Sustainable Strategies for Site-Selective C–C Bond Formations through Direct C–H Bond Functionalizations

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aus Homberg (Efze)

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Erklärung

Ich versichere, dass ich die vorliegende Dissertation in der Zeit
von August 2008 bis Januar 2012 am

Institut für Organische und Biomolekulare Chemie
Georg-August-Universität zu Göttingen

auf Anregung und unter Anleitung von

Herrn Prof. Dr. L. Ackermann

selbständig durchgeführt und keine anderen als die angegebenen Hilfsmittel
und Quellen benutzt habe.

Göttingen, den 02.01.2012

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Sabine Fenner

1. Gutachter: Prof. Dr. L. Ackermann
2. Gutachter: Prof. Dr. U. Diederichsen
Tag der mündlichen Prüfung: 25.01.2012

Die vorliegende Arbeit wurde in der Zeit von August 2008 bis Januar 2012 unter der Anleitung von Herrn Prof. Dr. Lutz Ackermann am Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen durchgeführt.

In Liebe meinem Papa

Hilmar Fenner

**14.08.1953 †13.08.2011*

Mut steht am Anfang des Handelns, Glück am Ende.

Demokrit

Contents

Abbreviations

Ac	acetyl
Ad	adamantyl
Alk	alkyl
aq	aqueous
Ar	aryl
ATP	attached proton test
Bn	benzyl
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
calcd.	calculated
cat.	catalytic
cf.	confer
CMD	concerted metalation-deprotonation
CM-phos	2-(2-(dicyclohexylphosphino)phenyl)-1-methyl-1*H*-indole
Coe	cyclooctene
conv	conversion
COSY	correlated spectroscopy
Cp	cyclopentadienyl
Cy	cyclohexyl
δ	chemical shift
Dave-Phos	2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	density function theory
DG	directing group
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxid
dppm	bis(diphenylphosphino)methane
Ed.	editor
e.g.	for example (lat.: exempli gratia)
EI	electron ionization
equiv	equivalents

ESI	electronspray ionization
Et	ethyl
et. al.	et alia
eV	electron-volt
FT	fourier transform
g	gramm
GC	gaschromatography
h	hours
HASPO	heteroatom substituted secondary phosphine oxide
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMBC	heteronuclear multiple bond correlation
n-Hex	*n*-hexyl
HRMS	high resolution mass spectrometry
Hz	Hertz
IMes	1,3-bis(mesityl)imidazolin-2-ylidene
i-Pr	*iso*-propyl
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IR	infrared spectroscopy
isol.	isolated
J	coupling constant
KIE	kinetic isotopic effect
L	ligand
$[M^+]$	molecular ion peak
M	metal
M	molar
m	meta
m	multiplett
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
Mes	mesityl
Min	minute
mL	milliliter
mmol	millimol
m.p.	melting point

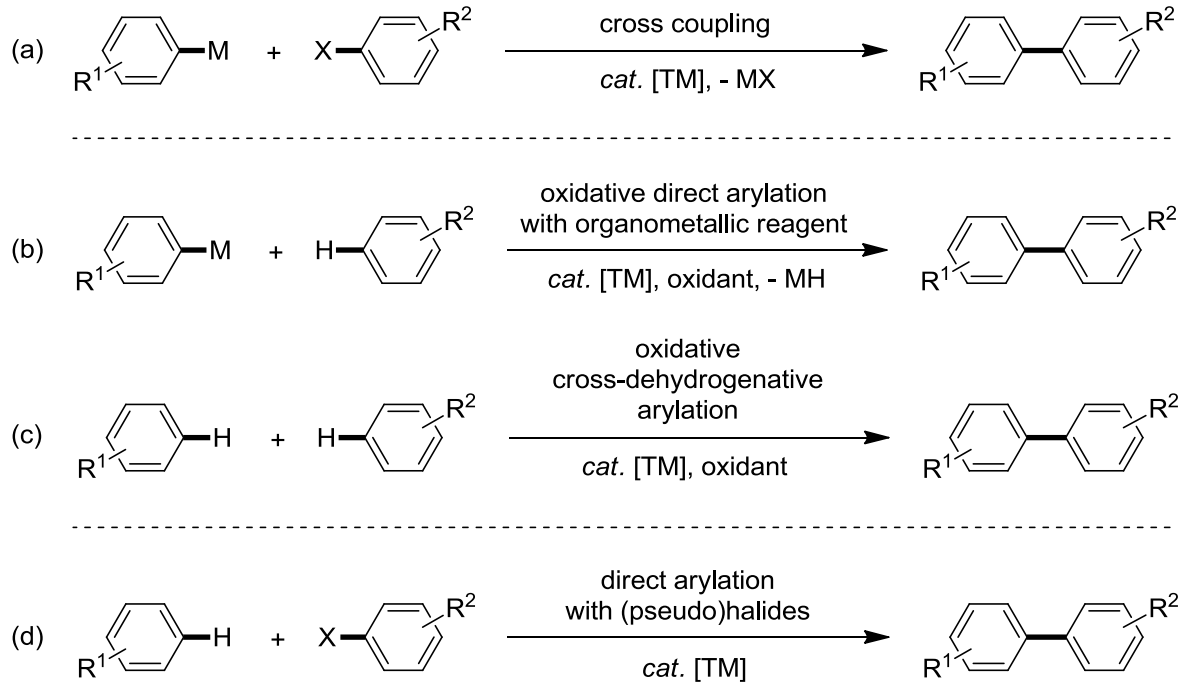
MPV	membrane pump vacuum
Ms	methanesulfonyl
MS	mass spectrometry
m/z	mass-to-charge ratio
N	nucleophilicity parameter
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance spectroscopy
NOESY	nuclear Overhauser enhancement spectroscopy
o	ortho
n-Oct	*n*-octyl
n-Pent	*n*-pentyl
OPV	oil pump vacuum
p	para
Ph	phenyl
PIDA	(diacetoxyiodo)benzene
PIFA	phenyliodo(III)-bis(trifluoroacetate)
Piv	pivalate
ppm	parts per million
Pr	propyl
PTS	polyoxyethanyl α-tocopheryl sebacate
p-Ts	*p*-toluenesulfonyl
py	pyridyl
R	rest
ref.	reference
RP	reversed phase
S_EAr	electrophilic aromatic substitution
sat.	saturated
SET	single electron transfer
solv.	solved
SPO	secondary phosphine oxide
t	(reaction) time
T	temperature
t-AmOH	*tert*-amyl alcohol
TBAB	tetra-*n*-butylammonium bromide

t-Bu	*tert*-butyl
TEMPO	2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
Tf	triflouromethanesulfonyl
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	transition metal
TMS	trimethyl silyl
Tol	tolyl
Ts	*p*-toluenesulfonyl
wt%	weight by volume
X	(pseudo)halide
X-Phos	2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

1 Introduction

1.1 Direct arylations *via* transition-metal-catalyzed C–H bond funtionalizations

The design of novel synthetic methodologies for sustainable, ecologically benign, chemical transformations represents a great challenge to organic chemists. Thus, over the past two decades transition-metal-catalyzed C–H bond functionalizations attracted much attention, as these strategies allow for streamlining organic syntheses.[1,2,3] The ubiquity and relatively low cost of hydrocarbons renders C–H bond functionalizations an attractive alternative to traditional C–C bond forming reactions, such as cross-couplings, where the synthesis of prefunctionalized coupling partners, organo(pseudo)halide, as well as organometallic nucleophile, is required (Scheme 1a).[4]



Scheme 1: Strategies for catalytic synthesis of bi(hetero)aryls.

The preparation of substrates from the corresponding arenes usually includes a number of synthetic operations, which lead to undesired by-products, as does the cross-coupling process itself (Scheme 1a).[5] Hence, direct C–H bond functionalization methodologies represent more atom- and step-economic tools for the construction of bi(hetero)arenes, which are important structural motifs in complex molecules like natural products and bioactive compounds.

Important pharmaceutical agents and agrochemicals like Vancomycin (**1**)[6] and Boscalid (**3**),[7] as well as the liquid-crystalline NCB807 (**2**)[8] comprise bi(hetero)aryl scaffolds (Figure 1).

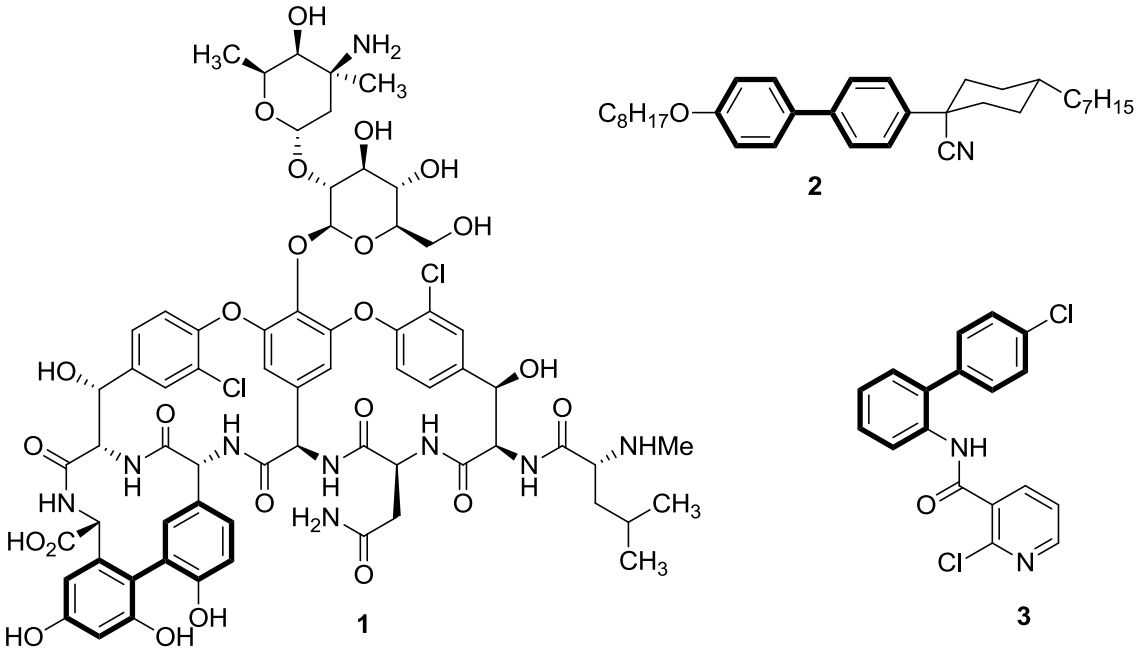


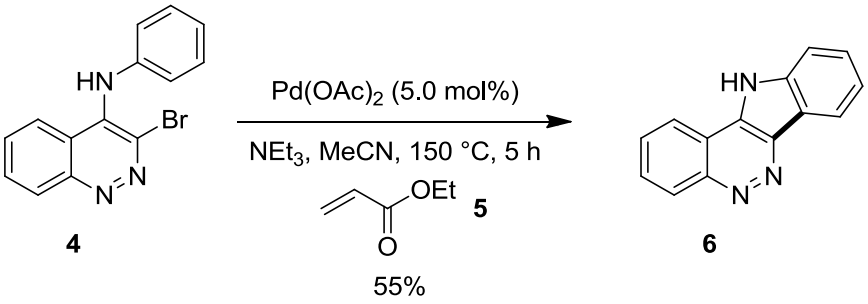
Figure 1: Selected industrially important bi(hetero)aryls.

However, the key challenge of C–H bond functionalizations is the selective cleavage of a specific C−H bond, in molecules, which possess numerous ones with comparable dissociation energies. Thus, the issue of site-selectivity is paramount in the development of any C−H bond functionalization methodology.

Generally, it has to be distinguished between different types of direct catalytic arylation processes, which are dependent on the nature of the coupling partners (Scheme 1). When using stoichiometric amounts of organometallic compounds2[f] or heteroarenes1 as arylating reagents, oxidative direct arylations can be accomplished (Scheme 1b and 1c). A major drawback of these transformations is the indispensability of an external oxidant, to warrant the catalysts regeneration. Furthermore, in cross-dehydrogenative arylations the achievement of site-selectivity is critical. A more convenient approach is represented by the use of (pseudo)halides in direct arylations (Scheme 1d).

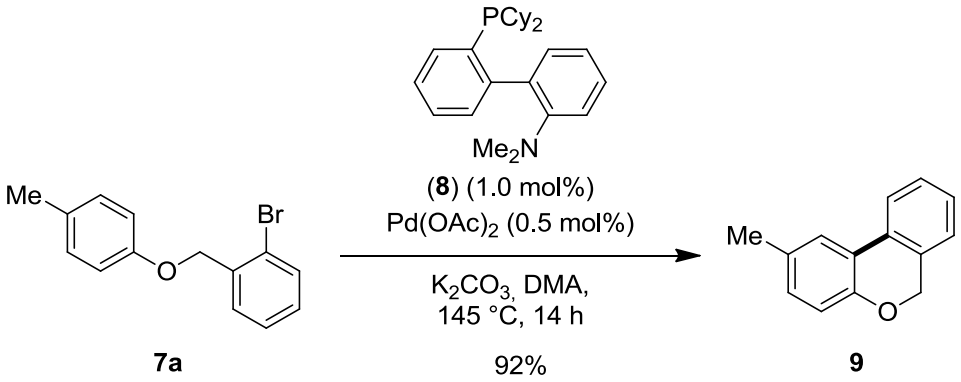
1.1.1 Intra- and intermolecular direct arylations

The regioselectivity in direct arylations of type (d) can be governed by electronic effects, when using aromatic heterocycles or electron-deficient arenes, like oligohalogenated aromatics, as substrates. During the last decades considerable progress has been achieved in this particular field of C–H bond functionalizations.2 However, the very first example of a palladium-catalyzed intramolecular direct arylation has already been presented in 1982 by *Ames*.[9] With the intent to perform a Mizoroki–Heck-reaction, Ames used cinnolin derivative **4** and ethyl acrylate **5** under palladium-catalysis, expecting the formation of an alkenylated product. Instead he obtained compound **6** as a result of an intramolecular direct arylation process (Scheme 2).



Scheme 2: Palladium-catalyzed intramolecular direct arylation by *Ames*.

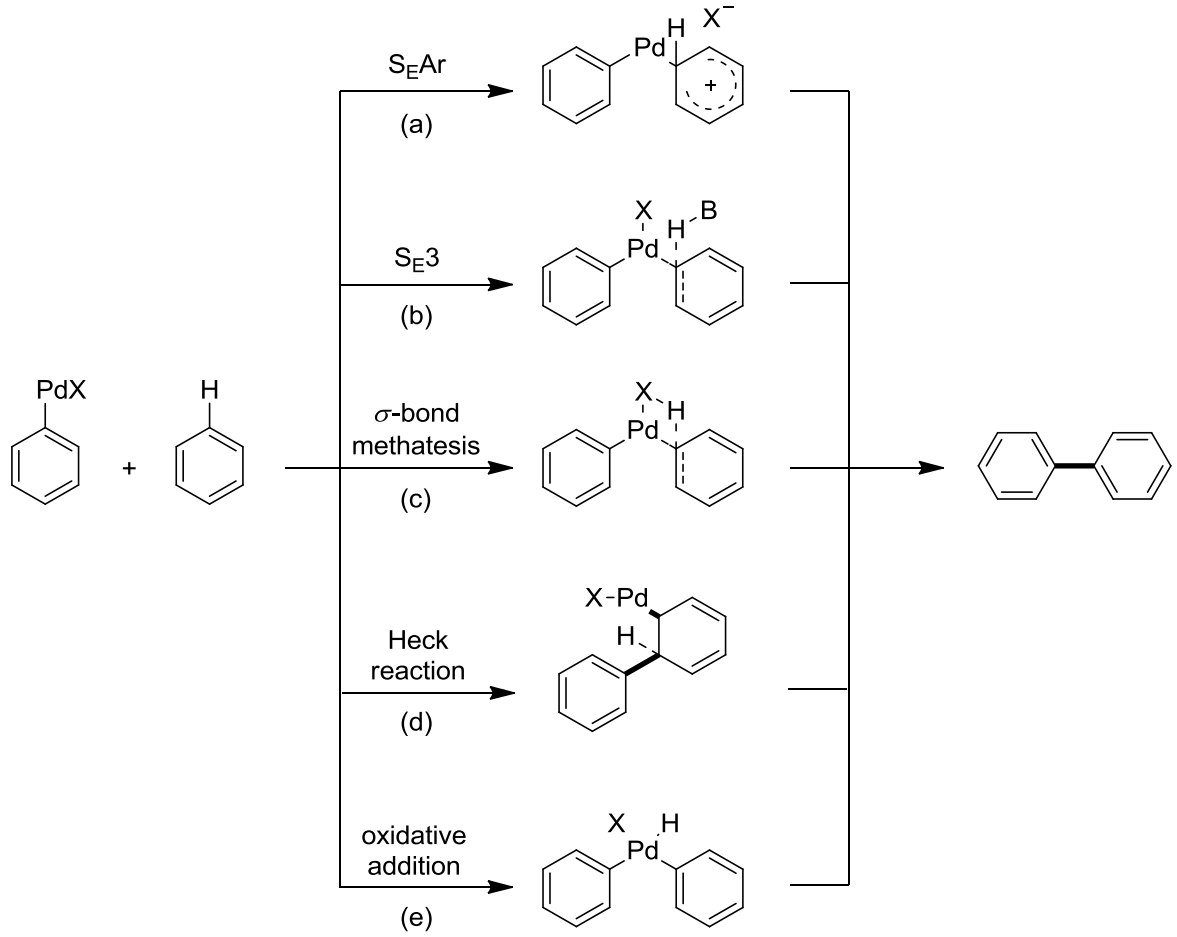
In 2004 *Fagnou* and coworkers succeeded in the development of a generally applicable methodology for palladium-catalyzed intramolecular direct arylations with aryl bromides **7** using palladium(II) acetate in combination with electron-rich biphenyl phosphine ligand **8** as efficient catalyst (Scheme 3).[10]



Scheme 3: Intramolecular C–H bond arylation with bromide **7a** by *Fagnou*.

In terms of mechanistical considerations, intra- and intermolecular direct arylations of arenes are proposed to occur *via* an initial oxidative addition step, in which the transition-metal inserts into the aryl–(pseudo)halide bond, followed by one of the illustrated key carbon–

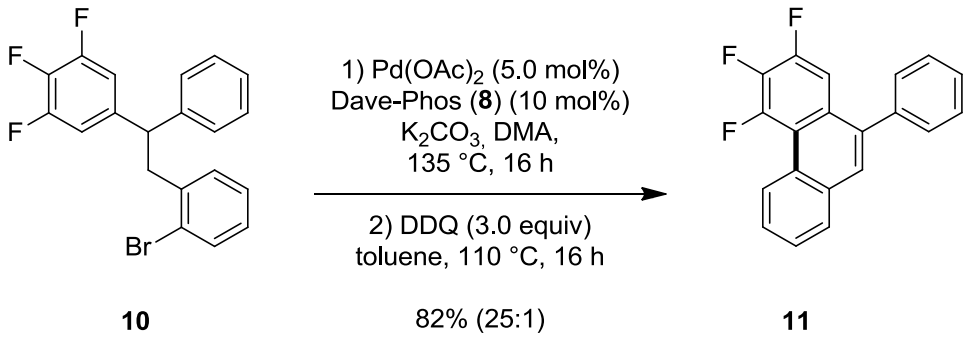
carbon bond-forming steps (Scheme 4):2[b,g] C–H bond metalation may proceed through (a) an electrophilic aromatic substitution at the transition-metal (S_EAr), (b) a concerted S_E3 process, (c) a σ-bond metathesis, (d) a carbometalation process (Heck-type) either through an unusual formal *anti* β-hydride elimination or *via* isomerization followed by a *syn* β-hydride elimination, or (e) a C–H bond oxidative addition.



Scheme 4: Proposed mechanisms for C–H bond palladations in catalytic direct arylations.

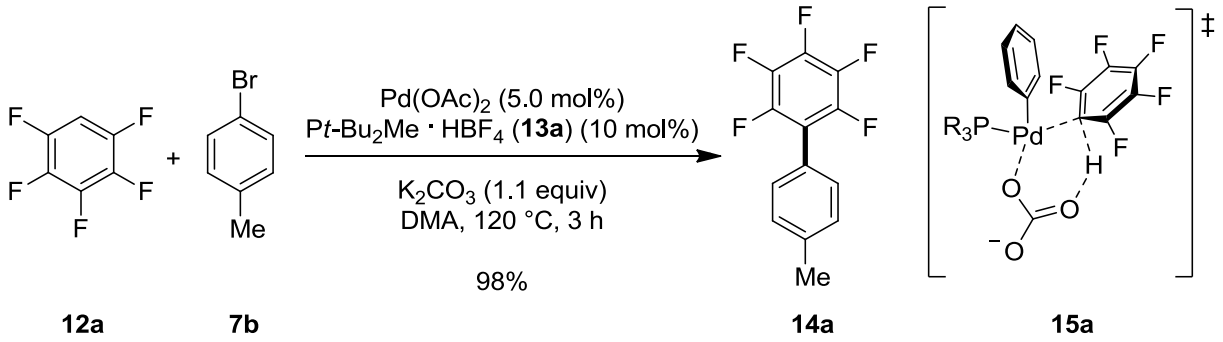
Importantly, the exact mechanism for any direct arylation reaction strongly depends on the substrates, catalyst, solvent, base and additives being used. Nevertheless, most commonly suggested hypotheses are paths (a), (d) and (e).

Striving for a better understanding of working modes in C–H bond functionalization reactions, in 2006, *Echavarren* and coworkers performed intramolecular competition experiments with fluorinated arenes **10** (Scheme 5). They observed preferential C–H bond functionalization at the less nucleohpilic, but more C–H acidic position.[11a] In accordance with computational studies by *Maseras*, a concerted metalation-deprotonation (CMD) mechanism instead of a S_EAr pathway, was hence postulated for this type of reaction.[11]



Scheme 5: Intramolecular competition experiment with fluorinated arene **10** by *Echavarren*.

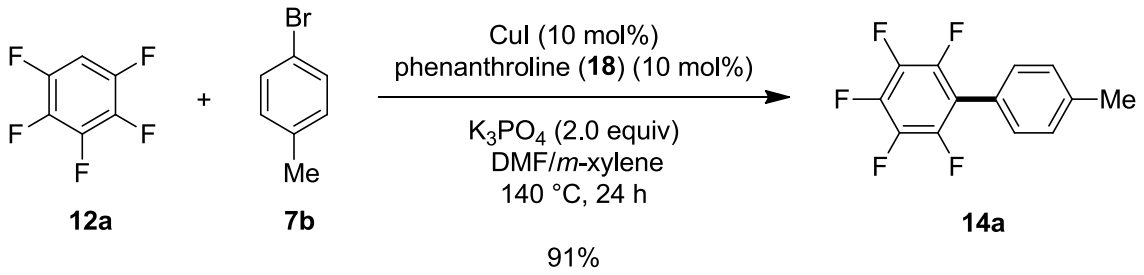
Independently, *Fagnou* reported on catalytic intermolecular direct arylations of perfluoroarenes **12** with aryl bromides **7**.[12] Likewise, he observed inversed reactivity compared to the common electrophilic aromatic substitution pathway, since electron-deficient, C−H acidic arenes **12** reacted preferentially. Computational studies indicated the C−H bond cleavage to occur *via* a concerted palladation-deprotonation pathway, which most likely involves a carbonate-assisted proton-abstraction transistion-state **15a** (Scheme 6).



Scheme 6: Catalytic intermolecular direct arylation of pentafluorobenzene (**12a**) with aryl bromide **7b** by *Fagnou.*

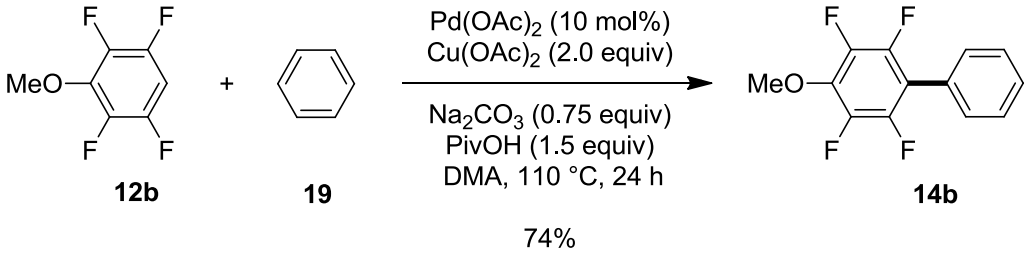
Later, in 2006, the methodology was extended to the use of other fluorinated arenes **12**, as well as the use of sterically demanding aryl bromides **7**, and even chlorides **16** as electrophiles.[13] Furthermore, the group of *Fagnou* found unsubstituted benzene (**19**) to undergo palladium-catalyzed C–H bond arylations in the presence of catalytic amounts of pivalic acid as a proton shuttle.[14] Only recently, the same group reported on ambient temperature direct arylations of fluoroarenes **12**. However, the protocol is restricted to more expensive aryl iodides **17** as arylating reagents.[15]

On the other hand, *Daugulis* presented copper-catalyzed direct arylations and alkenylations of polyfluoroarenes **12** (Scheme 7).[16a] The use of phenanthroline (**18**) as a ligand and potassium phosphate in a solvent mixture of DMF and *meta*-xylene at high temperature, allowed for C–H bond functionalizations of fluoroarenes **12** with iodides **17** and bromides **7**.



Scheme 7: Copper-catalyzed direct arylation of pentafluorobenzene (**12a**) by *Daugulis*.

A more general procedure for copper-catalyzed direct arylations of sp^2 C–H bonds with pK_a values below 35 was presented by the group of *Daugulis* in 2008.[16b] Therein, a variety of electron-rich and electron-poor heteroarenes, as well as substituted, electron-deficient arenes served as viable substrates for direct C–H bond arylations with aryl halides. Noteworthy, in some cases a strong lithium base was required for optimal results. Since 2009, a set of palladium-catalyzed strategies for efficient C–H bond functionalizations of fluorinated arenes **12** have been developed by different groups. *Su* and coworkers reported on direct arylations of fluorinated (hetero)aromatics with arylboronic acids in the presence of a silver(I) salt as a stoichiometric oxidant.[17] Moreover, the same group achieved oxidative, dehydrogenative couplings of fluoro(hetero)aryls **12** with simple arenes **19** employing stoichiometric amounts of copper acetate (Scheme 8).[18]



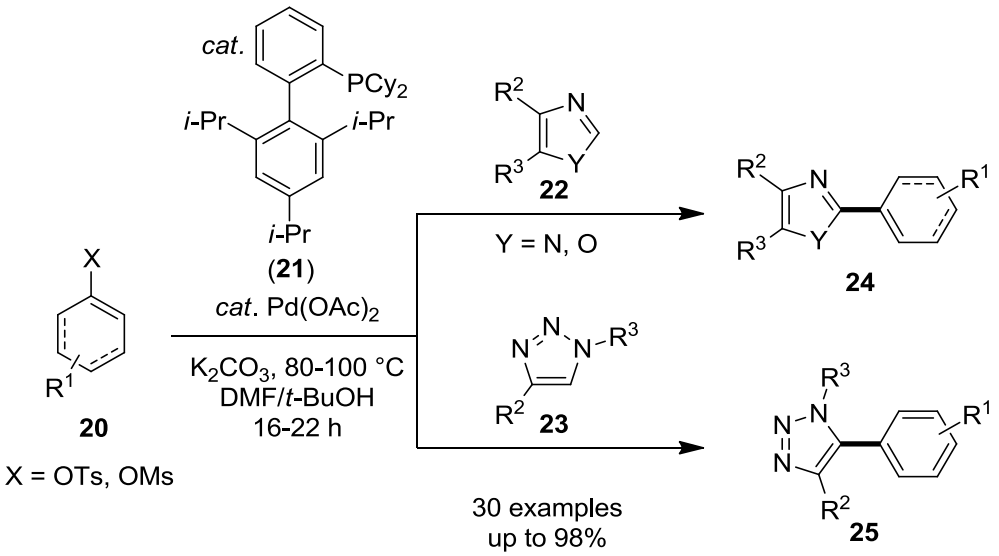
Scheme 8: Palladium-catalyzed oxidative C–H/C–H bond fucntionalization of tetrafluoroanisole **12b** with benzene (**19**) by *Su*.

Another example for cross-dehydrogenative direct arylations under palladium-catalysis with silver carbonate as an oxidant was shown by *Shi* and coworkers in 2011.[19] Indeed, large excess of the arene component was required in these particular transformations, which makes them less attractive from an economical point of view.

Elegant reports on the olefination[20] and benzylation[21] of electron-deficient perfluoroarenes **12** with moderate to good regioselectivities have been presented by *Zhang* and coworkers in 2010. However, when using arenes with less then five fluorine substituents, the use of pivalic acid proved to be pivotal to get high isolated yields of *mono*-arylated products. Very recently, the group of *Zhang* reported on palladium-catalyzed direct C–H bond arylations of

polyfluoroarenes **12** with heteroaryl tosylates **20a**.[22] A catalytic system, comprising palladium di(trifluoroacetate), a biphenyl phosphine ligand and a sterically demanding alkylcarboxylic acid allowed for the heteroarylation of fluorinated arenes **12** with high chemoselectivity and provided access to semiconducting materials.

Certainly, the use of sulfonates **20** as electrophiles in palladium-catalyzed direct arylations of heteroarenes was scarce, hitherto.[23,24] Their readily availability from inexpensive starting materials, like the corresponding phenols or ketones, and their high stability towards hydrolysis renders tosylates an attractive alternative for direct arylations, compared to typically used aryl triflates[25] or halides.2,[26] However, their high stability comes along with a significantly lower reactivity, hence posing a high challenge in their activation. A first example of palladium-catalyzed C–H bond arylations of electron-rich heteroarenes **22** and **23** with tosylates **20a** and mesylates **20b** was disclosed by the group of *Ackermann* in 2009 (Scheme 9).[27,28]

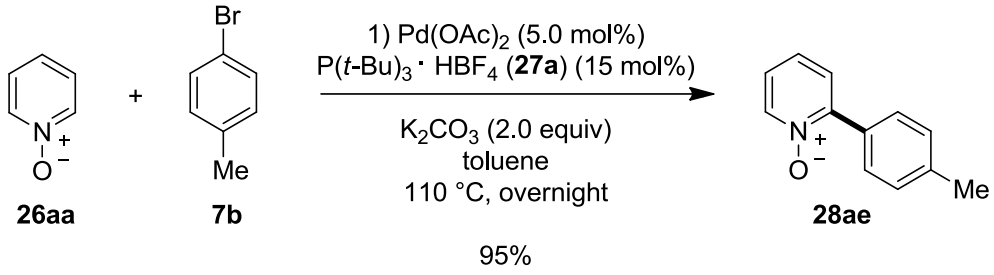


Scheme 9: Palladium-catalyzed direct arylations of heteroarenes **22** and **23** with tosylates **20a** and mesylates **20b**.

A highly active palladium complex enabled C–H bond functionalizations of heteroarenes **22** and **23** using tosylates **20a** or mesylates **20b** with ample scope. More recently, *Kwong* and coworkers reported on palladium-catalyzed direct arylations of electron-rich heteroarenes with mesylates **20b** using the indol-derived CM-phos as ligand.[29,30]

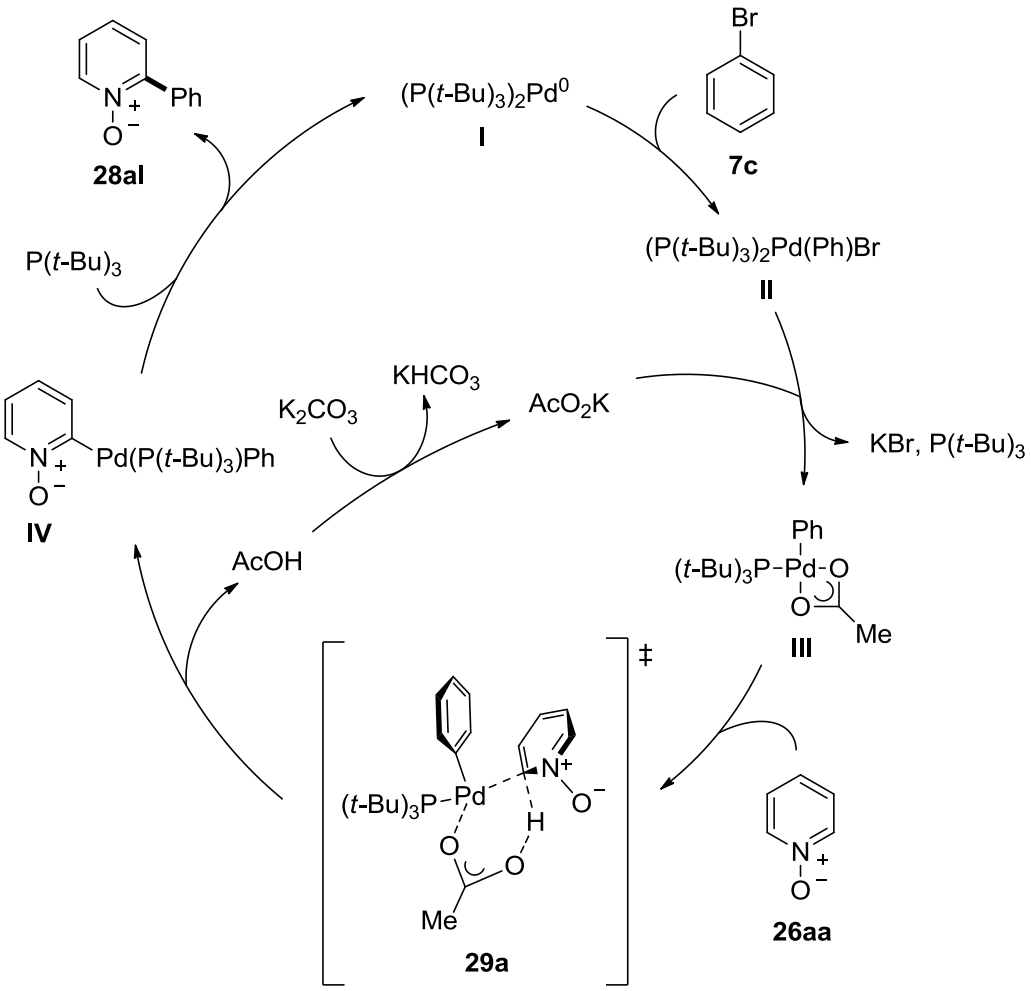
C–H bond functionalizations of electron-deficient heteroarenes were also examined carefully during the past decade.2 Caused by low reactivity or instability of substrates, like oranometallic pyridines, the use of such electron-deficient nucleophiles in cross-couplings is undoubtedly challenging.[31] Hence, the synthesis of bi(hetero)arenes comprising electron-

deficient (di)azine subunits *via* direct arylation constitutes an attractive approach.[32] In this context, palladium-catalyzed regioselective C–H bond functionalizations of pyridine *N*-oxides **26a** with aryl bromides **7** were presented by *Fagnou* and coworkers in 2005 (Scheme 10).[33]



Scheme 10: Palladium-catalyzed direct arylation of pyridine *N*-oxide (**26aa**) with aryl bromide **7b** by *Fagnou*.

Thereafter, numerous reports on transition metal-catalyzed direct arylations of electron-deficient (di)azine *N*-oxides **26** with halides and triflates were disclosed by the same group[34,35,36,37] and others.[26,38] Furthermore, *Fagnou* and coworkers reported on both palladium-catalyzed divergent C_{sp2}–H/C_{sp3}–H direct arylations and sequential C_{sp2}–H/C_{sp3}–H direct arylations.[39] In 2010 a mechanistic analysis of azine *N*-oxide direct arylations was disclosed by *Fagnou* et al., in which the authors point out the critical role of the acetate in the palladium precatalyst. On the basis of extensive mechanistical studies, C–H bond functionalizations were suggested to occur *via* an inner sphere acetate-assisted CMD pathway (Scheme 11).[40,41] In their article, the authors propose an initial fast oxidative addition of the aryl bromide **7c** to the palladium(0) species **I**, affording intermediate **II**. Ensuing, a κ^2-coordination by an acetate anion to the palladium centre provides intermediate **III**. One of the acetate oxygens is subsequently replaced by pyridine *N*-oxide (**26aa**) and C–H bond functionalization is assumed to proceed *via* an inner sphere acetate-assisted CMD transition-state **29a** leading to palladium biaryl species **IV**, which can eventually undergo reductive elimination releasing the arylated product **28al**, as well as the catalytically active palladium(0) species **I**.

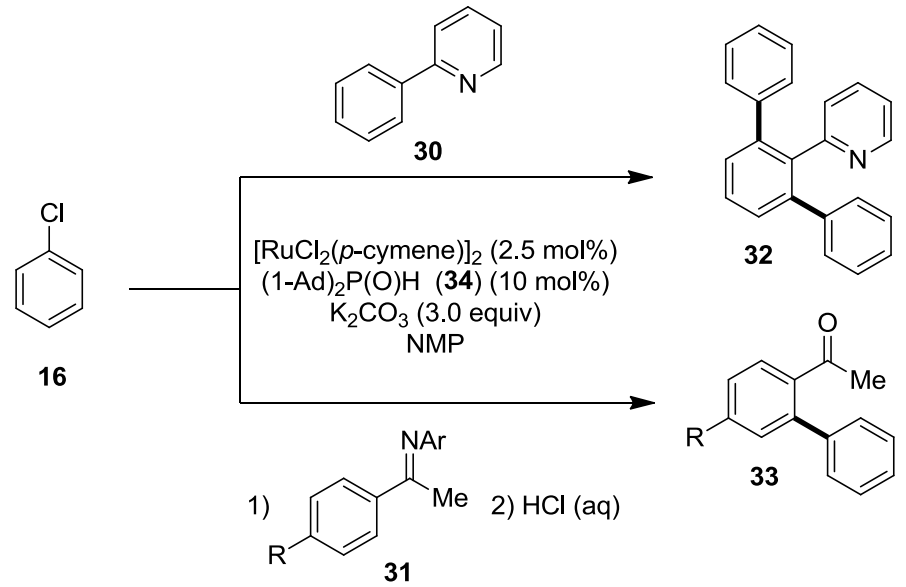


Scheme 11: Proposed catalytic cycle for direct arylations of pyridine *N*-oxides **26a** with aryl bromides **7** *via* a CMD transition-state **29a** by *Fagnou*.

Meanwhile, approaches towards substituted pyridines through C–H bond functionalizations of pyridine *N*-oxides **26a** with Grignard reagents were developed be *Almquist* and *Olsson*.[42] Moreover, metal-free aminiation reactions of (di)azine *N*-oxides **26** were accomplished recently,[43,44] as well as organocatalytic alkynylations and heteroarylations.[45] Palladium-catalyzed oxidative, highly selective alkenylations and direct (hetero)arylations were shown by the group of *Chang*[46] and others.[47,48,49,50,51,52] Importantly, not only *N*-oxides **26** but also other pyridinum derivatives, like *N*-iminopyridinium ylides or *N*-phenacylpyridinium bromides have been successfully employed as substrates in palladium-catalyzed direct arylations with (hetero)aryl halides in recent years.[53,54]

1.1.2 Direct arylations with directing groups

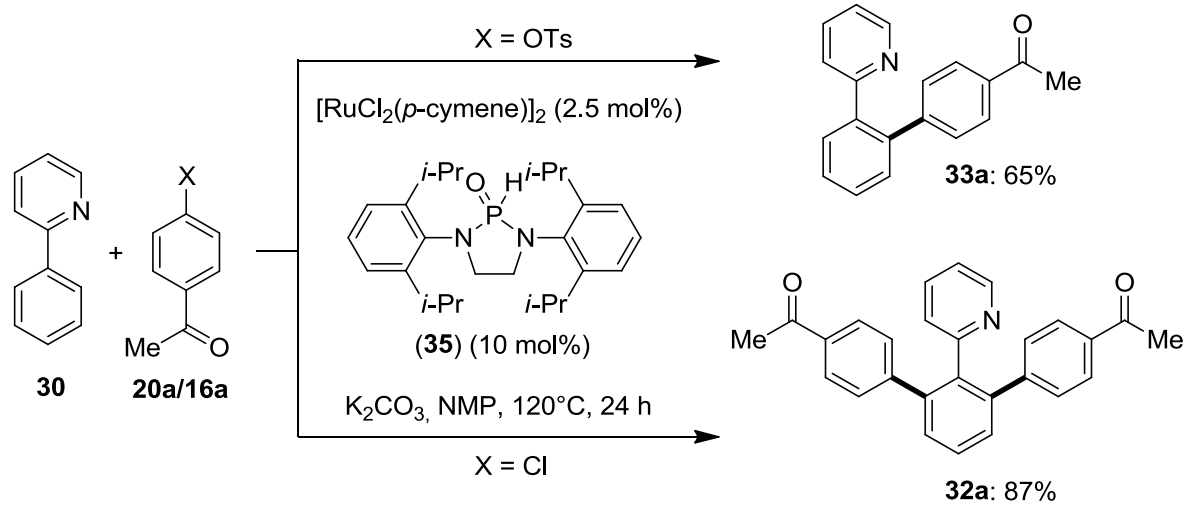
Transformations of electronically neutral arenes often lead to unsatisfactory selectivities. As a solution, strategies have been developed, which employ (potentially removable) directing groups, to coordinate to the transition-metal-catalyst with a lone pair of electrons, thus ensuring regioselectivity. Following this concept, allows intermolecular direct arylations *via* five- or six-membered cyclometalated intermediates in a highly regioselective fashion.[55] Seminal work in this field of research has been done by *Kleinman* and *Dubeck*, who reported on the regioselective formation of an *ortho*-cyclometalated azobenzene-nickel-complex in 1963.[56] Subsequently, valuable, early contributions to transition-metal-catalyzed C–H bond functionalizations have been made by *Murai* and coworkers in 1993, when they described ruthenium-catalyzed regioselective *ortho*-C–H bond alkylations of (hetero)aryl ketones with terminal olefins.[57,58] Ensuing, in 2001 *Oi* and *Inoue* accomplished first ruthenium-catalyzed direct arylations of phenylpyridines **30** with aryl bromides **7**.[59,60] Substantial progress in C–H bond functionalizations of phenylpyridines **30** and related compounds **31** was achieved by *Ackermann* in 2005, when he presented the first application of inexpensive aryl chlorides **16** in ruthenium-catalyzed direct arylations of such kind of pronucleophiles (Scheme 12).[61,62]



Scheme 12: Ruthenium-catalyzed direct arylations of phenylpyridines **30** and imines **31** with aryl chlorides **16** by *Ackermann*.

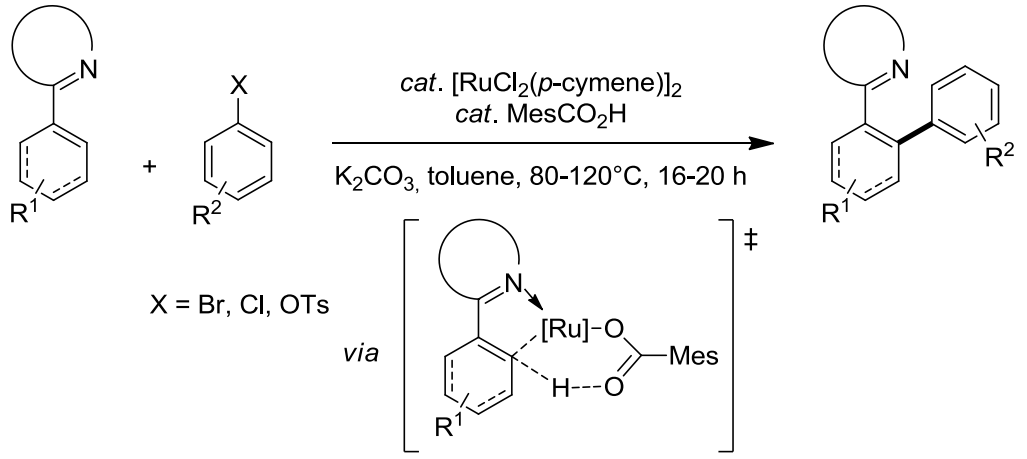
The use of an air-stable, electron-rich secondary phosphine oxide **34** as preligand allowed for unprecedented general ruthenium-catalyzed arylation reactions of phenylpyridines **30** and -imines **31** through C−H bond functionalizations with aryl chlorides **16**. Ongoing from theses results, the group of *Prof. Ackermann* presented the first highly efficient and selective direct

arylations with aryl tosylates **20a** as electrophiles in 2006 (Scheme 13).[63a] A ruthenium complex derived from air-stable diaminophosphine oxide **35** preligand set the stage for C−H bond arylations of pronucleophiles with different directing groups. Notably, the selective formation of either mono- or diarylated products could be controlled through the choice of the electrophile.



Scheme 13: Ruthenium-catalyzed intermolecular direct arylations with chloride **16a** and tosylate **20a** by *Ackermann*.

Further investigations led to the finding, that ruthenium-catalyst in combination with substoichiometric amounts of mesitylcarboxylic acid displays excellent activity in direct C–H bond functionalizations of a variety of pronucleophiles with (hetero)aryl halides as well as moisture-stable, inexpensive tosylates **20a** (Scheme 14).[63b] Regarding previous reports for transition-metal catalyzed direct arylations, a mechanism *via* concerted metallation-deprotonation was assumed by the authors.

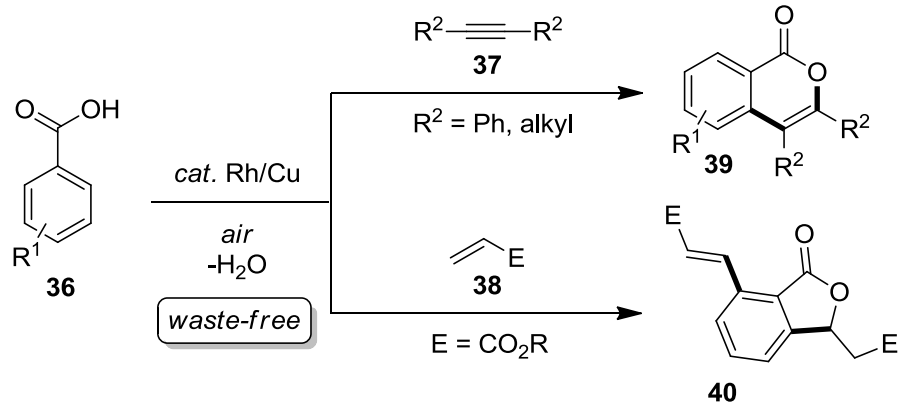


Scheme 14: Carboxylate-assisted, ruthenium-catalyzed C–H bond functionalizations *via* concerted metalation-deprotonation by *Ackermann.*

Moreover, in 2008 *Ackermann* and *Mulzer* found that broadly accessible phenols can be employed as proelectrophiles in ruthenium-catalyzed formal dehydrative direct arylations under similar reaction conditions, which represents an operationally simple and more sustainable approach.[64] Remarkably, recent advancements unfolded that the reaction also proceeds in environmentally benign water as solvent.[65]

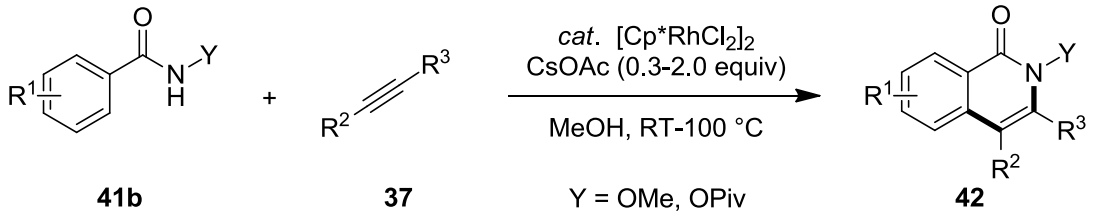
1.2 Transistion-metal-catalyzed directed oxidative transformations

Given the high impact on the development of sustainable chemical processes and striving for a minimized side-product formation, considerable progress was recently achieved in transition-metal-catalyzed oxidative transformations.[66,67] Excellent early work in the field of oxidative cross-dehydrogenative couplings has already been shown by *Miura* and *Satoh* in 2007 (Scheme 15).[68]



Scheme 15: Rhodium-catalyzed waste-free oxidative couplings of benzoic acids **36** with alkynes **37** and acrylates **38** under air by *Miura* and *Satoh*.

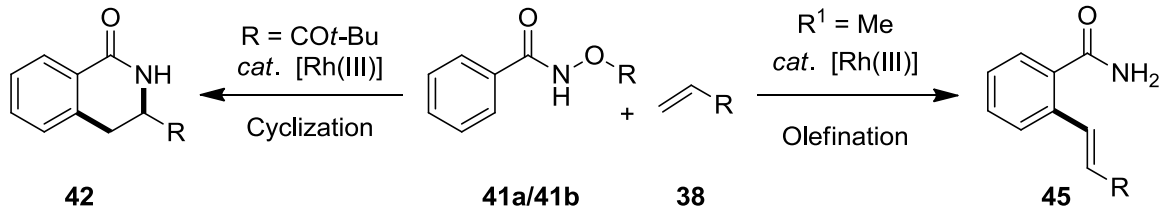
In an elegant report, the authors presented rhodium-catalyzed direct oxidative couplings of benzoic acids **36** with either internal alkynes **37**, or acrylates **38** in the presence of copper acetate as an oxidant under air. Ensuing, in 2010 a number of goups reported on rhodium-catalyzed oxidative synthesis of annulated lactames, such as isoquinolones **42**.[69,70] *Fangou* and coworkers disclosed rhodium-catalyzed redox-neutral isoquinolone **42** syntheses from benzhydroxamic acid esters **41b** through C–H/N–O bond cleavage (Scheme 16).[71,72] Catalytic annulations of alkynes **37** by benzhydroxamic acid esters **41b** proceeded well under rhodium(III)-catalysis and caesium acetate as additive in methanol, without any external oxidant.



Scheme 16: Rhodium-catalyzed annulations of alkynes **37** by benzhydroxamic acid esters **41b** by *Fagnou*.

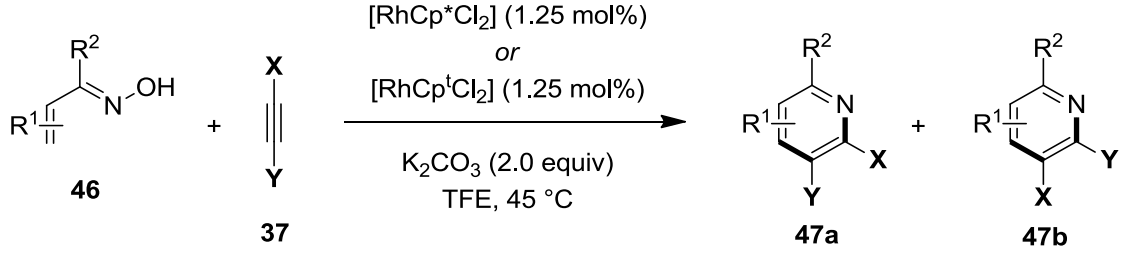
Notably, when using pivalate as a substituent on the nitrogen-atom, the reaction tolerated terminal alkynes and featured mild reaction conditions, as well as high functional group tolerance.[72] On the basis of extensive experimental, as well as computational studies the authors suggested C–H bond functionalizations to occur *via* an acetate-assisted CMD pathway. Labeling-experiments revealed the exact mechanism to strongly rely on the internal oxidant used.

Furthermore, the group of *Glorius* lately presented striking results in rhodium-catalysis, as they accomplished direct C–H olefinations of benzhydroxamic acid esters **41b** with an oxidizing directing group (Scheme 17).[73,74] The introduction of an *N*-methoxy substitutent on the benzamide moiety resulted in the dispensability of an external oxidant.



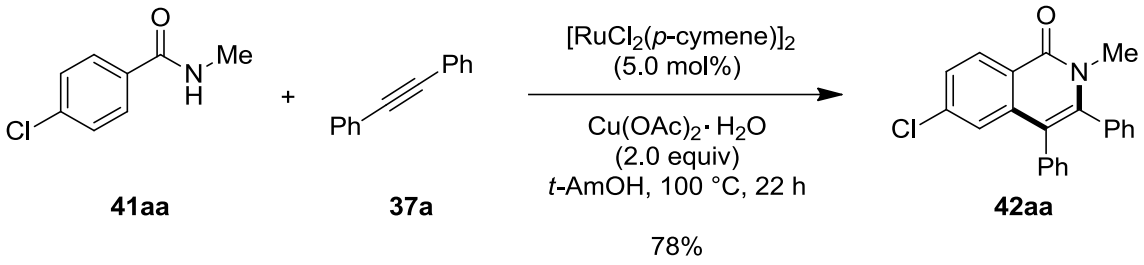
Scheme 17: Rhodium(III)-catalyzed directed C−H bond olefinations using an oxidizing directing group by *Glorius*.

On the other hand, *Hyster* and *Rovis* recently reported on the rhodium(III)-catalyzed synthesis of pyridines **47** from oximes **46** and alkynes **37** under mild conditions without the need of an external oxidant (Scheme 18).[75] Interstingly, different sterical demands of ligands provided complementary selectivities in the product formation.



Scheme 18: Rhodium(III)-catalyzed syntheses of pyridines **47** from oximes **46** and alkynes **37** by *Hyster* and *Rovis*.

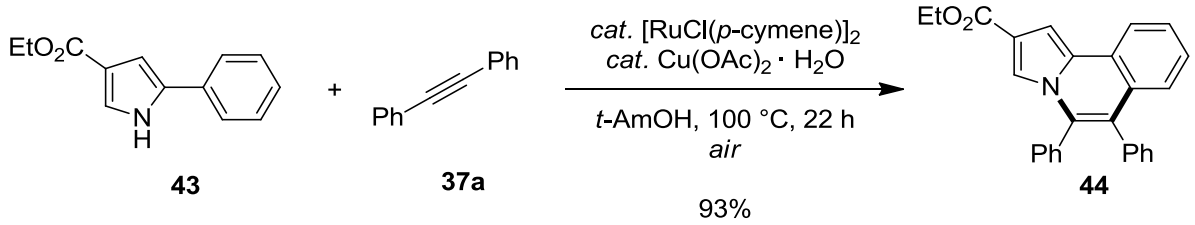
Along with these contributions in rhodium-catalysis, *Ackermann* and coworkers disclosed unprecedented ruthenium-catalyzed oxidative isoquinolone syntheses through C–H/N–H bond cleavage in 2011 (Scheme 19).[76] Intriguingly, less expensive ruthenium-catalyst allowed for oxidative annulations of alkynes **37** by benzamides **41a** with ample scope. Based on detailed experimental studies, a mechanism *via* rate-limiting acetate-assisted deprotonation-ruthenation and subsequent intramolecular oxidative C–N bond formation was proposed by the authors.



Scheme 19: Ruthenium-catalyzed oxidative annulations of alkynes **37a** *via* C–H/N–H bond cleavage by *Ackermann*.

More recently, the methodology was applied to the synthesis of pyridones from acrylamides.[77] Importantly, good chemo- and regioselectivites were achieved and an improved substrate scope, as compared to a related rhodium-catalyzed transformation[78] was accomplished. These results clearly illustrated the beneficial features and remarkable potential of thus far underexplored ruthenium-catalysts in oxidative annulative C–H bond functionalization processes. Besides, in a very recent work, the formation of isoquinolone motif by ruthenium-catalysis using benzhydroxamic acid esters **41b** in methanol as organic solvent was demonstrated by *Wang*.[79]

In 2011 ruthenium-catalyzed oxidative C–H bond alkenylations towards the synthesis of annulated lactones, in water as a reaction medium were disclosed by *Ackermann* and *Pospech*.[80a] Moreover, *Ackermann* and coworkers lately reported on an elegant protocol for ruthenium-catalyzed aerobic oxidative annulations of alkynes **37** with co-catalytic amounts of $Cu(OAc)_2 \cdot H_2O$ under air (Scheme 20).[81] A remarkably broad scope was exploited delivering structural analogues of bioactive marine alkaloids with unparalleled selectivities.



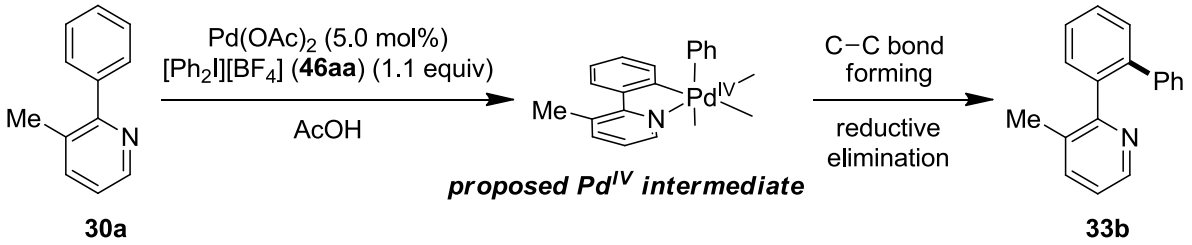
Scheme 20: Ruthenium-catalyzed aerobic oxidative coupling of tolane (**37a**) with 2-aryl-substituted pyrrole **43** by *Ackermann*.

1.3 Hypervalent iodine(III) reagents in C–H bond functionalizations of (hetero)arenes

1.3.1 Transition-metal-catalyzed C–H bond functionalizations

Heteroatom–substituted hypervalent iodine(III) compounds, like iodosobenzene or (diacetoxyiodo)benzene (PIDA) have recently attracted considerable interest as efficient alternatives to toxic heavy-metal-based oxidants and expensive organometallic catalysts for a large number of organic transformations.[82,83] Owing to their highly electron-deficient nature and excellent leaving-group ability, iodine(III) reagents with two carbon ligands have been employed as versatile arylating agents for a variety of nucleophiles in recent years.[84,85,86] While iodonium halides are generally sparingly soluble in organic solvents, the corresponding tetrafluoroborates or triflates display much higher solubility, which, accompanied by their weak to non-existing nucleophilicity, renders them valuable tools for organic syntheses.

Thus, in 2005 the group of *Sanford* reported on palladium-catalyzed oxidative C–H bond functionalization/C–C bond formations with hypervalent iodine(III) reagents (Scheme 21). The reaction was assumed to proceed *via* a P(II)/Pd(IV)-catalytic cycle, wherein the hypervalent iodine(III) compound acts not only as a reagent, but also as an oxidant.[87,88]

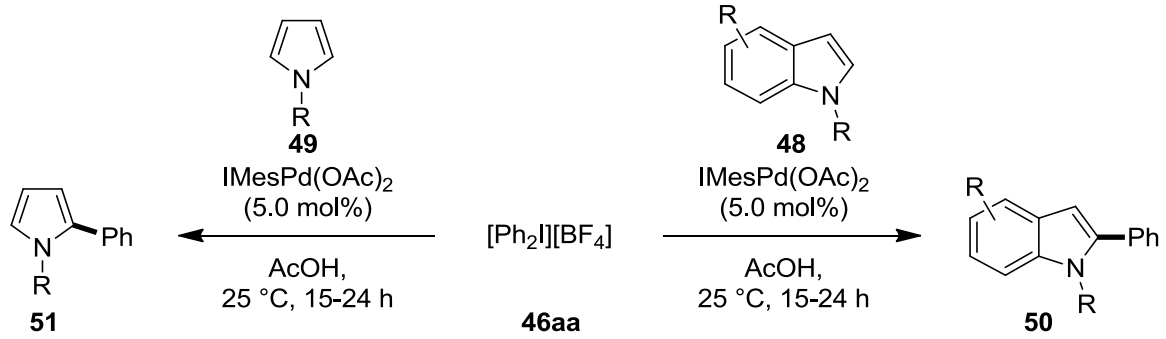


Scheme 21: Palladium-catalyzed direct arylation of phenylpyridine **30a** with iodonium tetrafluoroborate **46aa** by *Sanford*.

Later, in 2009 *Gaunt* and *Phipps* disclosed a *meta*-selective copper-catalyzed C–H bond arylation of anilides with iodonium triflates,[89] which in 2010, was extended to the use of α-arylacetamides.[90] Interstingly, in the latter communication it was supplemented, that pivanilides also undergo metal-free *meta*-selective direct arylations at elevated temperature.[91]

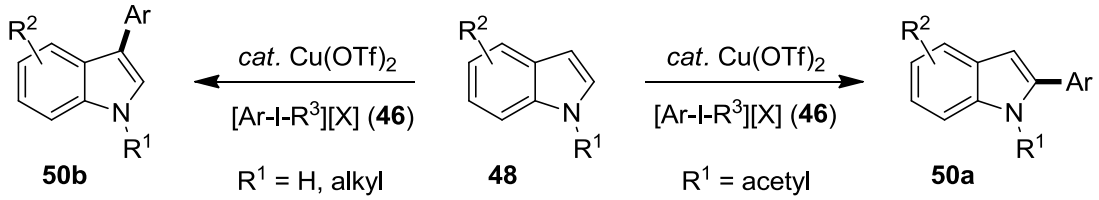
Iodine(III) reagents turned out to be beneficial also as arylating reagents in site-selective C–H bond functionalizations on electron-rich heteroarenes. Thus, in 2006 *Sanford* and coworkers presented a strategy for palladium-catalyzed regioselective C2-arylations of indoles **48** and pyrroles **49** with iodonium tetrafluoroborate **46a** at ambient temperature (Scheme 22).[92] The

reactions proceeded under remarkably mild conditions and the authors proposed these features to be the result of a Pd(II)/Pd(IV) mechanism operating in their presented system.



Scheme 22: Palladium-catalyzed C2-arylations of indoles **48** and pyrroles **49** with iodonium salt **46aa** at ambient temperature.

Besides, an elegant protocol for copper(II)-catalyzed site-selective arylations of indoles **48** with iodonium salts **46** under mild conditions was described by *Gaunt* et al. in 2008 (Scheme 23).[93]



Scheme 23: Copper(II)-catalyzed site-selective arylations of indoles **48** with iodonium salts **46** by *Gaunt*.

In this article, the mechanism of direct arylations was proposed to proceed *via* a Cu(III)-aryl species, which undergoes initial electrophilic addition at the C3-position of the indole **48** to provide intermediate **I** (Figure 2). The selectivity of the reaction is then assumed to result from the nature of the substituent on the nitrogen-atom, which may induce migration of the Cu(III)-aryl group from C3 to C2. With an acetyl group adjacent to the nitrogen-atom, intermediate **II** is proposed to be preferred, due to electronic properties and a directing effect of the carbonyl oxygen.

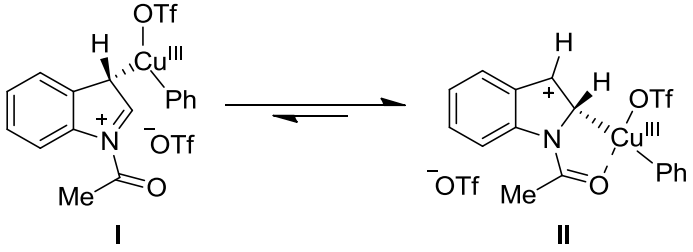
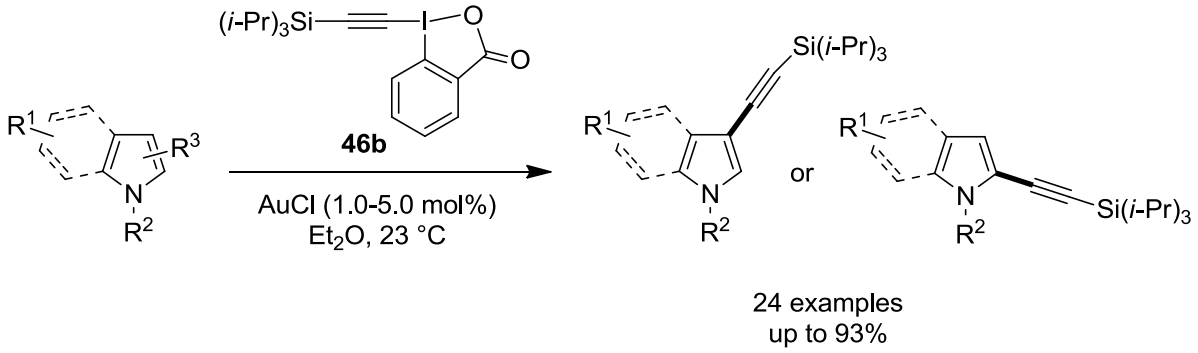


Figure 2: C3 to C2-migration of the Cu(III)-aryl group.

In 2011, *Sanford* accomplished C–H bond functionalizations on pyrroles **49** using diaryl iodonium salts **46** as arylating reagents under palladium-catalysis, with a broad scope of viable pyrrole **49** substrates.[94]

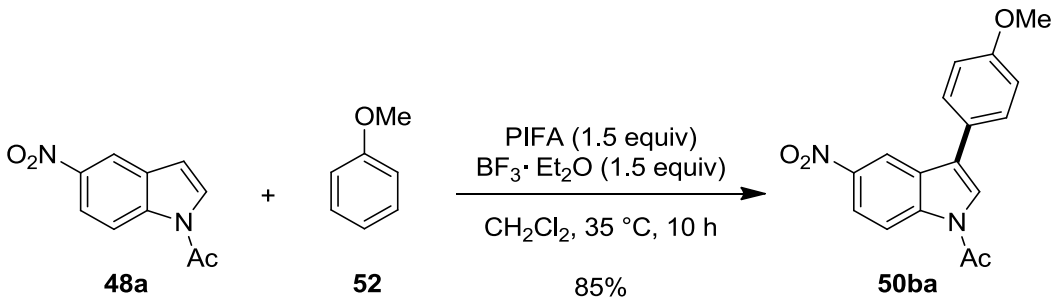
An innovative strategy for indole- and unprecedented pyrrole-alkynylations under gold-catalysis using benziodoxolone-based hypervalent iodine(III) reagent **46b** was reported by the group of *Waser* in 2009 (Scheme 24).[95] Low catalyst-loadings, mild reaction conditions and a high functional group tolerance renders this procedure an important contribution to synthetic organic chemistry.



Scheme 24: Gold-catalyzed direct alkynylations of indoles **48** and pyrroles **49** by *Waser*.

1.3.2 Transition-metal-free C–H bond functionalizations

An approach for metal-free oxidative direct C3-arylations of *N*-acetylindole **48a** with anisole **52** was demonstrated by *Gu* and *Wang* in 2010 (Scheme 25).[96] The use of phenyliodine bis(trifluoroacetate) and $BF_3 \cdot Et_2O$ provided the corresponding arylation product in a highly regioselective fashion *via* a SET process.

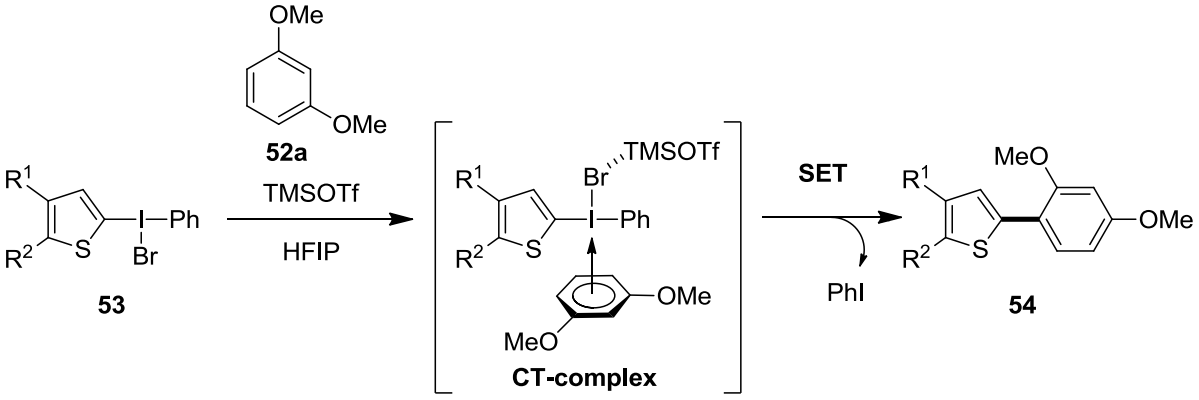


Scheme 25: Metal-free oxidative coupling of lindole **48a** and anisole **52** by *Gu* and *Wang*.

Moreover, a direct arylation process for the functionalization of heteroarenes with iodonium salts **46** was presented by *Zhang* and *Yu*, very recently.[97,98] Remarkably, the described arylation reactions are promoted by sodium hydroxide in the absence of a transistion-metal-

catalyst. Experiments with the radical traps TEMPO or 1,1-diphenylethylene resulted in trace amounts of product and low conversion, respectively. Based on these observations, the authors proposed a radical mechanism, which had previously been suggested by *Shi*.[91b]

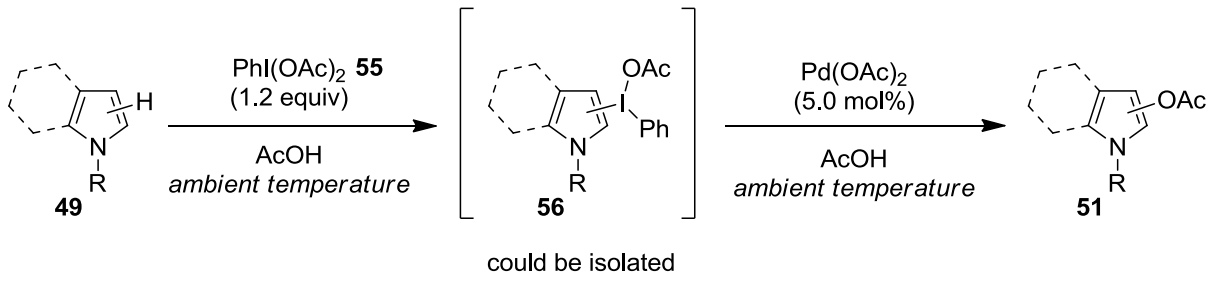
Besides, *Kita* et al. discovered a strategy for an unprecedented formal substitution process at the *ipso*-carbon-atom of heteroaromatic rings **53** in diaryliodonium salts **46**, *via* a SET mechanism, which enabled the synthesis of a variety of bi(hetero)aryl compounds **54** under metal-free conditions (Scheme 26).[98b]



Scheme 26: *ipso*-Substitution of diaryliodonium bromides **53** initiated by a SET oxidizing process by *Kita*.

1.3.3 Hypervalent iodine(III) reagents in C–O bond forming reactions

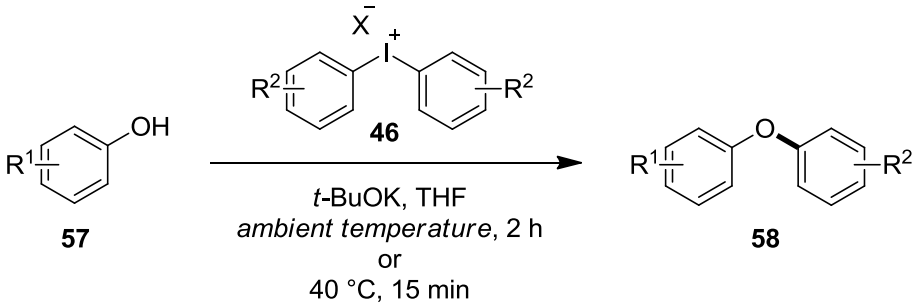
Recently, palladium-catalyzed regioselective C3-acetoxylations of 2,3-unsubstituted indoles with di(acetoxyiodo)benzene,[99] through C–H bond cleavage/C–O bond forming under mild conditions were described independently by the groups of *Kwong*[100] and *Lei*.[101] In addition, *Suna* et al. reported on palladium-catalyzed acetoxylations of pyrroles **49** under mild conditions (Scheme 27).[102] The authors were able to isolate pyrrolyl(aryl)iodonium acetates **56** as intermediates, which they suggested to be subsequently converted into the corresponding acetoxylation products **51** under palladium-catalysis.



Scheme 27: Palladium-catalyzed acetoxylations of pyrroles **49** by *Suna*.

Importantly, this type of mechanism differs from closely related palladium-catalyzed C2-arylations of pyrroles **49** with diaryliodonium salts **46** *via* initial carbopalladation of the pyrrole ring (cf. ref. 92).

Furthermore, *Olofsson* and coworkers reported on syntheses of diaryl ethers **58** at ambient temperature in the absence of any transition-metal-catalyst (Scheme 28).[98a] In the described procedure, simple phenols **57** were successfully reacted with differently substituted diaryl iodonim salts **46**.



Scheme 28: Metal-free syntheses of diaryl ethers **58** with the use of diaryliodonium salts **46** at ambient temperature by *Olofsson*.

1.4 Further site-selective C–H bond functionalization strategies on indoles and pyrroles

Indoles and pyrroles are integral parts in a large number of biologically active natural products, functional materials, agrochemicals, as well as in pharmaceuticals,[103] like Fluvastatin (**59**) or Lipitor (**60**) (Figure 3). Thus, the development of methodologies, which enable site-selective functionalizations of these heteroaromatics is of utmost importance.[104] Further strategies for efficient C–H bond functionalizations of indoles and pyrroles, beside the use of hypervalent iodonium salts will be illustrated in the following.

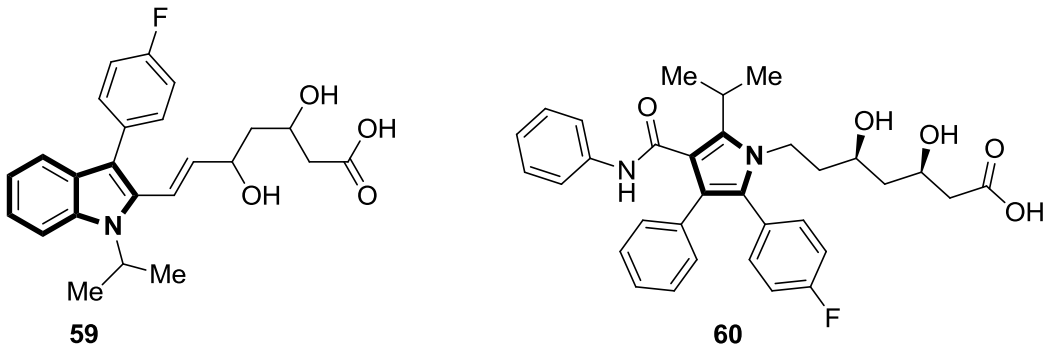
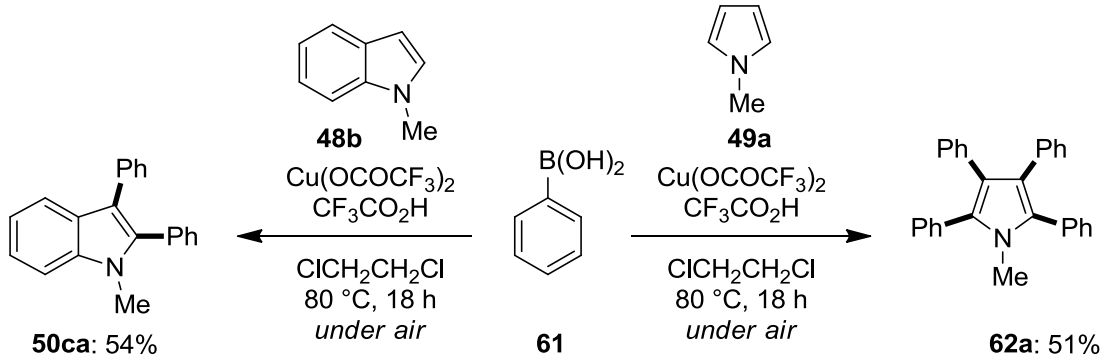


Figure 3: Indole- and pyrrole substructures in pharmaceuticals.

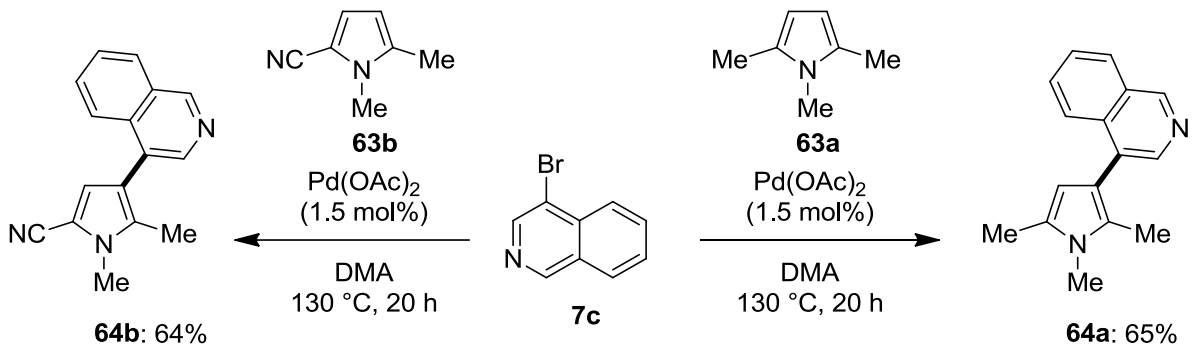
A pioneering early example of palladium-catalyzed, regioselective intermolecular direct arylation reactions of 2,3-unsubstituted indole derivatives with an electronically activated heteroaryl chloride was disclosed by *Otha* and coworkers.[105] They found the regioselectivity to be strongly depended on the substituents adjacent to the nitrogen-atom, as *N*-unsubstituted indoles and its *N*-alkylated derivatives provided 2-heteroarylated products, while the corresponding *N*-tosyl substituted indole derivatives resulted in functionalizations at the C3-position.

Since then, a plethora of C–H bond functionalization strategies has been developed among the organic chemical society. Various new techniques for the efficient, selective introduction of any kind of substitutents on indole and pyrrole cores have been published in esteemed natural science journals. A selected example illustrates copper(II)-mediated C–H bond functionalizations of *N*-methylindole **48b** and *N*-methylpyrrole **49a** using phenylboronic acid **61** under air, which was presented by the group of *Itami* in 2008.[106] Copper triflate enabled multiple C–H bond arylations. By this means 2,3-diarylated, as well as fully decorated pyrrole **62a** were obtained in reasonable yields (Scheme 29). Furthermore, electron-rich di-*ortho*-substituted arenes were successfully reacted with a range of boronic acids **61**.[106]



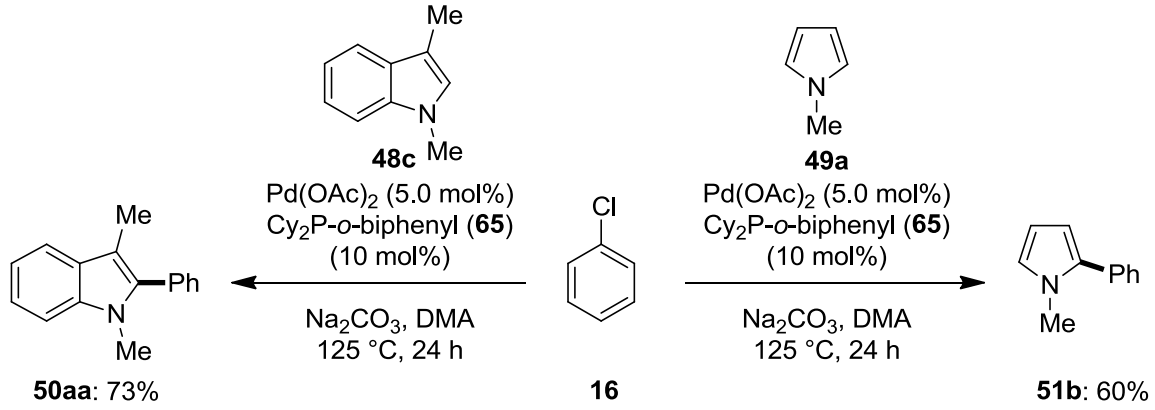
Scheme 29: Copper-mediated C–H bond arylations of *N*-methylindole **48b** and *N*-methylpyrrole **49a** by *Itami*.

Along with these contributions using organometallic arylating reagents, *Doucet*[107] reported on palladium-catalyzed direct C3- or C4-functionalizations of 2,5-disubstituted pyrroles **63** with bromides **7** (Scheme 30). Unfortunately, the methodology was restricted to activated aryl bromides **7**, whereas aryl chlorides **16** were found to be unreactive under the presented conditions. Notably, a wide range of functional groups like acetyl, formyl, nitro or trifluoromethyl groups on the electrophile were well tolerated in this reaction. Likewise, electron-deficient heteroaryl bromides **7** could be employed as electrophiles.



Scheme 30: Palladium-catalyzed direct functionalizations of 2,5-disubstituted pyrroles **49** with bromide **7c**.

Very recently, *Daugulis* demonstrated palladium-catalyzed C–H bond functionalizations of indoles, pyrroles and furanes with inexpensive aryl chlorides as arylating reagents (Scheme 31).[108] The reaction of 1,3-dimethylindole (**48c**) with chlorobenzene (**16**) afforded indole **50aa** in a good yield. A drawback of the methodology was displayed by modest selectivities. When 2,3-unsubstituted indoles, comprising more than one potential site for reactions, were employed as substrate, the C2-arylated product were preferentially formed, though C–H bond functionalizations at the C3-position, as well as the formation of 2,3-diarylated products in small amounts, could not be restrained entirely. In contrast, *N*-methylpyrrole **49a** afforded C2-substituted product **51b** exclusively (Scheme 31).

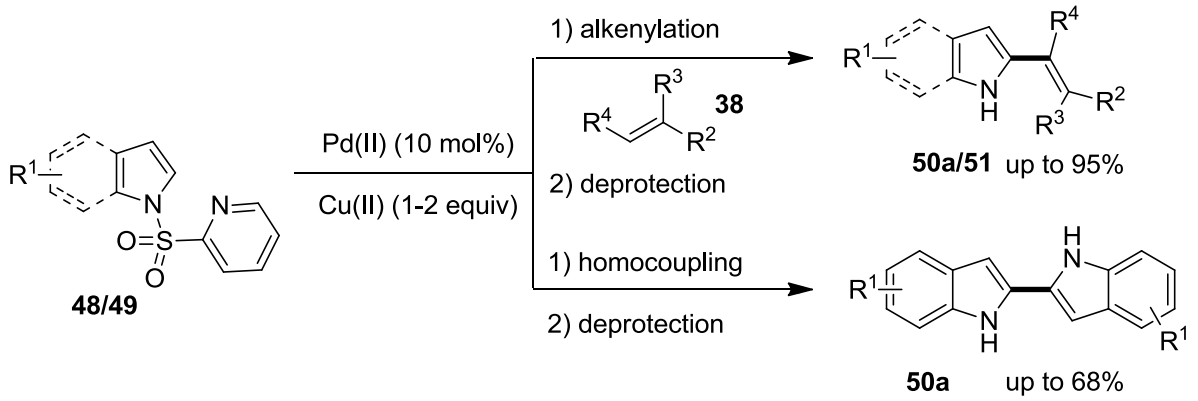


Scheme 31: Palladium-catalyzed arylations of indole **48c** and pyrrole **49a** with chlorobenzene (**16**) by *Daugulis*.

On the contrary, *Sames* and coworkers devised a protocol for phosphine-free palladium-catalyzed C2-selectiv direct arylations of indoles **48** and pyrroles **49** with aryl halides in 2007.[109] However, the procedure was restricted to the use of more expensive aryl iodides **17** and bromides **7**, but excellent regioselectivities were achieved.

Beside the recent progress in direct arylations, innovative strategies for oxidative C2-selective alkenylations of indoles **48** and pyrroles **49** were described. Efficient, palladium-catalyzed C–H bond functionalizations, assisted by a removable directing group, were accomplished by

Arrayás and *Carretero* in 2010.[110] A variety of substituted alkenes **38** were well tolerated in the reaction, and subsequent deprotection afforded free (*N*H)-indoles **50a** and -pyrroles **51** in good yields (Scheme 32). Indeed, the reactions only proceeded in the presence of copper acetate as an oxidant. Based on mechanistic studies, the authors suggested a chelation-assisted electrophilic aromatic-palladation pathway most likely to be operative in the presented oxidative coupling reaction.

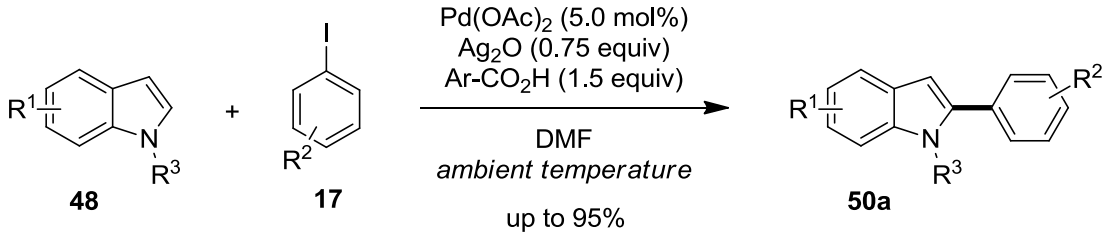


Scheme 32: Oxidative palladium-catalyzed, alkenylations of indoles **48** and pyrroles **49** by *Arrayás* and *Carretero.*

Furthermore, dehydrogenative homocoupling of indoles **48** was achieved under slightly modified reaction conditions.[110]

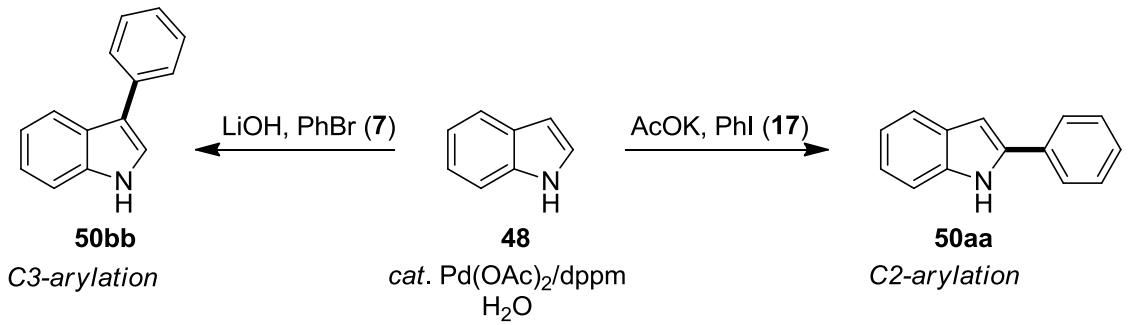
1.4.1 Site-selective palladium-catalyzed direct C–H bond arylations on indoles

In 2008, *Larossa* reported on highly efficient palladium-catalyzed regioselective direct arylations of indoles **48** by the use of aryl iodides **17** as arylating reagents, along with *p*-nitrobenzoic acid and Ag_2O as additives (Scheme 33).[111] The reaction proceeded well in the absence of phosphines or other ligands at ambient temperature. These mild conditions allowed a broad set of functionalities both in the indole **48** and the aryl iodide **17** moiety.



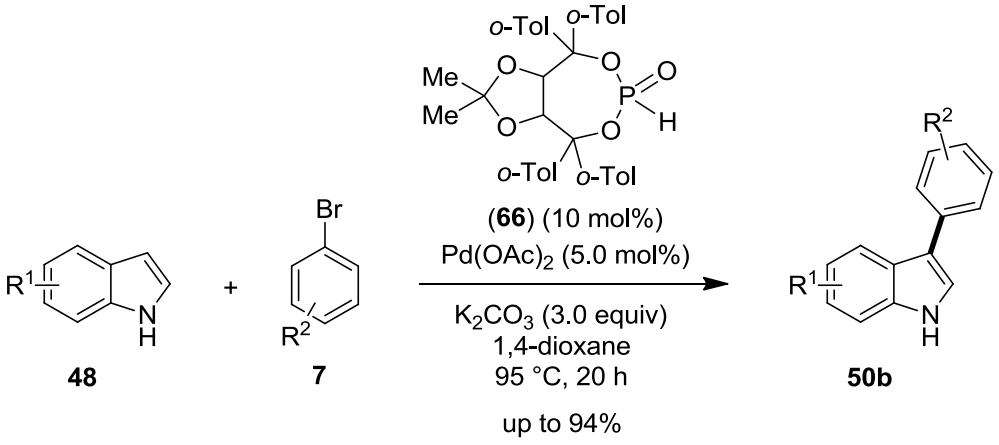
Scheme 33: Phosphine-free palladium-catalyzed direct C2-arylation of indoles **48** at ambient temperature by *Larossa*.

More recently, *Djakovitch* and coworkers reported on a versatile catalytic system based on palladium acetate/dppm for site-selective C–H bond arylations of (*N*H)-indoles **48** on environmentally benign, nontoxic water (Scheme 34).[112] The methodology showed high chemo- and regioselectivities and structural versatility with regard to either indole or aryl moieties. Employing bromobenzenes **7** in combination with lithium hydroxide afforded C3-arylation in a highly regioselective fashion, whereas the use of iodobenzenes **17** and potassium acetate resulted in exclusive C2-arylations of indoles.



Scheme 34: Tunable functionalizations of (*N*H)-indoles **48** through base/halide-controlled regioselective palladium-catalyzed C–H arylation by *Djakovitch*.

On the other hand, a procedure for palladium-catalyzed highly regioselective C3-arylation of (*N*H)-indoles **48** under ligand-free conditions with aryl bromides **7** was presented by *Bellina* and *Rossi*.[113] However, the methodology does not work for indoles containing electron-withdrawing substituents. Ensuing, in 2009 *Ackermann* and *Barfüßer* developed a highly efficient catalytic system comprising an *in-situ* generated palladium complex derived from air-stable HASPO preligand **66** for direct C3-arylations of indoles **48** (Scheme 35).[114] The active catalyst allowed for regioselective arylations of various indoles **48** employing divers aryl bromides **7** as electrophiles.

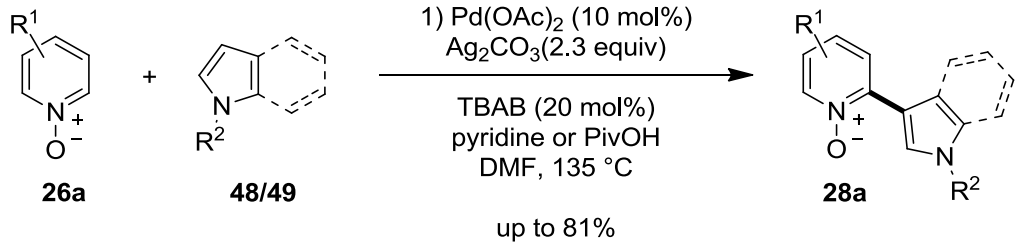


Scheme 35: Palladium-catalyzed direct C3-arylations of indoles **48** with air-stable HASPO preligand **66** by *Ackermann*.

In 2007 a breakthrough in catalytic direct oxidative couplings of unactivated arenes was accomplished by *Stuart* and *Fangou*.[115] The authors reported on first palladium-catalyzed C–H bond arylations of *N*-actylindoles **48a** with simple benzene derivatives **19**. High regioselectivities could be achieved with preferential formation of the C3-arylated products. It is noteworthy, that homo-coupling products of either indole or benzene were not observed under the optimized reaction conditions.

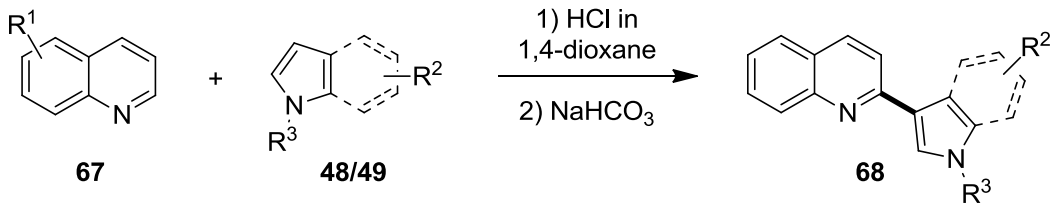
Subsequently, *DeBoef* and coworkers disclosed palladium-catalyzed oxidative arylations of *N*-acetylindoles **48a** with (pentafluoro)benzene **12a**.[116] Interestingly, the regioselectivity of the arylation process was controlled by the oxidant used. Copper acetate in stoichiometric amounts provided selective arylations at the C3-position, whereas the use of silver acetate led to the exclusive formation of C2-arylated products. However, the efficiency of the catalytic system turned out to be narrow, displayed by modest isolated yields of products.

A worthwhile contribution to oxidative couplings beween electronically distinct nitrogen containing heteroarenes was recently disclosed by *Zhang* and *Li*.[49] The catalytic system comprising palladium acetate, silver carbonate as an oxidant, and pyridine or pivalate as additives, featured high activity and provided a variety of biheteroaryls in moderate to good yields *via* two-fold C–H functionalization at the C2-position of the *N*-oxide **26** and the C3-position of the indole **48** or pyrrole **49** (Scheme 36). High regio- and chemoselectivities were achieved under the optimized reaction conditions. Experiments with deuterium-labeled substrates gave strong evidence for a rate-limiting cleavage of the *N*-oxide C–H bond. Moreover, the authors pointed out, that the corresponding 2-heteroarylpyridines are easily accessible *via* deoxygenation with trichlorophosphine in toluene.



Scheme 36: Palladium-catalyzed oxidative coupling between pyridine *N*-oxides **26a** and indoles **48** or pyrroles **49** by *Zhang* and *Li*.

Envisaging more ecological and economical strategies for the connection of two (hetero)aryl moieties,3 very lately an innovative methodology for metal-free autoxidative coupling of quinolines **67** with indoles **48** and pyrroles **49** was reported by *Bergman* and *Ellman* (Scheme 37).[117]



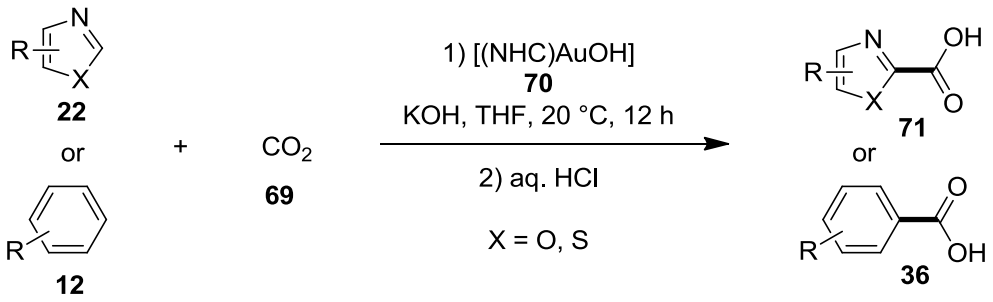
Scheme 37: Coupling of quinolines **67** with indoles **48** and pyrroles **49** by *Bergman* and *Ellman*.

Remarkably, regioselective oxidative formation of the C–C bond required no external oxidant catalyst or oxidizing reagent, but simple mineral acid, to provide indolyl- **68a** and pyrrolyl-quinolines **68b** *via* the formation of an isoquinolonium hydrochloride as electrophilic intermediate.

1.5 C–C bond forming strategies for convenient capture of carbon dioxide

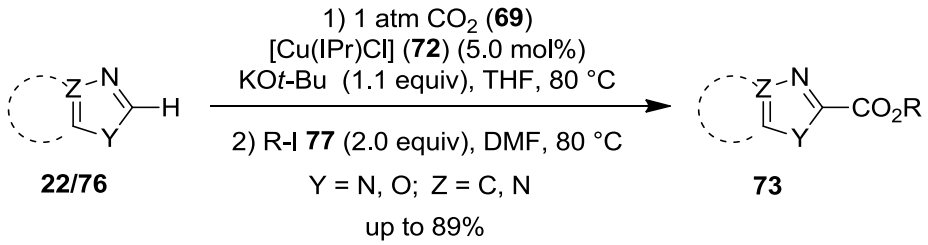
Carbon dioxide (**69**) as most abundant carbon source in the Earth's atmosphere has attracted much attention in recent years among the chemical society. Although it is relatively nontoxic, the steadily increasing concentration of carbon dioxide (**69**), basically boosted since the industrialization, is problematic as it contributes to the greenhouse effect, which is a major reason for global warming. Thus, the development of efficient methodologies for extensive capture and reuse of CO_2 (**69**) is of utmost importance.[118] Only few industrial applications, like the Kolbe-Schmitt synthesis of salicylic acid from sodium phenolate, have been developed so far.[119,120] Traditional methods for the fixation of carbon dioxide (**69**) unfortunately required the application of strongly nucleophilic Grignard or organolithium reagents,[121] which are incompatible with several sensitive functionalities. Less reactive zink- or boron-based nucleophiles on the contrary, often are in need of additional transition-metal-catalysts.[121] Therefore, over the past decade, substancial efforts have been made to overcome the thermodynamical stability of CO_2 (**69**), in order to give access to valuable polymers or complex organic molecules from an inexpensive, nontoxic, renewable C1 source.[118]

Particularly, the development of new methods for a direct approach towards (hetero)aromatic carboxylic acid derivatives through carbon dioxide fixation has attracted recent interest.[122,123,124] Lately, a protocol for direct carboxylations of (hetero)arene C–H bonds using well-defined *N*-heterocyclic carbene gold(I) complex **70** was presented by *Nolan* and *Boogaerts* (Scheme 38).[122a] The significant base strength of the Au−OH species (pK_{aDMSO} = 30.4)[125] permits facile functionalizations of C−H bonds without the use of other organometallic reagents.



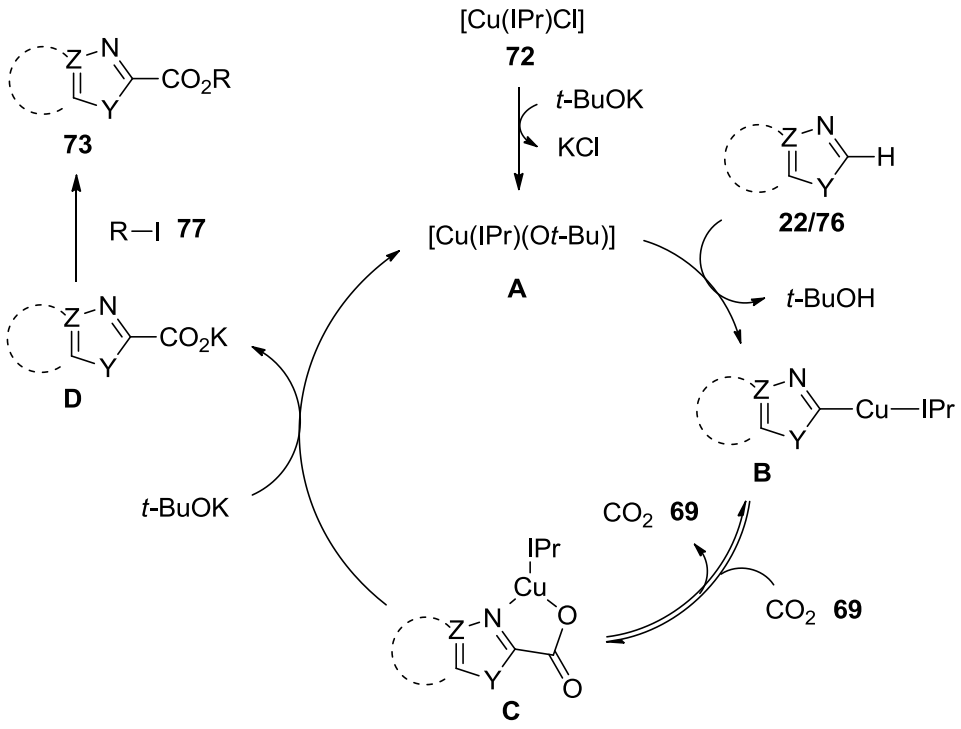
Scheme 38: Gold-catalyzed carboxylation of C–H bonds by *Nolan* and *Boogaerts*.

Thereupon, in 2010 the same authors, as well as *Hou* and coworkers independently demonstrated unprecedented carbon dioxide fixation to (hetero)arene C–H bonds with inexpensive *N*-heterocyclic carbene copper(I) complexes.[122b,c] Both groups gave detailed insight into their particularly postulated mechanism pathways, pointing out, that pK_a values of substrates and basicities of complexes play pivotal roles in the carboxylation reactions.[125] *Hou* identified a preformed copper(I) complex **72**, as well as the *in-situ* generated catalyst to be competent to catalyze carboxylation reactions (Scheme 39). More acidic benzoxazole (**22a**) (pK_a = 24.8)[125] and its derivatives were efficiently converted into the desired carboxylic acid esters **73**. Noteworthy, less acidic substrates, like *N*-methylbenzoimidazole (**74**) (pK_a = 32.5) or benzothiazole (**75**) (pK_a = 27.3) afforded only low yields or trace amounts of products.



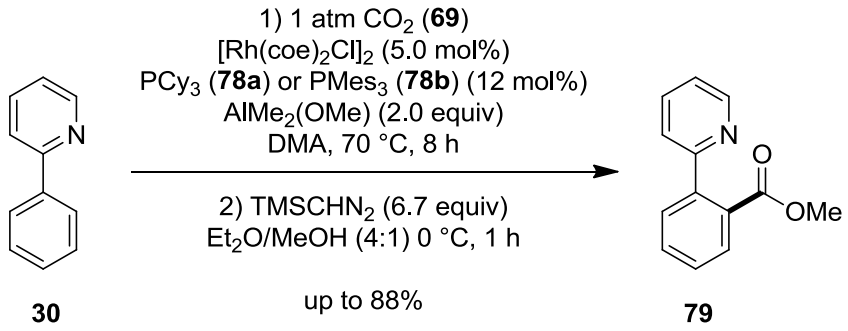
Scheme 39: Copper-catalyzed direct carboxylation of heteroarenes **22** and **76**.

Based on stoichiometric experiments, the following mechanism was proposed (Scheme 40). Copper alkoxide complex **A** is initially formed through salt-metathesis reaction between precursor **72** and potassium *tert*-butoxide. Subsequent reaction with a heteroarene **22** or **76** gives organocopper species **B** *via* deprotonation of the heteroaromatic C–H bond. Insertion of carbon dioxide (**69**) into the Cu–C bonds of **B** affords intermediate **C**, which can react with a further molecule of potassium *tert*-butoxide, to regenerate the copper alkoxide complex **A**. Concurrently, potassium carboxylate **D** is released, which provides the ester product **73**, after reaction with alkyl iodide **77**. Importantly, the authors were able to isolate and fully characterize intermediates **B** and **C**.



Scheme 40: Possible mechanism for the direct carboxylation of heteroarenes **22** and **76** with CO_2 (**69**) by *Hou.*

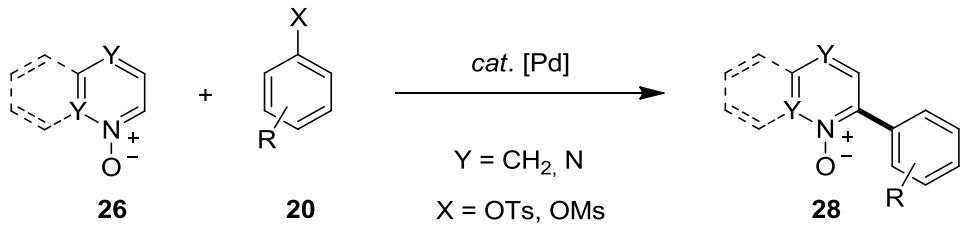
Very recently, unprecedented Rh-catalyzed direct carboxylations of unactivated aryl C−H bonds, under atmospheric pressure of carbon dioxide (**69**) were accomplished by *Iwasawa* and coworkers (Scheme 41).[122d] A variety of functionalized 2-arylpyridines **30** and 1-arylpyrazoles were successfully reacted in the presence of the rhodium catalyst and stoichiometric amounts of a methylating reagent, providing carboxylated products **79** in good yields. Although, detailed mechanistic studies have not been performed yet, the catalysis is proposed to proceed *via* chelation-assisted C–H bond functionalization and nucleophilic attack on carbon dioxide (**69**) by an aryl-Rh(I) species.



Scheme 41: Rhodium-catalyzed direct carboxylation of phenylpyridine **30** with carbon dioxide (**69**) by *Iwasawa*.

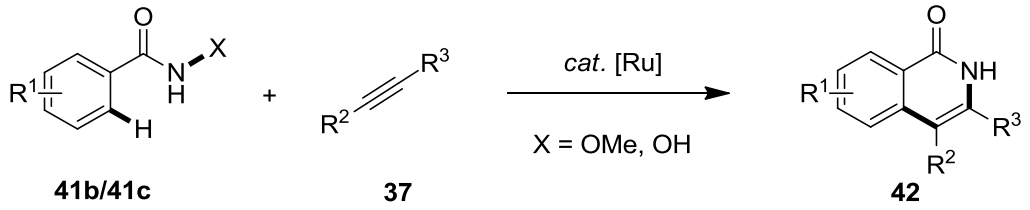
2 Objectives

On the basis of ongoing research directed towards the development of efficient transition-metal-catalyzed C–H bond functionalization methodologies, auspicious results were recently accomplished in direct arylations of electron-rich heteroarenes **22** and **23** with sufonates **20** in the group of *Prof. Ackermann.*[27] Hence, a major focus in the presented work was set on the development of a generally applicable methodology for efficient palladium-catalyzed direct arylations of electron-deficient (hetero)arenes **26** with sulfonates **20** as challenging, in that less reactive, electrophiles (Scheme 42).



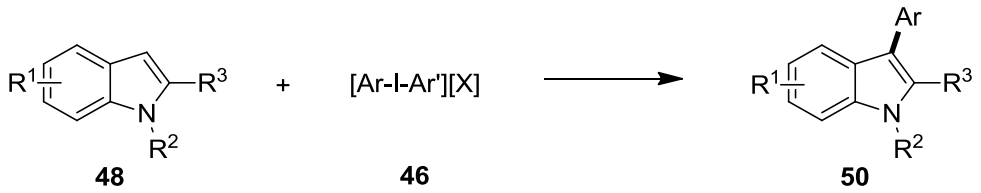
Scheme 42: Palladium-catalyzed direct arylations of electron-deficient heteroarenes **26** with moisture-stable sulfonates **20** as electrophiles.

Recently, unprecedented ruthenium-catalyzed oxidative annulations of alkynes **37** by benzamides **41a** and acrylamides **41d** through cleavage of C-H/N–H bonds were presented by the group of *Prof. Ackermann*.[33,76] Meanwhile, *Fagnou* and coworkers reported on rhodium-catalyzed external-oxidant-free syntheses of annulated lactames **42** through C–H/N–O bond functionalization.[71,72] Based on these results, the idea of a redox-neutral process towards the construction of isoquinolones **42** by advantageous, since less expensive ruthenium-catalysis came up. Thus, the elaboration of such a protocol was highly attractive (Scheme 43).



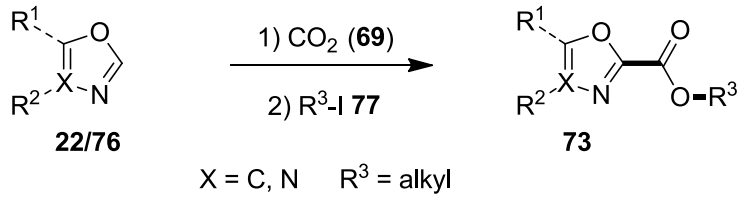
Scheme 43: Ruthenium-catalyzed redox-neutral syntheses of annulated lactames **42**.

In light of the demand for sustainable processes in organic chemistry, methodologies for direct arylations without the need of transition-metal-catalysts have attracted recent interest.[91,98] On the basis of observations by *Vicente*, which indicated the occurance of C–H bond arylations of indoles **48** in the absence of a transition-metal-catalyst, a third project of the present thesis was the development of an efficient procedure for metal-free, regioselective C–H bond functionalizations on ubiquitous indole framework (Scheme 44).



Scheme 44: Metal-free direct arylations of indoles **48** with diaryl-λ^3-iodanes **46**.

With regard to the perpetual abundance of carbon dioxide in the earth's atmosphere, chemists are currently challenged by devising processes that utilize CO_2 (**69**) as an inexpensive C1 source for the production of valuable chemical commodities.[118] Recently, tremendous efforts have been conducted to develop methodologies for a direct approach towards (hetero)aromatic carboxylic acid esters **73** through transition-metal-catalyzed carbon dioxide fixation.[122] As a part of this highly topical research area, an additional chapter in this work deals with the development of an economical and expedient procedure for direct carboxylation of heteroarenes **22** and **76** (Scheme 45).



Scheme 45: Economical and efficient direct carboxylations of heteroarenes **22** and **76** with CO_2 (**69**) as a C1 source.

3 Results and Discussion

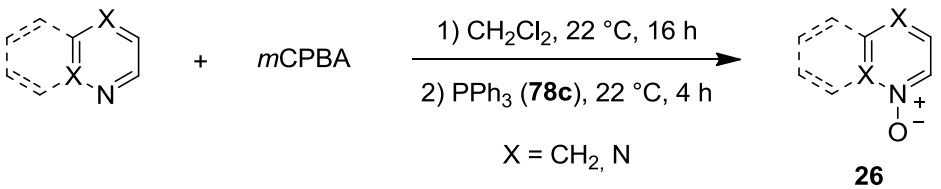
3.1 Palladium-catalyzed direct arylations of electron-deficient heteroarenes with moisture-stable sulfonates

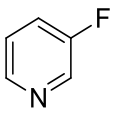
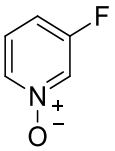
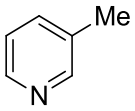
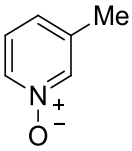
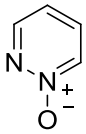
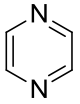
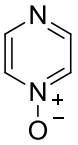
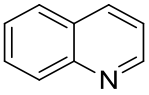
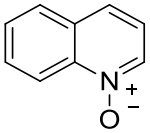
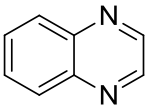
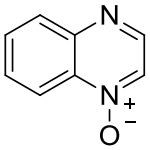
Several methods for the efficient direct C–H bond functionalization of electron-deficient heteroarenes with aryl halides[26,33,38,36,53a,54,126] or triflates[127] as electrophiles have been published in recent years by various groups. In 2009, a procedure for palladium-catalyzed C–H bond arylations of electron-rich heteroarenes with aryl sulfonates **20** was presented by the group of *Prof. Ackermann*.[27] Hitherto, no protocol for the application of sulfonates **20** in palladium-catalyzed direct arylations of electron-deficient heteroarenes had been presented. Sulfonates **20** are attractive electrophiles, as they are easily accessible from inexpensive starting materials and exhibit high stability. However, the high stability results in decreased reactivity compared to the corresponding triflates. Thus, activation of sulfonates in direct arylations is highly challenging. The quest for a generally applicable approach using sulfonates **20** as inexpensive, moisture-stable electrophiles for direct arylations of electron-deficient heteroarenes provided the impetus to develop a novel catalytic system.

3.1.1 Synthesis of (di)azine *N*-oxides

(Di)azine *N*-oxides **26** were synthesized *via* oxidation with peracid according to a published literature procedure (Table 1).[34] Substituted pyridines **47c** and **47d** as well as quinoline **67** provided the corresponding *N*-oxides **26ab**, **26ac** and **26b**, respectively, in good yields (entries 1, 2 and 5). Also, diazines **80**, **81** and **82** were efficiently converted into the corresponding *N*-oxides in good isolated yields (entries 3, 4 and 6).

Table 1: Synthesis of (di)azine *N*-oxides **26** *via* oxidation with *m*CPBA.[a]



entry	substrate		26		yield
1		**47c**		**26ab**	60%
2		**47d**		**26ac**	76%
3		**80**		**26c**	82%
4		**81**		**26d**	72%
5		**67**		**26b**	80%
6		**82**		**26e**	66%

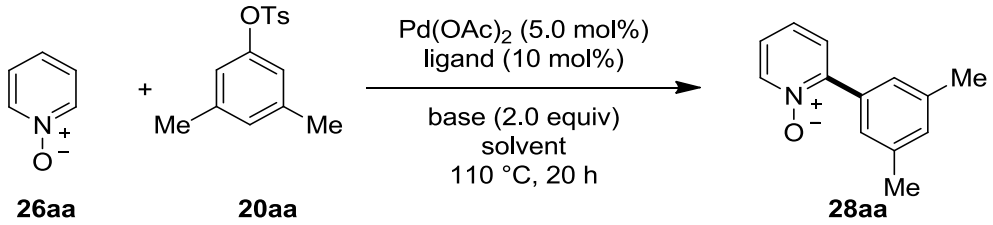
[a] Reaction conditions: (Di)azine (1.0 equiv), *m*CPBA (1.0 equiv), CH_2Cl_2 (0.2 M), 22 °C, 16 h; PPh_3 (**78c**) (0.5 equiv), 4 h; isolated yields.

3.1.2 Optimization of reaction conditions for direct arylations of (di)azine *N*-oxides with tosylates

Extensive screening was performed in order to establish effective reaction conditions for an unprecedented palladium-catalyzed direct arylation of electron-deficient (di)azine *N*-oxides **26** using aryl tosylates **20** as electrophiles (Table 2).[128] Initial studies were conducted applying the reaction conditions which were previously developed for palladium-catalyzed C–H bond functionalizations of electron-rich azoles **22** and **23**.[27] Unfortunately, low conversion was observed for the direct arylation of electron-deficient pyridine *N*-oxide **26aa** with aryl tosylate **20aa** under these conditions (entry 1). The use of toluene as solvent also showed a low yield (entry 2), whereas the addition of *tert*-butanol as co-solvent in

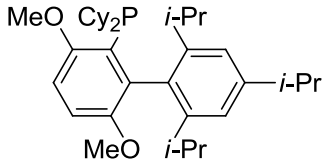
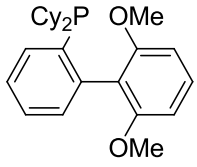
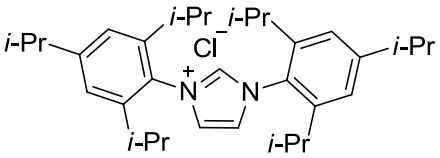
combination with toluene resulted in a significantly increased isolated yield of 33% of desired product **28aa** (entry 3). Notably, mixtures of *tert*-butanol and other polar solvents like 1,4-dioxane, DMA and NMP provided only trace amounts of the desired arylation product **28aa** (entries 4–8). Reaction conditions, which were previously described by *Fagnou* for the direct arylation of pyridine *N*-oxide **26aa** with aryl halides **7** led to no product formation (entry 9).[33] Ultimately, a considerably higher yield of **28aa** could be achieved, employing caesium fluoride as the base (entry 10). Several representative phosphine ligands (entries 11–15), as well as *N*-heterocyclic carbene precursor **85** (entry 16) were then studied. However, none of them furnished a satisfying outcome, but only very low conversion of substrate **20aa** was observed. Moreover, a reaction performed under microwave irradiation indicated no increased reactivity and the product **28aa** was formed in a significantly lower yield as compared to conventional heating (entry 17).

Table 2: Solvent and ligand optimization on the direct arylation of electron-deficient pyridine-*N*-oxide **26aa** with aryl tosylate **20aa**.[a]



26aa **20aa** **28aa**

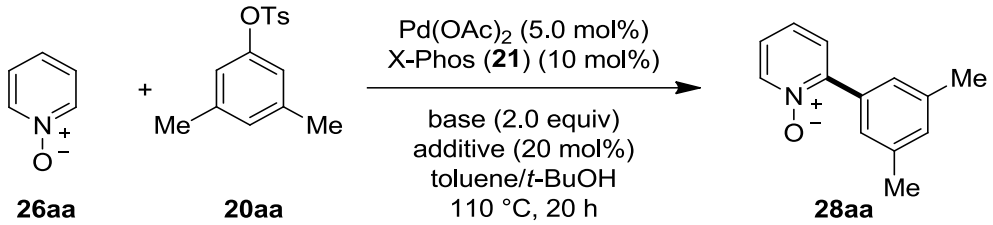
entry	ligand	base	solvent	yield
1	X-Phos (**21**)	K_2CO_3	DMF/*t*-BuOH (2:1)	9[b]
2	X-Phos (**21**)	K_2CO_3	toluene	11%
3	X-Phos (**21**)	K_2CO_3	toluene/*t*-BuOH (2:1)	33%
4	X-Phos (**21**)	K_2CO_3	toluene/*t*-BuOH (2:1)	26%[c]
5	X-Phos (**21**)	K_2CO_3	1,4-dioxane/*t*-BuOH (2:1)	traces[d]
6	X-Phos (**21**)	K_2CO_3	*o*-xylene/*t*-BuOH (2:1)	traces
7	X-Phos (**21**)	K_2CO_3	DMA/*t*-BuOH (2:1)	traces
8	X-Phos (**21**)	K_2CO_3	NMP/*t*-BuOH (2:1)	traces
9	$P(t\text{-Bu})_3 \cdot HBF_4$ (**27a**)	K_2CO_3	toluene	-[c]
10	**X-Phos** (**21**)	**CsF**	**toluene/*t*-BuOH (2:1)**	**64%**
11	PPh_3 (**78c**)	CsF	toluene/*t*-BuOH (2:1)	-

12	PCy_3 (**78a**)	CsF	toluene/*t*-BuOH (2:1)	-
13	 (**83**)	CsF	toluene/*t*-BuOH (2:1)	5%
14	Dave-Phos (**8**)	CsF	toluene/*t*-BuOH (2:1)	< 5%
15	 (**84**)	CsF	toluene/*t*-BuOH (2:1)	< 5%
16	 (**85**)	CsF	toluene/*t*-BuOH (2:1)	-
17	X-Phos (**21**)	CsF	*o*-xylene/*t*-BuOH (2:1)	30%[e]

[a] Reaction conditions: **26aa** (2.00 mmol), **20aa** (0.50 mmol), $Pd(OAc)_2$ (5.0 mol%), ligand (10 mol%), base (1.0 mmol) solvent (3.0 mL), 110 °C, 20 h; isolated yields. [b] Reaction at 130 °C. [c] Reaction with *t*-$BuCO_2H$ (20 mol%). [d] Reaction at 100 °C. [e] Microwave irradiation (170 °C, 20 min).

Further optimization studies were conducted diversifying the base used in the reaction (Table 3). Neither organic base di-*iso*-propylethylamine, nor inorganic potassium phosphate proved to be viable (entries 1 and 2). Among different *tert*-butoxide derivatives tested, sodium *tert*-butoxide delivered the product **28aa** in a comparatively good yield of 63% (entries 3–5, cf. entry 6). With regard to substrates bearing sensitive functionalities, which are desirable to be tolerated in C–H bond functionalization processes, it was outplayed by the milder ceasium fluoride. Representative carbonate bases such as sodium and caesium carbonate led to very low and modest conversions, respectively (entries 7 and 8), whereas rubidium carbonate afforded **28aa** in a comparable yield to ceasium fluoride (entries 9 and 6). Though, from an economical point of view the latter was favored and used henceforth.[129] Furthermore, neither the addition of substoichometric amounts of pivalic acid, nor of sodium tosylate, implicated a significant improvement in isolated yield of **28aa** (entries 10–12). Using two equivalents of **28aa** resulted in a somewhat lower isolated yield of **28aa** (entry 13). Moreover, a reduced reaction temperature resulted in trace amounts of **28aa** (entry 14). Accordingly, further reactions were performed using the conditions described in Table 2, entry 10**.**

Table 3: Optimization studies concerning the effect of base and additive on direct arylation of **26aa** with **20aa**.[a]



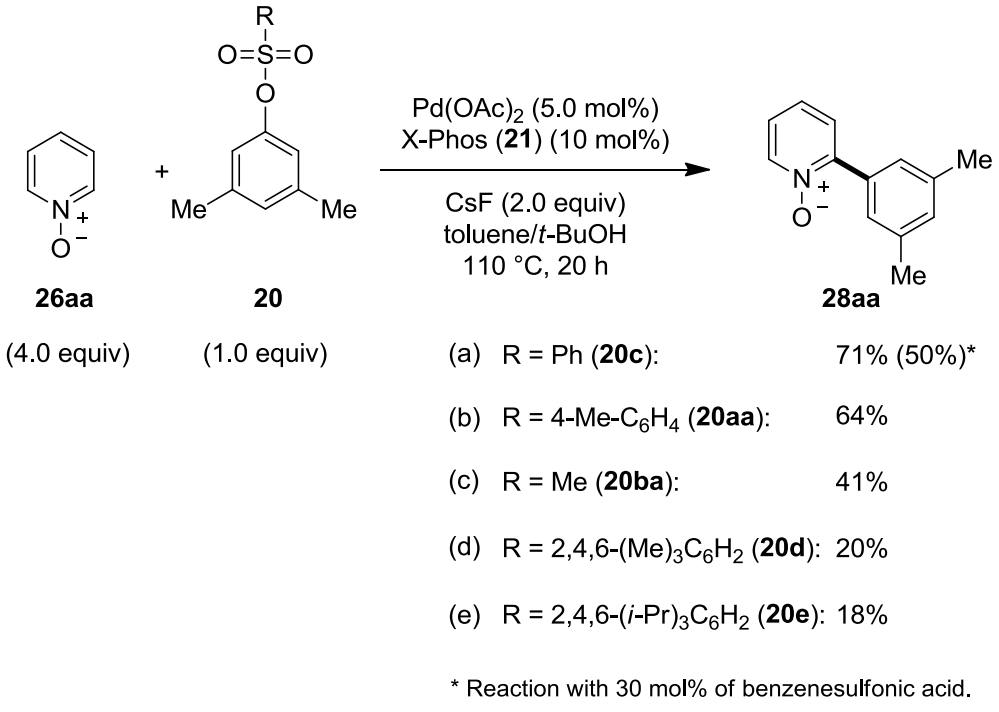
26aa **20aa** **28aa**

entry	additive	base	yield
1	-	EtN(*i*-Pr)$_2$	traces
2	-	K_3PO_4	19%
3	-	NaO*t*-Bu	63%
4	-	LiO*t*-Bu	41%
5	-	KO*t*-Bu	11%
6	-	**CsF**	**64%**
7	-	Na_2CO_3	traces
8	-	Cs_2CO_3	51%
9	-	Rb_2CO_3	62%
10	*t*-BuCO_2H	Rb_2CO_3	68%
11	*t*-BuCO_2H	CsF	62%
12	NaOTs	CsF	57%
13	-	CsF	56%[b]
14	-	CsF	traces[c]

[a] Reaction conditions: **26aa** (2.00 mmol), **20aa** (0.50 mmol), Pd(OAc)$_2$ (5.0 mol%), X-Phos (**21**) (10 mol%), CsF (1.0 mmol), additive (20 mol%), toluene (2.0 mL) *t*-BuOH (1.0 mL), 110 °C, 20 h; isolated yields. [b] Reaction with **26aa** (1.0 mmol). [c] Reaction at 80 °C.

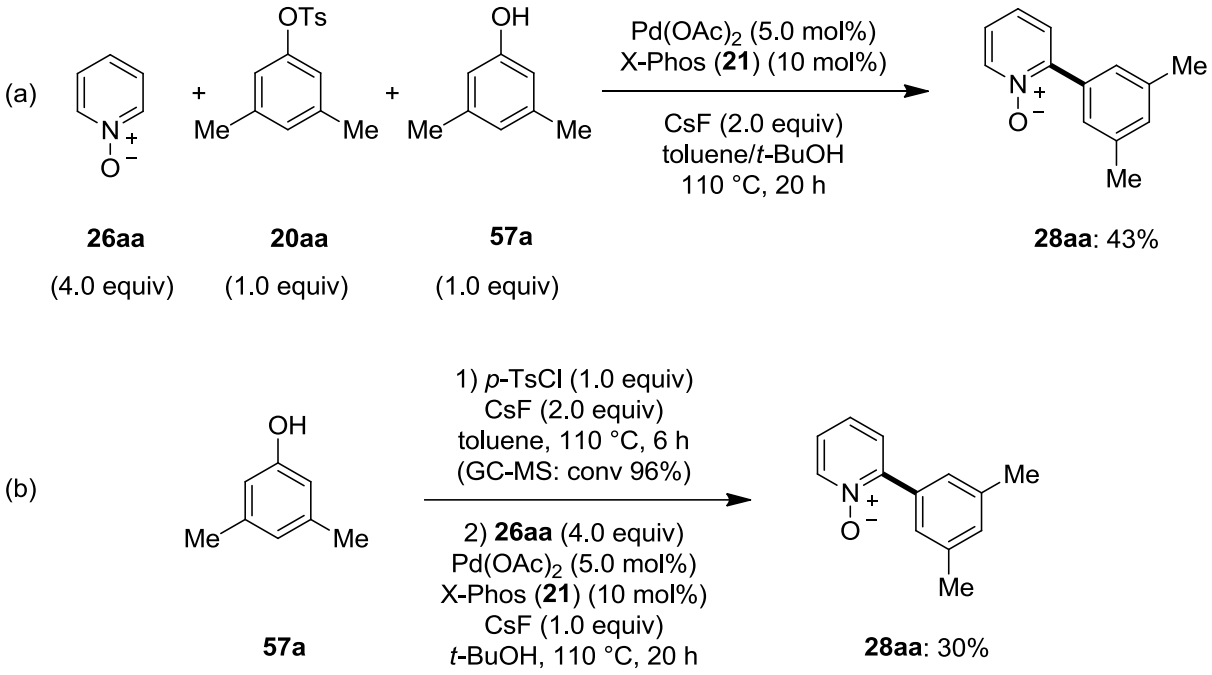
In the following, different leaving groups were evaluated (Scheme 46). Under establishd reaction conditions benzenesulfonate **20c** provided the arylation product **28aa** in 71% isolated yield (a). Noteworthy, in the presence of substoichiometric amounts of benzenesulfonic acid the yield dropped significantly (a[*]). 4-Methylbenzene sulfonate **20aa** afforded **28aa** in good, albeit slightly lower isolated yield of 64% (b). Notably, less reactive but valuable methane sulfonate **20ba**, in that offering an improved atom-economy of direct arylations, gave rise to

28aa in a reasonable yield of 41% (c). These results are in accordance with the expected reactivity of the sulfonate substrates, as the ability of the leaving group for nucleophilic substitution reactions is indirectly proportional to the pK_a value of the corresponding acid.[130] As expected, the use of sterically demanding mesityl sulfonate **20d** led to a significantly decreased formation of the desired product **28aa** (d). Likewise, the conversion of even more sterically hindered **20e** was low and a poor yield of product **28aa** was obtained (e).



Scheme 46: Reactivity studies concerning the ability of the leaving group.

Striving for a more sustainable approach towards biheteroaryl formation, further studies were conducted to be aimed at the direct use of phenols **57** as proelectrophilic arylating reagents, as it was shown by *Ackermann* and *Mulzer* for ruthenium-catalyzed formal dehydrative direct arylations of arenes in 2008.[64] A significantly lower isolated yield of **28aa** was obtained, when using equal amounts of tosylat **20aa** and phenol **57aa** under the standard reaction conditions. This observation indicated, that catalyst deactivation might occur due to coordination of phenol **57a** to the metal-center, resulting in a catalytically inactive palladium species. (Scheme 47a). Unfortunately, *in-situ* formation of the tosylate also resulted in a diminished yield of isolated product **28aa**, in spite of almost quantitative conversion of the corresponding phenol **57a** to tosylate **20aa**, which was monitored by GC-MS analysis (Scheme 47b). Thus, for exploiting the scope of direct arylation of electron-deficient heteroarenes **26**, the established protocol using preformed sulfonates **20** as electrophiles was followed.

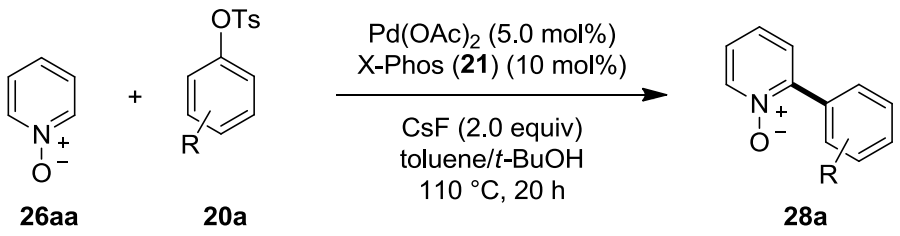


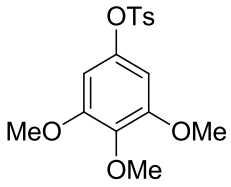
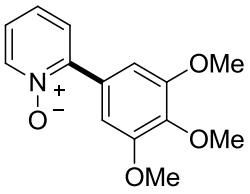
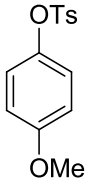
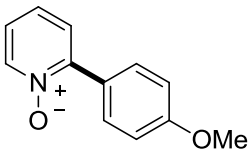
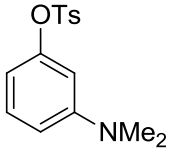
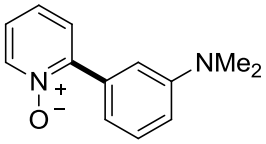
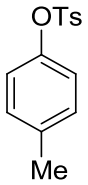
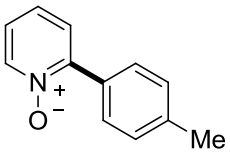
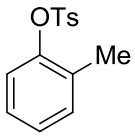
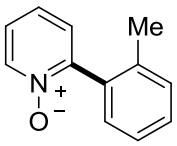
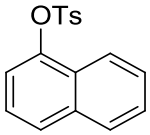
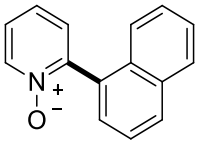
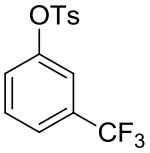
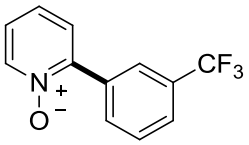
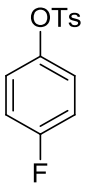
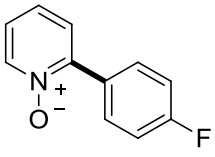
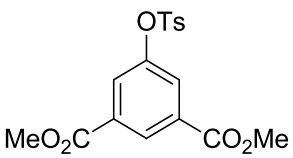
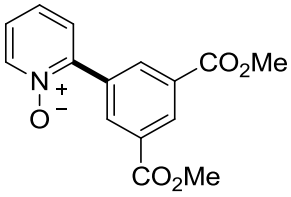
Scheme 47: Studies towards a sequential arylation process.

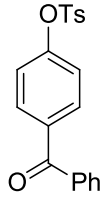
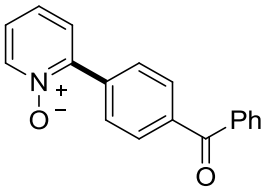
3.1.3 Scope and limitations

Under the optimized reaction conditions, representative aryl tosylates **20a** were probed (Table 4) in direct arylations of *N*-oxide **26aa**. Notably, both electron-deficient as well as electron-rich, hence deactivated aryl tosylates **20a** provided the corresponding mono-arylated products with high chemo- and regioselectivity in reasonable yields. Electron-donating methoxy or amine substituents on the electrophile proved to be compatible (entries 1–3), as did electron-withdrawing fluorine, ketone or ester substituents (entries 7–10). The diminished yield of **28af** can be attributed to the sterically demanding methyl substituent in the *ortho*-position of the electrophile (entry 5), though a comparatively high yield of 60% of **28ag** could be obtained using 1-naphtyl tosylate **20ag** (entry 6).

Table 4: Scope of direct arylation of pyridin *N*-oxide **26aa** with aryl tosylates **20a**.[a]

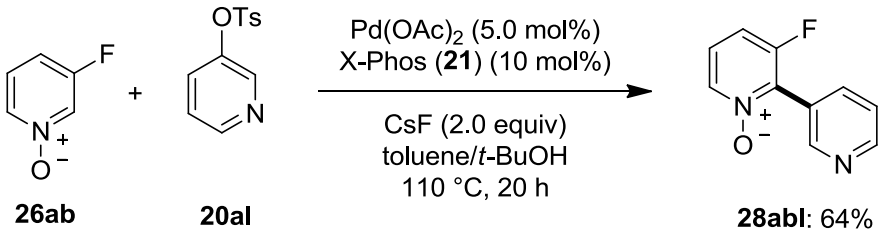


entry	20a		28a		yield
1		**20ab**		**28ab**	67%
2		**20ac**		**28ac**	52%
3		**20ad**		**28ad**	50%
4		**20ae**		**28ae**	58%
5		**20af**		**28af**	25%
6		**20ag**		**28ag**	60%
7		**20ah**		**28ah**	51%
8		**20ai**		**28ai**	60%
9		**20aj**		**28aj**	38%

10		**20ak**		**28ak**	49%

[a] Reaction conditions: **26aa** (2.00 mmol), **20a** (0.50 mmol), $Pd(OAc)_2$ (5.0 mol%), X-Phos (**21**) (10 mol%), CsF (1.0 mmol), toluene (2.0 mL), *t*-BuOH (1.0 mL), 110 °C, 20 h; isolated yields.

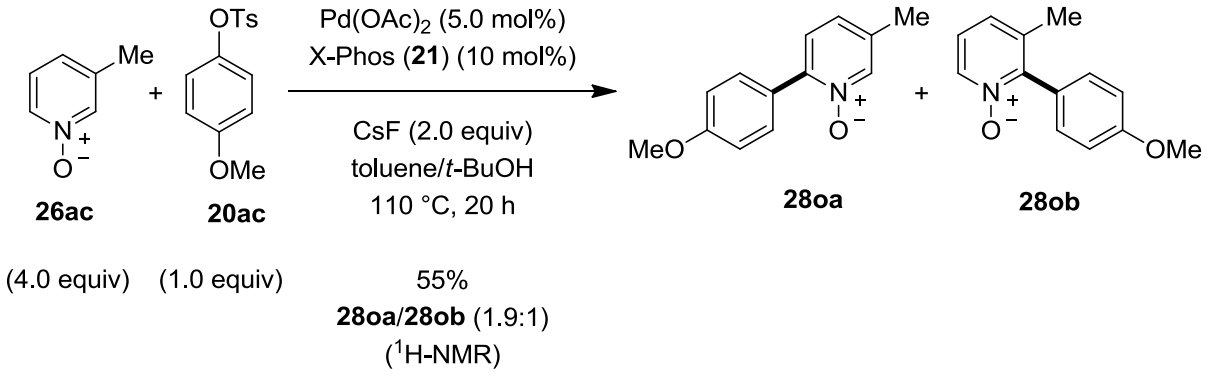
Remarkably, pyridyl tosylate **20al** served as viable substrate for the direct arylation of **26ab** under the optimized conditions, featuring a biheteroaryl scaffold in a highly regio- and chemoseletive manner, with the formation of **28abl** as sole product in good yield (Scheme 48). The unambiguous assignment of the molecular structure was supported by HMBC-NMR analysis.[131]



Scheme 48: Palladium-catalyzed direct arylation of *N*-oxide **26ab** with heteroaryl tosylate **20al**.

Notably, when using 3-fluoropyridine *N*-oxide (**26ab**) as substrate the electronic effect, predominats, as the more acidic C–H bond in the C2-position induced by the proximity of a strongly electronegative fluorine substituent, is exclusively arylated (Scheme 48).

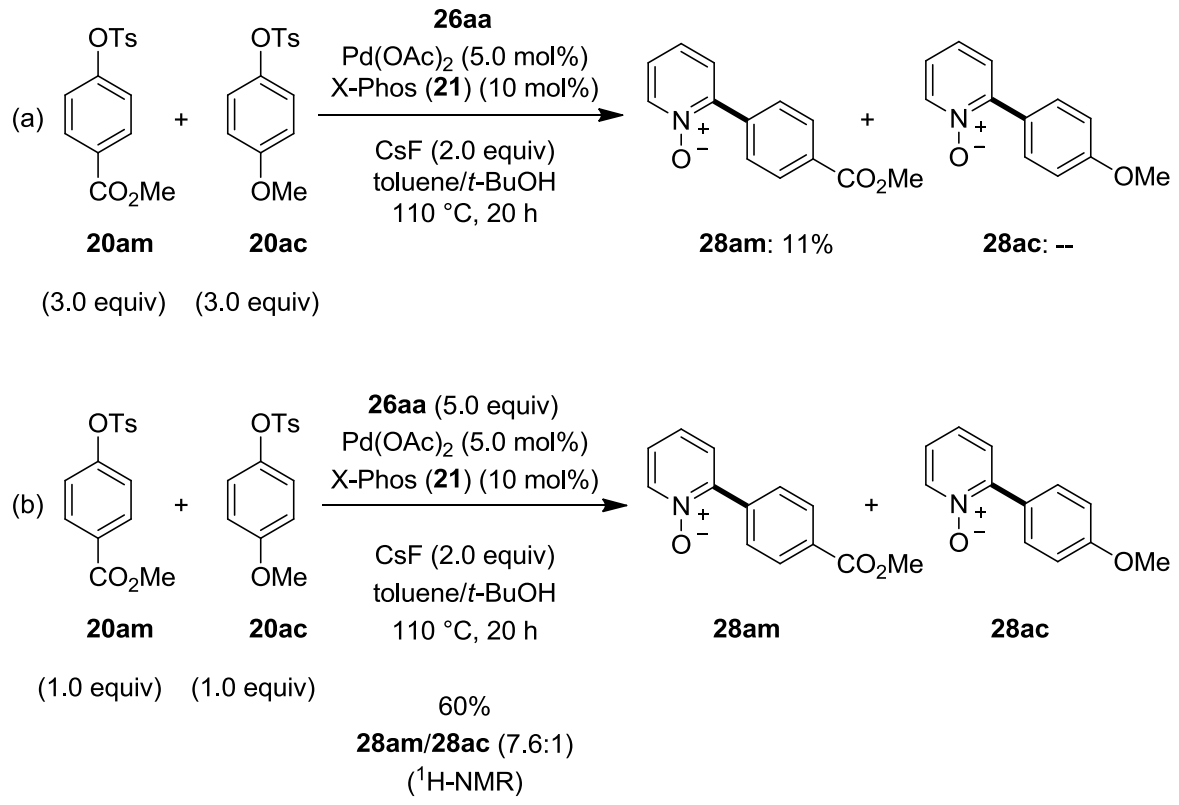
Interestingly, the reaction of 3-methyl substituted pyridine *N*-oxide **26ac** with **20ac** afforded a mixture of regioisomers **28oa** and **28ob** with a ratio of 1.9/1 as estimated by ^{1}H-NMR spectroscopy (Scheme 49).[132] The favored addressing of the sterically less hindered C6-position is contrary to the previously reported example (*vide supra*, see also: Table 8, entry 2) and gives strong evidence for the reaction outcome to be influenced by both, electronic as well as steric factors.



Scheme 49: Intramolecular competition experiment with 3-methylpyririne *N*-oxide (**26ac**).

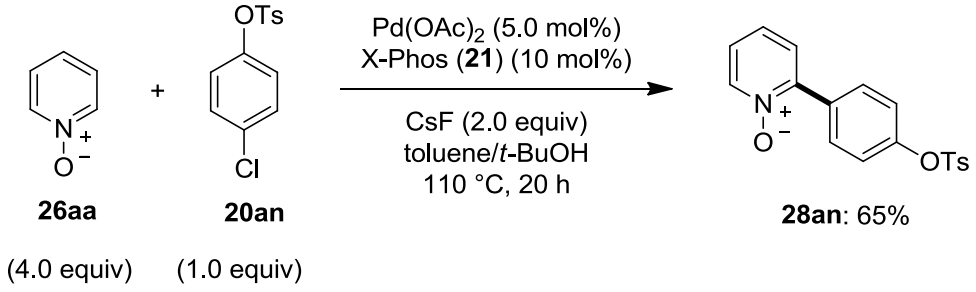
These results are consistent with previously reported observations from direct arylations of azine *N*-oxides **26** with aryl triflates, as well as a recent mechanistic analysis on direct arylations of azine *N*-oxides **26** with aryl bromides **7** by *Fagnou*.[40,127]

Intermolecular competition experiments between aryl tosylates **20am** and **20ac** revealed the electron-deficient tosylate **20am** to be converted in preference compared to the electron-rich derivative **20ac** (Scheme 50). In the presence of a large excess of differently substituted electrophiles the conversion was very low, however product **28am** was exclusively formed (Scheme 50a). A similar result with a predominant formation of the arylated product **28am** was observed when changing the stoichiometry, by using the *N*-oxide **26aa** in excess (Scheme 50b). Thus, a rate-determining oxidative addition step is suggested to be involved within the catalytic cycle.



Scheme 50: Intermolecular competition experiments between tosylates **20am** and **20ac**.

Furthermore, an intramolecular competition experiment was conducted, to reveal the relative reactivity of aryl tosylates **26a** compared to aryl chlorides **16** in palladium-catalyzed direct arylations of pyridine *N*-oxide (**26aa**) (Scheme 51). When 4-chlorophenyl tosylate (**20an**) was employed as an electrophile, direct arylation proceeded with high chemoselectivity, providing 2-{4-(tosyloxy)phenyl}pyridine *N*-oxide (**28an**) as the sole product. Hence, aryl tosylates **20a** display significantly decreased reactivity *versus* aryl chlorides **16** in this transformation.



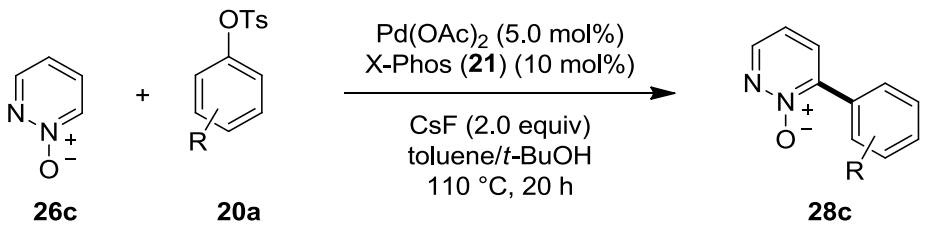
Scheme 51: Intramolecular competition experiment with aryl tosylate **20an**.

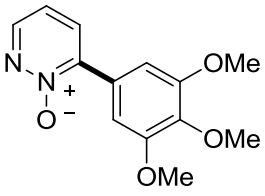
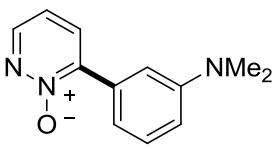
3.1.4 Palladium-catalyzed direct arylations of electron-deficient (di)azine *N*-oxides with tosylates as electrophiles

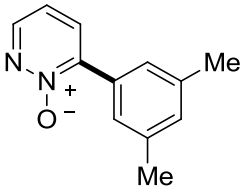
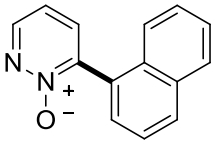
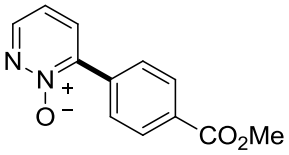
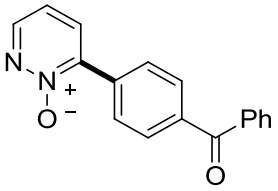
In an effort to enlarge the scope of palladium-catalyzed direct arylations with tosylates **20a** as electrophiles, different (di)azine *N*-oxides **26** were examined as substrates. Remarkably, the amount of the nucleophilic component **26** could be reduced significantly, still providing good isolated yields of the desired products in a highly chemo- and regioselective fashion.

Pyridazine *N*-oxide (**26c**) served as a viable substrate under the established reaction conditions, delivering the arylation products in acceptable to good yields (Table 5). Notably, electron-rich, thereby electronically deactivated methoxy- or dimethylamine-substituted aryl tosylates **20ab** and **20ad** were selectively converted into the corresponding products **28cb** and arylation product **20ca** in good isolated yield, as did more sterically encumbered 1-naphtyl tosylate (**20ag**) (entries 3 and 4). Likewise, tosylates bearing electron-withdrawing ester or ketone substituents proved to be suitable for C–H functionalization leading to **28cm** and **28ck** in synthetically useful isolated yields (entries 5 and 6).

Table 5: Scope of direct arylation of pyridazine *N*-oxide (**26c**) with aryl tosylates **20a**.[a]



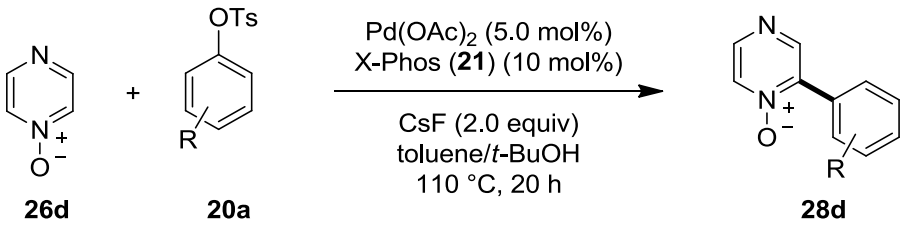
entry	20a		28		yield
1	3,4,5-$(MeO)_3$	**20ab**		**28cb**	69%
2	3-NMe_2	**20ad**		**28cd**	60%

3	3,5-Me_2	**20aa**		**28ca**	74%
4	1-naphtyl	**20ag**		**28cg**	71%
5	4-CO_2Me	**20am**		**28cm**	58%
6	4-C(O)Ph	**20ak**		**28ck**	50%

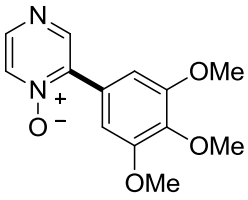
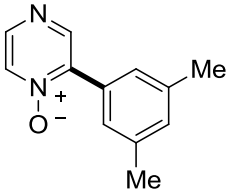
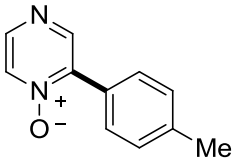
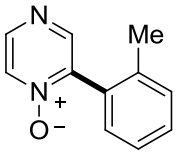
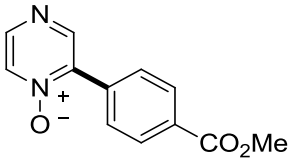
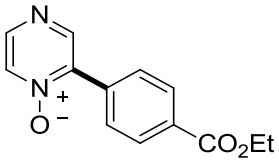
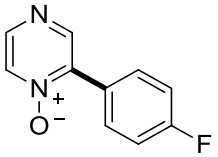
[a] Reaction conditions: **26c** (1.00 mmol), **20a** (0.50 mmol), $Pd(OAc)_2$ (5.0 mol%), X-Phos (**21**) (10 mol%), CsF (1.0 mmol), toluene (2.0 mL), *t*-BuOH (1.0 mL), 110 °C, 20 h; isolated yields.

While exploring the scope of palladium-catalyzed direct arylations, a number of reactions with pyrazine *N*-oxide (**26d**) as substrate were examined (Table 6). Again, different substitution patterns on the aryltosylate moiety were tolerated in the catalytic reaction yielding the appropriate products in reasonable yields. Importantly, a sterically congested *ortho*-methyl substituted tosylate **20as** gave rise to heterobiaryl **28ds** in 60% isolated yield, although a higher catalyst loading was required (entry 4).

Table 6: Scope of direct arylation of pyrazine *N*-oxide (**26d**) with aryl tosylates **20a**.[a]



26d **20a** **28d**

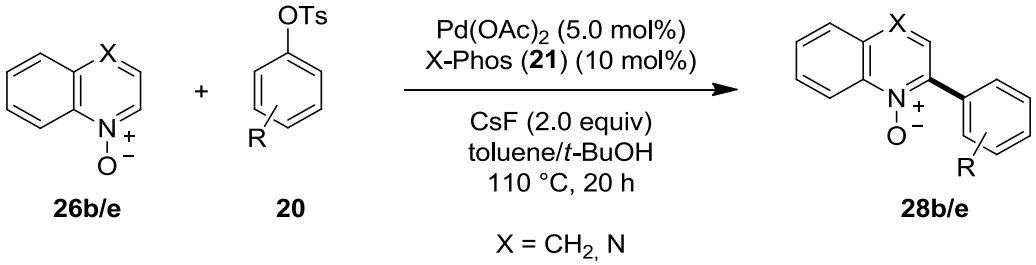
entry	20a		28		yield
1	3,4,5-$(MeO)_3$	**20ab**		**28db**	62%
2	3,5-Me_2	**20aa**		**28da**	51%
3	4-Me	**20ae**		**28de**	40%
4	2-Me	**20af**		**28df**	60%[b]
5	4-CO_2Me	**20am**		**28dm**	53%
6	4-CO_2Et	**20ao**		**28do**	57%
7	4-F	**20ai**		**28di**	48%

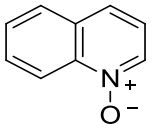
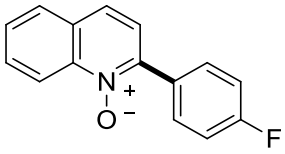
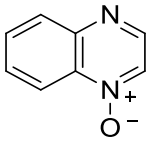
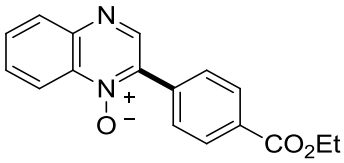
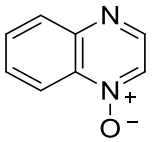
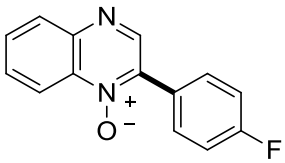
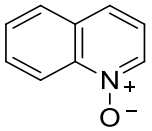
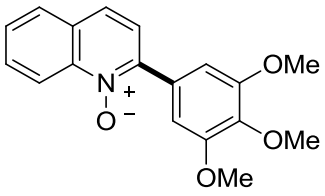
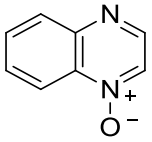
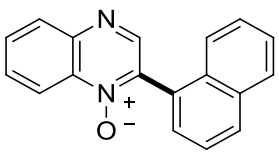
[a] Reaction conditions: **26d** (1.00 mmol), **20a** (0.50 mmol), $Pd(OAc)_2$ (5.0 mol%), X-Phos (**21**) (10 mol%), CsF (1.0 mmol), toluene (2.0 mL), *t*-BuOH (1.0 mL), 110 °C, 20 h; isolated yields. [b] $Pd(OAc)_2$ (10 mol%), X-Phos (**21**) (20 mol%).

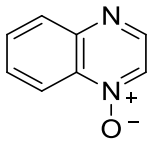
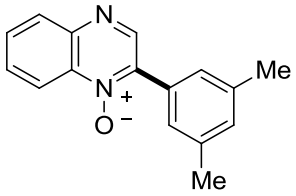
Additional experiments were conducted, using annulated substrates quinoline *N*-oxide (**26b**) and quinoxaline *N*-oxide (**26e**). Fortunately, both proved to be compatible and were chemoselectively mono-functionalized with a range of tosylates **20a** (Table 7). Flouro- and ester-substituted aryl tosylates **20ai** and **20ao** were efficiently converted with *N*-oxides **26b**

and **26e** into the corresponding products in moderate to good yields (entries 1–3). Furthermore, quinoline *N*-oxide (**26b**) and quinoxaline *N*-oxide (**26e**) smoothly underwent palladium-catalyzed direct arylations with challenging elcetrophilic substrates like electronically deactivated tosylate **20ab** and sterically congested 1-naphtyl tosylate (**20ag**), offering products **28bb** and **28eg** in good yields (entries 4 and 5).

Table 7: Scope of direct arylation of quinoline *N*-oxide (**26b**) and quinoxaline *N*-oxide (**26e**) with aryl tosylates **20a**.[a]

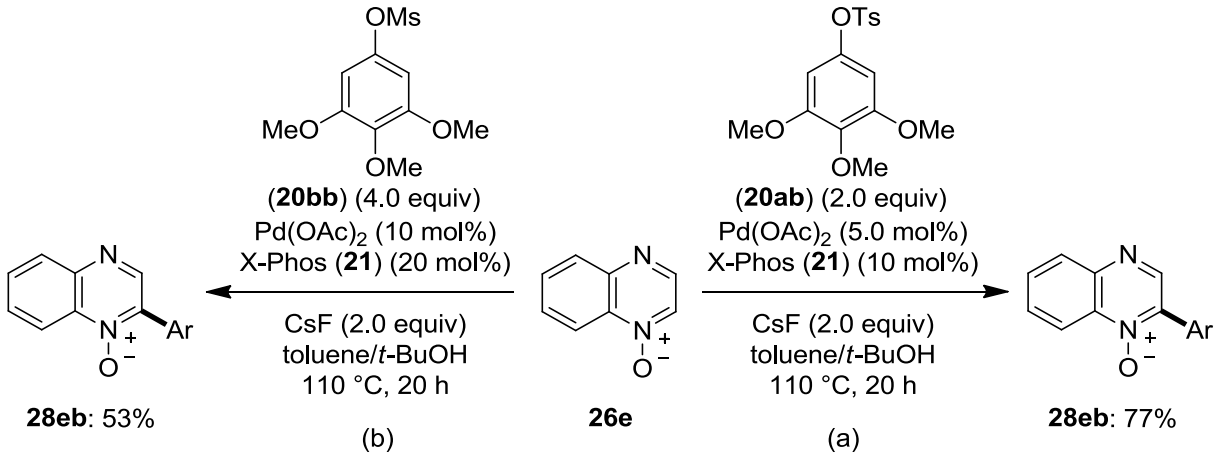


entry	26		20a	28		yield
1		**26b**	4-F **20ai**		**28bp**	50%
2		**26e**	4-CO_2Et **20ao**		**28eo**	68%
3		**26e**	4-F **20ai**		**28ei**	58%
4		**26b**	3,4,5-$(MeO)_3$ **20ab**		**28bb**	69%
5		**26e**	1-naphtyl **20ag**		**28eg**	73%[b]

6		**26e**	3,5-Me_2 **20aa**		**28ea**	51%

[a] Reaction conditions: **26** (1.00 mmol), **20a** (0.50 mmol), $Pd(OAc)_2$ (5.0 mol%), X-Phos (**21**) (10 mol%), CsF (1.0 mmol), toluene (2.0 mL), *t*-BuOH (1.0 mL), 110 °C, 20 h; isolated yields. [b] Reaction time 10 h.

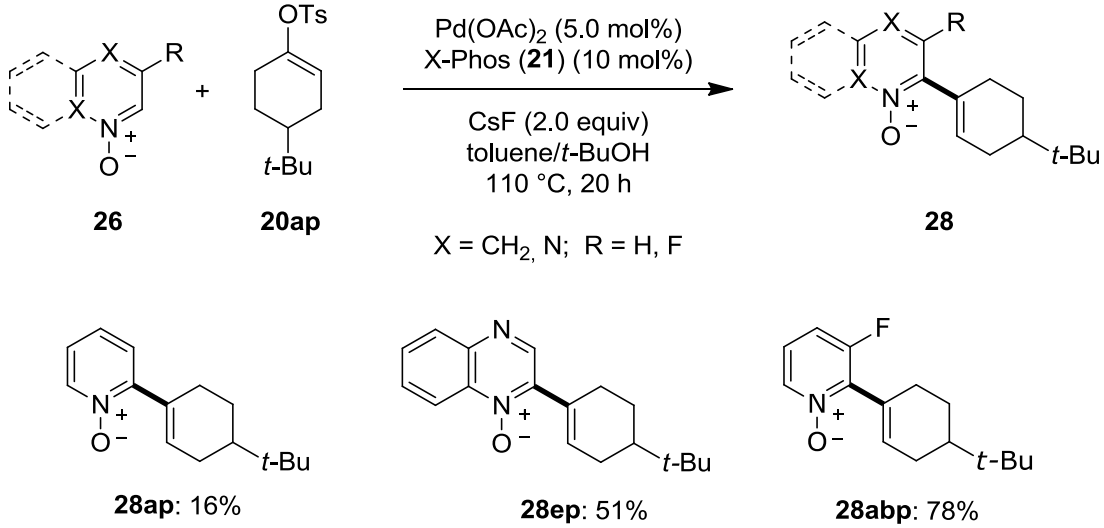
C–H bond functionalization of *N*-oxide **20e** with challenging, hence deactivated aryl tosylate **20ab** provided product **28eb** in 77% isolated yield (Scheme 52a). Remarkably, more atomeconomic mesylate **20bb** also served as viable substrate affording **28eb** in a reasonable yield of 53% (Scheme 52b).



Scheme 52: Direct arylations of quinoxaline *N*-oxide (**26e**) with aryl tosylate **20ab** and aryl mesylate **20bb**.

However, attempts to arylate pyrimidine *N*-oxide (**26f**) under the optimized reaction conditions were not successful. Neither the use of a large excess of *N*-oxide **26f**, nor the addition of copper(I) salts, as reported to be beneficial for the conversion of substrate **26f** by *Fagnou*,[34] were fruitful.

Notably, the catalytic system was not restricted to the use of aryl tosylates **20a** as electrophiles, but also set the stage for direct alkenylations of electron-deficient heteroarenes (Scheme 53).



Scheme 53: Palladium-catalyzed direct arylation of electron-deficient *N*-oxides **26** with alkenyl tosylate **20ap**.

Although unsubstituted pyridine *N*-oxide (**26aa**) furnished poor yield of **28ap**, the annulated diazine *N*-oxide **26e** and 3-fluoropyridine *N*-oxide (**26ab**) were efficiently converted with alkenyl tosylate **20ap** and gave rise to the corresponding alkenylation products in 51% and 78% isolated yield, respectively.

Previous examples on the use of alkenyl tosylates as electrophiles for either palladium-catalyzed traditional cross couplings have been reported by *Ackermann* and coworkers[133] and several other research groups[134,135,136] or for palladium-catalyzed amination reactions has been presented by *Buchwald*.[137] Moreover a first example for direct arylations of electron-rich heteroarenes with an alkenyl tosylate has been shown by the group of *Ackermann*.[27,138,139]

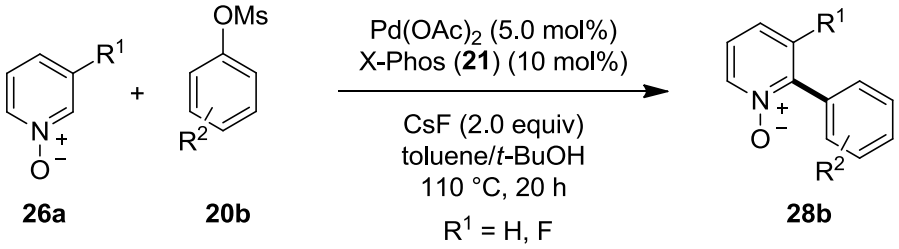
3.1.5 Palladium-catalyzed direct arylations of electron-deficient azine *N*-oxides with aryl mesylates as electrophiles

Intriguingly, the outstanding activity and chemoselectivity of the catalyst allowed for a significantly more sustainable[140] approach for direct arylations of electron-deficient heteroarenes **26** in that atom-economical aryl mesylates **20b** could be employed as substrates. This was achieved only once before in a report on direct arylations of electron-rich heteroarenes **22** and **23** by *Ackermann* and coworkers in 2009.[27] Until then, aryl mesylates **20b** have only been used as electrophiles in traditional metal-catalyzed cross-

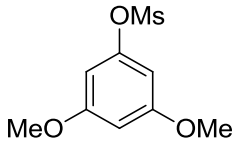
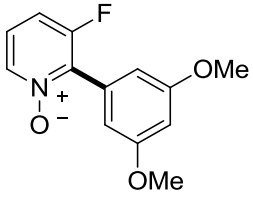
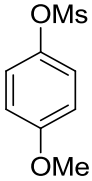
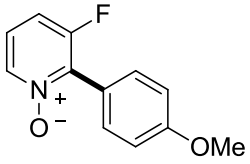
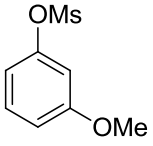
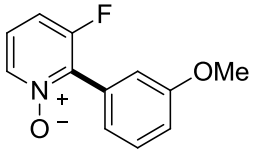
couplings[28,141,142,143,144] or amination reations.[145,146] Recent reports on palladium-catalyzed Suzuki–Miyaura cross-couplings with aryl mesylates **20b** have been published by *Buchwald* and *Kwong.*[135] Furthermore, an elegant approach for palladium-catalyzed amidation of aryl mesylates **20b** was presented by *Buchwald*.[147]

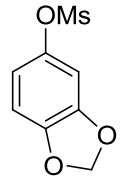
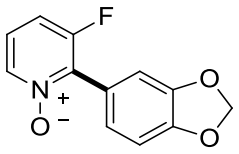
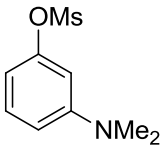
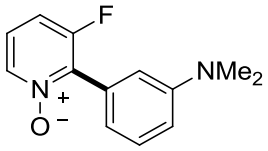
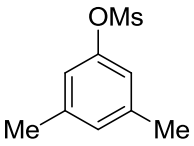
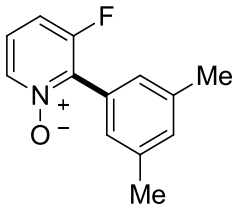
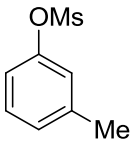
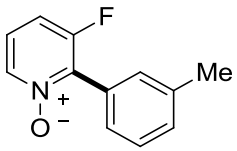
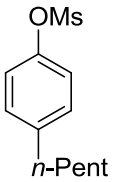
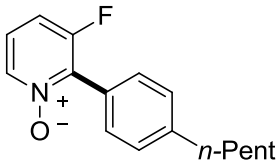
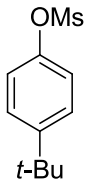
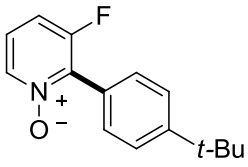
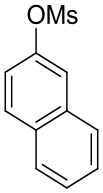
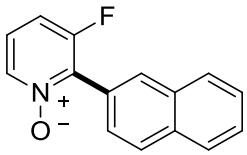
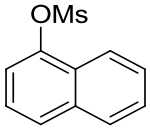
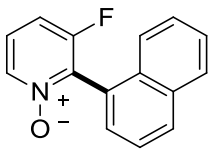
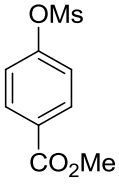
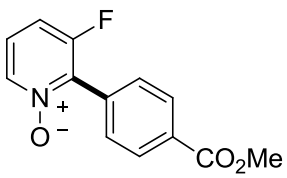
Remarkably, a broad sprectrum of aryl mesylates **20b** proved to be useful for C–H bond functionalization of pyridine *N*-oxids **26a** (Table 8). Various substituents in *para*-, *meta*- and even in the *ortho*-position of the mesylate moiety were well tolerated in the reaction. To our pleasure, the desired 2-mono-arylated products **28** were formed with high regioselectivity. As mentioned before, the electronegative fluorine substituent on the pyridine *N*-oxide increased the reactivity of the heteroarene, hence, providing the products in high isolated yields of up to 82% (entry 5). However, unsubstituted pyridine *N*-oxide (**26aa**) served as a viable substrate and gave rise to **28ab** and **28ad** in reasonable yields (entries 15 and 16).

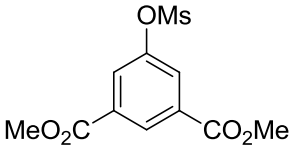
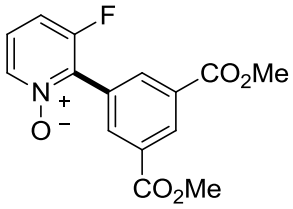
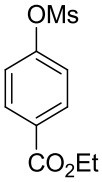
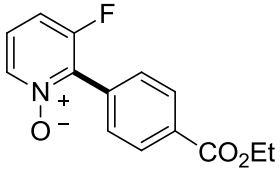
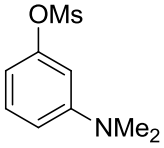
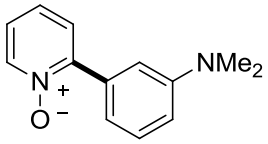
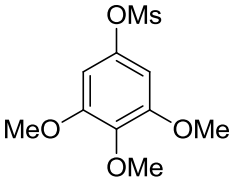
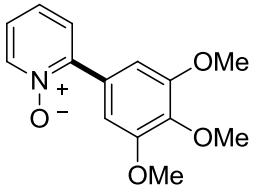
Table 8: Palladium-catalyzed direct arylation of pridine *N*-oxides **26a** with aryl mesylates **20b**.[a]



26a **20b** **28b**

entry	**20b**		**26**		**isolated yield**
1		**20bq**		**28bq**	78%
2		**20bc**		**28bc**	62%[b]
3		**20br**		**28br**	70%

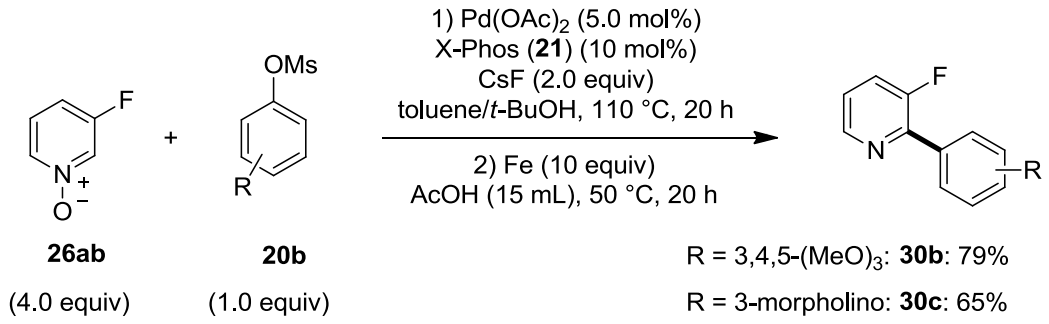
4		**20bs**		**28bs**	64%
5		**20bd**		**28bd**	82%
6		**20ba**		**28ba**	72%
7		**20bt**		**28bt**	69%
8		**20bu**		**28bu**	66%
9		**20bv**		**28bv**	69%
10		**20bx**		**28bx**	71%
11		**20bg**		**28bg**	66% 82%[c]
12		**20bm**		**28bm**	57%

13		**20by**		**28by**	46%
14		**20bo**		**28bo**	59%
15		**20bd**		**28ad**	52%[d]
16		**20bb**		**28ab**	41%[d]

[a] Reaction conditions: **26a** (2.00 mmol), **20b** (0.50 mmol), $Pd(OAc)_2$ (5.0 mol%), X-Phos (**21**) (10 mol%), CsF (1.0 mmol), toluene (2.0 mL), *t*-BuOH (1.0 mL), 110 °C, 20 h; isolated yields. [b] Reaction with **26ab** (1.5 mmol). [c] Reaction with aryl tosylate **20ag**. [d] Reaction with $Pd(OAc)_2$ (10 mol%), X-Phos (**21**) (20 mol%).

3.1.6 Reduction of arylated azine *N*-oxides

To emphasize the utility of the developed procedure, it was showcased, that the direct arylation products **28** can be easily deoxygenated releasing the corresponding 2-phenylpyridine derivatives **30** in a sequential procedure. Simple treatment of the crude arylation products **28** with iron powder in acetic acid, notably without the need of any prior purification step, provided the corresponding 2-arylpyridines **30** in high overall yields, as demonstrated in two representative examples (Scheme 54).[37,148]



Scheme 54: Direct arylations of 3-fluoro-*N*-oxide (**26ab**) and subsequent reduction to the corresponding pyridines **30**.

3.1.7 Plausible mechanism

The proposal for a plausible mechanism for the direct arylations of (di)azine *N*-oxides **26** with sulfonates **20** is not trivial. In a recent article by *Fagnou et al.* for azine *N*-oxide direct arylations, the authors proposed an acetate-assisted concerted metallation-deprotonation (CMD) pathway most likely to be operative.[11,40] Supported by experimental and computational studies, an electrophilic palladation process, which involves a rate-determining nucleophilic attack of the heteroarene on an electrophilic palladium(II)-arene species, was ruled out. This was confirmed by the observation that more electron-deficient substrates reacted preferentially. As for the present C–H bond functionalizations of (di)azine *N*-oxides **26** with sulfonates **20** there is no distinct effect of either using a carbonate base or pivalate additive (see Table 3), which proved to be beneficial for C–H bond activations *via* CMD path in previously reported examples2[b,12,14,37] yet, an acetate-assisted CMD pathway could also be involved in the direct arylation of (di)azine *N*-oxides **26** with tosylates **20a** and mesylates **20b** (Figure 4a, cf. Scheme 11). On the other hand, a sulfonate ligand, which coordinates to the palladium after oxidative addition, could assist the metalation-deprotonation-event, thus acting as a "proton-shuttle" (Figure 4b). By this means, an autocatalytic direct arylation process would be rationalized.

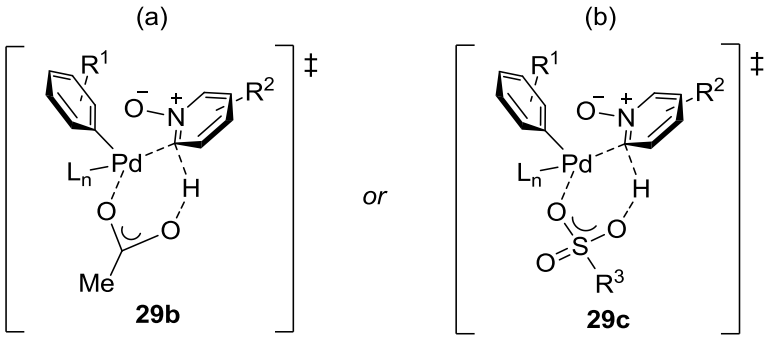


Figure 4: Possible transition-states **29b** and **29c** for CMD pathway.

Furthermore, the highly regioselective C–H bond functionalization of electron-deficient 3-fluoropyridine *N*-oxide (**26ab**) is consistent with six-membered inner sphere CMD transition-state **29**. Hence, a strongly electronegative fluorine substituent exerts a negative inductive effect resulting in an electropositive character at the C2-position of the heteroarene. Consequently, the developed negative charge in the CMD transistion-state **29** could be well stabilized by the fluorine substituent. Importantly, compared to direct arylations of *N*-oxides **26** with aryl halides, in case of using sulfonates **20** as electrophiles, the kinetics of the overall-procedure is probably different, due to lower reactivity of electrophiles **20**.

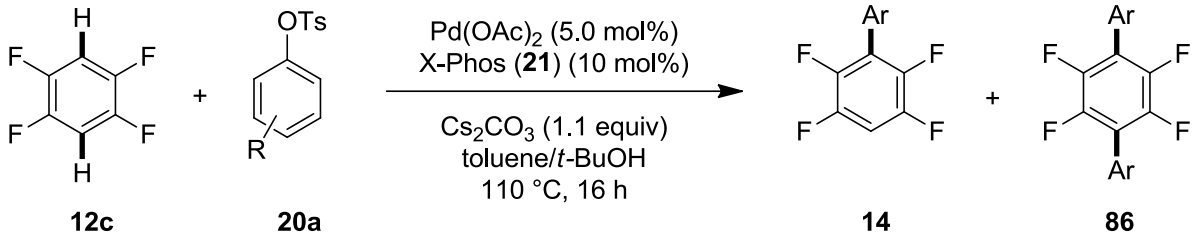
Compared to traditional cross-coupling reactions which are undoubtedly challenging for electron-deficient nucleophiles, caused by low reactivity or instability of substrates, the approach for heterobiaryl synthesis disclosed herein, illustrates a streamlining alternative.[31,149] Particularly, the avoidance of the formation of waste generated by organometallic substrates, as well as the applicability of atom-economical mesylates **20b** renders the presented procedure highly attractive.

3.2 Palladium-catalyzed direct arylation of electron-deficient arenes with aryl tosylates

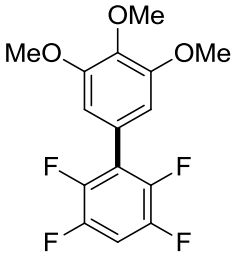
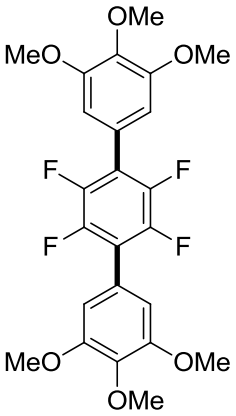
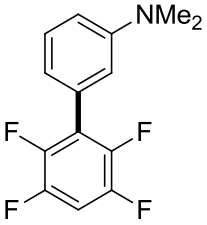
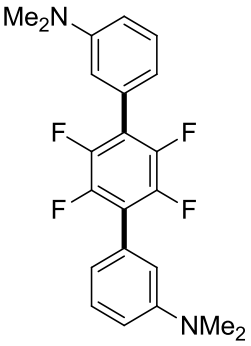
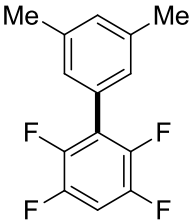
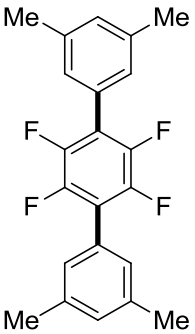
In recent years many efforts have been directed towards the selective functionalization of arenes possessing no conventional directing group.2 Palladium-catalyzed direct arylations of perfluoroarenes **12** with aryl or benzyl halides have been presented by *Fangou*[12,15,150] and others.[21] Furthermore, copper-catalyzed C–H bond functionalizations on perfluoroarenes **12** with aryl halides have been shown by *Daugulis*.[16] Considering the indispensibility of polyfluorobiphenyl motifs in medicinal and materials chemistry,[151,152] electron-deficient arene **12c** was probed as substrate for palladium-catalyzed C–H bond functionalizations (Table 9).

The use of caesium carbonate as a base under otherwise unchanged reaction conditions resulted in high conversions of the substrate **12c**.[153,154] Prodigiously, electron-rich thus deactivated aryl tosylates proved to be excellent electrophiles for direct arylations and the corresponding fluorinated bi- and tri-phenyls **14** and **86** could be isolated in good overall yields. In case of methoxy- or methyl-substituted tosylates **20ab** and **20aa** a mixture of mono- and di-arylation products (in a ratio of 1:1) were observed (entries 1 and 3), while dimethylamino-substituted **20ad** exhibited an enhanced selectivity favoring the monoarylation product **14d** in synthetically useful isolated yield (entry 2). In fact, the chemoselective access to one single isomer was pointed out to be elusive. Anyhow, changing the stoichiometry led to an improved product distribution with a preferential formation of monoarylated isomer **14c** in 68% isolated yield (entry 1).

Table 9: Palladium-catalyzed direct arylation of electron-deficient tetrafluorobenzene (**12c**) with deactivated aryl tosylates **20a**.[a]

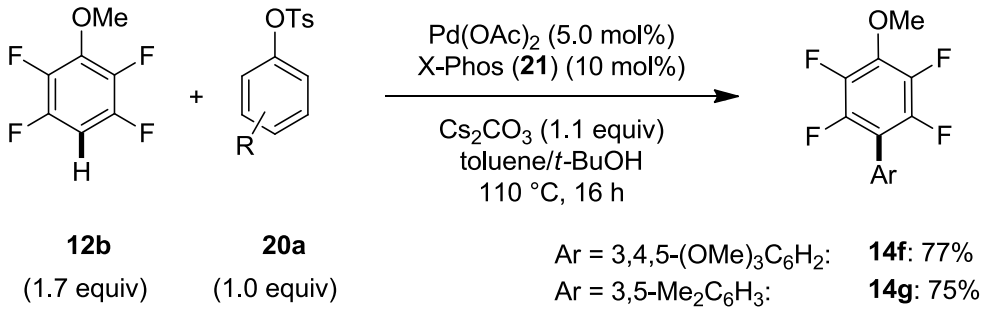


12c **20a** **14** **86**

entry	R	14	yield	86	yield	overall yield
1	3,4,5-$(OMe)_3$ **20ab**	 **14c**	45% 68%[b]	 **86c**	40% 18%[b]	85% 86%[b]
2	3-$N(Me)_2$ **20ad**	 **14d**	55%	 **86d**	18%	73%
3	3,5-Me_2 **20aa**	 **14e**	31%	 **86e**	30%	61%

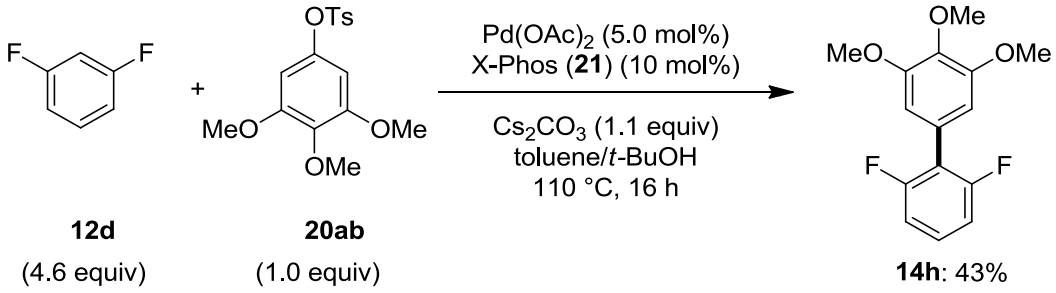
[a] Reaction conditions: **12c** (0.8 mmol), **20a** (0.5 mmol), $Pd(OAc)_2$ (5.0 mol%), X-Phos (**21**) (10 mol%), Cs_2CO_3 (0.55 mmol), toluene (1.5 mL), *t*-BuOH (0.5 mL), 110 °C, 16 h; isolated yields. [b] **12c** (2.5 mmol).

To our delight, tetrafluoroanisole (**12b**) turned out to be an excellent substrate for selective C–H bond functionalizations. The established highly active palladium catalyst allowed for direct arylations with either **20ab** or **20aa** as electrophiles (Scheme 55). Good isolated yields of the fluorinated biphenyls **14f** and **14g** of 77% and 75%, respectively were accomplished.



Scheme 55: Palladium-catalyzed direct arylation of electron-deficient tetrafluoroanisole **12b**.

Remarkably, 1,3-difluorobenzene (**12d**) comprising more than one potential site for reaction, delivered 2-monoarylated regioisomer **14h** in a reasonable yield (Scheme 56). Compared to a recently described palladium-catalyzed polyfluorobiphenyl construction methodology using arylboronic acids[17] by *Hong* and oxidative cross coupling procedures with simple arenes in high excess, reported by *Shi*[19] and *Su*,[18] the presented reaction using inexpensive, moisture-stable tosylates **20a** represents a competitive synthetic approach.



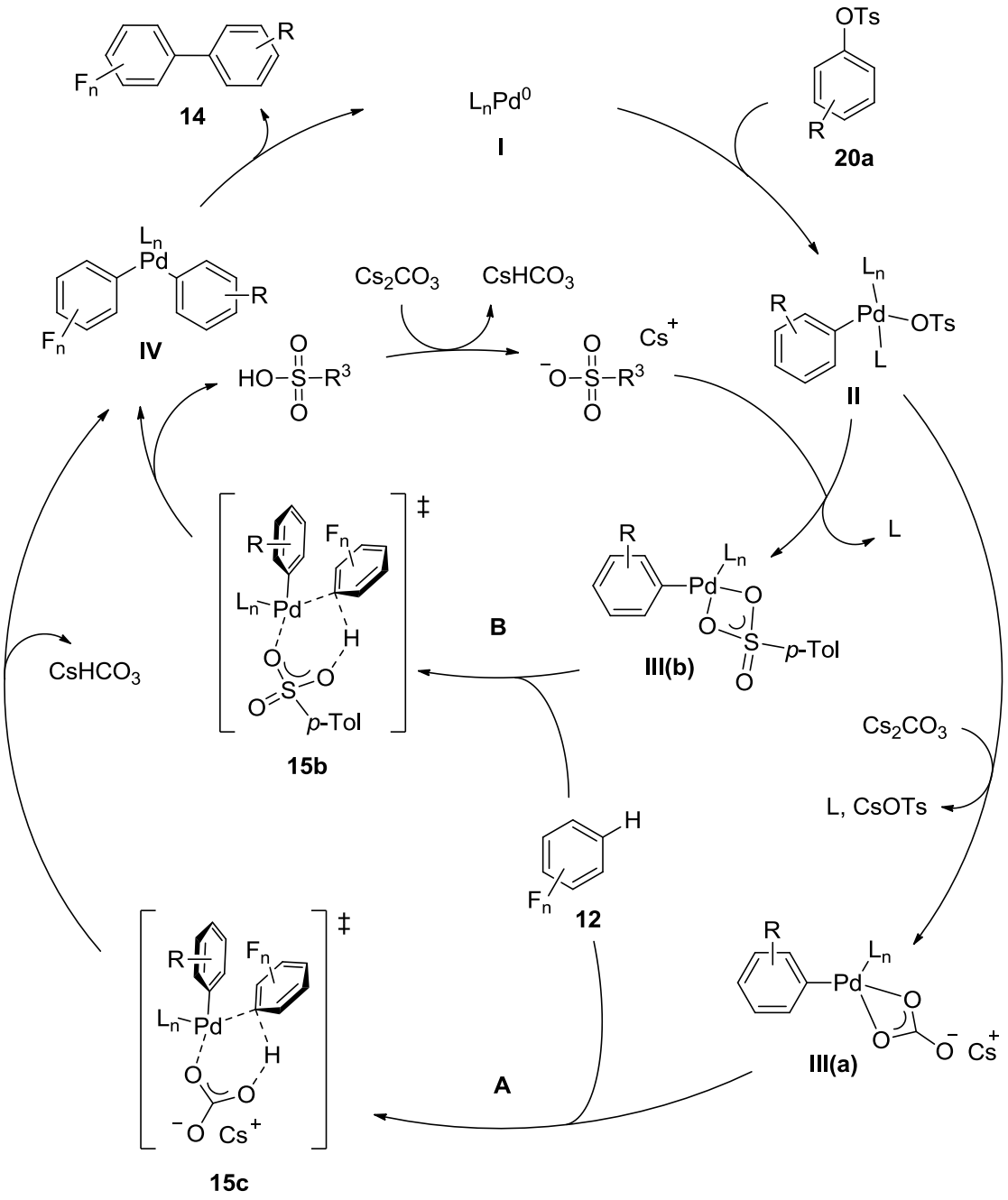
Scheme 56: Palladium-catalyzed regioselective direct arylation of 1,3-difluorobenzene (**12d**).

The regioselective arylation in the position between the two fluoro substituents indicates the acidity of the proton to play a crucial role in the catalytic reaction, which is consistent with previous observations for direct arylations of perfluoroarenes **12** with aryl bromides **7**.[12] Reports on the correlation of proton acidity with reactivity of perfluoroarenes **12** by *Fagnou* as well as the determination, that more electron-deficient arenes react preferentially, rendered an electrophilic aromatic substitution (S_EAr) pathway less likely to be operative. Rather, a mechanism *via* concerted carbonate-assisted metalation-deprotonation (CMD),[11] was postulated and supported by extensive DFT calculations.[12] The improved reactivity, when

using a carbonate base in C–H bond functionalizations of electron-deficient perfluoroarenes **12** with tosylates **20b**, could indicate an analougous pathway. Contrary, the sulfonate could participate in the concerted metalation-deprotonation step, as it was suggested for C–H bond functionalizations of (di)azine *N*-oxides **26** as depicted in Figure 4.

3.2.1 Mechanistic proposal

Based on these facts, the following possible mechanistic pathways are proposed (Scheme 57).



Scheme 57: Mechanistic proposals for direct arylations of electron-deficient perfluoroarenes **12** with aryl tosylates **20a**.

Initial oxidative addition of the aryl tosylate **20a** to the palladium(0) species **I** leads to intermediate **II**, which in the next step could undergo ligand exchange with the carboxylate anion providing intermediate **III(a)** (cycle A). Carbonate-assisted concerted metallation-deprotonation (CMD) *via* transition-state **15c** could then generate intermediate I**V**, from which the direct arylation product **14** eventually could reductively eliminate, releasing the active catalyst **I**. Alternatively, after the oxidative addition, **III(b)** could be formed through chelation of the sulfonate ligand (cycle B). Therafter, sulfonate-assisted CDM *via* transition-state **15b** could occur, providing intermediate I**V**. Finally, reductive elimination could release the active catalyst **I** and the arylation product **14**. Both models, carbonate-assisted, as well as autocatalytic sulfonate-assisted one, display possible reaction pathways.

Indeed, solubility of the base is ascribed to have a high impact on the catalytic reaction as it was described by *Fagnou* in 2006 for direct arylations of benzene **19** with aryl bromides **7**.[14] In a recent article by *Zhang* and coworkers the authors reported on a beneficial effect of sterically demanding carboxylic acid additives,[22] as was described before, for intra- as well as intermolecular direct arylation reactions.[14,41,115,150,155] However, the herein presented direct arylation does not show any improvement, when employing carboxylic acid additives.

3.3 Ruthenium-catalyzed synthesis of isoquinolones in water

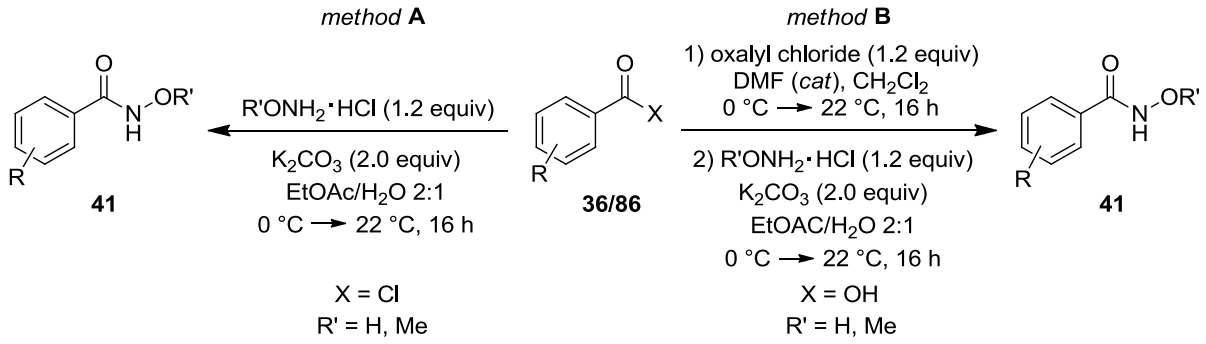
Transistion-metal-catalyzed oxidative C–H bond functionalizations have attracted significant interest in recent years, as tedious, multi-step preparation of preactivated starting materials can be avoided for this kind of transformations. Elegant reports on rhodium-catalyzed isoquinolone syntheses without the need of an external oxidant have been reported by *Fagnou et al.* in *2010* and *2011*.[71,72] In a very recent work, *Wang* presented the formation of isoquinolone motif by ruthenium-catalysis using benzhydroxamic acid esters **41b** in methanol as organic solvent.[79]

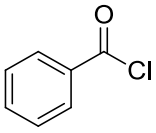
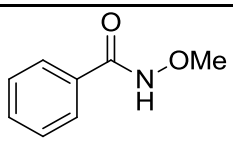
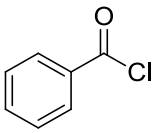
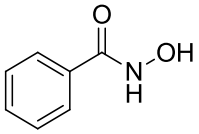
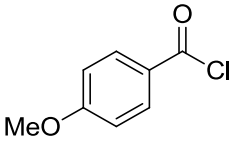
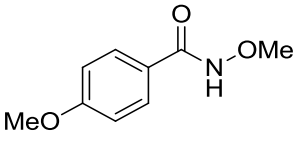
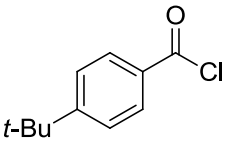
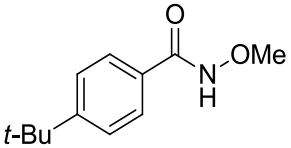
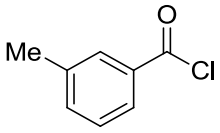
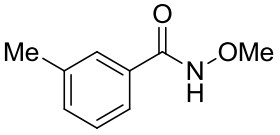
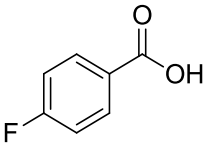
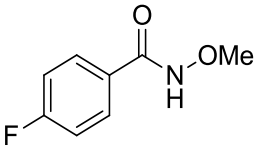
3.3.1 Synthesis of benzhydroxamic acid esters and acids

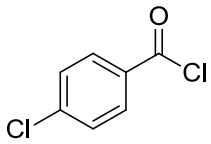
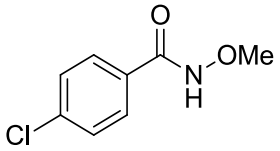
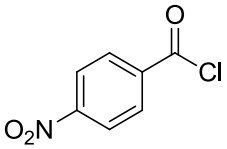
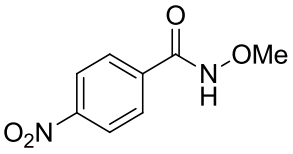
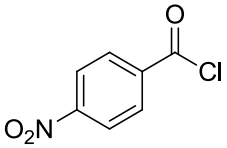
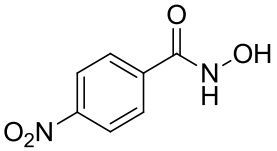
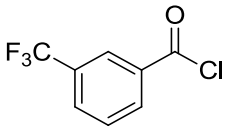
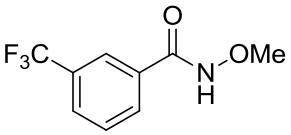
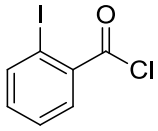
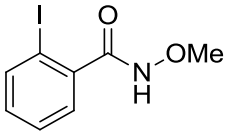
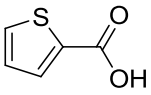
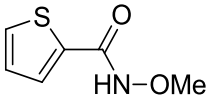
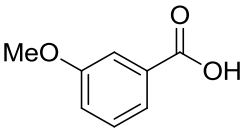
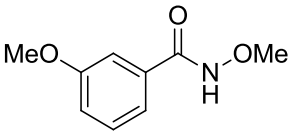
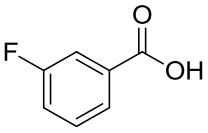
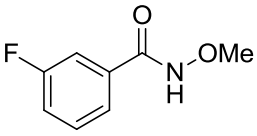
Benzyhydroxamic acid derivatives **41b** and **41c** were synthesized according to known literature procedures (Table 10).[73] The reactions of benzoyl chlorides **87** with *N*-methoxyamine hydrochlorides (**88a**) or *N*-hydroxyamine hydrochlorides (**88b**) afforded the benzyhydroxamic acid esters **41b** and acids **41c** (entries 1–5, 7–10 and 12). In some cases,

acid chlorides **87** were generated *in-situ* by treatment of the corresponding benzoic acids **36**, and reacted further with substituted hydroxylamines **88** providing **41b** and **41c** (entries 6, 11 and 13–15).

Table 10: Synthesis of benzhydroxamic acid esters **41b** and acids **41c** from the corresponding benzoic acids **36** or chlorides **87**.[a]



entry	substrate		meth.	41		yield
1		**87a**	A		**41ba**	75%
2		**87a**	A		**41ca**	33%
3		**87c**	A		**41bb**	66%
4		**87d**	A		**41bc**	97%
5		**87e**	A		**41bd**	93%
6		**36a**	B		**41be**	60%

7		**87f**	A		**41bf**	99%
8		**87g**	A		**41bg**	55%
9		**87g**	A		**41cb**	12%
10		**87i**	A		**41bh**	99%
11		**87j**	B		**41bj**	81%
12		**36b**	A		**41bi**	85%
13		**36c**	B		**41bk**	90%
14		**36d**	B		**41bl**	31%

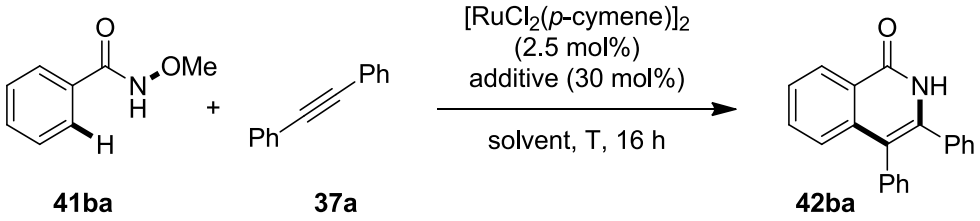
[a] Reaction conditions: A) **87** (1.0 equiv), R'ONH$_2$ · HCl **88** (1.5 equiv), K_2CO_3 (2.0 equiv), EtOAc/H_2O (2:1, 0.07 M), 0 °C to 22 °C, 16 h; B) **36** (1.0 equiv), oxalyl chloride (1.2 equiv), DMF (5 drops), CH_2Cl_2 (0.3 M), 0 to 22 °C, 4 h; R'ONH$_2$ · HCl **88** (1.1 equiv), K_2CO_3 (2.0 equiv), EtOAc/H_2O (2:1, 0.2 M), 0 to 22 °C, 16 h; isolated yields.

3.3.2 Optimization studies for ruthenium-catalyzed isoquinolone synthesis

Focusing on a highly efficient isoquinolone synthesis initial studies were conducted employing the [$RuCl_2$(*p*-cymene)]$_2$ complex, which has recently been reported by *Ackermann* to be suitable for oxidative annulations of internal alkynes **37** by secondary benzamides **41**.[76] Benzhydroxamic acid ester **41ba** and diphenylacetylene (**37a**) were chosen as standard

substrates in a ratio of 1:2 (Table 11).[156] Interestingly, the reaction occurred even at 60 °C with $[RuCl_2(p\text{-cymene})]_2$ as a catalyst using environmentally friendly, nonflammable and nontoxic water as reaction medium, albeit in low yield (entry 1). Among different additives tested, catalytic amounts of KO_2CMes proved to be the most efficient, delivering the desired product **42ba** in 81% isolated yield (entry 7). The use of polar organic solvents, such as DMF, *t*-AmOH or methanol (entries 8–10), as well as the addition of $Cu(OAc)_2 \cdot H_2O$ as an external oxidant (entry 6) resulted in lower yields of isoquinolone **42ba**. Further, a decreased yield was observed, with 1:1.2 ratio of substrates (entry 13). Although, the product **42ba** could be obtained in almost quantitative yield at 100 °C (entry 12), the lower reaction temperature of 60 °C, and therefore much milder reaction conditions, were chosen for the scope of the reaction.

Table 11: Optimization studies for ruthenium-catalyzed isoquinolone synthesis.[a]



41ba **37a** **42ba**

entry	additive	solvent	T [°C]	yield
1	-	H_2O	60	17%
2	KPF_6	H_2O	60	25%
3	KOAc	H_2O	60	11%
4	NaOAc	H_2O	60	17%
5	KOPiv	H_2O	60	56%
6	$Cu(OAc)_2 \cdot H_2O$	H_2O	60	9%
7	**KO_2CMes**	**H_2O**	**60**	**81%**
8	KO_2CMes	MeOH	60	65%
9	KO_2CMes	*t*-AmOH	60	19%
10	KO_2CMes	DMF	60	3%
11	KO_2CMes	H_2O	22	21%
12	KO_2CMes	H_2O	100	99%

13	KO_2CMes	H_2O	60	67%[b]
14	KO_2CMes	H_2O	60	76%[c]

[a] Reaction conditions: **41ba** (0.5 mmol), **37a** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), additive (30 mol%), solvent (2.0 mL), T, 16 h; isolated yields. [b] **37a** (0.6 mmol); [c] KO_2CMes (10 mol%).

3.3.3 Scope and limitations of ruthenium-catalyzed annulations of alkynes

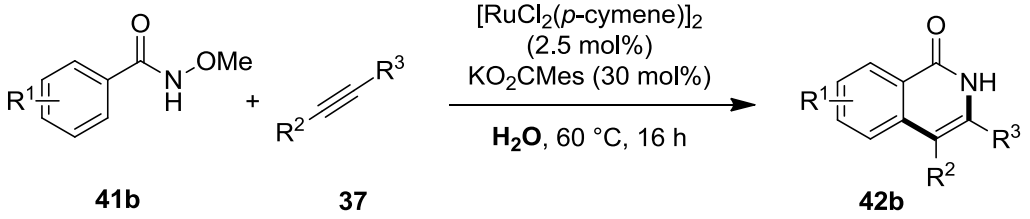
Under the optimized reaction conditions the formation of a variety of isoquinolone derivatives **42** was explored (Table 12). Ruthenium-catalyzed C–H/N–O bond functionalizations allowed for the efficient annulations of diffenrently substituted alkynes **37** by functionalized benzhyrdoxamic acid esters **41b** using water as a *green* solvent.

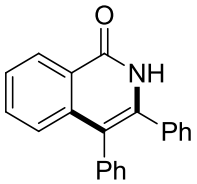
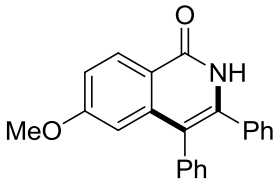
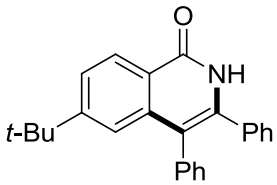
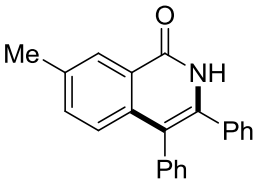
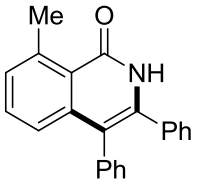
Electron-rich as well as electron-neutral benzhydroxamic acid esters were successfully converted into the corresponding isoquinolones **42ba**, **42bb** and **42bc** in high yields (entries 1–3). However, *ortho*-substituted ester **41bm** gave only low yield of the corresponding product **42bm**, even at elevated temperature, probably due to steric hinderance (entry 5). Actually, *ortho*-iodo substituted substrate **41bj** failed to react under the optimized conditions (entry 6). On the contrary, a valuable chlorine substituent on the benzamide moiety was well tolerated in the reaction, providing the possibility of further functionalization of isoquinolone **42bf** by cross-coupling reactions (entry 7). Moreover, electron-deficient fluorine- or worthwhile nitro-substituted benzhydroxamic acid esters **41be** and **41bg** served as suitable substrates, providing **42be** and **42bg** in high yields (entries 8 and 9). With the introduction of an electron-withdrawing fluorine substituent on the alkyne, an acceptable isolated yield of isoquinolone **42bn** was observed (entry 11), whereas the presence of a methoxy substituent resulted in a dramatical decrease of isolated yield, probably due to stronger binding of donor-substituted alkyne **37c** to the ruthenium center, which might decrease reactivity (entry 12).

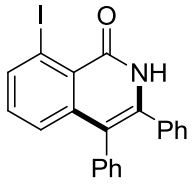
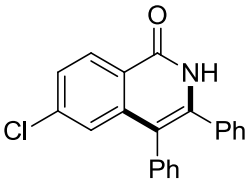
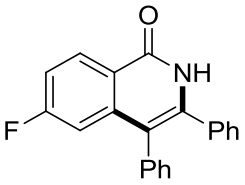
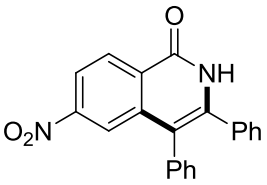
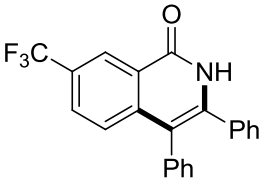
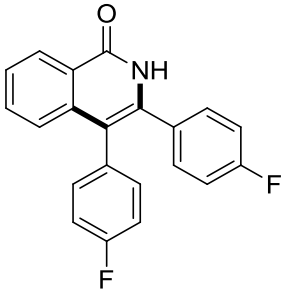
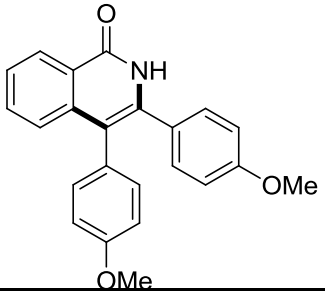
Fortunately, the catalytic system was not restricted to aryl-substituted alkynes, but also allowed for efficient annulations of alkyl substituted alkynes, albeit a higher catalyst loading was required to obtain the corresponding products **42bs**, **42bt**, **42bu**, **42bv** and **42bw** (entries 13–17). Remarkably, the annulation process occurred with excellent site-selectivity when using unsymmetrically substituted alkyl/aryl alkynes **37d**, **37e** and 3**7f,** resulting in an exclusive formation of the regioisomer with the sp^2-centre installed at the C3-position, delivering the corresponding products **42bp**, **42bq** and **42br** in good yields of up to 83% (entries 18–20). Well-established NOESY-NMR analysis confirmed the conformational

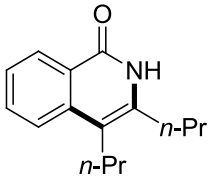
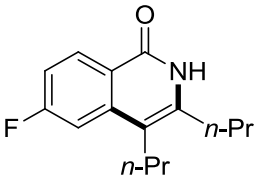
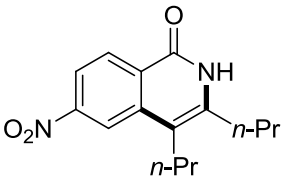
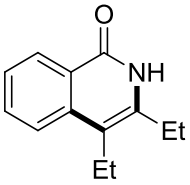
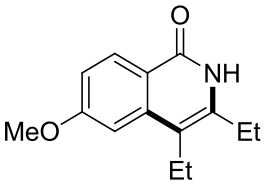
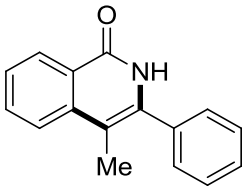
correlation at C3- and C4-position of the isoquinolones (see: experimental section). These results are in accordance with the previously observed selectivities for ruthenium-catalyzed reactions reported by *Ackermann*[76] and *Wang*[79] as well as by *Fagnou*[71,72] and *Rovis*[69a] for rhodium-catalyzed annulations of alkynes **37**. Sterical factors are therefore considered to govern the selectivity of alkyne insertion into the metal–carbon bond, which eventually defines the overall reaction outcome.

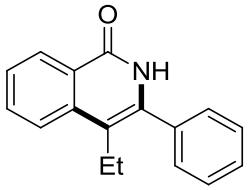
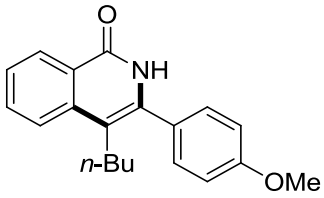
Table 12: Scope of ruthenium-catalyzed isoquinolone synthesis in water.[a]



entry	R^1	R^2	R^3	42		yield
1	H **41ba**	Ph **37a**	Ph		**42ba**	81%
2	4-MeO **41bb**	Ph **37a**	Ph		**42bb**	63%
3	4-*t*-Bu **41bc**	Ph **37a**	Ph		**42bc**	93%[b]
4	3-Me **41bd**	Ph **37a**	Ph		**42bd**	82%
5	2-Me **41bm**	Ph **37a**	Ph		**42bm**	19%[b]

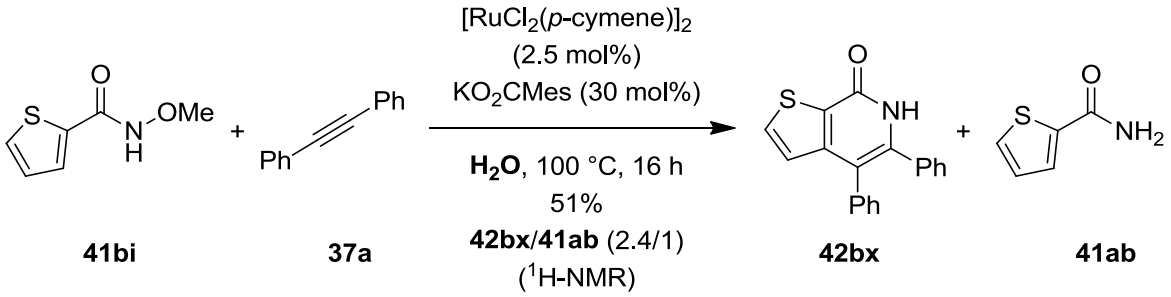
6	4-I **41bj**	Ph **37a**	Ph		**42bj**	-
7	4-Cl **41bf**	Ph **37a**	Ph		**42bf**	73%[c]
8	4-F **41be**	Ph **37a**	Ph		**42be**	72%
9	4-NO_2 **41bg**	Ph **37a**	Ph		**42bg**	86%
10	3-CF_3 **41bh**	Ph **37a**	Ph		**42bh**	79%[b]
11	H **41ba**	4-FC_6H_4 **37b**	4-FC_6H_4		**42bn**	50%
12	H **41ba**	4-$MeOC_6H_4$ **37c**	4-$MeOC_6H_4$		**42bo**	16%

13	H **41ba**	*n*-Pr **37g**	*n*-Pr		**42bs**	65%[d]
14	4-F **41be**	*n*-Pr **37g**	*n*-Pr		**42bt**	65%[d]
15	4-NO_2 **41bg**	*n*-Pr **37g**	*n*-Pr		**42bu**	79%[d]
16	H **41ba**	Et **37h**	Et		**42bv**	24%
17	4-OMe **41bb**	Et **37h**	Et		**42bw**	38%[d]
18	H **41ba**	Me **37d**	Ph		**42bp**	71%

19	H **41ba**	Et **37e**	Ph		**42bq**	83%
20	H **41ba**	*n*-Bu **37f**	4-MeOC$_6$H$_4$		**42br**	69%

[a] Reaction conditions: **41b** (0.5 mmol), **37** (1.0 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (2.5 mol%), KO$_2$CMes (30 mol%), H$_2$O (2.0 mL), 60 °C, 16 h; isolated yields. [b] Reaction at 100 °C. [c] Reaction with **37** (0.75 mmol). [d] Reaction with [RuCl$_2$(*p*-cymene)]$_2$ (5.0 mol%).

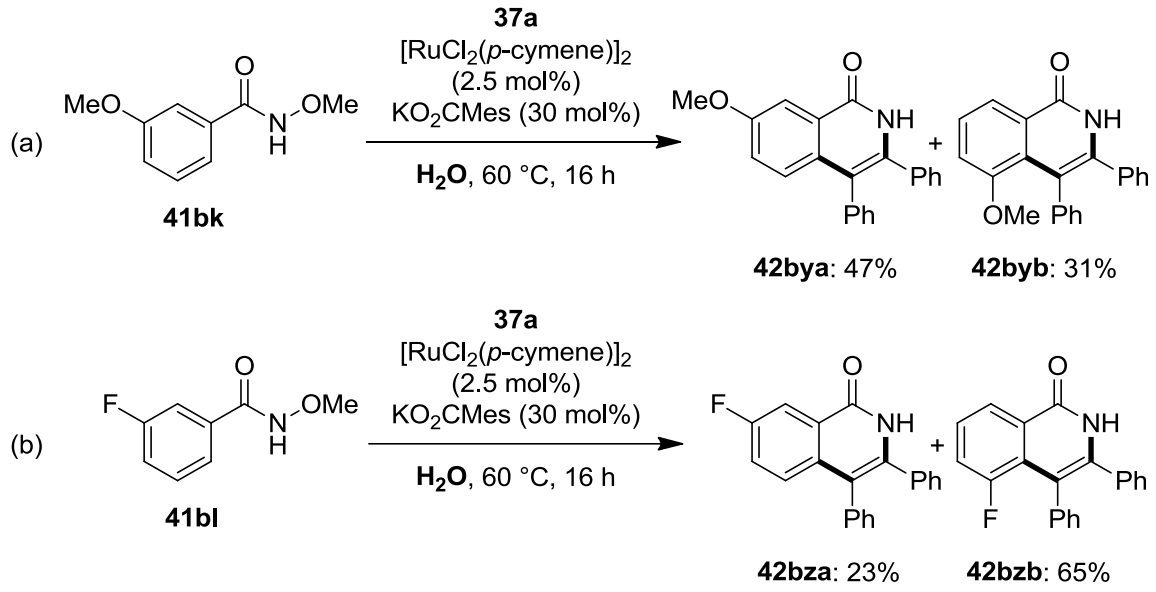
Interestingly, heterocycle **41bi** turned out to be a viable substrate for ruthenium-catalyzed annulation process as well. However, under the optimized reaction conditions a reduced yield of annulated product **42bx** was observed, which can be attributed to the formation of undesired thiophene-2-carboxamide (**41ab**). A mixture of **42bx** and **41ab** could be isolated in a ratio of 2.4:1 as estimated by ^{1}H-NMR spectroscopy (Scheme 58).[157]



Scheme 58: Ruthenium-catalyzed annulation with heterocyclic substrate **41bi**.

Importantly, reactions with *meta*-substituted substrates **41bd** and 41**bh** proceeded in a highly regioselective fashion with the C–H bond cleavage occuring at the sterically less hindered C6-position of the arene providing isoquinolones **42bd** and **42bh** in 82% and 79% isolated yields, respectively (Table 12, entries 4 and 9), which is in agreement with the previously described results.[76,79] In contrast, benzhydroxamic acid esters **41bk** and **41bl** bearing hetereoatoms in *meta*-position led to product mixtures with significant amounts of **42byb** and **42bzb**, respectively, through C–H bond functionalization at the C2-positon of the arenes (Scheme 59). These observations can be ascribed to an enhanced C–H bond acidity[125b] at the C2-

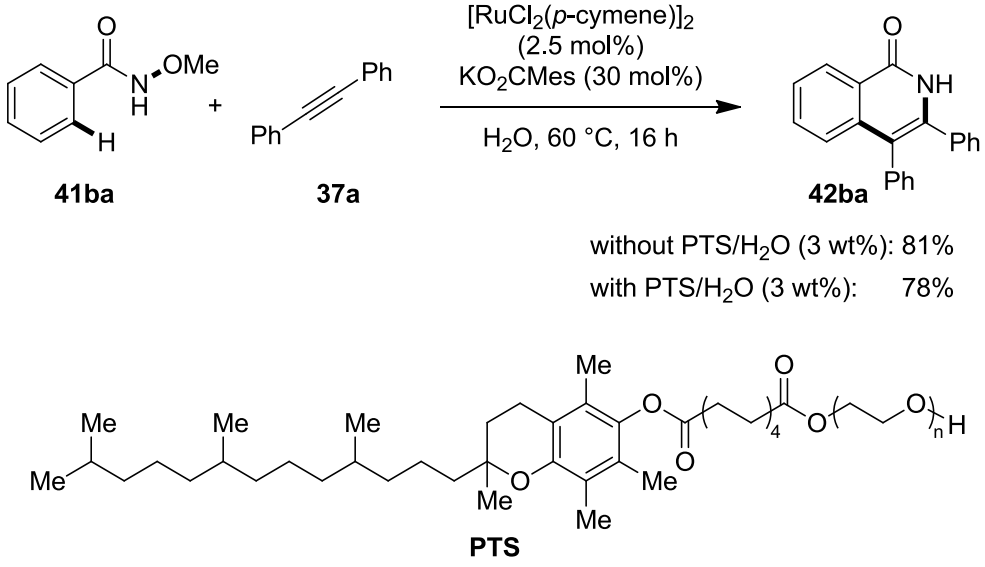
position, as well as the higher stability of Ru–C bonds in proximity of the heteroatoms,[158] governing the site-selectivity of the overall annulation process.



Scheme 59: Ruthenium-catalyzed annulations with *meta*-substituted benzhydroxamic acid esters **41bk** and **41bl**.

3.3.4 Mechanistic studies

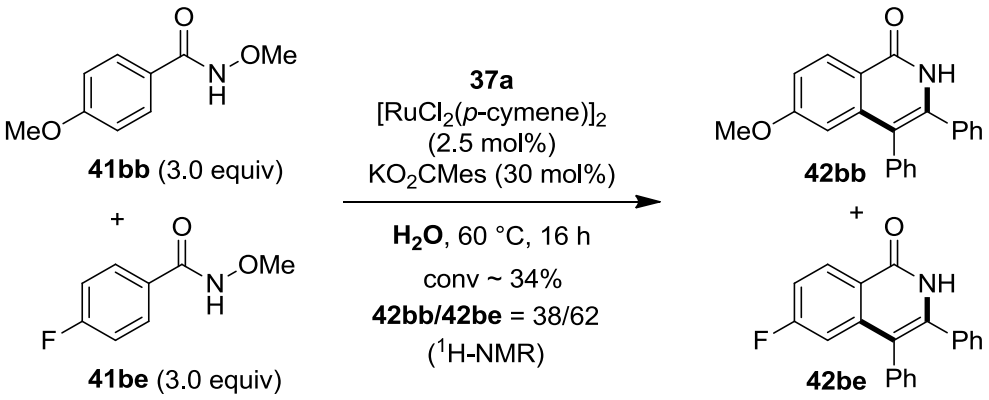
According to recent studies concerning comparative effects of water on organic reactions,[159] it has been probed, if the addition of a phase transfer catalyst PTS (*polyoxyethanyl α-tocopheryl sebacate*) has any influence on the annulations of alkynes **37** by benzhydroxamic acid esters **41b** (Scheme 60).



Scheme 60: Influences of phase transfer catalyst PTS on the annulation of alkyne **37a** by benzhydroxamic acid ester **41ba**.

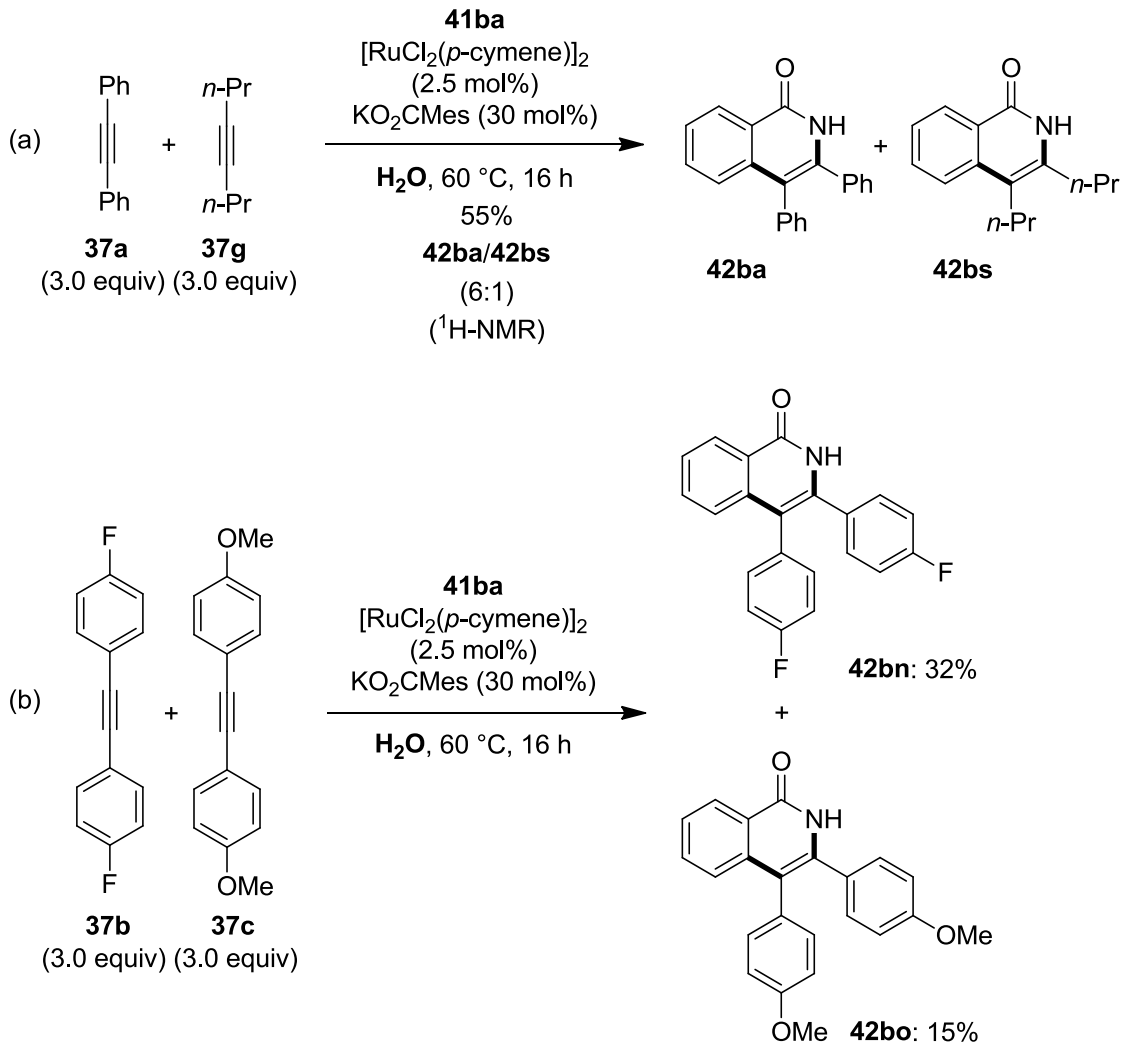
Under standard reaction conditions, using *N*-methoxybenzamide (**41ba**) and diphenylacetylene (**37a**) the addition of 3 wt% of PTS showed no distinct effect on the reaction outcome. Based on these results, the presented procedure is assumed to proceed in water but not on water, despite the solubility of **37a** in water is determined to be sparingly in a recent review by *Butler* and *Coyne*.[159d] Similarly, *Ackermann* and *Pospech* recently presented ruthenium-catalyzed oxidative C–H bond alkenylations of benzoic acids **36** in water.[80a]

In order to get a closer insight into the working mode of ruthenium-catalyzed C–H/N–O bond functionalizations, further mechanistic studies have been conducted. An intermolecular competition experiment between **41bb** and **41be** revealed the electron-deficient substrate **41be** to react preferentially, indicating that an electrophilic C–H bond activation pathway is less likely (Scheme 61).



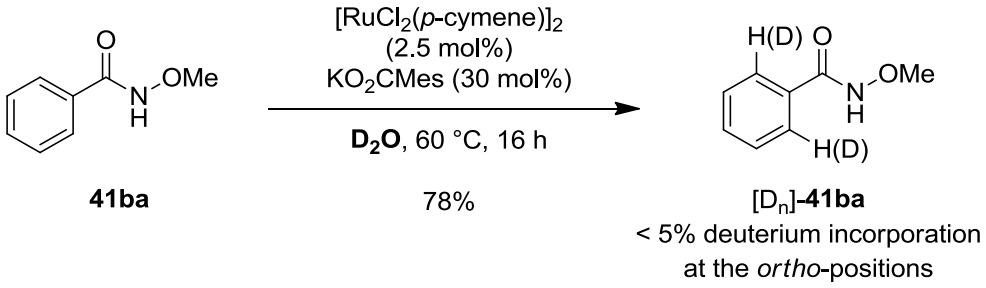
Scheme 61: Intermolecular competition experiment between **41bb** and **41be**.

Intermolecular competition experiments between phenylacetylene (**37a**) and 4-octyne (**37g**) (Scheme 62a), as well as between tolan derivatives **37b** and **37c** (Scheme 62b) illustrated preferential functionalization of more electron-deficient alkynes **37a** and **37b** respectively, which is in accordance with recently reported ruthenium-catalyzed annulations procedures[76,79] but differs considerably from rhodium-catalyzed oxidative annulations processes.[69a,69b,69c,]



Scheme 62: Intermolecular competition experiments between diaryl alkynes.

To verify the mode of action for the presented isoquinolone synthesis, experiments with isotopically-labeled solvent and substrate [D_5]-**41ba** have been performed (Scheme 63).



Scheme 63: Experiment with isotopically-labeled solvent.

Heating the mixture of **41ba**, ruthenium-catalyst and KO_2CMes in the absence of an alkyne **37** at 60 °C for 16 h in D_2O showed less than 5% deuterium incorporation at the two *ortho*-positions of the benzhydroxamic acid ester **41ba**, thus providing strong evidence for an irreversible C–H bond metalation (Figure 5). Notably, no cleavage of the N–O bond was observed in this case, excluding a mechanism involving an N–O bond oxidative addition, which has previously been demonstrated by *Hartwig* for palladium-catalyzed aromatic C−H bond amination with oxime esters.[160]

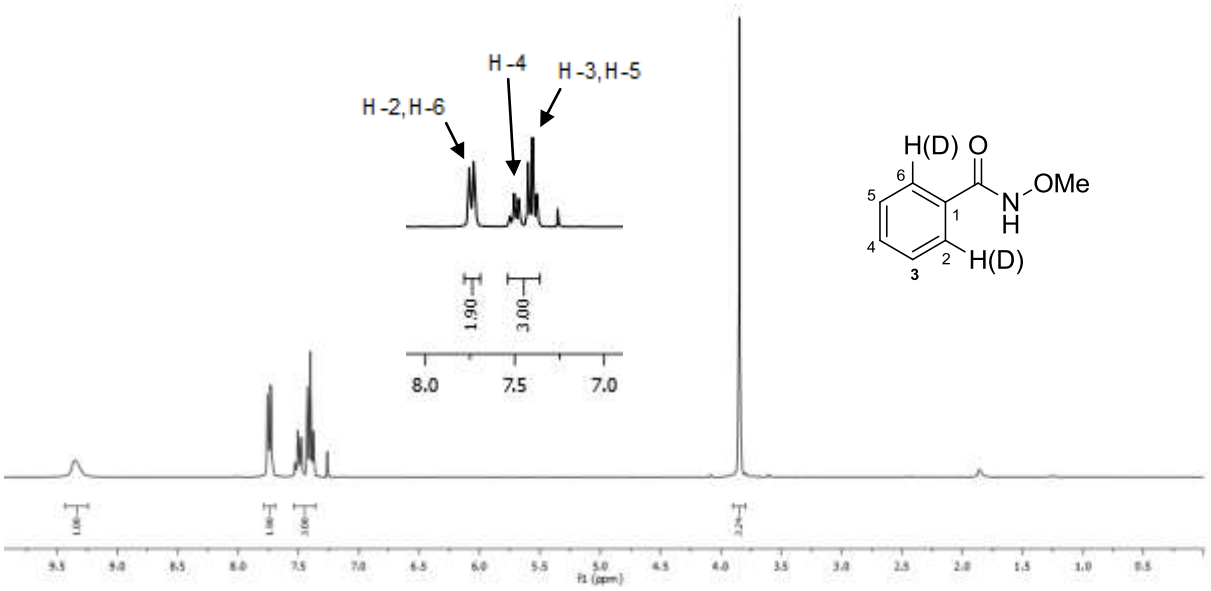
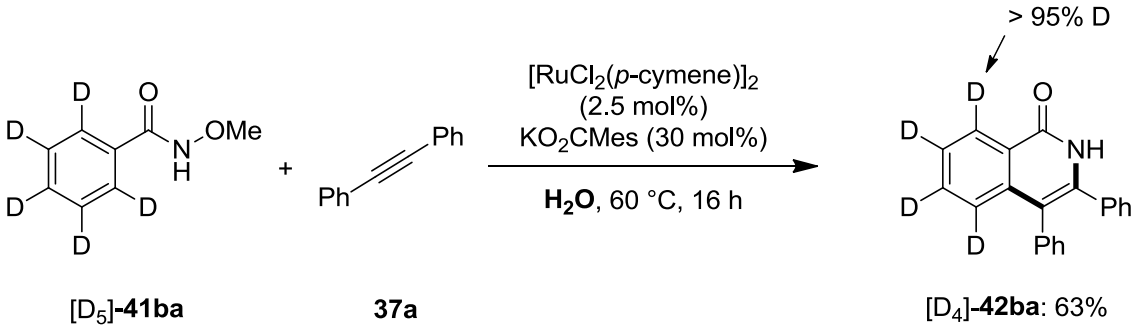


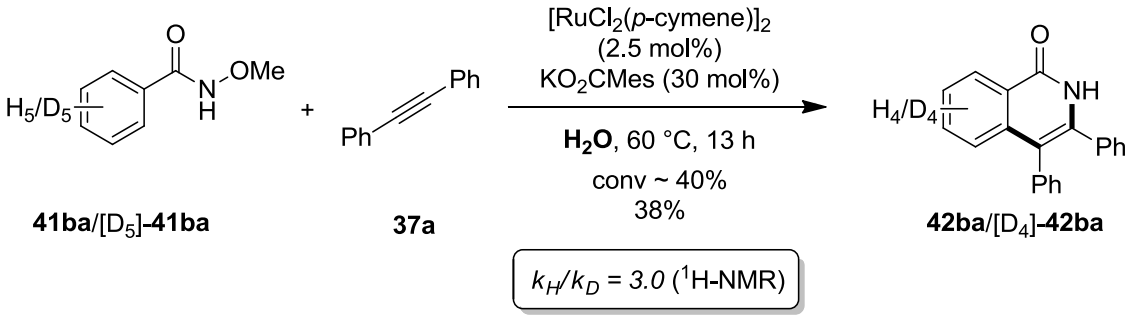
Figure 5: ^{1}H-NMR spectrum of [D_n]-**41ba**.

The utilization of [D_5]-**41ba** furnished isoquinolone [D_4]-**42ba** in 63% isolated yield (Scheme 64). According to ^{1}H-NMR spectroscopy only negligable H/D exchange at the *ortho*-positions of the arene core could be detected, which additionally confirmed the assumed irreversibility of the *ortho*-metallation step.



Scheme 64: Reaction with [D_5]-**41ba**.

Furthermore, an intermolecular competition experiment between **41ba** and [D_5]-**41ba** showed a primary kinetic isotope effect *(KIE)* of $k_H/k_D \approx 3.0$ (Scheme 65), rendering an irreversible rate-determining ruthenation-event through concerted carboxylate-assistance to be presumably operative.2[c]



Scheme 65: Intermolecular competition experiment between **41ba** and [D_5]-**41ba**.

The decisive sections of the corresponding ^{1}H-NMR spectra are depicted in Figure 6. Accordingly, the ratio of **42ba**/[D_4]-**42ba** in the mixture of products was determined to be 3:1.

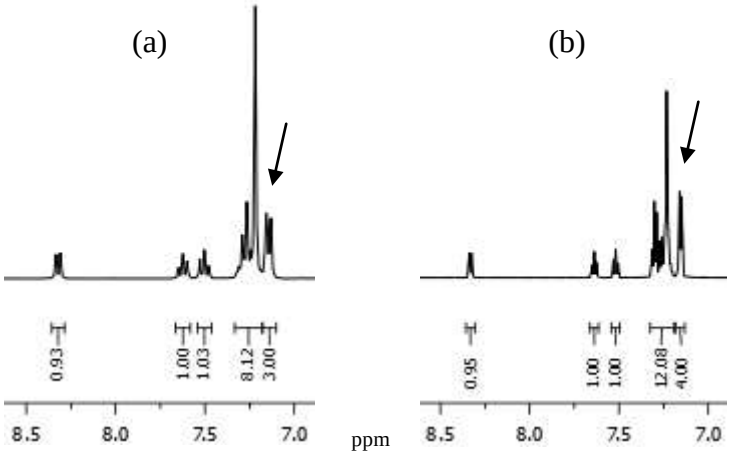
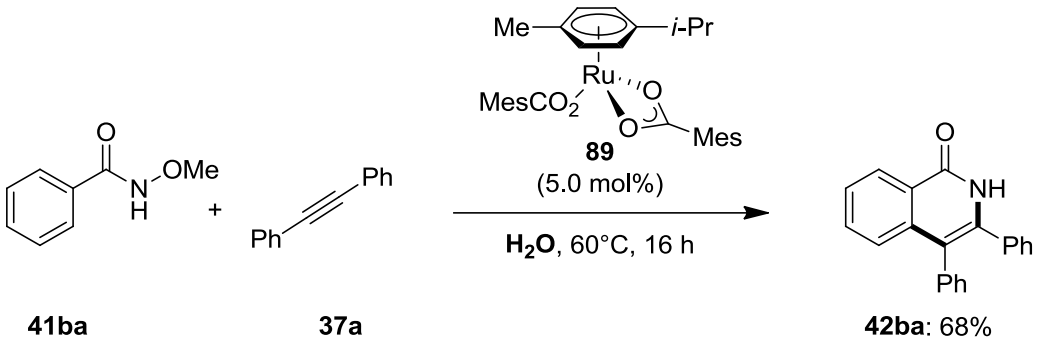


Figure 6: Decisive sections of ^{1}H-NMR spectra of (a) **42ba** and (b) the mixture of **42ba**/[D_4]-**42ba**.

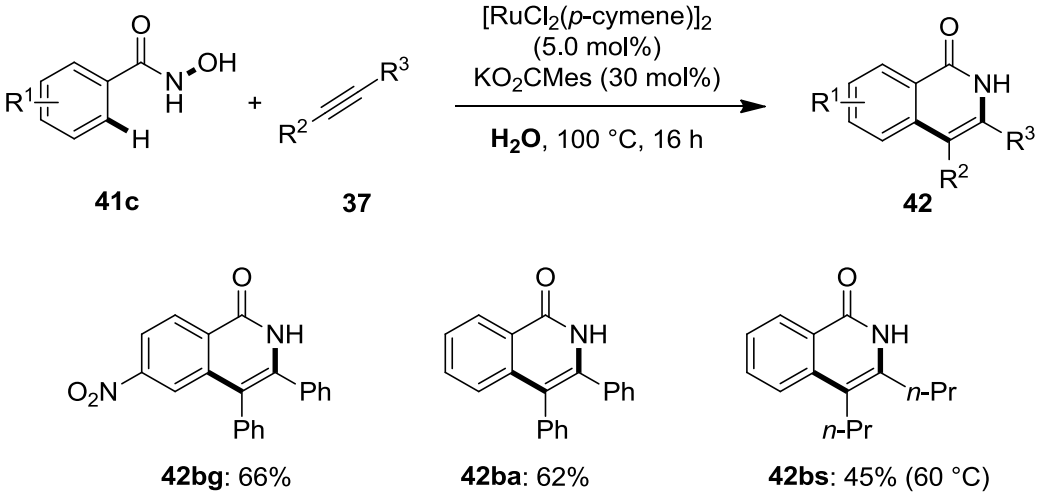
These results are consistent with *Wang's* observations for ruthenium-catalyzed isoquinolone synthesis,[79] but substantially differ from *Fagnou's* postulated mechanism for rhodium-catalyzed procedure using *N*-methoxy benzhydroxamic acid esters **41b**.[71]

Gratifyingly, well-defined ruthenium(II)-carboxylate-complex **89** was found to be catalytically competent for the annulation of tolane (**37a**) without the need of additional KO_2CMes, providing **42ba** in only slightly lower yield, when compared to the *in-situ* generated system (Scheme 66).



Scheme 66: Ruthenium-catalyzed isoquinolone synthesis using the well-defined ruthenium-complex **89**.

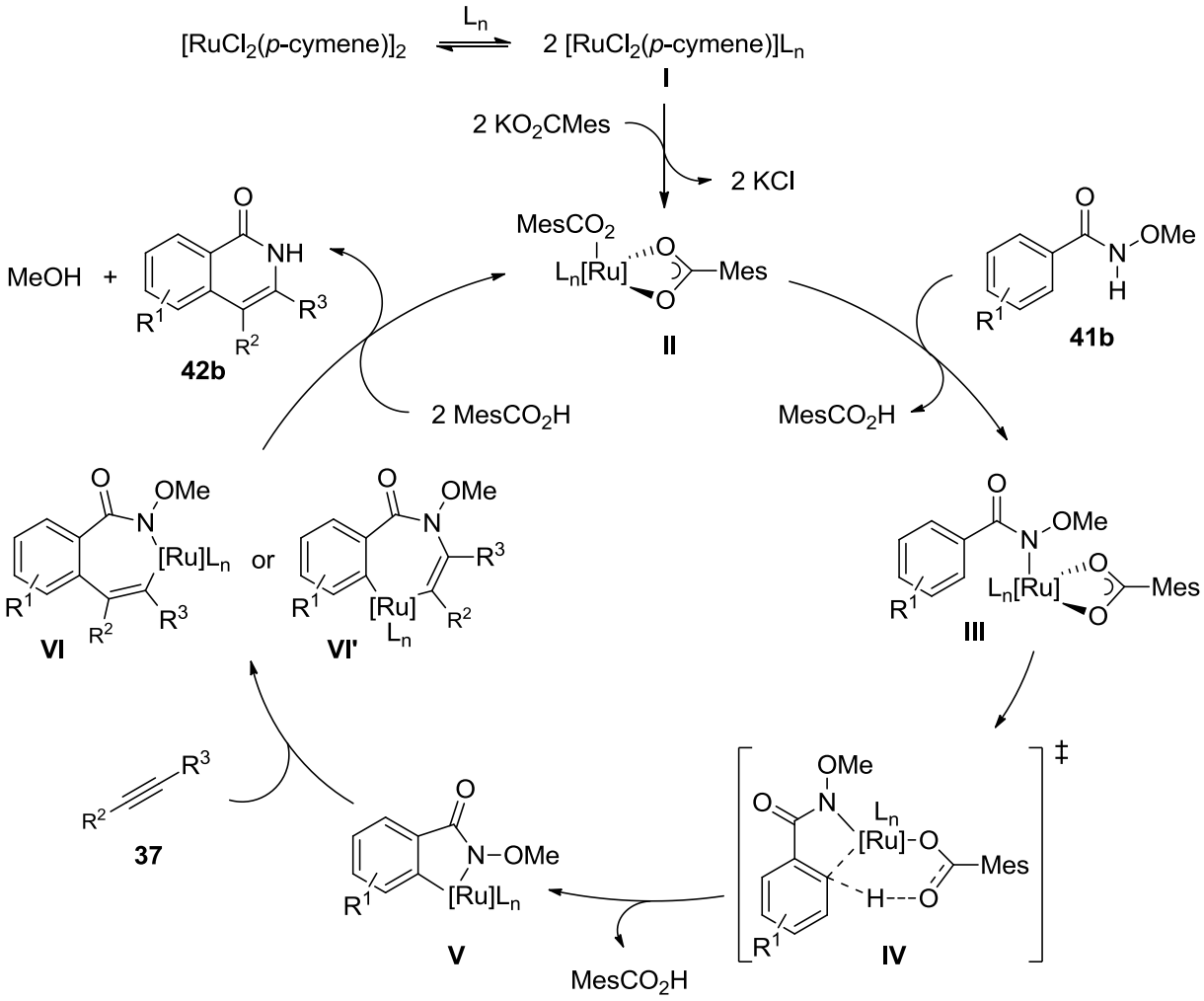
Strikingly, the newly developed system proved to be capable of catalyzing unprecedented annulations of alkynes **37** using free hydroxamic acids **41c** (Scheme 67). Valuable nitro-substituted substrate **41cb**, as well as unsubstituted benzhydroxamic acid (**41ca**) was efficiently converted to **42bg** and **42ba** in 66% and 62% isolated yields, respectively. The excellent catalytic activity led to the annulation of alkyl-substituted alkyne **37g** under relatively mild reaction conditions providing isoquinolone **42bs** in 45% isolated yield.



Scheme 67: Ruthenium-catalyzed annulation of benzhydroxamic acids **41c**.

3.3.5 Mechanistic proposal

Based on the experimental observations, the following mechanism for ruthenium-catalyzed carboxylate-assisted isoquinolone synthesis is proposed (Scheme 68).

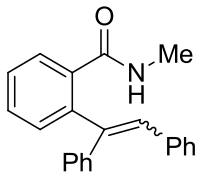


Scheme 68: Proposed mechanism for ruthenium(II)-catalyzed carboxylate-assisted isoquinolone synthesis.

Initially, the ruthenium dimer precatalyst presumably dissociates to coordinatively unsaturated species **I**, which can undergo ligand exchange, generating catalytically active ruthenium(II) species **II**. In the first step of the cycle ruthenium(II) species **II** gets coordinated by benzhydroxamic acid ester **41b** and releases one molecule of mesitylcarboxylic acid, providing **III**. Thereafter, irreversible carboxylate-assisted concerted deprotonation-ruthenation event *via* six-membered transistion state **IV** leads to five-membered ruthenacycle **V** with concomitant formation of mestitycarboxylic acid. After regioselective insertion of the alkyne **37** a seven-membered ruthenacycle **VI** or **VI'** is formed. Finally, reductive elimination

gives rise to isoquinolone **42b** as well as one equivalent of methanol, while two mesitylcarboxylate ligands coordinate to the ruthenium center, regenerating the catalytically active species **II**.

Currently, neither ruthenacycle **VI**, nor **VI'** can definitely be ruled out. In the previous report on ruthenium-catalyzed oxidative synthesis of isoquinolones, the formation of a ruthenacycle of type **VI** was proposed, based on the structure of uncyclized intermediate **90**, which was isolated as a side-product and fully characterized (Figure 7).[76]



90

Figure 7: Structure of 2-(1,2-diphenylvinyl)-*N*-methylbenzamide **90**.

At this point it is not yet clear, if the reaction proceeds *via* concerted or stepwise C–N bond formation/N–O bond cleavage. Indeed, a stepwise pathway has recently been postulated for rhodium-catalyzed annulations of alkynes **37** with *N*-pivalate substituted benzhydroxamic acid esters **41b** by *Fagnou*, which was supported by DFT calculations.[72]

3.4 Metal-free direct arylations of indoles and pyrroles with diaryliodonium salts

With respect to the indispensibility of indoles **48** and pyrroles **49** in pharmaceuticals, materials sciences and natural products,[161] the regioselective functionalization of these particular heterocycles is of paramount importance in organic chemistry.[103,104] Thus, in 2009 an efficient procedure for palladium-catalyzed direct C3-arylations of indoles **48** with aryl bromides **7** using an air-stable HASPO preligand, was developed in the *Ackermann* group.[114] Actually, caused by their low toxicity and mild reaction conditions, hypervalent iodine(III) compounds **46**, have received recent attention among organic chemists, as metal-free highly selective reagents in oxidative transformations.[85,86] In 2006 *Sanford* reported on the first palladium-catalyzed regioselective C2-arylation of indoles **48** with diaryl iodonium tetrafluoroborates **46a**.[92] Further, *Gaunt* presented copper(II)-catalyzed direct site-selective arylations of indoles **48** with diaryl iodonium reagents **46** in 2008.[93] Only recently, *Sanford*

reported on an elegant method for palladium-catalyzed direct arylations of pyrroles **49** with diaryl-λ^3-iodanes **46**.[94]

Endeavouring the development of new efficient ruthenium-catalyzed C–H bond functionalizations on heteroarenes,[58,162] *Vicente* recently made an interesting observation. He found that C–H bond arylation occurred on indoles **48** and pyrroles **49** even in the absence of any transistion-metal-catalyst. On the basis of these findings, extensive research-effort has been pursued to elaborate an effective direct arylation procedure.

3.4.1 Otimization studies on metal-free direct arylations of indoles

Initial studies on direct arylations of indoles **48** have been carried out by *Vicente*. With diphenyliodonium triflate **46c** as arylating reagent he explored the effect of solvents on the direct functionalization of 1,2-dimethyl-substituted indole **48d**.[163] Among various organic solvents dimethyl formamide provided superior results as compared to toluene, 1,4-dioxane, NMP, acetic acid or *tert*-amyl alcohol and was used as reaction medium, henceforth. Further studies, verifying different counterions, revealed iodonium tosylates **46d** as most useful arylating reagents for direct arylations of indoles **48**. Though, almost comparable results could be accomplished with diaryliodonium hexaflourophosphate **46e**, trifluoroacetate **46f** or tetrafluoroborate **46a**. *Sandmann* verified influences of the reaction temperature and the addition of different Brønstedt acids, as potential catalysts, on the reaction, concluding that no improvement on the reaction outcome could be achieved, either choosing higher reaction temperatures or adding any Brønstedt acid.[164]

Based on these findings, experiments on the stoichiometry of substrates **46da** and **46db** were pursued (Scheme 69). As showcased, a rario of 1:2 delivered the desired arylation products **50bc** and **50bd** in satisfactory yields of 54% (a) and 67% (c), respectively, whereas significantly lower isolated yields of **50bc** and **50bd** were achieved using a ratio of 1:1.1 (b) and (d). Consequently, for further direct arylations two equivalents of iodonium salts in relation to indoles were used.

48d (1.0 equiv)

(a) Ar = C_6H_5: **46da**: (2.0 equiv) **50bc**: 54%

(b) Ar = C_6H_5: **46da**: (1.1 equiv) **50bc**: 47%

(c) Ar = 4-$MeOC_6H_4$: **46db**: (2.0 equiv) **50bd**: 67%

(d) Ar = 4-$MeOC_6H_4$: **46db**: (1.1 equiv) **50bd**: 53%

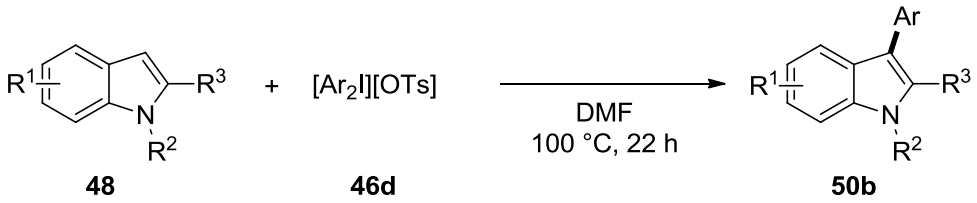
Scheme 69: Optimization studies on the ratio of substrates.

3.4.2 Scope of metal-free direct arylation of indoles with diaryliodonium salts

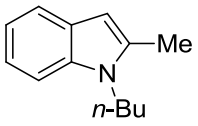
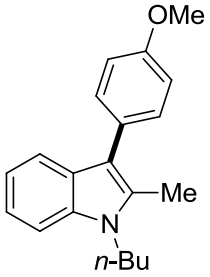
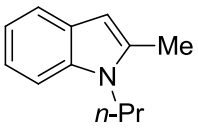
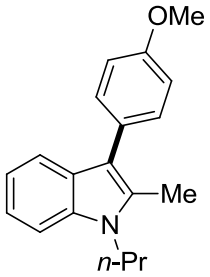
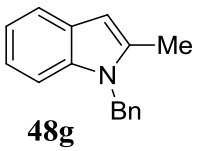
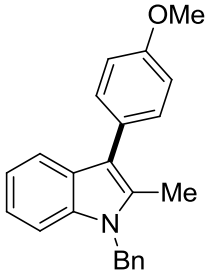
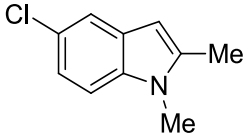
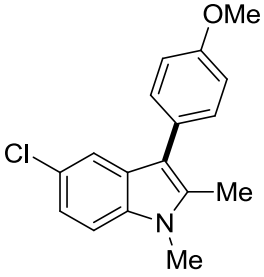
With optimized reaction conditions in hand, the scope of metal-free direct C–H bond functionalization of indoles was investigated (Table 13). 1,2-Disubstituted indoles **48e**, **48f** and **48g** were efficiently converted into the corresponding C3-arylated products **50be**, **50bf** and **50bg** with bis(4-methoxyphenyl)iodonium tosylate (**46db**). Different alkyl chains on nitrogen were well tolerated (entries 1 and 2), as was a benzyl substituent (entry 3). Noteworthy, no significant decrease of the isolated yield of **50bg** was observed, when performing the reaction under air (entry 3). Decoration on the aromatic moiety of the indoles proved to be compatible, which among others set the stage for the synthesis of chloro-substituted products **50bh** and **50bi** in reasonable yields (entries 4 and 5). C–H bond functionalization of 5-methoxy-1,2-dimethylindole (**48bi**) afforded the appropriate product **50bk** in a high yield of 81% (entry 7). Furthermore, diaryliodonium tosylates **46da** and **46dc** served as vialble arylating reagents (entries 5 and 6).

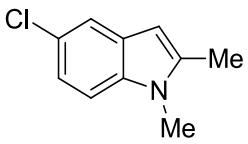
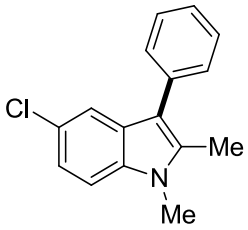
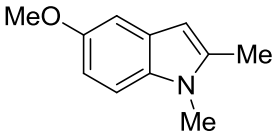
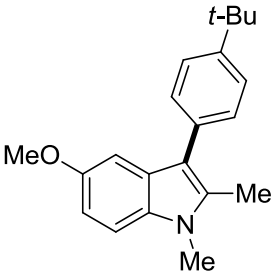
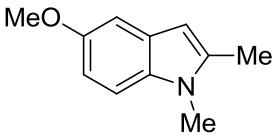
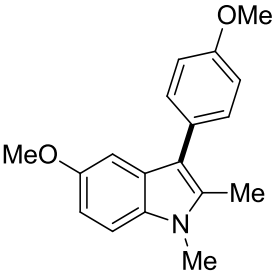
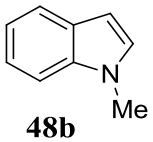
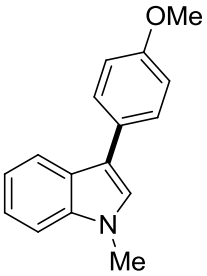
As expected, direct arylations proceeded with high site-selectivities to predominantly yield the C3-arylated products. The reaction of *N*-methylindole (**48b**) with bis(4-methoxy-phenyl)iodonium tosylate (**46bd**) gave rise to C3-regioisomer **50bl** in 55% isolated yield (entry 8). Thus, in spite of elevated temperature, our arylation-procedure and copper-promoted[93] C–H bond functionalization result in essentially the same regioselectivity.

Table 13: Scope of metal-free direct arylation of indoles **48** with diaryliodonium tosylates **46d**.[a]



48 **46d** **50b**

entry	48	Ar	50		yield
1	 **48e**	4-$MeOC_6H_4$ **46db**		**50be**	68%
2	 **48f**	4-$MeOC_6H_4$ **46db**		**50bf**	59%
3	 **48g**	4-$MeOC_6H_4$ **46db**		**50bg**	40% (37%)[b]
4	 **48h**	4-$MeOC_6H_4$ **46db**		**50bh**	61%

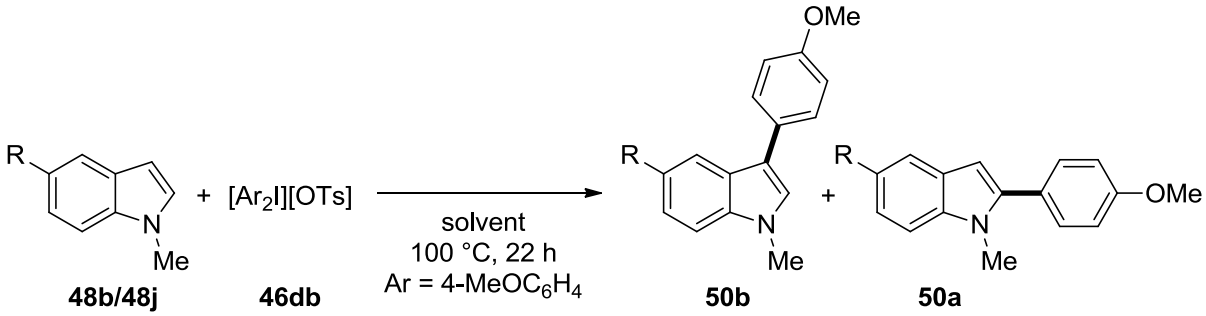
5	 **48h**	C_6H_5 **46da**		**50bi**	46%
6	 **48i**	4-*t*-BuC_6H_4 **46dc**		**50bj**	(74%)[c]
7	 **48i**	4-MeOC_6H_4 **46db**		**50bk**	81%
8	 **48b**	4-MeOC_6H_4 **46db**		**50bl**	55%[d,e]

[a] Reaction conditions: **48** (0.5 mmol), **46d** (1.0 mmol), DMF (2.0 mL), 100 °C, 22 h; isolated yields. [b] Under air. [c] GC-Yield, *n*-tridecane as internal standard. [d] **46db** (2.0 mmol). [e] Less then 10% of the corresponding C2-arylated product **50al** was formed (GC-MS analysis).

Prodigiously, the methodogly was not restricted to *N*-substituted indoles, but also allowed for C–H bond functionalizations of free (*NH*)-indoles, which was disclosed by *Dell'Acqua*, who collaborated in this particular project.[163]

A closer examination of solvent influences on the selectivity in the reactions of **48b** and **48j** is depicted in Scheme 70. Toluene is unveiled to provide an analogous result (a) compared to dimethyl formamide (Table 13, entry 8). Likewise, 1,4-dioxane delivered an comparable selectivity, but significantly inferior isolated yields of products **50bl** and **50al** (b) and **50bm**

and **50am** (d). Indeed, acetic acid proved to be an inadequate solvent as a low yield of 3-arylated product **50bl** was obtained (c).[116]

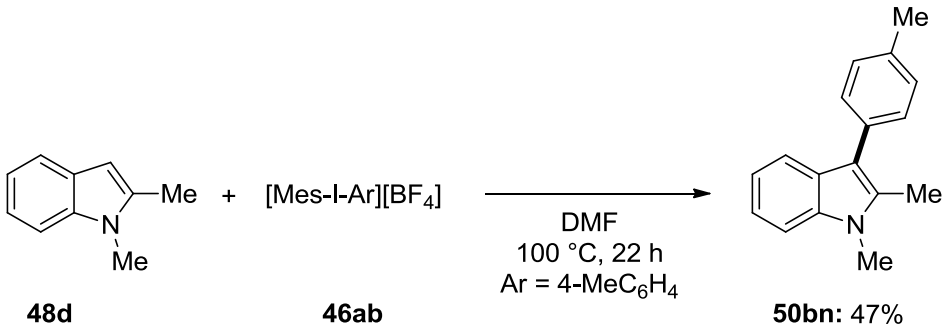


48b/48j **46db** **50b** **50a**

(1.0 equiv)	(2.0 equiv)	R = H	toluene:	**50bl**: 55%	**50al**: 12%	(a)
			1,4-dioxane:	**50bl**: 43%	**50bl**: 9%	(b)
			acetic acid:	**50bl**: 7%	**50al**: -	(c)
		R = Br	1,4-dioxane:	**50bm**: 31%	**50am**: 8%	(d)

Scheme 70: Solvent influences on *site*-selectivity of direct arylations of 2,3-unsubstituted indoles **48b** and **48j**.

Notably, unsymmetrically substituted diaryliodonium salt **46ab** was found to be suitable for direct arylation of indole **50bn**. The corresponding reaction resulted in the preferential transfer of the less sterically congested aromatic fragment (Scheme 71).

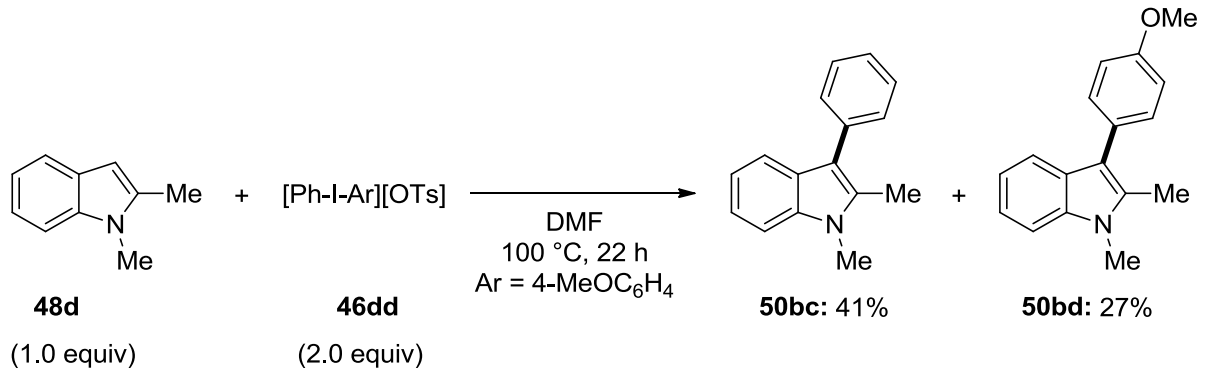


48d **46ab** **50bn:** 47%

(1.0 equiv) (2.0 equiv)

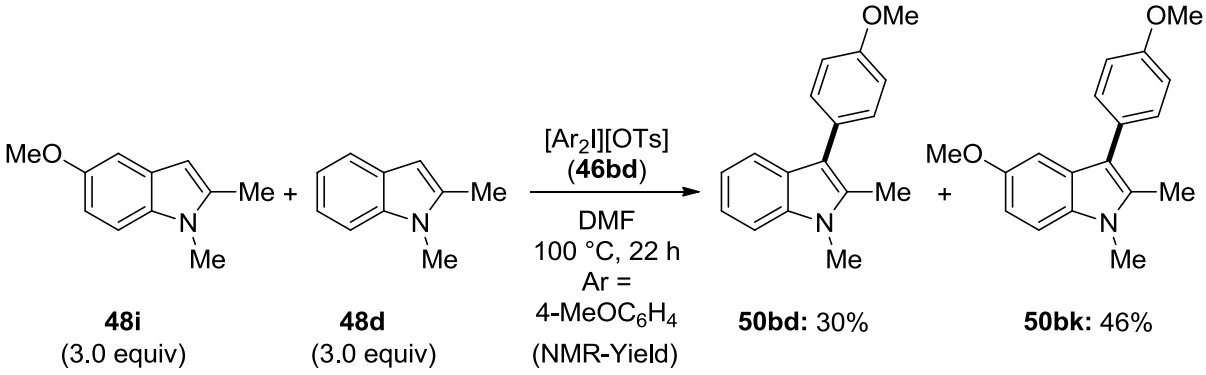
Scheme 71: Metal-free direct arylation of indole **48d** with diaryliodonium tetrafluoroborate **46ab**.

An additional intramolecular competition experiment with iodonium tosylate **46dd** bearing two different aryl substituents with comparable steric demands highlighted that the less electron-rich group is introduced predominantly resulting in a product distribution of 1:1.5 (Scheme 72).



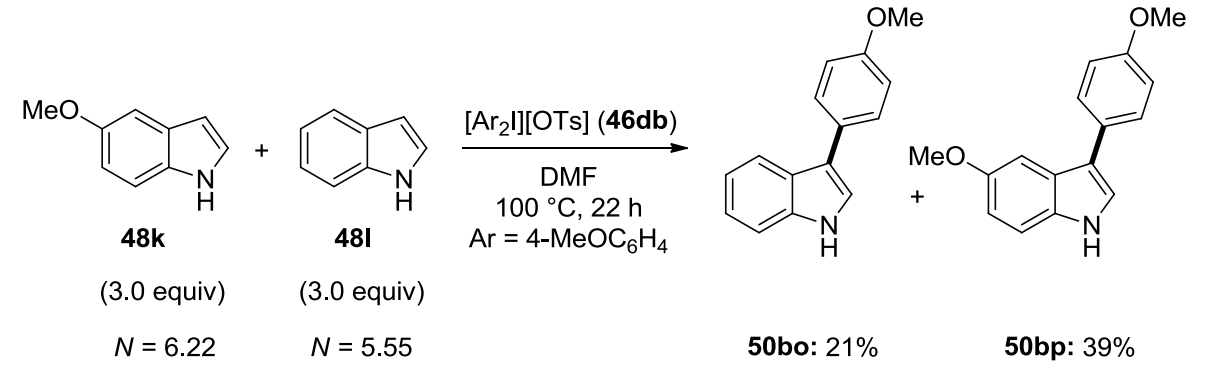
Scheme 72: Intramolecular competition experiment with iodonium salt **46dd**.

In order to get a clearer perception of the working mode of metal-free indole arylation with iodonium salts **46**, further mechanistic studies were conducted. An intermolecular competition experiment between a methoxy-substituted indole **48i** and indole **48d** with common electron-density, revealed **48i** to be preferentially arylated (Scheme 73).



Scheme 73: Intermolecular competition experiment between indoles **48i** and **48d**.

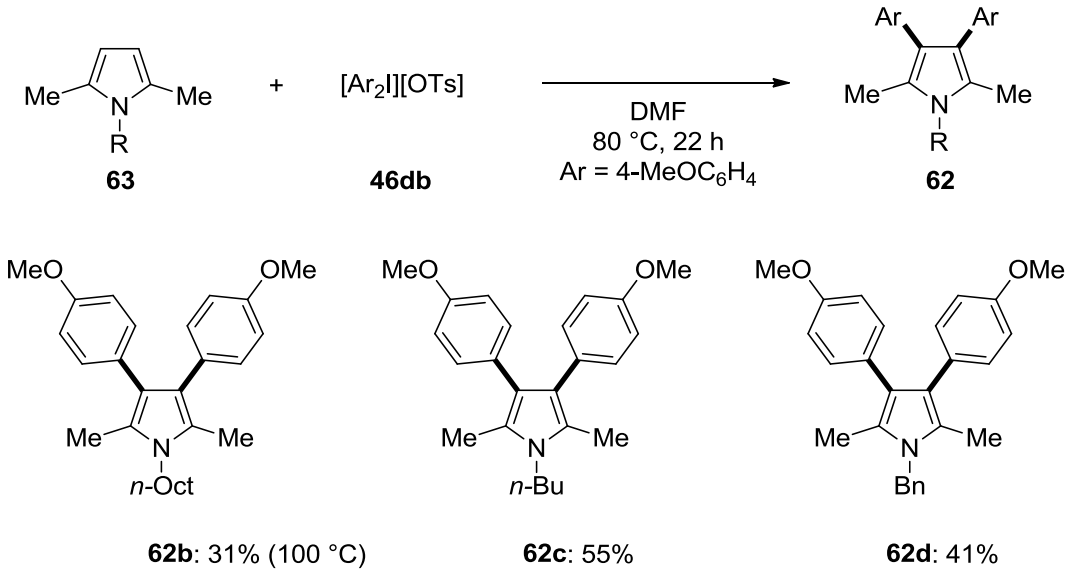
This result was verified when adopting free (*NH*)-indoles **48k** and **48l**, which featured distinct tendency towards the formation of **50bp** (Scheme 74), hence disclosing a strong correlation with previously compiled nucleophilicity parameters *N* by *Mayr* and coworkers.[165]



Scheme 74: Intermolecular competition experiment between indoles **48k** and **48l**.

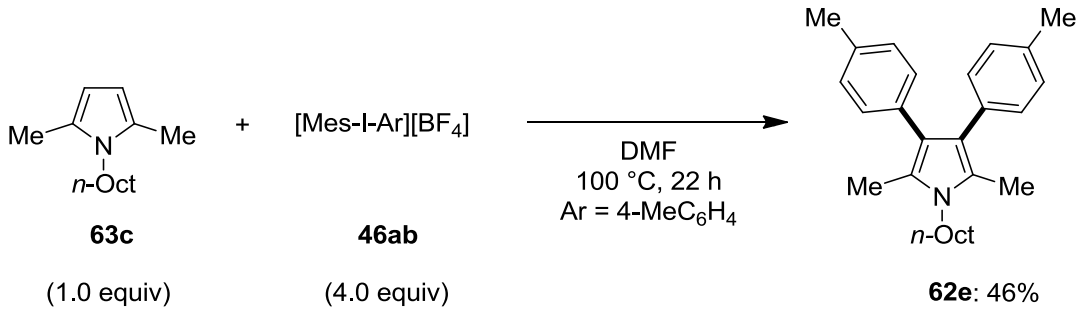
3.5 Metal-free direct arylations of pyrroles

Based on the achievements with indoles **48** in metal-free direct arylations, particularly regarding the relation with *Mayr's* nucleophilicity coefficients *N*[166] pyrroles **63** were probed as substrates in direct arylations with iodonium tosylate **46db** (Scheme 75). At this juncture, when using iodonium salt **46db** in excess, the syntheses of 1,2,3,4,5-*penta*-substituted pyrroles **62** in reasonable yields could be achieved.



Scheme 75: Metal-free direct arylation of pyrroles **63** using diaryliodonium tosylate **46db**.

Similar to previous observations for indole arylations (Scheme 71) an intramolecular competition experiment with iodonium tetrafluoroborate **46ab** resulted in the exclusive formation of pyrrole **62e** (Scheme 76). Likewise, the sterically less encumbered *para*-tolyl moiety was transfered to pyrrole **63c**.



Scheme 76: Metal-free direct arylation of pyrrole **63c** with diaryliodonium tetrafluoroborate **46ab**.

An efficient metal-free C–H bond functionalization methodology was presented herein, which sets the stage for a readily access to a number of C3-arylated indoles **48** under mild reaction conditions using versatile and nontoxic diaryl iodonium salts **46** as arylating reagents. Intriguingly, *N*-substituted as well as free (*NH*)-indoles proved to be viable substrates for chemo- and regioselective direct arylations. Furthermore, the protocol enabled the syntheses of fully-decorated pyrroles **62**.

Strong correlation with previously reported nucleophilicity parameters for indoles and pyrroles and the distinct electrophilic character of diaryl-λ^3-iodanes portends the reaction to proceed in analogy to an electrophilic aromatic substitution.

3.6 CO_2 as C1 building block for direct carboxylations of heteroaromatic C–H bonds

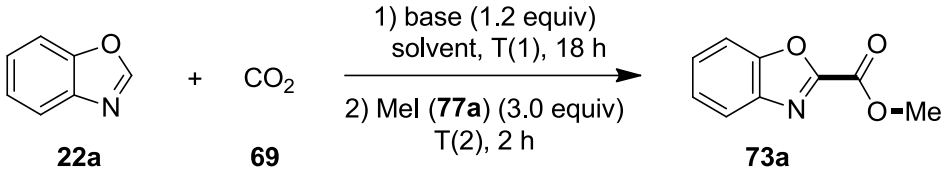
The development of efficient and sustainable strategies for the incorporation of carbon dioxide (**69**) as an inexpensive, abundant C1 source into valuable chemical commodities displays a great challenge to organic chemists. Although worthwhile methodologies have been disclosed in recent years,[118] the demand of further innovative approaches is still highly topical. With the ambition to develop an atom-economical approach and targeting a large number of heteroaromatic substrates for direct carboxylations, operating expenditures concerning catalysts and further reaction conditions have been conducted.

3.6.1 Optimization studies

At the ouset of optimization studies, reaction conditions were chosen, which are similar to previously described ones for the carboxylations of organoboronic esters and heterorarenes with carbon dioxide (**69**) by *Hou* (Table 14).[121d,122b] When reacting benzo[*d*]oxazole (**22a**) in the presence of 10 mol% of well-defined *N*-heterocyclic carbene copper(I) complex **91** in DMF at 80 °C under an atmosphere of carbon dioxide (**69**), 82% isolated yield of methylbenzo[*d*]oxazole-2-carboxylate (**73a**) were obtained after treatment with methyl iodide (**77a**) (entry 1). Focusing a more economical synthetic procedure, the reaction was conducted using simple copper chloride as catalyst, without any additional ligand, which provided **73a** in a comparable yield of 76% (entry 2).

Interestingly, when performing the reaction without any transistion-metal-catalyst, but with KO*t*-Bu (pK_a = 32.2)[125] as the base, in DMF at 100 °C, 80% of the desired product **73a** could be isolated (entry 3). Elevated temperature of 125 °C did not afford any improvement (entry 6), whereas 80 °C provided an almost comparable yield of 71% (entry 4). On the other hand, a further lowering of the reaction temperature showed a dramatical decrease of the isolated yield of **73a** (entry 5). Moreover, when performing the reaction at 40 °C at a longer reaction time and with the addition of catalytic amounts of copper(I) salt, the yield of **73a** could not be increased (entry 13). Other polar solvents, such as NMP or THF, provided less satisfactory results (entries 6, 7, 11 and 12), as did unpolar toluene (entry 9). On the contrary, the reaction in DMA furnished carboxylic acid ester **73a** in 77% isolated yield (entry 10), which was comparable to the reaction using DMF as the solvent.

Table 14: Optimization studies for direct carboxylations of heteroaromatic C–H bonds.[a]



22a **69** **73a**

entry	base	solvent	T(1) [°C]	T(2) [°C]	yield
1	KO*t*-Bu	DMF	80	65	82%[b]
2	KO*t*-Bu	DMF	100	65	76%[c]
3	**KO*t*-Bu**	**DMF**	**100**	**65**	**80%**
4	KO*t*-Bu	DMF	80	65	71%
5	KO*t*-Bu	DMF	40	40	(10%)
6	KO*t*-Bu	DMF	125	65	80%
7	KO*t*-Bu	NMP	100	65	69%
8	KO*t*-Bu	THF	65	65	(4%)
9	KO*t*-Bu	toluene	100	60	(11%)
10	KO*t*-Bu	DMA	100	60	77%
11	KO*t*-Bu	DMSO	100	60	52%
12	KO*t*-Bu	1,4-dioxane	100	60	-
13	KO*t*-Bu	DMF	40	40	(26%)[c,d]

14	Cs_2CO_3	DMF	100	60	69%
15	Cs_2CO_3	DMF	80	60	23%
16	Rb_2CO_3	DMF	100	60	8%

[a] Reaction conditions: **22a** (1.0 mmol), base (1.2 mmol), solvent (5.0 mL), balloon of CO_2 (**69**), T(1), 18 h; methyliodide (**77a**) (3.0 mmol), T(2), 2 h; isolated yields; GC-MS conversion in parentheses. [b] Reaction with copper(I) complex **91** (10 mol%). [c] Reaction with CuCl (10 mol%). [d] Reaction time T(1) = 22 h.

Considering a very recent publication by *Hu*,[124] in which the authors report on metal-free direct carboxylations of aromatic heterocycles, other bases like Cs_2CO_3 and Rb_2CO_3 were probed in the reaction. However, carboxylate bases proved to be less active compared to potassium *tert*-butoxide under our conditions (entries 14-16). When using Cs_2CO_3 at 100 °C compound **73a** was obtained in only 69% isolated yield (entry 14).

3.6.2 Scope of direct carboxylation of heteroaromatic C–H bonds

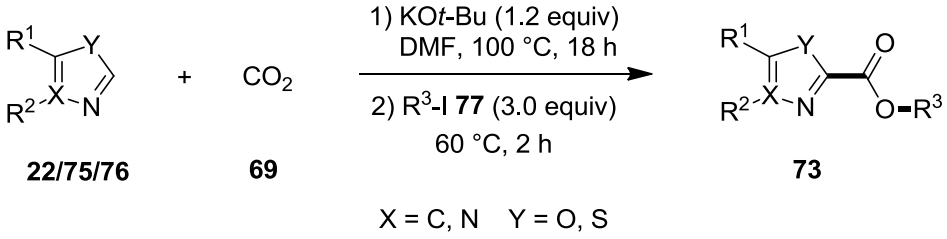
With the optimized catalytic system, the scope of direct carboxylation of heteroaromatic C–H bonds was exploited (Table 15). A series of heteroarenes was successfully converted into the corresponding carboxylic acid ester derivatives **73** without a metal-catalyst present, but simply using potassium *tert*-butoxide under one atmosphere of carbon dioxide (**69**) as C1 source. Alkyl carboxylates **73** were obtained on subsequent esterification with different alkyl iodides **77** under relatively mild reaction conditions.

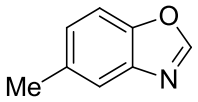
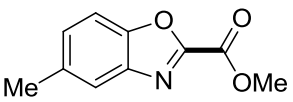
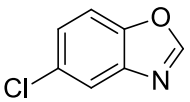
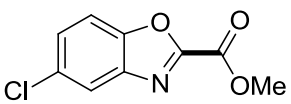
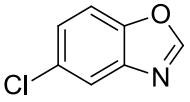
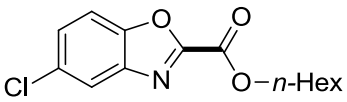
Methyl- as well as chloro-substituted benzoxazoles **22b** and **22c** were regioselectively functionalized affording the 2-substituted carboxylic acid esters **73b** and **73c** in good yields after treatment with methyl iodide (**77a**) (entries 1 and 2). Notably, the use of caesium carbonate as base under otherwise unchanged reaction conditions resulted in an inferior isolated yield of **73b**. Remarkably, 5-chlorobenzo[*d*]oxazole (**22c**) provided the related product **73e** in an excellent yield of 91%, whereas caesium carbonate furnished a significantly decreased yield of isolated **73e** (entry 3). As showcased in several examples, the established protocol was not restricted to the use of methyl iodide but also allowed esterification with longer-chain alkyl iodides like hexyl iodide (**77b**) or butyl iodide (**77c**) (entries 3, 4, 6, 9, 11 and 13). Benzothiazole (**75**) was efficiently converted into methyl ester **73g** and hexyl ester **73h** in 66% and 62% isolated yield, respectively (entries 5 and 6).

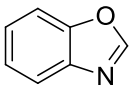
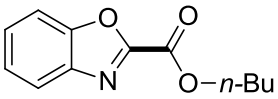
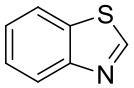
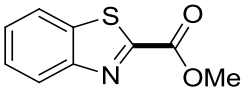
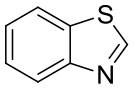
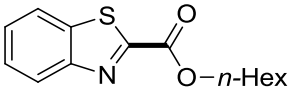
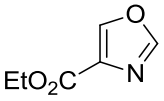
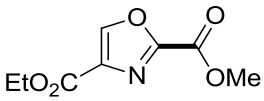
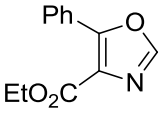
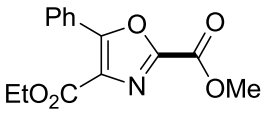
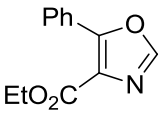
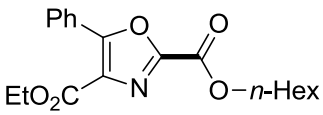
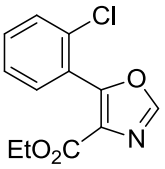
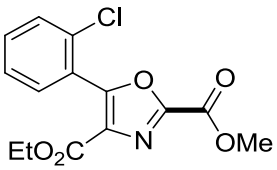
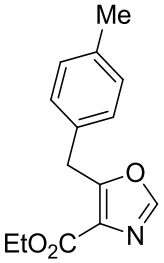
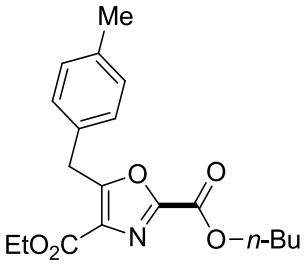
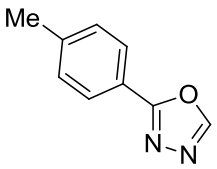
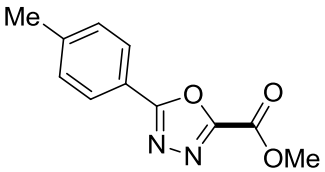
Furthermore, oxazoles **22e**, **22f** and **22g** served as viable substrates for direct carboxylation and the desired carboxylic acid esters **73j** **73k**, **73l** and **73m** were obtained in reasonable yields (entries 8–11). However, 4-mono substituted oxazole **22d** delivered only 25% of isolated product **73i** (entry 7). Unfortunately, when using **22e**, undesired side-product due to transesterification was formed in small amounts.[167] Nevertheless, the isolated yield of the desired product was still higher, compared to the reaction with caesium carbonate as base. With **22g** as substrate, an additional carboxylation in the benzylic position took place.[167] Though, the desired mono functionalized product **73m** could be obtained in a synthetically useful isolated yield (entry 11).

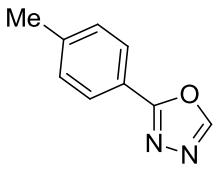
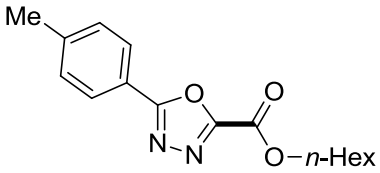
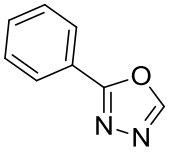
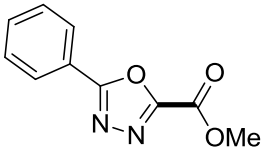
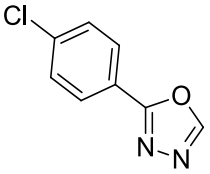
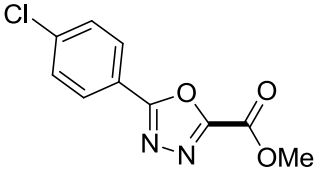
Finally, oxadiazoles **76a**, **76b** and **76c** proved to be applicable for direct carboxylation providing the corresponding carboxylic acid esters **73n**, **73o**, **73p** and **73q** in moderate yields (entries 12–15). Intriguingly, valuable chlorine substituents on the different heteroarenes were well tolerated under the optimized conditions, which set the stage for further functionalization of the carboxlic acid esters through traditional cross coupling chemistry.

Table 15: Scope for direct carboxylations of heteroarenes.[a]



entry	substrate		73		yield
1		**22b**		**73b**	66% (48%)[b]
2		**22c**		**73c**	63%
3		**22c**		**73e**	91% (55%)[b]

4		**22a**		**73f**	64%
5		**75**		**73g**	66%
6		**75**		**73h**	62%
7		**22d**		**73i**	25%
8		**22e**		**73j**	(61%)[c]
9		**22e**		**73k**	65% (58%)[b]
10		**22f**		**73l**	52%
11		**22g**		**73m**	51%
12		**76a**		**73n**	56%

13		**76a**		**73o**	51%
14		**76b**		**73p**	43%
15		**76c**		**73q**	38%

[a] Reaction conditions: **22**/**75**/**76** (1.0 mmol), KO*t*-Bu (1.2 mmol), DMF (5.0 mL), balloon of CO_2 (**69**), 100 °C, 18 h; alkyliodide (3.0 mmol), 60 °C, 2 h; isolated yields. [b] Reaction with Cs_2CO_3 (1.2 equiv). [c] GC-MS-conversion.

A straightforward method for the efficient carboxylation of various heteroarenes bearing moderately acidic C–H bonds was achieved, using CO_2 (**69**) as renewable C1 source. Remarkably, the reaction proceeds without any transistion-metal-catalyst, but solely potassium *tert*-butoxide as the base allows for direct C–H bond functionalizations.

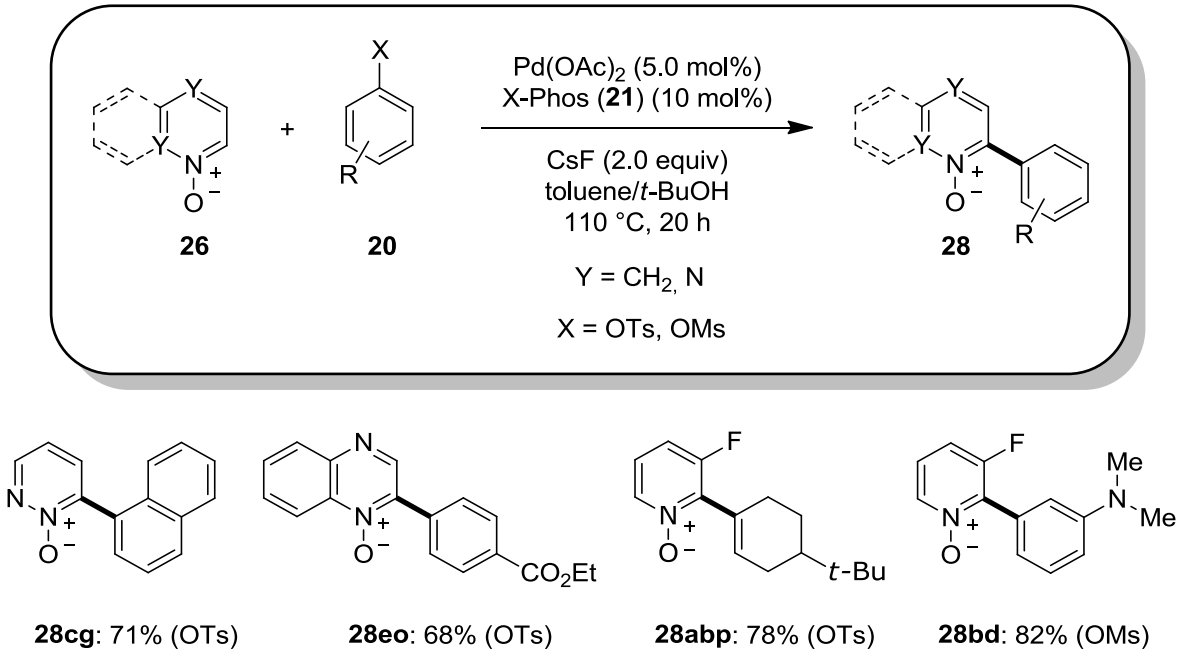
The majority of compounds listed in Table 15, was prepared by direct carboxylation of the corresponding heteroarenes for the first time. Methylcarboxylates **73b**, **73c** and **73q** have previously been synthesized by carboxylations applying caesium carbonate as a base[124] at elevated temperature in 83%, 92% and 88% yield, respectively. On the other hand, compound **73e** could be obtained in only 55% isolated yield with caesium carbonate at 100 °C (Table 15, entry 3) and 58% under copper(I)-catalysis (cf. ref. 122), whereas direct carboxylation under our optimized conditions with potassium *tert*-butoxide as the base provided **73e** in excellent 91% isolated yield (Table 15, entry 3).

Moreover, comparison of the lowest prices for potassium *tert*-butoxide and ceasium carbonate[168] makes our contribution not only of theoretical, but also of practical importance.

4 Summary and Outlook

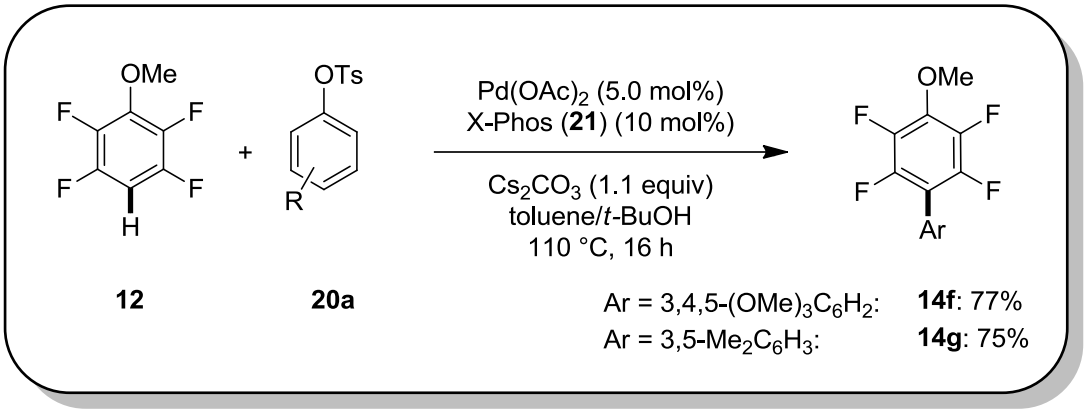
Transition-metal-catalyzed direct arylations have emerged as a viable alternative to traditional cross coupling chemistry in recent decades, as they constitute an economically attractive strategy for an overall streamlining of sustainable syntheses.2 Thus, the main focus of the present work was set on the development of generally applicable methodologies for site-selective formations of C–C bonds through direct C–H bond functionalizations.

In the first part an efficient and generally applicable protocol for palladium-catalyzed direct C–H bond arylations of electron-deficient heteroarenes **26** with aryl and alkenyl sulfonates **20** was elaborated (Scheme 77).



Scheme 77: Palladium-catalyzed direct C–H bond arylations of electron-deficient heteroarenes **26** with aryl sulfonates **20**.

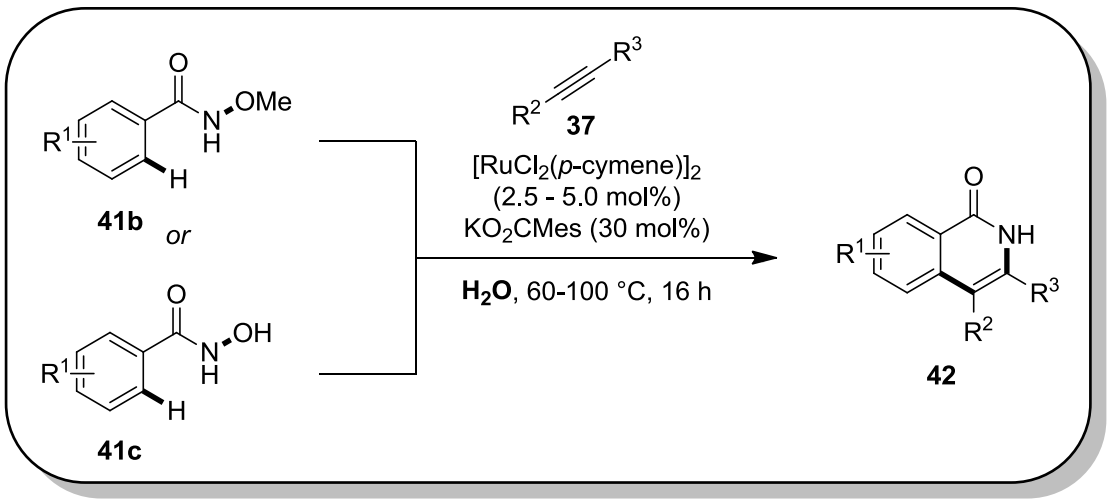
The optimized catalytic system provided the direct arylation products **28** with excellent chemo- and site-selectivites in high isolated yields. Various tosylates, as well as more atom-economical aryl mesylates **20b** could be successfully used as inexpensive, moisture-stable electrophiles for C–H bond functionalizations. Detailed studies could be exploited in a future project, to further provide evidence for the proposed CMD pathway in direct arylations of (di)azine *N*-oxides **26** with sulfonates **20**.Remarkably, the highly-active catalytic system also allowed the direct arylations of electron-deficient fluoroarenes **12** with deactivated tosylates **20a** (Scheme 78).

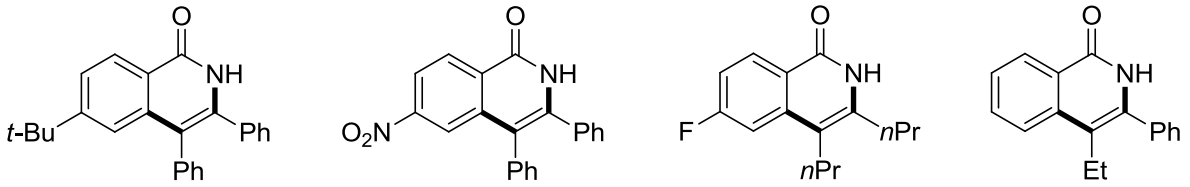


Scheme 78: Palladium catalyzed direct C–H bond functionalizations of electron-deficient fluoroarenes **12** with deactivated aryl tosylates **20a**.

Concerning future efforts, divergent direct C–H bond arylations of substrates bearing unactivated C_{sp3}–H bonds adjacent to the *N*-oxide **26**, like picolines, with sulfonates **20** as user-friendly arylating reagents, would be highly desirable. Furthermore, with respect to multisite-selectivity, sequential functionalizations of either (di)azine *N*-oxides **26** or polyfluoro-substituted arenes **12** could be a challenging assignment.

In a second project of this thesis, research efforts were directed towards sustainable ruthenium-catalyzed annulations of alkynes **37** by benzhydroxamic acid esters **41b**, through C–H/N–O bond functionalizations, under environmentally benign conditions. Intriguingly, ruthenium-catalyzed redox-neutral isoquinolone **42** syntheses with ample scope and excellent regioselectivities were accomplished *via* carboxylate-assistance in water as a *green* solvent (Scheme 79). The outstanding robustness and chemoselectivity of the ruthenium(II)-carboxylate complex **89** also set the stage for the direct use of free hydroxamic acids **41c** for the synthesis of annulated lactames **42**.



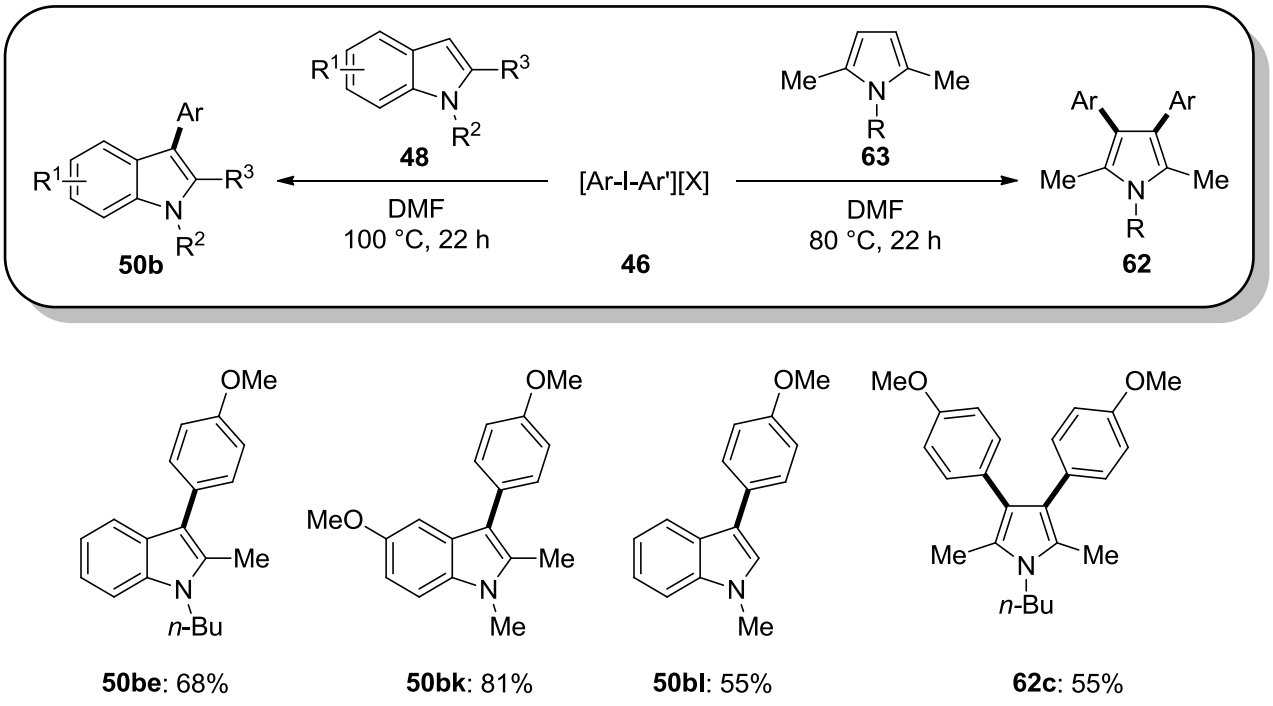


42bc: 93% **42bg**: 86% **42bt**: 65% **42bq**: 83%

Scheme 79: Ruthenium-catalyzed isoquinolone **42** syntheses in water as a *green* solvent.

The use of terminal alkynes **37** as prospective candidates for the annulation process would be highly desirable. Moreover, the exploration of other leaving groups on the nitrogen-atom, which could admit even lower reaction temperatures, would be of great interest.

It was further focused on the development of an efficient strategy for site-selective C–H bond funtionalizations on indoles **48** in the absence of a transition-metal-catalyst. Regioselective C3-arylations on various *N*-alkyl-substituted, as well as free (*NH*)-indoles were achieved using diaryliodonium salts **46** as mild arylating reagents (Scheme 80). The protocol was not restricted to the functionalization of indoles **48**, but also allowed for direct arylations of pyrroles **63**, hence featuring access to a large number of variously decorated, ubiquitous bioactive heterocycles.

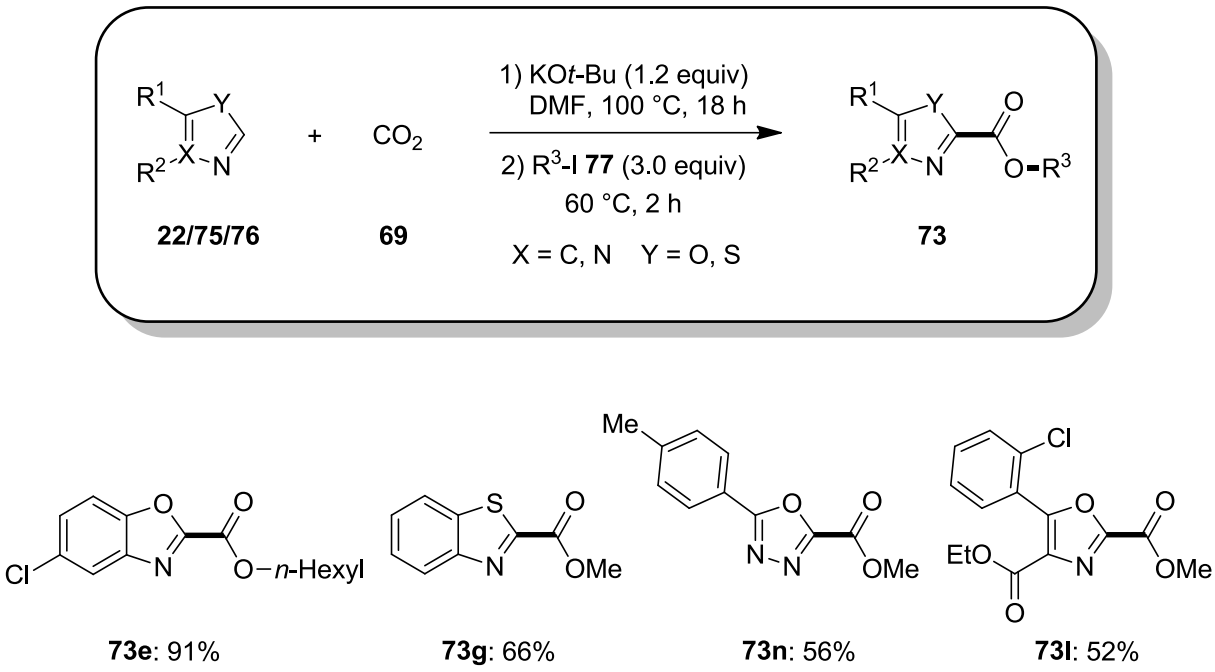


50be: 68% **50bk**: 81% **50bl**: 55% **62c**: 55%

Scheme 80: Metal-free direct arylations of indoles **48** and pyrroles **63** with diaryliodonium salts **46**.

The selective mono-arylation of pyrroles could be a challenging project for the future, as well as to extent direct metal-free C–H bond arylations to other less nucleophilic heterocycles like (benzo)thiophenes or (benzo)furanes.

In order to benefit from the abundance of carbon dioxide (**69**) in the earth's atmosphere, its use as an inexpensive, renewable C1 source for various chemical transformations constitutes a contemporary issue. Thus, in the last project of the presented work, a direct approach towards (hetero)aromatic carboxylic acid derivatives **73** by C–C bond formation through carbon dioxide fixation under mild conditions was investigated (Scheme 81).



Scheme 81: Direct carboxylations of heteroaromatic C–H bonds with CO_2 (**69**) as a C1 building block.

Carboxylic acid esters **73** derived from diverse heteroarenes with moderately acidic C–H bonds were obtained in good isolated yields in the absence of a transition-metal-catalyst, using inexpensive potassium *tert*-butoxide as the base.

Prospective endeavours could be directed towards the extent of the methodology to less acidic substrates, as well as to unactivated C_{sp3}–H bonds.

5 Experimental Section

5.1 General Remarks

All reactions involving moisture- or air-sensitive reagents or products were performed under an atmosphere of dry nitrogen using standard Schlenk techniques and predried glassware. Syringes for handling of dry solvents or liquid reagents were flushed with dry nitrogen threefold prior to use. Analytical data of substances that are known in literature (marked by corresponding references) were compared with those described in the literature.

5.1.1 Solvents

All solvents for reactions involving moisture-sensitive reagents were dried, distilled and stored under inert atmosphere (argon or nitrogen) according to following standard procedures.

***tert*-Butyl alcohol** was degassed, dried and distilled over Na under ambient pressure and stored over molecular sieves (4 Å).
***tert*-Amyl alcohol** was stirred over Na for 5 h at 120 °C and distilled under ambient pressure.
***N*,*N*-Dimethylacetamide** was dried over KH and distilled under ambient pressure.
***N*,*N*-Dimethylformamide** was dried over CaH_2 for 8 h, degassed and distilled under reduced pressure.
Dimethyl sulfoxide was dried over CaH_2 for 4 h, degassed and distilled under reduced pressure.
Methanol was stirred over Mg for 3 h at 65 °C prior to distillation.
***N*-Methyl-2-pyrrolidone** was stirred for 4 h at 150 °C and subsequently distilled under reduced pressure.
Tetrahydrofuran was purified using an SPS solvent purification system by MBRAUN.
Toluene was pre-dried over KH and distilled over Na/benzophenone.
Water was degassed for 2 h and ultrasonicated.
1,4-Dioxane was dried and distilled over Na/benzophenone.
***o*-Xylene** was stirred at 160 °C over Na/benzophenone and distilled under ambient pressure.

5.1.2 Vacuum

Following pressures were measured on the used vacuum pump and are not corrected: membrane pump vacuum (MPV): 5.0 mbar, oil pump vacuum (OPV): 0.1 mbar.

5.1.3 Melting Points

Melting points were measured using a Stuart® Melting Point Apparatus SMP3 from BARLOWORLD SCIENTIFIC or BÜCHI 540 Melting Point Apparatus. Reported values are uncorrected.

5.1.4 Chromatography

Analytical TLC was performed on 0.25 mm silica gel 60F plates (MACHEREY-NAGEL) with 254 nm fluorescent indicator from MERCK. Plates were visualized under ultraviolet light and developed by treatment with a $KMnO_4$ solution or an acidic Cer(IV)-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 (0.040–0.063 mm and 0.063–0.200 mm, 70–230 mesh ASTM).

5.1.5 High-Performance Liquid Chromatography

Preparative separations were performed on an HPLC-System from KNAUER (Smartline Pump 100, Dynamic Mixing Chamber, Injection- and Control-Valve, Smartline UV Detector 2500). Separation column VP C18 ec (RP) (250 x 16 mm, *Nucleodur,* 100-10) from MACHEREY-NAGEL was used. Organic solvents of HPLC-grade and bidistilled H_2O were employed. All samples were filtrated through Polytetrafluorethylen-(PTFE)-Filter from ROTH (Ø 25 mm, 0.2 μm), respectively VWR (Ø 13 mm, 0.2 μm) prior to separation.

5.1.6 Gas Chromatograpgy

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 x 0.25 mm, film 0.25 μm) were used.

5.1.7 Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) spectra were recorded at 250, 300 or 600 MHz (^{1}H-NMR) and 75 or 125 MHz (^{13}C-NMR, APT) on BRUKER AM 250, VARIAN Unity-300 and Inova 500 instruments. Chemical shifts are reported as δ-values in ppm relative to the residual proton peak of the deuterated solvent or its carbon atom, respectively.

	^{1}H-NMR	^{13}C-NMR
d_1-Chloroform	7.26 ppm	77.0 ppm
d_6-DMSO	2.49 ppm	49.5 ppm
d_4-Methanol	3.31 ppm	49.0 ppm

For characterization of the observed signal multiplicities the following abbrevations were applied: s (singlet), d (doublet), t (triplet), q (quartet), hept (heptet), m (multiplet). Coupling constants *J* are reported in Hertz (Hz).

5.1.8 Infrared Spectroscopy

Infrared spectra were recorded using BRUKER IFS 66 (FT-IR) spectrometer, solid probes measured as KBr pellets, liquid probes as film between KBr plates, or on BRUKER Alpha-P spectrometer, liquid probes measured as film and solid probes measured neat. Analysis of the spectra was carried out using OPUS 3.1 from BRUKER GMBH, respectively OPUS 6. Absorption is given in wave numbers (cm^{-1}). Spectra were recorded in the range of 4000–400 cm^{-1}. Following abbreviations were used for characterization: s (strong), m (medium), w (weak).

5.1.9 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.

5.1.10 Microwave Irradiation

Reactions under microwave irradiation were performed using an Initiator^{TM} Microwave Synthesizer from BIOTAGE. Reaction conditions were controlled by integrated software.

5.1.11 Reagents

Chemicals obtained from commercial sources (purity > 95%) were used without further purification.
3-Chloroperoxybenzoic acid (*m*CPBA) was purchased from ACROS ORGANICS with a purity of 70–75 % (rest: 3-chlorobenzoic acid and water) and was used as such.

The following compounds were synthesized according to known literature procedures:[169,170] 4-metylphenyl 4-methylbenzenesulfonate (**20ae**),[171] 2-metylphenyl 4-methyl-benzenesulfonate (**20af**),[171] naphthalen-1-yl 4-methylbenzenesulfonate (**20ag**),[171] 4-methoxyphenyl 4-methylbenzenesulfonate (**20ac**),[171] 4-chlorophenyl 4-methylbenzenesulfonate (**20an**),[172] methyl-4-(methylsulfonyloxy)benzoate (**20am**),[28c] pyridin-3-yl 4-methylbenzenesulfonate (**20al**),[173,24] 4-(*tert*-butyl)cyclohex-1-en-1-yl 4-methylbenzenesulfonate (**20ap**),[24] 3,4,5-trimethoxyphenyl methanesulfonate (**20bb**),[141] 3-morpholinophenyl methanesulfonate (**20bz**),[142] 3-(*N*,*N*-dimethylamino)phenyl 4-methylbenzenesulfonate (**20ad**),[174] ethyl-4-(tosyloxy)benzoate (**20at**),[174] 4-fluoro 4-methylbenzenesulfonate (**20ai**),[174] naphthalen-2-yl methanesulfonate (**20bx**),[175] methyl-4-(tosyloxy)benzoate (**20bm**),[175] naphthalen-1-yl methanesulfonate (**20bg**),[144] Ruthenium(II)-dimesitylcarboxylate-*para*-cymene complex (**89**),[176] bis(4-methoxyphenyl)iodonium 4-methyl-benzenesulfonate (**46db**),[177] 2,5-dimethyl-1-*n*-octylpyrrole (**63c**),[178] mesityl(*p*-tolyl)iodonium tetrafluoroborate (**46ab**),[93] 5-methyl-benzo[*d*]oxazole (**22b**),[179] 2-(4-chlorophenyl)-1,3,4-oxadiazole (**76c**).[124]

Dimethyl 5-(tosyloxy)isophthalate (**20aj**), 3-(trifluoromethyl)phenyl 4-methylbenzenesulfonate (**20ah**), 3-methylphenyl methanesulfonate (**20bt**), 3,5-dimethylphenyl methanesulfonate (**20ba**), 4-benzoylphenyl 4-methylbenzenesulfonate (**20ak**) and 3-(*N*,*N*-dimethylamino)phenyl methanesulfonate (**20bd**) by courtesy of *Dr. Andreas Althammer.*

2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (**21**) and Dichloro-(*p*-cymene)-ruthenium(II) dimer by courtesy of *Karsten Rauch*.

4-Methoxyphenyl methanesulfonate (**20bc**) by courtesy of *Dr. Atul Manvar*.

3-Methoxyphenyl methanesulfonate (**20br**) and ethyl-4-(methylsulfonyloxy)benzoate (**20bo**) by courtesy of *B.Sc. Jonathan Hubrich*.

4-*tert*-Butylphenyl methanesulfonate (**20bv**) by courtesy of *Dipl. Chem. Matthias Reckers*.

1,2-Dimethylindole (**48d**), 5-chloro-1,2-dimethylindole (**48h**), 1-benzyl-2-methylindole (**48g**), 1-*n*-butyl 2-methylindole (**48e**) and diphenyliodonium-4-methylbenzenesulfonate (**46da**) by courtesy of *Dr. René Sandmann*.

2-Methyl-1-*n*-propylindole (**48f**), 5-methoxy-1,2-dimethylindole (**48i**) and 5-bromo-*N*-methylindole (**48j**) by courtesy of *Monica Dell'Acqua*.

2,5-Dimethyl-1-*n*-butylpyrrole (**63d**) and 2,5-dimethyl-1-benzylpyrrole (**63e**)[178] by courtesy of *B.Sc. Michaela Bauer*.

5-Chlorobenzo[*d*]oxazole (**22c**) by courtesy of *Dipl. Chem. Christoph Kornhaaß*.

Ethyl-5-(4'-methylbenzyl)oxazole-4-carboxylate (**22g**), ethyl-5-phenyloxazole-4-carboxylate (**22e**) and ethyl-5-(2-chlorophenyl)oxazole-4-carboxylate (**22f**) by courtesy of *B.Sc. Thorben Schulte*.

2-(4-Methylphenyl)-1,3,4-oxadiazole (**76a**) by courtesy of *B.Sc. Wiebke Wackerow*.

Potassium 2,4,6-trimethylbenzoate by courtesy of *Dipl. Chem. Marvin Schinkel*.

1,2-Bis(4-methoxyphenyl)ethyne (**37b**), 1,2-bis(4-fluorophenyl)ethyne (**37c**) and *N*-methoxy-2-methylbenzamide (**87h**) by courtesy of *Fanzhi Yang*.

5.2 General Procedures

5.2.1 General Procedure A: Synthesis of aryl sulfonates

To a solution of phenol **57** (1.0 equiv.) in CH_2Cl_2 (0.3 M) and NEt_3 (1.5 equiv.) the sulforyl chloride (1.2 equiv.) was added and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was neutralized with HCl (2 M) and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with saturated Na_2CO_3-solution (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-pentane/EtOAc) or recrystallization from EtOH, concentrated and dried *in vacuo*.

5.2.2 General Procedure B: Oxidation of (di)azines[34]

The (di)azine (1.0 equiv.) and *m*CPBA (1.0 equiv.) in CH_2Cl (0.2 M) were stirred at ambient temperature for 16 h. PPh_3 (**78c**) (0.5 equiv.) was then added and the mixture was stirred for additional 4 h at ambient temperature. The volatiles were evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc/MeOH) or (CH_2Cl_2/acetone), concentrated and dried *in vacuo*.

5.2.3 General Procedure C: Palladium-catalyzed direct arylations of electron-deficient (di)azine *N*-oxides with aryl tosylates or mesylates

A mixture of aryl sulfonate **20** (1.0 equiv.), (di)azine *N*-oxide **26** (4.0 equiv.), $Pd(OAc)_2$ (5.0 mol%), X-Phos (**21**) (10 mol%) and CsF (2.0 equiv.) in toluene (2.0 mL) and *t*-BuOH (1.0 mL) was stirred at 110 °C for 20 h under nitrogen. At ambient temperature the reaction mixture was diluted with CH_2Cl_2, filtered over Celite® and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (CH_2Cl_2/acetone/MeOH), concentrated and dried *in vacuo*.

5.2.4 General Procedure D: Palladium-catalyzed direct arylations of electron-deficient fluoroarenes with aryl tosylates

A mixture of aryl tosylate **20b** (1.0 equiv.), fluoroarene **12** (1.6 equiv.), $Pd(OAc)_2$ (5.0 mol%), X-Phos (**21**) (10 mol%) and Cs_2CO_3 (1.1 equiv.) in toluene (1.5 mL) and *t*-BuOH (0.5 mL) was stirred at 110 °C for 16 h under nitrogen. At ambient temperature EtOAc (50 mL) and H_2O (50 mL) were added. The aqueous layer was extracted with EtOAc (2 x 50 mL), the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-pentane/EtOAc), concentrated and dried *in vacuo*.

5.2.5 General Procedure E1: Synthesis of *N*-methoxybenzamides and *N*-hydroxybenzamides from carboxylic acids[73a]

To a solution of carboxylic acid **36** (1.0 equiv.) in CH_2Cl_2 (0.3 M) at 0 °C under N_2 atmosphere was added dropwise oxalyl chloride (1.2 equiv.) *via* syringe followed by catalytic amounts of DMF (5 drops). The reaction was allowed to stir at ambient temperature until completion (typically 4 h). The solvent was then removed under reduced pressure to afford the corresponding crude acid chloride **87**.

N-Methoxyamine hydrochloride (**88a**) or *N*-hydroxyamine hydrochloride (**88b**) (1.1 equiv.) was added to a biphasic mixture of K_2CO_3 (2.0 equiv.) in a 2:1 mixture of EtOAc/H_2O (0.2 M). The resulting solution was cooled to 0 °C followed by addition of the crude acid chloride **87** (1.0 equiv.) dissolved in a minimum amount of EtOAc (5.0 mL) *via* syringe. The reaction was allowed to stir for 4 h, while reaching ambient temperature. Afterwards the layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (*n*-pentane/EtOAc), concentrated and dried *in vacuo*.

5.2.6 General Procedure E2: Synthesis of *N*-methoxybenzamides and *N*-hydroxybenzamides from acid chlorides[73]

N-Methoxyamine hydrochloride (**88a**) or *N*-hydroxyamine hydrochloride (**88b**) (1.5 equiv.) and K_2CO_3 (2.0 equiv.) were added to a mixture of EtOAc/H_2O (0.07 M, 2:1) and cooled to – 5 °C in an ice bath with NaCl. The acid chloride **87** (1.0 equiv.) was added dropwise *via* syringe and the reaction mixture was stirred to ambient temperature over 16 h. EtOAc (50 mL) was added and after separation of the layers the organic layer was washed with H_2O (2 x 100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered, evaporated under reduced pressure and dried *in vacuo*.

5.2.7 General Procedure F1: Ruthenium-catalyzed isoquinolone synthesis from *N*-methoxybenzamides

A mixture of *N*-methoxybenzamide **41** (1.0 equiv.), alkyne **37** (2.0 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%) and potassium 2,4,6-trimethylbenzoate (30 mol%) in H_2O (2.0 mL) was stirred at 60 °C under nitrogen atmosphere for 16 h. At ambient temperature, the reaction mixture was diluted with H_2O (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-pentane/EtOAc), concentrated and dried *in vacuo*.

5.2.8 General Procedure F2: Ruthenium-catalyzed isoquinolone synthesis from *N*-hydroxybenzamides

A mixture of *N*-hydroxybenzamide **41c** (1.0 equiv.), alkyne **37** (2.0 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol%) and potassium 2,4,6-trimethylbenzoate (30 mol%) in H_2O (2.0 mL) was stirred at 100 °C under nitrogen atmosphere for 16 h. At ambient temperature, the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-pentane/EtOAc), concentrated and dried *in vacuo*.

5.2.9 General Procedure G: Metal-free direct arylation of indoles[180]

In a glove box, a solution of indole **48** (1.0 equiv.) and iodonium salt **46** (2.0 equiv.) in DMF (2.0 mL) was set up in a glas tube equipped with a stirring bar. The tube was then sealed with a septum, taken out of the glove box and stirred at 100 °C for 22 h under nitrogen. At ambient temperature, H_2O (25 mL) was added and the reaction mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica (*n*-pentane/Et_2O), concentrated and dried *in vacuo*.

5.2.10 General Procedure H: Metal-free direct arylation of pyrroles[180]

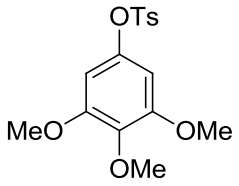
In a glove box, a solution of pyrrole **63** (1.0 equiv.) and iodonium salt **46** (4.0 equiv.) in DMF (2.0 mL) was set up in a glas tube equipped with a stirring bar. The tube was then sealed with a septum, taken out of the glove box and was stirred at 100 °C for 22 h under nitrogen. At ambient temperature, H_2O (25 mL) was added and the reaction mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica (*n*-pentane/Et_2O), concentrated and dried *in vacuo*.

5.2.11 General Procedure I: Direct carboxylation of heteroaromatic C–H bonds using CO_2

A mixture of heteroarene **22/75/76** (1.0 equiv.), KO*t*-Bu (1.2 equiv.) and DMF (5.0 mL) was degassed in a Schlenk-tube. The Schlenk-tube was then flushed with CO_2 (**69**) *via* a balloon and CO_2 (**69**) was bubbled through the reaction mixture for 10 – 20 minutes. After removal of the balloon, the reaction was heated to 100 °C for 18 h. It then cooled to 60 °C, alkyl iodide **77** (3.0 equiv.) was added and the reaction mixture was stirred at 60 °C for 2 h. At ambient temperature, the reaction mixture was diluted with H_2O (25 mL) and Et_2O (25 mL). The aqueous layer was extracted with Et_2O (3 x 25 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-pentane/Et_2O), concentrated and dried *in vacuo*.

6 Analytical Data

Synthesis of 3,4,5-Trimethoxyphenyl 4-methylbenzenesulfonate (20ab)



20ab

The general procedure **A** was followed using 3,4,5-trimethoxyphenol (1.84 g, 10.0 mmol), and tosyl chloride (2.31 g, 12.1 mmol). Purification by column chromatography (*n*-pentane/EtOAc: 20/1 → 5/1 → 2/1) yielded **20ab** (3.25 g, 96%) as a colorless solid.

M. p.: 120–123 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 6.18 (s, 2H), 3.79 (s, 3H), 3.69 (s, 6H), 2.45 (s, 3H).

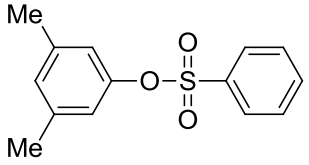
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 153.2 (C_q), 145.4 (C_q), 145.4 (C_q), 136.7 (C_q), 132.3 (C_q), 129.6 (CH), 128.7 (CH), 99.9 (CH), 60.9 (CH_3), 56.1 (CH_3), 21.7 (CH_3).

IR (neat, cm^{-1}): 2944 (w), 1604 (s), 1495 (m), 1373 (s), 1175 (s), 977 (s), 663 (m).

MS (EI) *m/z* (relative intensity): 338 ([M^+] 28), 183 (100), 168 (21), 91 (7).

HR-MS (EI) *m/z* for $C_{16}H_{18}O_6S$ calcd.: 338.0824.
found: 338.0817.

Synthesis of 3,5-Dimethylphenyl benzenesulfonate (20c)



20c

The general procedure **A** was followed using 3,5-dimethylphenol (2.32 g, 19.0 mmol), and benzene-1-sulfonyl chloride (3.69 g, 20.9 mmol). Recrystallization from EtOH yielded **20c** (4.68 g, 94%) as a colorless solid.

M. p.: 129–130 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.88 – 7.81 (m, 2H), 7.67 (m, 1H), 7.57 – 7.48 (m, 2H), 6.87 (s, 1H), 6.59 (s, 2H), 2.23 (s, 6H).

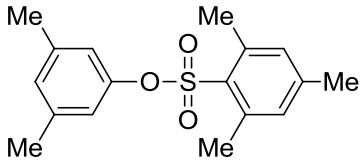
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 149.4 (C_q), 139.5 (C_q), 135.7 (C_q), 134.0 (CH), 129.0 (CH), 128.8 (CH), 128.5 (CH), 119.8 (CH), 21.1 (CH_3).

IR (KBr, cm^{-1}): 2911 (w), 1583 (m), 1452 (m), 1366 (s), 1185 (s), 934 (m), 689 (m).

MS (EI) *m/z* (relative intensity): 262 ([M^+] 100), 170 (29), 141 (51), 121 (35), 77 (59).

HR-MS (EI) *m/z* for $C_{14}H_{14}O_3S$ calcd.: 262.0664.
found: 262.0661.

Synthesis of 3,5-Dimethylphenyl 2,4,6-trimethylbenzenesulfonate (20d)



20d

The general procedure **A** was followed using 3,5-dimethylphenol (2.20 g, 18.3 mmol), and 2,4,6-trimethylbenzene-1-sulfonyl chloride (4.37 g, 20.0 mmol). Recrystallization from EtOH yielded **20d** (5.02 g, 92%) as a colorless solid.

M. p.: 109–110 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.97 (s, 2H), 6.85 (s, 1H), 6.60 (s, 2H), 2.58 (s, 6H), 2.33 (s, 3H), 2.22 (s, 6H).

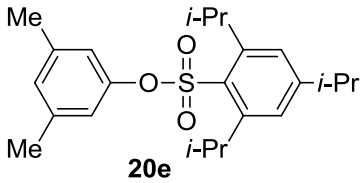
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 149.3 (C_q), 143.6 (C_q), 140.3 (C_q), 139.4 (C_q), 131.6 (CH), 130.9 (C_q), 128.5 (CH), 119.6 (CH), 22.8 (CH_3), 21.1 (CH_3), 21.1 (CH_3).

IR (KBr, cm^{-1}): 2946 (w), 1602 (m), 1456 (m), 1357 (s), 1181 (s), 942 (m), 668 (s).

MS (EI) *m/z* (relative intensity): 304 ([M^+] 8), 240 (16), 183 (13), 119 (100), 44 (32).

HR-MS (EI) *m/z* for $C_{17}H_{20}O_3S$ calcd.: 304.1133.
found: 304.1122.

Synthesis of 3,5-Dimethylphenyl 2,4,6-triisopropylbenzenesulfonate (20e)



20e

The general procedure **A** was followed using 3,5-dimethylphenol (2.44 g, 20.0 mmol), and 2,4,6-triisopropylbenzene-1-sulfonyl chloride (7.27 g, 24.0 mmol). Recrystallization from EtOH yielded **20e** (4.73 g, 61%) as a colorless solid.

M. p.: 142 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.20 (s, 2H), 6.85 (s, 1H), 6.59 (s, 2H), 4.10 (hept, *J* = 6.8 Hz, 2H), 2.94 (hept, *J* = 6.9 Hz, 1H), 2.22 (s, 6H), 1.27 (d, *J* = 6.9 Hz, 6H), 1.20 (d, *J* = 6.8 Hz, 12H).

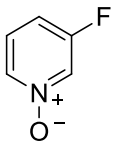
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 154.1 (C_q), 151.1 (C_q), 149.4 (C_q), 139.4 (C_q), 130.1 (C_q), 128.5 (CH), 123.8 (CH), 119.8 (CH), 34.3 (CH), 29.7 (CH), 24.6 (CH_3), 23.6 (CH_3), 21.1 (CH_3).

IR (KBr, cm^{-1}): 2960 (m), 1426 (s), 1351 (m), 1184 (s), 940 (s), 854 (s), 778 (s).

MS (EI) *m/z* (relative intensity): 338 ([M^+] 27), 267 (100), 203 (12), 122 (8).

HR-MS (ESI) *m/z* for $C_{23}H_{32}O_3S+H^+$ calcd.: 389.2145.
found: 389.2144.

Synthesis of 3-Fluoropyridine *N*-oxide (26ab)



26ab

The general procedure **B** was followed using 3-fluoropyridine (**47c**) (1.91 g, 19.7 mmol), *m*CPBA (4.63 g, 20.0 mmol), and triphenylphosphine (2.62 g, 9.99 mmol). Purification by column chromatography (EtOAc/MeOH: 30/1 → 20/1 → 7/1 → 4/1) yielded **26ab** (1.35 g, 60%) as a colorless solid.

M. p.: 61–63 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.14 (ddd, *J* = 4.2, 1.9, 1.9 Hz, 1H), 8.05 (ddt, *J* = 6.5, 1.7, 0.7 Hz, 1H), 7.25 (m, 1H), 7.06 (dddd, *J* = 8.9, 6.8, 2.2, 0.8 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.4 (C_q, *J* = 254 Hz), 136.1 (CH, *J* = 3 Hz), 129.7 (CH, *J* = 36 Hz), 125.7 (CH, *J* = 10 Hz), 113.6 (CH, *J* = 20 Hz).

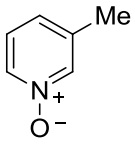
^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 120.4 (td, *J* = 6.8, 4.6 Hz).

IR (KBr, cm^{-1}): 3061 (w), 2774 (w), 2362 (m), 1949 (w), 1617 (s), 1562 (s), 1285 (s), 977 (s), 667 (s).

MS (EI) *m/z* (relative intensity): 113 ([M^+] 100), 97 (43), 86 (9), 70 (36), 57 (72).

HR-MS (ESI) *m/z* for $C_5H_4FNO+Na^+$ calcd.: 136.0169.
found: 136.0171.

Synthesis of 3-Methylpyridine *N*-oxide (26ac)



26ac

The general procedure **B** was followed using 3-methylpyridine (**47d**) (1.02 g, 10.9 mmol), *m*CPBA (2.54 g, 11.0 mmol), and triphenylphosphine (1.31 g, 5.00 mmol). Purification by column chromatography (EtOAc → EtOAc/MeOH: 20/1 → 7/1 → acetone/MeOH: 7/1) yielded **26ac** (0.91 g, 76%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.06 (s, 1H), 8.04 (d, J = 7.1 Hz, 1H), 7.15 (dd, J = 7.8, 7.1 Hz, 1H), 7.07 (d, J = 7.8 Hz, 1H), 2.30 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 139.3 (CH), 136.8 (C_q), 136.6 (CH), 127.1 (CH), 125.3 (CH), 18.3 (CH_3).

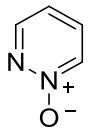
IR (KBr, cm^{-1}): 3392 (s), 3064 (s), 1603 (s), 1274 (s), 1164 (s), 1016 (s), 795 (s), 680 (s).

MS (EI) *m/z* (relative intensity): 109 ([M^+] 90), 93 (100), 66 (44), 53 (38).

HR-MS (EI) *m/z* for C_6H_7NO calcd.: 109.0528.
found: 109.0522.

The analytical data are in accordance with those reported in the literature.[181]

Synthesis of Pyridazine *N*-oxide (26c)



26c

The general procedure **B** was followed using pyridazine (**80**) (0.38 g, 4.73 mmol), *m*CPBA (1.16 g, 5.00 mmol), and triphenylphosphine (0.66 g, 2.50 mmol). Purification by column chromatography (EtOAc → EtOAc/MeOH: 10/1) yielded **26c** (0.37 g, 82%) as a brown solid.

M. p.: 34–36 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.45 (m, 1H), 8.14 (ddd, J = 6.5, 6.5, 1.0 Hz, 1H), 7.61 (ddd, J = 7.7, 6.5, 2.5 Hz, 1H), 7.06 (ddd, J = 7.7, 5.4, 1.0 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 150.5 (CH), 134.3 (CH), 134.0 (CH), 115.9 (CH).

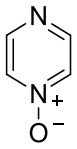
IR (KBr, cm^{-1}): 3442 (s), 3109 (m), 1650 (m), 1456 (s), 1314 (s), 1148 (m), 983 (s), 787 (s), 524 (m).

MS (EI) *m/z* (relative intensity): 96 ([M^+] 100), 66 (22), 40 (12).

HR-MS (EI) *m/z* for $C_4H_4N_2O$ calcd.: 96.0324.
found: 96.0322.

The analytical data are in accordance with those reported in the literature.[34]

Synthesis of Pyrazine *N*-oxide (26d)



26d

The general procedure **B** was followed using pyrazine (**81**) (0.40 g, 5.04 mmol), *m*CPBA (1.15 g, 5.00 mmol), and triphenylphosphine (0.66 g, 2.50 mmol). Purification by column chromatography (EtOAc → EtOAc/MeOH: 10/1) yielded **26d** (0.35 g, 72%) as a colorless solid.

M. p.: 113–114 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 4.9 Hz, 2H), 8.09 (d, *J* = 4.9 Hz, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 147.9 (CH), 134.1 (CH).

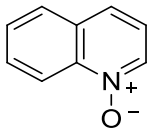
IR (KBr, cm^{-1}): 3394 (s), 3090 (s), 1596 (s), 1469 (s), 1314 (s), 1008 (s), 863 (s), 540 (s).

MS (EI) *m/z* (relative intensity): 96 ([M^+] 100), 80 (7), 52 (13), 40 (40).

HR-MS (EI) *m/z* for $C_4H_4N_2O$ calcd.: 96.0324.
found: 96.0324.

The analytical data are in accordance with those reported in the literature.[34]

Synthesis of Quinoline *N*-oxide (26b)



26b

The general procedure **B** was followed using quinoline (**67**) (1.23 g, 9.53 mmol), *m*CPBA (2.31 g, 10.0 mmol), and triphenylphosphine (1.34 g, 5.11 mmol). Purification by column chromatography (EtOAc → EtOAc/MeOH: 10/1 → 7/1) yielded **26b** (1.11 g, 80%) as a pale yellow solid.

M. p.: 57–60 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.74 (dd, J = 8.9, 1.0 Hz, 1H), 8.52 (dd, J = 6.0, 1.0 Hz, 1H), 7.86 (dd, J = 8.1, 1.2 Hz, 1H), 7.81 – 7.69 (m, 2H), 7.63 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 7.28 (dd, J = 8.5, 6.0 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 141.6 (C_q), 135.6 (CH), 130.5 (C_q), 130.4 (CH), 128.7 (CH), 128.1 (CH), 125.9 (CH), 120.9 (CH), 119.8 (CH).

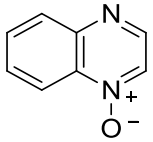
IR (KBr, cm^{-1}): 3057 (w), 1690 (w), 1571 (s), 1393 (s), 1229 (s), 1092 (m), 797 (s).

MS (EI) *m/z* (relative intensity): 145 ([M^+] 100), 117 (14), 90 (42), 63 (7).

HR-MS (EI) *m/z* for C_9H_7NO calcd.: 145.0528.
found: 145.0523.

The analytical data are in accordance with those reported in the literature.[182]

Synthesis of Quinoxaline *N*-oxide (26e)



26e

The general procedure **B** was followed using quinoxaline (**82**) (1.31 g, 10.1 mmol), *m*CPBA (2.31 g, 10.0 mmol), and triphenylphosphine (1.31 g, 5.00 mmol). Purification by column chromatography (EtOAc) yielded **26e** (0.97 g, 66%) as an off-white solid.

M. p.: 123–124 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.67 (d, J = 3.6 Hz, 1H), 8.58 (dd, J = 8.6, 1.5 Hz, 1H), 8.35 (d, J = 3.6 Hz, 1H), 8.13 (m, 1H), 7.83 (ddd, J = 8.6, 7.0, 1.5 Hz, 1H), 7.75 (ddd, J = 8.6, 7.0, 1.5 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 146.0 (C_q), 145.9 (C_q), 137.5 (CH), 131.8 (CH), 130.2 (CH), 130.1 (CH), 129.2 (CH), 118.9 (CH).

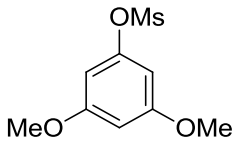
IR (KBr, cm^{-1}): 3404 (w), 3090 (w), 1575 (s), 1498 (s), 1318 (s), 890 (s), 759 (s).

MS (EI) *m/z* (relative intensity): 146 ([M^+] 100), 118 (17), 91 (54), 76 (27), 50 (20).

HR-MS (EI) *m/z* for $C_8H_6N_2O$ calcd.: 146.0480.
found: 146.0474.

The analytical data are in accordance with those reported in the literature.[183]

Synthesis of 3,5-Dimethoxyphenyl methanesulfonate (20bq)



20bq

The general procedure **A** was followed using 3,5-dimethoxyphenol (3.08 g, 20.0 mmol), and mesyl chloride (2.75 g, 24.0 mmol). Purification by column chromatography (*n*-pentane/EtOAc: 10/1 → 4/1 → 2/1) yielded **20bq** (4.48 g, 97%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.45 (d, J = 2.2 Hz, 2H), 6.41 (m, 1H), 3.79 (s, 3H), 3.14 (s, 3H).

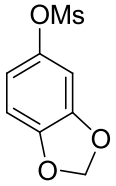
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.3 (C_q), 150.6 (C_q), 100.4 (CH), 99.4 (CH), 55.6 (CH_3), 37.3 (CH_3).

IR (film, cm^{-1}): 3019 (m), 2942 (m), 1616 (s), 1475 (s), 1366 (s), 1118 (s), 809 (s).

MS (EI) *m/z* (relative intensity): 232 ([M^+] 68), 154 (74), 125 (100), 69 (27), 52 (17).

HR-MS (ESI) *m/z* for $C_9H_{12}O_5S+H^+$ calcd.: 233.0484.
found: 233.0478.

Synthesis of Benzo[*d*]-[1,3]dioxol-5-yl methanesulfonate (20bs)



20bs

The general procedure **A** was followed using benzo[*d*][1,3]dioxol-5-ol (1.38 g, 10.0 mmol), and mesyl chloride (1.38 g, 12.0 mmol). Purification by column chromatography (*n*-pentane/EtOAc: 10/1 → 5/1 → 3/1 yielded **20bs** (2.10 g, 97%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.79 (d, J = 8.6 Hz, 1H), 6.80 (d, J = 2.1 Hz, 1H), 6.73 (dd, J = 8.6, 2.1 Hz, 1H), 6.01 (s, 2H), 3.12 (s, 3H).

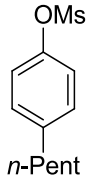
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.2 (C_q), 146.6 (C_q), 143.2 (C_q), 114.7 (CH), 108.1 (CH), 104.1 (CH), 102.1 (CH_2), 37.1 (CH_3).

IR (neat, cm^{-1}): 2908 (w), 1502 (s), 1358 (s), 1158 (s), 1033 (s), 830 (s), 597 (m).

MS (EI) *m/z* (relative intensity): 216 ([M^+] 19), 137 (100), 107 (35), 79 (25), 43 (42).

HR-MS (ESI) *m/z* for $C_8H_8O_5S+Na^+$ calcd.: 238.9986.
found: 238.9985.

Synthesis of 4-*n*-Pentylphenyl methanesulfonate (20bu)



20bu

The general procedure **A** was followed using 4-*n*-pentylphenole (3.46 g, 21.1 mmol), and mesyl chloride (2.75 g, 24.0 mmol). Purification by column chromatography (*n*-pentane/EtOAc: 15/1 → 10/1) yielded **20bu** (4.31 g, 84%) as a brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.25 – 7.14 (m, 4H), 3.12 (s, 3H), 2.67 – 2.53 (m, 2H), 1.59 (ddd, *J* = 13.6, 7.5, 1.5 Hz, 2H), 1.42 – 1.22 (m, 4H), 0.95 – 0.85 (t, *J* = 7.0 Hz, 3H).

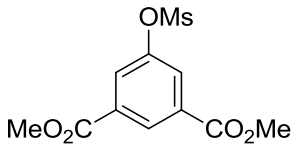
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 147.2 (C_q), 142.4 (C_q), 129.8 (CH), 121.7 (CH), 37.2 (CH_3), 35.3 (CH_2), 31.4 (CH_2), 31.0 (CH_2), 22.5 (CH_2), 14.0 (CH_3).

IR (film, cm^{-1}): 3034 (m), 2931 (s), 2860 (s), 1898 (w), 1597 (w), 1502 (m), 1371 (s), 971 (m), 684 (m).

MS (EI) *m/z* (relative intensity): 242 ([M^+] 18), 185 (41), 163 (12), 107 (100), 78 (10).

HR-MS (ESI) *m/z* for $C_{12}H_{18}O_3S+Na^+$ calcd.: 265.0869.
found: 265.0873.

Synthesis of Dimethyl 5-{(methylsulfonyl)oxy}isophthalate (20by)



20by

The general procedure **A** was followed using dimethyl 5-hydroxyisophthalate (2.11 g, 10.0mmol), and mesyl chloride (1.38 g, 12.0 mmol). Purification by column chromatography (*n*-pentane/EtOAc: 5/1 → 3/1 → 1/1 → 1/2 → 1/3 → EtOAc) yielded **20by** (2.60 g, 90%) as a colorless solid.

M. p.: 145–147 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.65 (t, *J* = 1.5 Hz, 1H), 8.12 (d, *J* = 1.5 Hz, 2H), 3.96 (s, 6H), 3.23 (s, 3H).

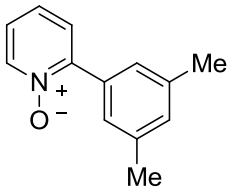
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 164.7 (C_q), 148.8 (C_q), 132.6 (C_q), 129.3 (CH), 127.3 (CH), 52.8 (CH_3), 38.1 (CH_3).

IR (neat, cm^{-1}): 3027 (w), 1719 (s), 1433 (m), 1365 (s), 1245 (m), 979 (m), 755 (s).

MS (ESI) *m/z* (relative intensity): 288 ([M^+] 66), 257 (46), 210 (100), 179 (45), 119 (4).

HR-MS (EI) *m/z* for $C_{11}H_{12}O_7S+Na^+$ calcd.: 311.0196.
found: 311.0197.

Synthesis of 2-(3,5-Dimethylphenyl)pyridine *N*-oxide (28aa)



28aa

The general procedure **C** was followed, using 3,5-dimethylphenyl 4-methyl-benzenesulfonate (**20aa**) (138 mg, 0.50 mmol) and pyridine *N*-oxide (**26aa**) (190 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/1 → CH_2Cl_2/acetone/MeOH: 86/86/1) yielded **28aa** (64 mg, 64%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.30 (ddd, *J* = 6.3, 1.4, 0.5 Hz, 1H), 7.41 – 7.32 (m, 3H), 7.25 (td, *J* = 7.7, 1.4 Hz, 1H), 7.18 (ddd, *J* = 7.5, 6.4, 2.3 Hz, 1H), 7.09 – 7.04 (m, 1H), 2.35 (s, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 149.6 (C_q), 140.3 (CH), 137.7 (C_q), 132.5 (C_q), 131.2 (CH), 127.3 (CH), 126.8 (CH), 125.4 (CH), 124.2 (CH), 21.4 (CH_3).

IR (film, cm^{-1}): 3395 (s), 3074 (w), 2947 (w), 1602 (s), 1406 (s), 1257 (s), 875 (s).

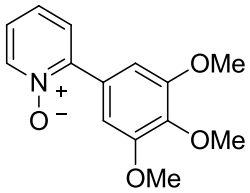
MS (EI) *m/z* (relative intensity): 199 ([M^+] 63), 170 (100), 130 (39), 78 (51), 58 (47).

HR-MS (EI) *m/z* for $C_{13}H_{13}NO$ calcd.: 199.0997.
found: 199.0991.

The analytical data are in accordance with those reported in the literature.[33]

The analogous reaction using 3,5-dimethylphenyl methanesulfonate (**20ba**) (101 mg, 0.50 mmol) and pyridine *N*-oxide (**26aa**) (207 mg, 2.17 mmol) yielded **28aa** (41 mg, 41%) as a brown oil.

Synthesis of 2-(3,4,5-Trimethoxyphenyl)pyridine *N*-oxide (28ab)



28ab

The general procedure **C** was followed, using 3,4,5-trimethoxyphenyl 4-methyl-benzenesulfonate (**20ab**) (169 mg, 0.50 mmol) and pyridine *N*-oxide (**26aa**) (195 mg, 2.05 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/1 → CH_2Cl_2/acetone/MeOH: 86/86/1) yielded **28ab** (88 mg, 67%) as a light yellow solid.

M. p.: 142–144 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.31 (dd, J = 6.4, 1.3 Hz, 1H), 7.42 (dd, J = 7.8, 2.2 Hz, 1H), 7.29 (td, J = 7.7, 1.4 Hz, 1H), 7.21 (m, 1H), 7.05 (s, 2H), 3.89 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 153.0 (C_q), 149.1 (C_q), 140.5 (CH), 139.1 (C_q), 127.8 (C_q), 127.3 (CH), 125.7 (CH), 124.4 (CH), 106.7 (CH), 60.8 (CH_3), 56.2 (CH_3).

IR (KBr, cm^{-1}): 3336 (s), 3112 (w), 2936 (m), 2832 (m), 2596 (w), 1991 (w), 1583 (s), 1397 (s), 1126 (s), 772 (m).

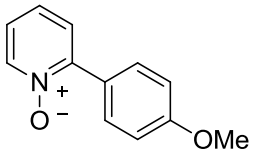
MS (EI) *m/z* (relative intensity): 261 ([M^+] 83), 172 (66), 104 (90), 78 (100), 51 (50).

HR-MS (EI) *m/z* for $C_{14}H_{15}NO_4$ calcd.: 261.1001.
found: 261.0999.

The analytical data are in accordance with those reported in the literature.[128]

The analogous reaction using 3,4,5-trimethoxyphenyl methanesulfonate (**20bb**) (131 mg, 0.50 mmol), pyridine *N*-oxide (**26aa**) (218 mg, 2.29 mmol), $Pd(OAc)_2$ (10 mol%) and X-Phos (**21**) (20 mol%) yielded **28ab** (53 mg, 41%) as a light yellow solid.

Synthesis of 2-(4-Methoxyphenyl)pyridine-*N*-oxide (28ac)



28ac

The general procedure **C** was followed, using 4-methoxyphenyl 4-methylbenzenesulfonate (**20ac**) (139 mg, 0.50 mmol) and pyridine-*N*-oxide (**26aa**) (190 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/1 → CH_2Cl_2/acetone/MeOH: 86/86/1) yielded **28ac** (52 mg, 52%) as a yellow solid.

M. p.: 136–137 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.29 (ddd, *J* = 6.4, 1.3, 0.5 Hz, 1H), 7.85 – 7.75 (m, 2H), 7.40 (m, 1H), 7.25 (ddd, *J* = 7.7, 7.7, 1.4 Hz, 1H), 7.15 (ddd, *J* = 7.5, 6.5, 2.2 Hz, 1H), 7.02 – 6.93 (m, 2H), 3.83 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.4 (C_q), 148.8 (C_q), 140.4 (CH), 130.7 (CH), 126.8 (CH), 125.5 (CH), 124.7 (C_q), 123.8 (CH), 113.6 (CH), 55.4 (CH_3).

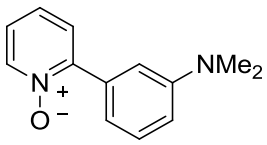
IR (KBr, cm^{-1}): 3102 (w), 3057 (m), 2935 (m), 2841 (m), 1608 (s), 1435 (s), 1243 (s), 830 (s), 761 (w).

MS (EI) *m/z* (relative intensity): 201 ([M^+] 100), 200 (92), 185 (38), 158 (25), 130 (24), 78 (15).

HR-MS (EI) *m/z* for $C_{12}H_{11}NO_2$ calcd.: 201.0790.
found: 201.0783.

The analytical data are in accordance with those reported in the literature.[33]

Synthesis of 2-{3-(*N*,*N*-Dimethylamino)phenyl}pyridine *N*-oxide (28ad)



28ad

The general procedure **C** was followed, using 3-(*N*,*N*-dimethylamino)phenyl 4-methyl-benzenesulfonate (**20ad**) (154 mg, 0.55 mmol) and pyridine *N*-oxide (**26aa**) (192 mg, 2.02 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/1 → CH_2Cl_2/acetone/MeOH: 70/70/1) yielded **28ad** (59 mg, 50%) as a brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.31 (dd, *J* = 6.4, 1.0 Hz, 1H), 7.41 (dd, *J* = 7.8, 2.1 Hz, 1H), 7.37 – 7.13 (m, 4H), 7.02 (m, 1H), 6.81 (ddd, *J* = 8.4, 2.7, 0.8 Hz, 1H), 2.97 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 150.3 (C_q), 150.2 (C_q), 140.4 (CH), 133.3 (C_q), 129.0 (CH), 127.5 (CH), 125.5 (CH), 124.2 (CH), 117.3 (CH), 113.8 (CH), 113.2 (CH), 40.6 (CH_3).

IR (film, cm^{-1}): 3389 (s), 3076 (w), 2886 (w), 2804 (w), 1601 (m), 1488 (m), 1229 (s), 850 (m), 772 (s).

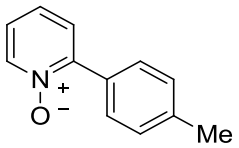
MS (EI) *m/z* (relative intensity): 214 ([M^+] 100), 199 (54), 171 (24), 117 (14), 78 (9).

HR-MS (EI) *m/z* for $C_{13}H_{14}N_2O$ calcd.: 214.1106.
found: 214.1098.

The analytical data are in accordance with those reported in the literature.[128]

The analogous reaction using 3-(*N*,*N*-dimethylamino)phenyl methanesulfonate (**20bd**) (108 mg, 0.50 mmol), pyridine *N*-oxide (**26aa**) (181 mg, 1.90 mmol), $Pd(OAc)_2$ (10 mol%) and X-Phos (**21**) (20 mol%) yielded **28ad** (56 mg, 52%) as a brown oil.

Synthesis of 2-(4-Methylphenyl)pyridine *N*-oxide (28ae)



28ae

The general procedure **C** was followed, using 4-methylphenyl 4-methyl-benzenesulfonate (**20ae**) (131 mg, 0.50 mmol) and pyridine *N*-oxide (**26aa**) (200 mg, 2.10 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/1 → CH_2Cl_2/acetone/MeOH: 68/68/1) yielded **28ae** (54 mg, 58%) as a pale yellow solid.

M. p.: 132–133 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.32 (dd, J = 6.4, 0.9 Hz, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.41 (dd, J = 7.8, 2.0 Hz, 1H), 7.34 – 7.24 (m, 3H), 7.19 (m, 1H), 2.40 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 149.3 (C_q), 140.4 (CH), 139.7 (C_q), 129.7 (C_q), 129.1 (CH), 128.9 (CH), 127.2 (CH), 125.6 (CH), 124.2 (CH), 21.4 (CH_3).

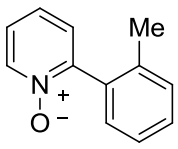
IR (KBr, cm^{-1}): 3066 (s), 3043 (s), 2915 (m), 1614 (m), 1430 (s), 1240 (s), 816 (m).

MS (EI) *m/z* (relative intensity): 185 ([M^+] 71), 184 (100), 156 (45), 117 (20), 78 (16).

HR-MS (EI) *m/z* for $C_{12}H_{11}NO$ calcd.: 185.0841.
found: 185.0835.

The analytical data are in accordance with those reported in the literature.[33]

Synthesis of 2-(2-Metylphenyl)pyridine *N*-oxide (28af)



28af

The general procedure **C** was followed, using 2-methylphenyl 4-methyl-benzenesulfonate (**20af**) (131 mg, 0.50 mmol) and pyridine *N*-oxide (**26aa**) (191 mg, 2.01 mmol). After 20 h,

purification by column chromatography (CH_2Cl_2/acetone: 2/1 → CH_2Cl_2/acetone/MeOH: 70/70/1) yielded **28af** (23 mg, 25%) as a pale yellow solid.

M. p.: 117–119 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.32 (ddd, J = 5.4, 3.5, 1.6 Hz, 1H), 7.41 – 7.18 (m, 7H), 2.23 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 150.8 (C_q), 140.0 (CH), 137.7 (C_q), 133.0 (C_q), 130.1 (CH), 129.5 (CH), 129.2 (CH), 127.9 (CH), 125.9 (CH), 125.1 (CH), 124.9 (CH), 19.5 (CH_3).

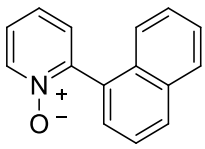
IR (KBr, cm^{-1}): 3055 (s), 2471 (w), 2082 (w), 1936 (w), 1469 (m), 1419 (m), 1245 (s), 1006 (m), 771 (s).

MS (EI) *m/z* (relative intensity): 185 ([M^+] 30), 168 (100), 141 (13), 115 (18), 51 (14).

HR-MS (EI) *m/z* for $C_{12}H_{11}NO$ calcd.: 185.0841.
found: 185.0841.

The analytical data are in accordance with those reported in the literature.[33]

Synthesis of 2-(1-Naphtyl)pyridine *N*-oxide (28ag)



28ag

The general procedure **C** was followed, using 1-naphthyl 4-methyl-benzenesulfonate (**20ag**) (149 mg, 0.50 mmol) and pyridine *N*-oxide (**26aa**) (191 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/1 → CH_2Cl_2/acetone/MeOH: 86/86/1) yielded **28ag** (66 mg, 60%) as an off-white solid.

M. p.: 161–162 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.43 (m, 1H), 7.97 (dd, J = 8.0, 1.3 Hz, 1H), 7.91 (m, 1H), 7.63 – 7.31 (m, 8H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 149.7 (C_q), 140.3 (CH), 133.4 (C_q), 131.1 (C_q), 130.8 (C_q), 130.1 (CH), 128.8 (CH), 128.5 (CH), 127.7 (CH), 126.8 (CH), 126.2 (CH), 125.3 (CH), 125.2 (CH).

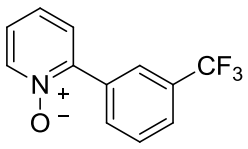
IR (KBr, cm^{-1}): 3418 (s), 3059 (s), 2473 (w), 1977 (w), 1550 (m), 1423 (m), 1243 (s), 966 (m), 778 (s), 494 (m).

MS (EI) *m/z* (relative intensity): 221 ([M^+] 71), 204 (100), 193 (89), 115 (58), 83 (72).

HR-MS (EI) *m/z* for $C_{15}H_{11}NO$ calcd.: 221.0841.
found: 221.0834.

The analytical data are in accordance with those reported in the literature.[33]

Synthesis of 2-{3-(Trifluoromethyl)phenyl}pyridine *N*-oxide (28ah)



28ah

The general procedure **C** was followed, using 3-(trifluoromethyl)phenyl 4-methyl-benzenesulfonate (**20ah**) (158 mg, 0.50 mmol) and pyridine *N*-oxide (**26aa**) (189 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 2/1 → 1/1) yielded **28ah** (61 mg, 51%) as a brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.34 (m, 1H), 8.10 – 8.01 (m, 2H), 7.71 (m, 1H), 7.61 (m, 1H), 7.45 (dd, *J* = 7.8, 2.2 Hz, 1H), 7.38 – 7.24 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 147.7 (C_q), 140.5 (CH), 133.2 (C_q), 132.6 (CH), 130.7 (C_q, *J* = 33 Hz), 128.7 (CH), 127.2 (CH), 126.2 (CH, *J* = 4 Hz), 126.1 (CH, *J* = 4 Hz), 126.0 (C_q, *J* = 275 Hz), 125.1 (CH), 124.9 (CH).

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

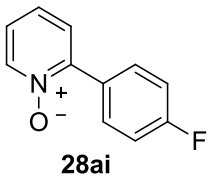
IR (film, cm^{-1}): 3402 (s), 3076 (m), 1482 (m), 1337 (m), 1241 (s), 1126 (s), 855 (m), 770 (m), 658 (m).

MS (EI) *m/z* (relative intensity): 239 ([M^+] 70), 238 (100), 190 (13), 117 (17), 78 (12).

HR-MS (EI) *m/z* for $C_{12}H_8F_3NO$ calcd.: 239.0558.
found: 239.0550.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-(4-Fluorophenyl)pyridine *N*-oxide (28ai)



28ai

The general procedure **C** was followed, using 4-fluorophenyl 4-methyl-benzenesulfonate (**20ai**) (133 mg, 0.50 mmol) and pyridine *N*-oxide (**26aa**) (195 mg, 2.05 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/1 → CH_2Cl_2/acetone/MeOH: 86/86/1) yielded **28ai** (57 mg, 60%) as a light yellow solid.

M. p.: 161–163 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.32 (dd, *J* = 6.5, 1.2 Hz, 1H), 7.90 – 7.78 (m, 2H), 7.41 (dd, *J* = 7.8, 2.2 Hz, 1H), 7.36 – 7.08 (m, 4H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ =163.5 (C_q, *J* = 250 Hz), 148.5 (C_q), 140.8 (CH), 131.6 (CH, *J* = 9 Hz), 128.8 (C_q, *J* = 4 Hz), 127.4 (CH), 125.9 (CH), 124.8 (CH), 115.6 (CH, *J* = 22 Hz).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 110.7 (tt, *J* = 8.5, 6.4 Hz).

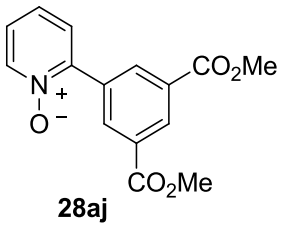
IR (KBr; cm^{-1}): 3064 (s), 3041 (s), 2463 (w), 1916 (w), 1595 (s), 1247 (s), 1018 (s), 760 (s), 572 (s).

MS (EI) *m/z* (relative intensity): 189 ([M^+] 71), 188 (100), 160 (18), 133 (13), 78 (4).

HR-MS (EI) *m/z* for $C_{11}H_8FNO$ calcd.: 189.0590.
found: 189.0583.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-{3,5-Bis(methoxycarbonyl)phenyl}pyridine *N*-oxide (28aj)



28aj

The general procedure **C** was followed, using 3,5-bis(methoxycarbonyl)phenyl 4-methyl-benzenesulfonate (**20aj**) (182 mg, 0.50 mmol) and pyridine *N*-oxide (**26aa**) (187 mg, 1.97 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/1 → CH_2Cl_2/acetone/MeOH: 68/68/1) yielded **28aj** (55 mg, 38%) as a pale yellow solid.

M. p.: 169 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.74 (dd, J = 1.6, 1.6 Hz, 1H), 8.66 (d, J = 1.7 Hz, 2H), 8.32 (m, 1H), 7.48 (m, 1H), 7.37 – 7.23 (m, 2H), 3.93 (s, 6H).

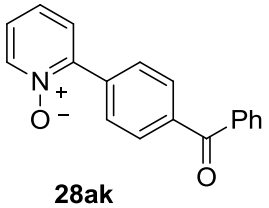
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.7 (C_q), 147.3 (C_q), 140.5 (CH), 134.5 (CH), 133.3(C_q), 131.6 (CH), 130.8 (C_q), 127.3 (CH), 125.8 (CH), 125.4 (CH), 52.5 (CH_3).

IR (KBr, cm^{-1}): 3416 (s), 2956 (m), 1720 (s), 1429 (m), 1232 (s), 993 (m), 760 (s).

MS (EI) *m/z* (relative intensity): 287 ([M^+] 60), 286 (100), 213 (33), 141 (11), 78 (11).

HR-MS (EI) *m/z* for $C_{15}H_{13}NO_5$ calcd.: 287.0794.
found: 287.0787.

Synthesis of 2-(4-Benzoylphenyl)pyridine *N*-oxide (28ak)



28ak

The general procedure **C** was followed, using 4-benzoylphenyl 4-methyl-benzenesulfonate (**20ak**) (153 mg, 0.50 mmol) and pyridine *N*-oxide (**26aa**) (191 mg, 2.01 mmol). After 20 h,

purification by column chromatography (CH_2Cl_2/acetone: 2/1 → CH_2Cl_2/acetone/MeOH: 70/70/1) yielded **28ak** (54 mg, 49%) as a pale yellow solid.

M. p.: 183–184. °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.34 (m, 1H), 7.97 – 7.80 (m, 6H), 7.59 (m, 1H), 7.53 – 7.43 (m, 3H), 7.33 (td, *J* = 7.7, 1.5 Hz, 1H), 7.26 (m, 1H).

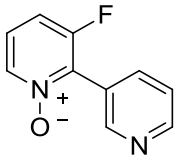
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 196.0 (C_q), 148.3 (C_q), 138.3 (C_q), 137.3 (C_q), 136.3 (C_q), 132.6 (CH), 130.1 (CH), 129.7 (CH), 129.2 (CH), 129.0 (CH), 128.4 (CH), 127.4 (CH), 125.7 (CH), 125.1 (CH).

IR (KBr, cm^{-1}): 3298 (w), 3049 (s), 2848 (w), 2087 (w), 1822 (w), 1623 (s), 1433 (m), 1245 (m), 844 (m).

MS (EI) *m/z* (relative intensity): 275 ([M^+] 100), 259 (19), 182 (24), 105 (50), 77 (35).

HR-MS (EI) *m/z* for $C_{18}H_{13}NO_2$ calcd.: 275.0946.
found: 275.0940.

Synthesis of 3-Fluoro-2-(pyrid-3-yl)pyridine *N*-oxide (28abl)



28abl

The general procedure **C** was followed, using pyridin-3-yl 4-methylbenzenesulfonate (**20al**) (124 mg, 0.50 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/1 → acetone/MeOH: 10/1) yielded **28abl** (61 mg, 64%) as an orange solid.

M. p.: 139–142 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.83 (s, 1H), 8.69 (d, *J* = 4.9, 1H), 8.23 (dd, *J* = 6.5, 1.1 Hz, 1H), 8.07 (d, *J* = 8.0, 1H), 7.45 (dd, *J* = 8.0, 4.9, 1H), 7.33 – 7.12 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.3 (C_q, J = 253 Hz), 150.6 (CH), 150.5 (CH, J = 4 Hz), 137.9 (CH, J = 2 Hz), 137.6 (C_q, J = 25 Hz), 136.7 (CH), 124.3 (CH, J = 11 Hz), 123.0 (CH), 122.9 (C_q, J = 3 Hz), 113.5 (CH, J = 23 Hz).

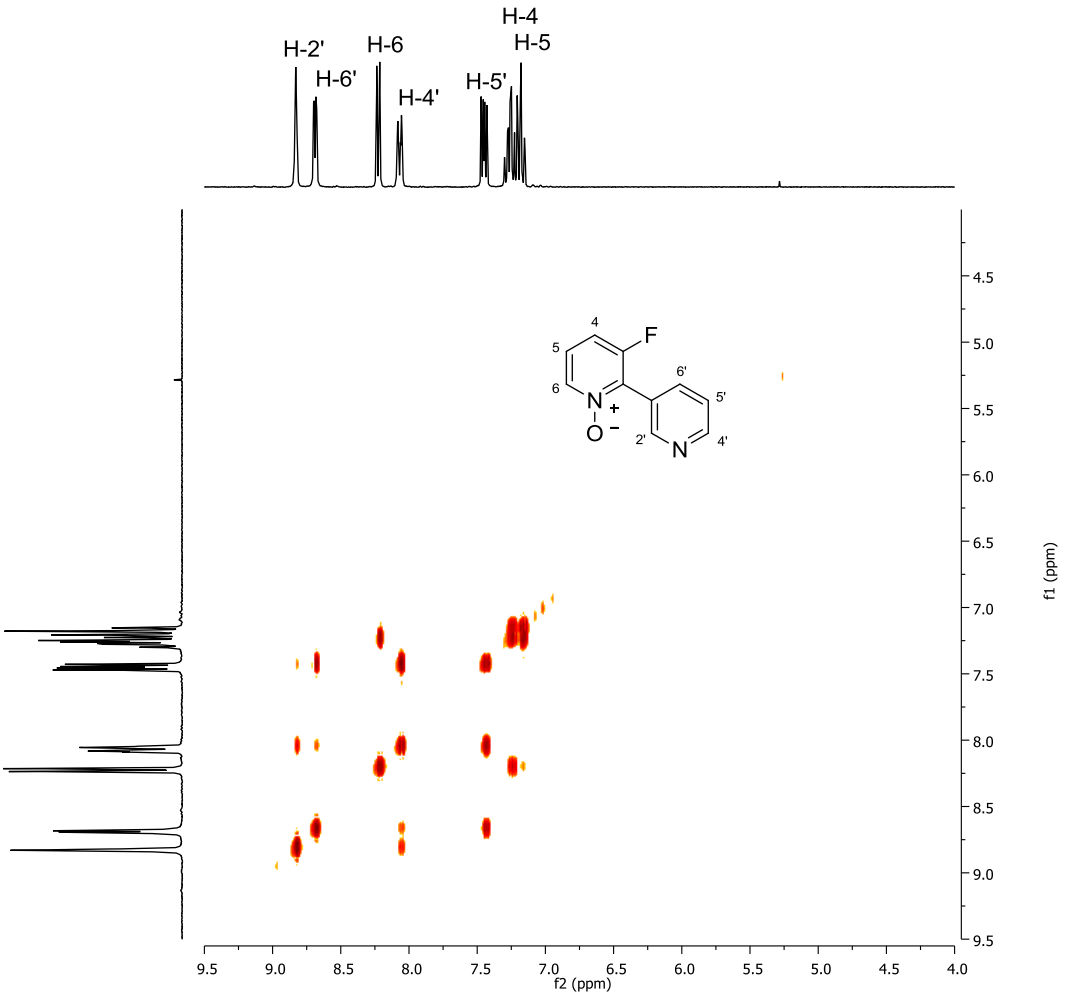
^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 116.5 (t, J = 7.0 Hz).

IR (KBr, cm^{-1}): 3045 (m), 2855 (w), 1570 (s), 1408 (s), 1235 (s), 1035 (s), 786 (s).

MS (EI) *m/z* (relative intensity): 190 ([M^+] 8), 174 (100), 148 (39), 97 (12), 51 (12).

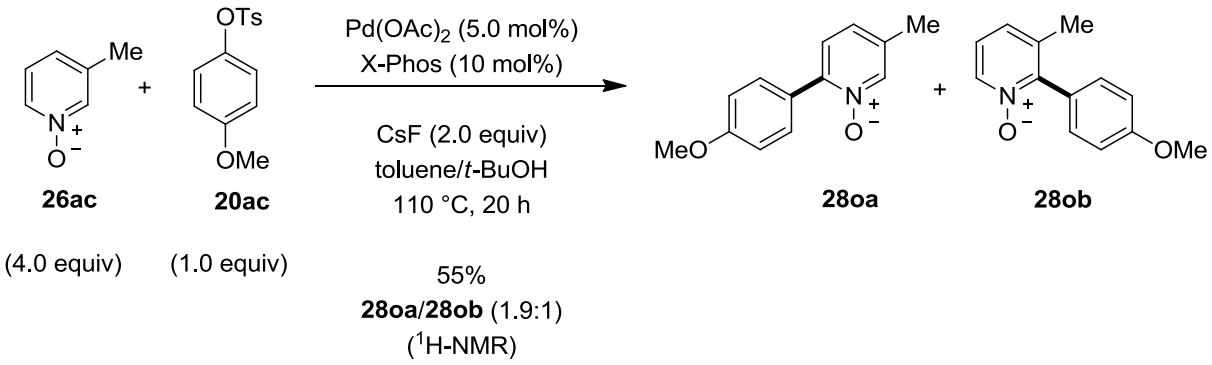
HR-MS (ESI) *m/z* for $C_{10}H_7FN_2O+H^+$ calcd.: 191.0615.
found: 191.0623.

COSY-NMR:



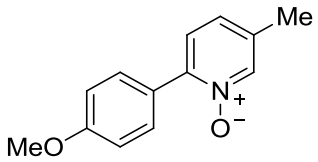
The analytical data are in accordance with those reported in the literature.[126]

Intramolecular Competition Experiment with 3-methylpyridine-*N*-oxide (26ac)



Synthesis of 2-(4-methoxyphenyl)-3-methylpyridine *N*-oxide (28ob) and 2-(4-methoxyphenyl)-5-methylpyridine *N*-oxide (28oa)

The general procedure **C** was followed, using 4-methoxyphenyl 4-methylbenzenesulfonate (**20ac**) (139 mg, 0.50 mmol) and 3-methylpyridine *N*-oxide (**26ac**) (219 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/1 → CH_2Cl_2/acetone/MeOH: 100/100/1) yielded **28oa** (36 mg, 34%) as pale yellow solid and a mixture of **28oa**/**28ob** (23 mg, 21%). The ratio of **28oa**/**28ob** was determined to be 1/25 by ^{1}H-NMR spectroscopy.



28oa

M. p.: 142–145 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.17 (s, 1H), 7.80 (d, J = 9.0 Hz, 2H), 7.29 (d, J = 8.1 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 6.98 (d, J = 9.0 Hz, 2H), 3.85 (s, 3H), 2.31 (s, 3H).

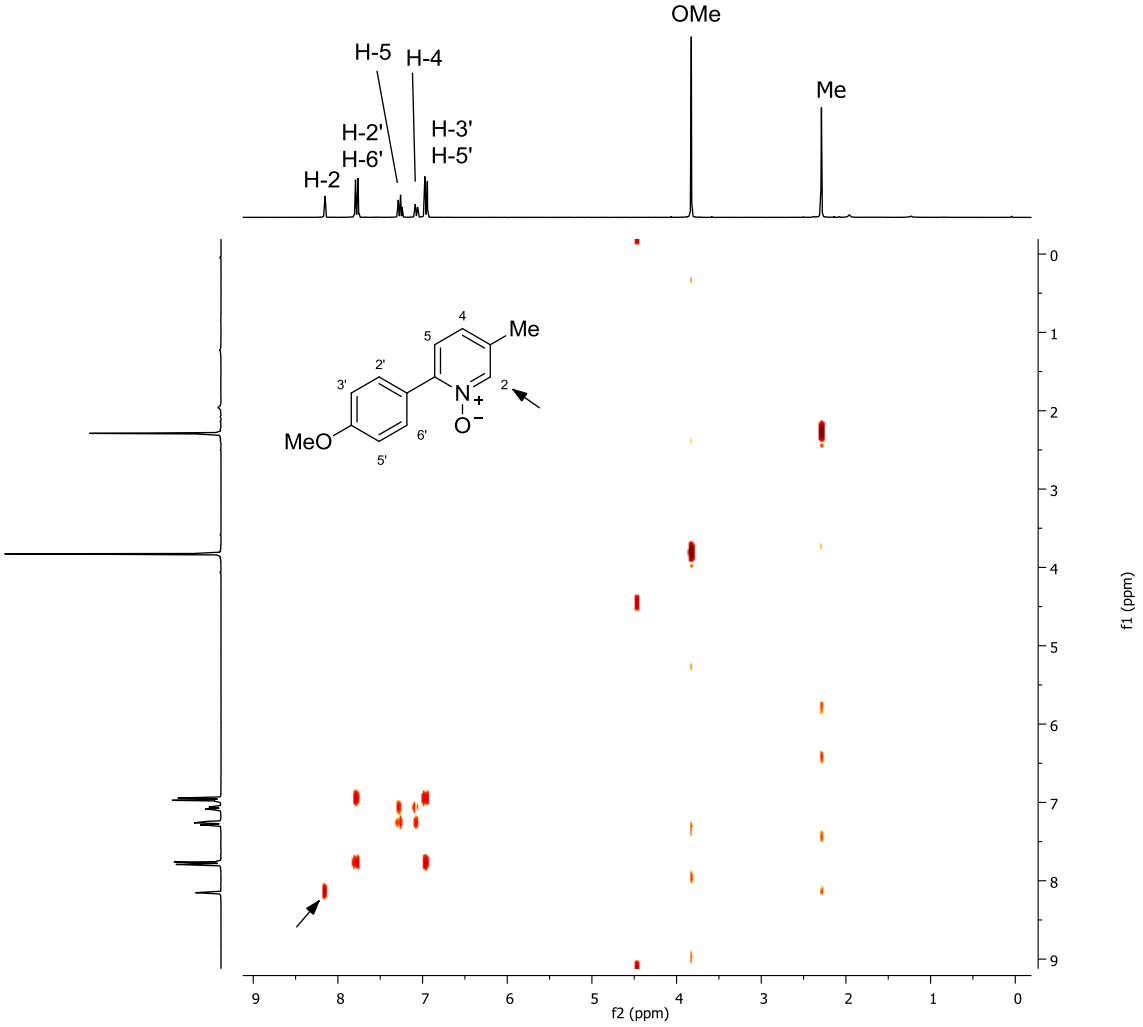
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.3 (C_q), 146.1 (C_q), 140.2 (CH), 134.4 (C_q), 130.7 (CH), 127.1 (CH), 126.2 (CH), 124.9 (C_q), 113.6 (CH), 55.3 (CH_3), 18.0 (CH_3).

IR (neat, cm^{-1}): 2924 (w), 1608 (s), 1492 (s), 1249 (s), 1172 (s), 1019 (m), 801 (s).

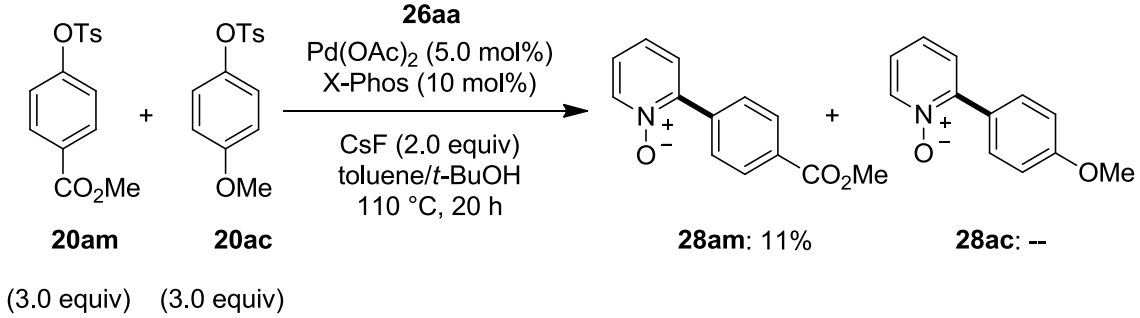
MS (EI) *m/z* (relative intensity): 215 ([M^+] 53), 199 (100), 184 (43), 156 (45), 63 (15).

HR-MS (EI) *m/z* for $C_{13}H_{13}NO_2$ calcd.: 215.0946.
found: 215.0947.

COSY-NMR:

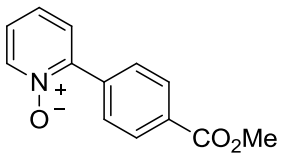


Intramolecular Competition Experiment between Tosylates 20am and 20ac



Synthesis of 2-{4-(Methoxycarbonyl)phenyl}pyridine *N*-oxide (28am)

The general procedure **C** was followed, using methyl-4-(tosyloxy)benzoate (**20am**) (459 mg, 1.50 mmol), 4-methoxyphenyl 4-methylbenzenesulfonate (**20ac**) (417 mg, 1.50 mmol) and pyridine *N*-oxide (**26aa**) (46.2 mg, 0.49 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone/MeOH: 75/75/1 → 63/63/1) yielded **28am** (12 mg, 11%) as pale yellow solid.



28am

M. p.: 205–207 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.30 (dd, J = 6.2, 1.6 Hz, 1H), 8.11 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 8.7 Hz, 2H), 7.42 (dd, J = 7.8, 2.2 Hz, 1H), 7.30 (td, J = 7.8, 1.6 Hz, 1H), 7.26 – 7.20 (m, 1H), 3.91 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.4 (C_q), 148.2 (C_q), 140.5 (CH), 136.8 (C_q), 130.8 (C_q), 129.4 (CH), 129.2 (CH), 127.3 (CH), 125.5 (CH), 125.0 (CH), 52.3 (CH_3).

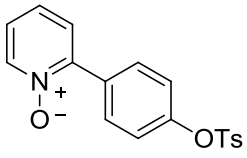
IR (neat, cm^{-1}): 3039 (m), 1715 (s), 1439 (s), 1247 (s), 1102 (s), 844 (m), 700 (m).

MS (EI) *m/z* (relative intensity): 229 ([M^+] 80), 213 (6), 184 (14), 141 (28), 78 (8).

HR-MS (ESI) *m/z* for $C_{13}H_{11}NO_3+H^+$ calcd.: 230.0812.
found: 230.0812.

The analytical data are in accordance with those reported in the literature.[33]

Synthesis of 2-{4-(Tosyloxy)phenyl}pyridine *N*-oxide (28an)



28an

The general procedure **C** was followed, using 4-chlorophenyl 4-methyl-benzenesulfonate (**20an**) (141 mg, 0.50 mmol) and pyridine *N*-oxide (**26aa**) (192 mg, 2.02 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/1 → CH_2Cl_2/acetone/MeOH: 70/70/1) yielded **28an** (111 mg, 65%) as a brown solid.

M. p.: 148–149 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.30 (m, 1H), 7.80 (d, J = 8.9 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.40 (dd, J = 7.7, 2.3 Hz, 1H), 7.36 – 7.20 (m, 4H), 7.10 (d, J = 8.9 Hz, 2H), 2.45 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 150.3 (C_q), 147.9 (C_q), 145.5 (C_q), 140.6 (CH), 132.3 (C_q), 131.3 (C_q), 130.9 (CH), 129.9 (CH), 128.5 (CH), 127.3 (CH), 125.7 (CH), 124.9 (CH), 122.2 (CH), 21.7 (CH_3).

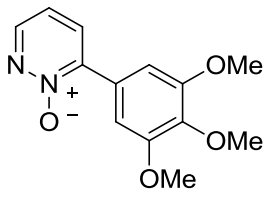
IR (KBr, cm^{-1}): 3134 (m), 2361 (m), 1373 (m), 1242 (m), 1150 (m), 762 (m).

MS (EI) *m/z* (relative intensity): 341 ([M^+] 100), 325 (18), 229 (14), 170 (39), 91 (21).

HR-MS (EI) *m/z* for $C_{18}H_{15}NO_4S$ calcd.: 341.0722.
found: 341.0715.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 6-(3,4,5-Trimethoxyphenyl)pyridazine *N*-oxide (28cb)



28cb

The general procedure **C** was followed, using 3,4,5-trimethoxyphenyl 4-methyl-benzenesulfonate (**20ab**) (169 mg, 0.50 mmol) and pyridazine *N*-oxide (**26c**) (104 mg, 1.08 mmol). After 20 h, purification by column chromatography (CH_2Cl_2 → CH_2Cl_2/acetone: 10/1) yielded **28cb** (90 mg, 69%) as a colorless solid.

M.p.: 161–163°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.41 (dd, *J* = 5.2, 2.5 Hz, 1H), 7.74 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.11 (dd, *J* = 8.0, 5.2 Hz, 1H), 7.02 (s, 2H), 3.87 (s, 3H), 3.87 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 153.2 (C_q), 149.0 (CH), 144.3 (C_q), 139.7 (C_q), 134.6 (CH), 126.5 (C_q), 116.2 (CH), 106.5 (CH), 60.9 (CH_3), 56.3 (CH_3).

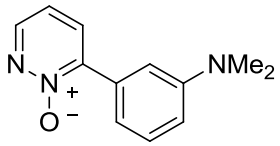
IR (KBr, cm^{-1}): 3096 (m), 2934 (s), 2836 (m), 1584 (s), 1344 (m), 1131 s), 908 (m).

MS (EI) *m/z* (relative intensity): 262 ([M^+] 100), 247 (27), 215 (53), 204 (6), 173 (2).

HR-MS (EI) *m/z* for $C_{13}H_{14}N_2O_4$ calcd.: 262.0954.
found: 262.0946.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 6-{3-(*N*,*N*-Dimethylamino)phenyl}pyridazine *N*-oxide (28cd)



28cd

The general procedure **C** was followed, using 3-(*N*,*N*-dimethylamino)phenyl 4-methyl-benzenesulfonate (**20ad**) (145 mg, 0.50 mmol) and pyridazine *N*-oxide (**26c**) (95.2 mg, 0.99 mmol). After 20 h, purification by column chromatography (CH_2Cl_2 → CH_2Cl_2/acetone: 40/1 → 20/1 → 15/1) yielded **28cd** (64 mg, 60%) as a brown solid.

M. p.: 75–78 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.40 (dd, *J* = 5.2, 2.5 Hz, 1H), 7.73 (dd, *J* = 7.9, 2.5 Hz, 1H), 7.37 – 7.27 (m, 1H), 7.14 (dd, *J* = 2.5, 1.7 Hz, 1H), 7.08 (dd, *J* = 7.9, 5.2 Hz, 1H), 6.98 (ddd, *J* = 7.6, 1.6, 0.9 Hz, 1H), 6.81 (ddd, *J* = 8.4, 2.7, 0.8 Hz, 1H), 2.97 (s, 6H).

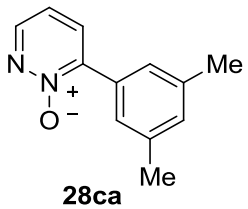
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 150.3 (C_q), 148.8 (CH), 145.3 (C_q), 134.7 (CH), 132.1 (C_q), 129.2 (CH), 116.8 (CH), 116.0 (CH), 114.1 (CH), 112.6 (CH), 40.6 (CH_3).

IR (KBr, cm^{-1}): 3097 (m), 3053 (s), 2860 (m), 2803 (m), 2669 (w), 1963 (w), 1609 (s), 1447 (s), 868 (m).

MS (EI) *m/z* (relative intensity): 215 ([M^+] 100), 200 (58), 172 (20), 118 (20), 63 (9).

HR-MS (EI) *m/z* for $C_{12}H_{13}N_3O$ calcd.: 215.1059.
found: 215.1052.

Synthesis of 6-(3,5-Dimethylphenyl)pyridazine *N*-oxide (28ca)



28ca

The general procedure **C** was followed, using 3,5-dimethylphenyl 4-methyl-benzenesulfonate (**20aa**) (138 mg, 0.50 mmol) and pyridazine *N*-oxide (**26c**) (96.5 mg, 1.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2 → CH_2Cl_2/acetone: 5/1) yielded **28ca** (74 mg, 74%) as a light yellow solid.

M. p.: 141–142 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.40 (dd, J = 5.2, 2.4 Hz, 1H), 7.70 (dd, J = 7.9, 2.5 Hz, 1H), 7.36 (s, 2H), 7.13 – 7.04 (m, 2H), 2.35 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 148.9 (CH), 144.9 (C_q), 138.2 (C_q), 134.7 (CH), 131.8 (CH), 131.3 (C_q), 126.6 (CH), 116.1 (CH), 21.3 (CH_3).

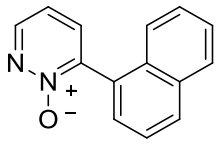
IR (KBr, cm^{-1}): 3105 (m), 3062 (s), 2918 (m), 2858 (m), 1600 (m), 1360 (m), 1135 (w), 980 (w), 813 (m).

MS (EI) *m/z* (relative intensity): 200 ([M^+] 100), 172 (57), 157 (32), 128 (33), 77 (12).

HR-MS (EI) *m/z* for $C_{12}H_{12}N_2O$ calcd.: 200.0950.
found: 200.0942.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 6-(1-Naphtyl)pyridazine *N*-oxide (28cg)



28cg

The general procedure **C** was followed, using 1-naphtyl 4-methylbenzenesulfonate (**20ag**) (149 mg, 0.50 mmol) and pyridazine *N*-oxide (**26c**) (96.8 mg, 1.01 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 30/1 → 20/1) yielded **28cg** (80 mg, 71%) as a brown solid.

M. p.: 177–179 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.55 (dd, *J* = 5.2, 2.4 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.90 (dd, *J* = 7.0, 1.8 Hz, 1H), 7.73 (dd, *J* = 7.8, 2.5 Hz, 1H), 7.61 – 7.37 (m, 5H), 7.15 (dd, *J* = 7.8, 5.3 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 150.0 (CH), 144.8 (C_q), 136.3 (CH), 133.4 (C_q), 130.7 (CH), 130.3 (C_q), 129.7 (C_q), 128.7 (CH), 127.8 (CH), 127.1 (CH), 126.5 (CH), 125.2 (CH), 124.7 (CH), 115.5 (CH).

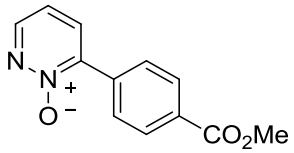
IR (KBr, cm^{-1}): 3097 (m), 3054 (m), 2674 (w), 2165 (w), 1948 (w), 1586 (m), 1370 (m), 1047 (m), 789 (m).

MS (EI) *m/z* (relative intensity): 222 ([M^+] 100), 205 (31), 194 (43), 140 (29), 63 (10).

HR-MS (EI) *m/z* for $C_{14}H_{10}N_2O$ calcd.: 222.0793.
found: 222.0785.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 6-(4-Methoxycarbonylphenyl)pyridazine *N*-oxide (28cm)



28cm

The general procedure **C** was followed, using methyl-4-(tosyloxy)benzoate (**20am**) (153 mg, 0.50 mmol) and pyridazine *N*-oxide (**26c**) (95.1 mg, 0.99 mmol). After 20 h, purification by column chromatography (CH_2Cl_2) yielded **28cm** (67 mg, 58%) as a light yellow solid.

M. p.: 207–209 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.46 (dd, *J* = 5.2, 2.4 Hz, 1H), 8.19 – 8.06 (m, 2H), 7.91 – 7.82 (m, 2H), 7.77 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.14 (dd, *J* = 8.0, 5.3 Hz, 1H), 3.93 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.2 (C_q), 149.7 (CH), 143.5 (C_q), 135.6 (C_q), 134.7 (CH), 131.5 (C_q), 129.7 (CH), 129.0 (CH), 116.2 (CH), 52.3 (CH_3).

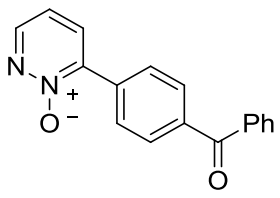
IR (KBr, cm^{-1}): 3064 (m), 1725 (s), 1545 (m), 1377 (s), 1278 (s), 1113 (s), 863 (m), 773 (m), 698 (m.).

MS (EI) *m/z* (relative intensity): 230 ([M^+] 83), 229 (100), 199 (13), 142 (15), 63 (10).

HR-MS (EI) *m/z* for $C_{12}H_{10}N_2O_3$ calcd.: 230.0691.
found: 230.0684.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 6-(4-Benzoylphenyl)pyridazine *N*-oxide (28ck)



28ck

The general procedure **C** was followed, using 4-benzoylphenyl 4-methyl-benzenesulfonate (**20ak**) (176 mg, 0.50 mmol) and pyridazine *N*-oxide (**26c**) (94.6 mg, 0.98 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 20/1) yielded **28ck** (68 mg, 50%) as a colorless solid.

M. p.: 149–151 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.48 (dd, *J* = 5.3, 2.5 Hz, 1H), 7.99 – 7.86 (m, 4H), 7.86 – 7.77 (m, 3H), 7.65 – 7.55 (m, 1H), 7.49 (ddt, *J* = 8.2, 6.6, 1.1 Hz, 2H), 7.17 (dd, *J* = 8.0, 5.3 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 196.1 (C_q), 150.0 (CH), 143.8 (C_q), 139.1 (C_q), 137.3 (C_q), 135.2 (C_q), 135.0 (CH), 133.1 (CH), 130.3 (CH), 130.3 (CH), 129.2 (CH), 128.7 (CH), 116.6 (CH).

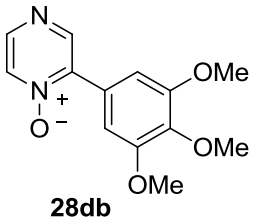
IR (KBr, cm^{-1}): 3369 (w), 3058 (m), 2857 (w), 2329 (w), 1648 (m), 1369 (s), 1283 (m), 988 (m), 690 (m).

MS (EI) *m/z* (relative intensity): 276 ([M^+] 100), 219 (10), 143 (9), 105 (43), 77 (34).

HR-MS (EI) *m/z* for $C_{17}H_{12}N_2O_2$ calcd.: 276.0899.
found: 276.0891.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-(3,4,5-Trimethoxyphenyl)pyrazine *N*-oxide (28db)



28db

The general procedure **C** was followed, using 3,4,5-trimethoxyphenyl 4-methyl-benzenesulfonate (**20ab**) (169 mg, 0.50 mmol) and pyrazine *N*-oxide (**26d**) (96.3 mg, 1.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/2) yielded **28db** (81 mg, 62%) as an orange solid.

M. p.: 117–120 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.61 (s, 1H), 8.35 (d, *J* = 4.1 Hz, 1H), 8.17 (d, *J* = 4.1 Hz, 1H), 7.02 (s, 2H), 3.88 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 153.3 (C_q), 148.3 (CH), 145.3 (CH), 144.4 (C_q), 139.9 (C_q), 134.5 (CH), 124.0 (C_q), 106.6 (CH), 60.9 (CH_3), 56.3 (CH_3).

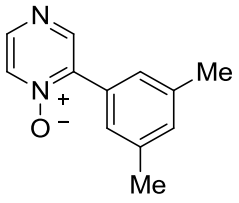
IR (KBr, cm^{-1}): 3416 (s), 3108 (m), 2949 (m), 2841 (m), 2146 (m), 1576 (s), 1298 (s), 1121 (s), 837 (s), 640 (m).

MS (EI) *m/z* (relative intensity): 262 ([M^+] 71), 247 (30), 215 (100), 173 (35), 105 (16).

HR-MS (EI) *m/z* for $C_{13}H_{14}N_2O_4$ calcd.: 262.0954.
found: 262.0948.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-(3,5-Dimethylphenyl)pyrazine *N*-oxide (28da)



28da

The general procedure **C** was followed, using 3,5-dimethylphenyl 4-methyl-benzenesulfonate (**20aa**) (138 mg, 0.50 mmol) and pyrazine *N*-oxide (**26d**) (96.9 mg, 1.01 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/2) yielded **28da** (52 mg, 51%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.56 (s, 1H), 8.33 (d, J = 4.1 Hz, 1H), 8.17 (dd, J = 4.1, 0.7 Hz, 1H), 7.40 – 7.31 (m, 2H), 7.12 (ddd, J = 2.2, 1.5, 0.7 Hz, 1H), 2.37 (d, J = 0.6 Hz, 6H).

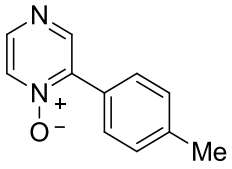
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 148.4 (CH), 145.3 (CH), 145.0 (C_q), 138.3 (C_q), 134.4 (CH), 132.1 (CH), 128.7 (C_q), 126.7 (CH), 21.3 (CH_3).

IR (KBr, cm^{-1}): 3012 (m), 2918 (s), 1603 (s), 1456 (s), 1390 (s), 1296 (s), 888 (s), 696 (s).
MS (EI) *m/z* (relative intensity): 200 ([M^+] 100), 171 (75), 132 (33), 88 (33), 47 (51).

HR–MS (EI) *m/z* for $C_{12}H_{12}N_2O$ calcd.: 200.0950.
found: 200.0942.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-(4-Methylphenyl)pyrazine *N*-oxide (28de)



28de

The general procedure **C** was followed, using 4-methylphenyl 4-methyl-benzenesulfonate (**20ae**) (131 mg, 0.50 mmol) and pyrazine *N*-oxide (**26d**) (96.0 mg, 1.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 10/1) yielded **28de** (37 mg, 40%) as a brown solid.

M. p.: 138.2–139.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.61 (s, 1H), 8.35 (d, J = 4.1 Hz, 1H), 8.19 (d, J = 4.1 Hz, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 2.42 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 148.3 (CH), 145.2 (CH), 144.7 (C_q), 140.8 (C_q), 134.4 (CH), 129.3 (CH), 129.0 (CH), 126.0 (C_q). 21.5 (CH_3).

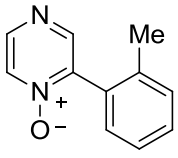
IR (KBr, cm^{-1}): 2361 (m), 1589 (s), 1457 (s), 1388 (m), 1320 (m), 1250 (m), 1007 (m), 869 (m), 822 (m).

MS (EI) *m/z* (relative intensity): 186 ([M^+] 100), 157 (70), 118 (29), 77 (17), 63 (23).

HR-MS (ESI) *m/z* for $C_{11}H_{10}N_2O+H^+$ calcd.: 187.0866.
found: 187.0865.

The analytical data are in accordance with those reported in the literature.[34]

Synthesis of 2-(2-Methylphenyl)pyrazine *N*-oxide (28df)



28df

The general procedure **C** was followed, using 2-methylphenyl 4-methyl-benzenesulfonate (**20af**) (131 mg, 0.50 mmol), pyrazine *N*-oxide (**26d**) (96.1 mg, 1.00 mmol), $Pd(OAc)_2$ (10 mol%) and X-Phos (**21**) (20 mol%). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 10/1) yielded **28df** (56 mg, 60%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.50 (s, 1H), 8.45 (d, J = 4.1 Hz, 1H), 8.22 (dd, J = 4.2, 0.8 Hz, 1H), 7.42 (m, 1H), 7.37 – 7.22 (m, 3H), 2.23 (s, 3H).

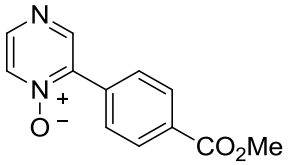
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 149.0 (CH), 146.3 (CH), 138.5 (C_q), 138.5 (C_q), 134.1 (CH), 130.4 (CH), 130.3 (CH), 129.7 (CH), 129.0 (C_q), 126.1 (CH), 19.4 (CH_3).

IR (film, cm^{-1}): 3456(s), 3058 (s), 2923 (m), 2595 (w), 2358 (w), 1924 (w), 1587 (m), 1308 (s), 762 (m).

MS (EI) *m/z* (relative intensity): 186 ([M^+] 26), 169 (100), 128 (12), 115 (16), 89 (6).

HR-MS (EI) *m/z* for $C_{11}H_{10}N_2O$ calcd.: 186.0793.
found: 186.0787.

Synthesis of 2-(4-Methoxycarbonylphenyl)pyrazine *N*-oxide (28dm)



28dm

The general procedure **C** was followed, using methyl-4-(tosyloxy)benzoate (**20am**) (153 mg, 0.50 mmol) and pyrazine *N*-oxide (**26d**) (96.5 mg, 1.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 6/1) yielded **28dm** (61 mg, 53%) as a pale yellow solid.

M. p.: 218–222 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.65 (s, 1H), 8.42 (d, J = 4.1 Hz, 1H), 8.24 – 8.14 (m, 3H), 7.93 – 7.86 (m, 2H), 3.95 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.2 (C_q), 148.3 (CH), 146.2 (CH), 143.7 (C_q), 134.5 (CH), 133.1 (C_q), 131.7 (C_q), 129.7 (CH), 129.2 (CH), 52.4 (CH_3).

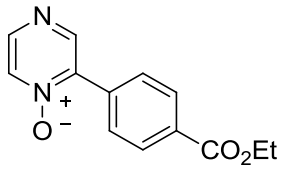
IR (KBr, cm^{-1}): 3070 (m), 3013 (m), 2576 (w), 1922 (w), 1719 (s), 1454 (m), 1286 (s), 1108 (m), 861 (m).

MS (EI) *m/z* (relative intensity): 230 ([M^+] 100), 202 (78), 183 (74), 143 (77), 75 (34).

HR-MS (EI) *m/z* for $C_{12}H_{10}N_2O_3$ calcd.: 230.0691.
found: 230.0694.

The analytical data are in accordance with those reported in the literature.[34]

Synthesis of 2-(4-Ethoxycarbonylphenyl)pyrazine *N*-oxide (28do)



28do

The general procedure **C** was followed, using ethyl-4-(tosyloxy)benzoate (**20at**) (160 mg, 0.50 mmol) and pyrazine *N*-oxide (**26d**) (96.4 mg, 1.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 7/1) yielded **28do** (69 mg, 57%) as a pale yellow solid.

M. p.: 160–162 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.65 (s, 1H), 8.42 (d, J = 4.1 Hz, 1H), 8.26 – 8.10 (m, 3H), 7.93 – 7.85 (m, 2H), 4.41 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.8 (C_q), 148.3 (CH), 146.2 (CH), 143.8 (C_q), 134.5 (CH), 133.0 (C_q), 132.1 (C_q), 129.7 (CH), 129.1 (CH), 61.3 (CH_2), 14.3 (CH_3).

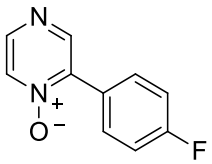
IR (KBr, cm^{-1}): 3413 (m), 3103 (m), 2992 (m), 1716 (s), 1459 (m), 1289 (s), 1111 (s), 1017 (s), 863 (s).

MS (EI) *m/z* (relative intensity): 244 ([M^+] 100), 216 (31), 199 (53), 171 (59), 143 (36), 89 (14).

HR-MS (EI) *m/z* for $C_{13}H_{12}N_2O_3$ calcd.: 244.0848.
found: 244.0840.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-(4-Fluorophenyl)pyrazine *N*-oxide (28di)



28di

The general procedure **C** was followed, using 4-fluorophenyl 4-methyl-benzenesulfonate (**20ai**) (133 mg, 0.50 mmol) and pyrazine *N*-oxide (**26d**) (96.2 mg, 1.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 10/1) yielded **28di** (45 mg, 48%) as a pale yellow solid.

M. p.: 174–175 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.59 (s, 1H), 8.37 (dd, J = 4.2, 1.3 Hz, 1H), 8.17 (m, 1H), 7.87 – 7.74 (m, 2H), 7.25 – 7.14 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.7 (C_q, J = 252 Hz), 148.13 (CH), 145.7 (CH), 143.7 (C_q), 134.5 (CH), 131.3 (CH, J = 9 Hz), 124.9 (C_q, J = 3 Hz), 115.9 (CH, J = 22 Hz).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 108.9 (tt, J = 8.9, 4.7 Hz).

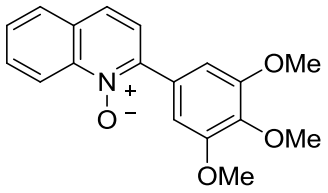
IR (KBr, cm^{-1}): 3104 (m), 3053 (m), 2577 (w), 2162 (w), 1910 (w), 1587 (s), 1248 (m), 1010 (m), 843 (m).

MS (EI) *m/z* (relative intensity): 190 ([M^+] 100), 162 (28), 121 (17), 107 (16), 75 (8).

HR-MS (EI) *m/z* for $C_{10}H_7FN_2O$ calcd.: 190.0542.
found: 190.0537.

The analytical data are in accordance with those reported in the literature.[34]

Synthesis of 2-(3,4,5-Trimethoxyphenyl)quinoline *N*-oxide (28bb)



28bb

The general procedure **C** was followed, using 3,4,5-trimethoxyphenyl 4-methyl-benzenesulfonate (**20ab**) (169 mg, 0.50 mmol) and quinoline *N*-oxide (**26b**) (148 mg, 1.02 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 5/1) yielded **28bb** (107 mg, 69%) as an orange solid.

M. p.: 137–139 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.83 (d, J = 8.7 Hz, 1H), 7.91 – 7.67 (m, 3H), 7.63 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.23 (s, 2H), 3.90 (s, 3H), 3.90 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 153.0 (C_q), 144.8 (C_q), 142.3 (C_q), 139.2 (C_q), 130.6 (CH), 129.4 (C_q), 128.7 (C_q), 128.4 (CH), 127.9 (CH), 125.2 (CH), 123.3 (CH), 120.2 (CH), 107.2 (CH), 60.9 (CH_3), 56.3 (CH_3).

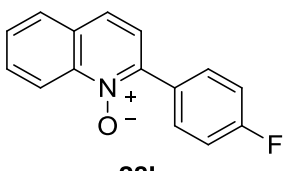
IR (KBr, cm^{-1}): 2931 (m), 1585 (s), 1499 (s), 1335 (s), 1127 (s), 999 (m), 823 (m).

MS (EI) *m/z* (relative intensity): 311 ([M^+] 14), 268 (11), 168 (100), 118 (42), 51 (31).

HR-MS (ESI) *m/z* for $C_{18}H_{17}NO_4+H^+$ calcd.: 312.1230.
found: 312.1242.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-(4-Fluorophenyl)quinoline *N*-oxide (28bp)



28bp

The general procedure **C** was followed, using 4-fluorophenyl 4-methyl-benzenesulfonate (**20ai**) (133 mg, 0.50 mmol) and quinoline *N*-oxide (**26b**) (145 mg, 1.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 10/1) yielded **28bp** (60 mg, 50%) as a light yellow solid.

M. p.: 162–164 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.84 (d, J = 8.6 Hz, 1H), 8.06 – 7.95 (m, 2H), 7.91 – 7.72 (m, 3H), 7.65 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.29 – 7.13 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.1 (C_q, J = 250 Hz), 143.9 (C_q), 142.2 (C_q), 131.6 (CH, J = 9 Hz), 130.6 (CH), 129.5 (C_q), 129.3 (C_q, J = 4 Hz), 128.4 (CH), 127.9 (CH), 125.2 (CH), 122.9 (CH), 120.2 (CH), 115.3 (CH, J = 22 Hz).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 110.6 (tt, J = 8.5, 5.4 Hz).

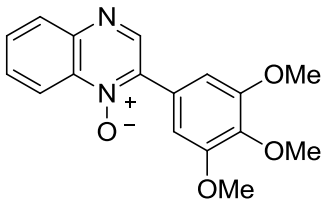
IR (KBr, cm^{-1}): 3066 (m), 3034 (m), 2361 (m), 1599 (s), 1501 (s), 1327 (s), 1234 (s), 1096 (m), 889 (m), 740 (s).

MS (EI) *m/z* (relative intensity): 239 ([M^+] 74), 210 (21), 183 (11), 128 (17), 75 (12).

HR-MS (ESI) *m/z* for $C_{15}H_{10}FNO+H^+$ calcd.: 240.0819.
found: 240.0819.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-(3,4,5-Trimethoxyphenyl)quinoxaline *N*-oxide (28eb)



28eb

The general procedure **C** was followed, using 3,4,5-trimethoxyphenyl 4-methyl-benzenesulfonate (**20ab**) (169 mg, 0.50 mmol) and quinoxaline *N*-oxide (**26e**) (146 mg, 1.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2 → CH_2Cl_2/acetone: 40/1 → 30/1) yielded **28eb** (120 mg, 77%) as a yellow solid.

M. p.: 124–126 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.90 (s, 1H), 8.67 (m, 1H), 8.14 (m, 1H), 7.89 – 7.69 (m, 2H), 7.25 (s, 2H), 3.93 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 153.3 (C_q), 147.3 (CH), 144.3 (C_q), 140.0 (C_q), 139.1 (C_q), 137.4 (C_q), 131.1 (CH), 130.5 (CH), 130.0 (CH), 125.0 (C_q), 119.3 (CH), 107.0 (CH), 60.9 (CH_3), 56.4 (CH_3).

IR (KBr, cm^{-1}): 3116 (w), 2931 (m), 2834 (m), 2361 (w), 1960 (w), 1586 (s), 1348 (s), 1138 (s), 845 (m).

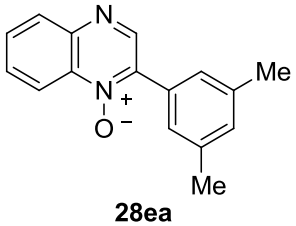
MS (EI) *m/z* (relative intensity): 312 ([M^+] 67), 265 (100), 223 (27), 155 (27), 49 (23).

HR-MS (EI) *m/z* for $C_{17}H_{16}N_2O_4$ calcd.: 312.1110.
found: 312.1102.

The analytical data are in accordance with those reported in the literature.[128]

The analogous reaction using 3,4,5-trimethoxyphenyl methanesulfonate (**20bb**) (131 mg, 0.50 mmol), quinoxaline *N*-oxide (**26e**) (146 mg, 1.90 mmol), $Pd(OAc)_2$ (10 mol%) and X-Phos (**21**) (20 mol%) yielded **28eb** (82 mg, 53%) as a yellow solid.

Synthesis of 2-(3,5-Dimethylphenyl)quinoxaline *N*-oxide (28ea)



28ea

The general procedure **C** was followed, using 3,5-dimethylphenyl 4-methyl-benzenesulfonate (**20aa**) (138 mg, 0.50 mmol) and quinoxaline *N*-oxide (**26e**) (146 mg, 1.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2) yielded **28ea** (64 mg, 51%) as an orange solid.

M. p.: 107–109 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.87 (s, 1H), 8.69 (m, 1H), 8.13 (m, 1H), 7.89 – 7.66 (m, 2H), 7.64 – 7.48 (m, 2H), 7.16 (dd, *J* = 1.4, 0.7 Hz, 1H), 2.42 (d, *J* = 0.7 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 147.5 (CH), 144.3 (C_q), 139.6 (C_q), 138.2 (C_q), 137.4 (C_q), 132.0 (CH), 130.9 (CH), 130.3 (CH), 129.9 (CH), 129.7 (C_q), 126.9 (CH), 119.3 (CH), 21.5 (CH_3).

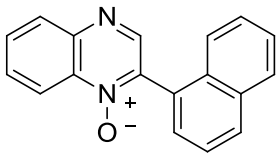
IR (KBr, cm^{-1}): 3058 (m), 2911 (s), 2856 (m), 1926 (w), 1601 (m), 1348 (s), 1087 (m), 854 (m), 756 (m).

MS (EI) *m/z* (relative intensity): 250 ([M^+] 100), 221 (64), 207 (34), 129 (10), 77 (11).

HR-MS (EI) *m/z* for $C_{16}H_{14}N_2O$ calcd.: 250.1106.
found: 250.1098.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-(1-Naphtyl)quinoxaline *N*-oxide (28eg)



28eg

The general procedure **C** was followed, using 1-naphtyl 4-methyl-benzenesulfonate (**20ag**) (149 mg, 0.50 mmol) and quinoxaline *N*-oxide (**26e**) (220 mg, 1.50 mmol). After 20 h, purification by column chromatography (CH_2Cl_2 → CH_2Cl_2/acetone: 100/1) yielded **28eg** (99 mg, 73%) as a light yellow solid.

M. p.: 139–140 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.86 (s, 1H), 8.71 (m, 1H), 8.22 (m, 1H), 8.04 (dd, *J* = 6.6, 2.9 Hz, 1H), 7.95 (d, *J* = 7.4 Hz, 1H), 7.92 – 7.75 (m, 2H), 7.70 – 7.38 (m, 5H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.3 (CH), 145.1 (C_q), 140.1 (C_q), 137.4 (C_q), 133.4 (C_q), 131.4 (CH), 130.8 (CH), 130.7 (C_q), 130.3 (CH), 130.1 (CH), 128.7 (CH), 128.5 (CH), 128.1 (C_q), 127.1 (CH), 126.4 (CH), 125.3 (CH), 125.0 (CH), 119.4 (CH).

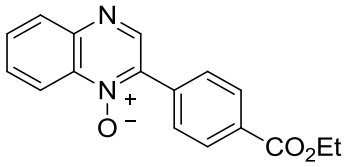
IR (KBr, cm^{-1}): 3054 (s), 2927 (m), 1575 (m), 1487 (m), 1350 (s), 1327 (s), 1099 (m), 899 (m), 778 (s).

MS (EI) *m/z* (relative intensity): 272 ([M^+] 99), 244 (100), 217(10), 115 (21), 76 (9).

HR-MS (ESI) *m/z* for $C_{18}H_{12}N_2O+H^+$ calcd.: 273.1022.
found: 273.1025.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-{4-(Ethoxycarbonyl)phenyl}quinoxaline *N*-oxide (28eo)



28eo

The general procedure **C** was followed, using ethyl-4-(tosyloxy)benzoate (**20at**) (160 mg, 0.50 mmol) and quinoxaline *N*-oxide (**26e**) (146 mg, 1.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 40/1) yielded **28eo** (100 mg, 68%) as a yellow solid.

M. p.: 215–217 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.89 (s, 1H), 8.67 (m, 1H), 8.26 – 8.17 (m, 2H), 8.13 (m, 1H), 8.09 – 8.00 (m, 2H), 7.88 – 7.72 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

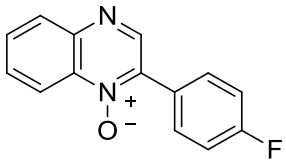
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 165.7 (C_q), 147.0 (CH), 144.6 (C_q), 138.4 (C_q), 137.3 (C_q), 134.0 (C_q), 131.8 (C_q), 131.4 (CH), 130.6 (CH), 130.0 (CH), 129.6 (CH), 129.3 (CH), 119.3 (CH), 61.3 (CH_2), 14.4 (CH_3).

IR (KBr, cm^{-1}): 3044 (w), 2978 (w), 1717 (s), 1489 (m), 1280 (s), 1128 (m), 901 (m), 774 (m), 703 (m).

MS (EI) *m/z* (relative intensity): 294 ([M^+] 100), 265 (32), 221 (26), 193 (27), 168 (8), 102 (8).

HR-MS (ESI) *m/z* for $C_{17}H_{14}N_2O_3$+Na^+ calcd.: 317.0897.
found: 317.0904.

Synthesis of 2-(4-Fluorophenyl)quinoxaline *N*-oxide (28ei)



28ei

The general procedure **C** was followed, using 4-fluorophenyl 4-methyl-benzenesulfonate (**20ai**) (133 mg, 0.50 mmol) and quinoxaline *N*-oxide (**26d**) (146 mg, 1.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2) yielded **28ei** (69 mg, 58%) as an orange solid.

M. p.: 162–164 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.87 (s, 1H), 8.65 (m, 1H), 8.12 (m, 1H), 8.04 – 7.96 (m, 2H), 7.85 – 7.72 (m, 2H), 7.29 – 7.19 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.6 (C_q, J = 252 Hz), 147.1 (CH), 144.5 (C_q), 138.4 (C_q), 137.4 (C_q), 131.6 (CH, J = 9 Hz), 131.2 (CH), 130.6 (CH), 130.0 (CH), 126.0 (C_q, J = 4 Hz), 119.3 (CH), 115.9 (CH, J = 22 Hz).

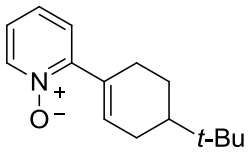
^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 108.9 (tt, J = 8.4, 5.3 Hz).

IR (KBr, cm^{-1}): 3110 (w), 1598 (s), 1487 (s), 1330 (s), 1236 (s), 1064 (m), 835 (s).

MS (EI) *m/z* (relative intensity): 240 ([M^+] 91), 211 (40), 120 (22), 76 (30).

HR-MS (EI) *m/z* for $C_{14}H_9FN_2O$ calcd.: 240.0699.
found: 240.0693.

Synthesis of 2-{4-(*tert*-Butyl)cyclohex-1-en-1-yl}pyridine *N*-oxide (28ap)



28ap

The general procedure **C** was followed, using 4-(*tert*-butyl)cyclohex-1-en-1-yl 4-methylbenzenesulfonate (**20ap**) (138 mg, 0.50 mmol) and pyridine *N*-oxide (**26aa**) (191 mg, 2.01 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/1 → CH_2Cl_2/acetone/MeOH: 86/86/1) yielded **28ap** (19 mg, 16%) as a light yellow solid.

M. p.: 115–116 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.17 (ddd, J = 6.3, 6.3, 1.0 Hz, 1H), 7.24 – 7.06 (m, 2H), 6.17 (m, 1H), 2.56 (ddq, J = 7.8, 3.9, 1.9 Hz, 2H), 2.33 – 2.18 (m, 1H), 2.09 – 1.88 (m, 2H), 1.53 – 1.21 (m, 3H), 0.89 (s, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 152.1 (C_q), 140.0 (CH), 133.4 (C_q), 132.1 (CH), 126.0 (CH), 125.4 (CH), 123.7 (CH), 43.5 (CH), 32.3 (C_q), 27.5 (CH_2), 27.3 (CH_2), 27.2 (CH_3), 23.8 (CH_2).

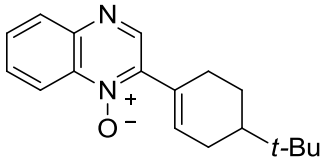
IR (KBr, cm^{-1}): 3371 (s), 3066 (w), 2950 (s), 2361 (m), 1648 (m), 1428 (m), 1233 (s), 833 (m), 585 (m).

MS (EI) *m/z* (relative intensity): 231 ([M^+] 100), 174 (61), 146 (93), 119 (47), 57 (36).

HR-MS (EI) *m/z* for $C_{15}H_{21}NO$ calcd.: 231.1623.
found: 231.1615.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-{4-(*tert*-Butyl)cyclohex-1-en-1-yl}quinoxaline *N*-oxide (28ep)



28ep

The general procedure **C** was followed, using 4-(*tert*-butyl)cyclohexene-2-yl 4-methyl-benzenesulfonate (**20ap**) (155 mg, 0.50 mmol) and quinoxaline *N*-oxide (**26e**) (220 mg, 1.50 mmol). After 20 h, purification by column chromatography (CH_2Cl_2 → CH_2Cl_2/acetone: 100/1 → 50/1) yielded **28ep** (69 mg, 51%) as an orange solid.

M. p.: 153–155 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.67 (s, 1H), 8.65 – 8.56 (m, 1H), 8.15 – 8.02 (m, 1H), 7.81 – 7.68 (m, 2H), 6.49 (dd, *J* = 4.9, 2.4 Hz, 1H), 2.81 – 2.54 (m, 2H), 2.36 (dt, *J* = 18.8, 5.2 Hz, 1H), 2.20 – 1.92 (m, 2H), 1.60 – 1.22 (m, 2H), 0.93 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 146.8 (CH), 144.2 (C_q), 141.9 (C_q), 137.2 (C_q), 134.9 (CH), 130.6 (C_q), 130.5 (CH), 130.1 (CH), 129.7 (CH), 118.9 (CH), 43.5 (CH), 32.4 (C_q), 27.8 (CH_2), 27.2 (CH_3), 27.1 (CH_2), 23.8 (CH_2).

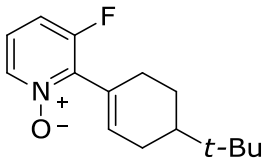
IR (KBr, cm^{-1}): 3123 (w), 2959 (m), 1574 (s), 1487 (s), 1343 (s), 1124 (s), 765 (s).

MS (EI) *m/z* (relative intensity): 282 ([M^+] 69), 225 (33), 197 (100), 169 (46), 129 (21), 57 (23).

HR-MS (ESI) *m/z* for $C_{18}H_{22}N_2O+H^+$ calcd.: 283.1805.
found: 283.1805.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-{4-(*tert*-Butyl)cyclohex-1-enyl}-3-fluoropyridine *N*-oxide (28abp)



28abp

The general procedure **C** was followed, using 4-(*tert*-butyl)cyclohex-1-enyl 4-methyl-benzene-sulfonate (**20ap**) (154 mg, 0.50 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/1) yielded **28abp** (97 mg, 78%) as a yellow solid.

M. p.: 144–145 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.06 (m, 1H), 7.16 – 6.89 (m, 2H), 5.96 (d, J = 2.7 Hz, 1H), 2.47 – 2.36 (m, 2H), 2.25 (m, 1H), 2.11 – 1.83 (m, 2H), 1.59 – 1.29 (m, 2H), 0.89 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.9 (C_q, J = 249 Hz), 143.0 (C_q, J = 27 Hz), 136.2 (CH, J = 4 Hz), 133.8 (CH, J = 3 Hz), 125.8 (C_q, J = 2 Hz), 122.5 (CH, J = 10 Hz), 113.1 (CH, J = 23 Hz), 43.2 (CH), 32.3 (C_q), 27.1 (CH_2), 27.0 (CH_3), 26.6 (CH_2), 23.5 (CH_2).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 117.4 (t, J = 6.8 Hz).

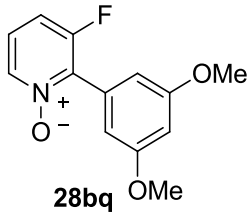
IR (KBr, cm^{-1}): 3045 (m), 1550 (s), 1479 (s), 1366 (m), 1228 (s), 1031 (s), 787 (s).

MS (EI) *m/z* (relative intensity): 249 ([M^+] 4), 176 (100), 148 (67), 111 (20), 57 (54).

HR-MS (ESI) *m/z* for $C_{15}H_{20}FNO+H^+$ calcd.: 250.1602.
found: 250.1604.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-(3,5-Dimethoxyphenyl)-3-fluoropyridine *N*-oxide (28bq)



28bq

The general procedure **C** was followed, using 3,5-dimethoxyphenyl methanesulfonate (**20bq**) (116 mg, 0.50 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (225 mg, 1.99 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/1) yielded **28bq** (97 mg, 78%) as a pale yellow solid.

M. p.: 111–113 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.18 (dt, J = 6.4, 1.1 Hz, 1H), 7.23 – 7.06 (m, 2H), 6.69 (dd, J = 2.3, 1.0 Hz, 2H), 6.55 (dd, J = 2.3 Hz, 1H), 3.79 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.7 (C_q), 158.3 (C_q, J = 252 Hz), 140.7 (C_q, J = 24 Hz), 136.7 (CH, J = 4 Hz), 127.9 (C_q, J = 2 Hz), 123.6 (CH, J = 10 Hz), 113.3 (CH, J = 23 Hz), 107.9 (CH, J = 2 Hz), 102.5 (CH), 55.4 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - (115.7 – 115.8) (m).

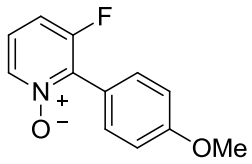
IR (KBr, cm^{-1}): 3050 (m), 1597 (s), 1421 (s), 1345 (s), 1157 (s), 1033 (s), 843 (s).

MS (EI) *m/z* (relative intensity): 233 (100), 203 (18), 173 (15), 147 (18), 87 (15).

HR-MS (ESI) *m/z* for $C_{13}H_{12}FNO_3+H^+$ calcd.: 250.0874.
found: 250.0879.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 3-Fluoro-2-(4-methoxyphenyl)pyridine *N*-oxide (28bc)



28bc

The general procedure **C** was followed, using 4-methoxyphenyl methanesulfonate (**20bc**) (101 mg, 0.50 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (169 mg, 1.50 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/1) yielded **28bc** (68 mg, 62%) as a pale yellow solid.

M. p.: 138–140 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.19 (m, 1H), 7.65 – 7.54 (m, 2H), 7.20 – 6.94 (m, 4H), 3.85 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 160.6 (C_q), 158.2 (C_q, J = 250 Hz), 140.4 (C_q, J = 25 Hz), 136.6 (CH, J = 3 Hz), 131.6 (CH, J = 2 Hz), 122.8 (CH, J = 11 Hz), 118.2 (C_q, J = 2 Hz), 114.4 (CH), 113.2 (CH, J = 23 Hz), 55.4 (CH_3).

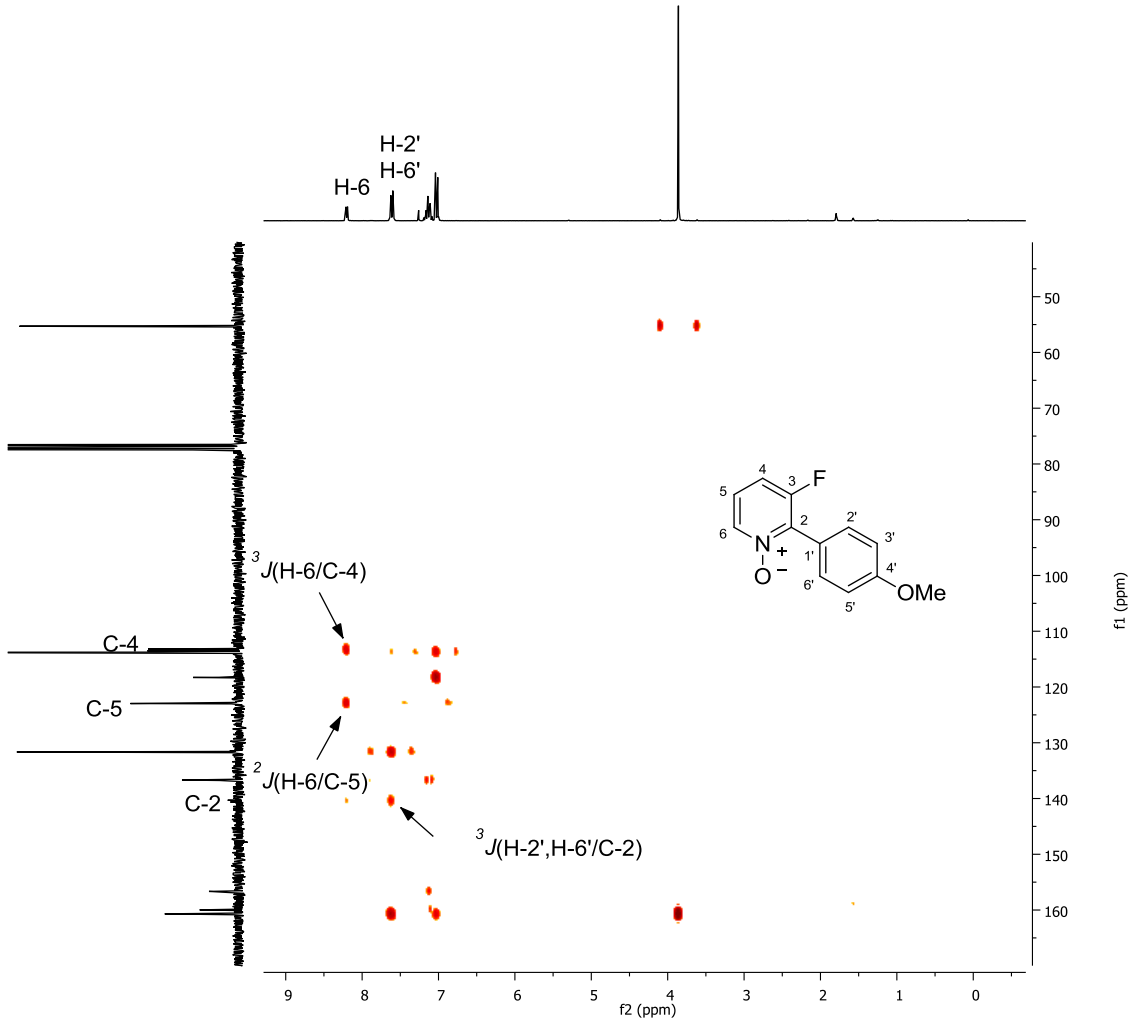
^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 116.6 (ddd, J = 7.1, 7.1, 1.6 Hz).

IR (KBr, cm^{-1}): 3009 (s), 2971 (s), 1577 (m), 1234 (s), 1129 (s), 833 (s), 725 (s).

MS (EI) *m/z* (relative intensity): 219 ([M^+] 6), 203 (100), 188 (33), 107 (9), 63 (7).

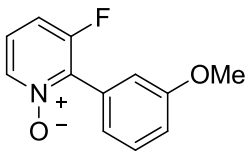
HR-MS (ESI) *m/z* for $C_{12}H_{10}FNO_2$-H^+ calcd.: 218.0623.
found: 218.0623.

HMBC-NMR:



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

Synthesis of 3-Fluoro-2-(3-methoxyphenyl)pyridine *N*-oxide (28br)



28br

The general procedure **C** was followed, using 3-methoxyphenyl methanesulfonate (**20br**) (125 mg, 0.62 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 4/1 → 3/1) yielded **28br** (95 mg, 70%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.19 (dt, *J* = 6.4, 1.2 Hz, 1H), 7.41 (m, 1H), 7.23 – 7.06 (m, 4H), 7.00 (ddd, *J* = 8.4, 2.5, 1.2 Hz, 1H), 3.81 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 159.3 (C_q), 158.2 (C_q, *J* = 251 Hz), 140.5 (C_q, *J* = 26 Hz), 136.6 (CH, *J* = 4 Hz), 129.4 (CH), 127.4 (C_q, *J* = 2 Hz), 123.5 (CH, *J* = 11 Hz), 122.3 (CH, *J* = 3 Hz), 116.0 (CH), 115.3 (CH, *J* = 2 Hz), 113.3 (CH, *J* = 23 Hz), 55.4 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 120.0 (td, *J* = 7.0, 1.2 Hz).

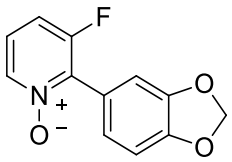
IR (film, cm^{-1}): 3112 (m), 3071 (m), 2837 (m), 2322 (w), 1584 (s), 1418 (s), 1030 (s), 791 (s).

MS (EI) *m/z* (relative intensity): 219 ([M^+] 50), 204 (94), 176 (76), 148 (100), 96 (14).

HR-MS (ESI) *m/z* for $C_{12}H_{10}FNO_2$+Na^+ calcd.: 242.0588.
found: 242.0590.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-(Benzo[*d*]-[1,3]dioxol-5'-yl)-3-fluoropyridine *N*-oxide (28bs)



28bs

The general procedure **C** was followed, using benzo[*d*]-[1,3]dioxol-5'-yl methanesulfonate (**20bs**) (113 mg, 0.52 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 4/1) yielded **28bs** (78 mg, 64%) as an orange solid.

M. p.: 156–158 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.18 (m, 1H), 7.20 – 7.01 (m, 4H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.00 (s, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 158.2 (C_q, *J* = 251 Hz), 148.9 (C_q), 147.5 (C_q), 140.2 (C_q, *J* = 25 Hz), 136.6 (CH, *J* = 3 Hz), 124.6 (CH, *J* = 3 Hz), 123.1 (CH, *J* = 11 Hz), 119.3 (C_q, *J* = 2 Hz), 113.3 (CH, *J* = 23 Hz), 110.4 (CH), 108.3 (CH), 101.4 (CH_2).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = **-** 120.1 (ddd, *J* = 8.5, 2.6, 1.2 Hz).

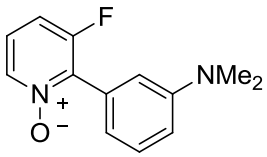
IR (KBr, cm^{-1}): 3050 (s), 2899 (s), 2507 (w), 1472 (s), 1234 (s), 1037 (s), 816 (s).

MS (EI) *m/z* (relative intensity): 233 ([M^+] 84), 217 (100), 147 (85), 122 (29), 63 (16).

HR-MS (ESI) *m/z* for $C_{12}H_8FNO_2$+Na^+ calcd.: 256.0380.
found: 256.0381.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-{3-(*N*,*N*-Dimethylamino)phenyl}-3-fluoropyridine *N*-oxide (28bd)



28bd

The general procedure **C** was followed, using 3-(*N*,*N*-dimethylamino)phenyl methanesulfonate (**20bd**) (108 mg, 0.50 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 1/2) yielded **28bd** (95 mg, 82%) as a yellow solid.

M. p.: 89–91 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.21 (dt, *J* = 6.3, 1.2 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.23 – 7.07 (m, 2H), 6.93 – 6.80 (m, 3H), 2.97 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.4 (C_q, *J* = 251 Hz), 150.4 (C_q), 141.5 (C_q, *J* = 86 Hz), 136.7 (CH, *J* = 3 Hz), 129.1 (CH), 127.0 (C_q, *J* = 2 Hz), 123.3 (CH, *J* = 10 Hz), 117.7 (CH, *J* = 2 Hz), 114.1 (CH), 113.5 (CH, *J* = 2 Hz), 113.3 (CH, *J* = 23 Hz), 40.5 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - (115.7 – 115.8) (m).

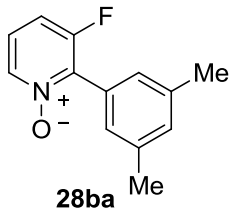
IR (KBr, cm^{-1}): 3078 (w), 2887 (s), 2806 (s), 1604 (s), 1355 (m), 1233 (s), 1031 (s), 788 (s), 688 (w).

MS (EI) *m/z* (relative intensity): 232 ([M^+] 9), 216 (100), 200 (43), 172 (34), 93 (16).

HR-MS (ESI), *m/z* for $C_{13}H_{13}FN_2O+H^+$ calcd.: 233.1085.
found: 233.1087.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-(3,5-Dimethylphenyl)-3-fluoropyridine *N*-oxide (28ba)



28ba

The general procedure **C** was followed, using 3,5-dimethylphenyl methanesulfonate (**20ba**) (100 mg, 0.50 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 2/1) yielded **28ba** (78 mg, 72%) as a yellow solid.

M. p.: 84–85 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.18 (dd, J = 6.3, 1.1 Hz, 1H), 7.23 – 7.02 (m, 5H), 2.35 (s, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 158.2 (C_q, J = 251 Hz), 141.1 (C_q, J = 25 Hz), 137.9 (C_q), 136.6 (CH, J = 4 Hz), 131.7 (CH), 127.4 (CH, J = 2 Hz), 126.1 (C_q, J = 2 Hz), 123.2 (CH, J = 10 Hz), 113.2 (CH, J = 23 Hz), 21.4 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 116.2 (dd, J = 10.1, 3.8 Hz).

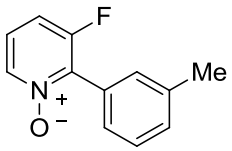
IR (KBr, cm^{-1}): 3111 (m), 2862 (m), 1609 (m), 1419 (s), 1290 (s), 1033 (s), 790 (m).

MS (EI) *m/z* (relative intensity): 217 ([M^+] 7), 201 (100), 184 (50), 105 (7), 77 (7).

HR-MS (ESI) *m/z* for $C_{13}H_{12}FNO+H^+$ calcd.: 218.0976.
found: 218.0983.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 3-Fluoro-2-(3-methylphenyl)pyridine *N*-oxide (28bt)



28bt

The general procedure **C** was followed, using 3-methylphenyl methanesulfonate (**20bt**) (95.5 mg, 0.51 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 4/1) yielded **28bt** (72 mg, 69%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.19 (dt, J = 6.3, 1.2 Hz, 1H), 7.46 – 7.01 (m, 6H), 2.39 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 158.2 (C_q, J = 251 Hz), 140.8 (C_q, J = 25 Hz), 137.9 (C_q), 136.6 (CH, J = 4 Hz), 130.7 (CH), 130.4 (CH, J = 2 Hz), 128.2 (CH), 127.0 (CH, J = 3 Hz), 126.2 (C_q, J = 2 Hz), 123.3 (CH, J = 11 Hz), 113.3 (CH, J = 23 Hz), 21.5 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = **-** (120.1 – 120.2) (m).

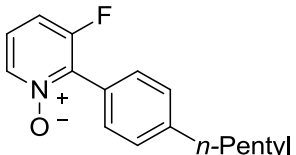
IR (film, cm^{-1}): 3113 (m), 3064 (m), 1616 (m), 1588 (m), 1430 (s), 1279 (m), 1237 (s), 793 (s).

MS (EI) *m/z* (relative intensity): 203 ([M^+] 63), 174 (100), 135 (39), 96 (9), 51 (11).

HR-MS (ESI) *m/z* for $C_{13}H_{10}FNO$-H^+ calcd.: 202.0674.
found: 202.0669.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 3-Fluoro-2-(4-*n*-pentylphenyl)pyridine *N*-oxide (28bu)



28bu

The general procedure **C** was followed, using 4-*n*-pentylphenyl methanesulfonate (**20bu**) (127 mg, 0.52 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 4/1 → 3/1 → 2/1) yielded **28bu** (90 mg, 66%) as a yellow solid.

M. p.: 88–90 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.19 (dt, *J* = 6.2, 1.2 Hz, 1H), 7.52 (dd, *J* = 8.2, 1.5 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.21 – 7.03 (m, 2H), 2.72 – 2.54 (m, 2H), 1.73 – 1.53 (m, 2H), 1.33 (m, 4H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 158.3 (C_q, *J* = 251 Hz), 145.1 (C_q), 140.8 (C_q, *J* = 25 Hz), 136.7 (CH, *J* = 4 Hz), 129.9 (CH, *J* = 3 Hz), 128.3 (CH), 123.4 (C_q, *J* = 2 Hz), 123.2 (CH, *J* = 11 Hz), 113.3 (CH, *J* = 23 Hz), 35.9 (CH_2), 31.5 (CH_2), 30.8 (CH_2), 22.5 (CH_2), 14.0 (CH_3).

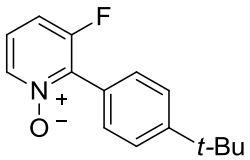
^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 116.4 (td, *J* = 7.2, 1.2 Hz).

IR (KBr, cm^{-1}): 3042 (m), 2930 (s), 2859 (s), 1910 (w), 1472 (s), 1033 (s), 787 (s), 723 (s).
MS (EI) *m/z* (relative intensity): 259 ([M^+] 3), 243 (25), 186 (100), 135 (7), 93 (2).

HR-MS (ESI) *m/z* for $C_{16}H_{18}FNO+H^+$ calcd.: 260.1445.
found: 260.1442.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-{4-(*tert*-Butyl)phenyl}-3-fluoropyridine *N*-oxide (28bv)



28bv

The general procedure **C** was followed, using 4-(*tert*-butyl)phenyl methanesulfonate (**20bv**) (111 mg, 0.49 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 2/1) yielded **28bv** (83 mg, 69 %) as a yellow solid.

M. p.: 118–120 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.20 (m, 1H), 7.62 – 7.46 (m, 4H), 7.21 – 7.04 (m, 2H), 1.33 (s, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 158.3 (C_q, *J* = 251 Hz), 153.0 (C_q), 140.6 (C_q, *J* = 25 Hz), 136.6 (CH, *J* = 4 Hz), 129.7 (CH, *J* = 3 Hz), 125.2 (CH), 123.2 (C_q, *J* = 2 Hz), 123.1 (CH, *J* = 11 Hz), 113.3 (CH, *J* = 23 Hz), 34.9 (C_q), 31.2 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = **-** 120.4 (ddd, *J* = 7.1, 7.0, 1.4 Hz).

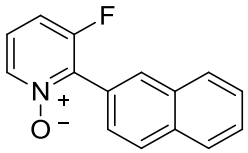
IR (KBr, cm^{-1}): 3047 (s), 2965 (s), 1912 (m), 1468 (s), 1234 (s), 1033 (s), 836 (s), 789 (s), 695.

MS (EI) *m/z* (relative intensity): 245 ([M^+] 2), 214 (100), 185 (21), 93 (15).

HR-MS (ESI) *m/z* for $C_{15}H_{16}FNO$-H^+ calcd.: 244.1143.
found: 244.1140.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 3-Fluoro-2-(2-naphtyl)pyridine *N*-oxide (28bx)



28bx

The general procedure **C** was followed, using 2-naphtyl methanesulfonate (**20bx**) (111 mg, 0.50 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 2/1) yielded **28bx** (85 mg, 71%) as a pale yellow solid.

M. p.: 179–181 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.24 (dt, *J* = 6.2, 1.2 Hz, 1H), 8.09 (s, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.92 – 7.82 (m, 2H), 7.75 – 7.67 (m, 1H), 7.59 – 7.46 (m, 2H), 7.18 (tdd, *J* = 8.7, 7.5, 3.6 Hz, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 158.4 (C_q, J = 251 Hz), 140.6 (C_q, J = 25 Hz), 136.7 (CH, J = 4 Hz), 133.7 (C_q), 132.7 (C_q), 130.4 (CH, J = 3 Hz), 128.4 (CH), 127.8 (CH), 127.6 (CH), 127.2 (CH), 126.5 (CH, J = 2 Hz), 126.2 (CH), 123.7 (C_q, J = 2 Hz), 123.5 (CH, J = 11 Hz), 113.4 (CH, J = 23 Hz).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - (116.3 – 116.4) (m).

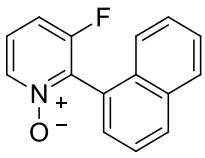
IR (KBr, cm^{-1}): 3052 (m), 1548 (m), 1425 (s), 1267 (s), 1228 (s), 1029 (s), 753 (s).

MS (EI) *m/z* (relative intensity): 223 (100), 194(5), 175 (6), 111 (36), 97 (7).

HR-MS (ESI) *m/z* for $C_{15}H_{10}FNO+H^+$ calcd.: 240.0819.
found: 240.0823.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 3-Fluoro-2-(1-naphtyl)pyridine *N*-oxide (28bg)



28bg

The general procedure **C** was followed, using 1-naphtyl methanesulfonate (**20bg**) (132 mg, 0.59 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 4/1 → 3/1 →2/1) yielded **28bg** (93 mg, 66%) as a yellow solid.

M. p.: 159–160 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.31 (dt, J = 6.5, 1.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.93 (dd, J = 7.2, 1.9 Hz, 1H), 7.66 – 7.39 (m, 5H), 7.39 – 7.17 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.1 (C_q, J = 252 Hz), 140.3 (C_q, 27 Hz), 136.8 (CH, J = 4 Hz), 133.6 (C_q), 130.9 (C_q), 130.7 (CH), 128.7 (CH), 128.6 (CH, J = 2 Hz), 127.0 (CH), 126.3 (CH), 125.3 (CH), 124.5 (CH), 124.4 (C_q, J = 2 Hz), 124.2 (CH, J = 11 Hz), 113.0 (CH, J = 23 Hz).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 114.3 (t, J = 7.2 Hz).

IR (KBr, cm^{-1}): 3051 (s), 1925 (w), 1552 (s), 1428 (s), 1241 (s), 1033 (s), 783 (s).

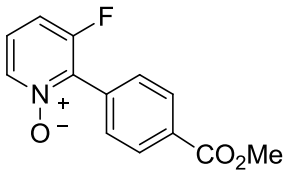
MS (EI) *m/z* (relative intensity): 239 ([M^+] 6), 222 (100), 175 (6), 110 (20).

HR-MS (ESI) *m/z* for $C_{15}H_{10}FNO+H^+$ calcd.: 240.0819.
found: 240.0825.

The analytical data are in accordance with those reported in the literature.[128]

The analogous reaction using 1-naphtyl 4-methylbenzenesulfonate (**20ag**) (149 mg, 0.50 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol) yielded **28bg** (98 mg, 82%) as a yellow solid.

Synthesis of 3-Fluoro-2-(4-methoxycarbonylphenyl)pyridine *N*-oxide (28bm)



28bm

The general procedure **C** was followed, using methyl-4-(methylsulfonyloxy)benzoate (**20bm**) (115 mg, 0.50 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 2/1) yielded **28bm** (71 mg, 57%) as a yellow solid.

M. p.: 164–166 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.20 (dt, J = 6.5, 1.1 Hz, 1H), 8.18 – 8.11 (m, 2H), 7.74 – 7.66 (m, 2H), 7.28 – 7.08 (m, 2H), 3.92 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.3 (C_q), 158.2 (C_q, J = 252 Hz), 139.6 (C_q, J = 25 Hz), 136.7 (CH, J = 4 Hz), 131.3 (C_q), 130.7 (C_q, J = 2 Hz), 130.2 (CH, J = 3 Hz), 129.3 (CH), 124.0 (CH, J = 11 Hz), 113.4 (CH, J = 23 Hz), 52.3 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - (116.2 – 116.3) (m).

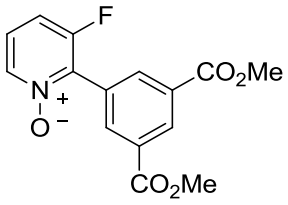
IR (KBr, cm^{-1}): 2954 (m), 1724 (s), 1516 (m), 1436 (s), 1282 (s), 1113 (s), 724 (s).

MS (EI) *m/z* (relative intensity): 247 ([M^+] 2), 231 (60), 200 (100), 172 (56), 86 (19).

HR-MS (ESI) *m/z* for $C_{13}H_{10}FNO_3+H^+$ calcd.: 248.0717.
found: 248.0723.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-{3,5-Bis(methoxycarbonyl)phenyl}-3-fluoropyridine *N*-oxide (28by)



28by

The general procedure **C** was followed, using 3,5-bis(methoxycarbonyl)phenyl methanesulfonate (**20by**) (145 mg, 0.50 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 2/1) yielded **28by** (71 mg, 46%) as a yellow solid.

M. p.: 212–213 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.77 (t, J = 1.6 Hz, 1H), 8.48 (dd, J = 1.4 Hz, 2H), 8.22 (dt, J = 6.5, 1.0 Hz, 1H), 7.38 – 7.06 (m, 2H), 3.94 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.5 (C_q), 158.3 (C_q, J = 253 Hz), 138.7 (C_q, J = 23 Hz), 136.8 (CH, J = 4 Hz), 135.6 (CH, J = 3 Hz), 132.1 (CH), 130.9 (C_q), 127.2 (C_q, J = 2 Hz), 124.4 (CH, J = 11 Hz), 113.6 (CH, J = 22 Hz), 52.5 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - (114.4 – 119.7) (m).

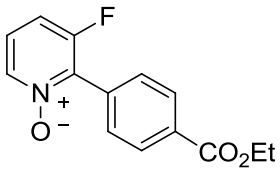
IR (KBr, cm^{-1}): 3084 (m), 3016 (m), 2961 (m), 1934 (w), 1728 (s), 1421 (s), 1253 (s), 749 (s).

MS (EI) *m/z* (relative intensity): 289 (27), 258 (54), 231 (100), 171 (19), 100 (14).

HR-MS (ESI) *m/z* for $C_{15}H_{12}FNO_5$+Na^+ calcd.: 328.0592.
found: 328.0593.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2-(4-Ethoxycarbonylphenyl)-3-fluoropyridine *N*-oxide (28bo)



28bo

The general procedure **C** was followed, using ethyl-4-(methylsulfonyloxy)benzoate (**20bo**) (122 mg, 0.50 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h, purification by column chromatography (CH_2Cl_2/acetone: 3/1) yielded **28bo** (78 mg, 59%) as a pale yellow solid.

M. p.: 141–143 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.31 – 8.06 (m, 3H), 7.81 – 7.62 (m, 2H), 7.27 – 7.09 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.7 (C_q), 158.2 (C_q, *J* = 252 Hz), 139.6 (C_q, *J* = 25 Hz), 136.7 (CH, *J* = 4 Hz), 131.6 (C_q), 130.6 (C_q, *J* = 2 Hz), 130.1 (CH, *J* = 3 Hz), 129.3 (CH), 124.0 (CH, *J* = 11 Hz), 113.3 (CH, *J* = 23 Hz), 61.2 (CH_2), 14.4 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 120.3 (td, *J* = 8.3, 7.1, 1.2 Hz).

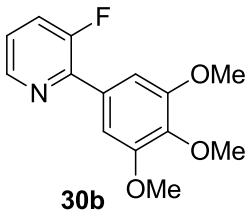
IR (KBr, cm^{-1}): 2983 (m), 1716 (s), 1551 (m), 1279 (s), 1109 (s), 1034 (s), 724 (s).

MS (EI) *m/z* (relative intensity): 261 ([M^+] 24), 245 (42), 200 (100), 172 (50), 43 (10).

HR-MS (ESI) *m/z* for $C_{14}H_{12}FNO_3$-H^+ calcd.: 260.0728.
found: 260.0722.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 3-Fluoro-2-(3,4,5-trimethoxyphenyl)pyridine (30b)



30b

The general procedure **C** was followed, using 3,4,5-trimethoxyphenyl methanesulfonate (**20bb**) (131 mg, 0.50 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h the reaction mixture was allowed to cool to ambient temperature, was diluted with CH_2Cl_2, filtered over Celite and concentrated *in vacuo*. The remaining residue was stirred in acetic acid (15.0 mL) with iron powder (10 equiv.) for 20 h at 50 °C.[37] After extraction with ethyl acetate purification by column chromatography (*n*-pentane/ethyl acetate: 4/1 → 3/1) yielded the reduced product **30b** (104 mg, 79%) as a colorless solid.

M. p.: 111–113 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.55 – 8.43 (m, 1H), 7.56 – 7.39 (m, 1H), 7.31 – 7.16 (m, 3H), 3.93 (s, 6H), 3.90 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.4 (C_q, J = 260 Hz), 153.1 (C_q), 145.6 (C_q, J = 10 Hz), 145.2 (CH, J = 5 Hz), 139.6 (C_q), 130.7 (C_q, J = 6 Hz), 124.1 (CH, J = 21 Hz), 123.3 (CH, J = 4 Hz), 106.1 (CH, J = 7 Hz), 60.9 (CH_3), 56.2 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = **-** 122.3 (ddd, J = 11.3, 3.4, 1.6 Hz).

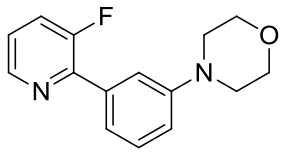
IR (KBr, cm^{-1}): 3055 (s), 2940 (s), 2307 (w), 1590 (s), 1267 (s), 1129 (s), 717 (s).

MS (EI) *m/z* (relative intensity): 263([M^+] 100), 248 (59), 220 (38), 190 (36), 134 (33).

HR-MS (ESI) *m/z* for $C_{14}H_{14}FNO_3+H^+$ calcd.: 264.1030.
found: 264.1033.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 3-Fluoro-2-(3-morpholinophenyl)pyridine (30c)



30c

The general procedure **C** was followed, using 3-morpholinophenyl methanesulfonate (**20bz**) (114 mg, 0.45 mmol) and 3-fluoropyridine *N*-oxide (**26ab**) (226 mg, 2.00 mmol). After 20 h the reaction mixture was allowed to cool to ambient temperature, was diluted with CH_2Cl_2, filtered over Celite and concentrated *in vacuo*. The remaining residue was stirred in acetic acid (15.0 mL) with iron powder (10 equiv.) for 20 h at 50 °C.[37] After extraction with ethyl acetate purification by column chromatography (*n*-pentane/ethyl acetate: 5/1 → 2/1) yielded the reduced product **30c** (74 mg, 65%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.49 (dt, J = 4.5, 1.6 Hz, 1H), 7.64 – 7.10 (m, 5H), 6.98 (ddd, J = 8.1, 2.5, 1.0 Hz, 1H), 3.95 – 3.75 (m, 4H), 3.34 – 3.04 (m, 4H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.4 (C_q, J = 260 Hz), 151.3 (C_q), 146.4 (C_q, J = 11 Hz), 145.1 (CH, J = 5 Hz), 136.1 (C_q, J = 5 Hz), 129.1, (CH), 124.0 (CH, J = 21 Hz), 123.3 (CH, J = 4 Hz), 120.6 (CH, J = 7 Hz), 116.6 (CH), 115.9 (CH, J = 5 Hz), 67.0 (CH_2), 49.4 (CH_2).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = **-** (122.4 **–** 122.5) (m).

IR (film, cm^{-1}): 3067 (m), 2962 (s), 2854 (s), 1599 (s), 1376 (s), 1065 (s), 801 (s).

MS (EI) *m/z* (relative intensity): 258 ([M^+] 100), 227 (12), 200 (78), 173 (61), 145 (9).

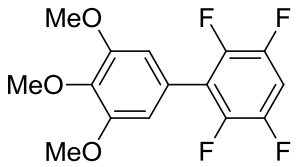
HR-MS (EI) *m/z* for $C_{15}H_{15}FN_2O$ calcd.: 258.1168.
found: 258.1165.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2,3,5,6-Tetrafluoro-3',4',5'-trimethoxy-1,1'-biphenyl (14c) and 1,4-Bis-(3',4',5'-trimethoxyphenyl)-2,3,5,6-tetrafluorobenzene (86c)

The general procedure **D** was followed, using 3,4,5-trimethoxyphenyl 4-methyl-benzenesulfonate (**20ab**) (169 mg, 0.50 mmol), 1,2,4,5-tetrafluorobenzene (**12c**) (121 mg, 0.80 mmol) and Cs_2CO_3 (180 mg, 0.55 mmol). After 16 h, purification by column chromatography (*n*-pentane/ethyl acetate: 50/1 → 30/1 → 20/1 → 10/1 → 7/1 → 4/1) yielded **14c** (71 mg, 45%) and **86c** (49 mg, 40%) as colorless solids.

2,3,5,6-Tetrafluoro-3',4',5'-trimethoxy-1,1'-biphenyl (14c)



14c

HPLC: VP C18 ec (RP) MeOH/H_2O: 1:1 → 100% MeOH, flow rate 16.0 mL/min, 254 nm, t_R = 22.1 min.

M. p.: 112–113 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.12 - 6.97 (m, 1H), 6.68 - 6.61 (m, 2H), 3.90 (s, 3H), 3.86 (s, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 153.3 (C_q), 146.2 (C_q, *J* = 248, 15, 11, 4 Hz), 143.7 (C_q, *J* = 247, 24, 4 Hz), 138.8 (C_q), 122.5 (C_q), 121.4 (C_q, *J* = 17 Hz), 107.5 (CH, 3 Hz), 104.7 (CH, *J* = 23 Hz), 60.9 (CH_3), 56.2 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - (139.0 – 139.2) (m), - (143.2 – 143.4) (m).

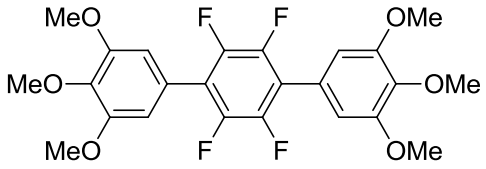
IR (KBr, cm^{-1}): 3188 (m), 3008 (s), 2941 (s), 1970 (w), 1585 (s), 1502 (s), 1243 (m), 1131 (s), 842 (s).

MS (EI) *m/z* (relative intensity): 316 ([M^+] 100), 301 (61), 273 (42), 213 (19), 187 (49).

HR-MS (EI) *m/z* for $C_{15}H_{12}F_4O_3$ calcd.: 316.0723.
found: 316.0712.

The analytical data are in accordance with those reported in the literature.[128]

1,4-Bis-(3',4',5'-trimethoxyphenyl)-2,3,5,6-tetrafluorobenzene (86c)



86c

M. p.: 196–198 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.69 (s, 4H), 3.91 (s, 6H), 3.88 (s, 12H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 153.3 (C_q), 144.0 (C_q, J = 250 Hz), 138.8 (C_q), 120.5 (C_q), 119.5 (C_q), 107.5 (CH), 60.9 (CH_3), 56.2 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = **-** 143.7 (s).

IR (KBr, cm^{-1}): 3008 (m), 2937 (m), 1654 (s), 1516 (s), 1128 (s), 1001 (m), 742 (s).

MS (EI) *m/z* (relative intensity): 482 ([M^+] 100), 467 (35), 439 (14), 407 (16).

HR-MS (EI) *m/z* for $C_{24}H_{22}F_4O_6$ calcd.: 482.1353.
found: 482.1358.

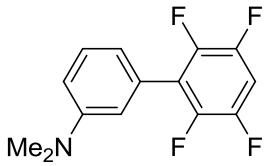
The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2,3,5,6-Tetrafluoro-3'-*N*,*N*-dimethyl-1,1'-biphenyl (14d) and 1,4-Bis-(3'-*N*,*N*-dimethylphenyl)-2,3,5,6-tetrafluorobenzene (86d)

The general procedure **D** was followed, using 2-*N*,*N*-dimethylphenyl 4-methyl-benzenesulfonate (**20ad**) (146 mg, 0.50 mmol), 1,2,4,5-tetrafluorobenzene (**12c**) (123 mg, 0.82 mmol) and Cs_2CO_3 (180 mg, 0.55 mmol). After 16 h, purification by column

chromatography (*n*-pentane → *n*-pentane/ethyl acetate: 100/1 → 70/1) yielded **14d** (74 mg, 55%) as a yellow oil and **86d** (17 mg, 18%) as a colorless solid.

2,3,5,6-Tetrafluoro-3'-*N*,*N*-dimethyl-1,1'-biphenyl (14d)



14d

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.35 (m, 1H), 7.05 (ddd, J = 9.5, 7.2, 2.6 Hz, 1H), 6.87 – 6.72 (m, 3H), 2.99 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 150.5 (C_q), 146.1 (C_q, J = 247, 15, 11, 4 Hz), 143.8 (C_q, J = 247, 13, 4 Hz), 129.2 (CH), 128.1 (C_q, J = 2 Hz), 122.5 (C_q, J = 17 Hz), 118.0 (CH, J = 2 Hz), 113.9 (CH, J = 2 Hz), 113.2 (CH), 104.4 (CH, J = 23 Hz), 40.5 (CH_3).

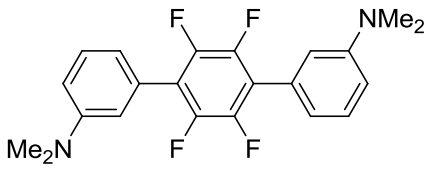
^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 143.3 (m), - (113.9 – 114.0) (m).

IR (film, cm^{-1}): 2923 (s), 1603 (s), 1494 (s), 1280 (m), 1177 (s), 936 (s), 649 (m).

MS (EI) *m/z* (relative intensity): 268 ([M^+] 100), 214 (30), 133 (16), 55 (30).

HR-MS (EI) *m/z* for $C_{14}H_{11}F_4N$ calcd.: 269.0828.
found: 269.0828.

1,4-Bis-(3'-*N*,*N*-dimethylphenyl)-2,3,5,6-tetrafluorobenzene (86d)



86d

M. p.: 164–169 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.37 (ddd, J = 7.5, 7.5, 1.4 Hz, 2H), 6.89 – 6.79 (m, 6H), 3.01 (s, 12H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 150.5 (C_q), 143.9 (C_q, J = 246 Hz), 129.2 (CH), 128.2 (C_q), 120.1 (C_q, J = 10 Hz), 118.2 (CH), 114.1 (CH), 113.1 (CH), 40.6 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = **-** 144.0 (s).

IR (KBr, cm^{-1}): 2920 (m), 1601 (s), 1462 (s), 1424 (s), 1183 (m), 977 (s), 775 (s).

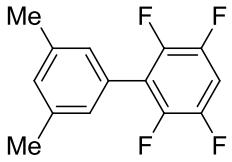
MS (EI) *m/z* (relative intensity): 388 ([M^+] 100), 371 (31), 193 (23), 171 (7).

HR-MS (EI) *m/z* for $C_{22}H_{20}F_4O_2$ calcd.: 388.1563.
found: 388.1546.

Synthesis of 2,3,5,6-Tetrafluoro-3,5-dimethyl-1,1'-biphenyl (14e) and 1,4-Bis-(3,5-dimethylphenyl)-2,3,5,6-tetrafluorobenzene (86e)

The general procedure **D** was followed, using 3,5-dimethylphenyl 4-methylbenzenesulfonate (**20aa**) (138 mg, 0.50 mmol), 1,2,4,5-tetrafluorobenzene (**12c**) (113 mg, 0.75 mmol) and Cs_2CO_3 (180 mg, 0.55 mmol). After 16 h, purification by column chromatography (*n*-pentane) yielded **14e** (39 mg, 31%) and **86e** (27 mg, 30%) as colorless solids.

2,3,5,6-Tetrafluoro-3',5'-dimethyl-1,1'-biphenyl (14e)



14e

HPLC: VP C18 ec (RP) MeOH/H_2O: 1:1 → 3:1), flow rate 16.0 mL/min, 254 nm, t_R = 6.5 min.

M. p.: 45–46 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.10 (s, 1H), 7.07 (s, 2H), 7.02 (m, 1H), 2.38 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 146.3 (C_q, J = 247, 15, 11, 4 Hz), 143.6 (C_q, J = 246, 14, 4 Hz), 138.1 (C_q), 130.8 (CH), 127.6 (CH, J = 2 Hz), 127.1 (C_q, J = 2 Hz), 121.8 (C_q, J = 17 Hz), 104.5 (CH, J = 23 Hz), 21.4 (CH_3).

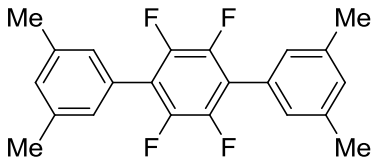
^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 139.5 (ddd, J = 22.5, 12.8, 9.6 Hz), - (143.5 – 143.8) (m).

IR (KBr, cm^{-1}): 3078 (m), 2922 (s), 1645 (m), 1500 (s), 1173 (m), 934 (m), 742 (s).

MS (EI) *m/z* (relative intensity): 254 ([M^+] 100), 239 (59), 219 (47), 119 (4), 43 (25).

HR-MS (EI) *m/z* for $C_{14}H_{10}F_4$ calcd.: 254.0719.
found: 254.0720.

1,4-Bis-(3',5'-dimethylphenyl)-2,3,5,6-tetrafluorobenzene (86e)



86e

M. p.: 215–217 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.12 (s, 6H), 2.40 (s, 12H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 144.0 (C_q, J = 249 Hz), 138.1 (C_q), 130.8 (CH), 127.8 (CH), 127.3 (C_q), 119.6 (C_q), 21.3 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 144.3 (s).

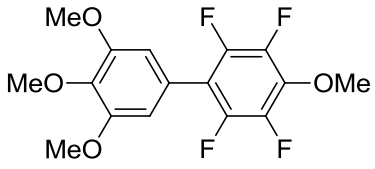
IR (KBr, cm^{-1}): 2956 (m), 2862 (m), 1602 (m), 1479 (s), 1423 (s), 983 (s), 708 (s).

MS (EI) *m/z* (relative intensity): 358 ([M^+] 100), 343 (13), 237 (2), 164 (7), 77 (3).

HR-MS (EI) *m/z* for $C_{22}H_{18}F_4$ calcd.: 358.1345.
found: 358.1347.

The analytical data are in accordance with those reported in the literature.[128]

Synthesis of 2,3,5,6-Tetrafluoro-3',4,4',5'-tetramethoxy-1,1'-biphenyl (14f)



14f

The general procedure **D** was followed, using 3,4,5-trimethoxyphenyl 4-methyl-benzenesulfonate (**20ab**) (169 mg, 0.50 mmol), 1,2,4,5-tetrafluoro-3-methoxybenzene (**12b**) (153 mg, 0.84 mmol) and Cs_2CO_3 (180 mg, 0.55 mmol). After 16 h, purification by column chromatography (*n*-pentane/ethyl acetate: 20/1) yielded **14f** (133mg, 77%) as a colorless solid.

M. p.: 117–120°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.63 (t, J = 1.3 Hz, 2H), 4.12 (t, J = 1.3 Hz, 3H), 3.91 (s, 3H), 3.88 (s, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 153.0 (C_q), 144.1 (C_q, J = 246, 12, 7, 4 Hz), 141.0 (C_q, J = 247, 16, 4 Hz), 138.4 (C_q), 137.2 (C_q, J = 12 Hz), 122.2 (C_q, J = 2 Hz), 114.0 (C_q, J = 17 Hz), 107.4 (CH, J = 2 Hz), 62.1 (CH_3, J = 4 Hz), 60.8 (CH_3), 56.2 (CH_3).

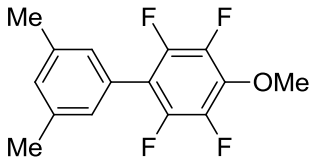
^{19}F-NMR (282 MHz, $CDCl_3$): δ = **-** (144.4 – 144.6) (m), **-** (158.1 – 158.3) (m).

IR (KBr, cm^{-1}): 2944 (w), 1583 (m), 1490 (s), 1245 (s), 1129 (s), 978 (s), 706 (s).

MS (EI) *m/z* (relative intensity): 346 ([M^+] 100), 331 (81), 271 (25), 217 (25), 69 (3).

HR-MS (EI) *m/z* for $C_{16}H_{14}F_4O_4$ calcd.: 346.0828.
found: 346.0836.

Synthesis of 2,3,5,6-Tetrafluoro-4-methoxy-3',5'-dimethyl-1,1'-biphenyl (14g)



14g

The general procedure **D** was followed, using 3,5-dimethylphenyl 4-methylbenzenesulfonate (**20aa**) (138 mg, 0.50 mmol), 1,2,4,5-tetrafluoro-3-methoxybenzene (**12b**) (152 mg, 0.84 mmol) and Cs_2CO_3 (180 mg, 0.55 mmol). After 16 h, purification by column chromatography (*n*-pentane) yielded **14g** (107 mg, 75%) as a colorless solid.

M. p.: 70–72°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.08 (s, 1H), 7.04 (s, 2H), 4.12 (t, J = 1.3 Hz, 3H), 2.38 (s, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ = 144.2 (C_q, J = 245, 12, 8, 4 Hz), 141.0 (C_q, J = 246, 16, 4 Hz), 138.0 (C_q), 137.2 (CH, J = 12 Hz), 130.5 (CH), 127.8 (C_q, J = 1.8 Hz), 126.9 (C_q), 114.5 (C_q, J = 18 Hz), 62.2 (CH_3, J = 4 Hz), 21.4 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - (144.6 – 145.3) (m), - (158.1 –158.9) (m).

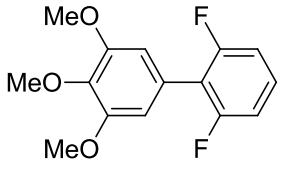
IR (KBr, cm^{-1}): 2922 (m), 1604 (m), 1505 (s), 1430 (s), 1097 (s), 918 (s), 850 (s).

MS (EI) *m/z* (relative intensity): 284 (57), 269 (51), 206 (9), 58 (25), 43 (100).

HR-MS (EI) *m/z* for $C_{15}H_{12}F_4O$ calcd.: 284.0824.
found: 284.0819.

The analytical data are in accordance with those reported in the literature.[17]

Synthesis of 2,6-Difluoro-3',4',5'-trimethoxy-1,1'-biphenyl (14h)



14h

The general procedure **D** was followed, using 3,4,5-trimethoxyphenyl 4-methyl-benzenesulfonate (**20ab**) (169 mg, 0.50 mmol), 1,3-difluorobenzene (**12d**) (276 mg, 2.34 mmol) and Cs_2CO_3 (180 mg, 0.55 mmol). After 16 h, purification by column chromatography (*n*-pentane/ethyl acetate: 30/1 → 15/1 → 10/1) yielded **14h** (60 mg, 43%) as a colorless solid.

M. p.: 107–108 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.26 (m, 1H), 7.02 – 6.91 (m, 2H), 6.65 (s, 2H), 3.89 (s, 3H), 3.86 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.1 (C_q, J = 245 Hz), 153.0 (C_q), 138.1 (C_q), 128.8 (CH, J = 11 Hz), 124.4 (C_q, J = 2 Hz), 118.5 (C_q, J = 19 Hz), 111.7 (CH, J = 29 Hz), 107.6 (CH), 60.9 (CH_3), 56.2 (CH_3).

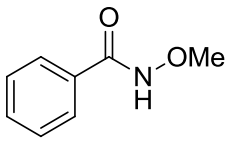
^{19}F-NMR (282 MHz, $CDCl_3$): δ = - (113.8 – 113.9) (m).

IR (KBr, cm^{-1}): 2935 (m), 1584 (s), 1461 (s), 1238 (s), 1125 (s), 992 (s), 569 (m).

MS (EI) *m/z* (relative intensity): 280 ([M^+] 100), 265 (73), 237 (40), 151 (51), 43 (18).

HR-MS (EI) *m/z* for $C_{15}H_{14}F_2O$ calcd.: 280.0911.
found: 280.0903.

Synthesis of *N*-Methoxybenzamide (41ba)



41ba

The general procedure **E2** was followed using *N*-methoxyamine hydrochloride (**88a**) (1.25 g, 15.0 mmol), benzoyl chloride (**87a**) (1.16 mL, 10.0 mmol) and K_2CO_3 (2.77 g, 20.0 mmol) yielding **41ba** (1.14 g, 75%) as a pale yellow solid.

M. p.: 60–63 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.32 (s, 1H), 7.77 – 7.71 (m, 2H), 7.50 (m, 1H), 7.44 – 7.36 (m, 2H), 3.85 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.5 (C_q), 132.0 (CH), 131.8 (C_q), 128.6 (CH), 127.1 (CH), 64.5 (CH_3).

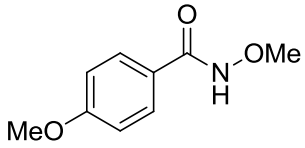
IR (neat, cm^{-1}): 3184 (s), 2979 (m), 1642 (s), 1481 (m), 1309 (m), 1042 (m) 1024 (m), 799 (w), 690 (m).

MS (EI) *m/z* (relative intensity): 151 ([M^+] 26), 121 (12), 105 (100), 77 (63), (51) 24.

HR-MS (EI) *m/z* for $C_8H_9NO_2$ calcd.: 151.0633.
found: 151.0629.

The analytical data are in accordance with those reported in the literature.[73,184]

Synthesis of 4,*N*-Dimethoxybenzamide (41bb)



41bb

The general procedure **E2** was followed using *N*-methoxyamine hydrochloride (**88a**) (1.26 g, 15.1 mmol), 4-methoxybenzoyl chloride (**87c**) (1.35 mL, 10.0 mmol) and K_2CO_3 (2.77 g, 20.0 mmol) yielding **41bb** (1.17 g, 66%) as a colorless solid.

M. p.: 102–105 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.98 (s, 1H), 7.71 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.4 (C_q), 162.6 (C_q), 128.9 (CH), 124.0 (C_q), 113.9 (CH), 64.5 (CH_3), 55.4 (CH_3).

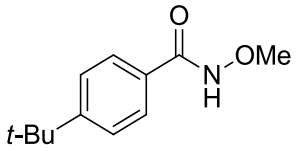
IR (neat, cm^{-1}): 3171 (s), 2959 (w), 1643 (s), 1489 (s), 1254 (s), 1016 (s), 842 (s), 672 (s), 610 (s).

MS (EI) *m/z* (relative intensity): 181 ([M^+] 18), 135 (100), 107 (12), 77 (18), 43 (12).

HR-MS (EI) *m/z* for $C_9H_{11}NO_3$ calcd.: 181.0739.
found: 181.0743.

The analytical data are in accordance with those reported in the literature.[184]

Synthesis of 4-*tert*-Butyl-*N*-methoxybenzamide (41bc)



41bc

The general procedure **E2** was followed using *N*-methoxyamine hydrochloride (**88a**) (1.25 g, 15.0 mmol), 4-*tert*-butylbenzoyl chloride (**87d**) (2.00 mL, 11.0 mmol) and K_2CO_3 (2.77 g, 20.0 mmol) yielding **41bc** (2.22g, 97%) as a pale yellow solid.

M. p.: 68–71 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.00 (s, 1H), 7.68 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 3.86 (s, 3H), 1.32 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.6 (C_q), 155.7 (C_q), 128.9 (C_q), 126.9 (CH), 125.6 (CH), 64.6 (C_q), 35.0 (CH_3), 31.1 (CH_3).

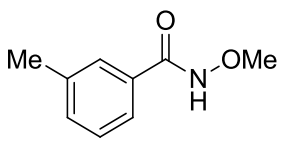
IR (neat, cm^{-1}): 3177 (s), 2960 (s), 1650 (s), 1491 (s), 1305 (s), 1045 (s), 852 (s), 706 (m), 550 (s).

MS (EI) *m/z* (relative intensity): 207 ([M^+] 25), 192 (65), 161 (100), 132 (24), 91 (20), 43 (11).

HR-MS (EI) *m/z* for $C_{12}H_{17}NO_2$ calcd.: 207.1259.
found: 207.1263.

The analytical data are in accordance with those reported in the literature.[79]

Synthesis of 3-Methyl-*N*-methoxybenzamide (41bd)



41bd

The general procedure **E2** was followed using *N*-methoxyamine hydrochloride (**88a**) (1.27 g, 15.2 mmol), 3-methylbenzoyl chloride (**87e**) (1.32 mL, 10.0 mmol) and K_2CO_3 (2.78 g, 20.1 mmol) yielding **41bd** (1.53 g, 93%) as a colorless solid.

M. p.: 62–64 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.10 (s, 1H), 7.55 (m, 1H), 7.49 (m, 1H), 7.32 – 7.20 (m, 2H), 3.83 (s, 3H), 2.34 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.7 (C_q), 138.6 (CH), 132.8 (C_q), 131.8 (CH), 128.5 (CH), 127.8 (CH), 64.5 (CH_3), 21.3 (CH_3).

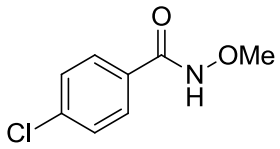
IR (neat, cm^{-1}): 3165 (s), 2978 (m), 1643 (s), 1504 (s), 1301 (s), 1052 (s), 945 (s), 797 (s), 668 (s).

MS (EI) *m/z* (relative intensity): 165 (28), 119 (100), 91 (52), 65 (14).

HR-MS (EI) *m/z* for $C_9H_{11}NO_2$ calcd.: 165.0790.
found: 165.0789.

The analytical data are in accordance with those reported in the literature.[73,185]

Synthesis of 4-Chloro-*N*-methoxybenzamide (41bf)



41bf

The general procedure **E2** was followed using *N*-methoxyamine hydrochloride (**88a**) (1.25 g, 15.0 mmol), 4-chlorobenzoyl chloride (**87f**) (1.28 mL, 10.0 mmol) and K_2CO_3 (2.76 g, 20.0 mmol) yielding **41bf** (1.87 g, 99%) as a colorless solid.

M. p.: 112–114 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.77 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 3.71 (s, 3H).

^{13}C-NMR (75 MHz, DMSO-d_6): δ = 163.0 (C_q), 136.3 (C_q), 131.0 (C_q), 128.9 (CH), 128.5 (CH), 63.2 (CH_3).

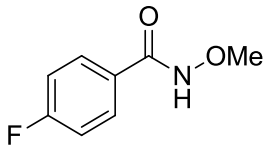
IR (neat, cm^{-1}): 3213 (s), 1643 (s), 1518 (m), 1440 (m), 1092 (m), 844 (m), 758 (m), 566 (s), 523 (s).

MS (EI) *m/z* (relative intensity): 185 ([M^+] 22), 139 (100), 111 (36), 75 (21), 43 (7).

HR-MS (EI) *m/z* for $C_8H_8ClNO_2$ calcd.: 185.0244.
found: 185.0242.

The analytical data are in accordance with those reported in the literature.[73]

Synthesis of 4-Fluoro-*N*-Methoxybenzamide (41be)



41be

The general procedure **E1** was followed using 4-fluorobenzoic acid (**36a**) (2.79 g, 19.9 mmol), oxalyl chloride (2.03 mL, 24.0 mmol), *N*-methoxyamine hydrochloride (**88a**) (1.84 g, 22.0 mmol) and K_2CO_3 (5.54 g, 40.1 mmol). Purification by column chromatography (*n*-pentane/EtOAc: 1/1) yielded **41be** (2.03 g, 60%) as a colorless solid.

M. p.: 102–105 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.13 (s, 1H), 7.77 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.10 (dd, *J* = 8.8, 8.8 Hz, 2H), 3.86 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.7 (C_q), 165.0 (C_q, *J* = 253 Hz), 129.5 (CH, *J* = 9 Hz), 127.9 (C_q, *J* = 3 Hz), 115.8 (CH, *J* = 22 Hz), 64.6 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 106.7 (s).

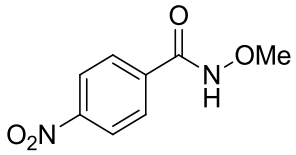
IR (neat, cm^{-1}): 3224 (s), 1644 (s), 1520 (s), 1228 (s), 1149 (s), 1035 (s), 940 (m), 843 (m), 582 (s).

MS (EI) *m/z* (relative intensity): 169 ([M^+] 23), 123 (100), 95 (40), 75 (14), 43 (8).

HR-MS (EI) *m/z* for $C_8H_8FNO_2$ calcd.: 169.0539.
found: 169.0542.

The analytical data are in accordance with those reported in the literature.[73]

Synthesis of 4-Nitro-*N*-methoxybenzamide (41bg)



41bg

The general procedure **E2** was followed using *N*-methoxyamine hydrochloride (**88a**) (1.26 g, 15.1 mmol), 4-nitrobenzoyl chloride (**87g**) (0.93 g, 5.00 mmol) and K_2CO_3 (2.77 g, 20.0 mmol) yielding **41bg** (0.54 g, 55%) as a pale yellow solid.

M. p.: 180–182 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.00 (s, 1H), 8.29 (d, J = 8.6 Hz, 1H), 7.97 (d, J = 8.6 Hz, 1H), 3.75 (s, 1H).

^{13}C-NMR (75 MHz, DMSO-d_6): δ = 184.6 (C_q), 149.1 (C_q), 137.9 (C_q), 128.4 (CH), 123.5 (CH), 63.2 (CH_3).

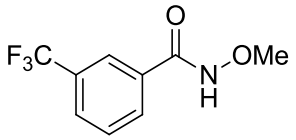
IR (neat, cm^{-1}): 3163 (m), 2991 (m), 1651 (s), 1598 (m), 1512 (s), 1326 (s), 1041 (m), 846 (m), 616 (s).

MS (EI) *m/z* (relative intensity): 196 ([M^+] 23), 150 (100), 104 (25), 76 (22), 50 (9).

HR-MS (EI) *m/z* for $C_8H_8N_2O_4$ calcd.: 196.0484.
found: 196.0479.

The analytical data are in accordance with those reported in the literature.[73]

Synthesis of 3-(Trifluoromethyl)-*N*-methoxybenzamide (41bh)



41bh

The general procedure **E2** was followed using *N*-methoxyamine hydrochloride (**88a**) (1.26 g, 15.1 mmol), 3-(trifluoromethyl)benzoyl chloride (**87i**) (1.51 mL, 10.0 mmol) and K_2CO_3 (2.77 g, 20.0 mmol) yielding **41bh** (2.20 g, 99%) as a colorless solid.

M. p.: 121–123 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.96 (s, 1H), 8.10 – 8.02 (m, 2H), 7.91 (d, J = 7.8 Hz, 1H), 7.72 (dd, J = 8.3, 7.2 Hz, 1H), 3.74 (s, 3H).

^{13}C-NMR (75 MHz, DMSO-d_6): δ = 162.5 (C_q), 133.1 (C_q), 131.0 (CH), 129.7 (CH), 129.2 (q, J = 32 Hz, C_q), 128.0 (CH), 123.8 (q, J = 272 Hz, C_q), 123.5 (CH), 63.2 (CH_3).

^{19}F-NMR (282 MHz, DMSO-d_6): δ = - 56.6 (s).

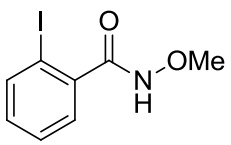
IR (neat, cm^{-1}):3162 (s), 3002 (m) 1649 (s), 1523 (m), 1335 (m), 1119 (s), 907 (m), 691 (s), 580 (m).

MS (EI) *m/z* (relative intensity): 219 ([M^+] 15), 173 (74), 145 (41), 95 (9), 75 (9).

HR-MS (EI) *m/z* for $C_9H_8F_3NO_2$ calcd.: 219.0507.
found: 219.0512.

The analytical data are in accordance with those reported in the literature.[73]

Synthesis of 2-Iodo-*N*-methoxybenzamide (41bj)



41bj

The general procedure **E2** was followed using *N*-methoxyamine hydrochloride (**88a**) (1.26 g, 15.0 mmol), 2-iodobenzoyl chloride (**87j**) (2.66 mg, 9.98 mmol) and K_2CO_3 (2.77 g, 20.1 mmol) yielding **41bj** (2.24 g, 81%) as a colorless solid.

M. p.: 103–105 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.55 (s, 1H), 7.85 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.43 – 7.30 (m, 2H), 7.12 (ddd, *J* = 8.0, 5.9, 3.3 Hz, 1H), 3.92 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.9 (C_q), 139.8 (CH), 138.7 (C_q), 131.7 (CH), 128.7 (CH), 128.1 (CH), 93.0 (C_q), 64.6 (CH_3).

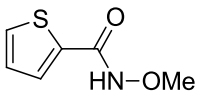
IR (neat, cm^{-1}): 3125 (s), 2934 (s), 1642 (s), 1514 (s), 1310 (s), 1012 (s), 872 (s), 686 (s), 638 (s).

MS (EI) *m/z* (relative intensity): 277 ([M+H$^+$] 19) 230 (100), 202 (31), 76 (29), 50 (18).

HR-MS (EI) *m/z* for $C_8H_8INO_2$ calcd.: 276.9600.
found: 276.9605.

The analytical data are in accordance with those reported in the literature.[71]

Synthesis of *N*-Methoxythiophene-2-carboxamide (41bi)



41bi

The general procedure **E1** was followed using thiophene-2-carboxylic acid (**36b**) (1.28 g, 10.0 mmol), oxalyl chloride (1.00 mL, 11.8 mmol), *N*-methoxyamine hydrochloride (**88a**) (0.97 g, 11.7 mmol) and K_2CO_3 (2.74 g, 19.8 mmol). Purification by column chromatography (*n*-pentane/EtOAc: 1/1) yielded **41bi** (1.33 g, 85%) as a colorless solid.

M. p.: 70–72 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.99 (s, 1H), 7.69 (d, *J* = 4.0 Hz, 1H), 7.54 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.09 (dd, *J* = 5.0, 4.0 Hz, 1H), 3.86 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.1 (C_q), 134.3 (C_q), 131.2 (CH), 130.4 (CH), 127.6 (CH), 64.9 (CH_3).

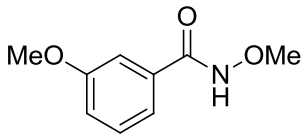
IR (neat, cm^{-1}): 3203 (s), 1624 (s), 1530 (s), 1416 (m), 1307 (s), 1142 (m), 934 (m), 825 (s), 550 (s).

MS (EI) *m/z* (relative intensity): 157 ([M^+] 17), 111 (100), 83 (8), 57 (6), 45 (7).

HR-MS (EI) *m/z* for $C_6H_7NO_2S$ calcd.: 157.0197.
found: 157.0197.

The analytical data are in accordance with those reported in the literature.[73]

Synthesis of 3,*N*-Dimethoxybenzamide (41bk)



41bk

The general procedure **E1** was followed using 3-methoxybenzoic acid (**36c**) (3.04 g, 20.0 mmol), oxalyl chloride (2.03 mL, 24.0 mmol), *N*-methoxyamine hydrochloride (**88a**) (1.85 g, 22.2 mmol) and K_2CO_3 (5.52 g, 39.9 mmol). Purification by column chromatography (*n*-pentane/EtOAc: 1/3) yielded **41bk** (3.27 g, 90%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.07 (s, 1H), 7.38 – 7.20 (m, 3H), 7.04 (ddd, *J* = 8.2, 2.7, 1.4 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.3 (C_q), 159.8 (C_q), 133.1 (C_q), 129.7 (CH), 118.9 (CH), 118.4 (CH), 112.2 (CH), 64.5 (CH_3), 55.4 (CH_3).

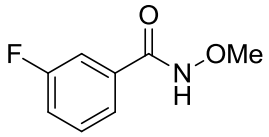
IR (neat, cm^{-1}): 3192 (s), 2837 (m), 1641 (s), 1581 (s), 1482 (m), 1240 (s), 1032 (s), 797 (s), 686 (s).

MS (EI) *m/z* (relative intensity): 181 ([M^+] 29), 135 (100), 107 (33), 77 (39), 43 (25).

HR-MS (EI) *m/z* for $C_9H_{11}NO_3$ calcd.: 181.0739.
found: 181.0740.

The analytical data are in accordance with those reported in the literature.[186]

Synthesis of 3-Fluoro-*N*-methoxybenzamide (41bl)



41bl

The general procedure **E1** was followed using 3-fluorobenzoic acid (**36d**) (1.40 g, 10.0 mmol), oxalyl chloride (1.00 mL, 11.8 mmol), *N*-methoxyamine hydrochloride (**88a**) (0.92 g, 11.0 mmol) and K_2CO_3 (2.76 g, 19.9 mmol). Purification by column chromatography (*n*-pentane/EtOAc: 1/3) yielded **41bl** (0.52 g, 31%) as a pale yellow solid.

M. p.: 66–68°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.92 (s, 1H), 7.57 – 7.34 (m, 3H), 7.23 (m, 1H), 3.88 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.3 (C_q), 162.7 (C_q, J = 249 Hz), 133.9 (C_q, J = 7 Hz), 130.5 (CH, J = 8 Hz), 122.6 (CH, J = 3 Hz), 119.2 (CH, J = 21 Hz), 114.5 (CH, J = 23 Hz), 64.7 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 111.3 (s).

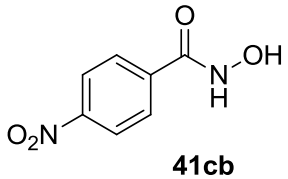
IR (neat, cm^{-1}): 3234 (s), 1651 (s), 1586 (m), 1478 (s), 1220 (d), 1043 (s), 937 (s), 797 (s), 676 (s).

MS (EI) *m/z* (relative intensity): 169 ([M^+] 32), 123 (100), 95 (46), 75 (18), 43 (3).

HR-MS (EI) *m/z* for $C_8H_8FNO_2$ calcd.: 169.0539.
found: 169.0538.

The analytical data are in accordance with those reported in the literature.[186]

Synthesis of 4-Nitro-*N*-Hydroxybenzamide (41cb)



41cb

The general procedure **E2** was followed using *N*-hydroxyamine hydrochloride (**88b**) (0.52 g, 7.50 mmol), 4-nitrobenzoyl chloride (**87g**) (0.93 g, 5.00 mmol) and K_2CO_3 (1.38 g, 10.0 mmol). After work-up **41cb** (0.11 g, 12%) was obtained as an off-white solid.

M. p.: > 170 °C (dec.).

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.50 (s, 1H), 9.28 (s, 1H), 8.29 (d, J = 8.3 Hz, 2H), 7.98 (d, J = 8.3 Hz, 2H), 3.32 (s, 3H).

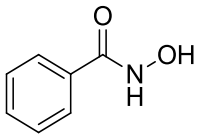
^{13}C-NMR (75 MHz, DMSO-d_6): δ = 162.2 (C_q), 148.9 (C_q), 138.5 (C_q), 128.3 (CH), 123.5 (CH).

IR (neat, cm^{-1}): 3113 (w), 1651 (s), 1514 (s), 1355 (s), 1034 (m), 849 (s), 663 (m).

MS (EI) *m/z* (relative intensity): 182 ([M^+] 19), 150 (100), 104 (41), 76 (44), 50 (33).

HR-MS (EI) *m/z* for $C_7H_6N_2O_4$ calcd.: 182.0328.
found: 182.0331.

Synthesis of *N*-Hydroxybenzamide (41ca)



41ca

The general procedure **E2** was followed using *N*-hydroxyamine hydrochloride (**88b**) (2.51 g, 36.2 mmol), benzoyl chloride (**87a**) (2.32 mL, 20.0 mmol) and K_2CO_3 (5.52 g, 40.0 mmol) in EtOAc/H_2O (300 mL, 2:1). After work-up **41ca** (0.89 g, 33%) was obtained as an off-white solid.

M. p.: 127–129 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.20 (s, 1H), 9.00 (s, 1H), 7.80 – 7.73 (m, 2H), 7.58 – 7.33 (m, 3H).

^{13}C-NMR (75 MHz, DMSO-d_6): δ = 164.3 (C_q), 132.8 (C_q), 131.0 (CH), 128.3 (CH), 126.8 (CH).

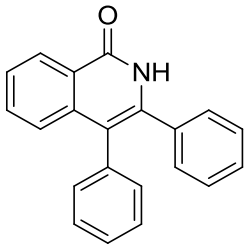
IR (neat, cm^{-1}): 3285 (s), 3037 (m), 2699 (s), 1554 (s), 1159 (m), 894 (m), 514 (m).

MS (EI) *m/z* (relative intensity): 137 ([M^+] 5), 121 (30), 105 (100), 77 (79), 43 (48).

HR-MS (EI) *m/z* for $C_7H_7NO_2$ calcd.: 137.0477.
found: 137.0470.

The analytical data are in accordance with those reported in the literature.[187]

Synthesis of 3,4-Diphenylisoquinolin-1(*2H*)-one (42ba)



42ba

The general procedure **F1** was followed using *N*-methoxybenzamide (**41ba**) (75.4 mg, 0.50 mmol), diphenylacetylene (**37a**) (178 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (30.8 mg, 31 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 2/1) yielded **42ba** (119 mg, 81%) as a colorless solid.

M. p.: 252–254 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.49 (s, 1H), 8.33 (d, J = 7.9 Hz, 1H), 7.63 (dd, J = 7.6, 7.6 Hz, 1H), 7.51 (dd, J = 7.2, 7.2 Hz, 1H), 7.36 – 7.09 (m, 11H).

^{13}C-NMR (75 MHz, DMSO-d_6): δ = 161.5 (C_q), 138.4 (C_q), 137.9 (C_q), 135.7 (C_q), 134.4 (C_q), 132.3 (CH), 131.5 (CH), 129.6 (CH), 128.0 (CH), 127.5 (CH), 126.8 (CH), 126.6 (CH), 126.0 (CH), 124.9 (CH), 124.7 (C_q), 124.7 (CH), 115.3 (C_q).

IR (neat, cm^{-1}): 3921 (w), 2887 (w), 1642 (s), 1489 (m), 1317 (m), 1155 (m), 779 (m), 694 (s), 557 (s).

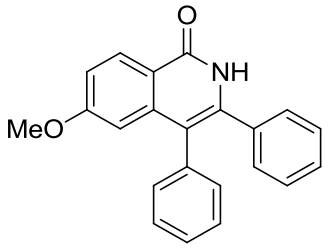
MS (EI) *m/z* (relative intensity): 297 ([M^+] 100), 278 (2), 252 (8), 165 (16), 104 (5), 77 (11).

HR-MS (EI) *m/z* for $C_{21}H_{15}NO$ calcd.: 297.1154.
found: 297.1164.

The analytical data are in accordance with those reported in the literature.[71]

Following general procedure **F2** using *N*-hydroxybenzamide (**41ca**) (68.8 mg, 0.50 mmol), diphenylacetylene (**37a**) (178 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.4 mg, 5.0 mol%) and potassium 2,4,6-trimethylbenzoate (30.2 mg, 30 mol%) yielded **42ba** (92 mg, 62%) as a colorless solid.

Synthesis of 4-Methoxy-3,4-diphenylisoquinolin-1(*2H*)-one (42bb)



42bb

The general procedure **F1** was followed using *N*-methoxy-4-methoxybenzamide (**41bb**) (90.3 mg, 0.50 mmol), diphenylacetylene (**37a**) (178 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (32.1 mg, 32 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 2/1 $\rightarrow$ 1/1 $\rightarrow$ 1/2 $\rightarrow$ 1/3) yielded **42bb** (103 mg, 63%) as an off-white solid.

M. p.: > 286 °C (dec.).

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.29 (s, 1H), 8.24 (d, J = 8.8 Hz, 1H), 7.40 – 6.96 (m, 11H), 6.51 (s, 1H), 3.66 (s, 3H).

^{13}C-NMR (75 MHz, DMSO-d_6): δ = 162.2 (C_q), 161.2 (C_q), 140.1 (C_q), 139.2 (C_q), 135.8 (C_q), 134.6 (C_q), 131.6 (CH), 129.7 (CH), 129.0 (CH), 128.1 (CH), 128.1 (CH), 127.5 (CH), 127.0 (CH), 118.9 (C_q), 115.0 (C_q), 114.4 (CH), 107.1 (CH), 55.1 (CH_3).

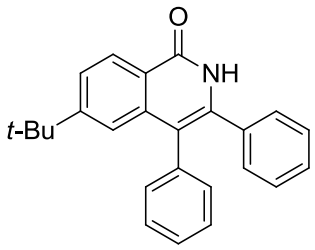
IR (neat, cm^{-1}): 3020 (w), 2845 (w), 1607 (s), 1511 (m), 1274 (m), 1106 (m), 766 (m), 695 (s), 543 (s).

MS (EI) *m/z* (relative intensity): 327 ([M^+] 100), 283 (8), 254 (7), 152 (9), 43 (28).

HR-MS (EI) *m/z* for $C_{22}H_{17}NO_2$ calcd.: 327.1259.
found: 327.1253.

The analytical data are in accordance with those reported in the literature.[79]

Synthesis of 6-*tert*-Butyl-3,4-diphenylisoquinolin-1(*2H*)-one (42bc)



42bc

The general procedure **F1** was followed using 4-*tert*-butyl-*N*-methoxybenzamide (**41bc**) (103 mg, 0.50 mmol), diphenylacetylene (**37a**) (178 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (30.0 mg, 30 mol%) in H_2O (2.0 mL) at 100 °C. Purification by column chromatography (*n*-pentane/EtOAc: 2/1 → 1/1→ 1/3) yielded **42bc** (164 mg, 93%) as a brown solid.

M. p.: 68–71 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.80 (s, 1H), 8.42 (dd, J = 8.5, 1.1 Hz, 1H), 7.58 (dd, J = 8.5, 1.8 Hz, 1H), 7.39 – 7.11 (m, 11H), 1.25 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.4 (C_q), 156.2 (C_q), 138.5 (C_q), 136.8 (C_q), 135.8 (C_q), 135.3 (C_q), 131.8 (CH), 129.1 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 127.3 (CH), 127.3 (CH), 124.7 (CH), 122.9 (C_q), 121.8 (CH), 117.5 (C_q), 35.3 (C_q), 31.0 (CH_3).

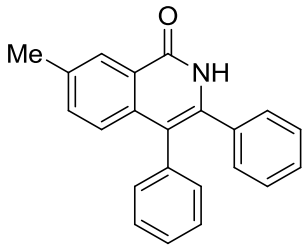
IR (neat, cm^{-1}): 2959 (w), 2865 (w), 1652 (s), 1489 (m), 1335 (m), 770 (s), 694 (s).

MS (EI) *m/z* (relative intensity): 353 ([M^+] 100), 338 (29), 296 (6), 165 (4), 77 (4).

HR-MS (EI) *m/z* for $C_{25}H_{23}NO$ calcd.: 353.1780.
found: 353.1778.

The analytical data are in accordance with those reported in the literature.[79]

Synthesis of 7-Methyl-3,4-diphenylisoquinolin-1(*2H*)-one (42bd)



42bd

The general procedure **F1** was followed using *N*-methoxy-3-methylbenzamide (**41bd**) (82.8 mg, 0.50 mmol), diphenylacetylene (**37a**) (178 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (28.8 mg, 29 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 2/1 $\rightarrow$ 1.5/1) yielded **42bd** (128 mg, 82%) as a colorless solid.

M. p.: > 283 °C (dec.).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.96 (s, 1H), 8.27 (s, 1H), 7.39 (dd, J = 8.4, 1.9 Hz, 1H), 7.32 – 7.11 (m, 11H), 2.48 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.6 (C_q), 136.8 (C_q), 136.3 (C_q), 135.9 (C_q), 135.8 (C_q), 135.2 (C_q), 134.1 (CH), 131.8 (CH), 129.1 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.2 (CH), 127.1 (CH), 125.7 (CH), 125.0 (C_q), 117.2 (C_q), 21.3 (CH_3).

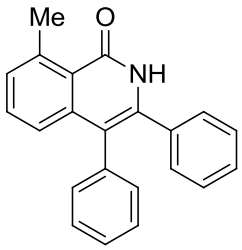
IR (neat, cm^{-1}): 3022 (w), 2917 (w), 1642 (s), 1488 (m), 1342 (m), 903 (m), 696 (s).

MS (EI) *m/z* (relative intensity): 311 ([M^+] 100), 292 (8), 267 (7), 178 (6), 43 (14).

HR-MS (EI) *m/z* for $C_{22}H_{17}NO$ calcd.: 311.1310.
found: 311.1312.

The analytical data are in accordance with those reported in the literature.[156]

Synthesis of 8-Methyl-3,4-diphenylisoquinolin-1(*2H*)-one (42bm)



42bm

The general procedure **F1** was followed using *N*-methoxy-2-methylbenzamide (**87h**) (82.7 mg, 0.50 mmol), diphenylacetylene (**37a**) (178 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (30.5 mg, 30 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 4/1) yielded **42bm** (29 mg, 19%) as an off-white solid.

M. p.: 284–285 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.70 (s, 1H), 7.39 (m, 1H), 7.31 – 7.13 (m, 12H), 2.91 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3/CD_3OD$): δ = 164.0 (C_q), 141.6 (C_q), 140.4 (C_q), 137.0 (C_q), 136.2 (C_q), 134.7 (C_q), 131.8 (CH), 131.7 (CH), 129.6 (CH), 129.1 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.1 (CH), 123.9 (CH), 123.3 (C_q), 117.5 (C_q), 23.7 (CH_3).

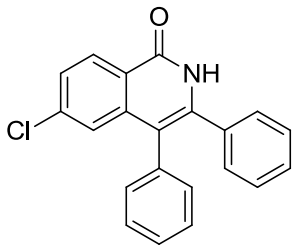
IR (neat, cm^{-1}): 3021 (w), 2869 (m), 1642 (s), 1440 (m), 1310 (s), 912 (m), 755 (m), 693 (s), 566 (s).

MS (EI) *m/z* (relative intensity): 311 ([M^+] 100), 267 (6), 182 (31), 167 (24), 107 (10), 77 (7).

HR-MS (EI) *m/z* for $C_{22}H_{17}NO$ calcd.: 311.1310.
found: 311.1302.

The analytical data are in accordance with those reported in the literature.[79]

Synthesis of 6-Chloro-3,4-diphenylisoquinolin-1(*2H*)-one (42bf)



42bf

The general procedure **F1** was followed using 4-chloro-*N*-methoxybenzamide (**41bf**) (92.5 mg, 0.50 mmol), diphenylacetylene (**37a**) (134 mg, 0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (30.3 mg, 30 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 2/1) yielded **42bf** (120 mg, 73%) as an off-white solid.

M. p.: 269–271 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.21 (s, 1H), 8.37 (d, J = 8.6 Hz, 1H), 7.42 (dd, J = 8.5, 1.9 Hz, 1H), 7.35 – 7.04 (m, 11H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.0 (C_q), 140.1 (C_q), 139.5 (C_q), 138.5 (C_q), 135.0 (C_q), 134.7 (C_q), 131.7 (CH), 129.3 (CH), 129.1 (CH), 128.9 (CH), 128.6 (CH), 128.4 (CH), 127.6 (CH), 127.2 (CH), 125.1 (CH), 123.5 (C_q), 116.4 (C_q).

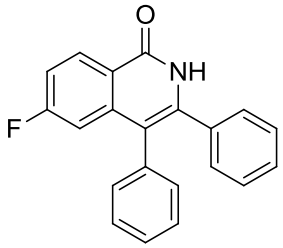
IR (neat, cm^{-1}): 3022 (m), 2891 (m), 1643 (s), 1593 (s), 1442 (s), 1079 (m), 883 (s), 695 (s), 556 (m).

MS (EI) *m/z* (relative intensity): 331 ([M^+] 100), 295 (16), 267 (11), 163 (11), 77 (9).

HR-MS (EI) *m/z* for $C_{21}H_{14}ClNO$ calcd.: 331.0764.
found: 331.0760.

The analytical data are in accordance with those reported in the literature.[79]

Synthesis of 6-Fluoro-3,4-diphenylisoquinolin-1(*2H*)-one (42be)



42be

The general procedure **F1** was followed using 4-fluoro-*N*-methoxybenzamide (**41be**) (84.5 mg, 0.50 mmol), diphenylacetylene (**37a**) (178 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (30.1 mg, 30 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 2/1) yielded **42be** (114 mg, 72%) as a colorless solid.

M. p.: 252–254 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.73 (s, 1H), 8.43 (dd, *J* = 8.9, 6.0 Hz, 1H), 7.37 – 7.10 (m, 11H), 6.96 (dd, *J* = 10.7, 2.5 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.6 (d, *J* = 252 Hz, C_q), 162.1 (C_q), 141.3 (d, *J* = 10 Hz, C_q), 138.5 (C_q), 135.2 (C_q), 134.7 (C_q), 131.6 (CH), 130.7 (d, *J* = 10 Hz, CH), 129.2 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH), 127.6 (CH), 121.7 (d, *J* = 2 Hz, C_q), 116.7 (d, *J* = 3 Hz, C_q), 115.2 (d, *J* = 24 Hz, CH), 110.9 (d, *J* = 24 Hz, CH).

^{19}F-NMR (282 MHz, $CDCl_3$) δ = - 105.0 (ddd, *J* = 10.8, 8.0, 6.0 Hz).

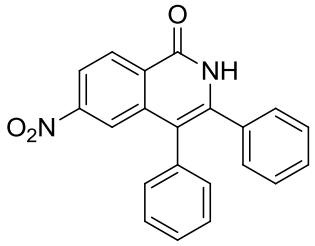
IR (neat, cm^{-1}): 3022 (w), 1643 (s), 1610 (s), 1447 (m), 1255 (m), 878 (m), 695 (s).

MS (EI) *m/z* (relative intensity): 315 ($[M^+]$ 100), 296 (18), 183 (12), 77 (8), 43 (11).

HR-MS (EI) *m/z* for $C_{21}H_{14}FNO$ calcd.: 315.1059.
found: 315.1067.

The analytical data are in accordance with those reported in the literature.[79]

Synthesis of 6-Nitro-3,4-diphenylisoquinolin-1(*2H*)-one (42bg)



42bg

The general procedure **F1** was followed using *N*-methoxy-4-nitrobenzamide (**41bg**) (98.1 mg, 0.50 mmol), diphenylacetylene (**37a**) (178 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (30.8 mg, 31 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 2/1) yielded **42bg** (147 mg, 86%) as a golden solid.

M. p.: 260–262 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.67 (s, 1H), 8.60 (md, J = 9.3 Hz, 1H), 8.43 – 8.00 (m, 2H), 7.40– 7.33 (m, 3H), 7.32 – 7.24 (m, 5H), 7.21 – 7.14 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.5 (C_q), 150.7 (C_q), 139.6 (C_q), 139.6 (C_q), 134.2 (C_q), 134.2 (C_q), 131.6 (CH), 129.6 (CH), 129.3 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.5 (C_q), 128.1 (CH), 121.2 (CH), 120.2 (CH), 117.1 (C_q).

IR (neat, cm^{-1}): 3025 (w), 1650 (s), 1526 (s), 1340 (s), 905 (m), 835 (m), 697 (s).

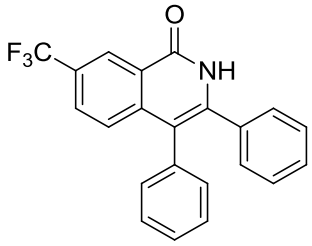
MS (EI) *m/z* (relative intensity): 342 ([M^+] 100), 295 (14), 267 (11), 190 (9), 165 (10), 77 (8).

HR-MS (EI) *m/z* for $C_{21}H_{14}N_2O_3$ calcd.: 342.1004.
found: 341.0996.

The analytical data are in accordance with those reported in the literature.[71]

Following general procedure **F2** using *N*-hydroxy-4-nitrobenzamide (**41cb**) (91.2 mg, 0.50 mmol), diphenylacetylene (**37a**) (178 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.4 mg, 5.0 mol%) and potassium 2,4,6-trimethylbenzoate (30.4 mg, 30.0 mol%) yielded **42bg** (113 mg, 66%) as a golden solid.

Synthesis of 7-(Trifluoromethyl)-3,4-diphenylisoquinolin-1(*2H*)-one (42bh)



42bh

The general procedure **F1** was followed using 3-trifluoromethyl-*N*-methoxybenzamide (**41bh**) (110 mg, 0.50 mmol), diphenylacetylene (**37a**) (178 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (30.7 mg, 30 mol%) at 100 °C. Purification by column chromatography (*n*-pentane/EtOAc: 4/1) yielded **42bh** (144 mg, 79%) as a colorless solid.

M. p.: > 232 °C (dec.).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.68 (s, 1H), 8.70 (m, 1H), 7.74 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.37 – 7.19 (m, 8H), 7.20 – 7.10 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.1 (C_q), 141.1 (C_q), 139.5 (C_q), 135.0 (C_q), 134.4 (C_q), 131.7 (CH), 129.2 (CH), 129.1 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 128.5 (q, *J* = 34 Hz, C_q), 127.7 (CH), 126.6 (CH), 125.2 (q, *J* = 4 Hz, CH), 124.9 (C_q), 123.9 (q, *J* = 272 Hz, C_q), 116.7 (C_q).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 62.4 (s).

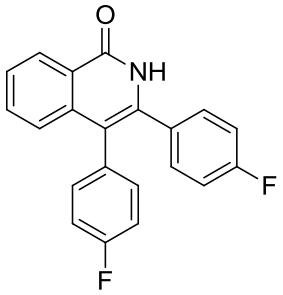
IR (neat, cm^{-1}): 3028 (w), 2865 (w), 1649 (s), 1619 (s), 1319 (s), 1113 (s), 835 (m), 675 (s), 464 (s).

MS (EI) *m/z* (relative intensity): 365 ([M^+] 100), 346 (21), 267 (7), 104 (4), 77 (6).

HR-MS (EI) *m/z* for $C_{22}H_{14}F_3NO$ calcd.: 365.1027.
found: 365.1020.

The analytical data are in accordance with those reported in the literature.[79]

Synthesis of 3,4-Di-(4'-fluorophenyl)isoquinolin-1(*2H*)-one (42bn)



42bn

The general procedure **F1** was followed using *N*-methoxybenzamide (**41ba**) (75.4 mg, 0.50 mmol), 1,2-bis(4-fluorophenyl)ethyne (**37b**) (214 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (30.4 mg, 30 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 3/1) yielded **42bn** (84 mg, 50%) as a colorless solid.

M. p.: > 293 °C (dec.).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.66 (s, 1H), 8.45 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.61 (ddd, *J* = 8.6, 7.1, 1.8 Hz, 1H), 7.51 (m, 1H), 7.31 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.27 – 7.18 (m, 2H), 7.18 – 7.08 (m, 2H), 7.09 – 6.92 (m, 4H).

^{13}C-NMR (75 MHz, $CDCl_3/CD_3OD$): δ = 163.0 (C_q), 162.5 (d, *J* = 250 Hz, C_q), 162.0 (d, *J* = 247 Hz, C_q), 138.4 (C_q), 136.5 (C_q), 133.3 (d, *J* = 8 Hz, CH), 132.9 (CH), 131.4 (C_q), 131.2 (d, *J* = 9 Hz, CH), 130.7 (d, *J* = 4 Hz, C_q), 127.4 (CH), 126.8 (CH), 125.3 (CH), 124.9 (C_q), 116.6 (C_q), 115.6 (d, *J* = 6 Hz, CH), 115.2 (d, *J* = 6 Hz, CH).

^{19}F-NMR (283 MHz, $CDCl_3$) δ = **-** (110.2 – 112.6) (m), **-** (113.4 – 116.5) (m).

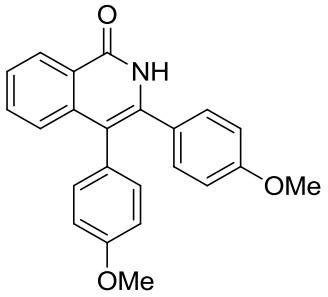
IR (neat, cm^{-1}): 3048 (w), 1649 (s), 1505 (s), 1222 (s), 1153 (m), 772 (s), 518 (s).

MS (EI) *m/z* (relative intensity): 333 ([M^+] 100), 314 (21), 182 (12), 122 (6), 95 (6).

HR-MS (EI) *m/z* for $C_{21}H_{13}F_2NO$ calcd.: 333.0965.
found: 333.0967.

The analytical data are in accordance with those reported in the literature.[79]

Synthesis of 3,4-Di-(4'-methoxyphenyl)isoquinolin-1(*2H*)-one (42bo)



42bo

The general procedure **F1** was followed using *N*-methoxybenzamide (**41ba**) (75.5 mg, 0.50 mmol), 1,2-bis(4-methoxyphenyl)ethyne (**37c**) (238 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (30.3 mg, 30 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 4/1) yielded **42bo** (29 mg, 16%) as an off-white solid.

M. p.: 265–257 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.16 (s, 1H), 8.46 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.57 (ddd, *J* = 8.3, 7.1, 1.5 Hz, 1H), 7.47 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.35 (m, 1H), 7.20 – 7.04 (m, 4H), 6.82 (dd, *J* = 27.6, 8.7 Hz, 4H), 3.82 (s, 3H), 3.78 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.7 (C_q), 159.5 (C_q), 158.7 (C_q), 139.1 (C_q), 136.9 (C_q), 132.8 (CH), 132.5 (CH), 130.4 (CH), 128.0 (C_q), 127.5 (C_q), 127.4 (CH), 126.3 (CH), 125.6 (CH), 124.9 (C_q), 116.3 (C_q), 113.9 (CH), 113.8 (CH), 55.2 (CH_3), 55.2 (CH_3).

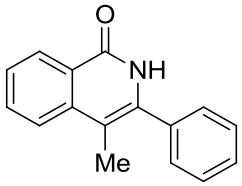
IR (neat, cm^{-1}): 3002 (w), 2833 (w), 1645 (s), 1509 (s), 1242 (s), 1111 (m), 1031 (s), 734 (m), 545 (s).

MS (EI) *m/z* (relative intensity): 357 ([M^+] 100), 342 (10), 282 (4), 152 (7), 44 (4).

HR-MS (EI) *m/z* for $C_{23}H_{19}NO_3$ calcd.: 357.1365.
found: 357.1361.

The analytical data is in accordance with those reported in the literature.[79]

Synthesis of 4-Methyl-3-phenylisoquinolin-1(*2H*)-one (42bp)



42bp

The general procedure **F1** was followed using *N*-methoxybenzamide (**41ba**) (75.8 mg, 0.50 mmol), 1-phenyl-1-propyne (**37d**) (119 mg, 1.03 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (29.0 mg, 29 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 2/1 → 1/2) yielded **42bp** (83 mg, 71%) as an off-white solid.

M. p.: 208–211 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.03 (s, 1H), 8.45 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 3.6 Hz, 2H), 7.58 – 7.41 (m, 6H), 2.27 (s, 3H).

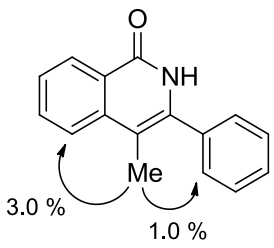
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.4 (C_q), 138.8 (C_q), 136.6 (C_q), 135.4 (C_q), 132.7 (CH), 129.2 (CH), 129.1 (CH), 128.8 (CH), 127.8 (CH), 126.4 (CH), 125.5 (C_q), 123.6 (CH), 109.1 (C_q), 13.8 (CH_3).

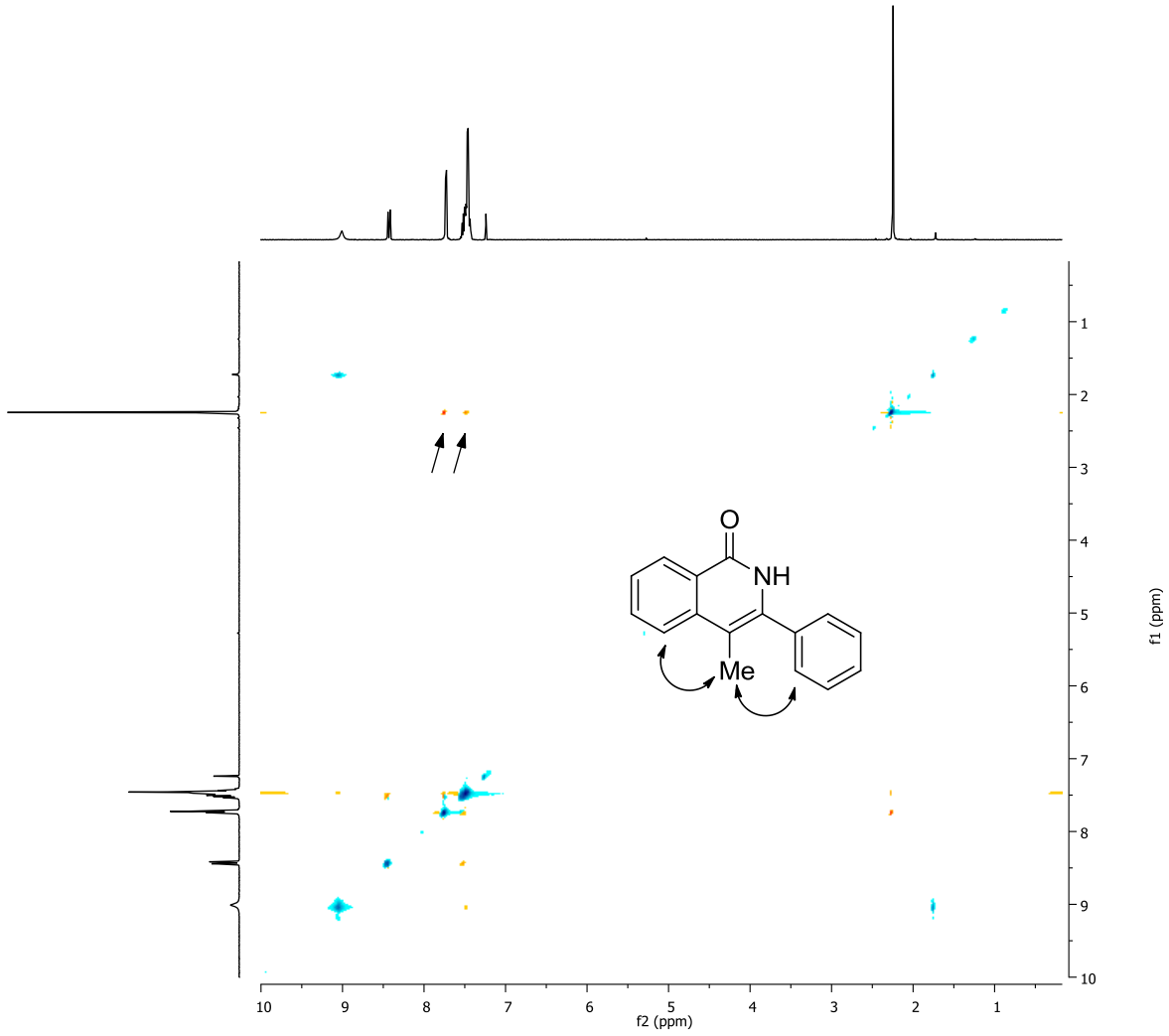
IR (neat, cm^{-1}): 3027 (w), 2913 (w), 1643 (s), 1489 (m), 1350 (m), 1154 (m), 758 (s), 700 (s), 482 (s).

MS (EI) *m/z* (relative intensity): 235 ([M^+] 89), 234 (100), 216 (21), 178 (8), 102 (9), 77 (20).

HR-MS (EI) *m/z* for $C_{16}H_{13}NO$ calcd.: 235.0997.
found: 235.1006.

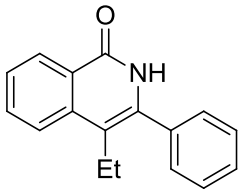
nOe:





The analytical data are in accordance with those reported in the literature.[71]

Synthesis of 4-Ethyl-3-phenylisoquinolin-1(*2H*)-one (42bq)



42bq

The general procedure **F1** was followed using *N*-methoxybenzamide (**41ba**) (75.6 mg, 0.50 mmol), 1-phenyl-1-butyne (**37e**) (0.14 mL, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (30.4 mg, 30 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 1/1) yielded **42bq** (104 mg, 83%) as an off-white solid.

M. p.: > 214 °C (dec.).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.09 (s, 1H), 8.44 (m, 1H), 7.82 – 7.68 (m, 2H), 7.56 – 7.41 (m, 6H), 2.67 (q, J = 7.5 Hz, 2H), 1.20 (t, J = 7.5 Hz, 3H).

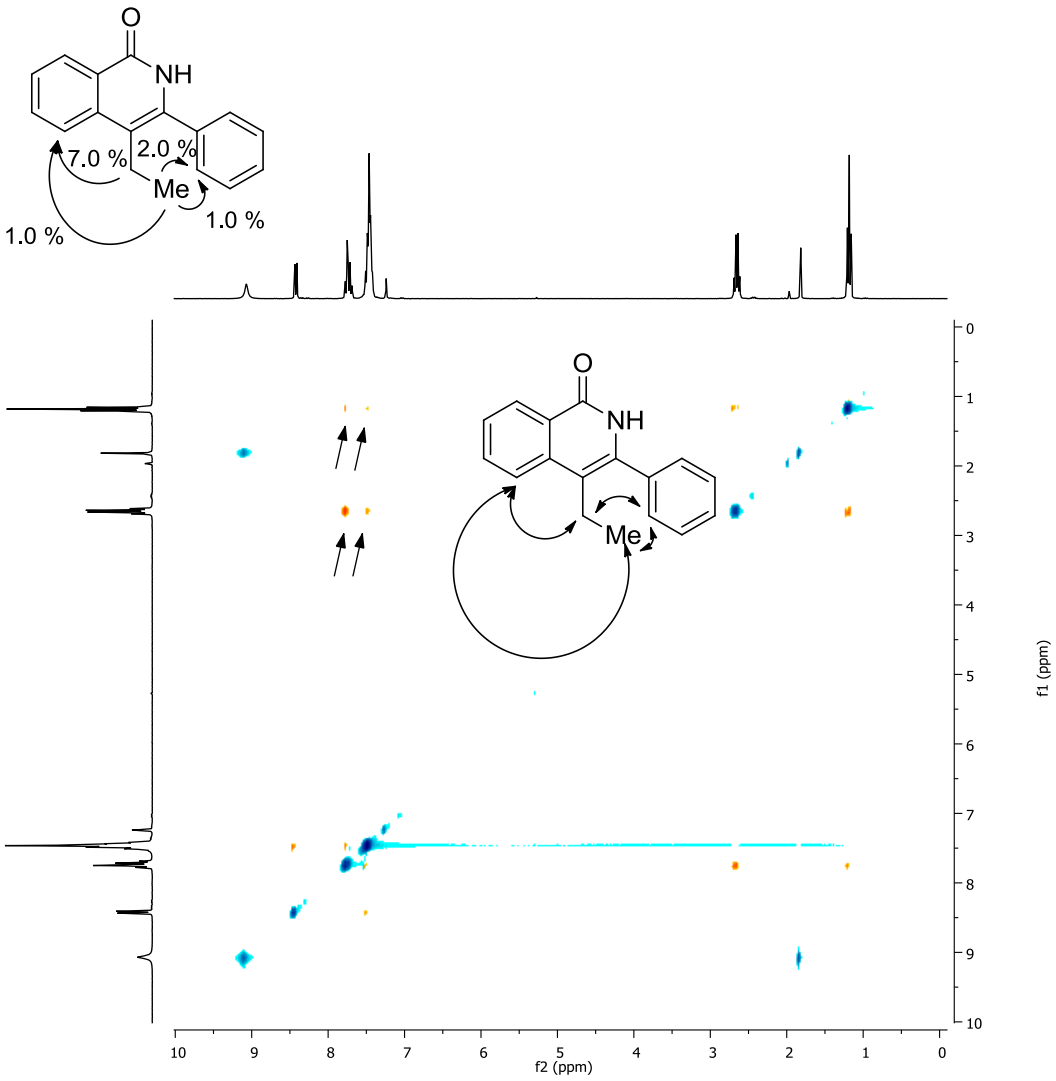
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.2 (C_q), 137.7 (C_q), 136.6 (C_q), 135.4 (C_q), 132.6 (CH), 129.1 (CH), 128.8 (CH), 128.8 (CH), 128.0 (CH), 126.2 (CH), 125.9 (C_q), 123.6 (CH), 115.5 (C_q), 20.5 (CH_2), 15.3 (CH_3).

IR (neat, cm^{-1}): 3164 (w), 2967 (w), 1642 (s), 1488 (m), 1350 (m), 758 (s), 693 (s).

MS (EI) *m/z* (relative intensity): 249 ([M^+] 59), 234 (100), 216 (29), 178 (8), 115 (9), 77(13).

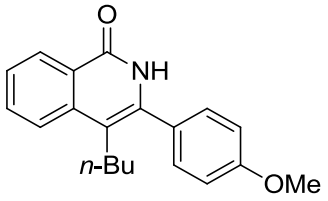
HR-MS (EI) *m/z* for $C_{17}H_{15}NO$ calcd.: 249.1154.
found: 249.1154.

nOe:



The analytical data are in accordance with those reported in the literature.[156]

Synthesis of 4-*n*-Butyl-3-(4'-methoxyphenyl)isoquinolin-1(*2H*)-one (42br)



42br

The general procedure **F1** was followed using *N*-methoxybenzamide (**41ba**) (72.7 mg, 0.48 mmol), 1-(4-methoxyphenyl)-1-hexyne (**37f**) (167 mg, 0.89 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (30.2 mg, 30 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 3/1 → 1/1) yielded **42br** (101 mg, 69%) as a colorless solid.

M. p.: 167–168 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.75 (s, 1H), 8.45 (d, J = 8.1 Hz, 1H), 7.77 – 7.67 (m, 2H), 7.49 (ddd, J = 8.1, 5.7, 2.6 Hz, 1H), 7.36 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 8.6 Hz, 2H), 3.90 (s, 3H), 2.69 – 2.56 (m, 2H), 1.61 – 1.46 (m, 2H), 1.41 – 1.18 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H).

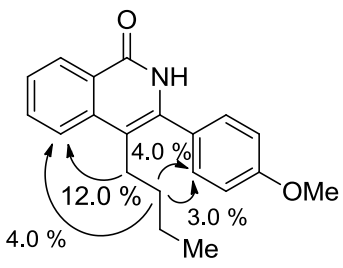
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.2 (C_q), 160.1 (C_q), 138.1 (C_q), 136.6 (C_q), 132.6 (CH), 130.2 (CH), 127.9 (CH), 127.9 (C_q), 126.1 (CH), 125.7 (C_q), 123.7 (CH), 114.3 (C_q), 114.1 (CH), 55.4 (CH_3), 32.8 (CH_2), 27.1 (CH_2), 22.8 (CH_2), 13.8 (CH_3).

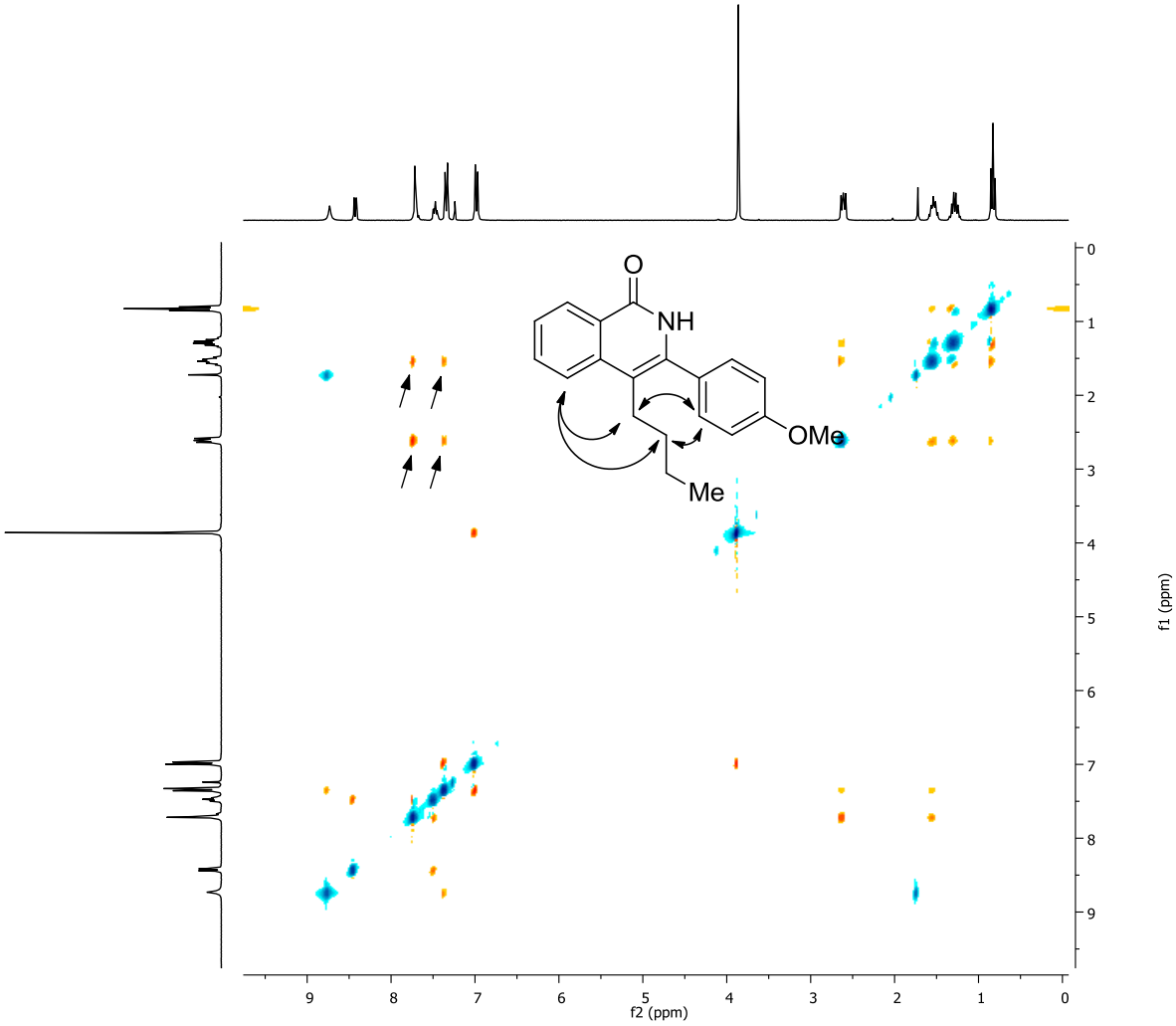
IR (neat, cm^{-1}): 2955 (m), 2868 (m), 1634 (s), 1511 (s), 1462 (m), 1245 (s), 1022 (m), 845 (m), 532 (s).

MS (EI) *m/z* (relative intensity): 307 ([M^+] 33), 264 (100), 233 (14), 165 (3), 43 (26).

HR-MS (EI) *m/z* for $C_{20}H_{21}NO_2$ calcd.: 307.1572.
found: 307.1583.

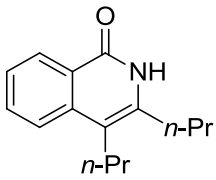
nOe:





The analytical data are in accordance with those reported in the literature.[156]

Synthesis of 3,4-Di-(*n*-propyl)isoquinolin-1(*2H*)-one (42bs)



42bs

The general procedure **F1** was followed using *N*-methoxybenzamide (**41ba**) (75.7 mg, 0.50 mmol), 4-octyne (**37g**) (0.15 mL, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol%) and potassium 2,4,6-trimethylbenzoate (29.5 mg, 29 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 2/1) yielded **42bs** (74 mg, 65%) as a colorless solid.

M. p.: 188–190 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.98 (s, 1H), 8.46 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 3.4 Hz, 2H), 7.44 (dt, *J* = 8.1, 4.4 Hz, 1H), 2.86 – 2.44 (m, 4H), 1.82 – 1.54 (m, 4H), 1.06 (t, *J* = 7.3 Hz, 3H), 1.04 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.6 (C_q), 138.5 (C_q), 138.0 (C_q), 132.3 (CH), 127.7 (CH), 125.3 (CH), 125.1 (C_q), 123.0 (CH), 112.9 (C_q), 32.9 (CH_2), 28.6 (CH_2), 23.6 (CH_2), 22.7 (CH_2), 14.3 (CH_3), 14.0 (CH_3).

IR (neat, cm^{-1}): 2955 (m), 2869 (m), 1652 (s), 1471 (m), 1321 (m), 1166 (m), 874 (m), 615 (m), 496 (m).

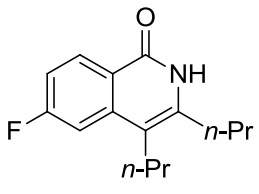
MS (EI) *m/z* (relative intensity): 229 ([M^+] 28), 200 (100), 172 (9), 115 (6), 77 (4).

HR-MS (EI) *m/z* for $C_{15}H_{19}NO$ calcd.: 229.1467.
found: 229.1462.

The analytical data are in accordance with those reported in the literature.[72]

Following general procedure **F2** using *N*-hydroxybenzamide (**41ca**) (68.6 mg, 0.50 mmol), 4-octyne (**37g**) (0.15 mL, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol%) and potassium 2,4,6-trimethylbenzoate (32 mg, 32 mol%) in H_2O (2.0 mL) at 60 °C yielded **42bs** (51 mg, 45%) as a colorless solid.

Synthesis of 6-Fluoro-3,4-di-(*n*-propyl)isoquinolin-1(*2H*)-one (42bt)



42bt

The general procedure **F1** was followed using 4-fluoro-*N*-methoxybenzamide (**41be**) (84.5 mg, 0.50 mmol), 4-octyne (**37g**) (0.14 mL, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and potassium 2,4,6-trimethylbenzoate (30.1 mg, 30 mol%). Purification by

column chromatography (*n*-pentane/EtOAc: 4/1) yielded **42bt** (80 mg, 65%) as an off-white solid.

M. p.: 170–172 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.28 (s, 1H), 8.45 (dd, *J* = 8.8, 6.3 Hz, 1H), 7.27 (dd, *J* = 10.8, 2.6 Hz, 1H), 7.13 (td, *J* = 8.5, 2.2 Hz, 1H), 2.75 – 2.53 (m, 4H), 1.82 – 1.68 (m, 2H), 1.66 – 1.51 (m, 2H), 1.06 (t, *J* = 6.6 Hz, 3H), 1.04 (t, *J* = 6.8 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.6 (d, *J* = 251 Hz, C_q), 163.1 (C_q), 141.0 (d, *J* = 10 Hz, C_q), 139.7 (C_q), 130.7 (d, *J* = 10 Hz, CH), 121.7 (C_q), 113.9 (d, *J* = 24 Hz, CH), 112.6 (d, *J* = 4 Hz, C_q), 108.3 (d, *J* = 23 Hz, CH), 33.0 (CH_2), 28.7 (CH_2), 23.3 (CH_2), 22.7 (CH_2), 14.2 (CH_3), 14.0 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$) δ = - 106.2 (ddd, *J* = 11.0, 8.1, 6.2 Hz).

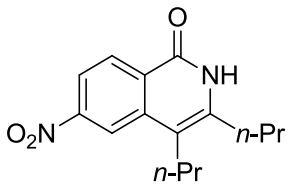
IR (neat, cm^{-1}): 2953 (m), 2870 (m), 1666 (s), 1613 (s), 1460 (m), 1186 (m), 981 (m), 862 (m), 477 (s).

MS (EI) *m/z* (relative intensity): 247 ([M^+] 25), 218 (100), 190 (11), 133 (5), 43 (2).

HR-MS (EI) *m/z* for $C_{15}H_{18}FNO$ calcd.: 247.1372.
found: 247.1372.

The analytical data are in accordance with those reported in the literature.[156]

Synthesis of 6-Nitro-3,4-di-(*n*-propyl)isoquinolin-1(*2H*)-one (42bu)



42bu

The general procedure **F1** was followed using *N*-methoxy-4-nitrobenzamide (**41bg**) (98.1 mg, 0.50 mmol), 4-octyne (**37g**) (0.14 mL, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and potassium 2,4,6-trimethylbenzoate (30.0 mg, 30 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 2/1) yielded **42bu** (108 mg, 79%) as a yellow solid.

M. p.: 200–203 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.59 (s, 1H), 8.57 (d, *J* = 8.8 Hz, 1H), 8.53 (d, *J* = 2.0 Hz, 1H), 8.18 (dd, *J* = 8.8, 2.1 Hz, 1H), 2.90 – 2.49 (m, 4H), 1.79 (dt, *J* = 7.3, 7.3 Hz, 2H), 1.64 (dt, *J* = 7.3, 7.3 Hz, 2H), 1.10 (t, *J* = 7.3 Hz, 3H), 1.08 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.7 (C_q), 150.5 (C_q), 141.0 (C_q), 139.2 (C_q), 129.7 (CH), 128.6 (C_q), 118.9 (CH), 118.9 (CH), 113.3 (C_q), 33.0 (CH_2), 28.5 (CH_2), 23.7 (CH_2), 22.7 (CH_2), 14.2 (CH_3), 14.0 (CH_3).

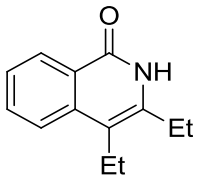
IR (neat, cm^{-1}): 2962 (m), 1667 (s), 1526 (m), 1338 (s), 1153 (m), 891 (m), 742 (s).

MS (EI) *m/z* (relative intensity): 274 ([M^+] 22), 245 (100), 199 (32), 115 (8), 43 (5).

HR-MS (EI) *m/z* for $C_{15}H_{18}N_2O_3$ calcd.: 274.1317.
found: 274.1307.

The analytical data are in accordance with those reported in the literature.[156]

Synthesis of 3,4-Diethylisoquinolin-1(*2H*)-one (42bv)



42bv

The general procedure **F1** was followed using *N*-methoxybenzamide (**41ba**) (75.5 mg, 0.50 mmol), 3-hexyne (**37h**) (0.11 mL, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (30.4 mg, 30 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 2/1 → 1/1 → 1/3) yielded **42bv** (24 mg, 24%) as a brown solid.

M. p.: 174–178 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.56 (s, 1H), 8.45 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.77 – 7.58 (m, 2H), 7.43 (ddd, *J* = 8.1, 5.5, 2.6 Hz, 1H), 2.73 (m, 4H), 1.32 (t, *J* = 7.6 Hz, 3H), 1.21 (t, *J* = 7.5 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.6 (C_q), 138.8 (C_q), 138.2 (C_q), 132.4 (CH), 127.8 (CH), 125.3 (CH), 125.2 (C_q), 122.8 (CH), 113.9 (C_q), 24.3 (CH_2), 19.5 (CH_2), 14.9 (CH_3), 13.9 (CH_3).

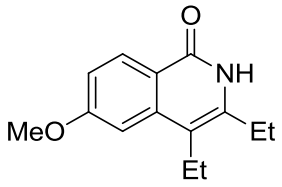
IR (neat, cm^{-1}): 3022 (m), 1649 (s), 1631 (s), 1474 (s), 1164 (m), 1055 (m), 769 (s), 691 (m), 521 (m).

MS (EI) *m/z* (relative intensity): 201 ([M^+] 40), 186 (100), 168 (6), 115 (10), 43 (16).

HR-MS (EI) *m/z* for $C_{13}H_{15}NO$ calcd.: 201.1154.
found: 201.1154.

The analytical data are in accordance with those reported in the literature.[79]

Synthesis of 6-Methoxy-3,4-diethylisoquinolin-1(*2H*)-one (42bw)



42bw

The general procedure **F1** was followed using *N*-methoxy-4-methoxybenzamide (**41bb**) (90.6 mg, 0.50 mmol), 3-hexyne (**37h**) (0.11 mL, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and potassium 2,4,6-trimethylbenzoate (30.3 mg, 30 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 2/1) yielded **42bw** (44 mg, 38%) as a brown solid.

M. p.: > 180 °C (dec.).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.80 (s, 1H), 8.39 (m, 1H), 7.07 – 6.98 (m, 2H), 3.93 (s, 3H), 2.79 – 2.65 (m, 4H), 1.32 (t, *J* = 7.6 Hz, 3H), 1.21 (t, *J* = 7.5 Hz, 3H).

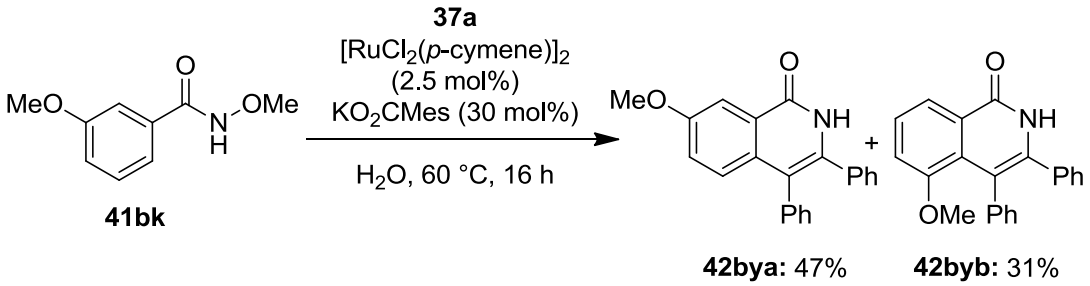
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.3 (C_q), 162.9 (C_q), 140.3 (C_q), 139.7 (C_q), 129.8 (CH), 119.1 (C_q), 113.9 (CH), 113.4 (C_q), 104.8 (CH), 55.4 (CH_3), 24.3 (CH_2), 19.6 (CH_2), 14.7 (CH_3), 13.9 (CH_3).

IR (neat, cm^{-1}): 2966 (m), 2872 (m), 1643 (s), 1606 (s), 1454 (s), 1204 (m), 1033 (m), 918 (s), 667 (m).

MS (EI) *m/z* (relative intensity): 231 ([M^+] 36), 216 (100), 173 (5), 115 (5), 77 (5).

HR-MS (EI) *m/z* for $C_{14}H_{17}NO_2$ calcd.: 231.1259.
found: 231.1265.

Synthesis of 5-Methoxy-3,4-diphenylisoquinolin-1(*2H*)-one (42byb) and 7-Methoxy-3,4-diphenylisoquinolin-1(*2H*)-one (42bya)

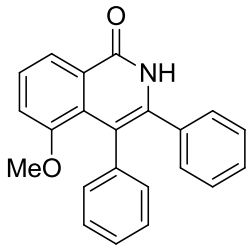


41bk

42bya: 47% **42byb:** 31%

The general procedure **F1** was followed using *N*-methoxy-3-methoxybenzamide (**41bk**) (90.2 mg, 0.50 mmol), diphenylacetylene (**37a**) (178 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.5 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (30.1 mg, 30 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 1/1) yielded **42byb** (51 mg, 31%) and **42bya** (77 mg, 47%) as off-white solids.

5-Methoxy-3,4-diphenylisoquinolin-1(*2H*)-one (42byb)



42byb

M. p.: 260–261 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.21 (s, 1H), 8.10 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.43 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.22 – 6.99 (m, 11H), 3.32 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.1 (C_q), 156.5 (C_q), 139.5 (C_q), 137.3 (C_q), 135.5 (C_q), 130.9 (CH), 129.4 (CH), 128.6 (C_q), 128.2 (CH), 128.0 (CH), 127.4 (CH), 127.0 (C_q), 126.7 (CH), 125.8 (CH), 120.0 (CH), 115.4 (C_q), 115.2 (CH), 55.9 (CH_3).

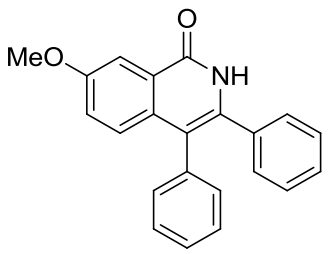
IR (neat, cm^{-1}): 3018 (w), 2883 (w), 1640 (s), 1550 (m), 1271 (m), 1046 (m), 897 (m), 698 (s).

MS (EI) *m/z* (relative intensity): 327 ([M^+] 100), 312 (24), 294 (13), 152 (8), 77 (13), 69 (15).

HR-MS (EI) *m/z* for $C_{22}H_{17}NO_2$ calcd.: 327.1259.
found: 327.1255.

The analytical data are in accordance with those reported in the literature.[79]

7-Methoxy-3,4-diphenylisoquinolin-1(*2H*)-one (42bya)



42bya

M. p.: 247–248 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.13 (s, 1H), 7.86 (d, *J* = 2.7 Hz, 1H), 7.34 – 7.10 (m, 12H), 3.93 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.3 (C_q), 158.6 (C_q), 135.8 (C_q), 135.1 (C_q), 134.6 (C_q), 132.7 (C_q), 131.7 (CH), 129.2 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 127.4 (CH), 127.3 (CH), 126.3 (C_q), 123.1 (CH), 117.2 (C_q), 107.2 (CH), 55.7 (CH_3).

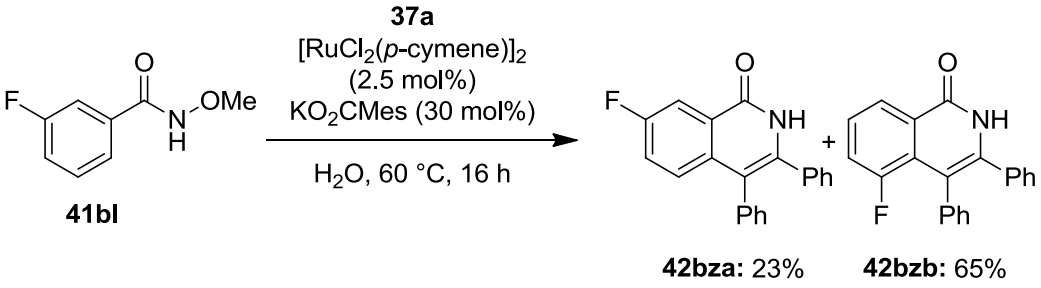
IR (neat, cm^{-1}): 3137 (w), 2966 (w), 1635 (s), 1490 (s), 1368 (m), 1248 (m), 1029 (m), 696 (s), 542 (s).

MS (EI) *m/z* (relative intensity): 327 ([M^+] 100), 312 (35), 254 (8), 152 (5), 77 (5).

HR-MS (EI) *m/z* for $C_{22}H_{17}NO_2$ calcd.: 327.1259.
found: 327.1261.

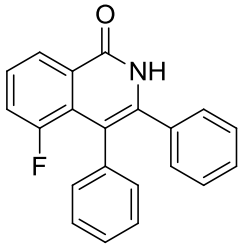
The analytical data are in accordance with those reported in the literature.[79]

Synthesis of 5-Fluoro-3,4-diphenylisoquinolin-1(*2H*)-one (42bzb) and 7-Fluoro-3,4-diphenylisoquinolin-1(*2H*)-one (42bza)



The general procedure **F1** was followed using 3-fluoro-*N*-methoxy-benzamide (**41bl**) (84.5 mg, 0.50 mmol), diphenylacetylene (**37a**) (178 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol%) and potassium 2,4,6-trimethylbenzoate (32.0 mg, 32 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 1/1) yielded **42bzb** (102 mg, 65%) and **42bza** (36 mg, 23%) as a colorless solids.

5-Fluoro-3,4-diphenylisoquinolin-1(*2H*)-one (42bzb)



42bzb

M. p.: 250–252 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.70 (s, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 7.44 (td, *J* = 8.0, 4.5 Hz, 1H), 7.32 – 7.12 (m, 11H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.5 (C_q, J = 3 Hz), 158.7 (C_q, J = 256 Hz), 138.4 (C_q), 137.4 (C_q,), 137.3 (C_q), 134.8 (C_q), 131.0 (CH, J = 4 Hz), 129.2 (CH), 128.7 (CH), 128.3 (CH), 127.5 (CH), 127.4 (CH, J = 3 Hz), 127.3 (C_q, J = 14 Hz), 126.9 (CH), 123.7 (CH, J = 4 Hz), 119.8 (CH, J = 23 Hz), 113.3 (C_q, J = 2 Hz).

^{19}F-NMR (282 MHz, $CDCl_3$) δ = - 107.2 (dd, J = 12.4, 4.5 Hz).

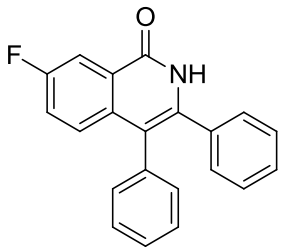
IR (neat, cm^{-1}): 3018 (w), 2883 (w), 1649 (s), 1489 (m), 1252 (m), 1065 (m), 696 (s), 569 (m).

MS (EI) *m/z* (relative intensity): 315 ([M^+] 100), 296 (7), 183 (11), 104 (4), 44 (23).

HR-MS (EI) *m/z* for $C_{21}H_{14}FNO$ calcd.: 315.1059.
found: 315.1054.

The analytical data are in accordance with those reported in the literature.[156]

7-Fluoro-3,4-diphenylisoquinolin-1(*2H*)-one (42bza)



42bza

M. p.: 258–260 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.74 (s, 1H), 8.06 (dd, J = 9.3, 2.4 Hz, 1H), 7.37 – 7.21 (m, 10H), 7.18 – 7.12 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.9 (d, J = 4 Hz, C_q), 161.1 (d, J = 248 Hz, C_q), 136.4 (d, J = 3 Hz, C_q), 135.5 (C_q), 135.2 (d, J = 2 Hz, C_q), 134.7 (C_q), 131.64 (CH), 129.2 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.2 (d, J = 8 Hz, CH), 127.4 (CH), 126.7 (d, J = 8 Hz, C_q), 121.1 (d, J = 23 Hz, CH), 116.7 (C_q), 112.4 (d, J = 23 Hz, CH).

^{19}F-NMR (282 MHz, $CDCl_3$) δ = - 113.6 (ddd, J = 9.2, 7.8, 5.2 Hz).

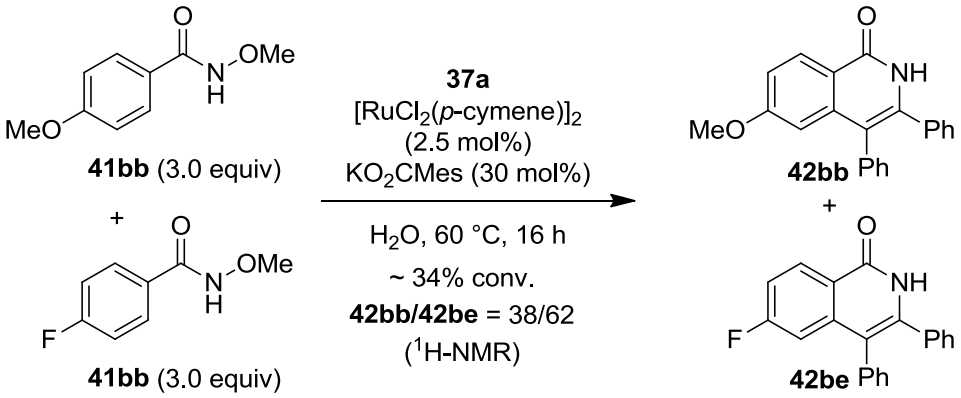
IR (neat, cm^{-1}): 3024 (w), 2923 (m), 1641 (s), 1486 (m), 1342 (m), 894 (m), 782 (m), 698 (s), 538 (s).

MS (EI) *m/z* (relative intensity): 315 ([M^+] 100), 296 (16), 183 (14), 104 (6), 77 (11).

HR-MS (EI) *m/z* for $C_{21}H_{14}FNO$ calcd.: 315.1059.
found: 315.1056.

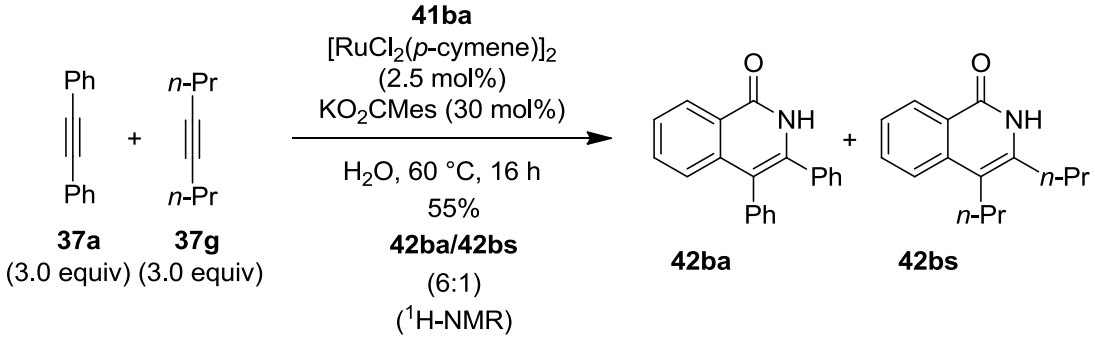
The analytical data are in accordance with those reported in the literature.[156]

Intermolecular Competition Experiment with Substituted *N*-Methoxybenzamides 41bb and 41be:



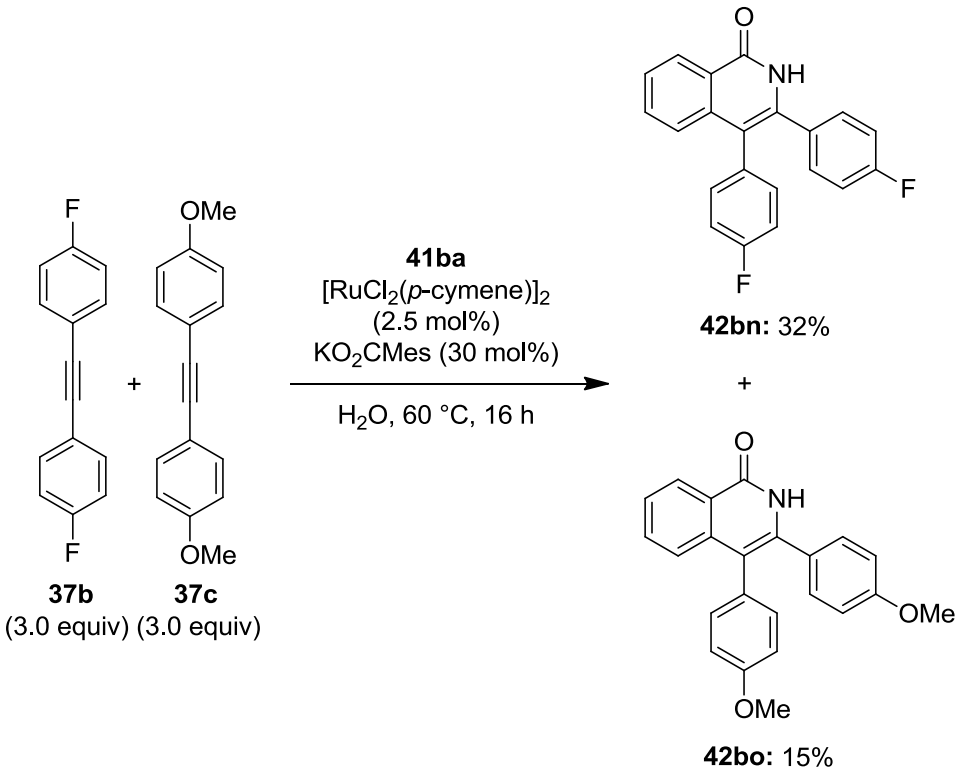
The general procedure **F1** was followed using *N*,4-dimethoxybenzamide (**41bb**) (272 mg, 1.50 mmol), 4-fluoro-*N*-methoxybenzamide (**41be**) (254 mg, 1.50 mmol), diphenylacetylene (**37a**) (89.1 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol %) and potassium 2,4,6-trimethylbenzoate (30.4 mg, 30 mol%). The ratio of **42bb** and **42be** in the crude mixture of products was determined to be 38/62 by ^{1}H-NMR spectroscopy.

Intermolecular Competition Experiment with Alkynes 37a and 37g:



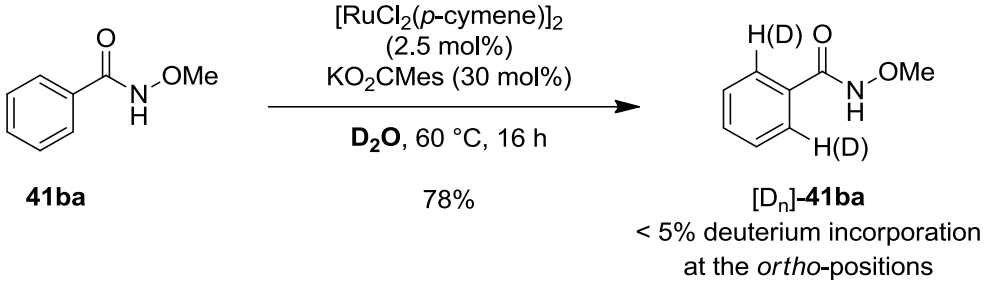
The general procedure **F1** was followed using *N*-methoxybenzamide (**41ba**) (75.6 mg, 0.50 mmol), diphenylacetylene (**37a**) (268 mg, 1.50 mmol), 4-octyne (**37g**) (0.22 mL, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol %) and potassium 2,4,6-tri-methylbenzoate (30.1 mg, 30 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 4/1) yielded a mixture of **42ba** and **42bs** (66 mg, 55%). The ratio of **42ba**/**42bs** was determined to be 6/1 by ^{1}H-NMR spectroscopy.

Intermolecular Competition Experiment with Alkynes 37b and 37c:



The general procedure **F1** was followed using *N*-methoxybenzamide (**41ba**) (75.5 mg, 0.50 mmol), 1,2-bis(4-fluorophenyl)ethyne (**37b**) (321 mg, 1.50 mmol), 1,2-bis(4-methoxyphenyl)ethyne (**37c**) (358 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol %) and potassium 2,4,6-trimethylbenzoate (30.2 mg, 30 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 3/1 → 1/2) yielded **42bn** (53 mg, 32%) and **42bo** (27 mg, 15%).

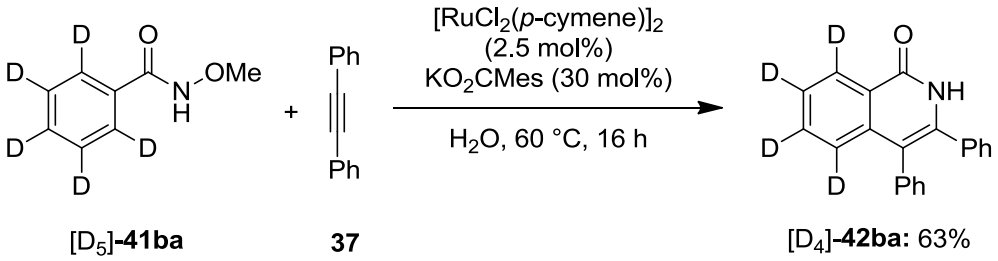
Experiment with isotopically-labeled solvent:



The general procedure **F1** was followed using *N*-methoxybenzamide (**41ba**) (75.5 mg, 0.50 mmol,) $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol %) and potassium 2,4,6-tri-methylbenzoate (30.3 mg, 30 mol%) in D_2O (2.0 mL). Purification by column chromatography (*n*-pentane/EtOAc: 1/1) yielded **41ba** (59 mg, 78%) with < 5% deuterium incorporation at the *ortho*-positions as estimated by ^{1}H-NMR spectroscopy.

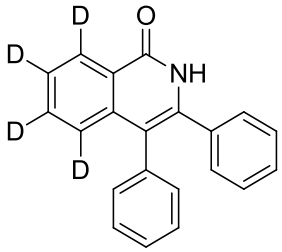
Ruthenium-Catalyzed Reaction with [D$_5$]-41ba

Synthesis of [D$_4$]-3,4-Diphenylisoquinolin-1(*2H*)-one ([D$_4$]-42ba)



The general procedure **F1** was followed using [D$_5$]-*N*-methoxybenzamide ([(D$_5$]-**41ba**) (84.7 mg, 0.54 mmol), diphenylacetylene (**37a**) (178 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$

(7.6 mg, 2.5 mol %) and potassium 2,4,6-trimethylbenzoate (30.3 mg, 30 mol%). Purification by column chromatography (*n*-pentane/EtOAc: 2/1) yielded [D_4]-**42ba** (103 mg, 63%) as colorless solid.



[D_5]-**42ba**

M. p.: 254–256 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.33 (s, 1H), 7.35 – 7.15 (m, 10H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 161.4 (C_q), 138.3 (C_q), 137.8 (C_q), 135.6 (C_q), 134.3 (C_q), 131.7 (t, *J* = 23 Hz, CD), 131.4 (CH), 129.6 (CH), 128.0 (CH), 127.9 (CH), 127.4 (CH), 126.8 (CH), 126.2 (t, *J* = 23 Hz, CD), 125.5 (t, *J* = 23 Hz, CD), 124.7 (C_q), 124.3 (t, *J* = 23 Hz, CD), 115.2 (C_q).

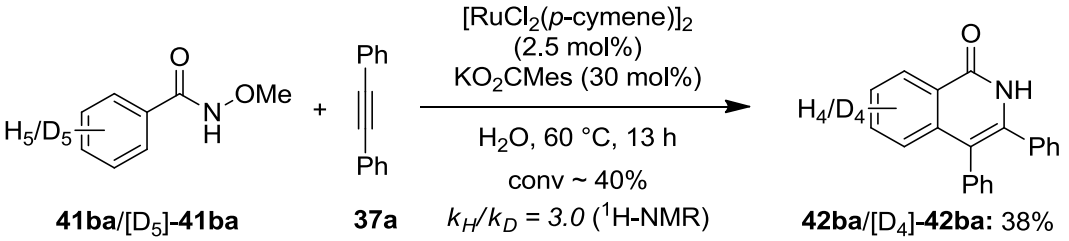
IR (neat, cm^{-1}): 3017 (w), 2897 (w), 1641 (s), 1443 (m), 1326 (s), 880 (m), 697 (s), 529 (m).

MS (EI) *m/z* (relative intensity): 301 ([M^+] 100), 282 (10), 169 (7), 105 (8), 77 (6).

HR-MS (EI) *m/z* for $C_{21}H_{11}D_4NO$ calcd.: 301.1405.
found: 301.1404.

The analytical data are in accordance with those reported in the literature.[156]

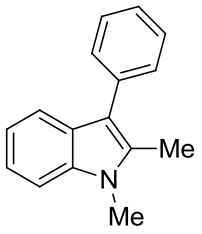
Intermolecular Competition Experiment with 41ba and [D_5]-41ba:



41ba/[D_5]-**41ba** **37a** **42ba**/[D_4]-**42ba:** 38%

The general procedure **F1** was followed using *N*-methoxybenzamide (**41ba**) (226 mg, 1.50 mmol), [D_5]-*N*-methoxybenzamide ([D_5]-**41ba**) (234mg, 1.50 mmol), diphenylacetylene (**37a**) (89.0 mg, 0.50 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (7.5 mg, 2.5 mol %) and potassium 2,4,6-trimethylbenzoate (30.3 mg, 0.15 mmol) in H_2O (2.0 mL) under nitrogen atmosphere for 13 h. Purification by column chromatography (*n*-pentane/EtOAc: 3/1) gave a mixture of products **42ba** and [D_4]-**42ba** (57 mg, 38%). The kinetic isotope effect of this reaction was thus determined to be $k_H/k_D \approx 3.0$ as estimated by ^{1}H-NMR spectroscopy.

Synthesis of 1,2-Dimethyl-3-phenylindole (50bc)



50bc

The general procedure **G** was followed, using 1,2-dimethylindole (**48d**) (72.9 mg, 0.50 mmol) and diphenyliodonium-4-methylbenzenesulfonate (**46da**) (452 mg, 1.00 mmol). Purification by column chromatography on silica (*n*-pentane → *n*-pentane/Et_2O: 50/1 → 40/1) yielded **50bc** (60 mg, 54%) as an off-white solid.

M. p.: 111–113 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, J = 7.8 Hz, 1H), 7.56 – 7.43 (m, 4H), 7.38 – 7.28 (m, 2H), 7.24 (m, 1H), 7.17 – 7.09 (m, 1H), 3.76 (s, 3H), 2.51 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 136.6 (C_q), 135.8 (C_q), 133.3 (C_q), 129.7 (CH), 128.4 (CH), 126.9 (C_q), 125.6 (CH), 121.1 (CH), 119.6 (CH), 118.7 (CH), 114.0 (C_q), 108.7 (CH), 29.6 (CH_3), 11.0 (CH_3).

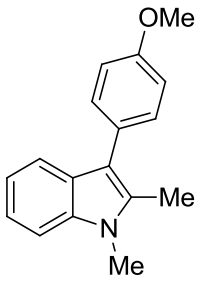
IR (neat, cm^{-1}): 3049 (m), 2938 (m), 1599 (s), 1468 (s), 1369 (s), 770 (s), 740 (s).

MS (EI) *m/z* (relative intensity): 221 ([M^+] 100), 204 (14), 178 (9), 144 (11), 43 (15).

HR-MS (EI) *m/z* for $C_{16}H_{15}N$ calcd.: 221.1204.
found: 221.1202.

The analytical data are in accordance with those reported in the literature.[188]

Synthesis of 3-(4'-Methoxyphenyl)-1,2-dimethylindole (50bd)



50bd

The general procedure **G** was followed, using 1,2-dimethylindole (**48d**) (72.6 mg, 0.50 mmol) and bis(4-methoxyphenyl)iodonium 4-methylbenzenesulfonate (**46db**) (512 mg, 1.00 mmol). Purification by column chromatography on silica (*n*-pentane → *n*-pentane/Et_2O: 100/1 → 70/1 → 50/1) yielded **50bd** (84 mg, 67%) as a colorless solid.

M. p.: 149–151 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 7.3 Hz, 1H), 7.23 – 7.16 (m, 1H), 7.13 – 7.05 (m, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.72 (s, 3H), 2.46 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.8 (C_q), 136.5 (C_q), 133.0 (C_q), 130.7 (CH), 128.1 (C_q), 127.2 (C_q), 121.0 (CH), 119.5 (CH), 118.6 (CH), 113.9 (CH), 113.6 (C_q), 108.6 (CH), 55.3 (CH_3), 29.6 (CH_3), 11.0 (CH_3).

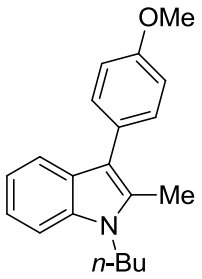
IR (neat, cm^{-1}): 3036 (w), 2932 (w), 1556 (s), 1464 (s), 1233 (s), 1032 (s), 835 (s), 740 (s), 560 (m).

MS (EI) *m/z* (relative intensity): 251 (100 [M^+]), 236 (93), 208 (8), 193 (13), 43 (4).

HR-MS (EI) *m/z* for $C_{17}H_{17}NO$ calcd.: 251.1310.
found: 251.1312.

The analytical data are in accordance with those reported in the literature.[163]

Synthesis of 1-*n*-Butyl-3-(4'-methoxyphenyl)-2-methylindole (50be)



50be

The general procedure **G** was followed, using 1-*n*-butyl 2-methylindole (**48e**) (93.2 mg, 0.50 mmol) and bis(4-methoxyphenyl)iodonium 4-methylbenzenesulfonate (**46db**) (512 mg, 1.00 mmol). Purification by column chromatography on silica (*n*-pentane → *n*-pentane/Et_2O: 100/1 → 70/1) yielded **50be** (99 mg, 68%) as a green oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.18 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.08 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 4.15 – 4.08 (t, *J* = 7.5 Hz, 2H), 3.86 (s, 3H), 2.45 (s, 3H), 1.78 (tt, *J* = 7.3, 7.3 Hz, 2H), 1.43 (tt, *J* = 7.3, 7.3 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.7 (C_q), 135.9 (C_q), 132.5 (C_q), 130.8 (CH), 128.2 (C_q), 127.3 (C_q), 120.8 (CH), 119.3 (CH), 118.7 (CH), 113.9 (CH), 113.6 (C_q), 108.9 (CH), 55.3 (CH_3), 43.2 (CH_2), 32.4 (CH_2), 20.4 (CH_2), 13.9 (CH_3), 11.0 (CH_3).

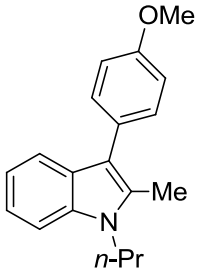
IR (neat, cm^{-1}): 3045 (m), 2957 (s), 1559 (s), 1510 (s), 1361 (s), 1241 (s), 1036 (s), 834 (s), 739 (s).

MS (EI) *m/z* (relative intensity): 293 ([M^+] 100), 250 (86), 206 (9), 192 (8), 77 (2).

HR-MS (EI) *m/z* for $C_{20}H_{23}NO$ calcd.: 293.1780.
found: 293.1785.

The analytical data are in accordance with those reported in the literature.[163]

Synthesis of 3-(4'-Methoxyphenyl)-2-methyl-1-*n*-propylindole (50bf)



50bf

The general procedure **G** was followed using 2-methyl-1-*n*-propylindole (**48f**) (86.7 mg, 0.50 mmol) and bis(4-methoxyphenyl)iodonium 4-methylbenzenesulfonate (**46db**) (513 mg, 1.00 mmol). Purification by column chromatography on silica (*n*-pentane → *n*-pentane/Et_2O: 200/1 → 100/1) yielded **50bf** (83 mg, 59%) as a yellow solid.

M. p.: 78–81°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, J = 7.7 Hz, 1H), 7.40 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.1 Hz, 1H), 7.17 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 7.08 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 4.16 – 4.00 (t, J = 7.4 Hz 2H), 3.86 (s, 3H), 2.45 (s, 3H), 1.83 (tq, J = 7.4, 7.4 Hz, 2H), 1.00 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.7 (C_q), 135.9 (C_q), 132.5 (C_q), 130.8 (CH), 128.2 (C_q), 127.3 (C_q), 120.8 (CH), 119.3 (CH), 118.7 (CH), 113.9 (CH), 113.6 (C_q), 108.9 (CH), 55.3 (CH_3), 45.0 (CH_2), 23.5 (CH_2), 11.6 (CH_3), 11.0 (CH_3).

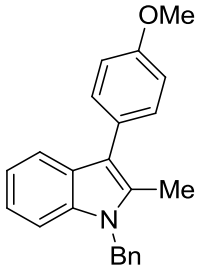
IR (neat, cm^{-1}): 2997 (m), 2916 (w), 1504 (s), 1242 (s), 1171 (m), 826(m), 732 (s).

MS (EI) *m/z* (relative intensity): 279 ([M^+] 100), 250 (87), 235 (12), 152 (5), 43 (2).

HR-MS (EI) *m/z* for $C_{19}H_{21}NO$ calcd.: 279.1623.
found: 279.1631.

The analytical data are in accordance with those reported in the literature.[163]

Synthesis of 1-Benyzl-3-(4'-methoxyphenyl)-2-methylindole (50bg)



50bg

The general procedure **G** was followed, using 1-benzyl-2-methylindole (**48g**) (110 mg, 0.50 mmol) and bis(4-methoxyphenyl)iodonium 4-methylbenzenesulfonate (**46db**) (512 mg, 1.00 mmol). Purification by column chromatography on silica (*n*-pentane → *n*-pentane/Et_2O: 100/1 → 70/1 → 50/1) yielded **50bg** (65 mg, 40%) as a colorless solid.

M. p.: 110−111 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.68 (m, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.34 – 7.23 (m, 4H), 7.20 – 7.09 (m, 2H), 7.09 – 6.99 (m, 4H), 5.39 (s, 2H), 3.88 (s, 3H), 2.42 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.9 (C_q), 137.8 (C_q), 136.5 (C_q), 132.8 (C_q), 130.8 (CH), 128.8 (CH), 128.0 (C_q), 127.5 (C_q), 127.3 (CH), 126.1 (CH), 121.3 (CH), 119.7 (CH), 118.8 (CH), 114.3 (C_q), 114.0 (CH), 109.1 (CH), 55.3 (CH_3), 46.7 (CH_2), 11.0 (CH_3).

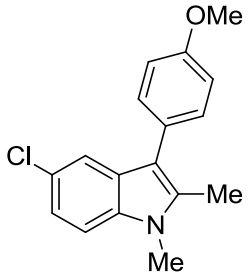
IR (neat, cm^{-1}): 3040 (w), 2999 (w), 1551 (s), 1466 (s), 1241 (s), 1175 (s), 1027 (s), 734 (s), 524 (m).

MS (EI) *m/z* (relative intensity): 327 ([M^+] 89), 236 (100), 192 (12), 91(31).

HR-MS (EI) *m/z* for $C_{23}H_{21}NO$ calcd.: 327.1623.
found: 327.1621.

The analytical data are in accordance with those reported in the literature.[163]

Synthesis of 5-Chloro-3-(4'-methoxyphenyl)-1,2-dimethylindole (50bh)



50bh

The general procedure **G** was followed using 5-chloro-1,2-dimethylindole (**48h**) (90.3 mg, 0.50 mmol) and bis(4-methoxyphenyl)iodonium 4-methylbenzenesulfonate (**46db**) (512 mg, 1.00 mmol). Purification by column chromatography on silica (*n*-pentane/Et_2O: 100/1 → 70/1 → 50/1) yielded **50bh** (87 mg, 61%) as a colorless solid.

M. p.: 130−133 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.55 (dd, *J* = 2.0, 0.4 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.19 (dd, *J* = 8.6, 0.5 Hz, 1H), 7.12 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.69 (s, 3H), 2.43 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.0 (C_q), 134.9 (C_q), 134.4 (C_q), 130.6 (CH), 128.2 (C_q), 127.3 (C_q), 125.2 (C_q), 121.1 (CH), 118.1 (CH), 114.1 (CH), 113.4 (C_q), 109.6 (CH), 55.3 (CH_3), 29.8 (CH_3), 11.0 (CH_3).

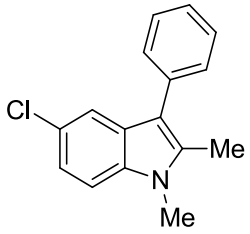
IR (neat, cm^{-1}): 3004 (w), 2910 (w), 1507 (s), 1473 (m), 1239 (s), 1031 (s), 793 (s).

MS (EI) *m/z* (relative intensity): 285 ([M^+] 10), 270 (68), 207 (21), 143 (8), 43 (5).

HR-MS (EI) *m/z* for $C_{17}H_{16}ClNO$ calcd.: 285.0920.
found: 285.0918.

The analytical data are in accordance with those reported in the literature.[163]

Synthesis of 5-Chloro-1,2-dimethyl-3-phenylindole (50bi)



50bi

The general procedure **G** was followed, using 5-chloro-1,2-dimethylindole (**48h**) (90.3 mg, 0.50 mmol) and diphenyliodonium-4-methylbenzenesulfonate (**46da**) (452 mg, 1.00 mmol). Purification by column chromatography on silica (*n*-pentane/Et_2O: 100/1 → 50/1) yielded **50bi** (59 mg, 46%) as a colorless solid.

M. p.: 120–122 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, J = 2.0 Hz, 1H), 7.52 – 7.39 (m, 4H), 7.36 – 7.27 (m, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (dd, J = 8.6, 2.0 Hz, 1H), 3.70 (s, 3H), 2.47 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 135.0 (C_q), 134.7 (C_q), 129.6 (CH), 128.6 (CH), 128.0 (C_q), 126.0 (CH), 125.4 (C_q), 121.2 (CH), 118.1 (CH), 113.8 (C_q), 109.7 (CH), 29.8 (CH_3), 11.1 (CH_3).

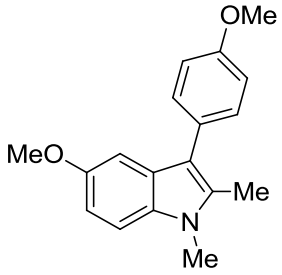
IR (neat, cm^{-1}): 3054 (w), 2920 (w), 1600 (m), 1471 (s), 1368 (m), 1061 (m), 789 (s), 764 (s), 700 (s).

MS (EI) *m/z* (relative intensity): 255 ([M^+] 100), 218 (13), 204 (12), 178 (14), 43 (4).

HR-MS (EI) *m/z* for $C_{16}H_{14}ClN$ calcd.: 255.0815.
found: 255.0816.

The analytical data are in accordance with those reported in the literature.[163]

Synthesis of 5-Methoxy-3-(4'-methoxyphenyl)-1,2-dimethylindole (50bk)



50bk

The general procedure **G** was followed using 5-methoxy-1,2-dimethylindole (**48i**) (87.9 mg, 0.50 mmol) and bis(4-methoxyphenyl)iodonium 4-methylbenzenesulfonate (**46db**) (513 mg, 1.00 mmol). Purification by column chromatography on silica (*n*-pentane/Et_2O: 20/1 → 15/1) yielded **50bk** (115 mg, 81%) as a colorless solid.

M. p.: 90–92°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.40 (md, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 7.03 (md, *J* = 8.8 Hz, 2H), 6.86 (dd, *J* = 8.8, 2.5 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.71 (s, 3H), 2.44 (s, 3H).

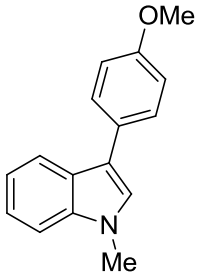
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.7 (C_q), 154.3 (C_q), 133.7 (C_q), 131.9 (C_q), 130.6 (CH), 128. (C_q), 127.4 (C_q), 114.0 (CH), 113.3 (C_q), 110.9 (CH), 109.3 (CH), 100.9 (CH), 56.0 (CH_3), 55.3 (CH_3), 29.7 (CH_3), 11.1 (CH_3).

IR (neat, cm^{-1}): 2915 (w), 2834 (w), 1612 (w), 1485 (s), 1154 (s), 1030 (s), 791 (s).

MS (EI) *m/z* (relative intensity): 281 ([M^+] 100), 266 (79), 238 (29), 194 (8), 140 (11).

HR-MS (EI) *m/z* for $C_{18}H_{19}NO_2$ calcd.: 281.1416.
found: 281.1413.

Synthesis of 3-(4'-methoxyphenyl)-1-methylindole (50bl)



50bl

The general procedure **G** was followed using 1-methylindole (**48b**) (65.5 mg, 0.50 mmol) and bis(4-methoxyphenyl)iodonium 4-methylbenzenesulfonate (**46db**) (1026 mg, 2.00 mmol). Purification by column chromatography on silica (*n*-pentane/Et_2O: 100/1 → 7071 → 60/1) yielded **50bl** (68 mg, 55%) as a colorless solid.

M. p.: 90–93 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.94 – 7.89 (m, 1H), 7.59 (md, *J* = 8.9 Hz, 2H), 7.37 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.33 – 7.25 (m, 1H), 7.23 – 7.14 (m, 2H), 7.01 (md, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.9 (C_q), 137.3 (C_q), 128.4 (CH), 128.2 (C_q), 126.2 (C_q), 125.9 (CH), 121.8 (CH), 119.8 (CH), 119.6 (CH), 116.4 (C_q), 114.2 (CH), 109.4 (CH), 55.3 (CH_3), 32.8 (CH_3).

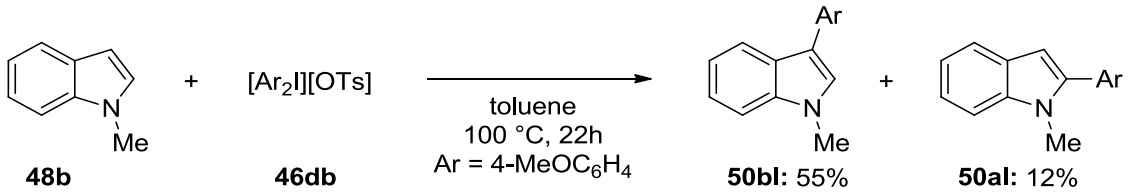
IR (neat, cm^{-1}): 2990 (w), 2836 (w), 1545 (m), 1469 (m), 1238 (s), 1028 (s), 743 (s).

MS (EI) *m/z* (relative intensity): 237 ([M^+] 99), 222 (100), 194 (24), 152 (15), 118 (10).

HR-MS (EI) *m/z* for $C_{16}H_{15}NO$ calcd.: 237.1154.
found: 237.1157.

The analytical data are in accordance with those reported in the literature.[189]

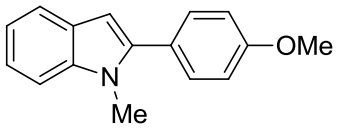
Synthesis of 3-(4'-Methoxyphenyl)-1-methylindole (50bl) and 2-(4'-Methoxyphenyl)-1-methylindole (50al)



48b **46db** **50bl:** 55% **50al:** 12%

The general procedure **G** was followed using using *N*-methylindole (**48b**) (65.7 mg, 0.50 mmol) and bis(4-methoxyphenyl)iodonium 4-methylbenzenesulfonate (**46db**) (512 mg, 1.00 mmol) in toluene (2.0 mL). Purification by column chromatography on silica (*n*-pentane/Et_2O: 100/1 → 90/1 → 80/1) yielded **50bl** (65 mg, 55%) and **50al** (15 mg, 12%) as colorless solids.

2-(4'-Methoxyphenyl)-1-methylindole (50al)



50al

M. p.: 119–120 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.63 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.44 (md, *J* = 8.8 Hz, 2H), 7.35 (m, 1H), 7.24 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.01 (md, *J* = 8.8 Hz, 2H), 6.51 (d, *J* = 0.8 Hz, 1H), 3.87 (s, 3H), 3.72 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.4 (C_q), 141.4 (C_q), 138.1 (C_q), 130.6 (CH), 128.0 (C_q), 125.3 (C_q), 121.4 (CH), 120.2 (CH), 119.7 (CH), 113.9 (CH), 109.5 (CH), 101.0 (CH), 55.4 (CH_3), 31.0 (CH_3).

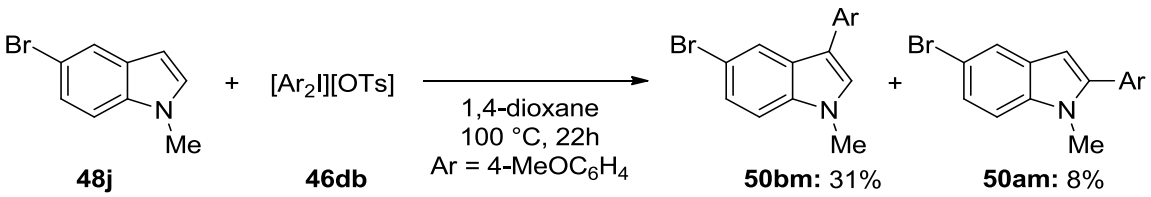
IR (neat, cm^{-1}): 2931 (w), 1609 (m), 1463 (s), 1242 (s), 1035 (m), 841 (m), 561 (m).

MS (EI) *m/z* (relative intensity): 237 ([M^+] 100), 222 (56), 194 (12), 167 (10), 63 (4).

HR-MS (EI) *m/z* for $C_{16}H_{15}NO$ calcd.: 237.1154.
found: 237.1157.

The analytical data are in accordance with those reported in the literature.[190]

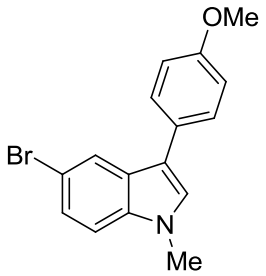
Intramolecular Competition Experiment with Indole 48j



Synthesis of 5-Bromo-3-(4'-methoxyphenyl)-1-methylindole (50bm) and 5-Bromo-2-(4'-methoxyphenyl)-1-methylindole (50am)

The general procedure **G** was followed using using 5-bromo-*N*-methylindole (**48j**) (120 mg, 0.50 mmol) and bis(4-methoxyphenyl)iodonium 4-methylbenzenesulfonate (**46db**) (512 mg, 1.00 mmol) in 1,5-dioxane (2.0 mL). Purification by column chromatography on silica (*n*-pentane/Et_2O: 200/1 → 180/1 → 140/1→ 100/1 → 80/1) yielded **50bm** (56 mg, 31%) and **50am** (15 mg, 8%) as pale yellow solids.

5-Bromo-3-(4'-methoxyphenyl)-1-methylindole (50bm)



50bm

M. p.: 88–89 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 1.7 Hz, 1H), 7.51 (md, *J* = 8.8 Hz, 2H), 7.34 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 7.14 (s, 1H), 7.00 (md, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.2 (C_q), 136.0 (C_q), 128.5 (CH), 127.9 (C_q), 127.4 (C_q), 126.9 (CH), 124.7 (CH), 122.4 (CH), 116.2 (C_q), 114.3 (CH), 113.2 (C_q), 110.9 (CH), 55.4 (CH_3), 33.0 (CH_3).

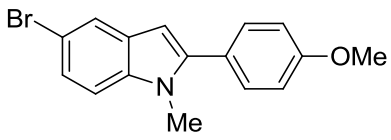
IR (neat, cm^{-1}): 2931 (m), 1737 (m), 1607 (s), 1471 (s), 1240 (s), 1030 (s), 788 (s).

MS (EI) *m/z* (relative intensity): 315 ([M^+] 100), 300 (88), 272 (16), 192 (31), 43 (27).

HR-MS (EI) *m/z* for $C_{16}H_{14}BrNO$ calcd.: 315.0259.
found: 315.0252.

The analytical data are in accordance with those reported in the literature.[163]

5-Bromo-2-(4'-methoxyphenyl)-1-methylindole (50am)



50am

M. p.: 120–122 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.73 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.42 (md, *J* = 8.9 Hz, 2H), 7.30 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.21 (dt, *J* = 8.6, 0.7 Hz, 1H), 7.01 (md, *J* = 8.9 Hz, 2H), 6.44 (d, *J* = 0.8 Hz, 1H), 3.88 (s, 3H), 3.70 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 159.4 (C_q), 142.5 (C_q), 136.7 (C_q), 130.5 (CH), 129.5 (C_q), 124.6 (C_q), 124.0 (CH), 122.6 (CH), 114.0 (CH), 112.9 (C_q), 110.9 (CH), 100.4 (CH), 55.4 (CH_3), 31.2 (CH_3).

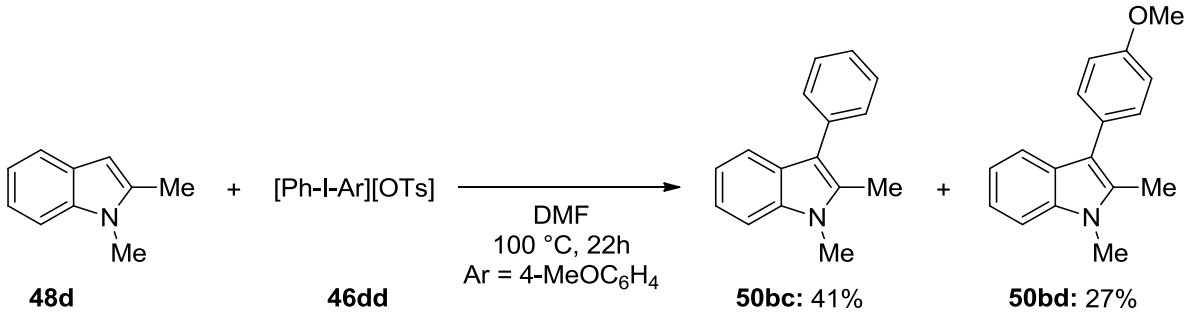
IR (neat, cm^{-1}): 2961 (m), 1608 (m), 1456 (s), 1238 (s), 1172 (m), 831 (s), 782 (s).

MS (EI) *m/z* (relative intensity): 315 ([M^+] 100), 300 (88), 272 (16), 192 (31), 43 (27).

HR-MS (EI) *m/z* for $C_{16}H_{14}BrNO$ calcd.: 315.0259.
found: 315.0253.

The analytical data are in accordance with those reported in the literature.[163]

Intramolecular Competition Experiment with Iodonium Salt 46dd

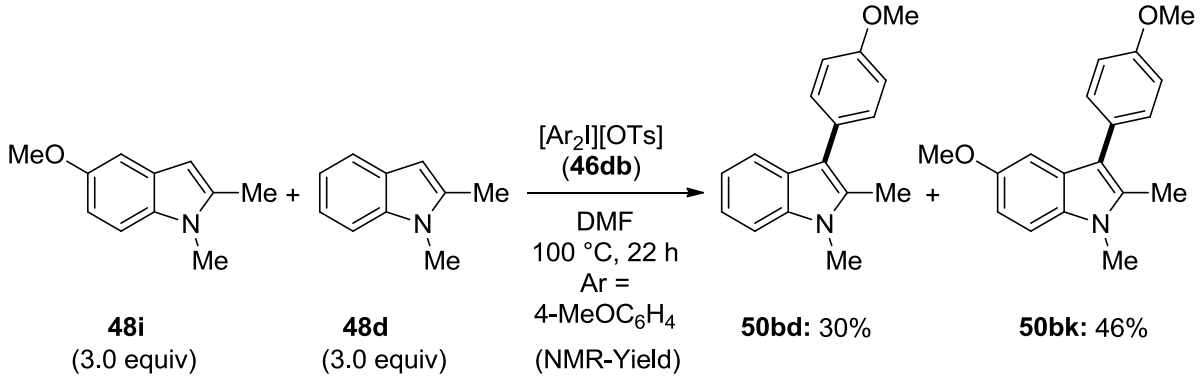


Synthesis of 1,2-Dimethyl-3-phenylindole (50bc) and 3-(4-Methoxyphenyl)-1,2-dimethylindole (50bd)

The general procedure **G** was followed using 1,2-dimethylindole (**48d**) (73 mg, 0.50 mmol) and (4-methoxyphenyl)(phenyl)iodonium 4-methylbenzenesulfonate (**46dd**) (482 mg, 1.00 mmol). Purification by column chromatography on silica (*n*-pentane → *n*-pentane/Et_2O: 200/1→ 150/1 → 100/1→ 70/1 → 60/1 → 50/1) yielded **50bc** (46 mg, 41%) and **50bd** (34 mg, 27%) as colorless solids.

The analytical data are in accordance with those previously reported.[188,163]

Intermolecular Competition Experiment between Indoles 48i and 48d



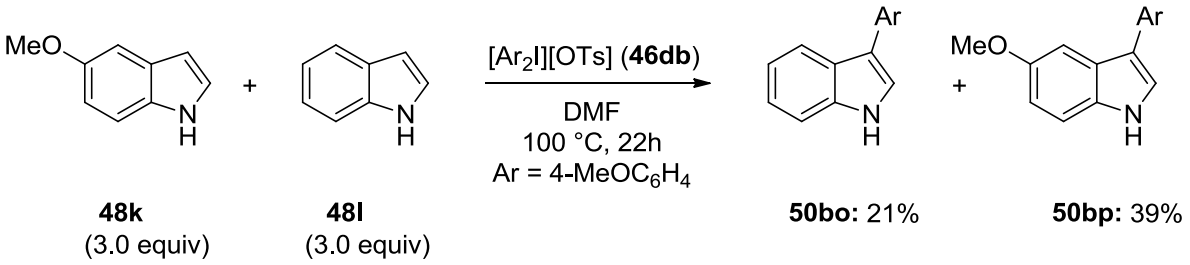
Synthesis of 3-(4'-Methoxyphenyl)-1,2-dimethylindole (50bd) and 5-Methoxy-3-(4'-methoxyphenyl)-1,2-dimethylindole (50bk)

The general procedure **G** was followed using 1,2-dimethylindole (**46d**) (131 mg, 0.90 mmol), 5-methoxy-1,2-dimethylindole (**48i**) (158 mg, 0.90 mmol) and bis(4-methoxyphenyl)iodonium 4-methylbenzenesulfonate (**46db**) (155 mg, 0.30 mmol). Purification by

column chromatography on silica (*n*-pentane → *n*-pentane/Et_2O: 100/1 → 70/1→ 50/1 → 20/1 → 15/1) yielded **50bd** (23 mg, 30%) and **50bk** (39 mg, 46%) as off-white solids.

The analytical data are in accordance with those previously reported.[163]

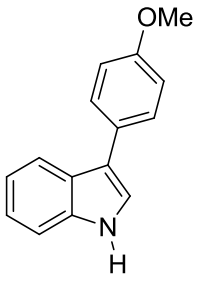
Intermolecular Competition Experiment between Indoles 48k and 48l



Synthesis of 3-(4'-Methoxyphenyl)indole (50bo) and 5-Methoxy-3-(4'-methoxyphenyl)indole (50bp)

The general procedure **G** was followed using using indole (**48l**) (106 mg, 0.90 mmol), 5-methoxyindole (**48k**) (132 mg, 0.90 mmol) and bis(4-methoxyphenyl)iodonium 4-methylbenzenesulfonate (**46db**) (153 mg, 0.30 mmol). Purification by column chromatography on silica (*n*-pentane/Et_2O: 20/1 → 15/1 → 10/1 → 5/1) yielded **50bo** (14 mg, 21%) and **50bp** (30 mg, 39%) as colorless solids.

3-(4'-Methoxyphenyl)indole (50bo)



50bo

M. p.: 133–134°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.16 (s, 1H), 7.90 (m, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.42 (m, 1H), 7.32 – 7.16 (m, 3H), 7.02 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H).

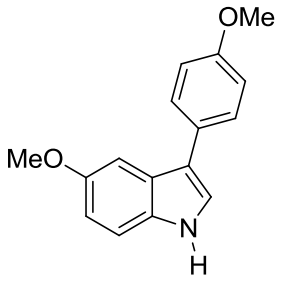
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 158.0 (C_q), 136.5 (C_q), 128.5 (CH), 128.0 (C_q), 125.8 (C_q), 122.2 (CH), 121.0 (CH), 120.1 (CH), 119.7 (CH), 118.0 (C_q), 114.2 (CH), 111.3 (CH), 55.4 (CH_3).

IR (neat, cm^{-1}): 3426 (s), 2953 (w), 1541 (m), 1241 (s), 1117 (s), 1029 (s), 736 (s).
MS (EI) *m/z* (relative intensity): 223 ([M^+] 99), 208 (100), 180 (48), 152 (36), 111 (12).

HR-MS (EI) *m/z* for $C_{15}H_{13}NO$ calcd.: 223.0997.
found: 223.0994.

The analytical data are in accordance with those reported in the literature.[113]

5-Methoxy-3-(4'-methoxyphenyl)indole (50bp)



50bp

M. p.: 102–103°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.08 (s, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.29 (m, 1H), 7.24 (d, *J* = 2.1 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.90 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.86 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.0 (C_q), 154.6 (C_q), 131.7 (C_q), 128.5 (CH), 128.2 (C_q), 126.3 (C_q), 122.0 (CH), 117.8 (C_q), 114.3 (CH), 112.6 (CH), 112.0 (CH), 101.5 (CH), 56.0 (CH_3), 55.3 (CH_3).

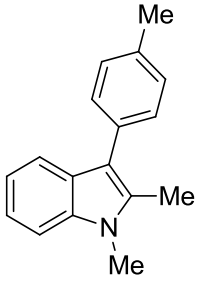
IR (neat, cm^{-1}): 3361 (s), 2931 (w), 1539 (m), 1480 (s), 1208 (s), 1028 (s), 782 (s), 611 (m), 517 (s).

MS (EI) *m/z* (relative intensity): 253 ([M^+] 100), 238 (85), 167 (32), 126 (22), 63 (6).

HR-MS (EI) *m/z* for $C_{16}H_{15}NO_2$ calcd.: 253.1103.
found: 253.1106.

The analytical data are in accordance with those reported in the literature.[113]

Synthesis of 1,2-Dimethyl-3-(4'methylphenyl)indole (50bn)



50bn

The general procedure **G** was followed, using 1,2-dimethylindole (**48d**) (72.6 mg, 0.50 mmol) and mesityl(*p*-tolyl)iodonium tetrafluoroborate (**46ab**) (425 mg, 1.00 mmol). Purification by column chromatography on silica (*n*-pentane/Et_2O: 70/1) yielded **50bn** (55 mg, 47%) as a colorless solid.

M. p.: 117–119 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.67 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.36 – 7.27 (m, 3H), 7.22 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.12 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 3.75 (s, 3H), 2.50 (s, 3H), 2.44 (s, 3H).

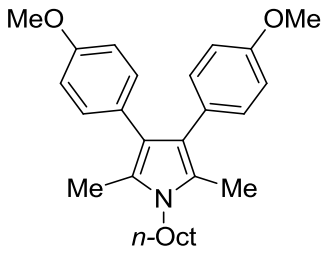
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 136.6 (C_q), 135.2 (C_q), 133.1 (C_q), 132.7 (C_q), 129.6 (CH), 129.2 (CH), 127.0 (C_q), 121.0 (CH), 119.5 (CH), 118.7 (CH), 113.9 (C_q), 108.6 (CH), 29.6 (CH_3), 21.2 (CH_3), 11.0 (CH_3).

IR (neat, cm^{-1}): 3027 (w), 2912 (m), 1469 (s), 1324 (s), 1208 (m), 816 (s), 735 (s).

MS (EI) *m/z* (relative intensity): 235 ([M^+] 100), 218 (10), 178 (5), 144 (7), 43 (3).

HR-MS (EI) *m/z* for $C_{17}H_{17}N$ calcd.: 325.1361.
. found: 325.1360.

Synthesis of 2,5-Dimethyl-3,4-bis(4-methoxyphenyl)-1-*n*-octylpyrrole (62b)



62b

The general procedure **H** was followed using 2,5-dimethyl-1-*n*-octylpyrrole (**63c**) (103 mg, 0.50 mmol) and bis(4-methoxyphenyl)iodonium 4-methylbenzenesulfonate (**46db**) (1026 mg, 2.00 mmol). Purification by column chromatography on silica (*n*-pentane/Et_2O: 100/1 → 70/1 → 40/1 → 207/1 → 10/1 → 5/1 → 4/1 → 3/1 → 2/1) yielded **62b** (64 mg, 31%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.02 (md, J = 8.7 Hz, 4H), 6.81 (md, J = 8.7 Hz, 4H), 3.91 – 3.82 (m, 2H), 3.80 (s, 6H), 2.31 (s, 6H), 1.75 (dd, J = 15.0, 7.4 Hz, 2H), 1.56 – 1.22 (m, 10H), 0.93 (t, J = 6.7 Hz, 3H).

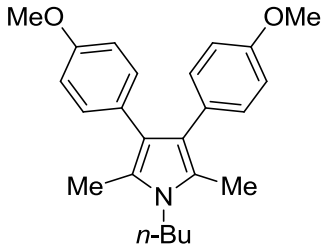
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.1 (C_q), 131.4 (CH), 129.0 (C_q), 123.8 (C_q), 119.6 (C_q), 113.2 (CH), 55.0 (CH_3), 44.2 (CH_2), 31.8 (CH_2), 31.1 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 10.7 (CH_3).

IR (neat, cm^{-1}): 2925 (s), 1543 (m), 1365 (m), 1239 (s), 1034 (s), 730 (m), 529 (m).

MS (EI) *m/z* (relative intensity): 419 ([M^+] 100), 321 (66), 178 (6), 43 (26).

HR-MS (EI) *m/z* for $C_{28}H_{37}NO_2$ calcd.: 419.2824.
found: 419.2839.

Synthesis of 2,5-Dimethyl-3,4-bis(4-methoxyphenyl)-1-*n*-butylpyrrole (62c)



62c

The general procedure **H** was followed using 2,5-dimethyl-1-*n*-butylpyrrole (**63d**) (79.6 mg, 0.53 mmol) and bis(4-methoxyphenyl)iodonium 4-methylbenzenesulfonate (**46db**) (1025 mg, 2.00 mmol) at 80 °C. Purification by column chromatography on silica (*n*-pentane/Et_2O: 20/1) yielded **62c** (105 mg, 55%) as an orange oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.99 (md, *J* = 8.8 Hz, 4H), 6.78 (md, *J* = 8.8 Hz, 4H), 3.88 – 3.81 (m, 2H), 3.78 (s, 6H), 2.28 (s, 6H), 1.72 (m, 2H), 1.46 (tt, *J* = 7.2 Hz, 2H), 1.01 (t, *J* = 7.3 Hz, 3H).

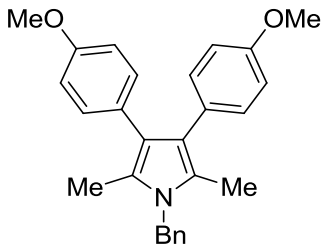
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 157.0 (C_q), 131.3 (CH), 128.9 (C_q), 123.7 (C_q), 119.6 (C_q), 113.1 (CH), 55.1 (CH_3), 44.0 (CH_2), 33.3 (CH_2), 20.4 (CH_2), 14.0 (CH_3), 10.8 (CH_3).

IR (neat, cm^{-1}): 2931 (m), 1644 (w), 1504 (s), 1365 (m), 1239 (s), 1031 (s), 832 (s).

MS (EI) *m/z* (relative intensity): 363 ([M^+] 100), 321 (57), 306 (36), 178 (8), 41 (15).

HR-MS (EI) *m/z* for $C_{24}H_{29}NO_2$ calcd.: 363.2198.
found: 363.2196.

Synthesis of 2,5-Dimethyl-3,4-bis(4-methoxyphenyl)-1-benzylpyrrole (62d)



62d

The general procedure **H** was followed using 2,5-dimethyl-1-benzylpyrrole (**63e**) (80.5 mg, 0.44 mmol) and bis(4-methoxyphenyl)iodonium 4-methylbenzenesulfonate (**46db**) (1025 mg, 2.00 mmol) at 80 °C. Purification by column chromatography on silica (*n*-pentane/Et_2O/NEt_3: 100/1/4) yielded **62d** (71 mg, 41%) as a colorless solid.

M. p.: 181−183 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.39 – 7.23 (m, 3H), 7.03 (md, J = 8.8 Hz, 6H), 6.80 (md, J = 8.8 Hz, 4H), 5.15 (s, 2H), 3.79 (s, 6H), 2.20 (s, 6H).

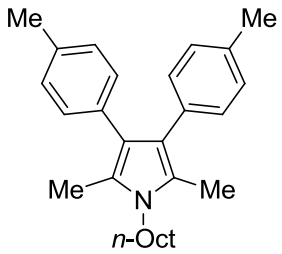
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.2 (C_q), 138.3 (C_q), 131.4 (CH), 129.0 (C_q), 128.8 (CH), 127.1 (CH), 125.8 (CH), 124.4 (C_q), 120.1 (C_q), 113.2 (CH), 55.1 (CH_3), 47.2 (CH_2), 10.8 (CH_3).

IR (neat, cm^{-1}): 2998 (w), 1609 (m), 1541 (s), 1238 (s), 1039 /m), 817 (m), 732 (s).

MS (EI) *m/z* (relative intensity): 397 ([M^+] 100), 306 (21), 265 (11), 91 (65), 65 (11).

HR-MS (EI) *m/z* for $C_{27}H_{27}NO_2$ calcd.: 397.2042.
found: 397.2042.

Synthesis of 2,5-Dimethyl-3,4-bis(*p*-tolyl)-1-*n*-octylpyrrole (62e)



62e

The general procedure **H** was followed using 2,5-dimethyl-1-*n*-octylpyrrole (**63c**) (110 mg, 0.50 mmol) and mesityl(*p*-tolyl)iodonium tetrafluoroborate (**46ab**) (849 mg, 2.00 mmol) in DMF (2.0 mL) for 20 h. Purification by column chromatography on silica (*n*-pentane/Et_2O: 100/1, NEt_3 0.5%) yielded **62e** (95 mg, 46%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.04 (md, *J* = 8.1 Hz, 4H), 6.97 (md, *J* = 8.1 Hz, 4H), 3.89–3.78 (m, 2H), 2.32 (s, 6H), 2.29 (s, 6H), 1.84–1.64 (m, 2H), 1.51–1.21 (m, 10H), 0.91 (t, *J* = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 134.2 (C_q), 133.6 (C_q), 130.3 (CH), 128.4 (CH), 124.1 (C_q), 120.0 (C_q), 44.2 (CH_2), 31.8 (CH_2), 31.1 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.1 (CH_2), 22.7 (CH_2), 21.1 (CH_3), 14.1 (CH_3), 10.8 (CH_3).

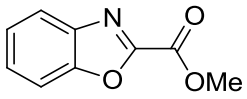
IR (neat, cm^{-1}): 2922 (w), 2855 (m), 1649 (m), 1364 (m), 1112 (m), 1108 (m), 808 (m).

MS (EI) *m/z* (relative intensity): 387 ([M+] 26), 288 (14), 198 (6), 58 (20), 43 (100).

HR-MS (EI) *m/z* for $C_{28}H_{37}N$ calcd.: 387.2926.
found: 387.2933.

The analytical data are in accordance with those reported in the literature.[163]

Synthesis of Methylbenzo[*d*]oxazole-2-carboxylate (73a)



73a

The general procedure **I** was followed using benzo[*d*]oxazole (**22a**) (118 mg, 0.99 mmol), and KO*t*-Bu (135 mg, 1.20 mmol). Purification by column chromatography (*n*-pentane/Et_2O: 20/1 → 10/1 → 7/1 → 5/1) yielded **73a** (141 mg, 80%) as a colorless solid.

M. p.: 102–104 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.88 (ddd, *J* = 7.7, 1.5, 0.7 Hz, 1H), 7.66 (m, 1H), 7.53 (m, 1H), 7.45 (m, 1H), 4.09 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 156.8 (C_q), 152.5, (C_q), 150.8 (C_q), 140.4 (C_q), 128.2 (CH), 125.8 (CH), 122.1 (CH), 111.7 (CH), 53.6 (CH_3).

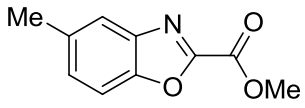
IR (neat, cm^{-1}):2956 (w), 1742 (s), 1538 (m), 1440, 1306 (s), 1106 (s), 744 (s), 626 (s).

MS (EI) *m/z* (relative intensity): 177 ([M^+] 100), 119 (24), 104 (45), 64 (69), 43 (99).

HR-MS (EI) *m/z* for $C_9H_7NO_3$ calcd.: 177.0426.
found: 177.0427.

The analytical data are in accordance with those reported in the literature.[124,191]

Synthesis of Methyl-5-methylbenzo[*d*]oxazole-2-carboxylate (73b)



73b

The general procedure **I** was followed using 5-methylbenzo[*d*]oxazole (**22b**) (134 mg, 1.00 mmol), and KO*t*-Bu (135 mg, 1.20 mmol). Purification by column chromatography (*n*-pentane/Et_2O: 20/1 → 10/1 → 8/1 → 5/1) yielded **73b** (129 mg, 66%) as a brown solid.

M. p.: 99–101 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.64 (dd, J = 1.6, 0.8 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.32 (m, 1H), 4.07 (s, 3H), 2.49 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 156.9 (C_q), 152.5 (C_q), 149.2 (C_q), 140.7 (C_q), 135.9 (C_q), 129.6 (CH), 121.6 (CH), 111.1 (CH), 53.6 (CH_3), 21.5 (CH_3).

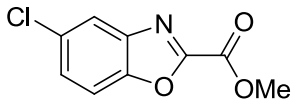
IR (neat, cm^{-1}): 3020 (w), 1746 (s), 1554 (m), 1435 (m), 1301 (s), 1110 (m), 807 (s), 631 (m), 433 (m).

MS (EI) *m/z* (relative intensity): 191 (100 [M^+]), 146 (65), 118 (62), 104 (41), 77 (74), 51 (48).

HR-MS (EI) *m/z* for $C_{10}H_9NO_3$ calcd.: 191.0582.
found: 191.0591.

The analytical data are in accordance with those reported in the literature.[124,191]

Synthesis of Methyl-6-chlorobenzo[*d*]oxazole-2-carboxylate (73c)



73c

The general procedure **I** was followed using 5-chlorobenzo[*d*]oxazole (**22c**) (154 mg, 1.00 mmol), and KO*t*-Bu (135 mg, 1.20 mmol). Purification by column chromatography (*n*-pentane/Et_2O: 20/1 → 10/1 → 7/1 → 6/1) yielded **73c** (133 mg, 63%) as a colorless solid.

M. p.: 122–124°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 2.1 Hz, 1H), 7.59 (d, *J* = 8.9, 1H), 7.49 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.09 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 156.5 (C_q), 153.6 (C_q), 149.4 (C_q), 141.4 (C_q), 131.5 (C_q), 128.8 (CH), 121.9 (CH), 112.6 (CH), 53.8 (CH_3).

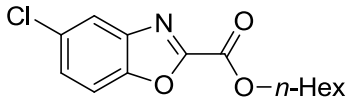
IR (neat, cm^{-1}): 3098 (m), 2961 (w), 1738 (s), 1544 (m), 1431 (m), 1300 (s), 1155 (s), 812 (m), 701 (m).

MS (EI) *m/z* (relative intensity): 211 ([M^+] 100), 167 (32), 124 (67), 104 (50), 98 (41), 63 (64).

HR-MS (EI) *m/z* for $C_9H_6ClNO_3$ calcd.: 211.0036.
found: 211.0035.

The analytical data are in accordance with those reported in the literature.[124,191]

Synthesis of *n*-Hexyl-5-chlorobenzo[*d*]oxazole-2-carboxylate (73e)



73e

The general procedure **I** was followed using 5-chlorobenzo[*d*]oxazole (**22c**) (153 mg, 1.00 mmol), and KO*t*-Bu (135 mg, 1.20 mmol). Purification by column chromatography (*n*-pentane/Et_2O: 40/1 → 20/1) yielded **73e** (255 mg, 91%) as a pale yellow solid.

M. p.: 48–50 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.48 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.48 (t, *J* = 6.8 Hz, 2H), 1.84 (dq, *J* = 8.4, 6.8 Hz, 2H), 1.53 – 1.22 (m, 6H), 0.93 – 0.86 (m, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 156.2 (C_q), 153.9 (C_q), 149.4 (C_q), 141.5 (C_q), 131.4 (C_q), 128.6 (CH), 121.8 (CH), 112.5 (CH), 67.5 (CH_2), 31.3 (CH_2), 28.4 (CH_2), 25.4 (CH_2), 22.5 (CH_2), 14.0 (CH_3).

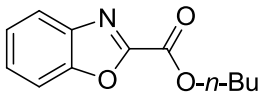
IR (neat, cm^{-1}): 3100 (w), 2928 (m), 1738 (s), 1541 (m), 1303 (s), 1154 (s), 919 (m), 813 (m), 637 (m).

MS (EI) *m/z* (relative intensity): 281 ([M^+] 23), 236 (11), 194 (30), 180 (74), 153 (100), 43 (80).

HR-MS (EI) *m/z* for $C_{14}H_{16}ClNO_3$ calcd.: 281.0819.
found: 281.0813.

The analytical data are in accordance with those reported in the literature.[122b]

Synthesis of *n*-Butyl-benzo[*d*]oxazole-2-carboxylate (73f)



73f

The general procedure **I** was followed using benzo[*d*]oxazole (**22a**) (119 mg, 1.00 mmol), and KO*t*-Bu (135 mg, 1.20 mmol). Purification by column chromatography (*n*-pentane/Et_2O: 20/1 → 10/1 → 7/1) yielded **73f** (139 mg, 64%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.89 (m, 1H), 7.66 (ddd, *J* = 8.3, 8.3, 0.9 Hz, 1H), 7.51 (m, 1H), 7.44 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H), 4.49 (t, *J* = 6.8 Hz, 2H), 1.91 – 1.74 (m, 2H), 1.59 – 1.37 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 156.6 (C_q), 152.8 (C_q), 150.9 (C_q), 140.5 (C_q), 128.1 (CH), 125.7 (CH), 122.1 (CH), 111.7 (CH), 67.0 (CH_2), 30.5 (CH_2), 19.0 (CH_2), 13.6 (CH_3).

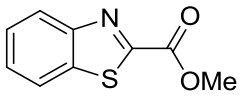
IR (neat, cm^{-1}): 2960 (m), 2874 (w), 1739 (s), 1545 (m), 1292 (s), 1138 (s), 842 (m), 744 (s), 429 (m).

MS (EI) *m/z* (relative intensity): 219 (32 [M^+]), 174 (11), 160 (17), 146 (56), 119 (100), 91 (42).

HR-MS (EI) *m/z* for $C_{12}H_{13}NO_3$ calcd.: 219.0895.
found. 219.0892.

The analytical data are in accordance with those reported in the literature.[192]

Synthesis of Methyl-benzo[*d*]thiazole-2-carboxylate (73g)



73g

The general procedure **I** was followed using benzo[*d*]thiazole (**75**) (138 mg, 1.00 mmol), and KO*t*-Bu (135 mg, 1.20 mmol). Purification by column chromatography (*n*-pentane/Et_2O: 20/1 → 10/1 → 7/1 → 5/1) yielded **73g** (131 mg, 66%) as a yellow solid.

M. p.: 92–94 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.24 (m, 1H), 7.97 (m, 1H), 7.55 (m, 2H), 4.08 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.1 (C_q), 158.0 (C_q), 153.1 (C_q), 136.8 (C_q), 127.6 (CH), 127.1 (CH), 125.5 (CH), 122.1 (CH), 53.6 (CH_3).

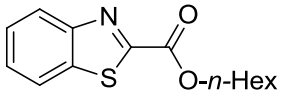
IR (neat, cm^{-1}): 2952 (w), 1711 (s), 1494 (s), 1287 (s), 1096 (s), 923 (m), 766 (s), 731 (s), 432 (s).

MS (EI) *m/z* (relative intensity): 193 ([M^+] 59), 162 (19), 135 (100), 108 (26), 90 (22), 69 (23).

HR-MS (EI) *m/z* for $C_9H_7NO_2S$ calcd.: 193.0197.
found: 193.0199.

The analytical data are in accordance with those reported in the literature.[124]

Synthesis of *n*-Hexyl-benzo[*d*]thiazole-2-carboxylate (73h)



73h

The general procedure **I** was followed using benzo[*d*]thiazole (**75**) (139 mg, 1.03 mmol), and KO*t*-Bu (135 mg, 1.20 mmol). Purification by column chromatography (*n*-pentane/Et_2O: 20/1) yielded **73h** (168 mg, 62%) as a yellow solid.

M. p.: 38–40 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.26 (m, 1H), 8.98 (m, 1H), 7.63 – 7.49 (m, 2H), 4.48 (t, *J* = 6.9 Hz, 2H), 1.94 – 1.75 (m, 2H), 1.55 – 1.25 (m, 6H), 0.94 – 0.87 (m, 3H).

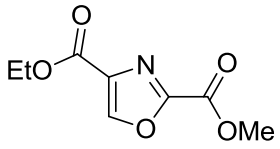
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.6 (C_q), 158.4 (C_q), 153.2 (C_q), 136.7 (C_q), 127.5 (CH), 127.0 (CH), 125.5 (CH), 122.0 (CH), 67.2 (CH_2), 31.4 (CH_2), 28.5 (CH_2), 25.5 (CH_2), 22.5 (CH_2), 14.0 (CH_3).

IR (neat, cm^{-1}): 3058 (w), 2918 (m), 1728 (s), 1496 (s), 1254 (s), 1099 (s), 865 (m), 765 (s), 583 (w).

MS (EI) *m/z* (relative intensity): 263 (10 [M^+]), 219 (30), 180 (33), 162 (82), 135 (100), 90 (11), 43 (29).

HR-MS (EI) *m/z* for $C_{14}H_{17}NO_2S$ calcd.: 263.0980.
found: 263.0988.

Synthesis of 4-Ethyl 2-methyloxazole-2,4-dicarboxylate (73i)



73i

The general procedure **I** was followed using ethyl oxazole-4-carboxylate (**22d**) (141 mg, 1.00 mmol), and KO*t*-Bu (135 mg, 1.20 mmol). Purification by column chromatography (*n*-pentane/Et_2O: 20/1 → 10/1 → 7/1 → 5/1 → 3/1 → 2/1 → 1/1) yielded **73i** (51 mg, 25%) as a colorless solid.

M. p.: 67–70 °C.

^{1}H-HMR (300 MHz, $CDCl_3$): δ = 8.36 (s, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.0 (C_q), 155.4 (C_q), 152.4 (C_q), 146.0 (CH), 135.3 (C_q), 61.7 (CH_2), 53.5 (CH_3), 14.2 (CH_2).

IR (neat, cm^{-1}): 3151 (w), 3004 (w), 1737 (s), 1543 (m), 1305 (s), 1145 (s), 982 (m), 772 (m), 649 (w).

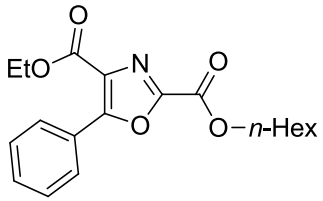
MS (EI) *m/z* (relative intensity): 199 ([M^+] 18), 184 (48), 171 (53), 143 (56), 59 (100), 43 (93).

HR-MS (EI) *m/z* for $C_8H_9NO_5$ calcd.: 199.0481.
found: 199.0484.

Synthesis of 2-*n*-Hexyl-4-ethyl-5-phenyloxazole-2,4-dicarboxylate (73k) and 2-*n*-Hexyl-4-*tert*-butyl-5-phenyloxazole-2,4-dicarboxylate (73ka)

The general procedure **I** was followed using ethyl 5-phenyloxazole-4-carboxylate (**22e**) (213 mg, 0.98 mmol), and KO*t*-Bu (135 mg, 1.20 mmol). Purification by column chromatography (*n*-pentane/Et_2O: 10/1 → 7/1 → 5/1) yielded **73k** (222 mg, 65%) and **73ka** (11 mg, 3%) as yellow oils.

2-*n*-Hexyl-4-ethyl-5-phenyloxazole-2,4-dicarboxylate (73k)



73k

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.19 – 8.06 (m, 2H), 7.56 – 7.44 (m, 3H), 4.53 – 4.34 (m, 4H), 1.81 (dq, *J* = 8.2, 6.9 Hz, 2H), 1.51 – 1.22 (m, 9H), 0.95 – 0.84 (m, 3H).

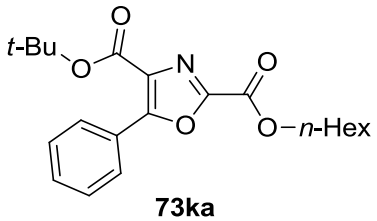
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.4 (C_q), 157.4 (C_q), 155.4 (C_q), 150.0 (C_q), 131.3 (CH), 128.9 (CH), 128.6 (C_q), 128.5 (CH), 125.9 (C_q), 67.1 (CH_2), 61.8 (CH_2), 31.3 (CH_2), 28.4 (CH_2), 25.4 (CH_2), 22.5 (CH_2), 14.2 (CH_3), 14.0 (CH_3).

IR (neat, cm^{-1}): 2931 (m), 2859 (w), 1721 (s), 1549 (m), 1334 (m), 1171 (s), 1093 (s), 763 (m), 690 (m).

MS (EI) *m/z* (relative intensity): 345 ([M^+] 23), 300 (18), 244 (45), 189 (28), 105 (100), 43 (99).

HR-MS (EI) *m/z* for $C_{19}H_{23}NO_5$ calcd.: 345.1576.
found: 345.1577.

2-*n*-Hexyl-4-*tert*-butyl-5-phenyloxazole-2,4-dicarboxylate (73ka)



73ka

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.06 – 7.98 (m, 2H), 7.53 – 7.44 (m, 3H), 4.42 (t, *J* = 6.9 Hz, 2H), 1.88 – 1.74 (m, 2H), 1.58 (s, 9H), 1.51 – 1.24 (m, 6H), 0.95 – 0.83 (m, 3H).

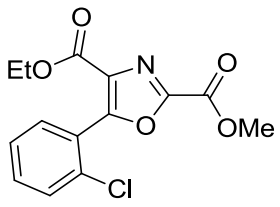
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.5 (C_q), 156.6 (C_q), 155.5 (C_q), 150.0 (C_q), 131.0 (CH), 129.9 (C_q), 129.0 (CH), 128.4 (CH), 126.3 (C_q), 83.1 (CH_2), 67.0 (C_q), 31.4 (CH_2), 28.4 (CH_2), 28.1 (CH_3), 25.4 (CH_2), 22.5 (CH_2), 14.0 (CH_3).

IR (neat, cm^{-1}): 2931 (m), 1716(s), 1547 (m), 1367 (m), 1236 (m), 1160 (s), 1094 (s), 844 (m), 690 (m).

MS (EI) *m/z* (relative intensity): 373 ([M^+] 46), 317 (80), 273 (56), 216 (100), 105 (61), 43 (45).

HR-MS (EI) *m/z* for $C_{21}H_{27}NO_5$ calcd.: 373.1889.
found: 373.1880.

Synthesis of 4-Ethyl-2-methyl-5-(2-chlorophenyl)oxazole-2,4-dicarboxylate (73l)



73l

The general procedure **I** was followed using ethyl 5-(2-chlorophenyl)oxazole-4-carboxylate (**22f**) (259 mg, 1.03 mmol), and KO*t*-Bu (135 mg, 1.20 mmol). Purification by column chromatography (*n*-pentane/Et_2O: 10/1 → 5/1 → 3/1 → 2/1) yielded **73l** (164 mg, 52%) as an off-white solid.

M. p.: 83–85 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.56 – 7.52 (m, 2H), 7.47 (ddd, *J* = 7.6, 7.6, 1.7 Hz, 1H), 7.39 (ddd, *J* = 7.3, 7.3, 1.7 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.03 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.3 (C_q), 155.6 (C_q), 155.0 (C_q), 151.1 (C_q), 134.4 (C_q), 132.2 (CH), 132.1 (CH), 131.5 (C_q), 130.0 (CH), 126.5 (CH), 125.7 (C_q), 61.6 (CH_2), 53.5 (CH_3), 14.0 (CH_3).

IR (neat, cm^{-1}): 2991 (w), 1738 (s), 1721 (s), 1551 (s), 1339 (s), 1194 (s), 1028 (m), 753 (s), 653 (s).

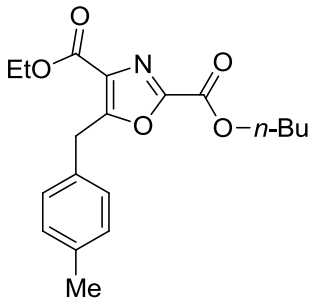
MS (EI) *m/z* (relative intensity): 274 (96), 246 (100), 214 (77), 139 (49), 59 (21).

HR-MS (EI) *m/z* for $C_{14}H_{12}ClNO_5$ calcd.: 309.0404.
found: 309.0410.

Synthesis of 2-*n*-Butyl-4-ethyl-5-(4-methylbenzyl)oxazole-2,4-dicarboxylate (73m) and 2-Butyl-4-ethyl-5-(1-(4-methylphenyl)pentyl)oxazole-2,4-dicarboxylate (73ma)

The general procedure **I** was followed using ethyl 5-(4-methylbenzyl)oxazole-4-carboxylate (**22g**) (242 mg, 0.99 mmol), and KO*t*-Bu (135 mg, 1.20 mmol). Purification by column chromatography (*n*-pentane/Et_2O: 10/1 → 7/1 → 5/1) yielded **73m** (174 mg, 51%) and **73ma** (25 mg, 6%) as yellow oils.

2-*n*-Butyl-4-ethyl-5-(4-methylbenzyl)oxazole-2,4-dicarboxylate (73m)



73m

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 4.49 – 4.33 (m, 6H), 2.31 (s, 3H), 1.68 – 1.82 (m, 2H), 1.49 – 1.33 (m, 5H), 0.94 (t, *J* = 7.4 Hz, 3H).

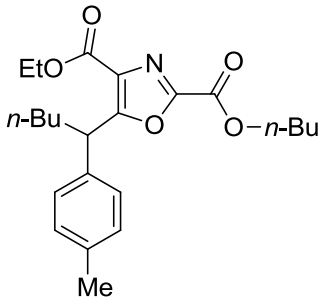
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.3 (C_q), 160.6 (C_q), 155.4 (C_q), 150.5 (C_q), 137.0 (C_q), 132.1 (C_q), 129.5 (CH), 129.2 (C_q), 128.7 (CH), 66.7 (CH_2), 61.5 (CH_2), 31.8 (CH_2), 30.4 (CH_2), 21.0 (CH_3), 18.9 (CH_2), 14.3 (CH_3), 13.6 (CH_3).

IR (neat, cm^{-1}): 2906 (m), 2874 (w), 1737 (s), 1549 (m), 1249 (s), 1154 (s), 1067 (s), 791 (m), 655 (m).

MS (EI) *m/z* (relative intensity): 345 (27 [M^+]), 299 (15), 243 (100), 199 (79), 105 (33), 41 (25).

HR-MS (EI) *m/z* for $C_{19}H_{23}NO_5$ calcd.: 345.1567.
found: 345.1572.

2-*n*-Butyl-4-ethyl-5-{1-(4-methylphenyl)pentyl}oxazole-2,4-dicarboxylate (73ma)



73ma

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 4.89 (t, *J* = 8.0 Hz, 1H), 4.49 – 4.32 (m, 4H), 2.30 (s, 3H), 2.22 – 1.97 (m, 2H), 1.83 – 1.70 (m, 2H), 1.52 – 1.13 (m, 9H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 7.1 Hz, 3H).

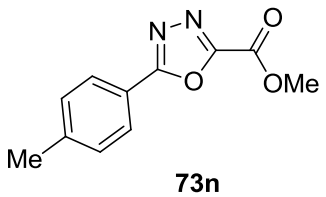
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.7 (C_q), 161.4 (C_q), 155.4 (C_q), 150.3 (C_q), 137.0 (C_q), 136.8 (C_q), 129.4 (CH), 128.6 (C_q), 127.9 (CH), 66.6 (CH_2), 61.4 (CH_2), 42.2 (CH), 33.6 (CH_2), 30.4 (CH_2), 29.7 (CH_2), 22.3 (CH_2), 21.0 (CH_3), 19.0 (CH_2), 14.3 (CH_3), 13.8 (CH_3), 13.6 (CH_3).

IR (neat, cm^{-1}): 2958 (m), 2872 (w), 1738 (s), 1549 (m), 1375 (m), 1158 (s), 1060 (s), 655 (m).

MS (EI) *m/z* (relative intensity): 401 ([M^+] 53), 355 (100), 312 (82), 256 (98), 212 (49), 105 (38).

HR-MS (EI) *m/z* for $C_{23}H_{31}NO_5$ calcd.: 401.2202.
found: 401.2192.

Synthesis of Methyl-5-(4-methylphenyl)-1,3,4-oxadiazole-2-carboxylate (73n)



73n

The general procedure **I** was followed using 2-(4-methylphenyl)-1,3,4-oxadiazole (**76a**) (160 mg, 1.00 mmol), and KO*t*-Bu (135 mg, 1.20 mmol). Purification by column chromatography (*n*-pentane/Et_2O: 10/1 → 5/1 → 4/1 → 3/1) yielded **73n** (121 mg, 56%) as a colorless solid.

M. p.: 118–120 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.08 (s, 3H), 2.44 (s, 3H).

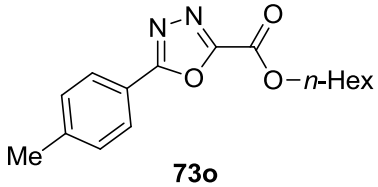
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.7 (C_q), 156.1 (C_q), 154.9 (C_q), 143.7 (C_q), 129.9 (CH), 127.6 (CH), 119.9 (C_q), 53.7 (CH_3), 21.7 (CH_3).

IR (neat, cm^{-1}): 2956 (w), 2854 (w), 1741 (s), 1529 (m), 1447 (s), 1202, (s), 1163 (s), 819 (s), 728 (s).

MS (EI) *m/z* (relative intensity): 218 ([M^+] 81), 159 (100), 131 (21), 117 (54), 91 (56), 65 (18).

HR-MS (EI) *m/z* for $C_{11}H_{10}N_2O_3$ calcd.: 218.0691.
found: 218.0693.

Synthesis of *n*-Hexyl-5-(4-methylphenyl)-1,3,4-oxadiazole-2-carboxylate (73o)



73o

The general procedure **I** was followed using 2-(4-methylphenyl)-1,3,4-oxadiazole (**76a**) (160 mg, 1.00 mmol), and KO*t*-Bu (135 mg, 1.20 mmol). Purification by column

chromatography (*n*-pentane/Et_2O: 20/1 → 15/1 → 10/1 → 8/1) yielded **73o** (146 mg, 51%) as a brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 4.47 (t, *J* = 6.8 Hz, 2H), 2.44 (s, 3H), 1.91 – 1.75 (m, 2H), 1.54 – 1.23 (m, 6H), 0.97 – 0.81 (m, 3H).

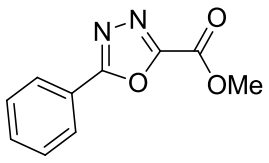
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.6 (C_q), 156.2 (C_q), 154.6 (C_q), 143.6 (C_q), 129.9 (CH), 127.6 (CH), 120.0 (C_q), 67.5 (CH_2), 31.3 (CH_2), 28.4 (CH_2), 25.4 (CH_2), 22.5 (CH_2), 21.70 (CH_3), 14.0 (CH_3).

IR (neat, cm^{-1}): 2928 (s), 2859 (m), 1743 (s), 1492 (m), 1272 (m), 1170 (s), 1090 (m), 825 (m), 732 (m).

MS (EI) *m/z* (relative intensity): 288 (13 [M^+]), 244 (16), 187 (69), 159 (100), 117 (73), 91 (57), 43 (59).

HR-MS (EI) *m/z* for $C_{16}H_{20}N_2O_3$ calcd.: 288.1474.
found: 288.1471.

Synthesis of Methyl-5-phenyl-1,3,4-oxadiazole-2-carboxylate (73p)



73p

The general procedure **I** was followed using 2-phenyl-1,3,4-oxadiazole (**76b**) (149 mg, 1.00 mmol), and KO*t*-Bu (135 mg, 1.20 mmol). Purification by column chromatography (*n*-pentane/Et_2O: 10/1 → 5/1 4/1) yielded **73p** (89 mg, 43%) as a colorless solid.

M. p.: 118–119 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.16 (m, 2H), 7.56 (m, 3H), 4.09 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.5 (C_q), 156.3 (C_q), 154.8 (C_q), 132.9 (CH), 129.2 (CH), 127.6 (CH), 122.7 (C_q), 53.8 (CH_3).

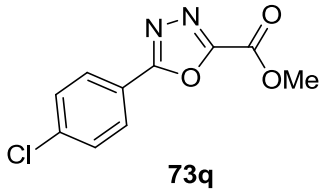
IR (neat, cm^{-1}): 2963 (w), 1737 (s), 1539 (m), 1378 (m), 1204 (s), 1094 (m), 811 (m), 710 (s), 642 (m).

MS (EI) *m/z* (relative intensity): 204 ([M^+] 44), 145 (100) 103 (20), 77 (64), 43 (17).

HR-MS (EI) *m/z* for $C_{10}H_8N_2O_3$ calcd.: 204.0535.
found: 204.0537.

The analytical data are in accordance with those reported in the literature.[193]

Synthesis of Methyl-5-(4-chlorophenyl)-1,3,4-oxadiazole-2-carboxylate (73q)



73q

The general procedure **I** was followed using 2-(4-chlorophenyl)-1,3,4-oxadiazole (**76c**) (182 mg, 1.01 mmol), and KO*t*-Bu (135 mg, 1.20 mmol). Purification by column chromatography (*n*-pentane/Et_2O: 5/1) yielded **73q** (90 mg, 38%) as a colorless solid.

M. p.: 156–159 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.10 (md, *J* = 8.7 Hz, 2H), 7.53 (md, *J* = 8.7 Hz, 2H), 4.09 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.7 (C_q), 156.3 (C_q), 154.7 (C_q), 139.4 (C_q), 129.7 (CH), 128.9 (CH), 121.1 (C_q), 53.9 (CH_3).

IR (neat, cm^{-1}): 3096 (w), 1740 (s), 1600 (m), 1164 (s), 1090 (m), 836 (m), 733 (m).

MS (EI) *m/z* (relative intensity): 238 ([M^+] 15), 179 (30), 137 (9), 111 (8), 43 (100).

HR-MS (EI) *m/z* for $C_{10}H_7ClNO_3$ calcd.: 238.0145.
found: 238.0138.

The analytical data are in accordance with those reported in the literature.[124]

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