Ruthenium(II) biscarboxylate-Catalyzed C(sp^2)–H and C(sp^3)–H Functionalizations by Chelation Assistance

Dissertation

for the award of the degree

Doctor of Philosophy (Ph.D.)

of the Georg-August-Universität Göttingen

within the doctoral program of chemistry

Catalysis for Sustainable Synthesis (CaSuS)

submitted by

Y Phani Kumar Nekkanti

from Ballatagi (India)

Göttingen, 2016

Thesis Committee

Prof. Dr. Lutz Ackermann, Institute of Organic and Biomolecular Chemistry

Prof. Dr. Ulf Diederichsen, Institute of Organic and Biomolecular Chemistry

Prof. Dr. Dietmar Stalke, Institute of Inorganic Chemistry

Members of the Examination Board

Reviewer: Prof. Dr. Lutz Ackermann, Institute of Organic and Biomolecular Chemistry

Second Reviewer: Prof. Dr. Ulf Diederichsen, Institute of Organic and Biomolecular Chemistry

Further members of the Examination Board

Prof. Dr. Dietmar Stalke, Institute of Inorganic Chemistry

Dr. Franziska Thomas, Institute of Organic and Biomolecular Chemistry

Dr. Alexander Breder, Institute of Organic and Biomolecular Chemistry

Dr. Shoubhik Das, Institute of Organic and Biomolecular Chemistry

Date of the oral examination: Nov 9th, 2016.

Table of Contents

List of Abbreviations

List of Abbreviations

Py   Pyridyl

Ac   acetyl

ACE   Angiotensin converting enzyme

acac   acetyl acetonate

Ad   adamantyl

Alk   alkyl

Am   amyl

AMLA   ambiphilic metal-ligand activation

aq.   aqueous

Ar   aryl

APT   attached proton test

atm   atmospheric pressure

ATR   attenuated total reflectance

ARB   Angiotensin receptor blocker

BHT   2,6-di-*tert*-butyl-4-methylphenol

pin   pinacolato

BINAP   2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Bn   benzyl

Bu   butyl

Bz   benzoyl

°C   degree Celsius

calc.   calculated

cat   catecholato

cat.   catalytic

CMD   concerted-metalation-deprotonation

cod   1,5-cyclooctadiene

conv.   conversion

Cp*	cyclopentadienyl
Cy	cyclohexyl
δ	chemical shift
d	doublet
DCE	1,2-dichloroethane
dd	doublet of doublet
DG	directing group
DMA	*N,N*-dimethylacetamide
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
E	electrophile
Ed.	edition
EI	electron ionization
eV	Electron Volt
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FG	functional group
FDA	Food and Drug Administration
g	gram
GC	gas chromatography
GVL	Gamma-Valerolactone
h	hour
Hal	halogen
HASPO	hetero-atom substituted secondary phosphine oxide
Het	hetero
Hept	heptyl
Hex	hexyl
HPLC	high performance liquid chromatography

HR-MS	high resolution mass spectrometry
HMBC	Heteronuclear Multiple Bond Correlation
HSQC	Heteronuclear Single Quantum Correlation
Hz	Hertz
i	*iso*
IR	infrared spectroscopy
IES	Internal electrophilic substitution
J	coupling constant
KIE	kinetic isotope effect
L	ligand
m	*meta*
m	multiplet
mmol	millimol
M	molar
$[M]^+$	molecular ion peak
Me	methyl
Mes	mesityl
mg	milligram
mm	millimeter
MHz	megahertz
min	Minute(s)
mL	milliliter
mmol	millimol
M. p.	melting point
MPV	membrane pump vacuum
MS	mass spectrometry
MTBE	methyl *tert*-butyl ether
m/z	mass-to-charge ratio
N_2	Nitrogen
NMP	*N*-methylpyrrolidinone

Introduction

1.1 Catalysis

Over the past century, catalysis has become an essential tool for chemical and material manufacturing and pollution control systems. In particular, the potential of this technology to efficiently produce specialty and fine chemicals, including many pharmaceuticals is proven.[1] The huge impact of catalysis on society was well recognized by the Nobel Foundation (Table 1).[2]

Table 1: Contributions in catalysis recognized by the Nobel Foundation

Awardees (year)	Research contribution
W. Ostwald (1909)	Catalysis, chemical equilibria, and reaction rates
P. Sabatier (1912)	Hydrogenation of organic compounds in presence of finely divided metals
F. Haber (1918)	Synthesis of ammonia from its elements
K. Ziegler and G. Natta (1963)	Discoveries in the field of chemistry and technology of high polymers
W. S. Knowles, R. Noyori, and K. Barry Sharpless (2001)	Chirally catalyzed hydrogenation and oxidation
Y. Chauvin, R. H. Grubbs, and R.R. Schrock (2005)	Development of metathesis method
G. Ertl (2007)	Studies of chemical processes on solid surfaces
R. F. Heck, E. Negishi and A. Suzuki (2010)	Palladium-catalyzed cross-coupling methods

1.2 Transition metal catalyzed C−H bond functionalization

Transition-metal-catalyzed reactions are vital to modern organic synthesis because the distinctive reactivity of transition metals allows highly selective and efficient transformations that are not possible with conventional methods. Synthesis of complex molecules using C–H bond functionalization[3] has become an essential tool in synthetic chemist's toolbox as it enables more straightforward and atom-economical synthetic routes (Scheme 1). This

approach provides a perfect opportunity for late stage diversification and is driven by environmental and economic requirements.
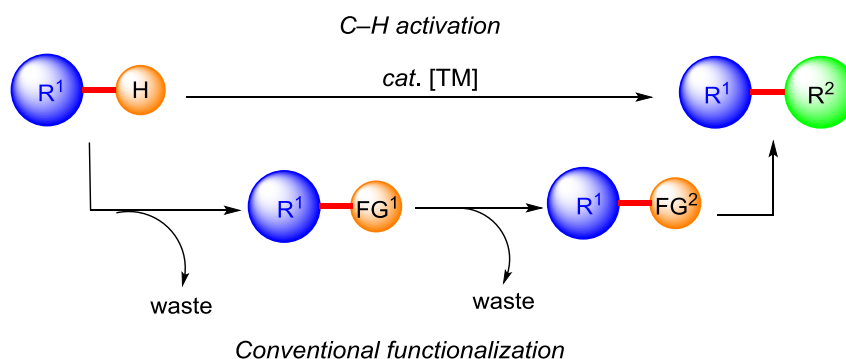
Scheme 1: Comparision of C–H activation *vs* conventional functional group interconversion

Owing to the presence of multiple C–H bonds in all kinds of organic molecules, achieving efficient, selective and predictable transformations is a challenging task. As organic molecules contain C–H bonds with comparable bond dissociation energies, the use of a Lewis basic directing group that coordinates to the transition metal is essential to achieve selectivity.[4] A directing group enables intramolecular cleavage of the C–H bond leading to a regioselective functionalization (Scheme 2).
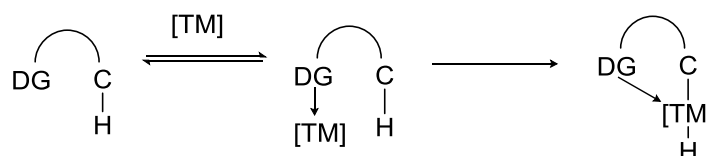
Scheme 2: Directing group(DG) strategy for intermolecular cleavage of C–H bond

1.3 Prices of transition metal catalysts

Efficient, selective, and direct functionalization of C−H bonds with less expensive transition metals under mild conditions remains the most difficult challenge. The prices of gold, platinum, rhodium, palladium, iridium, and ruthenium were 1326, 1049, 675, 665, 650, 42 US\$ per troy oz, respectively.[5] The demand for more abundant and less expensive complexes is very high for developing sustainable synthetic methods.[6]

1.4 Mechanisms of C−H bond functionalization

Depending on the nature of the transition metal M and ligand set L_n, the elementary step of C−H bond metalation was proposed to proceed via different pathways.[7] The four important classes, involving the formation of stable organometallic species are: a) Oxidative addition (OA) - characteristic for electron rich and low valent late transition metals; b) σ-bond metathesis (SBM) - characteristic for late transition metals with d^0 configuration; c) electrophilic activation (EA) - typical for late or a post-transition metal usually in strong polar medium; d) 1,2-addition - for addition to an unsaturated metal–non metal bond (Scheme 3).
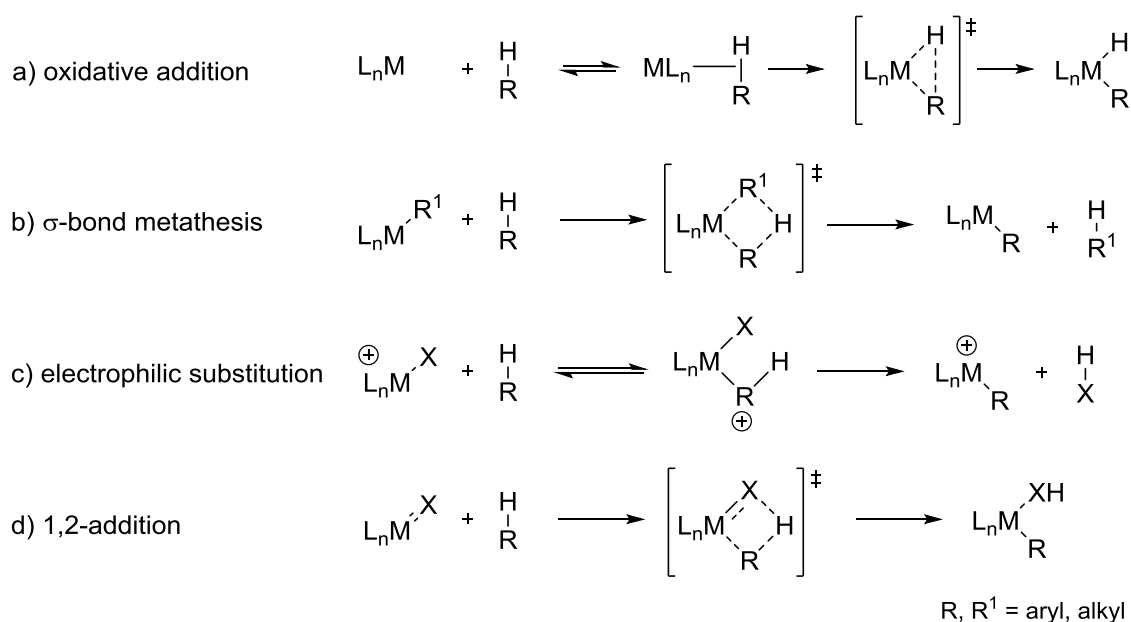
Scheme 3: Possible mechanisms for C–H bond metalation by transition metal complexes

1.5 General approach for the synthesis of biaryls

Regioselective syntheses of bi(hetero)aryls are mainly achieved by the use of highly efficient transition-metal-catalyzed cross-coupling reactions between organic (pseudo)halides and stoichiometric amounts of organometallic reagents.[8] A major drawback of these cross-coupling reactions is that the organometallic nucleophilic reagents are often not commercially available, relatively expensive and involve preparation from the corresponding arenes, during which undesired by-products are formed. Therefore, direct arylation reactions by direct cleavage of C–H bonds are more efficient regarding both atom- and step-economy. Tremendous savings in solvent, waste and energy enable the use of this strategy for the syntheses of bulk chemicals used in pharmaceutical and material science industry.

Approaches for biaryl synthesis are based on the nature of coupling partners: a) cross dehydrogenative coupling, b) cross coupling reactions and c) reactions with aryl (pseudo) halides (Scheme 4).

a) Cross-Dehydrogenative Coupling (CDC): Very challenging and highly desirable is the selective formation of carbon–carbon bonds directly from two different C–H bonds *via* the formal removal of two hydrogen atoms.[9] Controlling the chemo-selectivity of cross- versus homo dehydrogenative arylations and positional selectivity in intermolecular direct arylations are major limitations. Use of a stoichiometric oxidant and use of super stoichiometric arene also reduces the atom-economy of CDC coupling.

b) Cross coupling reactions make use of regioselective coupling between organometallic reagents as nucleophiles and aryl (pseudo)halides as electrophile. Generally, synthesis of organometallic reagents from corresponding aryl halides is tedious and expensive. Moreover, stoichiometric terminal oxidants like copper(II) or silver(I) salts are employed in the arylation step. Although this process is highly reliable, atom-economy and step-economy are still limitations for a sustainable approach.

c) Reactions in which unfunctionalized (hetero)arenes are directly employed as the starting materials and functionalized through C–H bond cleavages. Direct arylations with relatively inexpensive organic (pseudo)halides as the arylating reagents is definitely a more attractive option for the synthesis of biaryls due to the high efficiency as compared to oxidative arylations.[10]
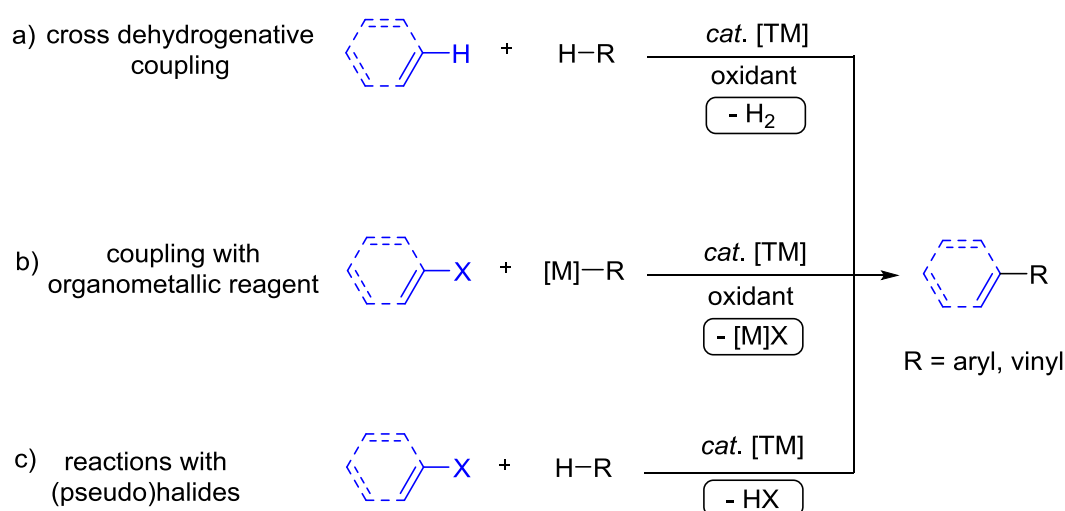
Scheme 4: Approaches for the synthesis of biaryls

1.6 Ruthenium catalyzed direct arylations of C(sp^2)–H bonds

The ruthenium-catalyzed direct arylation of C(sp^2)–H bonds using chelation assistance from pyridines was developed by Inoue and co-workers (Scheme 5).[11] Aryl bromides or aryl iodides were used as arylating agents. Subsequently, Inoue used the same reaction conditions for various other directing groups like imine[12] and oxazoline.[13] After few years, it was found researchers at Merck that these results could not be reproduced.[14] Aryl chlorides were ineffective under these reaction conditions.
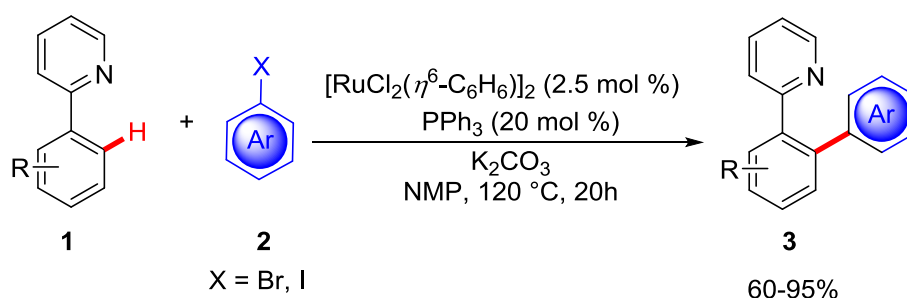
Scheme 5: Ruthenium-catalyzed direct arylation by Inoue using phosphine ligands

However, a major breakthrough in ruthenium-catalyzed direct arylations was achieved by Ackermann in 2005 (Scheme 5) overcoming the limitations of conditions developed by Inoue.[15] Reactions with aryl chlorides or tosylates proceeded with excellent chemo- and site-selectivity when phosphine oxides are used as ligands.[16] This approach is more economic as less expensive arylating agents and much inexpensive ruthenium catalyst was employed.
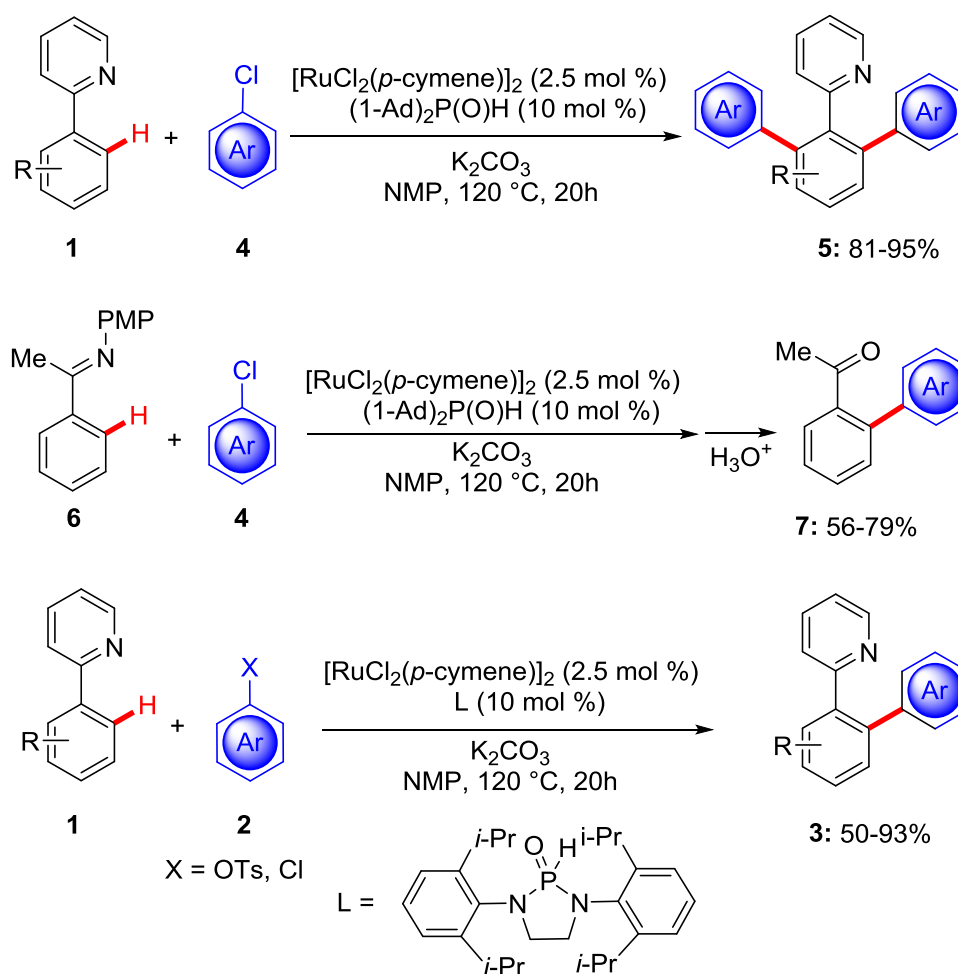
Scheme 6: Ruthenium-catalyzed direct arylation with phosphine oxide ligands

This catalytic system was further improved using carboxylic acids as co-catalysts instead of phosphine oxides (Scheme 7).[17] A variety of directing groups could be used to achieve $C(sp^2)$–H bond arylation using aryl(pseudo) halides with the highly robust catalytic system.
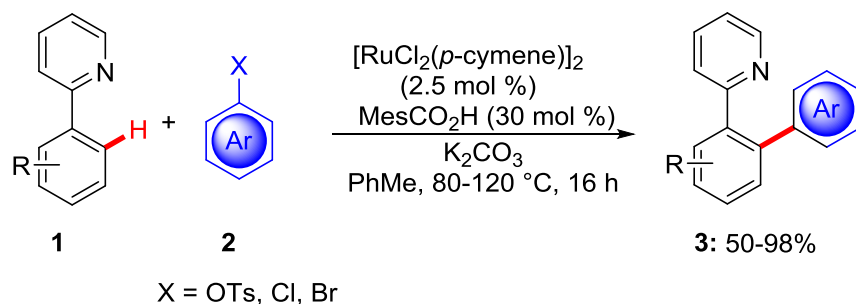
Scheme 7: Carboxylate-assisted ruthenium-catalyzed C–H arylation by Ackermann

Detailed mechanistic studies indicated that ruthenium carboxylate complexes are the actual catalysts in the reaction.[18] Using cheaper and more abundant carboxylic acids as co-catalysts will provide a chance to enhance the reactivity profile and robustness. The remarkable robustness of ruthenium carboxylate complexes was also proven ro be applicable for alkylations using primary, secondary and tertiary alkyl halides.[19]

1.7 Angiotensin II receptor blockers

Taking the advantages of direct arylation via C–H bond functionalization over cross-coupling chemistry methods into account, it would be very economical to apply this method to synthesize molecules of pharmaceutical interest. Angiotensin II receptor blockers (ARBs),[20] containing a biaryl tetrazole unit are identified as target molecules to apply ruthenium-catalyzed direct arylation methods (Figure 1).
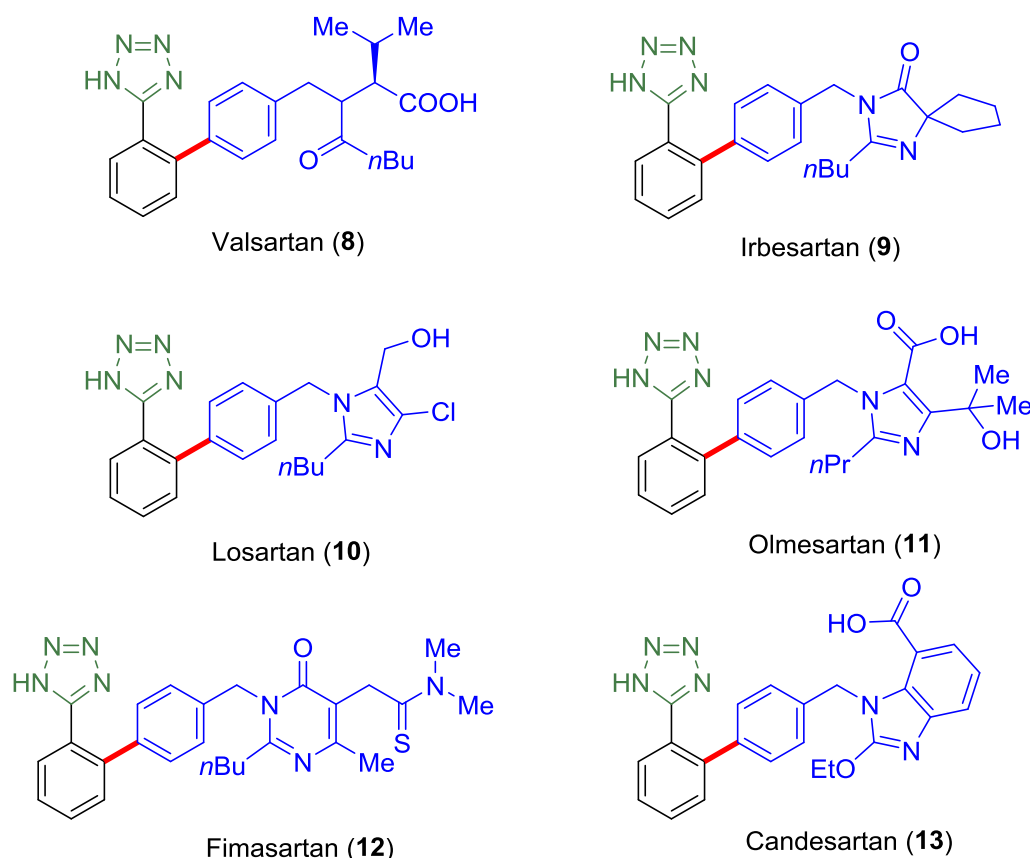

Figure 1: Blockbuster antihypertension drugs containing biaryl tetrazole unit

More than 1000 tons ARBs are produced per annum. Losartan (**10**) and Valsartan (**8**) are top selling drugs in this category. Previous synthetic methods suffer from several drawbacks as they use stoichiometric amounts of expensive and/or hazardous organometallic reagents (Figure 2).[21]
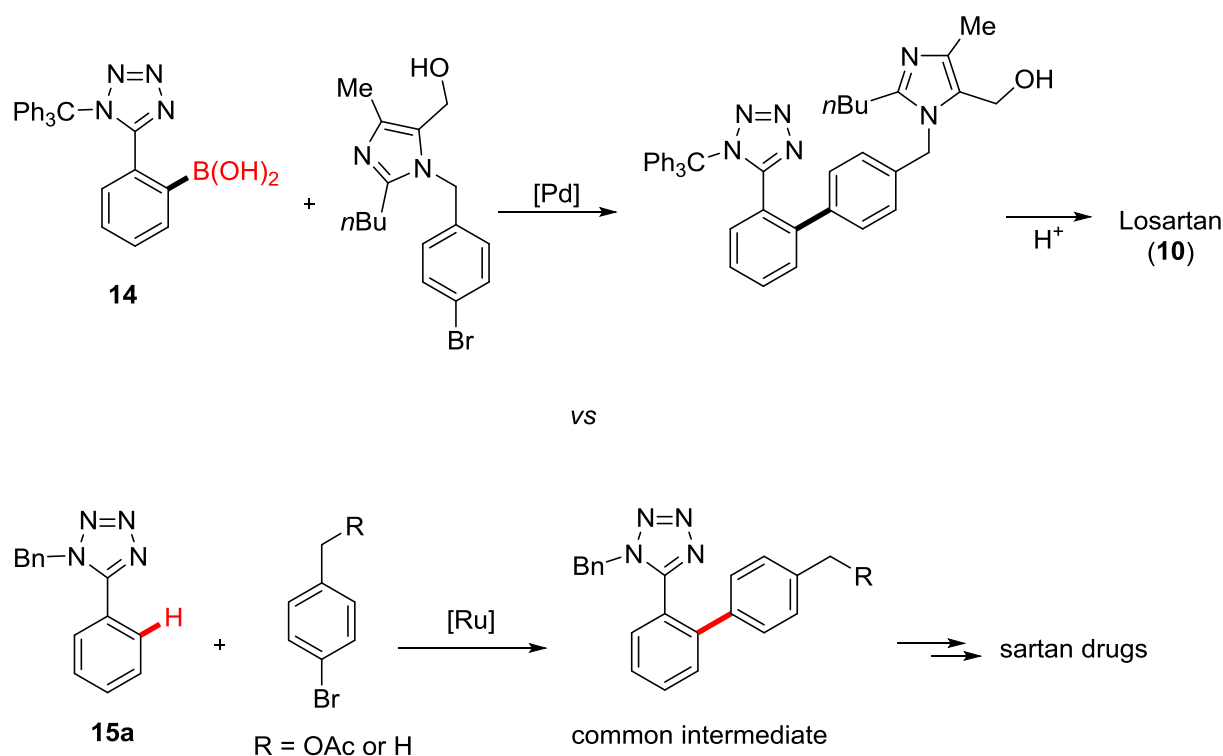
Figure 2: Cross-coupling with boron reagent vs direct arylation with aryl(pseudo)halide

The standard method to synthesize the biaryl unit in sartan drugs employs Suzuki-Miyaura coupling with boronic acid derivative **14** as the starting material and the reaction occurs with overall low effciency.[22] Therefore, there is an urgent need to develop a more sustainable method for the synthesis of ARBs using C–H bond arylation strategy. While efforts to synthesize biaryltetrazoles using carboxylate-assisted ruthenium catalyzed arylation were in progress in our group, Seki published a ruthenium-catalyzed direct arylation protocol to synthesize Valsartan with phosphine ligands developed by Oi and Inoue.[23] Later this reaction was found to be inefficient for pilot scale production of biaryl tetrazole. Similar results were observed by the process research division of Merck in the pilot scale synthesis of Anacetrapib when the Oi and Inoue phopshine-based ruthenium catalytic system failed to give reproducible results.[24] Extensive studies revealed that γ-butyrolactone, an impurity

present in NMP is the cause for irreproducibility and therefore a more robust catalytic system is needed. Exploring ruthenium(II) carboxylate complexes such as [Ru(O$_2$CMes)$_2$(*p*-cymene)] (**16**) might be beneficial as they were already proven to be efficient in direct arylations.[25]

1.8 Ruthenium catalyzed direct arylations of C(sp^3)–H bonds

Catalytic functionalization of C(sp^3)–H bonds in a selective fashion is very challenging due to the lack of π-orbitals that can interact with transition metals. As a result TM-catalyzed functionalization of C(sp^3)–H bonds are not very successful compared to functionalization of C(sp^2)–H bonds.[26] Considering the prevalence of functionalized saturated cyclic amines in molecules of pharmaceutical interest (Figure 3), it is very crucial to develop methods for the functionalization of cyclic amines to overcome the limitations of existing methods that involve the usage of stoichiometric lithiated reagents and cryogenic conditions.[27]
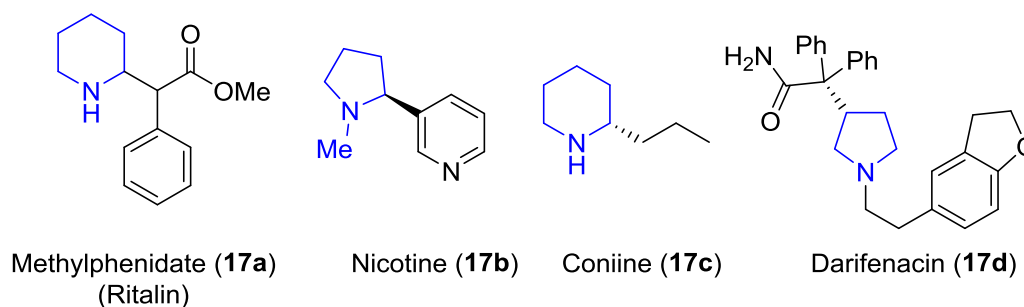
Figure 3: Representative examples of biologically active substituted cyclic amines

Molecules containing diarylmethylamine are also an important class of pharmaceutically active compounds (Figure 4).[28] They have a variety of biological activities such as antihistamanics[29] (e.g., Cetirizine) and antidepressants (e.g., Tianeptine).[30] Various strategies are available in the literature for the construction of this structural motif including imine hydrogenation.
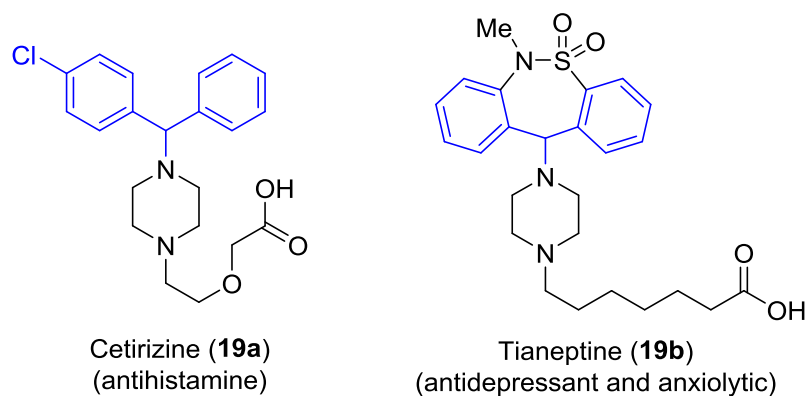
Figure 4: Representative examples of drugs containing diarylmethyl amine unit

Ruthenium catalyzed C(sp³)–H bond arylations are scarce in the literature (Scheme 8). Sames achieved chelation assisted α-arylation of pyrrolidines using removable (amidine) directing group.[31] Using similar reaction conditions as of Sames, and pyridine as the directing group, Maes developed a protocol for α-arylation of piperidines.[32] Schnurch also reported C(sp³)–H bond arylations in benzylic amines using pyridine as the directing group.[33] However, the use of rather expensive Ru(0) catalysts and aryl boronates as arylating agents are significant limitations.
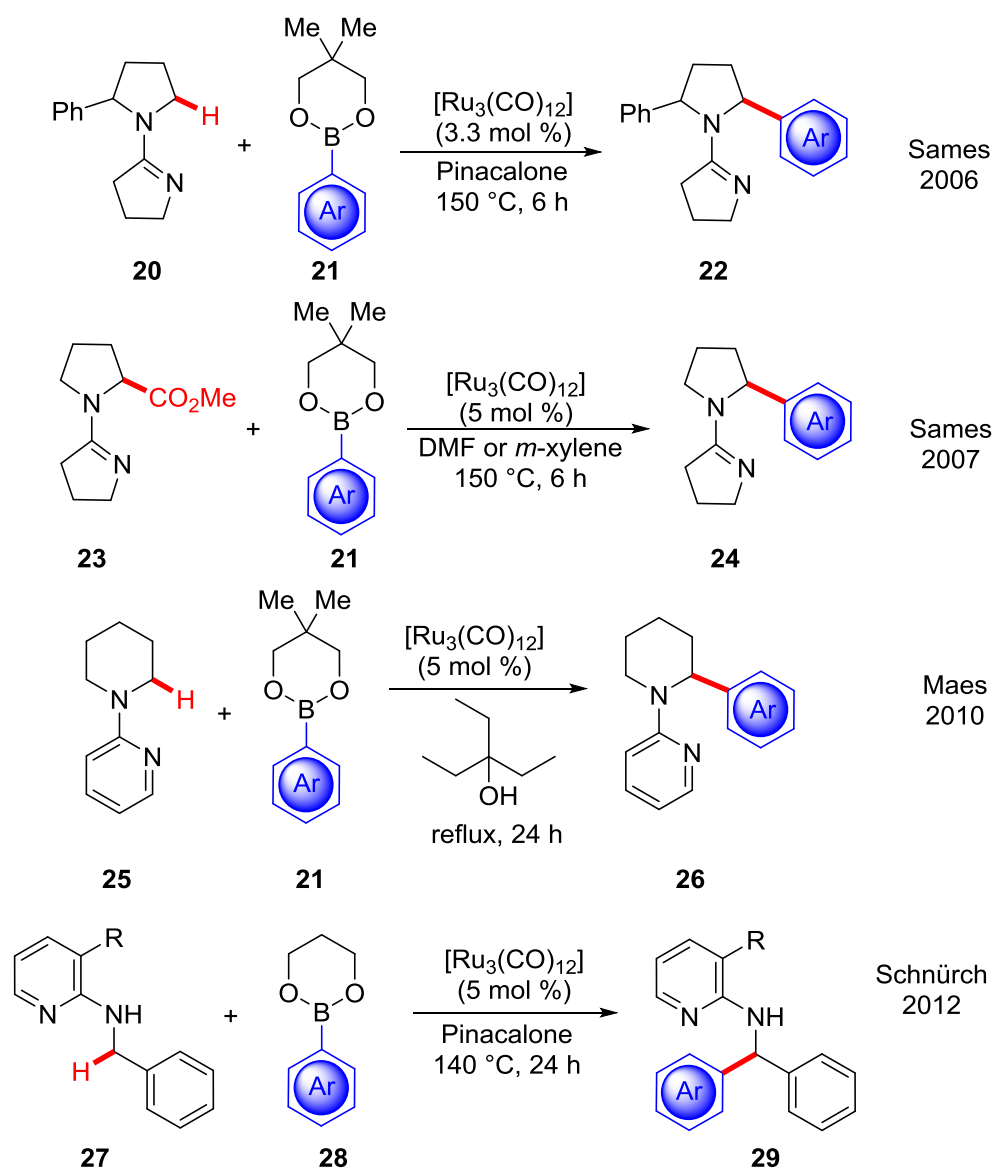
Scheme 8: Ruthenium-catalyzed arylation of C(sp^3)–H bonds using aryl boron reagents

Carboxylate assistance proved to overcome the drawbacks of this method (Scheme 9). However, pre-stirring of the catalyst with substoichiometric amount of co-catalyst is a limitation of this method.[34]
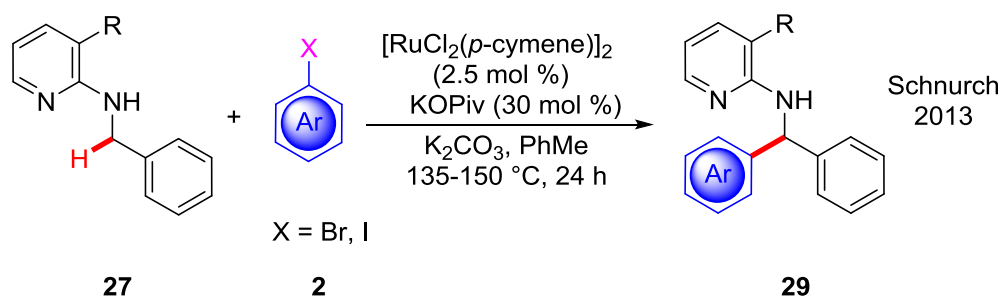
Scheme 9: Ruthenium-catalyzed arylation of C(sp^3)–H bonds using aryl halides

1.9 Ruthenium-Catalyzed Hydroarylation of Alkynes

Alkyl and vinyl arenes are produced on a large scale every year as they are useful intermediates for fine chemical synthesis and are key structural motifs in various important compounds in natural products,[35] in material sciences[36] and medicinal chemistry.[37] The addition of aromatic C–H bonds across alkene and across alkyne is an important synthetic method as it is the most efficient way to form a new C–C bond. A pioneering example of ruthenium-catalyzed addition of aromatic C–H bond in ketones (**30**) to internal alkynes was reported by Murai and coworkers in 1995 (Scheme 10).[38] The reaction occured with high site-selectively and regio-selectivity when trimethylsilyl substituted acetylenes were employed. Unfortunately, when other internal alkynes were used isomeric mixtures were obtained.
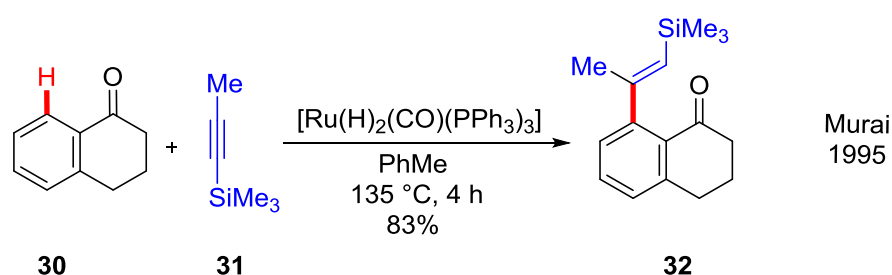
Scheme 10: Hydroarylation of internal alkynes using ketone as the DG

Much progress was not made for hydroarylation of alkynes using ruthenium catalysis until recently. Miura and coworkers reported amide directed regio- and stereo-selective hydroarylation in 2012 (Scheme 11).[39] Subsequently, Miura showed the efficiency of this catalytic system with various directing groups, such as imidazole, pyrazole, phosphine oxides and simple amines.[40]
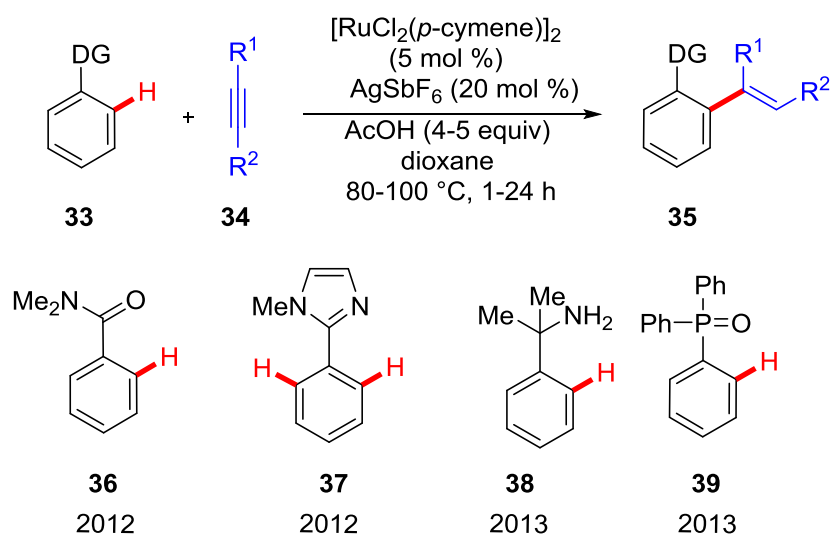
Scheme 11: Hydroarylation of alkynes by Miura

Jeganmohan could employ aryl carbamates, acetanilides and aromatic sulfoxides by a slight variation in the Miura's catalytic system (Scheme 12).[41]
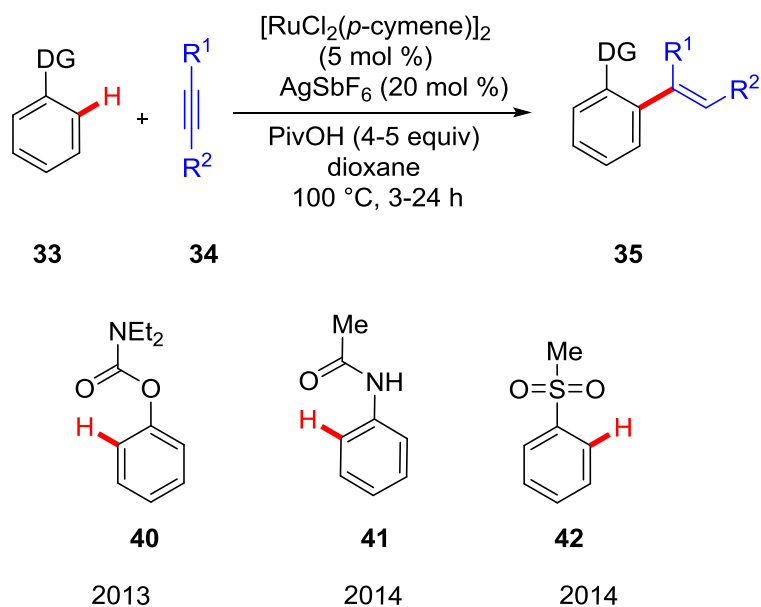
Scheme 12: Hydroarylation of alkynes with various directing groups by Jeganmohan

Pyridine was used as a removable directing group(rDG)[42] to achieve C2-functionalization of Indole by Zeng *et al*. (Scheme 13).[43]‵
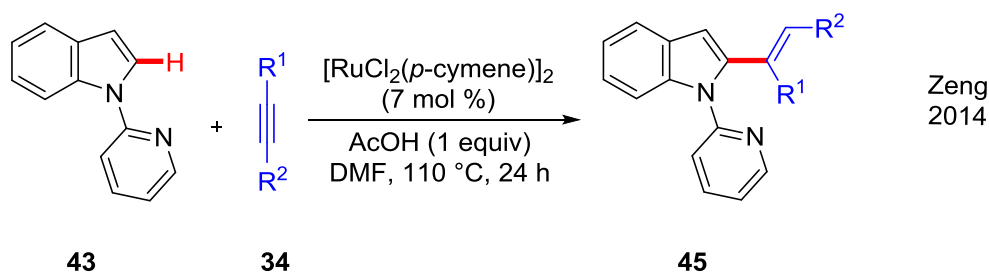
Scheme 13: C2-functionalization of Indole using removable directing group.

Hydroarylation of alkynes could be achieved employing triazole as directing group by Liu and Ackermann's group achieved the oxidative alkenylation with activated alkenes (Scheme 14).[44]
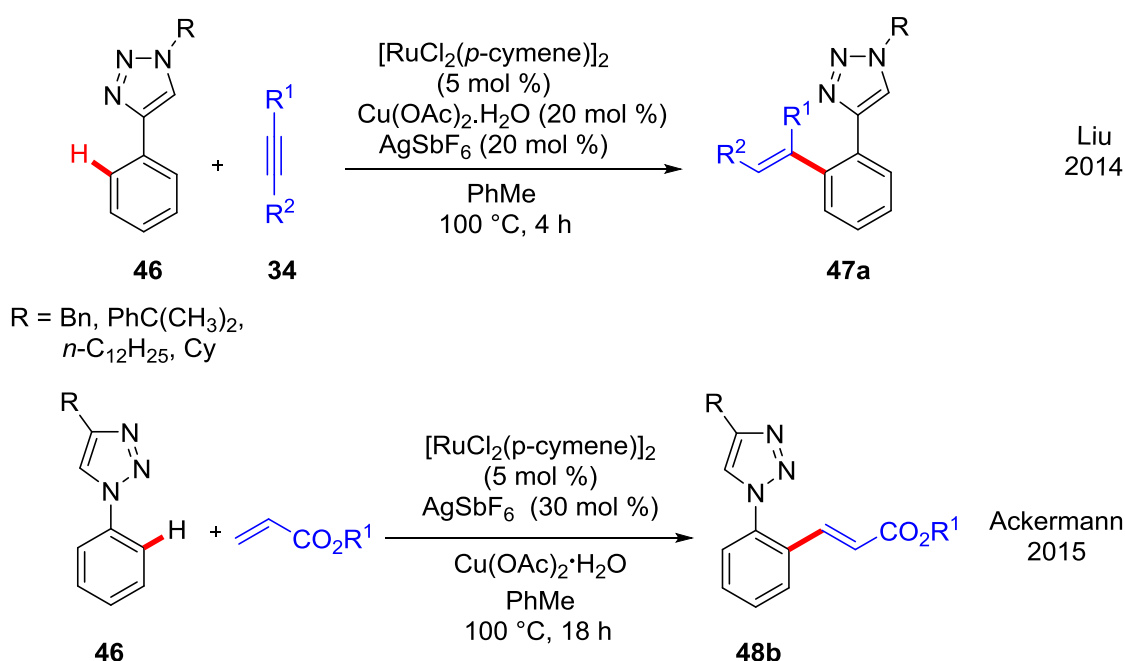
Scheme 14: Triazole-directed hydroarylation of alkynes.

Benzylthioethers were also used as substrates for hydroarylation of internal alkynes under microwave conditions.[45] Very recently, Ackermann and co-workers achieved aerobic oxidative C–H functionalization of weakly coordinating benzoic acids with oxygen or ambient air (Scheme 15). The alkenylation protocol with activated alkenes afforded phthalides[46] in a step-economic fashion.[47] Furthermore, the aerobic alkyne annulation method allowed the synthesis of isocoumarins.[48] Most importantly, use of oxygen as cheapest sacrificial oxidant obviates the use of stoichiometric copper(II) or silver(I) salts as oxidants and reduces the E factor.[49]
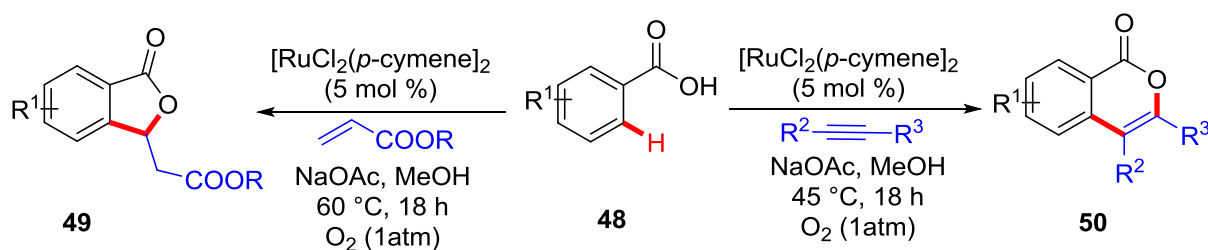
Scheme 15: Ruthenium catalyzed annulations with O_2 as oxidant

1.10 Transition metal catalyzed C–B bond formation

Boronic acids or their more stable derivatives, such as boronic esters and trifluoroborate salts are versatile compounds in organic synthesis as they can act as transient functional groups and intermediates in cross coupling technology,[50] enzyme inhibitors,[51] and boron neutron capture therapy agents.[52]
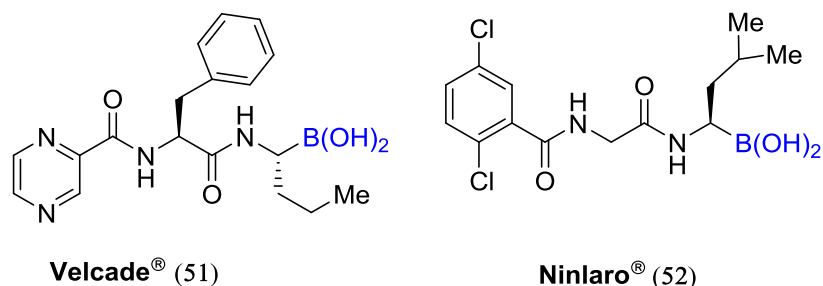
Figure 5: Boron-containing anti-cancer agents

While Velcade® and Ninlaro® are approved drugs (Figure 5), there are many other boron containing compounds showing promising activity as enzyme inhibitors. In particular, the enormous potential of compounds containing α-amino boronic acid in their structure has stimulated a great deal of interest (Figure 6).[53]

Talabostat (53)
DPP4 Inhibitor
(Phase II lung cancer, leukamia)

Delanzomib (54)
Phase I clinical trials
(solid tumours)

Dutogliptin (55)
DPP4 Inhibitor
(Phase III Type 2 diabetes mellitus)
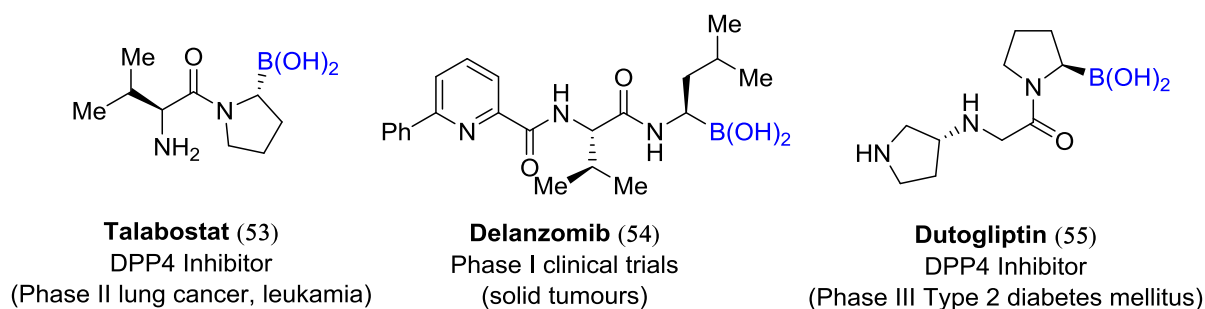
Figure 6: Pharmacologically relevant boron containing inhibitors

Traditional methods to synthesize boronic acids include: a) halogen-boron exchange with aryl halides and b) directed *ortho*-metallation along with subsequent borylation (Scheme 16).[54] The traditional methods are limited by functional group incompatibility, stoichiometric organometallic reagents, and the requirement of strict anhydrous and cryogenic conditions.

a) Halogen-Boron Exchange

X = Br, I
M = Li, Mg
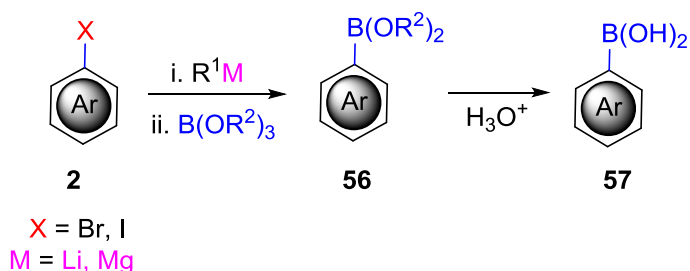
b) Directed *ortho*-metallation/borylation approach

DG = C(O)N(*i*-Pr)$_2$,
      OMOM,
      tetrazole
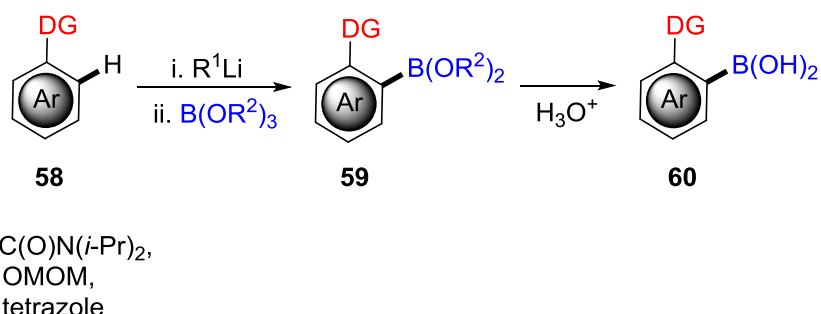
Scheme 16: Traditional approaches for the preparation of boronic acids

The first catalytic approach for the preparation of organo boronates was developed by Miyaura and co-workers in 1995 (Scheme 17).[55] The discovery of an efficient palladium

catalyzed cross-coupling reaction between B_2pin_2 and aryl (pseudo)-halides (Suzuki-Miyaura borylation) offered a more reliable approach for the synthesis of aryl/alkyl boronates. The use of preactivated substrates is a limitation in the Suzuki-Miyaura borylation. A more atom-economic approach by direct C–H bond functionalization is highly desirable.
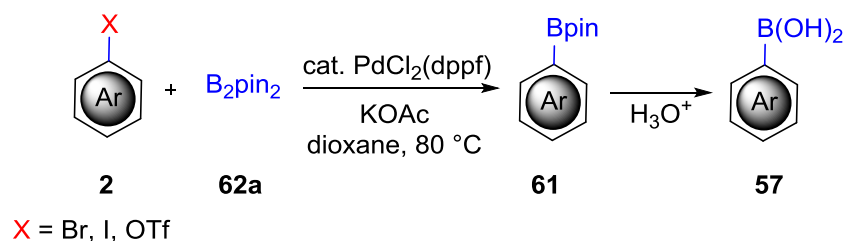
Scheme 17: Suzukui-Miyaura borylation

Early contributions from Hartwig, Smith, Miyaura and Marder include efficient procedures for arene and alkane borylation using expensive rhodium and iridium catalysts (Scheme 18).[56] Site-selectivity was mainly controlled by steric interactions in case of arene borylation, thus obviating the use of a directing group.
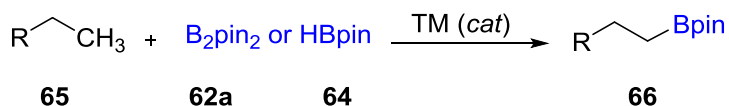
Scheme 18: Transition metal catalyzed C–H borylation

Considerable progress has been made in the last few years using a strategy involving directing group by Sawamura, Yu, Fernandez and others (Scheme 19).[57]
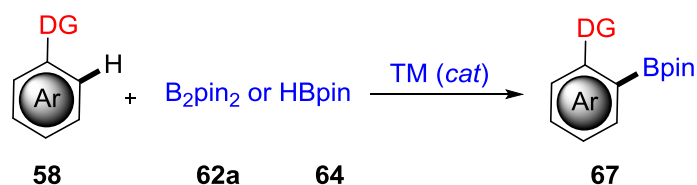
TM : Pd, Rh, Ir, Ru

Scheme 19: Transition metal-catalyzed chelation-assisted C–H borylation

1.11 Ruthenium-catalyzed C–H borylation

In 2006, Hartwig and co-workers reported the first ruthenium-catalyzed C–H borylation (Scheme 20). Regiospecific terminal borylation of alkanes was achieved using $[Cp*RuCl_2]_2$ at high temperatures under neat conditions.[58] Notably, preferential borylation was observed at the less hindered methyl group even when heteroatoms were present. The sensitive nature of the catalyst and the use of overstoichiometric reagent limit the practical applicability.
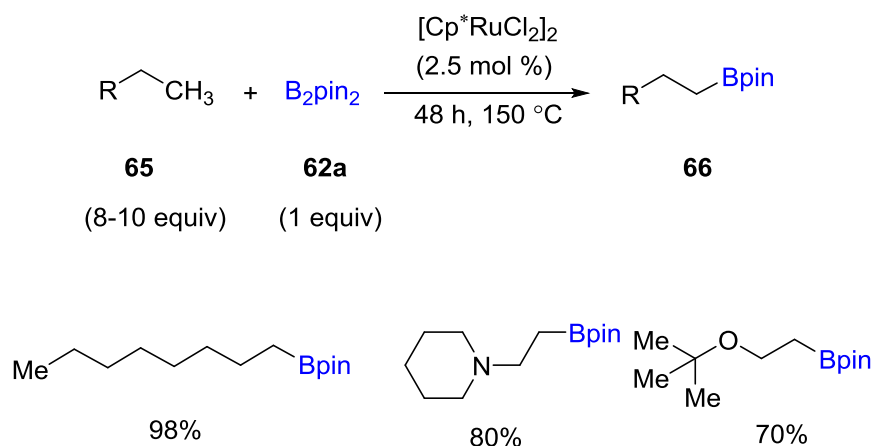
Scheme 20: Site-selective alkane borylation

Mullen and coworkers reported the ruthenium-catalyzed $C(sp^2)$–H borylation in 2011 (Scheme 21). The authors successfully achieved chelation-assisted tetraborylation in Perylenediimide (PDI) using $[RuH_2(CO)(PPh_3)_3]$.[59] Furthermore, boron derivatives of PDI were used for further functionalization.
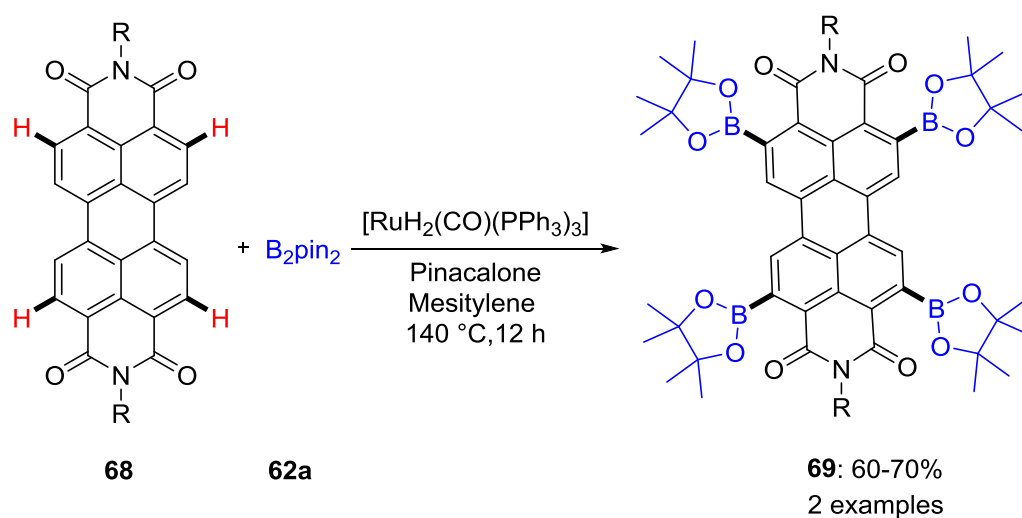
Scheme 21: Tetraborylation of PDI

Nolan *et al*. achieved ruthenium catalyzed *ortho*-selective C–H borylation of 2-phenyl pyridine derivatives using B_2pin_2 **62a** as the borylating agent (Scheme 22).[60] The authors employed 3-phenylindenyldihydridosilyl ruthenium complexes. However, the high cost of the precursor complex [RuCl(PPh$_3$)$_2$(3-phenylindenyl)] and the sensitive nature of the catalyst are major limitations of this method.[61]
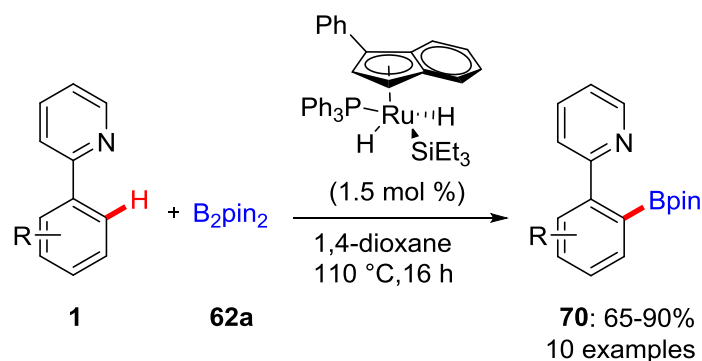
Scheme 22: Pyridine-directed borylation using B_2pin_2

Murata employed [RuH$_2$(CO)(PPh$_3$)$_3$] to achieve *ortho*-selective C–H borylation of 2-phenyl pyridine derivatives using HBpin at elevated temperature (150 °C) (Scheme 23).[62]
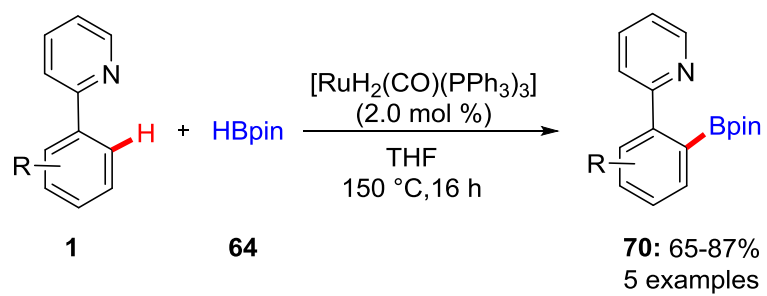
Scheme 23: Pyridine-directed borylation using HBpin

Objectives

Ruthenium(II) complexes have emerged as effective catalysts for C−H arylations of arenes by chelation assistance with organic halides or pseudohalides, which allowed for the step-economical synthesis of biaryl compounds. Ackermann's group reported the use of bifunctional additives, such as carboxylates and phosphates, as co-catalysts for ruthenium-catalyzed direct arylations in apolar solvents *via* a concerted metalation-deprotonation (CMD) mechanism.[63] Carboxylates are the first choice of additives in transition-metal catalyzed C–H bond fucntionalization due to their easy availability, low cost and stability. Continuing these efforts to apply carboxylate-assisted ruthenium-catalyzed direct arylation using tetrazoles as directing group is of critical importance as this potentially forms the key step in the syntheses of various block buster drugs, such as Losartan, Valsartan and Candesartan Cilexetil (Scheme 24).
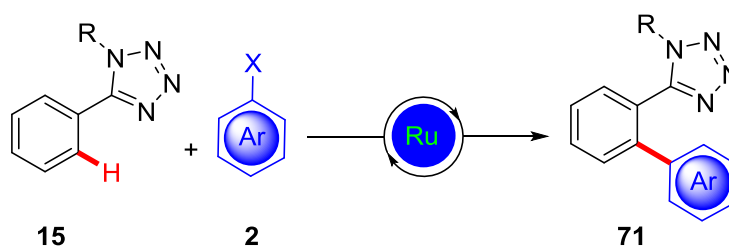
Scheme 24: Ruthenium-catalyzed C(sp^2)–H arylation

Transition metal-catalyzed functionalizations of C(sp^3)–H bonds are not very successful compared to direct C(sp^2)–H bond functionalizations due to the challenges involved in the catalytic functionalisation of C(sp^3)–H bonds. Developing user-friendly single component catalysts for C(sp^3)–H bond functionalization is a great challenge. Towards this goal probing various ruthenium(II) carboxylate complexes to achieve direct C(sp^3)–H bond functionalization might be advantageous. This project overcomes the challenges involved in direct arylations of C(sp^3)–H bonds using carboxylate-assisted ruthenium catalysis and its application to synthesize molecules containing the diarylmethylamine unit, an important class of pharmaceutically active compounds (Scheme 25).
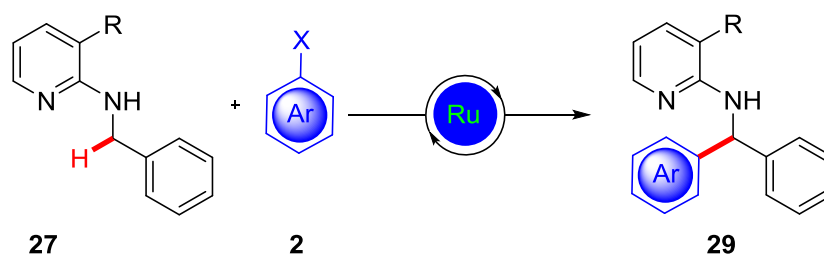
Scheme 25: Ruthenium-catalyzed C(sp^3)–H arylation

Ackermann and coworkers have disclosed ruthenium-catalyzed oxidative annulations of benzoic acids with activated alkenes and internal alkynes using oxygen as the terminal oxidant.[64] Benzoic acids are versatile starting materials for C–H bond fucntionalization due to their low cost and abundance.[65] Development of reactions using carboxylic acids as removable directing groups is very important as it provides a strategy to access *meta*-substituted arenes in a higly selective fashion obviating the use of templates.[66] We were interested in using readily available carboxylic acids as removable directing groups for hydroarylation reaction. More importantly, various *meta*-substituted arenes of high synthetic value should be prepared using this methodology (Scheme 26).
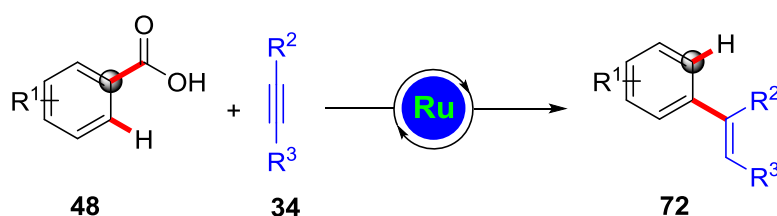
Scheme 26: Ruthenium-catalyzed C(sp^2)–H hydroarylation

The borylation of C–H bonds has received considerable attention in recent years because of the transformative nature of boronic acid derivatives as *inter alia* transient functional groups in cross-couplings technology and beyond. Site-selective borylations directed by sterics or directing groups are typically achieved using rather expensive iridium, rhodium, and palladium complexes.[67] Despite the power of organoboron compounds in organic synthesis, the use of ruthenium catalysts for formation of C–B bonds is underexplored. The

development of highly robust and inexpensive ruthenium(II) complexes as pre-catalysts for C–H borylation still remains a challenge in this field (Scheme 27).
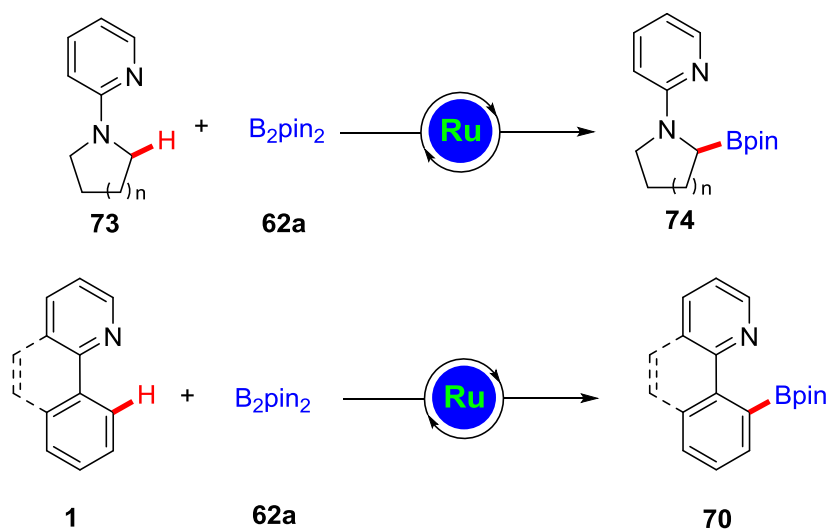
Scheme 27: Ruthenium-catalyzed borylation of $C(sp^3)$–H and $C(sp^2)$–H bonds

Results and discussion

3.1 Ruthenium-catalyzed C–H arylation of phenyltetrazoles

3.1.1 Scope of phenyltetrazoles in ruthenium-catalyzed direct arylation

Under optimized conditions by E.Diers,[68] the scope of the ruthenium-catalyzed arylation with tetrazoles as the directing group was explored. Initially, the scope of the reaction with respect to the electrophiles employed under the optimized reaction conditions was explored using *meta*-substituted derivatives **2** (Scheme 28). Aryl iodide **78**, aryl bromide **2b** and aryl triflate **80a** proved to be effective with similar reactivity. Unfortunately, more economical aryl chlorides **79** showed inferior reactivity.

X = I (**78**)	66%
X = Br (**2b**)	66%
X = Cl (**79**)	<10%
X = OTf (**80a**)	46%
X = OSO$_2$Im (**80b**)	10%
X = OTs (**80c**)	--
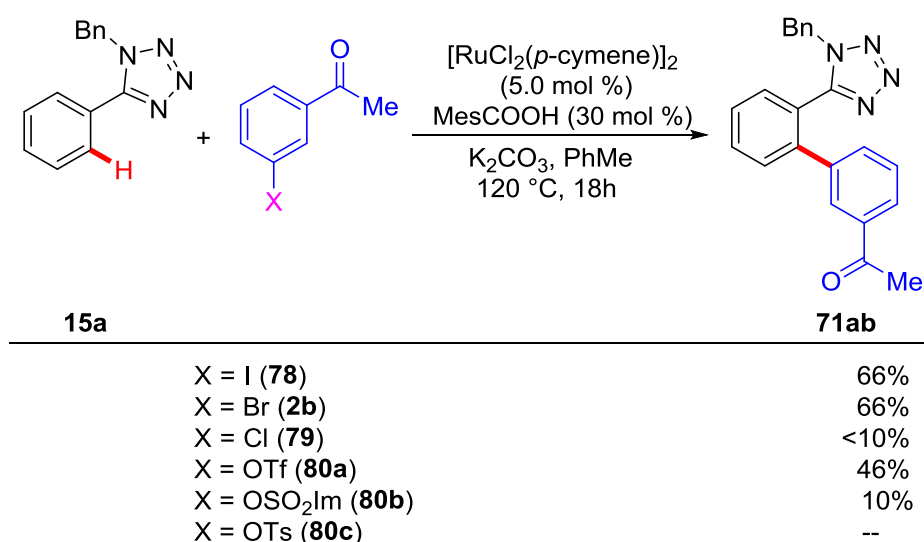
Scheme 28: Scope of tetrazole-directed C–H arylations with various aryl (pseudo)halides

Differently *N*-substituted tetrazoles were tested and a similar reactivity was observed with *N*-PMB substituted tetrazole **15b** compared to simple *N*-benzyl substitued tetrazole **15a**. Further scope was investigated with *N*-benzyl functional group on tetrazole **15a** as it is more atom economic and easily cleavable (Scheme 29).
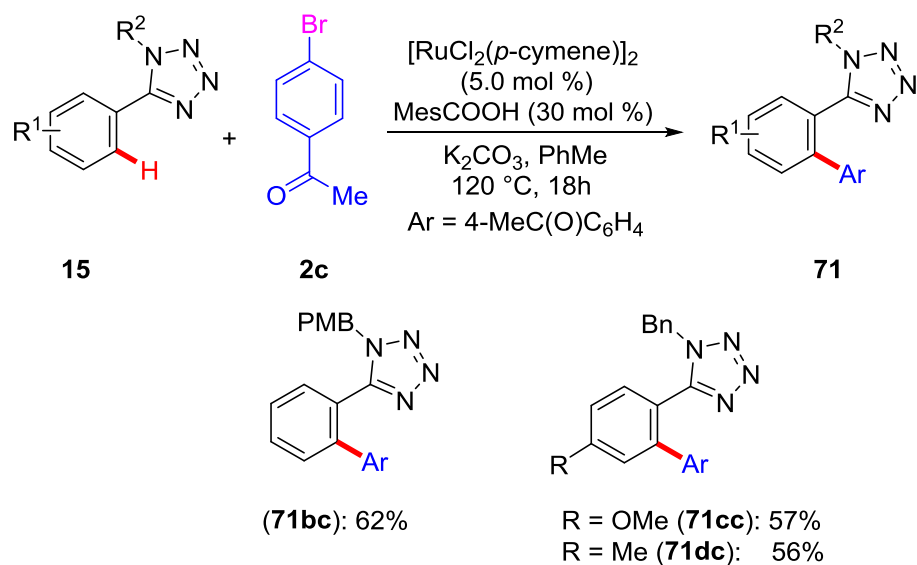
Scheme 29: Effect of the *N*-substituent on the tetrazole directing group

The versatility of the reaction was studied with electronically different aryl bromides **2** (Scheme 30). Aryl bromide **2c** with an enolizable ketone delivered the desired product **71ac**. The efficiency of the reaction was higher with electron-rich substrate **2e** than with electron deficient **2f**. Hetero-aryl bromides were also tested as electrophilic substrates. The reactivity profile was similar to that of aryl bromides, as the electron-rich electrophile **2h** was more reactive than **2g**.
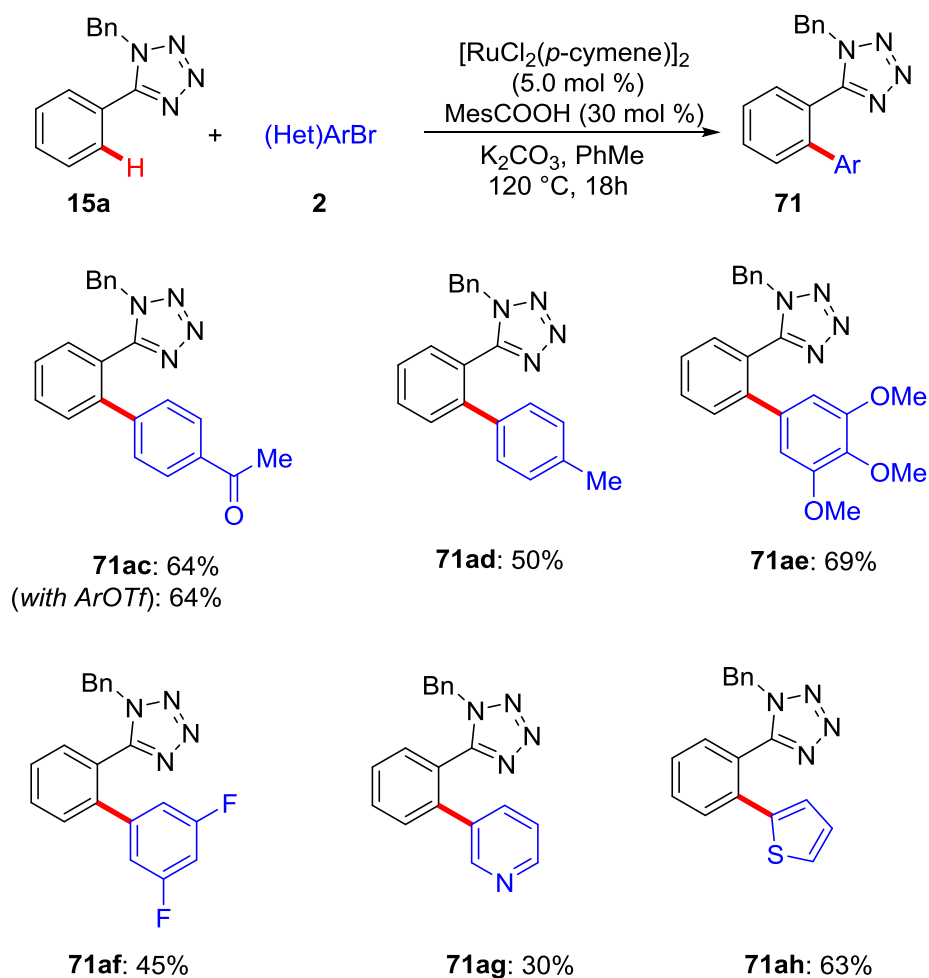
Scheme 30: Scope of tetrazole-directed arylations with aryl bromides

3.1.2 Arylation of phenyltetrazole with well-defined ruthenium(II) complex

To gain insight into the catalyst's mode of action, the well defined ruthenium(II) biscarboxylate complex (**16**) was employed as the catalyst. The catalyst **16** showed comparable reactivity and selectivity with the *in situ* formed catalytic system (Scheme 31). More importantly, the yield of the reaction showed only a slight decrease when the ruthenium loading was reduced to 5 mol % and delivered exclusively the monoarylated product **71ac**.
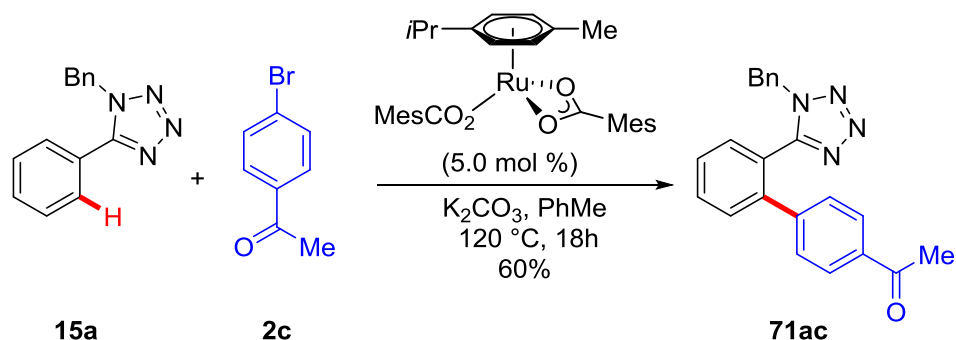
Scheme 31: C–H arylation with ruthenium(II) biscarboxylate complex

3.1.3 Proposed mechanism for C–H arylation of phenyltetrazole

Based on the mechanistic studies in our group,[69] the following mechanism is proposed. An initial reversible cyclometalation is plausible through chelation assistance from tetrazole to give complex **B** (Scheme 32) and subsequently formal oxidative addition of aryl(pseudo) halide **2** by a SET-type process give complex **C**. Reductive elimination from **C** delivers product **71**.
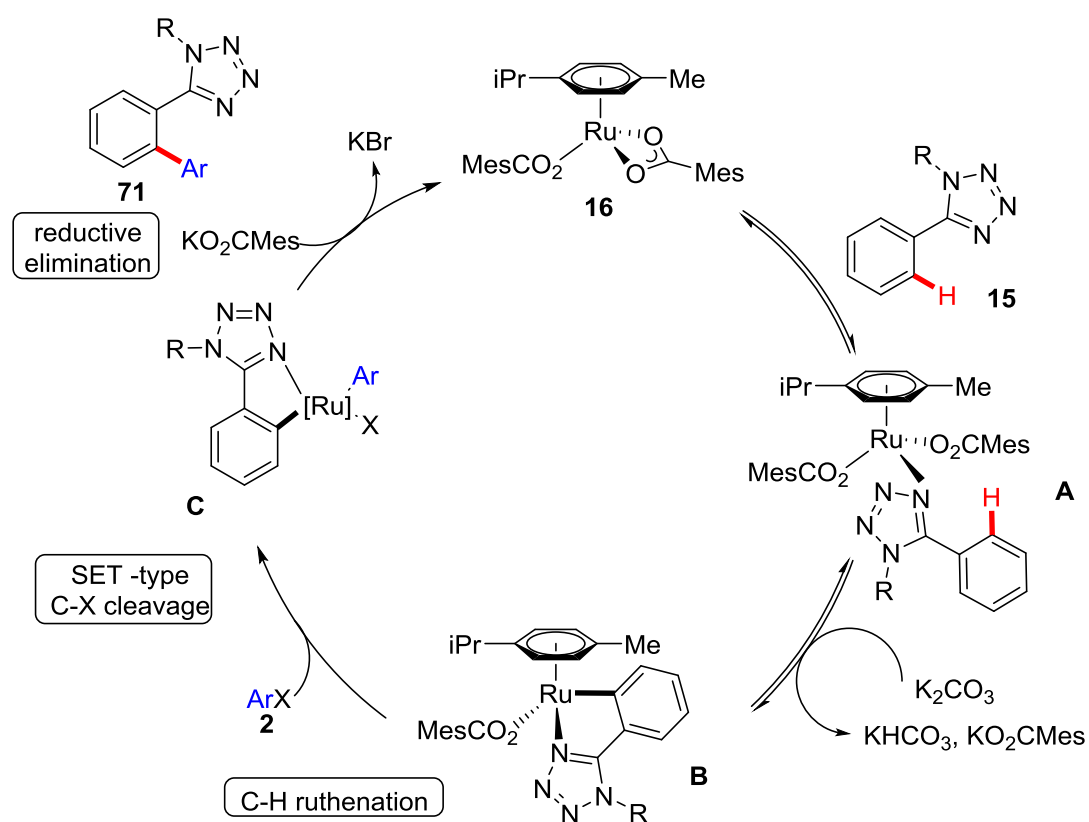
Scheme 32: Plausible mechanistic cycle for arylation of phenyltetrazole **15**. [Ru] = [Ru(O₂CMes)(p-cymene)

3.2 Ruthenium-catalyzed C(sp^3)–H arylation

3.2.1 Optimization studies for ruthenium-catalyzed C(sp^3)–H arylation

A variety of reaction conditions were tested for the envisioned ruthenium-catalyzed C(sp^3)–H arylation of benzyl amine **27a** with bromo benzene (**2i**) (Table 2).

Table 2. Optimization of C(sp^3)–H arylation
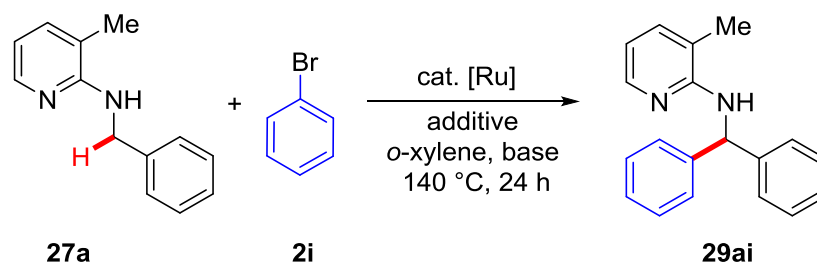
Entry	*Cat* [Ru]	Additive	Base	Yield (%)[a]
1	[Ru(O$_2$CMes)$_2$(*p*-cymene)]	--	K$_2$CO$_3$	60
2	[Ru(O$_2$CMes)$_2$(*p*-cymene)]	--	NaOAc	13
3	[Ru(O$_2$CMes)$_2$(*p*-cymene)]	--	KOAc	17
4	[Ru(O$_2$CMes)$_2$(*p*-cymene)]	--	K$_3$PO$_4$	46
5	[Ru(O$_2$CMes)$_2$(*p*-cymene)]	--	K$_2$CO$_3$	51[b]
6	**[Ru(O$_2$CMes)$_2$(*p*-cymene)]**	**--**	**Na$_2$CO$_3$**	**69**
7	[Ru(O$_2$CMes)$_2$(*p*-cymene)]	(1-Ad)$_2$P(O)H	Na$_2$CO$_3$	40
8	[Ru(O$_2$CMes)$_2$(*p*-cymene)]	1-AdCO$_2$H	Na$_2$CO$_3$	55
9	[Ru(O$_2$CMes)$_2$(*p*-cymene)]	MesCO$_2$K	K$_2$CO$_3$	55
10	[Ru(O$_2$CMes)$_2$(*p*-cymene)]	--	K$_2$CO$_3$	--[c]
11	[Ru(O$_2$CMes)$_2$(*p*-cymene)]	--	K$_2$CO$_3$	--[d]
12	[Ru(O$_2$CMes)$_2$(*p*-cymene)]	--	K$_2$CO$_3$	40[e]
13	[Ru(OPiv)$_2$(*p*-cymene)]	--	K$_2$CO$_3$	51
14	[Ru(OPiv)$_2$(*p*-cymene)]	KOPiv	K$_2$CO$_3$	58
15	[RuCl$_2$(*p*-cymene)]$_2$	--	Na$_2$CO$_3$	39
16	[RuCl$_2$(*p*-cymene)]$_2$	MesCO$_2$K	K$_2$CO$_3$	50
17	[RuCl$_2$(*p*-cymene)]$_2$	MesCO$_2$H	K$_2$CO$_3$	41

Entry	*Cat* [Ru]	Additive	Base	Yield $^{(\%)[a]}$
18	[RuCl$_2$(*p*-cymene)]$_2$	(1-Ad)$_2$P(O)H	K$_2$CO$_3$	36
19	[RuCl$_2$(*p*-cymene)]$_2$	(*t*-Bu)$_2$P(O)H	K$_2$CO$_3$	42
20	[RuCl$_2$(*p*-cymene)]$_2$	PCy$_3$	K$_2$CO$_3$	--
21	[RuCl$_2$(*p*-cymene)]$_2$	KOAc	K$_2$CO$_3$	47
22	[RuCl$_2$(*p*-cymene)]$_2$	--	K$_2$CO$_3$	36
23	[RuCl$_2$(*p*-cymene)]$_2$	--	KOAc	58
24	[RuCl$_2$(*p*-cymene)]$_2$	(1-Ad)$_2$P(O)H	Na$_2$CO$_3$	55
25	[RuBr$_2$(*p*-cymene)]$_2$	--	Na$_2$CO$_3$	51
26	[RuBr$_2$(*p*-cymene)]$_2$	--	K$_2$CO$_3$	48
27	--	--	Na$_2$CO$_3$	-

[a] Reaction conditions: 27a (0.50 mmol), 2i (0.75 mmol), [Ru] (5.0 mol %), additive (30 mol %), base (1.50 mmol), solvent (2.0 mL), 140 °C, 24 h; isolated yields. [b] [Ru] (2.5 mol %). [c] DMF as the solvent. [d] H$_2$O as solvent. [e] NMP as solvent.

Among the ruthenium(II) carboxylate complexes probed, [Ru(O$_2$CMes)$_2$(*p*-cymene)] showed superior reactivity as compared to [Ru(OPiv)$_2$(*p*-cymene)]. The reaction was shut down completely when polar solvents such as DMF or H$_2$O, were employed (entries 10 and 11). [RuCl$_2$(*p*-cymene)]$_2$ showed inferior reactivity even in presence of various additives such as phosphine oxides or carboxylates (entries 15-26). Among the various stoichiometric bases screened, Na$_2$CO$_3$ showed superior reactivity (entry 6) as compared to other bases, including K$_2$CO$_3,$ KOAc, NaOAc or K$_3$PO$_4$ (entries 1-4). A control experiment (entry 27) demonstrated that the reaction did not occur in the absence of a ruthenium catalyst.

3.2.2 Scope of C(sp^3)–H bond Arylation

After optimizing the reaction conditions, the effect of the substitution pattern of the pyridine moiety in substrates **27** was studied (Scheme 33). Pyridine **27b** without an additional substituent and other substituents (**27c**-**27e**) gave unsatisfactory results. Pyridine derivative **27a** bearing a 3-methyl group was found to be the best.
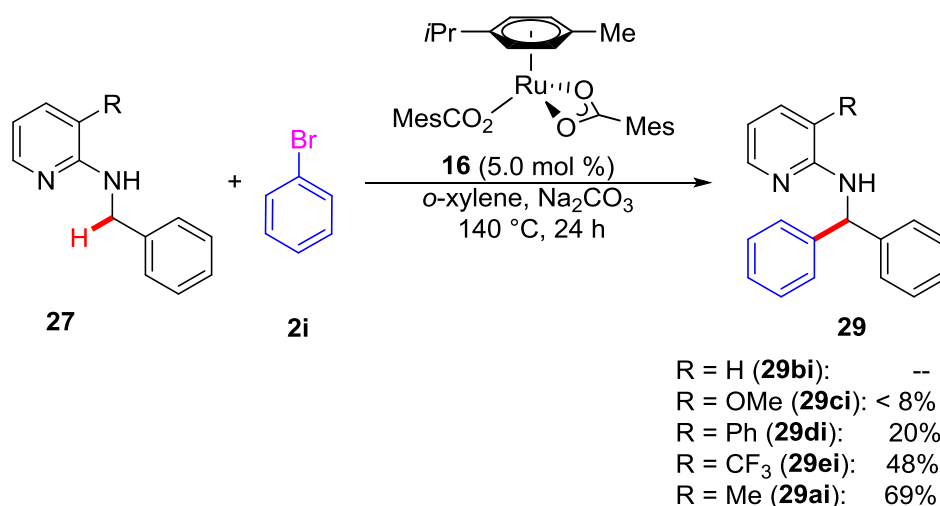
Scheme 33: Variation of pyridine substitution

With regard to the choice of electrophiles employed under the optimized reaction conditions, only aryl bromides **2** were efficient. Other electrophiles did not afford the desired product **29ai** (Scheme 34).
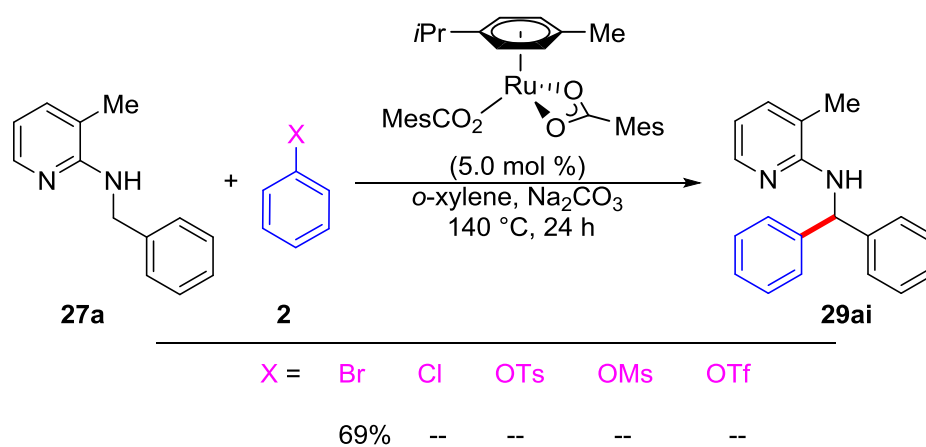
Scheme 34: Variation of Aryl(pseudo) halides **2**

With the optimized reaction conditions in hand, the scope of the reaction was studied with various (hetero)aryl bromides **2** as the electrophiles. The broad scope and remarkable functional group tolerance were exemplified by the synthetically useful chloride substituent, which should prove valuable for subsequent derivatization of **29al** as well as free (*NH*)-indole **29aq** (Scheme 35).
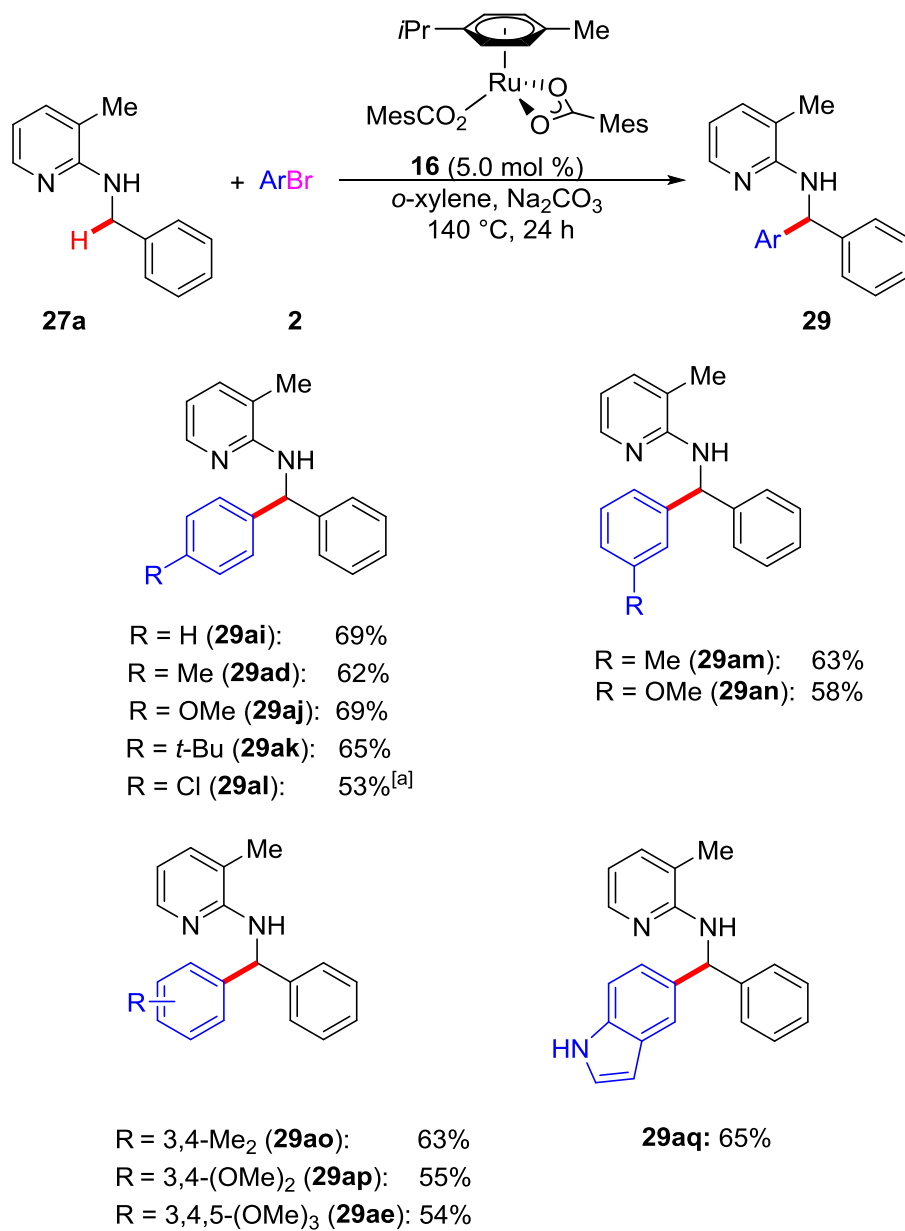
Scheme 35: Scope of C(sp^3)–H bond arylation with aryl bromides. [a] At 150 °C

3.2.3 Limitations of C(sp³)–H bond arylation

3.2.3.1 Unreactive *ortho*-aryl bromides

Reactions with *para*-substituted aryl bromides **2** and *meta*-substituted aryl bromides showed similar reactivity and good yields were obtained. However, when *ortho*-substituted aryl bromides **2r-t** were employed, no formation of products **29** was observed (Figure 7).

2r   **2s**   **2t**
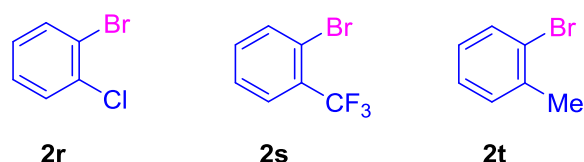
Figure 7: Unsuccessful *ortho* substituted aryl bromides

3.2.3.2 Unreactive amines

Various other substrates containing C(sp³)–H bond and a Lewis basic directing group were tested under the optimized reaction conditions (Figure 8). No conversion was observed for substrates (Figure 8). Based on these results, a free *NH* functionality and benzyl group are essential for effective arylations.

27f   **27g**   **27h**   **27i**

75   **73a**   **73b**   **73c**
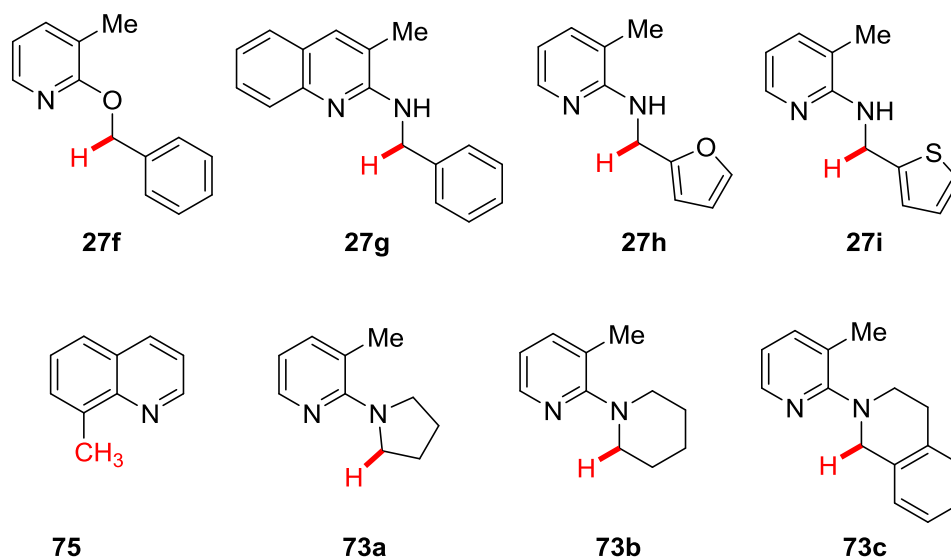
Figure 8: Unsuccesful amines for C(sp³)–H bond arylation

3.2.4 Mechanistic studies for C(sp³)–H arylation

3.2.4.1 Radical scavenger experiments for C(sp³)–H arylation

Experiments performed with TEMPO as a radical scavenger in catalytic amounts revealed that the reaction efficiency was reduced. Increasing the amount of TEMPO to superstoichiometric quantities led to no product (Scheme 36). This indicates that a single-electron transfer (SET) step might be involved in the catalytic cycle.

Standard conditions:	69%
TEMPO (5 mol %):	15% (64% of **27a** recovered)
TEMPO (120 mol %):	-- (78% of **27a** recovered)
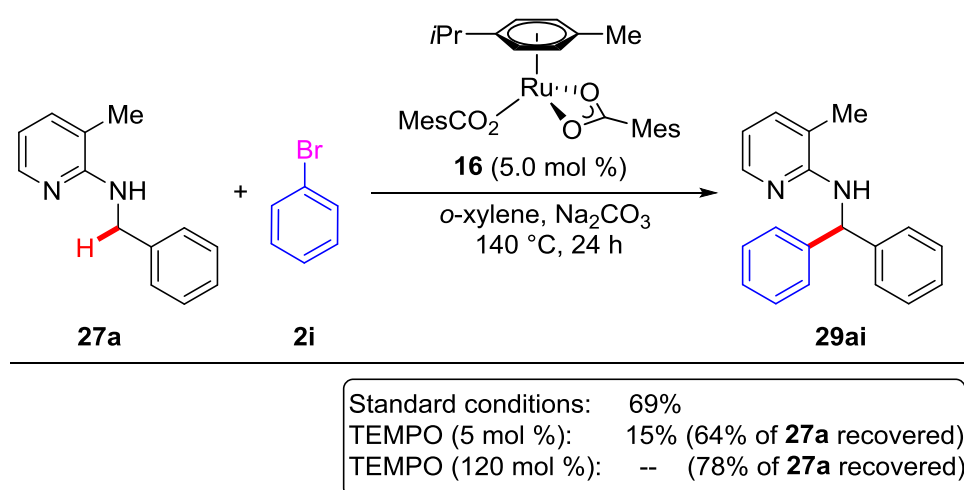
Scheme 36: Radical scavenger experiments with TEMPO as additives

3.2.4.2 H/D exchange

H/D exchange studies carried out in the presence of D_2O as a co-solvent revealed that a significant H/D scrambling occured (Scheme 37). These studies are in favor of a reversible C(sp³)–H bond cleavage.
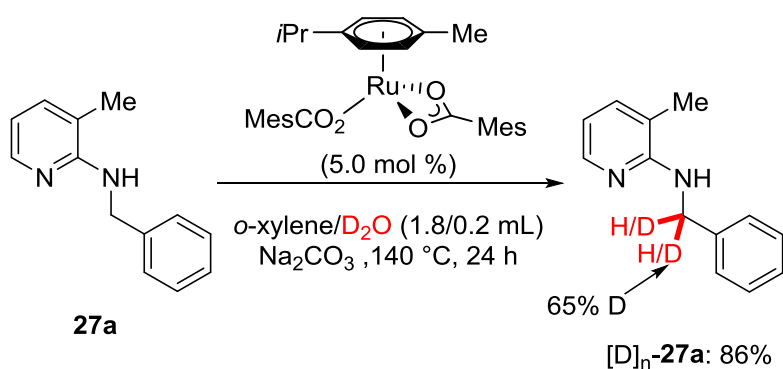
Scheme 37: H/D exchange in the presence of D_2O

3.2.4.3 Proposed mechanism for C(sp^3)–H arylation

Competition experiments performed by R. Jeyachandran revealed the importance of a Lewis basic directing group and also support a reversible C(sp^3)–H cleavage. Based on our mechanistic studies, the following mechanism is proposed. An initial reversible cyclometalation through pyridine assistance gives complex **P** (Scheme 37a) and subsequently carboxylate assisted C–H ruthenation via transition state **Q** delivers complex **R**. Formal oxidative addition of arylbromide **2** by a SET-type process furnishes complex **S**. Finally, complex **S** undergoes reductive elimination to deliver the desired product **29** and regenerates the active catalyst **16**.

[Ru] = [Ru(O$_2$CMes)(*p*-cymene)]
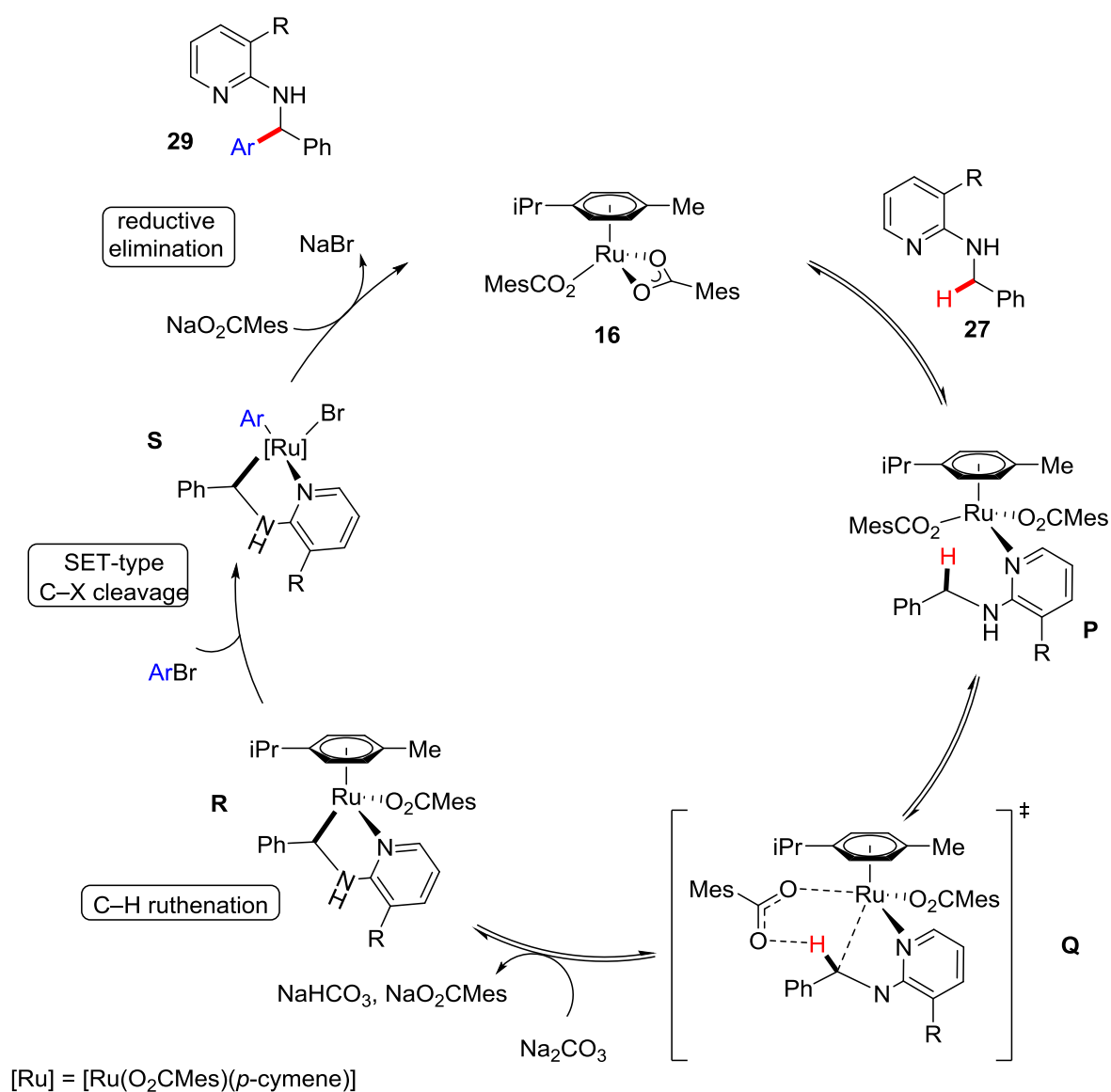
Scheme 37a: Plausible mechanism for C(sp^3)–H arylation

3.3 Decarboxylative Ruthenium-catalyzed Hydroarylation of Alkynes

3.3.1 Optimization studies for Decarboxylative Hydroarylation

At the outset of the studies, a variety of reaction conditions were tested for the envisioned hydroarylation reaction of diphenylacetylene **34a** with *o*-anisic acid **48a** (Table 3)**.** There was no conversion in the absence of a ruthenium catalyst (entry 1). Among the various ruthenium catalysts screened, simple [RuCl$_2$(*p*-cymene)]$_2$ showed no reactivity, while ruthenium(II) carboxylate complexes proved to be highly active. [Ru(O$_2$CMes)$_2$(*p*-cymene)] (**16**) showed similar reactivity as compared to [Ru(OPiv)$_2$(*p*-cymene)] (entries 4 and 6). We observed a significant decrease in the yield of the desired product **72aa** when reducing the reaction temperature (entry 3). Reducing the catalyst loading by half caused only a slight decrease in the yield of product **72aa** (entry 5). The reaction was efficient even in polar solvents such as water[70] and alcoholic solvents (entries 7, 8 and 13). However, a considerably low reactivity was observed when DMA was employed (entry 10). Toluene and 1,2-dichloroethane proved to be the best solvents for this transformation (entries 4 and 11). Carboxylate complexes from other transition metals, such as cobalt and palladium did not show any reactivity at all and the diphenylacetylene **34a** was reisolated in more than 95%). Therefore, ruthenium(II)-carboxylate complexes are critical for achieving the desired transformation.The optimized reaction conditions are very user friendly as only a single component catalyst is employed. No additives, such as copper(II) or silver(I) salts, were required and the reaction occured at rather low temperatures. Most importantly, readily available and inexpensive benzoic acids could be employed as starting materials to prepare *meta*-alkenylated arenes without the use of a template approach.

Table 3: Optimization Studies for Decarboxylative Hydroarylation
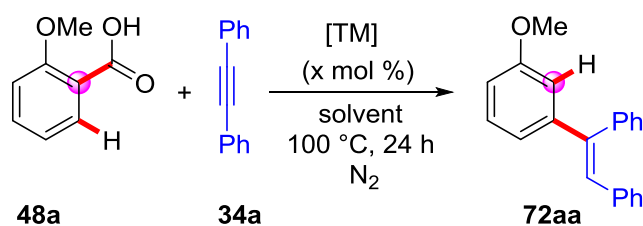
Entry	[TM] (x mol %)	Solvent	Yield [%][a]
1	-	PhMe	NR[b]
2	[RuCl$_2$(p-cymene)]$_2$ (5.0 mol %)	PhMe	NR[b]
3	[Ru(O$_2$CMes)$_2$(p-cymene)] (10.0 mol %)	PhMe	31[c]
4	**[Ru(O$_2$CMes)$_2$(p-cymene)] (10.0 mol %)**	**PhMe**	**95**
5	[Ru(O$_2$CMes)$_2$(p-cymene)] (5.0 mol %)	PhMe	87
6	[Ru(OPiv)$_2$(p-cymene)] (10.0 mol %)	PhMe	93
7	[Ru(O$_2$CMes)$_2$(p-cymene)] (10.0 mol %)	MeOH	50
8	[Ru(O$_2$CMes)$_2$(p-cymene)] (10.0 mol %)	H$_2$O	71
9	[Ru(O$_2$CMes)$_2$(p-cymene)] (10.0 mol %)	1,4-dioxane	50
10	[Ru(O$_2$CMes)$_2$(p-cymene)] (10.0 mol %)	DMA	10
11	**[Ru(O$_2$CMes)$_2$(p-cymene)] (10.0 mol %)**	**DCE**	**98**
12	[Ru(O$_2$CMes)$_2$(p-cymene)] (10.0 mol %)	tAmOH	56
13	Co(OAc)$_2$ (10.0 mol %)	PhMe	NR[d]
14	Co(OAc)$_2$ (10.0 mol %)	MeOH	NR[d]
15	Pd(OAc)$_2$ (10.0 mol %)	PhMe	NR[d]

[a] Reaction conditions: **48a** (0.50 mmol), **34a** (1.00 mmol), [TM] (x mol %), solvent (2.0 mL), 24 h, N$_2$, 100 °C, isolated yields. [b] **34a** recovered in 99%. [c] at 60 °C. [d] **34a** recovered in >95% yield.

3.3.2 Scope of Decarboxylative Hydroarylation

With the optimized reaction condition in hand, the versatility of the catalyst was studied using various *ortho*-substituted benzoic acids (Scheme 38). The functional group tolerance of the reaction was exemplified by having substituents, such as fluoro, chloro, and nitro, on the benzoic acid. Simple benzoic acid without an *ortho*-substituent also reacted, but with low efficiency. The optimized conditions furnished *meta*-alkenylated arenes **72** in a chemoselective fashion.
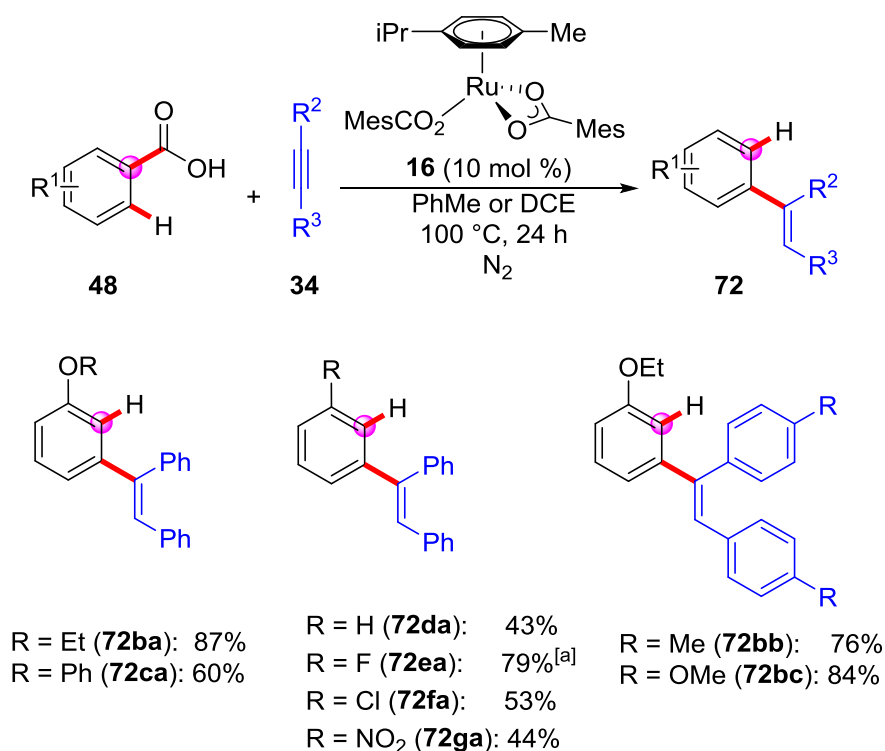
Scheme 38: Decarboxylative Hydroarylation of Alkynes **34**. [a] In DCE

The reactivity trend observed in the hydroarylation of alkynes **34** with benzoic acids **48** is difficult to explain as factors such as solubility of the substrates in the reaction medium and acidity of the benzoic acid are important, but can not be quantified easily. To verify if the efficiency of the reaction is dependent on the *ortho*-substituent, the scope of the reaction was also studied with *para*-substituted benzoic acids **48a'**, **48h** and **48**i (Scheme 39). Gratifyingly, the desired products **72** were obtained in good yields.
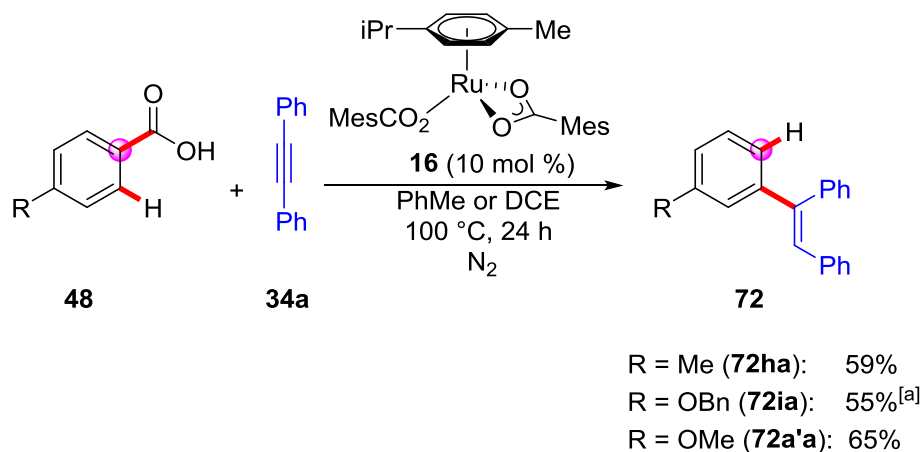
Scheme 39: Decarboxylative Hydroarylation with *para*-substituted Benzoic acids. [a] In DCE

To test the robustness of the novel decarboxylative method, more challenging substrates namely salicylic acid derivatives were employed. Interestingly, the desired product **72ja** was obtained in good to excellent yields (Scheme 40). Most importantly, a highly inexpensive and bio-renewable phenolic acid was used as a starting material to prepare a *meta*-anlaogue precursor for Zuclomiphene.[71] The free phenolic group in the product provides a handle for further functionalization.
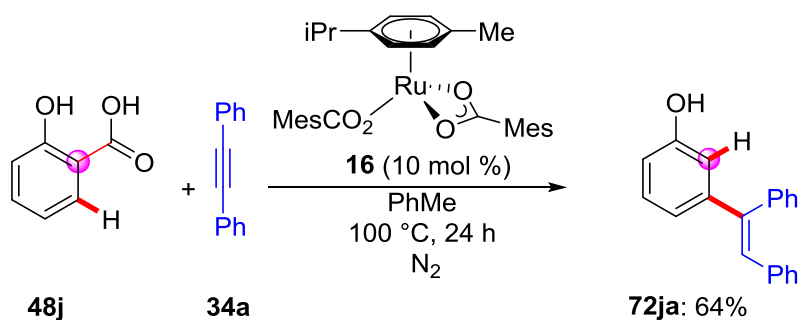
Scheme 40: Decarboxylative Hydroarylation with Salicylic acid **48j**

3.3.3 Mechanistic investigations for hydroarylation reaction

Several experiments were performed to clarify if the hydroarylation the formal loss of CO_2 proceeds in a simultaneous or a consecutive fashion. Hydroarylated products with carboxylic acid group intact **72ka'** could be isolated (Scheme 41). These results indicate that loss of CO_2 occurs most likely after the hydroarylation step.
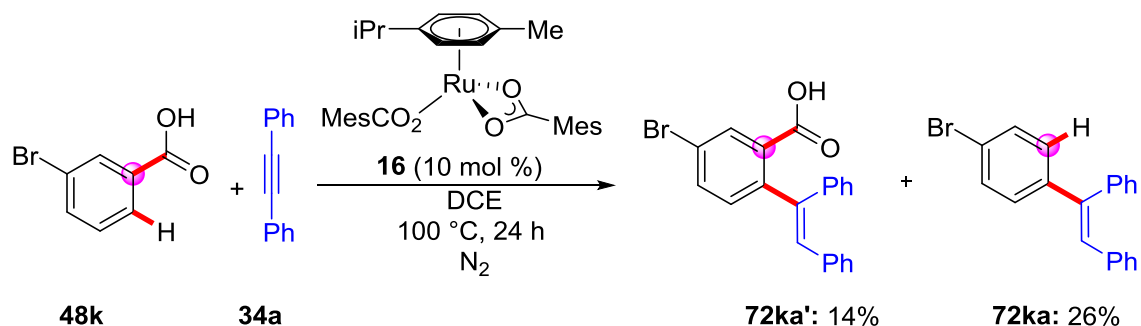
Scheme 41: Hydroarylation of alkyne **34a** with *m*- bromo benzoic acid **48k**

Moreover, an experiment performed with 2-napthoic acid **48m** under reaction conditions in the absence of alkyne did not show the formation of naphthalene, as judged by ^{1}H NMR spectroscopic and mass spectroscopic analysis.
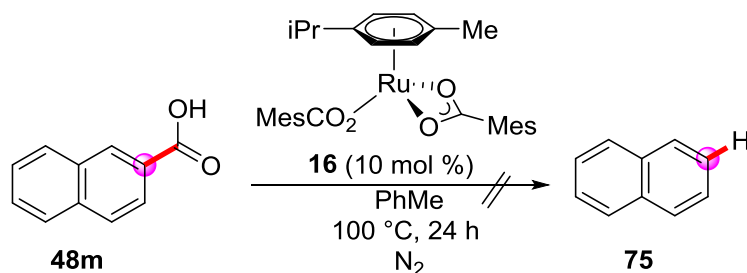
Scheme 42: Probing decarboxylation in the absence of an alkyne

3.3.4 Limitations of hydroarylation reactions

The steric and electronic nature of the carboxylic acids and solubility play a critical role in their reactivity towards the hydroarylation of alkyne **34a**. Cycloalkyl carboxylic acids and polyaromatic acids did thus far, not show any reactivity (Figure 9).
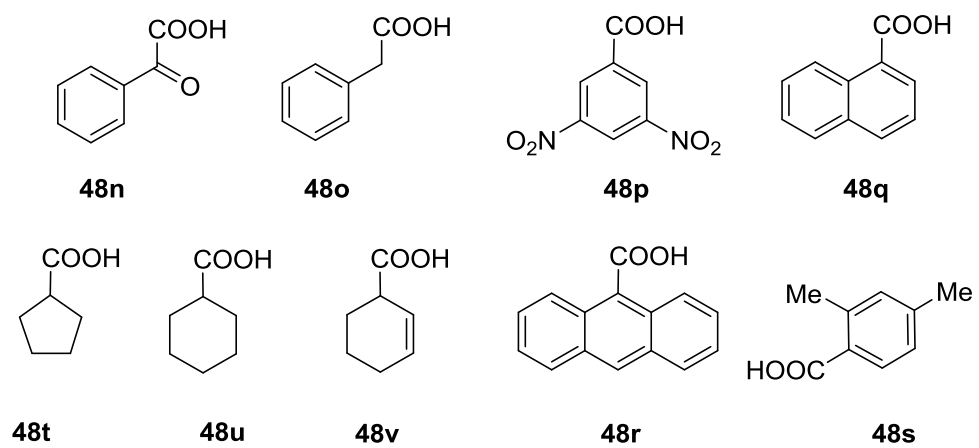
Figure 9: Thus far unsuccessful substrates **48**

3.4 Carboxylate-assisted ruthenium-catalyzed C–H borylation

3.4.1 Optimization of ruthenium-catalyzed C(sp^2)–H borylation

At the outset of our investigations, a variety of reaction conditions were tested for the envisioned borylation reaction of benzo[*h*]quinoline **1a** with bis pinacolato diboron **62a** (Table 4). No conversion was observed in the absence of a catalyst (entry 1). Inexpensive RuCl$_3$·xH$_2$O and [RuCl$_2$(*p*-cymene)]$_2$ were not effective for the desired transformation (entries 2 and 3) respectively. Various carboxylates were probed as additives (entries 4-8). Thus, the desired product **70aa** was observed with NaOAc as the addittive (entry 8). Next, well-defined ruthenium(II) carboxylates were explored (entries 10-22) in various solvents. The desired reaction was most efficient in 1,4-dioxane (entry 10).

Table 4: Optimization Studies for C(sp^2)–H Borylation
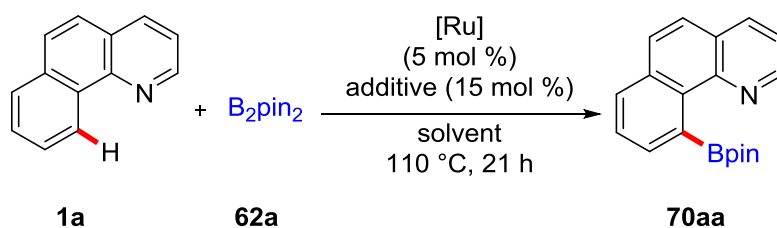
Entry	[TM] (x mol %)	Additive	Solvent	Yield [%][a]
1	-	-	1,4-dioxane	NR
2	RuCl$_3$·xH$_2$O	-	1,4-dioxane	NR
3	[RuCl$_2$(*p*-cymene)]$_2$	-	1,4-dioxane	NR
4	[RuCl$_2$(*p*-cymene)]$_2$	AgOAc	1,4-dioxane	NR
5	[RuCl$_2$(*p*-cymene)]$_2$	CsOAc	1,4-dioxane	NR
6	[RuCl$_2$(*p*-cymene)]$_2$	KOAc	1,4-dioxane	<5
7	[RuCl$_2$(*p*-cymene)]$_2$	KOPiv	1,4-dioxane	NR
8	[RuCl$_2$(*p*-cymene)]$_2$	NaOAc	1,4-dioxane	40
9	[RuCl$_2$(*p*-cymene)]$_2$	NaOTs	1,4-dioxane	NR

Entry	[TM] (x mol %)	Additive	Solvent	Yield [%][a]
10	**[Ru(O₂CMes)₂(p-cymene)]**	**-**	**1,4-dioxane**	**86**
11	[Ru(O₂CMes)₂(p-cymene)]	-	THF	NR[b]
12	[Ru(O₂CMes)₂(p-cymene)]	-	tAmOH	NR
13	[Ru(O₂CMes)₂(p-cymene)]	-	1,2-DCE	NR
14	[Ru(OPiv)₂(p-cymene)]	-	1,4-dioxane	76
15	**[Ru(O₂C1-Ad)₂(p-cymene)]**	**-**	**1,4-dioxane**	**90**
16	[Ru(O₂CMes)₂(p-cymene)]	-	1,4-dioxane	NR[c]
17	[Ru(O₂CMes)₂(p-cymene)]	MesCO₂H	1,4-dioxane	57
18	[Ru(O₂CMes)₂(p-cymene)]	-	PhMe	66[d]
19	[Ru(O₂CMes)₂(p-cymene)]	-	Benzene	58[e]
20	[Ru(O₂CMes)₂(p-cymene)]	-	o-xylene	trace[e]
21	RuCl₃·xH₂O	MesCO₂K	1,4-dioxane	62
22	[RuCl₂(p-cymene)]₂	MesCO₂K	1,4-dioxane	85
23	Pd(OAc)₂	-	1,4-dioxane	NR

[a] Reaction conditions: **1a** (0.25 mmol), **62a** (0.25 mmol), [TM] (5.0 mol %), additive (15 mol %), solvent (1.0 mL), 21 h, N₂, 110 °C, ¹H NMR yield (1,1,2,2 - tetrachloroethane as the internal standard). [b] at 80 °C. [c] 0.1 mL of H₂O added to reaction medium. [d] at 120 °C, borylation of solvent and unidentified side product was observed. [e] C–H Borylation of solvent observed.

Interestingly, there was no reactivity at all in other solvents (entries 11-13) and aromatic solvents delivered undesired products arising from the borylation of the solvent (entries 18-20). Upon addition of MesCOOH as an additive when employing well defined complex **16** as the catalyst, the efficiency of the reaction declined (entry 17). However, upon addition of MesCO₂K as an additive when RuCl₃·xH₂O or [RuCl₂(p-cymene)]₂ were employed (entries 21 and 22) the desired product was observed. These findings clearly suggested the beneficial effect of carboxylates. It is noteworthy that Pd(OAc)₂ did not show any catalytic activity (entry 24). Importantly, the optimized raection conditions are operationally simple and employs [Ru(O₂CMes)₂(p-cymene)] **16** as a single-component C–H activation catalyst (entry 10)

unlike other metal catalysts used for C–H borylation, which normally work in the presence of additives.

4.2 Scope of C(sp^2)–H borylation

With the optimized conditions in hand, we next examined the scope of the C(sp^2)–H borylation (Scheme 39). Pyridine and pyrazole could be used as directing groups to obtain monoborylated products **70** in good yields even with a lower catalyst loading of only 1.0 mol %. Controlling the site-slectivity in C–H borylations of heterocycles is very difficult with other metal catalysts.[72] However, site-selective diborylation was observed in case of 2-(1*H*-pyrrol-1-yl)pyridine (**1b**).

Furthermore, bis catecholato diboron (B$_2$cat$_2$) (**62b**) could also be used as the borylating agent to obtain boryalted products **70ab** and **70eb** in high yields.
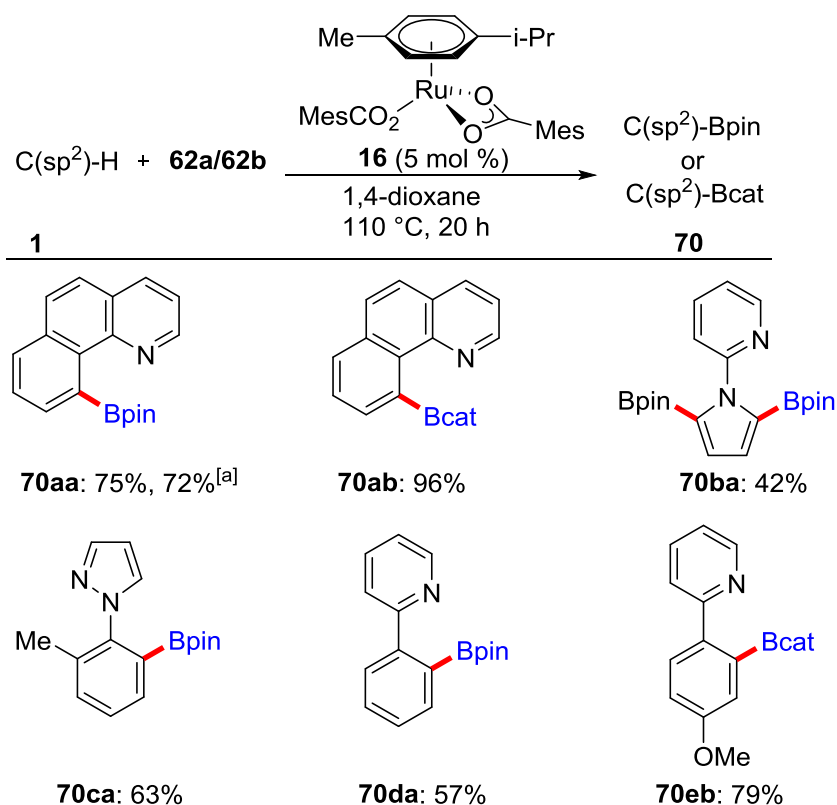
Scheme 39: Scope of C(sp^2)–H borylation. [a] 1 mol % of **16**

3.4.3 Optimization studies for ruthenium-catalyzed C(sp³)–H borylation

At the outset of our studies, we tested a variety of reaction conditions were screened for the envisioned borylation reaction of amine **73a** with bis pincolato diboron **62a** and (Table 5). Initial opyimization were performed by Dr. Suman De Sarkar (Table 5). Commerically available [RuCl$_2$(p-cymene)]$_2$ did not give the desired product (Table 5, entry 1). Upon addition of NaOAc as an additive the desired product **74aa** could be obtained in a low yield of 24%. An excess of diboorn reagent **62a** (1.5 equiv) is required to achieve a good conversion (Table 5, entries 7-10), when compared to C(sp²)–H borylation. Reducing the temperature and duration of the reaction gave better selectivity as the formation of undesired side products could be avoided (Table 5, entry 4 and entries 7-10). Reducing the catalyst loading gave less yield of the the desired product (Table 5, entry 11).

Table 5: Optimization studies performed by Dr. Suman De Sarkar[a]
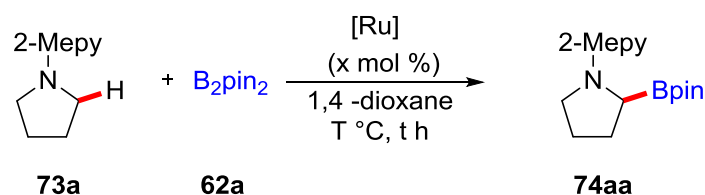
Entry	[Ru] cat.	Additive	T (°C)	**62a** [Equiv]	Time (t)	Yield [%][b]
1	[RuCl$_2$(p-cymene)]$_2$	-	120	1.5	20	0
2	[RuCl$_2$(p-cymene)]$_2$	NaOAc	120	1.5	20	24
3	-	NaOAc	120	1.5	20	0
4	[Ru(O$_2$CMes)$_2$(p-cymene)]	-	120	1.5	20	72
5	[Ru(O$_2$CMes)$_2$(p-cymene)]	-	120	1.2	20	69
6	[Ru(O$_2$CMes)$_2$(p-cymene)]	-	120	1.2	14	58

Entry	[Ru] cat.	Additive	*T* (°C)	62a [Equiv]	Time (t)	Yield [%][b]
7	[Ru(O$_2$CMes)$_2$(*p*-cymene)]	-	110	1.5	20	73
8	[Ru(O$_2$CMes)$_2$(*p*-cymene)]	-	100	1.5	20	31
9	[Ru(O$_2$CMes)$_2$(*p*-cymene)]	-	110	1.5	18	76
10	**[Ru(O$_2$CMes)$_2$(*p*-cymene)]**	**-**	**110**	**1.5**	**16**	**79**
11]	[Ru(O$_2$CMes)$_2$(*p*-cymene)]	-	110	1.5	20	41[c]

[a] Reaction conditions: **73a** (0.50 mmol), **62a** (0.50-0.75 mmol), [Ru] (10 mol %), additive (30 mol%), 1,4-dioxane (2.0 mL), under N$_2$ in pressure tube. [b] Isolated yield. [c] 5 mol % Ru-cat

Further optimization studies were performed by me (Table 6). There was no product observed in the absence of catalyst (Table 6, entry 1). With insights from optimization of C(sp^2)–H borylation, various ruthenium(II) carboxylate complexes were screened, which gave desired products in fair yields (Table 6, entries 2-4). However, a higher amount of catalyst loading was required compared to the C(sp^2)–H borylation. Inexpensive RuCl$_3$·xH$_2$O was not effective for the desired transformation even in the presence of MesCO$_2$K as an additive (Table 6, entries 5 and 6). Carboxylate complexes from other metals, such as Pd(OAc)$_2$[73]and Co(OAc)$_2$ were not effective (Table 6, entries 6 and 13). Other ruthenium complexes which are normally powerful in C(sp^3)–H functionalization, are futile in this case (Table 6,entries 8-11). Other boron reagents were employed, to verify the generality of the reaction. While HBpin **62c** (entry 14), B$_2$neop$_2$ **62d** (entry 15), pinB-Bdab **62e** (Table 6, entry 16) did not give encouraging results, employing two equivalents of pinB-Bdan **62f** (Table 6, entry 17) gave good conversion and the desired product could be isolated in good yield (61%). Interestingly, only Bpin from the pinB-Bdan reagent was transferred.

Table 6: Optimization Studies for C(sp³)–H bond Borylation[a]
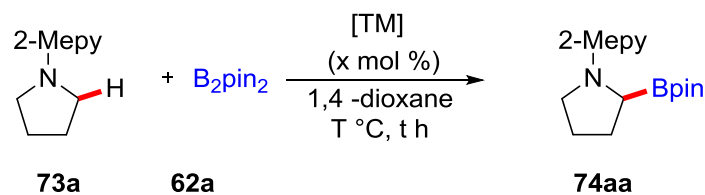
Entry	[TM] (x mol %)	T (°C)	t [h]	Yield [%][b]
1	-	110	16	NR
2	[Ru(O₂CMes)₂ (p-cymene)] (2.5 mol %)	110	20	24
3	[Ru(O₂CAd-1)₂ (p-cymene)] (10.0 mol %)	110	16	53
4	[Ru(OPiv)₂ (p-cymene)] (10.0 mol %)	110	16	56
5	RuCl₃·xH₂O (10.0 mol %)	110	16	NR
6	RuCl₃·xH₂O (10.0 mol %)	110	16	NR[c]
7	Pd(OAc)₂ (3.0 mol %)	110	16	NR
8	Ru(CO)H₂(PPh₃)₃ (5.0 mol %)	120	16	NR[d]
9	Ru₃(CO)₁₂ (3.3 mol %)	120	16	NR[e]
10	Ru(CO)H₂(PPh₃)₃ (5.0 mol %)	120	16	NR[d, e]
11	Ru₃(CO)₁₂ (3.3 mol %)	120	16	NR[d, e]
12	[Ru(O₂CMes)₂ (p-cymene)] (10.0 mol %)	120	16	NR[f]
13	Co(OAc)₂ (10.0 mol %)	110	16	NR
14	[Ru(O₂CMes)₂ (p-cymene)] (10.0 mol %)	110	16	< 4[g]
15	[Ru(O₂CMes)₂ (p-cymene)] (10.0 mol %)	110	16	< 10[h]

Entry	[TM] (x mol %)	T (°C)	t [h]	Yield [%][b]
16	[Ru(O$_2$CMes)$_2$ (p-cymene)] (10.0 mol %)	110	16	< 8[i]
17	[Ru(O$_2$CMes)$_2$ (p-cymene)] (10.0 mol %)	110	16	61[j]
18	[RuCl$_2$(p-cymene)]$_2$ (5.0 mol %)	110	16	34[c, k]

[a] Reaction conditions: **73a** (0.50 mmol), **62a** (0.75 mmol), [TM] (x mol %), 1,4-dioxane (2.0 mL), under N$_2$ in pressure tube, under N$_2$. [b] Isolated yield. [c] MesCO$_2$K (30 mol %). [d] 120°C under N$_2$ atmosphere. [e] Pinacolone (2.0 mL) as solvent. [f] PhCMe$_3$ (2.0 mL) as solvent [g] HBpin as the borylating agent. [h] B$_2$neop$_2$ as the borylating agent. [i] pinB-Bdab as the borylating agent. [j] pinB-Bdan (2.0 mmol) as the borylating agent [k] GC conversion with n-dodecane as internal standard.

3.4.4 Mechanistic investigations for C(sp³)–H borylation

We performed several experiments to get an insight into the reaction mechanism. During kinetic studies for the borylation of **73a** under standard conditions, we observed a significant induction period of 7-10 h. Long induction periods and irreproducible rates are known in literature for borylation reactions.[74] The reaction was not completely shut down on employing typical radical scavengers such as TEMPO and galvinoxyl, for the reaction between **62a** and **73a,** which is contrary to the observation made by Kuninobu and coworkers in an analogous palladium-catalyzed reaction (Scheme 40a).[75] We then speculated the formation of imine from amine **73a,** as the reason for long induction period. However, analysis of reaction mixtures by GC/GC-MS did not show any evidence for the imine as an intermediate. Formation of a black coating in the reaction tubes at the end of the reaction, prompted us to verify if the catalysis is heterogenous in nature. The mercury test[76] did not show any detrimental effect on the efficacy of the reaction with a 81% GC yield (Scheme 40b). The observation is similar for mercury test performed for reaction between benzo[h]quinoline (**1a**) and **62a**. (79% ¹H NMR yield). Interestingly, ¹¹B NMR studies for stoichiometric reaction between **62a** and **16** showed that the resonance corresponding to **62a** completely disappeared and a new signal at 21 ppm appeared. On addition of **73a** to this mixture, the formation of product **74aa** was observed (16% GC yield) (Scheme 40c).

a)
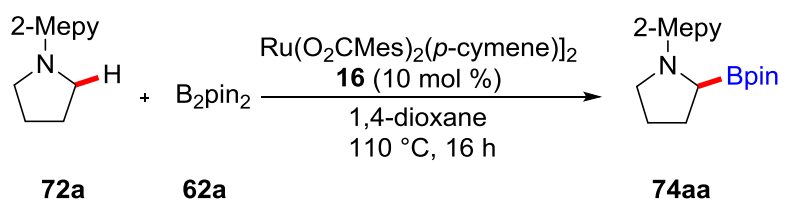
Standard conditons	: 79%
TEMPO (10 mol %)	: 42%[a]
TEMPO (100 mol %)	: 41%[a]
Galvinoxyl (100 mol %)	: 56%[a]

b)
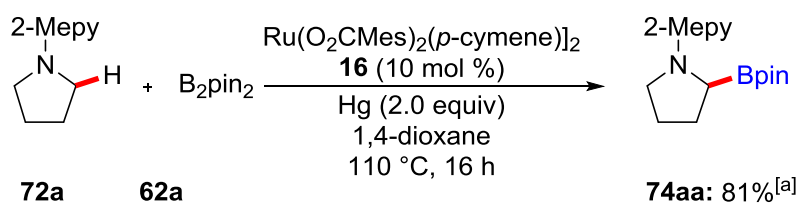
c)
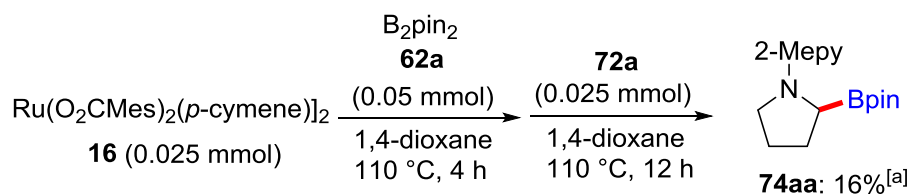
Scheme 40: Mechanistic investigations on C(sp^3)–H borylation. [a] GC yield with *n*-dodecane as the internal standard.

3.4.5 Mechanistic investigations for C(sp^2)–H bond borylation

To get insights in the mechanism of C(sp^2)–H bond borylation, cycloruthenated complex[77] **82** was synthesized and was probed as a catalyst in the C–H borylation. Interestingly, complex **82** was catalytically competent and the desired product was obtained in 82% yield (Scheme 41). This result suggested that complex **82** is most likely the intermediate involved in the catalytic cycle.
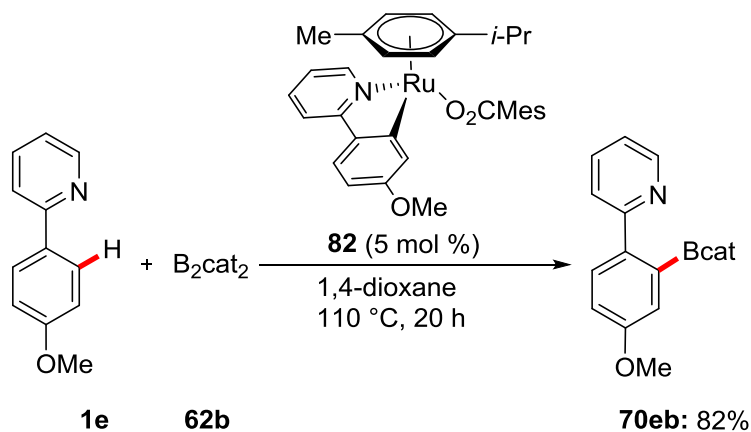
Scheme 40: Reaction with cycloruthenated complex **82** as catalyst

3.4.6 Limitations of C(sp^2)–H borylation

Investigations with other directing groups employing the optimized reaction conditions for the C(sp^2)–H borylation did not lead to any borylated products (Figure 11).
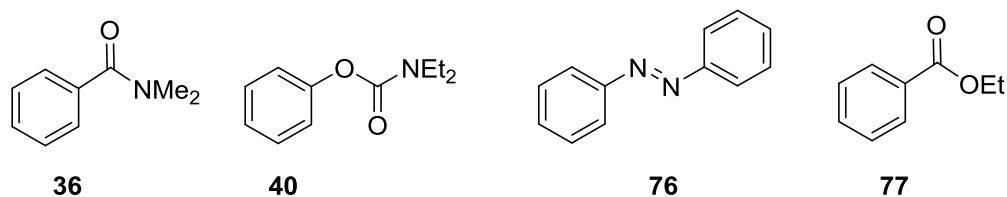
Figure 11: As of yet unsuccessful substrates for C(sp^2)–H borylations

3.4.7 Limitations of C(sp³)–H borylation:

Variation of the directing group in order to understand the reactivity pattern illustrated the superiority of pyridine as a directing group for C(sp³)–H borylations (Figure 12).
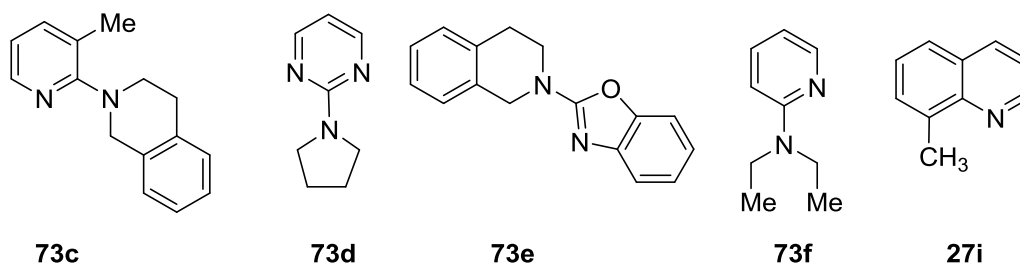
Figure 12: Thus far unsuccessful directing groups for C(sp²)–H borylations

Summary and Outlook

In the last decades ruthenium(II)-catalyzed C−H functionalizations have emerged as a reliable tool for the efficient chemo- and site-selective construction of C−C and C−X bonds in an atom and step-economic fashion. Within this thesis, efforts have been devoted to develop new synthetic methods to achieve the formation of C−C and C−B bonds using carboxylate-assisted ruthenium(II) catalysis.

In the first part of this thesis, direct C–H arylation of arenes was achieved using tetrazole as the directing group under carboxylate-assisted ruthenium(II) catalysis. A broad substrate scope was achieved using various aryl bromides and aryl pseudohalides. Importantly, our robust reaction conditions employed a single-component catalyst and toluene as the solvent to guarantee robust C–H functionalizations with remarkable selectivity.[78] Thus, a carboxylic acid derived ruthenium (II) catalyst enabled syntheses of biaryl tetrazoles, key structural motifs in various angiotensin II receptor blockers.[79] This paved the way for a more appealing catalytic system in the Ackermann group recently.[80]
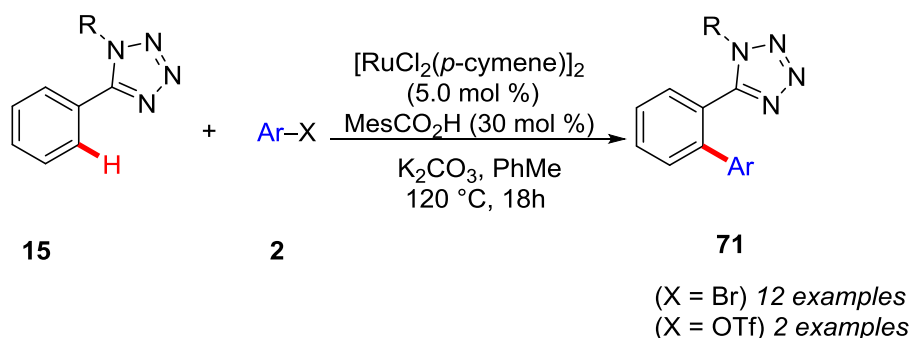
Reactivity order: ArI > ArBr > ArOTf

Scheme 43: Ruthenium-Catalyzed C(sp^2)–H Arylation

In the second part of this thesis, arylation of C(sp^3)–H bonds was achieved employing well-defined ruthenium(II) biscarboxylate complexes.[81] Variation of the removable directing group was examined and the importance of the Lewis basic directing group was established. Ample scope with various aryl and heteroaryl bromides was achieved. Detailed mechanistic studies provided strong evidence for an initial, reversible C(sp^3)–H bond activation.
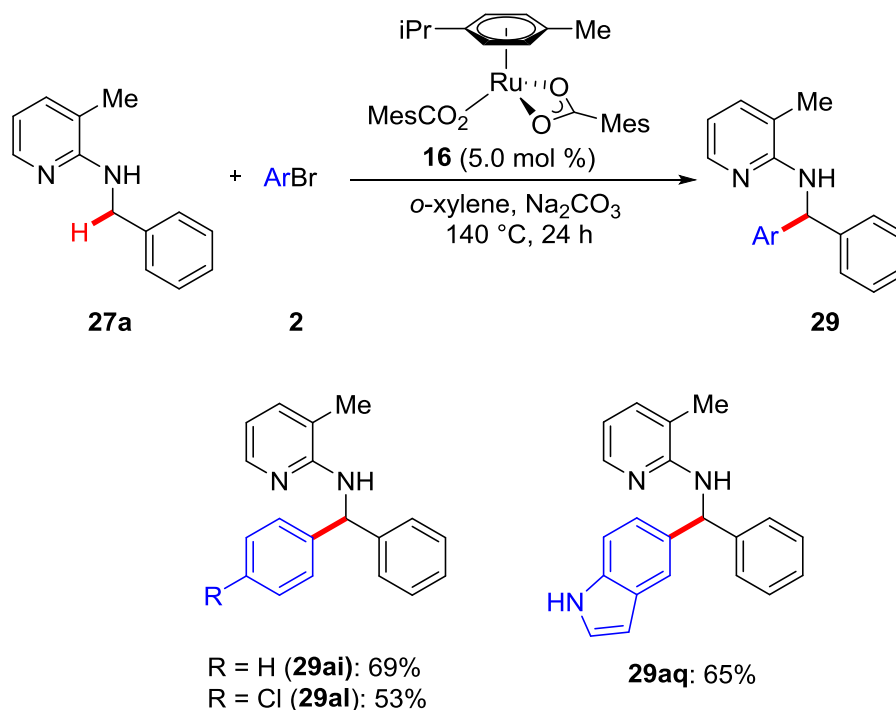
Scheme 44: Ruthenium-Catalyzed C(sp^3)–H Arylation

In the third part of this thesis, carboxylic acids were used as traceless directing groups to achieve redox-neutral hydroarylation of alkynes.[82] The scope with various internal alkynes and differently-substituted acids was studied. Key features of this highly useful method obviate the use of an external base and expensive silver salts. Moreover, removal of the directing group occurs in a domino fashion.[83] Further developments of this method to synthesize various compounds of pharmacological importance are currently under investigation in the Ackermann group.
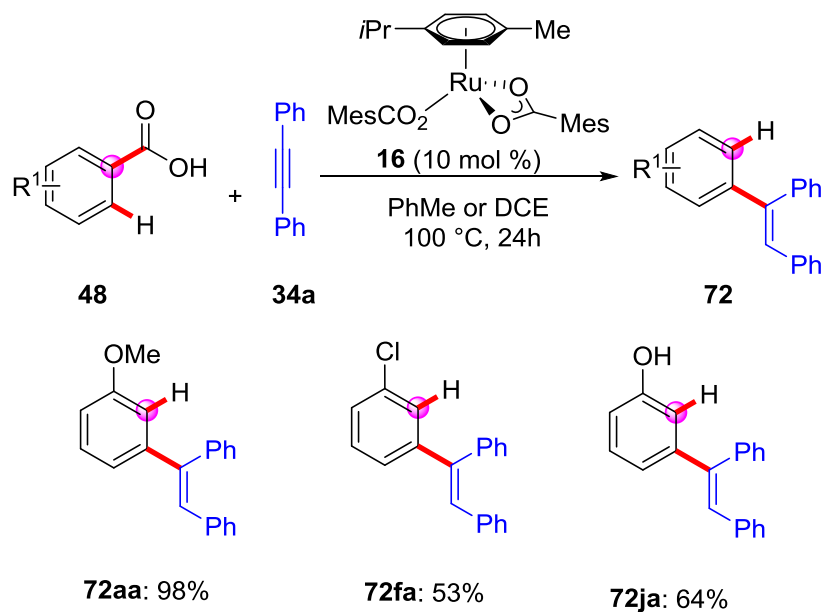
Scheme 45: Ruthenium(II) Catalyzed Decarboxylative Hydroarylation

In the fourth part of this thesis, chelation-assisted borylation of $C(sp^3)$–H and $C(sp^2)$–H bonds was achieved using ruthenium(II) biscarboxylate complexes. Stable diboron reagents such as B_2pin_2 and B_2cat_2 were the borylation agents of choice. Importantly, this method does not require any external base or oxidant, and occurs at relatively mild conditions. This economically attractive method allows for the preparation of highly useful pinacol boronate esters in an atom- and step-economic fashion and proves the unique power of ruthenium(II) biscarboxylate complexes over other ruthenium catalysts.
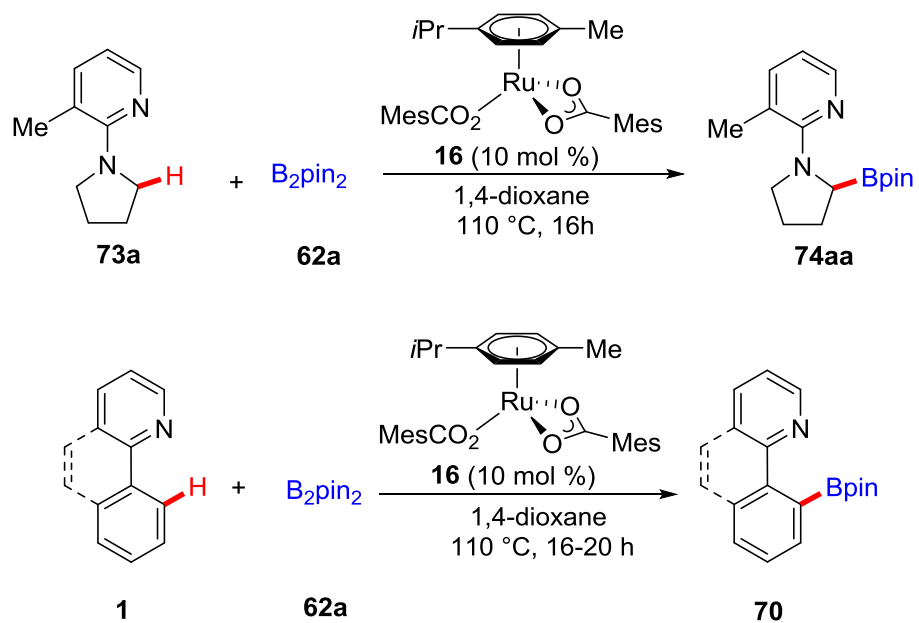
Scheme 46: Ruthenium(II)-Catalyzed Borylation of C(sp^3)–H and C(sp^2)–H bonds

Experimental section

5.1 General Remarks

Unless otherwise noticed, all reactions were performed under N_2 atmosphere using pre-dried glassware and standard Schlenk techniques. Syringes and needles for handling dry solvents or liquid reagents were washed with N_2 three times prior to their use.

Solvents

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

tert-Amyl alcohol (*t*-AmOH) was used stirred over sodium chips for 5 h at 120 °C and distilled under ambient pressure.

Water (H_2O) was degassed before its use applying repeated Freeze-Pump-Thaw degassing procedure.

1,2-dichloroethane (DCE) was dried over CaH_2 for 8 h, degassed and distilled under reduced pressure.

N,N-dimethylformamide (DMF) was dried over CaH_2 for 8 h, degassed and distilled under reduced pressure.

Acetonitrile (MeCN) was dried over CaH_2 for 8 h, degassed and distilled under reduced pressure.

Dimethylacetamide (DMA) was dried over CaH_2 for 8 h, degassed and distilled under reduced pressure.

Dichloromethane (DCM) was purified using a solvent purification system (SPS) from MBRAUN SPS-800.

Tetrahydrofuran (THF) was purified using a solvent purification system (SPS) from MBRAUN SPS-800.

N-methyl-2-pyrrolidone (NMP) was stirred over CaH_2 for 4 h at 150 °C and subsequently distilled under reduced pressure.

Methanol (MeOH) was stirred over magnesium for three hours at 65 °C prior to distillation.

Toluene (PhMe) was either pre-dried over KH followed by distillation from sodium/ benzophenone.

1,4-dioxane was dried by distillation from sodium/benzophenone.

o-Xylene was stirred at 160 °C over sodium/benzophenone and distilled under ambient pressure.

Vacuum

The following pressures were measured on the used vacuum pump and were not corrected: membrane pump vacuum (MPV): 0.5 mbar, oil pump vacuum (OPV): 0.1 mbar.

Melting Points (M. p.)

Melting points were measured using a *Stuart® Melting Point Apparatus SMP3.* Reported values are uncorrected.

Chromatography

Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60F-plates (MACHEREY-NAGEL) with 254 nm fluorescent indicator from MERCK. TLC plates were visualized under UV-light or developed by treatment with basic $KMnO_4$ solution followed by heating. Chromatographic purification of products was accomplished by flash column chromatography on MERCK silica gel, grade 60 (0.040–0.063 mm).

Gas Chromatograpghy (GC)

The conversion of the reactions was monitored applying coupled gas chromatography/mass spectrometry using *G1760C 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 equipped with *HP-5MS* columns (30 m × 0.25 mm × 0.25 m) were used.

Recycling Chromatograpghy

Recycling preparative HPLC was performed on a system from JAI (LC-92XX II Series, Injection- and Control-Valve, UV and RI Detector) connected to JAIGEL HH series columns. Chloroform (ethanol stabilized) of HPLC grade was employed.

Nuclear Magnetic Resonance Spectroscopy (NMR)

Nuclear magnetic resonance (NMR) spectroscopy was performed at 300, 400, 500 or 600 MHz (^{1}H-NMR), 75 or 125 MHz (^{13}C-NMR, APT) and 283 MHz (^{19}F-NMR) 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 resonance of the deuterated solvent or its carbon atom, respectively, or the standard trimethylsilyl (TMS) peak. For characterization of the observed resonance multiplicities the following abbreviations were applied: *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *m* (multiplet), *dd* (doublet of doublet), *dt* (doublet of triplet), or analogue representations. The coupling constants *J* are reported in Hertz (Hz).

Infrared Spectroscopy (IR)

Infrared spectra were recorded on a BRUKER *Alpha-P* ATR-spectrometer. Liquid probes have been measured as film and solid probes neat. Analysis of the spectral data has been done by using the *OPUS 6* software from BRUKER, respectively *OPUS 6*. Absorption (ṽ) is given in wave number (cm^{-1}). Spectra were recorded in the range of 4000 to 400 cm^{-1}.

Mass Spectrometry (MS)

MS (EI) and HR-MS (EI) 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-HR-MS spectra were recorded on a BRUKER *APEX IV* or a BRUKER *DALTONIC* {7T, Fourier Transform Ion Cyclotron Resonance (FTICR)} mass spectrometer. The ratios of mass to charge (*m/z*) are indicated, intensities relative to the base peak (I = 100) are written in parentheses.

Reagents

Chemicals obtained from commercial sources were used without further purification. Tetrazoles (**15**) are prepared according to described literature procedures.[84]

The following compounds were obtained by the generous courtesy of the persons named below:

[RuCl$_2$(*p*-cymene)]$_2$, [RuBr$_2$(*p*-cymene)]$_2$, [Ru(O$_2$CMes)$_2$(*p*-cymene)] **16**, [Ru(OPiv)$_2$(p-cymene)] by courtesy of Karsten Rauch.

2-(1*H*-pyrrol-1-yl)pyridine (**1b**), 2-(4-methoxyphenyl)pyridine (**1e**) by courtesy of Dr. Jie Li.

N-benzyl-3-methylpyridin-2-amine (**27a**), *N*-benzylpyridin-2-amine (**27b**), *N*-benzyl-3-methoxypyridin-2-amine (**27c**) and 2-(benzyloxy)-3-methylpyridine (**27f**) by courtesy of Jordi Creus.

3-methyl-2-(piperidin-1-yl)pyridine (**73b**), 2-(3-methylpyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline (**73c**), 2-(pyrrolidin-1-yl)pyrimidine (**73d**), *N,N*-diethylpyridin-2-amine (**73f**) by courtesy of Kris Bielefeld.

di(4-methylphenyl)acetylene (**34b**), 1,2-bis(4-methoxyphenyl)ethyne (**34c**) by courtesy of Dr. Sebastian Lackner.

N-benzyl-3-phenylpyridin-2-amine (**27d**), *N*-benzyl-3-methylquinolin-2-amine (**27g**), *N*-(furan-2-ylmethyl)-3-methylpyridin-2-amine (**27h**), 3-methyl-*N*-(thiophen-2-ylmethyl)pyridin-2-amine (**27i**) by courtesy of Daniel Zell

N-benzyl-3-(trifluoromethyl)pyridin-2-amine (**27e**) by courtesy of Rajkumar Jeyachandran

3-methyl-2-(pyrrolidin-1-yl)pyridine (**73a**) by courtesy of Dr. Marvin Schinkel

phenyl diethylcarbamate (**40**) by courtesy of Dr. Weiping Liu

1-(*o*-tolyl)-1*H*-pyrazole (**1c**) by courtesy of Keshav Raghuvanshi

2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzo[*d*]oxazole (**73e**) by courtesy of Marcus Thater

N,N-diethylpyridin-2-amine (**73f**) by courtesy of Dr. Suman Sarkar

5.2. General procedures

General Procedure A: Ruthenium(II)-catalyzed C–H arylations of phenyl tetrazoles

[RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), MesCO$_2$H (24.6 mg, 0.15 mmol, 30 mol %), tetrazoles **15** (0.50 mmol, 1.0 equiv), aryl bromides **2** (0.6 mmol, 1.2 equiv) and K$_2$CO$_3$ (138 mg, 1.00 mmol) were placed in a 25 mL Schlenk tube. The tube was evacuated and flushed with N$_2$ three times, PhMe (2 mL) (and if liquid, aryl bromide was also added at this point) was added. The reaction mixture was stirred for 18 h at 120 °C. Then, H$_2$O (50 mL) was added at ambient temperature. The aqueous layer was extracted with CH$_2$Cl$_2$ (3×40 mL), the combined organic layers were washed with brine (50 mL), dried over Na$_2$SO$_4$, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

General Procedure B: Ruthenium(II)-catalyzed C(sp^3)–H arylations:

[Ru(O$_2$CMes)$_2$(*p*-cymene)] (**16**) (14 mg, 0.025 mmol, 5.0 mol %), benzyl amines **27** (0.50 mmol, 1.0 equiv), Na$_2$CO$_3$ (159 mg, 1.50 mmol, 3.0 equiv) were placed in a 25 mL Schlenk tube. The tube was evacuated and flushed with N$_2$ three times, *o*-xylene (2 mL) and aryl bromides **2** (0.75 mmol, 1.5 equiv) was added. The reaction mixture was stirred at 140 °C for 24 h. At ambient temperature, the suspension was filtered through a short pad of Celite$^®$, which was further washed with CH$_2$Cl$_2$ (50 mL). All the volatiles were removed *in vacuo* and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

General Procedure C: Decarboxylative Hydroarylation of alkynes

[Ru(O$_2$CMes)$_2$(*p*-cymene)] (**16**) (28.0 mg, 0.05 mmol, 10 mol %), benzoic acids **48** (1.00 mmol, 2.0 equiv) and alkynes **34** (0.50 mmol, 1.0 equiv) were placed in a pre-dried pressure tube equipped with a rubber septum. The tube was evacuated and flushed with N$_2$ three times and either PhMe (2.0 mL) or DCE (2.0 mL) was added. The rubber septum was replaced by the pressure tube screw cap and the reaction mixture was stirred at 100 °C for 24 h. At ambient temperature, all volatiles were removed *in vacuo* and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

General Procedure D: Ruthenium(II)-catalyzed C(sp^2)–H borylations

[Ru(O$_2$CMes)$_2$(p-cymene)] (**16**) (14.0 mg, 0.025 mmol, 5 mol %), arenes **1** (0.50 mmol, 1.0 equiv) and B$_2$pin$_2$ **2a** (0.50 mmol, 1.0 equiv) were placed in a pre-dried pressure tube equipped with a rubber septum. The tube was evacuated and flushed with N$_2$ three times and 1,4-dioxane (2.0 mL) was added. The rubber septum was replaced by the pressure tube screw cap and the reaction mixture was stirred at 110 °C for 20 h. At ambient temperature, all volatiles were removed *in vacuo* and the residue was purified by column chromatography on silica gel (n-hexane/EtOAc/NEt$_3$).

General Procedure E: Ruthenium-catalyzed C(sp^3)–H borylations

[Ru(O$_2$CMes)$_2$(p-cymene)] (**16**) (28.0 mg, 0.05 mmol, 10 mol %), Amine **1a** (0.50 mmol, 1.0 equiv) and B$_2$pin$_2$ **2a** (0.75 mmol, 1.5 equiv) were placed in a pre-dried pressure tube equipped with a rubber septum. The tube was evacuated and flushed with N$_2$ three times and 1,4-dioxane (2.0 mL) was added. The rubber septum was replaced by the pressure tube screw cap and the reaction mixture was stirred at 110 °C for 16 h. At ambient temperature, all volatiles were removed *in vacuo* and the residue was purified by column chromatography on silica gel (n-hexane/EtOAc/NEt$_3$).

5.3 Ruthenium(II)-catalyzed C–H arylations of phenyl tetrazoles

Characterization data of products 71
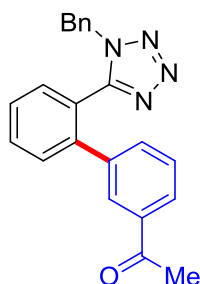
1-{2′-(1-Benzyl-1H-tetrazol-5-yl)-[1,1′-biphenyl]-3-yl}ethanone (71ab)

The general procedure **A** was followed using **15a** (118 mg, 0.50 mmol) and **2b** (109 mg, 0.55 mmol). Compound **71ab** (117 mg, 66%) was obtained as a colorless liquid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1).

¹H NMR (300 MHz, CDCl₃): δ = 7.85 (d, J = 7.6 Hz, 1H), 7.76 (s, 1H), 7.66 (dd, J = 7.5, 1.5 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.48 (td, J = 7.5, 1.4 Hz, 1H), 7.40–7.05 (m, 6H), 6.76 (d, J = 6.8 Hz, 2H), 4.87 (s, 2H), 2.49 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ = 197.4 (C$_q$), 154.3 (C$_q$), 140.8 (C$_q$), 139.1 (C$_q$), 137.4 (C$_q$), 133.1 (CH), 132.8 (C$_q$), 131.9 (CH), 131.1 (CH), 130.3 (CH), 129.1 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.7 (CH), 127.6 (CH), 122.6 (C$_q$), 50.9 (CH$_2$), 26.6 (CH$_3$).

IR (ATR): 1682, 1405, 1357, 1227, 1100, 758 cm⁻¹.

MS (EI) *m*/*z* (relative intensity): 354 ([M⁺] 28), 353 (41), 326 (21), 325 (68), 91 (100).

HRMS (EI) *m*/*z* calcd for C₂₂H₁₈N₄O [M−H⁺] 353.1402, found 353.1411.
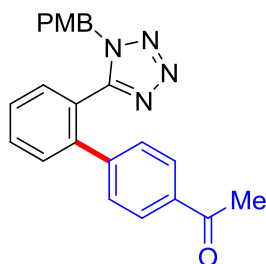
1-{2′-(1-(4-Methoxybenzyl)-1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl}ethanone (71bc)

The general procedure **A** was followed using **15b** (136 mg, 0.51 mmol) and **2c** (109 mg, 0.55 mmol). Compound **71bc** (121 mg, 62%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1).

Mp: 117–119 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.84–7.77 (m, 2H), 7.67 (td, *J* = 7.6, 1.4 Hz, 1H), 7.58 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.50 (td, *J* = 7.5, 1.4 Hz, 1H), 7.36 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.21–7.12 (m, 2H), 6.68–6.61 (m, 4H), 4.81 (s, 2H), 3.72 (s, 3H), 2.57 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 197.4 (C$_q$), 159.7 (C$_q$), 153.9 (C$_q$), 143.3 (C$_q$), 140.7 (C$_q$), 136.2 (C$_q$), 131.6 (CH), 131.2 (CH), 130.2 (CH), 129.2 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 124.8 (C$_q$), 122.8 (C$_q$), 114.0 (CH), 55.2 (CH$_3$), 50.5 (CH$_2$), 26.6 (CH$_3$).

IR (ATR): 1677, 1513, 1400, 1326, 1244, 1179, 1100, 1034, 775 cm^{-1}.

HRMS (EI) *m/z* calcd for C$_{23}$H$_{20}$N$_4$O$_2$ [M+H$^+$] 385.1659, found 385.1657
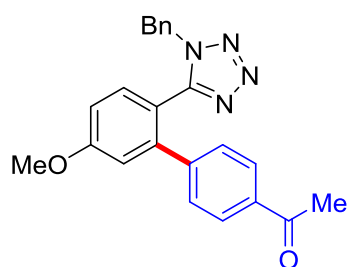
1-[2′-(1-Benzyl-1*H*-tetrazol-5-yl)-5′-methoxy-(1,1′-biphenyl)-4-yl]ethanone (71cc)

The general procedure **A** was followed using **15c** (136 mg, 0.51 mmol) and **2c** (109 mg, 0.60 mmol). Compound **71cc** (108 mg, 57%) was obtained as a green solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1).

Mp: 153–154 °C.

1H NMR (300 MHz, CDCl$_3$): *δ* = 7.80 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.24–7.09 (m, 5H), 7.05 (d, *J* = 2.6 Hz, 1H), 6.99 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.79 (d, 2H), 4.87 (s, 2H), 3.90 (s, 3H), 2.56 (s, 3H).

13C NMR (75 MHz, CDCl$_3$): *δ* = 197.3 (C$_q$), 161.8 (C$_q$), 154.1 (C$_q$), 143.3 (C$_q$), 142.2 (C$_q$), 136.2 (C$_q$), 132.9 (C$_q$), 132.6 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.6 (CH), 115.9 (CH), 114.4 (C$_q$), 113.8 (CH), 55.6 (CH$_3$), 50.7 (CH$_2$), 26.6 (CH$_3$).

IR (ATR): 1677, 1601, 1467, 1444, 1268, 1221, 848 cm^{-1}.

HRMS (ESI) *m*/*z* calcd for C$_{23}$H$_{20}$N$_4$O$_2$ [M+H$^+$] 385.1659, found 385.1658.
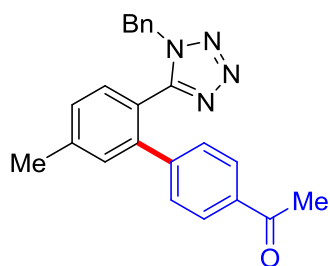
1-[2′-(1-Benzyl-1*H*-tetrazol-5-yl)-5′-methyl-(1,1′-biphenyl)-4-yl]ethanone (71dc)

The general procedure **A** was followed using **15d** (127 mg, 0.50 mmol) and **2c** (109 mg, 0.55 mmol). Compound **71dc** (104 mg, 56%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1).

Mp: 149–151 °C.

¹H NMR (300 MHz, CDCl₃): δ = 7.82 (d, *J* = 8.6 Hz, 2H), 7.36 (dt, *J* = 1.5, 0.8, 0.8 Hz, 1H), 7.32–7.06 (m, 7H), 6.80–6.74 (m, 2H), 4.85 (s, 2H), 2.56 (s, 3H), 2.48 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 197.4 (C$_q$), 154.3 (C$_q$), 143.6 (C$_q$), 142.0 (C$_q$), 140.6 (C$_q$), 136.2 (C$_q$), 132.9 (C$_q$), 131.1 (CH), 130.1 (CH), 129.3 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.7 (CH), 119.7 (C$_q$), 50.8 (CH$_2$), 26.6 (CH$_3$), 21.5 (CH$_3$).

IR (ATR): 1675, 1601, 1495, 1453, 1268, 1229, 833 cm⁻¹.

HRMS (ESI) *m/z* calcd for C₂₃H₂₀N₄O [M+H⁺] 369.1710; found 369.1708
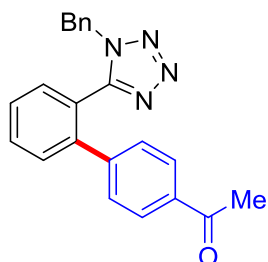
1-{2′-(1-benzyl-1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl}ethanone (71ac)

The general procedure **A** was followed using **15a** (119 mg, 0.50 mmol) and **2c** (109 mg, 0.60 mmol). Compound **71ac** (116 mg, 64%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1).

Mp: 157–159 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.87–7.78 (m, 2H), 7.67 (td, *J* = 7.7, 1.4 Hz, 1H), 7.57 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.49 (td, *J* = 7.7, 1.4 Hz, 1H), 7.37 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.24–7.09 (m, 5H), 6.85–6.69 (m, 2H), 4.88 (s, 2H), 2.58 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 197.4 (C$_q$), 154.2 (C$_q$), 143.3 (C$_q$), 140.7 (C$_q$), 136.3 (C$_q$), 132.8 (C$_q$), 131.7 (CH), 131.2 (CH), 130.3 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.7 (CH), 128.5 (CH), 127.7 (CH), 122.7 (C$_q$), 51.0 (CH$_2$), 26.6 (CH$_3$).

IR (ATR): 1680, 1496, 1437, 1402, 1357, 1265, 959, 849, 721, 700 cm^{-1}.

MS (EI) *m/z* (relative intensity): 354 (12), 353 (35), 325 (10), 206 (8), 192 (8), 179 (8), 164 (11), 151 (6), 91 (100), 65 (15), 43 (38).

HRMS (EI) *m/z* calcd for C$_{22}$H$_{18}$N$_4$O$^+$ [M$^+$] 354.1481, found 354.1468.
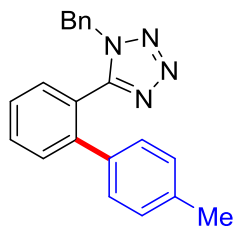
1-Benzyl-5-(4′-methyl-[1, 1′-biphenyl]-2-yl)-1*H*-tetrazole (71ad)

The general procedure **A** was followed using **15a** (118 mg, 0.50 mmol) and **2d** (97 mg, 0.57 mmol). Compound **71ad** (82 mg, 50%) was obtained as a colorless solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 6:1).

Mp: 143–144 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.67–7.52 (m, 2H), 7.45–7.30 (m, 2H), 7.23–7.06 (m, 5H), 7.06–7.00 (m, 2H), 6.81–6.64 (m, 2H), 4.77 (s, 2H), 2.34 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 154.7 (C$_q$), 141.6 (C$_q$), 138.0 (C$_q$), 135.9 (C$_q$), 133.1 (C$_q$), 131.5 (CH), 131.2 (CH), 130.1 (CH), 129.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.5 (CH), 122.6 (C$_q$), 50.8 (CH$_2$), 21.1 (CH$_3$).

IR (ATR): 1597, 1495, 1470, 1457, 1240, 1074, 756 cm^{-1}.

HRMS (ESI) *m/z* calcd for C$_{21}$H$_{18}$N$_4$ [M+H$^+$] 327.1604; found 327.1604.
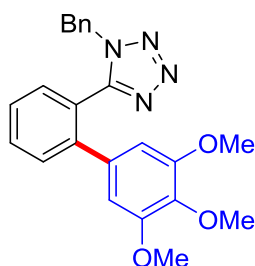
1-Benzyl-5-(3′,4′,5′-trimethoxy-[1,1′-biphenyl]-2-yl)-1*H*-tetrazole (71ae)

The general procedure **A** was followed using **15a** (118 mg, 0.50 mmol) and **2e** (136 mg, 0.60 mmol). Compound **71ae** (140 mg, 69%) was obtained as a colorless liquid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.67–7.57 (m, 2H), 7.42 (ddd, J = 7.8, 6.1, 2.5 Hz, 1H), 7.36–7.31 (m, 1H), 7.24–7.09 (m, 3H), 6.81–6.72 (m, 2H), 6.34 (s, 2H), 4.84 (s, 2H), 3.83 (s, 3H), 3.67 (s, 6H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 154.8 (C$_q$), 153.3 (C$_q$), 141.4 (C$_q$), 137.8 (C$_q$), 133.1 (C$_q$), 132.9 (C$_q$), 131.6 (CH), 131.2 (CH), 129.8 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 127.6 (CH), 122.5 (C$_q$), 105.7 (CH), 60.9 (CH$_3$), 56.1 (CH$_3$), 50.7 (CH$_2$).

IR (film): 1584, 1568, 1508, 1470, 1455, 1240, 1122, 1001, 763.

HRMS (ESI) *m/z* calcd for C$_{23}$H$_{22}$N$_4$O$_3$ [M+H$^+$] 403.1765, found 403.1766.

1-Benzyl-5-(3′,5′-difluoro-[1,1′-biphenyl]-2-yl)-1*H*-tetrazole (71af)

The general procedure **A** was followed using **15a** (118 mg, 0.50 mmol) and **2f** (110 mg, 0.57 mmol). Compound **71af** (78 mg, 45%) was obtained as a colorless liquid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1).

**¹H NMR** (300 MHz, CDCl₃): δ = 7.64 (td, J = 7.5, 1.4 Hz, 1H), 7.54–7.40 (m, 2H), 7.33 (dd, J = 8.0, 1.4 Hz, 1H), 7.27–7.10 (m, 3H), 6.85–6.73 (m, 2H), 6.66 (tt, J = 8.8, 2.3 Hz, 1H), 6.58–6.40 (m, 2H), 5.04 (s, 2H).

¹³C NMR (125 MHz, CDCl₃): δ = 162.7 (C$_q$, J_{C-F} = 250, 13 Hz), 153.8 (C$_q$), 141.8(C$_q$, J_{C-F} = 9 Hz), 139.8 (C$_q$, J_{C-F} = 2 Hz), 132.8 (C$_q$), 131.6 (CH), 130.1 (CH), 130.2 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.6 (CH), 122.7 (C$_q$), 111.71 (CH, J_{C-F} = 20, 7 Hz), 103.4 (CH, J_{C-F} = 25 Hz), 50.1 (CH₂).

¹⁹F NMR (282 MHz, CDCl₃): δ = −(108.16–108.33) (m).

IR (film): 1622, 1593, 1497, 1406, 1099, 987, 860, 689 cm⁻¹.

MS (EI) *m/z* (relative intensity): 348 ([M⁺] 38), 347 (48), 319 (32), 201 (48), 91 (100).

HRMS (EI) *m/z* calcd for C₂₀H₁₄N₄F₂ [M−H] 347.1108; found 347.1116.

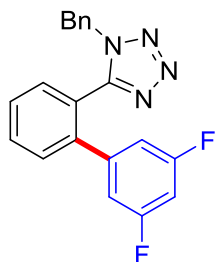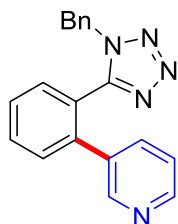**3-[2-(1-Benzyl-1*H*-tetrazol-5-yl)phenyl]pyridine (71ag)**

The general procedure **A** was followed using **15a** (118 mg, 0.50 mmol) and **2g** (98 mg, 0.62 mmol) Compound **71ag** (46 mg, 30%) was obtained as a green liquid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1).

¹H NMR (300 MHz, CDCl₃): δ = 8.49 (d, *J* = 4.6 Hz, 1H), 8.39 (s, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.59–7.44 (m, 2H), 7.40–7.04 (m, 6H), 6.78 (d, *J* = 7.0 Hz, 2H), 4.97 (s, 2H).

¹³C NMR (125 MHz, CDCl₃): δ = 153.7 (C$_q$), 148.9 (CH), 148.8 (CH), 138.3 (C$_q$), 135.8 (CH), 134.3 (C$_q$), 132.6 (C$_q$), 131.6 (CH), 130.8 (CH), 130.3 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.5 (CH), 122.8 (CH), 122.7 (C$_q$), 50.9 (CH₂).

IR (film): 1603, 1404, 1274, 1247, 1026, 791, 761.

HRMS (ESI) *m/z* calcd for C₁₉H₁₅N₅ [M+H⁺] 314.1400, found 314.1399.
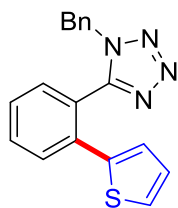
1-Benzyl-5-{2-(thiophen-2-yl)phenyl}-1*H*-tetrazole (71ah)

The general procedure **A** was followed using **15a** (118 mg, 0.50 mmol) and **2h** (99 mg, 0.60 mmol). Compound **71ah** (101 mg, 63%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 6:1).

Mp: 90–92 °C.

^{1}H NMR (300 MHz, CDCl$_3$): *δ* = 7.65 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.59–7.53 (m, 1H), 7.39–7.08 (m, 6H), 6.90 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.84–6.76 (m, 2H), 6.59 (dd, *J* = 3.6, 1.2 Hz, 1H), 4.90 (s, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): *δ* = 154.2 (C$_q$), 140.1 (C$_q$), 134.4 (C$_q$), 132.9 (C$_q$), 131.5 (CH), 131.4 (CH), 130.0 (CH), 128.7 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.0 (CH), 126.9 (CH), 122.2 (C$_q$), 50.9 (CH$_2$).

IR (ATR): 1494, 1470, 1457, 1240, 1159, 1098, 1074, 756 cm^{-1}.

MS (EI) *m/z* (relative intensity): 318 ([M$^+$] 28), 317 (53), 289 (30), 91 (100).

HRMS (EI) *m/z* calcd for C$_{18}$H$_{14}$N$_4$S [M−H$^+$] 317.0861; found 317.0872.

5.4 Ruthenium(II)-catalyzed C(sp^3)–H arylation
Characterization data of products 29
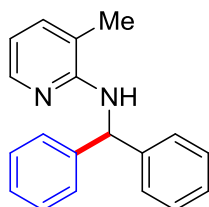
N-Benzhydryl-3-methylpyridin-2-amine (29ai)

The representative procedure **B** was followed using *N*-Benzyl-3-methylpyridin-2-amin (**27a**) (99 mg, 0.50 mmol, 1.0 equiv), and bromobenzene (**2i**) (118 mg, 0.75 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 99/1 → 98/2) yielded **29ai** (95 mg, 69%) as a colorless solid.

M.p: 91–93 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.98 (dd, *J* = 5.2, 1.7 Hz, 1H), 7.39–7.21 (m, 11H), 6.59–6.48 (m, 2H), 4.67 (d, *J* = 7.0 Hz, 1H), 2.15 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 155.6 (C$_q$), 145.6 (CH), 143.5 (C$_q$), 136.9 (CH), 128.4 (CH), 127.5 (CH), 126.1 (CH), 116.3 (C$_q$), 113.1 (CH), 58.4 (CH), 17.0 (CH$_3$).

IR (neat): 3438, 1595, 1485, 1465, 1057, 695 cm^{-1}.

MS (EI) *m/z* (relative intensity): 274 ([M$^+$], 87), 182 (55), 167 (100), 165 (52), 98 (50), 43 (69).

HR-MS (EI) *m/z* calcd for C$_{19}$H$_{18}$N$_2^+$ 274.1470, found 274.1462.

The spectral data were in accordance with those reported in the literature.[85]
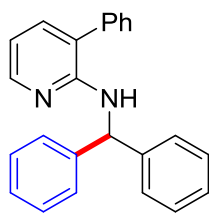
N-Benzhydryl-3-phenylpyridin-2-amine (**29di**)

The representative procedure **B** was followed using *N*-benzyl-3-phenylpyridin-2-amine (**27d**) (130 mg, 0.50 mmol) and bromobenzene (**2i**) (118 mg, 0.75 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 99/1 → 98/2) yielded **29di** (34 mg, 20%) as a colorless solid.

M.p: 90–92 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.08 (dd, *J* = 5.1, 1.8 Hz, 1H), 7.48–7.16 (m, 16H), 6.65 (dd, *J* = 7.3, 5.0 Hz, 1H), 6.52 (d, *J* = 7.5 Hz, 1H), 5.20 (d, *J* = 7.5 Hz, 1H).

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 154.4 (C$_q$), 147.2 (CH), 143.3 (C$_q$), 137.9 (C$_q$), 137.1 (CH), 129.2 (CH), 128.8 (CH), 128.4 (CH), 127.8 (CH), 127.4 (CH), 126.9 (CH), 122.2 (C$_q$), 113.2 (CH), 58.5 (CH). **IR** (neat): 3447, 3023, 1596, 1463, 1280, 767, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity): 336 ([M$^+$], 100), 335 (20), 182 (45), 167 (87), 165 (45).

HR-MS (EI) *m/z* calcd for C$_{24}$H$_{20}$N$_2$$^+$ 336.1626, found 336.1629.

The spectral data were in accordance with those reported in the literature.[85]

N-benzhydryl-3-(trifluoromethyl)pyridin-2-amine (29ei)

The representative procedure **B** was followed using *N*-benzyl-3-(trifluoromethyl)pyridin-2-amine (**27e**) (126 mg, 0.50 mmol) and bromobenzene (**2i**) (118 mg, 0.75 mmol). Purification by column chromatography on silica gel (*n*-pentane/EtOAc 50/1 → 40/1 → 30/1) yielded **29ei** (78 mg, 48%) as a yellow oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.20 (ddd, J = 5.0, 1.9, 1.0 Hz, 1H), 7.67 (ddd, J = 7.6, 1.8, 0.8 Hz, 1H), 7.38–7.15 (m, 9H), 6.70–6.46 (m, 2H), 5.46 (d, J = 6.5 Hz, 1H).

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 153.5 (C$_q$), 151.8 (CH), 142.6 (C$_q$), 134.9 (CH, J = 10.3 Hz), 128.6 (CH), 127.4 (CH), 127.2 (CH), 124.5 (C$_q$, J = 273.9 Hz), 111.9 (CH), 58.4 (CH).

^{19}F-NMR (282 MHz, CDCl$_3$): δ = –63.7 (s).

IR (neat): 3476, 1602, 1582, 1493, 1465, 1301, 1102, 1024, 697 cm^{-1}.

MS (EI) *m/z* (relative intensity): 328 ([M$^+$], 90), 251 (25), 182 (45), 167 (100), 152 (35), 128 (30), 104 (20), 77 (15).

HR-MS (EI) *m/z* calcd for C$_{19}$H$_{15}$F$_3$N$_2^+$ 328.1187, found 328.1176.

The spectral data were in accordance with those reported in the literature.[85]

3-Methyl-*N*-[phenyl(*p*-tolyl)methyl]pyridin-2-amine (29ad)

The representative procedure **B** was followed using *N*-benzyl-3-methylpyridin-2-amine (**27a**) (99 mg, 0.50 mmol) and 1-bromo-4-methylbenzene (**2d**) (128 mg, 0.75 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 99/1 → 98/2) yielded **29ad** (90 mg, 62%) as a colorless solid.

M.p. = 103–105 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.95 (dd, J = 5.1, 1.7 Hz, 1H), 7.36–7.09 (m, 10H), 6.55–6.46 (m, 2H), 4.63 (d, J = 7.0 Hz, 1H), 2.31 (s, 3H), 2.12 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 155.7 (C$_q$), 145.6 (CH), 143.6 (C$_q$), 140.5 (C$_q$), 136.9 (CH), 136.6 (C$_q$), 129.2 (CH), 128.4 (CH), 127.5 (CH), 127.4 (CH), 126.9 (CH), 116.3 (C$_q$), 112.9 (CH), 58.2 (CH), 21.0 (CH$_3$), 17.1 (CH$_3$).

IR (neat): 3446, 3024, 1597, 1464, 771, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity): 288 ([M$^+$], 75), 196 (33), 181 (100), 210 (35), 166 (38), 165 (40).

HR-MS (EI) *m/z* calcd for C$_{20}$H$_{20}$N$_2$$^+$ 288.1626, found 288.1637.
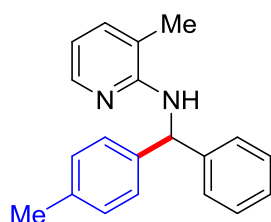
The spectral data were in accordance with those reported in the literature.[85]
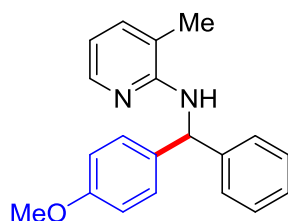
N-[(4-Methoxyphenyl)(phenyl)methyl]-3-methylpyridin-2-amine (29aj)

The representative procedure **B** was followed using *N*-benzyl-3-methylpyridin-2-amine (**27a**) (99 mg, 0.50 mmol) and 1-bromo-4-methoxybenzene (**2j**) (140 mg, 0.75 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 99/1 → 98/2) yielded **29aj** (105 mg, 69%) as a colorless solid.

M.p. = 60–62 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.95 (dd, *J* = 5.1, 1.7 Hz, 1H), 7.34–7.16 (m, 8H), 6.87–6.79 (m, 2H), 6.54–6.43 (m, 2H), 4.60 (d, *J* = 7.0 Hz, 1H), 3.76 (s, 3H), 2.12 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 158.6 (C$_q$), 155.7 (C$_q$), 145.6 (CH), 143.66 (C$_q$), 136.8 (CH), 135.7 (C$_q$), 128.7 (CH), 128.4 (CH), 127.4 (CH), 126.9 (CH), 116.2 (C$_q$), 113.8 (CH), 113.0 (CH), 57.8 (CH), 55.2 (CH$_3$), 17.1 (CH$_3$).

IR (neat): 3026, 1596, 1508, 1482, 1243, 1172, 1029, 697 cm^{-1}.

MS (EI) *m/z* (relative intensity): 304 ([M$^+$], 43), 198 (18), 197 (100), 153 (22).

HR-MS (EI) *m/z* calcd C$_{20}$H$_{20}$N$_2$O$^+$ 304.1576, found 304.1570.

The spectral data were in accordance with those reported in the literature.[85]
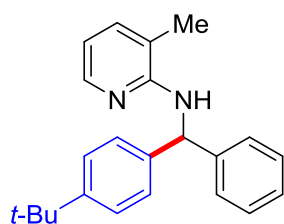
N-[{4-(tert-Butyl)phenyl}(phenyl)methyl]-3-methylpyridin-2-amine (29ak)

The representative procedure **B** was followed using *N*-benzyl-3-methylpyridin-2-amine (**27a**) (99 mg, 0.50 mmol) and 1-bromo-4-(*tert*-butyl)benzene (**2k**) (162 mg, 0.76 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 99/1 → 98/2) yielded **29ak** (108 mg, 65%) as a colorless solid.

M.p. = 121–123 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.96 (dd, *J* = 5.1, 1.7 Hz, 1H), 7.36–7.19 (m, 10H), 6.47–6.54 (m, 2H), 4.67 (d, *J* = 7.1 Hz, 1H), 2.13 (s, 3H), 1.29 (s, 9H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 155.7 (C$_q$), 149.8 (C$_q$), 145.6 (CH), 143.6 (C$_q$), 140.4 (C$_q$), 136.8 (CH), 128.4 (CH), 127.4 (CH), 127.3 (CH), 126.8 (CH), 125.4 (CH), 116.3 (C$_q$), 112.9 (CH), 58.0 (CH), 34.4 (C$_q$), 31.3 (CH$_3$), 17.1 (CH$_3$).

IR (neat): 3426, 2958, 1596, 1465, 785, 698 cm^{-1}.

MS (EI) *m/z* (relative intensity): 330 ([M$^+$], 100), 238 (32), 223 (93), 193 (20).

HR-MS (EI) *m/z* calcd C$_{23}$H$_{26}$N$_2$$^+$ 330.2096, found 330. 2100.

The spectral data were in accordance with those reported in the literature.[85]

N-[(4-Chlorophenyl)(phenyl)methyl]-3-methylpyridin-2-amine (29al)

The representative procedure **B** was followed using *N*-benzyl-3-methylpyridin-2-amine (**27a**) (99 mg, 0.50 mmol) and 1-bromo-4-chlorobenzene (**2l**) (143 mg, 0.75 mmol) at 150 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 99/1 → 98/2) yielded **29al** (82 mg, 53%) as a colorless solid.

M.p: 116–118 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.94 (dd, *J* = 5.2, 1.8 Hz, 1H), 7.36–7.21 (m, 10H), 6.56–6.43 (m, 2H), 4.58 (d, *J* = 6.7 Hz, 1H), 2.12 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 155.5 (C$_q$), 145.6 (CH), 143.0 (C$_q$), 141.1 (C$_q$), 136.1 (CH), 132.6 (C$_q$), 128.8 (CH), 128.7 (CH), 128.5 (CH), 127.6 (CH), 127.3 (CH), 116.4 (C$_q$), 113.4 (CH), 58.0 (CH), 17.0 (CH$_3$).

IR (neat): 3445, 2925, 1596, 1483, 1464, 1087, 755, 695 cm^{-1}.

MS (EI) *m/z* (relative intensity): 308 ([M$^+$], 100), 216 (40), 201 (65), 166 (43), 165 (77).

HR-MS (EI) *m/z* calcd for C$_{19}$H$_{17}$ClN$_2$$^+$ 308.1080, found 308. 1076.
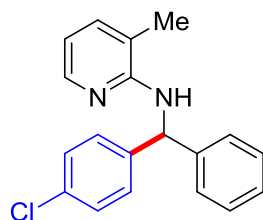
The spectral data were in accordance with those reported in the literature.[85]
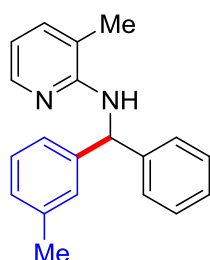
3-Methyl-*N*-[phenyl(*m*-tolyl)methyl]pyridin-2-amine (29am)

The representative procedure **B** was followed using *N*-benzyl-3-methylpyridin-2-amine (**27a**) (99 mg, 0.50 mmol) and 1-bromo-3-methylbenzene (**2m**) (135 mg, 0.78 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 99/1 → 98/2) yielded **29am** (91 mg, 63%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.97 (dd, *J* = 5.2, 1.7 Hz, 1H), 7.39–7.02 (m, 10H), 6.56–6.48 (m, 2H), 4.65 (d, *J* = 7.0 Hz, 1H), 2.32 (s, 3H), 2.14 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 155.7 (C$_q$), 145.6 (CH), 143.5 (C$_q$), 143.4 (C$_q$), 138.1 (C$_q$), 136.8 (CH), 128.4 (CH), 128.3 (CH), 127.8 (CH), 127.5 (CH), 127.5 (CH), 126.9 (CH), 124.5 (CH), 116.2 (C$_q$), 112.9 (CH), 58.4 (CH), 21.5 (CH$_3$), 17.1 (CH$_3$).

IR (neat): 3025, 1596, 1482, 1463, 1406, 773, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity): 288 ([M$^+$], 100), 287 (18), 196 (55), 181 (100), 165 (58).

HR-MS (EI) *m/z* calcd for C$_{20}$H$_{20}$N$_2^+$ 288.1626, found 288. 1619.

The spectral data were in accordance with those reported in the literature.[85]
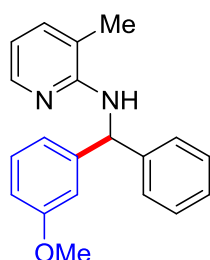
N-[(3-Methoxyphenyl)(phenyl)methyl]-3-methylpyridin-2-amine (29an)

The representative procedure **B** was followed using *N*-benzyl-3-methylpyridin-2-amine (**27a**) (99 mg, 0.50 mmol) and 1-bromo-3-methoxybenzene (**2n**) (143 mg, 0.76 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 99/1 → 98/2) yielded **29an** (88 mg, 58%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.96 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.36–7.18 (m, 7H), 6.94–6.86 (m, 2H), 6.81–6.74 (m, 1H), 6.60–6.45 (m, 2H), 4.64 (d, *J* = 6.9 Hz, 1H), 3.75 (s, 3H), 2.13 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.7 (C$_q$), 155.6 (C$_q$), 145.6 (CH), 145.1 (C$_q$), 143.3 (C$_q$), 136.9 (CH), 129.5 (CH), 128.5 (CH), 127.5 (CH), 127.0 (CH), 119.9 (CH), 116.3 (C$_q$), 113.5 (CH), 113.1 (CH), 112.0 (CH), 58.4 (CH), 55.1 (CH$_3$), 17.0 (CH$_3$).

IR (neat): 2934, 1595, 1482, 1463, 1252, 1043, 773, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity): 304 ([M$^+$], 100), 303 (16), 212 (68), 197 (84).

HR-MS (EI) *m/z* calcd for C$_{20}$H$_{20}$N$_2$O$^+$ 304.1576, found 304.1588.

The spectral data were in accordance with those reported in the literature.[86]
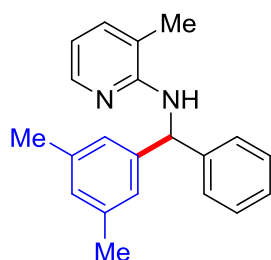
N-[(3,5-Dimethylphenyl)(phenyl)methyl]-3-methylpyridin-2-amine (29ao)

The representative procedure **B** was followed using *N*-benzyl-3-methylpyridin-2-amine (**27a**) (99 mg, 0.50 mmol) and 1-bromo-3,5-dimethylbenzene (**2o**) (142 mg, 0.76 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 99/1 → 98/2) yielded **29ao** (96 mg, 63%) as a colorless solid.

M.p: 117–119 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.96 (dd, *J* = 5.1, 1.7 Hz, 1H), 7.34–7.18 (m, 6H), 6.92 (s, 2H), 6.87 (s, 1H), 6.54–6.42 (m, 2H), 4.63 (d, *J* = 7.1 Hz, 1H), 2.26 (s, 6H), 2.13 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 155.7 (C$_q$), 145.7 (CH), 143.6 (C$_q$), 143.4 (C$_q$), 137.9 (C$_q$), 136.8 (CH), 128.8 (CH), 128.4 (CH), 127.4 (CH), 126.8 (CH), 125.4 (CH), 116.2 (C$_q$), 112.9 (CH), 108.7 (C$_q$, *J* = 31.4 Hz), 58.4 (CH), 21.4 (CH$_3$), 17.1 (CH$_3$).

IR (neat): 3446, 2918, 1596, 1465, 1404, 755, 698 cm^{-1}.

MS (EI) *m/z* (relative intensity): 302 ([M$^+$] 100), 301 (14), 210 (35), 195 (75), 165 (35).

HR-MS (EI) *m/z* calcd for C$_{21}$H$_{22}$N$_2^+$ 302.1783, found 302.1772.
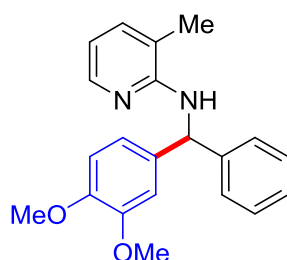
N-[(3,4-Dimethoxyphenyl)(phenyl)methyl]-3-methylpyridin-2-amine (29ap)

The representative procedure **B** was followed using *N*-benzyl-3-methylpyridin-2-amine (**27a**) (99 mg, 0.50 mmol) and 4-bromo-1,2-dimethoxybenzene (**2p**) (173 mg, 0.79 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 99/1 → 98/2) yielded **29ap** (91 mg, 55%) as a light brown solid.

M.p: 134–136 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.95 (dd, *J* = 5.2, 1.8 Hz, 1H), 7.37–7.15 (m, 6H), 6.87–6.74 (m, 3H), 6.55–6.41 (m, 2H), 4.59 (d, *J* = 7.0 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.11 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 155.7 (C$_q$), 148.9 (C$_q$), 148.0 (C$_q$), 145.6 (CH), 143.5 (C$_q$), 136.9 (CH), 136.1 (C$_q$), 128.4 (CH), 127.4 (CH), 126.9 (CH), 119.5 (CH), 116.2 (C$_q$), 113.1 (CH), 111.2 (CH), 111.0 (CH), 58.1 (CH), 55.8 (CH$_3$), 55.8 (CH$_3$), 17.1 (CH$_3$).

IR (neat): 3398, 3005, 2934, 1595, 1512, 1269, 1137, 1021, 701 cm^{-1}.

MS (EI) *m/z* (relative intensity): 334 ([M$^+$], 52), 228(16), 227 (100).

HR-MS (EI) *m/z* calcd for C$_{21}$H$_{22}$N$_2$O$_2^+$ 334.1681, found 334.1673.
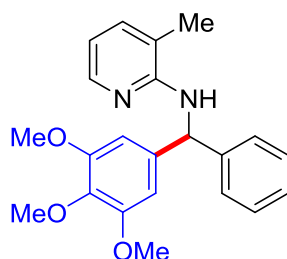
3-Methyl-*N*-[phenyl(3,4,5-trimethoxyphenyl)methyl]pyridin-2-amine (29ae)

The representative procedure **B** was followed using *N*-benzyl-3-methylpyridin-2-amine (**27a**) (99 mg, 0.50 mmol) and 5-bromo-1,2,3-trimethoxybenzene (**2e**) (185 mg, 0.75 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 99/1 → 95/5 → 90/10) yielded **29ae** (97 mg, 54%) as a violet solid.

M.p: 174–176 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): *δ* = 7.96 (dd, *J* = 5.1, 1.7 Hz, 1H), 7.34–7.19 (m, 6H), 6.55–6.49 (m, 3H), 6.44 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 6H), 2.13 (s, 3H).

^{13}C-NMR (125 MHz, CDCl$_3$): *δ* = 155.6 (C$_q$), 153.1 (C$_q$), 145.5 (CH), 143.2 (C$_q$), 139.0 (C$_q$), 136.9 (CH), 136.8 (C$_q$), 128.4 (CH), 127.3 (CH), 126.9 (CH), 116.2 (C$_q$), 113.1 (CH), 104.7 (CH), 60.7 (CH$_3$), 58.5 (CH), 55.9 (CH$_3$), 16.9 (CH$_3$).

IR (neat):.3399, 2970, 1589, 1487, 1460, 1157, 1008 cm^{-1}.

MS (EI) *m/z* (relative intensity): 364 ([M$^+$], 58), 349 (15), 258 (15), 257 (100).

HR-MS (EI) *m/z* calcd for C$_{22}$H$_{24}$N$_2$O$_3$$^+$ 364.1787, found 364.1783.
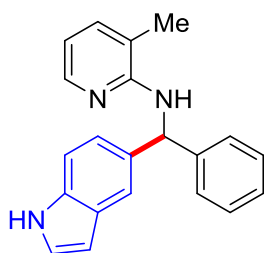
N-[(1H-Indol-5-yl)(phenyl)methyl]-3-methylpyridin-2-amine (29aq)

The representative procedure **B** was followed using *N*-benzyl-3-methylpyridin-2-amine (**27a**) (99 mg, 0.50 mmol) and 5-bromo-1*H*-indole (**2q**) (147 mg, 0.75 mmol). Purification by column chromatography on silica gel (*n*-pentane/EtOAc 5/1 → 2/1) yielded **29aq** (102 mg, 65%) as a colorless solid.

M.p: 148–149 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.57 (s$_{br}$, 1H), 7.98 (dd, *J* = 5.1, 1.7 Hz, 1H), 7.60–7.54 (m, 1H), 7.42–7.35 (m, 2H), 7.32–7.20 (m, 5H), 7.16–7.04 (m, 2H), 6.63 (d, *J* = 6.7 Hz, 1H), 6.52 (dd, *J* = 7.1, 5.1 Hz, 1H), 6.56–6.45 (m, 1H), 4.78 (d, *J* = 6.7 Hz, 1H), 2.15 (s, 3H).

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 155.8 (C$_q$), 145.5 (CH), 144.0 (C$_q$), 136.8 (CH), 135.0 (C$_q$), 134.9 (C$_q$), 128.2 (CH), 127.8 (C$_q$), 127.4 (CH), 126.6 (CH), 124.8 (CH), 122.1 (CH), 119.4 (CH), 116.3 (C$_q$), 112.8 (CH), 111.3 (CH), 102.4 (CH), 58.9 (CH), 17.1 (CH$_3$).

IR (neat): 3641, 3024, 1599, 1467, 1427, 1277, 1107, 896, 799, 772, 723, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity): 313 ([M$^+$], 85), 221 (45), 207 (45), 206 (100), 204 (55), 179 (40), 178 (30), 92 (25), 65 (10).

HR-MS (EI) *m/z* calcd for C$_{21}$H$_{19}$N$_3{}^+$ 313.1579, found 313.1574.

H/D Exchange in substrate 27a with D$_2$O as the co-solvent

27a

[D]$_n$-**27a**: 86%
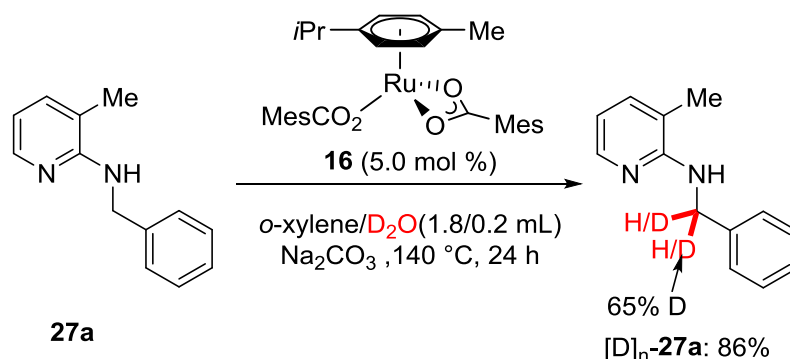
N-Benzyl-3-methylpyridin-2-amine (**1a**) (99 mg, 0.50 mmol, 1.0 equiv), [Ru(O$_2$CMes)$_2$(*p*-cymene)] (**16**) (14 mg, 0.025 mmol, 5.0 mol %) and Na$_2$CO$_3$ (159 mg, 1.50 mmol, 3.0 equiv) were placed in a 25 mL sealed tube with a septum screw cap under an inert atmosphere of nitrogen. After adding 1.8 mL *o*-xylene and 0.2 mL D$_2$O, the septum screw cap was removed and a teflon lined cap was fixed immediately. The reaction mixture was stirred at 140 °C for 24 h. At ambient temperature, the suspension was filtered through a short pad of Celite®, which was further washed with CH$_2$Cl$_2$ (50 mL). Evaporation of the solvent *in vacuo* and purification by column chromatography on silica gel (*n*-hexane/EtOAc 99/1 → 98/2) yielded [D$_n$]-**27a**) as a colorless oil (85 mg, 86%, 65%-D), as estimated by ^{1}H-NMR.

^{1}H NMR (300 MHz, CDCl$_3$): *δ* = 8.04 (dd, *J* = 5.1, 1.7 Hz, 1H), 7.43–7.19 (m, 6H), 6.55 (dd, *J* = 7.1, 5.1 Hz, 1H), 4.68 (d, *J* = 5.4 Hz, 2H), 4.35 (s$_{br}$, 1H), 2.07 (s, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): *δ* = 156.6 (C$_q$), 145.4 (CH), 140.0 (C$_q$), 136.8 (CH), 128.5 (CH), 127.8 (CH), 127.1 (CH), 116.4 (C$_q$), 112.9 (CH), 45.8 (CH$_2$), 45.5 (CHD, *J* = 21.0 Hz), 17.0 (CH$_3$).

IR (neat): 3447, 3027, 1597, 1490, 1466, 1381, 696 cm^{-1}

MS (EI) *m/z*(relative intensity): 200 (23), 199 (77), 198 (100), 197 (33), 108 (27), 107 (80), 106 (77), 93 (47), 92 (65), 91 (38), 65 (38).

HRMS (ESI) *m/z* calcd for [C$_{13}$H$_{12}$D$_2$N$_2$ + H]$^+$ 201.1355, found 201.1355
m/z calcd for [C$_{13}$H$_{13}$DN$_2$ + H]$^+$ 200.1293, found 200.1292,
m/z calcd for [C$_{13}$H$_{14}$N$_2$ + H]$^+$ 199.1230, found 199.1230

Me

NH

H/D

H/D

65% D

[D]$_n$-**27a**

(300 MHz, CDCl$_3$)

0.80

5.30

0.89

1.32

0.87

3.00

).0   9.5   9.0   8.5   8.0   7.5   7.0   6.5   6.0   5.5   5.0   4.5   4.0   3.5   3.0   2.5   2.0   1.5   1.0   0.5

f1 (ppm)

156.6   145.4   140.0   136.8   128.5   127.8   127.1   116.4   112.9   45.8   45.7   45.5   45.3   17.0

Me

NH

H/D

H/D

65% D

[D]$_n$-**27a**

(125 MHz, CDCl$_3$)

10   200   190   180   170   160   150   140   130   120   110   100   90   80   70   60   50   40   30   20   10

f1 (ppm)

85
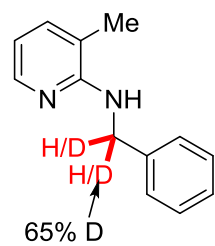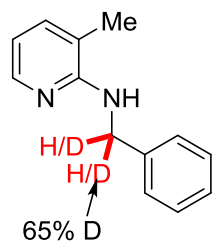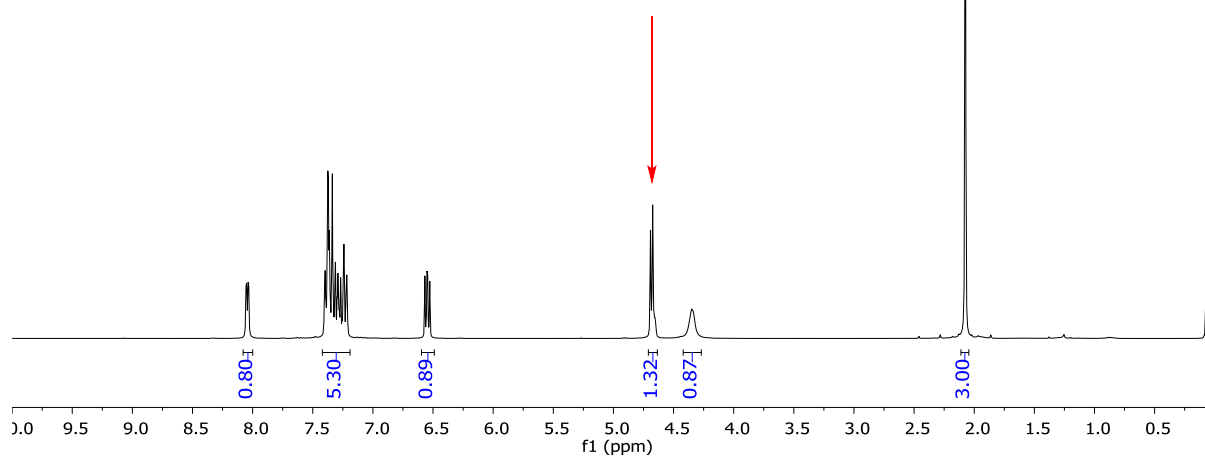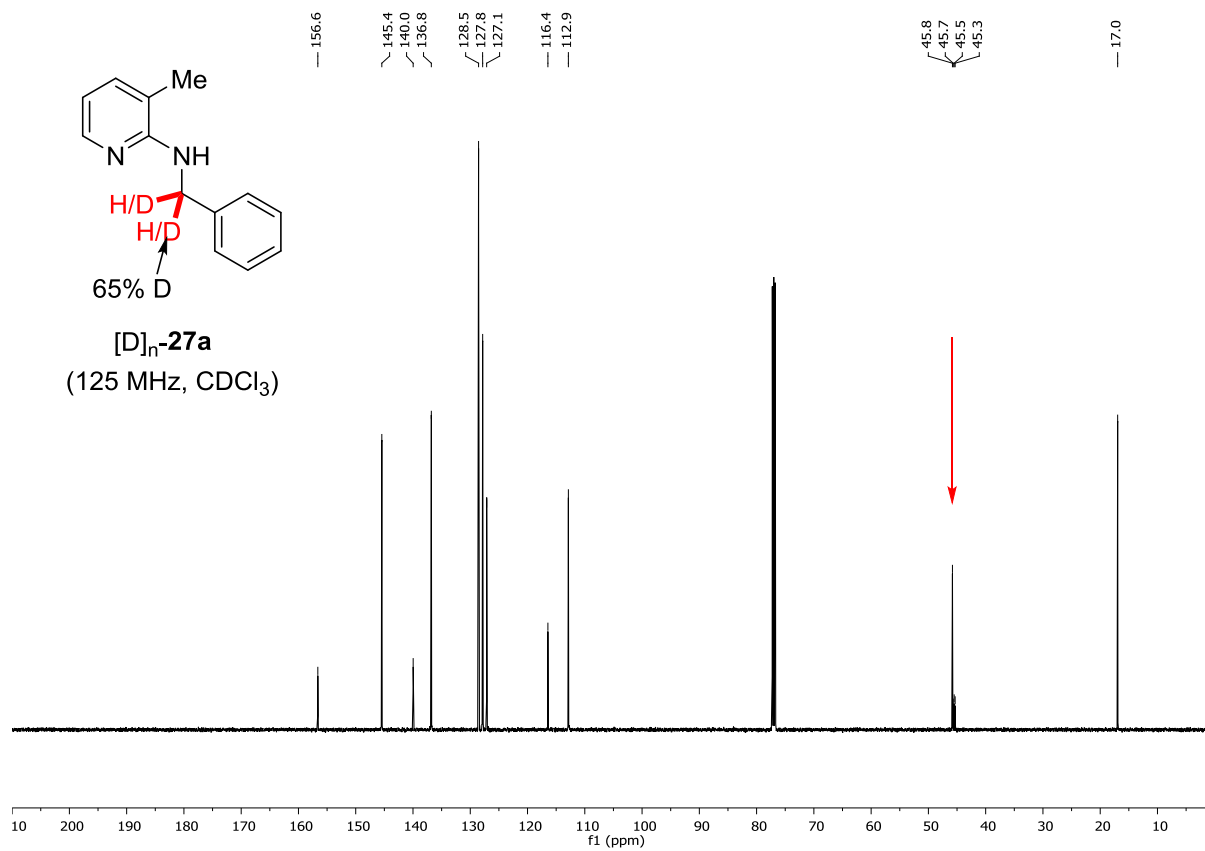
5.5 Hydroarylation of alkynes

Characterization data of products 72
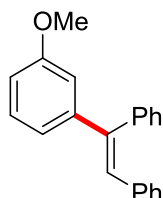
(*E*)-[1-(3-Methoxyphenyl)-1,2-diphenyl] ethene (72aa)

The general procedure **C** was followed using 2-methoxy benzoic acid (**48a**) (152 mg, 1.00 mmol) and diphenylacetylene (**34a**) (89 mg, 0.50 mmol) in DCE (2.0 mL). Purification by column chromatography (*n*hexane/EtOAc: 99/1) yielded **72aa** (140 mg, 98%) as light yellow oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.35–7.30 (m, 3H), 7.25–7.19 (m, 3H), 7.15–7.10 (m, 3H), 7.04–7.01 (m, 2H), 6.98 (s, 1H), 6.92 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1H), 6.88 (dd, *J* = 2.5, 1.7 Hz, 1H), 6.84 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 3.78 (s, 3H).

^{13}C NMR (126 MHz, CDCl$_3$): δ = 160.0 (C$_q$), 145.1 (C$_q$), 142.6 (C$_q$), 140.4 (C$_q$), 137.4 (C$_q$), 130.5 (CH), 129.7 (CH), 129.2 (CH), 128.7 (CH), 128.5 (CH), 128.1 (CH), 127.6 (CH), 126.9 (CH), 120.4 (CH), 113.6 (CH), 113.0 (CH), 55.4 (CH$_3$).

IR (ATR): 3020, 2832, 1593, 1576, 1483, 1260, 1074, 1000, 754, 691 cm^{-1}.

MS (EI) *m/z* (relative intensity): 286 (100) [M$^+$], 255 (15), 253 (22), 252 (14), 178 (14), 165 (14).

HR-MS (EI) *m/z* calcd for C$_{21}$H$_{18}$O, [M$^+$] 286.1358, found 286.1360.

The analytical data are in accordance with those reported in the literature.[87]
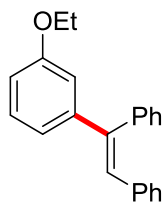
(*E*)-[1-(3-Ethoxyphenyl)-1,2-diphenyl] ethene (72ba)

The general procedure **C** was followed using 2-ethoxy benzoic acid (**48b**) (166 mg, 1.00 mmol) and diphenylacetylene (**34a**) (89 mg, 0.50 mmol) in PhMe (2.0 mL). Purification by column chromatography (*n*hexane) yielded **72ba** (131 mg, 87%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.27–7.22 (m, 3H), 7.18–7.11 (m, 3H), 7.07–7.01 (m, 3H), 6.95–6.93 (m, 2H), 6.89 (s, 1H), 6.83 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1H), 6.80–6.79 (m, 1H), 6.75 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 3.93 (q, *J* = 7.0 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ = 159.0 (C$_q$), 145.1 (C$_q$), 142.6 (C$_q$), 140.4 (C$_q$), 137.5 (C$_q$), 130.5 (CH), 129.7 (CH), 129.2 (CH), 128.7 (CH), 128.4 (CH), 128.1 (CH), 127.5 (CH), 126.9 (CH), 120.3 (CH), 114.2 (CH), 113.5 (CH), 63.5 (CH₂), 15.0 (CH₃).

IR (ATR): 3022, 2977, 1594, 1574, 1441, 1262, 1200, 1048, 772, 691 cm^{-1}.

MS (EI) *m/z* (relative intensity) 300 (100) [M⁺], 271 (22), 253 (18), 252 (15), 239 (12), 165 (15).

HR-MS (EI) *m/z* calcd for C₂₂H₂₀O, [M⁺] 300.1514, found 300.1505.
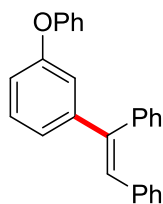
(*E*)-[1-(3-Pheoxyphenyl)-1,2-diphenyl] ethene (72ca)

The general procedure **C** was followed using 2-phenoxy benzoic acid (**48c**) (214 mg, 1.00 mmol) and diphenylacetylene (**34a**) (89 mg, 0.50 mmol) in PhMe (2.0 mL). Purification by column chromatography (*n*hexane) yielded **72ca** (105 mg, 60%) as a yellow oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.35–7.30 (m, 5H), 7.27–7.20 (m, 3H), 7.15–7.09 (m, 3H), 7.09–7.03 (m, 3H), 7.03–7.00 (m, 4H), 6.97 (s, 1H), 6.91 (ddd, J = 8.1, 2.4, 1.0 Hz, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ = 157.4 (C$_q$), 157.2 (C$_q$), 145.5 (C$_q$), 142.1 (C$_q$), 140.1 (C$_q$), 137.3 (C$_q$), 130.5 (CH), 129.8 (CH), 129.7 (CH), 129.5 (CH), 128.8 (CH), 128.7 (CH), 128.1 (CH), 127.7 (CH), 127.0 (CH), 123.3 (CH), 122.9 (CH), 118.8 (CH), 118.4 (CH), 118.0 (CH).

IR (ATR): 3055, 3022, 1589, 1573, 1487, 1478, 1261, 1217, 776, 689 cm^{-1}.

MS (EI) *m/z* (relative intensity) 348 (100) [M$^+$], 255 (33), 253 (28), 252 (18), 213 (15), 178 (18), 77 (18), 51 (12).

HR-MS (EI) *m/z* calcd for C$_{26}$H$_{20}$O, [M$^+$] 348.1514, found 348.1514.
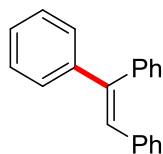
1,1,2- Triphenylethylene (72da)

The general procedure **C** was followed using benzoic acid (**48d**) (122 mg, 1.00 mmol) and diphenylacetylene (**34a**) (89 mg, 0.50 mmol) in PhMe (2.0 mL). Purification by column chromatography (*n*hexane) yielded **72da** (55 mg, 43%) as a colourless solid.

M.p: 71-73 °C.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.35–7.27 (m, 8H), 7.22–7.20 (m, 2H), 7.15–7.09 (m, 3H), 7.04–7.02 (m, 2H), 6.97 (s, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ = 143.6 (C$_q$), 142.7 (C$_q$), 140.5 (C$_q$), 137.5 (C$_q$), 130.5 (CH), 129.7 (CH), 128.8 (CH), 128.3 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 126.9 (CH).

IR (ATR): 3077, 3054, 3021, 1575, 1490, 775, 722, 690, 586 cm^{-1}.

MS (EI) *m/z* (relative intensity) 256 (100) [M$^+$], 255 (22), 179 (25), 178 (37), 43 (18).

HR-MS (EI) *m/z* calcd for C$_{20}$H$_{16,}$ [M$^+$] 256.1252, found 256.1254.

The analytical data are in accordance with those reported in the literature. [88]

(*E*)-[1-(3-Fluorophenyl)-1,2-diphenyl] ethene (72ea)

The general procedure C was followed using 2-fluorobenzoic acid (**48e**) (140 mg, 1.00 mmol), diphenylacetylene (**34a**) (89 mg, 0.50 mmol) in DCE (2.0 mL). Purification by column chromatography (*n*hexane) yielded **72ea** (108 mg, 79%) as colourless solid.
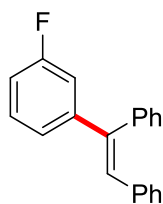
M.p: 67-69 °C.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.35–7.32 (m, 3H), 7.28–7.24 (m, 1H), 7.20–7.18 (m, 2H), 7.15–7.09 (m, 4H), 7.03–6.99 (m, 3H), 6.98 (s, 1H), 6.97–6.94 (m, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ = 163.0 (C$_q$, $^1J_{C\text{-}F}$ = 245.2 Hz), 145.9 (C$_q$, $^3J_{C\text{-}F}$ = 7.3 Hz), 141.6 (C$_q$, $^4J_{C\text{-}F}$ = 2.4 Hz), 139.9 (C$_q$), 137.0 (C$_q$), 130.4 (CH), 129.8 (CH), 129.7 (CH, $^3J_{C\text{-}F}$ = 8.4 Hz), 129.2 (CH), 128.9 (CH), 128.2 (CH), 127.8 (CH), 127.2 (CH), 123.3 (CH, $^4J_{C\text{-}F}$ = 2.6 Hz), 114.6 (CH, $^2J_{C\text{-}F}$ = 20.4 Hz), 114.4 (CH, $^2J_{C\text{-}F}$ = 19.7 Hz).

^{19}F{^{1}H} NMR (300 MHz, CDCl$_3$): δ = -114.7 (s).

IR (ATR): 3055, 3020, 1574, 1524, 1492, 1478, 1184, 1157, 872, 691 cm^{-1}.

MS (EI) *m/z* (relative intensity) 274 (100) [M$^+$], 273 (22), 259 (20), 196 (22), 178 (18), 43 (35).

HR-MS (EI) *m/z* calcd for C$_{20}$H$_{15}$F, [M$^+$] 274.1158, found 274.1158.
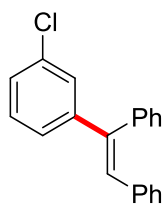
(*E*)-[1-(3-Chlorophenyl)-1,2-diphenyl] ethene (72fa)

The general procedure **C** was followed using 2-chloro benzoic acid (**48f**) (157 mg, 1.00 mmol) and diphenylacetylene (**34a**) (89 mg, 0.50 mmol) in PhMe (2.0 mL). Purification by column chromatography (*n*hexane) yielded **72fa** (77 mg, 53%) as a yellow oil.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.37–7.36 (m, 3H), 7.34–7.36 (m, 1H), 7.29–7.26 (m, 2H), 7.26–7.22 (m, 1H), 7.22–7.19 (m, 2H), 7.17–7.13 (m, 3H), 7.06–7.03 (m, 2H), 7.02 (s, 1H).

^{13}C NMR (126 MHz, CD$_2$Cl$_2$): δ = 145.7 (C$_q$), 141.6 (C$_q$), 140.1 (C$_q$), 137.3 (C$_q$), 134.4 (C$_q$), 130.5 (CH), 129.9 (CH), 129.8 (CH), 129.5 (CH), 129.1 (CH), 128.3 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 126.1 (CH).

IR (ATR): 3055, 3021, 1618, 1588, 1561, 1491, 1471, 1444, 741, 653 cm^{-1}.

MS (EI) *m/z* (relative intensity) 290 (100) [M$^+$], 253 (37), 252 (30), 239 (18), 179 (22), 178 (33), 176 (15), 126 (12).

HR-MS (EI) *m/z* calcd for C$_{20}$H$_{15}$Cl, [M$^+$] 290.0862, found 290.0872.
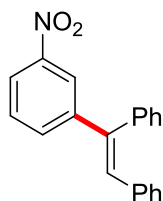
(*E*)-[1-(3-Nitrophenyl)-1,2-diphenyl] ethene (72ga)

The general procedure **C** was followed using 2-nitrobenzoic acid (**48g**) (167 mg, 1.00 mmol) and diphenylacetylene (**34a**) (89 mg, 0.50 mmol) in PhMe (2.0 mL). Purification by column chromatography (*n*hexane/EtOAc: 97/3) yielded **72ga** (66 mg, 44%) as yellow solid.

M.p: 148-150 °C.

^{1}H NMR (600 MHz, CD$_2$Cl$_2$): *δ* = 8.19 (dd, *J* = 2.1, 2.1 Hz, 1H), 8.13–8.11 (m, 1H), 7.67–7.63 (m, 1H), 7.49 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.42–7.38 (m, 3H), 7.23–7.20 (m, 2H), 7.17–7.15 (m, 3H), 7.11 (s, 1H), 7.09–7.06 (m, 2H).

^{13}C NMR (126 MHz, CD$_2$Cl$_2$): *δ* = 148.7 (C$_q$), 145.4 (C$_q$), 140.7 (C$_q$), 139.5 (C$_q$), 137.0 (C$_q$), 133.7 (CH), 130.7 (CH), 130.5 (CH), 130.0 (CH), 129.4 (CH), 129.1 (CH), 128.3 (CH), 128.3 (CH), 127.7 (CH), 122.4 (CH), 122.3 (CH).

IR (ATR): 3034, 3014, 1571, 1493, 1444, 1346, 860, 780, 740, 695 cm^{-1}.

MS (EI) *m/z* (relative intensity) 301 (100) [M$^+$], 253 (35), 252 (30), 239 (22), 179 (20).

HR-MS (EI) *m/z* calcd for C$_{20}$H$_{15}$NO$_2$, [M$^+$] 301.1103, found 301.1107.
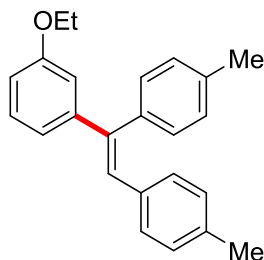
(*E*)-{1-(3-Ethoxyphenyl)-1,2-bis-[*p*-tolyl]} ethene (72bb)

The general procedure **C** was followed using 2-ethoxy benzoic acid (**48b**) (166 mg, 1.00 mmol), di(4-methylphenyl)acetylene (**34b**) (103 mg, 0.50 mmol) in PhMe (2.0 mL). Purification by column chromatography using (*n*hexane/EtOAc: 99/1) yielded **72bb** (126 mg, 76%) as a yellow oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.21 (dd, J = 7.9, 7.9 Hz, 1H), 7.17–7.07 (m, 4H), 6.98–6.84 (m, 7H), 6.80 (ddd, J = 8.2, 2.5, 0.9 Hz, 1H), 4.00 (q, J = 7.0 Hz, 2H), 2.38 (s, 3H), 2.26 (s, 3H), 1.38 (t, J = 7.0 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ = 158.9 (C$_q$), 145.5 (C$_q$), 141.7 (C$_q$), 137.5 (C$_q$), 137.1(C$_q$), 136.6 (C$_q$), 134.8 (C$_q$), 130.3 (CH), 129.6 (CH), 129.5 (CH), 129.1(CH), 128.8 (CH), 128.1 (CH), 120.3 (CH), 114.2 (CH), 113.3 (CH), 63.5 (CH₂), 21.5 (CH₃), 21.3 (CH₃), 15.0 (CH₃).

IR (ATR): 3021, 2977, 1593, 1574, 1262, 1198, 1050, 776, 729, 697 cm⁻¹.

MS (EI) *m/z* (relative intensity) 328 (100) [M⁺], 285 (18), 252 (10).

HR-MS (EI) *m/z* calcd for C₂₄H₂₄O, [M⁺] 328.1827, found 328.1817.

(*E*)-[1-(3-Ethoxyphenyl)-1,2-bis-(*p*-anisyl)] ethene (72bc)

The general procedure **C** was followed using 2-ethoxy benzoic acid (**48b**) (166 mg, 1.00 mmol), 1,2-bis(4-methoxyphenyl)ethyne (**34c**) (119 mg, 0.50 mmol) in PhMe (2.0 mL). Purification by column chromatography (*n*hexane/EtOAc: 49/1) yielded **72bc** (152 mg, 84%) as a colourless oil.
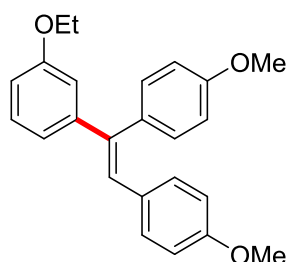
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.14–7.09 (m, 1H), 7.06–7.02 (m, 2H), 6.93–6.88 (m, 2H), 6.83–6.77 (m, 5H), 6.72 (ddd, *J* = 8.1, 2.6, 0.9 Hz, 1H), 6.63–6.56 (m, 2H), 3.92 (q, *J* = 7.0 Hz, 2H), 3.76 (s, 3H), 3.67 (s, 3H), 1.31 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 159.0 (C$_q$), 159.0 (C$_q$), 158.4 (C$_q$), 145.6 (C$_q$), 140.3 (C$_q$), 132.9 (C$_q$), 131.7 (CH), 130.9 (CH), 130.4 (C$_q$), 129.1 (CH), 127.6 (CH), 120.2 (CH), 114.2 (CH), 114.1 (CH), 113.6 (CH), 113.2 (CH), 63.5 (CH$_2$), 55.3 (CH$_3$), 55.3 (CH$_3$), 15.0 (CH$_3$).

IR (ATR): 2977, 2834, 1600, 1573, 1506, 1284, 1241, 1172, 1030, 826, 789 cm^{-1}.

MS (EI) *m/z* (relative intensity) 360 (100) [M$^+$], 345 (10), 209 (10), 181 (8).

HR-MS (EI) *m/z* calcd for C$_{24}$H$_{24}$O$_3$, [M$^+$] 360.1725, found 360.1714.

(*E*)-[1-(3-Benzyloxyphenyl)-1,2-diphenyl] ethene (72ia)

The general procedure **C** was followed using 4-benzyloxy benzoic acid (**48i**) (228 mg, 1.00 mmol) and diphenylacetylene (**34a**) (89 mg, 0.50 mmol) in DCE (2.0 mL). Purification by column chromatography (*n*hexane/EtOAc: 99/1) yielded **72ia** (100 mg, 55%) as a colourless oil.

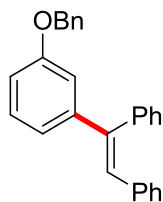**^{1}H NMR** (600 MHz, CD$_2$Cl$_2$): δ = 7.43–7.32 (m, 8H), 7.25–7.23 (m, 1H), 7.22–7.19 (m, 2H), 7.15–7.09 (m, 3H), 7.05–7.03 (m, 2H), 7.02 (s, 1H), 6.96–6.94 (m, 2H), 6.93–6.90 (m, 1H), 5.04 (s, 2H).

^{13}C NMR (76 MHz, CD$_2$Cl$_2$): δ = 159.1 (C$_q$), 145.3 (C$_q$), 142.8 (C$_q$), 140.7 (C$_q$), 137.8 (C$_q$), 137.5 (C$_q$), 130.7 (CH), 129.9 (CH), 129.5 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 128.3 (CH), 128.0 (CH), 127.8 (CH), 127.2 (CH), 120.7 (CH), 114.7 (CH), 114.1 (CH), 70.3 (CH$_2$).

IR (ATR): 3055, 3022, 1589, 1573, 1183, 1128, 873, 719, 689 cm^{-1}.

MS (EI) *m/z* (relative intensity) 362 (53) [M$^+$], 271 (15), 91 (100).

HR-MS (EI) *m/z* calcd for C$_{27}$H$_{22}$O, [M$^+$] 362.1671, found 362.1678.

(*E*)-[1-(*m*-Tolyl)-1,2-diphenyl] ethene (72ha)

The general procedure **C** was followed using 4-methylbenzoic acid (**48h**) (136 mg, 1.00 mmol) and diphenylacetylene (**34a**) (89 mg, 0.50 mmol) in PhMe (2.0 mL). Purification by column chromatography (*n*hexane) yielded **72ha** (80 mg, 59%) as a colourless oil.
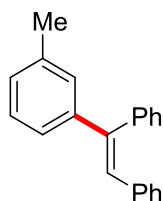
^{1}H NMR (600 MHz, CD_2Cl_2): δ = 7.41–7.37 (m, 3H), 7.26–7.22 (m, 4H), 7.19–7.13 (m, 5H), 7.10–7.07 (m, 2H), 7.03 (s, 1H), 2.37 (s, 3H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 143.7 (C_q), 143.1 (C_q), 140.9 (C_q), 138.2 (C_q), 137.9 (C_q), 130.6 (CH), 129.9 (CH), 128.9 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.7 (CH), 127.0 (CH), 125.1 (CH), 21.7 (CH_3).

IR (ATR): 3053, 3020, 1599, 1491, 1444, 781, 754, 717, 690, 595 cm^{-1}.

MS (EI) *m/z* (relative intensity) 270 (100) [M$^+$], 255 (38), 253 (18), 239 (12), 178 (28), 43 (21).
HR-MS (EI) *m/z* calcd for $C_{21}H_{18}$, [M$^+$] 270.1409, found 270.1411.

The analytical data are in accordance with those reported in the literature.[89]
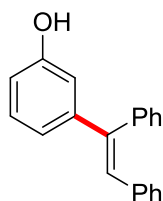
(*E*)-[1-(3-Hydroxyphenyl)-1,2-diphenyl] ethene (72ja)

The general procedure **C** was followed using salicylic acid (**48j**) (138 mg, 1.00 mmol) and diphenylacetylene (**34a**) (89 mg, 0.50 mmol) in PhMe (2.0 mL). Purification by column chromatography (*n*hexane/EtOAc: 97/3) yielded **72ja** (87 mg, 64%) as a beige solid.

M.p: 126-128 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.34–7.30 (m, 3H), 7.21–7.16 (m, 3H), 7.14–7.09 (m, 3H), 7.02–6.99 (m, 2H), 6.96 (s, 1H), 6.95–6.92 (m, 1H), 6.77–6.72 (m, 2H), 4.70 (s, 1H).

¹³C NMR (126 MHz, CDCl₃): δ = 155.4 (C$_q$), 145.3 (C$_q$), 142.2 (C$_q$), 140.3 (C$_q$), 137.3 (C$_q$), 130.5 (CH), 129.7 (CH), 129.5 (CH), 128.8 (CH), 128.5 (CH), 128.1 (CH), 127.6 (CH), 127.0 (CH), 120.4 (CH), 114.7 (CH), 114.6 (CH).

IR (ATR): 3250 (br), 3017, 1578, 1492, 1443, 1269, 1191, 753, 718, 690 cm⁻¹.

MS (EI) *m/z* (relative intensity) 272 [M⁺], 58 (18), 44 (21), 43 (100).

HR-MS (EI) *m/z* calcd for C₂₀H₁₆O, [M⁺] 272.1201, found 272.1208.
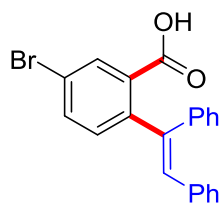
(*E*)-5-Bromo-2-(1,2-diphenylvinyl)benzoic acid (72ka)

The general procedure **C** was followed using 3-bromo benzoic acid (**48k**) (201 mg, 1.00 mmol) and diphenylacetylene (**34a**) (89 mg, 0.50 mmol) in DCE (2.0 mL). Purification by column chromatography (*n*hexane/EtOAc: 5/1) yielded **72ka'** (27 mg, 14%) as colorless solid and **72ka** as colorless viscous liquid (43 mg, 26%).

M.p: 190-192 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.92 (d, J = 2.2 Hz, 1H), 7.60 (dd, J = 8.2, 2.2 Hz, 2H), 7.22 (d, J = 8.2 Hz, 1H), 7.16–7.07 (m, 10H), 6.58 (s, 1H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 170.8 (C$_q$), 144.6 (C$_q$), 141.1 (C$_q$), 139.4 (C$_q$), 137.2 (C$_q$), 134.8 (CH), 133.1 (CH), 132.9 (CH), 132.0 (C$_q$), 130.6 (CH), 130.3 (CH), 129.5 (CH), 128.2 (CH), 127.6 (CH), 127.3 (CH), 121.2 (C$_q$).

IR (ATR): 1703, 1675, 1440, 1292, 1096, 1072, 775, 759, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity) 378 (100) [M$^+$], 361 (21), 334 (11), 252 (100), 165 (16), 105 (50), 77 (40).

HR-MS (EI) *m/z* calcd for C$_{20}$H$_{15}$^{79}BrO$_2$, [M$^+$] 378.0255, found 378.0265
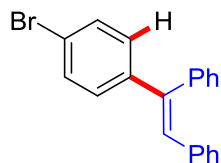
(*E*)-[1-(4-Bromophenyl)-1,2-diphenyl] ethene (72ka')

¹H NMR (600 MHz, CDCl₃): δ = 7.45–7.42 (m, 2H), 7.34 (dd, J = 5.0, 1.9 Hz, 3H), 7.22–7.17 (m, 4H), 7.16 – 7.11 (m, 3H), 7.03 (dd, J = 7.7, 1.9 Hz, 2H), 6.96 (s, 1H).

¹³C NMR (76 MHz, CDCl₃): δ = 142.5 (C$_q$), 141.6 (C$_q$), 140.0 (C$_q$), 137.2 (C$_q$), 131.4 (CH), 130.4 (CH), 129.7 (CH), 129.3 (CH), 128.9 (CH), 128.7 (CH), 128.1 (CH), 127.8 (CH), 127.1 (CH), 121.7 (C$_q$).
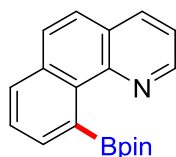
IR (ATR): 3021, 1487, 1443, 1072, 1007, 834, 728, 694, cm⁻¹.

MS (EI) *m/z* (relative intensity) 334 (100) [M⁺], 253 (17), 252 (13), 239 (9), 178 (16).

HR-MS (EI) *m/z* calcd for C$_{20}$H$_{15}$⁷⁹Br, [M⁺] 334.0357, found 334.0347

5.6 Ruthenium(II)-catalyzed C(sp^2)–H borylations

Characterization data of products 70

10-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*h*]quinoline (70aa)

The general procedure **D** was followed using benzo[*h*]quinoline (**1a**) (179 mg, 1.00 mmol) and B$_2$pin$_2$ (**62a**) (254 mg, 1.00 mmol) in 1,4-dioxane (2.5 mL). After 20 h, purification by Kuglerohr distillation yielded **70aa** (228 mg, 75%) as a colorless solid.

M.p.: 167-169 °C

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.90 (dd, *J* = 4.5, 1.6 Hz, 1H), 8.18 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.88 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.82–7.75 (m, 2H), 7.72–7.64 (m, 2H), 7.52 (dd, *J* = 8.0, 4.5 Hz, 1H), 1.55 (s, 12H)

^{13}C NMR (101 MHz, CDCl$_3$): δ = 146.8 (C$_q$), 146.5 (CH), 136.1 (CH), 134.5 (C$_q$), 132.7 (C$_q$), 130.9 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 126.4 (C$_q$), 124.6 (CH), 121.8 (CH), 83.4 (C$_q$), 25.4 (CH$_3$).

^{11}B NMR (128 MHz, CDCl$_3$): δ = 30.8

IR (neat): $\tilde{v}$ = 2976, 1511, 1368, 1341, 1314, 1132, 1101, 969, 852, 825 cm^{-1}.

HR-MS (ESI): *m/z* calcd for C$_{19}$H$_{21}$BNO$_2^+$ [M+H$^+$] 306.1660, found 306.1663.

Note: A resonance for the carbon directly attached to the boron atom was not observed.

The analytical data are in accordance with those reported in the literature.[90]
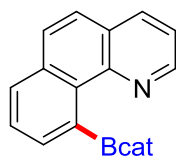
10-(Benzo[*d*][1,3,2]dioxaborol-2-yl)benzo[*h*]quinoline (70ab)

The general procedure **D** was followed using benzo[*h*]quinoline (**1a**) (45 mg, 0.25 mmol) and B$_2$cat$_2$ (**62b**) (59 mg, 0.25 mmol) in 1,4-dioxane (1.0 mL). After 20 h, purification by Kugelrohr distillation yielded **70ab** (72 mg, 97%) as a violet solid.

M.p.: 190-192 °C.

^{1}H NMR (400 MHz, CDCl$_3$): *δ* = 8.47–8.42 (m, 2H), 8.00–7.96 (m, 2H), 7.90 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.84 (dd, *J* = 8.0, 6.7 Hz, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.56 (dd, *J* = 8.0, 5.2 Hz, 1H), 7.01 (dd, *J* = 5.7, 3.3 Hz, 2H), 6.88 (dd, *J* = 5.7, 3.3 Hz, 2H).

^{13}C NMR (101 MHz, CDCl$_3$): *δ* = 152.0 (C$_q$), 145.6 (C$_q$), 141.3 (CH), 139.8 (CH), 134.5 (C$_q$), 132.0 (CH), 130.7 (C$_q$), 130.5 (CH), 129.5 (CH), 125.9 (CH), 124.8 (C$_q$), 122.6 (CH), 122.3 (CH), 119.9 (CH), 110.7 (CH).

^{11}B NMR (128 MHz, CDCl$_3$): *δ* = 16.6.

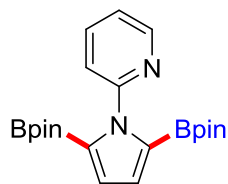**IR** (neat): *ṽ* = 3032, 1476, 1462, 1228, 1213, 1168, 1065, 743, 719 cm^{-1}.

MS (EI) *m/z* (relative intensity) 297 (100) [M$^+$], 253 (15), 207 (15), 191 (35), 164 (50), 91 (75), 84 (25), 77 (20), 65 (15), 43 (35).

HR-MS (EI) *m/z* calcd for C$_{19}$H$_{12}$BNO$_2$, [M$^+$] 297.0961, found 297.0959.

Note: A resonance for the carbon directly attached to the boron atom was not observed.

2-[2,5-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrol-1-yl]pyridine (70ba)

The general procedure **D** was followed using 2-(1*H*-pyrrol-1-yl)pyridine (**1b**) (36 mg, 0.25 mmol) and B$_2$pin$_2$ (**62a**) (63 mg, 0.25 mmol) in 1,4-dioxane (1.0 mL). After 20 h, purification by flash column chromatography on silica gel (EtOAc/NEt$_3$: 98/2) and HPLC yielded **70ba** (42 mg, 42%) as a red viscous liquid.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 8.38–8.36 (m, 1H), 8.34–8.32 (m, 1H), 7.87 (ddd, J = 8.8, 7.3, 1.7 Hz, 1H), 7.16–7.13 (m, 1H), 6.76 (s, 2H), 1.30 (s, 24H).

^{13}C NMR (126 MHz, CDCl$_3$): δ = 152.1 (C$_q$), 143.0 (CH), 141.8 (CH), 123.5 (CH), 119.5 (CH), 114.5 (CH), 82.4 (C$_q$), 25.4 (CH$_3$).

^{11}B NMR (128 MHz, CDCl$_3$): δ = 20.8.

IR (neat): $\tilde{v}$ = 2973, 1590, 1474, 1455, 1340, 1134, 925, 966, 675 cm^{-1}.

HR-MS (ESI): *m*/*z* calcd for C$_{21}$H$_{31}$B$_2$N$_2$O$_4^+$ [M+H$^+$] 397.2464, found 397.2472.

Note: A resonance for the carbon directly attached to the boron atom was not observed.
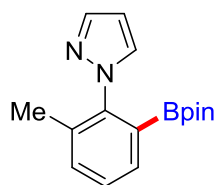
1-[2-Methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1H-pyrazole (70ca)

The general procedure **D** was followed using 1-(*o*-tolyl)-1*H*-pyrazole (**1c**) (40 mg, 0.25 mmol) and B$_2$pin$_2$ (**62a**) (63 mg, 0.25 mmol) in 1,4-dioxane (1.0 mL). After 20 h, purification by flash column chromatography on silica gel (EtOAc/NEt$_3$: 98/2) and HPLC yielded **70ca** (45 mg, 63%) as a light yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ =7.66 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.59–7.56 (m, 2H), 7.35–7.29 (m, 2H), 6.38 (t, *J* = 2.1 Hz, 1H), 2.11 (s, 3H), 1.19 (s, 12H).

^{13}C NMR (126 MHz, CDCl$_3$): δ = 143.7 (C$_q$), 138.9 (CH), 133.5 (C$_q$), 132.8 (CH), 132.3 (CH), 130.9 (CH), 128.2 (CH), 105.8 (CH), 83.5 (C$_q$), 25.0 (CH$_3$), 18.0 (CH$_3$).

^{11}B NMR (128 MHz, CDCl$_3$): δ = 28.6.

IR (neat): $\tilde{v}$ = 2977, 1590, 1460, 1354, 1138, 1112, 1080, 851, 746 cm^{-1}.

HR-MS (ESI): *m*/*z* calcd for C$_{16}$H$_{22}$BN$_2$O$_2$$^+$ [M+H$^+$] 285.1769, found 285.1772.

Note: A resonance for the carbon directly attached to the boron atom was not observed.

2-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyridine (70da)

The general procedure **D** was followed using 2-phenylpyridine (**1d**) (78 mg, 0.50 mmol) and B$_2$pin$_2$ (**62a**) (127 mg, 0.50 mmol) in 1,4-dioxane (2.0 mL). After 20 h, purification by flash column chromatography on silica gel (EtOAc/NEt$_3$: 99/1) and HPLC yielded 7**0da** (80 mg, 57%) was obtained as a white solid.

M.p.: 129-131 °C

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.65 (ddd, J = 5.6, 1.5, 0.9 Hz, 1H), 7.93 (ddd, J = 8.0, 7.4, 1.5 Hz, 1H), 7.78 (dt, J = 8.0, 1.1 Hz, 1H), 7.72 (dt, J = 7.2, 1.0 Hz, 1H), 7.64 (dt, J = 7.6, 0.9 Hz, 1H), 7.40 (td, J = 7.3, 1.1 Hz, 1H), 7.34 (ddd, J = 7.4, 5.6, 1.2 Hz, 1H), 7.27 (dd, J = 7.5, 1.2 Hz, 1H), 1.42 (s, 12H).

^{13}**C NMR** (101 MHz, CDCl$_3$): δ = 156.6 (C$_q$), 143.3 (CH), 141.9 (CH), 137.2 (C$_q$), 131.5 (CH), 131.5 (CH), 127.9 (CH), 122.8 (CH), 121.3 (CH), 117.5 (CH), 80.3 (C$_q$), 27.1 (CH$_3$).

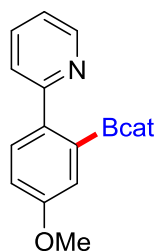^{11}**B NMR** (128 MHz, CDCl$_3$): δ = 13.7.

IR (neat): $\tilde{v}$ = 2974, 1519, 1359, 1318, 1138, 1128, 950, 859 cm^{-1}.

HR-MS (ESI): m/z calcd for C$_{17}$H$_{20}$BNNaO$_2$$^+$ [M+Na$^+$] 304.1479, found 304.1482.
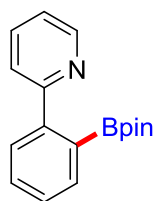
Note: A resonance for the carbon directly attached to the boron atom was not observed.

The analytical data are in accordance with those reported in the literature.[91]

2-{2-(Benzo[*d*][1,3,2]dioxaborol-2-yl)-4-methoxyphenyl}pyridine (70eb)

The general procedure **D** was followed using 2-(4-methoxyphenyl)pyridine (**1e**) (46 mg, 0.25 mmol) and B$_2$cat$_2$ (**62b**) (59 mg, 0.25 mmol) in 1,4-dioxane (1.0 mL). After 20 h, purification by flash column chromatography on silica gel (*n*-hexane/Et$_3$N/EtOAc: 8/2/90). yielded **70eb** (60 mg, 79%) as a grey color solid.

M.p.: 160-162 °C

^{1}H NMR (400 MHz, CDCl$_3$): *δ* = 8.10 (ddd, *J* = 5.6, 1.5, 0.9 Hz, 1H), 7.98 (ddd, *J* = 8.1, 7.5, 1.5 Hz, 1H), 7.74 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.66 (dd, *J* = 8.5, 0.5 Hz, 1H), 7.25 (d, *J* = 2.2 Hz, 1H), 7.20 (ddd, *J* = 7.5, 5.6, 1.1 Hz, 1H), 6.94–6.89 (m, 3H), 6.83–6.78 (m, 2H), 3.86 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): *δ* = 163.4 (C$_q$), 155.7 (C$_q$), 152.3 (C$_q$), 143.5 (CH), 142.2 (CH), 129.9 (C$_q$), 123.4 (CH), 122.1 (CH), 119.5 (CH), 117.2 (CH), 116.7 (CH), 115.3 (CH), 110.3 (CH), 55.6 (CH$_3$).

^{11}B NMR (128 MHz, CDCl$_3$): *δ* = 13.3

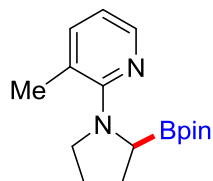**IR** (neat): *ṽ* = 2938, 1611, 1479, 1469, 1348, 1220, 1014, 865, 770 cm^{-1}.

MS (EI) *m/z* (relative intensity) 303 (100) [M$^+$], 302 (29), 288 (25), 260 (25), 259 (24), 230 (9).

HR-MS (EI) *m/z* calcd for C$_{18}$H$_{14}$BNO$_3$ [M$^+$] 303.1067, found 303.1079.

Note: A resonance for the carbon directly attached to the boron atom was not observed.

5.7 Ruthenium-catalyzed C(sp^3)–H bond borylations

Characterization data of products 74

3-Methyl-2-{2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl}pyridine (74aa)

The general procedure **E** was followed using substrate **73a** (81 mg, 0.50 mmol), B$_2$Pin$_2$ (**62a**) (190 mg, 0.75 mmol), in 1,4-dioxane (2 mL). After 16 h, purification by flash column chromatography (EtOAc/NEt$_3$: 98/2) yielded **74aa** (35 mg, 24%) as a brown solid.

M.p: 130-132 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.76 (ddd, J = 6.0, 1.6, 0.7 Hz, 1H), 7.21 (ddd, J = 7.0, 1.6, 0.9 Hz, 1H), 6.43 (dd, J = 7.0, 6.0 Hz, 1H), 3.68 (td, J = 9.1, 1.7 Hz, 1H), 3.24–3.14 (m, 1H), 2.75 (dd, J = 12.2, 6.0 Hz, 1H), 2.21 (s, 3H), 2.06 (dtt, J = 12.0, 6.8, 1.4 Hz, 1H), 1.92 (tddd, J = 12.1, 10.2, 8.8, 6.3 Hz, 1H), 1.80 (dtd, J = 12.4, 6.2, 1.2 Hz, 1H), 1.50 (qd, J = 12.2, 6.6 Hz, 1H), 1.16 (s, 12H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 159.6 (C$_q$), 142.2 (CH), 137.1 (CH), 120.1 (C$_q$), 112.2 (CH), 79.2 (C$_q$), 59.0 (CH), 49.9 (CH$_2$), 29.9 (CH$_2$), 27.4 (CH$_2$), 26.3 (CH$_3$), 18.9 (CH$_3$).

^{11}B NMR (128 MHz, CDCl$_3$): δ = 9.71 (s).

IR (neat): $\tilde{v}$ = 2962, 1619, 1498, 1478, 1240, 1079, 971, 780, 753 cm^{-1}.

HR-MS (ESI): m/z calcd for C$_{16}$H$_{26}$BN$_2$O$_2^+$ [M+H$^+$] 289.2082, found 289.2085

The analytical data are in accordance with those reported in the literature.[92]

Radical scavenger experiments

The general procedure **E** was followed using substrate **73a** (81 mg, 0.50 mmol), B_2Pin_2 (**62a**) (190 mg, 0.75 mmol), and radical scavenger in 1,4-dioxane (2 mL). After 16 h, an aliquot was removed and analyzed by GC and GC-MS with *n*-dodecane as internal standard.

| TEMPO (10 mol %) | : 42% |
| TEMPO (100 mol %) | : 41% |
| Galvinoxyl (100 mol %) | : 56% |
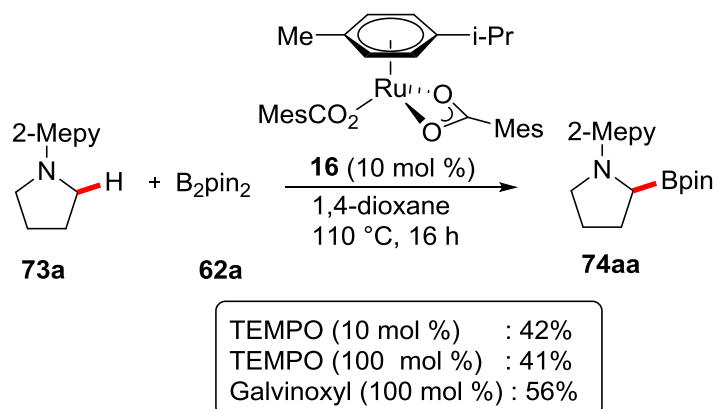
Mercury test

The general procedure **E** was followed using substrate **73a** (81 mg, 0.50 mmol), B_2Pin_2 (**62a**) (190 mg, 0.75 mmol), and Hg (200 mg, 1.00 mmol) in 1,4-dioxane (2.0 mL). After 16 h, an aliquot was removed and analyzed by GC and GC-MS with *n*-dodecane as internal standard. The GC yield of **74aa** was 81%.
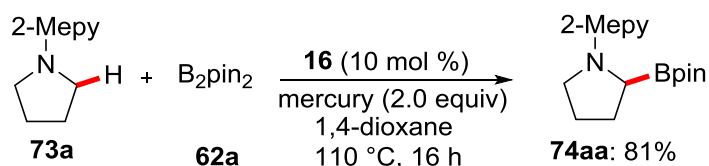
Stoichiometric transformation

B_2pin_2 (**62a**) (13 mg, 0.05 mmol) and [Ru(O$_2$CMes)$_2$(*p*-cymene)] (**16**) (14.0 mg, 0.025 mmol) were placed in a pre-dried pressure tube equipped with a rubber septum. The tube was evacuated and flushed with N_2 three times and 1,4-dioxane (0.3 mL) was added and the reaction mixture was stirred at 110 °C for 4 h and then **73a** (4.0 mg, 0.025 mmol) was added to the reaction mixture under N_2 atmosphere.

The rubber septum was replaced by the pressure tube screw cap, stirring was continued at 110 °C for 12 h and analyzed by GC and GC-MS with *n*-dodecane as internal standard. The GC yield of **74aa** was 16%.
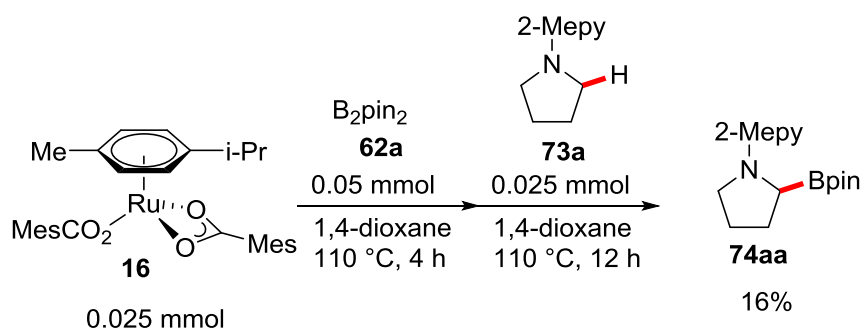
Reaction with cycloruthentaed complex 82

The general procedure **D** was followed using 2-(4-methoxyphenyl)pyridine (**1e**) (46 mg, 0.25 mmol), B_2cat_2 (**62b**) (59 mg, 0.25 mmol) and cycloruthenated compled (**82**) (7 mg, 5.0 mol %) in 1,4-dioxane (1.0 mL). After 20 h, purification by column chromatography on silica gel (*n*-hexane/Et$_3$N/EtOAc: 8/2/90) yielded **70eb** (62 mg, 82%) was obtained as a grey color solid.
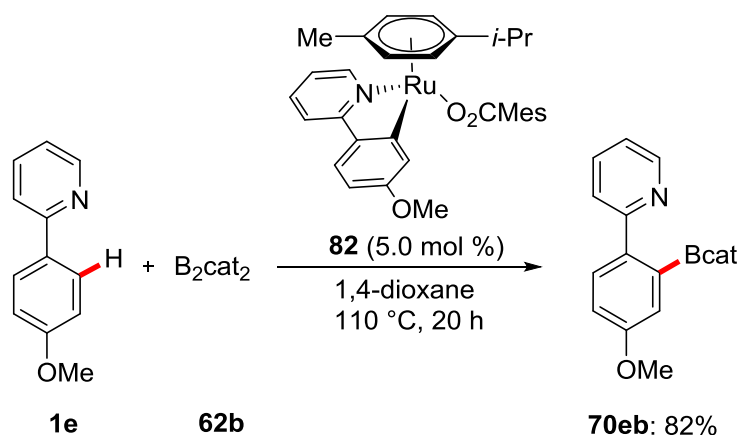
References

[1] a) K. P. de Jong, *Catal. Today* **1996**, *29*, 171-178; b) R. A. Sheldon, *Pure Appl. Chem.* **2000**, *72;* 1233-1246; c) R. A. Sheldon, *Chem. Commun.* **2008**, *29*, 3352-3356; d) C. A. Busacca, D. R. Fandrick, J. J. Song, C. H. Senanayake, *Adv. Synth. Catal.* **2011**, *353*, 1825-1864, and references cited therein.

[2] Data obtained from https://www.nobelprize.org/ on 05-10-16.

[3] General reviews on C–H activation: a) R. G. Bergman, *Nature* **2007**, *446*, 391-393; b) L. Ackermann, R. Vicente, A. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826; c) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242-3272; d) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212-11222; e) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960-9009; f) D. Y. K. Chen, S. W. Youn, *Chem. Eur. J.* **2012**, *18*, 9452-9474; g) J. Schranck, A. Tlili, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 9426-9428; h) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74-100; i) N. Kuhl, N. Schroeder, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 1443-1460; j) O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* **2015**, *48*, 1053-1064; k) Y. Segawa, T. Maekawa, K. Itami, *Angew. Chem. Int. Ed.* **2015**, *54*, 66-81; l) C. Borie, L. Ackermann, M. Nechab, *Chem. Soc. Rev.* **2016**, 1368-1386; m) J. K. Kim, K. Shin, S. Chang, *Top. Organomet. Chem.* **2016**, *55*, 29-51; n) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546-576; o) T. Gensch, M. N. Hopkinson, F. Glorius, J. Wencel-Delord, *Chem. Soc. Rev.* **2016**, *45*, 2900-2936; p) W. Liu, L. Ackermann, *ACS Catal.* **2016**, *6*, 3743-3752; q) M. Moselage, J. Li, L. Ackermann, *ACS Catal.* **2016**, *6*, 498-525, and references cited therein.

[4] a) L. Ackermann, *Top. Organomet. Chem.* **2007**, *24*, 35-60; b) G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **2011**, *50*, 2450-2494; c) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726-11743; d) G. Shi, Y. Zhang, *Adv. Synth. Catal.* **2014**, *356*, 1419-1442; e) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107-1295; f) L. Ackermann, J. Li, *Nat. Chem.* **2015**, *7*, 686-687; g) H. Tang, X.-R. Huang, J. Yao, H. Chen, *J. Org. Chem.* **2015**, *80*, 4672-4682; h) M. R. Yadav, R. K. Rit, M. Shankar, A. K. Sahoo, *Asian J. Org. Chem.* **2015**, *4*, 846-864; i) J. Li, S. De Sarkar, L. Ackermann, *Top. Organomet. Chem.* **2016**, *55*, 217-257; j) A. Dey, S. Agasti, D. Maiti, *Org. Biomol. Chem.* **2016**, *14*, 5440-5453.

[5] Prices of metals as of 12.09.2015 obtained from http://www.infomine.com/

[6]   For ruthenium catalyzed C–H bond functionalization reviews see: a) L. Ackermann, R. Vicente, *Top. Curr. Chem.* **2010***, 292*, 211-229; b) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879-5918; c) L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281-295; d) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356,* 1461-1479; e) V. S. Thirunavukkarasu, S. I. Kozhushkov, L. Ackermann, *Chem. Commun.* **2014**, *50*, 29-39; f) L. Ackermann, *Org. Process Res. Dev.* **2015**, *19*, 260-269; g) S. Ruiz, P. Villuendas, E. P. Urriolabeitia, *Tetrahedron Lett.* **2016**, *57*, 3413-3432, and references cited therein. For ruthenium catalyzed C– H bond functionalization using bidentate directing groups: h) K. Shibata, N. Hasegawa, Y. Fukumoto, N. Chatani, *ChemCatChem* **2012**, *4*, 1733-1736; i) Y. Aihara, N. Chatani, *Chem. Sci.* **2013**, *4*, 664-670; j) G. Rouquet, N. Chatani, *Chem. Sci.* **2013**, *4*, 2201-2208; k) H. H. Al Mamari, E. Diers, L. Ackermann, *Chem. Eur. J.* **2014**, *20*, 9739-9743.

[7]   a) Y. Boutadla, D. L. Davies, S. A. Macgregor, A. I. Poblador-Bahamonde, *Dalton Transactions* **2009**, 5820; b) J. A. Labinger, J. E. Bercaw, *Nature* **2002,** *417*, 507-514.

[8]   a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457-2483; b) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633-9695; c) R. Rossi, F. Bellina, A. Carpita, *Synthesis* **2004**, *2004*, 2419-2440; d) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461-1473.

[9]   C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335-344, and references cited therein.

[10]   L. Ackermann, R. Vicente, A. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826.

[11]   S. Oi, S. Fukita, N. Hirata, N. Watanuki, S. Miyano, Y. Inoue, *Org. Lett.* **2001**, *3*, 2 579-2581.

[12]   S. Oi, Y. Ogino, S. Fukita, Y. Inoue, *Org. Lett.* **2002**, *4*, 1783-1785.

[13]   S. Oi, E. Aizawa, Y. Ogino, Y. Inoue, *J. Org. Chem.* **2005***, 70,* 3113-3119.

[14]   S. p. G. Ouellet, A. I. Roy, C. Molinaro, R. m. Angelaud, J.-F. o. Marcoux, P. D. O'Shea, I. W. Davies, *J. Org. Chem.* **2011**, *76*, 1436-1439.

[15]   L. Ackermann, *Org. Lett.* **2005**, *7*, 3123-3125.

[16]   L. Ackermann, A. Althammer, R. Born, *Angew. Chem. Int. Ed.* **2006**, *45*, 2619-2622.

[17]   L. Ackermann, R. Vicente, A. Althammer, *Org. Lett.* **2008**, *10*, 2299-2302.

[18]   L. Ackermann, R. Vicente, H. K. Potukuchi, V. Pirovano, *Org. Lett.* **2010**, *12*, 5032-5035.

[19]   a) L. Ackermann, P. Novák, R. Vicente, N. Hofmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 6045-6048; b) L. Ackermann, *Chem. Commun.* **2010**, *46*, 4866-4877; c) L. Ackermann, N. Hofmann, R. Vicente, *Org. Lett.* **2011**, *13*, 1875-1877; d) N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.* **2013**, *135*, 5877-5884; e) J. Li, S. Warratz, D. Zell, S. De Sarkar, E. E. Ishikawa, L. Ackermann, *J. Am. Chem. Soc.* **2015**, *137*, 13894-13901.

[20]   a) J. V. Duncia, A. T. Chiu, D. J. Carini, G. B. Gregory, A. L. Johnson, W. A. Price, G. J. Wells, P. C. Wong, J. C. Calabrese, P. B. M. W. M. Timmermans, *J. Med. Chem.* **1990**, *33*, 1312-1329; b) K. Kubo, Y. Kohara, Y. Yoshimura, Y. Inada, Y. Shibouta, Y. Furukawa, T. Kato, K. Nishikawa, T. Naka, *J. Med. Chem.* **1993**, *36*, 2343-2349; c) P. Bühlmayer, P. Furet, L. Criscione, M. de Gasparo, S. Whitebread, T. Schmidlin, R. Lattmann, J. Wood, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 29-34; d) J. H. Kim, J. H. Lee, S. H. Paik, J. H. Kim, Y. H. Chi, *Arch. Pharmacal Res.* **2012**, *35*, 1123-1126.

[21]   G.-x. Wang, B.-p. Sun, C.-h. Peng, *Org. Process Res. Dev.* **2011,** *15*, 986-988.

[22]   a) R. D. Larsen, A. O. King, C. Y. Chen, E. G. Corley, B. S. Foster, F. E. Roberts, C. Yang, D. R. Lieberman, R. A. Reamer, D. M. Tschaen, T. R. Verhoeven, P. J. Reider, Y. S. Lo, L. T. Rossano, A. S. Brookes, D. Meloni, J. R. Moore, J. F. Arnett, *J. Org. Chem.* **1994**, *59*, 6391-6394; b) V. Pandarus, D. Desplantier-Giscard, G. Gingras, F. Béland, R. Ciriminna, M. Pagliaro, *Org. Process Res. Dev.* **2013**, *17*, 1492-1497.

[23]   M. Seki, M. Nagahama, *J. Org. Chem.* **2011**, *76*, 10198-10206.

[24]   S. p. G. Ouellet, A. I. Roy, C. Molinaro, R. m. Angelaud, J.-F. o. Marcoux, P. D. O'Shea, I. W. Davies, *J. Org. Chem.* **2011**, *76*, 1436-1439.

[25]   a) L. Ackermann, R. Vicente, A. Althammer, *Org. Lett.* **2008**, *10*, 2299-2302; b) L. Ackermann, R. Vicente, H. K. Potukuchi, V. Pirovano, *Org. Lett.* **2010**, *12*, 5032-5035; c) L. Ackermann, A. V. Lygin, *Org. Lett.* **2011**, *13*, 3332-3335; d) L. Ackermann, E. Diers, A. Manvar, *Org. Lett.* **2012**, *14*, 1154-1157.

[26]   a) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654-2672; b) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902-4911.

[27]   M. D. Moen, S. J. Keam, *CNS Drugs* **2009**, *23*, 1057-1083.

[28]   a) S. Jolidon, D. Alberati, A. Dowle, H. Fischer, D. Hainzl, R. Narquizian, R. Norcross, E. Pinard, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5533-5536; b) K.-S. Song, S.-H. Lee, H. J. Chun, J. Y. Kim, M. E. Jung, K. Ahn, S.-U. Kim, J. Kim, J. Lee, *Biorg. Med. Chem.* **2008**, *16*, 4035-4051; c) J. P. McCauley, C. L. Dantzman, M. M. King,

G. E. Ernst, X. Wang, K. Brush, W. E. Palmer, W. Frietze, D. W. Andisik, V. Hoesch, K. Doring, J. Hulsizer, K. H. Bui, J. Liu, T. J. Hudzik, S. S. Wesolowski, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1169-1173.

[29]   M. Gillard, *Mol. Pharmacol.* **2002**, *61*, 391-399.

[30]   S. S. Bilge, A. Bozkurt, F. İlkaya, E. Çiftcioğlu, Y. Kesim, T. I. Uzbay, *Eur. J. Pharmacol.* **2012**, *681*, 44-49.

[31]   a) S. J. Pastine, D. V. Gribkov, D. Sames, *J. Am. Chem. Soc.* **2006**, *128*, 14220-14221; b) D. V. Gribkov, S. J. Pastine, M. Schnürch, D. Sames, *J. Am. Chem. Soc.* **2007**, *129*, 11750-11755.

[32]   H. Prokopcová, S. D. Bergman, K. Aelvoet, V. Smout, W. Herrebout, B. Van der Veken, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2010**, *16*, 13063-13067.

[33]   N. Dastbaravardeh, M. Schnürch, M. D. Mihovilovic, *Org. Lett.* **2012**, *14*, 1930-1933.

[34]   N. Dastbaravardeh, M. Schnürch, M. D. Mihovilovic, *Org. Lett.* **2012**, *14*, 3792-3795.

[35]   a) A. Nitzsche, S. V. Tokalov, H. O. Gutzeit, J. Ludwig-Müller, *J. Agric. Food. Chem.* **2004**, *52*, 2915-2923; b) B. S. Siddiqui, H. Aslam, S. Begum, S. T. Ali, *Nat. Prod. Res.* **2007**, *21*, 736-741.

[36]   a) M. M. da Silva Paula, C. V. Franco, M. C. Baldin, L. Rodrigues, T. Barichello, G. D. Savi, L. F. Bellato, M. A. Fiori, L. da Silva, *Mater. Sci. Eng; C,* **2009**, *29*, 647-650; b) Q. Jiang, Z. Lei, *Biotechnol. Bioproc. E.* **2011**, *16*, 1187-1195.

[37]   a) B. Narasimhan, D. Belsare, D. Pharande, V. Mourya, A. Dhake, *Eur. J. Med. Chem.* **2004**, *39*, 827-834; b) J. Cheel, C. Theoduloz, J. Rodríguez, G. Saud, P. D. S. Caligari, G. Schmeda-Hirschmann, *J. Agric. Food. Chem.* **2005**, *53*, 8512-8518; c) M. Sova, *Mini Rev. Med. Chem.* **2012**, *12*, 749-767.

[38]   F. Kakiuchi, Y. Yamamoto, N. Chatani, S. Murai, *Chem. Lett.* **1995**, *24*, 681-682.

[39]   Y. Hashimoto, K. Hirano, T. Satoh, F. Kakiuchi, M. Miura, *Org. Lett.* **2012**, *14*, 2058-2061.

[40]   a) Y. Hashimoto, K. Hirano, T. Satoh, F. Kakiuchi, M. Miura, *J. Org. Chem.* **2013**, *78*, 638-646; b) M. Itoh, Y. Hashimoto, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2013**, *78*, 8098-8104; c) C. Suzuki, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2013**, *15*, 3990-3993.

[41]   a) M. C. Reddy, M. Jeganmohan, *Chem. Commun.* **2013**, *49*, 481-483; b) R. Manikandan, M. Jeganmohan, *Org. Lett.* **2014**, *16*, 912-915; c) K. Padala, M. Jeganmohan, *Chem. Commun.* **2014**, *50*, 14573-14576.

[42]   a) L. Ackermann, A. V. Lygin, *Org. Lett.* **2011**, *13*, 3332-3335; b) L. Ackermann, A. V. Lygin, *Org. Lett.* **2012**, *14*, 764-767.

[43]   L. Liang, S. Fu, D. Lin, X.-Q. Zhang, Y. Deng, H. Jiang, W. Zeng, *J. Org. Chem.* **2014**, *79*, 9472-9480.

[44]   X. G. Li, K. Liu, G. Zou, P. N. Liu, *Eur. J. Org. Chem.* **2014**, *2014*, 7878-7888.

[45]   P. Villuendas, E. P. Urriolabeitia, *Org. Lett.* **2015**, *17*, 3178-3181.

[46]   R. Karmakar, P. Pahari, D. Mal, *Chem. Rev.* **2014**, *114*, 6213-6284.

[47]   A. Bechtoldt, C. Tirler, K. Raghuvanshi, S. Warratz, C. Kornhaaß, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 264-267.

[48]   a) S. Warratz, C. Kornhaaß, A. Cajaraville, B. Niepötter, D. Stalke, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 5513-5517. For representative publications on biological activity of isocoumarins: b) M. Hussain, M. T. Hussain, N. H. Rama, S. Hameed, A. Malik, K. M. Khan, *Nat. Prod. Res.* **2003**, *17*, 207-214; c) S. Pal, V. Chatare, M. Pal, *Curr. Org. Chem.* **2011**, *15*, 782-800; d) M. Simic, N. Paunovic, I. Boric, J. Randjelovic, S. Vojnovic, J. Nikodinovic-Runic, M. Pekmezovic, V. Savic, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 235-239.

[49]   C.-J. Li, P. T. Anastas, *Chem. Soc. Rev.* **2012**, *41*, 1413-1414.

[50]   a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457-2483; b) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147-168; c) S. Darses, J.-P. Genet, *Eur. J. Org. Chem.* **2003**, *2003*, 4313-4327; d) G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275-286.

[51]   a) J. Adams, *Drug Discovery Today* **2003**, *8*, 307-315; b) J. Adams, M. Kauffman, *Cancer Invest.* **2009**, *22*, 304-311; c) P. Moreau, T. Masszi, N. Grzasko, N. J. Bahlis, M. Hansson, L. Pour, I. Sandhu, P. Ganly, B. W. Baker, S. R. Jackson, A.-M. Stoppa, D. R. Simpson, P. Gimsing, A. Palumbo, L. Garderet, M. Cavo, S. Kumar, C. Touzeau, F. K. Buadi, J. P. Laubach, D. T. Berg, J. Lin, A. Di Bacco, A.-M. Hui, H. van de Velde, P. G. Richardson, *New Engl. J. Med.* **2016**, *374*, 1621-1634.

[52]   a) T. K. Liao, E. G. Podrebarac, C. C. Cheng, *J. Am. Chem. Soc.* **1964**, *86*, 1869-1870; b) R. R. Srivastava, G. W. Kabalka, *J. Org. Chem.* **1997**, *62*, 8730-8734; c) M. F. Hawthorne, *Mol. Med. Today* **1998**, *4*, 174-181.

[53]   P. Andrés, G. Ballano, M. I. Calaza, C. Cativiela, *Chem. Soc. Rev.* **2016**, *45*, 2291-2307.

[54]   a) W. Seaman, J. R. Johnson, *J. Am. Chem. Soc.* **1931**, *53*, 711-723; b) F. R. Bean, J. R. Johnson, *J. Am. Chem. Soc.* **1932**, *54*, 4415-4425; c) M. J. Sharp, V. Snieckus, *Tetrahedron Lett.* **1985**, *26*, 5997-6000; d) M. J. Sharp, W. Cheng, V. Snieckus, *Tetrahedron Lett.* **1987**, *28*, 5093-5096.

[55]   T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508-7510.

[56]   J. F. Hartwig, *Acc. Chem. Res.* **2012,** *45*, 864-873.

[57]   A. Ros, R. Fernández, J. M. Lassaletta, *Chem. Soc. Rev.* **2014,** *43*, 3229-3243, and references cited therein.

[58]   J. M. Murphy, J. D. Lawrence, K. Kawamura, C. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 13684-13685.

[59]   . Battagliarin, C. i ,   . Enkelmann, K. M ll en, *Org. Lett.* **2011**, *13*, 3012-3015.

[60]   J. A. Fernández-Salas, S. Manzini, L. Piola, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2014**, *50*, 6782-6784.

[61]   The cost of complex [RuCl(PPh$_3$)$_2$(3-phenylindenyl)] is 225 Euro/gm as per Strem Chemicals.

[62]   S. Okada, T. Namikoshi, S. Watanabe, M. Murata, *ChemCatChem* **2015**, *7*, 1531-1534.

[63]   L. Ackermann, R. Vicente, A. Althammer, *Org. Lett.* **2008**, *10*, 2299-2302.

[64]   a) L. Ackermann, J. Pospech, *Org. Lett.* **2011**, *13*, 4153-4155; b) L. Ackermann, J. Pospech, K. Graczyk, K. Rauch, *Org. Lett.* **2012**, *14*, 930-933.

[65]   a) S. M. Bonesi, M. Fagnoni, *Chem. Eur. J.* **2010**, *16*, 13572-13589; b) N. Rodríguez, L. J. Goossen, *Chem. Soc. Rev.* **2011**, *40*, 5030-5048; c) W. I. Dzik, P. P. Lange, L. J. Gooßen, *Chem. Sci.* **2012**, *3*, 2671-2678.

[66]   a) D. H. Wang, K. M. Engle, B. F. Shi, J. Q. Yu, *Science* **2009**, *327*, 315-319; b) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518-522; c) H.-X. Dai, G. Li, X.-G. Zhang, A. F. Stepan, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 7567-7571; d) M. Bera, A. Modak, T. Patra, A. Maji, D. Maiti, *Org. Lett.* **2014**, *16*, 5760-5763; e) A. Deb, S.

Bag, R. Kancherla, D. Maiti, *J. Am. Chem. Soc.* **2014**, *136*, 13602-13605; f) R.-Y. Tang, G. Li, J.-Q. Yu, *Nature* **2014**, *507*, 215-220; g) G. Yang, P. Lindovska, D. Zhu, J. Kim, P. Wang, R.-Y. Tang, M. Movassaghi, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 10807-10813; h) Y.-F. Yang, G.-J. Cheng, P. Liu, D. Leow, T.-Y. Sun, P. Chen, X. Zhang, J.-Q. Yu, Y.-D. Wu, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 344-355; i) M. Bera, A. Maji, S. K. Sahoo, D. Maiti, *Angew. Chem. Int. Ed.* **2015**, *54*, 8515-8519; j) L. Chu, M. Shang, K. Tanaka, Q. Chen, N. Pissarnitski, E. Streckfuss, J.-Q. Yu, *ACS Cent. Sci.* **2015**, *1*, 394-399; k) Y. Deng, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2015**, *54*, 888-891; l) M. Bera, S. K. Sahoo, D. Maiti, *ACS Catal.* **2016**, *6*, 3575-3579; m) A. Dey, S. Agasti, D. Maiti, *Org. Biomol. Chem.* **2016**, *14*, 5440-5453; n) A. Maji, B. Bhaskararao, S. Singha, R. B. Sunoj, D. Maiti, *Chem. Sci.* **2016**, *7*, 3147-3153; o) T. Patra, S. Bag, R. Kancherla, A. Mondal, A. Dey, S. Pimparkar, S. Agasti, A. Modak, D. Maiti, *Angew. Chem. Int. Ed.* **2016**, *55*, 7751-7755; p) T. Patra, R. Watile, S. Agasti, T. Naveen, D. Maiti, *Chem. Commun.* **2016**, *52*, 2027-2030.

[67]   I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890-931.

[68]   E. Diers (2015). *Ruthenium-Catalyzed Synthesis of Biaryls through C–H Bond Functionalizations.* (Doctoral thesis, Georg-August-Universität Göttingen, Göttingen, Germany).

[69]   a) D. Zell, S. Warratz, D. Gelman, S. J. Garden, L. Ackermann, *Chem. Eur. J.* **2016**, *22*, 1248-1252; b) J. Hubrich, L. Ackermann, *Eur. J. Org. Chem.* **2016**, *2016*, 3700-3704.

[70]   a) J. E. Klijn, J. B. F. N. Engberts, *Nature* **2005**, *435*, 746-747; b) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095-3166; c) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2005**, *44*, 3275-3279; d) Y. Hayashi, *Angew. Chem. Int. Ed.* **2006**, *45*, 8103-8104; e) C.-J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68-82.

[71]   S. R. Goldstein, S. Siddhanti, A. V. Ciaccia, L. Plouffe, *Hum. Reprod. Update* **2000**, *6*, 212-224.

[72]   M. A. Larsen, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 4287-4299.

[73]   For palladium catalyzed C–H borylations: a) H.-X. Dai, J.-Q. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 134-137; b) B. Xiao, Y.-M. Li, Z.-J. Liu, H.-Y. Yang, Y. Fu, *Chem. Commun.* **2012**, *48*, 4854-4856; c) Y. Kuninobu, T. Iwanaga, T. Omura, K. Takai, *Angew. Chem. Int. Ed.* **2013**, *52*, 4431-4434; d) L.-S. Zhang, G. Chen, X. Wang, Q.-

Y. Guo, X.-S. Zhang, F. Pan, K. Chen, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2014**, *53*, 3899-3903; e) J. He, H. Jiang, R. Takise, R.-Y. Zhu, G. Chen, H.-X. Dai, T. G. M. Dhar, J. Shi, H. Zhang, P. T. W. Cheng, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2016**, *55*, 785-789.

[74]   a) C. N. Iverson, M. R. Smith, *J. Am. Chem. Soc.* **1999**, *121*, 7696-7697; b) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 390-391.

[75]   Kuninobu, Y.; Iwanaga, T.; Omura, T.; Takai, K., *Angew. Chem. Int. Ed.* **2013,** *52*, 4431-4434.

[76]   a) G. M. Whitesides, M. Hackett, R. L. Brainard, J. P. P. M. Lavalleye, A. F. Sowinski, A. N. Izumi, S. S. Moore, D. W. Brown, E. M. Staudt, *Organometallics* **1985**, *4*, 1819-1830; b) L. N. Lewis, *Chem. Rev.* **1993**, *93*, 2693-2730; c) R. H. Crabtree, *Chem. Rev.* **2012**, *112*, 1536-1554; d) J. F. Sonnenberg, R. H. Morris, *Catal. Sci. Technol.* **2014**, *4*, 3426-3438.

[77]   N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.* **2013**, *135*, 5877-5884.

[78]   Y.-J. Ding, Y. Li, S.-Y. Dai, Q. Lan, X.-S. Wang, *Org. Biomol. Chem.* **2015**, *13*, 3198-3201.

[79]   E. Diers, N. Y. P. Kumar, T. Mejuch, I. Marek, L. Ackermann, *Tetrahedron* **2013**, *69*, 4445-4453.

[80]   a) D. Zell, S. Warratz, D. Gelman, S. J. Garden, L. Ackermann, *Chem. Eur. J.* **2016**, *22*, 1248-1252; b) J. Hubrich, L. Ackermann, *Eur. J. Org. Chem.* **2016**, *2016*, 3700-3704.

[81]   N. Y. P. Kumar, R. Jeyachandran, L. Ackermann, *J. Org. Chem.* **2013**, *78*, 4145-4152.

[82]   N. Y. P. Kumar, A. Bechtoldt, K. Raghuvanshi, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 6929-6932.

[83]   a) R. Robinson, *J. Chem. Soc., Trans.* **1917**, *111*, 762-768; b) L. F. Tietze, U. Beifuss, *Angew. Chem. Int. Ed.* **1993**, *32*, 131-163; c) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115-136.

[84]   M. Seki, M. Nagahama, *J. Org. Chem.* **2011**, *76*, 10198-10206.

[85]   N. Dastbaravardeh, K. Kirchner, M. Schnürch, M. D. Mihovilovic, *J. Org. Chem.* **2013**, *78*, 658-672.

[86] N. Dastbaravardeh, M. Schnürch, M. D. Mihovilovic, *Org. Lett.* **2012**, *14*, 1930-1933.

[87] X. Xu, J. Chen, W. Gao, H. Wu, J. Ding, W. Su, *Tetrahedron* **2010**, *66*, 2433-2438.

[88] B.-J. Li, Y.-Z. Li, X.-Y. Lu, J. Liu, B.-T. Guan, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2008**, *47*, 10124-10127.

[89] D. Xu, C. Lu, W. Chen, *Tetrahedron* **2012**, *68*, 1466-1474.

[90] S. Kawamorita, T. Miyazaki, H. Ohmiya, T. Iwai, M. Sawamura, *J. Am. Chem. Soc.* **2011**, *133*, 19310-19313.

[91] S. Okada, T. Namikoshi, S. Watanabe, M. Murata, *ChemCatChem* **2015**, *7*, 1531-1534.

[92] S. Kawamorita, T. Miyazaki, T. Iwai, H. Ohmiya, M. Sawamura, *J. Am. Chem. Soc.* **2012**, *134*, 12924-12927.

Acknowledgements

Kanagaraj, Dr. Ravi, Dr. Penchu, Dr. Megha Joshi Yadav for their professional advice and hospitality.

Last, but not least my gratitude would go to my beloved family and friends for their love and understanding.

"A scientist in his laboratory is not a mere technician: he is also a child confronting natural phenomena that impress him as though they were fairy tales"- **Marie Curie**

I did find fairy tales.

svasti prajabhya: paripalayantham nyayeana margena mahim maheesah

gobrahmanebhya shubamsthu nityam lokah samastha sukhino bhavanthu