaturated M=X bonds (Scheme 1.3 d).

Related to the σ-bond metathesis mechanism, a number of reactions proceeds *via* "base-assisted" C−H activation.[19] For instance, a carboxylate-ligand on the transition metal can act as base to promote the abstraction of the proton after electrophilic activation of the C−H bond by the metal. Proton abstraction by the carboxylate and C−M bond formation take place simultaneously. Such transition states **5** have been described as "concerted-metalation-deprotonation" (CMD)[20] or "ambiphilic metal-ligand activation" (AMLA)[17] and the mechanism can be generalized as shown in Scheme 1.4.[21–24]



Scheme 1.4: Mechanism for the carboxylate-assisted C−H activation.

Various calculations showed that a six-membered transition state, where the carboxylate is still bound to the transition metal, is favoured over a four-membered transition state. Figure 1.2 for example, shows the differences in energy between the potential transition-states of the iridium-catalyzed C−H activation in benzene.[25]

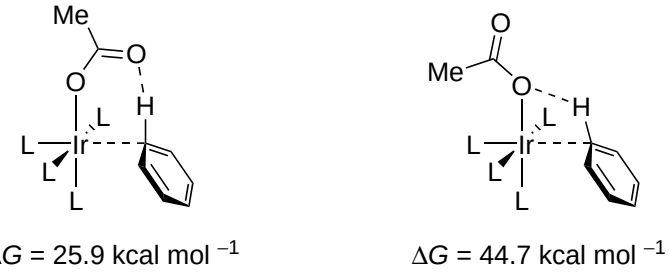
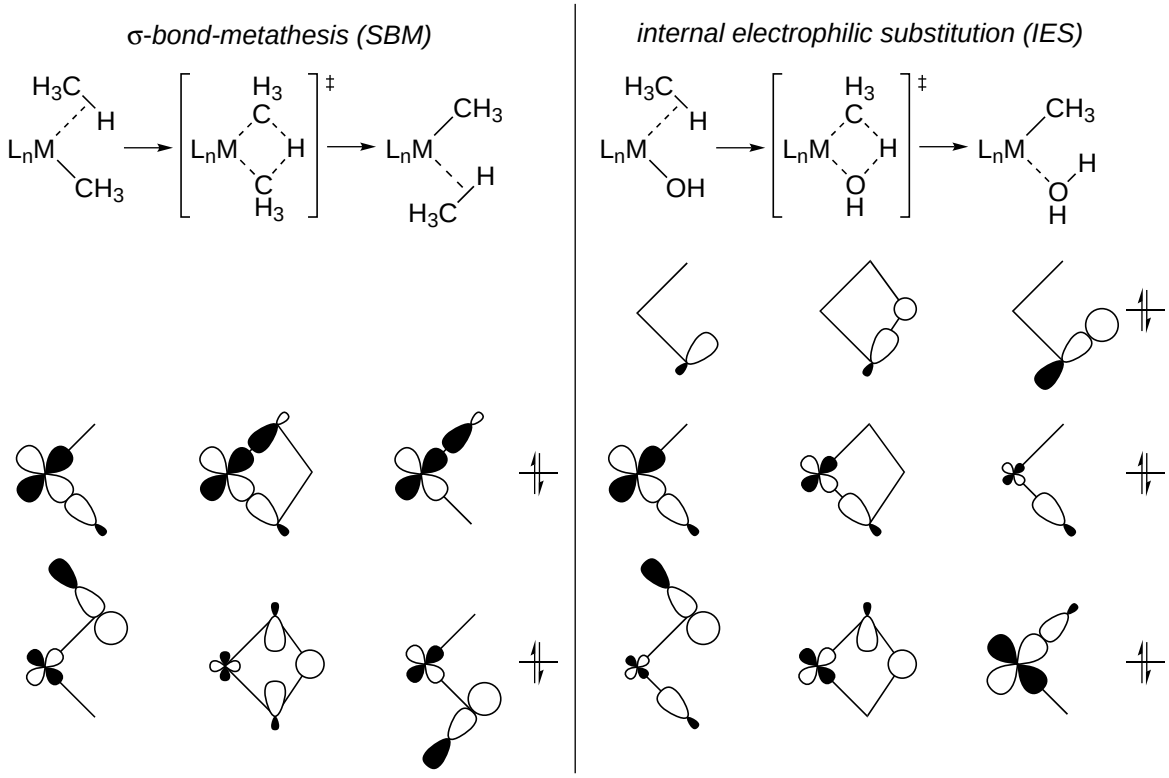


Figure 1.2: Differences in energy between a 4-membered and 6-membered TS.

Nevertheless, in case of hydroxyl- or alkoxyl-ligands only 4-membered transition states are possible. This transition state appears to be a SBM (Scheme 1.3 c). However, calculations by *Goddard III et. al.* revealed that, in contrast to SBM, the M−O bond is based on a different orbital than the newly formed H−O bond (Scheme 1.5).[26, 27] This mechanistic pathway is termed as "internal electrophilic substitution" (IES). Herein, the lonepair of the hydroxyl-ligand starts interacting with the proton and is finally converted into the new H−O bond. The M−O bond on the other hand is broken and results a new lone pair on the oxygen, which weakly donates to a d-orbital on the metal. Only the formerly bonding C−H bond orbital also delocalizes with the forming M−C bond during the transition state.

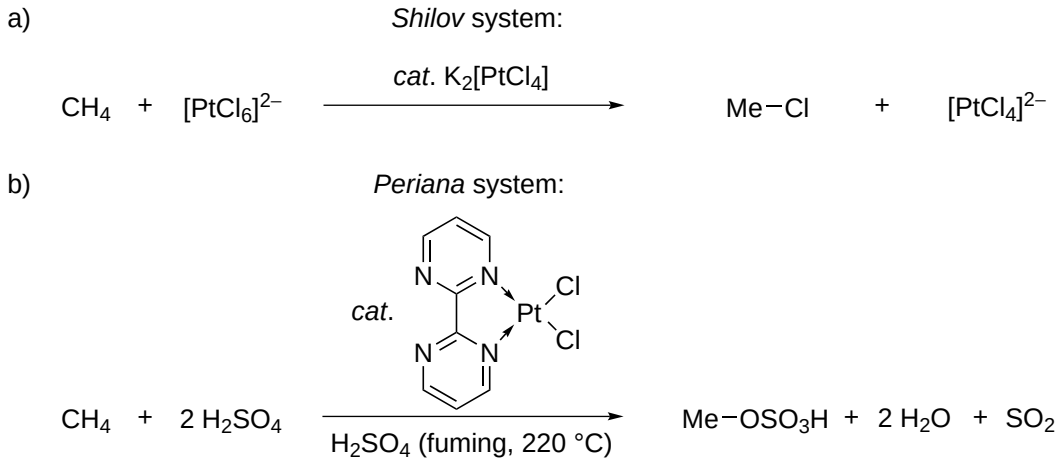


Scheme 1.5: Molecular orbital diagrams for the SBM- and the IES-mechanism.

Besides all generalizations mentioned above, it is important to note that the exact mechanism also strongly depends on the substrates and the solvent in each individual case.

1.2 Site-selectivity and Directing Groups in C−H Bond Functionalization

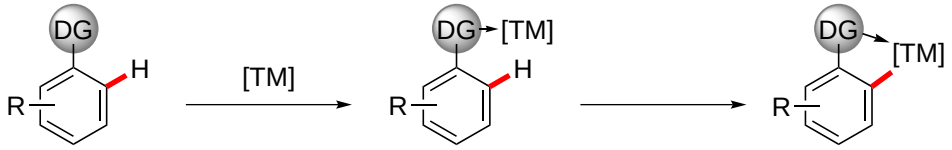
A big issue in C−H activation chemistry is the chemo- and site-selective cleavage of specific C−H bonds. The selective conversion of methane to methanol, for instance, is of great importance with respect to the potential use of methanol as a fuel.[28] However, the chemoselective oxidation of alkanes is still a challenging task, as alcohols and aldehydes tend to be more reactive than the hydrocarbons itself and thus resulting in overoxidation. Radical-based reactions, on the other side, are often not selective enough and lead to product mixtures. Scheme 1.6 a shows the early catalytic system which was developed by *Shilov* for the selective methane-activation.[16, 29] As stoichiometric amounts of Pt(IV) are required as oxidant, intensive studies by *Periana* led to an improved catalytic system where H_2SO_4 is the stoichiometric oxidant (Scheme 1.6 b). It is noteworthy to mention that these catalysts selectively oxidize the terminal methyl-group of longer aliphatic chains.[30, 31] Recently, *White* reported on the selective C−H oxidation of complex organic molecules by employing an iron-catalyst.[32, 33] However, the mode of action might be similar to those of haem-based enzymes.[34]



Scheme 1.6: Methane activation with the *Shilov*- and the *Periana*-systems.

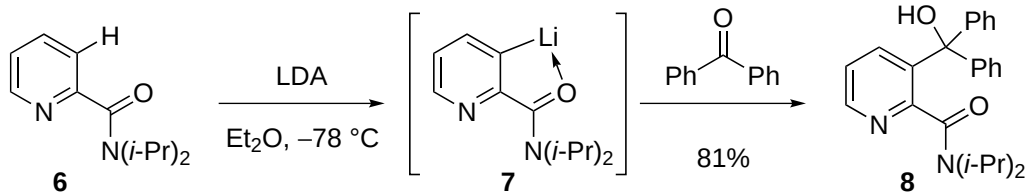
Besides the selective C−H activation of aliphatic compounds, the selective functionalization of aromatic and heteroaromatic C−H bonds is of significant importance, as an ample number of fine chemicals consists of aromatic moieties. On one hand, C−H activation on aromatic system might be accelerated due to precoordination of the aromatic π-system to the transition metal. On the other hand, the site-selective C−H bond cleavage of functionalized arenes and heteroarenes remains a challenging task.

The most common way to achieve site-selectivity in direct C−H bond activation on arenes is the use of a directing group, which is usually placed in the *ortho*-position to the C−H bond that should be functionalized (Scheme 1.7). The directing group bears a heteroatom with a lonepair of electrones and can thus coordinate to the transition metal complex [TM].



Scheme 1.7: Principle of a directing group in transition metal-catalyzed C−H activation.

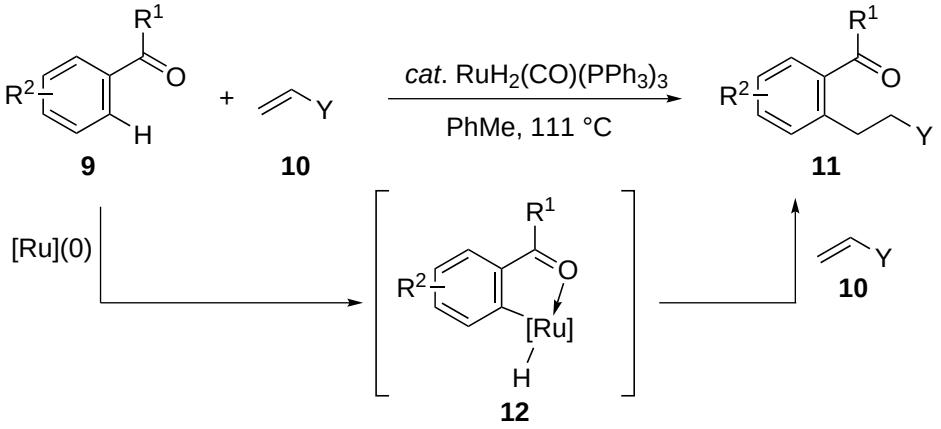
This principle is also utilized in the stoichiometric directed *ortho*-metalation (DoM) of arenes with organolithium compounds, such as *n*-BuLi, or lithiated bases, such as LDA.[35] The resulting stoichiometrically *ortho*-lithiated compound, for example **7**, is then usually reacted with an electrophile (Scheme 1.8).



Scheme 1.8: Directed *ortho*-metalation of a pyridine derivative **6**.[36]

Unfortunately, the functional group tolerance of this stoichiometric approach is very limited due to the high reactivity of the strong bases. More importantly, stoichiometric amounts of the strong base are necessary. This results in the formation of large quantities of undesired lithium salts as byproduct.

Based on pioneering work by *Lewis*,[37] in 1993 *Murai et al.* described the first example of a directed catalytic C−H bond functionalization of aromatic ketones **9** (Scheme 1.9).[38] This reaction can also be considered as a hydroarylation of olefin **10**. Herein the carbonyl-functionality served as the directing group for the ruthenium-catalyst. Further developments showed that also other directing groups and other ruthenium-catalysts can be used for this chemistry,[39] with recent examples from the groups of *Genet*[40, 41] and *Ackermann*.[42, 43]



Scheme 1.9: The *Murai*-reaction.

In the past decade, a variety of different directing groups, some of which are shown in Figure 1.3, have been successfully applied for palladium-, nickel-, rhodium-, ruthenium- or iridium-catalyzed direct arylations, alkylations, alkenylations and alkynylations.[14, 15, 44–46]

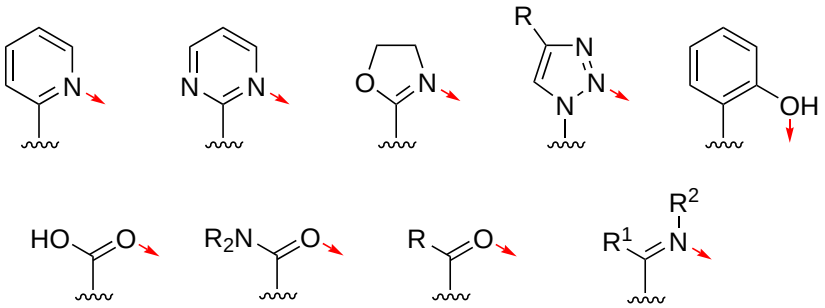
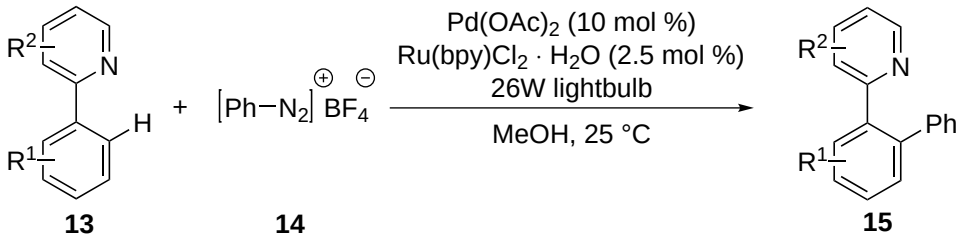
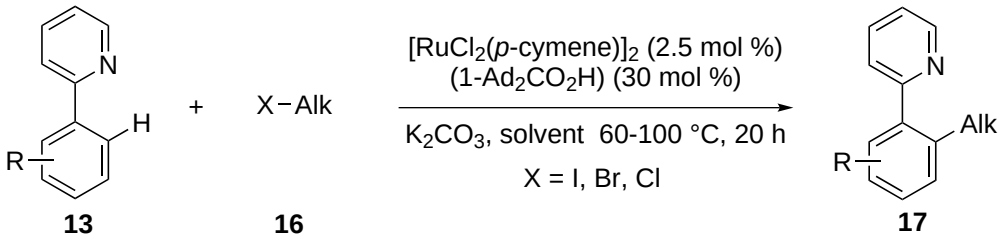


Figure 1.3: Different directing-groups in transition-metal catalyzed C−H activation.

One of the most commonly used directing groups is the 2-pyridyl-substituent.[47–50] For instance, it has recently been used in photo-redox-mediated palladium-catalyzed arlytions of phenylpyridines **13** with aryl diazonium salts **14** (Scheme 1.10).[51] Also ruthenium-catalyzed direct alkylations and benzylations with primary alkyl halides **16** and benzyl chlorides are possible with pyridine as the directing group (Scheme 1.11).[52, 53]

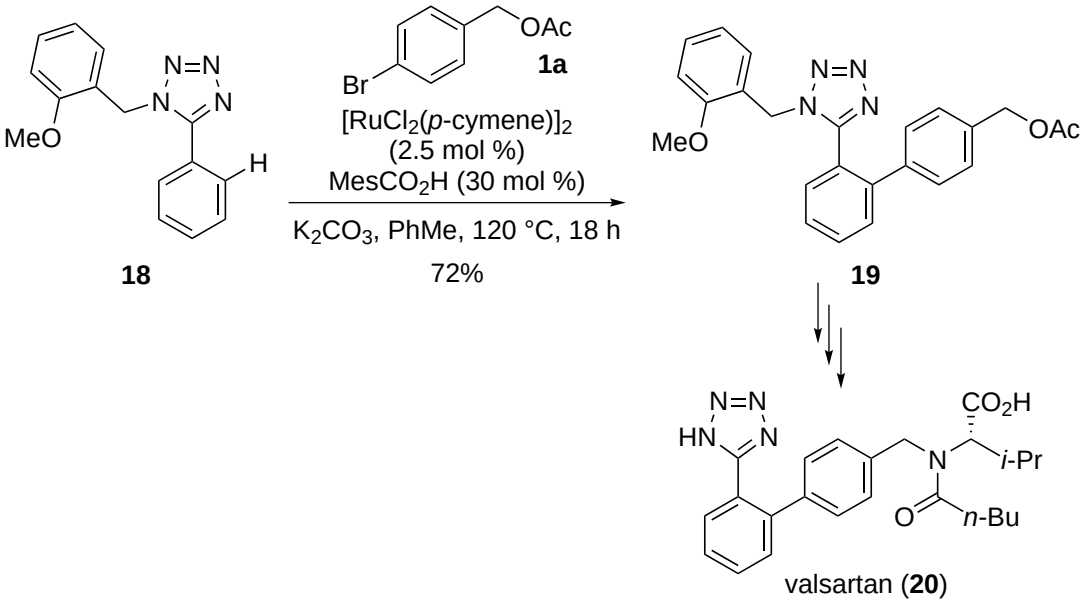


Scheme 1.10: Palladium-catalyzed direct arylations *via* vissible-light photocatalysis.



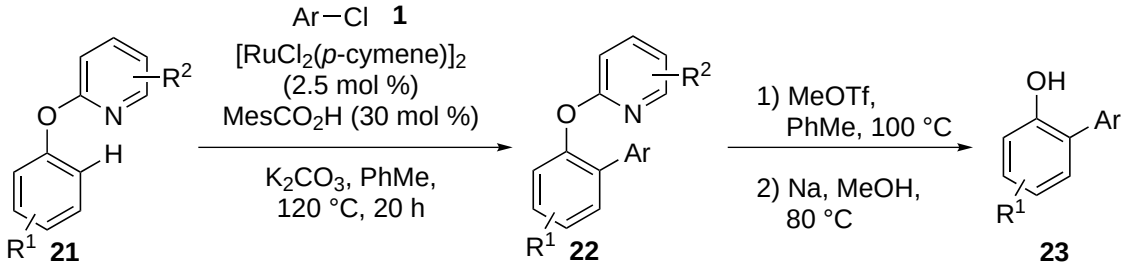
Scheme 1.11: Ruthenium-catalyzed direct alkylations of 2-phenylpyridines **13**.

More recently, even *meta*-selective alkylations with secondary alkyl halides have been described by the group of *Ackermann*.[54] Nevertheless, 2-pyridyl-substituents are difficult to remove. Therefore also significant efforts were invested to replace it with more synthetically useful or removable directing groups. Tetrazoles, for example, are usefull directing groups for direct arylations, as they are part of most AT_1-receptor antagonists. Scheme 1.12 shows the successful arylation of **18** by employing a relatively inexpensive ruthenium-catalyst. The product **19** is a direct precursor of the nonpeptidic angiotensin-II-receptor blocker valsartan (**20**).[55–57]



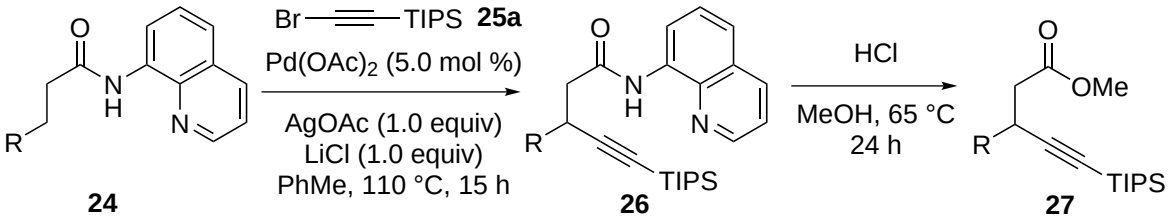
Scheme 1.12: Ruthenium-catalyzed direct arylation by tetrazole-assistance.[55]

Also the use of removable directing groups was extensively studied in recent years.[58, 59] Thus, the research group of *Ackermann* reported on 2-phenoxypyridine as a removable directing group for ruthenium-catalyzed arylations with aryl chlorides (Scheme 1.13).[60]



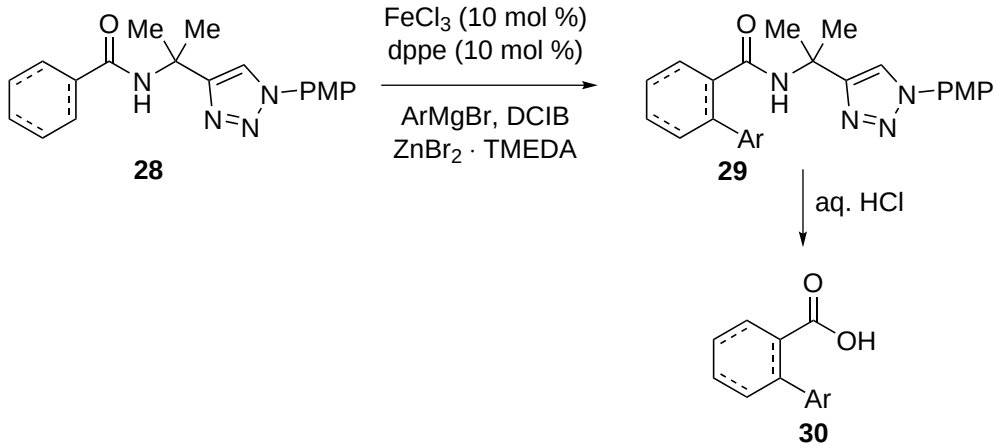
Scheme 1.13: Phenoxypyridine as a removable directing group.

Daugulis et al. developed a bidentade directing group based on 8-aminoquinoline.[61, 62] An example is represented by the palladium-catalyzed direct alkynylation of amides derived from aliphatic carboxylic acids **24** with **25a** as reported by *Chatani* (Scheme 1.14).[63, 64]



Scheme 1.14: 8-Aminoquinoline as a removable directing-group.

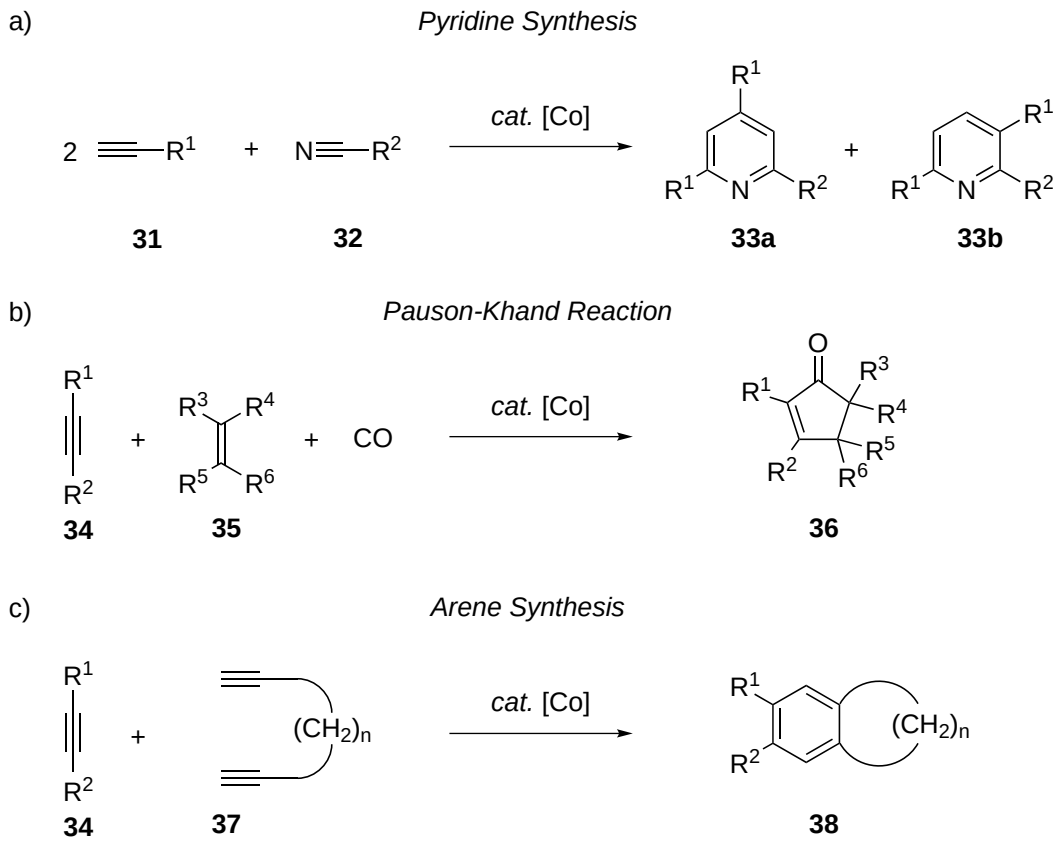
A modular bidentate directing group based on a triazole moiety was devised by *Ackermann* and coworkers for iron-catalyzed arylations of C(sp^2)− and C(sp^3)−H bonds (Scheme 1.15).[65]



Scheme 1.15: Iron-catalyzed direct arylations with a triazoles-based directing group.

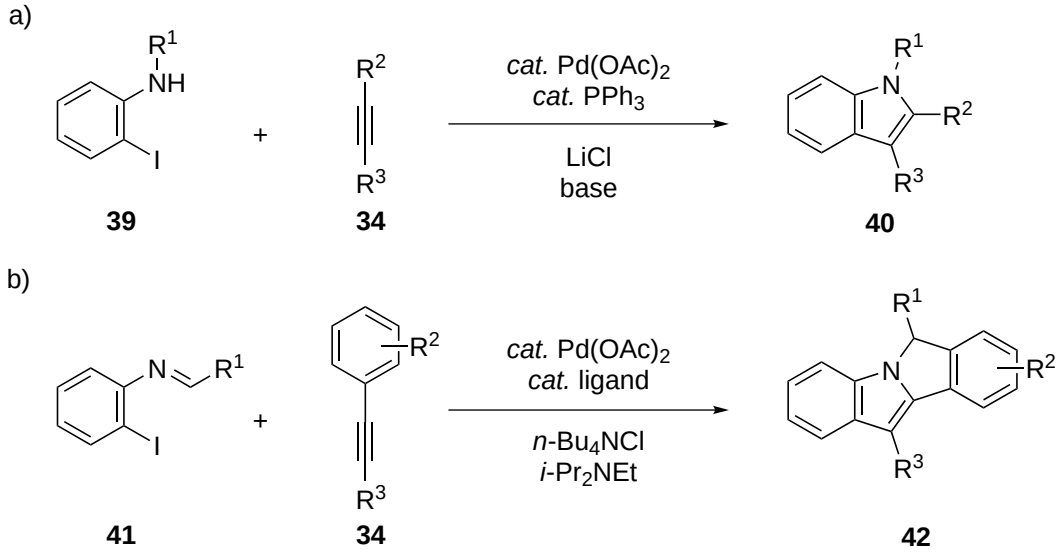
1.3 Syntheses of Heterocycles through Transistion Metal-Catalyzed Alkyne Annulations

Transition metal-catalyzed annulations of alkynes are among the most important methods to produce organic molecules with cyclic frameworks. Especially cobalt-catalyzed annulations, such as the *Bönnemann*-pyridine-synthesis, *Phauson-Khand*-reactions and *Vollhardt*-cyclizations, belong to the reactions showing the potential use of transition metal-catalyzed alkyne annulations (Scheme 1.16).[6, 66–70]



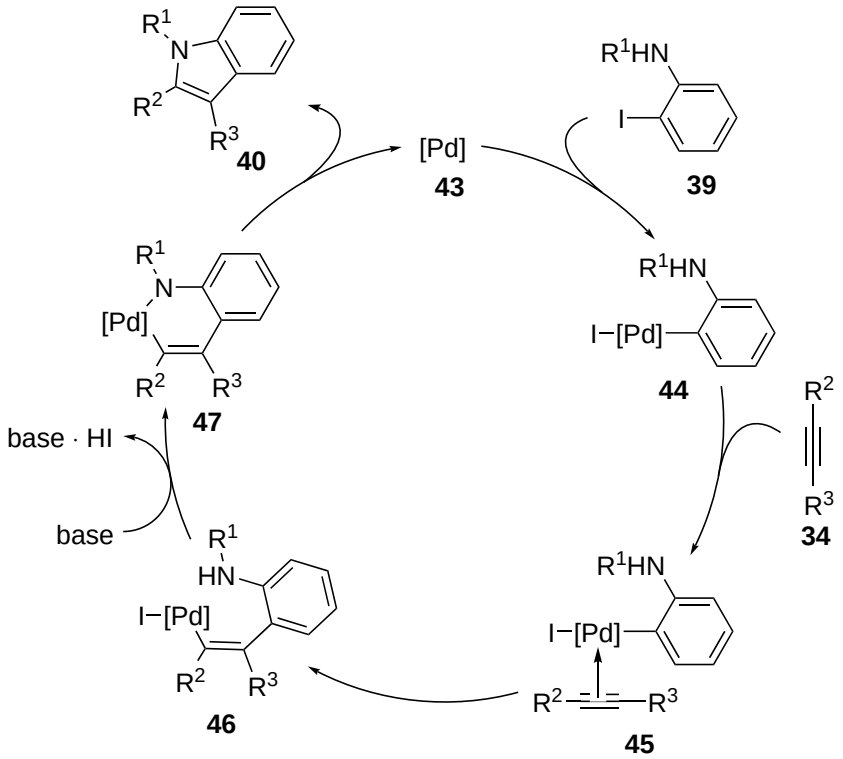
Scheme 1.16: Cobalt-catalyzed annulations of alkynes.

Based on the early advances in palladium-catalyzed cross-coupling reactions, *Larock* and others developed efficient catalysts for the alkyne annulation with substituted haloarenes.[71, 72] These reactions show some mechanistic similarities to palladium-catalyzed cross-coupling reactions and *Mizoroki-Heck*-couplings. The most famous example of these reactions is the *Larock*-indole-synthesis (Scheme 1.17 a). An *ortho*-iodoaniline **39** was reacted with the alkyne **34** in the presence of catalytic amounts of $Pd(OAc)_2$ ligated by a phosphine-ligand to yield the indole **40**.[73, 74] A complementary strategy was described by *Ackermann et al.*[75] The *Larock*-procedure can be modified for the synthesis of fused indoles **42** by using imines **41** derived from *ortho*-iodoaniline (Scheme 1.17 b).[76] The mechanism of this reaction can be described as shown in Scheme 1.18.[77]



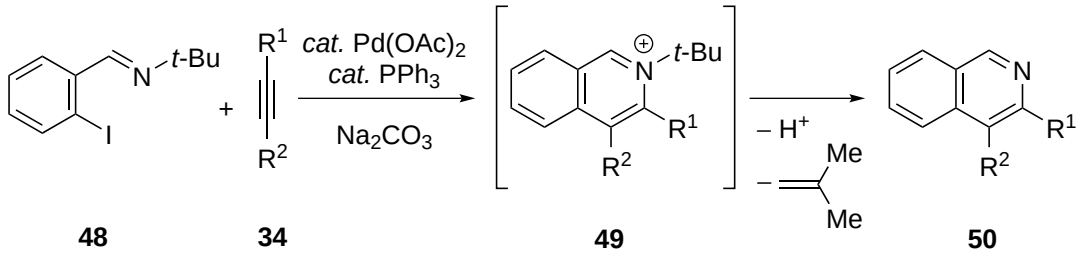
Scheme 1.17: The *Larock*-indole-synthesis.

The first step is the oxidative addition of the *ortho*-iodaniline **39** to the palladium-species **43**. The next step is the coordination of the alkyne **34** followed by regioselective insertion into the palladium−carbon bond. After deprotonation of the amino-group, intermediate **47** is formed, which undergoes reductive elimination, resulting in the formation of the product **40**.



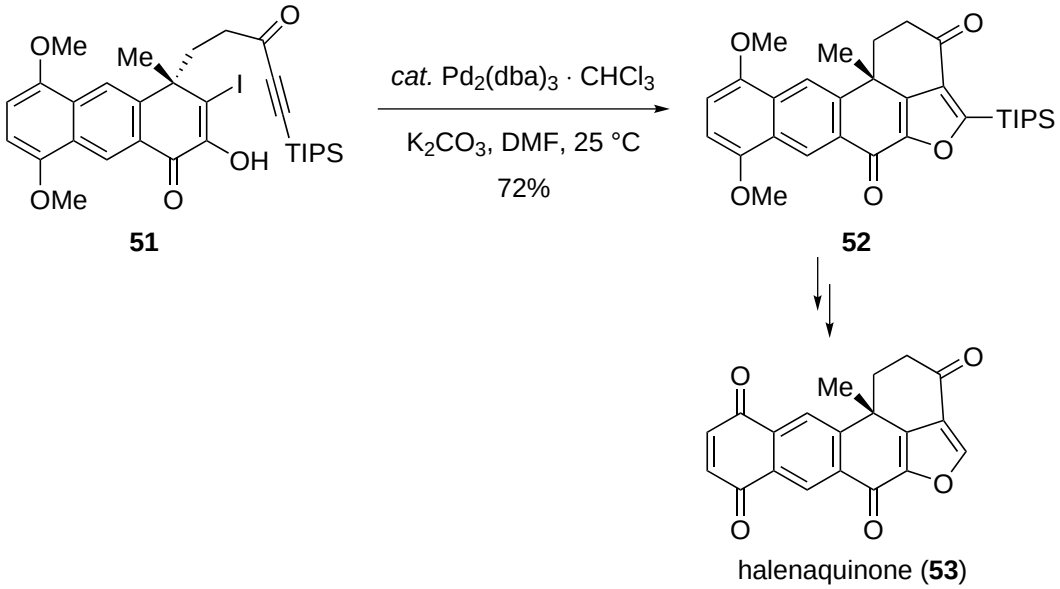
Scheme 1.18: Mechanism of the *Larock*-indole-synthesis.

A similar reaction is based on the *tert*-butylimines **48** of *ortho*-iodobenzaldehydes. The product is a *tert*-butylated isoquinolinium salt **49**, which is not stable and decomposes affording the isoquinoline **50** (Scheme 1.19).[78, 79]



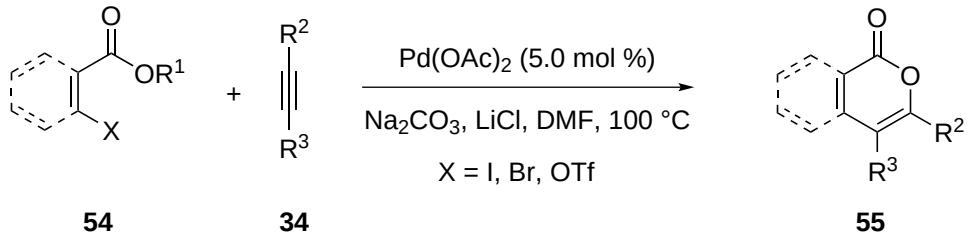
Scheme 1.19: Synthesis of isoquinolines **50** *via* palladium-catalyzed annulation of alkynes **34**.

The palladium-catalyzed annulations of haloarenes are not restricted to the synthesis of nitrogen-containing heterocycles. Oxygen-containing heterocycles are also accessible through the annulation of haloarenes. A very impressing example is *Shibasaki*'s synthesis of halenaquinone (**53**).[80] Here an intramolecular annulation-reaction takes place to furnish a furan moiety **52** (Scheme 1.20).



Scheme 1.20: Palladium-catalyzed annulation in the synthesis of halenaquinone (**53**).

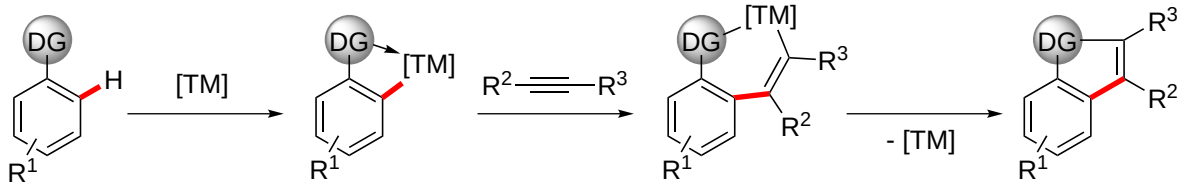
Another example is the synthesis of isocoumarins **55** through the annulation of halogen- or triflate-substituted esters **54** (Scheme 1.21).[81] The mechanism of these reactions are quite similar to the *Larock*-indole-synthesis. In most of these reactions the first step is the oxidative addition of the haloarene to the palladium(0)-catalyst followed by insertion of the alkyne.



54 **34** **55**

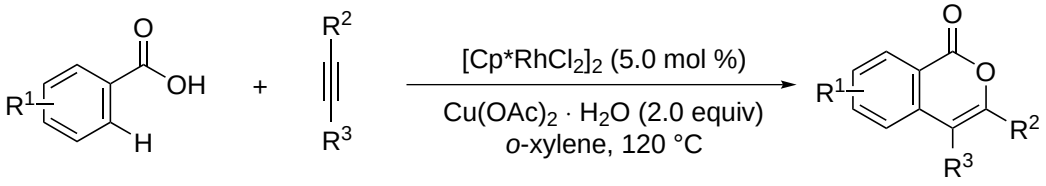
Scheme 1.21: Synthesis of isocoumarins **55** *via* palladium-catalyzed annulation of alkynes **34**.

Analogously to palladium-catalyzed cross-coupling reactions, the palladium-catalyzed annulations require prefunctionalized starting-materials. As a consequence, the development of transition metal-catalyzed C−H bond annulations received great attention within the last decade. These findings are again based on the directing group concept (Scheme 1.22). A transition metal coordinates to a directing group, which leads to a metalation of the C−H bond in the *ortho*-position to the directing group. Insertion of the alkyne and subsequent elimination lead to the desired heterocyclic product.
In contrast to direct C−H bond arylations or alkylations, the directing group does not only act as a donating *Lewis*-base but is also integral part of the newly formed cyclic framework which contains the heteroatom. This is of great advantage, as there is no necessity to remove a potential directing group.



Scheme 1.22: Transition metal-catalyzed direct C−H annulation.

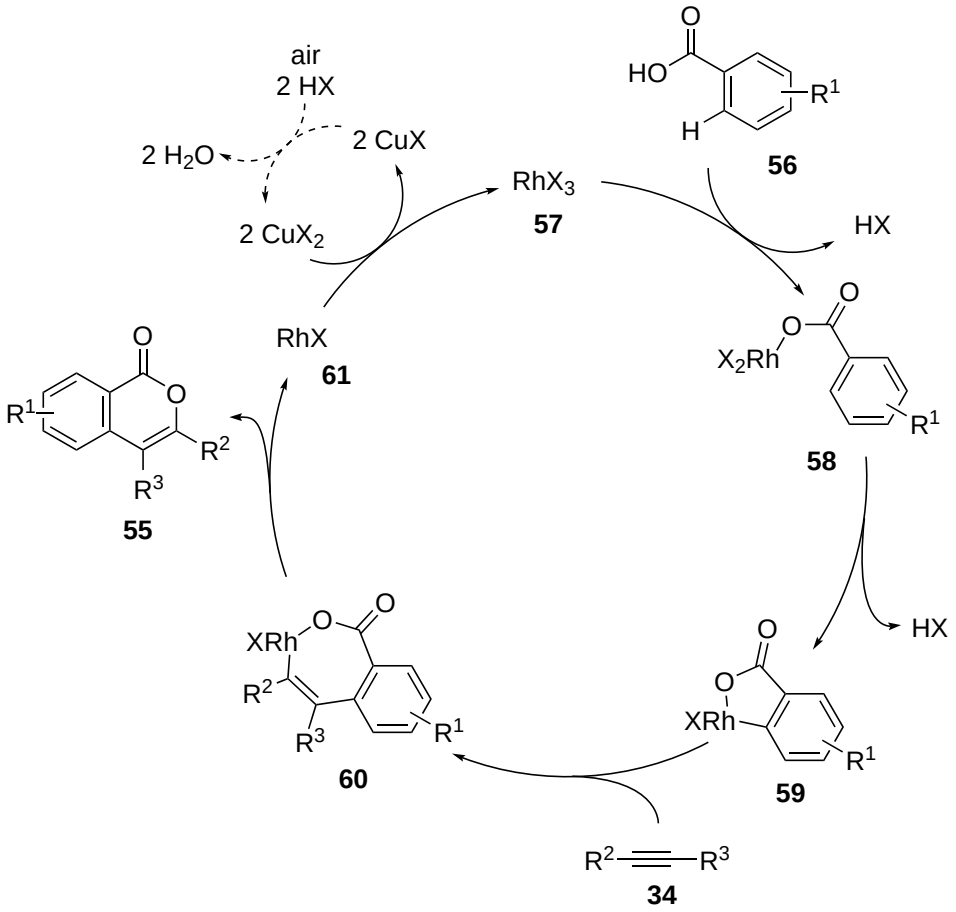
One of the first examples is the synthesis of isocoumarins employing the rhodium-catalyzed annulation of alkynes.[82, 83] As early as 1987 *Maitlis et al.* reported on the successful stoichiometric cyclometalation of benzoic acid with rhodium, iridium and osmium.[84] *Satoh* and *Miura* developed this concept further in order to achieve the annulation of benzoic acids **56** with catalytic amounts of a rhodium-complex (Scheme 1.23).[82, 83]



56 **34** **55**

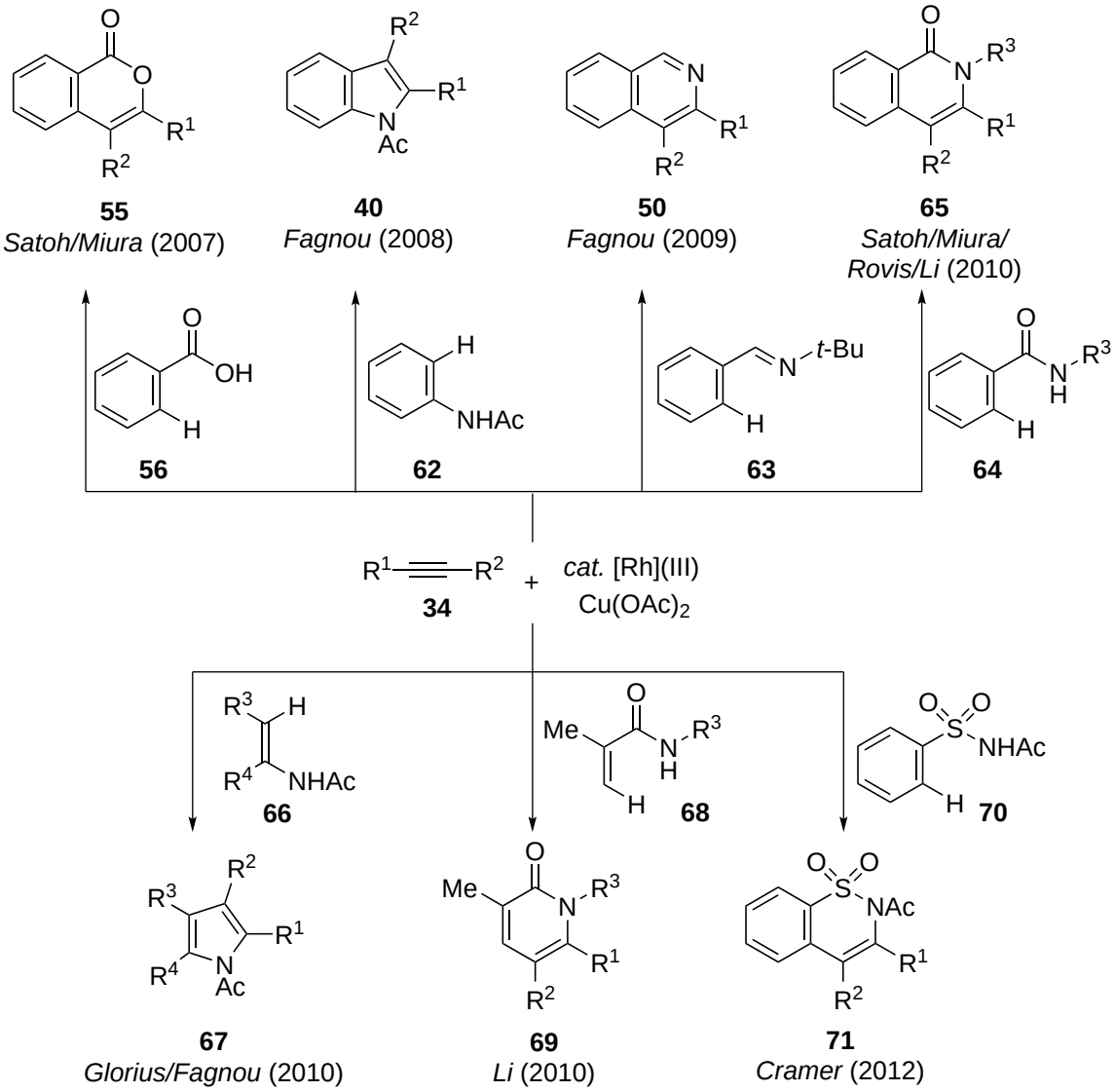
Scheme 1.23: Rhodium-catalyzed oxidative alkyne annulations with benzoic acids **56**.

The proposed mechanism of this transformation is shown in Scheme 1.24. The first step is a ligand-exchange reaction, after which the cyclometalation takes place. Insertion of the alkyne **34** leads to a seven-membered rhodacycle **60** which undergoes reductive elimination. At this stage copper(II)acetate is necessary to achieve reoxidation of the resulting rhodium(I)-species **61**. *Satoh* and *Miura* were able to reduce the amount of copper(II)acetate by performing the reaction under air. This concept shows some similarities to the *Wacker*-process.[6, 85]



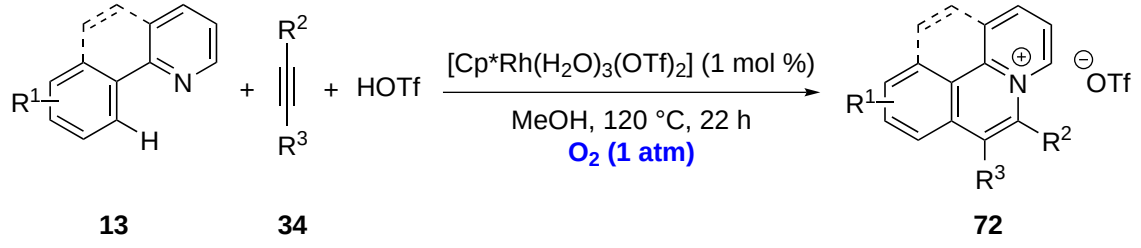
Scheme 1.24: Mechanism for rhodium-catalyzed oxidative alkyne annulations with benzoic acids **56**.

Subsequently similar rhodium-catalyzed reactions were developed, a few of which are shown in Scheme 1.25.[86, 87] The reactions with anilides **62** led to indoles **40**,[88, 89] with benzaldehyde-derived imines **63** to isoquinolines **50** and with benzamides **64** to isoquinolones **65**.[90–93] Enamines **66** and acyclic amides **68** were also valuable substrates as well as sulfonamides **70**.[89, 94–96] It is important to mention that all these transformations required copper(II)acetate as the reoxidant. In analogy to *Satoh*'s and *Miura*'s isocoumarin synthesis, it was possible to reduce the amount of copper(II) if air or oxygen was employed as the terminal oxidant.



Scheme 1.25: Heterocycles syntheses through rhodium-catalyzed oxidative alkyne annulations.

In 2013, *Huang et al.* reported on the first completely copper-free oxidative annulation.[97] Starting materials were the phenylpyridines **13**, which were converted to heterocycles **72** under rhodium(III)-catalysis with molecular oxygen as the terminal oxidant. Remarkably, no copper- or sivler-salts were required to trigger the reoxidation of the rhodium-catalyst.



Scheme 1.26: Copper-free oxidative annulation of phenylpyridines **13**.

All the annulation reactions described above were catalyzed with either rhodium or palladium and a few procedures made use of iridium as the catalyst.[82, 98] Albeit the effective catalytic activity of most noble metals, their prices are subject to major variations (Figure 1.4).[99] An exception is ruthenium, which is relatively inexpensive and attractive as a catalyst for C−H activation processes from an economical point of view.

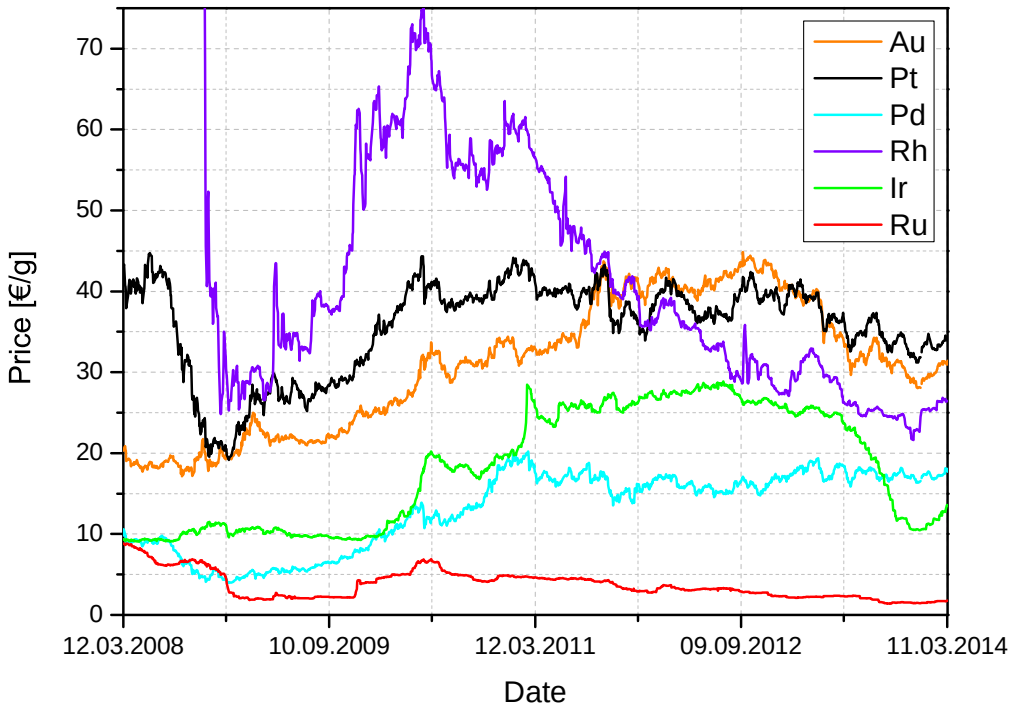
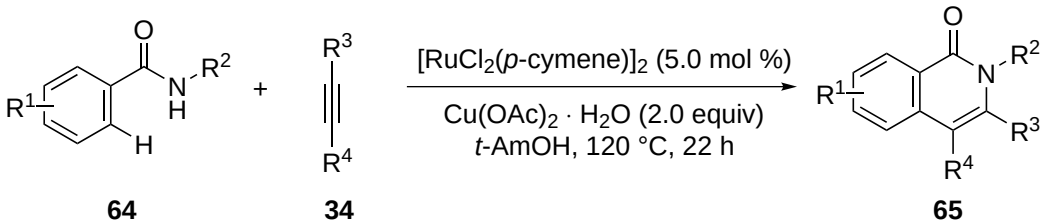


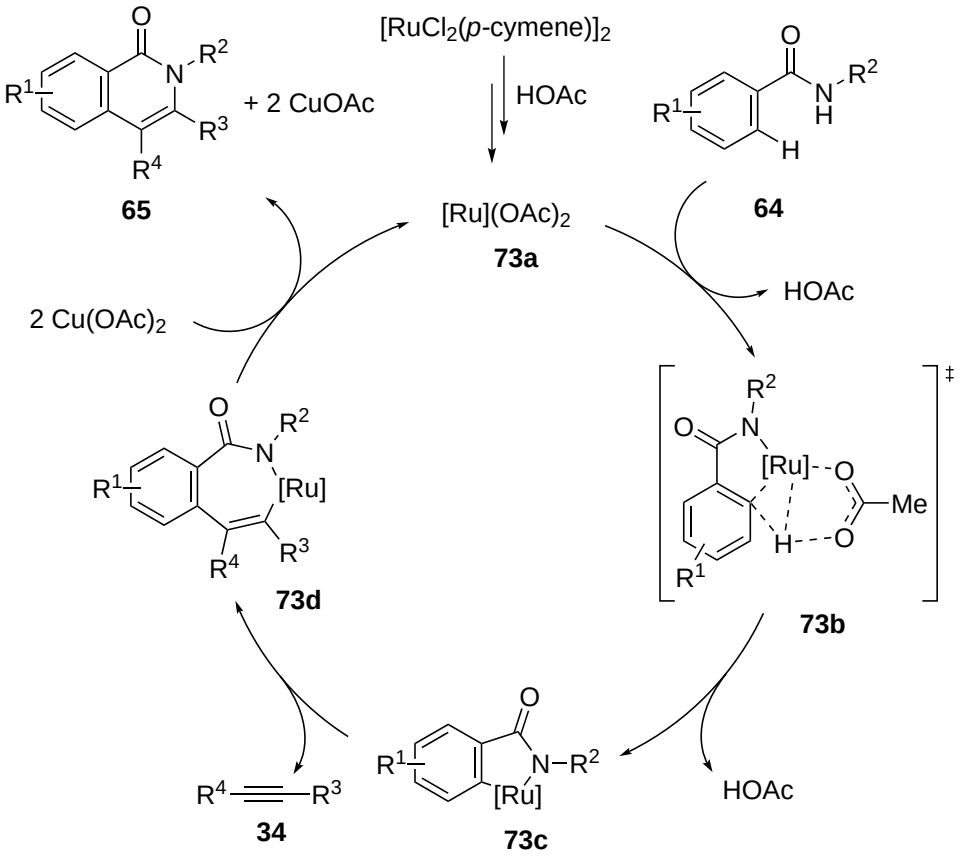
Figure 1.4: Prices of noble metals over the past 4 years.

As a consequence, *Ackermann et al.* developed the catalytic system for oxidative alkyne annulations with benzamides **64** based on the inexpensive complex $[RuCl_2(p\text{-cymene})]_2$ (Scheme 1.27).[100] The terminal oxidant was again copper(II)acetate.



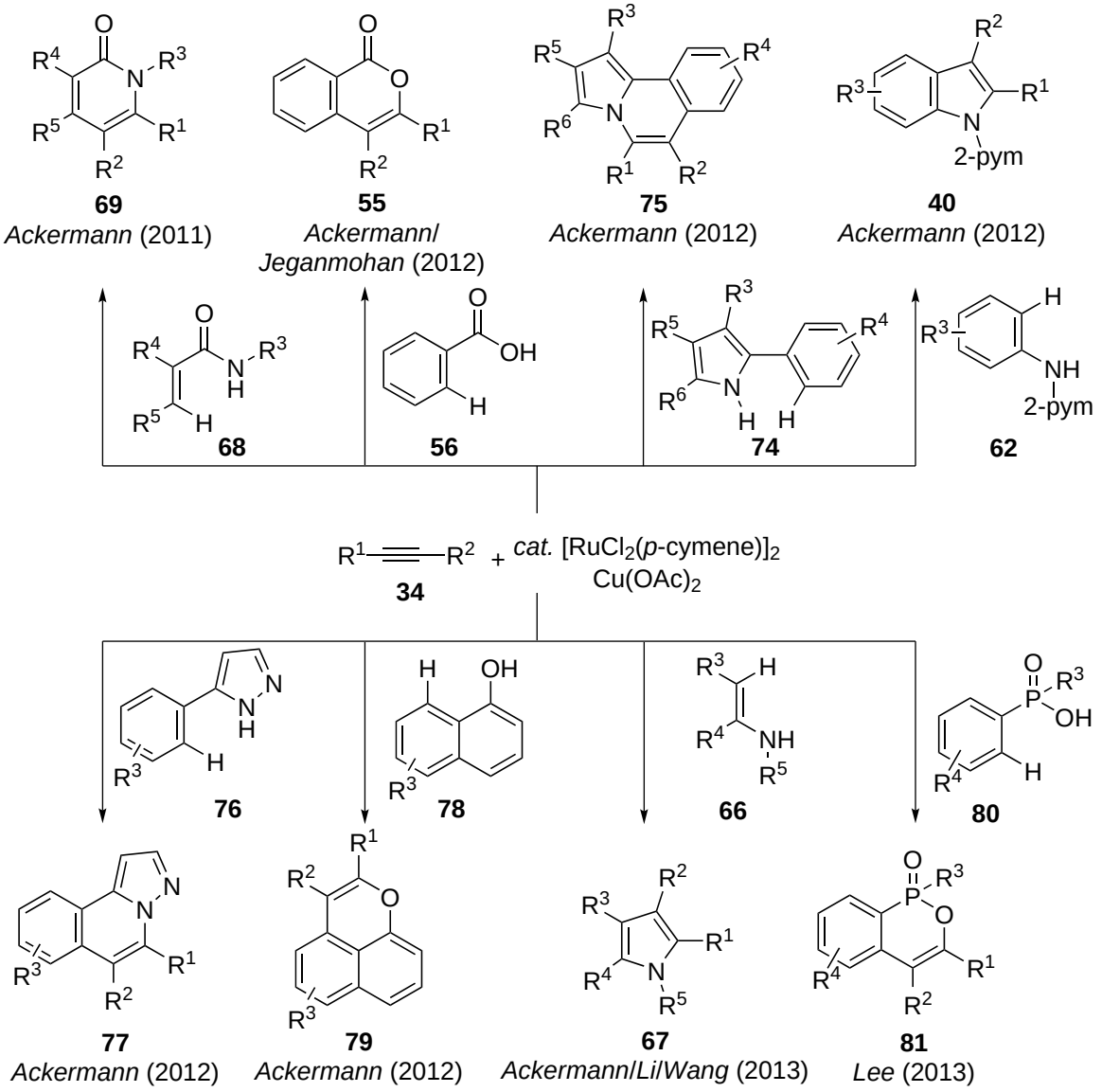
Scheme 1.27: Ruthenium-catalyzed annulation of alkynes **34** by benzamides **64**.

The mechanism of this reaction is presented in Scheme 1.28.[100–102] Analyzing the previously described catalytic system,[103] it was suggested that the catalytically active species is a carboxylate-complex **73a** which is formed *in situ*. The six-membered transition state **73b** for the C−H activation step is analogous to the previously discussed CMD- and AMLA-transition states. The insertion of the alkyne **34** to the ruthenated complex **73c** leads to a seven-membered ruthenacycle **73d**. The next step is the reductive elimination and, upon reoxidation with $Cu(OAc)_2$, the catalytically active species **73a** is formed again. Studies with deuterium-labelled substrates revealed that the C−H activation step is irreversible.



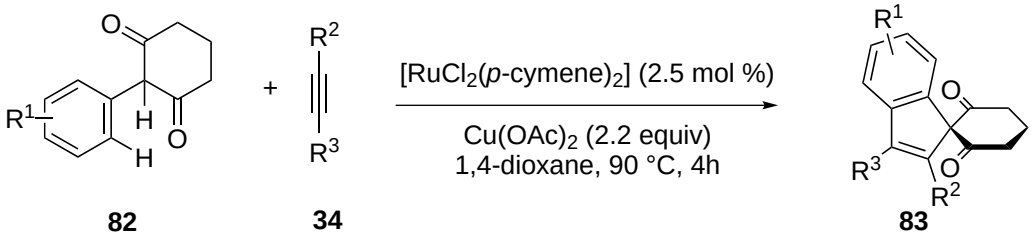
Scheme 1.28: Mechanism for the ruthenium-catalyzed alkyne annulation with benzamides **64**.

On the basis of these results, the research group of *Ackermann* and others made efforts to extend the rage of ruthenium-catalyzed oxidative annulation reactions for the synthesis of heterocycles (Scheme 1.29).[102, 104–108] Thus, pyridones **69** and isocoumarins **55** became accessible,[109–112] likewise indoles **40** and pyrroles **67**.[113–115] Interestingly, the group of *Ackermann* also managed to find appropriate reaction conditions for the successful alkyne annulation with 2-phenyl-pyrroles and 2-phenyl-indoles **74** as well as with 2-phenyl-1*H*-pyrazoles **77** and naphtholes **79** leading to polyheterocyclic structures.[116–119] Recently, *Lee* showed that the ruthenium-catalyzed annulation of phosphinic- and phosphonic-acids **80** gave rise to phosphaisocoumarins **81**.[120]



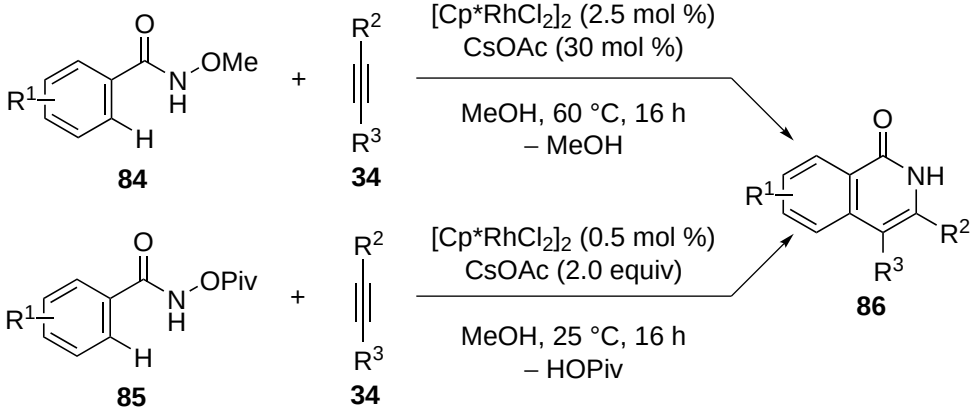
Scheme 1.29: Heterocycles through ruthenium-catalyzed C−H bond alkyne annulations.

In 2012 *Lam* reported on a remarkable synthesis of spiroindenes **83** *via* ruthenium-catalyzed oxidative alkyne annulation.[121] A quaternary carbon center is formed during the course of this $C(sp^2)^-$ and $C(sp^3)$−H bond functionalization reaction (Scheme 1.30).



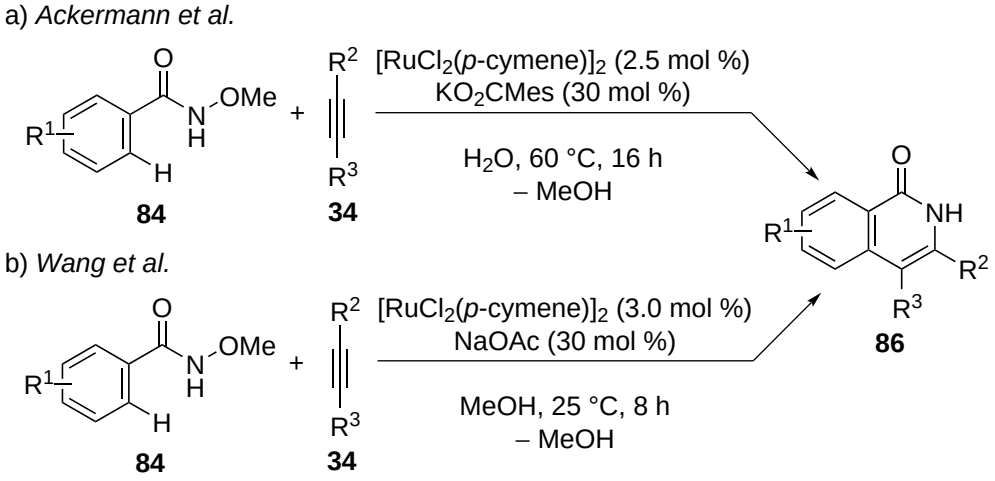
Scheme 1.30: Synthesis of spiroindenes **83** through ruthenium-catalyzed alkyne annulation.

The majority of alkyne annulations *via* rhodium- and ruthenium-catalyzed C−H activation discussed above required external oxidants. This is the result of the cleavage of one C−H bond and one Het−H bond, thus formally one equivalent of dihydrogen is formed. Parallel to the development of oxidative alkyne annulations some other attempts were focused on alkyne annulations involving C−H/N−O bond cleavages. These isohypsic approaches exhibit the advantage that the substrate itself acts as an "internal oxidant", therefore external oxidants, like copper(II)acetate, are not needed.



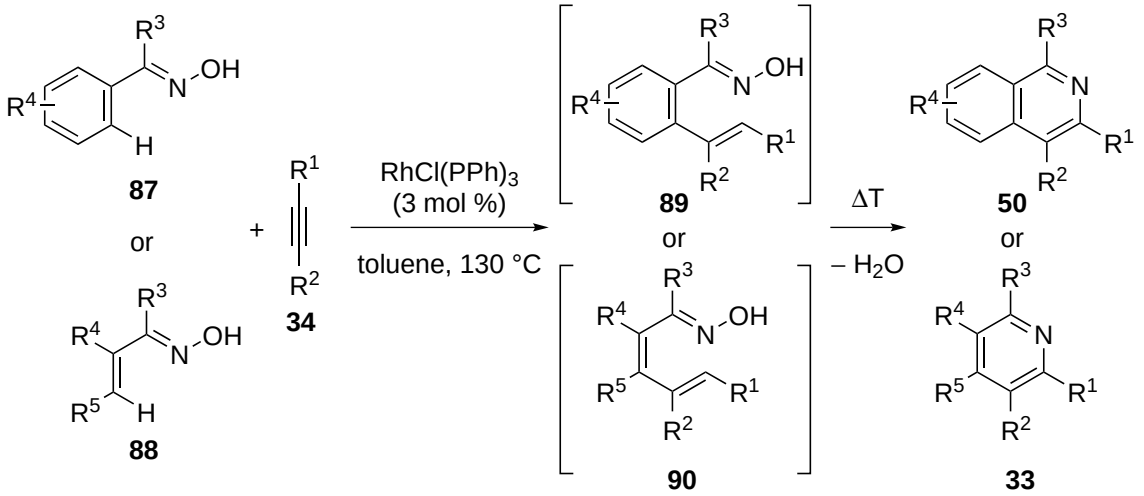
Scheme 1.31: Redox-neutral rhodium-catalyzed C−H annulations with hydroxamic acid esters **84** and **85**.

Fagnou and coworkers used hydroxamic acid esters **84** and **85** as substrates for the rhodium-catalyzed C−H annulation (Scheme 1.31).[122, 123] The only byproducts of this reaction were methanol and pivalic acid, respectively. It is noteworthy to mention that the pivalate esters **85**, in contrast to the *N*-methoxybenzamides **84**, could act as bidendate directing groups, and thus enable the process to proceed under milder reaction-conditions and with a lower catalyst-loading.



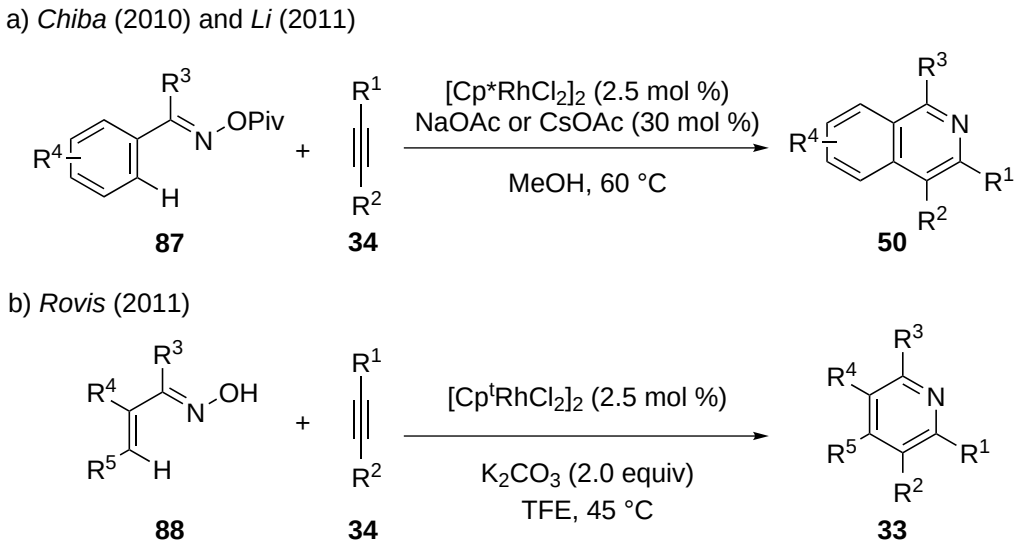
Scheme 1.32: Ruthenium-catalyzed C−H annulations with *N*-methoxybenzamides **84**.

Shortly thereafter, in 2011, also ruthenium-catalyzed versions of this reaction were independently published by the research group of *Ackermann* and the group of *Li* and *Wang* (Scheme 1.32).[124, 125] The reaction conditions of *Ackermann et al.* used water as a non-inflammable and non-toxic solvent, while *Wang* and *Li* were able to perform the reaction at ambient temperature of 25 °C. In 2008 and 2009, *Cheng et al.* reported on the successful rhodium(I)-catalyzed C−H annulation of aromatic and olefinic oximes leading to substituted pyridines **33** and isoquinolines **50** (Scheme 1.33).[126, 127] The rhodium complex employed in this reaction was the *Wilkinson*-catalyst. The reaction was assumed to proceed *via* the alkenylated oximes **89** and **90**, which were converted to the products **50** and **33** through the dehydrative electrocyclization.



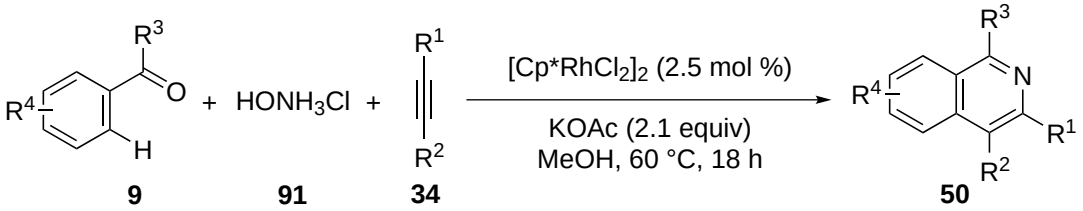
Scheme 1.33: *Cheng*'s procedure for the synthesis of pyridines **33** and isoquinolines **50**.

Shortly thereafter also rhodium(III)-catalyzed variants of these reactions were published by the groups of *Chiba*, *Rovis* and *Li*.[128–131]



Scheme 1.34: Rhodium(III)-catalyzed C−H annulations with oxime derivatives **87** and **88**.

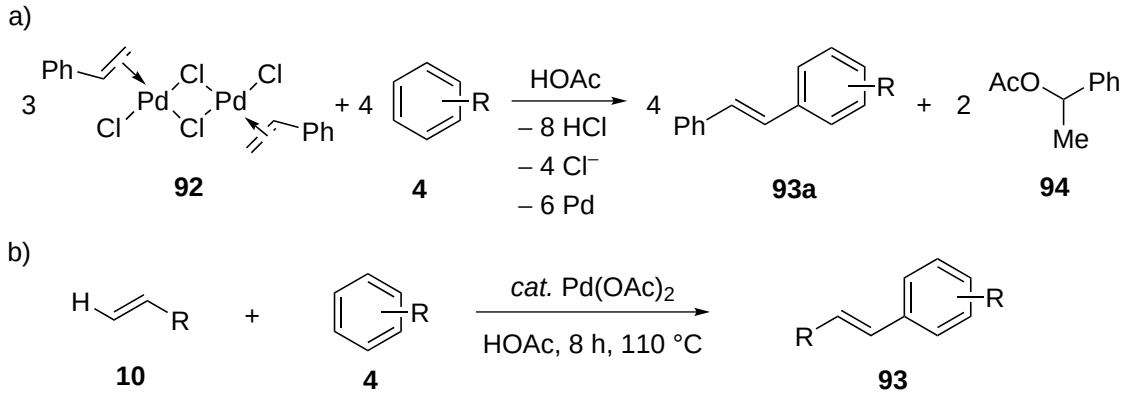
Recently, *Hua* and coworkers modified this reaction in a way that the oximes are formed *in situ* from the corresponding ketones **9** and hydroxylamine hydrochloride (**91**) (Scheme 1.35).[132]



Scheme 1.35: Rhodium(III)-catalyzed C−H annulations with *in situ* generated oximes.

1.4 Ruthenium-Catalyzed Oxidative C−H Bond Alkenylations

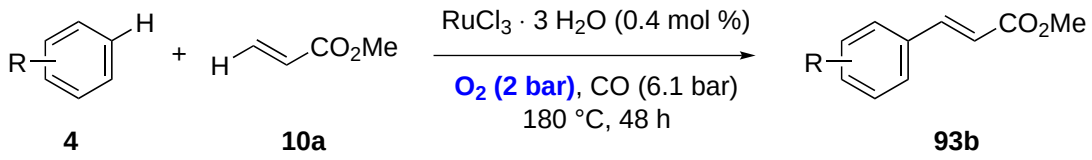
Transition metal-catalyzed oxidative alkenylations are related to oxidative alkyne annulations. The first example for such kind of reactions was published as early as 1967 by *Y. Fujiwara* and *I. Moritani*.[133, 134] Herein a palladium-styrene complex **92** reacts with an arene **4** to the corresponding stilbene **93a** (Scheme 1.36 a). Shortly after *Y. Fujiwara* and *I. Moritani* also reported on a catalytic version of this reaction (Scheme 1.36 b).[135]



Scheme 1.36: The *Fujiwara-Moritani*-reaction.

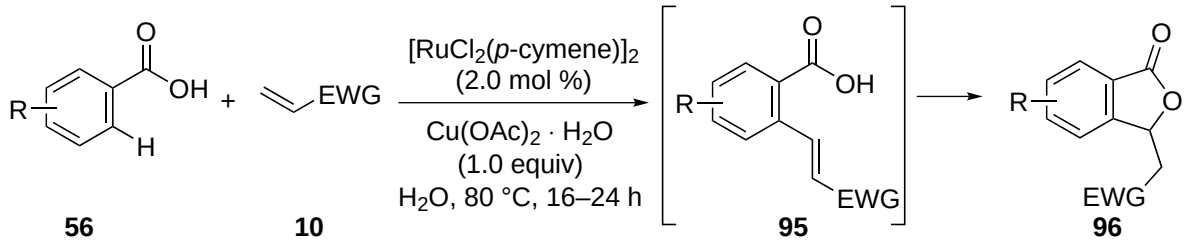
Inspired by this initial results, many research groups investigated other catalytic variations of this reaction.[136, 137] Due to some similarities with traditional cross-coupling reactions, the *Fujiwara-Moritani*-reaction is also described as a dehydrogenative or oxidative *Mizoroki-Heck*-coupling. Besides palladium, the rhodium catalysts were employed again during the past decade.[138–143] As in the case of oxidative alkyne annulations, the high costs of rhodium complexes led to an intense focus on inexpensive ruthenium catalysts for direct C−H olefinations.[46, 144]

The first ruthenium-catalyzed oxidative alkenylation was reported in 2001 by *Milstein* and coworkers.[145] Notably, they used molecular oxygen as the terminal oxidant (Scheme 1.37). The scope of this reaction was rather narrow and restricted to simple arenes **4**, like toluene and anisole, and methyl acrylate **10a**; however, no directing group was necessary.



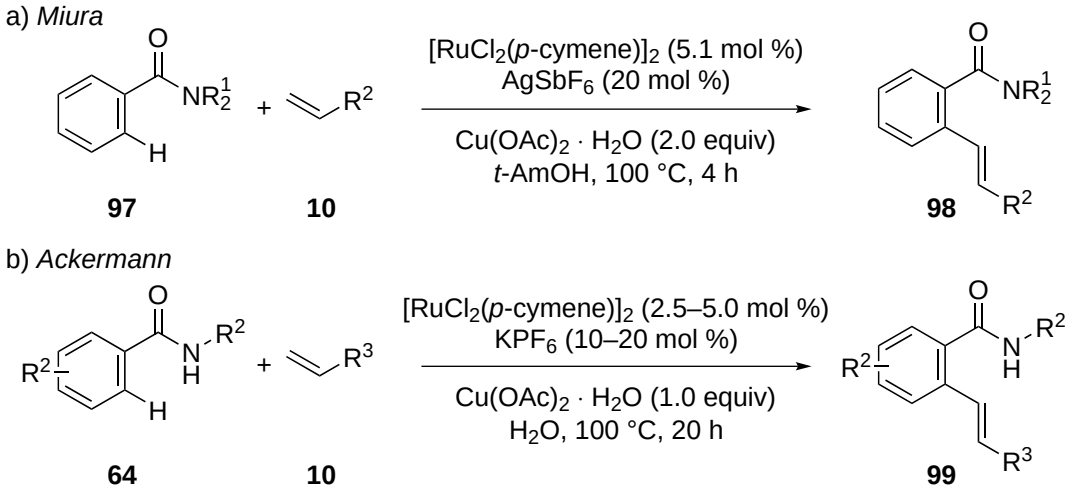
Scheme 1.37: Oxidative alkenylation of simple arenes **4** with oxygen as the oxidant.

Ackermann et al. published a procedure for the successful ruthenium-catalyzed direct alkenylation of benzoic acids **56** in nontoxic water as the solvent (Scheme 1.38).[146] Herein copper(II)acetate was used as the oxidant. Interestingly, after the alkenylation, the intermediates **95** underwent a subsequent cyclization *via* intramolecular oxa-*Michael*-addition. Similar observations were made in the ruthenium-catalyzed direct alkenylation of benzanilides.[147]



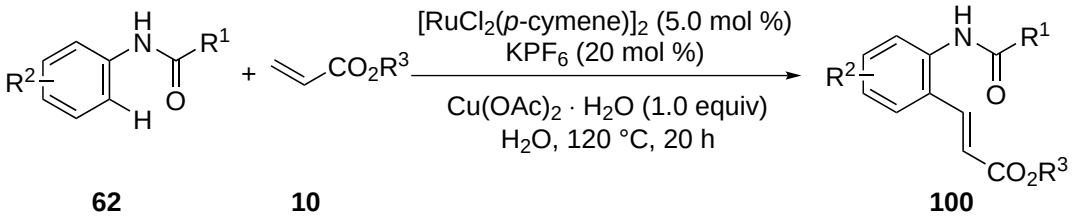
Scheme 1.38: Oxidative alkenylation of benzoic acids **56**.

Shortly after the groups of *Miura* and *Ackermann* independently disclosed the efficient ruthenium-catalyzed direct oxidative alkenylation of benzamides **64** and **97**.[148, 149] Both systems were based on *in situ* formed cationic ruthenium species generated with the aid of $AgSbF_6$ in *t*-AmOH under *Miura*'s conditions (Scheme 1.39, a), and with KPF_6 in water under *Ackermann*'s conditions (Scheme 1.39, b). *Li* and *Wang* described a similar reaction where they used an internal oxidant.[150]



Scheme 1.39: Oxidative alkenylation of benzamides **64** and **97**.

The catalytic system of *Ackermann et al.* was not restricted to benzamides, but could also be used for the successful olefination of benzanilides **62** (Scheme 1.40).[149] This is particularly interesting, because, in contrast to the previously discussed substrates, anilides can be considered as electron-rich substrates.

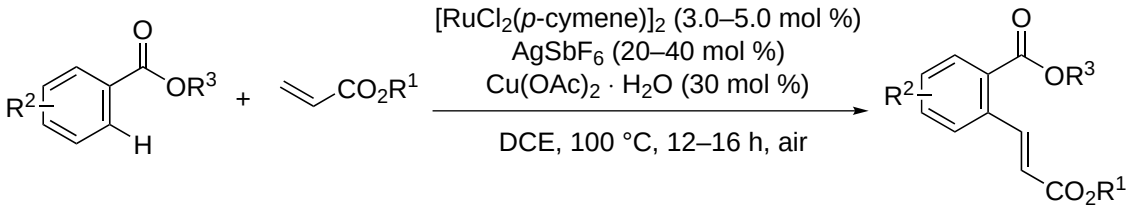


62 **10** **100**

Scheme 1.40: Oxidative alkenylation of anilides **62**.

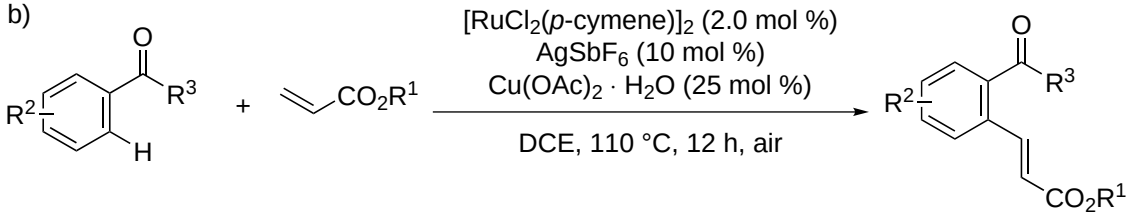
The scope of ruthenium-catalyzed annulations was further investigated by the groups of *Ackermann* and *Jeganmohan*.[151–154] Under almost the same conditions it was possible to functionalize esters **101**, phenones **9**, and benzaldehydes **104** (Scheme 1.41). In contrast to the reactions discussed above, copper(II)acetate was used in minor quantities, as the reactions were performed under air.

a)



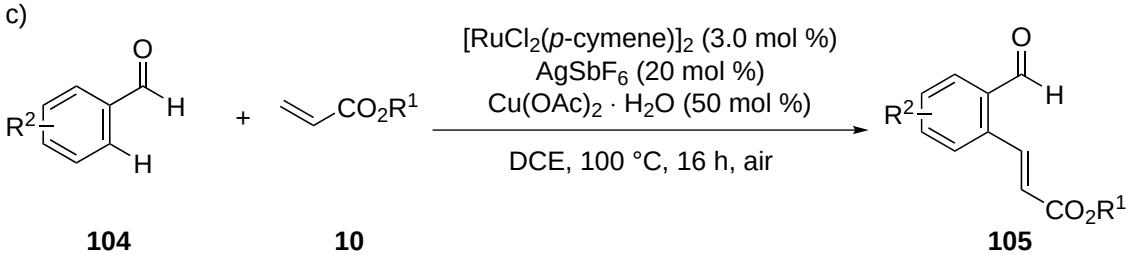
101 **10** **102**

b)



9 **10** **103**

c)



104 **10** **105**

Scheme 1.41: Oxidative alkenylation of esters **101**, phenones **9**, and benzaldehydes **104**.

1.5 Transition Metal-Catalyzed C−H-Bond Alkynylations of Azoles

The bond acidities of diversely positioned C−H bonds in heteroaromatic compounds exhibit significant differences, as indicated by their pK_a values (Figure 1.3).[155, 156] Therefore, it is more easy to perform site-selective C−H bond functionalization reactions on these compounds in comparison to carbocyclic arenes. Indeed directing groups are often not necessary for transition metal-catalyzed direct functionalizations in the more acidic C-2 position of oxazoles, thiazoles, imidazoles and related compounds.

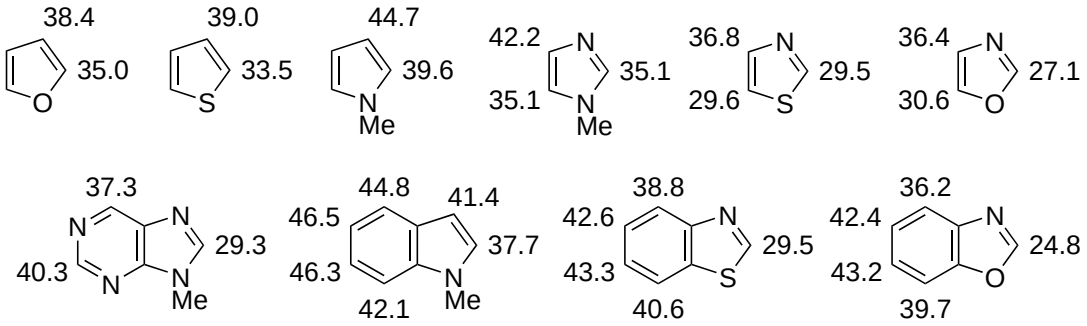
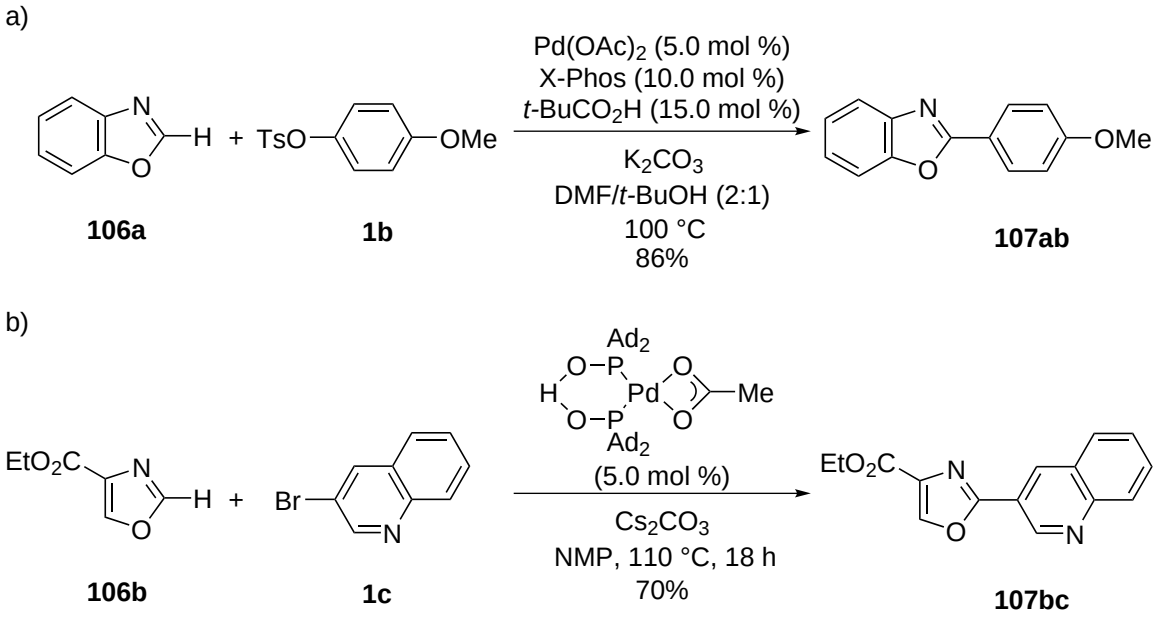


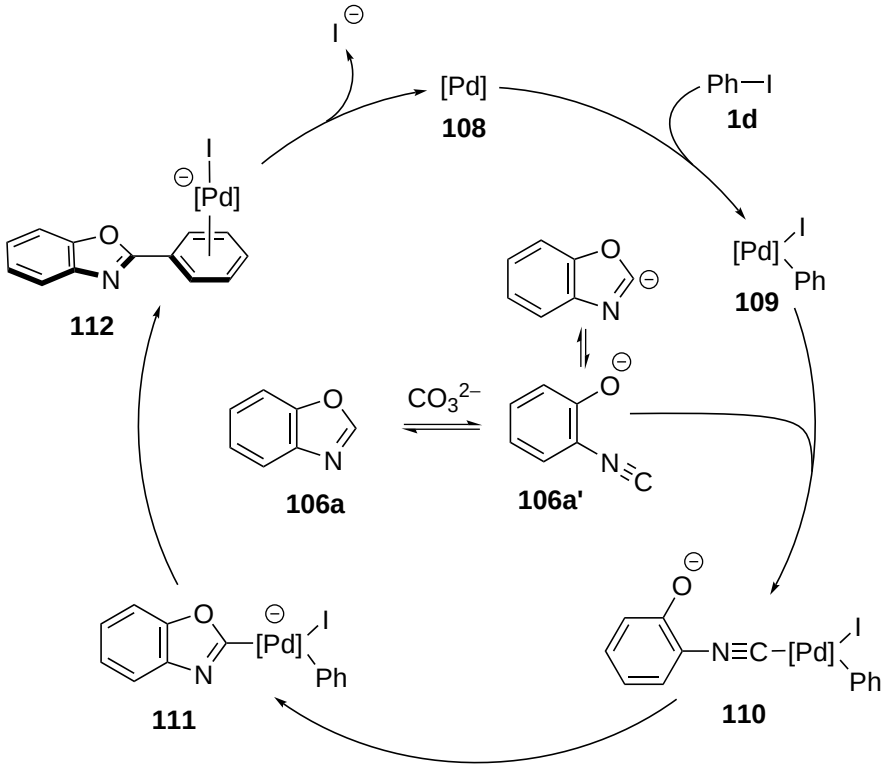
Figure 1.5: pK_a values of different heteroarenes in DMSO.[155]

Especially within the last decade, a huge variety of procedures for the palladium-catalyzed direct C-2 arylation of oxazoles was reported.[157] Scheme 1.42 shows two examples originated from the research group of *Ackermann et al.*[158, 159] In the first reaction, an aryl tosylate is employed for the direct arylation of benzoxazole (**106a**). The second example shows that also secondary phopshine oxide (SPO) derived palladium complexes, which were previously employed for transition metal-catalyzed cross-coupling reactions,[160–163] could be used as catalysts.



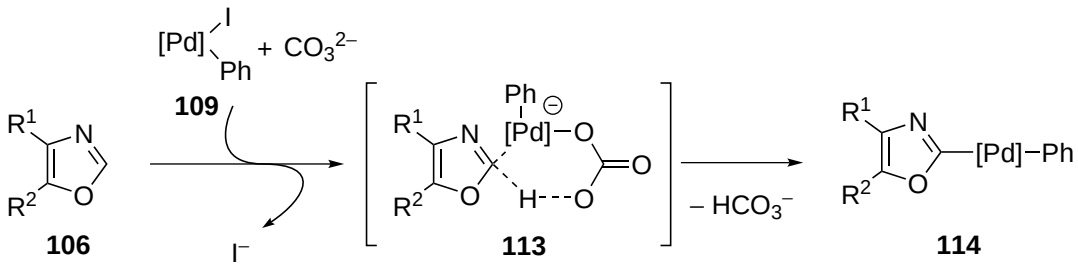
Scheme 1.42: Palladium-catalyzed direct arylations of oxazoles **106**.

Zhuravlev and *Sánchez* conducted mechanistic studies to devise a concise mechanism for palladium-catalyzed arylations of benzoxazole (**106a**) (Scheme 1.43).[164]



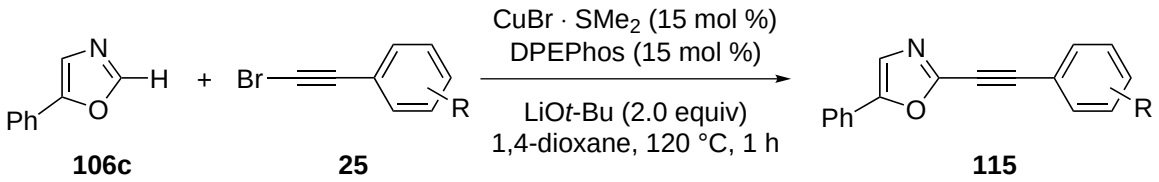
Scheme 1.43: Mechanism for the direct arylation of benzoxazole **106a**.

The first step is the oxidative addition of the haloarene **1d** to the palladium catalyst **108**. Benzoxazole (**106a**) is deprotonated by a base and undergoes ring-opening to the isonitrile **106a'**, which undergoes a coordination to the aryl-palladium species **109**. After cyclization and reductive elimination, the catalytically active species **108** is reformed. However, other studies suggested that the deprotonation occurs *via* a CMD-type mechanism (Scheme 1.44).[165, 166]



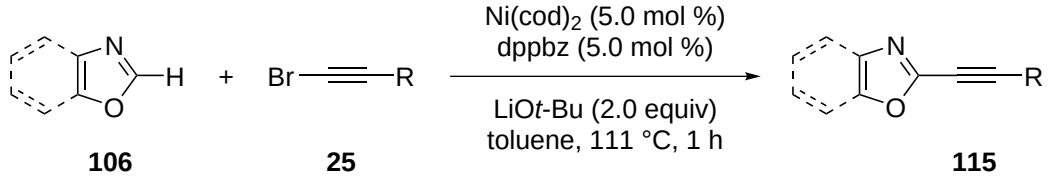
Scheme 1.44: CMD-type mechanism for the palladiation of oxazoles **106**.[166]

In contrast to direct arylations, transition metal-catalyzed direct alkynylations of oxazoles and related heterocycles have been less extensively studied. In 2009, *Piguel* reported on a copper(I)-catalyzed method for the direct alkynylation of 5-phenyloxazole (**106c**) with bromoalkynes **25** (Scheme 1.45).[167] This catalytic system is not restricted to substrate **106c**, but could also be used for alkynylations of other oxazoles as well as of other C−H-acidic heterocycles.



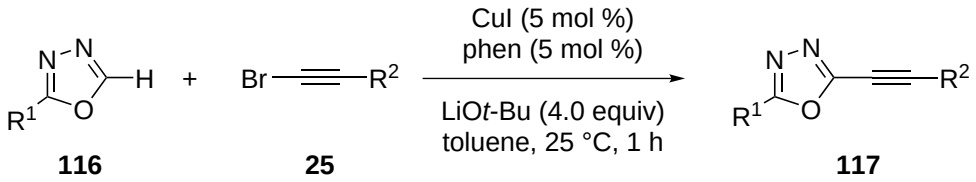
Scheme 1.45: Copper(I)-catalyzed alkynylation of oxazole **106c**.

Also in 2009, *Miura et al.* disclosed a nickel(0)-catalyzed alkynylation of oxazoles **106**.[168] Herein, also bromoalkynes **25** were used as the electrophiles (Scheme 1.46). *Miura* suggested a mechanism in analogy to the one shown in Scheme 1.43.



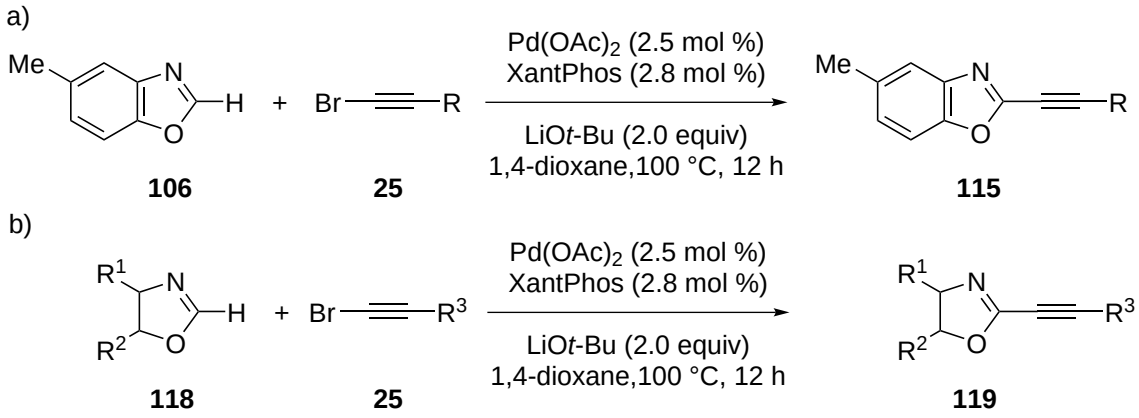
Scheme 1.46: Nickel(0)-catalyzed alkynylation of oxazoles **106**.

Miura also developed a copper(I)-catalyzed alkynylation of oxadiazoles **116**. The reaction is similar to the one described by *Piguel*. The electrophiles were once again bromoalkynes **25**, and the ligand was phenanthroline (Scheme 1.47).[169]



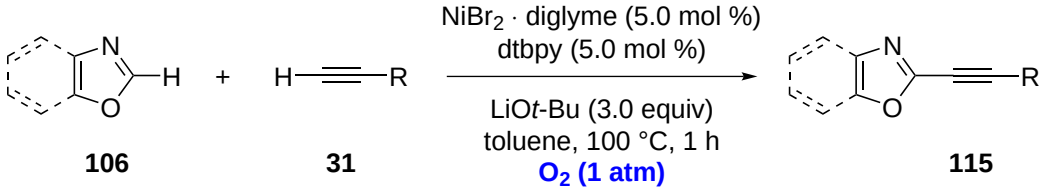
Scheme 1.47: Copper(I)-catalyzed alkynylations of oxadiazoles **116**.

A palladium-catalyzed version of these reactions was published by *Chang* in 2010.[170] It should be mentioned that under these conditions the alkynylation was not restricted to heteroaromatic oxazoles **106** (Scheme 1.48 a), but could also be used for the alkynylation of oxazolines **118** (Scheme 1.48 b).



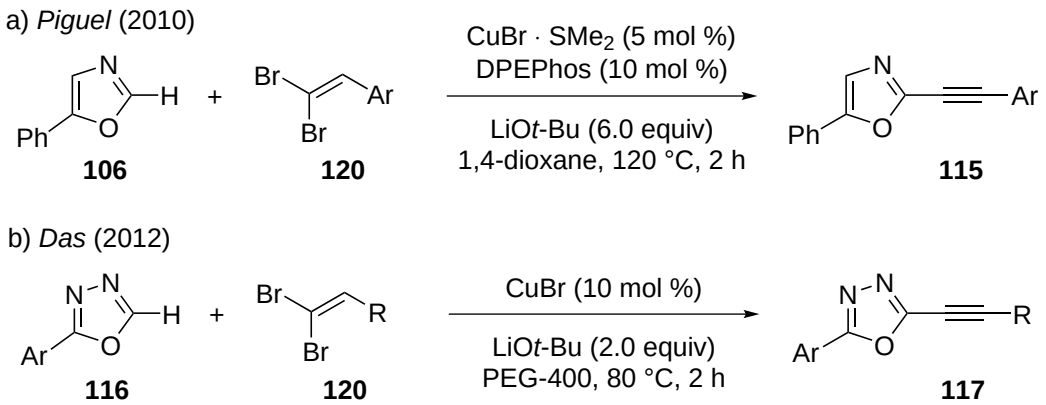
Scheme 1.48: Palladium-catalyzed alkynylations of oxazoles **106** and oxazolines **118**.

All reactions described above used bromoalkynes **25** as the electrophiles. However, *Miura* reported on an oxidative coupling for the synthesis of alkynylated oxazoles **115**.[171, 172] Benzoxazoles **106** and terminal alkynes **31** were coupled in a dehydrogenative fashion with a nickel-catalyst and oxygen as the oxidant (Scheme 1.49).



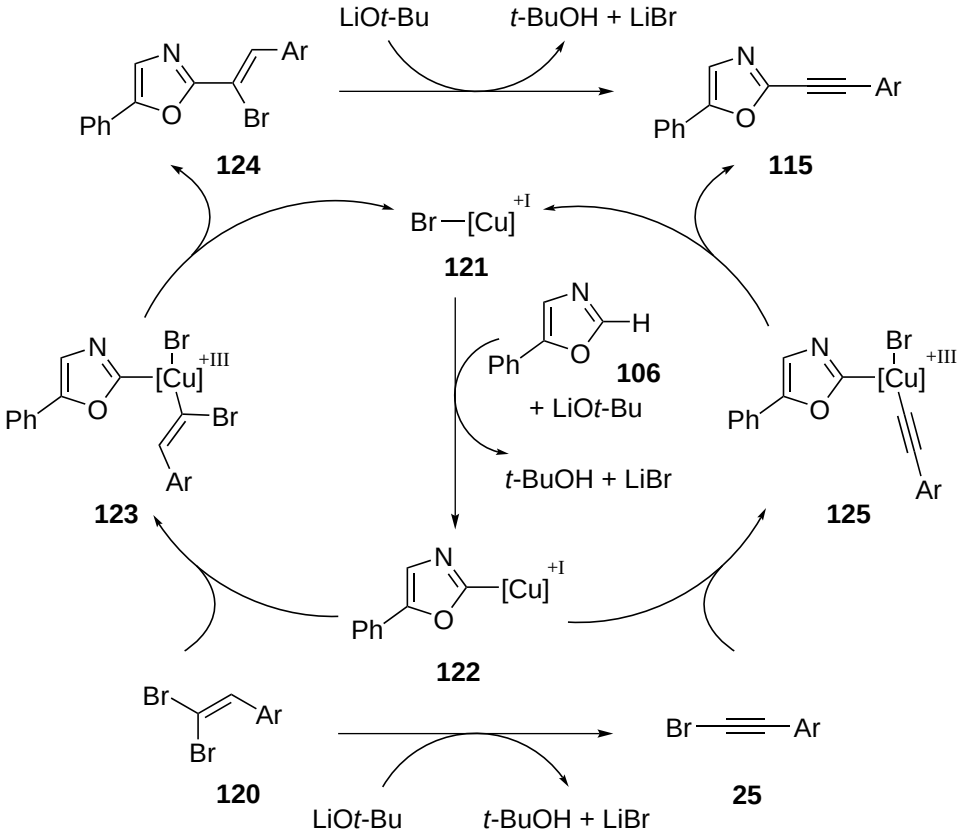
Scheme 1.49: Nickel-catalyzed oxidative alkynylation of oxazoles **106**.

In 2010 *Piguel et al.*, reported on an improved version of their copper(I)-catalyzed annulation of oxazoles **106**.[173] Instead of bromoalkynes, the more stable and easier accessible *gem*-dibromoalkenes **120** were used (Scheme 1.50 a). *Das et al.* modified the reaction conditions to use *gem*-dibromoalkenes **120** for the alkynylation of oxadiazoles **116** applying polyethylene glycol as the solvent (Scheme 1.50 b).[174]



Scheme 1.50: Copper(I)-catalyzed C−H alkynylations with *gem*-dibromoalkenes **120**.

The mechanism of this reaction is described in Scheme 1.51. According to *Piguel*, the first step is the deprotonative coordination of the oxazole **106**. From this point, two possible reaction pathways can be postulated. The first possibility (Scheme 1.51, left side) is the reaction between **122** and the *gem*-dibromoalkene **120**. After reductive elimination, the bromoalkenylated intermediate **124** is formed, which eliminates in the presence of LiO*t*-Bu to the product **115**. During the course of the second pathway (Scheme 1.51, right side), initial dehydrobromination of the *gem*-dibromoalkene **120** affords the corresponding bromoalkyne **25**, which undergoes reaction with **122** to **125**. The product **115** is directly formed from the latter through reductive elimination. It is important to mention that the LiO*t*-Bu is necessary for both, the deprotonation of the oxazole **106** and the elimination process.



Scheme 1.51: Plausible mechanism for alkynylations with *gem*-dibromoalkenes **120**.

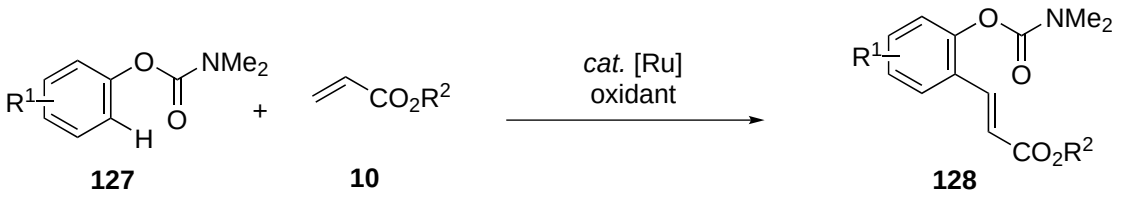
2 Objectives

The idea of using transition metals as catalysts for direct C−H bond funtionalizations opens up the pathway for the development of chemo- and site-selective ways to synthesize organic molecules and thus has been of central importance for the research of *Prof. Dr. Ackermann* and his coworkers. A majority of these works is focused on the efficient synthesis of heterocyclic molecules.

Within this context, major efforts were made to achieve efficient C2-arylations and benzylations of oxazoles **106** through palladium-catalyzed direct C−H bond functionalization. At the outset of this thesis, research should be continued in this direction by extending the methodology from sp^3- and sp^2-hybridized to sp-hybridized electrophiles, i.e. direct alkynylations. Especially the synthetic validity of *gem*-dihaloalkenes **120** and **126** as electrophiles should be tested, as they are more accessible and stable as compared to the corresponding haloalkynes (Scheme 2.1).[175–177]

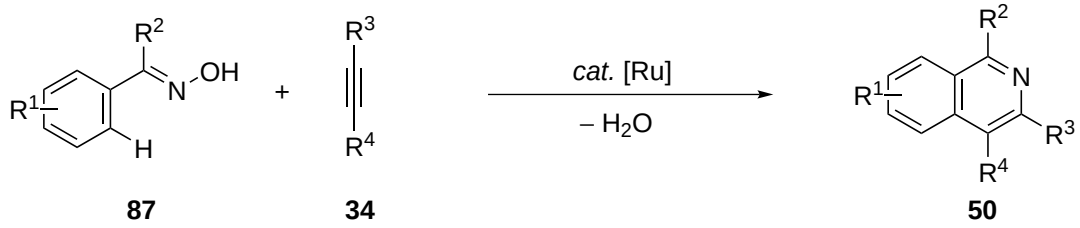
Scheme 2.1: Palladium-catalyzed direct alkynylations with *gem*-dihaloalkenes **120** and **126**.

Some further experiments should be performed by using different acrylates **10** for a ruthenium-catalyzed oxidative akenylation of arenes **127** with removable carbamates by utilizing previously developed reaction conditions (Scheme 2.2).[178]



Scheme 2.2: Ruthenium-catalyzed direct C−H alkenylations of aryl carbamates **127**.

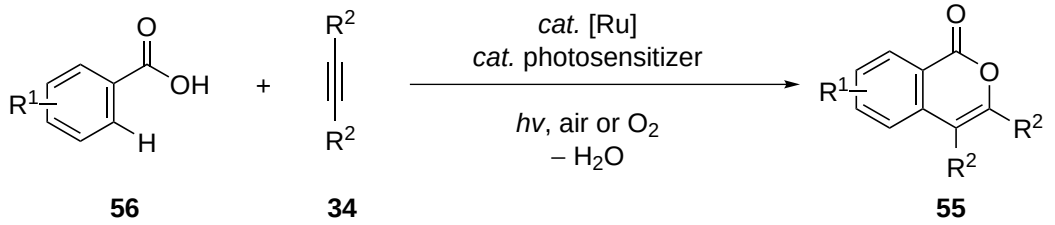
Given the success of the research on ruthenium-catalyzed annulations of alkynes pursued in the *Ackermann* group and on similar reactions with rhodium catalysts, another project should be directed towards the efficient synthesis of bioactive isoquinolines. Hence, an inexpensive ruthenium catalyst should be used for redox-neutral annulations of oximes **87** with alkynes **34** (Scheme 2.3). This approach would be of great advantage from the viewpoint of green chemistry, as the only byproduct would be water.



87 **34** **50**

Scheme 2.3: Synthesis of isoquinolines **50** *via* ruthenium-catalyzed alkyne-annulations.

If prosperous, the newly developed reaction should also be utilized for the annulation of redox-active ferrocenyl-substituted alkynes, besides the implementation of mechanistic studies.
Another goal, closely related to the previous project, was the further modification of the already examined synthesis of isocoumarins **55** through an oxidative annulation-reaction with benzoic acids **56**. As the use of copper(II)acetate as oxidant in stoichiometric quantities impeds the practical preparations on a large scale, it would be of great advantage if a photosensitizer could be used in catalytic amounts. Upon irradiation, this photosensitizer would mediate a redox-reaction between the ruthenium catalyst and air or oxygen as the terminal oxidant (Scheme 2.4).



56 **34** **55**

Scheme 2.4: Ruthenium-catalyzed aerobic alkyne-annulations employing photosensitizer.

Once the optimized reaction conditions would be established, insights into the mechanism should be gained through detailed kinetic studies employing deuterated substrates.

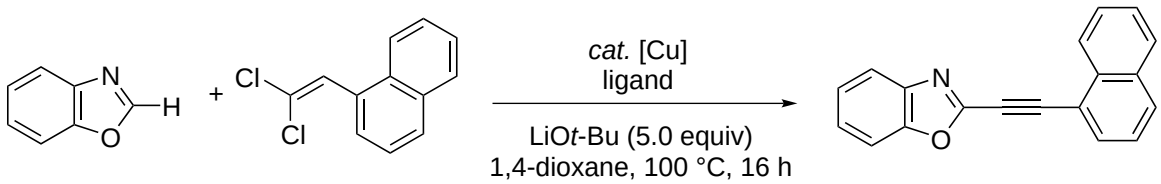
3 Results and Discussion

3.1 Palladium-Catalyzed Direct Alkynylations of Oxazoles and Thiazoles with *gem*-Dichloro- and *gem*-Dibromoalkenes

As discussed above, a plethora of methods for the direct alkynylation of oxazoles **106** and thiazoles **129** was developed by different research groups in the past few years.[167, 168, 170, 172, 179, 180] Most of these procedures either employed terminal alkynes, and thus required external oxidants, or made use of unstable 1-haloalkynes as the electrophiles. Nevertheless, *gem*-dihaloalkenes represent an interesting alternative to the latter, regarding their accessibility from aldehydes and improved stability. Only few procedures are using this concept by employing *gem*-dibromoolefins for the direct alkynylation of oxazoles.[173, 174, 181] Since one of the priorities of the *Ackermann* research group is focused on direct C−H bond functionalizations of oxazoles, the direct alkynylation of oxazoles applying *gem*-dichloroolefins seemed to be an attractive objective.

3.1.1 Optimization Studies for the Direct Alkynylation of Benzoxazole with *gem*-Dichloroalkenes

Table 3.1: Preliminary studies for the direct alkynylation with copper catalysts.[a]



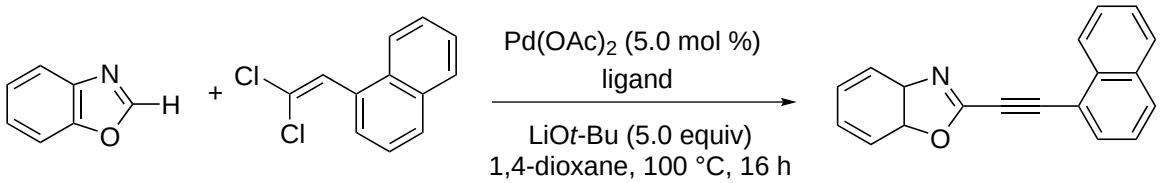
106a **126a** **115aa**

entry	catalyst	ligand	isolated yield (%)
1	CuI (5.0 mol %)	XantPhos (5.0 mol %)	13
2	CuBr · SMe_2 (5.0 mol %)	DPEPhos (5.0 mol %)	13
3	CuBr · SMe_2 (15 mol %)	DPEPhos (15 mol %)	17

[a] Reaction conditions: **106a** (1.0 equiv), **126a** (1.5 equiv), 1,4-dioxane (0.25 M), 100 °C, 16 h, N_2 (1 atm).

Given the fact that direct alkynylations of oxazoles can be achieved under copper(I)-catalysis using *gem*-dibromoalkenes,[173] some preliminary experiments were conducted by employing copper(I)-salts as catalysts for the direct alkynylation of benzoxazole (**106a**) with 1-(2,2-dichlorovinyl)naphthalene (**126a**). Nevertheless, both CuI (Table 3.1, entry 1) as well as the previously applied CuBr · SMe_2 (Table 3.1, entries 2 and 3), gave only unsatisfactory yields.
As a result, further optimization studies were focused on the use of palladium complexes as the catalysts. Replacing copper(I)iodid with palladium(II)acetate under otherwise identical reaction conditions already gave a promising result (Table 3.2, entry 1). Changing the ratio of **106a** and **126a** reduced the yield (entry 2), while adding copper(I)iodid led to a slightly better conversion (entry 3). Extensive ligand screening revealed that catalysts derived from bidentate phosphine-ligands showed superior activity compared to those derived from monodentate phosphines (entries 4–13). The use of *N*-heterocyclic carbenes and phosphine oxides, which were recently employed by *Ackermann et al.* as ligands for direct benzylations and arylations of oxazoles,[159] resulted in only poor conversions (entries 14–16). The best results were obtained with DPEPhos as ligand (entry 4). There seems to be a certain correlation, of the conversion to **115aa** to the bite-angle β_n of the ligand, with the optimum at 104 °, while ligands with a larger or smaller β_n decreased the yield.[182] This trend is, however, interrupted by dppe (β_n = 86 °) (entry 8). Without any metal, no product formation was observed (entry 17).

Table 3.2: Optimization studies for the direct alkynylation: Ligand-effect.[a]



106a **126a** **115aa**

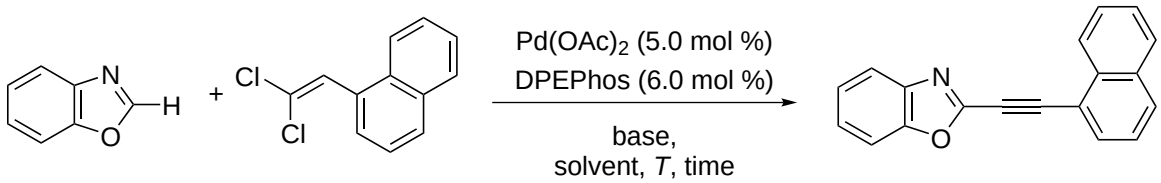
entry	ligand	β_n	isolated yield (%)
1	XantPhos (5.0 mol %)	108 °	47
2	XantPhos (5.0 mol %)	108 °	29[b]
3	XantPhos (5.0 mol %)	108 °	57[c]
4	DPEPhos (5.0 mol %)	104 °	68
5	DPEPhos (5.0 mol %)	104 °	43[c]
6	dppf (5.0 mol %)	99 °	56
7	dppp (5.0 mol %)	91 °	39
8	dppe (5.0 mol %)	86 °	62
9	PPh_3 (10 mol %)	-	38
10	PCy_3 (10 mol %)	-	20

entry	ligand	β_n	isolated yield
11	JohnPhos (10 mol %)	-	40
12	DavePhos (10 mol %)	-	40
13	XPhos (10 mol %)	-	(3)
14	HiPrCl (10 mol %)	-	19
15	PinP(O)H (10 mol %)	-	10
16	1-Ad$_2$P(O)H (10 mol %)	-	9
17	-		-[d]

[a] Reaction conditions: **106a** (1.0 equiv), **126a** (1.5 equiv), $Pd(OAc)_2$ (5.0 mol %), LiO*t*-Bu (5.0 equiv), 1,4-dioxane (0.25 M), 100 °C, 16 h, N_2 (1 atm); [b] **106a** (1.5 equiv), **126a** (1.0 equiv); [c] $Pd(OAc)_2$ (5.0 mol %) + CuI (5.0 mol %); [d] without catalyst, 120 °C, yields in parantheses refer to conversions determined by GC-MS.

Further experiments highlighted the necessity of using LiO*t*-Bu as the base. In the presence of other bases, including other *t*-butoxides, the reaction did not work (Table 3.3, entries 1–4). Solubility of the base as well as reactivity and stability of *in situ* formed organolithium intermediates could be possible explanations. The use of 5.0 equivalents of the base gave the best results (Table 3.3, entries 5–7). Increasing the reaction temperature to 120 °C led to a higher yield, while decreasing of the reaction temperature to 80 °C resulted in less product formation (Table 3.3, entries 8 and 9). When switching to more polar solvents as the reaction medium, no product was formed (Table 3.3, entries 10 and 11). The use of nonpolar aromatic solvents furnished the product in moderate yields, which, however, were lower than those obtained by performing the reaction in 1,4-dioxane (Table 3.3, entries 12–14).

Table 3.3: Optimization studies for the direct alkynylation: Solvent, base and reaction temperature.[a]



106a **126a** **115aa**

entry	solvent	base	T (°C)	time (h)	isolated yield (%)
1	1,4-dioxane	NaO*t*-Bu (5.0 equiv)	100	16	-[b]
2	1,4-dioxane	KO*t*-Bu (5.0 equiv)	100	16	-[b]
3	1,4-dioxane	K_3PO_4 (5.0 equiv)	100	16	-[b]
4	1,4-dioxane	$CsCO_3$ (5.0 equiv)	100	16	-[b]
5	1,4-dioxane	LiO*t*-Bu (5.0 equiv)	100	16	69

entry	solvent	base	T (°C)	time (h)	isolated yield (%)
6	1,4-dioxane	LiO*t*-Bu (4.0 equiv)	100	16	48
7	1,4-dioxane	LiO*t*-Bu (6.0 equiv)	100	16	27
8	1,4-dioxane	LiO*t*-Bu (5.0 equiv)	120	16	74
9	1,4-dioxane	LiO*t*-Bu (5.0 equiv)	80	16	49
10	DMA	LiO*t*-Bu (5.0 equiv)	120	16	-
11	NMP	LiO*t*-Bu (5.0 equiv)	120	16	-
12	toluene	LiO*t*-Bu (5.0 equiv)	120	16	62
13	*o*-xylene	LiO*t*-Bu (5.0 equiv)	120	16	41
14	*m*-xylene	LiO*t*-Bu (5.0 equiv)	120	16	39
15	1,4-dioxane	LiO*t*-Bu (5.0 equiv)	120	24	67
16	1,4-dioxane	LiO*t*-Bu (5.0 equiv)	120	13	75
17	1,4-dioxane	LiO*t*-Bu (5.0 equiv)	120	8	67
18	1,4-dioxane	LiO*t*-Bu (5.0 equiv)	120	4	56
19	1,4-dioxane	LiO*t*-Bu (5.0 equiv)	120	13	75[c]

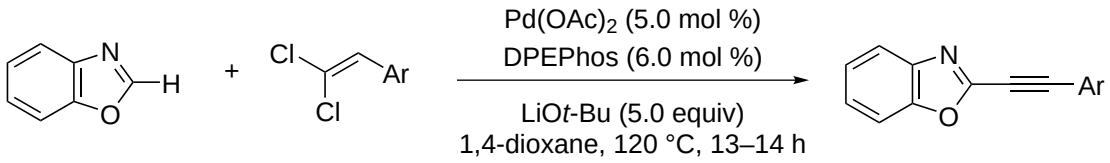
[a] Reaction conditions: **106a** (1.0 equiv), **126a** (1.5 equiv), $Pd(OAc)_2$ (5.0 mol %), DPEPhos (6.0 mol %), solvent (0.25 M), N_2 (1 atm) [b] DPEPhos (5.0 mol %); [c] $Pd(OAc)_2$ (2.5 mol %).

The efficacy appears to be in line with the longer reaction time (Table 3.3, entries 15–18). Thus, heating for 4 (entry 18), 6 (entry 17) and 13 h (entry 16) resulted in isolated yield of 56, 65 and 75%, respectively. However, prolonged heating for 24 h decreased the yield to 67% (entry 15). Lowering the catalyst loading to 2.5 mol % gave exactly the same result as with 5.0 mol % of $Pd(OAc)_2$ (Table 3.3, entries 17 and 19).

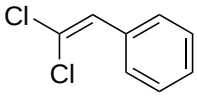
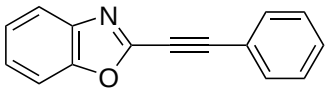
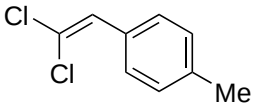
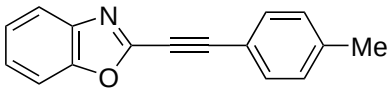
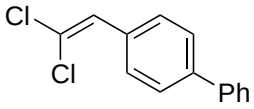
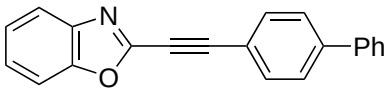
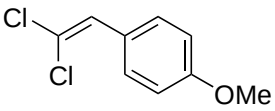
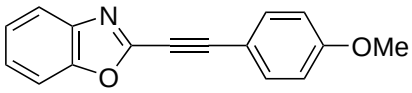
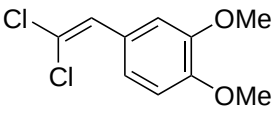
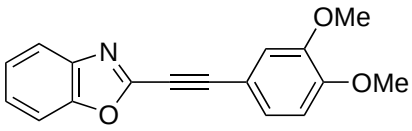
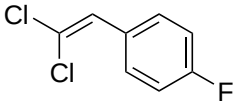
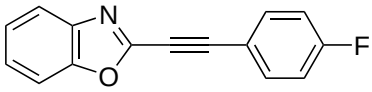
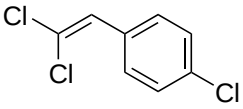
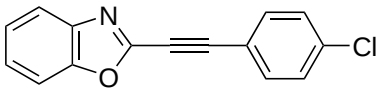
3.1.2 Scope and Limitations for Direct Alkynylation with *gem*-Dichloroalkenes

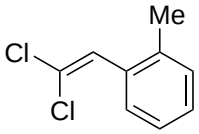
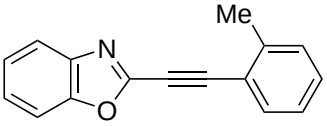
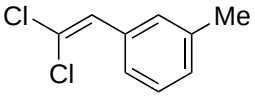
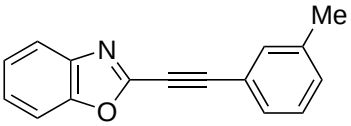
Under the optimized reaction conditions (Table 3.3, entry 17), a representative selection of *gem*-dichloroalkenes **126** was tested (Table 3.4). Most of the substituted *gem*-dichloroalkenes yielded the corresponding products in good to moderate yields. With alkyl- or aryl-substituents in *para*-position of the phenyl-ring, the yields ranged between 55% and 60% (Table 3.4, entries 2 and 3). Electron-rich methoxy-substituents in *meta*- and *para*-position furnished the alkynylated oxazoles **115ae** and **115af** with comparable yields (Table 3.4, entries 4 and 5). The same held true for halogen-substituted substrates **115ag** and **115ah**, which were also employed under the optimized reaction conditions (Table 3.4, entries 6 and 7). Notably, these reactions proceeded smoothly with high chemoselectivity, and the halogen atom in the aromatic backbone remained unaffected. Even sterically more congested substrates **126i** and **126j** furnished the desired product in 60% and 43% yield, respectively (Table 3.4, entries 8 and 9).Unfortunately, reactions with *gem*-dichloroalkenes other than **126a** gave inferior results with 2.5 mol % of the catalyst (Table 3.4, entries 4 and 6).

Table 3.4: Alkynylation of benzoxazole (**106a**) with *gem*-dichloroalkenes **126**.[a]



106a **126** **115**

entry	dichloroalkene **126**	product **115**	isolated yield (%)
1	 **126b**	 **115ab**	38
2	 **126c**	 **115ac**	60
3	 **126d**	 **115ad**	55
4	 **126e**	 **115ae**	40 (35)[b]
5	 **126f**	 **115af**	57
6	 **126g**	 **115ag**	55 (39)[b]
7	 **126h**	 **115ah**	52

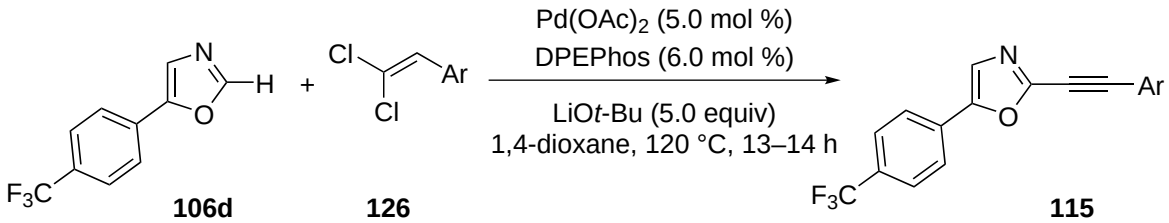
entry	dichloroalkene **126**	product **115**	isolated yield (%)
8	 **126i**	 **115ai**	68
9	 **126j**	 **115aj**	43

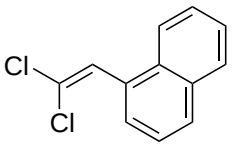
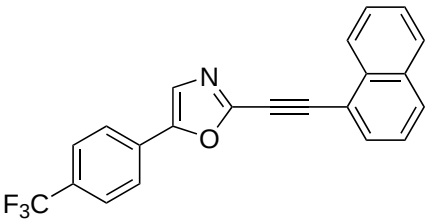
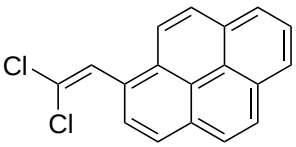
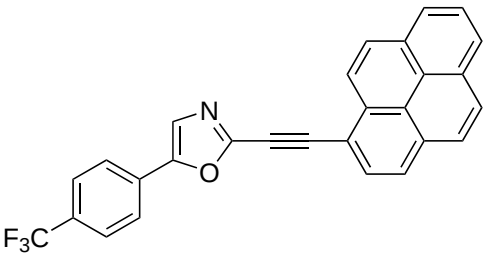
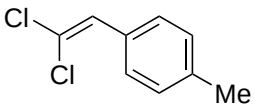
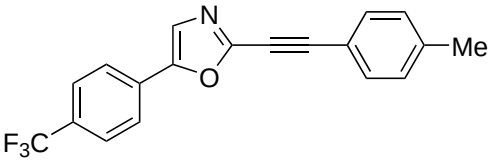
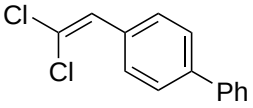
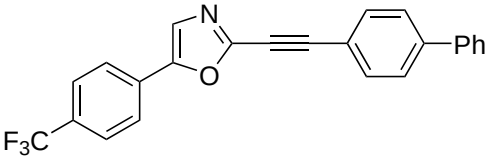
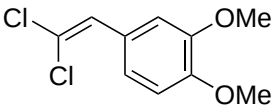
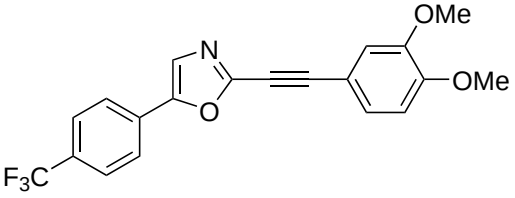
[a] Reaction conditions: **106a** (1.0 equiv), **126** (1.5 equiv), $Pd(OAc)_2$ (5.0 mol %), DPEPhos (6.0 mol %), LiO*t*-Bu (5.0 equiv), 1,4-dioxane (0.25 M), 120 °C, 13−14 h, N_2 (1 atm); [b] $Pd(OAc)_2$ (2.5 mol %)

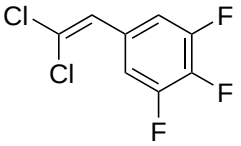
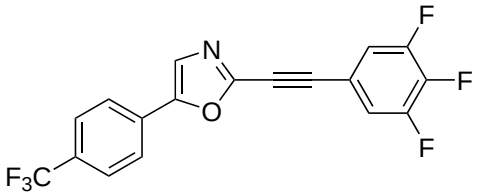
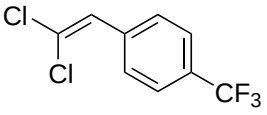
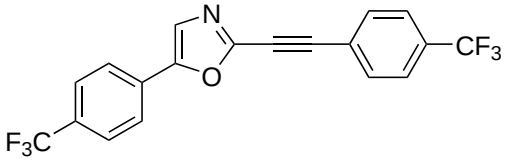
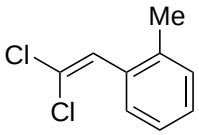
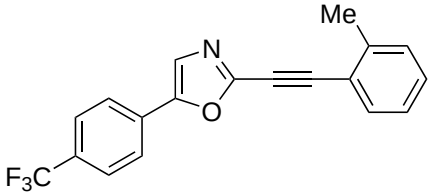
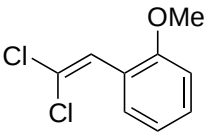
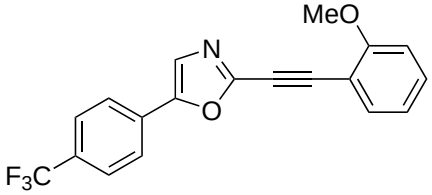
Furthermore, 5-[4-(trifluoromethyl)phenyl]oxazole (**106d**) was subjected to the *gem*-dichloroalkenes **126** under the optimized reaction conditions (Table 3.5). In general, these reactions worked really well and gave better yields compared to benzoxazole (**106a**). Considering that the H bond in substrate **106d** in position C-2 should have a lower pK_A-value than that one in benzoxazole (**106a**), the first-mentioned substrate should be deprotonated faster and thus be more reactive. Hence, *gem*-dichloroalkenes with polycyclic aromatic moieties afforded the desired products **115da** and **115dk** in very good yields of up to 78% (Table 3.5, entries 1 and 2). Similar to reactions with benzoxazole (**106a**), alkyl- or aryl-substituted *gem*-dichloroalkenes **126c** and **126d** also proved to be applicable for the direct alkynylation of **106d** (Table 3.5, entries 3 and 4).

Both electron-rich and electron-deficient substrates allowed for successful transformations under the optimized reaction conditions, (Table 3.5, entries 5–7) as well as the sterically demanding *ortho*-substituted *gem*-dichloroalkenes **126i** and **126n** (Table 3.5, entries 8 and 9).

Table 3.5: Alkynylation of substrate **106d** with *gem*-dichloroalkenes **126**.[a]



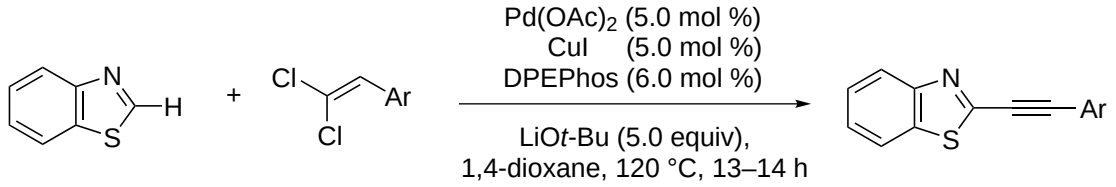
entry	dichloroalkene **126**	product **115**	isolated yield (%)
1	 **126a**	 **115da**	78
2	 **126k**	 **115dk**	75
3	 **126c**	 **115dc**	62
4	 **126d**	 **115dd**	58
5	 **126f**	 **115df**	64

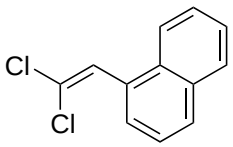
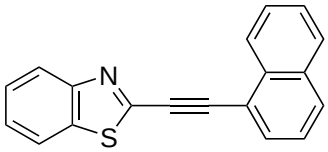
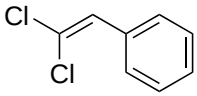
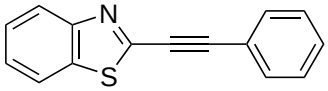
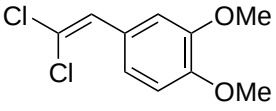
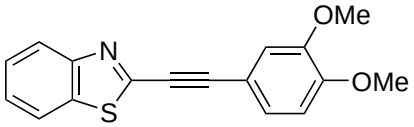
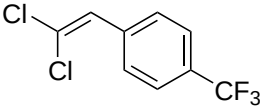
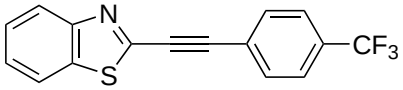
entry	dichloroalkene **126**	product **115**	isolated yield (%)
6	 **126l**	 **115dl**	62
7	 **126m**	 **115dm**	76
8	 **126i**	 **115di**	70
9	 **126n**	 **115dn**	64

[a] Reaction conditions: **106d** (1.0 equiv), **126** (1.5 equiv), $Pd(OAc)_2$ (5.0 mol %), DPEPhos (6.0 mol %), LiO*t*-Bu (5.0 equiv), 1,4-dioxane (0.25 M), 120 °C, 13−14 h, N_2 (1 atm).

The reaction was not restricted to oxazoles, but also proved to be applicable for the direct alkynylation of benzothiazole (**129a**) (Table 3.6). Nevertheless, a minor modification of the reaction conditions was mandatory to achieve good results. While the alkynylation with 1-(2,2-dichlorovinyl)naphthalene (**126a**) as a substrate resulted in poor conversion under the original conditions, product **130aa** could be obtained in 73% yield, when the reaction was performed in the presence of copper(I)iodid (Table 3.6, entry 1). A similar effect has already been described for palladium-catalyzed direct arylations of benzothiazole.[183] The yields with other *gem*-dichloroalkenes were somewhat lower, although electron-rich as well as electron-deficient substrates were well tolerated under the modified conditions (Table 3.6, entries 2–4).

Table 3.6: Alkynylation of benzothiazole (**129a**) with *gem*-dichloroalkenes **126**.[a]

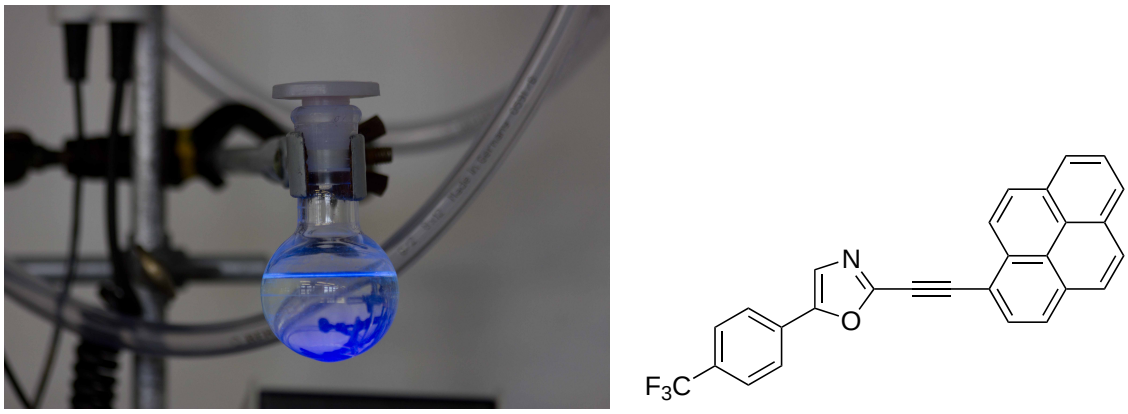


entry	dichloroalkene **126**	product **130**	isolated yield (%)
1	 **126a**	 **130aa**	73 (13)[b]
2	 **126b**	 **130ab**	54
3	 **126f**	 **130af**	50
4	 **126m**	 **130am**	53

[a] Reaction conditions: **128** (1.0 equiv), **126** (1.5 equiv), $Pd(OAc)_2$ (5.0 mol %), CuI (5.0 mol%), DPEPhos (6.0 mol %), LiO*t*-Bu (5.0 equiv), 1,4-dioxane (0.25 M), 120 °C, 13−14 h, N_2 (1 atm); [b] reaction without CuI, GC-MS-conversion.

Unfortunately, for some other substrates, such as caffeine and other imidazoles, no product formation was observed. The reason for this is probably the suppressed reactivity of electron-rich oxazoles and oxadiazoles under these conditions, as observed by *K. Runge.*[184] Some base-sensitive functionalities, such as nitro-groups and esters, led to a significant amount of side products. However, the products which are already accessible are interesting regarding the general usefulness of substituted (hetero)aryl acetylenes as key structural motifs in chemical biology and material sciences.[185, 186] Indeed, most compounds showed significant fluorescence, when objected to UV-light, especially compound **115dk** (Figure 3.1).

As a consequence, the emitted fluorescence of compound **115dk** was recorded as a function of the excitation radiation (Figure 3.2). The collected data showed high fluorescence for excitation wavelengths between 250 nm and 550 nm.



(a) (b)

Figure 3.1: Fluorescence of **115dk** in CH_2Cl_2.

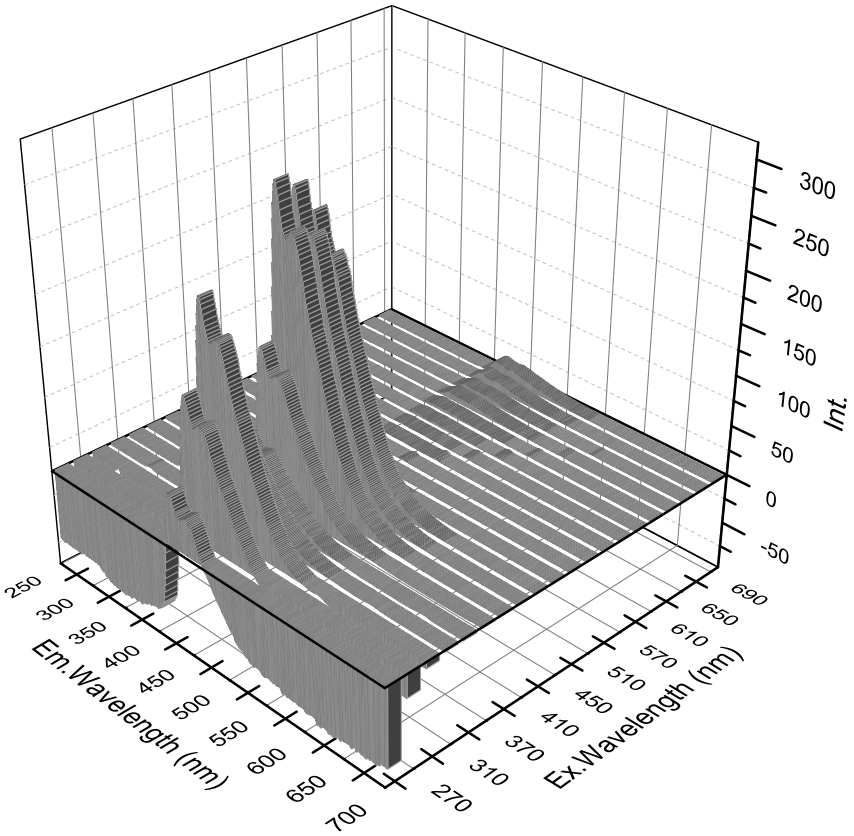
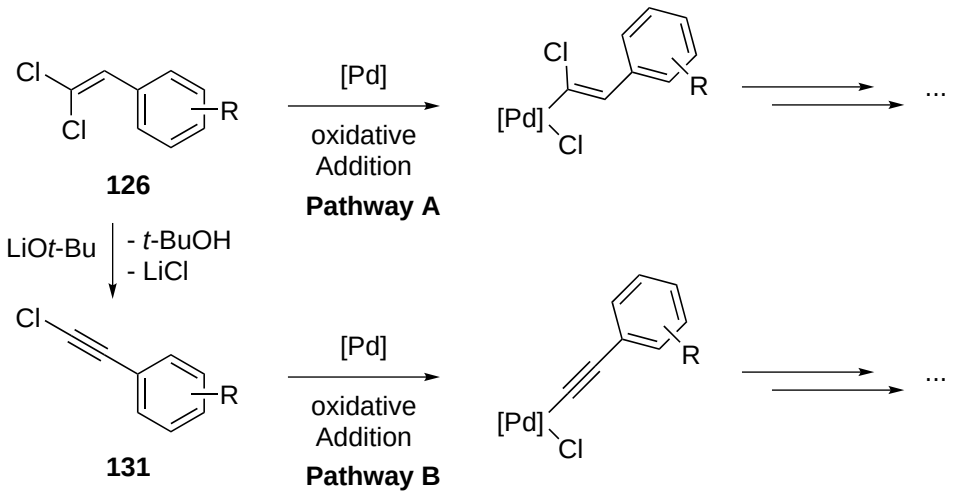


Figure 3.2: 3D-Plot of the fluorescence spectra of a 5μM solution of **115dk** in CH_2Cl_2.

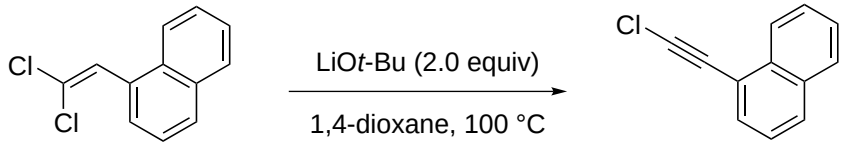
3.1.3 Proposed Mechanism of the Direct Alkynylation with *gem*-Dichloroalkenes

Extensive studies on palladium-catalyzed direct arylations of oxazoles and thiazoles unraveled some similarities to traditional cross-coupling chemistry. Hence, a numberous direct arylations also involve oxidative addition, transmetallation with a deprotonated heterocycle and reductive elimination.[157–159, 164, 187–190] Although some reports on copper(I)-catalyzed direkt alkynylations with *gem*-dibromoalkenes are known from the literature, none of them enclosed detailed mechanistical studies.[173, 174, 181] Thus, it is not obvious for the direct alkynylations with *gem*-dihaloalkenes, if the compound **126** initially undergoes direct oxidative addition (Scheme 3.1, Pathway A), or if the first step renders elimination to corresponding 1-chloroalkynes **131** followed by oxidative addition (Scheme 3.1, Pathway B).



Scheme 3.1: Pathways for the oxidative addition of *gem*-dichlorolkenes (**126**).

Table 3.7: Dehydrochlorination of the *gem*-dichloroalkene **126a** to the 1-chloroalkyne **131a**.[a]

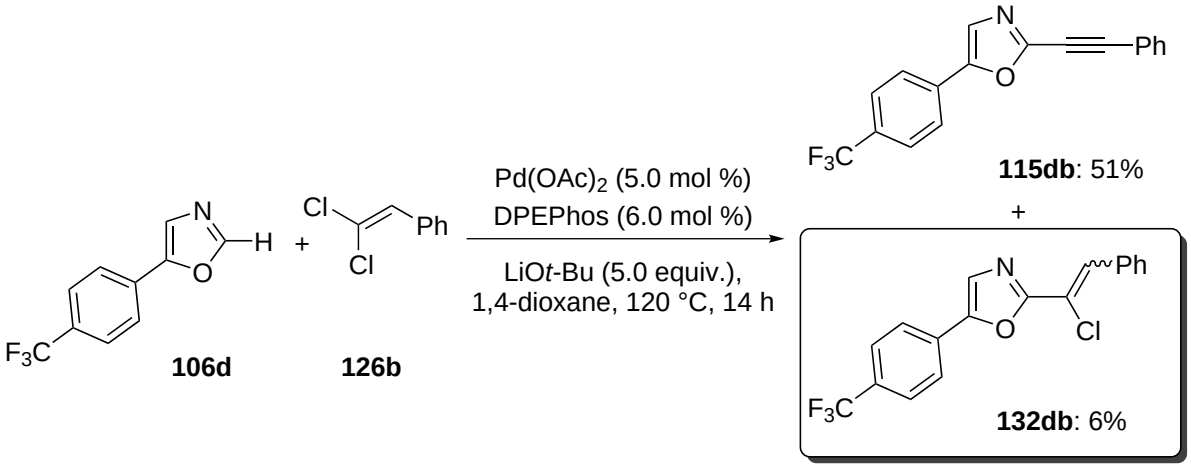


126a **131a**

entry	time (h)	conversion (%)
1	0.5	16
2	1	21
3	2	25
4	4	30

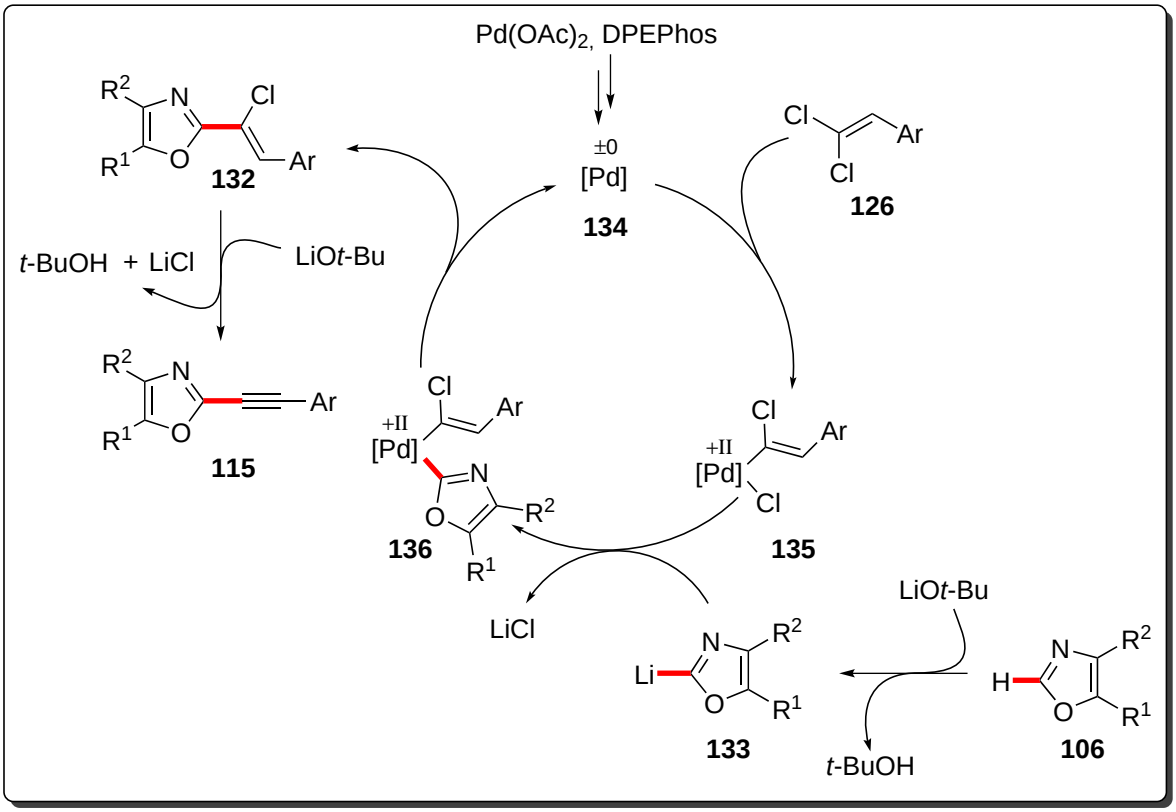
[a] Reaction conditions: **126a** (1.0 equiv), LiO*t*-Bu (2.0 equiv), 1,4-dioxane (0.25 M), 100 °C, N_2 (1 atm), all conversions determined by GC-MS.

In order to elucidate this question, some elimination experiments were conducted (Table 3.7). In the absence of the catalyst elimination proceeded very slowly. After 4 h only 30% of the *gem*-dichloroalkene **126a** were converted to the corresponding chloroalkyne **131a**. This indicates that the concentration of **126** is higher than that of **131**, and thus pathway A should be favoured, at least at the beginning of the reaction. An interesting observation was made, when 1-(2,2-dichlorovinyl)benzene (**126b**) was reacted with oxazole **106d**. In this particular case not only the alkynylated product **115db** was isolated, but also the chloroalkenylated intermediate **132db** (Scheme 3.2). For this reason, and taking into consideration also the previous observations, pathway B in Scheme 3.1 appears to be less likely, and the reaction might predominantly proceed through pathway A.



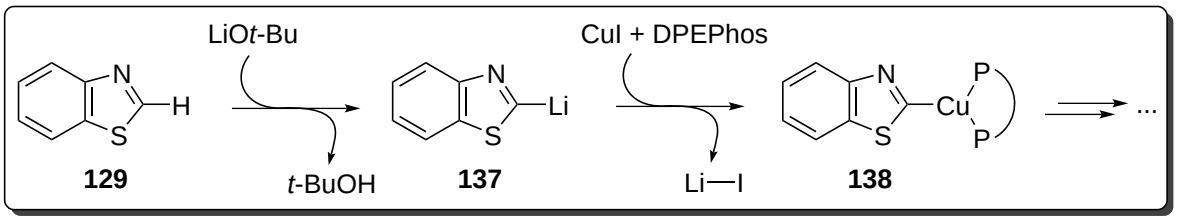
Scheme 3.2: Isolation of the chloroalkenylated intermediate **132db**.

Based on these observation, a plausible mechanism is shown in Scheme 3.3. At the beginning, the catalytic active palladium(0)-species is generated from palladium(II)-acetate and DPEPhos. Intermediate **135** is formed after oxidative addition of the *gem*-dichloroalkene **126**. Deprotonation of the oxazole **106** with LiO*t*-Bu results in the formation of a lithiated oxazole **133**. Now transmetallation can take place, giving rise to intermediate **136**, which can undergo reductive elimination, thus regenerating the catalytically active palladium(0)-species and thereby affording the chloroalkenylated intermediate **132**. The final step is the dehydrochlorination of the intermediate **132** with another equivalent of LiO*t*-Bu furnishing the product **115**.



Scheme 3.3: Plausible mechanism for the direct alkynylation of oxazoles **106**.

In the case of benzothiazole (**129**) the mechanism includes an additional step (Scheme 3.4). The lithiated benzothiazole **137** likely reacts with copper(I)iodid to form cuprate **138**, which finally undergoes transmetallation with the palladium catalyst. Reports in the literature indicated that the ligand also plays an important role in this process.[183]

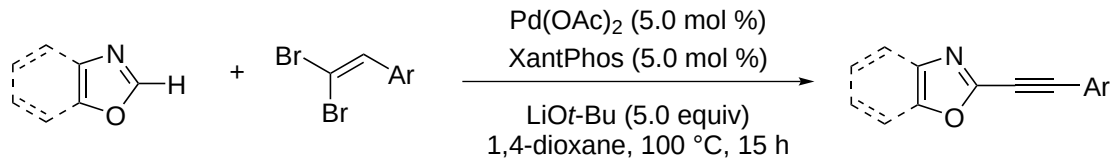


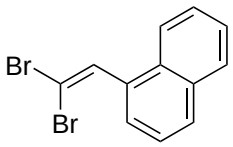
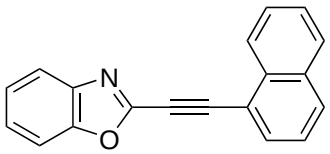
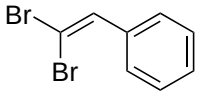
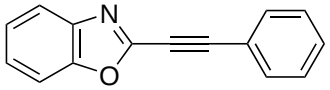
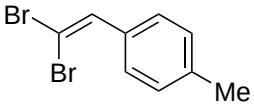
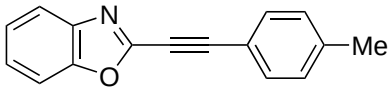
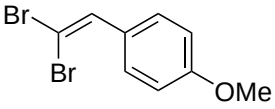
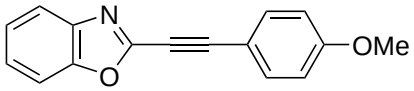
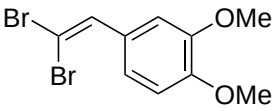
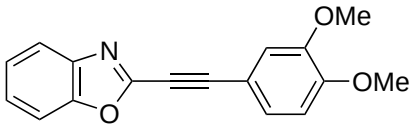
Scheme 3.4: Transmetalation with copper(I)iodid.

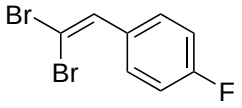
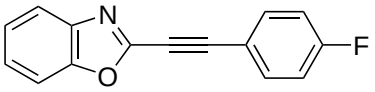
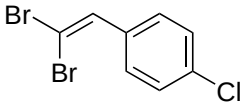
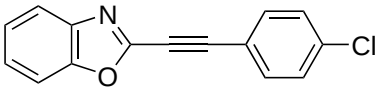
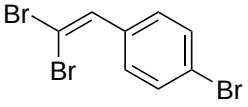
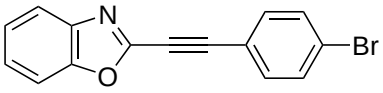
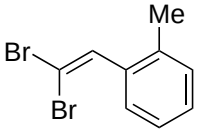
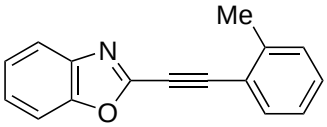
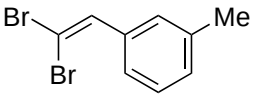
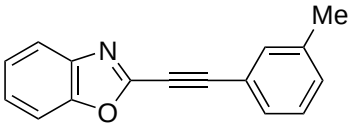
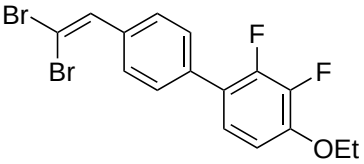
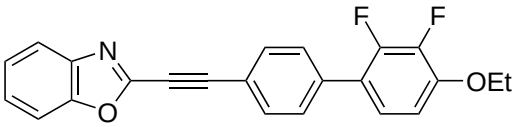
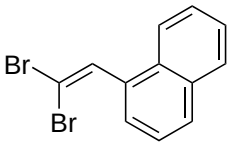
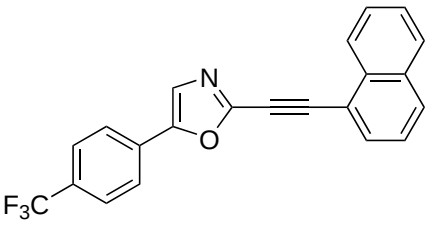
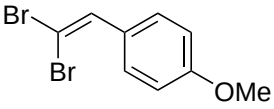
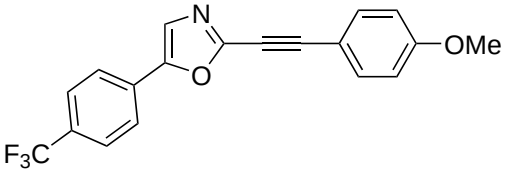
3.1.4 Direct Alkynylations with *gem*-Dibromoalkenes

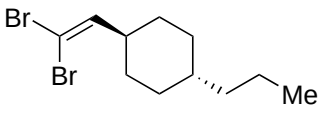
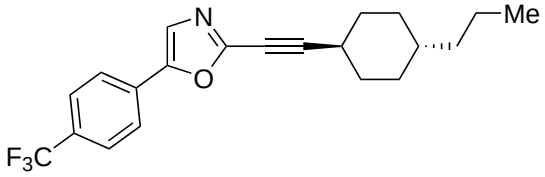
The procedure was consequently extended to *gem*-dibromoalkenes **120**. The reaction conditions were slightly modified by *S. Barfüßer*, utilizing XantPhos as the ligand of choice and decreasing the reaction temperature to 100 °C.[191] The results for the reactions of different oxazoles **106** with different *gem*-dibromoalkenes **120** are shown in Table 3.8.

Table 3.8: Alkynylations of oxazoles **106** with *gem*-dibromoalkenes **120**.[a]



entry	dibromoalkene **120**	product **115**	isolated yield (%)
1	 **120a**	 **115aa**	73
2	 **120b**	 **115ab**	66
3	 **120c**	 **115ac**	60
4	 **120e**	 **115ae**	63
5	 **120f**	 **115af**	64

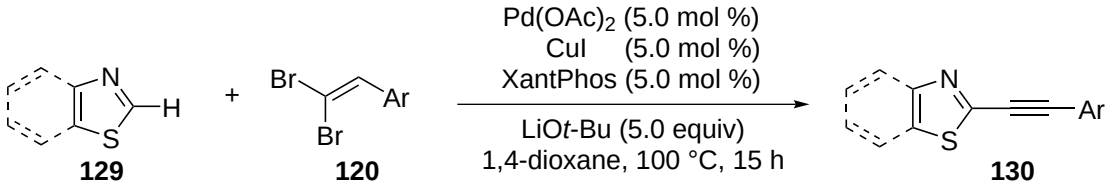
entry	dibromoalkene **120**	product **115**	isolated yield (%)
6	 **120g**	 **115ag**	51
7	 **120h**	 **115ah**	61
8	 **120o**	 **115ao**	53
9	 **120i**	 **115ai**	66
10	 **120j**	 **115aj**	69
11	 **120p**	 **115ap**	63
12	 **120a**	 **115da**	88
13	 **120e**	 **115de**	60

entry	dibromoalkene **120**	product **115**	isolated yield (%)
14	 **120q**	 **115dq**	49

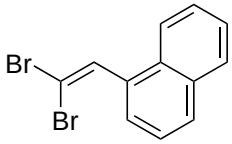
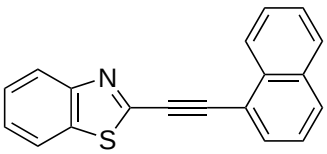
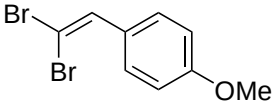
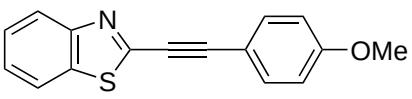
[a] Reaction conditions: **106** (1.0 equiv), **120** (1.5 equiv), $Pd(OAc)_2$ (5.0 mol %), XantPhos (5.0 mol %), LiO*t*-Bu (5.0 equiv), 1,4-dioxane (0.25 M), 100 °C, 15 h, N_2 (1 atm).

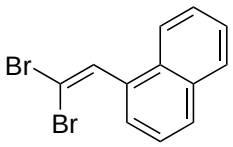
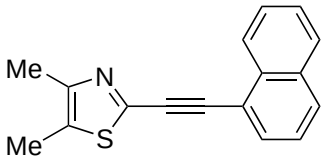
The yields were mostly similar or slightly better than those obtained with *gem*-dichloroalkenes. Besides the unfunctionalized *gem*-dibromoalkenes containing solely phenyl- or naphthyl-rings (Table 3.8, entries 1, 2 and 12), electron-rich substrates also furnished the desired products **115** in good yields (Table 3.8, entries 3–5 and 13). The same holds true for halogen-substituted substrates and *gem*-dibromostyrenes with *meta*- and *ortho*-substitution (Table 3.8, entries 6–8 and 9–10). Two examples are extraordinary interesting: the reactions with highly functionalized as well as with the non-aromatic *gem*-dibromoalkenes **120p** and **120q** led to practically useful products **115ap** and **115dq** in reasonable isolated yields (Table 3.8, entries 11 and 14). The latter example shows that even less-stabilized aliphatic *gem*-dibromoalkenes are tolerated under the optimized reaction conditions.

Table 3.9: Alkynylations of thiazoles **129** with *gem*-dibromoalkenes **120**.[a]



129 **120** **130**

entry	**129**	dibromoalkene **120**	product **130**	yield (%)
1	**129a**	 **120a**	 **130aa**	50
2	**129a**	 **120e**	 **130ae**	40

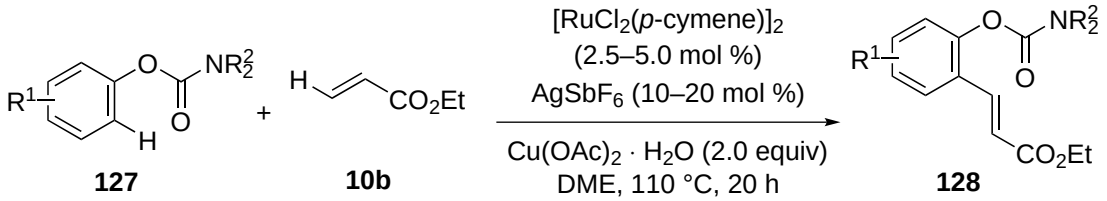
entry	**129**	dibromoalkene **120**	product **130**	yield (%)
3	**129b**	 **120a**	 **130ba**	11

[a] Reaction conditions: **129** (1.0 equiv), **120** (1.5 equiv), $Pd(OAc)_2$ (5.0 mol %), CuI (5.0 mol %), XantPhos (5.0 mol %), LiO*t*-Bu (5.0 equiv), 1,4-dioxane (0.25 M), 100 °C, 15 h, N_2 (1 atm).

As in the case of *gem*-dichloroalkenes **126**, alkynylation of thiazoles **129** with *gem*-dibromoalkenes **120** was also accelerated by addition of catalytic amounts of copper(I)iodid (Table 3.9). The reactions with benzothiazole **129a** furnished the desired products in moderate to good yields (Table 3.9, entries 1 and 2), whereas the direct alkynylation of 4,5-dimethylthiazole **129b** unfortunately resulted in a diminished yield of the corresponding product (Table 3.9, entry 3). In general, the results of the direct alkynylations with *gem*-dibromoalkenes **120** resembled those obtained employing *gem*-dichloroalkenes **126**. Although no additional experiments toward elucidation of the mechanistic pathway have been provided, it is conceivable that also for direct alkynylations with *gem*-dibromoalkenes **120**, the mechanism is alike the one discussed in Schemes 3.3 and 3.4.

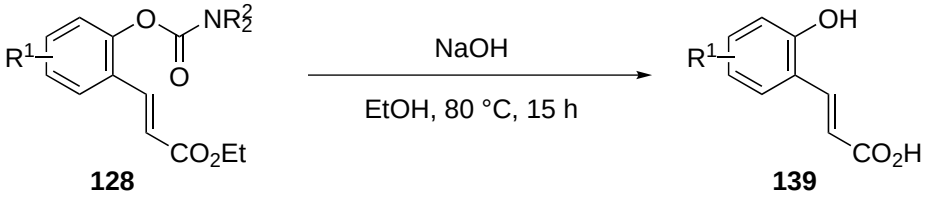
3.2 Ruthenium-Catalyzed Direct C−H Bond Alkenylations of Carbamates

The second project presented herein is a recent supplement to the ruthenium-catalyzed alkenylation reactions presented before. In recent years the *Ackermann*-research group developed various *Fujiwara-Moritani*-type ruthenium-catalyzed direct alkenylations.[146, 149, 151, 192] Based on these results, *J. Li* elaborated an oxidative direct alkenylation of carbamates **125** with ethyl acrylate (**10b**) (Scheme 3.5).[178]



Scheme 3.5: Alkenylation reaction optimized by *J. Li*.[178]

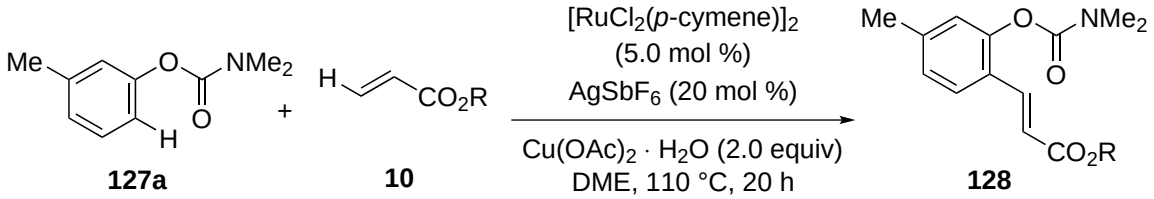
The catalytically active species is most likely a cationic ruthenium-complex, as catalytic amounts of $AgSbF_6$ also have a positive effect on the isolated yield. The reaction is of oxidative in nature. Therefore, a terminal oxidant is required to reoxidize the ruthenium-catalyst. Best results were obtained with copper(II)-acetate as the oxidant, however, extensive studies revealed that copper can also be used in catalytic amounts if the reactions are performed under air.[178]
The carbamate directing groups are also of great use, as they can be cleaved under basic conditions, thus leading to functionalized phenol-derivatives **139** (Scheme 3.6)



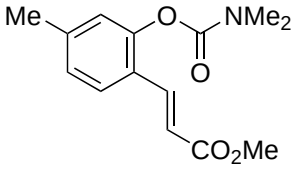
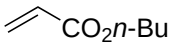
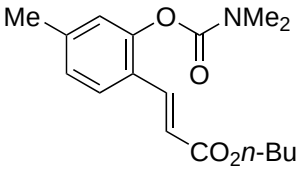
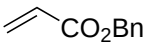
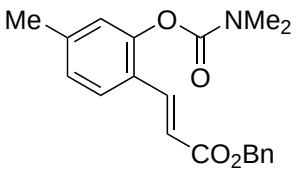
Scheme 3.6: Removal of the directing group (conducted by *J. Li*).[178]

As a consequence, the scope of this reaction was extended to certain practically interesting susbtrates such as *meta*-substituted carbamates and benzyl acrylate (**10d**). The results for the reactions of *meta*-tolyl *N*,*N*-dimethylcarbamate (**127a**) with different acrylates are shown in Table 3.10. As expected, all acrylates furnished the alkenylated products **128** in excellent yields between 87% and 97%. It is also noteworthy to mention, that alkenylation took place at the sterically less-hindered C−H position.

Table 3.10: Direct alkenylations of *meta*-tolyl *N*,*N*-dimethylcarbamate (**127a**) with acrylates **10**.[a]

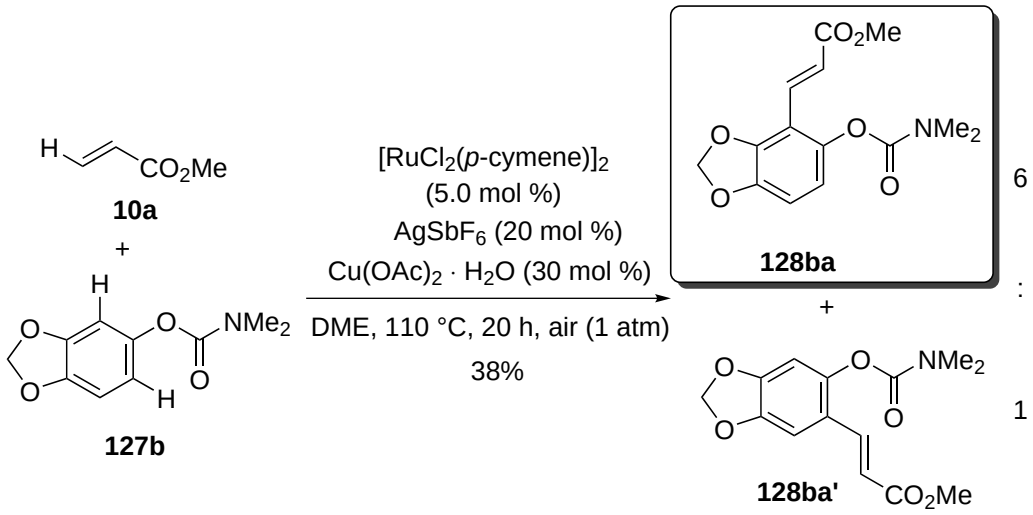


127a **10** **128**

entry	acrylate **10**	product **128**	isolated yield (%)
1	 **10a**	 **128aa**	87
2	 **10c**	 **128ac**	97
3	 **10d**	 **128ad**	95

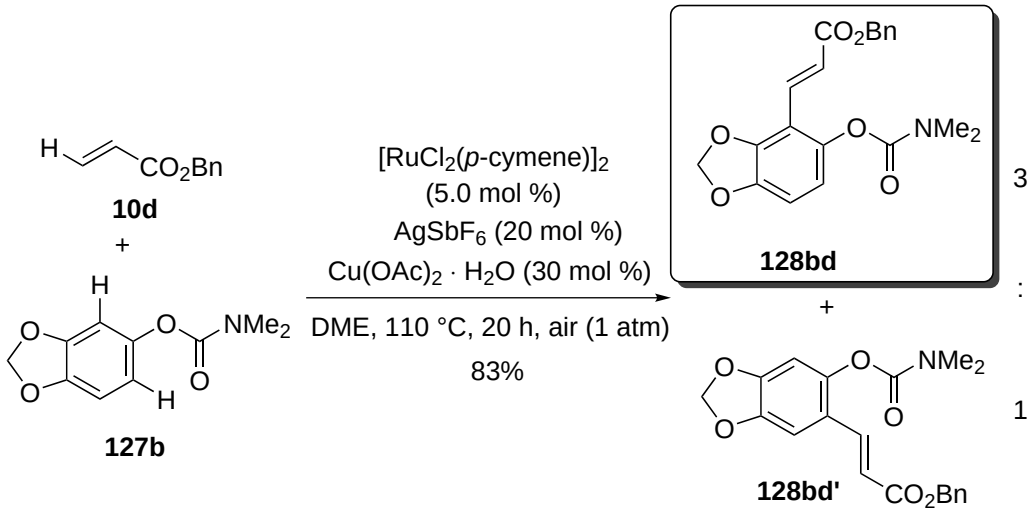
[a] Reaction conditions: **127** (1.0 equiv), **10** (2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv), DME (0.25 M), 110 °C, 20 h, N_2 (1 atm).

In order to verify if the methylenedioxy-group acts as a secondary directing group for this reaction, benzo[*d*][1,3]dioxol-5-yl *N*,*N*-dimethylcarbamate (**127b**) was employed as a substrate.[39, 193] For these experiments, the reaction conditions were also modified. As discussed above, the amount of copper(II)acetate was reduced to catalytic quantities, while air was used as the terminal oxidant. The reaction with methyl acrylate (**10a**) is shown in Scheme 3.7. After 20 h, a 6:1 mixture of **128ba** and **128ba'** was isolated in 38% yield. Even though the yield was only moderate, the major regioisomer was, indeed, the expected sterically-more hindered product **128ba**.



Scheme 3.7: Alkenylation with catalytic amounts of $Cu(OAc)_2 \cdot H_2O$ and air as the oxidant (ratio by ^{1}H-NMR).

Surprisingly, when benzyl acrylate (**10d**) had been used as the olefin, the yield was much higher, however, the chemoselectivity was lower and provided only a 3:1 selectivity in favour of the sterically more-hindered product **128bd** (Scheme 3.8).



Scheme 3.8: Alkenylation with catalytic amounts of $Cu(OAc)_2 \cdot H_2O$ and air as the oxidant (ratio by ^{1}H-NMR).

Some other experiments using an acetate directing group instead of a carbamate directing group led only to unsatisfactory yields.

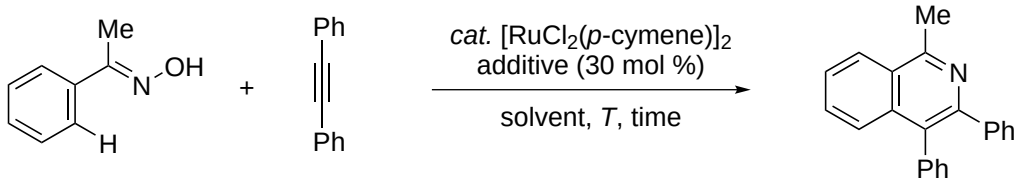
3.3 Annulation of Alkynes through Ruthenium-Catalyzed Direct C−H/N−O Bond Functionalizations of Oximes

Transition metal-catalyzed annulations of alkynes have become an important tool for the synthesis of fine chemicals. Within the last couple of years, a lot of publications illustrated the beneficial effect of alkyne annulations through transition metal-catalyzed direct C−H bond functionalizations. As a significant drawback of these reactions, the necessity to use external oxidants should be mentioned. Hence, the development of new methods avoiding external oxidants continues to be of importance. For instance, essential progress was achieved in the synthesis of isoquinoline scaffolds by redox-neutral direct annulations of alkynes with oximes employing efficient, yet rather expensive rhodium(I)- and rhodium(III)-catalysts.[127–132] As research in the *Ackermann*-research group has focussed on direct annulations of alkynes, a similar approach to isoquinolines was devised by employing less-expensive ruthenium-catalysts. Investigations were started on the basis of redox-neutral alkyne annulations with *N*-methoxybenzamides, independently reported by *Ackermann et al.* and *Wang et al.*[124, 125]

3.3.1 Optimization Studies for the Direct Annulation of Diphenylacetylene with Acetophenone Oxime

At the outset of the optimization studies, it was decided to use 2.5 mol % of $[RuCl_2(p\text{-cymene})]_2$ as the catalyst of choice, with catalytic amounts of different carboxylates as additives (Table 3.11). Acetophenone oxime (**87a**) and two equivalents of diphenylacetylene (**34a**) were selected as substrates of choice. The nitrogen-atom of the oxime **87a** should act as a directing group and should also be a part of the desired product, the isoquinoline **50aa**. In addition, one equivalent of water should be formed during the course of the reaction. In contrast to previous procedures,[100, 109, 110, 116] when *t*-amyl alcohol was used as the solvent, no product formation was observed regardless of whether CsOAc, NaOAc or CuOAc was used as the carboxylate additive (Table 3.11, entries 1–3). When switching to water or toluene as solvent and KO_2CMes as the additive, again only trace amounts of the product could be detected (entries 4 and 5), whereas the use of methanol as the solvent led to, still unsatisfactory, but isolable quantities of the product **50aa** (entry 6). Likewise also other carboxylates KOPiv, CsOAc and NaOAc, gave comparably low yields (entries 7–9). $Cu(OAc)_2 \cdot H_2O$, on the other hand, did not give any product at all (entry 10). By the use of CsOAc as carboxylate, with methanol as the solvent and by increasing the catalyst loading to 5.0 mol %, the conversion could be increased up to 40% (entry 12). An extended reaction time finally led to a reasonable yield of 58% (entry 13). Other carboxylates, as well as K_2CO_3, were tested under the new reaction conditions. However, besides NaOAc, which gave 39% of the desired product, they resulted again in low yields (entries 14 and 15).

Table 3.11: Optimization studies for the direct annulation of alkynes **34** with oximes **87**.[a]



87a **34a** **50aa**

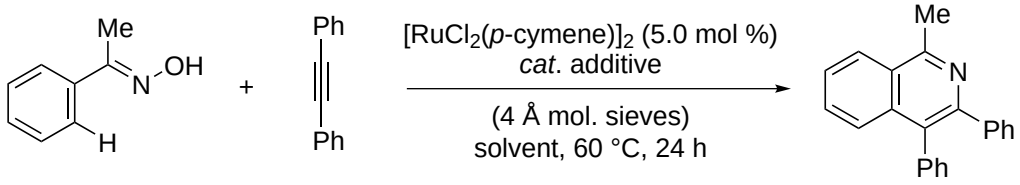
entry	catalyst loading (mol %)	additive	solvent	T °C	time (h)	isolated yield (%)
1	2.5	CsOAc	*t*-AmOH	110	16	-
2	2.5	NaOAc	*t*-AmOH	110	16	-
3	2.5	CuOAc	*t*-AmOH	110	16	-
4	2.5	KO_2CMes	H_2O	110	16	(7)
5	2.5	KO_2CMes	toluene	110	16	(5)
6	2.5	KO_2CMes	MeOH	60	16	14
7	2.5	KOPiv	MeOH	60	16	(18)
8	2.5	CsOAc	MeOH	60	16	15
9	2.5	NaOAc	MeOH	60	16	13
10	2.5	$Cu(OAc)_2 \cdot H_2O$	MeOH	60	16	-
11	2.5	CsOAc	DMF	60	16	-
12	5.0	CsOAc	MeOH	60	16	40
13	5.0	CsOAc	MeOH	60	24	58
14	5.0	NaOAc	MeOH	60	24	39
15	5.0	CuOAc	MeOH	60	24	(13)
16	5.0	AgOAc	MeOH	60	24	9
17	5.0	KO_2CMes	MeOH	60	24	23
18	5.0	KOPiv	MeOH	60	24	15
19	5.0	K_2CO_3	MeOH	60	24	9

[a] Reaction conditions: **87a** (1.0 equiv), **34a** (2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$, additive (30 mol %), solvent (0.25 M), N_2 (1 atm); yields in parentheses refer to conversions determined by GC-MS.

To investigate the influence of water, experiments in the presence of molecular sieves were undertaken. The results are shown in Table 3.12. Most of the reactions using acetates or K_2CO_3 as additives furnished the product **50aa** in comparable yields (Table 3.12, entries 1–4). Only in the reaction with sodium acetate a positive effect was observed (Table 3.12, entry 5). Next, the carboxylate additive was replaced with salts of weakly coordinating anions. While use of $AgSbF_6$ resulted in a moderate conversion (Table 3.12, entry 6), the reaction in the presence of KPF_6 furnished the desired product in remarkable 83% yield (Table 3.12, entry 7). Fortunately,

a comparable result was obtained without the addition of molecular sieves (Table 3.12, entry 8). However, if KPF_6 was replaced by $NaPF_6$ or $AgSbF_6$ the yield was reduced to 67% an 38%, respectively (Table 3.12, entries 9 and 10). With the knowledge that molecular sieves were not mandatory, an attempt was made to use environmentally benign water as a solvent. However, a significantly lower yield was observed after the reaction, but still higher compared to *t*-amyl alcohol (Table 3.12, entries 11 and 12). Furthermore it was possible to ensure that elevated temperatures are necessary for the reaction, as stirring at ambient temperature gave only trace amounts of the desired product (Table 3.12, entry 13). This assumption can also be assured by the observation that the initially heterogenous (suspension) reaction mixture became homogenous upon heating. A reduced catalyst-loading, as well as a a reduced amount of KPF_6 resulted in slightly lower, but still good conversions (Table 3.12, entires 14 and 15). Astonishingly the absence of any additive also led to a decent yield of 60% (Table 3.12, entry 16). This observation indicates that carboxylates are more likely to slow down the reaction, rather than enhancing its rate. Thus, when using both KPF_6 and CsOAc, the yield was dramatically decreased (Table 3.12, entry 17).

Table 3.12: Optimization studies for the direct annulation of alkynes **34** with oximes **87**.[a]



87a **34a** **50aa**

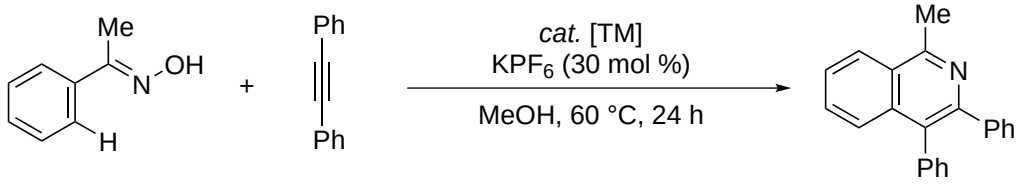
entry	additive (mol %)	4 Å mol. sieves	solvent	isolated yield (%)
1	CsOAc (30	yes	MeOH	58
2	CsOAc (30)	yes	MeOH	12[b]
3	AgOAc (30)	yes	MeOH	16
4	K_2CO_3 (30)	yes	MeOH	(12)
5	NaOAc (30)	yes	MeOH	68
6	$AgSbF_6$ (30)	yes	MeOH	53
7	KPF_6 (30)	yes	MeOH	83
8	KPF_6 (30)	-	MeOH	81
9	$NaPF_6$ (30)	-	MeOH	67
10	$AgSbF_6$ (30)	-	MeOH	38
11	KPF_6 (30)	-	H_2O	30

entry	additive (mol %)	mol. sieves 4Å	solvent	isolated yield (%)
12	KPF_6 (30)	-	*t*-AmOH	(9)
13	KPF_6 (30)	-	MeOH	(5)[c]
14	KPF_6 (30)	-	MeOH	65[b]
15	KPF_6 (10)	-	MeOH	72
16	-	-	MeOH	60
17	KPF_6 (10) + CsOAc (30)	-	MeOH	19[d]

[a] Reaction conditions: **87a** (1.0 equiv), **34a** (2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), additive, solvent (0.25 M), 60 °C, 24 h, N_2 (1 atm), 4 Å mol. sieves (100 mg per 0.5 mmol) **34a**; [b] $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %); [c] 25 °C; [d] + CsOAC (30 mol %); yields in parentheses refer to conversions determined by GC-MS.

Thereafter, some other precatalysts were examined under the optimized reaction conditions (Table 3.13).

Table 3.13: Precatalysts for the direct annulation of alkynes **34** with oximes **87**.[a]



87a **34a** **50aa**

entry	*cat.* [TM] (mol %)	isolated yield (%)
1	$[RuCl_2(p\text{-cymene})]_2$ (5.0)	81
2	$[Ru_2Cl_3(p\text{-cymene})_2][PF_6]$ (4.0)	68
3	$[RuBr_2(p\text{-cymene})]_2$ (5.0)	60
4	$[RuCl_2(C_6H_6)]_2$ (5.0)	7
5	$RuCl_3 \cdot 4\,H_2O$ (10)	(15)
6	$[RhCl_2(Cp^*)]_2$ (5.0)	28
7	-	-

[e] Reaction conditions: **87a** (1.0 equiv), **34a** (2.0 equiv), KPF_6 (30 mol %), MeOH (0.25 M), 60 °C, 24 h, N_2 (1 atm); yield in parentheses refer to conversion determined by GC-MS.

During the course of this reaction, a cationic ruthenium species is most likely formed through abstraction of a chlorine-atom from the precatalyst with a non-coordinating $[PF_6]^-$ anion (Scheme 3.9). In order to support this concept, the preformed cationic complex $[Ru_2Cl_3(p\text{-cymene})_2][PF_6]$[113] was tested as the catalyst and also furnished the desired product in good yield (Table 3.12, entry 2). Further details concerning the mode of action of the cationic ruthenium-

species will be discussed below in the mechanistic section.

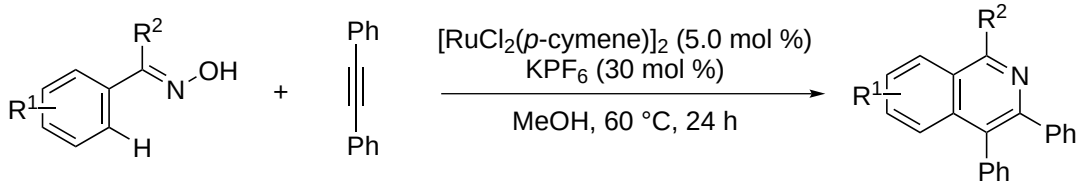
Scheme 3.9: Formation of the cationic ruthenium species.

If the chlorine in the precatalyst was replaced by bromine, the yield was somewhat lower, but still acceptable (Table 3.12, entry 3). On the other hand, if the *p*-cymene ligand was exchanged by benzene, the yield dropped dramatically (Table 3.12, entry 4). With the readily accessible $RuCl_3$ as the catalyst, only poor conversion to the product could be observed (Table 3.12, entry 5). The rhodium(III)-complex provided the product **50aa** in 28% yield, which was significantly lower compared to $[RuCl_2(p\text{-cymene})]_2$. Finally, the reaction was performed without any catalyst and, as expected, product formation was not observed (Table 3.12, entry 7).

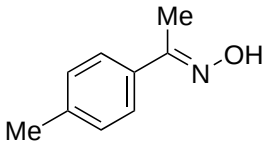
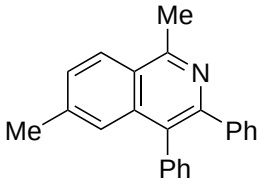
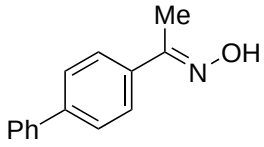
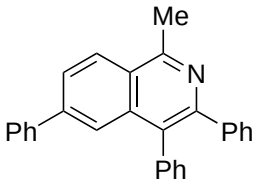
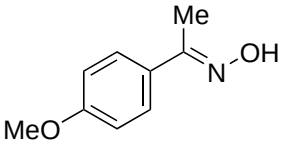
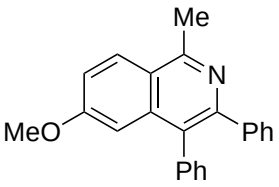
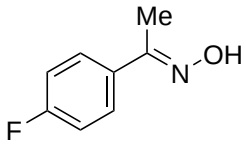
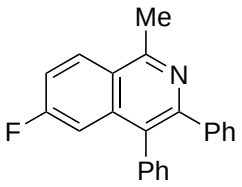
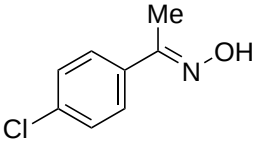
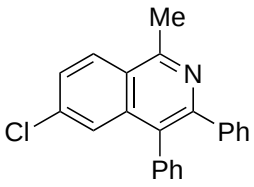
3.3.2 Scope and Limitations of Direct Annulations of Alkynes with Oximes

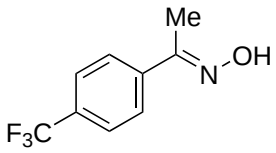
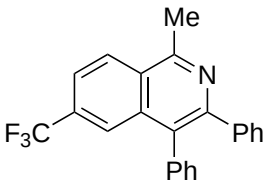
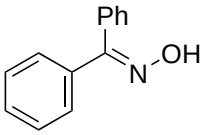
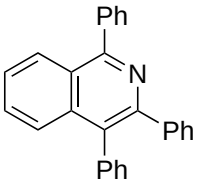
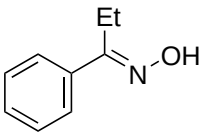
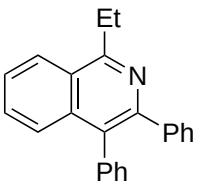
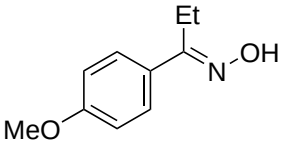
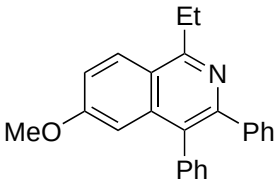
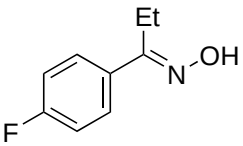
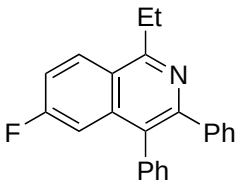
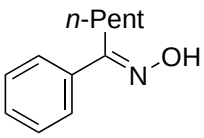
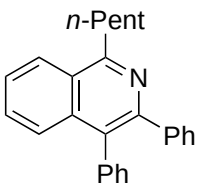
Under the optimized reaction conditions, shown in entry 1 of Table 3.13, a variety of differently substituted oximes **87** were examined regarding the functional group-tolerance of the reaction (Table 3.14). As shown in entry 1, an alkyl-substituent does not interfere the catalytic activity, while an aryl-substituent decreased the yield, but still afforded reasonable amounts of the product (Table 3.14, entry 2). Certain substituted acetophenone oximes demanded addition of molecular sieves in order to achieve decent yields (Table 3.14, entries 3–5). The reason for the low reactivity of these substrates is not completely clear, particularly since the electron-deficient oxime **87g** bearing a *p*-CF_3-group was converted to the product **50ga** with good chemo selectivity (Table 3.14, entry 6). It is still an open question, if the enhanced hygroscopicity of oximes **87d**–**87f** can be responsible for their suppressed reactivity. In contrast, benzophenone oxime (**87h**), gave a very good result, which was comparable to the one obtained from the experiment with acetophenone oxime (Table 3.12, entry 1). Reactions with electron-rich propiophenone oximes gave rise to rather high yields of the corresponding isoquinolines (Table 3.14, entries 8 and 9), whereas the electron-deficient fluoro-substituted oxime **87k** gave a slightly decreased yield (Table 3.14, entry 10). Further elongation of the aliphatic chain in the oxime had no negative effect, as **50la** was obtained in an excellent yield of 96% (Table 3.14, entry 11). Unfortunately, oximes with certain functionalities, such as nitro-groups, nitriles or 1-substituted naphthalenes, were not tolerated under the optimized reaction conditions (Figure 3.3). The same chemical behavior was detected for heteroaromatic (**87p**–**87r**), the *O*-methylated aromatic oxime **87s** and the olefinic oxime **88a**, which gave just trace amounts of the corresponding product.

Table 3.14: Scope of direct annulations of diphenylacetylene (**34a**) by oximes **87**.[a]



87 **34a** **50**

entry	oxime **87**	product **50**	isolated yield (%)
1	 **87b**	 **50ba**	85
2	 **87c**	 **50ca**	54
3	 **87d**	 **50da**	31 (50)[b]
4	 **87e**	 **50ea**	36 (52)[b]
5	 **87f**	 **50fa**	25 (49)[b]

entry	oxime **87**	product **50**	isolated yield (%)
6	 **87g**	 **50ga**	70[c]
7	 **87h**	 **50ha**	82
8	 **87i**	 **50ia**	91
9	 **87j**	 **50ja**	95
10	 **87k**	 **50ka**	57
11	 **87l**	 **50la**	96

[a] Reaction conditions: **87** (1.0 equiv), **34a** (2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), KPF_6 (30 mol %), MeOH (0.25 M), 60 °C, 24 h, N_2 (1 atm); [b] 4 Å mol. sieves (100 mg per 0.5 mmol **87**); [c] average yield from 2 different reactions.

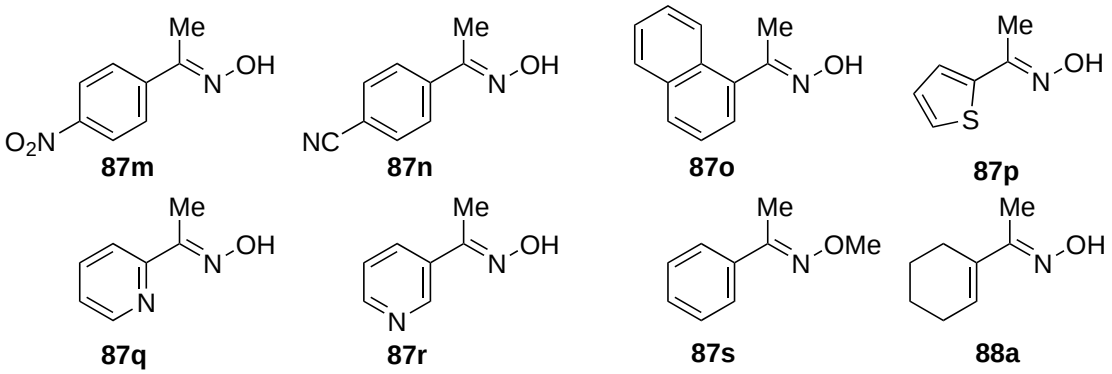
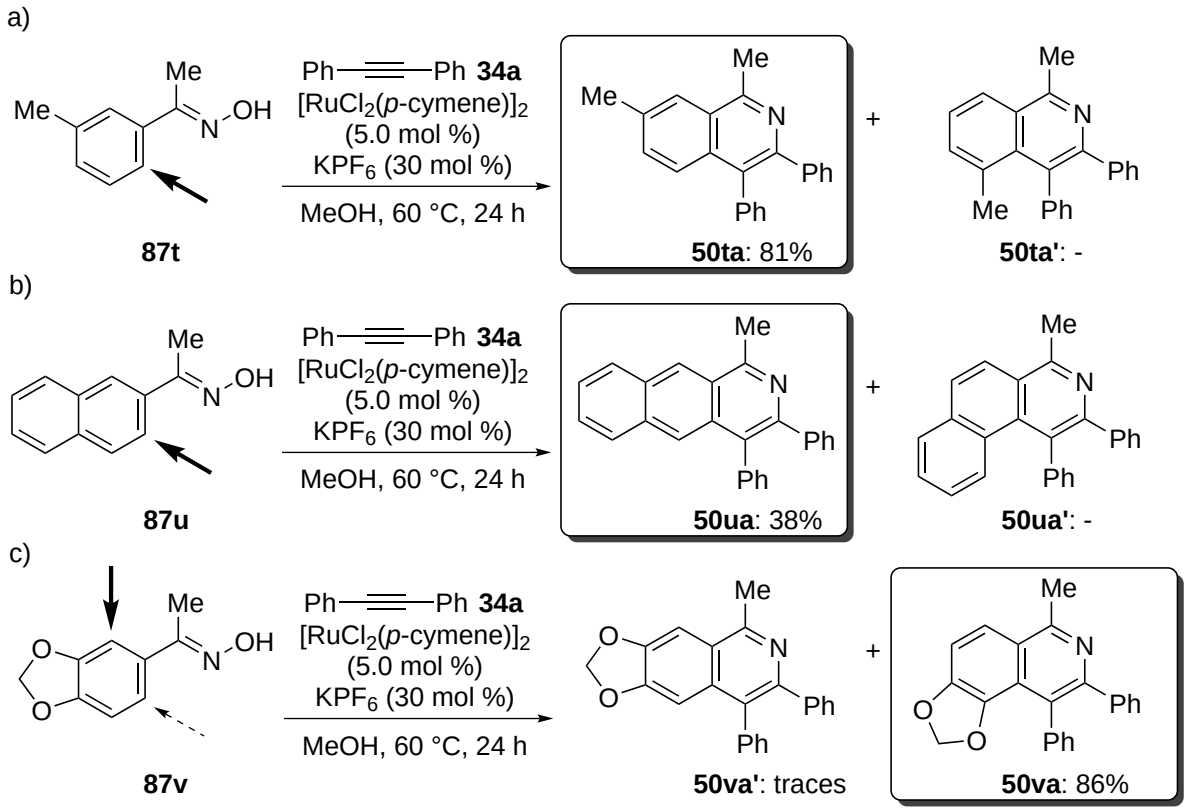


Figure 3.3: Unreactive oximes **87** and **88a**.

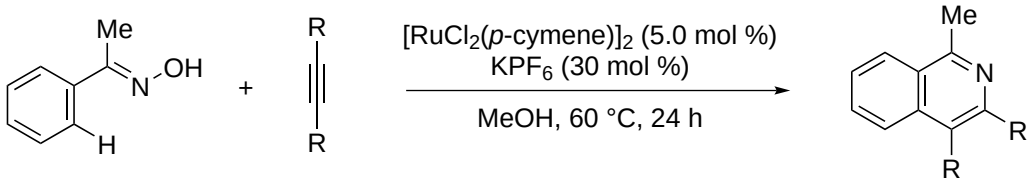
When *meta*-substituted oximes were subjected to the reaction conditions, some interesting observations were made. With *m*-methylacetophenone oxime (**87t**) as substrate, only the sterically less hindered product **50ta** was formed (Scheme 3.10 a). In spite of the lower yield, the reaction shows the same regioselectivity if benzannulated oxime **87u** was employed (Scheme 3.10 b). The opposite effect was observed when the oxime contains a fused dioxolane-moiety (Scheme 3.10 c). Herein, the annulation took place at the sterically more congested C−H bond. This finding can be explained by the influence of the oxygen-atom in 3-position, which can act as a secondary directing group through lone pair donation to the metal-center. Such secondary directing group effects have already been reported for ruthenium-catalyzed hydroarylations of olefins.[39, 193]



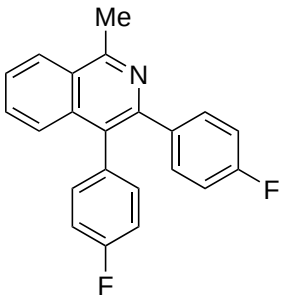
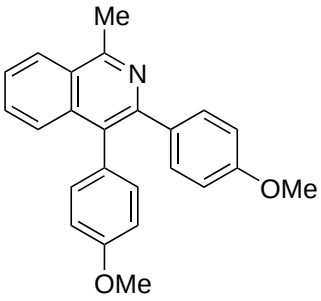
Scheme 3.10: Annulations with *meta*-substituted oximes.

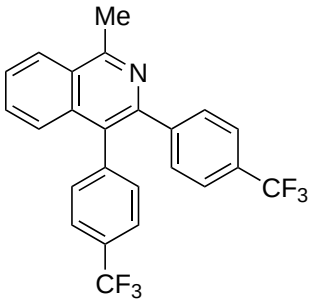
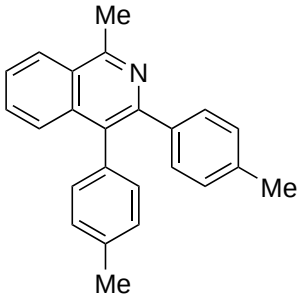
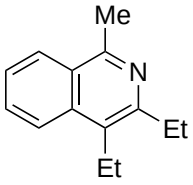
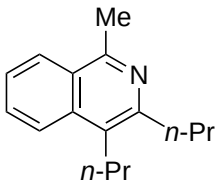
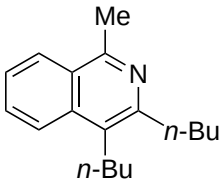
Besides diphenylacetylene (**34a**), the scope of the ruthenium-catalyzed annulation was also extended to include other alkynes **34** (Table 3.15). In the reactions with 1,2-bis(4-fluorophenyl)acetylene (**34b**) and 1,2-bis(4-methoxyphenyl)acetylene (**34c**), the corresponding products could be isolated in 70%, and 53% yield, respectively (Table 3.15, entries 1 and 2). The outcome of the reactions with **34d** and **34e**, however, was unexpectedly low and provided only unsatisfactory amounts of the desired products **50ad** and **50ae** (Table 3.15, entries 3 and 4). These intriguing results cannot be explained by electronic properties and could be a consequence of the extremely poor solubility of these two alkynes in methanol, even at elevated reaction temperatures. Symmetrical dialkylacetylenes **34f**–**34h** with completely aliphatic side chains, in turn, furnished the isoquinoline products **50af**–**50ah** in very good yields (Table 3.15, entries 5–7). In this context, the chain length does not seem to have a significant influence on the overall reactivity.

Table 3.15: Scope of direct annulation with alkynes **34**.[a]



87a **34** **50**

entry	**R**	product **50**	isolated yield (%)
1	*p*-(C_6H_4)F		70
	34b	**50ab**	
2	*p*-(C_6H_4)OMe		53
	34c	**50ac**	

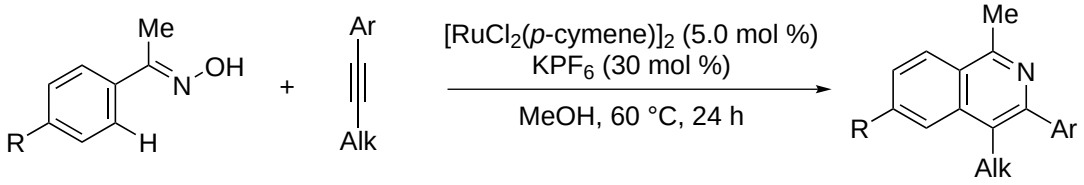
entry	**R**	product **50**	isolated yield (%)
3	*p*-(C_6H_4)CF_3		12
	34d	**50ad**	
4	*p*-(C_6H_4)Me		32
	34e	**50ae**	
5	Et		86
	34f	**50af**	
6	*n*-Pr		87
	34g	**50ag**	
7	*n*-Bu		79
	34h	**50ah**	

[a] Reaction conditions: **87a** (1.0 equiv), **34** (2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), KPF_6 (30 mol %), MeOH (0.25 M), 60 °C, 24 h, N_2 (1 atm).

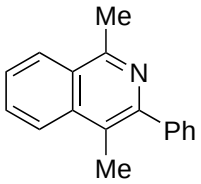
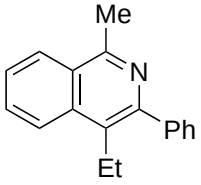
With these promising results in hand, several unsymmetrically substituted alkynes **34**, bearing one alkyl- and one aryl-substituent, were tested under the optimized reaction conditions (Table 3.16).

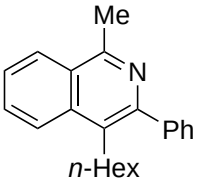
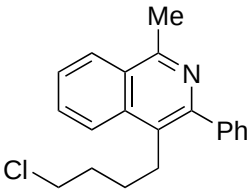
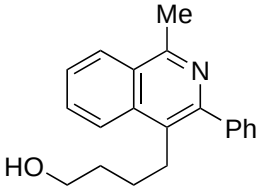
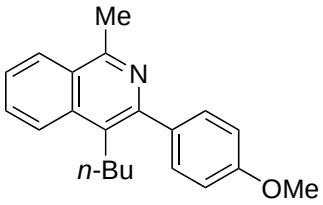
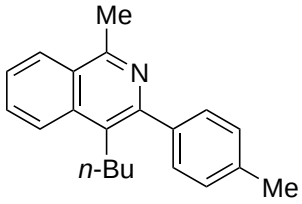
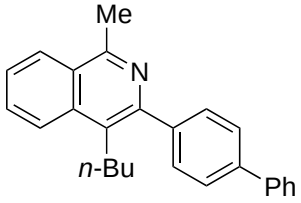
A common feature among all of these reactions was their excellent regioselectivity. The arene substituent in all reaction products was always placed proximal to the nitrogen. For example, the compound **50ai**, could be obtained in 69% by employing prop-1-ynylbenzene (**34i**) (Table 3.16, entry 1). Further side-chain homologation resulted in comparable outcomes (Table 3.16, entry 2 and 3). Fortunately, sensitive functionalities such as aliphatic alcohols and aliphatic halides were also tolerated under the reaction conditions, allowing further side-chain manipulation of the isoquinoline-product (Table 3.16, entries 4 and 5). Subsequently, variously decorated aryl-substituents on the other side of the alkyne were examined. The results indicated no significant differences in reactivity regardless of the electronic properties of the aromatic system (Table 3.16, entries 6–9). Another observation was that esters and ketones were also tolerated without any side-reactions occuring on the carbonyl-functionality (Table 3.16, entry 10 and 11). Annulation of the cyclopropyl-substituted alkyne **34t** was less efficient (Table Table 3.16, entry 12). Such a result is in line with the values of steric substituent constants for the alkyl groups, which are equal to 0 (Me, entry 1), 0.86 (Et, entry 2), 0.85 (*n*-hexyl, entry 3) and 1.33 (cyclopropyl, entry 12),[194] but cannot be completely explained as a consequence of the increased steric demands only.[112]

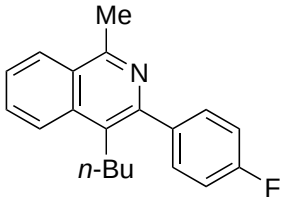
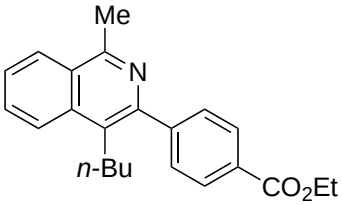
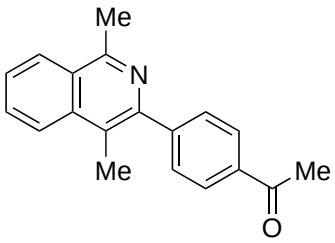
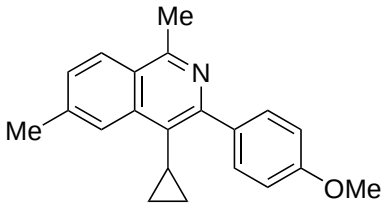
Table 3.16: Direct annulation of unsymmetrical alkynes **34** by oximes **87**.[a]



87 **34** **50**

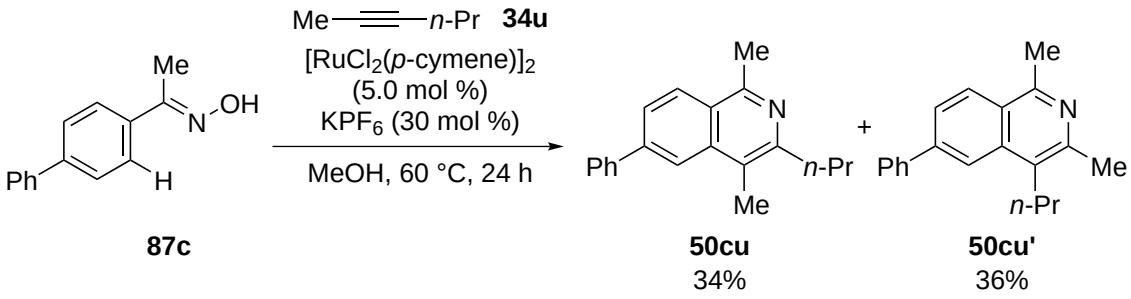
entry	**R**	**Ar**	**Alk**	product **50**	isolated yield (%)
1	H	Ph	Me		69
	87a	**34i**		**50ai**	
2	H	Ph	Et		63
	87a	**34j**		**50aj**	

entry	**R**	**Ar**	**Alk**	product **50**	isolated yield (%)
3	H	Ph	*n*-Hex		52[b]
	87a	**34k**		**50ak**	
4	H	Ph	$(CH_2)_4$−Cl		67
	87a	**34l**		**50al**	
5	H	Ph	$(CH_2)_4$−OH		73
	87a	**34m**		**50am**	
6	H	*p*-(C_6H_4)OMe	*n*-Bu		57
	87a	**34n**		**50an**	
7	H	*p*-(C_6H_4)Me	*n*-Bu		68[c]
	87a	**34o**		**50ao**	
8	H	*p*-(C_6H_4)Ph	*n*-Bu		51
	87a	**34p**		**50ap**	

entry	**R**	**Ar**	**Alk**	product **50**	isolated yield (%)
9	H	*p*-(C_6H_4)F	*n*-Bu		60
	87a	**34q**		**50aq**	
10	H	*p*-(C_6H_4)CO_2Et	*n*-Bu		47
	87a	**34r**		**50ar**	
11	H	*p*-(C_6H_4)C(O)Me	Me		70
	87a	**34s**		**50as**	
12	Me	*p*-(C_6H_4)OMe	*c*-Pr		26
	87b	**34t**		**50bt**	

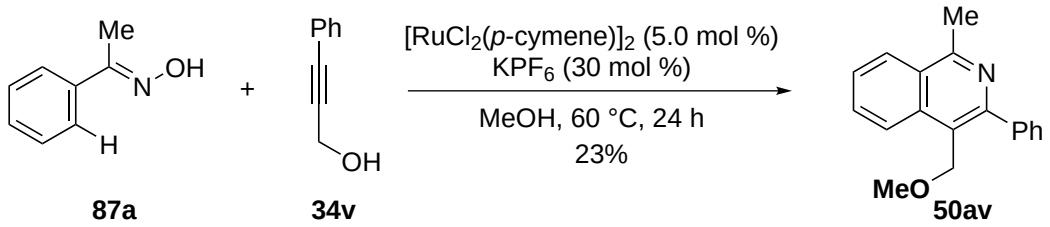
[a] Reaction conditions: **87** (1.0 equiv), **34** (2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), KPF_6 (30 mol %), MeOH (0.25 M), 60 °C, 24 h, N_2 (1 atm); [b] the other regio-isomer was also isolated in 6% yield; [c] the other regio-isomer was also isolated in 8% yield.

The reason for this high regioselectivity is not completely clear, further details will be discussed below. However, when 2-hexyne (**34u**) was used as the substrate, a 1:1-mixture of both regioisomers was obtained (Scheme 3.11). This result revealed that the catalyst is not able to distinguish between the two aliphatic side-chains of the alkyne, which show comparable electronic and steric properties. This result indicated the importance of electronic interaction between the ruthenium atom and the substituent on an alkyne moiety for the stabilization of intermediates. Such an interaction with the neighboring aryl substituent appeared to be rather efficient, but negligible in a case of aliphatic side chains with comparable electronic and steric properties.[112]



Scheme 3.11: Annulation of alkyne **34u** with oxime **87c**.

Another interesting effect was observed when alkyne **34v** was subjected to the reaction conditions (Scheme 3.12). In this special case methylation of the free OH-group takes place. This effect was only detected for the propargylic alcohol **34v** but not for **34m** and can be explained by coordination of the alkyne to the ruthenium-catalyst followed by an attack of methanol.



Scheme 3.12: Annulation of phenylpropargyl alcohol **34v**.

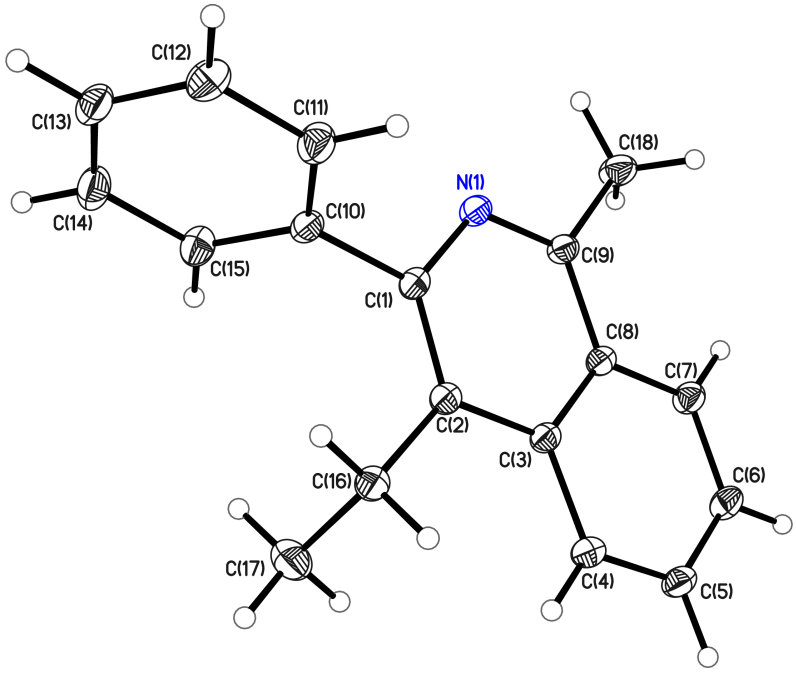


Figure 3.4: Crystal-structure of compound **50aj**.

In order to assign the structures of compounds **50ai**–**50av** to the correct regioisomers, NOE NMR-spectra or 2-dimensional NOESY-spectra were recorded for each product of Table 3.16. In addition, the structure of **50aj** was undoubtedly verified by X-ray structure analysis (Figure 3.4). The x-ray structure reveals the aromatic ring structure of the isoquinoline perfectly with bond lengths between 1.32 Å (N1–C9) and 1.43 Å (C8–C9). The phenyl-ring in position-3 avoids steric interaction with the ethyl-group in position 4 and is, at least in solid phase, distorted by nearly 180 °. **50aj** crystallizes in the monoclinic space-group $P2_1/c$.

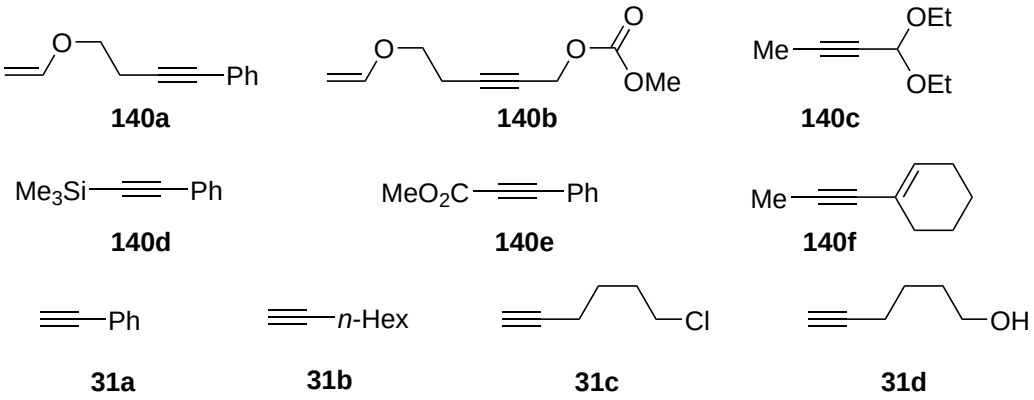
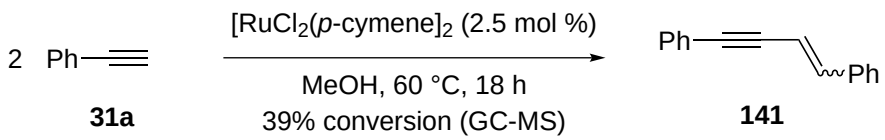


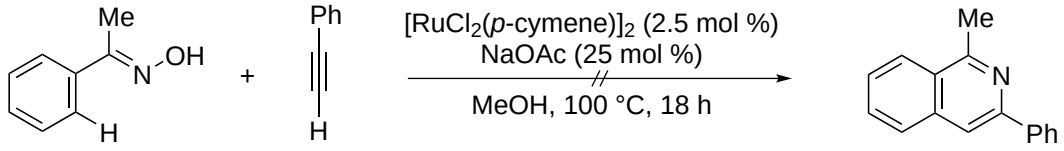
Figure 3.5: Unreactive alkynes.

Certain alkynes could not be converted to the corresponding isoquinolines. As shown in Scheme 3.5, enynes as well as alkynes with esters or TMS-groups directly attached to the triple bond did not furnish the desired products. Unfortunately, terminal alkynes also did not work, as they were prone to dimerization under the reaction conditions. As shown in Scheme 3.13, the ruthenium complex catalysed the addition of phenylacetylene (**31a**) to the triple bond of a second molecule of **31a**. Compound **141** was clearly identified by GC-MS and appeared to be a mixture of both *E* and *Z*-isomer, as determined by NMR-spectroscopy.[195, 196]



Scheme 3.13: Ruthenium-catalyzed "dimerization" of phenylacetylene **31a**.

It is also important to mention that a similar reaction was independently published by the group of *Jeganmohan*.[197, 198] The authors claimed that they could also convert terminal alkynes, including phenylacetylene **31a**, into the corresponding isoquinolines. However, several attemps to reproduce these results failed (Scheme 3.14).

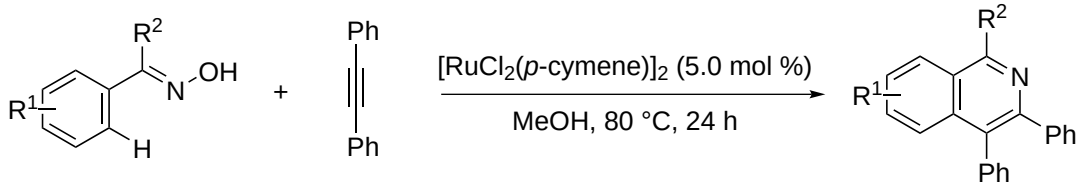


87a **31a** **50a**

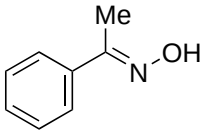
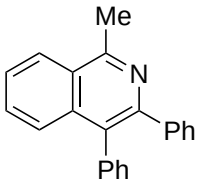
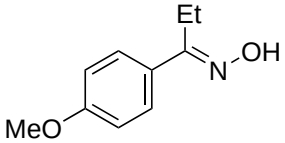
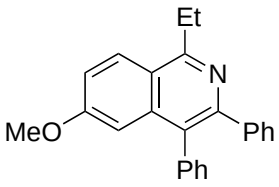
Scheme 3.14: Unsuccessful annulation of **31a** by **87a**.[197]

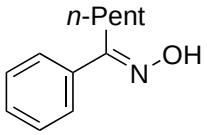
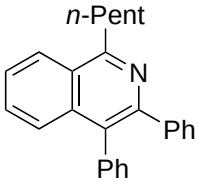
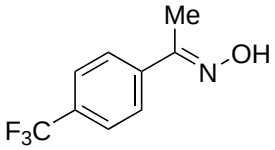
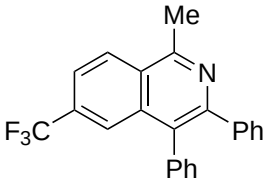
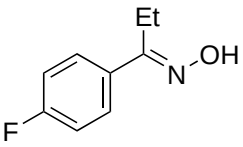
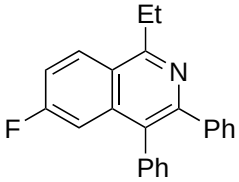
Finally, several experiments were conducted in the absence of KPF_6. As already shown in Table 3.12 (entry 16), at 60 °C the product **50aa** was obtained in 81% yield with (entry 8) and in 60% yield without KPF_6 (entry 16). At a slightly elevated reaction temperature (80 °C), oxime **87a** (Table 3.17, entry 1) and the electron-rich substrates **87j** and **87l** (Table 3.17, entries 2 and 3) showed essentially the same reactivity as at 60 °C in the presence of KPF_6 (Table 3.14, entries 9 and 11). With electron-deficient oximes, however, the yields were slightly reduced (Table 3.17, entries 4 and 5; *cf.* Table 3.14, entries 6 and 10). Nevertheless the reaction conditions without KPF_6 at elevated temperature also proved to be applicable for the synthesis of isoquinolines.

Table 3.17: Direct annulation of diphenylacetylene (**34a**) with oximes **87** scope without KPF_6.[a]



87 **34a** **50**

entry	oxime **87**	product **50**	isolated yield (%)
1	 **87a**	 **50aa**	63
2	 **87j**	 **50ja**	95

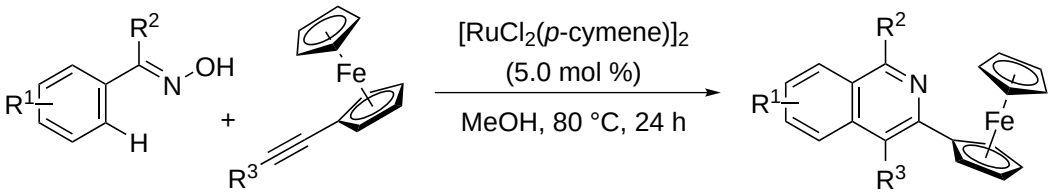
entry	oxime **87**	product **50**	isolated yield (%)
3	 **87l**	 **50la**	92
4	 **87g**	 **50ga**	56
5	 **87k**	 **50ka**	39

[a] Reaction conditions: **87** (1.0 equiv), **34a** (2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), MeOH (0.25 M), 80 °C, 24 h, N_2 (1 atm).

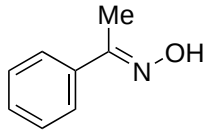
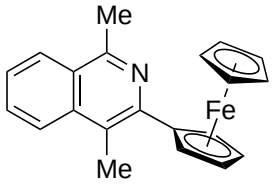
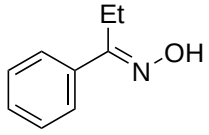
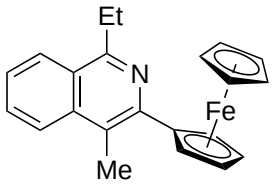
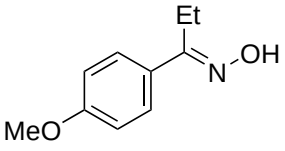
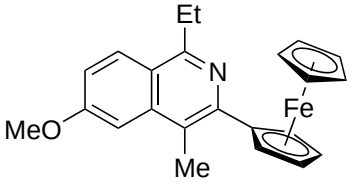
3.3.3 Direct Annulations of Ferrocenylalkynes with Oximes.

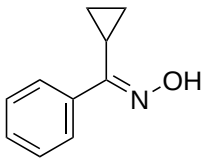
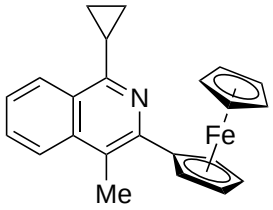
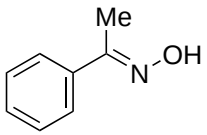
Ferrocenyl-substituted compounds are important precursors for chiral ligands in asymmetric catalysis and gained recent interest, for example, in material sciences due to their redox-active properties.[199–201] Moreover, ferrocenyl-moieties recently attracted some attraction as they have been utilized for modifying the bioactivity of peptides, steroids and oncological drugs.[202–206] Despite these advances, the introduction of redox-active ferrocenyl-units into complex molecules still remains a challenging task. As a consequence, it was decided to apply the newly developed ruthenium-catalyzed reaction for a straightforward synthesis of ferrocenyl-substituted isoquinolines, particularly because the corresponding ferrocenylalkynes **34w** and **34x** are easily accessible through modification of iodoferrocene and acetylferrocene.[207–209] The results are shown in Table 3.18.

Table 3.18: Direct annulation of ferrocenylalkynes **34w 34x** with oximes **87** - Scope.[a]



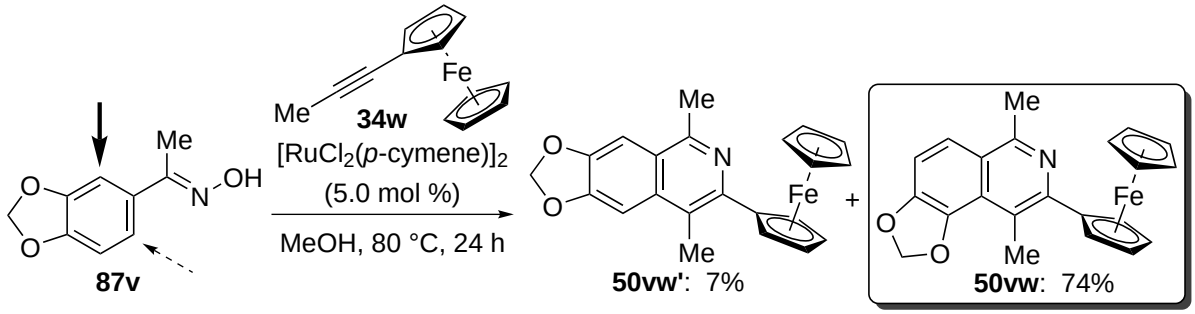
87 **34w** and **34x** **50**

entry	oxime **87**	R^3	product **140**	isolated yield (%)
1	 **87a**	Me	 **50aw**	58 (57)[b]
2	 **87i**	Me	 **50iw**	59
3	 **87j**	Me	 **50jw**	55

entry	oxime **87**	R^3	product **140**	isolated yield (%)
4	 **87w**	Me	 **50ww**	60
5	 **87a**	Ph	-	traces

[a] Reaction conditions: **87** (1.0 equiv), **34** (2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), MeOH (0.25 M), 80 °C, 24 h, N_2 (1 atm); [b] in the presence of KPF_6 (30 mol %), 60 °C.

The reaction between 1-propyn-1-ylferrocene (**34w**) and acetophenone oxime (**87a**) furnished the desired product **50aw** in 58% yield under the modified reaction conditions without KPF_6 (Table 3.18, entry 1). As the yield could not be improved by applying the original reaction conditions with KPF_6, all reactions were carried out under KPF_6-free conditions. Reactions performed with propiophenone oximes **87i** and **87j** as well as with the sterically more congested cyclopropyl-substituted oxime **87w** also furnished the desired product in moderate yields (Table 3.18, entries 2–4). However, when 2-ferrocenyl-phenylacetylene (**34x**) was used instead of 1-propyn-1-ylferrocene (**34w**), unfortunately only traces of the desired product **50ax** were detected (Table 3.18, entry 5). All examples with 1-propyn-1-ylferrocene (**34w**) in Table 3.18 illustrate the high regioselectivity of the annulation-reaction, which always provided the isoquinolines **50** with the aromatic ferrocene-substituent proximal to nitrogen and the aliphatic methyl-group in 4-position. This observation is in accordance with those one discussed above for annulations of alkyl-aryl-alkynes. When the *meta*-substituted oxime dioxolano-fused **87v** was reacted under these reaction conditions, the sterically-more hindered product **50vw** was formed preferentially (Scheme 3.15).

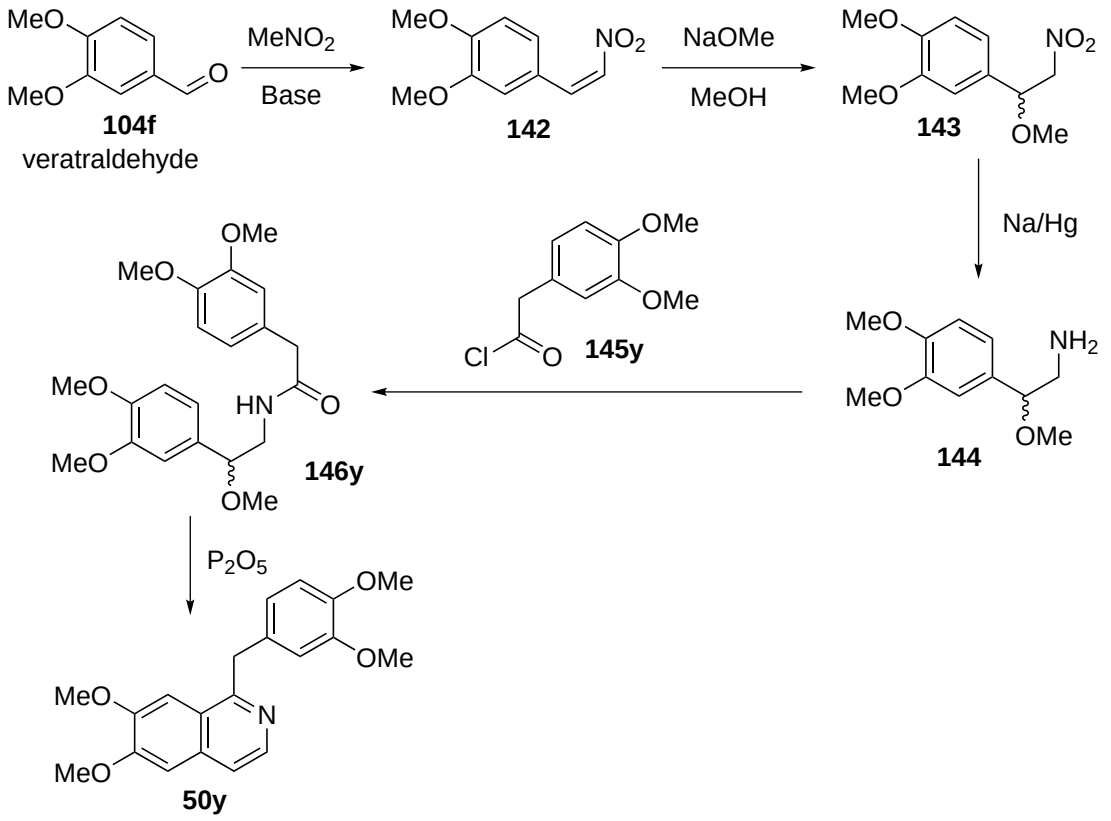


Scheme 3.15: Annulation of ferrocenylalkyne **87v** with oxime **50vw**.

This observation is in good agreement with the previous results (Schemes 3.7, 3.8 and 3.10, c) and confirms the secondary directing effect of the dioxole moiety. Overall, the described methodology proved to be a valuable tool for the synthesis of ferrocenyl-substituted isoquinolines. More experiments between ferrocenylalkynes **34w** and **34x** and oximes **87** were conducted by *C. Kuper* and exhibited comparable results.[210]

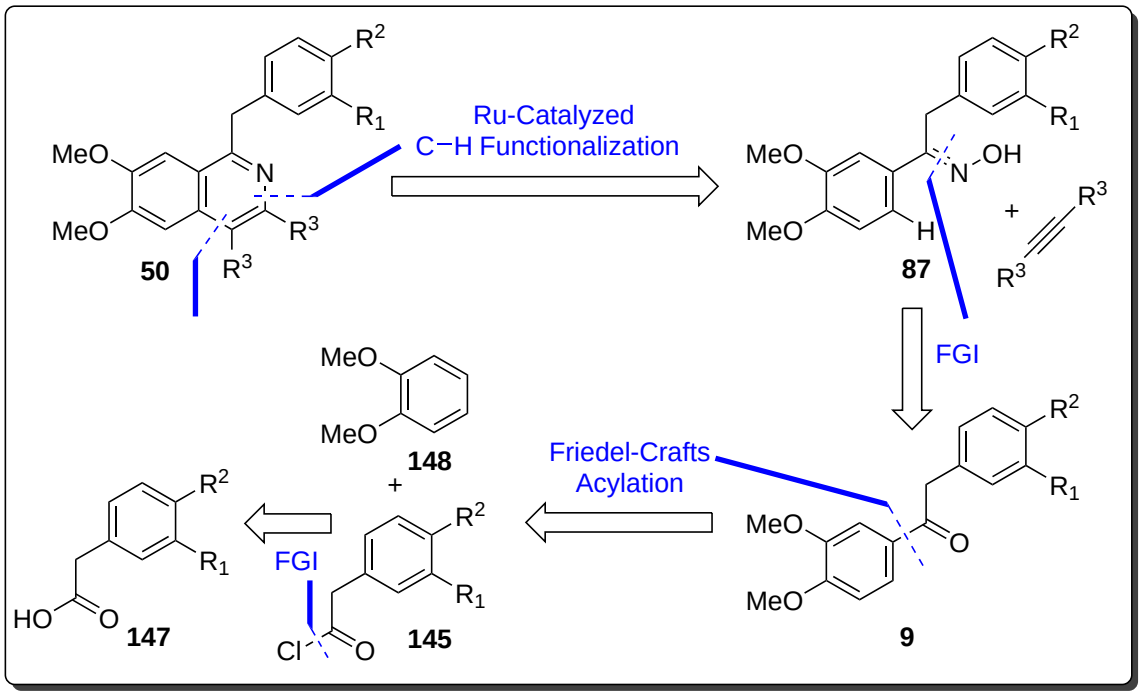
3.3.4 Synthesis of Isoquinolines Derived from Biologically Active Natural Products

Isoquinolines are important structural motifs in many biologically active natural products. The opiate papaverine and its synthetic analog moxaverine are used as vasodilators and as smooth muscle relaxants in many medicinal applications, *inter alia* in coronary artery bypass surgery and in treatment of erectile dysfunction.[211–214] Opium contains only 1% of papaverine, therefore papaverine is also obtained by total synthesis. Scheme 3.16 shows a traditional way of synthesizing papaverine (**50y**), starting from veratraldehyde (**104f**). After 4 steps the key intermediate, an amide **146y** is formed, which can be cyclized applying a *Bischler-Napieralski*-reaction.[2] However, this synthesis consists of several steps involving toxic chemicals like nitromethane and mercury amalgam.

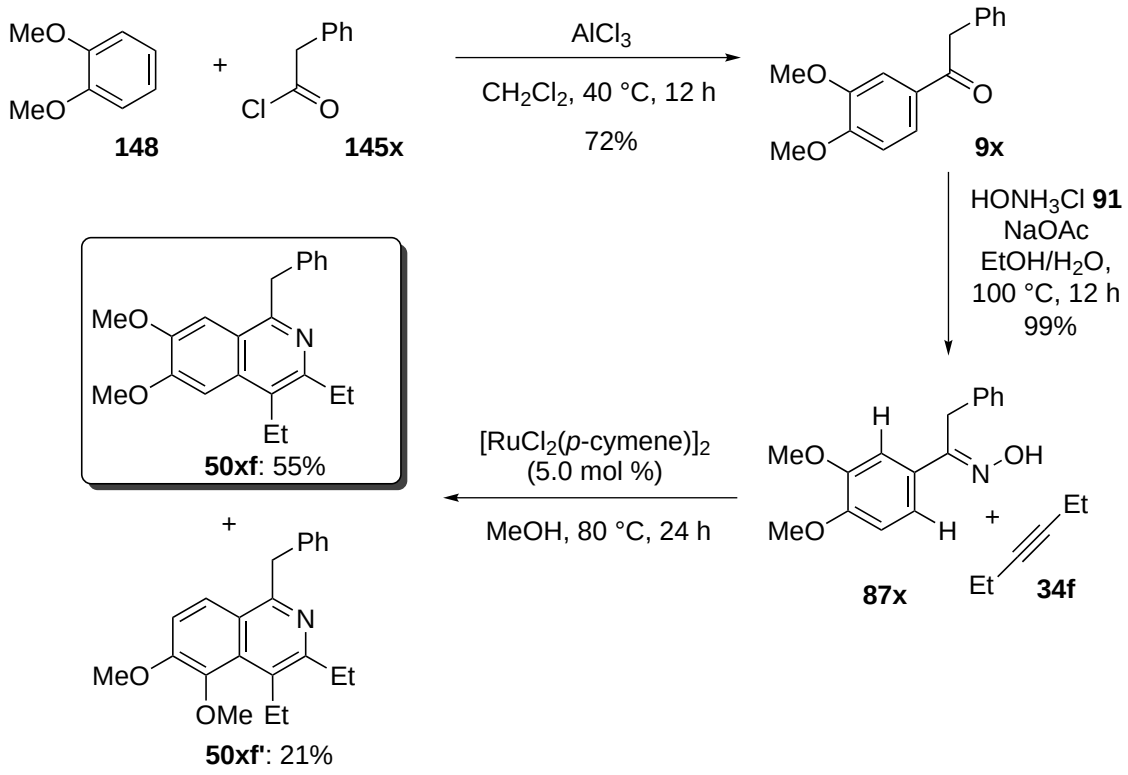


Scheme 3.16: A classic synthesis of papaverine (**50y**).

As a consequence, it was decided to apply the newly developed ruthenium-catalyzed annulation with oximes for the synthesis of isoquinolines derived from papaverine and moxaverine. Scheme 3.17 shows a very short and simple retrosynthetic analysis. Herein, the final product **50** is directly formed through the ruthenium-catalyzed C−H/N−O bond formation. After retrosynthetic disconnection, an oxime **87** is identified, which can be traced back to the corresponding ketone **9**. This ketone **9** can be easily prepared in a *Friedel-Crafts*-acylation of veratrole (**148**) with an acid chloride **145** derived from the corresponding phenylacetic acid **147**.

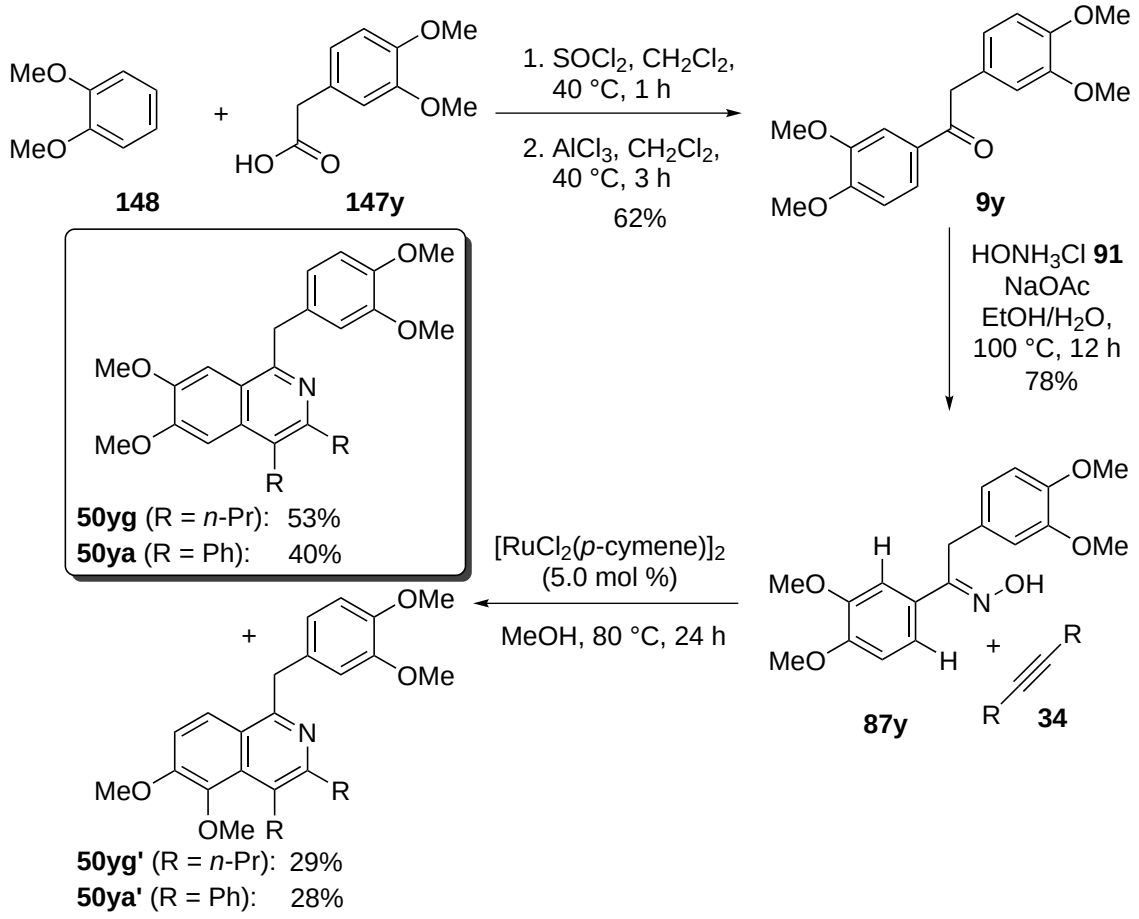


Scheme 3.17: Retrosynthetic analysis for the synthesis of papaverine- and moxaverine-derivatives **50**.



Scheme 3.18: Synthesis of 4-ethylmoxaverine **50xf**.

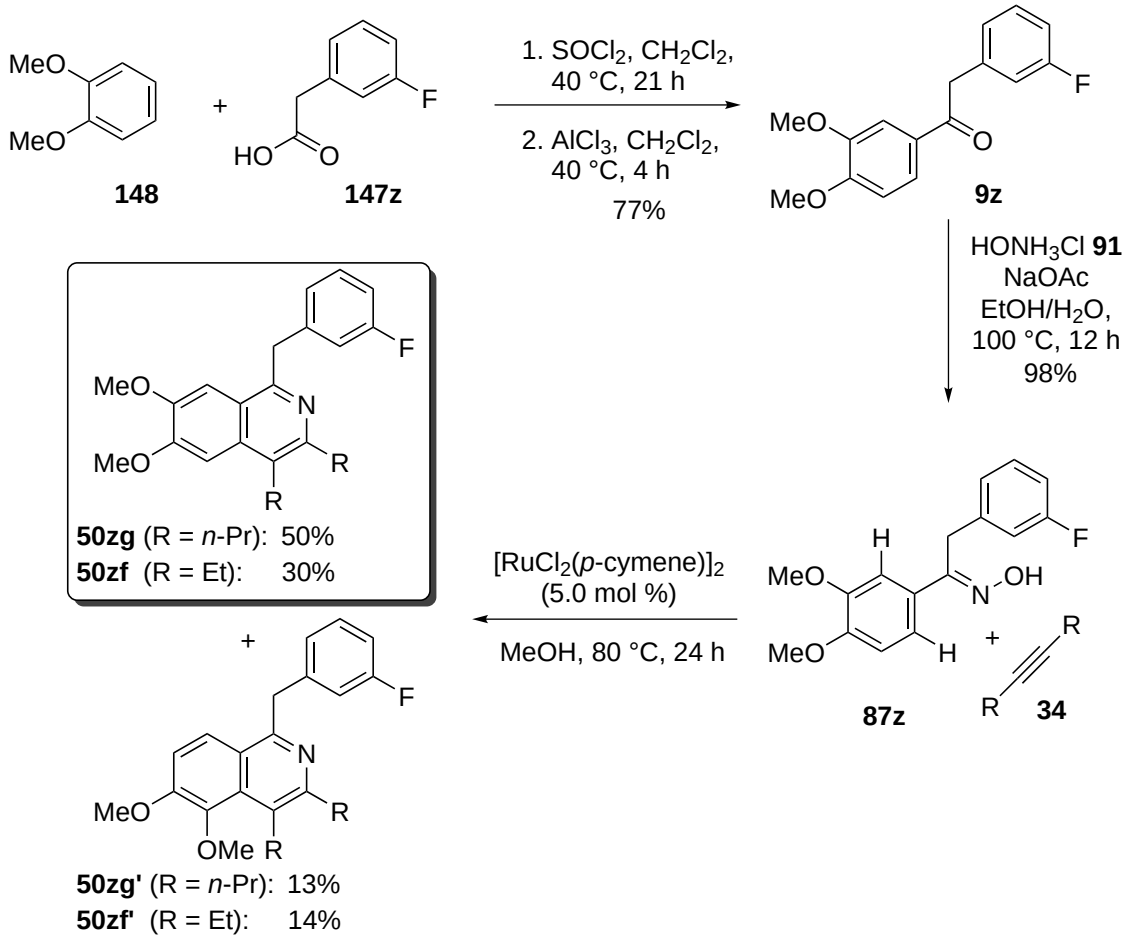
The synthesis of 4-ethylmoxaverine **50xf** is shown in Scheme 3.18. Veratrole (**148**) was reacted with phenyl acetic acid chloride (**145x**) to form ketone **9x**. The latter was then transformed to the corresponding oxime **87x** in quantitative yield. To select proper conditions for the annulation, several preliminary studies were conducted by *K. Dienst* and revealed that the reaction conditions without KPF_6 at elevated temperature proofed to be superior with regard to reactivity and selectivity.[215] The reaction afforded the 4-ethylmoxaverine **50xf** in 55% yield. Unfortunately, the other regioisomer was also formed in 21% yield. In analogy to the reaction with the 1,3-dioxolane-fused oxime **87v** (Scheme 3.10 c), the methoxy-group in *meta*-position acted as a directing group. However, the buttressing effect between the two methoxy-groups in the positions 3 and 4 resulted in increased steric demands compared to the 1,3-dioxolane moiety and, therefore, to the preferential formation of the desired product **50xf**.[39, 193, 216]



Scheme 3.19: Synthesis of 3,4-di-*n*-propylpapaverine **50yg** and 3,4-diphenylpapaverine **50ya**.

The synthesis of 3,4-di-*n*-propylpapaverine **50yg** and 3,4-diphenylpapaverine **50ya** was slightly modified (Scheme 3.19), as the 3,4-dimethoxyphenyl acetic acid chloride is not commercially available and was thus prepared *in situ*. Formation of the oxime **87y** and the ruthenium-catalyzed annulation were performed under the same conditions as already used for the synthesis of 4-ethylmoxaverine (**50xf**). Also in these two cases, 3,4-di-*n*-propylpapaverine **50yg** and 3,4-diphenylpapaverine **50ya** were formed as the main-products, even though the other regioi-

somers **50yg'** and **50ya'** were formed as well in 29% and 28% yield, respectively. The same approach was also used to synthesize fluorinated analogues of papaverine (Scheme 3.20), keeping in mind that fluorinated pharmaceuticals are getting more important, due to their physiological properties.[217] The synthesis followed the same route as discussed above and yielded the fluorinated isoquinolines **50zg** and **50zf** in moderate yields. Again, the alternative regioisomers **50zg'** and **50zf'** were also formed.

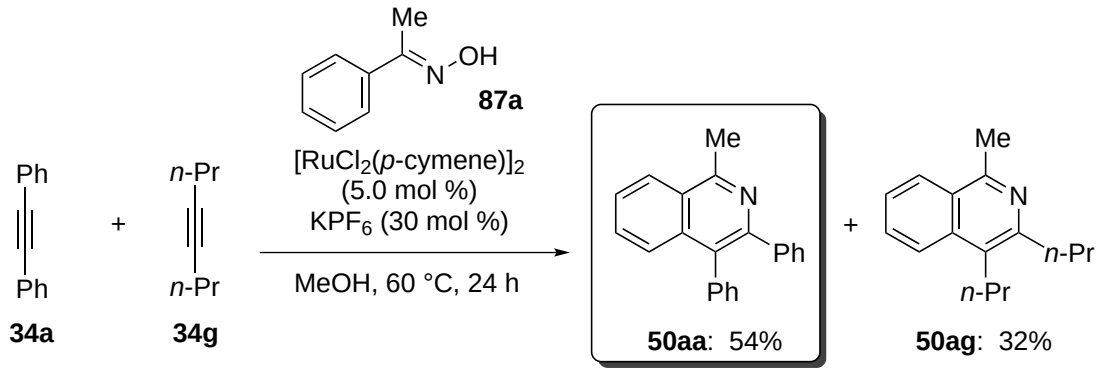


Scheme 3.20: Synthesis of fluorinated analogues of papaverine.

In summary, the C−H activation approach was a powerful tool for the short synthesis of diversely substituted papaverine-derivatives using readily available starting materials, in spite of the formation of byproducts in significant amounts. However, the parent naturally occurring compounds themselves were not accessible through this procedure since the terminal and TMS-protected alkynes did not undergo annulations under the reaction conditions.

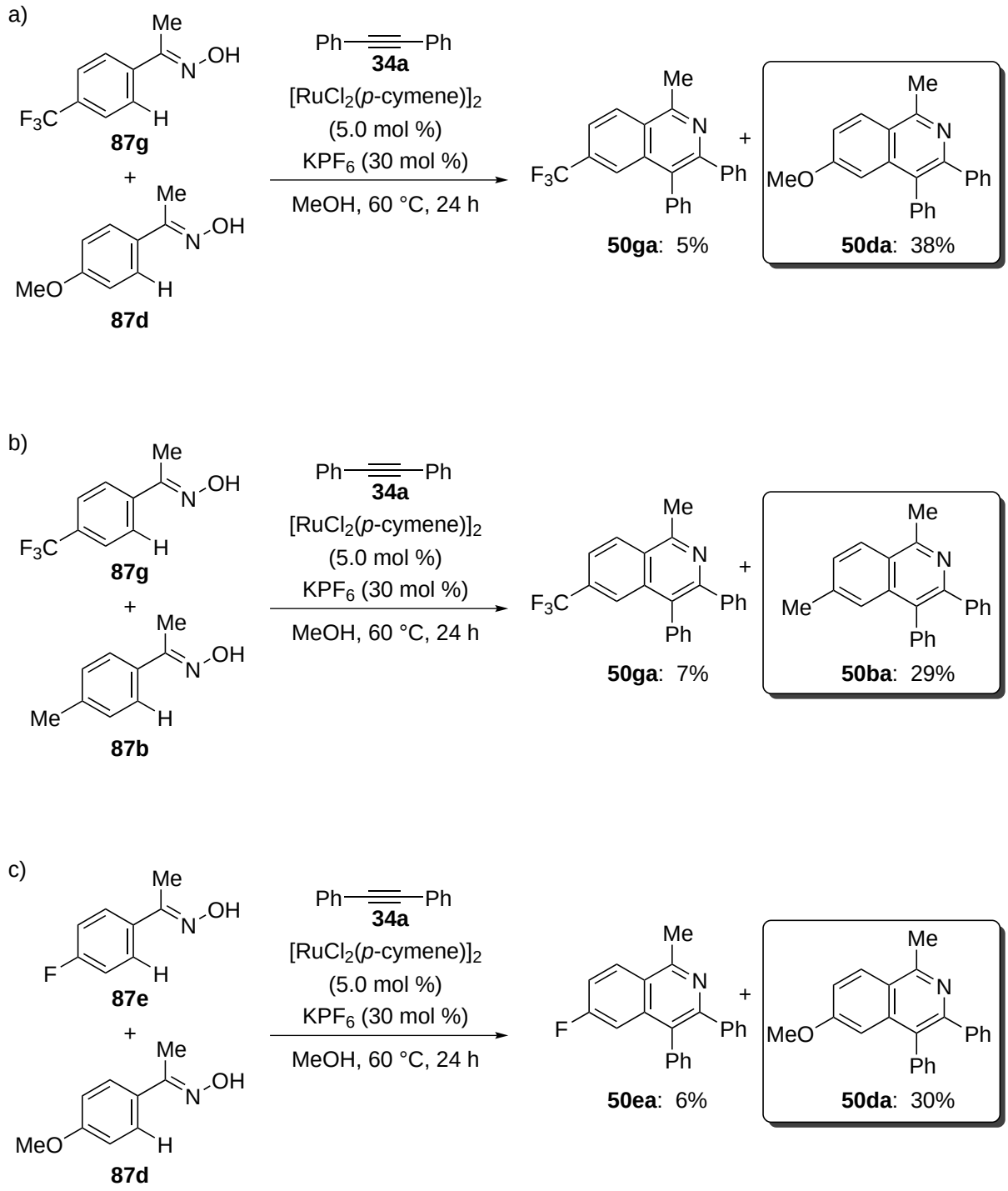
3.3.5 Direct Annulations of Alkynes with Oximes: Mechanistical Studies

Several competition experiments were conducted with the aim to gain more insight into the reaction mechanism. To begin with, oxime **87a** was reacted with 4.0 equivalents of diphenylacetylene (**34a**) and 4.0 equivalents of 4-octyne (**34g**) (Scheme 3.21). After 24 h, both products **50aa** and **50ag** were isolated in 54% and 32% yield, respectively. This result indicated that the diaryl-alkynes reacted faster than the dialkylsubstituted ones. Most probably, this was a consequence of a better ruthenium-alkyne coordination in the former case as well as of an additional stabilization in the intermediates through conjugation between the ruthenium-atom and the π-systems of the aromatic ring. The same effect could also be responsible for the high regioselectivity observed in the reaction with unsymmetrical alkynes.



Scheme 3.21: Competition experiment with alkynes **34a** and **34g**.

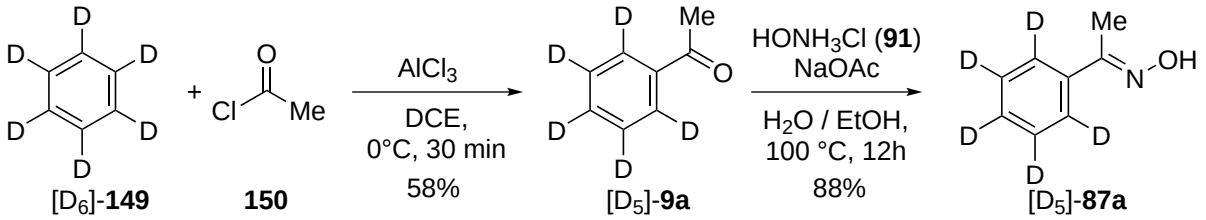
The results of the competition experiments between electron-rich and electron-deficient oximes are presented in Scheme 3.22. The competition between *p*-(trifluoromethyl)acetophenone oxime (**87g**) and *p*-methoxyacetophenone oxime (**87d**), obviously indicated that the electron-rich oxime reacted faster (Scheme 3.22 a). Also, in the second reaction between *p*-methylacetophenone oxime (**87b**) and *p*-(trifluoromethyl)acetophenone oxime (**87g**), a significantly larger amount of the electron-rich isoquinoline was formed (Scheme 3.22 b). Finally, the third experiment between *p*-fluoroacetophenone oxime (**87e**) and *p*-methoxyacetophenone oxime (**87d**) was conducted and revealed the same selectivity (Scheme 3.22 c). All these experiments gave a significantly reduced yields, which resulted from the inverse ratio of the alkyne to the oximes. Nevertheless, these experiments clearly showed that electron-rich oximes reacted faster than electron-deficient ones.



Scheme 3.22: Competition experiments with oximes **87b**, **87d**, **87e** and **87g**.

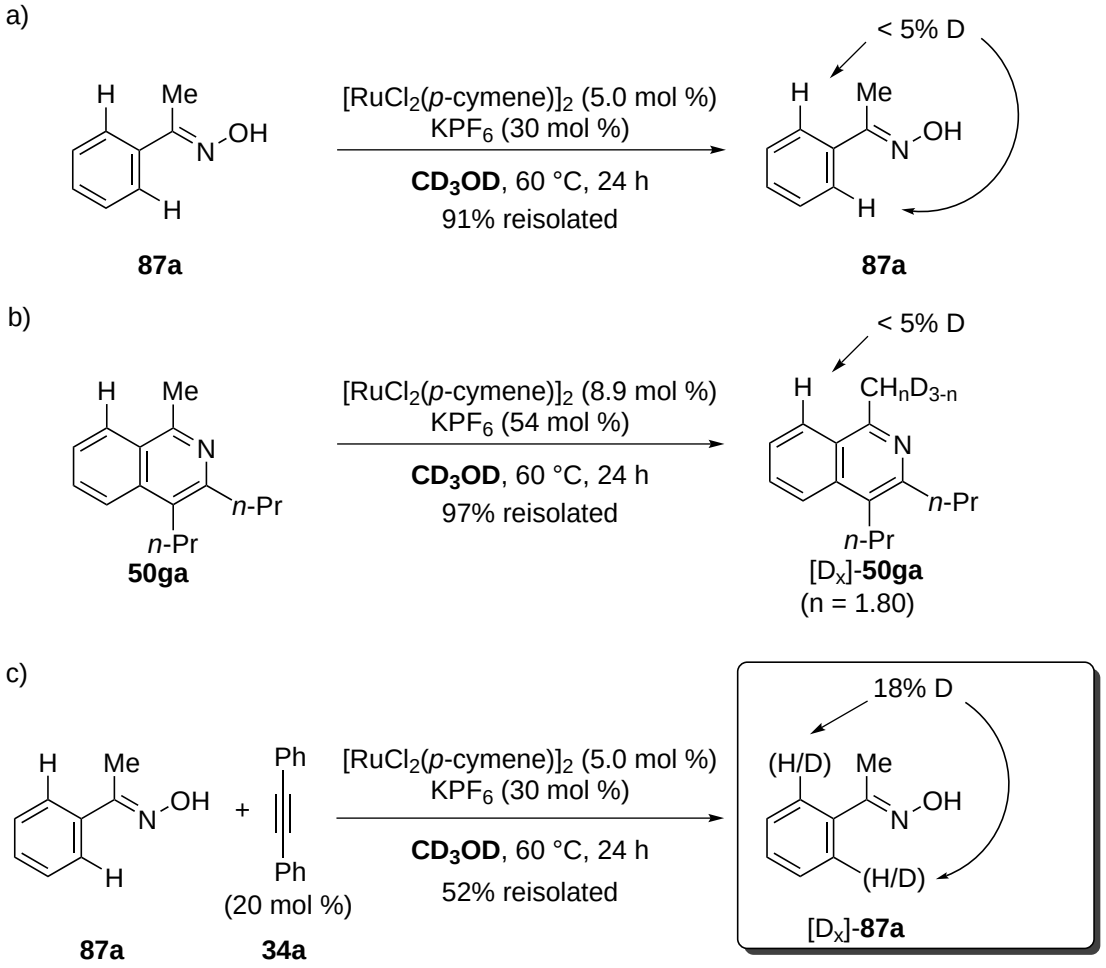
To gain further insight into the reaction mechanism, experiments with isotopically labelled substrates were conducted.[218, 219] As C−H and C−D bonds differ in their bond strenght and energy, this approach is of great importance for determining the kinetics of reactions involving C−H bond cleavages.[220] Most of the experiments presented herein are perfomed with 4-octyne (**34g**) rather than with diphenylacetylene (**34a**), in order to avoid interference with the aromatic proton-signals in the ^{1}H NMR-spectra.

With regard to this, the deuterated [D_5]-acetophenone oxime [D_5]-**87a** was synthesized. [D_5]-**87a** was obtained after a short two-step synthesis starting with the *Friedel-Crafts*-acylation of [D_5]-benzene as the first step followed by the oxime synthesis as the second step (Scheme 3.23).



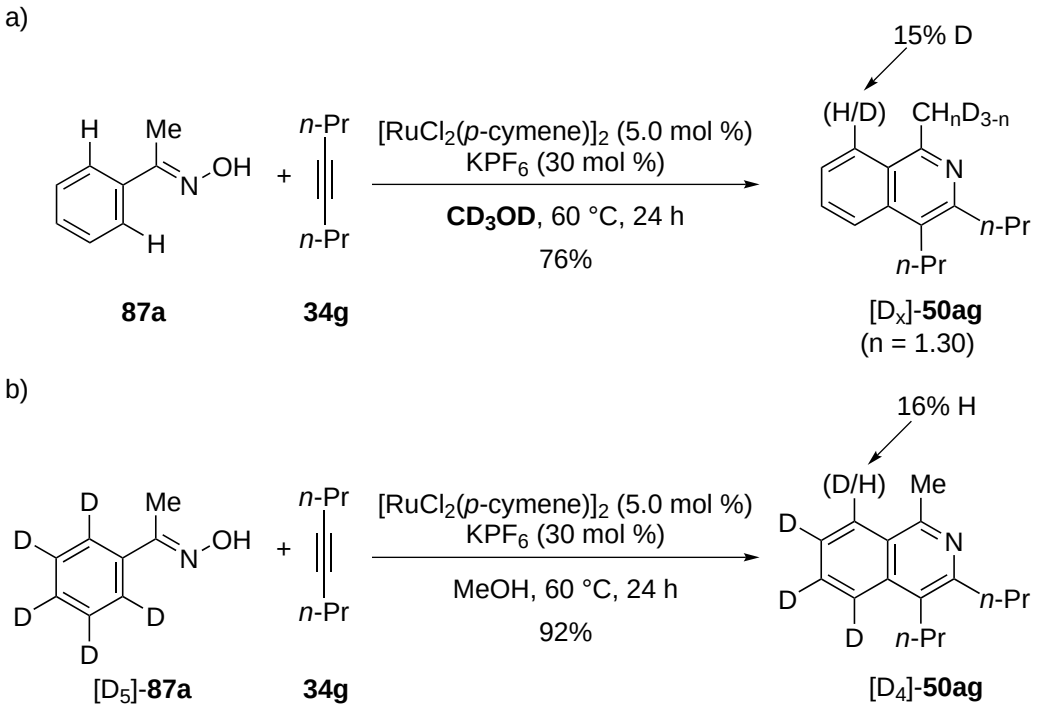
Scheme 3.23: Synthesis of [D_5]-acetophenone oxime [D_5]-**87a**.

Scheme 3.24 illustrates some experiments, that were performed in [D_4]-MeOH as the solvent. For instance, if the oxime **87a** was solely stirred in [D_4]-MeOH under the optimized reaction conditions without alkyne, no H/D-exchange occured in the *ortho*-position of the oxime **87a** (Scheme 3.24 a). The same observation was made when the isoquinoline **50ag** was subjected to the reaction conditions (Scheme 3.24 b).



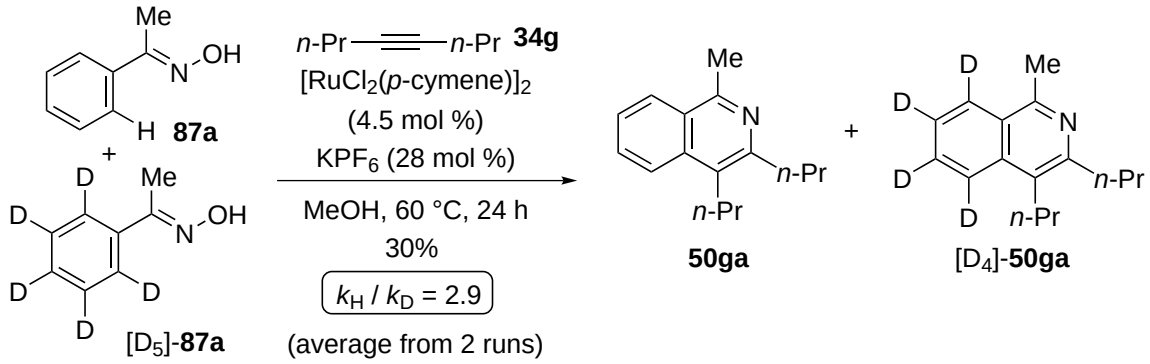
Scheme 3.24: Mechanistic experiments with [D_4]-MeOH.

Even though there was no deuterium incorporation in the 8-position of the isoquinoline, H/D-scrambling was observed for the methyl-group in position 1. This is not surprising, as 1-methyl-substituted isoquinolines are prone for enolization.[1] However, if the oxime was stirred in the presence of the catalyst and with substoichiometric amounts of the alkyne **34a** in [D_4]-MeOH, a significant deuterium-incorporation of 18% was observed in the *ortho*-position of the reisolated oxime (Scheme 3.24 c). These observations indicated that the C−H bond cleavage in the oxime can only occur in the presence of the alkyne. Most likely, the alkyne coordinates to the ruthenium catalyst before the oxime comes into action, i. e. the catalytically-active ruthenium species contains a precoordinated alkyne. Another conclusion from the latter experiment would be that the C−H bond cleavage step might be reversible, as there is significant H/D scrambling in the *ortho*-position of the oxime. In order to verify this assumption, two more experiments were performed (Scheme 3.25). When acetophenone oxime (**87a**) was reacted with stoechiometric amounts of 4-octyne (**34g**) in [D_4]-MeOH, the product [D_x]-**50ag** was obtained in 76% yield and a deuterium incorporation of 15% was observed in position 8 of [D_x]-**50ag** (Scheme 3.25 a). As presented before in Scheme 3.24 b, also in this reaction an enolization of the isoquinoline led to H/D-scrambling in the methyl-group at position 1. A quite similar experiment was performed with the deuterated acetophenone oxime [D_5]-**87g**, but this time in nondeuterated methanol (Scheme 3.25 b). This reaction afforded a deuterated isoquinoline [D_4]-**50ag** with 16% hydrogen-incorporation in position 8. In conclusion, the two experiments in scheme 3.25 showed indeed that the C−H bond cleavage is most likely reversibel and thus not the turnover-determining step of the catalytic cycle.



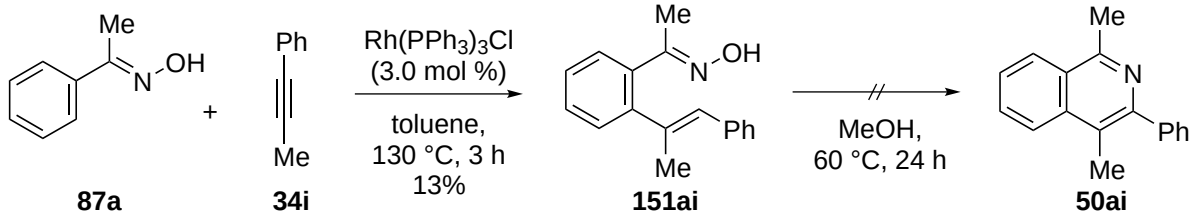
Scheme 3.25: Mechanistic experiments with oximes **87a** and [D_5]-**87a**.

Finally, a competition experiment between **87a** and [D_5]-**87a** revealed a significant kinetic isotopic effect (KIE) (Scheme 3.26). Herein the nondeuterated product is formed 2.9 times faster than the deuterated product. This result indicated the C−H bond cleavage step to be irreversible and seemed to be in contradiction with the observations discussed above. However, extensive kinetic studies performed by *D. Zell* revealed an induction-period, which can be traced back to a kinetically relevant equilibrium between the coordinated and the non-coordinated oximes directly before the reversible C−H bond clevage.[221]



Scheme 3.26: Competition-experiment between oximes **87a** and oximes [D_5]-**87a**.

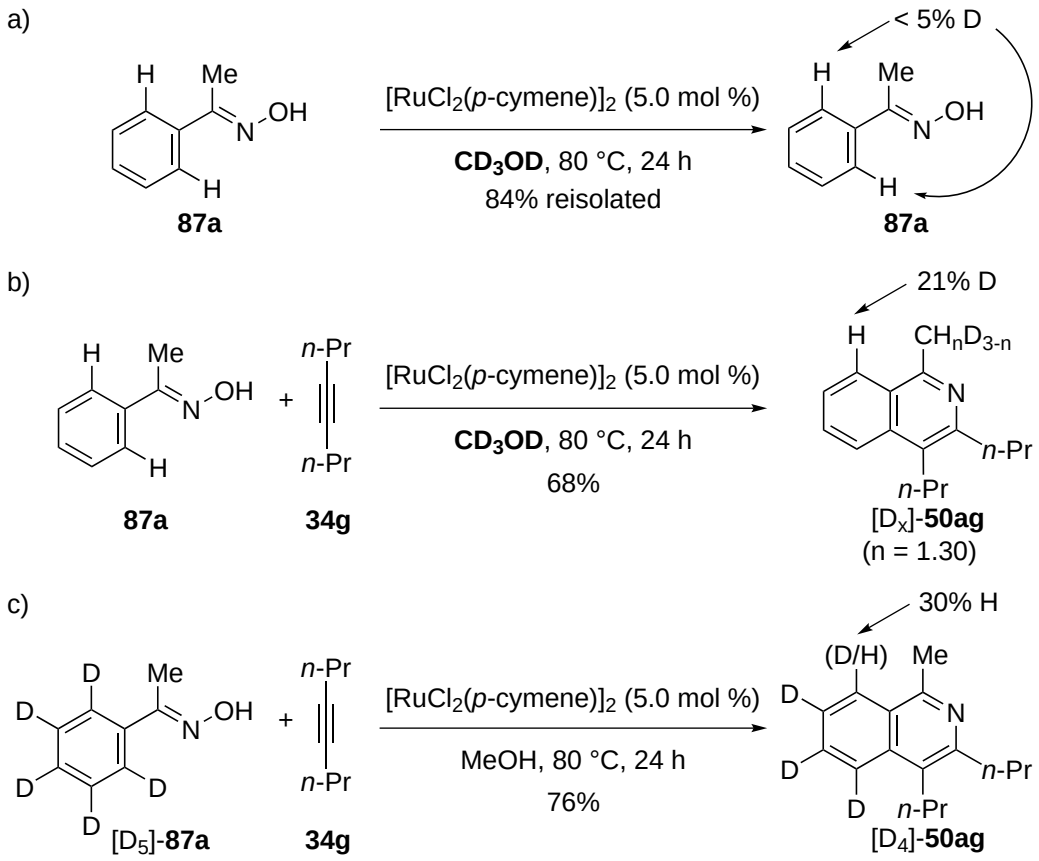
Another experiment was performed to test whether the final cyclization-step, which furnishes the isoquinoline, involves a thermal electrocyclization (Scheme 3.27). In the first step, the alkyne **34i** was hydroarylated with oxime **87a** employing the *Wilkinson*-catalyst.[127] The alkenylated oxime **151ai** was then heated in methanol for 24 h to see, if the cyclization can take place without the ruthenium-catalyst, but it turned out, that this what not the case. This result and the fact, that the uncyclized intermediates were never isolated in any of the above mentioned reactions, led to the conclusion, that the final C−N bond forming reductive elimination is part of the catalytic cycle.



Scheme 3.27: Checking the possibility of an electrocyclic reaction.

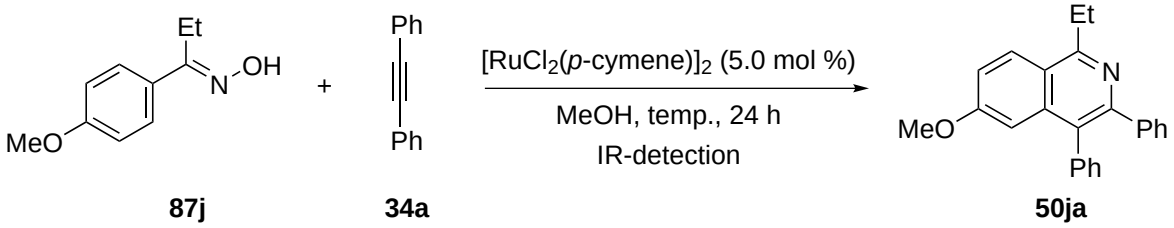
As some reactions were performed without KPF_6 and at elevated temperature, several additional labeling-studies were conducted under this modified reaction conditions (Scheme 3.28). Once again, no H/D-scrambling in the *ortho*-position took place without addition of the alkyne (Scheme 3.28 a). When the oximes **87a** or [D_5]-**87a** were treated with 4-octyne **34g** in [D_4]-MeOH and non-deuterated MeOH, respectivly, deuterium-incorporation did occur (Schemes 3.28 b and c).

As a consequence, it can be assumed, that the reactions without KPF_6 followed a similar mechanism compared to the one performed in the presence of KPF_6.



Scheme 3.28: H/D-exchange-experiments without KPF_6.

Additional information was gained from kinetic reaction-profiles of the reaction of oxime **87j** with diphenylacetylene (**34a**), which were recorded under different conditions using *in situ* IR technology (Figure 3.6). Oxime **87j** was chosen for these measurements, because of its high reactivity. Figure 3.7 shows the formation of the product **50ja** as a function of the time. The y-axis shows the relative intensity of the peak at 1622 cm^{-1} compared to the baseline. The diagrams of the annulations in the presence of KPF_6 at 60 °C and without additive at 80 °C showed, that both transformations were almost finished after 11 and 7 h, respectively. On the other hand, the reaction without KPF_6 at 60 °C was still not completed even after 24 h.



Scheme 3.29: Annulation of alkyne **34a** with oxime **87j** under IR monitoring.

Figure 3.6: Reaction setup using *in situ* IR Technology.

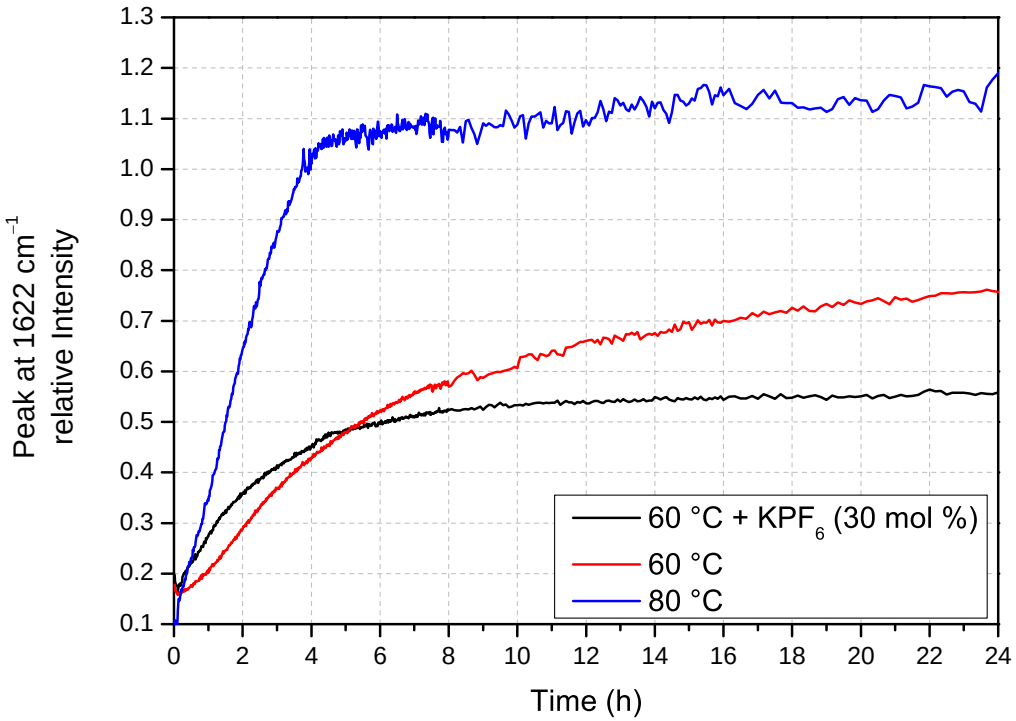
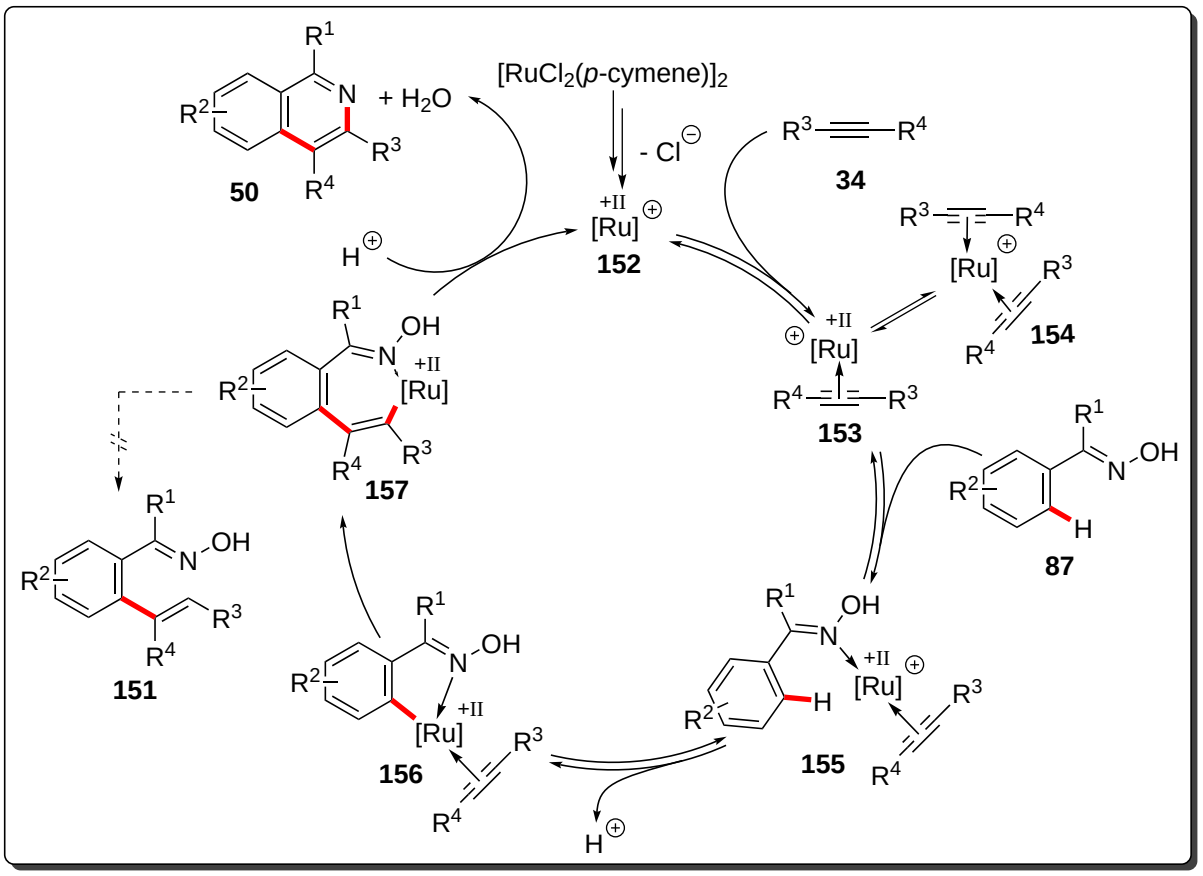


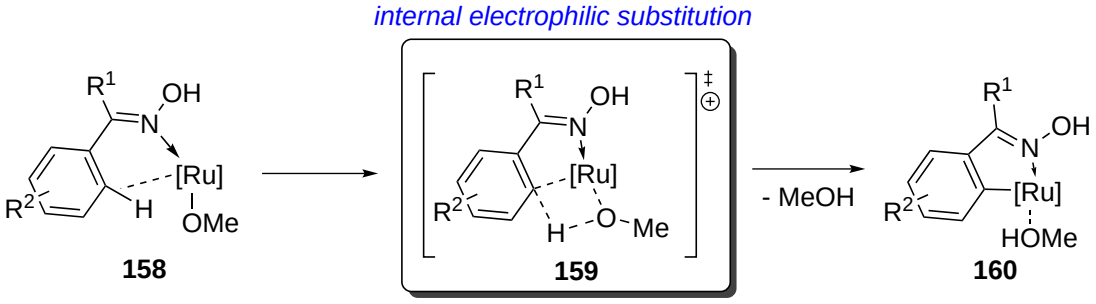
Figure 3.7: Kinetic profiles for the reaction of alkyne **34a** with oxime **87j**.

Summarizing the information, a reaction mechanism can be ultimatelly proposed for the ruthenium-catalyzed alkyne annulation (Scheme 3.30). At first, the catalytically-active cationic ruthenium species **152** is formed by abstraction of one chlorine-ligand assisted by KPF_6. The next step is the coordination of the alkyne **34**, which occurs most likely reversibly. After this, the oxime **87** reversibly coordinates to the ruthenium-alkyne complex **153**. Mechanistic studies conducted by *D. Zell* also revelead, that an increased concentration of the alkyne **34** leads to a bis-alkyne complex **154**, which acts as a resting state and thus slows down the reaction.[221] The nitrogen atom of the oxime directs the ruthenium to the *ortho*-position of the arene, the complex **155** then undergoes cyclometalation to yield **156**. This step is also reversible as indicated by the previously discussed H/D-exchange experiments. After insertion of the alkyne, the seven-membered ruthenacycle **157** is formed, which, in turn, dissociates into the product **50** and the cationic-ruthenium-species **152**. The cationic complex **152** can then undergo another catalytic cycle. As mentioned before the alkenylated oxime **151** was never isolated. This indicates that the last step is a very fast process. The observed KIE of about 3, can be reasoned by saturation kinetics connected to the cyclometalated species **156**. Thus, the migratory insertion of the alkyne into the ruthenium-carbon bond is, presumably, the turnover-determining step.[220]



Scheme 3.30: Mechanism of the ruthenium-catalyzed synthesis of isoquinolines.

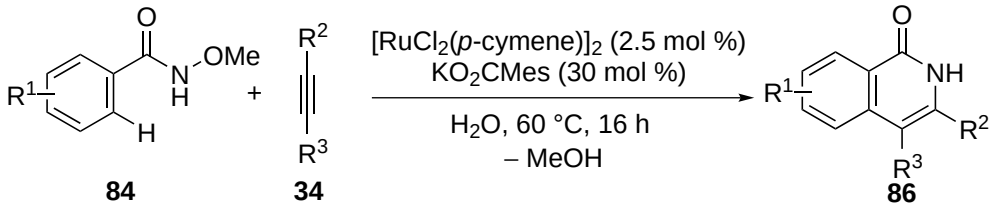
From several different transition states proposed for the working mode of metal-catalyzed C−H activation and discussed above in Chapter 1.1, an electrophilic aromatic substitution mechanism appears to be appropriate at first sight, due to the cationic nature of the catalytically active ruthenium-species.[14, 15, 19] The observed KIE of about 3 is, however, too high to support an S_EAr-type mechanism.[219] Therefore it is more likely that the C−H bond activation step proceeds through base-assisted cyclometalation, in which one coordination-site of the ruthenium is first occupied by a methanolate. The proton is then abstracted *via* a 4-membered transition-state **159** by the methanolate (Scheme 3.31). The latter proposal is similar to the internal electrophilic substitution (IES) mechanism described by *Goddard III.*[26, 27]



Scheme 3.31: Possible transition state **159** for the C−H activation.

3.4 Ruthenium-Catalyzed Synthesis of Ferrocenyl-Substituted Isoquinolones through Direct Annulations with *N*-Methoxybenzamides

The idea for the ruthenium-catalyzed synthesis of ferrocenyl-substituted isoquinolones **86** arose from a reaction, which was priorly developed by *S. Fenner* (Scheme 3.32).[124]

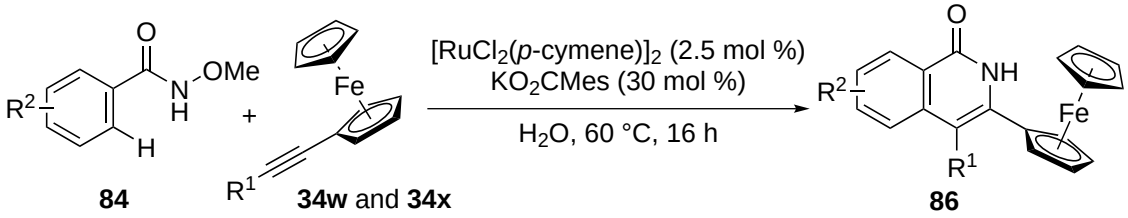


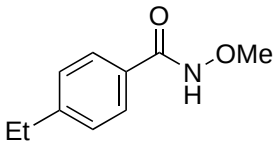
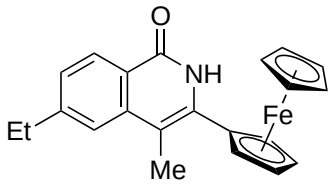
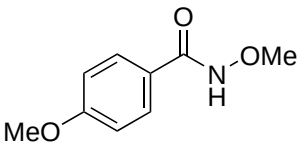
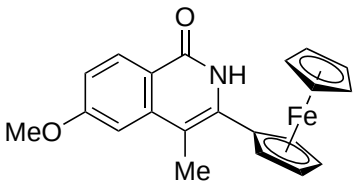
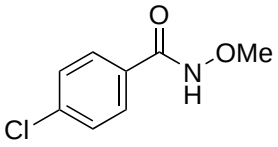
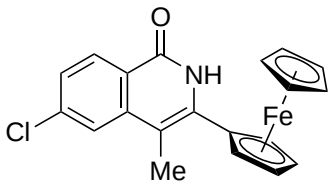
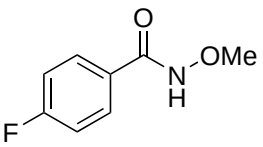
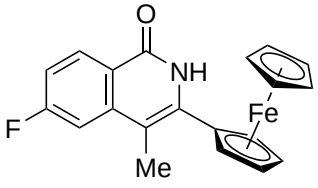
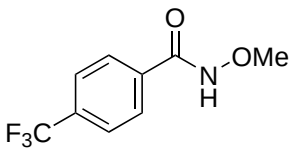
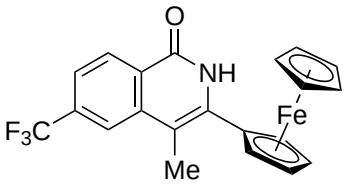
Scheme 3.32: Ruthenium-catalyzed synthesis of isoquinolones **86**.

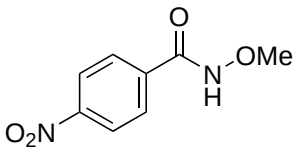
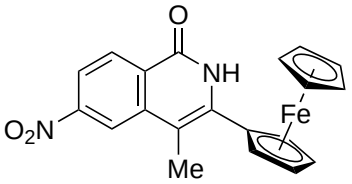
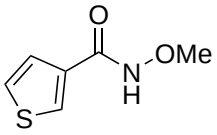
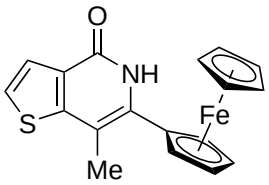
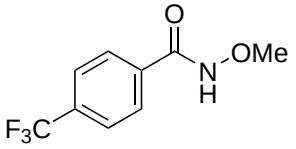
As the annulation-reaction with *N*-methoxybenzamides **84** proceeded smoothly without the need of an external oxidant, it appeared worthwhile to check, if the annulation of the previously employed redox-active ferrocenyl-substituted alkyne **34w** was also possible under the conditions shown in Scheme 3.32. Some initial experiments performed by *C. Kuper* indicated,[210] that it was not necessary to modify the original reaction conditions. The scope for this reaction is shown in Table 3.19.

These reactions gave surprisingly good results. The yields were higher compared to those obtained with oximes (Table 3.18). The electron-rich substrates **84a** and **84b**, for instance, gave the desired isoquinolones **86aw** and **86bw** with 80% and 78% yield, respectively (Table 3.19, entries 1 and 2). Also halogen-substituted *N*-methoxybenzamides **84c** and **84d** furnished the ferrocenyl-substituted isoquinolones **86cw** and **86dw** in good to very good yield (Table 3.19, entries 3 and 4). Excellent yields were obtained when electron-deficient substrates **84e** and **84f** were used (Table 3.19 entries 5 and 6). Moreover, it was also possible to employ *N*-methoxythiophene-3-carboxamide (**84g**) under the reaction conditions (Table 3.19, entry 7). With this substrate, the functionalization regioselectivly occurred at the more C−H acidic bond in position 2. As in the annulation with oximes (Table 3.18, entry 5), the reaction with 2-ferrocenyl-phenylacetylene (**34x**) did not yield the desired product (Table 3.19, entry 8).

Table 3.19: Scope of direct annulations of ferrocenylalkynes **34w** and **34x** with *N*-methoxybenzamides **84**.[a]



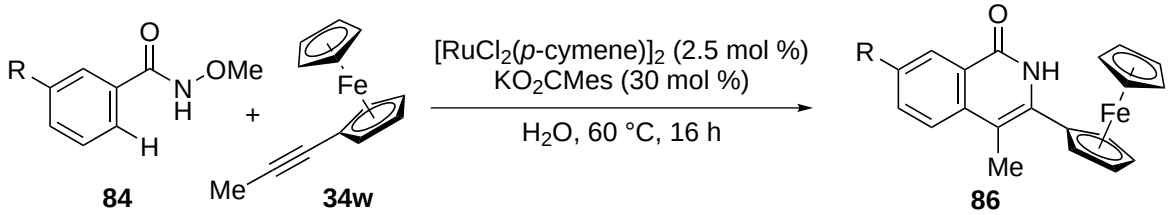
entry	benzamide **84**	R^1	product **86**	isolated yield (%)
1	 **84a**	Me	 **86aw**	80
2	 **84b**	Me	 **86bw**	78
3	 **84c**	Me	 **86cw**	60
4	 **84d**	Me	 **86dw**	88
5	 **84e**	Me	 **86ew**	89

entry	benzamide **84**	R^1	product **86**	yield (%)
6	 **84f**	Me	 **86fw**	84
7	 **84g**	Me	 **86gw**	78
8	 **84e**	Ph	-	-

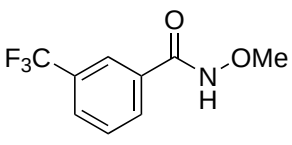
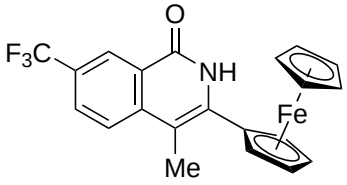
[a] Reaction conditions: **84** (1.0 equiv), **34** (2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), KO_2CMes (30 mol %), H_2O (0.25 M), 60 °C, 16 h, N_2 (1 atm).

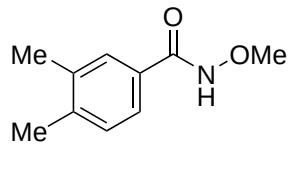
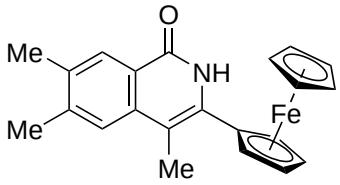
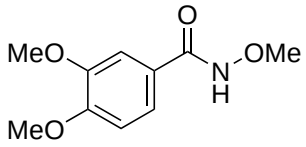
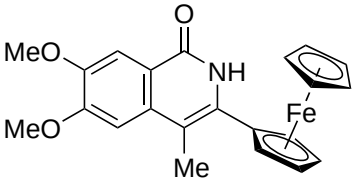
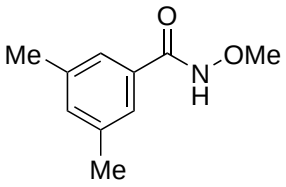
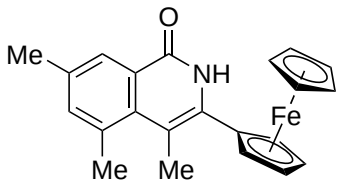
In addition to the results shown in Table 3.19, another set of experiments was based on *N*-methoxybenzamides with substituents in the *meta*-position (Table 3.20).

Table 3.20: Direct annulation of ferrocenylalkyne **34w** with *meta*-substituted benzamides **84**.[a]



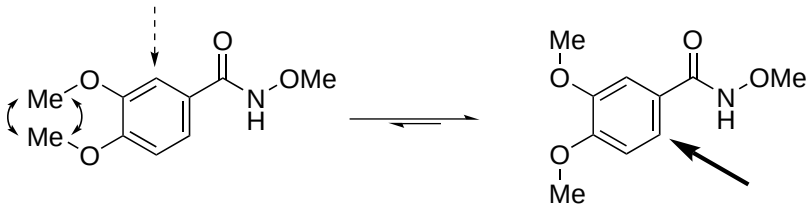
84 **34w** **86**

entry	benzamide **84**	product **86**	isolated yield (%)
1	 **84h**	 **86hw**	86

entry	benzamide **84**	product **86**	isolated yield (%)
2	 **84i**	 **86iw**	83
3	 **84j**	 **86jw**	46[b]
4	 **84k**	 **86kw**	37

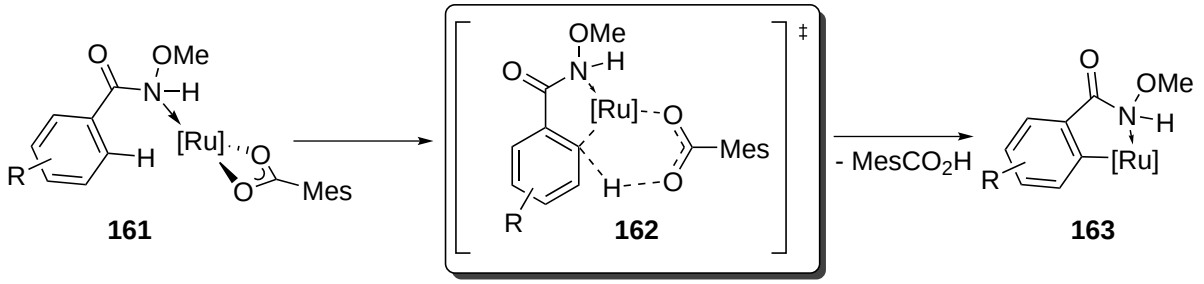
[a] Reaction conditions: **84** (1.0 equiv), **34** (2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), KO_2CMes (30 mol %), H_2O (0.25 M), 60 °C, 16 h. N_2 (1 atm); [b] The other 5,6-dimethoxy-substituted isomer was also isolated in 6% yield.

Entries 1 and 2 in Table 3.20 show that electron-deficient as well as electron-rich substrates (**84h** and **84i**) were functionalized at the sterically-less hindered position. The corresponding products **86hw** and **86iw** were obtained in excellent yields. *N*,3,4-Trimethoxybenzamide (**84j**) gave a reduced yield of 46% (Table 3.20 entry 3). Notwithstanding that the methoxy-group in the *meta*-position can act as a secondary directing group. Once again, the buttressing effect between the two methoxy-groups in positions 3 and 4 led to an increased steric demand (Scheme 3.33), that inhibited the secondary directing effect.[39, 193] When both *meta*-positions were blocked with non-directing substituents, the yield was also decreased. The latter can be explained by the increased steric demand in the transition state (Table 3.20, entry 4).



Scheme 3.33: The buttressing effect between the two methoxy-groups.

While no mechanistic investigations were conducted, previous studies revealed the need of carboxylate additives.[100, 124, 125] Therefore, one can assume a six-membered carboxylate-assisted transition state **162** for the key C−H activation step (Scheme 3.34).[19, 23, 24, 102, 103]



Scheme 3.34: Transition state for the carboxylate-assisted C−H activation.

3.5 Aerobic Alkyne Annulations through Ruthenium-Catalyzed Direct C−H/O−H Bond Functionalizations of Benzoic Acids

The previously described annulations with oximes and *N*-methoxybenzamides did not require any external oxidant. However, most annulations of alkynes proceeding through ruthenium-, rhodium- and iridium-catalyzed C−H bond functionalizations also involved the cleavage of a Het−H bond. For this reason external oxidants are required in order to reoxidize the catalytic active species. Most often stoichiometric amounts of copper(II)- or silver(I)-salts are used as external oxidants. However, several procedures managed to use substoichiometric amounts of Cu(II)-salts in combination with molecular oxygen or air as the terminal oxidant. In order to perform the reaction at a reduced temperature and to avoid a second transition metal, it was decided to use a photocatalyst as a trigger and also air or molecular oxygen as the terminal oxidant.[222] Herein, the well-studied reaction between benzoic acids and internal alkynes should serve as a model-system.[82, 98, 110, 111, 223]

3.5.1 Optimization Studies for the Aerobic Annulation of Diphenylacetylene with *ortho*-Toluic Acid

At the outset of this project, the optimization studies were started with *o*-toluic acid (**56a**) and diphenylacetylene (**34a**) as substrates. The $[RuCl_2(p\text{-cymene})]_2$ complex was used as the catalyst with substoichiometric amounts of KPF_6 as the additive. $Ru(bpy)_3Cl_2 \cdot 6\,H_2O$ should serve as the photocatalyst, as it was already established for visible light mediated C−H bond functionalizations.[51, 224] Irradiation of the reaction-mixture was carried out with RGB-LED's, emitting blue light with $\lambda = 450{-}500$ nm. The setup is shown in Figure 3.8.

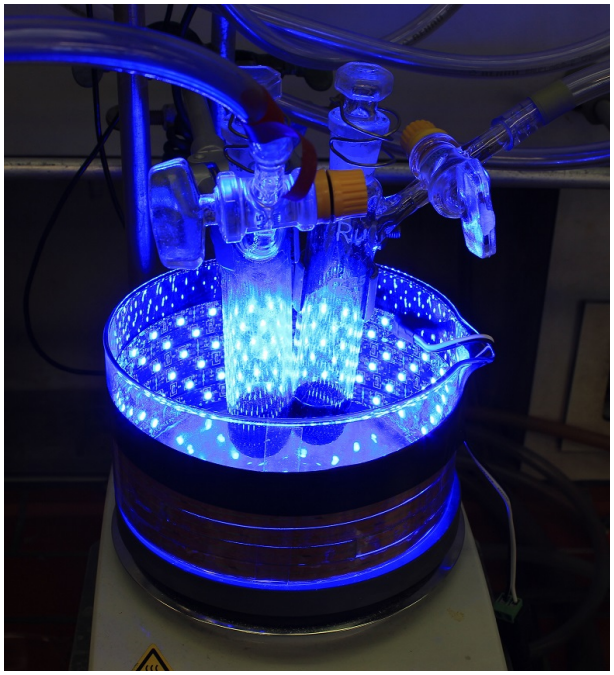
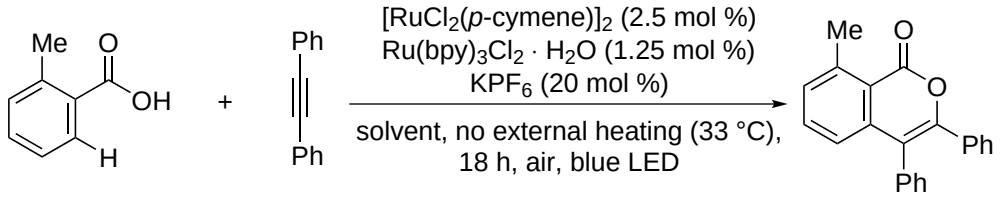


Figure 3.8: Reaction setup for photoredox-mediated C−H annulations.

Table 3.21 shows the initial experiments. As pointed out in entries 1–3, no product formation was noticed with MeCN, MeOH or *t*-AmOH as the solvent. Only the addition of NaOAc led to the formation of trace amounts of the poduct (Table 3.21, entry 4). One explanation for the unexpected low catalytic activity could be a possible ligand exchange, which might occur between the two ruthenium catalysts.

Table 3.21: Optimization studies for the direct annulation of **34a** with benzoic acid **56a**.[a]



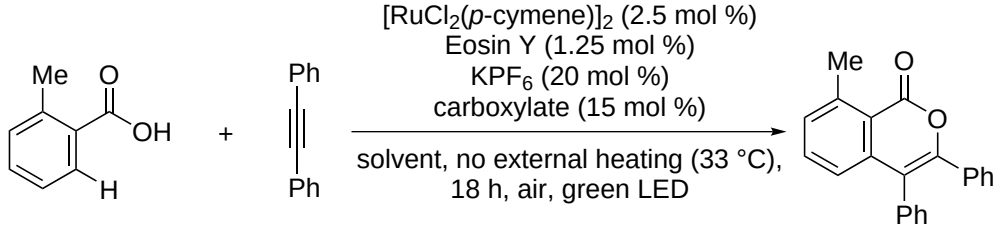
56a **34a** **55aa**

entry	solvent	conversion (%)
1	MeCN	-
2	MeOH	-
3	*t*-AmOH	-
4	*t*-AmOH	8[b]

[a] Reaction conditions: **56a** (2.0 equiv), **34a** (1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $Ru(bpy)_3Cl_2 \cdot 6\,H_2O$ (1.25 mol %), KPF_6 (20 mol %), solvent (0.33 M), no external heating (33 °C), 18 h, air, irradiation with blue LED's; [b] + NaOAc (15 mol %); conversion determined by GC-MS.

For this reason, Eosyn Y, which optical absorption properties allowed to switch the irradiation wavelength of the LED's to $\lambda = 500$–570 nm (green light), was applied for further optimization studies as the photocatalyst in the presence of a carboxylate-additive. The results are shown in Table 3.22. Entry 1 in Table 3.22 illustrates that just by switching from $Ru(bpy)_3Cl_2 \cdot 6\,H_2O$ to Eosin Y, the yield could be raised to 19%. Variation of the carboxylate-additive gave comparable conversions (Table 3.22, entries 2 and 3). However, if $Cu(OAc)_2 \cdot H_2O$ was employed as the carboxylate-additive, the reaction shut down and only trace amounts of the product were formed (Table 3.22, entry 4). Interestingly, the desired product was also obtained without irradiation of the reaction mixture, (Table 3.22, entry 5). Also the preformed carboxylate-complex $[Ru(O_2CMes)_2(p\text{-cymene})]$ showed some catalytic activity and gave a result comparable to the *in situ* formed system (Table 3.22, entry 6). A reduced conversion was observed, when *i*-PrOH was used as the solvent instead of MeOH (Table 3.22, entry 7). Other polar solvents did not result in any product formation (Table 3.22, entries 8 and 9). The same observation was made, when no carboxylate-additive was used (Table 3.22, entries 10 and 11). On the other hand, varying the ratio of the benzoic acid **56a** and the alkyne **34a** did not affect the yield (Table 3.22, entry 12). Surprisingly, the reaction proceeded even in the absence of any photocatalyst (Table 3.22, entry 13).

Table 3.22: Optimization studies for the direct annulation of alkyne **34a** with benzoic acid **56a** in the presence of Eosin Y.[a]



56a **34a** **55aa**

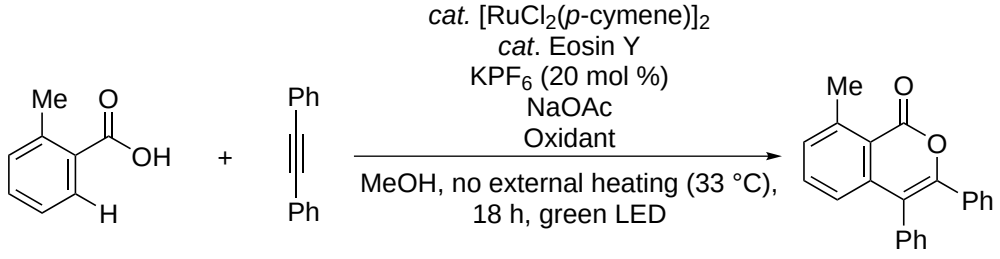
entry	carboxylate	solvent	yield (%)
1	NaOAc	MeOH	19
2	CsOAc	MeOH	18
3	KOPiv	MeOH	16
4	$Cu(OAc)_2 \cdot H_2O$	MeOH	(3)
5	NaOAc	MeOH	11[b]
6	-	MeOH	17[c]
7	NaOAc	*i*-PrOH	(8)
8	NaOAc	MeCN	-
9	NaOAc	DMSO	-
10	-	MeOH	-
11	-	MeOH	-[d]
12	NaOAc	MeOH	16[e]
13	NaOAc	MeOH	14[f]

[a] Reaction conditions: **56a** (2.0 equiv), **34a** (1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), Eosin Y (1.25 mol %), KPF_6 (20 mol %), solvent (0.33 M), no external heating (33 °C), 18 h, air, irradiation with green LED's; [b] no irradiation; [c] $[Ru(O_2CMes)_2(p\text{-cymene})]$ (5.0 mol %) instead of $[RuCl_2(p\text{-cymene})]_2$ as catalyst; [d] no KPF_6; [e] **56a** (1.0 equiv.), **34a** (2.0 equiv); [f] without Eosin Y; yield in parantheses refers to conversion determined by GC-MS.

However, although all the reactions furnished the desired product, the yields never exceeded 20%. Therefore, several other oxidants were tested (Table 3.23). At first, certain tertiary amines were examined as oxidants, as they have already been used for photocatalytic reactions with $[Ru(bpy)_3]^{2+}$.[225–228] As shown in the entries 1 and 2 of Table 3.23, this approach did not lead to any product formation. The use of sodium ascorbate, again, did not furnish the desired product (Table 3.23, entry 3). When acetone was employed as the oxidant, traces of the product were observed, while the use of molecular oxygen gave the same result as obtained in the reaction performed under air (Table 3.23, entries 4 and 5, Table 3.22 entry 1). Next the catalyst loading and thus also the amount of NaOAc was increased. With this reaction conditions the yield could be increased up to 29% (Table 3.23, entry 6) and even further to 36% when NaOAc was utilized

in stoichiometric quantities (Table 3.23, entry 7).
With the increased catalyst-loading, molecular oxygen was employed again, as the terminal oxidant, and an isolated yield of 67% was obtained (Table 3.23, entry 8). The addition of molecular sieves, however, had no positive effect on the yield (Table 3.23, entry 9). If the reaction was completely performed under a nitrogen atmosphere the yield was significantly reduced. This indicated the important role of the oxygen for the catalytic cycle (Table 3.23, entry 10).

Table 3.23: Optimization studies for the direct annulation of alkyne **34a** with benzoic acid **56a**: oxidants.[a]



56a **34a** **55aa**

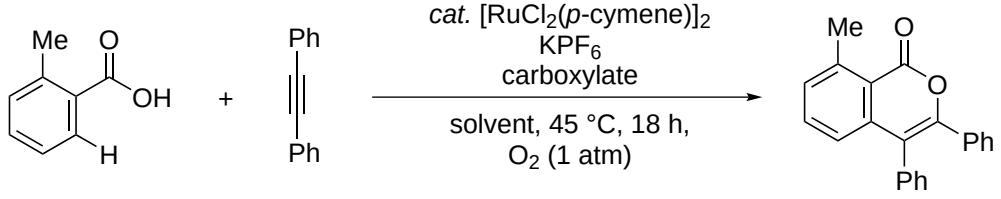
entry	[Ru]	Eosin Y	NaOAc	oxidant	yield (%)
1	2.5 mol %	1.25 mol %	15 mol %	NEt_3	-[b]
2	2.5 mol %	1.25 mol %	15 mol %	i-Pr_2NEt	-[b]
3	2.5 mol %	1.25 mol %	15 mol %	Na-ascorbate (1.0 equiv.)	-
4	2.5 mol %	1.25 mol %	15 mol %	acetone	(6)[b]
5	2.5 mol %	1.25 mol %	15 mol %	O_2 (1 atm)	19
6	5.0 mol %	1.25 mol %	30 mol %	air (1 atm)	29
7	5.0 mol %	1.25 mol %	2.0 equiv	air (1 atm)	36
8	5.0 mol %	1.25 mol %	2.0 equiv	O_2 (1 atm)	67
9	5.0 mol %	1.25 mol %	2.0 equiv	O_2 (1 atm)	56[c]
10	5.0 mol %	1.25 mol %	2.0 equiv	no oxidant (1 atm N_2)	14
11	5.0 mol %	2.5 mol %	2.0 equiv	O_2 (1 atm)	65
12	5.0 mol %	-	2.0 equiv	O_2 (1 atm)	61
13	5.0 mol %	-	2.0 equiv	O_2 (1 atm)	43[d]
14	5.0 mol %	-	2.0 equiv	no oxidant (1 atm N_2)	-[d]

[a] Reaction conditions: **56a** (2.0 equiv), **34a** (1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$, Eosin Y (1.25 mol %), KPF_6 (20 mol %), MeOH (0.33 M), no external heating (33 °C), 18 h, irradiation with green LED's; [b] solvent consists of 5/6 MeOH and 1/6 oxidant; [c] + 4 Å mol. sieves (100 mg); [d] without irradiation; yields in parantheses refer to conversions determined by GC-MS.

An increased loading of the photocatalyst gave nearly the same result (Table 3.23, entry 11). Hence the reaction was conducted without Eosin Y, which surprisingly also gave a yield of 61%

(Table 3.23, entry 12). For this reaction, the temperature was monitored, and it was revealed that irradiation with the LED-lamps led to an increased temperature of 33 °C within the reaction vessel. As a consequence, another reaction was performed in the absence of the photocatalyst, but this time even without irradiation. The reduced yield of 43% proofed that the yield is indeed related to the reaction temperature (Table 3.23, entry 13).

Table 3.24: Optimization studies for the direct annulation of alkyne **34a** with benzoic acid **56a** without irradiation.[a]



56a **34a** **55aa**

entry	[Ru]	KPF_6	carboxylate	solvent	yield (%)
1	5.0 mol %	20 mol %	NaOAc (2.0 equiv)	MeOH	87[b]
2	5.0 mol %	20 mol %	NaOAc (2.0 equiv, 99.997%)	MeOH	89
3	5.0 mol %	20 mol %	NaOAc (2.0 equiv, 99.997%)	MeOH	80[c]
4	5.0 mol %	20 mol %	$Cu(OAc)_2 \cdot H_2O$ (15 mol%)	MeOH	(3)
5	5.0 mol %	20 mol %	$Cu(OAc)_2 \cdot H_2O$ (2.0 equiv)	MeOH	(10)
6	2.5 mol %	20 mol %	NaOAc (2.0 equiv)	MeOH	20
7	5.0 mol %	20 mol %	NaOAc (1.0 equiv)	MeOH	78
8	5.0 mol %	-	NaOAc (2.0 equiv)	MeOH	77
9	5.0 mol %	-	NaOAc (1.0 equiv)	MeOH	78
10	5.0 mol %	-	NaOAc (1.0 equiv)	MeOH	49[d]
11	5.0 mol %	-	NaOAc (1.0 equiv)	EtOH	-
12	5.0 mol %	-	NaOAc (1.0 equiv)	*i*-PrOH	-
13	5.0 mol %	-	NaOAc (1.0 equiv)	*t*-AmOH	-
14	5.0 mol %	-	NaOAc (1.0 equiv)	MeOH	72[e]
15	5.0 mol %	-	NaOAc (1.0 equiv)	MeOH	76[f]
16	-	-	NaOAc (1.0 equiv)	MeOH	-

[a] reaction conditions: **56a** (2.0 equiv.), **34a** (1.0 equiv.), $[RuCl_2(p\text{-cymene})]_2$, solvent (0.33 M), 45 °C, 18 h, O_2 (1 atm); [b] average from two runs; [c] reaction performed in a new *Schlenk*-tube; [d] air (1 atm) was used instead of O_2; [e] $[RuBr_2(p\text{-cymene})]_2$ as catalyst; [f] $[RuCl_2(C_6H_6)]_2$ as catalyst; yields in parantheses refer to conversions determined by GC-MS.

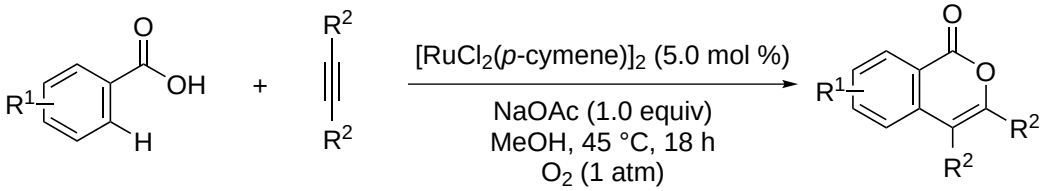
As the photocatalyst appears to be redundant, it is likely that reoxidation of the ruthenium-catalyst occurs under aerobic conditions at elevated temperatures. For this reason it was decided to carry out some more optimization experiments (Table 3.24). When the reaction was performed

at a slightly increased temperature of 45 °C, an excellent yield of 87% was obtained (Table 3.24, entry 1). As a hypothesis, the participation of trace amounts of copper(II) in the reoxidation of the ruthenium catalyst was considered as well. To exclude this possibility, two additional experiments were performed with NaOAc of 99.997% metal-based purity. One of the reactions was carried out in a newly made Schlenk tube. Both reactions gave again yields of 80% and more. These results excluded the participation of copper(II)-impurities in the reoxidation step (Table 3.24, entries 2 and 3). The idea of the direct reoxidation was also supported by the fact, that the use of $Cu(OAc)_2 \cdot H_2O$ in catalytic as well as in stoichiometric quantities, instead of NaOAc, afforded only traces of the desired product (Table 3.24, entries 4 and 5). A lower catalyst loading also gave a significantly reduced yield (Table 3.24, entry 6). After that, the reactions with reduced amount of NaOAc (Table 3.24, entries 7 and 9) or without KPF_6 (Table 3.24, entries 8 and 9) were tested. As the isloated yields were only slightly decreased, all further reactions were run without KPF_6 and with just 1.0 equivalents of sodium acetate. Once again, the reaction performed under air instead of an O_2-atmosphere furnished **55aa** in only a moderate yield of 49% (Table 3.24, entry 10). Other alcohols than MeOH were not suitable as the solvent (Table 3.24, entries 11–13). At last $[RuBr_2(p\text{-cymene})]_2$ and $[RuCl_2(C_6H_6)]_2$ were used as precatalysts (Table 3.24, entry 14 and 15). Both complexes showed similar catalytic activity as $[RuCl_2(p\text{-cymene})]_2$, but no product formation occured in the absence of an ruthenium source (Table 3.24, entry 16). Ultimately, the reaction conditions in entry 9 were applied in testing the scope of the reaction.

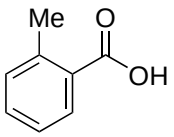
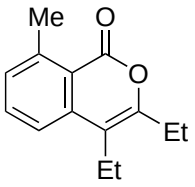
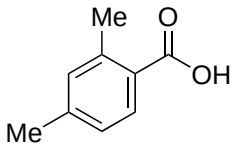
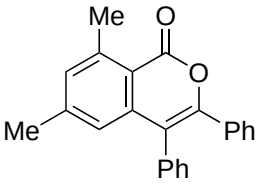
3.5.2 Aerobic Annulations of Alkynes with Benzoic acids: Scope and Limitations

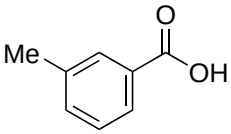
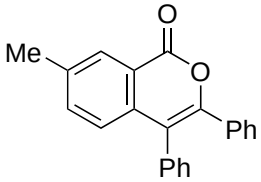
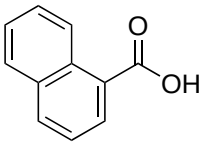
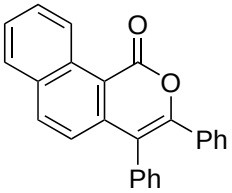
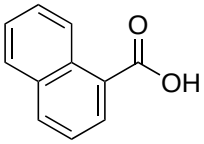
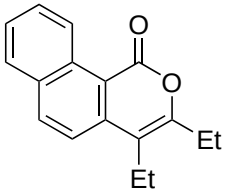
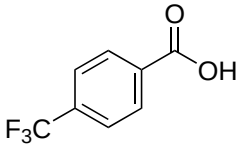
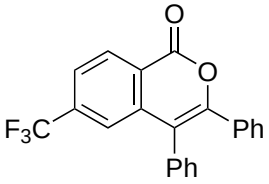
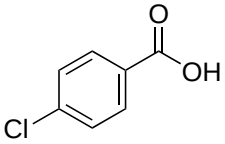
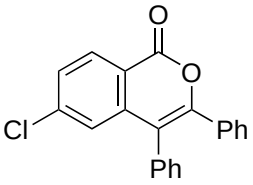
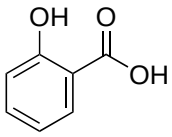
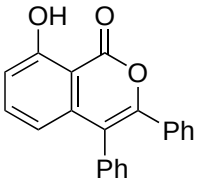
Several differently substituted benzoic acids **56** and alkynes **34** were examined under the optimized reaction conditions (Table 3.25). The reaction between electron-rich benzoic acids with 3-hexyne (**34f**) and diphenylacetylene (**34a**) furnished the desired isocoumarins in good yields (Table 3.25, entries 1 and 2). In analogy to the annulation with *meta*-substituted oximes, the reaction with *meta*-toluic acid (**56c**) resulted in the functionalization of the sterically less-hindered C−H bond (Table 3.25, entry 3). The reactions with 1-naphthoic acid (**56d**) also furnished the desired product, however, only in a reduced yield of 32% when diphenylacetylene (**34a**) was employed as the substrate, while 3-hexyne (**34f**) gave the product **55df** in 64% yield (Table 3.25, entries 4 and 5). The electron-deficient substrate **56e** was converted to the product **55ea** with a diminished yield of 25%. On the other hand, a chlorine atom in the *para*-position was tolerated somewhat better (Table 3.25, entries 6 and 7). Unfortunately, a free hydroxyl-group in the *ortho*-position was not well tolerated (Table 3.25, entry 8).

Table 3.25: Aerobic direct annulation of alkynes **34** with benzoic acids **56** - Scope.[a]



56 **34** **55**

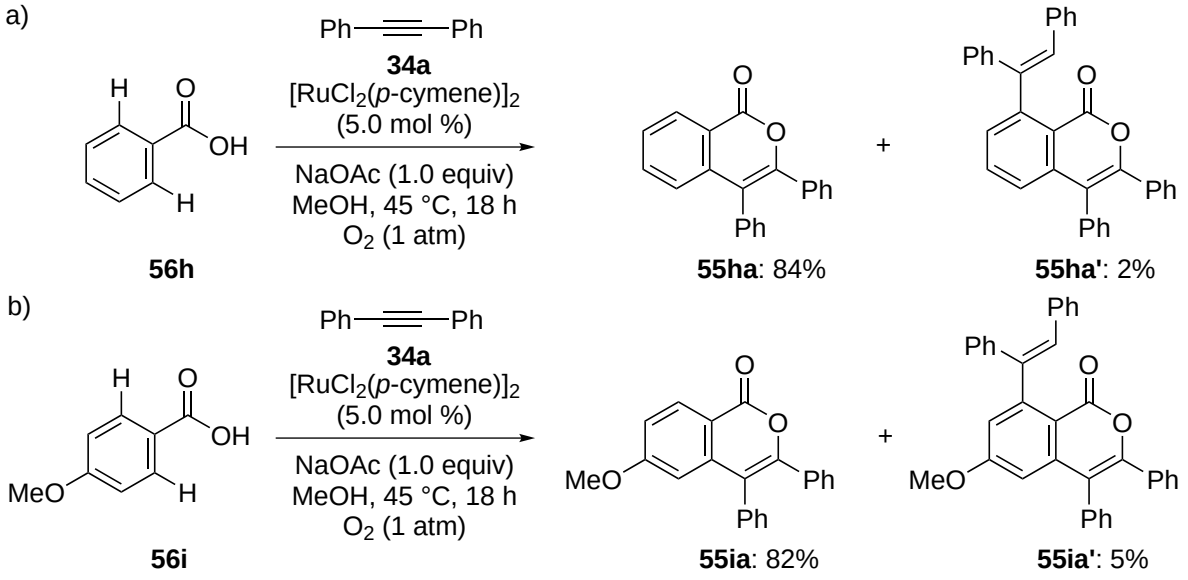
entry	benzoic acid **56**	R^2	product **55**	isolated yield (%)
1		Et		78
	56a	**34f**	**55af**	
2		Ph		84
	56b	**34a**	**55ba**	

entry	benzoic acid **56**	R^2	product **55**	isolated yield (%)
3		Ph		70
	56c	**34a**	**55ca**	
4		Ph		32
	56d	**34a**	**55da**	
5		Et		64
	56d	**34f**	**55df**	
6		Ph		25
	56e	**34a**	**55ea**	
7		Ph		47
	56f	**34a**	**55fa**	
8		Ph		26
	56g	**34a**	**55ga**	

[a] Reaction conditions: **56** (2.0 equiv), **34** (1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), MeOH (0.33 M), 45 °C, 18 h, O_2 (1 atm).

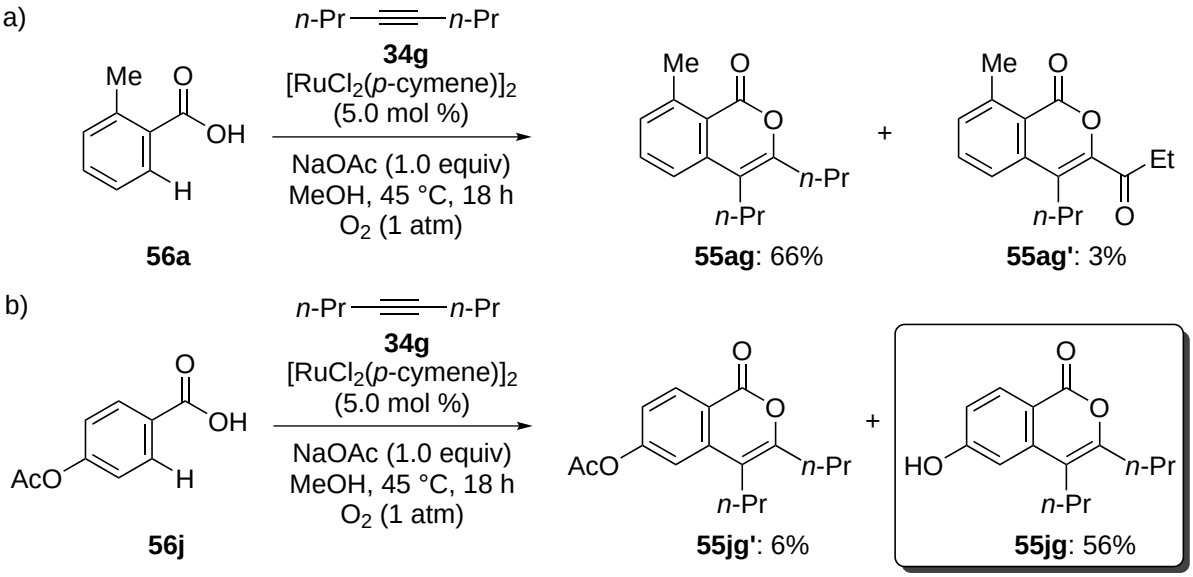
Surprisingly, the products of the reactions with unsubstituted benzoic acid (**56h**) and its *para*-methoxy substituted analogue **56i** reacted with another equivalent of the alkyne **34a**, yielding

the corresponding alkenylated products **55ha'** and **55ia'** (Scheme 3.35). Nevertheless, due to the excess of the acid **56**, these unexpected side-products were only formed in minor quantities.



Scheme 3.35: Reactions with benzoic acids **56h** and **56i**.

Two interesting observation were made for the reactions with 4-octyne (**34g**) as the substrate (Scheme 3.36). For instance, in the isocoumarin-product of the reaction between **56a** and **34g**, partial oxidation of the side-chain occured (Scheme 3.36 a). The structure of the corresponding ketone was assigned through 2-dimensional NOESY-NMR spectroscopy. A possible explanation for this side-product is the existence of ruthenium-oxo-complexes during the catalytic cycle.

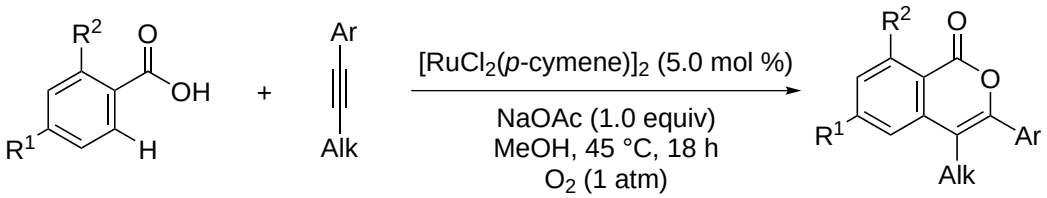


Scheme 3.36: Reactions with 4-octyne (**34g**).

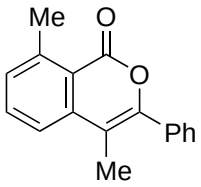
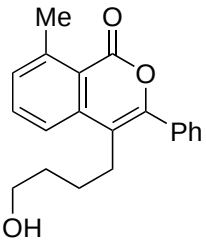
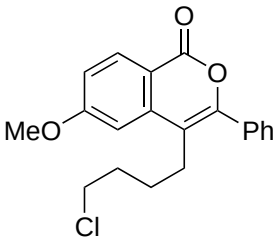
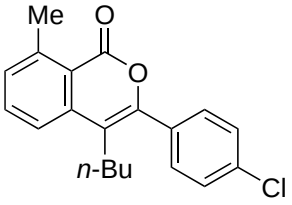
The other observation was that when 4-acetoxybenzoic acid **56j** was subjected to the reaction conditions, deacetylation took place and furnished compound **55jg** with the free hydroxyl-group

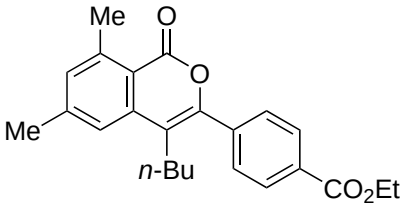
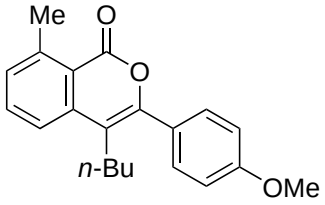
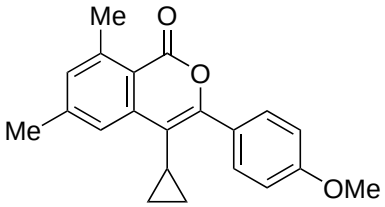
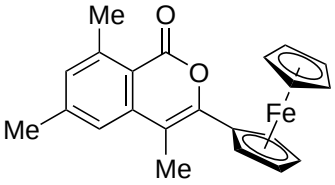
as the main product (Scheme 3.36 b).

Table 3.26: Aerobic direct annulation of alkynes **34** with benzoic acids **56** - unsymmetrical alkynes.[a]



56 **34** **55**

entry	alkyne **34** Ar	alkyne **34** Alk	product **55**	isolated yield (%)
1	Ph	Me		79 (6)[b]
	34i		**55ai**	
2	Ph	$(CH_2)_4OH$		69
	34m		**55am**	
3	Ph	$(CH_2)_4Cl$		74 (8)[b]
	34l		**55il**	
4	4-Cl(C_6H_4)	*n*-Bu		70
	34y		**55ay**	

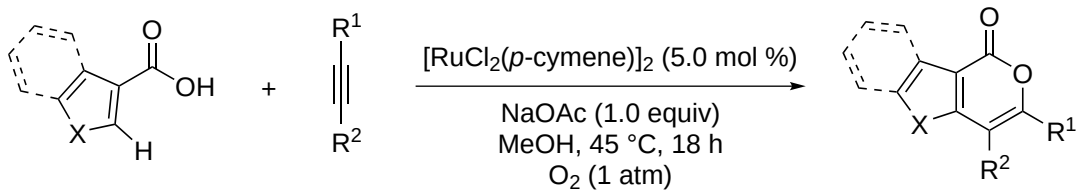
entry	alkyne **34** Ar	Alk	product **55**	isolated yield (%)
5	4-CO_2Et(C_6H_4)	*n*-Bu		67
	34r		**55br**	
6	4-MeO(C_6H_4)	*n*-Bu		54 (5)[b]
	34n		**55an**	
7	4-MeO(C_6H_4)	*c*-Pr		56 (7)[b]
	34t		**55bt**	
8	Fc	Me		16
	34w		**55bw**	

[a] Reaction conditions: **56** (2.0 equiv), **34** (1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), MeOH (0.33 M), 45 °C, 18 h, O_2 (1 atm); [b] yields in parantheses refer to the other regioisomer which was also isolated.

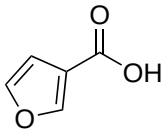
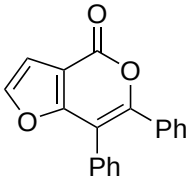
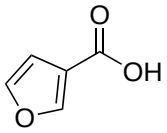
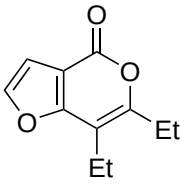
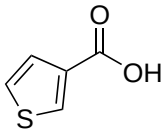
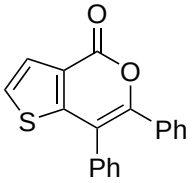
As previously tested with oximes **87**, the annulations of unsymmetrically substituted alkylarylalkynes with benzoic acids **56** were examined as well (Table 3.26). The first reaction with 1-phenylpropyne (**34i**) revealed, that, as in the annulations with oximes **87** (cf. Table 3.16), the major isolated regioisomer was the one with a phenyl-moiety attachet to the position 3 (Table 3.26, entry 1). The other regioisomer was formed in only minor quantities. Furthermore, it was also gratifying to observe that aliphatic alcohols and aliphatic halides were tolerated under the reaction conditions (Table 3.26, entries 2 and 3). With regard to the electronic properties of the alkynes, it should be mentioned, that alkynes, bearing electron-deficient substituents on the aromatic ring, gave slightly better results than the ones with an electron-donating methoxy-substituent (Table 3.32, entries 4–6). Also the more sterically-demanding cyclopropyl-substituted alkyne **34t** could successfully be converted to the isocoumarin **55bt**, without ring

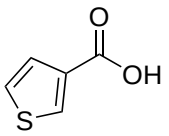
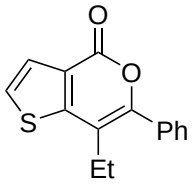
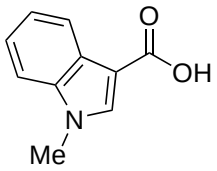
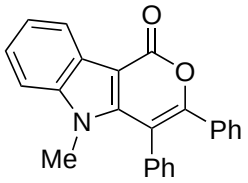
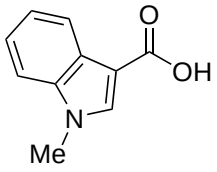
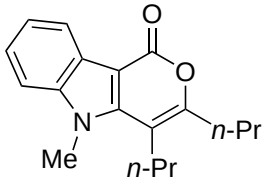
opening of the cyclopropane moiety,[112] which gives a prospect for interesting structural architectures (Table 3.26, entry 7). The reaction with the previously employed ferrocenyl-substituted alkyne **34w** afforded **55bw** in only diminished yield of 16% (Table 3.26, entry 8). In contrast to the annulations with oximes, the aerobic annulation could also be successfully applied to heteroaromatic substrates (Table 3.27). Thus, furan-3-carboxylic acid (**56k**) was converted to the corresponding furo[3,2-*c*]pyranones **55ka** and **55kg** in moderate to good yields (Table 3.27, entries 1 and 2). With thiophene-3-carboxylic acid (**56l**) the yields were even higher and, as with the benzoic acids, also the unsymmetrical alkyne **34j** was regioselectively converted to the product **55lj** (Table 3.27, entries 3 and 4). Moreover, this methodology also gave access to 3,4-disubstitued pyrano[4,3-*b*]indol-1(5*H*)-ones **55ma** and **55mg** in yields above 80% (Table 3.27, entries 5 and 6). It is noteworthy to mention, that in all of these reactions the most acidic C−H bond was functionalized in a site-selective manner.

Table 3.27: Aerobic direct annulation of alkynes **34** with heteroaromatic acids.[a]



56k–m **34** **55**

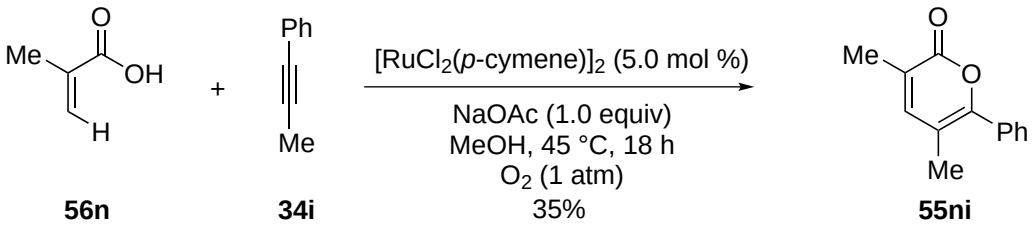
entry	acid **56**	alkyne **34** R^1	alkyne **34** R^2	product **55**	isolated yield (%)
1		Ph	Ph		66
	56k		**34a**	**55ka**	
2		Et	Et		56
	56k		**34g**	**55kg**	
3		Ph	Ph		93
	56l		**34a**	**55la**	

entry	acid **56**	alkyne **34** R^1	R^2	product **55**	isolated yield (%)
4	 **56l**	Ph	Et	 **55lj**	95 (2)[b]
5	 **56m**	Ph	Ph	 **55ma**	83
6	 **56m**	*n*-Pr	*n*-Pr	 **55mg**	94

[a] Reaction conditions: **56** (2.0 equiv), **34** (1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), MeOH (0.33 M), 45 °C, 18 h, O_2 (1 atm); [b] yield in parantheses refers to the other regioisomer which was also isolated.

In order to assign the correct structures of compounds **55ai**–**55lj**, NOE NMR-spectra, 2-dimensional NOESY-spectra or HMBC-spectra were recorded for the products of Tables 3.26 and 3.27.

Finally, attempts were made to extend the scope of the aerobic C−H annulation also towards non-aromatic substrates. However, the pyranone **55ni** could be obtained from methacrylic acid (**56n**) in only 35% yield (Scheme 3.37). Unfortunately, reactions with other alkynes or acrylate derivatives showed even lower conversion.



56n **34i** **55ni**

Scheme 3.37: Reaction with methacrylic acid (**56n**).

Nevertheless, aerobic annulation of alkynes with benzoic acids and heteroaromatic carboxylic acids proceeded with ample scope and large functional group tolerance.

3.5.3 Synthesis of Isocoumarins Derived from Biologically Active Thunberginols

Isocoumarins occur as parts of compounds synthesized by nature. For example, the plant *Hydrangea macrophylla*, commonly known as hortensia, produces a class of natural products with isocoumarin and dihydroisocoumarin substructures (Figure 3.9). These compounds show antiallergic and antimicrobial properties.[229–231] As a consequence the total synthesis of thunberginol A gained some attraction and several procedures involving palladium-catalyzed transformations as key reactions have been described in the literature.[232–234]

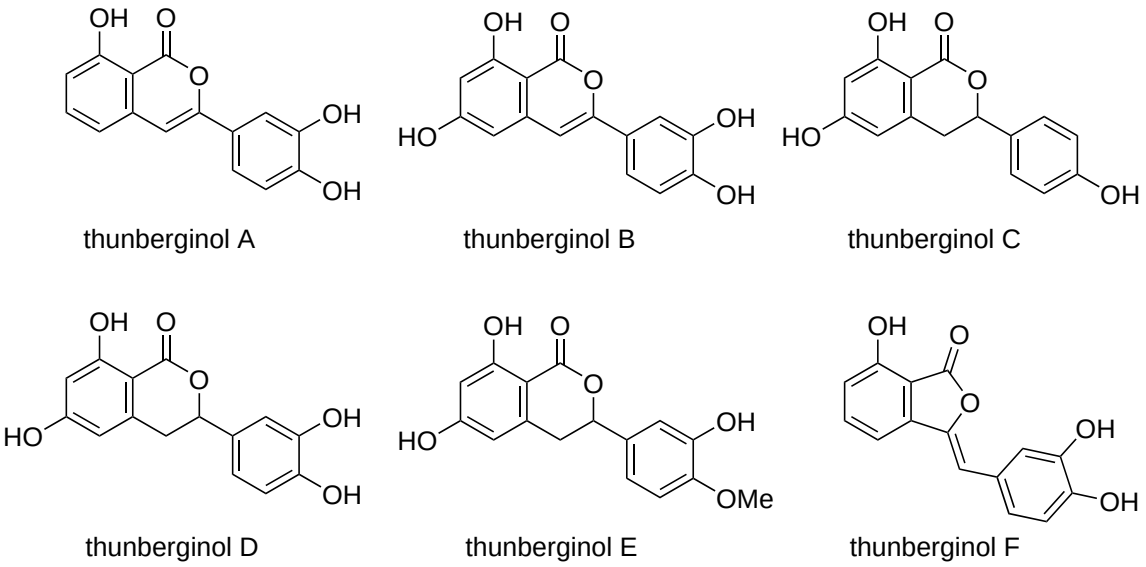
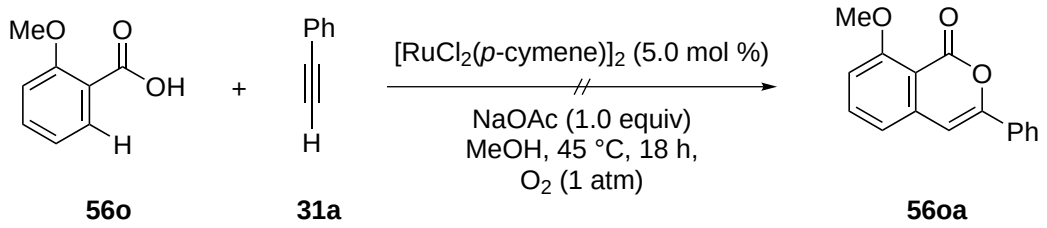


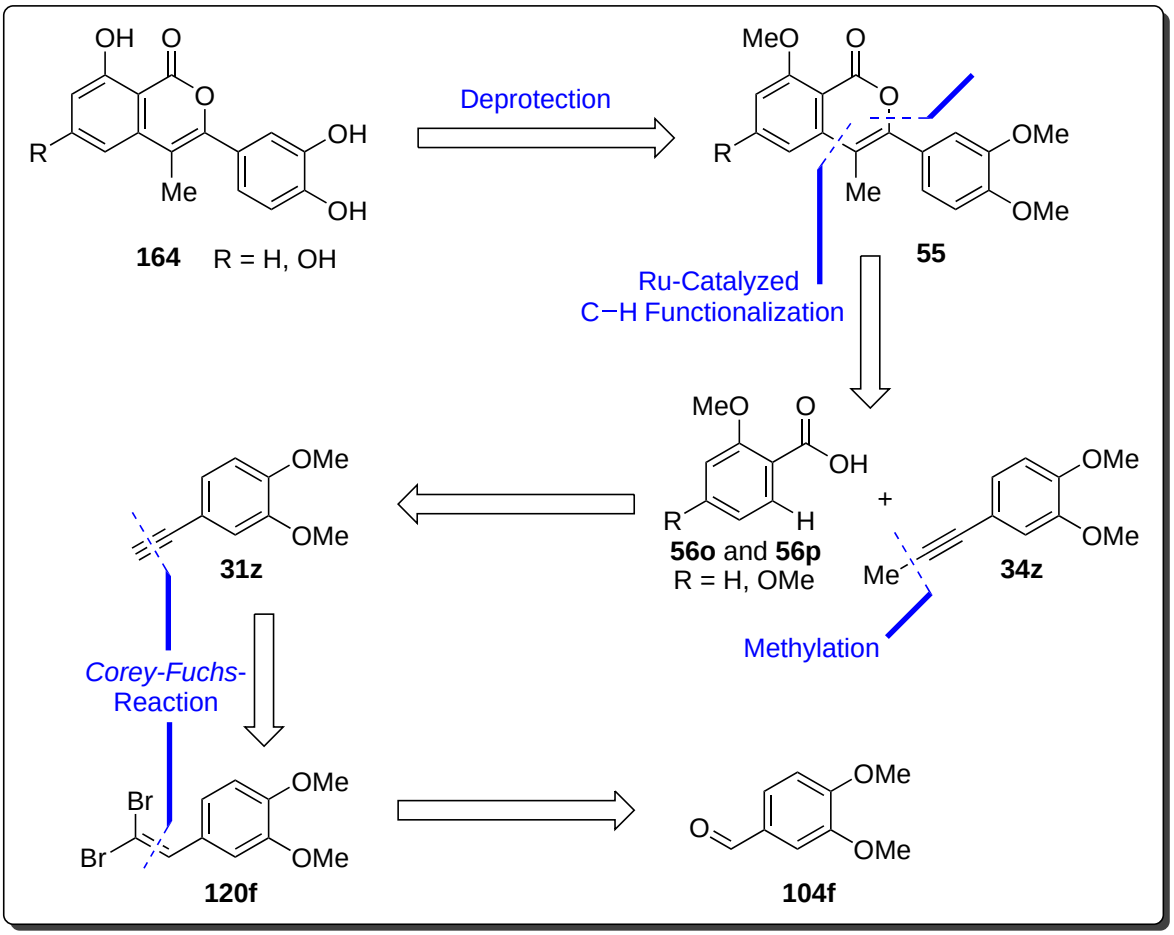
Figure 3.9: Natural occurring thunberginols.

For this reason, it was decided to use the structures of thunberginol A and B as potential target-structures to proof the applicability of the newly developed ruthenium-catalyzed aerobic annulation reaction. At the beginning, studies with a model-system revealed, that terminal alkynes do not work in the ruthenium-catalyzed aerobic annulation with benzoic acids (Scheme 3.38). As in the reaction with the oximes, phenylacetylene (**31a**) tends to dimerize in the presence of the ruthenium-catalyst.



Scheme 3.38: Test reaction with phenylacetylene (**31a**).

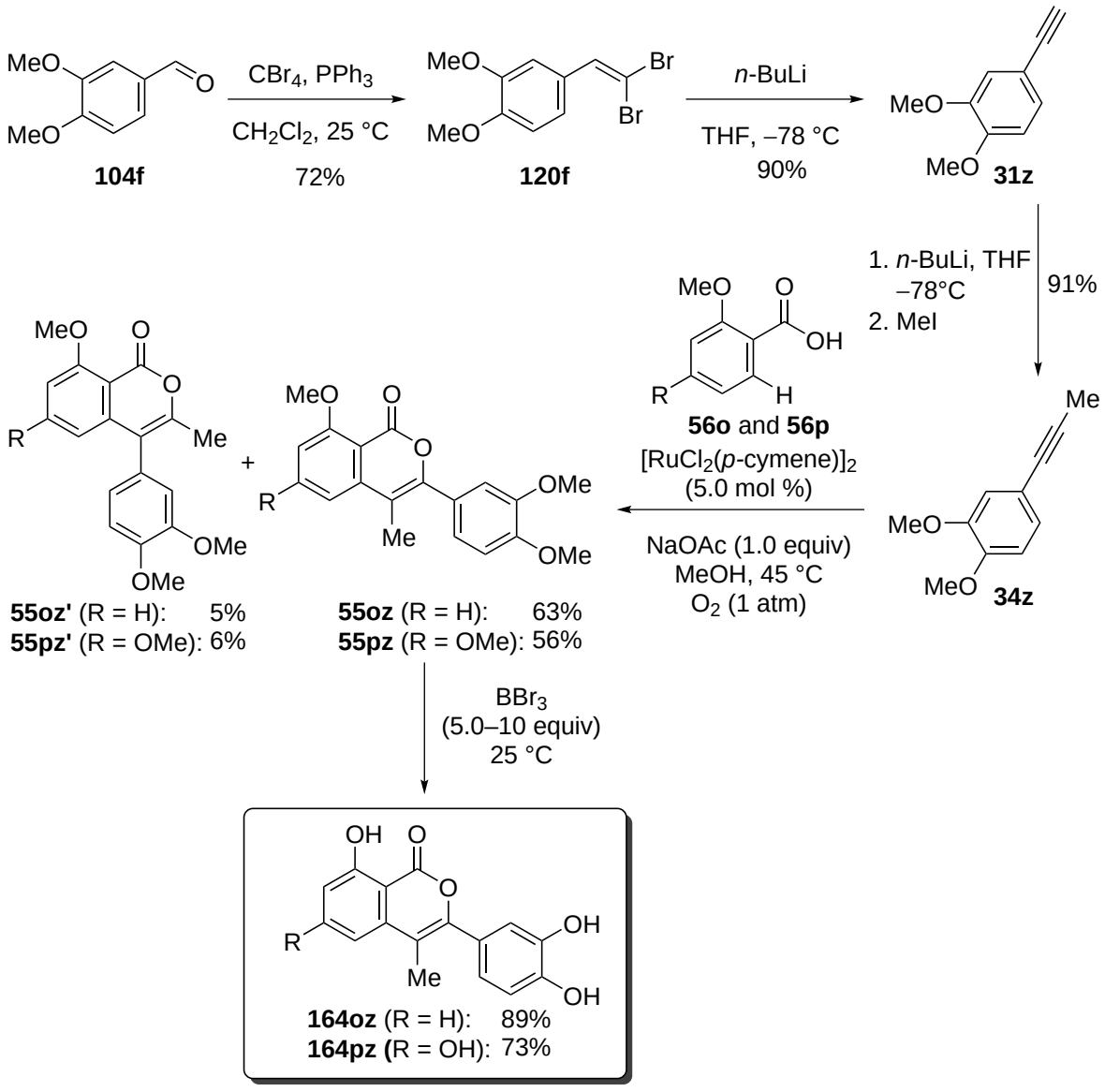
As a consequence, the synthesis was directed towards methylated derivatives of thunberginols A and B (Scheme 3.39). The first step in the retrosynthetic analysis is a deprotection step. In order to avoid any functional group tolerance problems, it seemed favourable to use methoxy-groups instead of the free hydroxyl-functionalities during the course of the synthesis. The next retrosynthetic step would be the crucial annulation through C−H functionalization of the alkyne **34z** with benzoic acids **56o** or **56p**, both of which are commercially available. Through simple demethylation one would arrive at the terminal alkyne **31z**, which in turn can be traced back to veratraldehyde (**104f**) through a *Corey-Fuchs*-reaction.[175]



Scheme 3.39: Retrosynthetic analysis for the synthesis of thunberginol derivatives.

The synthesis of both 4-methylthunberginol A and 4-methylthunberginol B is outlined in Scheme 3.40. The first step was the transformation of veratraldehyde (**104f**) into the corresponding di-bromoalkene **120f**.[235] The second stage of the *Corey-Fuchs*-alkynylation also went smoothly and furnished **31z** with 90% yield.[236] The next step was a simple methylation, through deprotonation of the alkyne **31z** and subsequent quenching of the generated organolithium compound with methyl iodide. After that, the generated alkyne **34z** was used for the ruthenium-catalyzed C−H bond functionalization reactions with 2-methoxybenzoic acid (**56o**) and 2,4-dimethoxybenzoic acid (**56p**).

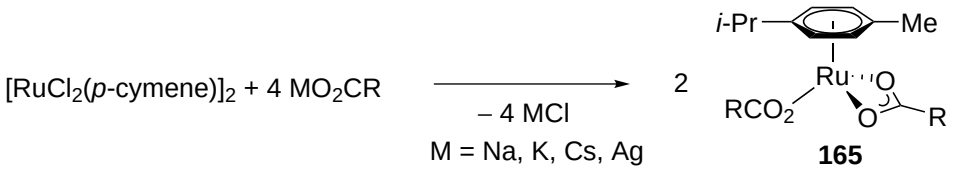
As anticipated, the desired regiosomers **55oz** and **55pz** were isolated in 63% and 56% yield, respectively, with only small quantities of the undesired regioisomers **55oz'** and **55pz'** as the side-products. Finally, deprotection of the hydroxyl-groups with a large excess of BBr_3 furnished the desired products: 4-methylthunberginol A (**164oz**) and 4-methylthunberginol B (**164pz**).[232] Overall, the synthesis of **164oz** and **164pz** was very effecient and straightforward from easy accessible starting materials. The correct structures were, again, assigned *via* NOE-NMR spectroscopy.



Scheme 3.40: Synthesis of 4-methylthunberginol A (**164oz**) and 4-methylthunberginol B (**164pz**).

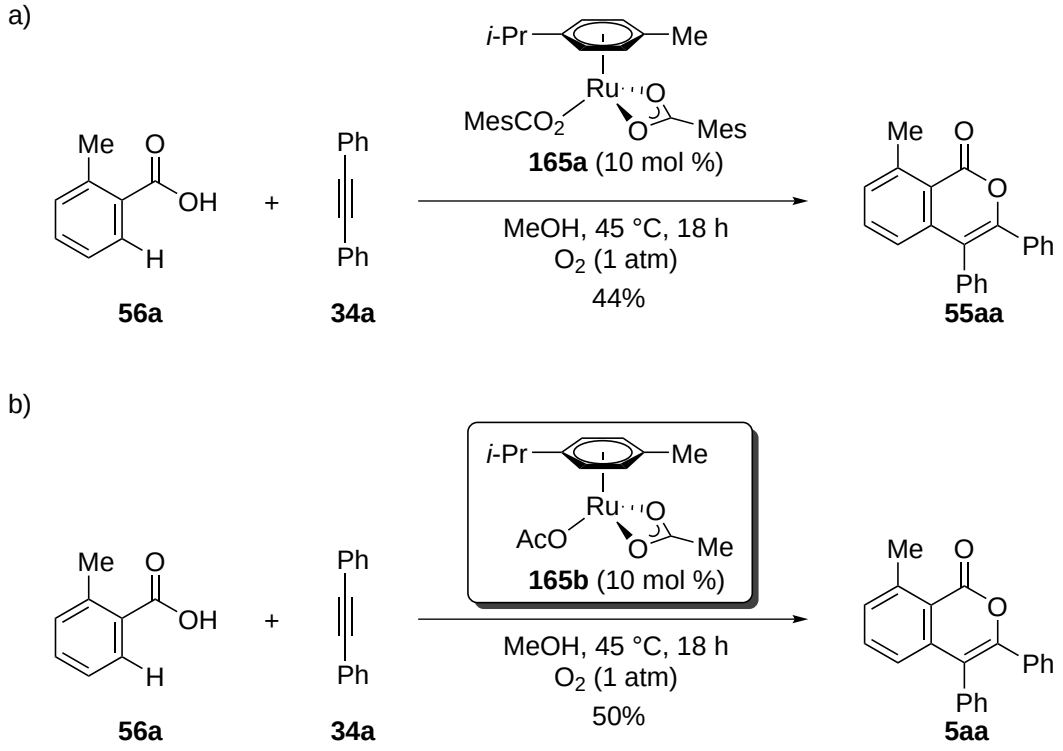
3.5.4 Mechanistic Studies on Aerobic Annulations of Alkynes with Benzoic Acids

Previous studies from the *Ackermann*-research group revealed, that in most of the carboxylate-assisted ruthenium-catalyzed C−H bond functionalizations, the catalytically active species is a biscarboxylate-complex **165**, which is formed *in situ* (Scheme 3.41).[43, 52, 54, 55, 103, 124]



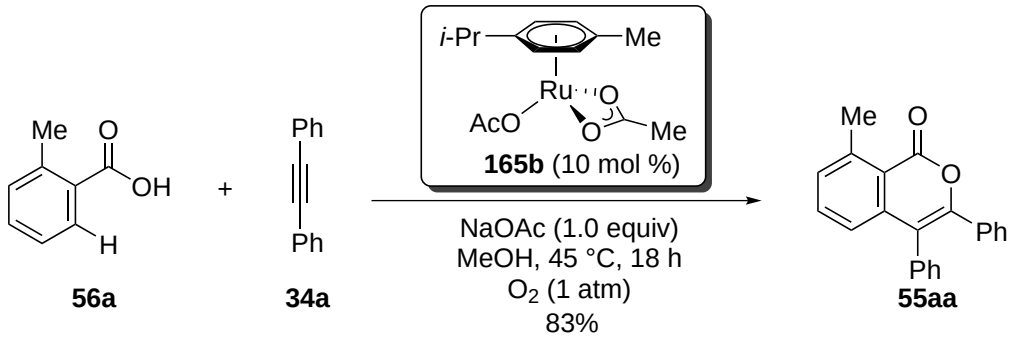
Scheme 3.41: *In situ* formed catalytically active species.

In order to explore, if this statement also holds true for the newly developed aerobic annulation, the previously employed bis(mesitylcarboxylate) complex **165a** was tested with the standard substrates (Scheme 3.41 a). It is also important to mention, that no external carboxylate-source had been used in this reaction. The conversion was not as high as with the *in situ* generated system, but the isocoumarin **55aa** could be isolated in a moderate yield of 44%. However, one has to keep in mind, that reactions with the *in situ* generated catalytic system work with sodium acetate and not with mesitylcarboxylate. For that reason, the corresponding bis(acetate)-complex **165b** was also investigated (Scheme 3.41 b).



Scheme 3.42: Aerobic annulation with the previously employed complexes **165a** and **165b**.

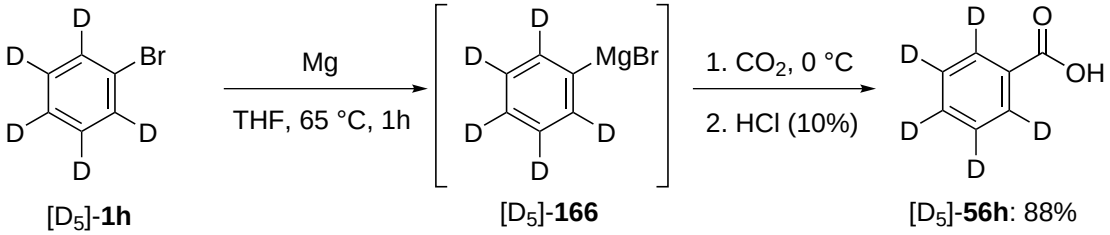
The yield was slightly higher (50%). In order to further stabilize the catalytically active complex, additional sodium acetate was added to the reaction mixture. Indeed, a positive effect on the conversion was observed, and the product could finally be obtained in a yield comparable to those obtained with the *in situ* generated system.



Scheme 3.43: Aerobic annulation with the acetate complex **165b**.

The fact that the carboxylate-complexes **165a** and **165b** can act as catalysts as well, leads to the conclusion that the active catalyst is most likely the complex **165b**, which is stabilized by additional sodium acetate. The sodium acetate is also important for another reason which will be discussed later.

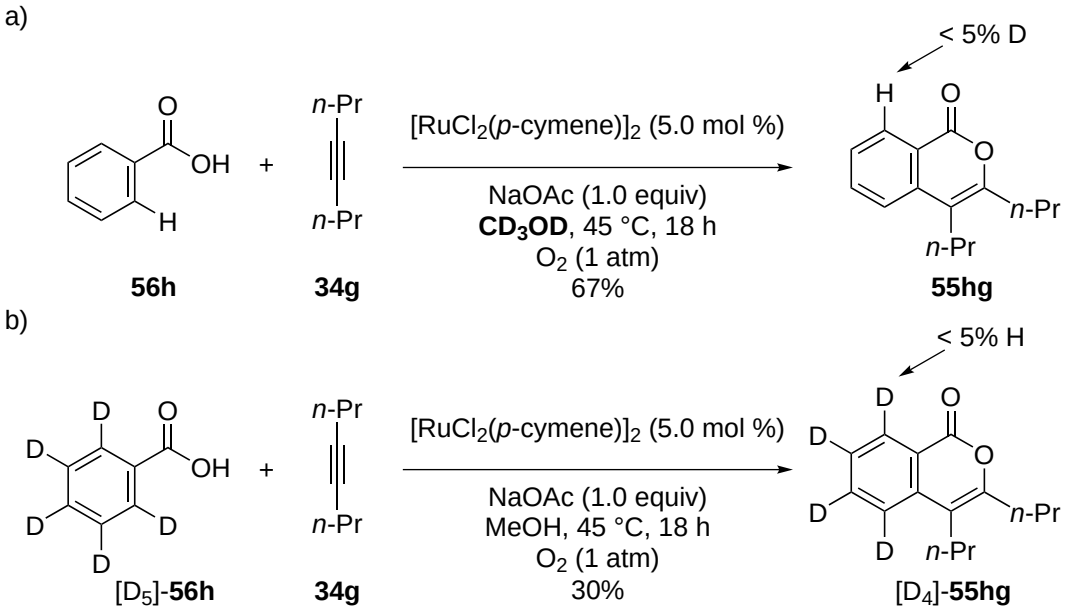
After that, several additional experiments involving reactions with isotopically labeled substrates were conducted. Thus, the deuterated benzoic acid [D_5]-**56h** was synthesized by conversion of [D_5]-bromobenzene into a *Grignard*-reagent, which was simply reacted with CO_2 to afford [D_5]-**56h**.[100]



Scheme 3.44: Preparation of [D_5]-**56h**.

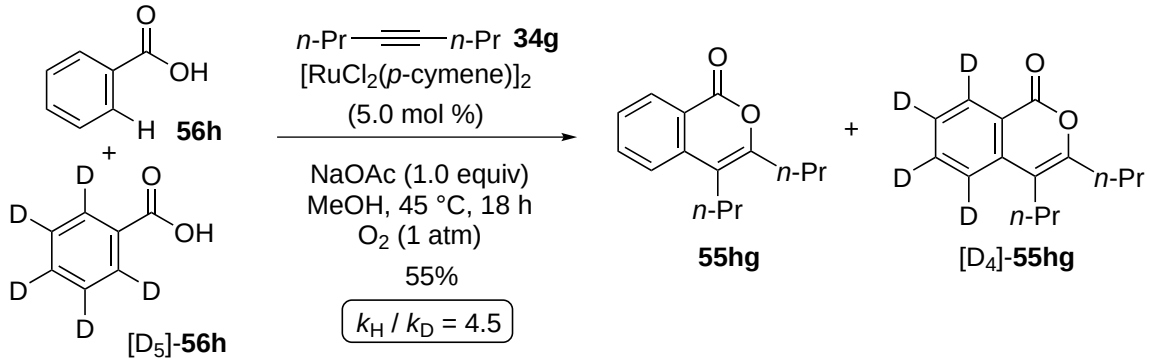
As methanol is a polar-protic solvent, and thus is a valuable proton- or deuterium-source, two simple experiments were performed to see if there was any H/D-scrambling in the *ortho*-position of the product. In case of a reversible C−H bond cleavage, a significant deuterium-incorporation should be observed. The experiment shown in Scheme 3.45 a, between benzoic acid (**56h**) and 4-octyne (**34g**) in [D_4]-MeOH led to the product in 67% yield, and less than 5% deuterium-incorporation was observed in position 8. The second experiment, which is displayed in Scheme 3.45 b, is the alternative reaction between [D_5]-**56h** and **34g** in nondeuterated MeOH. Even in this experiment, no significant H/D-scrambling could be detected in position 8 of the final product. Nevertheless, the yield of the isolated product [D_4]-**55hg** was significantly lower. This

indicated that substrate **56h** is reacting faster than [D_5]-**56h** and thus it is possible that the C−H bond cleavage is of significant importance for the mechanism.



Scheme 3.45: H/D-exchange experiments.

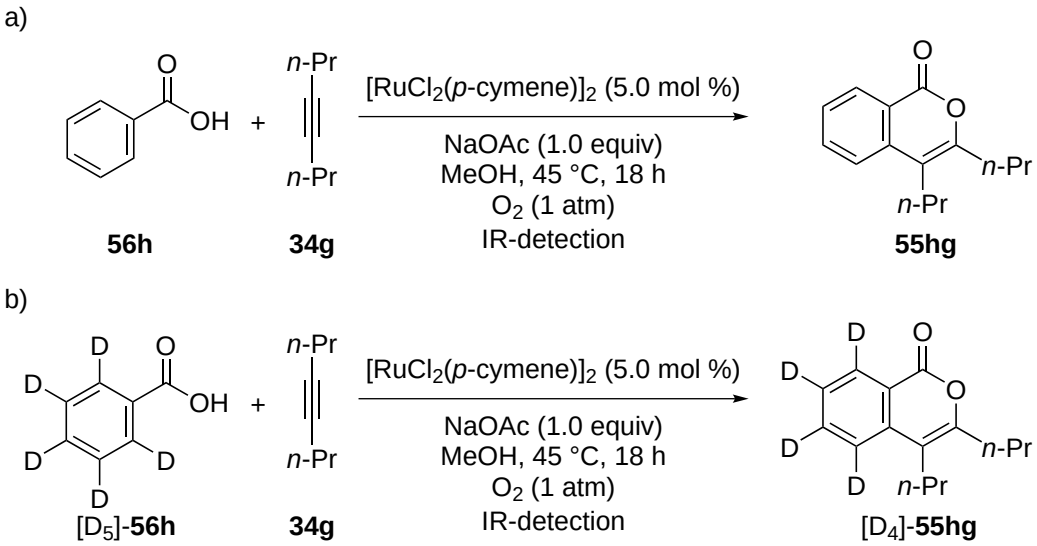
To gain further information, a competition experiment between **56h** and [D_5]-**56h** was performed (Scheme 3.46). After 18 h, a mixture of **55hg** and [D_4]-**55hg** was obtained and analyzed, revealing a KIE of 4.5. This was lower compared to the KIE of 7.3 of the previously published nonaerobic System.[110] Nevertheless, it was high enough to indicate that the C−H bond cleavage is indeed kinetically relevant for the mechanism.



Scheme 3.46: Competition experiment between **56h** and [D_5]-**56h**.

In order to confirm this hypothesis, the kinetic profiles for the formation of **55hg** and [D_4]-**55hg** were recorded from independant experiments under otherwise identical reaction conditions (Scheme 3.47). The data was again obtained via *in situ* IR spectroscopy and the results are shown in Figure 3.10. For both reactions, the product-formation was followed by monitoring the intensity of the signal at 1650 cm^{-1}.

From the curves shown in Figure 3.10 it is indeed obvious that the formation of the nondeuterated product **55hg** proceeded much faster in comparison to the deuterated isocoumarin [D_4]-**55hg**. In order to determine the KIE, the gradient of the initial rate was calculated for both reactions.



Scheme 3.47: Reactions of **56h** and [D_5]-**56h** monitored by *in situ* IR spectroscopy.

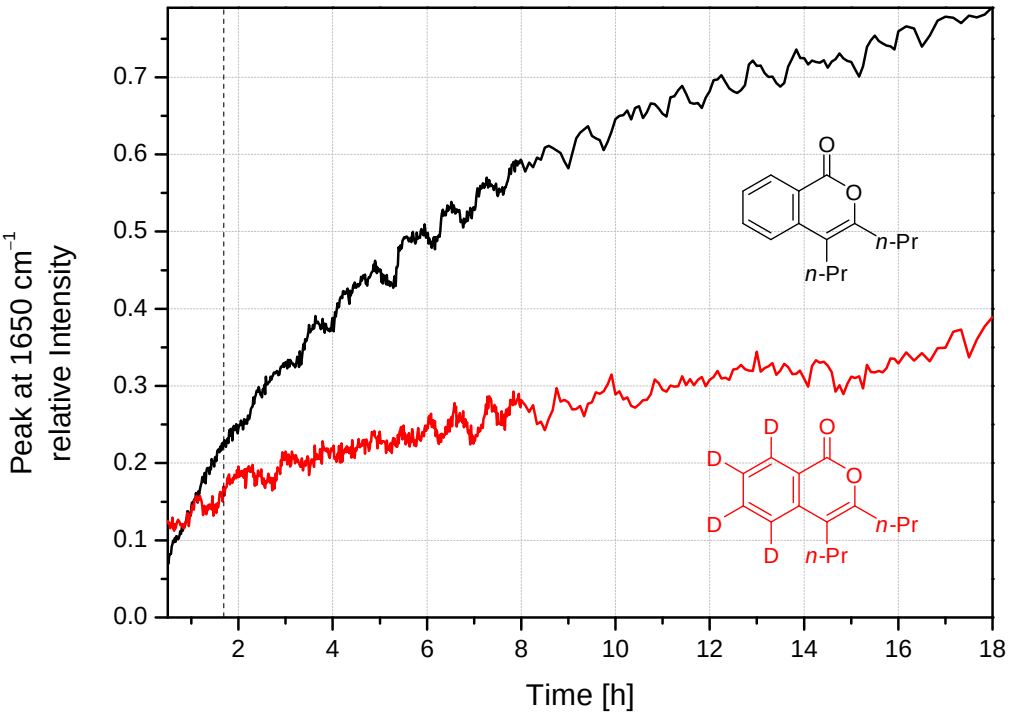


Figure 3.10: Kinetic profiles for the reactions of **56h** and [D_5]-**56h** with **34g**.

During the first 30 min the intensity of the signal at 1650 cm^{-1} is decreasing instead of increasing. This is a thermal effect, as it takes some time till the reaction mixture reaches the final reaction temperature, even though the oil-bath was preheated. To exclude any errors from this heating-phase, the range of data used for the calculation of the initial rate-constants spreads from 30 min to 2 h (Figure 3.11). The linear fits were calculated with *OriginPro 8.5G*:

$$k_{\mathrm{H}} = 0.11674 \pm 0.00178$$

$$k_{\mathrm{D}} = 0.04705 \pm 0.00254$$

$$\mathrm{KIE} = \frac{k_{\mathrm{H}}}{k_{\mathrm{D}}} = 2.48119 \pm 0.17178$$

This kinetic isotope effect was lower than the one observed in the competition experiments between **56h** and [D_5]-**56h**, but with 2.5 it was still significant. These are strong hints to conclude that the C−H bond cleavage is most likely the turnover-determining step (TDS).

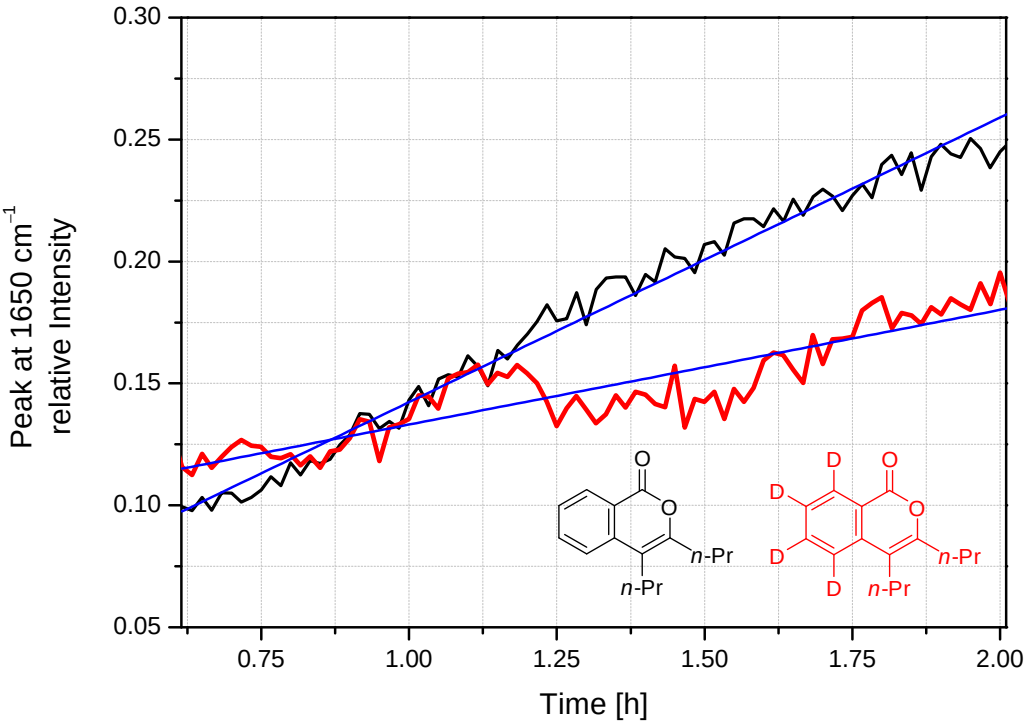
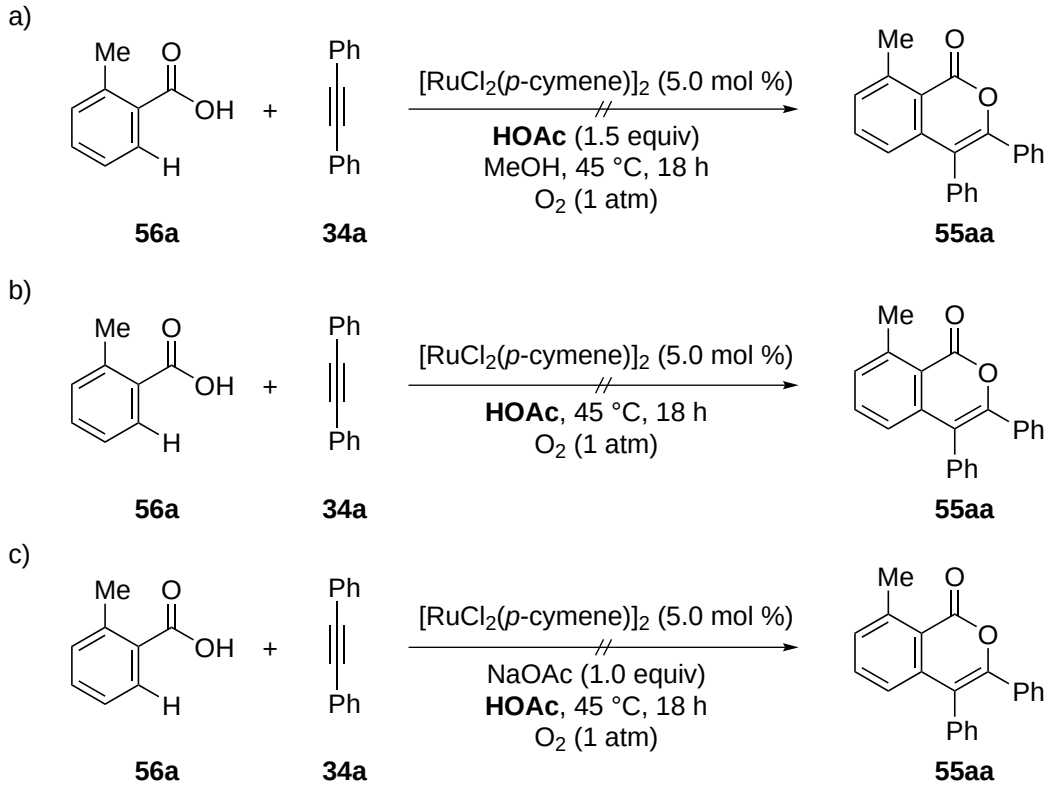


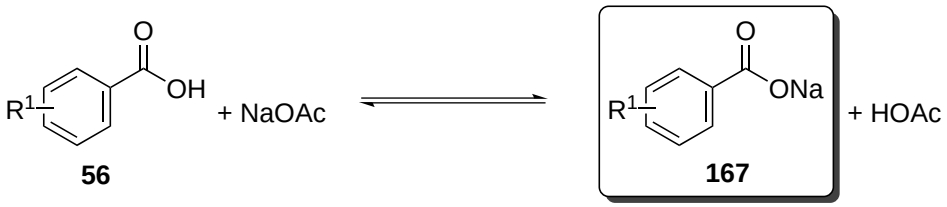
Figure 3.11: Initial rates for the reactions of **56h** and [D_5]-**56h** with **34g**.

The acetic acid seems to be indispensable for the reoxidation of the ruthenium catalyst. However, if acetic acid was used under the optimized reaction conditions as a replacement of sodium acetate, or even as solvent, no product formation was observed (Scheme 3.48).



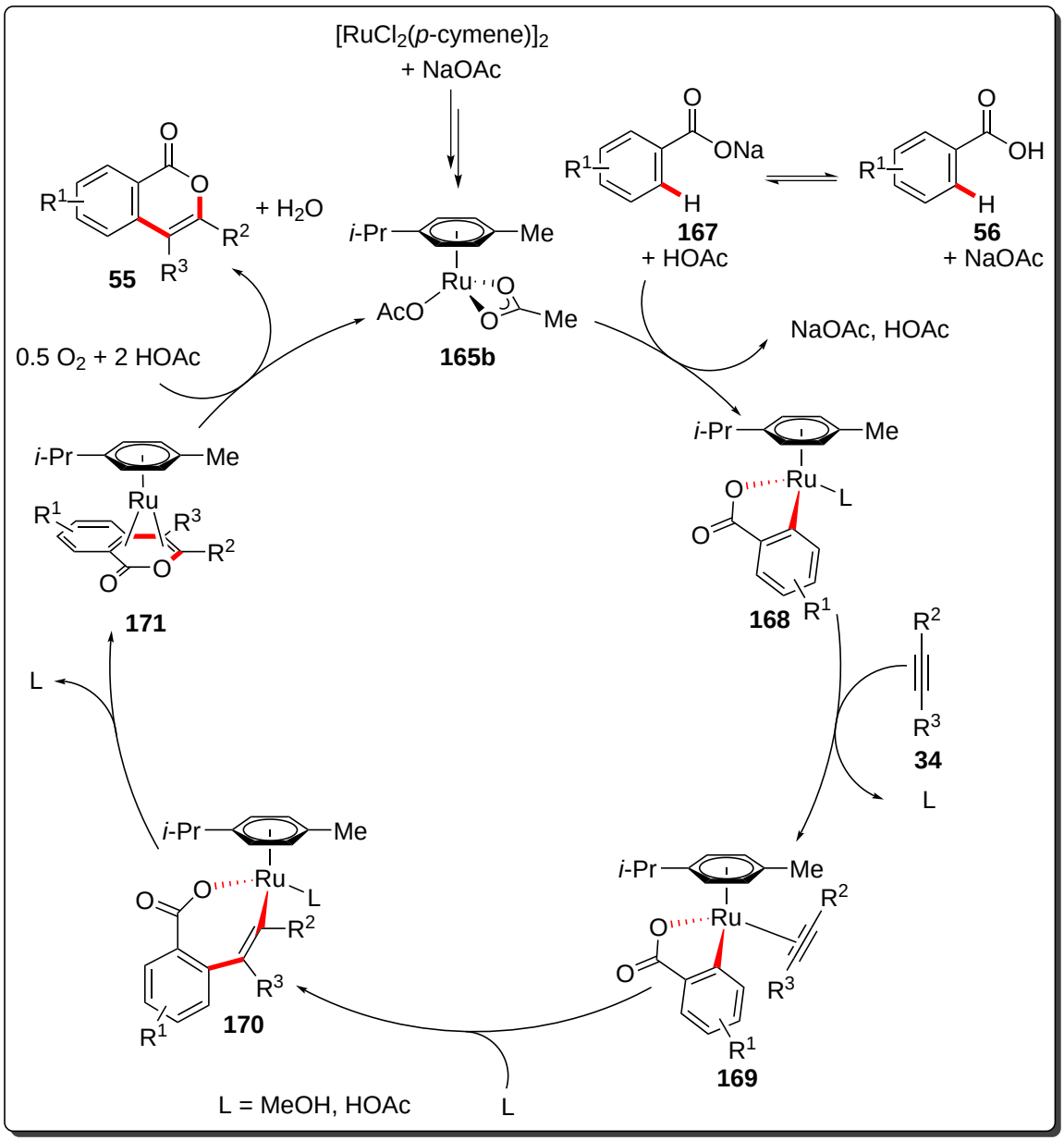
Scheme 3.48: Attempted ruthenium-catalyzed annulations in the presence of HOAc.

On one hand, acetic acid was indispensable for the reoxidation of the ruthenium catalyst, and, on the other hand, large quantities of HOAc seemed to hamper the reaction. These apparent contradictory results can be explained with a pre-equilibrium between the benzoic acid **56** and sodium acetate (Scheme 3.49). The ruthenium-acetate complex **164b** is most likely undergoing ligand exchange with the sodium benzoate **167**. Thus, a large excess of HOAc will shift the equilibrium to the left side and thus to the protonated benzoic acid **56**, which hardly coordinates to the catalyst.



Scheme 3.49: Pre-equilibrium between **56** and NaOAc.

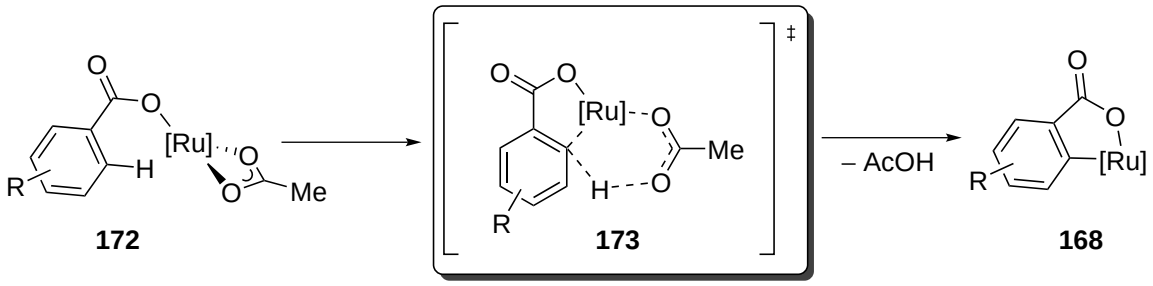
With the information gained from all these experiments and based on the previously nonaerobic system,[110] it is finally possible to devise a mechanism for the ruthenium-catalyzed aerobic annulation of alkynes with benzoic acids (Scheme 3.50).



Scheme 3.50: Mechanism for the aerobic annulation of alkynes **34** with benzoic acids **56**.

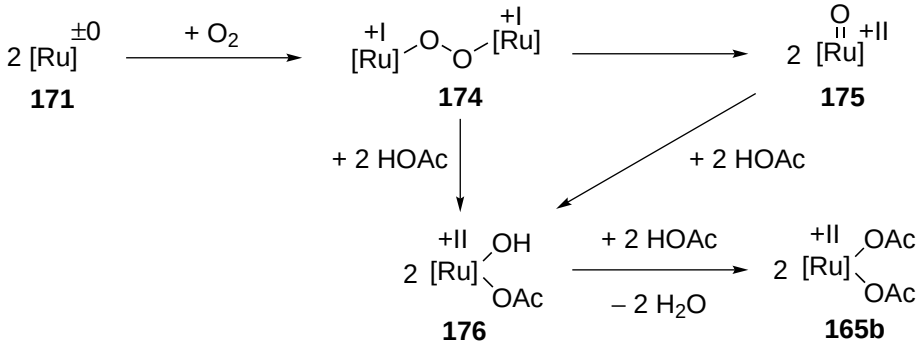
At first, the catalytically active species is formed. This is the carboxylate complex **165b**. The previously discussed equilibrium leads to a sodium benzoate **167**, which reacts with the catalytically active species **165b** to form the cyclometallated-complex **168**. The previous discussed results on the H/D-exchange experiments also suggest that this step of the catalytic cycle is most likely the turnover-determining step (TDS), as long as the reaction is performed under a completely saturated oxygen atmosphere. Moreover, it should be mentioned that 2 equivalents of HOAc are formed during the course of the catalytic cycle, one through deprotonation of the benzoic acid **56** and the second one during the carboxylate-assisted C−H activation step. The next step of the catalytic cycle is the coordination of the alkyne which subsequently undergoes migratory insertion into the carbon−ruthenium bond.

The resulting seven-membered ruthenacycle **170** is relatively unstable and immediately undergoes reductive elimination to yield a ruthenium(0)-sandwich complex **171**. Such ruthenium(0)-sandwich complexes were isolated by *S. Warratz* in stoichiometric experiments.[237] In the absence of HOAc and O_2 this species is stable, however, under the reaction conditions this ruthenium(0)-species is prone to oxidation. The 2 equivalents of HOAc, which are formed earlier in the catalytic cycle, are consumed within the regeneration of the carboxylate complex **165b**. During this process the product **55** is released and oxygen presumably reduced to water. The suggested CMD-typ transition state for the turnover-determining C−H activation step is shown in Scheme 3.51.



Scheme 3.51: Transition state **173** for the carboxylate-assisted C−H activation of benzoic acids.

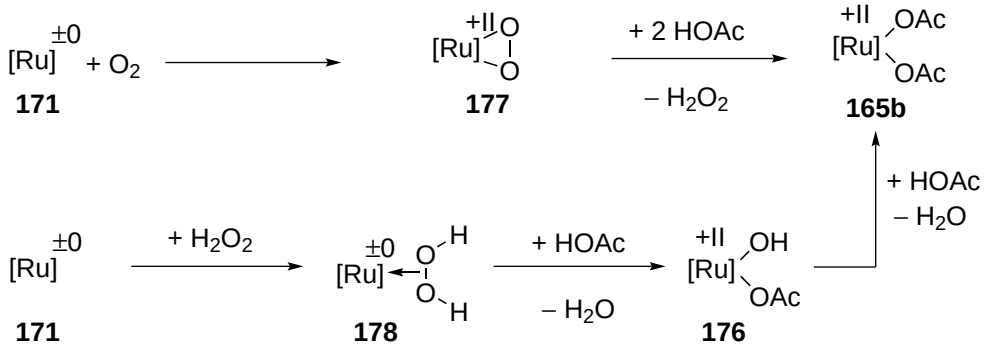
One aspect is still not completely clarified: the exact mechanism for the reoxidation of the ruhenium(0)-species to the ruthenium(II)-species. Herein, two possible reoxidation pathways are elucidated. The first one proceeds *via* a bisruthenium(I)-(μ-η^1:η^1)peroxo species **174** (Scheme 3.52).[238] Complex **174** can undergo disproportionation into two monomeric ruthenium(II)-oxo complexes **175** followed by subsequent attack of HOAc and formation of the complex **165b**, or direct transformation to **176** *via* oxidative addition of HOAc. The hydroxide-ligand in **176** is replaced by another equivalent of acetic acid to form the biscarboxylate complex **165b**.



Scheme 3.52: Reoxidation pathway *via* bisruthenium(I)-(μ-η^1:η^1)peroxo species **174**.

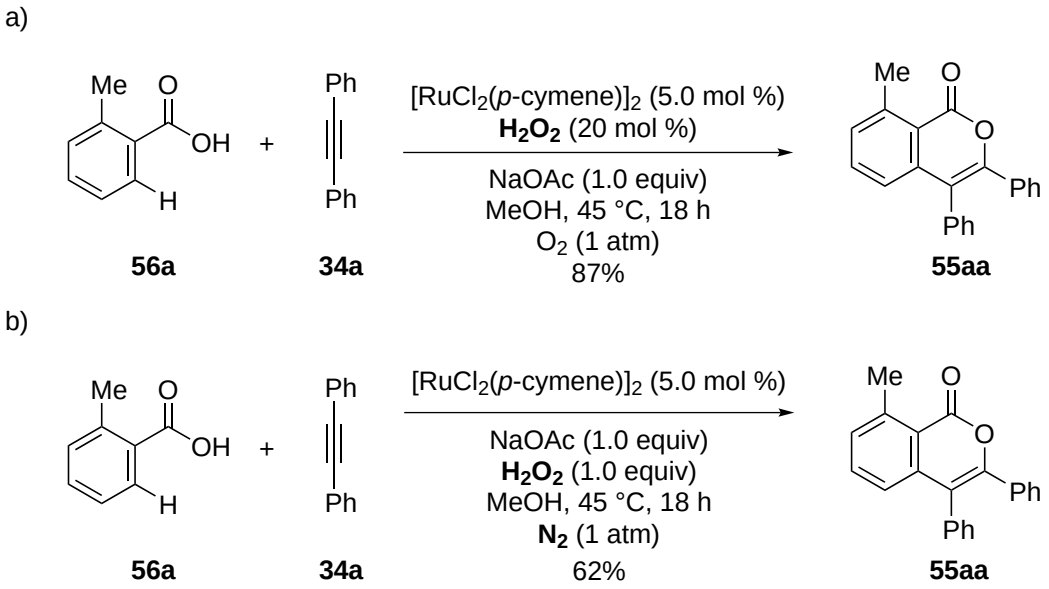
The second pathway involves the formation of a monomeric ruthenium(II)-(η^2)peroxo species **177**, where the oxygen coordinates side-on to the metal-center (Scheme 3.53).[239–241] Upon nucleophilic attack of HOAc, hydrogen peroxide is released and biscarboxylate complex **165b**

is formed. The hydrogen peroxid can than react with a second ruthenium(0) metal-center to furnish the side-on coordinated complex **178**, which reacts with HOAc to form **176**.



Scheme 3.53: Reoxidation pathway *via* the monomeric ruthenium(II)-(η^2)peroxo species **177**.

In order to see, if hydrogen peroxide might be involved into the reoxidation pathway as shown in Scheme 3.53, two additional experiments were performed. As illustrated in Scheme 3.54, H_2O_2 is not only tolerated under the reaction conditions (Scheme 3.54 a), but can even serve as the sole oxidant in the absence of oxygen (Scheme 3.54 b)

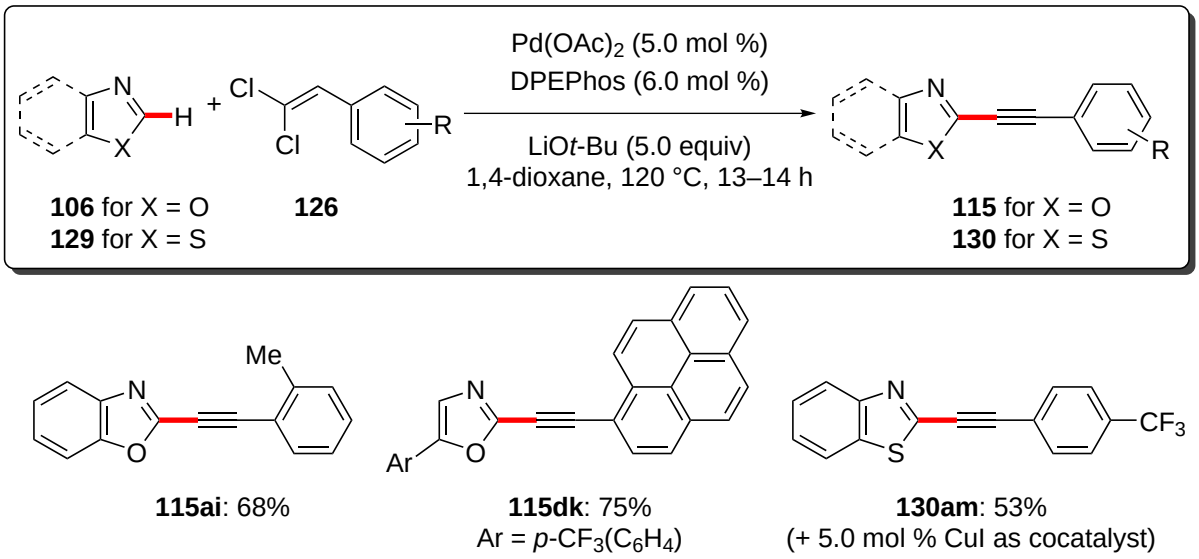


Scheme 3.54: Experiments with H_2O_2.

4 Summary and Outlook

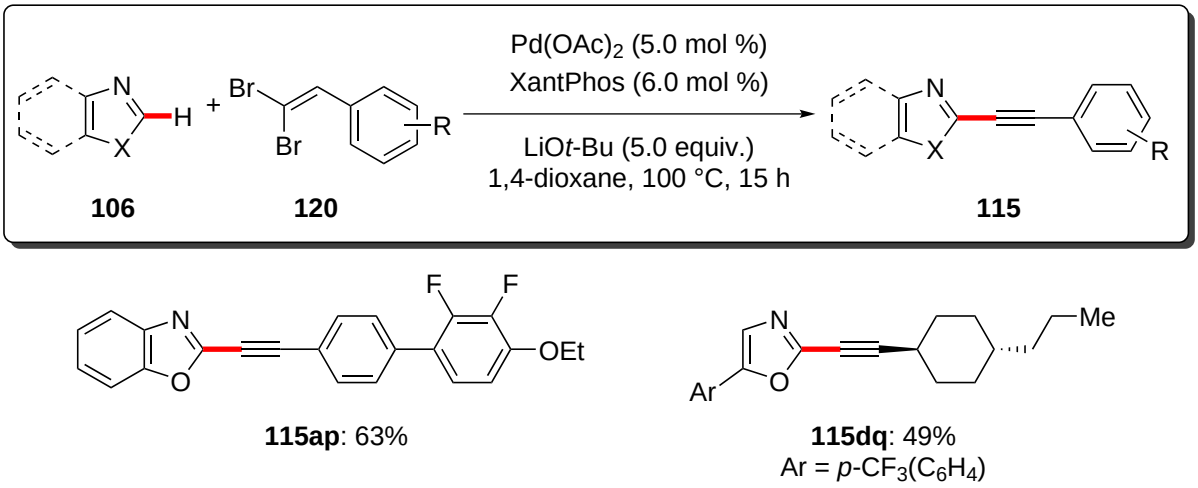
The development of sustainable procedures for the synthesis of highly functionalized heterocycles is of great importance for the preparation of pharmaceuticals, agrochemicals and functional materials. Therefore, the work presented within this thesis focused on the construction of heterocyclic frameworks based on step-economical palladium- or ruthenium-catalyzed direct C−H bond functionalizations.

In the first part of this thesis, an effective protocol for the direct alkynylation of oxazoles **106** and thiazoles **129** with easily accessible *gem*-dichloroalkenes **126** was elaborated and the catalytic system based on $Pd(OAc)_2$ and DPEPhos tolerated various functional groups (Scheme 4.1).



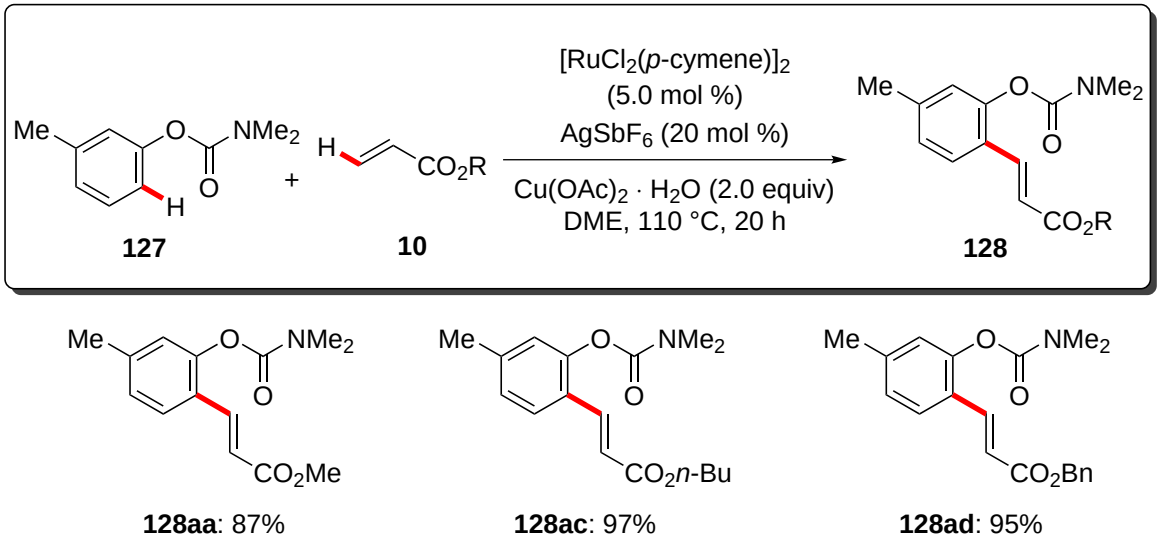
Scheme 4.1: Palladium-catalyzed direct alkynylations with *gem*-dichloroalkenes **126**.

Moreover, the reaction was proposed to proceed through a chloroalkenylated species which underwent β-elimination in the presence of LiO*t*-Bu. With slightly modified reaction conditions, the direct alkynylations were also achieved with *gem*-dibromoalkenes **120** as the electrophiles (Scheme 4.2). Notably, highly functionalized as well as aliphatic *gem*-dibromoalkenes were successfully converted to the corresponding products **115ap** and **115dq**.



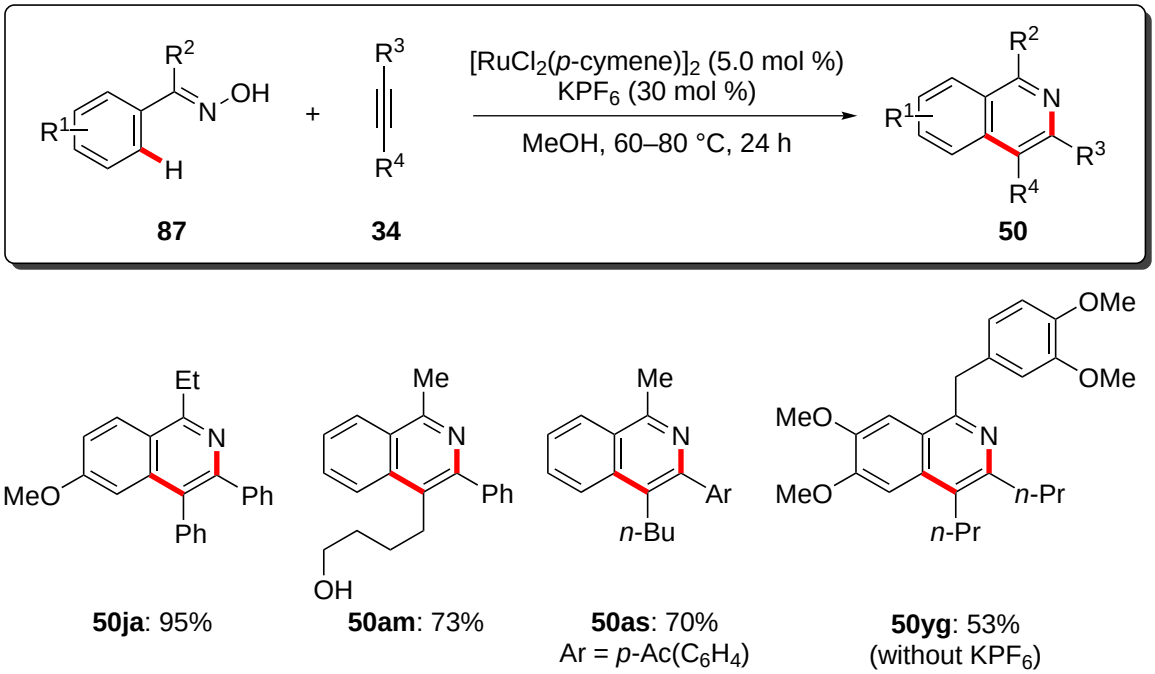
Scheme 4.2: Palladium-catalyzed direct alkynylations with *gem*-dibromoalkenes **120**.

The second part of this thesis elucidated phenol-derived carbamates **127** as directing groups for ruthenium-catalyzed direct alkenylation with differently substituted acrylates **10** (Scheme 4.3).



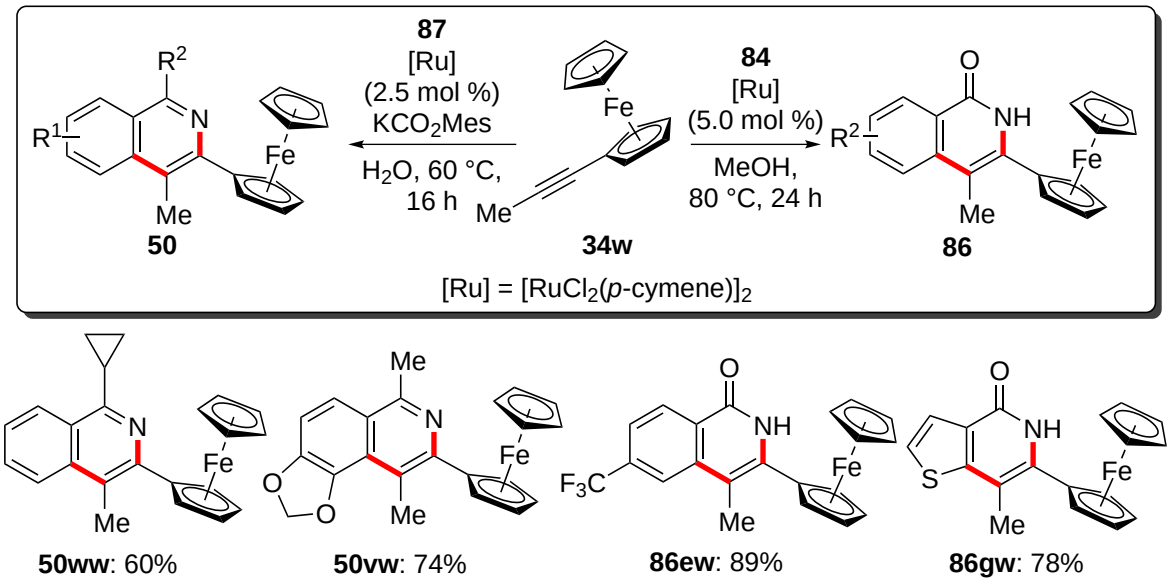
Scheme 4.3: Ruthenium-catalyzed direct C−H alkenylations of aryl carbamates **127**.

The third project focused on redox-neutral annulations of alkynes **34** *via* ruthenium-catalyzed C−H/N−O bond functionalization of oximes **87**. The aim of this study was to devise a short and efficient synthesis of highly substituted isoquinolines **50** (Scheme 4.4). Electron-rich as well as electron-deficient oximes were tolerated with ample scope. Unsymmetrical aryl-alkyl-alkynes, bearing sensitive functionalities, were regioselectively transformed to the corresponding isoquinolines, as for instance **50am** and **50as**. Pleasantly, the method proved also valuable for the synthesis of papaverine- and moxaverine-derivatives such, as isoquinoline **50yg**.



Scheme 4.4: Synthesis of isoquinolines **50** *via* ruthenium-catalyzed alkyne-annulations.

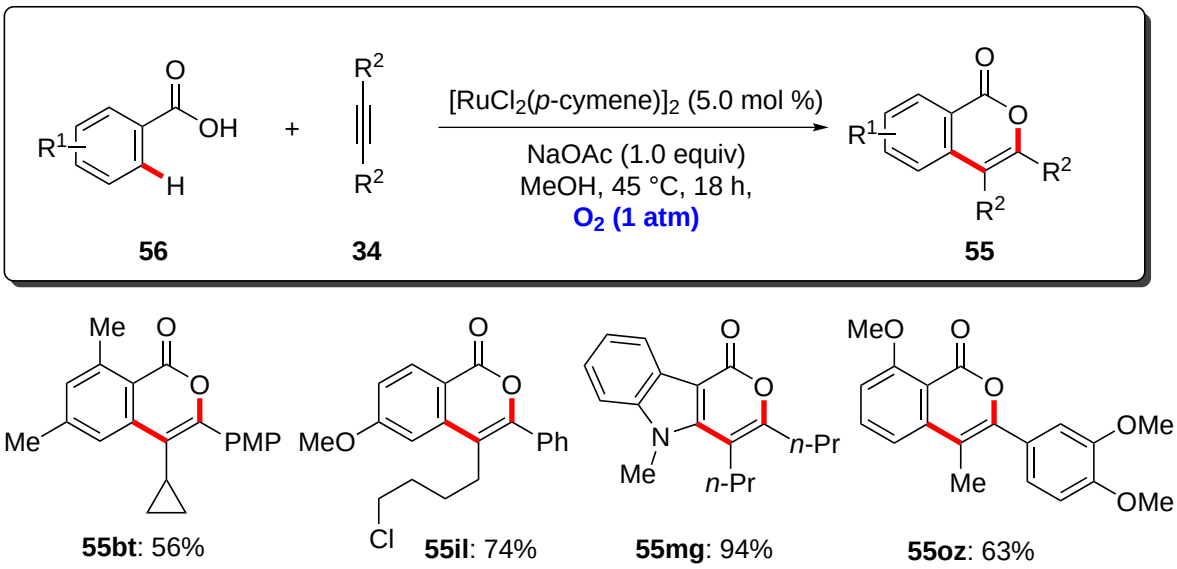
Electron-rich oximes generally reacted faster than the electron-poor analogs. The sterically-less hindered C−H bond was preferentially functionalized in *meta*-substituted substrates unless the substituent was bearing a free electron pair and thus displayed a secondary directing effect. Detailed mechanistic studies, involving experiments with isotopically labeled substrates, revealed that the reaction likely proceeded *via* an alkyne-coordinated cationic ruthenium-species and that the C−H bond cleavage was reversible in nature.



Scheme 4.5: Ruthenium-catalyzed annulations of ferrocenyl-substituted alkyne **34w** through C−H/N−O bond cleavage.

Consequently, the reaction was modified for annulations of a redox-sensitive ferrocenylalkyne **34w** (Scheme 4.5). This reaction showed the same regioselectivity as with aryl-alkyl-alkynes. Notably, the ferrocenylalkyne could also be employed for a previously developed annulation of *N*-methoxybenzamides **84** yielding ferrocenyl-substituted isoquinolones, for instance **86ew**, and heterocyclic analog **86gw**.[124]

Thereafter, the last project was dealing with ruthenium-catalyzed oxidative annulations of alkynes **34** with benzoic acids **56**, based on a modification of a previously devised reaction.[110] The initial concept was aimed towards a photochemically triggered reoxidation of the ruthenium catalyst instead of using stoichiometric amounts of copper(II)-salts. In the course of the studies it was revealed, that reoxidation simply occured in the presence of molecular oxygen under very mild reaction conditions (Scheme 4.6).



Scheme 4.6: Synthesis of isocoumarins **55** *via* ruthenium-catalyzed aerobic alkyne annulations.

With unsymmetrical alkynes the reaction is again highly regioselective, yielding 3-aryl substituted isocoumarins, such as **55bt** and **55il**, even in the presence of sterically demanding cyclopropyl-substituents and sensitive functionalities. Notably also heterocyclic analogues, for example **55mg**, and precursors of naturally-derived isocoumarins (**55oz**) were prepared in high yields.

Within extensive kinetic studies, involving also deuterium-labeled compounds, it was shown that the C−H bond cleavage is the turnover-determining step of the catalytic cycle.

The rather poor yields, which were obtained with terminal alkynes in all of the ruthenium-catalyzed annulation reactions and attributed dimerization of the terminal alkyne, is an issue that should be addressed in further studies, as well as modification of the catalyst in order to tolerate other reactive functionalities.

5 Experimental Section

5.1 General Remarks

All reactions involving moisture- or air-sensitive reagents or products were performed under a nitrogen atmosphere using pre-dried glassware and standard Schlenk techniques. Syringes for handling of dry solvents or liquid reagents were flushed with dry nitrogen threefold prior to use. Analytical data of known substances were compared with those described in the literature.

Vacuum

The following pressures were measured on the used vacuum pump and are uncorrected: oil pump vacuum (OPV): 0.1 mbar, membrane pump vacuum (MPV): 5.0 mbar.

Melting Points

Melting points were measured using a *Stuart® Melting Point Apparatus SMP3* from BARLOWORLD SCIENTIFIC or BÜCHI *540 Melting Point Apparatus*. The reported values are not corrected.

Chromatography

Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel *60F-plate* (MACHEREY-NAGEL) with 254 nm fluorescent indicator from MERCK. Plates were either visualized under ultraviolet light or developed by treatment with a $KMnO_4$ solution followed by careful warming with a heat gun. Chromatographic purification of products was accomplished by flash column chromatography on MERCK silica gel, *grade 60* (40–63 μm and 63–200 μm, 70–230 mesh ASTM).

Gas Chromatography

Monitoring of reaction processes *via* coupled gas chromatography-mass spectrometry was performed using *G1800C GCDplus* with mass detector *HP 5971, 5890 Series II* with mass detector *HP 5972* from HEWLETT-PACKARD and *7890A* GC-System with mass detector *5975C* (*Triplex-Axis-Detector*) from AGILENT TECHNOLOGIES. *HP-5MS* columns (30 m $\times$ 0.25 mm, film 0.25 μm) were used.

Infrared Spectroscopy

Infrared spectra were recorded using a BRUKER *Alpha-P ATR* spectrometer. Liquid samples were measured as film and solid samples neat. Analysis of the spectral data was carried out using *OPUS 6*. Absorption is given in wave numbers (cm^{-1}). Spectra were recorded in the range from 4000 to 400 cm^{-1}. Kinetic profiles of reactions were recorded using a METLER TOLEDO *ReactIR™ 15* spectrometer with a *DiComp* (Diamond) probe (AgX 9.5 mm × 1.5 mm fiber, 3000–650 cm^{-1}, 8 cm^{-1} resolution). Analysis of the recorded data was carried out using *IC IR™ 4.3* and *Origin Pro 8.5G* software.

Fluorescence-Spectroscopy

The fluorescence-emission spectra of **115dk** were recorded on a JASCO *FP-6200* spectroscope with an *ETC 27 LCT* heater. Spectra were recorded as 5μM-solutions of **115dk** in CH_2Cl_2. Analyses of the recorded spectra was carried out using *Origin Pro 8.5G*.

Nuclear Magnetic Resonance Spectroscopy (NMR)

Nuclear magnetic resonance (NMR) spectra were recorded at 300 or 600 MHz (^{1}H NMR), 75 or 125 MHz (^{13}C NMR and APT) and 282 MHz (^{19}F NMR) on VARIAN *Unity-300*, *AMX 300*, *Inova-500* and *Inova-600* instruments. Chemical shifts are reported as δ-values in ppm relative to the residual proton peak or the carbon peak of the deuterated solvent.

	^{1}H NMR	^{13}C NMR
$CDCl_3$	7.26 ppm	77.2 ppm
DMSO-d_6	2.54 ppm	40.5 ppm
Acetone-d_6	2.09 ppm	30.6 ppm

For characterization of the observed resonance multiplicities the following abbrevations were applied: s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), hept (heptet), m (multiplet) or analogous representations. The coupling constants J are reported in Hertz (Hz). Analysis of the recorded spectra were carried out using *MestReNova 7.1* software.

Mass Spectrometry

EI and EI-HRMS spectra were measured on a Time-of-Flight mass spectrometer *AccuTOF* from JOEL. ESI mass spectra were recorded on an Ion-Trap mass spectrometer *LCQ* from FINNIGAN or on a Time-of-Flight mass spectrometer *microTOF* from BRUKER. ESI-HRMS spectra were recorded on a BRUKER *APEX IV* or a BRUKER *DALTONIC 7T*, Transform Ion Cyclotron Resonance (FTICR) mass spectrometer. The ratios of mass to charge are indicated, intensities relative to the base peak ($I = 100$) are written in parentheses. In the case of oligohalocompounds, only the peaks of major isotopomers are listed for the simplicity.

Solvents

Solvents for column chromatography were purified *via* distillation under reduced pressure prior to use. All solvents for reactions involving moisture-sensitive reagents were dried, distilled and stored under inert atmosphere (argon or nitrogen) according to following standard procedures.
Dichloromethane was purified using a solvent purification system (SPS-800) from M. BRAUN.
Toluene was purified using a solvent purification system (SPS-800) from M. BRAUN.
Tetrahydrofuran was purified using a solvent purification system (SPS-800) from M. BRAUN.
Diethyl ether was purified using a solvent purification system (SPS-800) from M. Braun.
Methanol was stirred over magnesium turnings at 65 °C for 3 h prior to distillation from $Mg(OMe)_2$.
***t*-Amylalcohol** was stirred over sodium chips at 103 °C for 5 h prior to distillation.
***t*-Butylalcohol** was stirred over sodium chips 83 °C for several hours at prior to distillation.
Triethylamine was stirred over CaH_2 at 90 °C for 4 h prior to distillation.
Water was degased before its use applying repeated Freeze-Pump-Thaw degasing procedure.
1,4-Dioxane was distilled from sodium benzophenone ketyl.
1,2-Dimethoxyethane was distilled from sodium benzophenone ketyl.
***N*-Methyl-2-pyrrolidone** was stirred over CaH_2 at 204 °C for 4 h and subsequently distilled under reduced pressure.

Reagents

Chemicals obtained from commercial sources (wit a purity > 95%) were used without further purification. The following compounds are known and were synthesized according to previously described literature protocols:
gem-dichloroalkenes **126**,[176] *gem*-dibromoalkenes **120**,[235] oximes **87**,[242] 1-propyn-1-yl-ferrocene (**34w**),[208] ethynylferrocene (**31f**),[207] arylalkyl-alkynes **34**,[243] ruthenium(acetato-κO)-(acetato-κO,κO')[(1,2,3,4,5,6-η)(*p*-cymene)],[244] 1-([1,1'-biphenyl]-4-yl)ethan-1-one (**9c**),[245] 1-phenyl-*n*-hexan-1-one (**9l**),[246] 5-[4-(Trifluoromethyl)phenyl]oxazole (**106d**),[247], 2-ferrocenyl-phenylacetylene (**34x**),[209] *N*-methoxybenzamides **84**.[122]
Several compounds were used with the kind permission of the following people:
Karsten Rauch: $[RuCl_2(p\text{-cymene})]_2$, $[RuBr_2(p\text{-cymene})]_2$, $[Ru(O_2CMes)_2(p\text{-cymene})]$.
M.Sc. Kris Runge: 1-(2,2-dichlorovinyl)-4-methoxybenzene (**126e**), 1-(2,2-dichlorovinyl)-4-methylbenzene (**126c**), 1-chloro-4-(2,2-dichlorovinyl)benzene (**126h**), 1-(2,2-dichlorovinyl)-3-methylbenzene (**126j**), 1-(2,2-dichlorovinyl)-4-fluorobenzene (**126g**), 4-(2,2-dichlorovinyl)-1,2-dimethoxybenzene (**126f**), 5-(2,2-dichlorovinyl)-1,2,3-trifluorobenzene (**126l**).
B.Sc. Kathrin Dienst: oct-1-ynylbenzene (**34k**), 1-(hex-1-ynyl)-4-methylbenzene (**34o**), 1,2-bis[4-(trifluoromethyl)phenyl]acetylene (**34d**), 1,2-di-*p*-tolylacetylene (**34e**), 4-(hex-1-ynyl)-biphenyl (**34p**).
M.Sc. Jie Li: 1-(4-fluorophenyl)ethanone oxime (**87e**), acetophenone *O*-methyloxime (**87s**), cyclopropyl(phenyl)methanone oxime (**87w**), *m*-tolyl *N*,*N*-dimethylcarbamate (**127a**),

benzo[*d*][1,3]dioxol-5-yl *N*,*N*-dimethyl-carbamate (**127b**), 1-(4-chlorophenyl)ethanone oxime (**87f**).
M.Sc. Fanzhi Yang: 1-fluoro-4-(hex-1-ynyl)benzene (**34r**), 4-ethyl-*N*-methoxybenzamide (**84a**).
M.Sc. Karolina Graczyk: KO_2CMes.
Dr. Alexander V. Lygin: $[Ru_2Cl_3(p\text{-cymene})_2][PF_6]$.
M.Sc. Sebastian Lackner: 1-[4-(prop-1-ynyl)phenyl]ethanone (**34s**).
M.Sc. Jie (Jack) Li: 1,2-bis(4-methoxyphenyl)acetylene (**34c**).
Margherita Donati: 1,2-bis(4-fluorophenyl)acetylene (**34b**).

5.2 General Procedures

General Procedure A: Synthesis of *gem*-Dichloroalkenes 126

Aldehyde **104** (10.0 mmol, 1.0 equiv) and PPh_3 (7.90 g, 30.1 mmol, 3.0 equiv) were placed in a 250-mL flask, and MeCN (100 mL) was added. The mixture was stirred at ambient temperature for 5 min, followed by the addition of $BrCCl_3$ (3.57 g, 18.0 mmol, 1.8 equiv). The resulting mixture was stirred at ambient temperature for 7 h. A mixture of Et_2O/*n*-pentane (3:1, 500 mL) was added and the resulting suspension was filtered through a pad of silica gel to seperate the precipitated $Ph_3P{=}O$. The solvents were removed in vacuo and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

General Procedure B: Synthesis of *gem*-Dibromoalkenes 120

Aldehyde **104** (10.0 mmol, 1.0 equiv) and CBr_4 (5.00 g, 15.1 mmol, 1.5 equiv) were placed in a two-necked 250-mL flask equipped with a dropping-funnel and CH_2Cl_2 (80 mL) was added. The reaction mixture was cooled down to 0 °C and a solution of PPh_3 (7.90 30.1 mmol, 3.0 equiv) in CH_2Cl_2 (70 mL) was added dropwise over a period of 20 min. Thereafter, the resulting solution was stirred at ambient temperature for 2 h. The solvent was removed *in vacuo*. $CHCl_3$ (20 mL) was added, the precipitade was filtered off and washed with $CHCl_3$ (2 × 25 mL). The filtrates were combined and the solvent was removed *in vacuo*. The product was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

General Procedure C: Synthesis of Oximes 87

Hydroxylamine hydrochloride (**91**) (2.61 g, 37.5 mmol, 1.50 equiv) and NaOAc (5.13 g, 62.5 mmol, 2.5 equiv) were placed in a 100-mL flask equipped with a reflux condenser, EtOH (10 mL), H_2O (30 mL) and ketone **9** (25 mmol, 1.00 equiv) were added. The resulting mixture was stired at 100 °C overnight. After cooling to 0 °C, the precipitated crude product was filtered off and washed with H_2O. Recrystallization from EtOH yielded the pure oxime **87**.

General Procedure D: Palladium-Catalyzed Direct Alkynylations of Oxazoles 106 with *gem*-Dichloroalkenes 126

Solid oxazole **106** (0.50 mmol, 1.0 equiv), solid *gem*-dichloroalkene **126** (0.75 mmol, 1.5 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %), DPEPhos (16.2 mg, 0.030 mmol, 6.0 mol %) and LiO*t*-Bu (200 mg, 2.50 mmol, 5.0 equiv) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. Dry 1,4-dioxane (2.0 mL, 0.25 M) was added (and if liquid, the oxazole **106** and the *gem*-dichloroalkene **126** were also added at this point) and the reaction mixture was stirred at 120 °C for 13–14 h. At ambient temperature, H_2O (5 mL) was added and the aqueous layer was extracted with EtOAc (4 × 20 mL). The organic layers were combined and the solvents were removed *in vacuo*. The product was purified by column chromatography on silica gel (*n*-hexane/EtOAc) or by recrystallization from EtOH.

General Procedure E: Palladium-Catalyzed Direct Alkynylations of Benzothiazole 129a with *gem*-Dichloroalkenes 126

Solid *gem*-dichloroalkene **126** (0.75 mmol, 1.5 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %), CuI (4.8 mg, 0.025 mmol, 5.0 mol %), DPEPhos (16.2 mg, 0.030 mmol, 6.0 mol %) and LiO*t*-Bu (200 mg, 2.50 mmol, 5.0 equiv) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. Dry 1,4-dioxane (2.0 mL, 0.25 M) and benzothiazole (**129a**) (0.50 mmol, 1.0 equiv) were added (and if liquid, the *gem*-dichloroalkene **126** was also added at this point) and the reaction mixture was stirred at 120 °C for 13–14 h. At ambient temperature, H_2O (5 mL) was added and the aqueous layer was extracted with EtOAc (4 × 20 mL). The organic layers were combined and the solvents were removed *in vacuo*. The product was purified by column chromatography on silica gel (*n*-hexane/EtOAc) or by recrystallization from EtOH.

General Procedure F: Palladium-Catalyzed Direct Alkynylations of Oxazoles 106 with *gem*-Dibromoalkenes 120

Solid oxazole **106** (0.50 mmol, 1.0 equiv), solid *gem*-dibromoalkene **120** (0.75 mmol, 1.5 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %), XantPhos (14.5 mg, 0.025 mmol, 5.0 mol %) and LiO*t*-Bu (200 mg, 2.50 mmol, 5.0 equiv) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. Dry 1,4-dioxane (2.0 mL, 0.25 M) was added (and if liquid, the oxazole **106** and the *gem*-dibromoalkene **120** were also added at this stage) and the reaction mixture was stirred at 100 °C for 15 h. At ambient temperature, H_2O (5 mL) was added and the aqueous layer was extracted with EtOAc (4 × 20 mL). The organic layers were combined and the solvents were removed *in vacuo*. The product was purified by column chromatography on silica gel (*n*-hexane/EtOAc) or by recrystallization from EtOH.

General Procedure G: Ruthenium-Catalzyed direct C−H Bond Alkenylations of Carbamates 127

$[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol, 2.5 mol %), $AgSbF_6$ (17 mg, 0.05 mmol, 20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (100 mg, 0.5 mmol, 1.0 equiv) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. Dry DME (3 mL, 0.17 M), carbamate **127** (0.5 mmol, 1.0 equiv) and the acrylate **10** (1.0 mmol, 2.0 equiv) were added and the reaction mixture was stirred at 110 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. The product was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

General Procedure H: Synthesis of Isoquinolines 50 *via* Ruthenium-Catalyzed C−H/N−O-Bond Functionalization

Oxime **87** (0.50 mmol, 1.0 equiv), solid alkyne **34** (1.00 mmol, 2.0 equiv) $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %) and KPF_6 (28 mg, 0.15 mmol, 30 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. Dry MeOH (2.0 mL, 0.25 M) was added (and if liquid, the alkyne **34** was also added at this stage) and the reaction mixture was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. The product was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

General Procedure I: Modified Procedure for the Synthesis of Isoquinolines 50 *via* Ruthenium-Catalyzed C−H/N−O-Bond Functionalization

Oxime **87** (0.50 mmol, 1.0 equiv), solid alkyne **34** (1.00 mmol, 2.0 equiv) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. Dry MeOH (2.0 mL, 0.25 M) was added (and if liquid, the alkyne **34** was also added at this stage) and the reaction mixture was stirred at 80 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. The product was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

General Procedure J: Ruthenium-Catalyzed C−H Annulations of 1-Propyn-1-yl-ferrocene 34w with *N*-Methoxybenzamides 84

N-Methoxybenzamide **84** (0.50 mmol, 1.0 equiv), 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol, 2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol, 2.5 mol %) and KO_2CMes (30 mg, 0.15 mmol, 30 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. Degassed H_2O (2.0 mL, 0.25 M) was added and the reaction mixture was stirred at 60 °C for 16 h. At ambient, temperature CH_2Cl_2 (15 mL) and H_2O (5 mL) were added and the mixture was transferred into a 100-mL separation funnel. CH_2Cl_2 (10 mL) and H_2O (10 mL) were added and the layers were separated. The aqueous layer

was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* and the product was purified by column chromatography on silica gel.

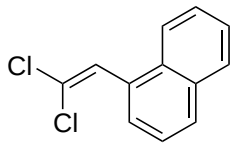
General Procedure K: Synthesis of Isocoumarins 55 *via* Ruthenium-Catalyzed C−H Bond Functionalization

Benzoic acid **55** (2.00 mmol, 2.0 equiv), solid alkyne (**34**) (1.00 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (30.6 mg, 0.05 mmol, 5.0 mol %) and NaOAc (82 mg, 1.00 mmol, 1.0 equiv) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with O_2 for 3 times. Dry MeOH (3.0 mL, 0.33 M) was added (and if liquid, the alkyne **34** was also added at this stage) and the reaction mixture was stirred at 45 °C for 18 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. The product was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

5.3 Experiments

5.3.1 Syntheses of *gem*-Dihaloalkenes 126 and 120

Synthesis of 1-(2,2-Dichlorovinyl)naphthalene (126a)



The general procedure **A** was followed using 1-naphthaldehyde (**104a**) (1.56 g, 10.0 mmol). After 7 h, purification by column chromatography (*n*-hexane) yielded **126a** as a white solid (2.037 g, 91%, m.p.: 49–52 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.98$–7.81 (m, 3H), 7.68–7.47 (m, 4H), 7.38 (d, $J = 0.6$ Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 133.5$ (C_q), 131.1 (C_q), 130.7 (C_q), 128.9 (CH), 128.6 (CH), 127.0 (CH), 126.9 (CH), 126.5 (CH), 126.1 (CH), 125.2 (CH), 124.0 (CH), 123.4 (C_q).

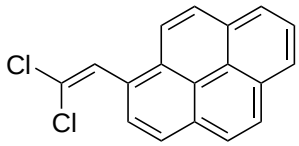
IR (ATR, cm^{-1}): 3063, 3027, 1591, 1505, 1346, 1294, 1171, 920, 899, 852, 793, 772, 732, 665, 605, 553, 474.

MS (EI): 222 (15) $[M]^+$, 187 (50) $[M-Cl]^+$, 152 (100) $[M-2Cl]^+$, 126 (7) $[C_{10}H_6]^+$, 98 (6), 93 (8), 86 (11), 75 (15), 63 (11).

$[\mathbf{C_{12}H_8Cl_2}]^+$ (EI) HRMS: calcd.: 222.0003.
found: 222.0006.

The spectral data are in accordance with those reported in the literature.[248]

Synthesis of 1-(2,2-Dichlorovinyl)pyrene (126k)



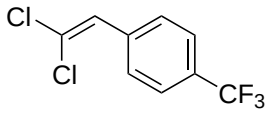
Pyrene-1-carbaldehyde (**104k**) (520 mg, 2.26 mmol) and PPh_3 (1.762 g, 6.72 mmol) were placed in a 100-mL flask and MeCN (40 mL) was added. The mixture was stirred at ambient temperature for 5 min, followed by the addition of $BrCCl_3$ (800 mg, 4.03 mmol). The reaction mixture was stirred at ambient temperature overnight. A mixture of Et_2O/*n*-pentane (3:1, 300 mL) was added and the resulting suspension was filtered through a pad of silica gel to separate the precipitated $Ph_3P{=}O$. The solvents were removed *in vacuo* and purification by column chromatography (*n*-hexane) yielded **126k** as a yellow solid (564 mg, 84%, m.p.: 121–125 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.24$–7.98 (m, 9H), 7.63 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 131.3$ (C_q), 131.1 (C_q), 130.7 (C_q), 128.6 (C_q), 128.1 (CH), 127.9 (CH), 127.8 (C_q), 127.4 (CH), 127.2 (CH), 126.5 (CH), 126.1 (CH), 125.6 (CH), 125.5

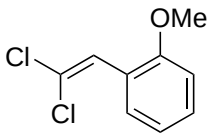
(CH), 124.6 (C_q), 124.5 (C_q), 124.4 (CH), 123.5 (C_q), 123.4 (CH).
IR (ATR, cm^{-1}): 3024, 1602, 1262, 1186, 913, 850, 835, 770, 745, 730, 708, 678, 665, 593, 491.
MS (EI): 296 (37) $[M]^+$, 261 (28) $[M-Cl]^+$, 226 (100) $[M-2Cl]^+$, 130 (11), 112 (16).
$[\mathbf{C_{18}H_{10}Cl_2}]^+$ (EI) HRMS: calcd.: 296.0160.
found: 296.0167.

Synthesis of 1-(2,2-Dichlorovinyl)-4-(trifluoromethyl)benzene (126m)



The general procedure **A** was followed using 4-(trifluoromethyl)benzaldehyde (**104m**) (1.74 g, 10.0 mmol). After 7 h, purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded **126m** as a pale yellow oil (1.717 g, 71%).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.62$ (s, 4H), 6.88 (s, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 136.8$ (C_q), 130.2 (d, $^2J_{C-F} = 33$ Hz, C_q), 128.9 (CH), 127.3 (CH), 125.4 (q, $^3J_{C-F} = 4$ Hz, CH), 123.9 (d, $^1J_{C-F} = 272$ Hz, C_q), 123.6 (C_q).
141.4 (C_q), 140.5 (C_q), 132.6 (C_q), 129.3 (CH), 129.1 (CH), 128.4 (CH), 127.9 (CH), 127.3 (CH), 127.3 (CH), 121.2 (C_q).
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.8$ (s).
IR (ATR, cm^{-1}): 1730, 1612, 1412, 1320, 1165, 1111, 1017, 915, 863, 830, 756, 673, 627, 514.
MS (EI): 240 (100) $[M]^+$, 221 (9) $[M-F]^+$, 205 (37) $[M-2Cl]^+$, 185 (32), 170 (30) $[M-2Cl]^+$, 151 (9), 136 (13), 120 (5), 99 (7), 75 (13), 58 (11), 43 (38).
$[\mathbf{C_9H_5Cl_2F_3}]^+$ (EI) HRMS: calcd.: 239.9720.
found: 239.9710.

Synthesis of 1-(2,2-Dichlorovinyl)-2-methoxybenzene (126n)



The general procedure **A** was followed using 2-methoxybenzaldehyde (**104n**) (1.36 g, 10.0 mmol). After 7 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **126n** as a pale yellow oil (1.48 g, 73%).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.72$ (dd, $J = 7.6$, 1.6 Hz, 1H), 7.30 (ddd, $J = 8.2$, 7.6, 1.6 Hz, 1H), 7.11 (s, 1H), 6.97 (td, $J = 7.6$, 1.1 Hz, 1H), 6.87 (dd, $J = 8.2$, 1.1 Hz, 1H), 3.83 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 156.6$ (C_q), 129.8 (CH), 129.1 (CH), 123.9 (CH), 122.4 (C_q), 120.9 (C_q), 120.2 (CH), 110.4 (CH), 55.5 (CH_3).

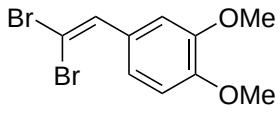
IR (ATR, cm^{-1}): 2837, 1598, 1484, 1462, 1435, 1246, 1111, 1051, 906, 829, 746, 660, 599, 562, 493.

MS (EI): 202 (73) $[M]^+$, 167 (22) $[M-Cl]^+$, 159 (30), 152 (65) $[M-Cl-Me]^+$, 139 (32), 131 (100) $[M-H-2Cl]^+$, 125 (30), 103 (33), 89 (55), 78 (14), 75 (13), 63 (25), 43 (26).

$[\mathbf{C_9H_8Cl_2O}]^+$ (EI) HRMS: calcd.: 201.9952.
found: 201.9953.

The spectral data are in accordance with those reported in the literature.[249]

Synthesis of 4-(2,2-Dibromovinyl)-1,2-dimethoxybenzene (120f)



The general procedure **B** was followed using 3,4-dimethoxybenzaldehyde (**104f**) (1.66 g, 10.0 mmol). After 2 h, purification by column chromatography (*n*-hexane/EtOAc: 4/1) yielded **120f** as a red oil (2.31 g, 72%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$ (s, 1H), 7.13 (d, $J = 2.1$ Hz, 1H), 7.04 (dd, $J = 8.4$, 2.1 Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 149.1$ (C_q), 148.3 (C_q), 136.2 (CH), 127.7 (C_q), 121.7 (CH), 110.9 (CH), 110.6 (CH), 87.1 (C_q), 55.7 (CH_3), 55.7 (CH_3).

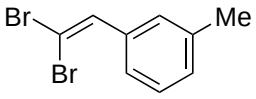
IR (ATR, cm^{-1}): 3002, 2933, 2834, 1599, 1510, 1461, 1440, 1418, 1258, 1233, 1140, 1022, 869, 837, 820, 799, 766, 717, 569, 551, 480, 460, 439.

MS (EI): 322 (100) $[M]^+$, 307 (43) $[M-Me]^+$, 279 (9), 198 (21), 162 (23), 147 (25), 119 (50), 91 (32), 76 (29), 58 (17), 50 (24), 43 (77).

$[\mathbf{C_{10}H_{10}Br_2O_2}]^+$ (EI) HRMS: calcd.: 319.9048
found: 319.9048.

The spectral data are in accordance with those reported in the literature.[250]

Synthesis of 1-(2,2-Dibromovinyl)-3-methylbenzene (120j)



The general procedure **B** was followed using 3-mehtylbenzaldehyde (**104j**) (1.20 g, 10.0 mmol). After 2 h, purification by column chromatography (*n*-hexane) yielded **120j** as a yellow oil (1.818 g, 66%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.45$ (s, 1H), 7.40–7.30 (m, 2H), 7.26 (t, $J = 7.5$ Hz, 1H), 7.18–7.10 (m, 1H), 2.37 (s, 3H).

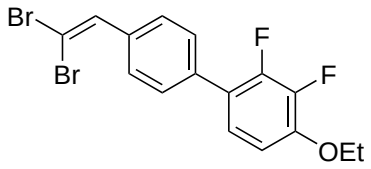
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 138.0$ (C_q), 137.0 (CH), 135.2 (C_q), 129.3 (CH), 129.0 (CH), 128.3 (CH), 125.4 (CH), 89.3 (C_q), 21.4 (CH_3).

IR (ATR, cm^{-1}): 3015, 2919, 1603, 1483, 1449, 1271, 1092, 936, 908, 882, 833, 815, 773, 729, 690, 602, 564, 521, 441.

MS (EI): 276 (90) $[M]^+$, 195 (18) $[M-Br]^+$, 116 (100) $[M-2Br]^+$, 89 (16), 63 (15), 58 (12), 50 (8), 43 (27).

$[\mathbf{C_9H_8Br_2}]^+$ (EI) HRMS: calcd.: 273.8993
found: 273.8958.

Synthesis of 4'-(2,2-Dibromovinyl)-4-ethoxy-2,3-difluoro-1,1'-biphenyl (120p)



4'-Ethoxy-2',3'-difluoro-1,1'-biphenyl-4-carbaldehyde (**104p**) (1.31 g, 5.0 mmol) and CBr_4 (2.49 g, 7.51 mmol) were placed in a two-necked 100 mL-flask equiped with a dropping funnel and CH_2Cl_2 (40 mL) was added. The reaction mixture was cooled to 0 °C and a solution of PPh_3 (3.93 g, 15 mmol) in CH_2Cl_2 (35 mL) was added dropwise over a period of 20 min. Thereafter, the resulting solution was stirred at ambient temperature for 2 h. The solvent was removed *in vacuo*. $CHCl_3$ (20 mL) was added, the precipitade was filtered off and washed with $CHCl_3$ (2 × 25 mL). The filtrates were combined and the solvent was removed *in vacuo*. Purification by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **120p** as a beige-yellow solid (1.797 g, 86%, m.p.: 80–81 °C)

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.60$ (d, $J = 8.3$ Hz, 2H), 7.53–7.47 (m, 2H), 7.49 (s, 1H), 7.09 (ddd, $J = 8.9, 8.1, 2.4$ Hz, 1H), 6.78 (ddd, $J = 8.9, 7.5, 2.0$ Hz, 1H), 4.15 (q, $J = 7.0$ Hz, 2H), 1.47 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 148.9$ (dd, $^1J_{C-F} = 249$ Hz, $^2J_{C-F} = 11$ Hz, C_q), 147.9 (dd, $^2J_{C-F} = 8$ Hz, $^3J_{C-F} = 3$ Hz, C_q), 141.8 (dd, $^1J_{C-F} = 247$ Hz, $^2J_{C-F} = 15$ Hz, C_q), 136.3 (CH), 135.07 (dd, $^3J_{C-F} = 2$ Hz, $^4J_{C-F} = 2$ Hz, C_q), 134.5 (C_q), 128.6 (t, $^3J_{C-F} = 3$ Hz, CH), 128.6 (CH), 123.4 (t, $^3J_{C-F} = 4$ Hz, CH), 122.2 (d, $^2J_{C-F} = 11$ Hz, C_q), 109.5 (CH), 89.9 (C_q), 65.4 (CH_2), 14.7 (CH_3).

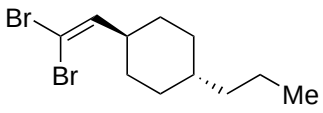
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -141.5$ (ddd, $J = 20.4, 9.2, 2.8$ Hz), -158.6 (ddd, $J = 18.9, 8.5, 2.8$ Hz).

IR (ATR, cm^{-1}): 2994, 2938, 1624, 1523, 1502, 1470, 1400, 1286, 1199, 1103, 1068, 874, 844, 796, 781, 726, 670, 626, 552, 525.

MS (EI): 418 (72) $[M]^+$, 390 (90) $[M-C_2H_4]^+$, 230 (100) $[M-C_2H_4-2Br]^+$, 201 (37), 181 (33), 175 (8), 151 (8), 115 (7), 75 (6), 43 (13).

$[\mathbf{C_{16}H_{12}Br_2F_2O}]^+$ (EI) HRMS: calcd.: 415.9223
found: 415.9218.

Synthesis of (1*s*,4*r*)-1-(2,2-Dibromovinyl)-4-*n*-propylcyclohexane (120q)



The general procedure **B** was followed using 4-*n*-propylcyclohexane-1-carbaldehyde (**104j**) (1.54 g, 10.0 mmol). After 2 h, purification by column chromatography (*n*-hexane) yielded **120q** as a yellow oil (2.008 g, 65%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.20$ (d, $J = 9.0$ Hz, 1H), 2.29–2.14 (m, 1H), 1.83–1.71 (m, 4H), 1.61–0.82 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 143.8$ (CH), 87.0 (C_q), 42.8 (CH), 39.6 (CH_2), 36.6 (CH), 32.3 (CH_2), 31.2 (CH_2), 19.9 (CH_2), 14.3 (CH_3).

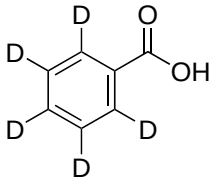
IR (ATR, cm^{-1}): 2918, 2849, 1447, 948, 900, 834, 801, 765, 551.

MS (EI): 310 (9) $[M]^+$, 267 (15) $[M-C_3H_7]^+$, 212 (13), 199 (16), 159 (10), 149 (60), 133 (20), 123 (53), 107 (20), 95 (24), 81 (88), 79 (35), 67 (45), 55 (62), 43 (76), 41 (100).

$[C_{11}H_{18}Br_2]^+$ (EI) HRMS: calcd.: 307.9775
found: 307.9777.

5.3.2 Syntheses of Ketones 9, Oximes 87 and Alkynes 34

Synthesis of [D_5]-Benzoic acid ([D_5]-56h)



Magnesium turnings (440 mg, 18.1 mmol, 1.29 equiv) were placed in a pre-dried, three-necked 50-mL flask equipped with a reflux condenser. The flask was degassed, purged with N_2 for 3 times and heated up to 85 °C. [D_5]-Bromobenzene (2.27 g, 14.0 mmol, 1.00 equiv) was dissolved in dry THF (15 mL). 1 mL of this solution was added under stirring to the magnesium turnings and the mixutre was heated to 65 °C. When the reaction initiated (the solvend startet changing colour) the rest of the [D_5]-Bromobenzene/THF-solution was added dropwise over 15 min. The resulting mixture was stirred at 65 °C for 1 h. A huge excess of dry ice was placed in pre-dried and nitrogen-purged 100-mL Schlenk flask. The *Grignard* solution was added dropwise, the resulting mixture was slowly heated up to ambient temperature and quenched with aq. HCl (10%, 15 mL). The mixture was extracted with toluene (3 × 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concetrated *in vacuo*. The crude product was dissolved in toluene (20 mL) again and extracted with aqueous KOH-solution (1 M, 4 × 20 mL). The combined aqueous layers were brought to a pH 3 conc. HCl and extracted with toluene (3 × 75 mL) again. The combined organic layers were dried over Na_2SO_4 and filtered. After evaporation of the solvent the pure product [D_5]-**56h** was obtained as a white solid (1.569 g, 88%, m.p.: 122–124 °C).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.9$ (C_q), 133.2 (t, $J = 24$ Hz, CD), 129.7 (t, $J = 24$ Hz, CD), 129.1 (C_q), 127.9 (t, $J = 24$ Hz, CD).

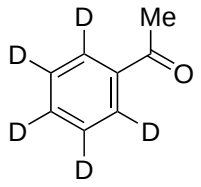
IR (ATR, cm^{-1}): 2847, 2785, 2681, 2616, 2523, 1674, 1566, 1431, 1332, 1270, 1087, 930, 839, 822, 775, 727, 646, 534.

MS (EI): 127 (84) $[M]^+$, 110 (80) $[M-OH]^+$, 98 (15), 82 (70) $[C_6D_5]^+$, 71 (43), 58 (31), 54 (34), 52 (17), 43 (100).

$[C_7HD_5NO_2 + H]^+$ (ESI) HRMS: calcd.: 128.0754.
found: 127.0751.

The spectral data are in accordance with those reported in the literature.[100]

Synthesis of [D_5]-Acetophenone ([D_5]-9a)



$AlCl_3$ (8.00 g, 60.0 mmol, 1.20 equiv) was placed in a two-necked 100-mL flask equipped with a reflux condenser. Dry 1,2-dichloroethane (20 mL) was added and the mixture was cooled to 0 °C. Acetylchloride (**150**) (4.12 g, 3.73 mL, 52.5 mmol, 1.05 equiv) was added dropwise under stirring at this temperature. Stirring was continued at the same temperature while [D_6]-benzene (4.21 g, 4.43 mL, 50.0 mmol, 1.00 equiv) was added dropwise over a period of 30 min. The resulting reaction mixture was allowed to warm up to ambient temperature overnight and poured onto ice (70 g). Conc. HCl (30 mL) was added and the phases were separated. The aqueous layer was extraced with CH_2Cl_2 (2 × 100 mL) and the combined organic layers were washed with H_2O (100 mL), aqueous NaOH solution (2%, 100 mL) and again with H_2O (100 mL). After drying over K_2CO_3 the solvents were removed *in vacuo*. Fractional distillation (15 mbar) yielded [D_5]-**9a** as a colourless oil (3.64 g, 58%, b.p.: 79–80 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.56$ (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 197.8$ (C_q), 136.8 (C_q), 132.4 (t, $J = 24$ Hz, CD), 127.8 (t, $J = 24$ Hz, CD), 127.6 (t, $J = 24$ Hz, CD), 26.5 (CH_3).

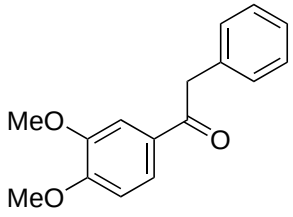
IR (ATR, cm^{-1}): 2291, 1679, 1566, 1429, 1381, 1352, 1328, 1295, 1226, 1018, 951, 832, 818, 770, 579, 526.

MS (EI): 125 (22) $[M]^+$, 110 (100) $[M-Me]^+$, 82 (66) $[C_6D_5]^+$, 54 (24), 43 (37).

$[C_8H_3D_5O]^+$ (EI) HRMS: calcd.: 125.0889.
found: 125.0891.

The spectral data are in accordance with those reported in the literature.[251]

Synthesis of 1-(3,4-Dimethoxyphenyl)-2-phenylethan-1-one (9x)



A solution of veratrole (**148**) (16.16 g, 117.0 mmol, 1.50 equiv) in dry CH_2Cl_2 (200 mL) was placed in a two-necked 500-mL flask equipped with a reflux condenser and 2-phenylacetyl chloride (**145x**) (12.06 g, 78.0 mmol, 1.00 equiv) was added. Unter stirring $AlCl_3$ (15.6 g, 117.0 mmol, 1.50 equiv) was added in small portions. The resulting reaction mixture was stirred at 40 °C over night and poured into an ice-water mixture (1:1, 200 mL). Conc. HCl (30 mL) was added

and the phases were separated. The aqueous layer was extraced with CH_2Cl_2 (3 × 75 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Recrystallization from EtOH yielded **9x** as a white solid (14.41 g, 72%, m.p.: 87–88 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.64$ (dd, $J = 8.4$, 2.0 Hz, 1H), 7.54 (d, $J = 2.0$ Hz, 1H), 7.35–7.18 (m, 5H), 6.86 (d, $J = 8.4$ Hz, 1H), 4.22 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 196.2$ (C_q), 153.3 (C_q), 149.0 (C_q), 135.0 (C_q), 129.8 (C_q), 129.3 (CH), 128.6 (CH), 126.8 (CH), 123.4 (CH), 110.7 (CH), 110.0 (CH), 56.0 (CH_3), 55.9 (CH_2), 45.2 (CH_2).

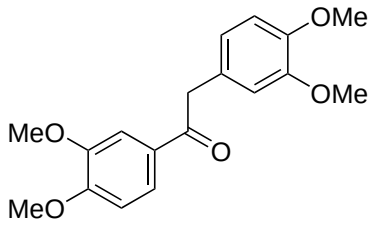
IR (ATR, cm^{-1}): 2952, 2907, 1673, 1583, 1515, 1417, 1313, 1260, 1236, 1157, 1141, 1024, 864, 813, 719, 695, 627, 546.

MS (EI): 256 (4) $[M]^+$, 165 (100) $[M\text{-}Bn]^+$, 137 (10), 122 (5), 107 (5), 91 (9), 79 (10), 65 (6), 51 (5), 43 (9).

$\mathbf{[C_{16}H_{16}O_3 + H]^+}$ (ESI) HRMS: calcd.: 257.1172.
found: 257.1171.

The spectral data are in accordance with those reported in the literature.[252]

Synthesis of 1,2-Bis(3,4-dimethoxyphenyl)ethanone (9y)



A two-necked 100-mL flask equipped with a reflux condenser was degassed, purged with N_2 for 3 times and charged with 2-(3,4-dimethoxyphenyl)acetic acid (**147y**) (15.7 g, 80.0 mmol, 1.00 equiv). Dry CH_2Cl_2 (30 mL) was added. Under stirring, $SOCl_2$ (10.8 mL, 149.0 mmol, 1.86 equiv) was added dropwise. The resulting mixture was stirred at 40 °C for 1 h. The solvents were removed *in vacuo* yielding the crude acid chlorid. The latter was transferred into a second 250-mL flask equipped with a reflux condenser and contained a solution of veratrole (**148**) (15.48 g, 112 mmol, 1.40 equiv) in anhydrous CH_2Cl_2 (120 mL). Unter stirring, $AlCl_3$ (14.93 g, 112.0 mmol, 1.40 equiv) was added in small portions. The resulting mixture was stirred at 40 °C for 3 h and poured onto ice (100 mL). Aqueous HCl (6 M, 30 mL) was added and the phases were separated. The aquaeous layer was extraced with CH_2Cl_2 (4 × 50 mL) and the combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Recrystallization from EtOH yielded **9y** as a yellow solid (15.69 g, 62%, m.p.: 96–100 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.64$ (dd, $J = 8.4$, 2.0 Hz, 1H), 7.54 (d, $J = 2.0$ Hz, 1H), 6.86 (d, $J = 8.4$ Hz, 1H), 6.82–6.75 (m, 3H), 4.16 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 196.5$ (C_q), 153.3 (C_q), 149.1 (C_q), 149.1 (C_q), 148.0 (C_q),

129.8 (C_q), 127.5 (C_q), 123.4 (CH), 121.4 (CH), 112.4 (CH), 111.4 (CH), 110.7 (CH), 110.0 (CH), 56.0 (CH_3), 55.9 (CH_3), 55.9 (CH_3), 55.8 (CH_3), 44.8 (CH_2).

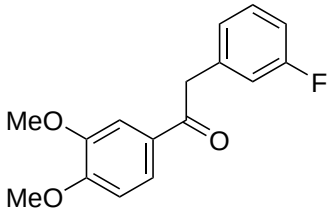
IR (ATR, cm^{-1}): 2946, 2839, 1675, 1584, 1515, 1469, 1452, 1439, 1416, 1324, 1262, 1236, 1146, 1134, 1015, 871, 804, 780, 766, 717, 630, 555.

MS (EI): 316 (14) $[M]^+$, 165 (100) $[M-(MeO)_2C_6H_3CH_2]^+$, 151 (12) $[(MeO)_2C_6H_3CH_2]^+$, 137 (6) $[(MeO)_2C_6H_3]^+$, 122 (4) $[(MeO)_2C_6H_3-Me]^+$, 107 (6), 77 (7).

$[\mathbf{C_{18}H_{20}O_5}]^+$ (EI) HRMS: calcd.: 316.1311.
found: 316.1313.

The spectral data are in accordance with those reported in the literature.[252]

Synthesis of 1-(3,4-Dimethoxyphenyl)-2-(3-fluorophenyl)ethan-1-one (9z)



A two-necked 50-mL flask equipped with a reflux condenser was degassed, purged with N_2 for 3 times and charged with 2-(3-fluorophenyl)acetic acid (**147z**) (3.85 g, 25.0 mmol, 1.00 equiv). Dry CH_2Cl_2 (12 mL) was added. Under stirring, $SOCl_2$ (3.37 mL, 46.5 mmol, 1.86 equiv) was added dropewise. The resulting mixture was stirred at 40 °C for 21 h. The solvents were removed *in vacuo* yielding the crude acid chlorid. The latter was transferred into a second 100-mL flask equipped with a reflux condenser and contained a solution of veratrole (**148**) (4.84 g, 35 mmol, 1.40 equiv) in anhydrous CH_2Cl_2 (40 mL). Unter stirring, $AlCl_3$ (4.67 g, 35.0 mmol, 1.40 equiv) was added in small portions. The resulting mixture was stirred at 40 °C for 4 h and poured onto ice (100 g). Conc. HCl (50 mL) was added and the phases were separated. The aquaeous layer was extraced with CH_2Cl_2 (3 × 50 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Recrystallization from EtOH yielded **9z** as a white solid (5.31 g, 77%, m.p.: 118–120 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.61$ (dd, $J = 8.4$, 2.0 Hz, 1H), 7.52 (d, $J = 2.0$ Hz, 1H), 7.30–7.21 (m, 1H), 7.06–6.99 (m, 1H), 6.99–6.86 (m, 2H), 6.86 (d, $J = 8.4$ Hz, 1H), 4.21 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 195.5$ (C_q), 162.8 (d, $^1J_{C-F} = 246$ Hz, C_q), 153.5 (C_q), 149.1 (C_q), 137.3 (d, $^3J_{C-F} = 8$ Hz, C_q), 130.0 (d, $^3J_{C-F} = 8$ Hz, CH), 129.5 (C_q), 125.0 (d, $^4J_{C-F} = 3$ Hz, CH), 123.3 (CH), 116.3 (d, $^2J_{C-F} = 22$ Hz, CH), 113.7 (d, $^2J_{C-F} = 21$ Hz, CH), 110.5 (CH), 110.0 (CH), 56.0 (CH_3), 55.9 (CH_3), 44.6 (d, $^4J_{C-F} = 2$ Hz, CH_2).

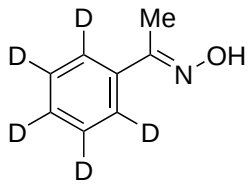
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -113.1$ (ddd, $J = 9.7$, 8.8, 6.1 Hz).

IR (ATR, cm^{-1}): 2996, 2962, 2935, 2907, 2834, 1673, 1585, 1514, 1445, 1322, 1238, 1181, 1143, 1018, 958, 890, 873, 795, 728, 684, 627, 549, 520.

MS (EI): 274 (11) $[M]^+$, 165 (100) $[M-FC_6H_4CH_2]^+$, 137 (23) $[(MeO)_2C_6H_3]^+$, 122 (10) $[(MeO)_2C_6H_3-Me]^+$, 109 (26) $[FC_6H_4CH_2]^+$, 92 (11), 83 (11), 79 (23), 63 (6), 51 (10).

$[\mathbf{C_{16}H_{15}FO_3}]^+$ (EI) HRMS: calcd.: 274.1005.
found: 274.1010.

Synthesis of [D_5]-Acetophenone Oxime ([D_5]-87a)



The general procedure **C** was followed, using [D_5]-acetophenone [D_5]-**9a** (3.13 g, 25.0 mmol). After 12 h, [D_5]-**87a** was obtained as a pale-yellow solid (3.096 g, 88%, m.p.: 57–59 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.07$ (s_{br}, 1H), 2.32 (s, 3H).

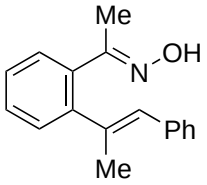
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 155.9$ (C_q), 136.2 (C_q), 128.6 (t, $J = 24$ Hz, CD), 127.9 (t, $J = 24$ Hz, CD), 125.5 (t, $J = 24$ Hz, CD), 12.3 (CH_3).

IR (ATR, cm^{-1}): 3226, 2922, 1681, 1566, 1429, 1383, 1383, 1255, 1230, 998, 918, 824, 753, 648, 631, 558, 515, 451.

MS (EI): 140 (95) $[M]^+$, 123 (18) $[M-OH]^+$, 108 (18) $[M-NOH-H]^+$, 99 (37), 82 (100) $[C_6D_5]^+$, 71 (18), 54 (39), 43 (39).

$[\mathbf{C_8H_4D_5NO}]^+$ (EI) HRMS: calcd.: 140.0998.
found: 140.0994.

Synthesis of (2-((*E*)-1-phenylprop-1-en-2-yl)phenyl)ethanone Oxime (151ai)



Acetophenone oxime (**87a**) (270 mg, 2.00 mmol, 1.0 equiv), prop-1-yn-1-ylbenzene (**34i**) (256 mg, 2.20 mmol, 2.2 equiv) and $[Rh(PPh_3)_3Cl]$ (56 mg, 0.06 mmol, 3.0 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. Dry toluene (6.0 mL) was added and the reaction mixture was stirred at 130 °C for 3 h. At ambient the mixture was filtered through a pad of Celites and rinsed with CH_2Cl_2 (50 mL) and the solvents were removed *in vacuo*. Purification of the residue by column chromatography on silica gel (*n*-hexane/EtOAc: 12/1) yielded **151ai** as a pale-brown solid (63 mg, 13%, m.p.: 111–113 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.15$ (s_{br}, 1H), 7.57–7.05 (m, 9H), 6.51 (d, $J = 1.5$ Hz, 1H), 2.21 (d, $J = 1.5$ Hz, 3H), 2.17 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.6$ (C_q), 144.3 (C_q), 137.9 (C_q), 137.7 (C_q), 136.1 (C_q), 130.8 (CH), 128.9 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 127.0 (CH), 126.6 (CH), 19.6 (CH_3), 15.9 (CH_3).

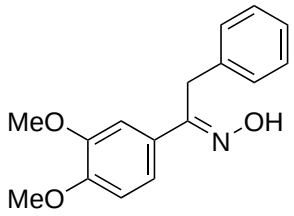
IR (ATR, cm^{-1}): 3220, 3054, 2913, 1488, 1364, 1307, 1011, 916, 862, 758, 731, 696, 657, 642, 559, 506.

MS (EI): 251 (20) $[M]^+$, 234 (100) $[M-OH]^+$, 219 (28) $[M-NOH-H]^+$, 204 (22), 174 (90), 157 (31), 115 (32), 91 (22), 77 (19), 51 (9).

$[\mathbf{C_{17}H_{17}NO + H}]^+$ (ESI) HRMS: calcd.: 252.1383.
found: 252.1383.

The spectral data are in accordance with those reported in the literature.[127]

Synthesis of 1-(3,4-Dimethoxyphenyl)-2-phenylethan-1-one Oxime (87x)



The general procedure **C** was followed using 1-(3,4-dimethoxyphenyl)-2-phenylethan-1-one (**9x**) (6.41 g, 25.0 mmol). After 12 h, recrystallization from EtOH yielded **87x** as a pale brown solid (6.69 g, 99%, m.p.: 123–126 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.15$ (s_{br}, 1H) 7.35–7.17 (m, 6H), 7.15 (dd, $J = 8.4$, 2.2 Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 1H), 4.20 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H).

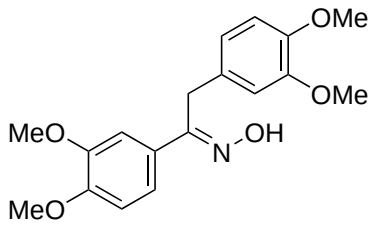
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 196.3$ (C_q), 153.3 (C_q), 149.1 (C_q), 135.0 (C_q), 129.8 (C_q), 129.3 (CH), 128.6 (CH), 126.8 (CH), 123.5 (CH), 110.7 (CH), 110.0 (CH), 56.0 (CH_3), 55.9 (CH_3), 45.2 (CH_2).

IR (ATR, cm^{-1}): 3134, 3006, 2968, 2923, 2830, 1599, 1579, 1515, 1496, 1456, 1416, 1331, 1310, 1277, 1254, 1228, 1146, 1078, 1021, 973, 882, 806, 761, 718, 625, 612, 477.

MS (EI): 271 (92) $[M]^+$, 254 (15) $[M-OH]^+$, 180 (9), 163 (100) $[M-NOH-Ph]^+$, 148 (16), 138 (12), 120 (10), 91 (82) $[Bn]^+$, 77 (14), 65 (23), 51 (9).

$[\mathbf{C_{16}H_{17}NO_3}]^+$ (EI) HRMS: calcd.: 271.1208.
found: 271.1210.

Synthesis of 1,2-Bis(3,4-dimethoxyphenyl)ethan-1-one Oxime (87y)



The general procedure **C** was followed using 1,2-bis(3,4-dimethoxyphenyl)ethan-1-one (**9y**) (7.91 g, 25.0 mmol). After 12 h, recrystallization from EtOH yielded **87y** as a pale brown solid (6.49 g, 78%, m.p.: 127–129 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.32$ (s_{br}, 1H), 7.26 (d, $J = 1.8$ Hz, 1H), 7.15 (dd, $J = 8.4$, 2.1 Hz, 1H), 6.85–6.71 (m, 4H), 4.13 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H).

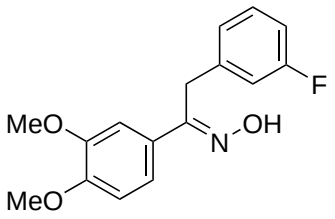
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 157.3$ (C_q), 150.1 (C_q), 149.0 (C_q), 148.9 (C_q), 147.6 (C_q), 129.2 (C_q), 128.3 (C_q), 120.4 (CH), 119.7 (CH), 111.9 (CH), 111.3 (CH), 110.6 (CH), 109.0 (CH), 55.8 (CH_3), 55.8 (CH_3), 55.8 (CH_3), 55.8 (CH_3), 31.4 (CH_2).

IR (ATR, cm^{-1}): 3478, 2961, 2839, 2039, 1513, 1455, 1329, 1253, 1221, 1134, 1021, 967, 863, 851, 825, 811, 767, 733, 615, 596, 575.

MS (EI): 331 (60) $[M]^+$, 313 (10) $[M-OH-H]^+$, 298 (18) $[M-OH-H-Me]^+$, 283 (9), 163 (18) $[M-OH-(MeO)_2C_6H_3CH_2]^+$, 151 (100) $[(MeO)_2C_6H_3CH_2]^+$, 120 (6), 107 (14), 77 (11), 65 (10), 51 (5).

$[\mathbf{C_{18}H_{21}NO_5}]^+$ (EI) HRMS: calcd.: 331.1420.
found: 331.1415.

Synthesis of 1-(3,4-Dimethoxyphenyl)-2-(3-fluorophenyl)ethan-1-one Oxime (87z)



Hydroxylamine hydrochloride (1.04 g, 15.0 mmol, 1.50 equiv.) and NaOAc (2.05 g, 25 mmol, 2.5 equiv) were placed in a 50-mL flask equipped with a reflux condenser and EtOH (5 mL), H_2O (15 mL) and 1-(3,4-dimethoxyphenyl)-2-(3-fluorophenyl)ethan-1-one (**9z**) (2.74 g, 10.0 mmol, 1.00 equiv) were added. The resulting mixture was heated at 100 °C overnight. After cooling down to 0 °C, the precipitated crude product was filtered off and washed with H_2O. Recrystallization from EtOH yielded **87z** as a white solid (2.85 g, 98%, m.p.: 69–73 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.73$ (s_{br}, 1H), 7.24–7.22 (m, 1H), 7.20 (dd, $J = 7.9$, 1.9 Hz, 1H), 7.10 (dd, $J = 8.4$, 2.1 Hz, 1H), 7.02 (ddd, $J = 7.7$, 1.7, 0.9 Hz, 1H), 6.97 (ddd, $J = 10.2$,

2.5, 1.6 Hz, 1H), 6.86 (tdd, J = 8.6, 2.7, 1.0 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 4.17 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.9 (d, $^1J_{C-F}$ = 246 Hz, C_q), 156.4 (C_q), 150.2 (C_q), 148.9 (C_q), 139.1 (d, $^3J_{C-F}$ = 8 Hz, C_q), 129.9 (d, $^3J_{C-F}$ = 8 Hz, CH), 127.8 (C_q), 124.1 (d, $^4J_{C-F}$ = 3 Hz, CH), 119.5 (CH), 115.4 (d, $^2J_{C-F}$ = 22 Hz, CH), 113.2 (d, $^2J_{C-F}$ = 21 Hz, CH), 110.6 (CH), 108.7 (CH), 55.8 (CH_3), 55.7 (CH_3), 31.56 (d, $^4J_{C-F}$ = 2 Hz, CH_2).

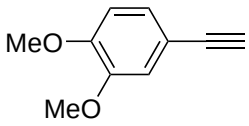
^{19}F NMR (282 MHz, $CDCl_3$): δ = −(110.2–115.3) (m).

IR (ATR, cm^{-1}): 3155, 3002, 2965, 2923, 2830, 1579, 1516, 1490, 1415, 1324, 1277, 1254, 1227, 1146, 1021, 973, 919, 886, 869, 798, 758, 741, 678, 626, 613, 524, 501, 461.

MS (EI): 289 (96) $[M]^+$, 272 (15) $[M-OH]^+$, 163 (100) $[M-OH\text{-}FC_6H_4CH_2]^+$, 148 (17), 138 (15), 120 (12), 109 (62), 92 (11), 83 (17), 77 (12), 65 (8), 51 (8).

$[C_{16}H_{16}FNO_3]^+$ (EI) HRMS: calcd.: 289.1114.
found: 289.1117.

Synthesis of 4-Ethynyl-1,2-dimethoxybenzene (31z)



A two-necked 100-mL flask equipped with a reflux-condenser was degassed and purged with nitrogen for 3 times. Dry THF (25 mL) and 4-(2,2-dibromovinyl)-1,2-dimethoxybenzene (**120f**) (1.61 g, 5.0 mmol, 1.0 equiv) were added and the mixture was cooled to −78 °C. Under stirring *n*-BuLi (4.8 mL, 2.5 M in *n*-hexane, 12.0 mmol, 2.4 equiv) was added dropwise at −78 °C. The reaction mixture was stirred for 15 h at this temperature and for an additional 2.5 h at ambient temperature. The mixture was cooled again to −78 °C, quenched with saturated aqueous NH_4Cl solution (15 mL) and extractet with EtOAc (2 × 125 mL). The combined organic layers were washed with brine (100 mL) and the solvent was removed *in vacuo*. Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **31z** as a pale yellow solid (733 mg, 90%, m.p.: 73–75 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08 (dd, J = 8.3, 1.9 Hz, 1H), 6.97 (d, J = 1.9 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.98 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.8 (C_q), 148.6 (C_q), 125.5 (CH), 114.7 (CH), 114.2 (C_q), 110.9 (CH), 83.8 (C_q), 75.6 (CH), 55.9 (CH_3), 55.9 (CH_3).

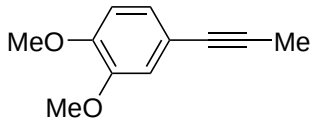
IR (ATR, cm^{-1}): 3249, 2970, 2939, 2843, 1596, 1578, 1507, 1445, 1407, 1321, 1259, 1234, 1150, 1135, 1023, 859, 819, 809, 726, 653, 616, 532, 494, 444.

MS (EI): 162 (100) $[M]^+$, 147 (34) $[M-Me]^+$, 119 (25), 117 (84), 91 (34), 76 (17), 65 (13), 58 (17), 50 (15), 43 (59).

$[C_{10}H_{10}O_2]^+$ (EI) HRMS: calcd.: 162.0681.
found: 162.0676.

The spectral data are in accordance with those reported in the literature.[253]

Synthesis of 1-2-Dimethoxy-4-(prop-1-ynyl)benzene (34z)



4-Ethynyl-1,2-dimethoxybenzene (**31z**) (681 mg, 4.2 mmol, 1.0 equiv) was placed in a two-necked 250-mL flask equipped with a reflux-condenser and degassed and purged with nitrogen for 3 times. Dry THF (60 mL) was added the mixture was cooled to −78 °C. Under stirring, *n*-BuLi (2.7 mL, 2.5 M in *n*-hexane, 6.75 mmol, 1.61 equiv) was added dropwise at −78 °C and the tesulting mixture was stirred for 10 min at this temperature. Methyliodid (2.38 g, 16.8 mmol, 4.0 equiv) was added, the reaction mixture was stirred for additional 20 min at −78 °C and then for another 1.5 h at ambient temperature. The mixture was cooled to 0 °C, quenched with H_2O (100 mL) and extracted with CH_2Cl_2 (2 × 80 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **34z** as a white solid (671 mg, 91%, m.p.: 55–57 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.96$ (dd, $J = 8.2$, 1.9 Hz, 1H), 6.89 (d, $J = 1.9$ Hz, 1H), 6.75 (d, $J = 8.2$ Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.02 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 148.8$ (C_q), 148.5 (C_q), 124.4 (CH), 116.2 (C_q), 114.2 (CH), 110.9 (CH), 84.1 (C_q), 79.5 (C_q), 55.8 (CH_3), 55.8 (CH_3), 4.3 (CH_3).

IR (ATR, cm^{-1}): 3002, 2912, 2839, 1600, 1578, 1509, 1463, 1443, 1324, 1241, 1210, 1169, 1133, 1018, 862, 805, 762, 647, 622.

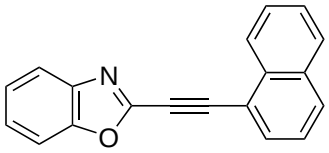
MS (EI): 176 (100) $[M]^+$, 161 (51) $[M-Me]^+$, 133 (29), 115 (17), 105 (30), 89 (25), 77 (23), 63 (23).

$[\mathbf{C_{11}H_{12}O_2}]^+$ (EI) HRMS: calcd.: 176.0837.
found: 176.0840.

The spectral data are in accordance with those reported in the literature.[254]

5.3.3 Syntheses of Alkynylated Heterocycles 115 and 130

2-(Naphthalen-1-ylethynyl)benzoxazole (115aa)



The general procedure **D** was followed using benzoxazole (**106a**) (60 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)naphthalene (**126a**) (167 mg, 0.75 mmol). After 13 h, purification by column chromatography (*n*-hexane/EtOAc: 35/1) yielded **115aa** as a pale-yellow solid (101 mg, 75%, m.p.: 116–118 °C). **115aa** was also obtained following general procedure **F** from 1-(2,2-bromovinyl)naphthalene (**120a**) (234 mg, 0.75 mmol). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded **115aa** as a pale-yellow solid (98 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.46$ (dq, $J = 7.5$, 1.0 Hz, 1H), 7.95–7.82 (m, 3H), 7.81–7.78 (m, 1H), 7.64 (ddd, $J = 8.4$, 6.9, 1.4 Hz, 1H), 7.58–7.53 (m, 2H), 7.47 (dd, $J = 8.2$, 7.2 Hz, 1H), 7.42–7.36 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.4$ (C_q), 147.8 (C_q), 141.2 (C_q), 133.3 (C_q), 133.0 (C_q), 132.3 (CH), 131.0 (CH), 128.5 (CH), 127.6 (CH), 126.9 (CH), 126.3 (CH), 125.8 (CH), 125.2 (CH), 125.1 (CH), 120.4 (CH), 117.8 (C_q), 110.6 (CH), 91.9 (C_q), 82.1 (C_q).

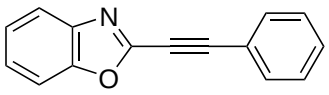
IR (ATR, cm^{-1}): 3046, 2212, 1542, 1448, 1238, 1140, 935, 799, 772, 746, 453.

MS (EI): 269 (100) $[M]^+$, 240 (30), 177 (15), 150 (10), 63 (16).

$[\mathbf{C_{19}H_{11}NO}]^+$ (EI) HRMS: calcd.: 269.0841.
found: 269.0847.

The spectral data are in accordance with those reported in the literature.[168]

2-(Phenylethynyl)benzoxazole (115ab)



The general procedure **D** was followed using benzoxazole (**106a**) (60 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)benzene (**126b**) (130 mg, 0.75 mmol). After 14 h, purification by column chromatography (*n*-hexane/EtOAc: 35/1) yielded **115ab** as an off-white solid (42 mg, 38%, m.p.: 97 °C). **115ab** was also obtained following general procedure **F** from 1-(2,2-bromovinyl)benzene (**120b**) (196 mg, 0.75 mmol). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **115ab** as an off-white solid (72 mg, 66%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.80$–7.70 (m, 1H), 7.66–7.61 (m, 2H), 7.55–7.49 (m, 1H), 7.45–7.31 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.3$ (C_q), 147.7 (C_q), 141.0 (C_q), 132.4 (CH), 130.3 (CH), 128.6 (CH), 126.3 (CH), 125.0 (CH), 120.4 (CH), 120.2 (C_q), 110.6 (CH), 93.4 (C_q), 77.4 (C_q).

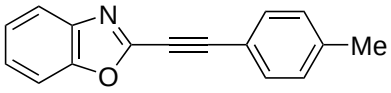
IR (ATR, cm^{-1}): 2221, 1605, 1538, 1444, 1304, 1238, 1135, 943, 762, 748, 683, 622, 528, 445, 403.

MS (EI): 219 (100) $[M]^+$, 191 (51), 163 (10), 127 (11), 95 (11), 63 (42), 51 (10), 43 (25).

$[\mathbf{C_{15}H_9NO}]^+$ (EI) HRMS: calcd.: 219.0684.
found: 219.0680.

The spectral data are in accordance with those reported in the literature.[168]

2-(*para*-Tolylethynyl)benzoxazole (115ac)



The general procedure **D** was followed using benzoxazole (**106a**) (60 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)-4-methylbenzene (**126c**) (140 mg, 0.75 mmol). After 13 h, purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded **115ac** as a white solid (70 mg, 60%, m.p.: 153–155 °C). **115ac** was also obtained following general procedure **F** from 1-(2,2-bromovinyl)-4-methylbenzene (**120c**) (207 mg, 0.75 mmol). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **115ac** as a white solid (70 mg, 60%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.78$–7.72 (m, 1H), 7.57–7.51 (m, 3H), 7.43–7.33 (m, 2H), 7.20 (d, $J = 7.8$ Hz, 2H), 2.39 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.2$ (C_q), 147.9 (C_q), 141.1 (C_q), 140.9 (C_q), 132.3 (CH), 129.4 (CH), 126.1 (CH), 124.9 (CH), 120.3 (CH), 117.1 (C_q), 110.5 (CH), 109.2 (C_q), 93.8 (C_q), 21.7 (CH_3).

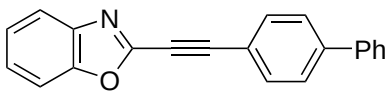
IR (ATR, cm^{-1}): 2914, 2213, 1548, 1445, 1299, 1240, 1131, 937, 803, 734, 525.

MS (EI): 233 (100) $[M]^+$, 205 (20), 190 (18), 140 (18), 63 (35).

$[\mathbf{C_{16}H_{11}NO}]^+$ (EI) HRMS: calcd.: 233.0841.
found: 233.0836.

The spectral data are in accordance with those reported in the literature.[168]

2-[(1,1'-Biphenyl)-4-ylethynyl]benzoxazole (115ad)

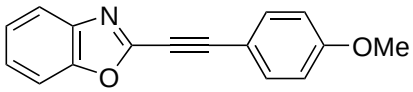


The general procedure **D** was followed using benzoxazole (**106a**) (60 mg, 0.50 mmol) and 4-(2,2-dichlorovinyl)-1,1'-biphenyl (**126d**) (187 mg, 0.75 mmol). After 13 h, purification by column chromatography (*n*-hexane/EtOAc: 35/1) yielded **115ad** as an off-white solid (81 mg, 55%, m.p.: 139–140 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.81$–7.71 (m, 1H), 7.74 (d, $J = 8.4$ Hz, 2H), 7.69–7.59 (m, 2H), 7.64 (d, $J = 8.4$ Hz, 2H), 7.58–7.52 (m, 1H), 7.51–7.35 (m, 5H).

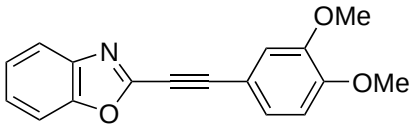
^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.3 (C_q), 147.7 (C_q), 143.1 (C_q), 141.1 (C_q), 139.8 (C_q), 132.9 (CH), 128.9 (CH), 128.1 (CH), 127.2 (CH), 127.1 (CH), 126.3 (CH), 125.0 (CH), 120.4 (CH), 118.9 (C_q), 110.6 (CH), 93.4 (C_q), 78.1 (C_q).
IR (ATR, cm^{-1}): 2215, 1548, 1448, 1300, 1239, 1133, 936, 842, 760, 743, 721, 692, 560, 504.
MS (EI): 295 (100) $[M]^+$, 267 (8), 203 (10), 63 (12).
$[\mathbf{C_{21}H_{13}NO}]^+$ (EI) HRMS: calcd.: 295.0997.
found: 295.0991.

2-[(4-Methoxyphenyl)ethynyl]benzoxazole (115ae)



The general procedure **D** was followed using benzoxazole (**106a**) (60 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)-4-methoxybenzene (**126e**) (152 mg, 0.75 mmol). After 13 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **115ae** as an off-white solid (50 mg, 40%, m.p.: 110–112 °C). **115ae** was also obtained following general procedure **F** from 1-(2,2-bromovinyl)-4-methoxybenzene (**120e**) (219 mg, 0.75 mmol). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **115ae** as a off-white solid (79 mg, 63%).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77–7.69 (m, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.54–7.47 (m, 1H), 7.42−7.31 (m, 2H), 6.90 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3 (C_q), 150.4 (C_q), 148.1 (C_q), 141.3 (C_q), 134.2 (CH), 126.0 (CH), 124.9 (CH), 120.3 (CH), 114.4 (CH), 112.2 (C_q), 110.5 (CH), 94.0 (C_q), 76.7 (C_q), 55.4 (CH_3).
IR (ATR, cm^{-1}): 2835, 2212, 1599, 1547, 1500, 1447, 1305, 1289, 1250, 1133, 1103, 1034, 940, 820, 734, 623, 594, 528, 498.
MS (EI): 249 (100) $[M]^+$, 234 (35) $[M-Me]^+$, 206 (24), 177 (12), 151 (12), 63 (16).
$[\mathbf{C_{16}H_{11}NO_2}]^+$ (EI) HRMS: calcd.: 249.0790.
found: 249.0792.
The spectral data are in accordance with those reported in the literature.[179]

2-[(3,4-Dimethoxyphenyl)ethynyl]benzoxazole (115af)



The general procedure **D** was followed using benzoxazole (**106a**) (60 mg, 0.50 mmol) and 4-(2,2-dichlorovinyl)-1,2-dimethoxybenzene (**126f**) (175 mg, 0.75 mmol). After 13 h, purification by column chromatography (*n*-hexane/EtOAc: 15/1→8/1→4/1) yielded **115af** as a pale yellow solid (80 mg, 57%, m.p.: 105–107 °C). **115af** was also obtained following general procedure **F**

from 4-(2,2-bromovinyl)-1,2-dimethoxybenzene (**120f**) (241 mg, 0.75 mmol). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **115af** as a pale yellow solid (90 mg, 64%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.68 (m, 1H), 7.54–7.47 (m, 1H), 7.41−7.31 (m, 2H), 7.27 (dd, J = 8.3, 1.9 Hz, 1H), 7.12 (d, J = 1.9 Hz 1H), 6.85 (d, J = 8.3 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H).

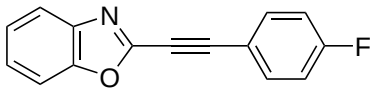
^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.2 (C_q), 150.2 (C_q), 148.8 (C_q), 148.0 (C_q), 141.1 (C_q), 126.4 (CH), 126.1 (CH), 124.9 (CH), 120.3 (CH), 114.7 (CH), 112.1 (C_q), 111.1 (CH), 110.5 (CH), 94.1 (C_q), 76.5 (C_q), 56.0 (CH_3), 55.9 (CH_3).

IR (ATR, cm^{-1}): 2910, 2210, 1547, 1508, 1327, 1245, 1126, 1016, 839, 805, 732, 609.

MS (EI): 279 (100) $[M]^+$, 264 (26) $[M-Me]^+$, 236 (41), 221 (15), 193 (20), 63 (19).

$[\mathbf{C_{17}H_{13}NO_3}]^+$ (EI) HRMS: calcd.: 279.0895.
found: 279.0896.

2-[(4-Fluorophenyl)ethynyl]benzoxazole (115ag)



The general procedure **D** was followed using benzoxazole (**106a**) (60 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)-4-fluorobenzene (**126g**) (143 mg, 0.75 mmol). After 13 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **115ag** as an off-white solid (65 mg, 55%, m.p.: 135–136 °C). **115ag** was also obtained following general procedure **F** from 1-(2,2-bromovinyl)-4-fluorobenzene (**120g**) (210 mg, 0.75 mmol). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **115ag** as an off-white solid (61 mg, 51%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77–7.71 (m, 1H), 7.66–7.59 (m, 2H), 7.55–7.48 (m, 1H), 7.43–7.32 (m, 2H), 7.08 (t, J = 8.6 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7 (d, $^1J_{C-F}$ = 252 Hz, C_q), 150.3 (C_q), 147.5 (C_q), 141.0 (C_q), 134.6 (d, $^3J_{C-F}$ = 9 Hz, CH), 126.3 (CH), 125.0 (CH), 120.4 (CH), 116.3 (d, $^4J_{C-F}$ = 3 Hz, C_q), 116.1 (d, $^2J_{C-F}$ = 23 Hz, CH), 110.6 (CH), 92.3 (C_q), 77.3 (d, $^5J_{C-F}$ = 2 Hz, C_q).

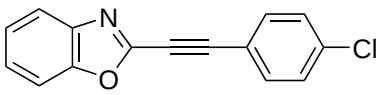
^{19}F NMR (282 MHz, $CDCl_3$): δ = −(106.8–108.8) (m).

IR (ATR, cm^{-1}): 3049, 2215, 1545, 1450, 1447, 1218, 1155, 1131, 940, 831, 740, 528.

MS (EI): 237 (100) $[M]^+$, 209 (35), 181 (6), 145 (10), 123 (7), 92 (6), 63 (39).

$[\mathbf{C_{15}H_8FNO}]^+$ (EI) HRMS: calcd.: 237.0590.
found: 237.0593.

2-[(4-Chlorophenyl)ethynyl]benzoxazole (115ah)



The general procedure **D** was followed using benzoxazole (**106a**) (60 mg, 0.50 mmol) and 1-chloro-4-(2,2-dichlorovinyl)benzene (**126h**) (156 mg, 0.75 mmol). After 13 h, purification by column chromatography (*n*-hexane/EtOAc: 40/1) yielded **115ah** as a white solid (66 mg, 52%, m.p.: 200 °C). **115ah** was also obtained following general procedure **F** from 1-(2,2-bromovinyl)-4-chlorobenzene (**120h**) (222 mg, 0.75 mmol). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **115ah** as a white solid (77 mg, 61%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77–7.71 (m, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.56–7.49 (m, 1H), 7.43–7.33 (m, 2H), 7.37 (d, J = 8.5 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.3 (C_q), 147.4 (C_q), 140.9 (C_q), 136.7 (C_q), 133.6 (CH), 129.1 (CH), 126.4 (CH), 125.1 (CH), 120.5 (CH), 118.7 (C_q), 110.6 (CH), 92.1 (C_q), 78.4 (C_q).

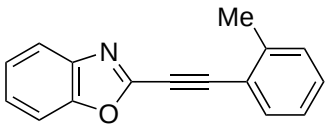
IR (ATR, cm^{-1}): 2213, 1542, 1446, 1340, 1304, 1133, 1082, 939, 818, 736, 522.

MS (EI): 253 (100) $[M]^+$, 225 (17), 190 (16), 161 (9), 63 (26).

$[\mathbf{C_{15}H_8ClNO}]^+$ (EI) HRMS: calcd.: 253.0294.
found: 253.0300.

The spectral data are in accordance with those reported in the literature.[168]

2-(*ortho*-Tolylethynyl)benzoxazole (115ai)



The general procedure **D** was followed using benzoxazole (**106a**) (60 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)-2-methylbenzene (**126i**) (140 mg, 0.75 mmol). After 14 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **115ai** as an off-white solid (79 mg, 68%, m.p.: 59–61 °C). **115ai** was also obtained following general procedure **F** from 1-(2,2-bromovinyl)-2-methylbenzene (**120i**) (207 mg, 0.75 mmol). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 100/1) yielded **115ai** as an off-white solid (77 mg, 66%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81–7.73 (m, 1H), 7.63 (dd, J = 7.7, 1.4 Hz, 1H), 7.59–7.52 (m, 1H), 7.46–7.37 (m, 2H), 7.35 (dd, J = 7.3, 1.5 Hz, 1H), 7.31–7.19 (m, 2H), 2.58 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.3 (C_q), 147.8 (C_q), 141.7 (C_q), 141.1 (C_q), 132.9 (CH), 130.3 (CH), 129.7 (CH), 126.2 (CH), 125.8 (CH), 125.0 (CH), 120.3 (CH), 120.0 (C_q), 110.5 (CH), 92.5 (C_q), 81.1 (C_q), 20.6 (CH_3).

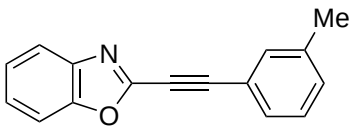
IR (ATR, cm^{-1}): 3058, 2217, 1546, 1449, 1241, 1140, 938, 858, 804, 740, 455.

MS (EI): 233 (100) $[M]^+$, 204 (55), 140 (35), 115 (75), 63 (46).

$[\mathbf{C_{16}H_{11}NO}]^+$ (EI) HRMS: calcd.: 233.0841.
found: 233.0833.

The spectral data are in accordance with those reported in the literature.[171]

2-(*meta*-Tolylethynyl)benzoxazole (115aj)



The general procedure **D** was followed, using benzoxazole (**106a**) (60 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)-3-methylbenzene (**126j**) (140 mg, 0.75 mmol). After 13 h, purification by column chromatography (*n*-hexane/EtOAc: 35/1) yielded **115aj** as an off-white solid (50 mg, 43%, m.p.: 93–94 °C). **115aj** was also obtained following general procedure **F** from 1-(2,2-bromovinyl)-3-methylbenzene (**120j**) (207 mg, 0.75 mmol). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 100/1) yielded **115aj** as an off-white solid (80 mg, 69%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.79$–7.70 (m, 1H), 7.56–7.50 (m, 1H), 7.48–7.22 (m, 6H), 2.36 (s, 3H).

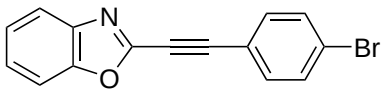
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.3$ (C_q), 147.8 (C_q), 141.1 (C_q), 138.4 (C_q), 132.9 (CH), 131.3 (CH), 129.6 (CH), 128.5 (CH), 126.2 (CH), 125.0 (CH), 120.4 (CH), 120.0 (C_q), 110.6 (CH), 93.7 (C_q), 77.2 (C_q), 21.2 (CH3).

IR (ATR, cm^{-1}): 2224, 1600, 1532, 1446, 1336, 1306, 1229, 1131, 1003, 956, 818, 779, 762, 749, 682, 452.

MS (EI): 233 (100) $[M]^+$, 205 (15), 190 (9), 140 (8), 63 (17).

$[\mathbf{C_{16}H_{11}NO}]^+$ (EI) HRMS: calcd.: 233.0841.
found: 233.0839.

2-[(4-Bromophenyl)ethynyl]benzoxazole (115ao)



The general procedure **F** was followed using benzoxazole (**106a**) (60 mg, 0.50 mmol) and 1-bromo-4-(2,2-dibromovinyl)benzene (**120o**) (156 mg, 0.75 mmol). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 150/1→8/1→100/1) yielded **115ao** as a white solid (79 mg, 53%, m.p.: 209–210 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.78$–7.72 (m, 1H), 7.58−7.46 (m, 5H), 7.44–7.33 (m, 2H).

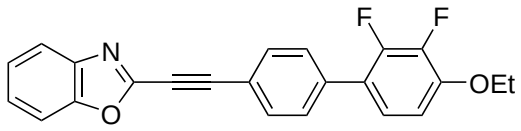
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.3$ (C_q), 147.5 (C_q), 141.0 (C_q), 133.7 (CH), 132.0 (CH), 126.5 (CH), 125.1 (CH), 125.1 (C_q), 120.5 (CH), 119.2 (C_q), 110.6 (CH), 92.2 (C_q), 78.5 (C_q).

IR (ATR, cm^{-1}): 2219, 1541, 1475, 1446, 1393, 1340, 1302, 1240, 1151, 1133, 1067, 939, 852, 810, 736, 521, 421.

MS (EI): 299/297 (97/100) $[M]^+$, 271/269 (16/17), 207 (7), 190 (20), 163 (8), 126 (15), 99 (8), 63 (44), 51 (8).

$[\mathbf{C_{15}H_8BrNO}]^+$ (EI) HRMS: calcd.: 296.9789.
found: 296.9785.

2-{[4'-Ethoxy-2',3'-difluoro-(1,1'-biphenyl)-4-yl]ethynyl}benzoxazole (115ap)



The general procedure **F** was followed using benzoxazole (**106a**) (60 mg, 0.50 mmol) and 4'-(2,2-dibromovinyl)-4-ethoxy-2,3-difluoro-1,1'-biphenyl (**120p**) (314 mg, 0.75 mmol). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 50/1→25/1→10/1→5/1) yielded **115ap** as a pale-yellow solid (118 mg, 63%, m.p.: 156–161 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.80$–7.67 (m, 3H), 7.61–7.52 (m, 3H), 7.46–7.35 (m, 2H), 7.12 (td, $J = 8.4$, 2.4 Hz, 1H), 6.82 (ddd, $J = 9.1$, 7.4, 1.9 Hz, 1H), 4.17 (q, $J = 7.0$ Hz, 2H), 1.49 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.3$ (C_q), 148.9 (dd, $^1J_{C-F} = 250$ Hz, $^2J_{C-F} = 11$ Hz, C_q), 148.3 (dd, $^2J_{C-F} = 8$ Hz, $^3J_{C-F} = 3$ Hz, C_q), 147.7 (C_q), 141.8 (dd, $^1J_{C-F} = 250$ Hz, $^2J_{C-F} = 15$ Hz, C_q), 141.1 (C_q), 137.0 (C_q), 137.0 (d, $^3J_{C-F} = 4$ Hz, C_q), 132.6 (CH), 128.9 (q, $^3J_{C-F} = 3$ Hz, CH), 126.3 (CH), 125.0 (CH), 123.5 (t, $^3J_{C-F} = 4$ Hz, CH), 121.7 (d, $^2J_{C-F} = 11$ Hz, C_q), 120.4 (CH), 119.3 (C_q), 110.6 (CH), 109.6 (d, $^4J_{C-F} = 2$ Hz, CH), 78.2 (C_q), 65.4 (CH_2), 14.7 (CH_3).

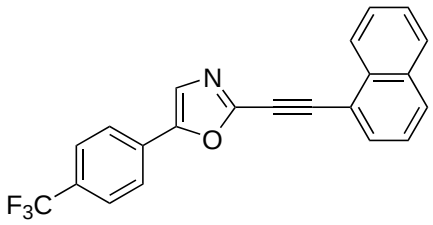
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -141.31$ (ddd, $J = 19.3$, 8.1, 1.7 Hz), -158.36 (ddd, $J = 19.4$, 7.4, 2.4 Hz).

IR (ATR, cm^{-1}): 2219, 1623, 1548, 1520, 1500, 1471, 1447, 1401, 1301, 1200, 1100, 1071, 942, 894, 845, 805, 759, 747, 622, 590, 535, 432.

MS (EI): 375 (77) $[M]^+$, 347 (100), 318 (17), 255 (8), 174 (11), 63 (23).

$[\mathbf{C_{23}H_{15}F_2NO_2}]^+$ (EI) HRMS: calcd.: 375.1071.
found: 375.1064.

2-(Naphthalen-1-ylethynyl)-5-[4-(trifluoromethyl)phenyl]oxazole (115da)



The general procedure **D** was followed using 5-[4-(trifluoromethyl)phenyl]oxazole (**106d**) (107 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)naphthalene (**126a**) (167 mg, 0.75 mmol). After 13 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1) and recrystallization from EtOH yielded **115da** as an orange solid (141 mg, 78%, m.p.: 136–139 °C). **115da** was also obtained following general procedure **F** from 1-(2,2-bromovinyl)naphthalene (**120a**) (234 mg,

0.75 mmol). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **115da** as an orange solid (160 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.43$ (d, $J = 8.3$ Hz, 1H), 7.93 (d, $J = 8.3$ Hz, 1H), 7.89 (dd, $J = 7.5$, 1.2 Hz, 2H), 7.80 (d, $J = 8.3$ Hz, 2H), 7.69 (d, $J = 8.3$ Hz, 2H), 7.66–7.53 (m, 2H), 7.56 (s, 1H), 7.52–7.45 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.6$ (C_q), 146.9 (C_q), 133.1 (C_q), 133.0 (C_q), 131.9 (CH), 130.7 (CH), 130.5 (d, $^2J_{C-F} = 32$ Hz, C_q), 130.4 (C_q), 130.4 (C_q), 128.4 (CH), 127.5 (CH), 126.8 (CH), 126.0 (q, $^3J_{C-F} = 4$ Hz, CH), 125.8 (CH), 125.1 (CH), 125.1 (CH), 124.5 (CH), 123.8 (d, $^1J_{C-F} = 270$ Hz, C_q), 91.0 (C_q), 81.6 (C_q).

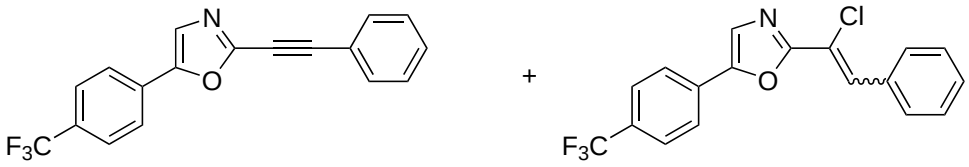
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.7$ (s).

IR (ATR, cm^{-1}): 2212, 1524, 1416, 1319, 1167, 1122, 1070, 827, 799, 773, 709, 564.

MS (EI): 363 (100) $[M]^+$, 307 (23), 239 (38), 173 (12), 163 (38), 145 (25), 95 (5), 63 (4).

$[\mathbf{C_{22}H_{12}F_3NO}]^+$ (EI) HRMS: calcd.: 363.0871.
found: 363.0865.

2-(Phenylethynyl)-5-[4-(trifluoromethyl)phenyl]oxazole (115db) and 2-(1-Chloro-2-phenylvinyl)-5-[4-(trifluoromethyl)phenyl]oxazole (132db)



The general procedure **D** was followed using 5-[4-(trifluoromethyl)phenyl]oxazole (**106d**) (107 mg, 0.50 mmol) and (2,2-dichlorovinyl)benzene (**126b**) (130 mg, 0.75 mmol). After 14 h, purification by column chromatography (*n*-hexane/EtOAc: 15/1) yielded **115db** as a pale yellow solid (80 mg, 51%, m.p.: 110–111 °C) and **132db** as a pale yellow solid (10 mg, 6%, m.p.: 125–127 °C).

115db:

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.78$ (d, $J = 8.1$ Hz, 2H), 7.68 (d, $J = 8.1$ Hz, 2H), 7.65–7.60 (m, 2H), 7.50 (s, 1H), 7.47–7.34 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.1$ (C_q), 146.8 (C_q), 132.1 (CH), 130.6 (d, $^2J_{C-F} = 32$ Hz, C_q), 130.5 (C_q), 130.5 (C_q), 130.1 (CH), 128.6 (CH), 126.1 (q, $^3J_{C-F} = 4$ Hz, CH), 125.0 (CH), 124.6 (CH), 123.8 (d, $^1J_{C-F} = 271$ Hz, C_q), 120.4 (C_q), 92.5 (C_q).

^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.8$ (s).

IR (ATR, cm^{-1}): 3057, 2207, 1681, 1321, 1157, 1108, 1069, 1016, 943, 830, 761, 694, 595, 462.

MS (EI): 313 (100) $[M]^+$, 258 (70), 189 (36), 173 (26), 145 (38), 129 (22), 110 (30), 75 (11), 63 (13).

$[\mathbf{C_{18}H_{10}F_3NO}]^+$ (EI) HRMS: calcd.: 313.0714.
found: 313.0719.

The spectral data are in accordance with those reported in the literature.[168]

132db:

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.57$ (d, $J = 8.3$ Hz, 2H), 7.49 (s, 1H), 7.41 (d, $J = 8.2$ Hz, 2H), 7.37–7.27 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.6$ (C_q), 150.4 (C_q), 136.1 (CH), 134.5 (C_q), 130.6 (d, $^2J_{C-F} = 32$ Hz, C_q), 130.3 (C_q), 128.8 (CH), 128.6 (CH), 128.4 (CH), 125.9 (q, $^3J_{C-F} = 4$ Hz, CH), 124.8 (CH), 124.4 (CH), 123.8 (d, $^1J_{C-F} = 272$ Hz, C_q), 118.8 (C_q).

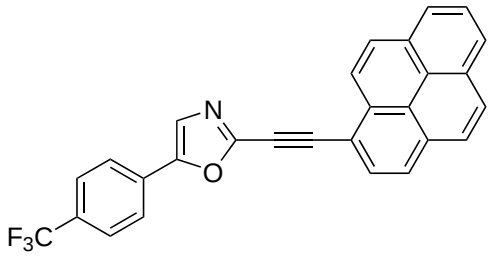
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -63.3$ (s).

IR (ATR, cm^{-1}): 2927, 1728, 1685, 1609, 1471, 1366, 1322, 1167, 1125, 1066, 1014, 843, 757, 690, 593, 550.

MS (EI): 350/348 (30/100) $[M-H]^+$, 314 (20) $[M-Cl]^+$, 190 (21), 173 (81), 149 (26), 145 (67), 129 (11), 114 (12), 102 (18), 91 (12), 75 (15), 51 (13).

$\mathbf{[C_{18}H_{11}ClF_3NO-H]^+}$ (EI) HRMS: calcd.: 348.0403.
found: 348.0412.

2-(Pyren-1-ylethynyl)-5-[4-(trifluoromethyl)phenyl]oxazole (115dk)



The general procedure **D** was followed using 5-[4-(trifluoromethyl)phenyl]oxazole (**106d**) (107 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)pyrene (**126k**) (223 mg, 0.75 mmol). After 13 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **115dk** as a brown solid (165 mg, 75%, m.p.: 178–181 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.60$ (d, $J = 9.1$ Hz, 1H), 8.26–8.16 (m, 4H), 8.12–7.97 (m, 4H), 7.76 (d, $J = 8.3$ Hz, 2H), 7.67 (d, $J = 8.3$ Hz, 2H), 7.53 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.5$ (C_q), 147.1 (C_q), 132.7 (C_q), 132.4 (C_q), 131.0 (C_q), 130.8 (C_q), 130.4 (d, $^2J_{C-F} = 32$ Hz, C_q), 130.4 (C_q), 130.1 (CH), 129.1 (CH), 127.0 (CH), 126.4 (CH), 126.2 (CH), 126.1 (CH), 126.0 (q, $^3J_{C-F} = 4$ Hz, CH), 125.1 (CH), 124.9 (CH), 124.5 (CH), 124.5 (CH), 124.4 (CH), 124.1 (C_q), 123.9 (C_q), 123.8 (d, $^1J_{C-F} = 270$ Hz, C_q), 114.3 (C_q), 92.3 (C_q), 82.3 (C_q).

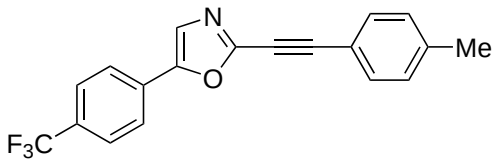
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.7$ (s).

IR (ATR, cm^{-1}): 2206, 1533, 1417, 1319, 1161, 1119, 1071, 944, 853, 843, 831, 764, 720, 708, 692, 593.

MS (EI): 437 (100) $[M]^+$, 381 (20), 313 (20), 237 (23), 191 (5), 173 (8), 145 (12).

$\mathbf{[C_{28}H_{14}F_3NO]^+}$ (EI) HRMS: calcd.: 437.1027.
found: 437.1026.

2-(*para*-Tolylethynyl)-5-[4-(trifluoromethyl)phenyl]oxazole (115dc)



The general procedure **D** was followed using 5-[4-(trifluoromethyl)phenyl]oxazole (**106d**) (107 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)-4-methylbenzene (**126c**) (140 mg, 0.75 mmol). After 13 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **115dc** as a white solid (101 mg, 62%, m.p.: 118–122 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.77$ (d, $J = 8.3$ Hz, 2H), 7.67 (d, $J = 8.3$ Hz, 2H), 7.51 (d, $J = 7.8$ Hz, 2H), 7.49 (s, 1H), 7.19 (d, $J = 7.8$ Hz, 2H), 2.37 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.4$ (C_q), 147.0 (C_q), 140.6 (C_q), 132.1 (CH), 130.5 (C_q), 130.5 (C_q), 130.5 (d, $^2J_{C-F} = 32$ Hz, C_q), 129.3 (CH), 126.0 (q, $^3J_{C-F} = 4$ Hz, CH), 125.0 (CH), 124.5 (CH), 123.8 (d, $^1J_{C-F} = 270$ Hz, C_q), 117.3 (C_q), 92.9 (C_q), 21.7 (CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.8$ (s).

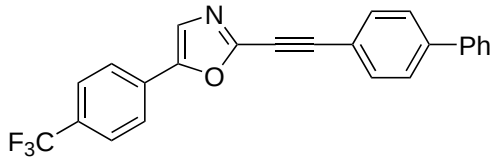
IR (ATR, cm^{-1}): 2204, 1674, 1535, 1414, 1321, 1160, 1108, 1068, 1017, 942, 834, 817, 709, 694, 598, 530.

MS (EI): 327 (100) $[M]^+$, 272 (16), 173 (24), 145 (26), 127 (11), 119 (12), 91 (8), 69 (10), 63 (6).

$[\mathbf{C_{19}H_{12}F_3NO_3}]^+$ (EI) HRMS: calcd.: 327.0871.
found: 327.0868.

The spectral data are in accordance with those reported in the literature.[255]

2-[(1,1'-Biphenyl)-4-ylethynyl]-5-[4-(trifluoromethyl)phenyl]oxazole (115dd)



The general procedure **D** was followed using 5-[4-(trifluoromethyl)phenyl]oxazole (**106d**) (107 mg, 0.50 mmol) and 4-(2,2-dichlorovinyl)-1,1'-biphenyl (**126d**) (187 mg, 0.75 mmol). After 13 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **115dd** as an off-white solid (113 mg, 58%, m.p.: 122–125 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.81$ (d, $J = 8.3$ Hz, 2H), 7.75–7.68 (m, 4H), 7.67–7.59 (m, 4H), 7.54 (s, 1H), 7.51–7.44 (m, 2H), 7.43−7.35 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 151.0$ (C_q), 146.9 (C_q), 142.9 (C_q), 139.9 (C_q), 132.7 (CH), 130.6 (d, $^2J_{C-F} = 32$ Hz, C_q), 130.5 (C_q), 128.8 (CH), 128.0 (CH), 127.2 (CH), 127.1 (CH),

126.0 (q, $^{3}J_{C-F} = 4$ Hz, CH), 125.0 (CH), 124.6 (CH), 123.8 (d, $^{1}J_{C-F} = 270$ Hz, C_q), 119.2 (C_q), 92.6 (C_q), 77.6 (C_q).

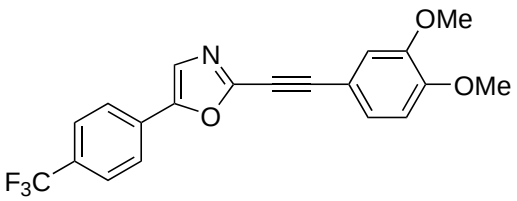
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.8$ (s).

IR (ATR, cm^{-1}): 2210, 1677, 1538, 1482, 1415, 1323, 1107, 1070, 1016, 843, 825, 689, 591, 501.

MS (EI): 389 (100) $[M]^+$, 334 (50), 265 (20), 189 (25), 173 (12), 145 (20), 44 (15).

$[\mathbf{C_{24}H_{14}F_3NO}]^+$ (EI) HRMS: calcd.: 389.1027.
found: 389.1033.

2-[(3,4-Dimethoxyphenyl)ethynyl]-5-[4-(trifluoromethyl)phenyl]oxazole (115df)



The general procedure **D** was followed using 5-[4-(trifluoromethyl)phenyl]oxazole (**106d**) (107 mg, 0.50 mmol) and 4-(2,2-dichlorovinyl)-1,2-dimethoxybenzene (**126f**) (175 mg, 0.75 mmol). After 13 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1→6/1) and recrystallization from EtOH yielded **115df** as a white solid (119 mg, 64%, m.p.: 162–164 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.75$ (d, $J = 8.3$ Hz, 2H), 7.65 (d, $J = 8.3$ Hz, 2H), 7.48 (s, 1H), 7.23 (dd, $J = 8.4$, 1.9 Hz, 1H), 7.09 (d, $J = 1.9$ Hz, 1H), 6.84 (d, $J = 8.4$ Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.9$ (C_q), 150.3 (C_q), 148.7 (C_q), 147.0 (C_q), 130.5 (C_q), 130.4 (d, $^{2}J_{C-F} = 32$ Hz, C_q), 126.0 (CH), 126.0 (q, $^{3}J_{C-F} = 4$ Hz, CH), 125.0 (CH), 124.5 (CH), 123.8 (d, $^{1}J_{C-F} = 270$ Hz, C_q), 114.4 (CH), 112.3 (C_q), 111.0 (CH), 93.1 (C_q), 75.9 (C_q), 55.9 (CH_3), 55.9 (CH_3).

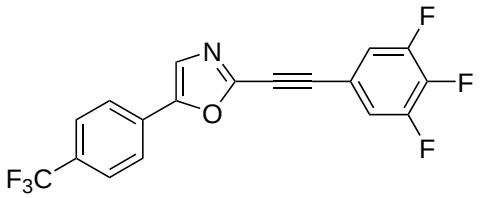
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.8$ (s).

IR (ATR, cm^{-1}): 2947, 2212, 1618, 1598, 1580, 1538, 1510, 1417, 1322, 1266, 1168, 1110, 1072, 1019, 829, 708, 592, 458.

MS (EI): 373 (100) $[M]^+$, 358 (13) $[M\text{-}Me]^+$, 330 (15), 318 (14), 173 (22), 145 (21).

$[\mathbf{C_{20}H_{14}F_3NO_3}]^+$ (EI) HRMS: calcd.: 373.0926.
found: 373.0932.

5-[4-(Trifluoromethyl)phenyl]-2-[(3,4,5-trifluorophenyl)ethynyl]oxazole (115dl)



The general procedure **D** was followed using 5-[4-(trifluoromethyl)phenyl]oxazole (**106d**) (107 mg, 0.50 mmol) and 5-(2,2-dichlorovinyl)-1,2,3-trifluorobenzene (**126l**) (170 mg, 0.75 mmol). After 14 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1) and recrystallization from EtOH yielded **115dl** as a white solid (114 mg, 62%, m.p.: 128–129 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.80$ (d, $J = 8.4$ Hz, 2H), 7.71 (d, $J = 8.4$ Hz, 2H), 7.54 (s, 1H), 7.34–7.19 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 151.1$ (ddd, $^1J_{C-F} = 251$ Hz, $^2J_{C-F} = 11$ Hz, $^3J_{C-F} = 4$ Hz, C_q), 151.1 (C_q), 145.9 (C_q), 141.5 (d, $^1J_{C-F} = 257$ Hz, C_q), 130.9 (d, $^2J_{C-F} = 32$ Hz, C_q), 130.2 (C_q), 126.1 (q, $^3J_{C-F} = 4$ Hz, CH), 125.1 (CH), 124.7 (CH), 123.8 (d, $^1J_{C-F} = 271$ Hz, C_q), 116.7 (dd, $^2J_{C-F} = 15$ Hz, $^3J_{C-F} = 8$ Hz, CH), 116.2 (d, $^3J_{C-F} = 10$ Hz, C_q), 89.0 (d, $^4J_{C-F} = 3$ Hz, C_q), 78.3 (d, $^5J_{C-F} = 2$ Hz, C_q).

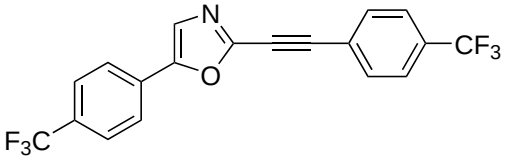
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.9$ (s), -132.5 (s), -155.1 (s).

IR (ATR, cm^{-1}): 2924, 2216, 1612, 1538, 1519, 1324, 1165, 1125, 1072, 1043, 846, 831, 706.

MS (EI): 367 (100) $[M]^+$, 348 (8) $[M\text{-}F]^+$, 312 (85), 277 (12), 243 (37), 173 (15), 167 (28), 145 (37).

$[\mathbf{C_{18}H_7F_6NO}]^+$ (EI) HRMS: calcd.: 367.0432.
found: 367.0432.

5-[4-(Trifluoromethyl)phenyl]-2-{[4-(trifluoromethyl)phenyl]ethynyl}oxazole (115dm)



The general procedure **D** was followed using 5-[4-(trifluoromethyl)phenyl]oxazole (**106d**) (107 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)-4-(trifluoromethyl)benzene (**126m**) (181 mg, 0.75 mmol). After 14 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **115dm** as an off-white solid (144 mg, 76%, m.p.: 102–103 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.81$–7.62 (m, 8H), 7.53 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 151.0$ (C_q), 146.2 (C_q), 132.5 (CH), 131.7 (d, $^2J_{C-F} = 32$ Hz, C_q), 130.8 (d, $^2J_{C-F} = 32$ Hz, C_q), 130.3 (C_q), 126.1 (q, $^3J_{C-F} = 4$ Hz, CH), 125.6 (q,

$^{3}J_{C-F}$ = 4 Hz, CH), 125.1 (CH), 124.6 (CH), 124.2 (C_q), 123.6 (d, $^{1}J_{C-F}$ = 271 Hz, C_q), 123.1 (d, $^{1}J_{C-F}$ = 270 Hz, C_q), 90.7 (C_q), 78.9 (C_q).

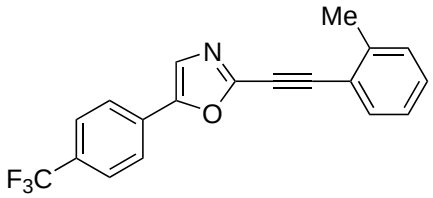
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.9$ (s), -63.1 (s).

IR (ATR, cm^{-1}): 2222, 1681, 1615, 1408, 1319, 1105, 1065, 1016, 945, 831, 709, 592, 470.

MS (EI): 381 (50) $[M]^+$, 326 (100), 257 (22), 181 (16), 173 (20), 145 (30).

$[\mathbf{C_{19}H_9F_6NO_3}]^+$ (EI) HRMS: calcd.: 381.0588.
found: 381.0580.

2-(*ortho*-Tolylethynyl)-5-[4-(trifluoromethyl)phenyl]oxazole (115di)



The general procedure **D** was followed using 5-[4-(trifluoromethyl)phenyl]oxazole (**106d**) (107 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)-2-methylbenzene (**126i**) (140 mg, 0.75 mmol). After 14 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1→4/1) yielded **115di** as a pale yellow solid (114 mg, 70%, m.p.: 87–88 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.80$ (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.60 (dd, J = 7.6, 1.4 Hz, 1H), 7.53 (s, 1H), 7.34 (td, J = 7.5, 1.4 Hz, 1H), 7.30−7.16 (m, 2H), 2.56 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.5$ (C_q), 147.0 (C_q), 141.4 (C_q), 132.7 (CH), 130.5 (d, $^{2}J_{C-F}$ = 33 Hz, C_q), 130.5 (C_q), 130.1 (CH), 129.7 (CH), 126.0 (q, $^{3}J_{C-F}$ = 4 Hz, CH), 125.8 (CH), 125.0 (CH), 124.6 (CH), 123.8 (d, $^{1}J_{C-F}$ = 271 Hz, C_q), 120.2 (C_q), 91.7 (C_q), 80.6 (C_q), 20.7 (CH_3).

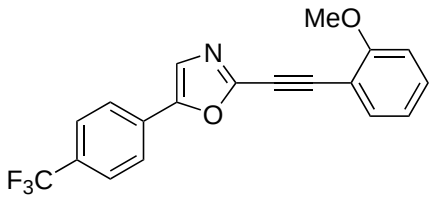
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.8$ (s).

IR (ATR, cm^{-1}): 3123, 2220, 1615, 1528, 1322, 1159, 1104, 1070, 966, 941, 840, 761, 710, 594, 461.

MS (EI): 327 (100) $[M]^+$, 272 (25), 202 (27), 173 (14), 154 (13), 145 (32), 127 (31), 115 (15), 77 (14).

$[\mathbf{C_{19}H_{12}F_3NO}]^+$ (EI) HRMS: calcd.: 327.0871.
found: 327.0869.

2-[(2-Methoxyphenyl)ethynyl]-5-[4-(trifluoromethyl)phenyl]oxazole (115dn)



The general procedure **D** was followed using 5-[4-(trifluoromethyl)phenyl]oxazole (**106d**) (107 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)-2-methoxybenzene (**126n**) (152 mg, 0.75 mmol). After 14 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **115dn** as an off-white solid (110 mg, 64%, m.p.: 99−100 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.79$ (d, $J = 8.4$ Hz, 2H), 7.68 (d, $J = 8.4$ Hz, 2H), 7.58 (dd, $J = 7.5$, 1.7 Hz, 1H), 7.52 (s, 1H), 7.45−7.37 (m, 1H), 7.01–6.91 (m, 2H), 3.93 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.0$ (C_q), 150.4 (C_q), 147.1 (C_q), 134.1 (CH), 131.7 (CH), 130.4 (d, $^2J_{C-F} = 32$ Hz, C_q), 130.2 (C_q), 126.0 (q, $^3J_{C-F} = 4$ Hz, CH), 125.0 (CH), 124.5 (CH), 123.8 (d, $^1J_{C-F} = 270$ Hz, C_q), 120.6 (CH), 110.8 (CH), 109.7 (C_q), 89.5 (C_q), 80.7 (C_q), 55.8 (CH_3).

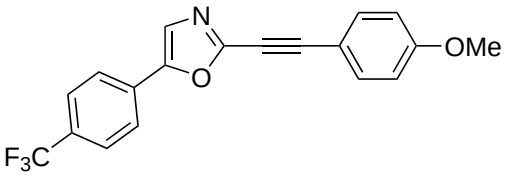
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.8$ (s).

IR (ATR, cm^{-1}): 2217, 1679, 1618, 1531, 1482, 1463, 1435, 1320, 1282, 1164, 1069, 1015, 944, 845, 828, 751, 709.

MS (EI): 343 (100) $[M]^+$, 314 (25), 170 (76), 145 (45), 131 (16), 115 (42), 89 (18), 74 (16), 63 (14).

$[\mathbf{C_{19}H_{12}F_3NO_2}]^+$ (EI) HRMS: calcd.: 343.0820.
found: 323.0821.

2-([4-Methoxyphenyl]ethynyl])-5-(4-[Trifluoromethyl]phenyl)oxazole (115de)



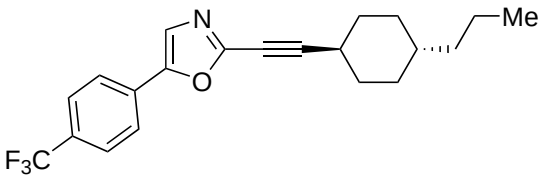
The general procedure **F** was followed using 5-[4-(trifluoromethyl)phenyl]oxazole (**106d**) (107 mg, 0.50 mmol) and 4-(2,2-dibromovinyl)-1-methoxybenzene (**120e**) (219 mg, 0.75 mmol). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1→6/1→4/1) yielded **115de** as a pale-yellow solid (103 mg, 60%, m.p.: 121–122 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.77$ (d, $J = 8.3$ Hz, 2H), 7.67 (d, $J = 8.3$ Hz, 2H), 7.56 (d, $J = 8.9$ Hz, 2H), 7.49 (s, 1H), 6.90 (d, $J = 8.9$ Hz, 2H), 3.83 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.0$ (C_q), 150.3 (C_q), 147.2 (C_q), 133.9 (CH), 130.6 (C_q), 130.4 (d, $^2J_{C-F} = 33$ Hz, C_q), 126.0 (q, $^3J_{C-F} = 4$ Hz, CH), 124.9 (CH), 124.5 (CH), 123.8 (d,

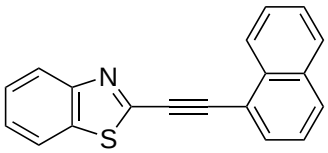
$^{1}J_{C-F}$ = 272 Hz, C_q), 114.3 (CH), 112.3 (C_q), 93.0 (C_q), 76.1 (C_q), 55.4 (CH_3).
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.8$ (s).
IR (ATR, cm^{-1}): 2845, 2219, 1604, 1531, 1464, 1416, 1318, 1250, 1159, 1105, 1069, 1053, 1032, 972, 943, 830, 820, 709, 693, 593, 571, 539, 504.
MS (EI): 343 (100) $[M]^+$, 288 (54), 273 (15), 173 (17), 143 (36), 100 (11), 74 (10), 69 (10).
$[\mathbf{C_{19}H_{12}F_3NO_2}]^+$ (EI) HRMS: calcd.: 343.0820.
found: 343.0810.

2-{[(1*S*,4*R*)-4-*n*-Propylcyclohexyl]ethynyl}-5-[4-(trifluoromethyl)phenyl]oxazole (115dq)



The general procedure **F** was followed using 5-[4-(trifluoromethyl)phenyl]oxazole (**106d**) (107 mg, 0.50 mmol) and (1*S*,4*R*)-1-(2,2-Dibromovinyl)-4-*n*-propylcyclohexane (**120q**) (233 mg, 0.75 mmol). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 15/1) yielded **115dq** as a yellow oil (88 mg, 49%).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.73$ (d, $J = 8.3$ Hz, 2H), 7.64 (d, $J = 8.3$ Hz, 2H), 7.40 (s, 1H), 2.44 (tt, $J = 11.9$, 3.6 Hz, 1H), 2.13–2.02 (m, 2H), 1.85–1.74 (m, 2H), 1.58–1.37 (m, 2H), 1.35–1.10 (m, 5H), 0.99–0.87 (m, 2H), 0.86 (t, $J = 7.1$ Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 149.9$ (C_q), 147.1 (C_q), 130.7 (C_q), 130.4 (d, $^{2}J_{C-F} = 33$ Hz, C_q), 126.0 (q, $^{3}J_{C-F} = 4$ Hz, CH), 124.5 (CH), 124.4 (CH), 123.8 (d, $^{1}J_{C-F} = 271$ Hz, C_q), 98.9 (C_q), 68.6 (C_q), 39.3 (CH_2), 36.4 (CH), 32.3 (CH_2), 32.0 (CH_2), 30.2 (CH), 19.9 (CH_2), 14.3 (CH_3).
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.8$ (s).
IR (ATR, cm^{-1}): 2931, 2860, 2228, 1683, 1618, 1526, 1450, 1415, 1321, 1163, 1122, 1110, 1070, 1016, 946, 856, 827, 713, 594.
MS (EI): 361 (28) $[M]^+$, 332 (26), 318 (19), 304 (15), 264 (100), 240 (15), 227 (9), 208 (9), 188 (12), 173 (28), 145 (36), 122 (32), 105 (8), 91 (11), 79 (21), 55 (13), 41 (33).
$[\mathbf{C_{21}H_{22}F_3NO}]^+$ (EI) HRMS: calcd.: 361.1653.
found: 361.1653.

2-(Naphthalen-1-ylethynyl)benzothiazole (130aa)



The general procedure **E** was followed using benzothiazole (**129a**) (68 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)naphthalene (**126a**) (167 mg, 0.75 mmol). After 13 h, purification by column chromatography (*n*-hexane/EtOAc: 35/1) and recrystallization from EtOH yielded **130aa** as a yellow solid (104 mg, 73%, m.p.: 108–109 °C). **130aa** was also obtained following general procedure **F** from 1-(2,2-bromovinyl)naphthalene (**120a**) (234 mg, 0.75 mmol) and CuI (4.8 mg, 5.0 mol %). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded **130aa** as a yellow solid (71 mg, 50%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.46$ (d, $J = 8.3$ Hz, 1H), 8.16–8.11 (m, 1H), 7.96–7.85 (m, 4H), 7.65 (ddd, $J = 8.4, 6.8, 1.4$ Hz, 1H), 7.60–7.51 (m, 2H), 7.53–7.43 (m, 2H).

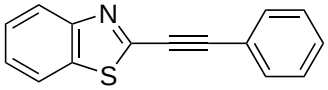
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 153.1$ (C_q), 148.6 (C_q), 135.4 (C_q), 133.1 (C_q), 133.0 (C_q), 131.8 (CH), 130.5 (CH), 128.4 (CH), 127.4 (CH), 126.8 (CH), 126.7 (CH), 126.2 (CH), 126.0 (CH), 125.2 (CH), 123.6 (CH), 121.3 (CH), 118.6 (C_q), 94.4 (C_q), 87.3 (C_q).

IR (ATR, cm^{-1}): 3052, 2199, 1484, 1430, 1328, 1250, 1129, 1023, 885, 801, 775, 758, 726, 679.

MS (EI): 285 (100) $[M]^+$, 253 (15), 241 (10), 177 (7), 150 (7), 108 (8), 69 (10).

$[\mathbf{C_{19}H_{11}NS}]^+$ (EI) HRMS: calcd.: 285.0612.
found: 285.0607.

2-(Phenylethynyl)benzothiazole (130ab)



The general procedure **E** was followed using benzothiazole (**129a**) (68 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)benzene (**126b**) (130 mg, 0.75 mmol). After 14 h, purification by column chromatography (*n*-hexane/EtOAc: 35/1) and recrystallization from EtOH yielded **130ab** as a pale yellow solid (64 mg, 54%, m.p.: 75–76 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.06$ (d, $J = 7.4$ Hz, 1H), 7.85 (d, $J = 7.4$ Hz, 1H), 7.68–7.58 (m, 2H) 7.55–7.33 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 152.9$ (C_q), 148.6 (C_q), 135.3 (C_q), 132.2 (CH), 129.9 (CH), 128.5 (CH), 126.7 (CH), 126.1 (CH), 123.6 (CH), 121.6 (CH), 121.0 (C_q), 95.9 (C_q), 82.7 (C_q).

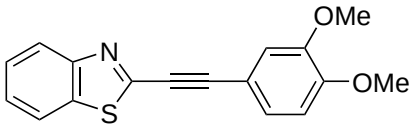
IR (ATR, cm^{-1}): 2923, 2203, 1469, 1453, 1442, 1428, 1313, 1258, 1102, 1056, 876, 749, 722, 680, 521.

MS (EI): 235 (100) $[M]^+$, 190 (10), 108 (17), 82 (11), 69 (23).

$[\mathbf{C_{15}H_9NS}]^+$ (EI) HRMS: calcd.: 235.0456.
found: 235.0457.

The spectral data are in accordance with those reported in the literature.[168]

2-[(3,4-Dimethoxyphenyl)ethynyl]benzothiazole (130af)



The general procedure **E** was followed using benzothiazole (**129a**) (68 mg, 0.50 mmol) and 4-(2,2-dichlorovinyl)-1,2-dimethoxybenzene (**126f**) (175 mg, 0.75 mmol). After 13 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1→4/1) yielded **130af** as a pale yellow solid (74 mg, 50%, m.p.: 104–105 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.03$ (d, $J = 8.3$ Hz, 1H), 7.82 (d, $J = 8.3$ Hz, 1H), 7.48 (ddd, $J = 8.2$, 7.2, 1.4 Hz, 1H), 7.43–7.36 (m, 1H), 7.23 (dd, $J = 8.3$, 1.9 Hz, 1H), 7.10 (d, $J = 1.9$ Hz, 1H), 6.84 (d, $J = 8.4$ Hz, 1H), 3.88 (s, 3H), 3.88 (s, 3H).

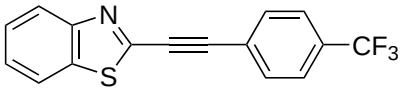
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 153.0$ (C_q), 150.8 (C_q), 148.8 (C_q), 148.8 (C_q), 135.2 (C_q), 126.6 (CH), 126.0 (CH), 126.0 (CH), 132.4 (CH), 121.2 (CH), 114.5 (CH), 113.0 (C_q), 111.1 (CH), 96.4 (C_q), 81.7 (C_q), 55.9 (CH_3), 55.9 (CH_3).

IR (ATR, cm^{-1}): 2934, 2191, 1595, 1516, 1453, 1249, 1220, 1142, 1097, 1019, 855, 809, 760, 725, 676, 614.

MS (EI): 295 (100) $[M]^+$, 280 (25) $[M-Me]^+$, 252 (24), 223 (15), 209 (11), 183 (9), 69 (8), 43 (15).

$[\mathbf{C_{17}H_{13}NO_2S}]^+$ (EI) HRMS: calcd.: 295.0667.
found: 295.0665.

2-{[4-(Trifluoromethyl)phenyl]ethynyl}benzothiazole (130am)



The general procedure **E** was followed using benzothiazole (**129a**) (68 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)-4-(trifluoromethyl)benzene (**126m**) (181 mg, 0.75 mmol). After 14 h, purification by column chromatography (*n*-hexane/EtOAc: 35/1) and recrystallization from EtOH yielded **130am** as a white solid (80 mg, 53%, m.p.: 170–171 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.10$ (d, $J = 7.5$ Hz, 1H), 7.88 (d, $J = 7.5$ Hz, 1H), 7.73 (d, $J = 8.3$ Hz, 2H), 7.64 (d, $J = 8.3$ Hz, 2H), 7.57–7.42 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 152.9$ (C_q), 147.8 (C_q), 135.4 (C_q), 132.4 (CH), 132.4 (CH), 131.4 (d, $^2J_{C-F} = 32$ Hz, C_q), 126.7 (d, $^3J_{C-F} = 27$ Hz, CH), 125.5 (q, $^4J_{C-F} = 4$ Hz, CH), 124.8 (C_q), 123.8 (CH), 121.4 (CH), 120.0 (d, $^1J_{C-F} = 271$ Hz, C_q), 93.7 (C_q), 84.6 (C_q).

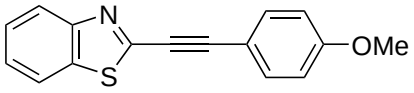
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -63.0$ (s).

IR (ATR, cm^{-1}): 3060, 2208, 1608, 1476, 1405, 1319, 1162, 1102, 1065, 1012, 836, 755, 725, 598, 542.

MS (EI): 303 (100) $[M]^+$, 108 (20), 82 (10), 69 (28), 63 (8), 43 (10).

$[\mathbf{C_{16}H_8F_3NS}]^+$ (EI) HRMS: calcd.: 303.0330.
found: 303.0326.

2-[(4-Methoxyphenyl)ethynyl]benzothiazole (130e)



The general procedure **F** was followed using benzothiazole (**129a**) (68 mg, 0.50 mmol), 4-(2,2-dibromovinyl)-1-methoxybenzene (**120e**) (219 mg, 0.75 mmol) and CuI (4.8 mg, 5.0 mol %). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **130ae** as a yellow oil (53 mg, 40%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.07$–8.00 (m, 1H), 7.83 (ddt, $J = 7.9$, 1.5, 0.7 Hz, 1H), 7.56 (d, $J = 9.0$ Hz, 2H), 7.52–7.46 (m, 1H), 7.44–7.38 (m, 1H), 6.89 (d, $J = 9.0$ Hz, 2H), 3.82 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 160.9$ (C_q), 153.0 (C_q), 149.0 (C_q), 135.3 (C_q), 133.9 (CH), 126.6 (CH), 126.0 (CH), 123.4 (CH), 121.2 (CH), 114.3 (CH), 113.0 (C_q), 96.5 (C_q), 81.9 (C_q), 55.3 (CH_3).

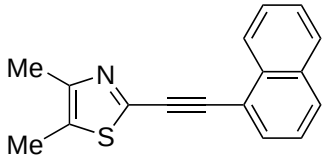
IR (ATR, cm^{-1}): 2205, 1601, 1516, 1476, 1300, 1255, 1172, 1103, 1059, 1023, 836, 756, 726, 679.

MS (EI): 265 (100) $[M]^+$, 250 (40) $[M-Me]^+$, 222 (21) $[M-OMe-H]^+$, 190 (5), 146 (7), 69 (9).

$[\mathbf{C_{16}H_{11}NOS}]^+$ (EI) HRMS: calcd.: 265.0561.
found: 265.0557.

The spectral data are in accordance with those reported in the literature.[256]

4,5-Dimethyl-2-(naphthalen-1-ylethynyl)thiazole (130ba)



The general procedure **F** was followed using 4,5-dimethylthiazole (**129b**) (57 mg, 0.50 mmol), 1-(2,2-bromovinyl)naphthalene (**120a**) (234 mg, 0.75 mmol) and CuI (4.8 mg, 5.0 mol %). After 15 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **130ba** as a yellow oil (15 mg, 11%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.40$ (dt, $J = 8.6$, 1.0 Hz, 1H), 7.91–7.84 (m, 2H), 7.81 (dd, $J = 7.2$, 1.2 Hz, 1H), 7.64–7.50 (m, 2H), 7.46 (dd, $J = 8.3$, 7.2 Hz, 1H), 2.42 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 149.7$ (C_q), 143.9 (C_q), 133.1 (C_q), 133.0 (C_q), 131.1 (CH), 129.7 (CH), 129.0 (C_q), 128.3 (CH), 127.1 (CH), 126.6 (CH), 126.2 (CH), 125.2 (CH), 119.4 (C_q), 91.3 (C_q), 87.3 (C_q), 14.8 (CH_3), 11.4 (CH_3).

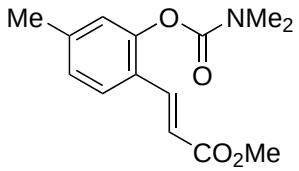
IR (ATR, cm^{-1}): 2917, 2200, 1584, 1529, 1503, 1432, 1387, 1281, 1244, 1138, 1024, 886, 797, 766, 731, 634, 587, 567, 443.

MS (EI): 263 (100) $[M]^+$, 177 (43), 150 (23), 86 (50), 71 (71), 59 (24), 43 (18).

$\mathbf{[C_{17}H_{13}NS]^+}$ (EI) HRMS: calcd.: 263.0769.
found: 263.0767.

5.3.4 Ruthenium-Catalzyed Direct C−H Bond Alkenylations of Carbamates

Synthesis of (*E*)-Methyl 3-[2-(*N*,*N*-Dimethylcarbamoyloxy)-4-methylphenyl]acrylate (128aa)



The general procedure **G** was followed using *meta*-tolyl *N*,*N*-dimethylcarbamate (**127a**) (90 mg, 0.50 mmol) and methyl acrylate (**10a**) (86 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 4/1) yielded **128aa** as a white solid (114 mg, 87%, m.p.: 77–80 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.79$ (d, $J = 16.1$ Hz, 1H), 7.49 (d, $J = 8.0$ Hz, 1H), 7.01 (dd, $J = 8.0$, 1.6 Hz, 1H), 6.97 (d, $J = 1.6$ Hz, 1H), 6.39 (d, $J = 16.1$ Hz, 1H), 3.77 (s, 3H), 3.15 (s, 3H), 3.01 (s, 3H), 2.34 (s, 3H).

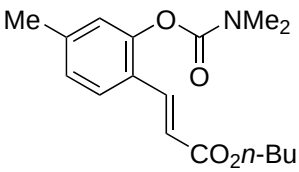
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.4$ (C_q), 154.3 (C_q), 150.0 (C_q), 141.9 (C_q), 138.6 (CH), 127.1 (CH), 126.6 (CH), 124.3 (C_q), 123.8 (C_q), 118.1 (CH), 51.5 (CH_3), 36.7 (CH_3), 36.4 (CH_3), 21.3 (CH_3).

IR (ATR, cm^{-1}): 2949, 1737, 1715, 1631, 1383, 1321, 1276, 1161, 985, 807, 746.

MS (EI): 263 (5) $[M]^+$, 175 (58) $[M-Me_2NCO_2]^+$, 160 (5) $[M-Me_2NCO_2-Me]^+$, 132 (13), 72 (100) $[Me_2NCO]^+$.

$[C_{14}H_{17}NO_4 + H]^+$ (ESI) HRMS: calcd.: 264.1230.
found: 264.1230.

Synthesis of (*E*)-*n*-Butyl 3-[2-(*N*,*N*-Dimethylcarbamoyloxy)-4-methylphenyl]acrylate (128ac)

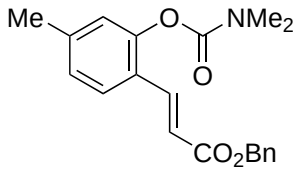


The general procedure **G** was followed using *meta*-tolyl *N*,*N*-dimethylcarbamate (**127a**) (90 mg, 0.50 mmol) and *n*-butyl acrylate (**10c**) (128 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 4/1) yielded **128ac** as a colourless oil (148 mg, 97%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.77$ (d, $J = 16.1$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.00 (dd, $J = 8.0$, 1.6 Hz, 1H), 6.96 (d, $J = 1.6$ Hz, 1H), 6.37 (d, $J = 16.1$ Hz, 1H), 4.16 (t, $J = 6.6$ Hz, 2 H), 3.14 (s, 3 H), 3.00 (s, 3 H), 2.33 (s, 3H), 1.74–1.58 (m, 2H), 1.50–1.30 (m, 2H), 0.94 (t, $J = 7.4$ Hz, 3H).

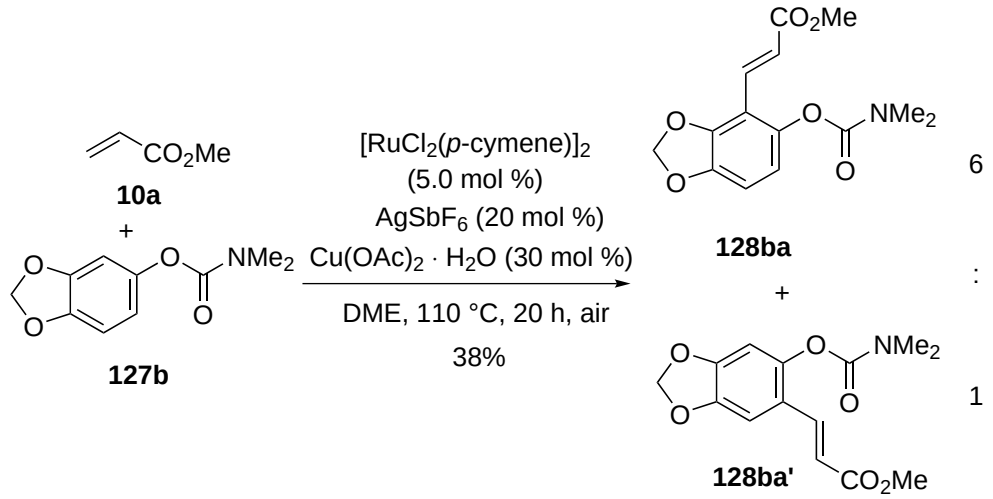
^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1 (C_q), 154.4 (C_q), 150.0 (C_q), 141.9 (C_q), 138.2 (CH), 127.0 (CH), 126.7 (CH), 124.5 (C_q), 123.9 (CH), 118.6 (CH), 64.3 (CH_2), 36.8 (CH_3), 36.5 (CH_3), 30.7 (CH_2), 21.4 (CH_3), 19.2 (CH_2), 13.7 (CH_3).
IR (ATR, cm^{-1}): 2958, 1709, 1633, 1381, 1269, 1244, 1150, 813, 732.
MS (EI): 304 (4) $[M-H]^+$, 217 (58) $[M-Me_2NCO_2]^+$, 161 (32), 132 (21), 103 (8), 72 (100) $[Me_2NCO]^+$, 56 (8), 41 (18).
$[C_{17}H_{23}NO_4 + H]^+$ (ESI) HRMS: calcd.: 306.1700.
found: 306.1702.
The spectral data are in accordance with those reported in the literature.[257]

Synthesis of (*E*)-Benzyl 3-[2-(*N*,*N*-Dimethylcarbamoyloxy)-4-methylphenyl]acrylate (128ad)



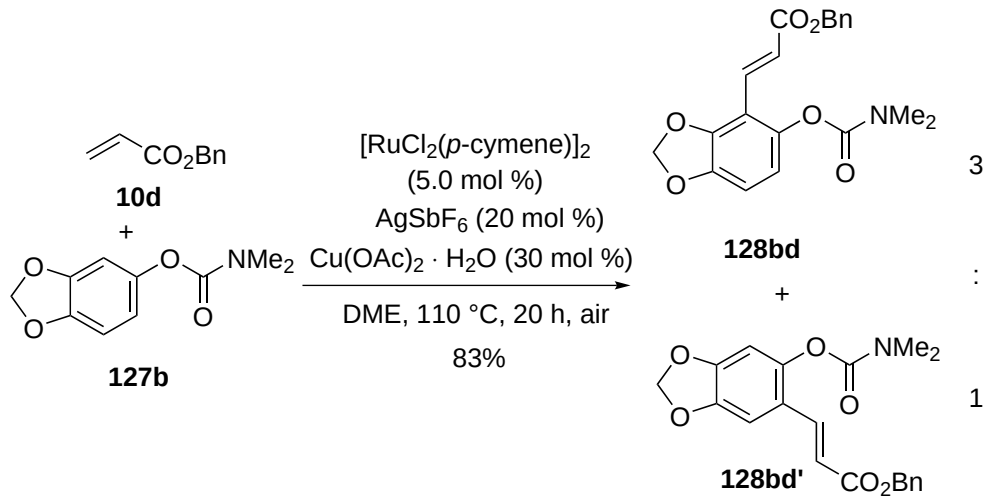
The general procedure **G** was followed using *meta*-tolyl *N*,*N*-dimethylcarbamate (**127a**) (90 mg, 0.50 mmol) and benzyl acrylate (**10d**) (162 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 4/1) yielded **128ad** as a colourless oil (161 mg, 95%).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, J = 16.1 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.43–7.27 (m, 5H), 7.01 (d, J = 8.0 Hz, 1H), 6.98 (s, 1H), 6.43 (d, J = 16.1 Hz, 1H), 5.22 (s, 2H), 3.11 (s, 3H), 2.99 (s, 3H), 2.34 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7 (C_q), 154.3 (C_q), 150.0 (C_q), 142.0 (C_q), 138.8 (CH), 136.0 (C_q), 128.5 (CH), 128.1 (CH),128.1 (CH), 127.0 (CH), 126.7 (CH), 124.3 (C_q), 123.8 (CH), 118.1 (CH), 66.2 (CH_2), 36.7 (CH_3), 36.4 (CH_3), 21.3 (CH_3).
IR (ATR, cm^{-1}): 2937, 1710, 1631, 1380, 1245, 1147, 982, 813, 734, 696.
MS (EI): 339 (1) $[M]^+$, 248 (5) $[M-Bn]^+$, 160 (36) $[M-Bn-Me_2NCO_2]^+$, 132 (23), 91 (38) $[Bn]^+$, 72 (100)$[Me_2NCO]^+$.
$[C_{20}H_{21}NO_4 + H]^+$ (ESI) HRMS: calcd.: 340.1543.
found: 340.1547.

C−H Alkenylation of Benzo[*d*][1,3]dioxol-5-yl *N*,*N*-Dimethylcarbamate (127b) with Methyl Acrylate (10a)



$[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.05 mmol, 20 mol %), $Cu(OAc)_2 \cdot H_2O$ (30 mg, 0.15 mmol, 30 mol %) and benzo[*d*][1,3]dioxol-5-yl *N*,*N*-dimethylcarbamate (**127b**) (105 mg, 0.50 mmol) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. Dry DME (3 mL) and methyl acrylate (**10a**) (86 mg, 1.0 mmol) were added and the reaction mixture was stirred at ambient temperature for 5 min, thereafter purged with air for 10 min. The resulting mixture was stirred at 110 °C for 20 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1 → 2.5/1) to yield a mixture of **128ba** and **128ba'** (56 mg 38%, 6:1, as determined by ^{1}H NMR).

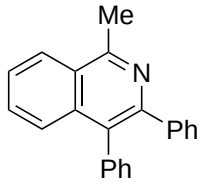
C−H Alkenylation of Benzo[*d*][1,3]dioxol-5-yl *N*,*N*-Dimethylcarbamate (127b) with Benzyl Acrylate (10d)



$[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), $AgSbF_6$ (34 mg, 0.05 mmol, 20 mol %), $Cu(OAc)_2 \cdot H_2O$ (30 mg, 0.15 mmol, 30 mol %) and benzo[*d*][1,3]dioxol-5-yl *N*,*N*-dimethylcarbamate (**127b**) (105 mg, 0.50 mmol) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. Dry DME (3 mL) and benzyl acrylate (**10d**) (162 mg, 1.0 mmol) were added and the reaction mixture was stirred at ambient temperature for 5 min, thereafter purged with air for 10 min. The resulting mixture was stirred at 110 °C for 20 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 3/1) to yield a mixture of **128bd** and **128bd'** (153 mg 83%, 3:1, as determined by ^{1}H NMR).

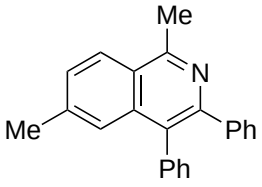
5.3.5 Syntheses of Isoquinolines 50

Synthesis of 1-Methyl-3,4-diphenylisoquinoline (50aa)



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **50aa** as a white solid (119 mg, 81%, m.p.: 152–155 °C).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.23$–8.20 (m, 1H), 7.71–7.67 (m, 1H), 7.63–7.57 (m, 2H), 7.44–7.32 (m, 5H), 7.29–7.17 (m, 5H), 3.11 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.7$ (C_q), 149.4 (C_q), 141.0 (C_q), 137.6 (C_q), 136.0 (C_q), 131.4 (CH), 130.2 (CH), 129.9 (CH), 129.1 (C_q), 128.1 (CH), 127.6 (CH), 127.1 (CH), 126.9 (CH), 126.5 (CH), 126.2 (CH), 126.1 (C_q), 125.5 (CH), 22.7 (CH_3).
IR (ATR, cm^{-1}): 3025, 1567, 1389, 1334, 1072, 1026, 765, 695, 612, 563, 496.
MS (EI): 295 (50) $[M]^+$, 294 (100) $[M-H]^+$, 278 (5), 252 (17), 177 (15), 146 (6), 43 (14).
$[\mathbf{C_{22}H_{17}N}]^+$ (EI) HRMS: calcd.: 295.1361.
found: 295.1348.
The spectral data are in accordance with those reported in the literature.[127]

Synthesis of 1,6-Dimethyl-3,4-diphenylisoquinoline (50ba)



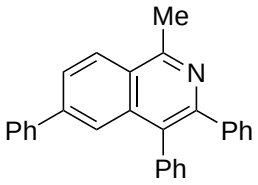
The general procedure **H** was followed using 1-*para*-tolylethanone oxime (**87b**) (75 mg, 0.50 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **50ba** as a white solid (131 mg, 85%, m.p.: 160–163 °C).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.09$ (d, $J = 9.2$ Hz, 1H), 7.44–7.39 (m, 2H), 7.39–7.30 (m, 5H), 7.25–7.14 (m, 5H), 3.05 (s, 3H), 2.43 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.3$ (C_q), 149.5 (C_q), 141.1 (C_q), 140.1 (C_q), 137.7 (C_q), 136.2 (C_q), 131.4 (CH), 130.2 (CH), 128.7 (C_q), 128.6 (CH), 128.1 (CH), 127.5 (CH), 127.0 (CH), 126.8 (CH), 125.4 (CH), 125.0 (CH), 124.5 (C_q), 22.6 (CH_3), 22.1 (CH_3).
IR (ATR, cm^{-1}): 3062, 1495, 1444, 1385, 1336, 1071, 1029, 813, 767, 755, 696, 614.

MS (EI): 309 (40) $[M]^+$, 308 (100) $[M-H]^+$, 293 (5) $[M-H-Me]^+$, 265 (5), 252 (12), 146 (5), 43 (4).

$\mathbf{[C_{23}H_{19}N + H]^+}$ (ESI) HRMS: calcd.: 310.1590.
found: 310.1592.

The spectral data are in accordance with those reported in the literature.[127]

Synthesis of 1-Methyl-3,4,6-triphenylisoquinoline (50ca)



The general procedure **H** was followed using 1-([1,1'-biphenyl]-4-yl)ethanone oxime (**87c**) (106 mg, 0.50 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 15/1) yielded **50ca** as a pale orange solid (101 mg, 54%, m.p.: 176–178 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.28$ (dd, $J = 8.2, 1.1$ Hz, 1H), 7.87 (s, 1H), 7.86 (d, $J = 8.2, 1.8$ Hz 1H), 7.62−7.53 (m, 2H), 7.49–7.14 (m, 13H), 3.11 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.5$ (C_q), 150.0 (C_q), 142.5 (C_q), 141.0 (C_q), 140.4 (C_q), 137.5 (C_q), 136.3 (C_q), 131.4 (CH), 130.2 (CH), 129.3 (C_q), 128.9 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 126.9 (CH), 126.2 (CH), 126.2 (CH), 125.2 (C_q), 124.0 (CH), 22.7 (CH_3).

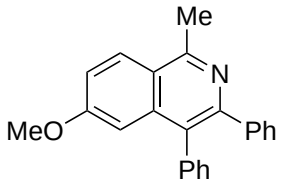
IR (ATR, cm^{-1}): 3058, 1611, 1567, 1434, 1339, 955, 893, 831, 760, 751, 690, 611.

MS (EI): 371 (68) $[M]^+$, 370 (100) $[M-H]^+$, 354 (3), 327 (5), 292 (2), 252 (4), 77 (3).

$\mathbf{[C_{28}H_{21}N]^+}$ (EI) HRMS: calcd.: 371.1674.
found: 371.1657.

The spectral data are in accordance with those reported in the literature.[128]

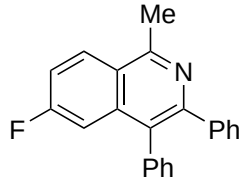
Synthesis of 6-Methoxy-1-methyl-3,4-diphenylisoquinoline (50da)



The general procedure **H** was followed using 1-([1,1'-biphenyl]-4-yl)ethanone oxime 1-(4-Methoxyphenylethanone oxime (**87d**) (83 mg, 0.50 mmol), diphenylacetylene (**34a**) (178 mg, 1.00 mmol) and additional molecular sieves 4 Å (100 mg). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50da** as a pale yellow solid (81 mg, 50%, m.p.: 175–177 °C).

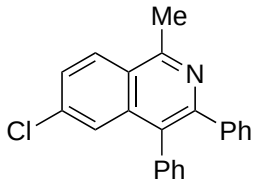
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.09$ (d, $J = 9.1$ Hz, 1H), 7.38–7.28 (m, 5H), 7.25–7.13 (m, 6H), 6.91 (d, $J = 2.6$ Hz, 1H), 3.71 (s, 3H), 3.01 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 160.5$ (C_q), 156.9 (C_q), 150.1 (C_q), 141.2 (C_q), 138.0 (C_q), 137.8 (C_q), 131.2 (CH), 130.2 (CH), 128.5 (C_q), 128.2 (CH), 127.5 (CH), 127.4 (CH), 127.0 (CH), 126.8 (CH), 121.8 (C_q), 118.6 (CH), 104.4 (CH), 55.2 (CH_3), 22.6 (CH_3).
IR (ATR, cm^{-1}): 2923, 1618, 1500, 1410, 1273, 1229, 1205, 1070, 1024, 853, 823, 767, 696, 611.
MS (EI): 325 (55) $[M]^+$, 324 (100) $[M-H]^+$, 281 (32), 239 (6), 139 (5), 43 (10).
$\mathbf{[C_{23}H_{19}NO]^+}$ (EI) HRMS: calcd.: 325.1467.
found: 325.1471.
The spectral data are in accordance with those reported in the literature.[127]

Synthesis of 6-Fluoro-1-methyl-3,4-diphenylisoquinoline (50ea)



The general procedure **H** was followed using 1-(4-fluorophenyl)ethanone oxime (**87e**) (77 mg, 0.50 mmol), diphenylacetylene (**34a**) (178 mg, 1.00 mmol) and additional molecular sieves 4 Å(100 mg). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50ea** as a white solid (81 mg, 52%, m.p.: 139–142 °C).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.20$ (ddd, $J = 9.1, 5.7, 0.5$ Hz, 1H), 7.40–7.12 (m, 12H), 3.05 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 163.1$ (d, $^1J_{C-F} = 249$ Hz, C_q), 157.5 (d, $^4J_{C-F} = 1$ Hz, C_q), 150.4 (C_q), 140.6 (C_q), 138.0 (d, $^3J_{C-F} = 10$ Hz, C_q), 137.1 (C_q), 131.2 (CH), 130.2 (CH), 128.9 (d, $^4J_{C-F} = 6$ Hz, C_q), 128.6 (d, $^3J_{C-F} = 9$ Hz, CH), 128.4 (CH), 127.6 (CH), 127.3 (CH), 127.1 (CH), 123.4 (C_q), 116.7 (d, $^2J_{C-F} = 23$ Hz, CH), 109.9 (d, $^2J_{C-F} = 23$ Hz, CH), 22.8 (CH_3).
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -107.57$ (ddd, $J = 10.9, 8.1, 5.7$ Hz).
IR (ATR, cm^{-1}): 3034, 1622, 1571, 1504, 1260, 1182, 1151, 978, 874, 830, 772, 756, 713, 700, 613.
MS (EI): 313 (57) $[M]^+$, 312 (100), 270 (22), 207 (6), 155 (15), 51 (6).
$\mathbf{[C_{22}H_{16}FN + H]^+}$ (ESI) HRMS: calcd.: 314.1340.
found: 314.1340.
The spectral data are in accordance with those reported in the literature.[258]

Synthesis of 6-Chloro-1-methyl-3,4-diphenylisoquinoline (50fa)



The general procedure **H** was followed using 1-(4-chlorophenyl)ethanone oxime (**87f**) (83 mg, 0.50 mmol), diphenylacetylene (**34a**) (178 mg, 1.00 mmol) and additional molecular sieves 4 Å (100 mg). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50fa** as a white solid (80 mg, 49%, m.p.: 181–183 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.12$ (dd, $J = 8.9, 0.6$ Hz, 1H), 7.62 (dd, $J = 2.1, 0.5$ Hz, 1H), 7.51 (dd, $J = 8.9, 2.1$ Hz, 1H), 7.40–7.29 (m, 5H), 7.23−7.13 (m, 5H), 3.04 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.6$ (C_q), 150.6 (C_q), 140.6 (C_q), 137.1 (C_q), 136.9 (C_q), 136.3 (C_q), 131.3 (CH), 130.2 (CH), 128.4 (C_q), 128.4 (CH), 127.6 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 127.1 (CH), 125.1 (CH), 124.4 (C_q), 22.7 (CH_3).

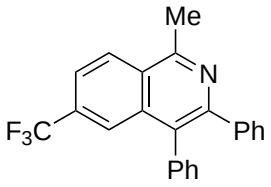
IR (ATR, cm^{-1}): 3065, 3027, 1602, 1562, 1385, 1329, 1093, 1071, 1030, 957, 885, 816, 792, 765, 696, 608.

MS (EI): 328 (100) $[M-H]^+$, 293 (8) $[M-H-Cl]^+$, 252 (15), 146 (8), 43 (18).

$\mathbf{[C_{22}H_{16}NCl]^+}$ (EI) HRMS: calcd.: 329.0971.
found: 329.0966.

The spectral data are in accordance with those reported in the literature.[127]

Synthesis of 1-Methyl-3,4-diphenyl-6-(trifluoromethyl)isoquinoline (50ga)



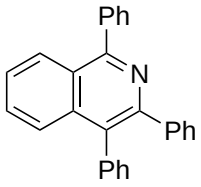
The general procedure **H** was followed using 1-[4-(trifluoromethyl)phenyl]ethanone oxime (**87g**) (102 mg, 0.50 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50ga** as an orange solid (134 mg, 74%, m.p.: 109–114 °C). The repeated synthesis furnished 118 mg (65%). Average Yield of two runs: 70%.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.31$ (d, $J = 8.8$ Hz, 1H), 7.96 (d, $J = 1.8$ Hz, 1H), 7.75 (dd, $J = 8.8, 1.8$ Hz, 1H), 7.40–7.33 (m, 5H), 7.23–7.16 (m, 5H), 3.10 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.8$ (C_q), 150.9 (C_q), 140.4 (C_q), 136.5 (C_q), 135.4 (C_q), 131.5 (q, $^2J_{C-F} = 32$ Hz, C_q), 131.2 (CH), 130.2 (CH), 129.7 (C_q), 128.5 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 127.0 (C_q), 126.8 (CH), 123.9 (q, $^3J_{C-F} = 5$ Hz, CH), 123.8 (d, $^1J_{C-F} = 272$ Hz, C_q), 122.2 (q, $^3J_{C-F} = 3$ Hz, CH), 22.8 (CH_3).

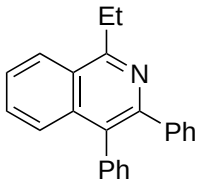
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.8$ (s).
IR (ATR, cm^{-1}): 2958, 1555, 1336, 1305, 1257, 1176, 1155, 1134, 1082, 909, 769, 696, 618.
MS (EI): 363 (50) $[M]^+$, 362 (100) $[M-H]^+$, 252 (8), 146 (5), 43 (5).
$[\mathbf{C_{23}H_{16}F_3N}]^+$ (EI) HRMS: calcd.: 363.1235.
found: 363.1219.
The spectral data are in accordance with those reported in the literature.[128]

Synthesis of 1,3,4-Triphenylisoquinoline (50ha)



The general procedure **H** was followed using benzophenone oxime (**87h**) (99 mg, 0.50 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **50ha** as a pale yellow solid (147 mg, 82%, m.p.: 181–184 °C).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.20$ (dm, $J = 8.5$ Hz, 1H), 7.84 (dd, $J = 8.0$, 1.6 Hz, 2H), 7.74 (dm, $J = 8.7$ Hz, 1H), 7.67–7.10 (m, 15H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.9$ (C_q), 149.6 (C_q), 140.9 (C_q), 139.8 (C_q), 137.5 (C_q), 136.9 (C_q), 131.3 (CH), 130.4 (CH), 130.2 (CH), 129.9 (CH), 129.7 (C_q), 128.5 (CH), 128.3 (CH), 128.3 (CH), 127.5 (CH), 127.5 (CH), 127.3 (CH), 127.0 (CH), 126.6 (CH), 126.0 (CH), 125.4 (C_q).
IR (ATR, cm^{-1}): 3054, 1540, 1494, 1442, 1384, 1336, 1073, 1030, 980, 761, 700, 668, 633, 567.
MS (EI): 357 (50) $[M]^+$, 356 (100) $[M-H]^+$, 278 (11) $[M-2H-Ph]^+$, 252 (10), 177 (5).
$[\mathbf{C_{27}H_{19}N}]^+$ (EI) HRMS: calcd.: 357.1517.
found: 357.1493.
The spectral data are in accordance with those reported in the literature.[127]

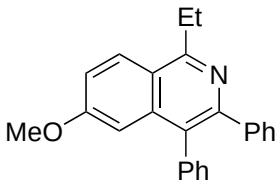
Synthesis of 1-Ethyl-3,4-diphenylisoquinoline (50ia)



The general procedure **H** was followed using propiophenone oxime (**87i**) (75 mg, 0.50 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 15/1) yielded **50ia** as a pale brown solid (141 mg, 91%, m.p.: 113–115 °C).

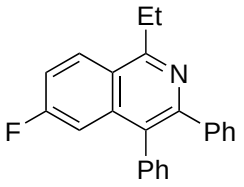
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.29$–8.20 (m, 1H), 7.70–7.62 (m, 1H), 7.61–7.50 (m, 2H), 7.42–7.30 (m, 5H), 7.26–7.12 (m, 5H), 3.44 (q, $J = 7.6$ Hz, 2H), 1.53 (t, $J = 7.6$ Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.2$ (C_q), 149.2 (C_q), 141.1 (C_q), 137.7 (C_q), 136.3 (C_q), 131.4 (CH), 130.3 (CH), 129.7 (CH), 128.9 (C_q), 128.2 (CH), 127.5 (CH), 127.1 (CH), 126.8 (CH), 126.4 (CH), 126.4 (CH), 125.3 (C_q), 125.1 (CH), 28.8 (CH_2), 13.9 (CH_3).
IR (ATR, cm^{-1}): 2935, 1552, 1445, 1382, 1260, 1072, 1028, 753, 694, 607, 561.
MS (EI): 309 (55) $[M]^+$, 308 (100) $[M-H]^+$, 293 (14) $[M-H-Me]^+$, 280 (8) $[M-Et]^+$, 252 (5), 146 (5), 69 (6).
$[\mathbf{C_{23}H_{19}N}]^+$ (EI) HRMS: calcd.: 309.1517.
found: 309.1505.
The spectral data are in accordance with those reported in the literature.[127]

Synthesis of 1-Ethyl-6-methoxy-3,4-diphenylisoquinoline (50ja)



The general procedure **H** was followed using 1-(4-methoxyphenyl)propan-1-one oxime (**87j**) (94 mg, 0.52 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50ja** as a pale yellow solid (168 mg, 95%, m.p.: 158–161 °C).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.14$ (d, $J = 9.2$ Hz, 1H), 7.40–7.28 (m, 5H), 7.26–7.11 (m, 6H), 6.91 (d, $J = 2.6$ Hz, 1H), 3.71 (s, 3H), 3.37 (q, $J = 7.6$ Hz, 2H), 1.50 (t, $J = 7.6$ Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.6$ (C_q), 160.3 (C_q), 150.0 (C_q), 141.3 (C_q), 138.4 (C_q), 138.0 (C_q), 131.3 (CH), 130.3 (CH), 128.3 (C_q), 128.2 (CH), 127.5 (CH), 127.0 (CH), 127.0 (CH), 126.8 (CH), 121.0 (C_q), 119.0 (CH), 104.6 (CH), 55.1 (CH_3), 28.8 (CH_2), 14.1 (CH_3).
IR (ATR, cm^{-1}): 2970, 1617, 1574, 1454, 1411, 1232, 1146, 1018, 757, 699, 662, 527.
MS (EI): 339 (55) $[M]^+$, 338 (100) $[M-H]^+$, 323 (5) $[M-H-Me]^+$, 295 (10) $[M-Et-Me]^+$, 280 (12) $[M-Et-OMe-H]^+$, 267 (7), 239 (8).
$[\mathbf{C_{24}H_{21}NO}]^+$ (EI) HRMS: calcd.: 339.1623.
found: 339.1613.

Synthesis of 1-Ethyl-6-fluoro-3,4-diphenylisoquinoline (50ka)



The general procedure **H** was followed using 1-(4-fluorophenyl)propan-1-one oxime (**87k**) (83 mg, 0.50 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 15/1 ⟶ 12/1) yielded **50ka** as a white solid (94 mg, 57%, m.p.: 141–142 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.27$ (dd, $J = 9.2, 5.7$ Hz, 1H), 7.45–7.10 (m, 12H), 3.42 (q, $J = 7.5$ Hz, 2H), 1.53 (t, $J = 7.5$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 163.0$ (d, $^1J_{C-F} = 245$ Hz, C_q), 162.0 (C_q), 150.7 (C_q), 140.8 (C_q), 138.4 (d, $^3J_{C-F} = 10$ Hz, C_q), 137.3 (C_q), 131.2 (CH), 130.3 (CH), 128.7 (d, $^4J_{C-F} = 5$ Hz, C_q), 128.4 (CH), 128.2 (d, $^3J_{C-F} = 10$ Hz, CH), 127.6 (CH), 127.3 (CH), 127.1 (CH), 122.5 (d, $^4J_{C-F} = 1$ Hz, C_q), 116.6 (d, $^2J_{C-F} = 25$ Hz, CH), 110.0 (d, $^2J_{C-F} = 22$ Hz, CH), 28.9 (CH_2), 13.9 (CH_3).

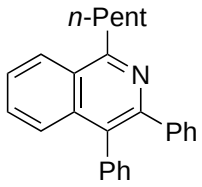
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -107.9$ (s).

IR (ATR, cm^{-1}): 2973, 1619, 1573, 1447, 1386, 1182, 1072, 876, 788, 753, 697.

MS (EI): 327 (53) $[M]^+$, 326 (100) $[M-H]^+$, 311 (12) $[M-H-Me]^+$, 298 (10) $[M-Et]^+$, 98 (10), 74 (6), 57 (10), 43 (20).

$[C_{23}H_{18}FN + H]^+$ (ESI) HRMS: calcd.: 328.1496.
found: 328.1498.

Synthesis of 1-*n*-Pentyl-3,4-diphenylisoquinoline (50la)



The general procedure **H** was followed using 1-phenylhexan-1-one oxime (**87l**) (96 mg, 0.50 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded **50la** as a yellow oil (168 mg, 96%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.31$–8.19 (m, 1H), 7.71–7.63 (m, 1H), 7.61–7.53 (m, 2H), 7.42–7.28 (m, 5H), 7.27–7.12 (m, 5H), 3.40 (t, $J = 7.5$ Hz, 2H), 2.07–1.89 (m, 2H), 1.66–1.37 (m, 4H), 0.96 (t, $J = 7.1$ Hz, 3H).

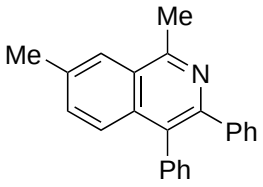
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.5$ (C_q), 149.3 (C_q), 141.1 (C_q), 137.7 (C_q), 136.3 (C_q), 131.4 (CH), 130.3 (CH), 129.6 (CH), 128.9 (C_q), 128.2 (CH), 127.5 (CH), 127.5 (CH), 127.1 (CH), 126.8 (CH), 126.3 (CH), 125.5 (C_q), 125.2 (CH), 35.8 (CH_2), 32.2 (CH_2), 29.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

IR (ATR, cm^{-1}): 3058, 2927, 2858, 1613, 1551, 1504, 1443, 1383, 1073, 1030, 763, 696, 612.

MS (EI): 351 (5) $[M]^+$, 322 (10) $[M-Et]^+$, 308 (12) $[M-n\text{-}Pr]^+$, 295 (100) $[M-n\text{-}Bu-H]^+$, 252 (5), 216 (5).

$[C_{26}H_{25}N]^+$ (EI) HRMS: calcd.: 351.1987.
found: 351.1998.

Synthesis of 1,7-Dimethyl-3,4-diphenylisoquinoline (50ta)



The general procedure **H** was followed using 1-*meta*-tolylethanone oxime (**87t**) (75 mg, 0.50 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50ta** as a pale orange solid (125 mg, 81%, m.p.: 134–139 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.96$ (dq, $J = 1.8, 0.9$ Hz, 1H), 7.57 (d, $J = 8.6$ Hz, 1H), 7.45–7.30 (m, 6H), 7.26–7.14 (m, 5H), 3.06 (s, 3H), 2.57 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 156.9$ (C_q), 148.6 (C_q), 141.0 (C_q), 137.7 (C_q), 136.3 (C_q), 134.1 (C_q), 132.0 (CH), 131.3 (CH), 130.2 (CH), 129.0 (C_q), 128.1 (CH), 127.5 (CH), 127.0 (CH), 126.7 (CH), 126.2 (C_q), 126.0 (CH), 124.4 (CH), 22.7 (CH_3), 21.8 (CH_3).

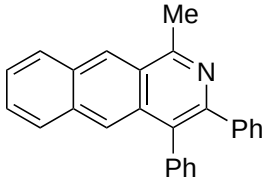
IR (ATR, cm^{-1}): 3023, 2914, 1551, 1504, 1442, 1386, 1321, 1073, 1027, 831, 767, 755, 696, 567.

MS (EI): 309 (100) $[M]^+$, 293 (8) $[M-H-Me]^+$, 265 (5), 252 (15), 146 (5), 43 (6).

$[\mathbf{C_{23}H_{19}N + H}]^+$ (ESI) HRMS: calcd.: 310.1590.
found: 310.1592.

The spectral data are in accordance with those reported in the literature.[258]

Synthesis of 1-Methyl-3,4-diphenylbenzo[*g*]isoquinoline (50ua)



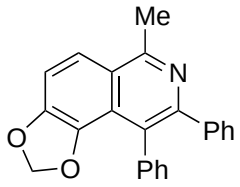
The general procedure **H** was followed using 1-(naphthalen-2-yl)ethanone oxime (**87u**) (93 mg, 0.50 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 15/1) yielded **50ua** as a red-brown solid (66 mg, 38%, m.p.: 115–117 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.81$ (s, 1H), 8.19 (s, 1H), 8.15–8.08 (m, 1H), 7.90–7.81 (m, 1H), 7.57–7.47 (m, 2H), 7.46–7.37 (m, 5H), 7.36–7.30 (m, 2H), 7.23–7.16 (m, 2H), 7.09–6.96 (m, 1H), 3.23 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 198.1$ (C_q), 197.2 (C_q), 137.5 (C_q), 137.5 (C_q), 137.0 (C_q), 135.5 (C_q), 133.9 (C_q), 133.9 (C_q), 132.7 (CH), 132.6 (C_q), 132.1 (CH), 130.7 (CH), 129.4 (CH), 129.3 (CH), 129.0 (CH), 128.6 (CH), 128.3 (CH), 128.3 (CH), 128.0 (CH), 127.3 (CH), 27.3 (CH), 27.3 (CH_3).

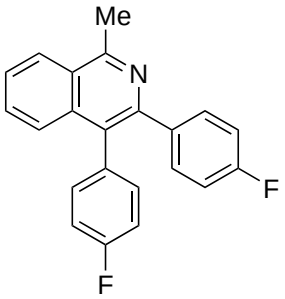
IR (ATR, cm^{-1}): 3057, 2926, 1669, 1446, 1411, 1263, 1024, 874, 754, 695, 560, 476.
MS (EI): 344 (90) $[M\text{-}H]^+$, 259 (100), 202 (33), 197 (23), 105 (36), 77 (50), 43 (57).
$[\mathbf{C_{26}H_{19}N - H}]^+$ (EI) HRMS: calcd.: 344.1439.
found: 344.1446.

Synthesis of 6-Methyl-8,9-diphenyl-[1,3]dioxolo[4,5-*f*]isoquinoline (50va)



The general procedure **H** was followed using 1-(benzo[*d*][1,3]dioxol-5-yl)ethanone oxime (**87v**) (100 mg, 0.56 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 10/1 → 8/1 → 6/1 → 2/1) yielded **50va** as a white solid (164 mg, 86%, m.p.: 251–254 °C).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.82$ (d, $J = 8.8$ Hz, 1H), 7.37–7.06 (m, 11H), 5.83 (s, 2H), 2.99 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.7$ (C_q), 150.2 (C_q), 147.6 (C_q), 141.7 (C_q), 140.8 (C_q), 138.4 (C_q), 131.1 (CH), 130.2 (CH), 127.5 (CH), 127.0 (CH), 126.8 (CH), 126.7 (CH), 124.8 (C_q), 123.2 (C_q), 122.5 (C_q), 120.9 (CH), 110.8 (CH), 101.4 (CH_2), 23.4 (CH_3).
IR (ATR, cm^{-1}): 2899, 1626, 1549, 1512, 1432, 1383, 1353, 1279, 1209, 1119, 1049, 891, 794, 760, 744, 698, 644.
MS (EI): 339 (100) $[M]^+$, 338 (98) $[M-H]^+$, 310 (18) $[M-CH_2-Me]^+$, 292 (14) $[M-OCH_2-H]^+$, 278 (9) $[M-O_2CH_2-Me]^+$, 267 (6), 239 (6), 176 (5), 139 (9), 77 (7), 43 (8).
$[\mathbf{C_{23}H_{17}NO_2}]^+$ (EI) HRMS: calcd.: 339.1259.
found: 339.1252.

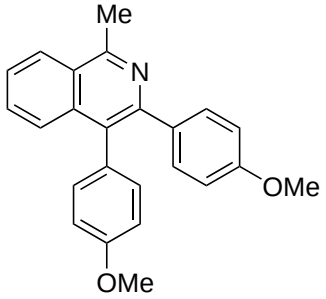
Synthesis of 3,4-Bis(4-fluorophenyl)-1-methylisoquinoline (50ab)



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and 1,2-bis(4-fluorophenyl)acetylene (**34b**) (214 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **50ab** as an orange oil (116 mg, 70%).

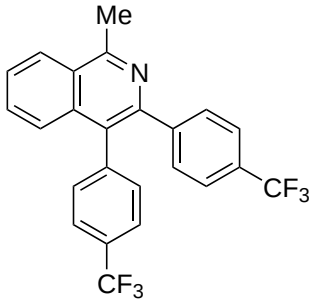
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.23$–8.15 (m, 1H), 7.65–7.55 (m, 3H), 7.37–7.27 (m, 2H), 7.22–7.12 (m, 2H), 7.11–7.00 (m, 2H), 6.95–6.84 (m, 2H), 3.06 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.9$ (d, $^1J_{C-F} = 247$ Hz, C_q), 161.8 (d, $^1J_{C-F} = 247$ Hz, C_q), 157.9 (C_q), 148.5 (C_q), 136.8 (d, $^4J_{C-F} = 4$ Hz, C_q), 135.9 (C_q), 133.2 (d, $^4J_{C-F} = 4$ Hz, C_q), 132.8 (d, $^3J_{C-F} = 8$ Hz, CH), 131.9 (d, $^3J_{C-F} = 8$ Hz, CH), 130.1 (CH), 128.0 (C_q), 126.6 (CH), 126.1 (C_q), 125.8 (CH), 125.5 (CH), 115.4 (d, $^2J_{C-F} = 21$ Hz, CH), 114.6 (d, $^2J_{C-F} = 21$ Hz, CH), 22.8 (CH_3).
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -114.6$ (tt, $J = 8.8$, 5.6 Hz), -115.2 (tt, $J = 8.7$, 5.5 Hz).
IR (ATR, cm^{-1}): 3035, 1603, 1508, 1390, 1334, 1221, 1154, 1093, 907, 836, 759, 728, 594, 560, 547.
MS (EI): 331 (55) $[M]^+$, 330 (100) $[M-H]^+$, 315 (4) $[M-Me-H]^+$, 288 (15), 268 (4).
$[\mathbf{C_{22}H_{15}F_2N}]^+$ (EI) HRMS: calcd.: 331.1173.
found: 331.1150.
The spectral data are in accordance with those reported in the literature.[258]

Synthesis of 3,4-Bis(4-methoxyphenyl)-1-methylisoquinoline (50ac)



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and 1,2-bis(4-methoxyphenyl)acetylene (**34c**) (238 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 10/1 ⟶ 8/1) yielded **50ac** as an orange solid (95 mg, 53%, m.p.: 106–110 °C).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.20$–8.11 (m, 1H), 7.73–7.62 (m, 1H), 7.60–7.49 (m, 2H), 7.32 (d, $J = 8.9$ Hz, 2H), 7.13 (d, $J = 8.8$ Hz, 2H), 6.90 (d, $J = 8.8$ Hz, 2H), 6.74 (d, $J = 8.9$ Hz, 2H), 3.83 (s, 3H), 3.75 (s, 3H), 3.04 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.6$ (C_q), 158.5 (C_q), 157.3 (C_q), 149.1 (C_q), 136.4 (C_q), 133.6 (C_q), 132.4 (CH), 131.5 (CH), 129.9 (C_q), 129.7 (CH), 128.2 (C_q), 126.2 (CH), 126.1 (CH), 125.9 (C_q), 125.5 (CH), 113.7 (CH), 113.1 (CH), 55.2 (CH_3), 55.1 (CH_3), 22.7 (CH_3).
IR (ATR, cm^{-1}): 2937, 2838, 1604, 1510, 1287, 1243, 1170, 1027, 837, 814, 760, 598, 557, 530.
MS (EI): 355 (80) $[M]^+$, 354 (100) $[M-H]^+$, 340 (10) $[M-Me]^+$, 311 (20), 296 (5), 268 (15), 239 (4), 226 (4), 43 (3).
$[\mathbf{C_{24}H_{21}NO_2}]^+$ (EI) HRMS: calcd.: 355.1572.
found: 355.1539.
The spectral data are in accordance with those reported in the literature.[131]

Synthesis of 1-Methyl-3,4-bis[4-(trifluoromethyl)phenyl]isoquinoline (50ad)



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and 1,2-bis[4-(trifluoromethyl)phenyl]acetylene (**34d**) (314 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50ad** as a white solid (26 mg, 12%, m.p.: 147–148 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.27$–8.19 (m, 1H), 7.69–7.60 (m, 4H), 7.59–7.53 (m, 1H), 7.50–7.41 (m, 4H), 7.35 (d, $J = 7.9$ Hz, 2H), 3.09 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.9$ (C_q), 147.8 (C_q), 143.9 (C_q), 141.0 (C_q), 135.5 (C_q), 131.7 (CH), 130.7 (CH), 130.5 (CH), 129.5 (d, $^{1}J_{C-F} = 265$ Hz, C_q), 129.5 (d, $^{2}J_{C-F} = 23$ Hz, C_q), 128.4 (C_q), 127.4 (CH), 126.4 (C_q), 125.8 (CH), 125.8 (CH), 125.4 (d, $^{1}J_{C-F} = 265$ Hz, C_q), 125.4 (q, $^{3}J_{C-F} = 4$ Hz, CH), 124.8 (q, $^{3}J_{C-F} = 4$ Hz, CH), 122.3 (d, $^{2}J_{C-F} = 23$ Hz, C_q), 22.6 (CH_3).

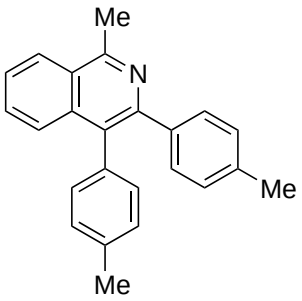
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.5$ (s), -62.60 (s).

IR (ATR, cm^{-1}): 2924, 1618, 1320, 1160, 1105, 1064, 1018, 848, 834, 762, 629.

MS (EI): 430 (55) $[M-H]^+$, 412 (3) $[M-F]^+$, 361 (3) $[M-H-CF_3]^+$, 320 (5), 146 (3), 69 (2).

$[\mathbf{C_{24}H_{15}F_6N}]^+$ (EI) HRMS: calcd.: 431.1109.
found: 431.1085.

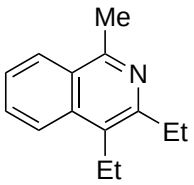
Synthesis of 1-Methyl-3,4-bis(*para*-tolyl)isoquinoline (50ae)



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and 1,2-di-*para*-tolylacetylene (**34e**) (206 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 15/1) yielded **50ae** as a pale orange solid (52 mg, 32%, m.p.: 148–150 °C).

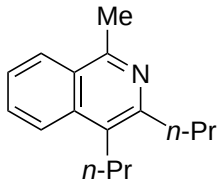
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.23$–8.14 (m, 1H), 7.72–7.62 (m, 1H), 7.57 (dt, $J =$ 6.5, 3.4 Hz, 2H), 7.29 (d, $J = 8.1$ Hz, 2H), 7.21–7.09 (m, 4H), 7.02 (d, $J = 8.1$ Hz, 2H), 3.07 (s, 3H), 2.40 (s, 3H), 2.29 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 157.3$ (C_q), 149.2 (C_q), 138.1 (C_q), 136.5 (C_q), 136.3 (C_q), 136.2 (C_q), 134.6 (C_q), 131.1 (CH), 130.0 (CH), 129.6 (CH), 128.8 (CH), 128.7 (C_q), 128.2 (CH), 126.2 (CH), 126.2 (CH), 125.9 (C_q), 125.4 (CH), 22.8 (CH_3), 21.4 (CH_3), 21.2 (CH_3).
IR (ATR, cm^{-1}): 2917, 1569, 1511, 1370, 1183, 1022, 817, 756, 728, 565, 494.
MS (EI): 322 (100) $[M-H]^+$, 307 (10) $[M-H-Me]^+$, 292 (5) $[M-H-2Me]^+$, 279 (4), 265 (8), 152 (8), 146 (7).
$[\mathbf{C_{24}H_{21}N + H}]^+$ (ESI) HRMS: calcd.: 324.1747.
found: 324.1752.
The spectral data are in accordance with those reported in the literature.[258]

Synthesis of 3,4-Diethyl-1-methylisoquinoline (50af)



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and 3-hexyne (**34f**) (82 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50af** as an orange oil (86 mg, 86%).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.06$ (ddd, $J = 8.5$, 1.3, 0.8 Hz, 1H), 7.96 (dt, $J = 8.5$, 0.8 Hz, 1H), 7.64 (ddd, $J = 8.5$, 6.8, 1.3 Hz, 1H), 7.48 (ddd, $J = 8.5$, 6.8, 1.3 Hz, 1H), 3.03 (q, $J = 7.7$ Hz, 2H), 2.95 (q, $J = 7.7$ Hz, 2H), 2.90 (s, 3H), 1.33 (t, $J = 7.7$ Hz, 3H), 1.27 (t, $J = 7.7$ Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 155.7$ (C_q), 152.5 (C_q), 135.1 (C_q), 129.4 (CH), 127.1 (C_q), 126.1 (CH), 126.0 (C_q), 125.2 (CH), 123.3 (CH), 28.5 (CH_2), 22.3 (CH_3), 20.6 (CH_2), 15.2 (CH_3), 14.9 (CH_3).
IR (ATR, cm^{-1}): 2963, 1614, 1566, 1451, 1391, 1311, 1054, 963, 769, 692, 616.
MS (EI): 199 (31) $[M]^+$, 198 (100) $[M-H]^+$, 184 (23) $[M-Me]^+$, 170 (9) $[M-Et]^+$, 128 (10), 115 (20), 77 (8), 69 (8).
$[\mathbf{C_{14}H_{17}N}]^+$ (EI) HRMS: calcd.: 199.1361.
found: 199.1355.
The spectral data are in accordance with those reported in the literature.[127]

Synthesis of 1-Methyl-3,4-di-*n*-propylisoquinoline (50ag)



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and 4-octyne (**34g**) (110 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50ag** as a yellow oil (99 mg, 87%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.06$ (dd, $J = 8.5, 0.8$ Hz, 1H), 7.94 (dd, $J = 8.5, 0.8$ Hz, 1H), 7.63 (ddd, $J = 8.2, 6.9, 1.2$ Hz, 1H), 7.47 (ddd, $J = 8.2, 6.9, 1.2$ Hz, 1H), 3.01–2.92 (m, 2H), 2.92–2.84 (m, 2H), 2.89 (s, 3H), 1.84–1.72 (m, 2H), 1.71–1.58 (m, 2H), 1.07 (t, $J = 6.7$ Hz, 3H), 1.03 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 155.6$ (C_q), 151.7 (C_q), 135.4 (C_q), 129.3 (CH), 126.1 (C_q), 126.1 (CH), 126.0 (C_q), 125.2 (CH), 123.5 (CH), 37.4 (CH_2), 29.8 (CH_2), 24.2 (CH_2), 23.8 (CH_2), 22.4 (CH_3), 14.6 (CH_3), 14.4 (CH_3).

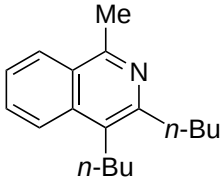
IR (ATR, cm^{-1}): 2957, 2870, 1617, 1568, 1454, 1391, 1333, 1027, 754, 614.

MS (EI): 227 (40) $[M]^+$, 212 (80) $[M-Me]^+$, 198 (100) $[M-Et]^+$, 184 (50) $[M-n\text{-}Pr]^+$, 171 (55), 128 (23), 115 (16), 77 (6), 43 (31).

$[\mathbf{C_{16}H_{21}N}]^+$ (EI) HRMS: calcd.: 227.1674.
found: 227.1669.

The spectral data are in accordance with those reported in the literature.[127]

Synthesis of 3,4-Di-*n*-butyl-1-methylisoquinoline (50ah)



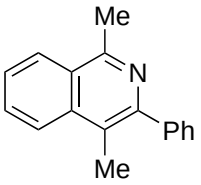
The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and 5-decyne (**34h**) (138 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50ah** as a yellow oil (101 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.05$ (dd, $J = 8.5, 1.0$ Hz, 1H), 7.94 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.62 (ddd, $J = 7.8, 6.8, 1.1$ Hz, 1H), 7.46 (ddd, $J = 7.8, 6.8, 1.1$ Hz, 1H), 3.04–2.86 (m, 4H), 2.90 (s, 3H), 1.79−1.65 (m, 2H), 1.65–1.40 (m, 6H), 0.99 (t, $J = 7.1$ Hz, 3H), 0.97 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 155.5$ (C_q), 151.7 (C_q), 135.3 (C_q), 129.3 (CH), 126.1 (C_q), 126.0 (CH), 126.0 (C_q), 125.1 (CH), 123.4 (CH), 35.2 (CH_2), 33.1 (CH_2), 32.8 (CH_2), 27.4 (CH_2), 23.2 (CH_2), 23.0 (CH_2), 22.3 (CH_3), 14.1 (CH_3), 13.9 (CH_3).

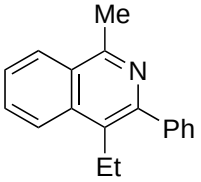
IR (ATR, cm^{-1}): 2955, 2858, 1617, 1568, 1504, 1441, 1391, 1336, 1028, 754, 614.
MS (EI): 255 (8) $[M]^+$, 240 (9) $[M-Me]^+$, 226 (31) $[M-Et]^+$, 213 (28), 198 (45), 184 (28), 171 (100), 128 (12), 115 (6), 43 (11).
$[\mathbf{C_{18}H_{25}N}]^+$ (EI) HRMS: calcd.: 255.1987.
found: 255.1992.

Synthesis of 1,4-Dimethyl-3-phenylisoquinoline (50ai)



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and prop-1-ynylbenzene (**34i**) (116 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50ai** as a pale red solid (81 mg, 69%, m.p.: 83–87 °C).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.15$ (dd, $J = 8.5, 0.9$ Hz, 1H), 8.04 (dd, $J = 8.5, 0.9$ Hz, 1H), 7.73 (ddd, $J = 8.5, 6.8, 1.3$ Hz, 1H), 7.64−7.54 (m, 3H), 7.52–7.45 (m, 2H), 7.42–7.33 (m, 1H), 2.98 (s, 3H), 2.59 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 155.8$ (C_q), 150.6 (C_q), 141.5 (C_q), 136.2 (C_q), 129.8 (CH), 129.8 (CH), 128.0 (CH), 127.4 (CH), 126.2 (CH), 126.1 (C_q), 126.0 (CH), 124.1 (CH), 122.1 (C_q), 22.5 (CH_3), 15.4 (CH_3).
IR (ATR, cm^{-1}): 2947, 1683, 1561, 1504, 1437, 1388, 1336, 1159, 1020, 760, 699, 603, 539.
MS (EI): 233 (50) $[M]^+$, 232 (100) $[M-H]^+$, 217 (10) $[M-H-Me]^+$, 202 (4) $[M-H-2Me]^+$, 189 (7), 128 (5), 115 (8), 77 (6), 43 (11).
$[\mathbf{C_{17}H_{15}N}]^+$ (EI) HRMS: calcd.: 233.1204.
found: 233.1186.
The spectral data are in accordance with those reported in the literature.[127]

Synthesis of 4-Ethyl-1-methyl-3-phenylisoquinoline (50aj)



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and but-1-ynylbenzene (**34j**) (130 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50aj** as a pale yellow solid (78 mg, 63%, m.p.: 117–120 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (ddd, J = 8.4, 1.4, 0.7 Hz, 1H), 8.07 (dd, J = 8.6, 1.0 Hz, 1H), 7.73 (ddd, J = 8.4, 6.8, 1.3 Hz, 1H), 7.59 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.54–7.33 (m, 5H), 2.99 (q, J = 7.5 Hz, 2H), 2.97 (s, 3H), 1.26 (t, J = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8 (C_q), 150.7 (C_q), 141.8 (C_q), 135.1 (C_q), 129.8 (CH), 129.2 (CH), 128.5 (C_q), 128.1 (CH), 127.4 (CH), 126.7 (C_q), 126.3 (CH), 126.1 (CH), 124.1 (CH), 22.5 (CH_3), 21.6 (CH_2), 15.7 (CH_3).

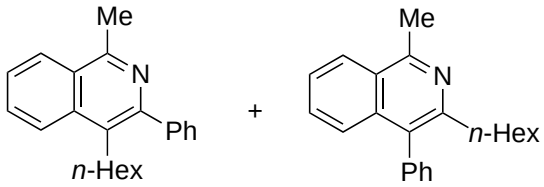
IR (ATR, cm^{-1}): 2963, 1562, 1435, 1390, 1333, 1162, 1027, 861, 771, 748, 685, 620, 590.

MS (EI): 247 (54) $[M]^+$, 246 (100) $[M-H]^+$, 231 (21) $[M-H-Me]^+$, 217 (10) $[M-H-Et]^+$, 202 (6) $[M-H-Et-Me]^+$, 189 (5), 128 (5), 115 (7), 77 (6).

$[\mathbf{C_{18}H_{17}N}]^+$ (EI) HRMS: calcd.: 247.1361.
found: 247.1349.

The spectral data are in accordance with those reported in the literature.[127]

Synthesis of 4-*n*-Hexyl-1-methyl-3-phenylisoquinoline (50ak) and 3-*n*-Hexyl-1-methyl-4-phenylisoquinoline (50ak')



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and oct-1-ynylbenzene (**34k**) (186 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50ak** as an orange oil (79 mg, 52%) and **50ak'** as an orange oil (9 mg, 6%).

50ak:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (ddd, J = 8.4, 1.3, 0.8 Hz, 1H), 8.05 (dd, J = 8.4, 0.8 Hz, 1H), 7.72 (ddd, J = 8.4, 6.8, 1.3 Hz, 1H), 7.58 (ddd, J = 8.4, 6.8, 1.3 Hz, 1H), 7.53–7.34 (m, 5H), 3.01–2.89 (m, 2H), 2.97 (s, 3H), 1.70–1.56 (m, 2H), 1.38–1.14 (m, 6H), 0.84 (t, J = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.7 (C_q), 150.9 (C_q), 141.9 (C_q), 135.4 (C_q), 129.7 (CH), 129.3 (CH), 128.1 (CH), 127.4 (C_q), 127.3 (CH), 126.6 (C_q), 126.2 (CH), 126.1 (CH), 124.2 (CH), 31.4 (CH_2), 31.2 (CH_2), 29.5 (CH_2), 28.5 (CH_2), 22.5 (CH_2), 22.5 (CH_3), 14.0 (CH_3).

IR (ATR, cm^{-1}): 2924, 2856, 1614, 1562, 1504, 1436, 1391, 1333, 1029, 755, 698, 616, 592.

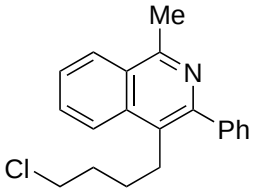
MS (EI): 303 (35) $[M]^+$, 260 (10) $[M-n\text{-Pr}]^+$, 246 (50) $[M-n\text{-Bu}]^+$, 232 (100) $[M-n\text{-Pent}]^+$, 217 (15) $[M-n\text{-Pent}-Me]^+$, 189 (5).

$[\mathbf{C_{22}H_{25}N}]^+$ (EI) HRMS: calcd.: 303.1987.
found: 303.1982.

50ak':

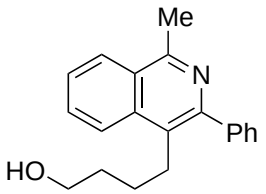
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.14$–8.07 (m, 1H), 7.53–7.38 (m, 5H), 7.37–7.30 (m, 1H), 7.30–7.22 (m, 2H), 2.99 (s, 3H), 2.69–2.58 (m, 2H), 1.77–1.55 (m, 2H), 1.28–1.08 (m, 6H), 0.79 (t, $J = 7.0$ Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.4$ (C_q), 151.7 (C_q), 137.9 (C_q), 136.0 (C_q), 130.4 (CH), 129.5 (CH), 128.9 (C_q), 128.3 (CH), 127.3 (CH), 125.8 (CH), 125.6 (CH), 125.4 (C_q), 125.3 (CH), 35.7 (CH_2), 31.6 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 22.5 (CH_2), 22.5 (CH_3), 14.0 (CH_3).
IR (ATR, cm^{-1}): 2925, 2855, 1713, 1563, 1505, 1442, 1392, 1336, 1028, 758, 699, 626, 599.
MS (EI): 303 (4) $[M]^+$, 288 (4) $[M-Me]^+$, 274 (5) $[M-Et]^+$, 260 (15) $[M-n\text{-}Pr]^+$, 246 (20) $[M-n\text{-}Bu]^+$, 232 (100) $[M-n\text{-}Pent]^+$, 217 (10) $[M-n\text{-}Pent-Me]^+$, 189 (8), 43 (7).
$[\mathbf{C_{22}H_{25}N}]^+$ (EI) HRMS: calcd.: 303.1987.
found: 303.1976.

Synthesis of 4-(4-Chloro-*n*-butyl)-1-methyl-3-phenylisoquinoline (50al)



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and (6-chlorohex-1-ynyl)benzene (**34l**) (193 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50al** as a yellow oil (104 mg, 67%).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.16$ (ddd, $J = 8.4, 1.3, 0.8$ Hz, 1H), 8.04 (dd, $J = 8.4, 0.8$ Hz, 1H), 7.73 (ddd, $J = 8.4, 6.9, 1.3$ Hz, 1H), 7.59 (ddd, $J = 8.4, 6.9, 1.3$ Hz, 1H), 7.53–7.34 (m, 5H), 3.42 (t, $J = 6.2$ Hz, 2H), 3.03–2.95 (m, 2H), 2.97 (s, 3H), 1.86–1.68 (m, 4H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 156.1$ (C_q), 151.1 (C_q), 141.6 (C_q), 135.2 (C_q), 129.9 (CH), 129.2 (CH), 128.2 (CH), 127.5 (CH), 126.6 (C_q), 126.4 (C_q), 126.3 (CH), 126.2 (CH), 124.0 (CH), 44.4 (CH_2), 32.3 (CH_2), 28.1 (CH_2), 27.5 (CH_2), 22.5 (CH_3).
IR (ATR, cm^{-1}): 2953, 1614, 1561, 1504, 1437, 1391, 1331, 1027, 756, 699, 648, 616, 592.
MS (EI): 309 (41) $[M]^+$, 246 (95) $[M-(CH_2)_2Cl]^+$, 232 (100) $[M-(CH_2)_3Cl]^+$, 217 (16) $[M-(CH_2)_3Cl-Me]^+$, 202 (6), 189 (6), 115 (6), 77 (5).
$[\mathbf{C_{20}H_{20}ClN}]^+$ (EI) HRMS: calcd.: 309.1284.
found: 309.1297.

Synthesis of 4-(1-Methyl-3-phenylisoquinolin-4-yl)butan-1-ol (50am)



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and 6-phenylhex-5-yn-1-ol (**34m**) (174 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **50am** as a pale brown solid (106 mg, 73%, m.p.: 96–101 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.17$ (ddd, $J = 8.5$, 1.3, 0.8 Hz, 1H), 8.06 (dd, $J = 8.5$, 0.8 Hz, 1H), 7.73 (ddd, $J = 8.5$, 6.8, 1.3 Hz, 1H), 7.59 (ddd, $J = 8.1$, 6.8, 1.2 Hz, 1H), 7.52–7.34 (m, 5H), 3.48 (t, $J = 6.5$ Hz, 2H), 3.06–2.90 (m, 2H), 2.97 (s, 3H), 1.75–1.45 (m, 5H).

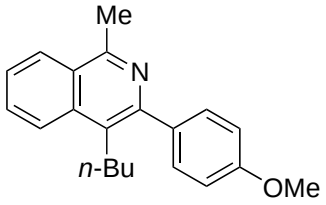
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 156.0$ (C_q), 151.0 (C_q), 141.7 (C_q), 135.3 (C_q), 130.0 (CH), 129.3 (CH), 128.1 (CH), 127.4 (CH), 126.9 (C_q), 126.6 (C_q), 126.3 (CH), 126.2 (CH), 124.1 (CH), 62.2 (CH_2), 32.5 (CH_2), 29.0 (CH_2), 27.2 (CH_2), 22.4 (CH_3).

IR (ATR, cm^{-1}): 3273, 2936, 2863, 1615, 1564, 1444, 1395, 1335, 1141, 1053, 1030, 982, 759, 707, 628.

MS (EI): 291 (50) $[M]^+$, 246 (68) $[M-(CH_2)_2OH]^+$, 232 (100) $[M-(CH_2)_3OH]^+$, 217 (14) $[M-(CH_2)_3OH-Me]^+$, 202 (6), 189 (7), 115 (5), 77 (5), 43 (6).

$[C_{20}H_{21}NO]^+$ (EI) HRMS: calcd.: 291.1623.
found: 291.1623.

Synthesis of 4-*n*-Butyl-1-methyl-3-(4-methoxyphenyl)isoquinoline (50an)



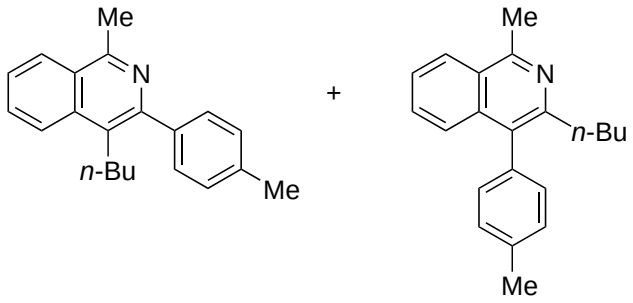
The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and 1-(*n*-hex-1-ynyl)-4-methoxybenzene (**34n**) (188 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50an** as a red oil (87 mg, 57%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.14$ (ddd, $J = 8.4$, 1.3, 0.7 Hz, 1H), 8.03 (dd, $J = 8.6$, 0.7 Hz, 1H), 7.70 (ddd, $J = 8.2$, 6.8, 1.3 Hz, 1H), 7.56 (ddd, $J = 8.2$, 6.8, 1.1 Hz, 1H), 7.44 (d, $J = 8.8$ Hz, 2H), 6.99 (d, $J = 8.8$ Hz, 2H), 3.86 (s, 3H), 3.06–2.90 (m, 2H), 2.95 (s, 3H), 1.71–1.54 (m, 2H), 1.35 (dd, $J = 7.3$ Hz, 2H), 0.86 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.9$ (C_q), 155.6 (C_q), 150.5 (C_q), 135.4 (C_q), 134.4 (C_q), 130.5 (CH), 129.6 (CH), 127.2 (C_q), 126.5 (C_q), 126.2 (CH), 125.9 (CH), 124.1 (CH), 113.5

(CH), 55.3 (CH_3), 33.4 (CH_2), 28.3 (CH_2), 22.9 (CH_2), 22.5 (CH_3), 13.8 (CH_3).
IR (ATR, cm^{-1}): 2957, 2926, 2868, 1609, 1567, 1512, 1463, 1436, 1391, 1376, 1291, 1250, 1176, 1021, 836, 753, 615, 588, 574, 541.
MS (EI): 305 (72) $[M]^+$, 276 (71) $[M-Et]^+$, 262 (100) $[M-n\text{-}Pr]^+$, 247 (35) $[M-Pr-Me]^+$, 230 (6), 218 (23), 43 (8).
$[\mathbf{C_{21}H_{23}NO}]^+$ (EI) HRMS: calcd.: 305.1780.
found: 305.1771.

Synthesis of 4-*n*-Butyl-1-methyl-3-(*p*-tolyl)isoquinoline (50ao) and 3-*n*-Butyl-1-methyl-4-(*p*-tolyl)isoquinoline (50ao')



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and 1-(*n*-hex-1-ynyl)-4-methylbenzene (**34o**) (172 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50ao** as a red oil (98 mg, 68%) and **50ao'** as a red oil (11 mg, 8%).

50ao:

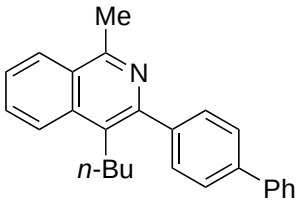
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.14$ (dd, $J = 8.6$, 0.9 Hz, 1H), 8.04 (dt, $J = 8.6$, 0.9 Hz, 1H), 7.70 (ddd, $J = 8.3$, 6.8, 1.3 Hz, 1H), 7.56 (ddd, $J = 8.3$, 6.8, 1.2 Hz, 1H), 7.39 (d, $J = 8.1$ Hz, 2H), 7.25 (d, $J = 8.1$ Hz, 2H), 3.03–2.91 (m, 2H), 2.95 (s, 3H), 2.41 (s, 3H), 1.70–1.56 (m, 2H), 1.34 (dt, $J = 7.3$, 7.3 Hz, 2H), 0.86 (t, $J = 7.3$ Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 155.6$ (C_q), 150.9 (C_q), 139.0 (C_q), 136.9 (C_q), 135.4 (C_q), 129.6 (CH), 129.1 (CH), 128.7 (CH), 127.2 (C_q), 126.5 (C_q), 126.2 (CH), 126.0 (CH), 124.2 (CH), 33.4 (CH_2), 28.3 (CH_2), 23.0 (CH_2), 22.5 (CH_3), 21.2 (CH_3), 13.8 (CH_3).
IR (ATR, cm^{-1}): 2955, 2923, 2869, 1614, 1563, 1513, 1438, 1391, 1333, 1026, 825, 755, 726, 615, 587, 539, 497.
MS (EI): 289 (50) $[M]^+$, 260 (70) $[M-Et]^+$, 246 (100) $[M-n\text{-}Pr]^+$, 231 (30) $[M-n\text{-}Pr-Me]^+$, 216 (8) $[M-n\text{-}Pr-2Me]^+$, 202 (10), 115 (5), 43 (11).
$[\mathbf{C_{21}H_{23}N}]^+$ (EI) HRMS: calcd.: 289.1830.
found: 289.1833.

50ao':

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.13$–8.05 (m, 1H), 7.51–7.43 (m, 2H), 7.39–7.32 (m, 1H), 7.28 (d, $J = 8.0$ Hz, 2H), 7.14 (d, $J = 8.0$ Hz, 2H), 2.98 (s, 3H), 2.70–2.61 (m, 2H), 2.45 (s, 3H), 1.70–1.55 (m, 2H), 1.31–1.16 (m, 2H), 0.78 (t, $J = 7.3$ Hz, 3H).

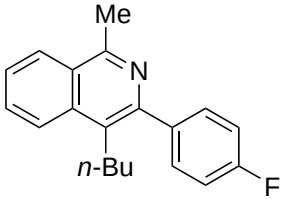
^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2 (C_q), 151.8 (C_q), 136.8 (C_q), 136.2 (C_q), 134.8 (C_q), 130.3 (CH), 129.4 (CH), 129.0 (CH), 128.9 (C_q), 125.9 (CH), 125.6 (CH), 125.4 (C_q), 125.3 (CH), 35.5 (CH_2), 32.7 (CH_2), 22.7 (CH_2), 22.5 (CH_3), 21.3 (CH_3), 13.9 (CH_3).
IR (ATR, cm^{-1}): 2955, 2924, 1614, 1563, 1517, 1439, 1391, 1336, 1107, 1024, 965, 817, 758, 613.
MS (EI): 289 (5) $[M]^+$, 274 (10) $[M-Me]^+$, 260 (15) $[M-Et]^+$, 246 (100) $[M-n\text{-}Pr]^+$, 231 (15) $[M-n\text{-}Pr-Me]^+$, 216 (5) $[M-n\text{-}Pr-2Me]^+$, 202 (8), 189 (6), 122 (5), 43 (12).
$[\mathbf{C_{21}H_{23}N}]^+$ (EI) HRMS: calcd.: 289.1830.
found: 289.1822.

Synthesis of 3-[(1,1'-Biphenyl)-4-yl]-4-*n*-butyl-1-methylisoquinoline (50ap)



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and 4-(hex-1-ynyl)-1,1'-biphenyl (**34p**) (234 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50ap** as a pale yellow solid (90 mg, 51%, m.p.: 129–130 °C).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.78–7.55 (m, 8H), 7.51–7.43 (m, 2H), 7.41–7.33 (m, 1H), 3.10–2.96 (m, 2H), 2.99 (s, 3H), 1.76–1.60 (m, 2H), 1.38 (dt, J = 7.4, 7.4 Hz, 2H), 0.88 (t, J = 7.4 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9 (C_q), 150.5 (C_q), 141.1 (C_q), 140.9 (C_q), 140.1 (C_q), 135.4 (C_q), 129.7 (CH), 129.7 (CH), 128.7 (CH), 127.4 (C_q), 127.2 (CH), 127.1 (CH), 126.9 (CH), 126.6 (C_q), 126.2 (CH), 126.1 (CH), 124.2 (CH), 33.5 (CH_2), 28.3 (CH_2), 23.0 (CH_2), 22.5 (CH_3), 13.8 (CH_3).
IR (ATR, cm^{-1}): 2926, 2870, 1563, 1436, 1387, 1334, 1006, 927, 814, 761, 732, 692, 598, 485.
MS (EI): 351 (25) $[M]^+$, 322 (45) $[M-Et]^+$, 308 (100) $[M-n\text{-}Pr]^+$, 231 (6), 77 (10).
$[\mathbf{C_{26}H_{25}N}]^+$ (EI) HRMS: calcd.: 351.1987.
found: 351.1979.

Synthesis of 4-*n*-Butyl-3-(4-fluorophenyl)-1-methylisoquinoline (50aq)



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and 1-fluoro-4-(hex-1-ynyl)benzene (**34q**) (176 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50aq** as a pale brown solid (88 mg, 60%, m.p.: 58–60 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (ddd, J = 8.4, 1.3, 0.7 Hz, 1H), 8.04 (dd, J = 8.4, 0.7 Hz, 1H), 7.72 (ddd, J = 8.4, 6.8, 1.3 Hz, 1H), 7.58 (ddd, J = 8.4, 6.8, 1.3 Hz, 1H), 7.51–7.41 (m, 2H), 7.20–7.07 (m, 2H), 3.01–2.89 (m, 2H), 2.95 (s, 3H), 1.67–1.53 (m, 2H), 1.40–1.25 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3 (d, $^1J_{C-F}$ = 246 Hz, C_q), 155.9 (C_q), 149.8 (C_q), 137.9 (d, $^4J_{C-F}$ = 3 Hz, C_q), 135.3 (C_q), 131.0 (d, $^3J_{C-F}$ = 8 Hz, CH), 129.9 (CH), 127.5 (C_q), 126.7 (C_q), 126.3 (CH), 126.3 (CH), 124.2 (CH), 115.0 (d, $^2J_{C-F}$ = 21 Hz, CH), 33.3 (CH_2), 28.2 (CH_2), 22.9 (CH_2), 22.5 (CH_3), 13.7 (CH_3).

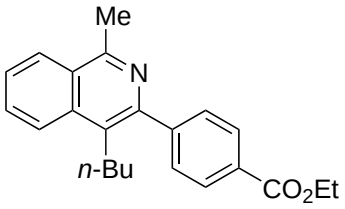
^{19}F NMR (282 MHz, $CDCl_3$): δ = −115.3 (tt, J = 8.8, 5.5 Hz).

IR (ATR, cm^{-1}): 2931, 2868, 1603, 1434, 1387, 1335, 1218, 1091, 837, 761, 727, 711, 616.

MS (EI): 293 (40) $[M]^+$, 264 (36) $[M-Et]^+$, 250 (100) $[M-n\text{-}Pr]^+$, 235 (15) $[M-n\text{-}Pr-Me]^+$, 220 (4) [M−*n*-Pr−2Me], 207 (4), 147 (4).

$[\mathbf{C_{20}H_{20}FN}]^+$ (EI) HRMS: calcd.: 293.1580.
found: 293.1584.

Synthesis of Ethyl 4-(4-*n*-Butyl-1-methylisoquinolin-3-yl)benzoate (50ar)



The general procedure **H** was followed, using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and ethyl 4-(*n*-hex-1-ynyl)benzoate (**34r**) (230 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50ar** as a red oil (81 mg, 47%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (dd, J = 8.6, 0.9 Hz, 1H) 8.13 (d, J = 8.1 Hz, 2H), 8.04 (dd, J = 8.6, 0.9 Hz, 1H), 7.73 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.64–7.54 (m, 3H), 4.40 (q, J = 7.1 Hz, 2H), 3.00–2.86 (m, 2H), 2.95 (s, 3H), 1.65–1.53 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H), 1.30 (dt, J = 7.4, 7.4 Hz, 2H), 0.82 (t, J = 7.3 Hz, 3H).

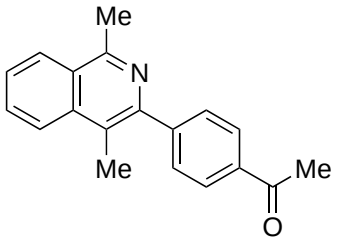
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6 (C_q), 156.1 (C_q), 149.7 (C_q), 146.4 (C_q), 135.2 (C_q), 129.9 (CH), 129.4 (CH), 129.4 (CH), 129.3 (C_q), 127.6 (C_q), 126.8 (C_q), 126.5 (CH), 126.2 (CH), 124.2 (CH), 60.9 (CH_2), 33.4 (CH_2), 28.2 (CH_2), 22.9 (CH_2), 22.5 (CH_3), 14.3 (CH_3), 13.7 (CH_3).

IR (ATR, cm^{-1}): 2957, 2871, 1713, 1611, 1563, 1508, 1391, 1366, 1267, 1174, 1098, 1019, 866, 757, 712, 616.

MS (EI): 347 (64) $[M]^+$, 318 (100) $[M-Et]^+$, 304 (15) $[M-n\text{-}Pr]^+$, 290 (14) $[M-n\text{-}Pr-Me]^+$, 276 (8), 260 (25), 244 (11), 231 (61), 216 (11), 202 (10), 189 (5), 115 (5), 43 (18).

$[\mathbf{C_{23}H_{25}NO_2}]^+$ (EI) HRMS: calcd.: 347.1885.
found: 347.1870.

Synthesis of 1-[4-(1,4-Dimethylisoquinolin-3-yl)phenyl]ethanone (50as)



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and 1-[4-(prop-1-ynyl)phenyl]ethanone (**34s**) (158 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **50as** as a yellow solid (97 mg, 70%, m.p.: 149–153 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.17$ (ddd, $J = 8.3, 1.3, 0.7$ Hz, 1H), 8.09−8.04 (m, 1H), 8.07 (d, $J = 8.5$ Hz, 2H), 7.76 (ddd, $J = 8.3, 6.9, 1.3$ Hz, 1H), 7.69 (d, $J = 8.5$ Hz, 2H), 7.63 (ddd, $J = 8.2, 6.9, 1.2$ Hz, 1H), 2.98 (s, 3H), 2.66 (s, 3H), 2.60 (s, 3H).

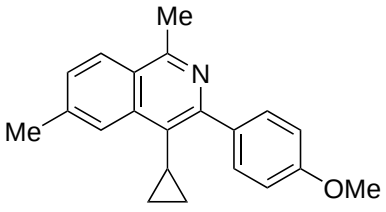
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.9$ (C_q), 156.2 (C_q), 149.3 (C_q), 146.3 (C_q), 136.1 (C_q), 135.9 (C_q), 130.2 (CH), 130.0 (CH), 128.1 (CH), 126.7 (CH), 126.3 (C_q), 126.1 (CH), 124.1 (CH), 122.6 (C_q), 26.7 (CH_3), 22.5 (CH_3), 15.3 (CH_3).

IR (ATR, cm^{-1}): 2920, 1681, 1605, 1565, 1261, 1012, 957, 853, 834, 762, 733, 599, 540.

MS (EI): 275 (59) $[M]^+$, 274 (100) $[M-H]^+$, 231 (27) $[M-H-Ac]^+$, 217 (8) $[M-Me-Ac]^+$, 188 (6), 129 (5), 115 (5), 43 (13).

$[\mathbf{C_{19}H_{17}NO}]^+$ (EI) HRMS: calcd.: 275.1310.
found: 275.1299.

Synthesis of 4-Cyclopropyl-3-(4-methoxyphenyl)-1,6-dimethylisoquinoline (50bt)



The general procedure **H** was followed using 1-*p*-tolylethanone oxime (**87b**) (75 mg, 0.50 mmol) and 1-(cyclopropylethynyl)-4-methoxybenzene (**34t**) (172 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **50bt** as a red oil (39 mg, 26%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.27$ (dt, $J = 1.7$, 0.9 Hz, 1H), 7.99 (d, $J = 8.5$ Hz, 1H), 7.67 (d, $J = 8.8$ Hz, 2H), 7.38 (ddd, $J = 8.5$, 1.7, 0.5 Hz, 1H), 6.97 (d, $J = 8.8$ Hz, 2H), 3.86 (s, 3H), 2.92 (s, 3H), 2.59 (s, 3H), 2.21–2.12 (m, 1H), 0.99–0.89 (m, 2H), 0.26–0.16 (m, 2H).

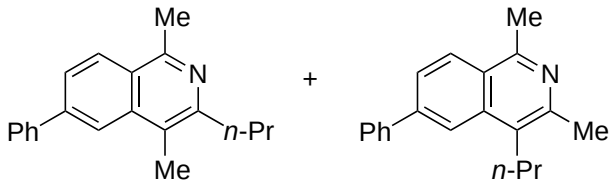
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.9$ (C_q), 156.1 (C_q), 151.3 (C_q), 139.6 (C_q), 138.1 (C_q), 134.3 (C_q), 131.2 (CH), 128.1 (CH), 126.0 (C_q), 125.7 (CH), 124.4 (C_q), 124.3 (CH), 113.1 (CH), 55.3 (CH_3), 22.5 (CH_3), 22.4 (CH_3), 11.2 (CH), 10.2 (CH_2).

IR (ATR, cm^{-1}): 2935, 1676, 1603, 1572, 1510, 1378, 1250, 1170, 1026, 773, 695, 592.

MS (EI): 303 (100) $[M]^+$, 288 (78) $[M-Me]^+$, 275 (20) $[M-(CH_2)_2]^+$, 260 (15), 245 (20), 231 (10), 202 (5), 196 (10), 43 (18).

$[\mathbf{C_{21}H_{21}NO}]^+$ (EI) HRMS: calcd.: 303.1623.
found: 303.1627.

Synthesis of 1,4-Dimethyl-6-phenyl-3-*n*-propylisoquinoline (50cu) and 1,3-dimethyl-6-phenyl-4-*n*-propylisoquinoline (50cu')



The general procedure **H** was followed using 1-[(1,1'-biphenyl)-4-yl]ethanone oxime (**87c**) (106 mg, 0.50 mmol) and 2-hexyne (**34c**) (82 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **50cu** as a yellow solid (47 mg, 34%, m.p.: 74–79 °C) and **50cu'** as a yellow solid (49 mg, 36%, m.p.: 80–82 °C).

50cu:

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.17$–8.10 (m, 2H), 7.78–7.68 (m, 3H), 7.54–7.46 (m, 2H), 7.45–7.37 (m, 1H), 3.02–2.90 (m, 2H), 2.93 (s, 3H), 2.61 (s, 3H), 1.85–1.68 (m, 2H), 1.03 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 155.3$ (C_q), 152.3 (C_q), 142.1 (C_q), 141.0 (C_q), 136.3 (C_q), 128.9 (CH), 127.9 (CH), 127.6 (CH), 126.6 (CH), 125.1 (CH), 124.7 (C_q), 121.5 (CH), 109.2 (C_q), 38.1 (CH_2), 23.4 (CH_2), 22.2 (CH_3), 14.2 (CH_3), 13.7 (CH_3).

IR (ATR, cm^{-1}): 2949, 2866, 1615, 1568, 1454, 1390, 1347, 1261, 1090, 1018, 879, 826, 760, 690.

MS (EI): 275 (18) $[M]^+$, 260 (25) $[M-Me]^+$, 247 (100), 202 (10) $[M-2Me-n\text{-}Pr]^+$, 152 (10), 124 (7), 77 (7).

$[\mathbf{C_{20}H_{21}N}]^+$ (EI) HRMS: calcd.: 275.1674.
found: 275.1677.

50cu':

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.17$–8.08 (m, 2H), 7.76–7.66 (m, 3H), 7.55–7.46 (m, 2H), 7.45–7.38 (m, 1H), 3.07–2.97 (m, 2H), 2.92 (s, 3H), 2.69 (s, 3H), 1.78–1.62 (m, 2H), 1.08 (t,

$J = 7.4$ Hz, 3H).

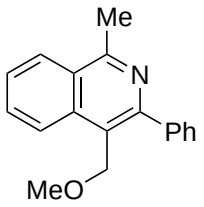
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 155.3$ (C_q), 148.1 (C_q), 142.1 (C_q), 141.0 (C_q), 135.6 (C_q), 128.9 (CH), 127.9 (CH), 127.6 (CH), 126.8 (C_q), 126.7 (CH), 125.0 (C_q), 125.0 (CH), 121.3 (CH), 30.0 (CH_2), 23.4 (CH_2), 22.3 (CH_3), 22.3 (CH_3), 14.5 (CH_3).

IR (ATR, cm^{-1}): 2953, 2869, 1617, 1567, 1486, 1470, 1443, 1373, 1336, 1267, 1077, 1019, 978, 892, 824, 762, 693, 613.

MS (EI): 275 (35) $[M]^+$, 247 (100), 202 (12) $[M-2Me-Pr]^+$, 77 (5), 43 (20).

$[\mathbf{C_{20}H_{21}N}]^+$ (EI) HRMS: calcd.: 275.1674.
found: 275.1680.

Synthesis of 4-(Methoxymethyl)-1-methyl-3-phenylisoquinoline (50av)



The general procedure **H** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and 3-phenylprop-2-yn-1-ol (**34v**) (132 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **50av** as a yellow oil (30 mg, 23%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.24$–8.09 (m, 2H), 7.76 (ddd, $J = 8.2$, 6.9, 1.3 Hz, 1H), 7.70–7.65 (m, 2H), 7.60 (ddd, $J = 8.2$, 6.9, 1.2 Hz, 1H), 7.52–7.37 (m, 3H), 4.72 (s, 2H), 3.44 (s, 3H), 2.99 (s, 3H).

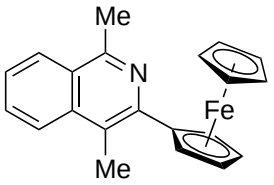
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.7$ (C_q), 152.3 (C_q), 140.6 (C_q), 136.2 (C_q), 130.4 (CH), 129.8 (CH), 128.1 (CH), 127.9 (CH), 126.6 (CH), 126.5 (C_q), 125.9 (CH), 124.6 (CH), 122.0 (C_q), 69.2 (CH_2), 58.3 (CH_3), 22.8 (CH_3).

IR (ATR, cm^{-1}): 3076, 2973, 2919, 2805, 1614, 1564, 1503, 1436, 1392, 1369, 1333, 1091, 1062, 947, 759, 748, 724, 693, 614, 586.

MS (EI): 263 (40) $[M]^+$, 248 (100), 232 (47), 230 (32), 217 (12), 115 (12).

$[\mathbf{C_{22}H_{17}N}]^+$ (EI) HRMS: calcd.: 263.1310.
found: 263.1314.

Synthesis of 3-Ferrocenyl-1,4-dimethylisoquinoline (50aw)



The general procedure **I** was followed using acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **50aw** as a red solid (99 mg, 58%, m.p.: 129–133 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.10$ (d, $J = 8.4$ Hz, 1H), 8.02 (d, $J = 8.4$ Hz, 1H), 7.69 (t, $J = 7.6$ Hz, 1H), 7.55 (t, $J = 7.6$ Hz, 1H), 4.92 (d, $J = 3.2$ Hz, 2H), 4.40 (dd, $J = 3.9$, 2.2 Hz, 2H), 4.16 (s, 5H), 2.98 (s, 3H), 2.84 (s, 3H).

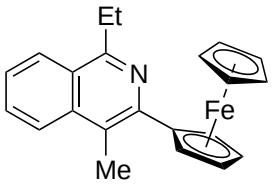
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 154.7$ (C_q), 148.2 (C_q), 136.4 (C_q), 129.5 (CH), 125.9 (CH), 125.5 (C_q), 125.4 (CH), 123.6 (CH), 121.1 (C_q), 87.2 (C_q), 70.6 (CH), 69.4 (CH), 68.7 (CH), 22.6 (CH_3), 15.0 (CH_3).

IR (ATR, cm^{-1}): 3094, 2918, 1611, 1564, 1389, 1329, 1103, 1022, 999, 813, 758, 479.

MS (EI): 341 (100) $[M]^+$, 276 (40) $[M-C_5H_5]^+$, 248 (7), 218 (15), 178 (5), 121 (10), 60 (8).

$[\mathbf{C_{21}H_{19}FeN}]^+$ (EI) HRMS: calcd.: 341.0867.
found: 341.0871.

Synthesis of 1-Ethyl-3-ferrocenyl-4-methylisoquinoline (50iw)



The general procedure **I** was followed using propiophenone oxime (**87i**) (75 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 70/1) yielded **50iw** as a red solid (104 mg, 59%, m.p.: 102–107 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.12$ (ddd, $J = 8.2$, 1.3, 0.6 Hz, 1H), 7.99 (ddd, $J = 8.4$, 1.2, 0.6 Hz, 1H), 7.65 (ddd, $J = 8.4$, 6.9, 1.3 Hz, 1H), 7.51 (ddd, $J = 8.2$, 6.9, 1.2 Hz, 1H), 4.91 (t, $J = 1.9$ Hz, 2H), 4.36 (t, $J = 1.9$ Hz, 2H), 4.10 (d, $J = 0.4$ Hz, 5H), 3.32 (q, $J = 7.5$ Hz, 2H), 2.75 (s, 3H), 1.52 (t, $J = 7.5$ Hz, 3H).

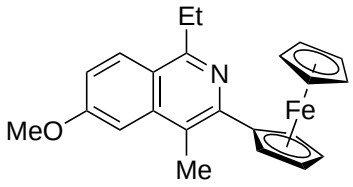
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.6$ (C_q), 148.2 (C_q), 136.5 (C_q), 129.3 (CH), 125.3 (CH), 125.3 (CH), 124.8 (C_q), 123.8 (CH), 120.6 (C_q), 87.5 (C_q), 70.7 (CH), 69.4 (CH), 68.5 (CH), 28.0 (CH_2), 15.1 (CH_3), 12.9 (CH_3).

IR (ATR, cm^{-1}): 3066, 2974, 2932, 1610, 1568, 1454, 1306, 1232, 1105, 1054, 1026, 999, 900, 812, 752, 744, 479.

MS (EI): 355 (100) $[M]^+$, 290 (32) $[M-C_5H_5]^+$, 177 (10), 121 (8), 60 (6).

$[\mathbf{C_{22}H_{21}FeN}]^+$ (EI) HRMS: calcd.: 355.1023.
found: 355.1024.

Synthesis of 1-Ethyl-3-ferrocenyl-6-methoxy-4-methylisoquinoline (50jw)



The general procedure **I** was followed using 1-(4-methoxyphenyl)propan-1-one oxime (**87j**) (90 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **50jw** as a red-orange solid (106 mg, 55%, m.p.: 132–135 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.03$ (d, $J = 9.1$ Hz, 1H), 7.19 (d, $J = 2.5$ Hz, 1H), 7.14 (dd, $J = 9.1$, 2.5 Hz, 1H), 4.92–4.86 (m, 2H), 4.35 (t, $J = 1.9$ Hz, 2H), 4.11 (s, 5H), 3.96 (s, 3H), 3.26 (q, $J = 7.5$ Hz, 2H), 2.71 (s, 3H), 1.49 (t, $J = 7.5$ Hz, 3H).

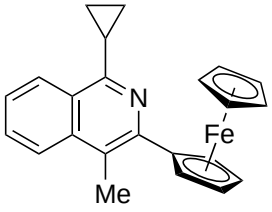
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 160.1$ (C_q), 158.2 (C_q), 148.8 (C_q), 138.4 (C_q), 127.3 (CH), 120.3 (C_q), 120.0 (C_q), 117.2 (CH), 102.4 (CH), 87.7 (C_q), 70.7 (CH), 69.4 (CH), 68.5 (CH), 55.3 (CH_3), 28.0 (CH_2), 15.3 (CH_3), 13.1 (CH_3).

IR (ATR, cm^{-1}): 3064, 2933, 1614, 1569, 1502, 1404, 1381, 1221, 1022, 998, 941, 818, 786, 728, 707, 499, 486.

MS (EI): 385 (100) $[M]^+$, 320 (25) $[M-C_5H_5]^+$, 264 (5), 192 (8), 121 (14), 60 (5).

$[\mathbf{C_{23}H_{23}FeNO}]^+$ (EI) HRMS: calcd.: 385.1129.
found: 385.1125.

Synthesis of 1-Cyclopropyl-3-ferrocenyl-4-methylisoquinoline (50ww)



The general procedure **I** was followed using cyclopropyl(phenyl)methanone oxime (**87w**) (81 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 70/1) yielded **50ww** as a red solid (110 mg, 60%, m.p.: 73–77 °C).

^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.37$ (d, $J = 8.4$ Hz, 1H), 7.97 (d, $J = 8.5$ Hz, 1H), 7.66 (ddd, $J = 8.3$, 6.9, 1.2 Hz, 1H), 7.54 (ddd, $J = 8.0$, 6.8, 1.1 Hz, 1H), 4.89–4.84 (m, 2H), 4.34 (t, $J = 1.7$ Hz, 2H), 4.07 (s, 5H), 2.75–2.69 (m, 1H), 2.70 (s, 3H), 1.40–1.34 (m, 2H), 1.11–1.06 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 157.5$ (C_q), 148.1 (C_q), 136.5 (C_q), 129.3 (CH), 125.6 (C_q), 125.4 (CH), 125.2 (CH), 123.8 (CH), 119.9 (C_q), 87.7 (C_q), 70.7 (CH), 69.5 (CH), 68.6 (CH),

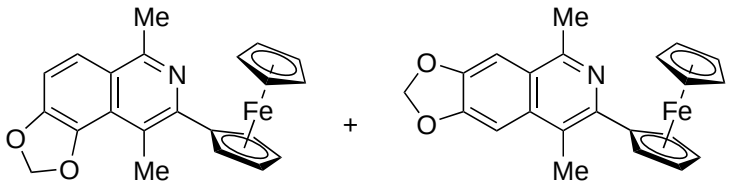
15.1 (CH_3), 13.1 (CH), 9.1 (CH_2).

IR (ATR, cm^{-1}): 3089, 3001, 2919, 1611, 1561, 1410, 1314, 1258, 1105, 1023, 999, 902, 878, 811, 754, 700, 668, 479.

MS (EI): 367 (100) $[M]^+$, 300 (15), 285 (7), 242 (8), 183 (5), 121 (10), 60 (8), 43 (21).

$[\mathbf{C_{23}H_{21}FeN}]^+$ (EI) HRMS: calcd.: 367.1023.
found: 367.1020.

Synthesis of 8-Ferrocenyl-6,9-dimethyl-[1,3]dioxolo[4,5-*f*]isoquinoline (50vw) and 7-Ferrocenyl-5,8-dimethyl-[1,3]dioxolo[4,5-*g*]isoquinoline (50vw')



The general procedure **I** was followed using 1-(benzo[*d*][1,3]dioxol-5-yl)ethanone oxime (**87v**) (90 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50vw** as a red-orange solid (143 mg, 74%, decomposition > 190 °C) and **50vw'** as a red-orange solid (14 mg, 7%, decomposition > 160 °C).

50vw:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H), 6.12 (s, 2H), 4.87 (t, J = 1.9 Hz, 2H), 4.38−4.33 (m, 2H), 4.11 (s, 5H), 2.88 (d, J = 0.7 Hz, 3H), 2.86 (d, J = 0.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.4 (C_q), 148.4 (C_q), 146.8 (C_q), 141.6 (C_q), 124.3 (C_q), 123.0 (C_q), 120.9 (CH), 118.7 (C_q), 109.7 (CH), 101.1 (CH_2), 86.8 (C_q), 70.5 (CH), 69.4 (CH), 68.6 (CH), 23.2 (CH_3), 17.4 (CH_3).

IR (ATR, cm^{-1}): 3092, 2886, 1627, 1560, 1428, 1411, 1378, 1350, 1273, 1106, 1043, 989, 877, 821, 774, 501, 484.

MS (EI): 385 (100) $[M]^+$, 320 (22) $[M-C_5H_5]^+$, 292 (5), 264 (6), 204 (5), 121 (12), 60 (7).

$[\mathbf{C_{22}H_{19}FeNO_2}]^+$ (EI) HRMS: calcd.: 385.0765.
found: 385.0758.

50vw':

^{1}H NMR (300 MHz, $CDCl_3$): δ =7.30 (s, 1H), 7.26 (s, 1H), 6.07 (s, 2H), 4.82 (t, J = 1.8 Hz, 2H), 4.34 (q, J = 1.8 Hz, 2H), 4.12 (s, 5H), 2.82 (s, 3H), 2.73 (s, 3H).

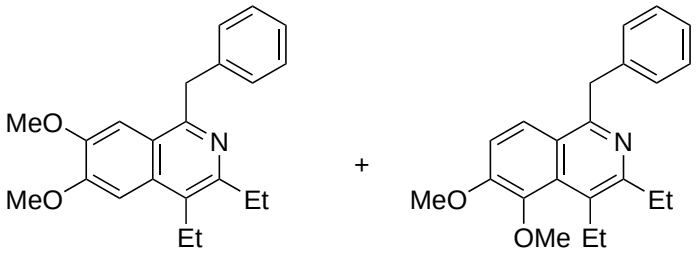
^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.8 (C_q), 150.3 (C_q), 147.5 (C_q), 146.9 (C_q), 134.6 (C_q), 122.4 (C_q), 121.2 (C_q), 102.1 (CH), 101.4 (CH_2), 101.1 (C_q), 100.3 (CH), 70.4 (CH), 69.4 (CH), 68.5 (CH), 22.9 (CH_3), 15.5 (CH_3).

IR (ATR, cm^{-1}): 3090, 2910, 1628, 1564, 1459, 1427, 1279, 1236, 1104, 1028, 999, 937, 854, 805, 775, 735, 485, 469.

MS (EI): 385 (100) $[M]^+$, 320 (30) $[M-C_5H_5]^+$, 292 (6), 264 (10), 204 (5), 121 (14), 60 (7).

$[\mathbf{C_{22}H_{19}NO_2Fe}]^+$ (EI) HRMS: calcd.: 385.0765.
found: 385.0771.

Synthesis of 1-Benzyl-3,4-diethyl-6,7-dimethoxyisoquinoline (4-Ethylmoxaverine) (50xf) and 1-Benzyl-3,4-diethyl-5,6-dimethoxyisoquinoline (50xf')



The general procedure **I** was followed using 1-(3,4-dimethoxyphenyl)-2-phenylethan-1-one oxime (**87x**) (136 mg, 0.50 mmol) and 3-hexyne (**34f**) (82 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1 ⟶ 5/1) yielded **50xf** as a pale brown solid (92 mg, 55%, m.p.: 100–103 °C) and **50xf'** as a yellow oil (36 mg, 21%).

50xf:

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.37-7.05$ (m, 7H), 4.54 (s, 2H), 3.98 (s, 3H), 3.81 (s, 3H), 2.98 (pent, $J = 7.6$ Hz, 4H), 1.35 (t, $J = 7.6$ Hz, 3H), 1.29 (t, $J = 7.6$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 154.9$ (C_q), 152.0 (C_q), 151.7 (C_q), 148.5 (C_q), 140.1 (C_q), 132.4 (C_q), 128.5 (CH), 128.4 (CH), 126.9 (C_q), 126.0 (CH), 121.4 (C_q), 105.0 (CH), 102.0 (CH), 55.8 (CH_3), 55.7 (CH_3), 42.8 (CH_2), 28.4 (CH_2), 21.1 (CH_2), 15.0 (CH_3), 14.8 (CH_3).

IR (ATR, cm^{-1}): 2963, 1621, 1566, 1426, 1248, 1203, 1152, 1030, 840, 794, 720, 700.

MS (EI): 335 (35) $[M]^+$, 320 (100) $[M-Me]^+$, 306 (15) $[M-Et]^+$, 292 (8), 276 (8), 165 (8), 91 (15).

$[\mathbf{C_{22}H_{25}NO_2}]^+$ (EI) HRMS: calcd.: 335.1885.
found: 335.1891.

50xf':

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.86$ (d, $J = 9.3$ Hz, 1H), 7.29–7.22 (m, 4H), 7.21–7.11 (m, 1H), 7.18 (d, $J = 9.3$ Hz, 1H), 4.57 (s, 2H), 3.95 (s, 3H), 3.90 (s, 3H), 3.22 (q, $J = 7.5$ Hz, 2H), 3.03 (q, $J = 7.5$ Hz, 2H), 1.39 (t, $J = 7.5$ Hz, 3H), 1.30 (s, $J = 7.5$ Hz, 3H).

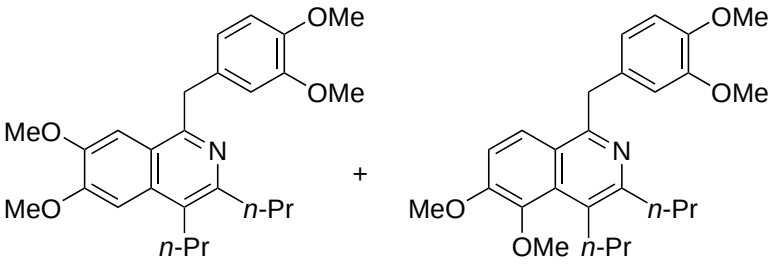
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 156.7$ (C_q), 154.1 (C_q), 152.3 (C_q), 143.9 (C_q), 140.0 (C_q), 131.4 (C_q), 128.4 (CH), 128.3 (CH), 127.1 (C_q), 126.0 (CH), 123.3 (CH), 122.7 (C_q), 113.5 (CH), 61.1 (CH_3), 56.3 (CH_3), 42.6 (CH_2), 28.5 (CH_2), 22.7 (CH_2), 16.1 (CH_3), 15.0 (CH_3).

IR (ATR, cm^{-1}): 2932, 1606, 1496, 1451, 1381, 1274, 1225, 1128, 1059, 1012, 791, 715, 696.

MS (EI): 335 (65) $[M]^+$, 320 (100) $[M-Me]^+$, 306 (42) $[M-Et]^+$, 290 (28), 276 (10), 211 (15), 91 (20), 59 (12), 43 (65).

$[\mathbf{C_{22}H_{25}NO_2}]^+$ (EI) HRMS: calcd.: 335.1885.
found: 335.1884.

Synthesis of 1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3,4-di-*n*-propylisoquinoline (3,4-Di-*n*-propylpapaverine) (50yg) and 1-(3,4-Dimethoxybenzyl)-5,6-dimethoxy-3,4-di-*n*-propylisoquinoline (50yg')



The general procedure **I** was followed using 1,2-bis(3,4-dimethoxyphenyl)ethan-1-one oxime (**87y**) (166 mg, 0.50 mmol) and 4-octyne (**34g**) (110 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 3/1 → 2/1) yielded **50yg** as a beige solid (112 mg, 53%, m.p.: 111–115 °C) and **50yg'** as a yellow oil (62 mg, 29%).

50yg:

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.29$ (s, 1H), 7.14 (s, 1H), 6.85 (d, $J = 1.9$ Hz, 1H), 6.80 (dd, $J = 8.2$, 1.9 Hz, 1H), 6.72 (d, $J = 8.2$ Hz, 1H), 4.46 (s, 2H), 3.98 (s, 3H), 3.86 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H), 2.99–2.88 (m, 4H), 1.82 (dq, $J = 14.9$, 7.4 Hz, 2H), 1.68 (dq, $J = 15.0$, 7.4 Hz, 2H), 1.08 (t, $J = 7.1$ Hz, 3H), 1.03 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 154.8$ (C_q), 151.8 (C_q), 150.5 (C_q), 148.8 (C_q), 148.4 (C_q), 147.2 (C_q), 132.6 (C_q), 132.5 (C_q) 125.8 (C_q), 121.2 (C_q), 120.2 (CH), 111.7 (CH), 110.9 (CH), 104.6 (CH), 102.1 (CH), 55.7 (CH_3), 55.6 (CH_3), 55.6 (CH_3), 55.5 (CH_3), 42.0 (CH_2), 37.1 (CH_2), 30.0 (CH_2), 23.8 (CH_2), 23.6 (CH_2), 14.6 (CH_3), 14.2 (CH_3).

IR (ATR, cm^{-1}): 2955, 2869, 1567, 1509, 1457, 1426, 1252, 1203, 1152, 1137, 1028, 841, 812, 788, 767, 626, 548.

MS (EI): 423 (53) $[M]^+$, 408 (100) $[M-Me]^+$, 395 (35), 380 (95) $[M-n\text{-}Pr]^+$, 367 (35), 165 (14), 151 (12).

$[\mathbf{C_{26}H_{33}NO_4}]^+$ (EI) HRMS: calcd.: 423.2410.
found: 423.2403.

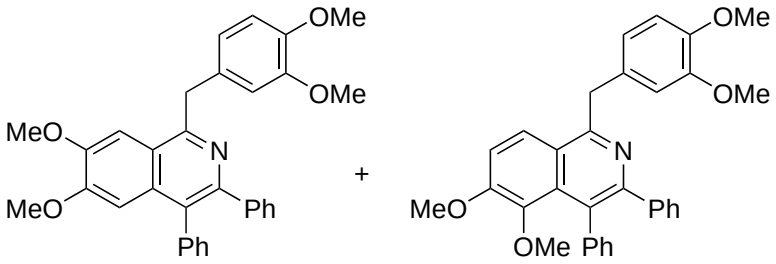
50yg':

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.90$ (d, $J = 9.2$ Hz, 1H), 7.19 (d, $J = 9.2$ Hz, 1H), 6.86 (d, $J = 1.9$ Hz, 1H), 6.77 (dd, $J = 8.2$, 1.9 Hz, 1H), 6.72 (d, $J = 8.2$ Hz, 1H), 4.48 (s, 2H), 3.96 (s, 3H), 3.88 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.16–3.07 (m, 2H), 3.00–2.92 (m, 2H), 1.83 (dq, $J = 14.9$, 7.4 Hz, 2H), 1.64 (dq, $J = 14.7$, 7.3 Hz, 2H), 1.06 (t, $J = 7.3$ Hz, 3H), 1.06 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 156.7$ (C_q), 152.9 (C_q), 152.4 (C_q), 148.8 (C_q), 147.3 (C_q), 143.9 (C_q), 132.6 (C_q), 131.5 (C_q), 126.0 (C_q), 123.2 (CH), 122.5 (C_q), 120.2 (CH), 113.4 (CH), 111.7 (CH), 111.0 (CH), 61.1 (CH_3), 56.2 (CH_3), 55.8 (CH_3), 55.6 (CH_3), 42.0 (CH_2), 37.4 (CH_2), 31.9 (CH_2), 25.2 (CH_2), 23.9 (CH_2), 14.8 (CH_3), 14.4 (CH_3).

IR (ATR, cm^{-1}): 2957, 2869, 1607, 1512, 1451, 1376, 1272, 1233, 1133, 1067, 1012, 792, 765.
MS (EI): 423 (38) $[M]^+$, 408 (60) $[M-Me]^+$, 392 (70) $[M-OMe]^+$, 380 (90) $[M-n\text{-}Pr]^+$, 364 (100), 352 (30), 226 (5), 151 (8).
$[\mathbf{C_{26}H_{33}NO_4}]^+$ (EI) HRMS: calcd.: 423.2410.
found: 423.2422.

Synthesis of 1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3,4-diphenylisoquinoline (3,4-Diphenylpapaverine) (50ya) and 1-(3,4-Dimethoxybenzyl)-5,6-dimethoxy-3,4-diphenylisoquinoline (50ya')



The general procedure **I** was followed using 1,2-bis(3,4-dimethoxyphenyl)ethan-1-one oxime (**87y**) (166 mg, 0.50 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 3.5/1) yielded **50ya** as a pale yellow solid (98 mg, 40%, m.p.: 167–170 °C) and **50ya'** as a pale yellow solid (68 mg, 28%, m.p.: 134–136 °C).

50ya:

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.42$ (s, 1H), 7.39–7.28 (m, 5H), 7.25–7.13 (m, 5H), 7.01 (d, $J = 2.0$ Hz, 1H), 6.92 (dd, $J = 8.2$, 2.0 Hz, 1H), 6.88 (s, 1H), 6.78 (d, $J = 8.2$ Hz, 1H), 4.63 (s, 2H), 3.91 (s, 3H), 3.82 (s, 3H), 3.82 (s, 3H), 3.71 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 156.8$ (C_q), 152.1 (C_q), 149.3 (C_q), 148.9 (C_q), 148.5 (C_q), 147.5 (C_q), 141.2 (C_q), 137.9 (C_q), 133.3 (C_q), 132.4 (C_q), 131.1 (CH), 130.2 (CH), 128.8 (C_q), 128.2 (CH), 127.5 (CH), 127.1 (CH), 126.7 (CH), 121.7 (C_q), 120.6 (CH), 112.1 (CH), 111.1 (CH), 104.6 (CH), 104.1 (CH), 55.8 (CH_3), 55.8 (CH_3), 55.8 (CH_3), 55.6 (CH_3), 42.4 (CH_2).
IR (ATR, cm^{-1}): 2952, 1508, 1465, 1425, 1250, 1229, 1203, 1140, 1025, 1001, 844, 762, 699.
MS (EI): 491 (50) $[M]^+$, 476 (100) $[M-Me]^+$, 460 (30) $[M-OMe]^+$, 445 (10) $[M-OMe-Me]^+$, 432 (6), 267 (4), 238 (4), 151 (5), 77 (8), 55 (13), 43 (46).
$[\mathbf{C_{32}H_{29}NO_4}]^+$ (EI) HRMS: calcd.: 491.2097.
found: 491.2086.

50ya':

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.07$ (d, $J = 9.3$ Hz, 1H), 7.30 (d, $J = 9.3$ Hz, 1H), 7.28–7.22 (m, 2H), 7.20–7.11 (m, 8H), 7.02 (d, $J = 2.0$ Hz, 1H), 6.89 (dd, $J = 8.2$, 2.0 Hz, 1H), 6.77 (d, $J = 8.2$ Hz, 1H), 4.63 (s, 2H), 3.91 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.04 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.1$ (C_q), 153.0 (C_q), 151.5 (C_q), 148.8 (C_q), 147.5 (C_q), 143.9 (C_q), 141.6 (C_q), 140.3 (C_q), 132.3 (C_q), 131.8 (C_q), 130.8 (CH), 130.2 (CH), 127.3 (CH),

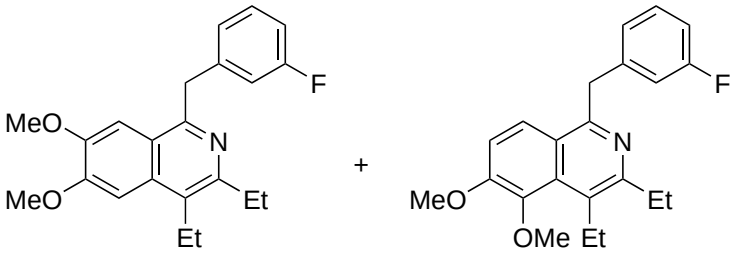
127.0 (C_q), 126.5 (CH), 126.5 (CH), 125.8 (CH), 123.0 (CH), 122.4 (C_q), 120.5 (CH), 114.5 (CH), 112.1 (CH), 111.1 (CH), 60.3 (CH_3), 56.2 (CH_3), 55.8 (CH_3), 55.8 (CH_3), 42.1 (CH_2).

IR (ATR, cm^{-1}): 2934, 1510, 1495, 1441, 1256, 1231, 1136, 1072, 1023, 1005, 793, 750, 696, 600.

MS (EI): 491 (100) $[M]^+$, 476 (65) $[M-Me]^+$, 460 (10) $[M-OMe]^+$, 445 (20) $[M-OMe-Me]^+$, 432 (5), 294 (4), 238 (7), 151 (8), 77 (9), 55 (8), 43 (38).

$[\mathbf{C_{32}H_{29}NO_4}]^+$ (EI) HRMS: calcd.: 491.2097.
found: 491.2085.

Synthesis of 3,4-Diethyl-1-(3-fluorobenzyl)-6,7-dimethoxyisoquinoline (50zf) and 3,4-Diethyl-1-(3-fluorobenzyl)-5,6-dimethoxyisoquinoline (50zf')



The general procedure **I** was followed using 1-(3,4-dimethoxyphenyl)-2-(3-fluorophenyl)ethan-1-one oxime (**87z**) (145 mg, 0.50 mmol) and 3-hexyne (**34f**) (82 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 6/1) yielded **50zf** as a yellow solid (53 mg, 30%, m.p.: 93–96 °C) and **50zf'** as a yellow oil (25 mg, 14%).

50zf:

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.23$–7.13 (m, 1H), 7.16 (s, 2H), 7.04 (d, $J = 7.9$ Hz, 1H), 6.91 (d, $J = 10.2$ Hz, 1H), 6.87–6.78 (m, 1H), 4.52 (s, 2H), 3.99 (s, 3H), 3.83 (s, 3H), 3.00 (q, $J = 7.5$ Hz, 2H), 2.96 (q, $J = 7.5$ Hz, 2H), 1.34 (t, $J = 7.5$ Hz, 3H), 1.29 (t, $J = 7.5$ Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 162.9$ (d, $^1J_{C-F} = 245$ Hz, C_q), 156.0 (C_q), 154.2 (C_q), 152.5 (C_q), 144.1 (C_q), 142.5 (d, $^3J_{C-F} = 7$ Hz, C_q), 131.5 (C_q), 129.7 (d, $^3J_{C-F} = 8$ Hz, CH), 127.4 (C_q), 124.1 (d, $^4J_{C-F} = 3$ Hz, CH), 123.0 (C_q), 122.6 (CH), 115.3 (d, $^2J_{C-F} = 22$ Hz, CH), 113.7 (CH), 112.9 (d, $^2J_{C-F} = 21$ Hz, CH), 61.1 (CH_3), 56.3 (CH_3), 42.2 (CH_2), 28.5 (CH_2), 22.8 (CH_2), 16.1 (CH_3), 14.9 (CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -113.7$ (td, $J = 9.4$, 6.0 Hz).

IR (ATR, cm^{-1}): 2964, 2931, 1615, 1587, 1566, 1510, 1471, 1448, 1427, 1250, 1204, 1151, 1032, 947, 840, 793, 773, 684.

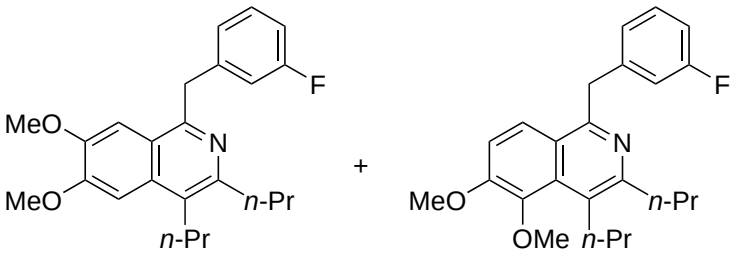
MS (EI): 353 (55) $[M]^+$, 338 (100) $[M-Me]^+$, 322 (20) $[M-OMe]^+$, 310 (6), 294 (10), 165 (16), 109 (6), 43 (5).

$[\mathbf{C_{22}H_{24}FNO_2}]^+$ (EI) HRMS: calcd.: 353.1791.
found: 353.1778.

50zf':

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.78$ (d, $J = 9.2$ Hz, 1H), 7.22–7.13 (m, 1H), 7.18 (d, $J = 9.3$ Hz, 1H), 7.02 (d, $J = 7.7$ Hz, 1H), 6.91 (d, $J = 10.0$ Hz, 1H), 6.82 (td, $J = 8.5, 2.6$ Hz, 1H), 4.54 (s, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 3.19 (q, $J = 7.3$ Hz, 2H), 3.00 (q, $J = 7.5$ Hz, 2H), 1.36 (t, $J = 7.5$ Hz, 3H), 1.27 (t, $J = 7.3$ Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 162.9$ (d, $^1J_{C-F} = 245$ Hz, C_q), 156.0 (C_q), 154.2 (C_q), 152.5 (C_q), 144.1 (C_q), 142.5 (d, $^3J_{C-F} = 7$ Hz, C_q), 131.5 (C_q), 129.7 (d, $^3J_{C-F} = 8.3$ Hz, CH), 127.4 (C_q), 124.07 (d, $^4J_{C-F} = 3$ Hz, CH), 123.0 (CH), 122.6 (C_q), 115.3 (d, $^2J_{C-F} = 22$ Hz, CH), 113.7 (CH), 112.9 (d, $^2J_{C-F} = 21$ Hz, CH), 61.1 (CH_3), 56.3 (CH_3), 42.2 (CH_2), 28.5 (CH_2), 22.8 (CH_2), 16.1 (CH_3), 14.9 (CH_3).
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -113.6$ (td, $J = 9.3, 5.9$ Hz).
IR (ATR, cm^{-1}): 2935, 1608, 1588, 1487, 1449, 1416, 1380, 1276, 1130, 1061, 1012, 789, 756, 684.
MS (EI): 353 (75) $[M]^+$, 338 (100) $[M-Me]^+$, 324 (75) $[M-Et]^+$, 308 (35), 294 (12), 109 (15), 43 (6).
$[C_{22}H_{24}FNO_2]^+$ (EI) HRMS: calcd.: 353.1791.
found: 353.1783.

Synthesis of 1-(3-Fluorobenzyl)-6,7-dimethoxy-3,4-di-*n*-propylisoquinoline (50zg) and 1-(3-Fluorobenzyl)-5,6-dimethoxy-3,4-di-*n*-propylisoquinoline (50zg')



The general procedure **I** was followed using 1-(3,4-dimethoxyphenyl)-2-(3-fluorophenyl)ethan-1-one oxime (**87z**) (145 mg, 0.50 mmol) and 4-octyne (**34g**) (110 mg, 1.00 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **50zg** as a yellow solid (95 mg, 50%, m.p.: 103–108 °C) and **50zg'** as a yellow oil (24 mg, 13%).
50zg:
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.22$–7.13 (m, 1H), 7.16 (s, 1H), 7.14 (s 1H), 7.03 (d, $J = 7.7$ Hz, 1H), 6.90 (d, $J = 10.0$ Hz, 1H), 6.82 (td, $J = 8.3, 2.3$ Hz, 1H), 4.52 (s, 2H), 3.98 (s, 3H), 3.82 (s, 3H), 3.01−2.84 (m, 4H), 1.80 (dq, $J = 12.3, 6.1, 4.7$ Hz, 2H), 1.68 (td, $J = 15.2, 13.8, 6.2$ Hz, 2H), 1.08 (t, $J = 7.8$ Hz, 3H), 1.03 (t, $J = 7.4$ Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.9$ (d, $^1J_{C-F} = 245$ Hz, C_q), 153.9 (C_q), 152.0 (C_q), 150.9 (C_q), 148.6 (C_q), 142.6 (d, $^3J_{C-F} = 7$ Hz, C_q), 132.7 (C_q), 129.7 (d, $^3J_{C-F} = 8$ Hz, CH), 126.2 (C_q), 124.1 (d, $^4J_{C-F} = 3$ Hz, CH), 121.3 (C_q), 115.3 (d, $^2J_{C-F} = 21$ Hz, CH), 113.0 (d, $^2J_{C-F} = 21$ Hz, CH), 104.5 (CH), 102.3 (CH), 55.8 (CH_3), 55.7 (CH_3), 42.3 (CH_2), 37.3 (CH_2), 30.1 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 14.7 (CH_3), 14.3 (CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -113.5$ (td, $J = 9.7, 6.5$ Hz).

IR (ATR, cm^{-1}): 2956, 2869, 1613, 1587, 1566, 1508, 1449, 1334, 1251, 1172, 1071, 1044, 995, 865, 841, 808, 688, 442.

MS (EI): 381 (40) $[M]^+$, 366 (100) $[M-Me]^+$, 353 (30), 338 (95) $[M-n\text{-}Pr]^+$, 325 (38), 308 (8), 235 (14), 109 (14), 43 (19).

$[\mathbf{C_{24}H_{28}FNO_2}]^+$ (EI) HRMS: calcd.: 381.2104.
found: 381.2114.

50zg':

^{1}H NMR (300 MHz, $CDCl_3$): δ =7.78 (d, $J = 9.2$ Hz, 1H), 7.21–7.13 (m, 1H), 7.18 (d, $J = 9.2$ Hz, 1H), 7.01 (dq, $J = 7.7, 0.9$ Hz, 1H), 6.90 (dt, $J = 10.1, 1.9$ Hz, 1H), 6.81 (td, $J = 8.6, 2.5$ Hz, 1H), 4.53 (s, 2H), 3.95 (s, 3H), 3.88 (s, 3H), 3.17–3.04 (m, 2H), 3.00–2.88 (m, 2H), 1.81 (dq, $J = 14.9, 7.4$ Hz, 2H), 1.63 (dq, $J = 14.6, 7.4$ Hz, 2H), 1.06 (t, $J = 7.3$ Hz, 3H), 1.05 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.8$ (d, $^1J_{C-F} = 245$ Hz, C_q), 155.8 (C_q), 153.1 (C_q), 152.4 (C_q), 144.0 (C_q), 142.5 (d, $^3J_{C-F} = 7$ Hz, C_q), 131.5 (C_q), 129.7 (d, $^3J_{C-F} = 8$ Hz, CH), 126.3 (C_q), 124.0 (d, $^4J_{C-F} = 3$ Hz, CH), 123.1 (CH), 122.5 (C_q), 115.3 (d, $^2J_{C-F} = 21$ Hz, CH), 113.5 (CH), 112.9 (d, $^2J_{C-F} = 21$ Hz, CH), 61.2 (CH_3), 56.3 (CH_3), 42.2 (CH_2), 37.5 (CH_2), 32.0 (CH_2), 25.2 (CH_2), 23.8 (CH_2), 14.8 (CH_3), 14.4 (CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -113.6$ (td, $J = 9.2, 5.9$ Hz).

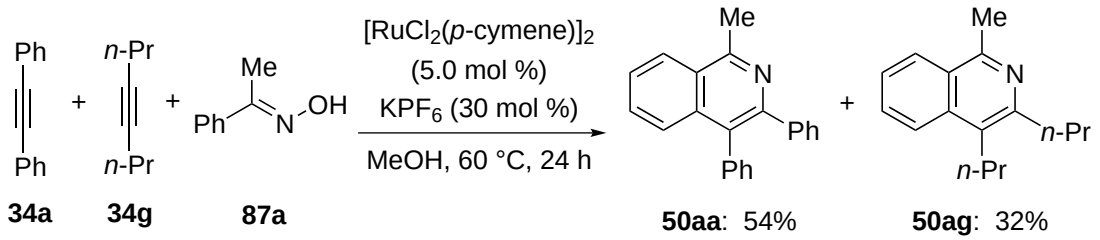
IR (ATR, cm^{-1}): 2959, 2870, 1609, 1589, 1489, 1450, 1275, 1133, 1067, 1012, 786, 757, 683, 521.

MS (EI): 381 (35) $[M]^+$, 366 (45) $[M-Me]^+$, 350 (63) $[M-OMe]^+$, 338 (82) $[M-n\text{-}Pr]^+$, 322 (100), 310 (29), 235 (6), 109 (11), 43 (5).

$[\mathbf{C_{24}H_{28}FNO_2}]^+$ (EI) HRMS: calcd.: 381.2104.
found: 381.2105.

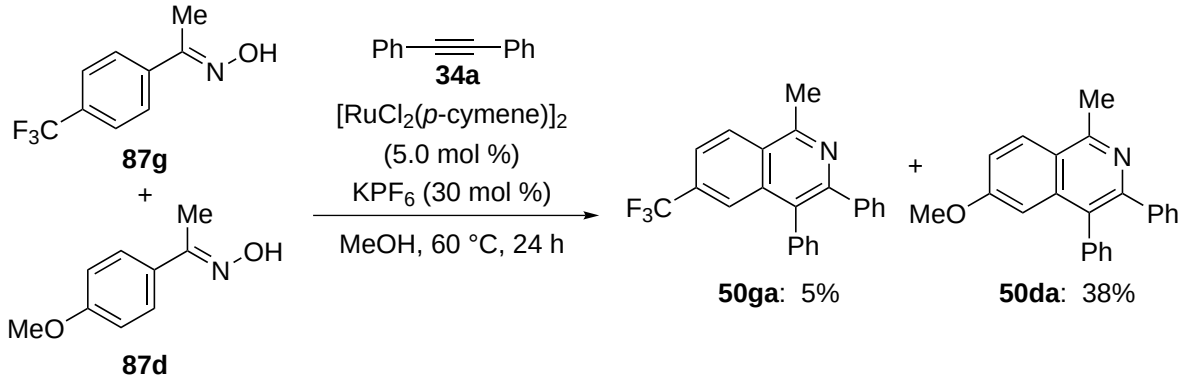
5.3.6 Intermolecular Competition Experiments for the Ruthenium-Catalyzed Synthesis of Isoquinolines

Competition Experiment between Alkynes 34a and 34g



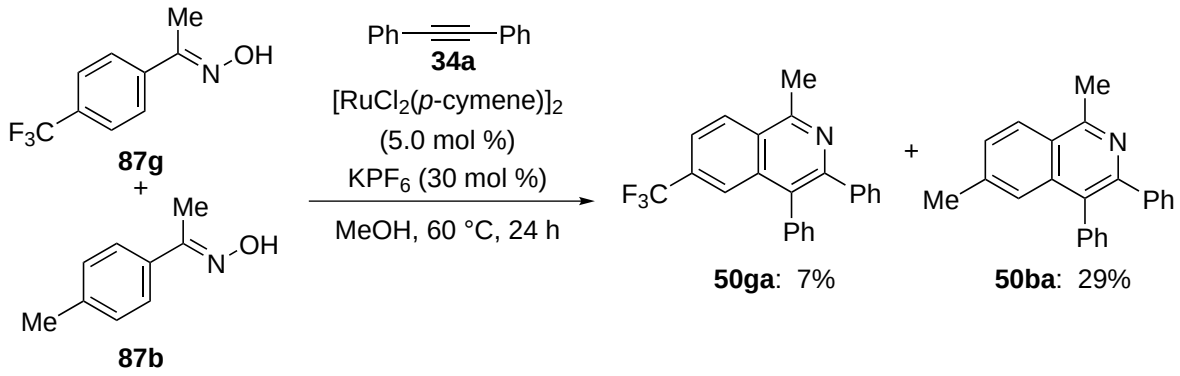
Acetophenone oxime (**87a**) (68 mg, 0.50 mmol), diphenylacetylene (**34a**) (356 mg, 2.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF_6 (28 mg, 0.15 mmol, 30 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. Dry MeOH (2.0 mL, 0.25 M) and 4-octyne (**34g**) (220 mg, 2.00 mmol) were added and the reaction mixture was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50aa** (80 mg, 54%) as a white solid and **50ag** (36 mg, 32%) as a yellow oil.

Competition Experiment between Oximes 87g and 87d



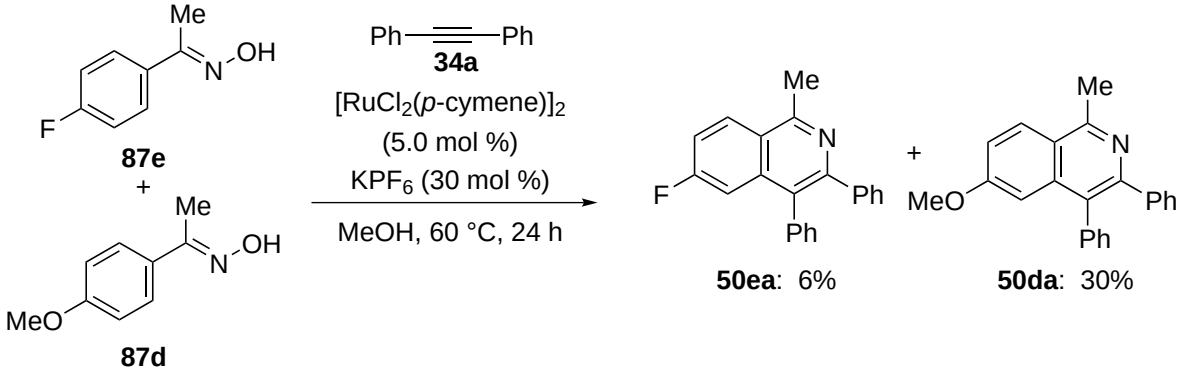
1-[4-(Trifluoromethyl)phenyl]ethanone oxime (**87g**) (112 mg, 0.55 mmol), 1-(4-methoxyphenyl)-ethanone oxime (**87d**) (91 mg, 0.55 mmol), diphenylacetylene (**34a**) (89 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF_6 (28 mg, 0.15 mmol, 30 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. Dry MeOH (2.0 mL, 0.25 M) was added and the reaction mixture was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50ga** (9 mg, 5%) as an orange solid and **50da** (62 mg, 38%) as a pale yellow solid.

Competition Experiment between Oximes 87g and 87b



1-[4-(Trifluoromethyl)phenyl]ethanone oxime (**87g**) (112 mg, 0.55 mmol), 1-*para*-tolylethanone oxime (**87b**) (82 mg, 0.55 mmol), diphenylacetylene (**34a**) (89 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF_6 (28 mg, 0.15 mmol, 30 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. Dry MeOH (2.0 mL, 0.25 M) was added and the reaction mixture was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50ga** (13 mg, 7%) as an orange solid and **50ba** (45 mg, 29%) as a pale orange solid.

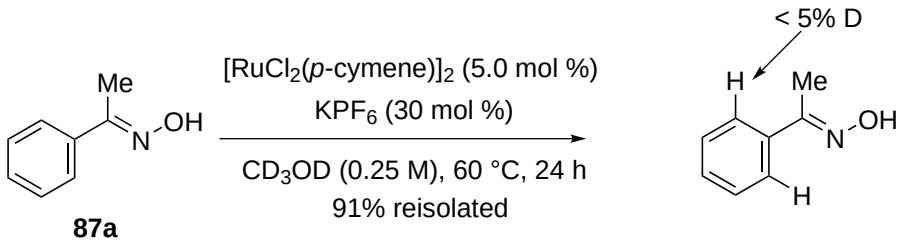
Competition Experiment between Oximes 87e and 87d



1-(4-Fluorophenyl)ethanone oxime (**87e**) (84 mg, 0.55 mmol), 1-(4-methoxyphenyl)ethanone oxime (**87d**) (91 mg, 0.55 mmol), diphenylacetylene (**34a**) (89 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF_6 (28 mg, 0.15 mmol, 30 mol %) were placed in a pre-dried 25-mL Schlenkt ube. The mixture was degassed and purged with N_2 for 3 times. Dry MeOH (2.0 mL, 0.25 M) was added and the reaction mixture was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **50ea** (10 mg, 6%) as a white solid and **50da** (45 mg, 30%) as a pale yellow solid.

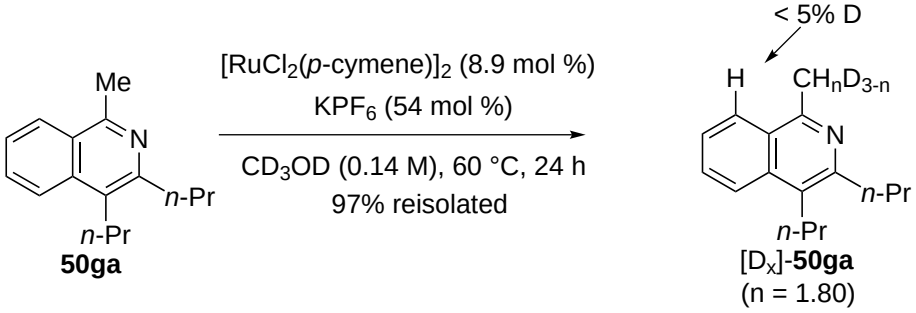
5.3.7 Mechanistical Studies of the Ruthenium-Catalyzed Synthesis of Isoquinolines through Isotopic Labeling

Ruthenium-Catalyzed H/D Exchange in 887a upon Reaction in [D_4]-MeOH



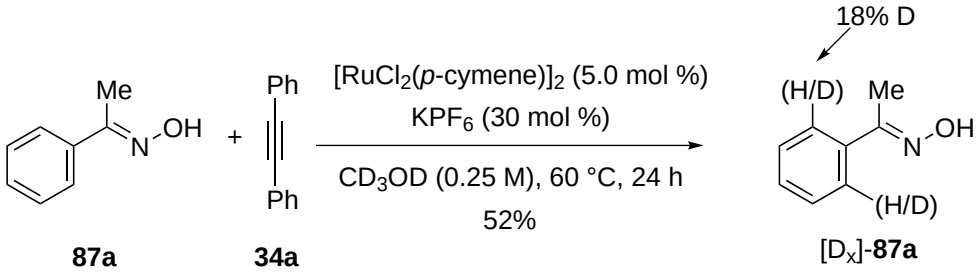
Acetophenone oxime (**87a**) (68 mg, 0.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF_6 (28 mg, 0.15 mmol, 30 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. D_3COD (2.0 mL, 0.25 M) was added and the reaction mixture was stirred at 60 °C for 24 h. At ambient temperature, H_2O (20 mL) was added and the mixture was extracted with EtOAc (2 × 80 mL). The combined organic layers wered dried over Na_2SO_4, filtered and the solvents were removed *in vacuo* to yield the oxime (62 mg, 91%) with less then 5% deuterium-incorporation in the *ortho*-position.

Ruthenium-Catalyzed H/D Exchange in Isoquinoline 50ga upon Reaction in [D_4]-MeOH



50ga (32 mg, 0.14 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol, 8.9 mol %), and KPF_6 (13.8 mg, 0.075 mmol, 54 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. CD_3OD (1.0 mL, 0.14 M) was added and the reaction mixture was stirred at 60 °C for 24 h. At ambient temperature, brine (75 mL) was added and the mixture was extracted wit EtOAc (75 mL). The organic layer was dried over Na_2SO_4, filtered and the solvents were removed *in vacuo* to yield [D_x]-**50ga** (31 mg, 97%) with less then 5% deuterium-incorporation in the *ortho*-position and 40% deuterium incorporation at the methyl-group, as estimated by ^{1}H NMR-spectroscopy.

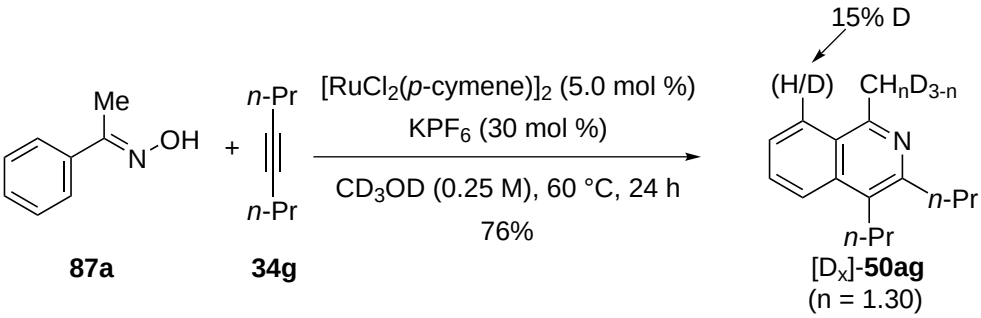
Ruthenium-Catalyzed H/D Exchange in Oxime 87a upon Reaction in [D_4]-MeOH in the Presence of Substoechiometric Amounts of 34a



87a **34a** [D_x]-**87a**

Acetophenone oxime (**87a**) (68 mg, 0.50 mmol), diphenylacetylene (**34a**) (17.8 mg, 0.10 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF_6 (28 mg, 0.15 mmol, 30 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. CD_3OD (2.0 mL, 0.25 M) was added and the reaction mixture was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 12/1) yielded [D_x]-**87a** (35 mg, 52%) with 18% deuterium incorporation in the *ortho*-position estimated by ^{1}H NMR-spectroscopy.

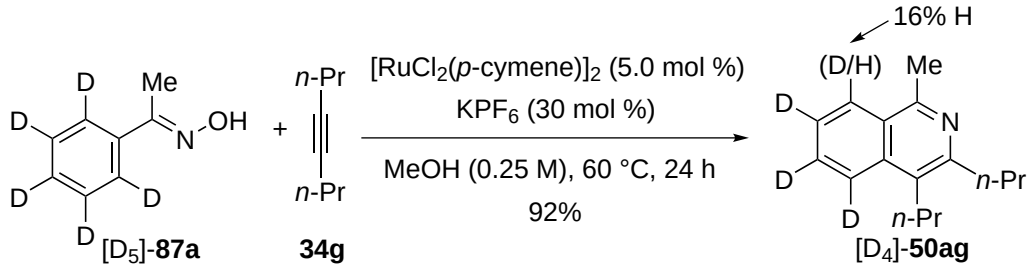
Ruthenium-Catalyzed Annulation of Alkyne 34g with Oxime 87a in [D_4]-MeOH



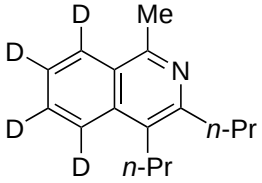
87a **34g** [D_x]-**50ag** (n = 1.30)

Acetophenone oxime (**87a**) (68 mg, 0.50 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF_6 (28 mg, 0.15 mmol, 30 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. CD_3OD (2.0 mL, 0.25 M) and 4-octyne (**34g**) (110 mg, 1.00 mmol) were added and the reaction mixture was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL)was added and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 12/1) yielded [D_x]-**50ag** (86 mg, 76%) as a yellow oil with 15% deuterium incorporation in the *ortho*-position and 57% deuterium incorporation at the methyl-group as estimated by ^{1}H NMR-spectroscopy.

Ruthenium-Catalyzed Annulation of Alkyne 34g with Oxime [D_5]-87a in MeOH



[D_5]-Acetophenone oxime ([D_5]-**87a**) (70 mg, 0.50 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), and KPF_6 (28 mg, 0.15 mmol, 30 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. MeOH (2.0 mL, 0.25 M) and 4-octyne (**34g**) (110 mg, 1.00 mmol) were added and the reaction mixture was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 12/1) yielded [D_4]-**50ag** (107 mg, 92%) as a yellow oil with 16% hydrogen incorporation in the *ortho*-position, as estimated by ^{1}H NMR-spectroscopy.



^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 3.07-2.81$ (m, 4H), 2.89 (s, 3H), 1.86−1.72 (m, 2H) 1.73−1.59 (m, 2H), 1.08 (t, $J = 7.3$ Hz, 3H), 1.04 (t, $J = 7.3$ Hz, 3H).

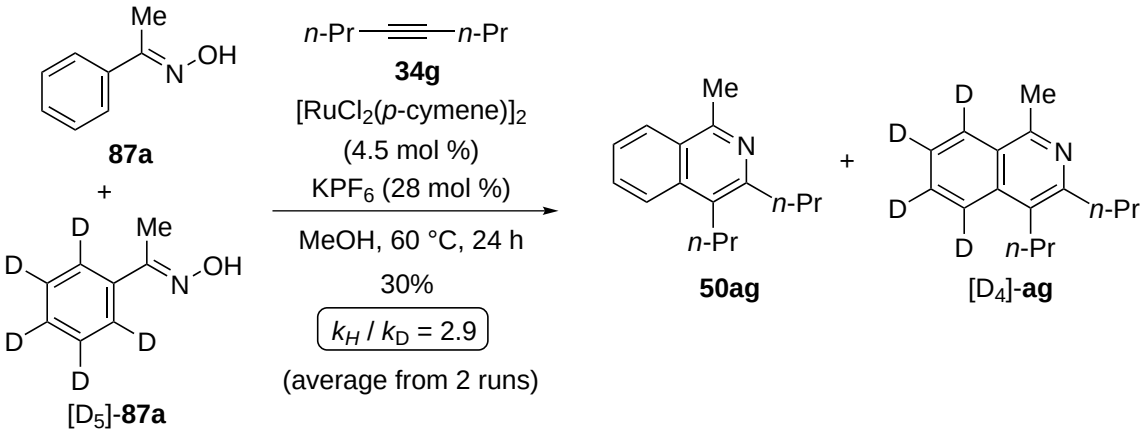
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 155.5$ (C_q), 151.5 (C_q), 135.2 (C_q), 128.8 (t, $J = 24$ Hz, CD), 126.0 (C_q), 125.8 (C_q), 125.2 (t, $J = 24$ Hz, CD), 124.6 (t, $J = 24$ Hz, CD), 123.1 (t, $J = 24$ Hz, CD), 37.4 (CH_2), 29.7 (CH_2), 24.1 (CH_2), 23.8 (CH_2), 22.3 (CH_3), 14.5 (CH_3), 14.3 (CH_3).

IR (ATR, cm^{-1}): 2957, 2930, 2871, 1593, 1555, 1451, 1402, 1376, 1307, 1275, 1089, 878, 647, 559.

MS (EI): 231 (65) [M]$^+$, 216 (100) [M−Me]$^+$, 201 (82) [M−2Me]$^+$, 184 (73), 175 (88), 160 (23), 145 (13), 131 (33), 118 (20), 92 (10), 79 (10), 41 (10).

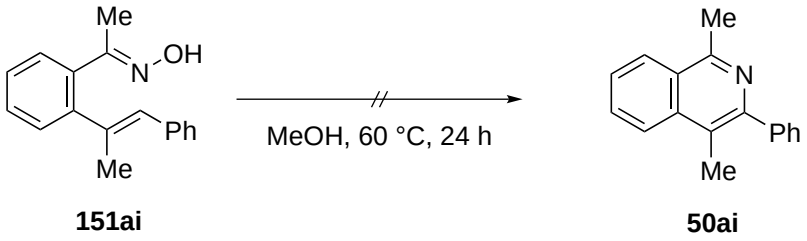
[$C_{16}H_{17}D_4N$ + H]$^+$ (ESI) HRMS: calcd.: 232.1998.
found: 232.1998.

Competition Experiment between Oximes 87a and [D_5]-87a



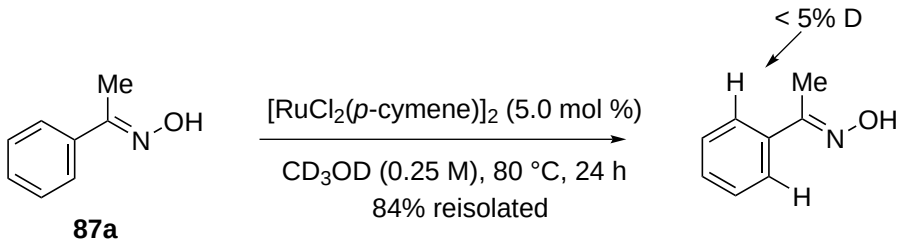
Acetophenone oxime (**87a**) (74 mg, 0.55 mmol), [D_5]-acetophenone oxime ([D_5]-**87a**) (77 mg, 0.55 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 0.025 mmol, 4.5 mol %), and KPF_6 (28 mg, 0.15 mmol, 28 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. MeOH (2.0 mL, 0.25 M) and 4-octyne (**34g**) (110 mg, 1.00 mmol) were added and the reaction mixture was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 12/1) yielded a mixture of **50ga** and [D_4]-**50ga** (50 mg, 40%) as a yellow oil with a ratio of 3.3 to 1 (**50ga**/[D_4]-**50ga**), as determined by ^{1}H NMR-spectroscopy. The reaction was repeated yielding a mixture of **50ga** and [D_4]-**50ga** (25 mg, 20%) with a ratio of 2.5 to 1 (**50ga**/[D_4]-**50ga**), as determined by ^{1}H NMR-spectroscopy.

Attempted Cyclyzation of Oxime 151ai in MeOH



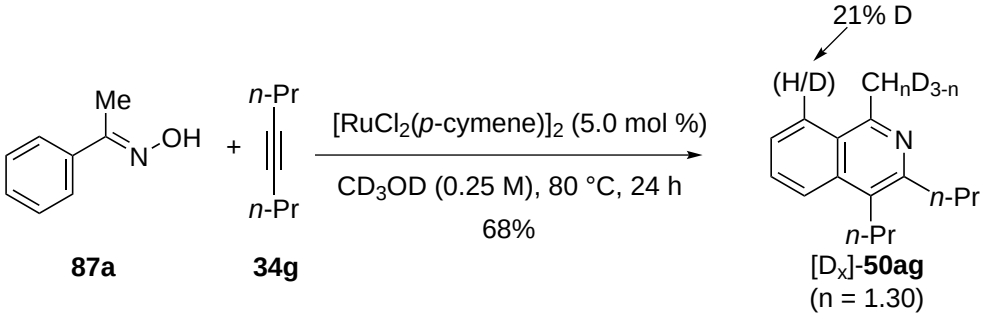
(2-((*E*)-1-phenylprop-1-en-2-yl)phenyl)ethan-1-one oxime (**151ai**) (45 mg, 0.18 mmol) was placed in a pre-dried 25-mL Schlenk tube and degassed and purged with N_2 for 3 times. MeOH (2.0 mL) was added and mixture was stirred at 60 °C for 24 h. The starting material was reisolated by evaporation of the solvent.

Ruthenium-Catalyzed H/D Exchange in Acetophenone Oxime (87a) in [D_4]-MeOH without KPF_6



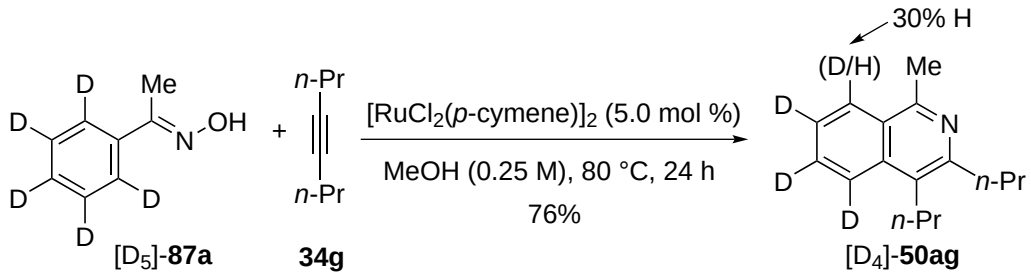
Acetophenone oxime (**87**) (68 mg, 0.50 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. CD_3OD (2.0 mL, 0.25 M) was added and the reaction mixture was stirred at 80 °C for 24 h. At ambient temperature, H_2O (20 mL) was added and the mixture was extracted with EtOAc (2 × 80 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo* to yield the oxime (57 mg, 84%) with less then 5% deuterium-incorporation in the *ortho*-position.

Ruthenium-Catalyzed Annulation of Alkyne 34g with Oxime 87a in [D_4]-MeOH without KPF_6



Acetophenone oxime (**87a**) (68 mg, 0.50 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. CD_3OD (2.0 mL, 0.25 M) and 4-octyne (**34g**) (110 mg, 1.00 mmol) were added and the reaction mixture was stirred at 80 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 12/1) yielded [D_x]-**50ag** (77 mg, 68%) as a yellow oil with 21% deuterium incorporation in the *ortho*-position and 57% deuterium-incorporation at the methyl-group as estimated by ^1H NMR-spectroscopy.

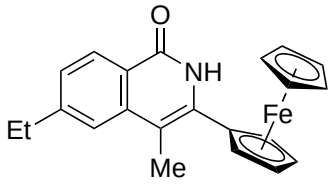
Ruthenium-Catalyzed Annulation of Alkyne 34g with Oxime [D_5]-87a in MeOH without KPF_6



[D_5]-Acetophenone oxime ([D_5]-**87a**) (70 mg, 0.50 mmol) and [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 0.025 mmol, 5.0 mol %) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. MeOH (2.0 mL, 0.25 M) and 4-octyne (**34g**) (110 mg, 1.00 mmol) were added and the reaction mixture was stirred at 80 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 12/1) yielded [D_4]-**50ag** (88 mg, 76%) as a yellow oil with 30% hydrogen incorporation in the *ortho*-position as estimated by ^{1}H NMR-spectroscopy.

5.3.8 Syntheses of Ferrrocenyl-Substituted Isoquinolones 86

Synthesis of 6-Ethyl-3-ferrocenyl-4-methylisoquinolin-1(2*H*)-one (86aw)



The general procedure **J** was followed using 4-ethyl-*N*-methoxybenzamide (**84a**) (90 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1 → EtOAc) yielded **86aw** as a red-orange solid (148 mg, 80%, decomposition > 190 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.80$ (s_{br}, 1H), 8.35 (d, $J = 8.1$ Hz, 1H), 7.44 (d, $J = 1.7$ Hz, 1H), 7.33 (dd, $J = 8.1$, 1.7 Hz, 1H), 4.58–4.49 (m, 2H), 4.44–4.36 (m, 2H), 4.26 (s, 5H), 2.79 (q, $J = 7.6$ Hz, 2H), 2.28 (s, 3H), 1.30 (t, $J = 7.6$ Hz, 3H).

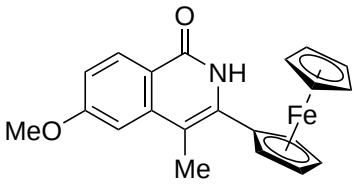
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 161.6$ (C_q), 149.4 (C_q), 139.0 (C_q), 133.5 (C_q), 127.8 (CH), 126.4 (CH), 123.0 (C_q), 122.1 (CH), 109.4 (C_q), 81.6 (C_q), 69.5 (CH), 69.4 (CH), 69.0 (CH), 29.6 (CH_2), 15.6 (CH_3), 14.0 (CH_3).

IR (ATR, cm^{-1}): 3167, 2966, 2930, 2863, 1634, 1603, 1556, 1456, 1347, 1105, 1061, 999, 917, 862, 819, 681, 598, 585, 486, 473.

MS (EI): 371 (100) $[M]^+$, 306 (8) $[M-C_5H_5]^+$, 248 (6), 178 (5), 121 (12), 60 (8).

$[\mathbf{C_{22}H_{21}FeNO}]^+$ (EI) HRMS: calcd.: 371.0973.
found: 371.0968.

Synthesis of 3-Ferrocenyl-6-methoxy-4-methylisoquinolin-1(2*H*)-one (86bw)



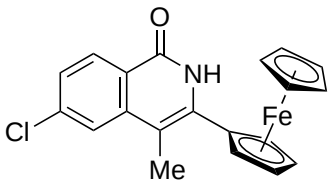
The general procedure **J** was followed using *N*,4-dimethoxybenzamide (**84b**) (91 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc: 3/1) yielded **86bw** as a red solid (145 mg, 78%, decomposition > 240 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.69$ (s_{br}, 1H), 8.36 (d, $J = 8.9$ Hz, 1H), 7.05 (dd, $J = 8.9$, 2.5 Hz, 1H), 6.98 (d, $J = 2.5$ Hz, 1H), 4.59–4.47 (m, 2H), 4.45–4.36 (m, 2H), 4.26 (s, 5H), 3.92 (s, 3H), 2.24 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 163.1$ (C_q), 161.2 (C_q), 140.9 (C_q), 134.2 (C_q), 129.8 (CH), 118.9 (C_q), 114.4 (CH), 109.1 (C_q), 105.6 (CH), 81.5 (C_q), 69.6 (CH), 69.4 (CH), 69.1 (CH),

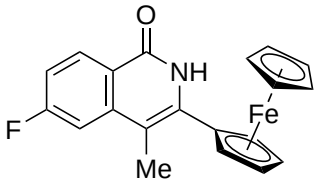
55.5 (CH_3), 14.1 (CH_3).
IR (ATR, cm^{-1}): 3107, 3011, 2862, 1633, 1598, 1499, 1456, 1422, 1332, 1228, 1104, 1028, 939, 845, 814, 795, 700, 507, 484, 448.
MS (EI): 371 (100) $[M]^+$, 308 (10), 250 (5) $[M-FeC_5H_5]^+$, 121 (12), 57 (10), 43 (15).
$[\mathbf{C_{21}H_{19}FeNO_2}]^+$ (EI) HRMS: calcd.: 373.0765.
found: 373.0758.

Synthesis of 6-Chloro-3-ferrocenyl-4-methylisoquinolin-1(2*H*)-one (86cw)



The general procedure **J** was followed using 4-chloro-*N*-methoxybenzamide (**84c**) (93 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1 → CH_2Cl_2/EtOAc: 2/1) yielded **86cw** as an orange solid (114 mg, 60%, decomposition > 235 °C).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.85 (s_{br}, 1H), 8.36 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 1.9 Hz, 1H), 7.41 (dd, J = 8.5, 1.9 Hz, 1H), 4.54 (t, J = 1.9 Hz, 2H), 4.42 (t, J = 1.9 Hz, 2H), 4.27 (s, 5H), 2.24 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.0 (C_q), 140.2 (C_q), 139.3 (C_q), 135.2 (C_q), 129.5 (CH), 126.4 (CH), 123.4 (C_q), 123.0 (CH), 108.6 (C_q), 81.0 (C_q), 69.6 (CH), 69.5 (CH), 69.3 (CH), 13.9 (CH_3).
IR (ATR, cm^{-1}): 3168, 3029, 2958, 2917, 1647, 1596, 1461, 1435, 1331, 1150, 1095, 1003, 913, 860, 792, 771, 587, 568, 485, 422.
MS (EI): 377 (100) $[M]^+$, 312 (14) $[M-C_5H_5]^+$, 256 (5), 191 (5), 165 (7), 121 (13), 60 (9).
$[\mathbf{C_{20}H_{16}ClFeNO}]^+$ (EI) HRMS: calcd.: 377.0270.
found: 377.0270.

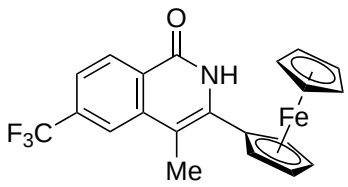
Synthesis of 3-Ferrocenyl-6-fluoro-4-methylisoquinolin-1(2*H*)-one (86dw)



The general procedure **J** was followed using 4-fluoro-*N*-methoxybenzamide (**84d**) (85 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 16 h, purification by column chromatography (CH_2Cl_2/EtOAc: 3/1 → 2/1) yielded **86dw** as a red solid (159 mg, 88%, decomposition > 235 °C).

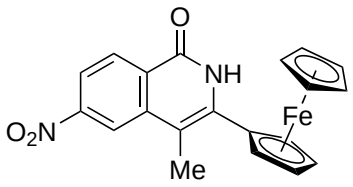
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.79$ (s_{br}, 1H), 8.44 (dd, $J = 8.8$, 6.1 Hz, 1H), 7.29–7.21 (m, 1H), 7.17 (td, $J = 8.5$, 2.5 Hz, 1H), 4.59–4.51 (m, 2H), 4.46–4.39 (m, 2H), 4.27 (s, 5H), 2.23 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 165.7$ (d, $^1J_{C-F} = 252$ Hz, C_q), 160.9 (C_q), 141.4 (d, $^3J_{C-F} = 10$ Hz, C_q), 135.2 (C_q), 130.8 (d, $^3J_{C-F} = 10$ Hz, CH), 121.7 (d, $^4J_{C-F} = 2$ Hz, C_q), 114.4 (d, $^2J_{C-F} = 23$ Hz, CH), 108.9 (d, $^4J_{C-F} = 3$ Hz, C_q), 108.8 (d, $^2J_{C-F} = 23$ Hz, CH), 81.1 (C_q), 69.6 (CH), 69.5 (CH), 69.3 (CH), 14.0 (CH_3).
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -105.3$ (ddd, $J = 10.5$, 8.0, 5.9 Hz).
IR (ATR, cm^{-1}): 2950, 2853, 1641, 1605, 1432, 1335, 1182, 1136, 1104, 946, 851, 817, 797, 473.
MS (EI): 361 (100) $[M]^+$, 296 (12) $[M-C_5H_5]^+$, 238 (8), 121 (12), 60 (8), 43 (14).
$[\mathbf{C_{20}H_{16}FFeNO}]^+$ (EI) HRMS: calcd.: 361.0565.
found: 361.0559.

Synthesis of 3-Ferrocenyl-4-methyl-6-(trifluoromethyl)isoquinolin-1(2*H*)-one (86ew)



The general procedure **J** was followed using *N*-methoxy-4-(trifluoromethyl)benzamide (**84e**) (110 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc: 5/1 → EtOAc) yielded **86ew** as a red-orange solid (184 mg, 89%, decomposition > 232 °C).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.07$ (s_{br}, 1H), 8.57 (d, $J = 8.3$ Hz, 1H), 7.91 (s, 1H), 7.69 (dd, $J = 8.3$, 1.3 Hz, 1H), 4.60 (t, $J = 1.9$ Hz, 2H), 4.46 (t, $J = 1.9$ Hz, 2H), 4.30 (d, $J = 0.6$ Hz, 5H), 2.34 (d, $J = 0.6$ Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 160.7$ (C_q), 138.9 (C_q), 135.5 (C_q), 134.2 (q, $^2J_{C-F} = 32$ Hz, C_q), 128.8 (CH), 127.3 (C_q), 123.79 (d, $^1J_{C-F} = 273$ Hz, C_q), 121.9 (q, $^3J_{C-F} = 3$ Hz, CH), 120.7 (q, $^3J_{C-F} = 4$ Hz, CH), 109.1 (C_q), 80.8 (C_q), 69.7 (CH), 69.5 (CH), 69.4 (CH), 13.9 (CH_3).
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.9$ (s).
IR (ATR, cm^{-1}): 3185, 3142, 1639, 1605, 1561, 1362, 1309, 1174, 1155, 1117, 914, 817, 795, 741, 704, 682, 491.
MS (EI): 411 (100) $[M]^+$, 346 (8) $[M-C_5H_5]^+$, 270 (5), 121 (5), 60 (4).
$[\mathbf{C_{21}H_{16}F_3FeNO}]^+$ (EI) HRMS: calcd.: 411.0533.
found: 411.0521.

Synthesis of 3-Ferrocenyl-4-methyl-6-nitroisoquinolin-1(2*H*)-one (86fw)



The general procedure **J** was followed using *N*-methoxy-4-nitrobenzamide (**84f**) (98 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1 → CH_2Cl_2/EtOAc: 2/1 → CH_2Cl_2) yielded **86fw** as a red solid (163 mg, 84%, decomposition > 230 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.99$ (s_{br}, 1H), 8.60 (d, $J = 8.7$ Hz, 1H), 8.52 (d, $J = 2.2$ Hz, 1H), 8.23 (dd, $J = 8.7$, 2.2 Hz, 1H), 4.59 (t, $J = 1.9$ Hz, 2H), 4.48 (t, $J = 1.9$ Hz, 2H), 4.31 (s, 5H), 2.36 (s, 3H).

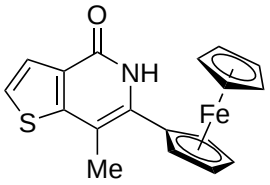
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 160.2$ (C_q), 150.6 (C_q), 139.6 (C_q), 136.6 (C_q), 129.8 (CH), 128.8 (C_q), 119.5 (CH), 119.0 (CH), 109.2 (C_q), 80.5 (C_q), 69.7 (CH), 69.6 (CH), 69.6 (CH), 14.0 (CH_3).

IR (ATR, cm^{-1}): 3174, 3083, 2861, 1646, 1605, 1521, 1337, 1296, 1106, 1069, 998, 852, 804, 735, 701, 481, 416.

MS (EI): 388 (100) $[M]^+$, 358 (20), 342 (22), 267 (16), 293 (11), 134 (25), 112 (15), 98 (46), 84 (23), 74 (27), 57 (61), 43 (77).

$[\mathbf{C_{20}H_{16}FeN_2O_3}]^+$ (EI) HRMS: calcd.: 388.0510.
found: 388.0503.

Synthesis of 6-Ferrocenyl-7-methylthieno[3,2-*c*]pyridin-4(5*H*)-one (86gw)



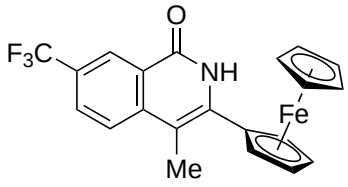
The general procedure **J** was followed using *N*-methoxythiophene-3-carboxamide (**84g**) (79 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 16 h, purification by column chromatography (CH_2Cl_2/EtOAc: 3/1) yielded **86gw** as an orange solid (137 mg, 78%, decomposition > 230 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.02$ (s_{br}, 1H), 7.68 (dd, $J = 5.3$, 0.6 Hz, 1H), 7.30 (dd, $J = 5.3$, 0.6 Hz, 1H), 4.64–4.54 (m, 2H), 4.47–4.39 (m, 2H), 4.26 (d, $J = 0.6$ Hz, 5H), 2.30 (d, $J = 0.6$ Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 158.3$ (C_q), 152.9 (C_q), 134.8 (C_q), 128.3 (C_q), 125.3 (CH), 124.0 (CH), 108.4 (C_q), 79.9 (C_q), 69.7 (CH), 69.3 (CH), 69.1 (CH), 16.1 (CH_3).

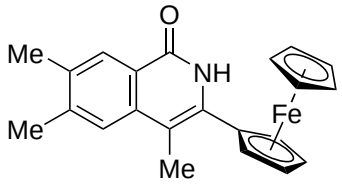
IR (ATR, cm^{-1}): 3112, 2982, 2939, 2914, 1628, 1583, 1522, 1263, 1175, 1103, 1038, 945, 869, 813, 762, 688, 622, 604, 515, 479, 441.
MS (EI): 349 (100) $[M]^+$, 284 (20) $[M-C_5H_5]^+$, 226 (5), 121 (14), 60 (10).
$[\mathbf{C_{18}H_{15}FeNOS}]^+$ (EI) HRMS: calcd.: 349.0224.
found: 349.0224.

Synthesis of 3-Ferrocenyl-4-methyl-7-(trifluoromethyl)isoquinolin-1(2*H*)-one (86hw)



The general procedure **J** was followed using *N*-methoxy-3-(trifluoromethyl)benzamide (**84h**) (110 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc: 3/1 → CH_2Cl_2/EtOAc: 3/1) yielded **86hw** as a red solid (177 mg, 86%, decomposition > 235 °C).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.06$ (s_{br}, 1H), 8.72 (d, $J = 1.9$ Hz, 1H), 7.86 (dd, $J = 8.8$, 1.9 Hz, 1H), 7.73 (d, $J = 8.8$ Hz, 1H), 4.58 (t, $J = 1.9$ Hz, 2H), 4.44 (t, $J = 1.9$ Hz, 2H), 4.27 (s, 5H), 2.30 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 160.9$ (C_q), 141.2 (C_q), 136.5 (C_q), 128.7 (q, $^3J_{C-F} = 3$ Hz, CH), 127.8 (q, $^2J_{C-F} = 33$ Hz, C_q), 125.4 (q, $^3J_{C-F} = 4$ Hz, CH), 124.9 (C_q), 124.2 (CH), 124.0 (d, $^1J_{C-F} = 272$ Hz, C_q), 108.9 (C_q), 80.7 (C_q), 69.7 (CH), 69.6 (CH), 69.5 (CH), 14.0 (CH_3).
^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -62.7$ (s).
IR (ATR, cm^{-1}): 3168, 3094, 2923, 1650, 1616, 1553, 1323, 1156, 115, 1084, 1000, 820, 792, 653, 625, 486, 472, 419.
MS (EI): 411 (100) $[M]^+$, 346 (5) $[M-C_5H_5]^+$, 270 (22), 244 (6), 121 (5), 60 (5), 43 (18).
$[\mathbf{C_{21}H_{16}F_3FeNO}]^+$ (EI) HRMS: calcd.: 411.0533.
found: 411.0536.

Synthesis of 3-Ferrocenyl-4,6,7-trimethylisoquinolin-1(2*H*)-one (86iw)



The general procedure **J** was followed using *N*-methoxy-3,4-dimethylbenzamide (**84i**) (90 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 16 h, purification by

column chromatography (CH_2Cl_2/EtOAc: 3/1) yielded **86iw** as an orange solid (155 mg, 83%, decomposition > 245 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.72 (s_{br}, 1H), 8.18 (s, 1H), 7.39 (s, 1H), 4.51 (t, J = 1.9 Hz, 2H), 4.38 (t, J = 1.9 Hz, 2H), 4.25 (s, 5H), 2.41 (s, 3H), 2.38 (s, 3H), 2.25 (s, 3H).

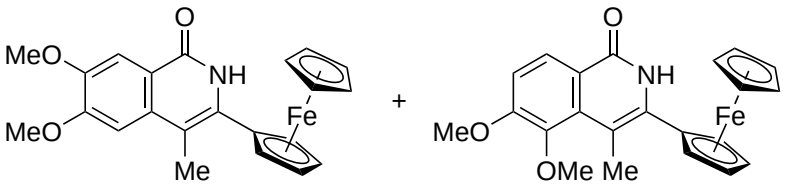
^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.5 (C_q), 142.5 (C_q), 137.0 (C_q), 135.4 (C_q), 132.4 (C_q), 127.8 (CH), 123.9 (CH), 123.1 (C_q), 109.3 (C_q), 81.7 (C_q), 69.5 (CH), 69.3 (CH), 68.9 (CH), 20.7 (CH_3), 19.7 (CH_3), 13.9 (CH_3).

IR (ATR, cm^{-1}): 3164, 3024, 2962, 2916, 2867, 1638, 1604, 1478, 1442, 1330, 1105, 1000, 905, 872, 807, 761, 718, 540, 483.

MS (EI): 371 (100) $[M]^+$, 306 (9) $[M-C_5H_5]$, 248 (8), 121 (10), 98 (8), 69 (7), 57 (8), 43 (23).

$[C_{22}H_{21}FeNO]^+$ (EI) HRMS: calcd.: 371.0973.
found: 371.0975.

Synthesis of 3-Ferrocenyl-6,7-dimethoxy-4-methylisoquinolin-1(2*H*)-one (86jw) and 4-Ferrocenyl-5,6-dimethoxy-4-methylisoquinolin-1(2*H*)-one (86jw')



The general procedure **J** was followed using *N*-methoxy-3,4-dimethoxybenzamide (**84j**) (106 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 16 h, purification by column chromatography (CH_2Cl_2/EtOAc: 3/2) yielded **86jw** as an orange solid (92 mg, 46%, decomposition > 240 °C) and **86jw'** as a brown-orange solid (12 mg, 6%, decomposition > 150 °C).

86jw:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.75 (s_{br}, 1H), 7.82 (s, 1H), 6.96 (s, 1H), 4.51 (t, J = 1.8 Hz, 2H), 4.38 (t, J = 1.8 Hz, 2H), 4.26 (s, 5H), 4.01 (s, 3H), 4.00 (s, 3H), 2.26 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.8 (C_q), 153.5 (C_q), 148.5 (C_q), 134.3 (C_q), 132.2 (C_q), 118.9 (C_q), 109.0 (C_q), 107.7 (CH), 103.9 (CH), 81.7 (C_q), 69.5 (CH), 69.3 (CH), 68.9 (CH), 56.2 (CH_3), 56.0 (CH_3), 14.2 (CH_3).

IR (ATR, cm^{-1}): 3076, 3001, 2960, 1631, 1604, 1509, 1435, 1263, 1213, 1072, 808, 782, 503, 470.

MS (ESI): 2442 (50) $[6M+H+Na]^+$, 2040 (73) $[5M+2H+Na]^+$, 1636 (100) $[4M+H+Na]^+$, 1232 (77) $[3M+Na]^+$, 807 (99) $[2M+H]^+$, 404 (19) $[M+H]^+$.

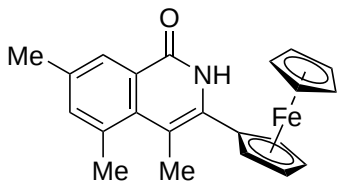
$[C_{22}H_{21}FeNO_3+H]^+$ (ESI) HRMS: calcd.: 404.0944.
found: 404.0942.

86jw':

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.70 (s_{br}, 1H), 8.26 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 4.50 (t, J = 1.9 Hz, 2H), 4.39 (t, J = 1.9 Hz, 2H), 4.27 (s, 5H), 3.97 (s, 3H), 3.81 (s, 3H),

2.42 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.9 (C_q), 156.6 (C_q), 144.7 (C_q), 133.7 (C_q), 133.5 (C_q), 124.9 (CH), 120.3 (C_q), 111.5 (CH), 109.0 (C_q), 82.4 (C_q), 69.9 (CH), 69.5 (CH), 68.9 (CH), 61.3 (CH_3), 56.1 (CH_3), 17.2 (CH_3).
IR (ATR, cm^{-1}): 2965, 2933, 1644, 1593, 1454, 1419, 1274, 1257, 1026, 809, 789, 724, 660, 502.
MS (EI): 2443 (5) $[6M+2H+Na]^+$, 2040 (15) $[5M+2H+Na]^+$, 1723 (27), 1636 (77), 1232 (73) $[3M+Na]^+$, 893 (26), 807 (100) $[2M+H]^+$, 426 (100) $[M+Na]^+$.
$[C_{22}H_{21}FeNO_3+H]^+$ (ESI) HRMS: calcd.: 404.0944.
found: 404.0949.

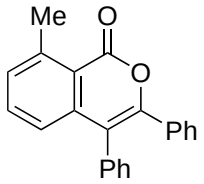
Synthesis of 3-Ferrocenyl-4,5,7-trimethylisoquinolin-1(2*H*)-one (86kw)



The general procedure **J** was followed using *N*-methoxy-3,5-dimethylbenzamide (**84k**) (90 mg, 0.50 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc: 3/1 → EtOAc) yielded **86kw** as a red solid (69 mg, 37%, decomposition > 183 °C).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (s_{br}, 1H), 8.16 (s, 1H), 7.28 (s, 1H), 4.50 (t, J = 1.8 Hz, 2H), 4.39 (t, J = 1.8 Hz, 2H), 4.26 (s, 5H), 2.71 (s, 3H), 2.40 (s, 3H), 2.37 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.6 (C_q), 138.4 (CH), 136.5 (C_q), 135.7 (C_q), 134.4 (C_q), 132.8 (C_q), 126.8 (C_q), 125.9 (CH), 110.6 (C_q), 82.3 (C_q), 69.8 (CH), 69.5 (CH), 68.9 (CH), 24.9 (CH_3), 20.9 (CH_3), 19.7 (CH_3).
IR (ATR, cm^{-1}): 3179, 3079, 2921, 2854, 1634, 1602, 1463, 1106, 1052, 1031, 1001, 807, 794, 724, 699, 479.
MS (EI): 371 (100) $[M]^+$, 304 (5), 248 (6), 213 (6), 169 (6), 121 (43), 115 (11), 56 (21).
$[C_{22}H_{21}FeNO]^+$ (EI) HRMS: calcd.: 371.0973.
found: 371.0967.

5.3.9 Syntheses of Isocoumarins 55

Synthesis of 8-Methyl-3,4-diphenyl-1*H*-isochromen-1-one (55aa)



The general procedure **K** was followed using *ortho*-toluic acid (**56a**) (272 mg, 2.00 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55a** as a white solid (245 mg, 78%, m.p.: 142–144 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.51$–7.37 (m, 4H), 7.35–7.28 (m, 3H), 7.27–7.14 (m, 5H), 7.01 (ddd, $J = 8.1$, 1.3, 0.7 Hz, 1H), 2.92 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.4$ (C_q), 150.5 (C_q), 143.4 (C_q), 140.4 (C_q), 134.9 (C_q), 133.7 (CH), 132.9 (C_q), 131.3 (CH), 131.0 (CH), 129.0 (CH), 129.0 (CH), 128.7 (CH), 128.0 (CH), 127.8 (CH), 123.6 (CH), 118.9 (C_q), 116.9 (C_q), 23.5 (CH_3).

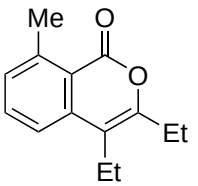
IR (ATR, cm^{-1}): 2929, 1727, 1623, 1564, 1487, 1467, 1443, 1304, 1201, 1089, 1028, 803, 762, 693, 670, 574, 548, 508, 490.

MS (EI): 312 (100) $[M]^+$, 297 (10) $[M-Me]^+$, 284 (25) $[M-CO]^+$, 235 (15) $[M-Ph]^+$, 207 (8), 179 (25), 152 (11), 105 (46), 77 (35) $[Ph]^+$, 51 (6).

$[\mathbf{C_{22}H_{16}O_2}]^+$ (EI) HRMS: calcd.: 312.1150.
found: 312.1145.

The spectral data are in accordance with those reported in the literature.[82]

Synthesis of 3,4-Diethyl-8-methyl-1*H*-isochromen-1-one (55af)



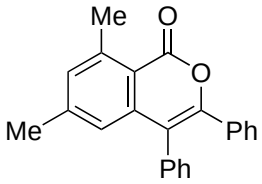
The general procedure **K** was followed using *ortho*-toluic acid (**56a**) (272 mg, 2.00 mmol) and 3-hexyne (**34f**) (82 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55af** as a colourless oil (168 mg, 78%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.53$ (dd, $J = 8.2$, 7.5 Hz, 1H), 7.35 (d, $J = 8.2$ Hz, 1H), 7.21 (dt, $J = 7.5$, 1.0 Hz, 1H), 2.80 (s, 3H), 2.58 (pent, $J = 7.5$ Hz, 4H), 1.24 (t, $J = 7.5$ Hz, 3H), 1.15 (t, $J = 7.5$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.2$ (C_q), 154.6 (C_q), 143.7 (C_q), 139.2 (C_q), 133.6 (CH), 130.0 (CH), 120.4 (CH), 119.3 (C_q), 112.8 (C_q), 23.9 (CH_2), 23.7 (CH_3), 19.6 (CH_2), 14.2 (CH_3), 12.5 (CH_3).

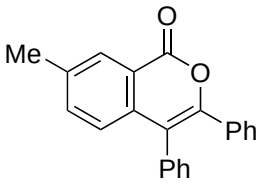
IR (ATR, cm^{-1}): 2969, 2933, 2876, 1715, 1648, 1591, 1571, 1469, 1299, 1268, 1180, 1126, 1073, 1022, 830, 805, 706, 680.
MS (EI): 216 (100) $[M]^+$, 201 (75) $[M-Me]^+$, 173 (30) $[M-Me-CO]^+$, 159 (31) $[M-Et-CO]^+$, 145 (13), 178 (65), 128 (16), 115 (39), 91 (15), 57 (15).
$[\mathbf{C_{14}H_{16}O_2}]^+$ (EI) HRMS: calcd.: 216.1150.
found: 216.1146.
The spectral data are in accordance with those reported in the literature.[110]

Synthesis of 6,8-Dimethyl-3,4-diphenyl-1*H*-isochromen-1-one (55ba)



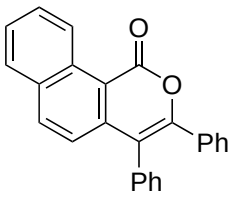
The general procedure **K** was followed using 2,4-dimethylbenzoic acid (**56b**) (300 mg, 2.00 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55ba** as a white solid (274 mg, 84%, m.p.: 158–161 °C).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.44$–7.35 (m, 3H), 7.33–7.27 (m, 2H), 7.26–7.20 (m, 2H), 7.20–7.09 (m, 4H), 6.78 (dq, $J = 1.6$, 0.7 Hz, 1H), 2.86 (s, 3H), 2.27 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.4$ (C_q), 150.5 (C_q), 144.5 (C_q), 143.2 (C_q), 140.4(C_q), 135.0 (C_q), 133.0 (C_q), 132.3(CH), 131.3 (CH), 129.0 (CH), 128.9 (CH), 128.6 (CH), 127.8 (CH), 127.6 (CH), 123.6 (CH), 116.8 (C_q), 116.4 (C_q), 23.3 (CH_3), 21.8 (CH_3).
IR (ATR, cm^{-1}): 3054, 2974, 2928, 1721, 1601, 1557, 1489, 1463, 1305, 1216, 1028, 1015, 1000, 854, 782, 767, 715, 695, 670.
MS (EI): 326 (100) $[M]^+$, 311 (18) $[M-Me]^+$, 298 (26) $[M-CO]^+$, 249 (15) $[M-Ph]^+$, 221 (13), 193 (24), 178 (13), 105 (36), 77 (28) $[Ph]^+$, 51 (4).
$[\mathbf{C_{23}H_{18}O_2}]^+$ (EI) HRMS: calcd.: 326.1307.
found: 326.1310.
The spectral data are in accordance with those reported in the literature.[110]

Synthesis of 7-Methyl-3,4-diphenyl-1*H*-isochromen-1-one (55ca)



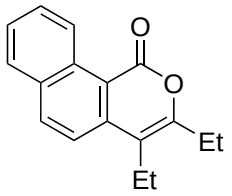
The general procedure **K** was followed using *meta*-toluic acid (**56c**) (272 mg, 2.00 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55ca** as a white solid (219 mg, 70%, m.p.: 170–173 °C).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.18$ (dt, $J = 1.7$, 0.8 Hz, 1H), 7.46–7.34 (m, 4H), 7.33–7.28 (m, 2H), 7.27–7.11 (m, 5H), 7.07 (d, $J = 8.2$ Hz, 1H), 2.44 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.3$ (C_q), 149.9 (C_q), 138.3 (C_q), 136.3 (C_q), 135.8 (CH), 134.3 (C_q), 132.9 (C_q), 131.1 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 127.9 (CH), 127.7 (CH), 125.2 (CH), 120.2 (C_q), 116.8 (C_q), 21.1 (CH_3).
IR (ATR, cm^{-1}): 3058, 1722, 1495, 1443, 1165, 1142, 1074, 963, 836, 786, 776, 693, 557, 496.
MS (EI): 312 (100) $[M]^+$, 284 (30) $[M-CO]^+$, 255 (28), 235 (40) $[M-Ph]^+$, 207 (13), 178 (17), 105 (51), 77 (23) $[Ph]^+$, 51 (4).
$[\mathbf{C_{22}H_{16}O_2}]^+$ (EI) HRMS: calcd.: 312.1150.
found: 312.1151.
The spectral data are in accordance with those reported in the literature.[82]

Synthesis of 3,4-Diphenyl-1*H*-benzo[*h*]isochromen-1-one (55da)



The general procedure **K** was followed using 1-naphthoic acid (**56d**) (344 mg, 2.00 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55da** as a white solid (112 mg, 32%, m.p.: 191–194 °C).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.85$ (dq, $J = 8.7$, 0.9 Hz, 1H), 7.98 (d, $J = 8.8$ Hz, 1H), 7.86 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.78 (ddd, $J = 8.6$, 6.9, 1.5 Hz, 1H), 7.61 (ddd, $J = 8.1$, 7.0, 1.2 Hz, 1H), 7.49–7.35 (m, 5H), 7.32–7.16 (m, 6H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.4$ (C_q), 152.5 (C_q), 141.0 (C_q), 135.8 (CH), 134.7 (C_q), 132.7 (C_q), 132.6 (C_q), 131.5 (C_q), 131.5(CH), 129.4 (CH), 129.2 (CH), 129.2 (CH), 129.1 (CH), 129.1 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.0 (CH), 122.6 (CH), 117.4 (C_q), 113.9 (C_q).
IR (ATR, cm^{-1}): 3054, 2922, 1708, 1591, 1489, 1229, 1216, 1157, 1100, 1049, 1021, 833, 803, 754, 733, 703, 692, 522, 502, 486.
MS (EI): 348 (100) $[M]^+$, 320 (18) $[M-CO]^+$, 289 (10), 271 (25), 215 (47), 105 (47), 77 (25) $[Ph]^+$, 43 (28).
$[\mathbf{C_{25}H_{16}O_2}]^+$ (EI) HRMS: calcd.: 348.1150.
found: 348.1155.
The spectral data are in accordance with those reported in the literature.[111]

Synthesis of 3,4-Diethyl-1*H*-benzo[*h*]isochromen-1-one (55df)



The general procedure **K** was followed using 1-naphthoic acid (**56d**) (344 mg, 2.00 mmol) and 3-hexyne (**34f**) (82 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55df** as a pale yellow solid (162 mg, 64%, m.p.: 133–136 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.75$ (dq, $J = 8.7$, 0.9 Hz, 1H), 8.05 (dt, $J = 8.9$, 0.6 Hz, 1H), 7.81 (ddt, $J = 8.0$, 1.2, 0.6 Hz, 1H), 7.69 (ddd, $J = 8.6$, 6.9, 1.5 Hz, 1H), 7.54 (ddd, $J = 8.1$, 6.9, 1.2 Hz, 1H), 7.54 (d, $J = 8.9$ Hz, 1H), 2.66 (q, $J = 7.5$ Hz, 4H), 1.29 (t, $J = 7.5$ Hz, 3H), 1.19 (t, $J = 7.5$ Hz, 3H).

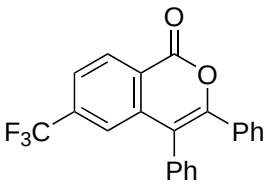
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.0$ (C_q), 156.8 (C_q), 140.1 (C_q), 135.9 (CH), 132.0 (C_q), 131.9 (C_q), 129.0 (CH), 128.2 (CH), 126.7 (CH), 126.4 (CH), 120.1 (CH), 114.0 (C_q), 113.5 (C_q), 24.2 (CH_2), 19.6 (CH_2), 14.5 (CH_3), 12.5 (CH_3).

IR (ATR, cm^{-1}): 2970, 2936, 1692, 1640, 1613, 1594, 1552, 1432, 1218, 1112, 1057, 993, 831, 769, 757, 503, 439.

MS (EI): 252 (100) $[M]^+$, 237 (40) $[M-Me]^+$, 209 (32) $[M-Me-CO]^+$, 195 (32) $[M-Et-CO]^+$, 181 (39), 165 (44), 152 (33), 57 (11).

$[\mathbf{C_{17}H_{16}O_2}]^+$ (EI) HRMS: calcd.: 252.1150.
found: 252.1147.

Synthesis of 3,4-Diphenyl-6-(trifluoromethyl)-1*H*-isochromen-1-one (55ea)



The general procedure **K** was followed using 4-(trifluoromethyl)benzoic acid (**56e**) (380 mg, 2.00 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55ea** as a white solid (91 mg, 25%, m.p.: 188–192 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.51$ (dt, $J = 8.2$, 0.8 Hz, 1H), 7.72 (ddd, $J = 8.3$, 1.7, 0.7 Hz, 1H), 7.50–7.38 (m, 4H), 7.35–7.28 (m, 2H), 7.28–7.14 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.1$ (C_q), 152.4 (C_q), 139.3 (C_q), 136.1 (q, $^2J_{C-F} = 33$ Hz, C_q), 133.2 (C_q), 132.3 (C_q), 131.0 (CH), 130.5 (CH), 129.4 (CH), 129.4 (CH), 129.2 (CH), 128.6

(CH), 127.9 (CH), 124.3 (q, $^{3}J_{C-F} = 4$ Hz, CH), 123.2 (d, $^{1}J_{C-F} = 272$ Hz, C_q), 122.7 (C_q), 122.3 (q, $^{3}J_{C-F} = 4$ Hz, CH), 116.3 (C_q).

^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -63.4$ (s).

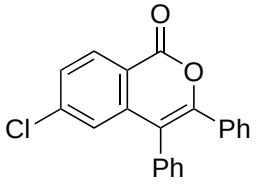
IR (ATR, cm^{-1}): 3064, 1734, 1622, 1564, 1484, 1427, 1313, 1124, 1071, 964, 905, 846, 779, 767, 691, 539, 508.

MS (EI): 366 (100) $[M]^+$, 338 (30) $[M-CO]^+$, 289 (25) $[M-Ph]^+$, 260 (13) $[M-Ph-F]^+$, 239 (13), 233 (16), 183 (7), 163 (7), 105 (46), 77 (40) $[Ph]^+$, 51 (6).

$[\mathbf{C_{22}H_{13}F_3O_2}]^+$ (EI) HRMS: calcd.: 366.0868.
found: 366.0874.

The spectral data are in accordance with those reported in the literature.[82]

Synthesis of 6-Chloro-3,4-diphenyl-1*H*-isochromen-1-one (55fa)



The general procedure **K** was followed using 4-chlorobenzoic acid (**56f**) (312 mg, 2.00 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55fa** as a pale yellow solid (155 mg, 47%, m.p.: 163–167 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.30$ (dd, $J = 8.5$, 0.4 Hz, 1H), 7.50–7.37 (m, 4H), 7.34–7.27 (m, 2H), 7.27–7.10 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.3$ (C_q), 152.2 (C_q), 141.5 (C_q), 140.3 (C_q), 133.5 (C_q), 132.5 (C_q), 131.2 (CH), 131.0 (CH), 129.2 (CH), 129.2 (CH), 129.2 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 124.9 (CH), 118.7 (C_q), 116.0 (C_q).

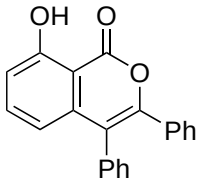
IR (ATR, cm^{-1}): 3065, 1725, 1590, 1473, 1461, 1444, 1311, 1192, 1093, 1072, 1047, 962, 772, 693, 662, 571, 546, 512.

MS (EI): 322 (100) $[M]^+$, 304 (26), 269 (17), 255 (28), 239 (23), 226 (10), 199 (16), 163 (27), 105 (76), 77 (66) $[Ph]^+$, 51 (13).

$[\mathbf{C_{21}H_{13}ClO_2}]^+$ (EI) HRMS: calcd.: 332.0604.
found: 332.0599.

The spectral data are in accordance with those reported in the literature.[82]

Synthesis of 8-Hydroxy-3,4-diphenyl-1*H*-isochromen-1-one (55ga)



The general procedure **K** was followed using 2-hydroxybenzoic acid (**56g**) (276 mg, 2.00 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **55ga** as a white solid (83 mg, 26%, m.p.: 151–153 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 11.28$ (d, $J = 0.4$ Hz, 1H), 7.51 (td, $J = 8.1$, 0.5 Hz, 1H), 7.42–7.36 (m, 3H), 7.33–7.27 (m, 2H), 7.25–7.14 (m, 5H), 6.99 (dd, $J = 8.3$, 1.0 Hz, 1H), 6.61 (dd, $J = 8.0$, 1.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.1$ (C_q), 161.7 (C_q), 150.3 (C_q), 139.4 (C_q), 137.1 (CH), 134.1 (C_q), 132.3 (C_q), 131.0 (CH), 129.1 (CH), 129.1 (CH), 129.0 (CH), 128.2 (CH), 127.9 (CH), 118.0 (C_q), 116.1 (CH), 115.3 (CH), 105.9 (C_q).

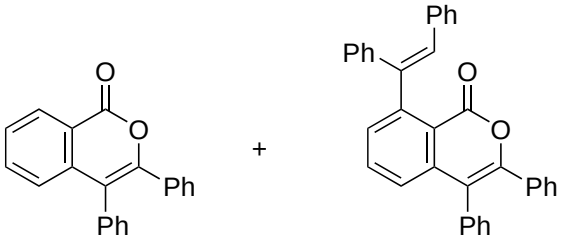
IR (ATR, cm^{-1}): 2925, 1678, 1611, 1563, 1454, 1240, 1196, 1111, 917, 745, 691, 681, 554, 522, 468.

MS (EI): 314 (100) $[M]^+$, 297 (9) $[M-OH]^+$, 286 (10) $[M-CO]^+$, 237 (26) $[M-Ph]^+$, 209 (9), 181 (12), 152 (18), 105 (64), 77 (30) $[Ph]^+$, 51 (5).

$[\mathbf{C_{21}H_{14}O_3}]^+$ (EI) HRMS: calcd.: 314.0943.
found: 314.0947.

The spectral data are in accordance with those reported in the literature.[110]

Synthesis of 3,4-Diphenyl-1*H*-isochromen-1-one (55ha) and 8-(1,2-Diphenylvinyl)-3,4-diphenyl-1*H*-isochromen-1-one (55ha')



The general procedure **K** was followed using benzoic acid (**56h**) (244 mg, 2.00 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55ha** as a white solid (252 mg, 84%, m.p.: 170–173 °C) and **55ha'** as a yellow oil (8 mg, 2%).

55ha:

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.38$ (ddd, $J = 7.9$, 1.5, 0.6 Hz, 1H), 7.61 (ddd, $J = 8.1$, 7.2, 1.5 Hz, 1H), 7.49 (ddd, $J = 7.8$, 7.3, 1.2 Hz, 1H), 7.44–7.36 (m, 3H), 7.36–7.29 (m, 2H), 7.28–7.22 (m, 2H), 7.22–7.12 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.1$ (C_q), 150.8 (C_q), 138.7 (C_q), 134.5 (CH), 134.2 (C_q), 132.8 (C_q), 131.1 (CH), 129.4 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.0 (CH), 128.0 (CH), 127.7 (CH), 125.2 (CH), 120.3 (C_q), 116.8 (C_q).

IR (ATR, cm^{-1}): 2923, 2852, 1723, 1603, 1479, 1443, 1077, 1021, 962, 781, 757, 710, 686, 668, 556, 540.

MS (EI): 298 (100) $[M]^+$, 270 (32) $[M-CO]^+$, 239 (20), 221 (31), 193 (10), 165 (29), 105 (56), 77 (36) $[Ph]^+$, 51 (6).

$[\mathbf{C_{21}H_{14}O_2}]^+$ (EI) HRMS: calcd.: 298.0994.
found: 298.0997.

The spectral data are in accordance with those reported in the literature.[82]

55ha':

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.59$ (dd, $J = 8.1$, 7.4 Hz, 1H), 7.49 (dd, $J = 7.4$, 1.4 Hz, 1H), 7.44–7.37 (m, 3H), 7.31–7.22 (m, 7H), 7.19–7.10 (m, 11H), 6.61 (s, 1H).

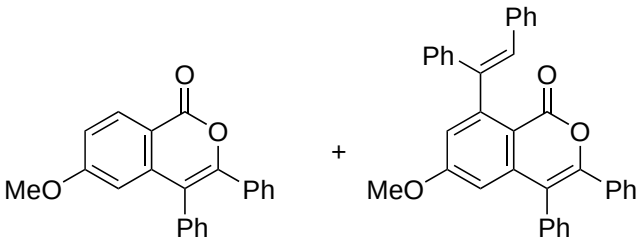
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.6$ (C_q), 151.0 (C_q), 147.7 (C_q), 143.0 (C_q), 140.5 (C_q), 139.3 (C_q), 137.4 (C_q), 134.8 (C_q), 133.5 (CH), 132.8 (C_q), 131.4 (CH), 131.3 (CH), 130.4 (CH), 129.4 (CH), 129.1 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 127.7 (CH), 127.1 (CH), 126.7 (CH), 125.0 (CH), 118.3 (C_q), 116.5 (C_q).

IR (ATR, cm^{-1}): 3049, 3024, 2923, 2852, 1736, 1578, 1564, 1490, 1444, 1211, 1074, 1024, 1011, 760, 691, 542.

MS (EI): 476 (100) $[M]^+$, 448 (53) $[M-CO]^+$, 399 (20) $[M-Ph]^+$, 385 (15), 371 (30), 339 (15), 298 (30), 265 (27), 239 (12), 221 (10), 165 (18), 105 (65), 77 (47) $[Ph]^+$.

$[\mathbf{C_{35}H_{24}O_2}]^+$ (EI) HRMS: calcd.: 476.1776.
found: 476.1775.

Synthesis of 6-Methoxy-3,4-diphenyl-1*H*-isochromen-1-one (55ia) and 8-(1,2-Diphenylvinyl)-6-methoxy-3,4-diphenyl-1*H*-isochromen-1-one (55ia')



The general procedure **K** was followed using 4-methoxybenzoic acid (**56i**) (304 mg, 2.00 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 16/1 → 10/1 → 5/1) yielded **55ia** as a white solid (268 mg, 82%, m.p.: 178–179 °C) and **55ia'** as a yellow oil (25 mg, 5%).

55ia:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35–8.25 (m, 1H), 7.42–7.34 (m, 3H), 7.33–7.27 (m, 2H), 7.26–7.11 (m, 5H), 7.03 (dd, J = 8.8, 2.5 Hz, 1H), 6.56 (d, J = 2.5 Hz, 1H), 3.72 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.5 (C_q), 161.9 (C_q), 151.4 (C_q), 141.1 (C_q), 134.3 (C_q), 132.9 (C_q), 131.8 (CH), 131.1 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.1 (CH), 127.7 (CH), 116.7 (C_q), 115.6 (CH), 113.6 (C_q), 108.4 (CH), 55.4 (CH_3).

IR (ATR, cm^{-1}): 3056, 3017, 2947, 1715, 1600, 1562, 1465, 1441, 1258, 1229, 1070, 1052, 1014, 850, 829, 780, 765, 724, 696, 676.

MS (EI): 328 (100) $[M]^+$, 300 (24) $[M-CO]^+$, 251 (28) $[M-Ph]^+$, 223 (10) $[M-CO-Ph]^+$, 195 (14), 152 (20), 105 (45), 77 (27) $[Ph]^+$, 51 (5).

$[\mathbf{C_{22}H_{16}O_3}]^+$ (EI) HRMS: calcd.: 328.1099.
found: 328.1100.

The spectral data are in accordance with those reported in the literature.[110]

55ia':

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.07 (m, 20H), 7.05 (d, J = 2.5 Hz, 1H), 6.62 (s, 1H), 6.55 (d, J = 2.6 Hz, 1H), 3.75 (s, 3H).

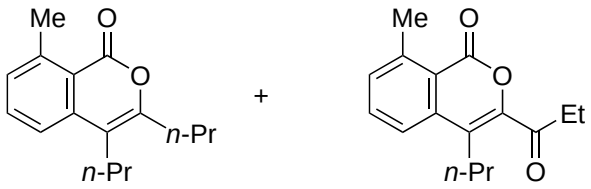
^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.2 (C_q), 159.2 (C_q), 151.4 (C_q), 150.1 (C_q), 142.9 (C_q), 142.9 (C_q), 139.1 (C_q), 137.3 (C_q), 134.9 (C_q), 132.9 (C_q), 131.3 (CH), 130.4 (CH), 129.4 (CH), 129.1 (CH), 129.1 (CH), 128.8 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 127.7 (CH), 127.1 (CH), 126.8 (CH), 118.6 (CH), 116.4 (C_q), 111.8 (C_q), 108.3 (CH), 55.5 (CH_3).

IR (ATR, cm^{-1}): 3055, 2954, 2927, 2859, 1731, 1584, 1445, 1320, 1258, 1204, 1155, 1049, 1025, 932, 763, 723, 690.

MS (EI): 506 (100) $[M]^+$, 478 (40) $[M-CO]^+$, 429 (40) $[M-Ph]^+$, 401 (25) $[M-CO-Ph]^+$, 252 (13), 105 (41), 77 (30) $[Ph]^+$.

$[\mathbf{C_{36}H_{26}O_3}]^+$ (EI) HRMS: calcd.: 506.1882.
found: 506.1881.

Synthesis of 8-Methyl-3,4-di-*n*-propyl-1*H*-isochromen-1-one (55ag) and 8-Methyl-3-propionyl-4-*n*-propyl-1*H*-isochromen-1-one (55ag')

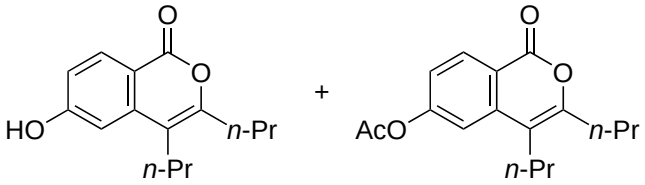


The general procedure **K** was followed using *ortho*-toluic acid (**56a**) (272 mg, 2.00 mmol) and 4-octyne (**34g**) (110 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **55ag** as a pale yellow oil (162 mg, 66%) and **55ag'** as a yellow oil (9 mg, 3%).

55ag:

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.53$ (dd, $J = 8.1$, 7.4 Hz, 1H), 7.33 (d, $J = 8.1$ Hz, 1H), 7.21 (dt, $J = 7.4$, 1.0 Hz, 1H), 2.80 (s, 3H), 2.60–2.46 (m, 4H), 1.71 (dq, $J = 14.8$, 7.4 Hz, 2H), 1.55 (dq, $J = 15.0$, 7.4 Hz, 2H), 1.00 (t, $J = 7.4$ Hz, 3H), 0.97 (t, $J = 7.4$ Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.2$ (C_q), 153.8 (C_q), 143.7 (C_q), 139.4 (C_q), 133.6 (CH), 130.0 (CH), 120.6 (CH), 119.3 (C_q), 112.0 (C_q), 32.6 (CH_2), 28.5 (CH_2), 23.7 (CH_3), 22.7 (CH_2), 21.1 (CH_2), 14.1 (CH_3), 13.8 (CH_3).
IR (ATR, cm^{-1}): 2961, 2931, 2872, 1714, 1593, 1572, 1469, 1300, 1265, 1180, 1128, 1083, 1022, 805, 784, 702.
MS (EI): 244 (70) $[M]^+$, 215 (100) $[M-Et]^+$, 159 (10), 145 (76), 128 (10), 115 (27), 43 (11).
$\mathbf{[C_{16}H_{20}O_2]^+}$ (EI) HRMS: calcd.: 244.1463.
found: 244.1463.
The spectral data are in accordance with those reported in the literature.[110]
55ag':
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.70$–7.61 (m, 2H), 7.41 (ddt, $J = 5.7$, 3.1, 0.8 Hz, 1H), 3.06–2.93 (m, 4H), 2.84 (d, $J = 0.8$ Hz, 3H), 1.69–1.54 (m, 2H), 1.15 (t, $J = 7.2$ Hz, 3H), 1.05 (t, $J = 7.3$ Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 197.6$ (C_q), 159.9 (C_q), 145.2 (C_q), 144.1 (C_q), 138.3 (C_q), 134.0 (CH), 133.0 (CH), 123.2 (CH), 122.4 (C_q), 121.4 (C_q), 33.7 (CH_2), 27.3 (CH_2), 23.6 (CH_3), 23.2 (CH_2), 14.2 (CH_3), 7.5 (CH_3).
IR (ATR, cm^{-1}): 2966, 2932, 2872, 1726, 1693, 1605, 1587, 1455, 1306, 1147, 1031, 801, 786, 701, 669.
MS (EI): 258 (15) $[M]^+$, 202 (100), 173 (15), 145 (47), 129 (11), 119 (10), 115 (26), 105 (7), 91 (7), 54 (18).
$\mathbf{[C_{16}H_{18}O_3 + H]^+}$ (ESI) HRMS: calcd.: 259.1329.
found: 259.1334.

Synthesis 6-Hydroxy-3,4-di-*n*-propyl-1*H*-isochromen-1-one (55jg) and 1-Oxo-3,4-di-*n*-propyl-1*H*-isochromen-6-yl Acetate (55jg')



The general procedure **K** was followed using 4-acetoxybenzoic acid (**56j**) (360 mg, 2.00 mmol) and 4-octyne (**34g**) (110 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **55jg** as a white solid (138 mg, 56%, m.p.: 131–135 °C) and **55jg'** as a colourless oil (16 mg, 6%).
55jg:
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.69$ (s_{br}, 1H), 8.18 (d, $J = 8.7$ Hz, 1H), 7.07 (dd, $J = 8.7$,

2.2 Hz, 1H), 7.00 (d, J = 2.2 Hz, 1H), 2.57–2.45 (m, 4H), 1.74–1.60 (m, 2H), 1.59–1.45 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.1 (C_q), 162.9 (C_q), 154.2 (C_q), 140.7 (C_q), 132.2 (CH), 116.5 (CH), 112.8 (C_q), 112.7 (C_q), 108.1 (CH), 32.7 (CH_2), 28.3 (CH_2), 22.7 (CH_2), 21.2 (CH_2), 14.2 (CH_3), 13.8 (CH_3).

IR (ATR, cm^{-1}): 3124, 2963, 2934, 2873, 1674, 1613, 1557, 1471, 1340, 1261, 1207, 1150, 1105, 867, 782, 692.

MS (EI): 246 (40) $[M]^+$, 217 (100) $[M-Et]^+$, 189 (10) $[M-Et-CO]^+$, 175 (8) $[M-n\text{-}Pr-CO]^+$, 161 (21), 147 (65), 119 (12), 91 (11), 43 (39).

$[\mathbf{C_{15}H_{18}O_3}]^+$ (EI) HRMS: calcd.: 246.1256.
found: 246.1259.

The spectral data are in accordance with those reported in the literature.[110]

55jg':

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (dd, J = 8.5, 0.5 Hz, 1H), 7.20–7.13 (m, 2H), 2.58–2.47 (m, 4H), 2.33 (s, 3H), 1.78–1.64 (m, 2H), 1.62–1.48 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H).

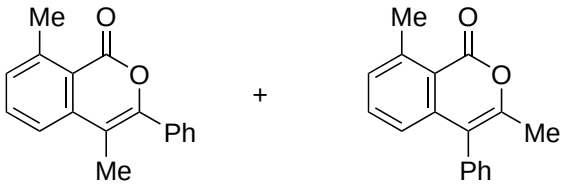
^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.5 (C_q), 162.0 (C_q), 155.5 (C_q), 155.0 (C_q), 139.8 (C_q), 131.7 (CH), 120.9 (CH), 118.3 (C_q), 115.2 (CH), 111.9 (C_q), 32.8 (CH_2), 28.3 (CH_2), 22.8 (CH_2), 21.3 (CH_3), 21.2 (CH_2), 14.2 (CH_3), 13.8 (CH_3).

IR (ATR, cm^{-1}): 2962, 2933, 2873, 1767, 1720, 1639, 1611, 1487, 1369, 1315, 1179, 1156, 1080, 1011, 917, 783, 732, 692.

MS (EI): 288 (45) $[M]^+$, 259 (432) $[M-Et]^+$, 246 (46), 217 (100), 189 (11), 161 (12), 147 (38), 43 (38).

$[\mathbf{C_{17}H_{20}O_4}]^+$ (EI) HRMS: calcd.: 288.1362.
found: 288.1358.

Synthesis of 4,8-Dimethyl-3-phenyl-1*H*-isochromen-1-one (55ai) and 3,8-Dimethyl-4-phenyl-1*H*-isochromen-1-one (55ai')



The general procedure **K** was followed using *ortho*-toluic acid (**56a**) (272 mg, 2.00 mmol) and prop-1-ynylbenzene (**34i**) (116 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55ai** as a white solid (198 mg, 79%, m.p.: 136–138 °C) and **55ai'** as a white semi-solid (15 mg, 6%).

55ai:

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.64$–7.53 (m, 3H), 7.48–7.38 (m, 4H), 7.30 (dt, $J = 7.6$, 1.0 Hz, 1H), 2.85 (s, 3H), 2.24 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.6$ (C_q), 150.8 (C_q), 143.5 (C_q), 140.2 (C_q), 133.8 (CH), 133.3 (C_q), 130.8 (CH), 129.4 (CH), 129.1 (CH), 128.1 (CH), 121.3 (CH), 119.1 (C_q), 108.9 (C_q), 23.5 (CH_3), 13.0 (CH_3).

IR (ATR, cm^{-1}): 2925, 1716, 1592, 1471, 1376, 1243, 1183, 1093, 1047, 1026, 797, 786, 764, 962, 654, 480.

MS (EI): 250 (95) $[M]^+$, 222 (100) $[M-CO]^+$, 178 (17), 145 (7), 115 (21), 105 (59), 91 (9), 77 (41), 51 (10).

$[\mathbf{C_{17}H_{14}O_2}]^+$ (EI) HRMS: calcd.: 250.0994.
found: 250.0996.

The spectral data are in accordance with those reported in the literature.[259]

55ai':

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.51$–7.34 (m, 5H), 7.24–7.18 (m, 2H), 6.77 (d, $J = 8.2$ Hz, 1H), 2.84 (s, 3H), 2.06 (s, 3H).

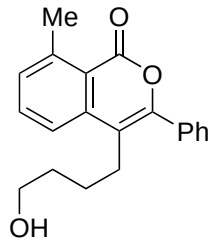
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.9$ (C_q), 151.3 (C_q), 143.4 (C_q), 140.3 (C_q), 135.2 (C_q), 133.6 (CH), 130.6 (CH), 130.3 (CH), 128.9 (CH), 127.9 (CH), 122.7 (CH), 118.5 (C_q), 116.3 (C_q), 23.5 (CH_3), 17.9 (CH_3).

IR (ATR, cm^{-1}): 3060, 2963, 2925, 2925, 1715, 1651, 1493, 1470, 1445, 1188, 1062, 1003, 804, 765, 699, 554, 510.

MS (EI): 250 (100) $[M]^+$, 235 (80) $[M-Me]^+$, 223 (12), 208 (40), 179 (54), 165 (18), 152 (17), 105 (11), 77 (11), 43 (27).

$[\mathbf{C_{17}H_{14}O_2}]^+$ (EI) HRMS: calcd.: 250.0994.
found: 250.0999.

Synthesis of 4-(4-Hydroxy-*n*-butyl)-8-methyl-3-phenyl-1*H*-isochromen-1-one (55am)



The general procedure **K** was followed using *ortho*-toluic acid (**56a**) (272 mg, 2.00 mmol) and 6-phenylhex-5-yn-1-ol (**34m**) (174 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 5/1 → 3/1) yielded **55am** as a white solid (213 mg, 69%, m.p.: 110–113 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.60$ (t, $J = 7.8$ Hz, 1H), 7.55–7.47 (m, 3H), 7.47–7.39 (m, 3H), 7.30 (d, $J = 7.3$ Hz, 1H), 3.57 (t, $J = 6.3$ Hz, 2H), 2.84 (s, 3H), 2.72–2.59 (m, 2H), 1.74–1.61

(m, 2H), 1.61–1.49 (m, 2H), 1.43 (s_{br}, 1H).

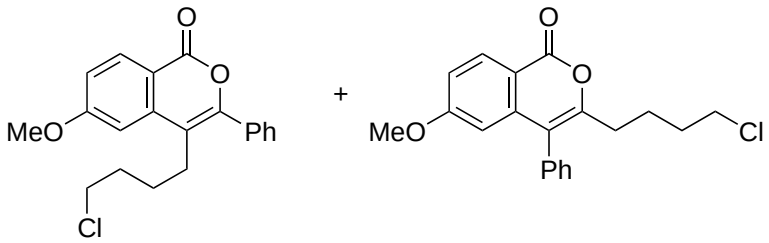
^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.6 (C_q), 151.4 (C_q), 143.9 (C_q), 139.1 (C_q), 133.8 (CH), 133.5 (C_q), 130.9 (CH), 129.3 (CH), 129.0 (CH), 128.3 (CH), 121.4 (CH), 119.7 (C_q), 113.6 (C_q), 62.2 (CH_2), 32.2 (CH_2), 26.7 (CH_2), 26.0 (CH_2), 23.7 (CH_3).

IR (ATR, cm^{-1}): 3531, 2931, 2860, 1705, 1640, 1569, 1445, 1387, 1293, 1219, 1182, 1096, 1074, 1052, 1037, 980, 808, 763, 697, 671, 483.

MS (EI): 308 (72) $[M]^+$, 249 (85) $[M-(CH_2)_3OH]^+$, 221 (100) $[M-CO-(CH_2)_3OH]^+$, 178 (34), 115 (17), 105 (32), 77 (38).

$[\mathbf{C_{20}H_{20}O_3}]^+$ (EI) HRMS: calcd.: 308.1412.
found: 308.1404.

Synthesis of 4-(4-Chloro-*n*-butyl)-6-methoxy-3-phenyl-1*H*-isochromen-1-one (55il) and 3-(4-Chloro-*n*-butyl)-6-methoxy-4-phenyl-1*H*-isochromen-1-one (55il')



The general procedure **K** was followed using 4-methoxybenzoic acid (**56i**) (304 mg, 2.00 mmol) and (6-chlorohex-1-ynyl)benzene (**34l**) (193 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55il** as a white solid (255 mg, 74%, m.p.: 79–83 °C) and **55il'** as a yellow solid (29 mg, 8%, m.p.: 64–68 °C).

55il:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (d, J = 8.8 Hz, 1H), 7.55–7.39 (m, 5H), 7.06 (dd, J = 8.8, 2.4 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 3.93 (s, 3H), 3.48 (t, J = 5.9 Hz, 2H), 2.71–2.58 (m, 2H), 1.83–1.74 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8 (C_q), 162.0 (C_q), 152.5 (C_q), 139.8 (C_q), 133.4 (C_q), 132.3 (CH), 129.4 (CH), 129.0 (CH), 128.4 (CH), 115.3 (CH), 114.4 (C_q), 113.1 (C_q), 106.7 (CH), 55.7 (CH_3), 44.3 (CH_2), 31.9 (CH_2), 26.5 (CH_2), 26.0 (CH_2).

IR (ATR, cm^{-1}): 2954, 1718, 1604, 1488, 1253, 1232, 1098, 1078, 1027, 909, 771, 726, 696.

MS (EI): 342 (60) $[M]^+$, 265 (100) $[M-CO-(CH_2)_3Cl]^+$, 237 (85) $[M-CO-(CH_2)_3Cl]^+$, 194 (15), 165 (15), 105 (27), 77 (36).

$[\mathbf{C_{20}H_{19}ClO_3}]^+$ (EI) HRMS: calcd.: 342.1023.
found: 342.1029.

55il:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (d, J = 8.8 Hz, 1H), 7.51–7.37 (m, 3H), 7.29–7.19 (m, 2H), 6.98 (dd, J = 8.8, 2.5 Hz, 1H), 6.31 (d, J = 2.5 Hz, 1H), 3.70 (s, 3H), 3.40 (t, J = 6.4 Hz, 2H), 2.36 (t, J = 7.2 Hz, 2H), 1.86–1.62 (m, 4H).

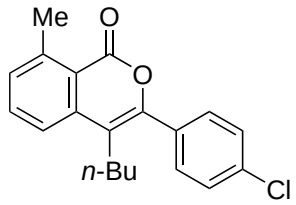
^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.5 (C_q), 162.2 (C_q), 154.6 (C_q), 140.9 (C_q), 134.1 (C_q), 131.7 (CH), 130.4 (CH), 128.9 (CH), 128.2 (CH), 116.5 (C_q), 115.0 (CH), 113.2 (C_q), 107.9 (CH), 55.4 (CH_3), 44.4 (CH_2), 31.9 (CH_2), 30.6 (CH_2), 24.9 (CH_2).

IR (ATR, cm^{-1}): 2933, 2870, 1710, 1609, 1566, 1491, 1327, 1272, 1255, 1227, 1118, 1041, 1021, 1005, 768, 718, 701, 678, 538, 501.

MS (EI): 342 (100) $[M]^+$, 251 (70) $[M-CO-(CH_2)_2Cl]^+$, 237 (24) $[M-CO-(CH_2)_3Cl]^+$, 224 (53), 195 (30), 181 (15), 165 (19), 152 (45), 55 (25).

$[\mathbf{C_{20}H_{19}ClO_3}]^+$ (EI) HRMS: calcd.: 342.1023.
found: 342.1030.

Synthesis of 4-*n*-Butyl-3-(4-chlorophenyl)-8-methyl-1*H*-isochromen-1-one (55ay)



The general procedure **K** was followed using *ortho*-toluic acid (**56a**) (272 mg, 2.00 mmol) and 1-chloro-4-(hex-1-ynyl)benzene (**34y**) (193 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 30/1) yielded **55ay** as a white solid (229 mg, 70%, m.p.: 97–100 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (t, J = 7.8 Hz, 1H), 7.50–7.38 (m, 5H), 7.30 (d, J = 7.4 Hz, 1H), 2.84 (s, 3H), 2.65–2.54 (m, 2H), 1.60–1.54 (m, 2H), 1.33 (dq, J = 14.6, 7.3 Hz, 2H), 0.87 (t, J = 7.3 Hz, 3H).

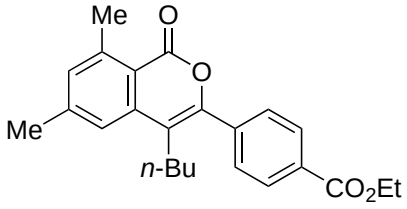
^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.2 (C_q), 149.9 (C_q), 143.8 (C_q), 139.0 (C_q), 135.1 (C_q), 133.7 (CH), 131.9 (C_q), 130.9 (CH), 130.3 (CH), 128.5 (CH), 121.4 (CH), 119.7 (C_q), 114.2 (C_q), 32.0 (CH_2), 26.9 (CH_2), 23.7 (CH_3), 22.7 (CH_2), 13.8 (CH_3).

IR (ATR, cm^{-1}): 2954, 2928, 2867, 1717, 1590, 1302, 1284, 1093, 1078, 1032, 1016, 843, 801, 729, 701, 672, 502.

MS (EI): 326 (58) $[M]^+$, 283 (55) $[M-n\text{-Pr}]^+$, 248 (100) $[M-n\text{-Pr}-Cl]^+$, 192 (16), 139 (23), 115 (18), 111 (22).

$[\mathbf{C_{20}H_{19}ClO_2}]^+$ (EI) HRMS: calcd.: 326.1074.
found: 326.1066.

Synthesis of Ethyl 4-(4-*n*-Butyl-6,8-dimethyl-1-oxo-1*H*-isochromen-3-yl)benzoate (55br)



The general procedure **K** was followed using 2,4-dimethylbenzoic acid (**56b**) (300 mg, 2.00 mmol) and ethyl 4-(hex-1-yn-1-yl)benzoate (**34r**) (230 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55br** as a white solid (254 mg, 67%, m.p.: 110–113 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.10$ (d, $J = 8.6$ Hz, 2H), 7.60 (d, $J = 8.6$ Hz, 2H), 7.24 (s, 1H), 7.15 (s, 1H), 4.39 (q, $J = 7.1$ Hz, 2H), 2.81 (s, 3H), 2.64–2.55 (m, 2H), 2.46 (s, 3H), 1.58 (dt, $J = 15.3$, 7.5 Hz, 2H), 1.40 (t, $J = 7.1$ Hz, 3H), 1.31 (dt, $J = 14.6$, 7.4 Hz, 2H), 0.86 (t, $J = 7.3$ Hz, 3H).

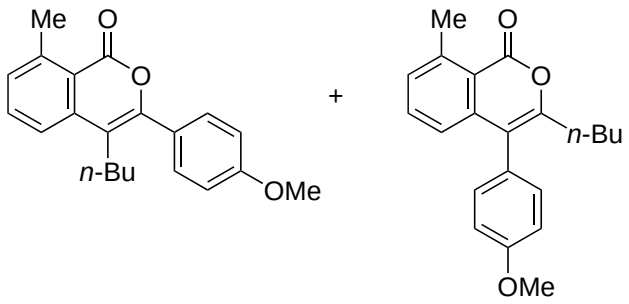
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.9$ (C_q), 161.3 (C_q), 150.0 (C_q), 144.5 (C_q), 143.7 (C_q), 138.9 (C_q), 137.8 (C_q), 132.4 (CH), 130.8 (C_q), 129.3 (CH), 128.9 (CH), 121.7 (CH), 117.3 (C_q), 114.5 (C_q), 61.1 (CH_2), 31.9 (CH_2), 26.6 (CH_2), 23.4 (CH_3), 22.5 (CH_2), 22.0 (CH_3), 14.2 (CH_3), 13.6 (CH_3).

IR (ATR, cm^{-1}): 2960, 2934, 2874, 1709, 1605, 1471, 1268, 1180, 1102, 1081, 1040, 1020, 864, 775, 722, 699, 666, 630, 560, 494.

MS (EI): 378 (100) $[M]^+$, 335 (14) $[M-n\text{-Pr}]^+$, 307 (23) $[M-n\text{-Pr}-CO]^+$, 291 (10), 263 (86), 247 (12), 235 (18), 191 (10), 177 (10), 145 (13).

$[\mathbf{C_{24}H_{26}O_4}]^+$ (EI) HRMS: calcd.: 378.1831.
found: 378.1827.

Synthesis of 4-*n*-Butyl-3-(4-methoxyphenyl)-8-methyl-1*H*-isochromen-1-one (55an) and 3-*n*-Butyl-4-(4-methoxyphenyl)-8-methyl-1*H*-isochromen-1-one (55an')



The general procedure **K** was followed using *ortho*-toluic acid (**56a**) (272 mg, 2.00 mmol) and 1-(hex-1-ynyl)-4-methoxybenzene (**34n**) (188 mg, 1.00 mmol). After 18 h, purification by column

chromatography (*n*-hexane/EtOAc: 20/1) yielded **55an** as a pale yellow solid (175 mg, 54%, m.p.: 70–75 °C) and **55an'** as a yellow oil (16 mg, 5%).

55an:

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.62$–7.56 (m, 1H), 7.50–7.42 (m, 1H), 7.47 (d, $J = 8.9$ Hz, 2H), 7.28 (ddd, $J = 7.4$, 1.2, 0.7 Hz, 1H), 6.95 (d, $J = 8.9$ Hz, 2H), 3.85 (s, 3H), 2.85 (s, 3H), 2.68–2.58 (m, 2H), 1.65–1.52 (m, 2H), 1.34 (dq, $J = 14.5$, 7.3 Hz, 2H), 0.87 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.8$ (C_q), 160.1 (C_q), 151.2 (C_q), 143.7 (C_q), 139.5 (C_q), 133.7 (CH), 130.6 (CH), 130.4 (CH), 126.1 (C_q), 121.4 (CH), 119.6 (C_q), 113.6 (CH), 113.4 (C_q), 55.3 (CH_3), 32.0 (CH_2), 26.9 (CH_2), 23.7 (CH_3), 22.7 (CH_2), 13.8 (CH_3).

IR (ATR, cm^{-1}): 2949, 2921, 2871, 1710, 1626, 1607, 1586, 1567, 1510, 1468, 1450, 1329, 1227, 1094, 1039, 909, 834, 704, 536.

MS (EI): 322 (50) $[M]^+$, 294 (30) $[M-CO]^+$, 279 (35) $[M-CO-Me]^+$, 251 (100) $[M-CO-n\text{-Pr}]$, 208 (10), 165 (6), 135 (20), 115 (11), 92 (6), 77 (8).

$\mathbf{[C_{21}H_{22}O_3]^+}$ (EI) HRMS: calcd.: 322.1569.
found: 322.1565.

55an':

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.37$ (t, $J = 7.7$ Hz, 1H), 7.20 (dt, $J = 7.5$, 1.1 Hz, 1H), 7.12 (d, $J = 8.7$ Hz, 2H), 6.98 (d, $J = 8.7$ Hz, 2H), 6.77 (ddd, $J = 8.1$, 1.3, 0.7 Hz, 1H), 3.86 (s, 3H), 2.84 (s, 3H), 2.37–2.23 (m, 2H), 1.66–1.53 m, 2H), 1.24 (dq, $J = 14.6$, 7.3 Hz, 2H), 0.80 (t, $J = 7.3$ Hz, 3H).

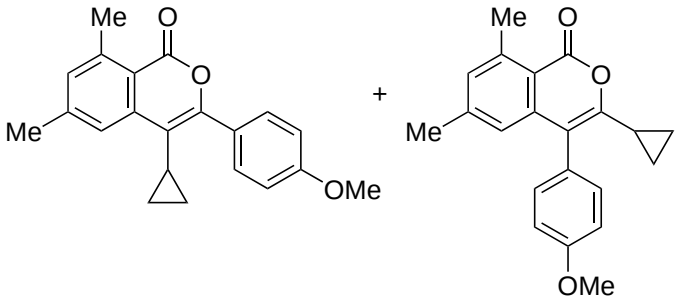
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.1$ (C_q), 159.2 (C_q), 155.1 (C_q), 143.3 (C_q), 140.8 (C_q), 133.5 (CH), 131.8 (CH), 130.2 (CH), 127.1 (C_q), 123.0 (CH), 118.5 (C_q), 115.8 (C_q), 114.2 (CH), 55.3 (CH_3), 31.0 (CH_2), 29.7 (CH_2), 23.5 (CH_3), 22.2 (CH_2), 13.8 (CH_3).

IR (ATR, cm^{-1}): 2958, 2932, 2872, 1766, 1722, 1598, 1510, 1250, 1172, 1024, 835, 756, 600, 524.

MS (EI): 322 (100) $[M]^+$, 265 (100) $[M-n\text{-Bu}]^+$, 253 (43), 237 (76), 209 (30), 165 (35), 135 (15), 57 (13).

$\mathbf{[C_{21}H_{22}O_3]^+}$ (EI) HRMS: calcd.: 322.1569.
found: 322.1581.

Synthesis of 4-Cyclopropyl-3-(4-methoxyphenyl)-6,8-dimethyl-1*H*-isochromen-1-one (55bt) and 3-Cyclopropyl-4-(4-methoxyphenyl)-6,8-dimethyl-1*H*-isochromen-1-one (55bt')



The general procedure **K** was followed using 2,4-dimethylbenzoic acid (**56b**) (300 mg, 2.00 mmol) and 1-(cyclopropylethynyl)-4-methoxybenzene (**34t**) (172 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1 → 15/1) yielded **55bt** as a white solid (181 mg, 56%, m.p.: 156–159 °C) and **55bt'** as a yellow oil (21 mg, 7%).

55bt:

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.71$ (s, 1H), 7.66 (d, $J = 8.9$ Hz, 2H), 7.08 (s, 1H), 6.92 (d, $J = 8.9$ Hz, 2H), 3.84 (s, 3H), 2.78 (s, 3H), 2.45 (s, 3H), 1.86–1.74 (m, 1H), 0.95–0.86 (m, 2H), 0.19–0.10 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 161.7$ (C_q), 160.1 (C_q), 153.1 (C_q), 144.2 (C_q), 142.9 (C_q), 141.5 (C_q), 131.7 (CH), 130.9 (CH), 125.8 (C_q), 122.5 (CH), 116.4 (C_q), 113.3 (C_q), 113.0 (CH), 55.2 (CH_3), 23.2 (CH_3), 22.0 (CH_3), 10.3 (CH_2), 9.5 (CH).

IR (ATR, cm^{-1}): 2960, 2927, 2835, 1708, 1600, 1513, 1459, 1250, 1176, 1071, 1030, 835, 798, 670, 525.

MS (EI): 320 (75) $[M]^+$, 305 (45) $[M-Me]^+$, 276 (66) $[M-CO_2]^+$, 261 (100) $[M-Me-CO_2]^+$, 245 (60), 141 (26), 135 (87), 128 (25), 115 (22), 92 (30), 77 (43) $[Ph]^+$, 43 (29).

$[\mathbf{C_{21}H_{20}O_3}]^+$ (EI) HRMS: calcd.: 320.1412.
found: 320.1418.

55bt':

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.23$ (d, $J = 8.8$ Hz, 2H), 7.01 (d, $J = 8.8$ Hz, 2H), 6.98 (s, 1H), 6.57 (s, 1H), 3.87 (s, 3H), 2.76 (s, 3H), 2.24 (s, 3H), 1.63–1.51 (m, 1H), 1.16–1.07 (m, 2H), 0.80–0.65 (m, 2H).

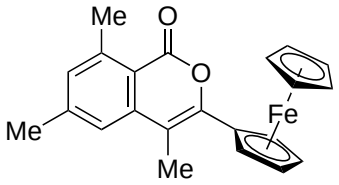
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 161.6$ (C_q), 159.1 (C_q), 154.1 (C_q), 144.4 (C_q), 143.1 (C_q), 141.0 (C_q), 132.3 (CH), 131.0 (CH), 127.1 (C_q), 122.4 (CH), 115.8 (C_q), 114.6 (C_q), 114.3 (CH), 55.3 (CH_3), 23.3 (CH_3), 21.8 (CH_3), 11.7 (CH), 7.2 (CH_2).

IR (ATR, cm^{-1}): 3009, 2925, 2837, 1717, 1637, 1605, 1561, 1511, 1287, 1240, 1174, 1029, 995, 835, 730, 677, 566, 532.

MS (EI): 320 (100) $[M]^+$, 305 (29) $[M-Me]^+$, 292 (30) $[M-CO]^+$, 277 (30) $[M-Me-(CH_2)_2]^+$, 251 (47) $[M-CO-C_3H_5]$, 223 (33), 178 (15), 165 (22), 70 (13), 41 (16).

$[\mathbf{C_{21}H_{20}O_3}]^+$ (EI) HRMS: calcd.: 320.1412.
found: 320.1415.

Synthesis of 3-Ferrocenyl-4,6,8-trimethyl-1*H*-isochromen-1-one (55bw)



The general procedure **K** was followed using 2,4-dimethylbenzoic acid (**56b**) (300 mg, 2.00 mmol) and 1-propyn-1-yl-ferrocene (**34w**) (224 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **55bw** as an orange solid (60 mg, 16%, m.p.: 140–143 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.16$ (s, 1H), 7.08 (s, 1H), 4.71 (t, $J = 1.9$ Hz, 2H), 4.36 (t, $J = 1.9$ Hz, 2H), 4.20 (s, 5H), 2.81 (s, 3H), 2.43 (s, 3H), 2.27 (s, 3H).

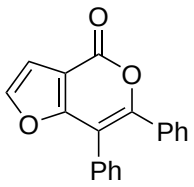
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.7$ (C_q), 150.8 (C_q), 144.4 (C_q), 143.4 (C_q), 140.8 (C_q), 131.4 (CH), 121.1 (CH), 116.4 (C_q), 107.5 (C_q), 78.3 (C_q), 69.7 (CH), 69.5 (CH), 69.2 (CH), 23.4 (CH_3), 22.0 (CH_3), 13.7 (CH_3).

IR (ATR, cm^{-1}): 2959, 2919, 1717, 1629, 1604, 1560, 1303, 1255, 1232, 1121, 1066, 1038, 996, 848, 820, 795, 675, 479.

MS (EI): 372 (100) $[M]^+$, 263 (9), 179 (9), 165 (6), 121 (16), 60 (10).

$[\mathbf{C_{22}H_{20}FeO_2}]^+$ (EI) HRMS: calcd.: 372.0813.
found: 372.0813.

Synthesis of 6,7-Diphenyl-4*H*-furo[3,2-*c*]pyran-4-one (55ka)



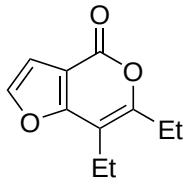
The general procedure **K** was followed using furan-3-carboxylic acid (**56k**) (224 mg, 2.00 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55ka** as a white solid (191 mg, 66%, m.p.: 185–188 °C).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.49$ (d, $J = 2.0$ Hz, 1H), 7.40–7.16 (m, 10H), 6.96 (d, $J = 2.0$ Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.2$ (C_q), 158.8 (C_q), 155.1 (C_q), 144.5 (CH), 131.8 (C_q), 130.5 (C_q), 130.3 (CH), 129.6 (CH), 129.3 (CH), 128.8 (CH), 128.4 (CH), 128.0 (CH), 110.6 (C_q), 109.5 (C_q), 107.8 (CH).

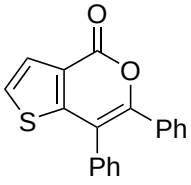
IR (ATR, cm^{-1}): 3148, 3124, 3055, 2923, 1739, 1547, 1493, 1441, 1368, 1144, 1097, 1067, 990, 939, 888, 776, 744, 717, 691, 587, 538, 523, 492.
MS (EI): 288 (100) $[M]^+$, 260 (11) $[M-CO]^+$, 231 (13), 211 (35) $[M-Ph]^+$, 182 (15), 126 (13), 105 (35), 77 (47) $[Ph]^+$, 51 (12).
$[\mathbf{C_{19}H_{12}O_3}]^+$ (EI) HRMS: calcd.: 288.0786.
found: 288.0789.
The spectral data are in accordance with those reported in the literature.[259]

Synthesis of 6,7-Diethyl-4*H*-furo[3,2-*c*]pyran-4-one (55kg)



The general procedure **K** was followed using furan-3-carboxylic acid (**56k**) (224 mg, 2.00 mmol) and 3-hexyne (**34g**) (82 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 15/1) yielded **55kg** as a white solid (108 mg, 56%, m.p.: 119–112 °C).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.45$ (d, $J = 2.1$ Hz, 1H), 6.82 (d, $J = 2.1$ Hz, 1H), 2.58 (q, $J = 7.5$ Hz, 4H), 1.22 (t, $J = 7.5$ Hz, 3H), 1.17 (t, $J = 7.6$ Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.4$ (C_q), 160.1 (C_q), 159.8 (C_q), 143.5 (CH), 109.0 (C_q), 108.6 (C_q), 107.6 (CH), 23.6 (CH_2), 17.8 (CH_2), 14.3 (CH_3), 12.6 (CH_3).
IR (ATR, cm^{-1}): 3133, 3115, 2933, 1705, 1567, 1469, 1367, 1231, 1128, 1046, 980, 943, 896, 761, 591, 448.
MS (EI): 192 (65) $[M]^+$, 177 (100) $[M-Me]^+$, 135 (22), 121 (20), 79 (15), 77 (27), 57 (18).
$[\mathbf{C_{11}H_{12}O_3}]^+$ (EI) HRMS: calcd.: 192.0786.
found: 192.0784.

Synthesis of 6,7-Diphenyl-4*H*-thieno[3,2-*c*]pyran-4-one (55la)



The general procedure **K** was followed using thiophene-3-carboxylic acid (**56l**) (256 mg, 2.00 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55la** as a pale yellow solid (282 mg, 93%, m.p.: 159–163 °C).
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.64$ (d, $J = 5.4$ Hz, 1H), 7.41–7.29 (m, 8H), 7.28–7.14 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.2 (C_q), 154.6 (C_q), 151.7 (C_q), 134.8 (C_q), 131.9 (C_q), 129.7 (CH), 129.3 (CH), 129.2 (CH), 129.2 (CH), 128.7 (CH), 128.0 (CH), 126.4 (CH), 126.0 (CH), 123.5 (C_q), 115.0 (C_q).

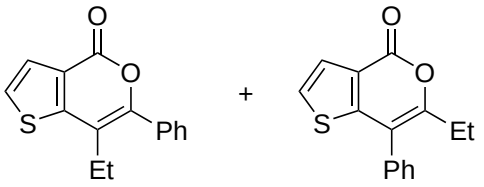
IR (ATR, cm^{-1}): 3106, 3083, 2923, 1732, 1587, 1488, 1441, 1339, 1282, 1197, 1067, 1050, 1026, 975, 902, 767, 714, 695, 545, 497.

MS (EI): 304 (100) $[M]^+$, 276 (20) $[M-CO]^+$, 247 (15), 227 (31) $[M-Ph]^+$, 199 (13) $[M-Ph-CO]^+$, 171 (14), 105 (35), 77 (41) $[Ph]^+$, 51 (10), 45 (14), 43 (18).

$[\mathbf{C_{19}H_{12}O_2S}]^+$ (EI) HRMS: calcd.: 304.0558.
found: 304.0547.

The spectral data are in accordance with those reported in the literature.[223]

Synthesis of 7-Ethyl-6-phenyl-4*H*-thieno[3,2-*c*]pyran-4-one (55lj) and 6-Ethyl-7-phenyl-4*H*-thieno[3,2-*c*]pyran-4-one (55lj')



The general procedure **K** was followed using thiophene-3-carboxylic acid (**56l**) (256 mg, 2.00 mmol) and but-1-ynylbenzene (**34j**) (130 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55lj** as a white solid (243 mg, 95%, m.p.: 95–101 °C) and **55lj'** as a red solid (6 mg, 2%, m.p.: 53–56 °C).

55lj:

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.57 (d, J = 5.3 Hz, 1H), 7.54–7.51 (m, 2H), 7.43–7.36 (m, 3H), 7.33 (d, J = 5.3 Hz, 1H), 2.65 (q, J = 7.6 Hz, 2H), 1.28 (dd, J = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.4 (C_q), 153.0 (C_q), 152.1 (C_q), 132.3 (C_q), 129.4 (CH), 128.6 (CH), 128.3 (CH), 125.9 (CH), 125.5 (CH), 124.0 (C_q), 114.4 (C_q), 22.7 (CH_2), 13.8 (CH_3).

IR (ATR, cm^{-1}): 3119, 2980, 2925, 1707, 1607, 1594, 1490, 1256, 1053, 1028, 916, 770, 718, 701, 649, 598, 576, 501, 482, 461.

MS (EI): 256 (85) $[M]^+$, 241 (18) $[M-Me]^+$, 228 (25) $[M-CO]^+$, 213 (100) $[M-Me-CO]^+$, 184 (15), 105 (30), 77 (53) $[Ph]^+$, 51 (16).

$[\mathbf{C_{15}H_{12}O_2S}]^+$ (EI) HRMS: calcd.: 256.0558.
found: 256.0564.

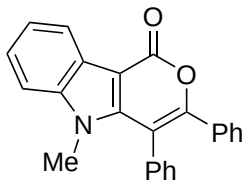
55lj':

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, J = 5.2 Hz, 1H), 7.51–7.42 (m, 3H), 7.39–7.33 (m, 2H), 7.23 (d, J = 5.2 Hz, 1H), 2.49 (q, J = 7.5 Hz, 2H), 1.22 (t, J = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1 (C_q), 157.5 (C_q), 154.3 (C_q), 134.5 (C_q), 129.5 (CH), 129.2 (CH), 128.8 (CH), 126.0 (CH), 125.5 (CH), 123.0 (C_q), 114.4 (C_q), 24.4 (CH_2), 12.5 (CH_3).

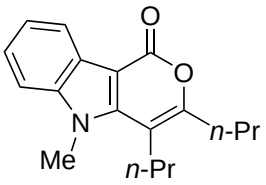
IR (ATR, cm^{-1}): 3109, 2922, 1714, 1613, 1596, 1512, 1490, 1456, 1441, 1251, 1062, 1006, 905, 762, 725, 701, 581, 532, 507.
MS (EI): 256 (100) $[M]^+$, 227 (90) $[M-Et]^+$, 215 (19), 199 (50), 187 (29), 171 (43), 127 (19), 115 (18), 77 (14) $[Ph]^+$, 57 (19), 45 (30).
$[\mathbf{C_{15}H_{12}O_2S}]^+$ (EI) HRMS: calcd.: 256.0558.
found: 256.0553.

Synthesis of 5-Methyl-3,4-diphenylpyrano[4,3-*b*]indol-1(5*H*)-one (55ma)



The general procedure **K** was followed using 1-methylindole-3-carboxylic acid (**56m**) (350 mg, 2.00 mmol) and diphenylacetylene (**34a**) (178 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **55ma** as a white solid (293 mg, 83%, m.p.: 206–208 °C).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35–8.27 (m, 1H), 7.46–7.11 (m, 13H), 3.16 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2 (C_q), 155.6 (C_q), 144.7 (C_q), 139.8 (C_q), 133.3 (C_q), 133.0 (C_q), 131.6 (CH), 129.3 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 127.7 (CH), 124.6 (CH), 123.7 (C_q), 122.7 (CH), 121.3 (CH), 110.4 (C_q), 109.3 (CH), 100.7 (C_q), 32.1 (CH_3).
IR (ATR, cm^{-1}): 3059, 2942, 1716, 1492, 1462, 1444, 1384, 1348, 1252, 1191, 1052, 993, 946, 916, 779, 752, 709, 689, 649, 519.
MS (EI): 351 (100) $[M]^+$, 274 (23) $[M-Ph]^+$, 246 (25) $[M-Ph-CO]^+$, 217 (18), 105 (23), 77 (20) $[Ph]^+$.
$[\mathbf{C_{24}H_{17}NO_2}]^+$ (EI) HRMS: calcd.: 351.1259.
found: 351.1252.
The spectral data are in accordance with those reported in the literature.[223]

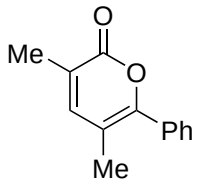
Synthesis of 5-Methyl-3,4-di-*n*-propylpyrano[4,3-*b*]indol-1(5*H*)-one (55mg)



The general procedure **K** was followed using 1-methylindole-3-carboxylic acid (**56m**) (350 mg, 2.00 mmol) and 4-octyne (**34a**) (110 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **55mg** as an orange solid (266 mg, 94%, m.p.: 153–156 °C).

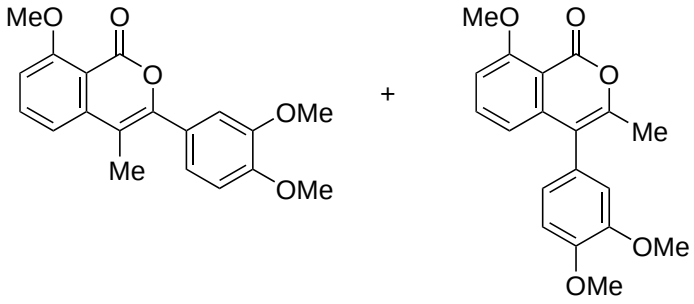
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21–8.16 (m, 1H), 7.32–7.23 (m, 3H), 3.89 (s, 3H), 2.78–2.63 (m, 2H), 2.62–2.52 (m, 2H), 1.74 (dq, J = 14.9, 7.4 Hz, 2H), 1.60 (dq, J = 15.2, 7.4 Hz, 2H), 1.05 (t, J = 7.4 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.8 (C_q), 159.1 (C_q), 145.6 (C_q), 139.3 (C_q), 124.0 (CH), 123.8 (C_q), 122.3 (CH), 120.9 (CH), 109.1 (CH), 107.1 (C_q), 100.9 (C_q), 32.8 (CH_2), 31.8 (CH_3), 28.0 (CH_2), 24.5 (CH_2), 21.6 (CH_2), 13.9 (CH_3), 13.9 (CH_3).
IR (ATR, cm^{-1}): 2955, 2926, 2867, 1707, 1596, 1520, 1465, 1384, 1354, 1257, 1161, 1068, 970, 949, 779, 752.
MS (EI): 283 (53) $[M]^+$, 254 (100) $[M-Et]^+$, 226 (14) $[M-Et-CO]^+$, 212 (14), 198 (13), 184 (25), 168 (14), 154 (21), 140 (11), 127 (11), 115 (10), 77 (9), 57 (10), 43 (20).
$[\mathbf{C_{18}H_{21}NO_2}]^+$ (EI) HRMS: calcd.: 283.1572.
found: 283.1577.
The spectral data are in accordance with those reported in the literature.[110]

Synthesis of 3,5-Dimethyl-6-phenyl-2*H*-pyran-2-one (55ni)



The general procedure **K** was followed using methacrylic acid (**56n**) (172 mg, 2.00 mmol) and prop-1-ynylbenzene (**34i**) (116 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **55ni** as an off-white solid (70 mg, 35%, m.p.: 93–96 °C).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.51 (m, 2H), 7.45–7.36 (m, 3H), 7.08 (q, J = 1.0 Hz, 1H), 2.11 (s, 3H), 2.11 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.6 (C_q), 154.9 (C_q), 144.7 (CH), 132.6 (C_q), 129.4 (CH), 128.5 (CH), 128.3 (CH), 123.8 (C_q), 111.3 (C_q), 16.7 (CH_3), 16.4 (CH_3).
IR (ATR, cm^{-1}): 2924, 1704, 1562, 1494, 1444, 1379, 1335, 1062, 1025, 914, 756, 696, 654, 476.
MS (EI): 200 (55) $[M]^+$, 172 (100) $[M-CO]^+$, 157 (15) $[M-CO-Me]^+$, 129 (52), 105 (32), 77 (45) $[Ph]^+$, 51 (19), 41 (14).
$[\mathbf{C_{13}H_{12}O_2}]^+$ (EI) HRMS: calcd.: 200.0837.
found: 200.0836.
The spectral data are in accordance with those reported in the literature.[260]

Synthesis of 3-(3,4-Dimethoxyphenyl)-8-methoxy-4-methyl-1*H*-isochromen-1-one (55oz) and 4-(3,4-Dimethoxyphenyl)-8-methoxy-3-methyl-1*H*-isochromen-1-one (55oz')



The general procedure **K** was followed using 2-methoxybenzoic acid (**56o**) (304 mg, 2.00 mmol) and 1,2-dimethoxy-4-(prop-1-ynyl)benzene (**34z**) (176 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **55oz** as a white solid (206 mg, 63%, m.p.: 196–200 °C) and **55oz'** as a white solid (15 mg, 5%, m.p.: 197–200 °C).

55oz:

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.64$ (t, $J = 8.2$ Hz, 1H), 7.14–7.04 (m, 3H), 6.94 (dd, $J = 8.5$, 1.0 Hz, 1H), 6.87 (d, $J = 8.8$ Hz, 1H), 3.97 (s, 3H), 3.88 (s, 3H), 3.88 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.6$ (C_q), 159.1 (C_q), 151.5 (C_q), 149.7 (C_q), 148.5 (C_q), 141.7 (C_q), 135.4 (CH), 125.7 (C_q), 122.6 (CH), 115.1 (CH), 112.2 (CH), 110.3 (CH), 109.6 (CH), 109.3 (C_q), 107.9 (C_q), 56.2 (CH_3), 55.9 (CH_3), 55.8 (CH_3), 14.2 (CH_3).

IR (ATR, cm^{-1}): 3002, 2958, 2931, 2839, 1720, 1650, 1597, 1569, 1514, 1479, 1328, 1251, 1214, 1171, 1140, 1092, 1047, 1022, 996, 805, 763, 681, 619, 453.

MS (EI): 326 (61) $[M]^+$, 298 (100) $[M-CO]^+$, 283 (50) $[M-CO-Me]^+$, 252 (14), 165 (15), 149 (7), 77 (10).

$[\mathbf{C_{19}H_{18}O_5}]^+$ (EI) HRMS: calcd.: 326.1154.
found: 326.1150.

The spectral data are in accordance with those reported in the literature.[261]

55oz':

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.46$ (t, $J = 8.2$ Hz, 1H), 6.94 (d, $J = 8.1$ Hz, 1H), 6.88 (d, $J = 8.3$ Hz, 1H), 6.77 (dd, $J = 8.1$, 2.0 Hz, 1H), 6.71 (d, $J = 2.0$ Hz, 1H), 6.54 (dd, $J = 8.1$, 0.9 Hz, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 3.85 (s, 3H), 2.06 (s, 3H).

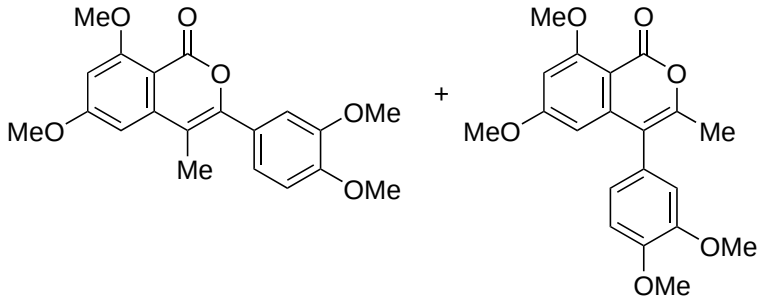
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 161.5$ (C_q), 159.2 (C_q), 152.3 (C_q), 149.1 (C_q), 148.6 (C_q), 141.8 (C_q), 135.3 (CH), 127.3 (C_q), 122.9 (CH), 116.6 (CH), 115.6 (C_q), 113.4 (CH), 111.4 (CH), 109.1 (CH), 108.8 (C_q), 56.4 (CH_3), 56.0 (CH_3), 55.9 (CH_3), 18.1 (CH_3).

IR (ATR, cm^{-1}): 2924, 2841, 1727, 1565, 1510, 1349, 1255, 1340, 1215, 1191, 1165, 1135, 1022, 963, 812, 797, 762, 704, 591.

MS (EI): 326 (100) $[M]^+$, 311 (80) $[M-Me]^+$, 283 (65) $[M-CO-Me]^+$, 255 (15), 135 (20), 43 (18).

$[\mathbf{C_{19}H_{18}O_5}]^+$ (EI) HRMS: calcd.: 326.1154.
found: 326.1149.

Synthesis of 3-(3,4-Dimethoxyphenyl)-6,8-dimethoxy-4-methyl-1*H*-isochromen-1-one (55pz) and 4-(3,4-Dimethoxyphenyl)-6,8-dimethoxy-3-methyl-1*H*-isochromen-1-one (55pz')



The general procedure **K** was followed using 2,4-dimethoxybenzoic acid (**56p**) (364 mg, 2.00 mmol) and 1,2-dimethoxy-4-(prop-1-ynyl)benzene (**34z**) (176 mg, 1.00 mmol). After 18 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **55pz** as a white solid (201 mg, 56%, m.p.: 197−200 °C) and **55pz'** as a white solid (21 mg, 6%, m.p.: 196–200 °C).

55pz:

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.11$–7.06 (m, 2H), 6.88 (d, $J = 8.9$ Hz, 1H), 6.53 (d, $J = 2.2$ Hz, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 2.20 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.2$ (C_q), 163.6 (C_q), 159.0 (C_q), 152.1 (C_q), 149.8 (C_q), 148.5 (C_q), 143.6 (C_q), 126.0 (C_q), 122.7 (CH), 112.4 (CH), 110.3 (CH), 107.8 (C_q), 103.5 (C_q), 98.6 (CH), 97.8 (CH), 56.3 (CH_3), 56.0 (CH_3), 55.9 (CH_3), 55.5 (CH_3), 14.3 (CH_3).

IR (ATR, cm^{-1}): 3000, 2963, 1717, 1597, 1516, 1468, 1441, 1374, 1335, 1246, 1207, 1172, 1139, 1077, 1017, 993, 828, 817, 764, 677, 594.

MS (EI): 356 (45) $[M]^+$, 328 (100) $[M-CO]^+$, 313 (40) $[M-CO-Me]^+$, 284 (10), 165 (14), 77 (10).

$[\mathbf{C_{20}H_{20}O_6}]^+$ (EI) HRMS: calcd.: 356.1260.
found: 356.1266.

The spectral data are in accordance with those reported in the literature.[261]

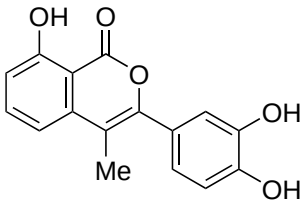
55pz':

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.93$ (d, $J = 8.1$ Hz, 1H), 6.76 (dd, $J = 8.1$, 1.9 Hz, 1H), 6.71 (d, $J = 1.9$ Hz, 1H), 6.40 (d, $J = 2.3$ Hz, 1H), 5.96 (d, $J = 2.3$ Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.84 (s, 3H), 3.65 (s, 3H), 2.03 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.1$ (C_q), 163.4 (C_q), 159.2 (C_q), 152.8 (C_q), 149.1 (C_q), 148.6 (C_q), 143.7 (C_q), 127.4 (C_q), 123.0 (CH), 115.6 (C_q), 113.3 (CH), 111.4 (CH), 102.9 (C_q), 99.9 (CH), 97.5 (CH), 56.3 (CH_3), 55.9 (CH_3), 55.8 (CH_3), 55.4 (CH_3), 18.1 (CH_3).

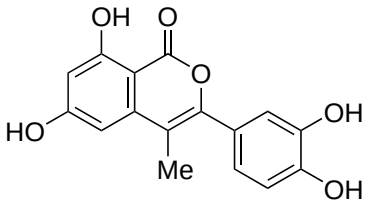
IR (ATR, cm^{-1}): 2919, 2839, 1723, 1709, 1600, 1574, 1516, 1458, 1350, 1241, 1218, 1169, 1137, 1112, 1072, 1017, 971, 883, 839, 805, 759, 703, 588, 567, 543.
MS (EI): 356 (100) $[M]^+$, 341 (70) $[M-Me]^+$, 323 (15), 313 (71) $[M-CO-Me]^+$, 285 (16), 43 (32).
$[\mathbf{C_{20}H_{20}O_6}]^+$ (EI) HRMS: calcd.: 356.1260.
found: 356.1252.

Synthesis of 3-(3,4-Dihydroxyphenyl)-8-hydroxy-4-methyl-1*H*-isochromen-1-one (4-Methylthunberginol A) (164oz)



3-(3,4-Dimethoxyphenyl)-8-methoxy-4-methyl-1*H*-isochromen-1-one (**55oz**) (130 mg, 0.40 mmol, 1.0 equiv) was placed in a pre-dried 5-mL Schlenk flask and degassed and purged with N_2 for 3 times. **55oz** was cooled to 0 °C and BBr_3 (2.1 mL, 1 M in CH_2Cl_2, 2.1 mmol, 5.25 equiv) was added dropwise. The resulting solution was stirred at ambient temperature for 22 h. The mixture was poured onto ice water (100 mL) and extracted with EtOAc (5 × 75 mL). The combined organic layers were washed with water (100 mL), dried over Na_2SO_4 and filtered. The solvents were removed *in vacuo*. Purification by column chromatography (toluene/THF: 3/2) yielded **164oz** as a pale orange solid (101 mg, 89%, m.p.: 202–205 °C).
^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 11.19$ (s_{br}, 1H), 9.32 (s_{br}, 2H), 7.75 (t, $J = 8.1$ Hz, 1H), 7.12 (dd, $J = 8.0$, 0.9 Hz, 1H), 7.03–6.96 (m, 2H), 6.90–6.86 (m, 2H), 2.20 (s, 3H).
^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 165.5$ (C_q), 160.8 (C_q), 150.5 (C_q), 146.9 (C_q), 145.0 (C_q), 139.2 (C_q), 137.5 (CH), 123.2 (C_q), 121.0 (CH), 116.4 (CH), 115.3 (CH), 114.4 (CH), 114.1 (CH), 108.9 (C_q), 105.3 (C_q), 13.6 (CH_3).
IR (ATR, cm^{-1}): 3290, 3044, 1662, 1603, 1512, 1492, 1458, 1292, 1232, 1174, 1115, 1098, 1021, 1000, 970, 809, 777, 679, 568, 541, 468.
MS (EI): 284 (75) $[M]^+$, 256 (100) $[M-CO]^+$, 239 (6) $[M-CO-OH]^+$, 181 (6), 137 (10), 109 (9) $[C_6H_3(OH)_2]^+$.
$[\mathbf{C_{16}H_{12}O_5}]^+$ (EI) HRMS: calcd.: 284.0685.
found: 284.0693.
The spectral data are in accordance with those reported in the literature.[261]

Synthesis of 3-(3,4-dihydroxyphenyl)-6,8-dihydroxy-4-methyl-1*H*-isochromen-1-one (4-Methylthunberginol B) (164pz)



3-(3,4-Dimethoxyphenyl)-6,8-dimethoxy-4-methyl-1*H*-isochromen-1-one (**55pz**) (143 mg, 0.40 mmol, 1.0 equiv) was placed in a pre-dried 5-mL Schlenk flask and degassed and purged with N_2 for 3 times. **55pz** was cooled to 0 °C and BBr_3 (4.0 mL, 1 M in CH_2Cl_2, 4.00 mmol, 10.0 equiv) was added dropwise. The resulting solution was stirred at ambient temperature for 96 h. The mixture was poured onto ice water (100 mL). The precipitate was filtered off and dried *in vacuo*. Purification by column chromatography (toluene/THF: 3/2) yielded **164pz** as an off-white solid (88 mg, 73%, m.p.: 288–290 °C).

^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 11.30$ (s_{br}, 1H), 9.65 (s_{br}, 3H), 7.02–6.95 (m, 1H), 6.91–6.82 (m, 2H), 6.45 (d, $J = 2.1$ Hz, 1H), 6.36 (dd, $J = 2.1$, 0.6 Hz, 1H), 2.12 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 165.7$ (C_q), 165.2 (C_q), 163.1 (C_q), 150.6 (C_q), 146.8 (C_q), 145.0 (C_q), 140.9 (C_q), 123.5 (C_q), 121.1 (CH), 116.5 (CH), 115.3 (CH), 108.6 (C_q), 101.4 (CH), 101.3 (CH), 98.1 (C_q), 13.5 (CH_3).

IR (ATR, cm^{-1}): 3336, 3066, 1659, 1602, 1583, 1507, 1298, 1179, 1110, 1007, 972, 901, 804, 777, 720, 678, 658, 566, 491.

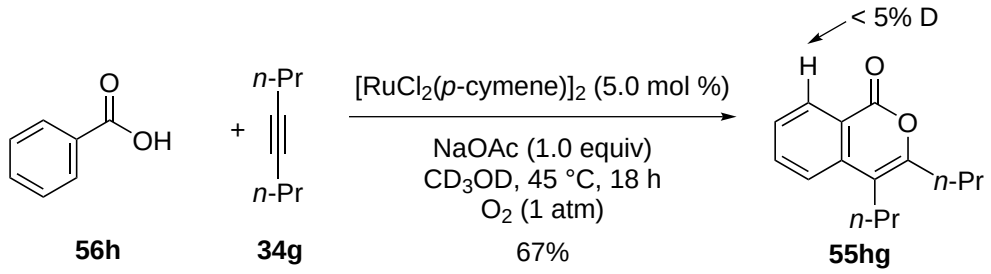
MS (EI): 300 (63) $[M]^+$, 272 (100) $[M-CO]^+$, 255 (12), 229 (5), 197 (5), 137 (13), 109 (11) $[C_6H_3(OH)_2]^+$, 81 (10), 77 (10), 43 (10).

$[C_{16}H_{12}O_6]^+$ (EI) HRMS: calcd.: 300.0634.
found: 300.0631.

The spectral data are in accordance with those reported in the literature.[261]

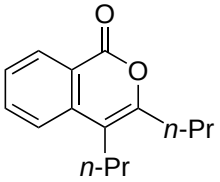
5.3.10 Mechanistic Studies on Ruthenium-catalyzed Syntheses of Isocoumarins through Isotopic Labeling

Reaction of 56h and 34g in [D_4]-MeOH



56h **34g** 67% **55hg**

Benzoic acid (**56h**) (244 mg, 2.00 mmol, 2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (30.6 mg, 0.05 mmol, 5.0 mol %) and NaOAc (82 mg, 1.00 mmol, 1.0 equiv) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with O_2 for 3 times. CD_3OD (3.0 mL, 0.33 M) and 4-octyne (**34g**) (110 mg, 1.00 mmol, 1.00 equiv) were added and the reaction mixture was stirred at 45 °C for 18 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 20/1) yielded 3,4-di-*n*-propyl-1*H*-isochromen-1-one **55hg** (154 mg, 67%) as a colourless oil with less than 5% deuterium incorporation in the *ortho*-position, as estimated by ^{1}H NMR-spectroscopy.



^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.26$ (ddd, $J = 7.0, 1.5, 0.6$ Hz, 1H), 7.68 (ddd, $J = 8.2, 7.2, 1.5$ Hz, 1H), 7.48 (ddd, $J = 8.0, 1.0, 0.6$ Hz, 1H), 7.41 (ddd, $J = 8.2, 7.2, 1.0$ Hz, 1H), 2.61–2.49 (m, 4H), 1.71 (dq, $J = 14.8, 7.4$ Hz, 2H), 1.56 (dq, $J = 15.0, 7.4$ Hz, 2H), 1.00 (t, $J = 7.4$ Hz, 3H), 0.96 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 162.7$ (C_q), 153.9 (C_q), 137.8 (C_q), 134.3 (CH), 129.6 (CH), 126.9 (CH), 122.5 (CH), 120.7 (C_q), 112.1 (C_q), 32.7 (CH_2), 28.2 (CH_2), 22.9 (CH_2), 21.2 (CH_2), 14.2 (CH_3), 13.8 (CH_3).

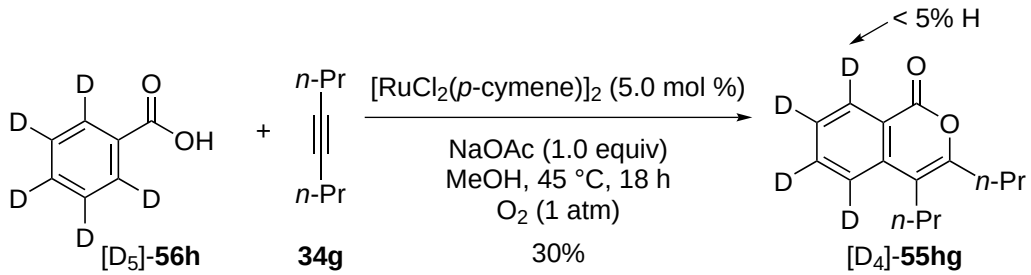
IR (ATR, cm^{-1}): 2960, 2932, 2872, 1719, 1638, 1605, 1565, 1486, 1457, 1319, 1246, 1182, 1149, 1115, 1080, 1026, 768, 690.

MS (EI): 230 (50) $[M]^+$, 201 (100) $[M-Et]^+$, 173 (10) $[M-Et-CO]^+$, 159 (7) $[M-n\text{-}Pr-CO]^+$, 145 (16), 131 (65), 115 (12), 102 (11), 91 (8), 77 (6), 43 (16).

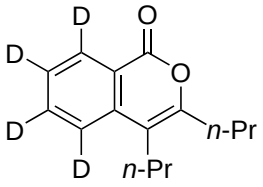
$[\mathbf{C_{15}H_{18}O_2}]^+$ (EI) HRMS: calcd.: 230.1307.
found: 230.1313.

The spectral data are in accordance with those reported in the literature.[110]

Ruthenium-Catalyzed Annulation of Alkyne 34g with Pentadeuterated Acid [D_5]-56h in MeOH

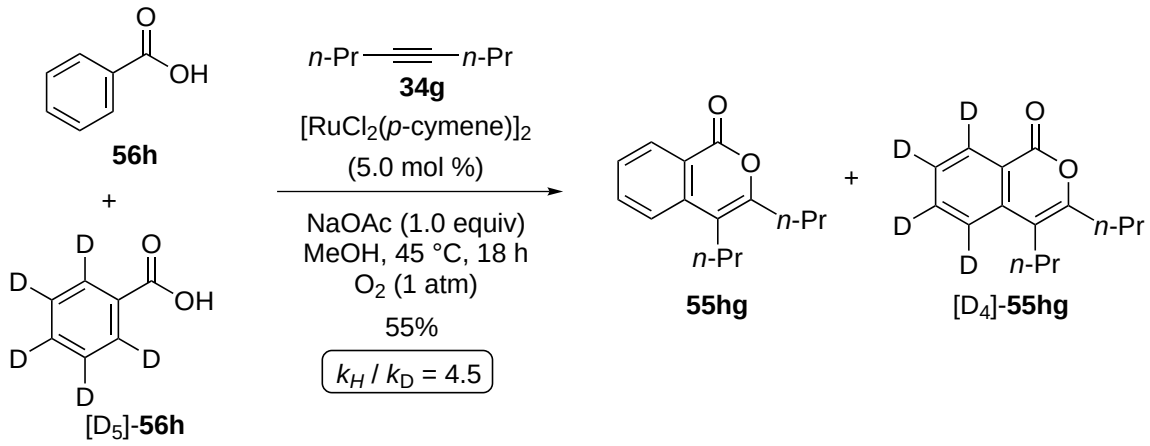


[D_5]-Benzoic acid ([D_5]-**56h**) (254 mg, 2.00 mmol, 2.0 equiv), [$RuCl_2$(*p*-cymene)]$_2$ (30.6 mg, 0.05 mmol, 5.0 mol %) and NaOAc (82 mg, 1.00 mmol, 1.0 equiv) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with O_2 for 3 times. Dry MeOH (3.0 mL, 0.33 M) and 4-octyne (**34g**) (110 mg, 1.00 mmol, 1.00 equiv) were added and the reaction mixture was stirred at 45 °C for 18 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 20/1) yielded [D_4]-**55hg** (70 mg, 30%) as a colourless oil with less than 5% hydrogen incorporation in the *ortho*-position, as estimated by ^{1}H NMR-spectroscopy.



^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.61–2.49 (m, 4H), 1.71 (tq, J = 7.4, 7.4 Hz, 2H), 1.56 (tq, J = 7.5, 7.4 Hz, 2H), 1.00 (t, J = 7.4 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.7 (C_q), 153.9 (C_q), 137.7 (C_q), 133.8 (t, J = 24 Hz, CD), 129.3 (t, J = 24 Hz, CD), 126.4 (t, J = 24 Hz, CD), 121.1 (t, J = 24 Hz, CD), 120.6 (C_q), 112.1 (C_q), 32.7 (CH_2), 28.2 (CH_2), 22.9 (CH_2), 21.2 (CH_2), 14.2 (CH_3), 13.8 (CH_3).
IR (ATR, cm^{-1}): 2961, 2932, 2873, 1721, 1638, 1576, 1442, 1458, 1412, 1375, 1314, 1241, 1207, 1160, 1126, 1085, 1043, 1022, 579.
MS (EI): 231 (55) $[M]^+$, 205 (100) $[M-Et]^+$, 177 (10) $[M-Et-CO]^+$, 163 (9) $[M-n\text{-}Pr-CO]^+$, 149 (20), 135 (75), 119 (15), 106 (16), 93 (7), 80 (7), 43 (23).
$[\mathbf{C_{15}H_{14}D_4O_2}]^+$ (EI) HRMS: calcd.: 234.1558.
found: 234.1564.

Competition Experiment between 56h and [D_5]-56h



Benzoic acid (**56h**) (122 mg, 1.00 mmol, 1.0 equiv.), [D_5]-Benzoic acid ([D_5]-**56h**) (127 mg, 2.00 mmol, 1.0 equiv), [$RuCl_2$(*p*-cymene)]$_2$ (30.6 mg, 0.05 mmol, 5.0 mol %) and NaOAc (82 mg, 1.00 mmol, 1.0 equiv) were placed in a pre-dried 25-mL Schlenk tube. The mixture was degassed and purged with O_2 for 3 times. Dry MeOH (3.0 mL, 0.33 M) and 4-octyne (**34g**) (110 mg, 1.00 mmol, 1.00 equiv) were added and the reaction mixture was stirred at 45 °C for 18 h. At ambient temperature, EtOAc (15 mL) was added and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 20/1) yielded a mixture of **55hg** and [D_4]-**55hg** (126 mg, 55%) with a ratio of 4.5 to 1 (**55hg**/[D_4]-**55hg**), as determined by ^{1}H NMR-spectroscopy.

6 Crystallographic Data

X-ray structure analysis of 4-ethyl-1-methyl-3-phenylisoquinoline (**50aj**).

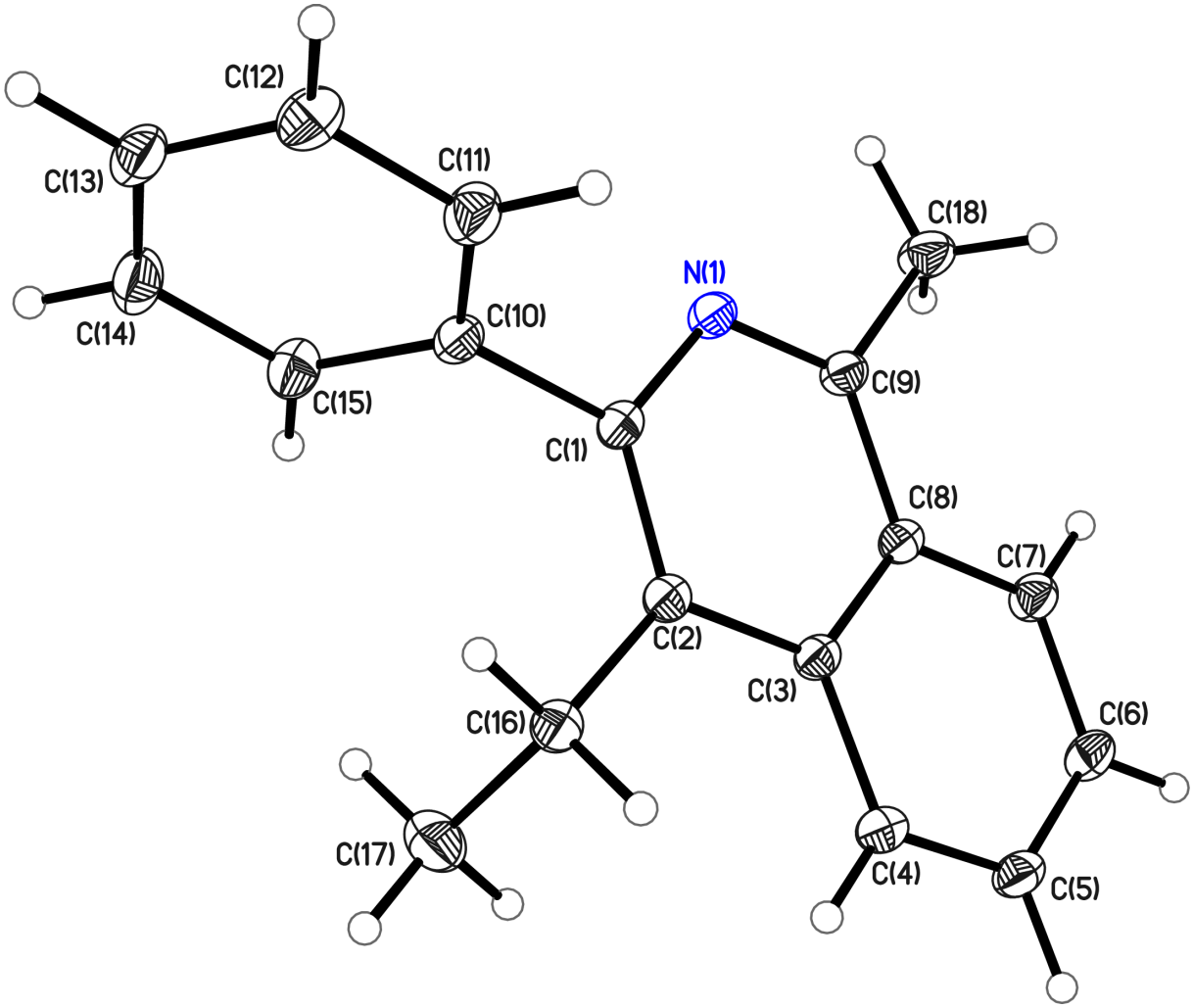


Figure 6.1: crystal-structure of compound **50aj** (numbering does not correspond to the IUPAC rules).

CCDC no.	987880
Empirical formula	$C_{18}H_{17}N$
Molecular weight	247.33
Temperature	101(2) K
Wavelength	0.71073 Å

Crystall system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	$a = 8.333(2)$ Å $\quad \alpha = 90\,^\circ$
	$b = 23.452(3)$ Å $\quad \beta = 115.99(2)\,^\circ$
	$c = 7.629(2)$ Å $\quad \gamma = 90\,^\circ$
Volume	$1340.1(5)$Å^3
Z	4
Density (calculated)	1.226 Mg/mm^3
Absorption coefficient	0.071 mm^{-1}
$F(000)$	528
Crystal size	$0.15 \times 0.05 \times 0.05$ mm^3
Theta range for data collection	$1.737-32.038\,^\circ$
Index ranges	-12 <h < 12, -34 <k <34, -11 <l <11
Reflections collected	48511
Independent reflections	4678 [R(int) = 0.0377]
Completeness to theta = $25.242\,^\circ$	99.9%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7463 and 0.7023
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4678 / 0 / 174
Goodness-of-fit on F^2	1.026
Final R indices [I>2sigma(I)]	$R_1 = 0.0447$, w$R_2 = 0.1201$
R indices (all data)	$R_1 = 0.0542$, w$R_2 = 0.1273$
Largest diff. peak and hole	0.522 and -0.193 e.Å^{-3}

Table 6.1: Bond lengths [Å] in **50aj**.

atoms	bond length	atoms	bond length
N(1)−C(9)	1.3184(11)	N(1)−C(1)	1.3720(11)
C(1)−C(2)	1.3786(12)	C(1)−C(10)	1.4948(12)
C(2)−C(3)	1.4302(12)	C(2)−C(16)	1.5096(12)
C(3)−C(8)	1.4182(12)	C(3)−C(4)	1.4234(12)
C(5)−C(4)	1.3733(13)	C(5)−C(6)	1.4105(13)
C(5)−H(5)	0.9500	C(4)−H(4)	0.9500
C(7)−C(6)	1.3719(13)	C(7)−C(8)	1.4180(12)
C(7)−H(7)	0.9500	C(6)−H(6)	0.9500
C(8)−C(9)	1.4279(13)	C(9)−C(18)	1.5001(13)
C(10)−C(15)	1.3915(13)	C(10)−C(11)	1.3932(13)
C(11)−C(12)	1.3915(14)	C(11)−H(11)	0.9500
C(12)−C(13)	1.3870(15)	C(12)−H(12)	0.9500
C(13)−C(14)	1.3835(15)	C(13)−H(13)	0.9500
C(14)−C(15)	1.3951(14)	C(14)−H(14)	0.9500
C(15)−H(15)	0.9500	C(16)−C(17)	1.5299(14)
C(16)−H(16A)	0.9900	C(16)−H(16B)	0.9900
C(17)−H(17A)	0.9800	C(17)−H(17B)	0.9800
C(17)−H(17C)	0.9800	C(18)−H(18A)	0.9800
C(18)−H(18B)	0.9800	C(18)−H(18C)	0.9800

Table 6.2: Bond angles [°] in **50aj**.

atoms	angle	atoms	angles
C(9)-N(1)-C(1)	119.31(8)	N(1)-C(1)-C(2)	123.80(8)
N(1)-C(1)-C(10)	113.23(7)	C(2)-C(1)-C(10)	122.96(8)
C(1)-C(2)-C(3)	117.55(8)	C(1)-C(2)-C(16)	121.46(8)
C(3)-C(2)-C(16)	120.99(8)	C(8)-C(3)-C(4)	118.32(8)
C(8)-C(3)-C(2)	118.75(8)	C(4)-C(3)-C(2)	122.93(8)
C(4)-C(5)-C(6)	120.51(8)	C(4)-C(5)-H(5)	119.7
C(6)-C(5)-H(5)	119.7	C(5)-C(4)-C(3)	120.81(8)
C(5)-C(4)-H(4)	119.6	C(3)-C(4)-H(4)	119.6
C(6)-C(7)-C(8)	120.61(8)	C(6)-C(7)-H(7)	119.7
C(8)-C(7)-H(7)	119.7	C(7)-C(6)-C(5)	120.05(8)

atoms	angle	atoms	angles
C(7)-C(6)-H(6)	120.0	C(5)-C(6)-H(6)	120.0
C(7)-C(8)-C(3)	119.63(8)	C(7)-C(8)-C(9)	122.02(8)
C(3)-C(8)-C(9)	118.35(8)	N(1)-C(9)-C(8)	122.16(8)
N(1)-C(9)-C(18)	116.54(8)	C(8)-C(9)-C(18)	121.30(8)
C(15)-C(10)-C(11)	119.07(8)	C(15)-C(10)-C(1)	121.24(8)
C(11)-C(10)-C(1)	119.64(8)	C(12)-C(11)-C(10)	120.54(9)
C(12)-C(11)-H(11)	119.7	C(10)-C(11)-H(11)	119.7
C(13)-C(12)-C(11)	119.95(9)	C(13)-C(12)-H(12)	120.0
C(11)-C(12)-H(12)	120.0	C(14)-C(13)-C(12)	119.98(9)
C(14)-C(13)-H(13)	120.0	C(12)-C(13)-H(13)	120.0
C(13)-C(14)-C(15)	120.11(9)	C(13)-C(14)-H(14)	119.9
C(15)-C(14)-H(14)	119.9	C(10)-C(15)-C(14)	120.34(9)
C(10)-C(15)-H(15)	119.8	C(14)-C(15)-H(15)	119.8
C(2)-C(16)-C(17)	113.22(8)	C(2)-C(16)-H(16A)	108.9
C(17)-C(16)-H(16A)	108.9	C(2)-C(16)-H(16B)	108.9
C(17)-C(16)-H(16B)	108.9	H(16A)-C(16)-H(16B)	107.7
C(16)-C(17)-H(17A)	109.5	C(16)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5	C(16)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5	H(17B)-C(17)-H(17C)	109.5
C(9)-C(18)-H(18A)	109.5	C(9)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5	C(9)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5	H(18B)-C(18)-H(18C)	109.5

Table 6.3: Torsion angles [°] in **50aj**.

atoms	angle	atoms	angles
C(9)-N(1)-C(1)-C(2)	2.31(13)	C(9)-N(1)-C(1)-C(10)	-178.70(8)
N(1)-C(1)-C(2)-C(3)	−1.25(13)	C(10)-C(1)-C(2)-C(3)	179.85(8)
N(1)-C(1)-C(2)-C(16)	178.98(8)	C(10)-C(1)-C(2)-C(16)	0.09(13)
C(1)-C(2)-C(3)-C(8)	−1.22(12)	C(16)-C(2)-C(3)-C(8)	178.55(8)
C(1)-C(2)-C(3)-C(4)	178.16(8)	C(16)-C(2)-C(3)-C(4)	−2.08(13)
C(6)-C(5)-C(4)-C(3)	−1.56(14)	C(8)-C(3)-C(4)-C(5)	−0.81(13)
C(2)-C(3)-C(4)-C(5)	179.82(8)	C(8)-C(7)-C(6)-C(5)	−0.10(14)
C(4)-C(5)-C(6)-C(7)	2.03(14)	C(6)-C(7)-C(8)-C(3)	−2.27(13)
C(6)-C(7)-C(8)-C(9)	177.25(9)	C(4)-C(3)-C(8)-C(7)	2.69(12)

atoms	angle	atoms	angles
C(2)-C(3)-C(8)-C(7)	−177.91(8)	C(4)-C(3)-C(8)-C(9)	−176.84(8)
C(2)-C(3)-C(8)-C(9)	2.56(12)	C(1)-N(1)-C(9)-C(8)	−0.81(13)
C(1)-N(1)-C(9)-C(18)	179.69(8)	C(7)-C(8)-C(9)-N(1)	178.89(8)
C(3)-C(8)-C(9)-N(1)	−1.59(13)	C(7)-C(8)-C(9)-C(18)	−1.63(13)
C(3)-C(8)-C(9)-C(18)	177.89(8)	N(1)-C(1)-C(10)-C(15)	101.45(10)
C(2)-C(1)-C(10)-C(15)	−79.55(12)	N(1)-C(1)-C(10)-C(11)	−76.06(11)
C(2)-C(1)-C(10)-C(11)	102.94(11)	C(15)-C(10)-C(11)-C(12)	0.93(15)
C(1)-C(10)-C(11)-C(12)	178.49(9)	C(10)-C(11)-C(12)-C(13)	−1.06(16)
C(11)-C(12)-C(13)-C(14)	0.46(15)	C(12)-C(13)-C(14)-C(15)	0.26(15)
C(11)-C(10)-C(15)-C(14)	−0.21(14)	C(1)-C(10)-C(15)-C(14)	−177.73(9)
C(13)-C(14)-C(15)-C(10)	−0.38(15)	C(1)-C(2)-C(16)-C(17)	100.04(10)
C(3)-C(2)-C(16)-C(17)	−79.72(11)		

References

[1] T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles*, 2. Aufl., Wiley-VCH, Weinheim, **2003**.

[2] G. Habermehl, P. Hammann, H. C. Krebs, W. Ternes, *Naturstoffchemie: Eine Einführung*, 3. Aufl., Springer, Heidelberg, **2008**.

[3] M. Brasholz, S. Sörgel, C. Azap, H.-U. Reißig, *Eur. J. Org. Chem.* **2007**, 3801–3814.

[4] A. C. Whyte, J. B. Gloer, *J. Nat. Prod.* **1996**, *59*, 765–769.

[5] B. A. Weissman, L. Raveh, *J. Neurochem.* **2003**, *84*, 432–437.

[6] A. Behr, *Angewandte homogene Katalyse*, Wiley-VCH, Weinheim, **2008**.

[7] *Modern Arylation Methods*, (Ed.: L. Ackermann), Wiley-VCH, Weinheim, **2009**.

[8] G. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555–1564.

[9] R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461–1473.

[10] "The Nobel Prize in Chemistry 2010 - Press Release". Nobelprize.org. Nobel Media AB 2013. Web. 25 Feb 2014. http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/press.html.

[11] B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500–1511.

[12] X. Hu, *Chem. Sci.* **2011**, *2*, 1867–1886.

[13] B. A. Arndtsen, R. G. Bergman, T. A. Mobley, T. H. Peterson, *Acc. Chem. Res.* **1995**, *28*, 154–162.

[14] D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238.

[15] L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826.

[16] A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879–2932.

[17] Y. Boutadla, D. L. Davies, S. A. Macgregor, A. I. Poblador-Bahamonde, *Dalton Trans.* **2009**, 5820–5831.

[18] D. Balcells, E. Clot, O. Eisenstein, *Chem. Rev.* **2010**, *110*, 749–823.

[19] L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345.

[20] D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118–1126.

[21] B. Biswas, M. Sugimoto, S. Sakaki, *Organometallics* **2000**, *19*, 3895–3908.

[22] D. L. Davies, S. M. A. Donald, S. A. Macgregor, *J. Am. Chem. Soc.* **2005**, *127*, 13754–13755.

[23] D. García-Cuadrado, P. de Mendoza, A. A. C. Bragan, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886.

[24] S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.

[25] D. H. Ess, S. M. Bischof, J. Oxgaard, R. A. Periana, W. A. Goddard III, *Organometallics* **2008**, *27*, 6440–6445.

[26] J. Oxgaard, W. J. Tenn III, R. J. Nielsen, R. A. Periana, W. A. Goddard III, *Organometallics* **2007**, *26*, 1565–1567.

[27] J. R. Webb, T. Bolano, T. B. Gunnoe, *ChemSusChem* **2011**, *4*, 37–49.

[28] G. A. Olah, A. Goeppert, G. K. S. Prakash, *Beyond Oil and Gas: The Methanol Economy*, 2. Aufl., Wiley-VCH, **2009**.

[29] R. H. Crabtree, *J. Chem. Soc., Dalton Trans.* **2001**, 2437–2450.

[30] R. A. Periana, G. Bhalla, W. J. Tenn III, K. J. Young, X. Y. Liu, O. Mironov, C. Jones, V. R. Ziatdinov, *J. Mol. Catal. A* **2004**, *220*, 7–25.

[31] B. G. Hashiguchi, S. M. Bischof, M. M. Konnick, R. A. Periana, *Acc. Chem. Res.* **2012**, *45*, 885–898.

[32] M. S. Chen, M. C. White, *Science* **2007**, *318*, 783–787.

[33] M. S. Chen, M. C. White, *Science* **2010**, *327*, 566–571.

[34] M. A. Bigi, S. A. Reed, M. C. White, *J. Am. Chem. Soc.* **2012**, *134*, 9721–9726.

[35] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933.

[36] J. Epsztajn, Z. Berski, J. Z. Brzezinski, A. Jóźwiak, *Tetrahedron Lett.* **1980**, *21*, 4739–4742.

[37] L. N. Lewis, J. F. Smith, *J. Am. Chem. Soc.* **1986**, *108*, 2728–2735.

[38] S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529–531.

[39] F. Kakiuchi, N. Chatani, *Activation of Inert C-H Bonds*, in *Ruthenium Catalysts and Fine Chemistry*, *Vol. 11* (Eds.: C. Bruneau and P. H. Dixneuf), Springer, Berlin-Heidelberg, **2004**, pp. 45–79.

[40] R. Martinez, R. Chevalier, S. Darses, J.-P. Genet, *Angew. Chem. Int. Ed.* **2006**, *45*, 8232–8235.

[41] R. Martinez, M.-O. Simon, R. Chevalier, C. Pautigny, J.-P. Genet, S. Darses, *J. Am. Chem. Soc.* **2009**, *131*, 7887–7895.

[42] S. I. Kozhushkov, D. S. Yufit, L. Ackermann, *Org. Lett.* **2008**, *10*, 3409–3412.

[43] M. Schinkel, I. Marek, L. Ackermann, *Angew. Chem. Int. Ed.* **2013**, *52*, 3977–3980.

[44] L. Ackermann, *Chem. Commun.* **2010**, *46*, 4866–4877.

[45] S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936–946.

[46] S. I. Kozhushkov, L. Ackermann, *Chem. Sci.* **2013**, *4*, 886–896.

[47] S. Oi, S. Fukita, N. Hirato, N. Watanuki, S. Miyano, Y. Inoue, *Org. Lett.* **2001**, *3*, 2579–2581.

[48] L. Ackermann, *Org. Lett.* **2005**, *7*, 3123–3125.

[49] D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331.

[50] L. Ackermann, A. Althammer, R. Born, *Angew. Chem. Int. Ed.* **2006**, *45*, 2619–2622.

[51] D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18566–18569.

[52] L. Ackermann, P. Novák, R. Vincente, N. Hofmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 6045–6048.

[53] L. Ackermann, P. Novák, *Org. Lett.* **2009**, *11*, 4966–4969.

[54] N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.* **2013**, *135*, 5877–5884.

[55] E. Diers, N. Y. P. Kumar, T. Mejuch, I. Marek, L. Ackermann, *Tetrahedron* **2013**, *69*, 4445–4453.

[56] M. Seki, M. Nagahama, *J. Org. Chem.* **2011**, *76*, 10198–10206.

[57] M. Seki, *ACS Catal.* **2011**, *1*, 607–610.

[58] C. Wang, Y. Huang, *Synlett* **2013**, *24*, 145–149.

[59] F. Mo, J. R. Tabor, G. Dong, *Chem. Lett.* **2014**, *43*, 264–271.

[60] L. Ackermann, E. Diers, A. Manvar, *Org. Lett.* **2012**, *14*, 1154–1157.

[61] V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155.

[62] D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972.

[63] Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 12984–12986.

[64] G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726–11743.

[65] Q. Gu, H. A. Mamari, K. Graczyk, E. Diers, L. Ackermann, *Angew. Chem. Int. Ed.* **2014**, *53*, 3868–3871.

[66] H. Bönnemann, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 505–515.

[67] K. P. Vollhardt, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 539–556.

[68] S. E. Gibson, A. Stevenazzi, *Angew. Chem.* **2003**, *115*, 1844–1854.

[69] J. Blanco-Urgoiti, L. A. norbe, L. Pérez-Serrano, G. Domínguez, J. Pérez-Castells, *Chem. Soc. Rev.* **2004**, *33*, 32–42.

[70] T. Shibata, *Adv. Synth. Catal.* **2006**, *348*, 2328–2336.

[71] R. C. Larock, *Top. Organomet. Chem.* **2005**, *14*, 147–182.

[72] G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644–4680.

[73] R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6690–6692.

[74] R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652–7662.

[75] L. Ackermann, L. T. Kaspar, C. Gschrei, *Chem. Commun.* **2004**, *40*, 2824–2825.

[76] K. R. Roesch, R. C. Larock, *Org. Lett.* **1999**, *1*, 1551–1553.

[77] L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Ltd, Oxford, **2004**.

[78] G. Wu, A. L. Rheingold, S. J. Geib, R. F. Heck, *Organometallics* **1987**, *6*, 1941–1946.

[79] K. R. Roesch, R. C. Larock, *J. Org. Chem.* **1998**, *63*, 5306–5307.

[80] A. Kojima, T. Takemoto, M. Sodeoka, M. Shibasaki, *Synthesis* **1998**, 581–589.

[81] R. C. Larock, M. J. Doty, X. Han, *J. Org. Chem.* **1999**, *64*, 8770–8779.

[82] K. Ueura, T. Satoh, M. Miura, *J. Org. Chem.* **2007**, *72*, 5362–5367.

[83] K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407–1409.

[84] J. M. Kisenyi, G. J. Sunley, J. A. Cabeza, A. J. Smith, H. Adams, N. J. Salt, P. M. Maitlis, *J. Chem. Soc. Dalton Trans.* **1987**, 2459–2466.

[85] D. Steinborn, *Grundlagen der metallorganischen Komplexkatalyse*, 1. Aufl., Teubner Verlag, Wiesbaden, **2007**.

[86] T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212–11222.

[87] G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651–3678.

[88] D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474–16475.

[89] D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326–18339.

[90] N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050–12051.

[91] T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 10565–10569.

[92] S. Mochida, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2010**, *39*, 744–746.

[93] G. Song, D. Chen, C.-L. Pan, R. H. Crabtree, X. Li, *J. Org. Chem.* **2010**, *75*, 7487–7490.

[94] Y. Su, M. Zhao, K. Han, G. Song, X. Li, *Org. Lett.* **2010**, *12*, 5462–5465.

[95] S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585–9587.

[96] M. V. Pham, B. Ye, N. Cramer, *Angew. Chem. Int. Ed.* **2012**, *51*, 10610–10614.

[97] G. Zhang, L. Yang, Y. Wang, Y. Xie, H. Huang, *J. Am. Chem. Soc.* **2013**, *135*, 8850–8853.

[98] D. A. Frasco, C. P. Lilly, P. D. Boyle, E. A. Ison, *ACS Catal.* **2013**, *3*, 2421–2429.

[99] Heraeus-edelmetallhandel.de. Web. 12 Mar 2014. http://heraeus-edelmetallhandel.de/de/marktinformationen/edelmetallcharts/edelmetallcharts.aspx.

[100] L. Ackermann, A. V. Lygin, N. Hofmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 6379–6382.

[101] N. Hofmann, Dissertation, Georg-August-Universität Göttingen, **2013**.

[102] L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281–295.

[103] L. Ackermann, R. Vicente, H. K. Potukuchi, V. Pirovano, *Org. Lett.* **2010**, *12*, 5032–5035.

[104] K. Parthasarathy, N. Senthilkumar, J. Jayakumar, C.-H. Cheng, *Org. Lett.* **2012**, *14*, 3478–3481.

[105] P. Villuendas, E. P. Urriolabeitia, *J. Org. Chem.* **2013**, *78*, 5254–5263.

[106] C.-Z. Luo, P. Gandeepan, C.-H. Cheng, *Chem. Commun.* **2013**, *49*, 8528–8530.

[107] H. Lu, Q. Yang, Y. Zhou, Y. Guo, Z. Deng., Q. Ding, Y. Peng, *Org. Biomol. Chem.* **2014**, *12*, 758–764.

[108] R. Wang, J. Falck, *J. Organomet. Chem.* **2014**, *759*, 33–36.

[109] L. Ackermann, A. V. Lygin, N. Hofmann, *Org. Lett.* **2011**, *13*, 3278–3281.

[110] L. Ackermann, J. Pospech, K. Graczyk, K. Rauch, *Org. Lett.* **2012**, *14*, 930–933.

[111] R. K. Chinnagolla, M. Jeganmohan, *Chem. Commun.* **2012**, *48*, 2030–2032.

[112] M. Deponti, S. I. Kozhushkov, D. S. Yufit, L. Ackermann, *Org. Biomol. Chem.* **2013**, *11*, 142–148.

[113] L. Ackermann, A. V. Lygin, *Org. Lett.* **2012**, *14*, 764–767.

[114] B. Li, N. Wang, Y. Liang, S. Xu, B. Wang, *Org. Lett.* **2013**, *15*, 136–139.

[115] L. Wang, L. Ackermann, *Org. Lett.* **2013**, *15*, 176–179.

[116] L. Ackermann, L. Wang, A. V. Lygin, *Chem. Sci.* **2012**, *3*, 177–180.

[117] W. Ma, K. Graczyk, L. Ackermann, *Org. Lett.* **2012**, *14*, 6318–6321.

[118] V. S. Thirunavukkarasu, M. Donati, L. Ackermann, *Org. Lett.* **2012**, *14*, 3416–3419.

[119] N. Kavitha, G. Sukumar, V. P. Kumar, P. S. Mainkar, S. Chandrasekhar, *Tetrahedron Lett.* **2013**, *54*, 4198–4201.

[120] Y. Park, I. Jeon, S. Shin, J. Min, P. H. Lee, *J. Org. Chem.* **2013**, *78*, 10209–10220.

[121] S. R. Chidipudi, I. Khan, H. W. Lam, *Angew. Chem. Int. Ed.* **2012**, *51*, 12115–12119.

[122] N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908–6909.

[123] N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011**, *133*, 6449–6457.

[124] L. Ackermann, S. Fenner, *Org. Lett.* **2011**, *13*, 6548–6551.

[125] B. Li, H. Feng, S. Xu, B. Wang, *Chem. Eur. J.* **2011**, *17*, 12573–12577.

[126] K. Parthasarathy, M. Jeganmohan, C.-H. Cheng, *Org. Lett.* **2008**, *10*, 325–328.

[127] K. Parthasarathy, C.-H. Cheng, *J. Org. Chem.* **2009**, *74*, 9359–9364.

[128] P. C. Too, Y.-F. Wang, S. Chiba, *Org. Lett.* **2010**, *12*, 5688–5691.

[129] P. C. Too, S. H. Chua, S. H. Wong, S. Chiba, *J. Org. Chem.* **2011**, *76*, 6159–6168.

[130] T. K. Hyster, T. Rovis, *Chem. Commun.* **2011**, *47*, 11846–11848.

[131] X. Zhang, D. Chen, M. Zhao, J. Zhao, A. Jia, X. Li, *Adv. Synth. Catal.* **2011**, *353*, 719–723.

[132] L. Zheng, J. Ju, Y. Bin, R. Hua, *J. Org. Chem.* **2012**, *77*, 5794–5800.

[133] I. Moritani, Y. Fujiwara, *Tetrahedron Lett.* **1967**, *12*, 1119–1122.

[134] Y. Fujiwara, I. Moritani, M. Matsuda, *Tetrahedron* **1968**, *4819-4824*, 24.

[135] Y. Fujiwara, I. Moritani, S. Danno, R. Asano, S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169.

[136] J. L. Bras, J. Muzart, *Chem. Rev.* **2011**, *111*, 1170–1214.

[137] C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292.

[138] S. Mochida, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2011**, *76*, 3024–3033.

[139] S. Rakshit, C. Grohmann, T. Besset, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2350–2353.

[140] F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9982–9983.

[141] A. S. Tsai, M. Brasse, R. G. Bergman, J. A. Ellman, *Org. Lett.* **2011**, *13*, 540–542.

[142] T. Matsumoto, R. A. Periana, D. J. Taube, H. Yoshida, *J. Catal.* **2002**, *206*, 272–280.

[143] T. Matsumoto, H. Yoshida, *Chem. Lett.* **2000**, *29*, 1064–1065.

[144] P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879–5918.

[145] H. Weissman, X. Song, D. Milstein, *J. Am. Chem. Soc.* **2001**, *123*, 337–338.

[146] L. Ackermann, J. Pospech, *Org. Lett.* **2011**, *13*, 4153–4155.

[147] Y. Hashimoto, T. Ueyama, T. Fukutani, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2011**, *40*, 1165–1166.

[148] Y. Hashimoto, T. Ortloff, K. Hirano, T. Satoh, C. Bolm, M. Miura, *Chem. Lett* **2012**, *41*, 151–153.

[149] L. Ackermann, L. Wang, R. Wolfram, A. V. Lygin, *Org. Lett.* **2012**, *14*, 728–731.

[150] B. Li, J. Ma, N. Wang, H. Feng, S. Xu, B. Wang, *Org. Lett.* **2012**, *14*, 736–739.

[151] K. Graczyk, W. Ma, L. Ackermann, *Org. Lett.* **2012**, *14*, 4110–4113.

[152] K. Padala, S. Pimparkar, P. Madasamy, M. Jeganmohan, *Chem. Commun.* **2012**, *48*, 7140–7142.

[153] K. Padala, M. Jeganmohan, *Org. Lett.* **2011**, *13*, 6144–6147.

[154] K. Padala, M. Jeganmohan, *Org. Lett.* **2012**, *14*, 1134–1137.

[155] K. Shen, Y. Fu, J.-N. Li, L. Liu, Q.-X. Guo, *Tetrahedron* **2007**, *63*, 1568–1576.

[156] Bordwell pKa Table (Acidity in DMSO), 05 May 2014. http://www.chem.wisc.edu/areas/reich/pkatable/l.

[157] C. Verrier, P. Lassalas, L. Théveau, G. Quéguiner, F. Trécourt, F. Marsais, C. Hoarau, *Beilstein J. Org. Chem.* **2011**, *7*, 1584–1601.

[158] L. Ackermann, A. Althammer, S. Fenner, *Angew. Chem. Int. Ed.* **2009**, *48*, 201–204.

[159] L. Ackermann, S. Barfüßer, C. Kornhaaß, A. R. Kapdi, *Org. Lett.* **2011**, *13*, 3082–3085.

[160] L. Ackermann, A. R. Kapdi, S. Fenner, C. Kornhaaß, C. Schulzke, *Chem. Eur. J.* **2011**, *17*, 2965–2971.

[161] L. Ackermann, *Synthesis* **2006**, 1557–1571.

[162] L. Ackermann, A. Althammer, *Org. Lett.* **2006**, *8*, 3457–3460.

[163] L. Ackermann, R. Born, *Angew. Chem. Int. Ed.* **2005**, *44*, 2444–2447.

[164] R. F. Sanchez, F. A. Zhuravlev, *J. Am. Chem. Soc.* **2007**, *129*, 5824–5825.

[165] B. Liégault, I. Petrov, S. I. Gorelsky, K. Fagnou, *J. Org. Chem.* **2010**, *75*, 1047–1060.

[166] L. Théveau, C. Verrier, P. Lassalas, T. Martin, G. Dupas, O. Querolle, L. V. Hijfte, F. Marsais, C. Hoarau, *Chem. Eur. J.* **2011**, *17*, 14450–14463.

[167] F. Besselièvre, S. Piguel, *Angew. Chem. Int. Ed.* **2009**, *48*, 9553–9556.

[168] N. Matsuyama, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2009**, *11*, 4156–4159.

[169] T. Kawano, N. Matsuyama, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2010**, *75*, 1764–1766.

[170] S. H. Kim, S. Chang, *Org. Lett.* **2010**, *12*, 1868–1871.

[171] N. Matsuyama, M. Kitahara, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2358–2361.

[172] M. Kitahara., K. Hirano, H. Tsurugi, T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 1772–1775.

[173] B. P. Berciano, S. Lebrequier, F. Besselièvre, S. Piguel, *Org. Lett.* **2010**, *12*, 4038–4041.

[174] G. C. Reddy, P. Balasubramanyam, N. Salvanna, B. Das, *Eur. J. Org. Chem.* **2012**, 471–474.

[175] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *36*, 3769–3772.

[176] S. G. Newman, C. S. Bryan, D. Perez, M. Lautens, *Synthesis* **2011**, 342–346.

[177] H. Hofmeister, K. Annen, H. Laurent, R. Wiechert, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 727–729.

[178] J. Li, C. Kornhaaß, L. Ackermann, *Chem. Commun.* **2012**, *48*, 11343–11345.

[179] N. Matsuyama, M. Kitahara, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2358–2361.

[180] L. Lu, H. Yan, P. S. S. Zhu, H. Yang, D. L. L. Rong, J. Mao, *Eur. J. Org. Chem.* **2013**, 1644–1648.

[181] K. Jouvin, A. Coste, A. Bayle, F. Legrand, G. Karthikeyan, K. Tadiparthi, G. Evano, *Organometallics* **2012**, *31*, 7933–7947.

[182] M.-N. Birkholz, Z. Freixa, P. W. N. M. van Leeuwen, *Chem. Soc. Rev.* **2008**, *38*, 1099–1118.

[183] J. Huang, J. Chan, Y. Chen, C. J. Borths, K. D. Baucom, R. D. Larsen, M. M. Faul, *J. Am. Chem. Soc.* **2010**, *132*, 3674–3675.

[184] K. Runge, Bachelor Thesis, Georg-August-Universität Göttingen, **2011**.

[185] A. J. Zucchero, P. L. McGrier, U. H. F. Bunz, *Acc. Chem. Res.* **2010**, *43*, 397–408.

[186] P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem. Int. Ed.* **2000**, *39*, 2632–2657.

[187] S. Pivsa-Art, T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467–473.

[188] C. Hoarau, A. D. F. de Kerdaniel, N. Bracq, P. Grandclaudon, A. Coutureb, F. Marsais, *Tetrahedron Lett.* **2005**, *46*, 8573–8577.

[189] L. Ackermann, S. Barfüsser, J. Pospech, *Org. Lett.* **2010**, *12*, 724–726.

[190] N. A. Strotman, H. R. Chobanian, Y. Guo, J. He, J. E. Wilson, *Org. Lett.* **2010**, *12*, 3578–3581.

[191] S. Barfüßer, L. Ackermann, unpublished results.

[192] W. Ma, L. Ackermann, *Chem. Eur. J.* **2013**, *19*, 13925–13928.

[193] M. Sonoda, F. Kakiuchi, N. Chatani, S. Murai, *J. Organomet. Chem.* **1995**, *504*, 151–152.

[194] H. D. Beckhaus, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 593–594.

[195] M. Picquet, C. Bruneau, P. H. Dixneuf, *Tetrahedron* **1999**, *55*, 3937–3948.

[196] S. Chang, Y. Na, E. Choi, S. Kim, *Org. Lett.* **2001**, *3*, 2089–2091.

[197] R. K. Chinnagolla, S. Pimparkar, M. Jeganmohan, *Org. Lett.* **2012**, *14*, 3032–3035.

[198] R. K. Chinnagolla, S. Pimparkar, M. Jeganmohan, *Chem. Commun.* **2013**, *49*, 3703–3705.

[199] A. Togni, T. Hayashi, *Ferrocenes*, VCH, Weinheim, **1995**.

[200] P. Štěpnička, *Ferrocenes: Ligands, Materials, Biomolecules*, John Wiley & Sons, Chichester, **2008**.

[201] L.-X. Dai, X.-L. Hou, *Chiral Ferrocenes in Asymmetric Catalysis*, Wiley-VCH, Weinheim, **2009**.

[202] F. Hessler, I. Císařová, D. Sedlák, P. Bartůněk, M. Kotora, *Chem. Eur. J.* **2012**, *18*, 5515 –5518.

[203] K. N. Tiwari, J.-P. Monserrat, F. de Montigny, G. Jaouen, M.-N. Rager, E. Hillard, *Organometallics* **2011**, *30*, 5424–5432.

[204] T. Moriuchi, T. Hirao, *Acc. Chem. Res.* **2010**, *43*, 1040–1051.

[205] D. R. van Staveren, N. Metzler-Nolte, *Chem. Rev.* **2004**, *104*, 5931–5985.

[206] S. Top, A. Vessiéres, G. Leclercq, J. Quivy, J. Tang, J. Vaissermann, M. Huché, G. Jaouen, *Chem. Eur. J.* **2003**, *9*, 5223–5236.

[207] J. Polin, H. Schottenberger, *Org. Synth.* **1996**, *73*, 262–266.

[208] D.-L. An, Z. Zhang, A. Orita, H. Mineyama, J. Otera, *Synlett* **2007**, 1909–1912.

[209] P. Štěpnička, L. Trojan, J. Kubišta, J. Ludvík, *J. Organomet. Chem.* **2001**, *637-639*, 291–299.

[210] C. Kuper, Master Thesis, Georg-August-Universität Göttingen, **2013**.

[211] K. Takeuchi, S. Sakamoto, Y. Nagayoshi, H. Nishizawa, J. Matsubara, *Eur. J. Cardiothorac. Surg.* **2004**, *26*, 956–9.

[212] J. K. Liu, W. T. Couldwell, *Neurocrit. Care* **2005**, *2*, 124–32.

[213] A. J. Bella, G. B. Brock, *Endocrine* **2004**, *23*, 149–155.

[214] E. D. Kim, R. El-Rashidy, K. T. McVary, *J. Urol.* **1995**, *153*, 361–365.

[215] K. Dienst, Bachelor Thesis, Georg-August-Universität Göttingen, **2012**.

[216] F. H. Westheimer, in *Steric Effects in Organic Chemistry* (Ed.: N. S. Newman), John Wiley & Sons, New York, **1956**, pp. 523.

[217] J. Wang, M. Sánchez-Roselló, J. L. A. na, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.

[218] W. D. Jones, *Acc. Chem. Res.* **2003**, *36*, 140–146.

[219] M. Gómez-Gallego, M. A. Sierra, *Chem. Rev.* **2011**, *111*, 4857–4963.

[220] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066–3072.

[221] D. Zell, Master-Thesis, Georg-August-Universität Göttingen, **2013**.

[222] Y. Xi, H. Yi, A. Lei, *Org. Biomol. Chem.* **2013**, *11*, 2387–2403.

[223] M. Shimizu, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 3478–3483.

[224] P. Schroll, D. P. Hari, B. König, *ChemistryOpen* **2012**, *1*, 130–133.

[225] M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, *J. Am. Chem. Soc* **2008**, *130*, 12886–12887.

[226] J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2009**, *131*, 8756–8757.

[227] L. Furst, B. S. Matsuura, J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *Org. Lett.* **2010**, *2010*, 3104–3107.

[228] R. S. Andrews, J. J. Becker, M. R. Gagné, *Angew. Chem. Int. Ed.* **2010**, *49*, 7274–7276.

[229] M. Yoshikawa, E. Uchida, N. Chatani, N. Murakami, J. Yamahara, *Chem. Pharm. Bull.* **1992**, *40*, 3121–3123.

[230] M. Yoshikawa, E. Uchida, N. Chatani, H. Kobayashi, Y. Naitoh, Y. Okuno, H. Matsuda, J. Yamahara, N. Murakami, *Chem. Pharm. Bull.* **1992**, *40*, 3352–3354.

[231] H. Matsuda, H. Shimoda, J. Yamahara, M. Yoshikawa, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 215–220.

[232] R. Rossi, A. Carpita, F. Bellina, P. Stabile, L. Mannina, *Tetrahedron* **2003**, *59*, 2067–2081.

[233] M. Uchiyama, H. Ozawa, K. T. Y. Matsumoto, M. Y. K. Hiroya, T. Sakamoto, *Org. Lett.* **2006**, *24*, 5517–5520.

[234] A. C. Tadd, M. R. Fielding, M. C. Willis, *Chem. Commun.* **2009**, *45*, 6744–6746.

[235] D. H. Huh, J. S. Jeong, H. B. Lee, H. Ryu, Y. G. Kim, *Tetrahedron* **2002**, *58*, 9925–9932.

[236] Z. Fang, Y. Song, T. Sarkar, E. Hamel, W. E. Fogler, G. E. Agoston, P. E. Fanwick, M. Cushman, *J. Org. Chem.* **2008**, *73*, 4241–4244.

[237] S. Warratz, L. Ackermann, unpublished results.

[238] R. Neumann, M. Dahan, *J. Am. Chem. Soc.* **1998**, *120*, 11969–11976.

[239] E. Lindner, M. Haustein, R. Fawzi, M. Steimann, P. Wegner, *Organometallics* **1994**, *13*, 5021–5029.

[240] J. Shen, E. D. Stevens, S. P. Nolan, *Organometallics* **1998**, *17*, 3875–3882.

[241] H. Yu, Y. Fu, Q. Guo, Z. Lin, *Organometallics* **2009**, *28*, 443–4451.

[242] G. Zhang, X. Wen, Y. Wang, W. Mo, C. Ding, *J. Org. Chem.* **2011**, *76*, 4665–4668.

[243] B. Lu, C. Li, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 14070–14072.

[244] V. K.-Y. Lo, Z. Guo, M. K.-W. Choi, W.-Y. Yu, J.-S. Huang, C.-M. Che, *J. Am. Chem. Soc.* **2012**, *134*, 7588–7591.

[245] L. M. Long, H. R. Henze, *J. Am. Chem. Soc.* **1941**, *63*, 1939–1940.

[246] R. Beckert, E. Fanghänel, W. D. Habicher, P. Metz, D. Pavel, K. Schwetlick, *Organikum*, 22. Aufl., Wiley-VCH, Weinheim, **2004**.

[247] A. M. van Leusen, B. E. Hoogenboom, H. Siderius, *Tetrahedron Lett.* **1972**, *23*, 2369–2372.

[248] V. G. Nenajdenko, A. V. Shastin, V. N. Korotchenko, E. S. Balenkova, *Russ. Chem. Bull.* **2001**, *50*, 1047–1050.

[249] C. Villieras, C. Bacquet, J. F. Normant, *J. Organomet. Chem.* **1975**, *97*, 355–374.

[250] S. J. O'Malley, K. L. Tan, A. Watzke, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2005**, *127*, 13496–13497.

[251] W. D. Ollis, M. Rey, I. O. Sutherland, *J. Chem. Soc. Perkin Trans. I* **1983**, *5*, 1009–1027.

[252] R. Short, M. Carta, C. G. Bezzu, D. Fritsch, B. M. Kariuki, N. B. McKeown, *Chem. Commun.* **2011**, *47*, 6822–6824.

[253] Z. Fang, Y. Song, T. Sarkar, E. Hamel, W. E. Fogler, G. E. Agoston, P. E. Fanwick, M. Cushman, *J. Org. Chem.* **2008**, *73*, 4241–4244.

[254] T. A. Engler, K. D. Combrink, J. E. Ray, *Synth. Commun.* **1989**, *19*, 1735–1744.

[255] M. Kitahara, K. Hirano, H. Tsurugi, T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 1772–1775.

[256] L. Lu, H. Yan, P. Sun, Y. Zhu, H. Yang, D. Liu, G. Rong, J. Mao, *Eur. J. Org. Chem.* **2013**, 1644–1648.

[257] T.-J. Gong, B. Xiao, Z.-J. Liu, J. Wan, J. Xu, D.-F. Luo, Y. Fu, L. Liu, *Org. Lett.* **2011**, *13*, 3235–3237.

[258] S.-C. Chuang, P. Gandeepan, C.-H. Cheng, *Org. Lett.* **2013**, *15*, 5750–5753.

[259] Q. Li, Y. Yan, X. Wang, B. Gong, X. Tang, J. Shi, H. E. Xu, W. Yi, *RSC Advances* **2013**, *3*, 23402–23408.

[260] S. Mochida, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 6295–6298.

[261] R. Rossi, A. Carpita, F. Bellina, P. Stabilea, L. Manninab, *Tetrahedron* **2003**, *59*, 2067–2081.