Ruthenium- and Cobalt-Catalyzed C–H Activation

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Contents

Abbreviations

Ac	acetyl
Ad	adamantyl
Alk	alkyl
Aq.	aqueous
Ar	aryl
atm	atmospheric pressure
ATR	attenuated total reflectance
BIES	base-assisted internal electrophilic substitution
Bn	benzyl
Bu	butyl
cat	catalytic
CMD	concerted metalation-deprotonation
conv.	conversion
Cp	cyclopentadienyl
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
Cy	cyclohexyl
δ	chemical shift
δ	doublet
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublet
DFT	density functional theory
DG	directing group
DMA	*N*,*N*-dimethylformamide
DMF	*N*,*N*-dimethylacetamide
DMSO	Dimethylsulfoxide

dt	doublet of triplet
EDG	electron-donating group
EI	electron ionization
equiv	equivalents
ESI	electronspray ionization
Et	ethyl
EWG	electron-withdrawing group
FG	functional group
g	gram
GC-MS	gas chromatography-mass spectrometry
GVL	γ-valerolactone
h	hour
Het	hetero(aryl)
Hept	heptyl
Hex	hexyl
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
i	*iso*
IES	internal electrophilic substitution
IR	infrared
J	coupling constant
KIE	kinetic isotope effect
L	ligand
m	*meta*
m	multiplet
M	metal

Abbreviations

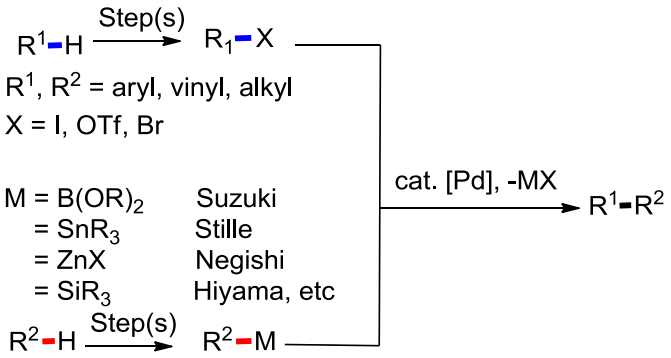
$[M]^+$	molecular ion peak
Me	methyl
Mes	2,4,6-trimethylphenyl
Mg	Milligram
MHz	megahertz
mL	milliliter
mmol	millimol
M.p.	melting point
MS	mass spectrometry
m/z	mass-to-charge ratio
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
o	*ortho*
P	*para*
P	$PhI(TFA)_2$
PEG	polyethylene glycol
Ph	phenyl
Piv	2,2-dimethylpropanoyl
ppm	parts per million
pKa	logarithmic acid dissociation constant
Pr	propyl
py	pyridine
AQ	aminoquinolin
Q	Quartet
ref.	reference
RT	room temperature
s	singlet

sat.	saturated
t	*tert*
t	triplet
T	temperature
t-Am	tert-Amyl
Tf	trifluoromethanesulfonyl
TFE	2,2,2,-trifluoroethanol
TFA	trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	tetrahydrofuran
TM	transition metal
TS	transition state
Ts	tosyl
X	(pseudo)halide

1 Introduction

1.1 Transition Metal-Catalyzed C–H Functionalizations

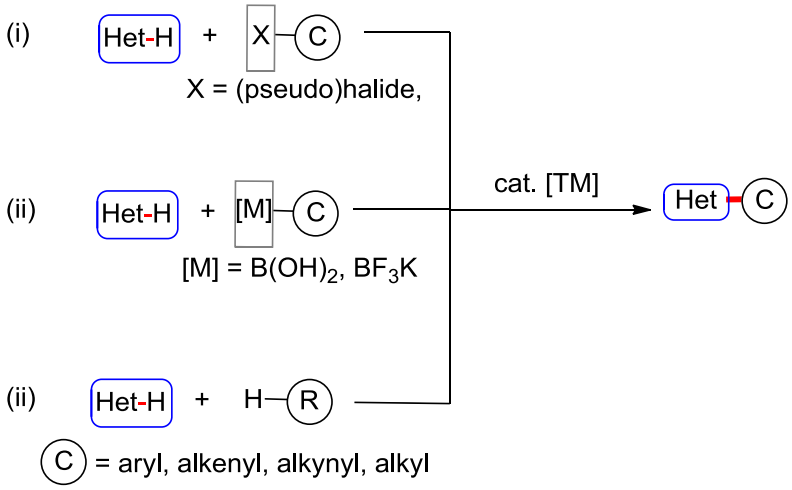
Carbon–carbon (C−C) and carbon–heteroatom (C−X) bonds are the basis of organic molecules in medicinal agents, functional materials, and natural products.[1] Therefore, many organic chemists have focused on the development of novel methods for the construction of these bonds. In the past few decades, transition metal-catalyzed transformations, such as cross-coupling reactions, became one of the most powerful and reliable tools for the formation of C–C and C–X bonds (Scheme 1).[2] In particular, the importance of this class of reactions was recognized with the Nobel Prize for Chemistry in 2010, the Mizoroki–Heck reaction,[3] the Negishi coupling,[4] and the Suzuki-Miyaura coupling.[5] Despite the indisputable advances, the major drawback of cross-coupling reactions is the necessity for pre-activation of both reactive components, which add costly chemical steps to the overall synthesis. Inspired by the need for green and sustainable chemistry, synthetic chemists hence seek more efficient ways to construct C−C and C−X bonds.



Scheme 1. Palladium-catalyzed cross-coupling reactions.

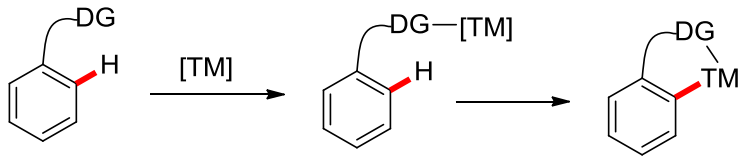
Recently, transition metal-catalyzed C−H bond activation has emerged as an attractive alternative for C−C and C−X bond formation. This approach avoids the need of prefunctionalization of starting materials, and reduces or eliminates salt wastes, which result in high atom- and step-economy. Various transition metal catalysts such as palladium,[6] ruthenium,[7] rhodium,[8] copper,[9] iridium,[10] manganese,[11] and others,[12] have made a significant progress in enhancing the efficiency of C–H bond transformation of heteroaromatic compounds. The direct C–H bond functionalization of

heterocycles can be arbitrarily classified into the following three general types (Scheme 2): (i) coupling of heteroarenes with electrophilic reactants, such as aryl-, alkyl-, alkenyl-, or alkynyl (pseudo)halides,[13] (ii) reactions of heteroarenes with nucleophilic coupling partners, including aryl-, alkyl-, or alkenyl boronic acids,[14] and (iii) cross-dehydrogentative couplings of heteroarenes with either another type of heteroarenes or hydrocarbons, including arenes, alkenes, alkynes, or alkanes.[15]



Scheme 2. The general methods for C–C/C–Het formation.

The challenges in transition metal-catalyzed C−H activation chemistry are mostly the chemo- and site-selectivities. Site selectivity can be controlled by the close proximity of C–H bonds to the reactive metal center. In the most cases, this is achieved by the introduction of directing group into the substrate core, which contains heteroatoms able to coordinate to metal center. The interaction of substrates and catalyst is then promoted through the coordination of heteroatoms to the transition metal catalysts (Scheme 3).[16] Consequently, coordination of transition metals with directing groups, namely the chelation-assisted C–H activation strategy, is usually considered as an essential step involved in these catalytic C–H bond activation processes.



Scheme 3. Site-selective C–H activation by chelation-assistance.

Various functional groups, including amide,[17] anilide,[18] imine,[19] heterocycles,[20] as well as weakly coordinating functional group, like carboxylic acid,[21] ester,[22] ketone,[23] and hydroxyl groups,[24] have been employed as directing groups for catalytic C–H bond activation (Figure 1).

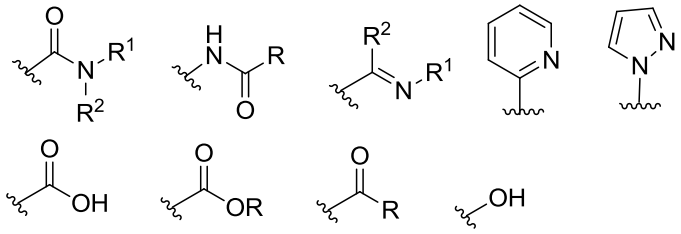


Figure 1. Selected examples of important directing groups employed in C–H activation reactions.

1.2 Ruthenium-Catalyzed C–H Functionalizations

In the past decades, the catalytic functionalization of C−H bonds has emerged as a powerful tool for the production of pharmaceuticals and natural products and also it opened new routes for synthesis of materials and polymers.[25] The regioselective direct transformation of C−H bonds to C−C bonds offers a unique opportunity to replace the classical catalytic cross-coupling reactions.[3, 5b, 26] Tremendous progress has been made in transition metal-catalysed C−H activation, most notably in the area of palladium and rhodium catalysis.[6c, 8c] Futermore, inexpensive ruthenium complexes (Figure 2) also have been widely explored for efficient catalytic conversion of C−H bonds.[7c, 27]

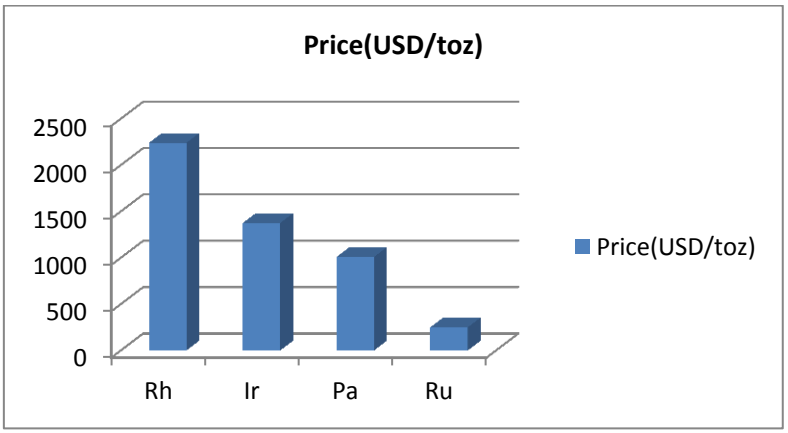
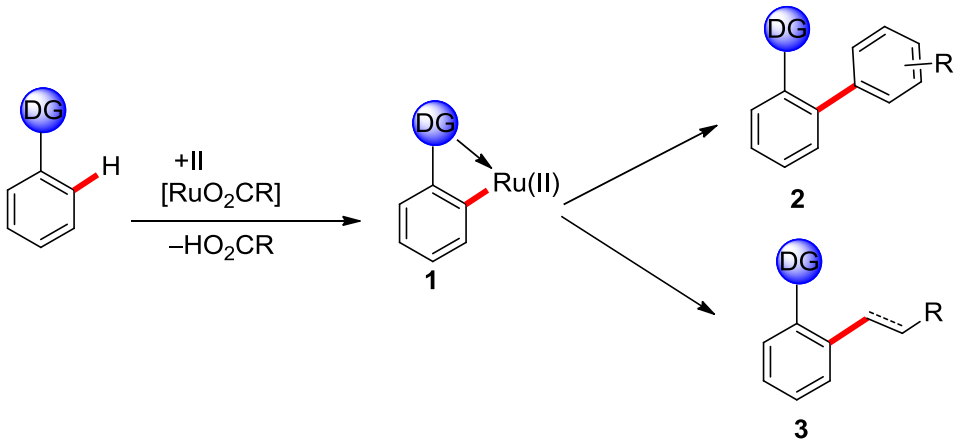


Figure 2. The prices of transition metals in 06.2018.

For example, the inert C(sp^2)−H bonds have been successfully functionalized by inexpensive and active ruthenium(0) catalyst [$RuH_2(CO)(PCy_3)_2$].[28] It was shown that an organometallic ruthenium complex can insert into C−H bonds to generate a reactive C−Ru−H species via unsaturated substrate insertion processes. Versatile ruthenium(II) complexes have also been employed as the catalysts in C−H activation transformations. The major contribution into this area have made by the Ackermann group, they focused on the application of ruthenium(II) complexes for C–H bond activations,[29] following the pioneering but not robust work of Oi and Inoune in 2001.[30] The ruthenium(II)-catalyzed C–H activation procceeds *via* a chelation-assisted C–H metalation to deliver cyclometalated ruthenium(II) complex **1**.[31] Then, further activation steps for C–H activation *via* oxidative addition of organohalides or insertion of unsaturated substrates delivered the products **2** or **3** respectively (Scheme 4).[27a, 32]



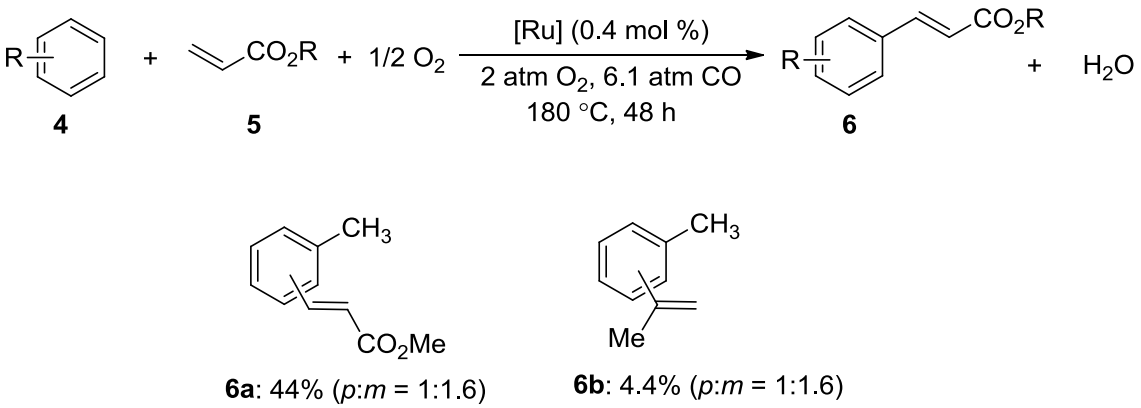
Scheme 4. Ruthenium-catalyzed C–H activation.

1.2.1 Ruthenium Catalyzed C–H Alkenylation

Styrene derivatives are useful intermediates in synthetic organic chemistry.[33] They can be obtained by Mizoroki-Heck reaction between arylhalides and alkenes in the presence of a palladium catalyst and base.[15a] In the most atom- and step-economical fashion, synthesis of alkenylarenes can be achieved by a C–H activation reaction.

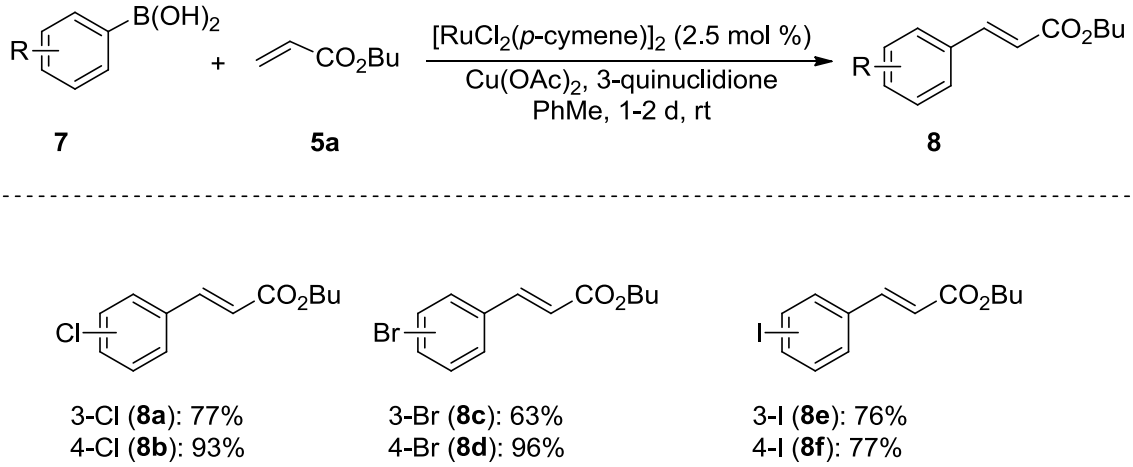
Based on an early report by Fujiwara and Moritani,[34] a wealth of palladium- and rhodium-catalyzed oxidative alkenylations were developed. Less expensive ruthenium complexes were also explored in oxidative C–H alkenylations reactions.[35]

In 2001, an early example of oxidative alkenylaton of an alkene **5** with aromatic C–H bond was reported by Milstein and co-workers using $RuCl_3 \cdot 3H_2O$, $[Ru(CO)_3Cl_2]_2$, $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$ or $Ru(NO)Cl_3 \cdot 5H_2O$ catalyst complexes under an atmosphere of CO and O_2 at 180 °C (Scheme 5).[36] low yield of up to 40% of alkenylated arenes **6** were obtained. The optimizied results show that O_2 or alkene can serve as oxidant and ruthenium(II) and ruthenium(III) had the same catalytic activity, whereas the ruthenium(0) precursor $Ru_3(CO)_{12}$ was much less active. Directing groups were not required under the reaction conditions, however only poor site-selectivities were obtained.



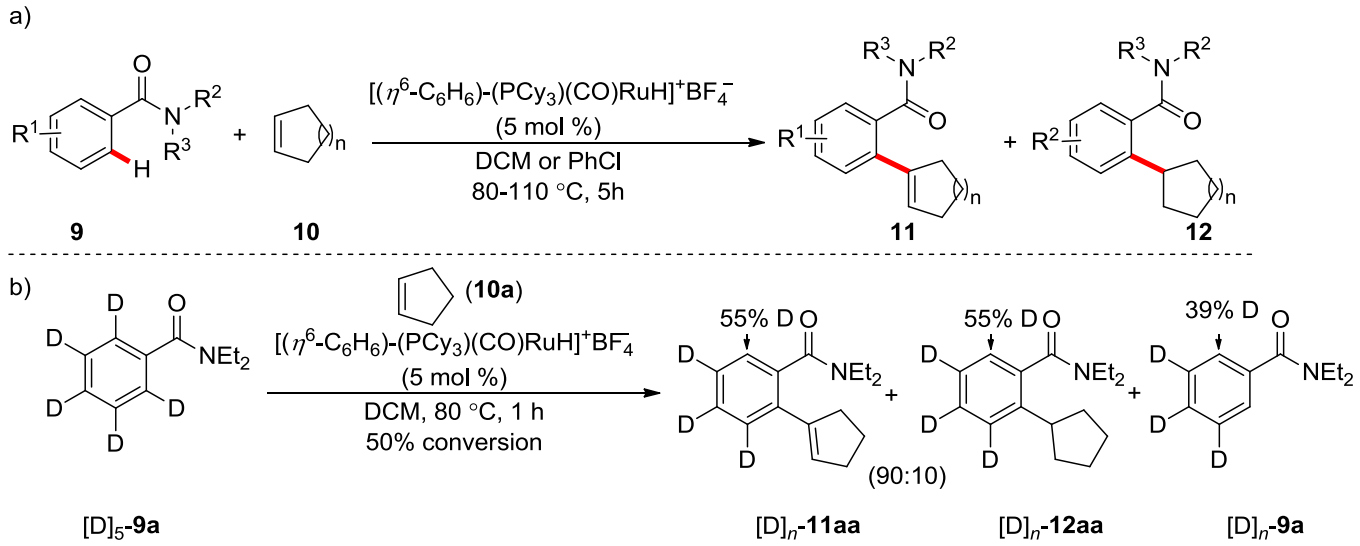
Scheme 5. Ruthenium-catalyzed C–H alkenylation of arenes **4** with olefins **5**.

Later, Brown and co-workers reported the oxidative Heck reaction of arene boronic acids **7** with acrylate **5a** catalyzed by $[RuCl_2(p\text{-cymene})_2]_2$ in the presence of $Cu(OAc)_2$ as the oxidant (Scheme 6).[37] In contrast to palladium catalyst system, in this reaction halides on the arenes **7** were tolerated.



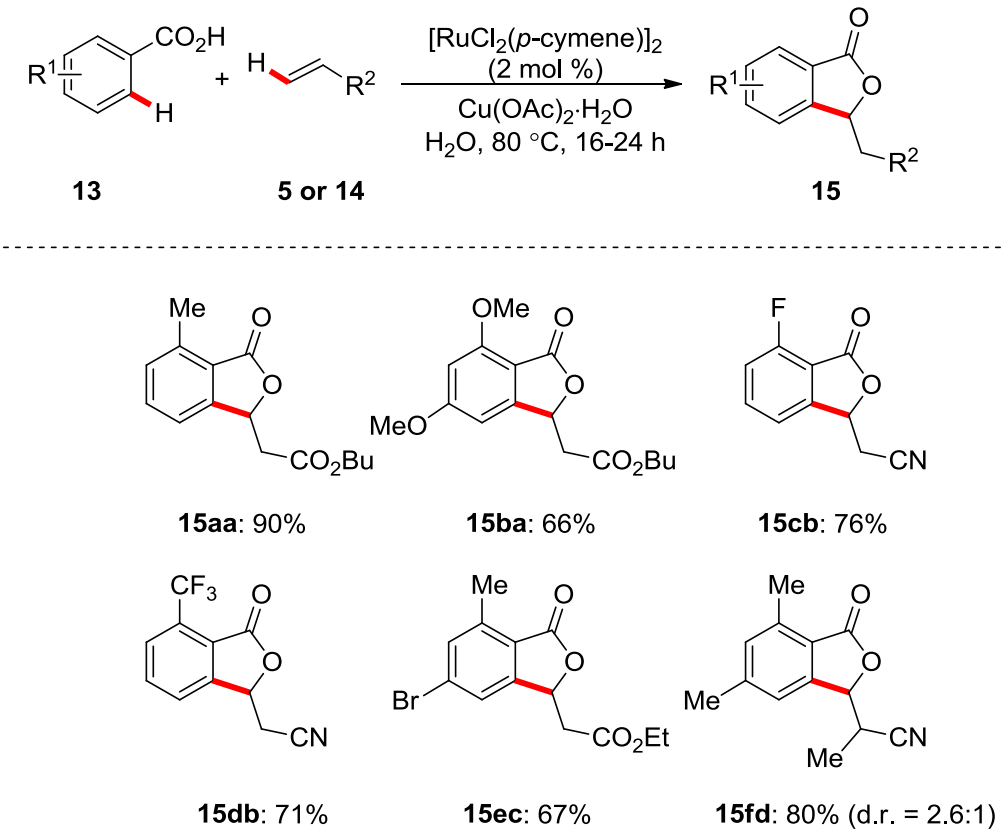
Scheme 6. Ruthenium-catalyzed oxidation Heck reaction.

Later, the cross-coupling of $C(Sp^2)$–H bonds between an alkene and an arene was achieved by Yi and co-workers using cationic ruthenium hydride complex $[(\eta^6\text{-}C_6H_6)\text{-}(PCy_3)(CO)RuH]^+BF_4^-$ as the catalyst precursor.[38] The cationic ruthenium hydride complex was found to be a highly site-selective catalyst for the oxidative C–H bond alkenylation of aryl-substituted amides **9** and unactivated alkenes **10** to give *o*-alkenylamide products **11** (Scheme 7a). In addition, kinetic experiments were performed to gain mechanistic insights into the coupling reaction. To examine the H/D exchange pattern on the amide substrate, the treatment of $C_6D_5C(O)NEt_2$ ($[D]_5$-**9a)** and cyclopentene (**10a)** in the presence of the catalyst was performed. The result indicated a reversible arene C–H activation step (Scheme 7b). In support of this notion, a negligible isotope effect of k_H/k_D = 1.1 was found for the competition reaction between $C_6H_5C(O)NEt_2$ (**9a**) and $C_6D_5C(O)NEt_2$ ($[D]_5$-**9a**) with cyclopentene (**10a**). Further detailed kinetic studies supported a mechanism involving a rapid vinyl C–H activation followed by a rate-limiting C–C bond forming reductive elimination. In these reactions, no external oxidant was added, the alkene as well as the newly formed alkenylated product severed here as hydrogen scavenger. Therefore the alkenylated product **11** was formed along with hydrogenated benzamides **12** as an insepeable mixture.



Scheme 7. Ruthenium-catalyzed oxidative alkenylations of benzamides **9**.

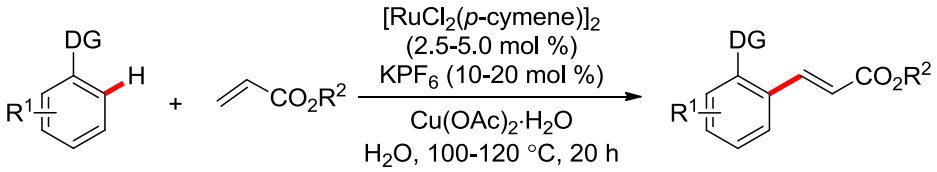
In 2011, the Ackermann group showed that the weakly-coordinating carboxylic group could direct the alkenylation with ruthenium(II) catalyst at the *ortho*-position of benzoic acid derivatives **13** with acrylates **5** or acrylonitrile **14** with 2 equivalent of oxidant $Cu(OAc)_2 \cdot H_2O$ (Scheme 8).[39] This reaction occurred efficiently in environmentally benign water, in contrast to related palladium- or rhodium-catalyzed reactions,[40] which were thus far could have been performed only in organic solvents. The alkenylated product underwent oxo-Michael addition, thus leading to a variety of lactones **15**. The catalytic system tolerated valuable electrophilic functional groups, such as fluoro or bromo substituents, and even sterically hindered *ortho*-substituted acids **13a-13f** were also accepted.



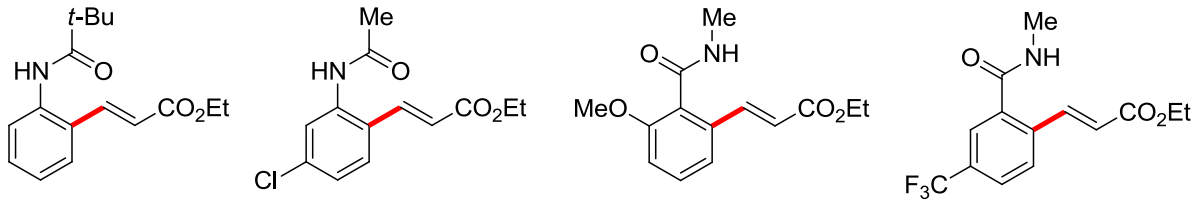
Scheme 8. Ruthenium-catalyzed oxidative alkenylation of benzoic acid in water.

Furthermore, the Ackermann group expanded the ruthenium(II)-catalyzed oxidative alkenylations process to other valuable substrates, such as anilides **16** and amides **9** (Scheme 9a). The high selectivity monoalkenylated products **18** were achieved using the $[RuCl_2(p\text{-cymene})]_2$ **17** catalyst with the non-coordinating salt KPF_6 (20 mol %) in the presence of $Cu(OAc)_2 \cdot H_2O$.[41] The intermolecular competition experiments revealed electron-rich anilides **16b** to be preferentially functionalized (Scheme 9b). However, when using *N*-benzoyl anilines **19** as the substrates, the alkenylation reaction peformed only at the *ortho* C–H bond of the aromatic ring linked to the amide carbonyl showing the preferential activation/alkenylation by the –C(O)NHPh than the –NHC(O)Ph group (Scheme 9c).

a)

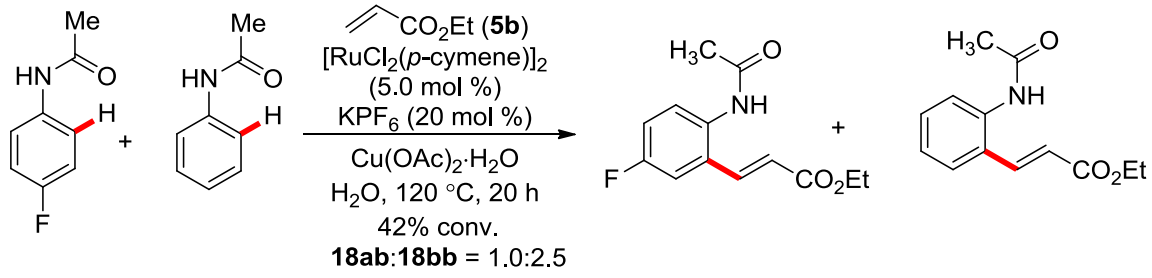


16 or 9 **5** **18**



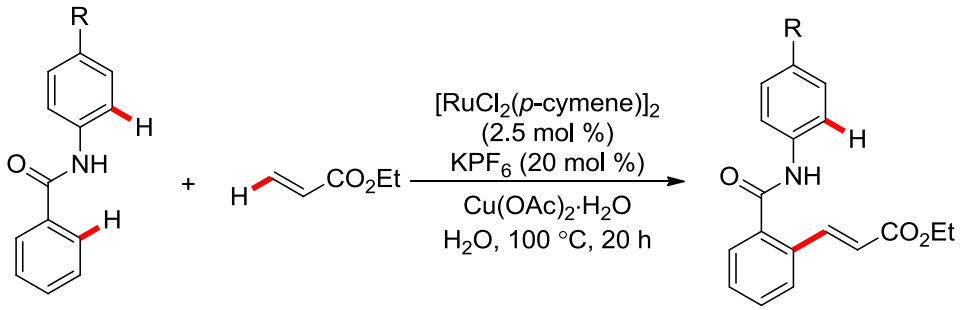
18a: 62% **18b**: 66% **18c**: 65% **18d**: 51%

b)



16a **16b** **18ab** **18bb**

c)

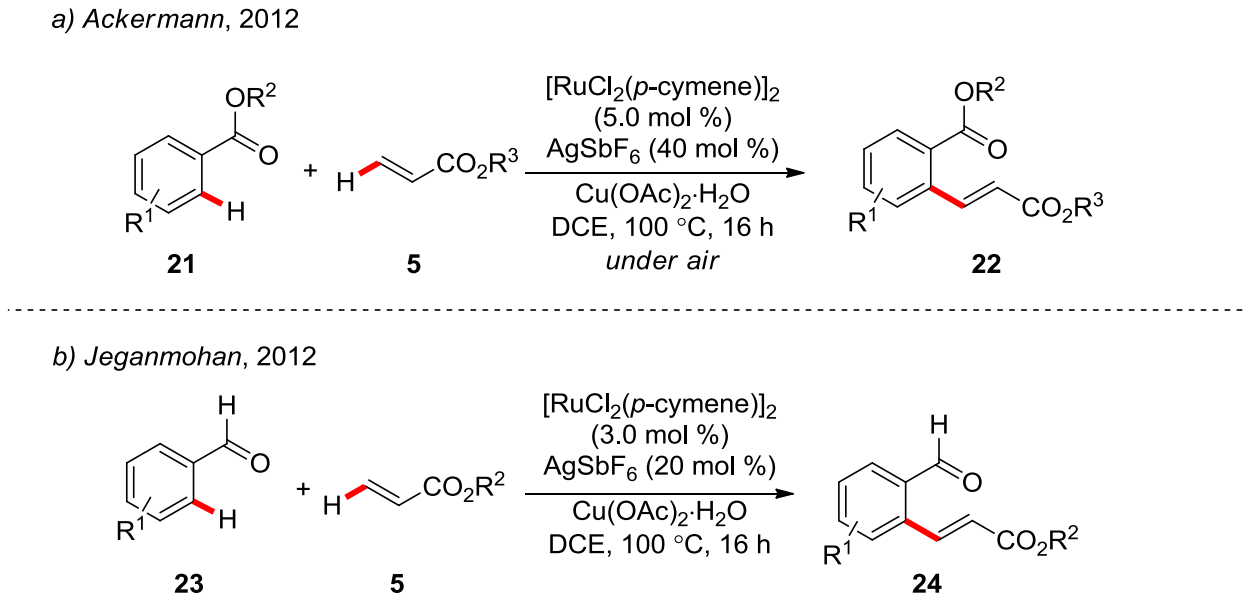


19 **5b**

R = H (**20ab**), 46%
R = F (**20bb**), 47%

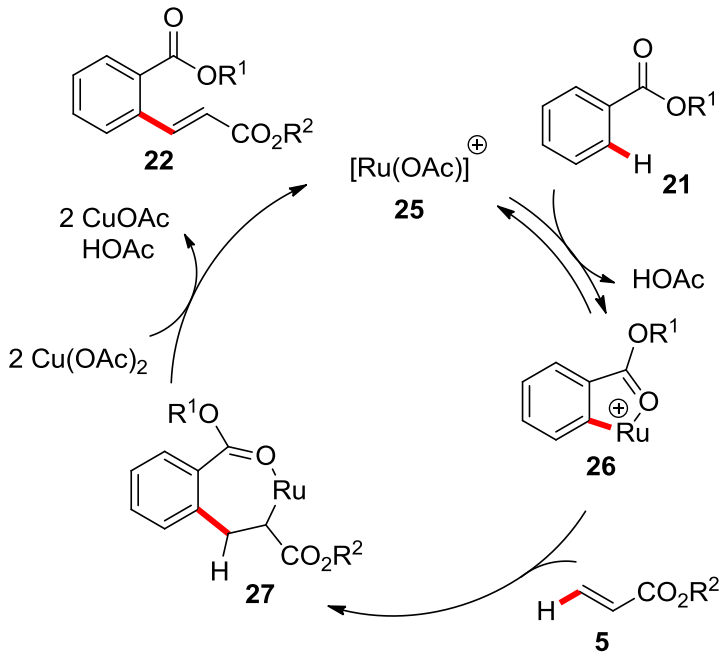
Scheme 9. Ruthenium-catalyzed C–H alkenylation of anilides and amides.

In contrast to the chelation-assisted alkenylations of benzamides, ruthenium-catalyzed oxidative functionalizations of weakly coordinating esters **21**,[42] aldehydes **23**[43] have also been reported by the research groups of Ackermann and Jeganmohan. By reacting the catalyst $[RuCl_2(p\text{-cymene})]_2$ with $AgSbF_6$ to abstract the chlorides from the ruthenium(II) complex, in the presence of $Cu(OAc)_2 \cdot H_2O$ as an acetate provider and oxidant, they succeeded here towards the alkenylation process (Scheme 10).



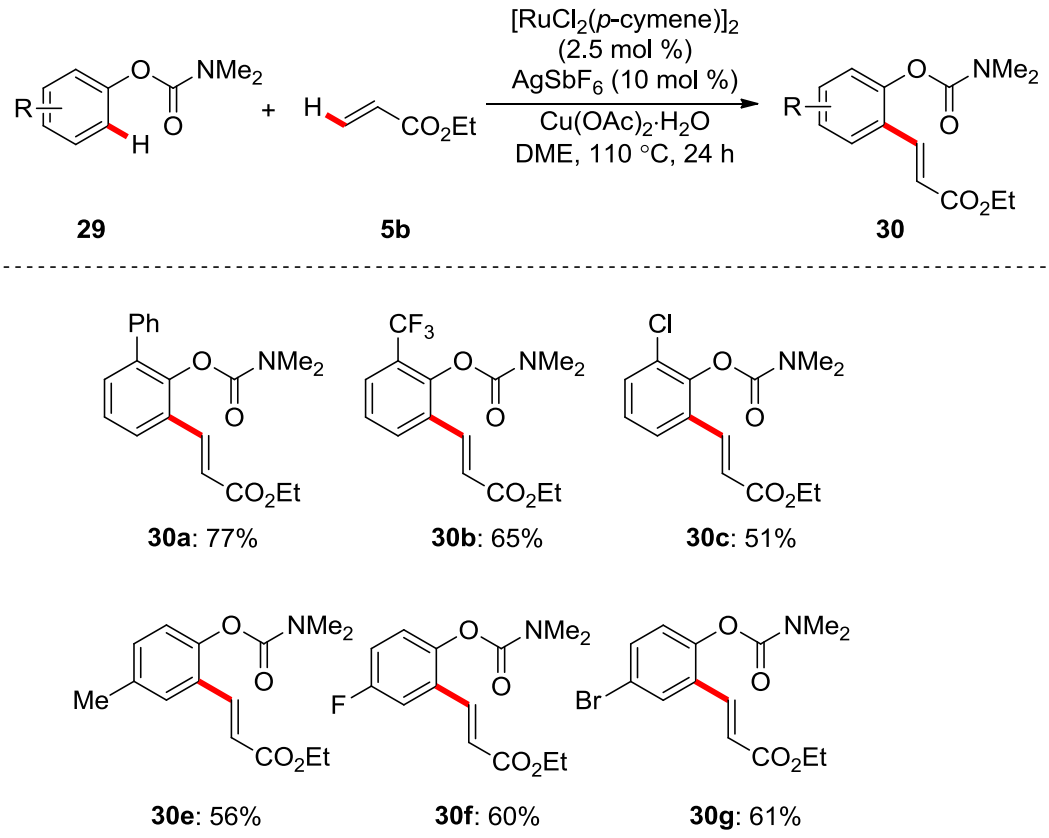
Scheme 10. Ruthenium(II)-catalyzed C–H alkenylation with weakly coordinating esters **21** and aldehydes **23** as directing groups.

Based on H/D-exchange experiments of ruthenium(II)-catalyzed C–H alkenylation, the Ackermann group proposed the catalytic cycle to involve an initial reversible acetate-assisted cycloruthenation to form complex **26** (Scheme 11). Subsequent migratory insertion of alkene **5** and *β*-hydride elimination furnish desired product **22**, while reductive elimination and reoxidation by $Cu(OAc)_2$ regenerate the catalytically active cationic species **25**.



Scheme 11. Proposed catalytic cycle of ruthenium(II)-catalyzed C–H alkenylation of arenes.

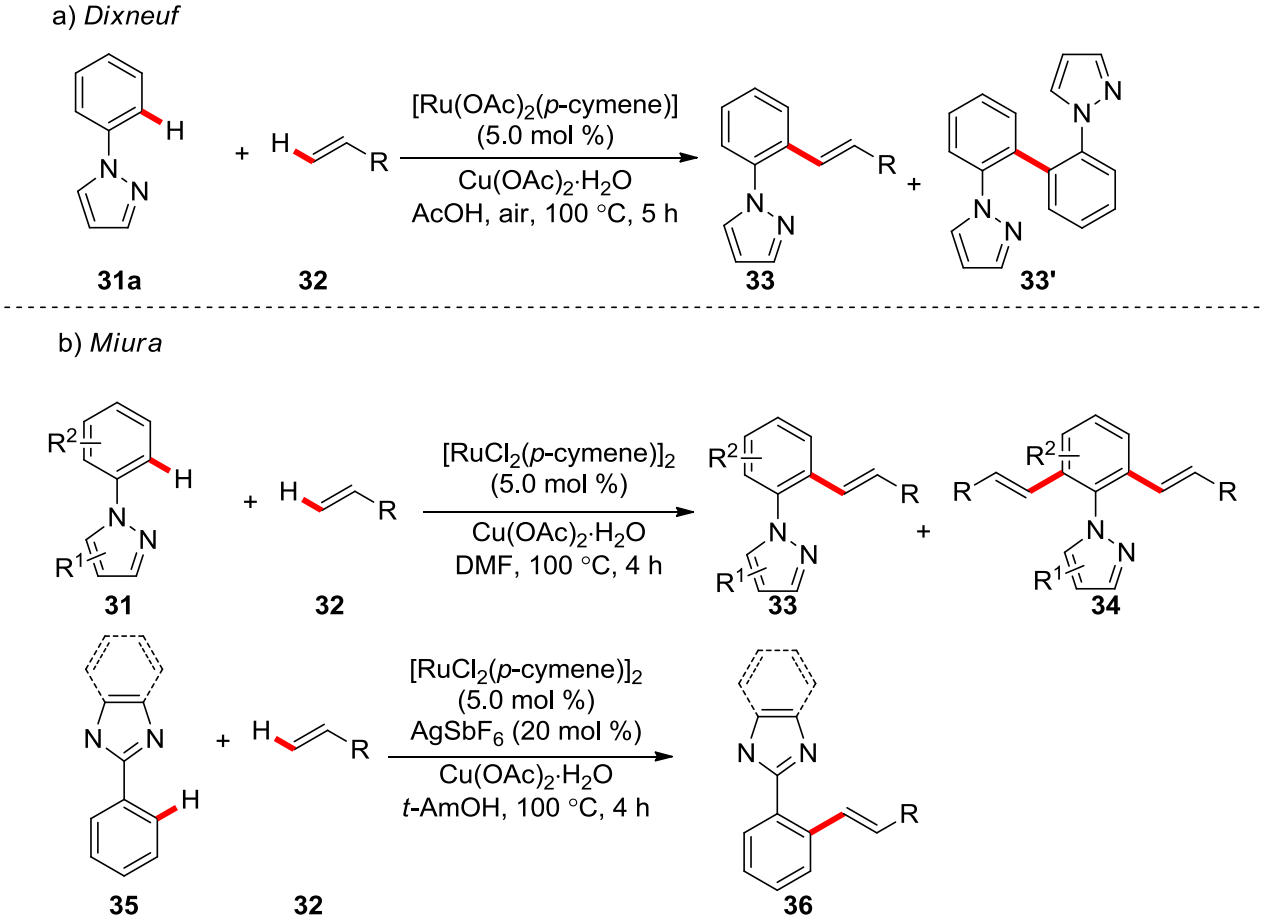
The hydroxyl group of phenols does not direct ruthenium(II)-catalyzed C–H bond activation, but it's derivatives such as carbamates[44]] and the strongly coordinating 2-pyridyl group[45] have been shown to direct the *ortho*-selective C–H cleavage to obtain the alkenylated products **28**. In 2012, the Ackermann group showed that carbamate derivatives of phenols **29** could undergo *ortho*-alkenylation with acrylates **5b** in the presence of catalytic amount of $[RuCl_2(p\text{-cymene})]_2$ and $AgSbF_6$ with $Cu(OAc)_2$ as oxidant in DME. The reaction was compatibles with a wide range of functional groups, including alkyl fluoro, chloro or bromo (Scheme 12).[44] The carbamate directing group was easily removed to provide *ortho*-alkenylated phenol under basic reaction condition.



Scheme 12. Oxidative C–H alkenylation of aryl carbamates **29**.

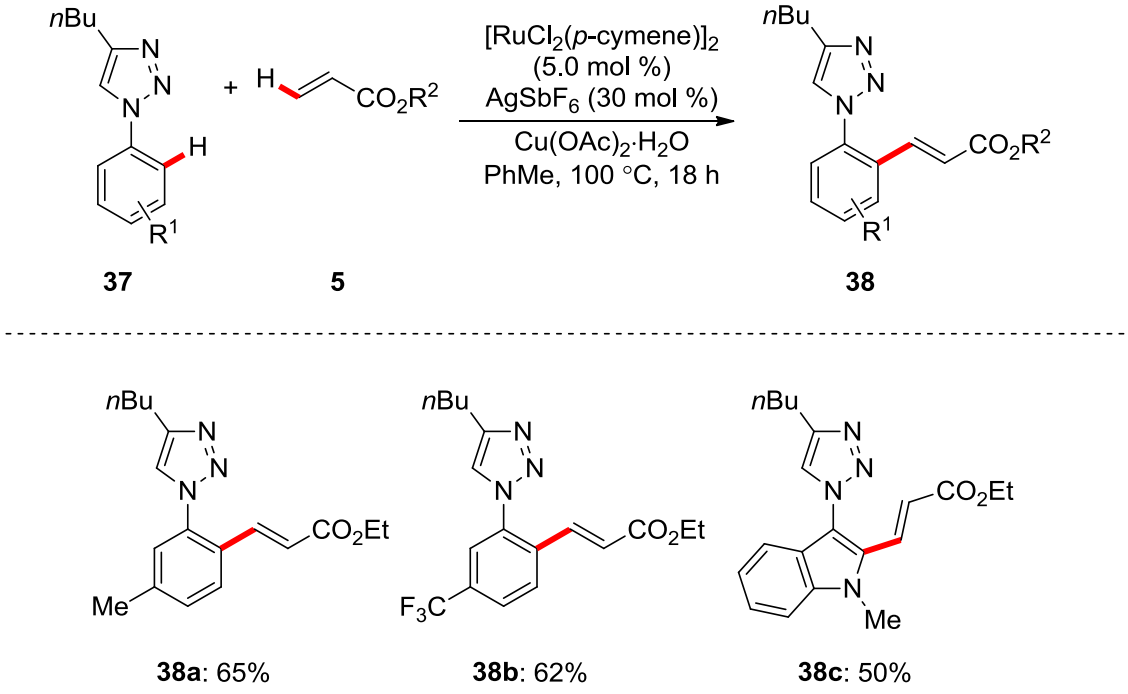
Oxidative alkenylations of arenes with heterocyclic directing groups were also achieved in recent years. Dixneuf and co-workers reported on the synthesis of *ortho*-alkenylated *N*-arylpyrazoles **33** *via* ruthenium-catalyzed oxidative C–H alkenylation of *N*-phenylpyrazole **31a** using [Ru(OAc)$_2$(*p*-cymene)] as the catalyst in HOAc at 100 °C (Scheme 13a).[46] For this reaction, in many cases the alkenylated products **33** were obtained with by-product **33'** generated through dehydrogenative homocoupling. Later, Miura and Satoh reported the direct alkenylation of 1-phenylpyrazoles **31** with alkenes **32** using [RuCl$_2$(*p*-cymene)]$_2$ instead of [Ru(OAc)$_2$(*p*-cymene)] as catlyst in the presence of a copper (II) oxidant (Scheme 13b).[47] The reaction was shown to tolerate various substituents on the arene ring, such as chloro, ester and nitrile groups.[48] Here the formation of mixtures of mono- and bisalkenylated product (**33** and **34**) was observed. Under the same reaction conditions, a low yield was obtained for the phenylbenzothiazole **35** with acrylate **5**.

The C–H alkenylation efficiency was considerably improved by the addition of $AgSbF_6$ as the cocatalyst (Scheme13b).



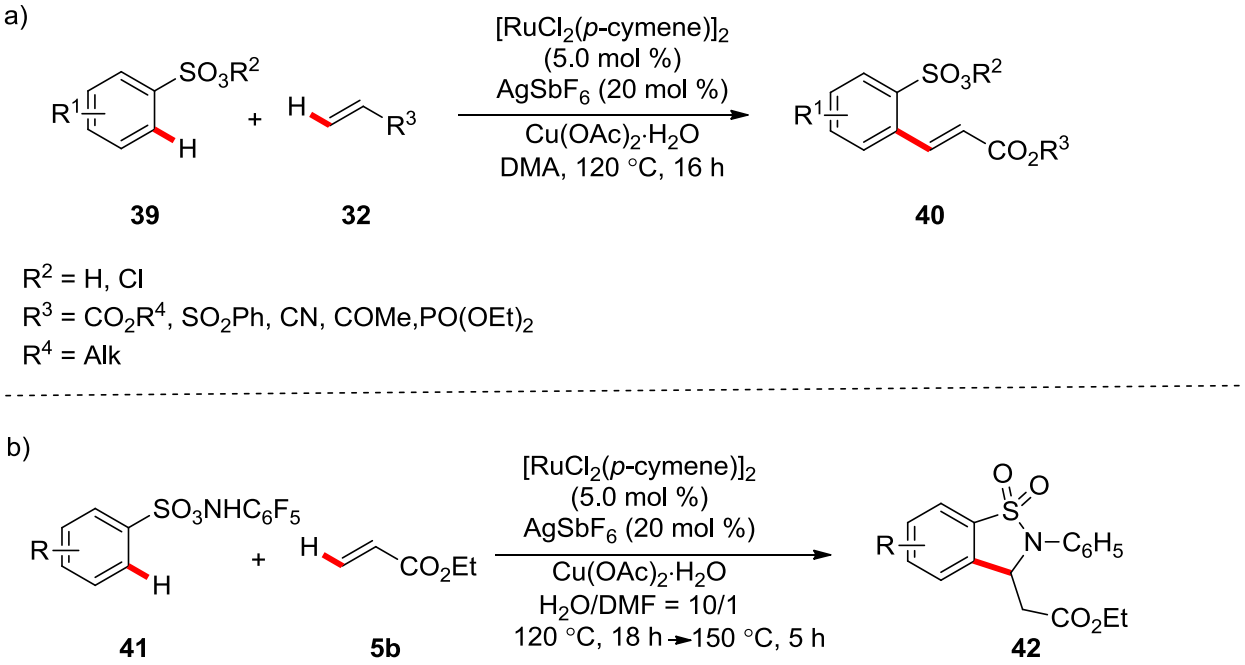
Scheme 13. Ruthenium-catalyzed C–H alkenylation.

Futhermore, in 2015, the Ackermann group reported the C–H alkenylation of aromatic compounds with alkenes assisted by the 1,2,3-triazole group (Scheme 14).[49] Under the optimal reaction conditions, the authors showed that various acrylates **5** and functional groups substituted aromatic rings **37** were tolerated. Particularly, a very good site-slectivity at a less hindered side of aromatics for the *meta* Me and CF_3 substituted aromatics was observed. It is worth to note that heteroarenes **37c** can be succesfully converted to indol derivative **38c**.



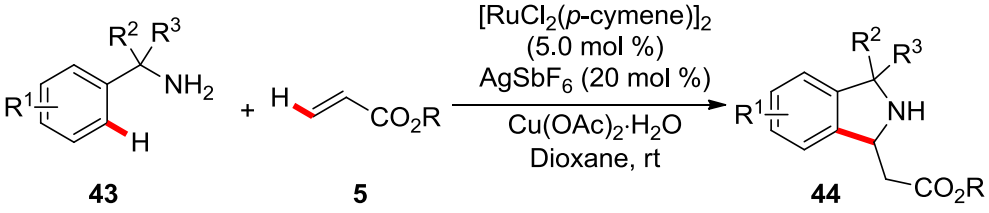
Scheme 14. Ruthenium-catalyzed alkenylation of triazole derivatives **37**.

Subsequently, the Ackermann group reported the efficient oxidative C–H alkenylation of sulfonic acid, sulfonyl chlorides, and sulfonamides (**39** and **41**) with ample substrate scope. For the alkenylation of sulfonic acids, not only acrylates, but also vinyl sulfones, nitriles, phosphonates and ketones proved to be viable substrates. For the reaction of sulfonamides **41**, the alkenylation was followed by intramolecular *aza*-Michael reaction leading to cyclization into sultams **42** in good yields when increasing the temperature to 150 °C (Scheme 15).[50]



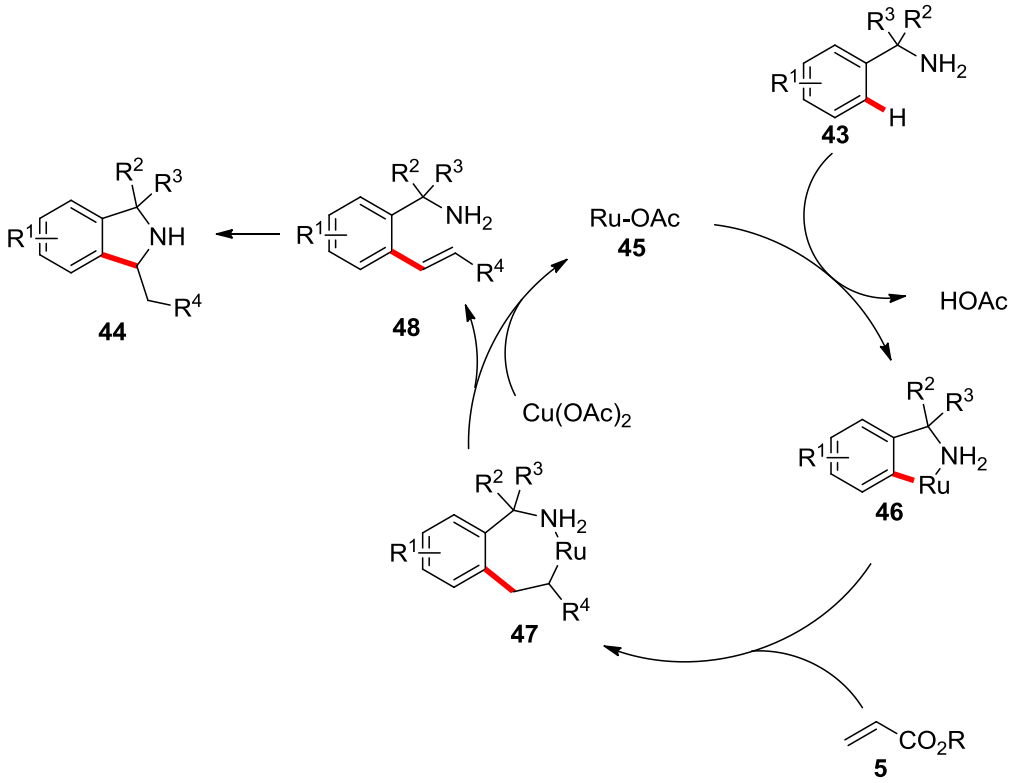
Scheme 15. Ruthenium-catalyzed C–H alkenylation of sulfonic acid, sulfonyl chlorides, and sulfonamides **39**.

Recently, the direct alkenylation of *α*,*α*-disubstituted benzylamines catalyzed by $[RhCp^*Cl_2]_2$ or low-cost $[RuCl_2(p\text{-cymene})]_2$ in the presence of $Cu(OAc)_2$ as oxidant was reported by Miura and co-workers.[51] This was the first example of ruthenium(II)-catalysed C–H bond functionalisation directed by a free NH_2 group. When treating the *α*,*α*-disubstituted benzylamines **43** with alkenes **5** in the presence of $[RuCl_2(p\text{-cymene})]_2$ and $Cu(OAc)_2$ in dioxane at room temperature, the cyclization product **44** was formed in good yield (Scheme 16).



Scheme 16. Ruthenium-catalyzed alkenylation of *α*,*α*-disubstituted benzylamines **43**.

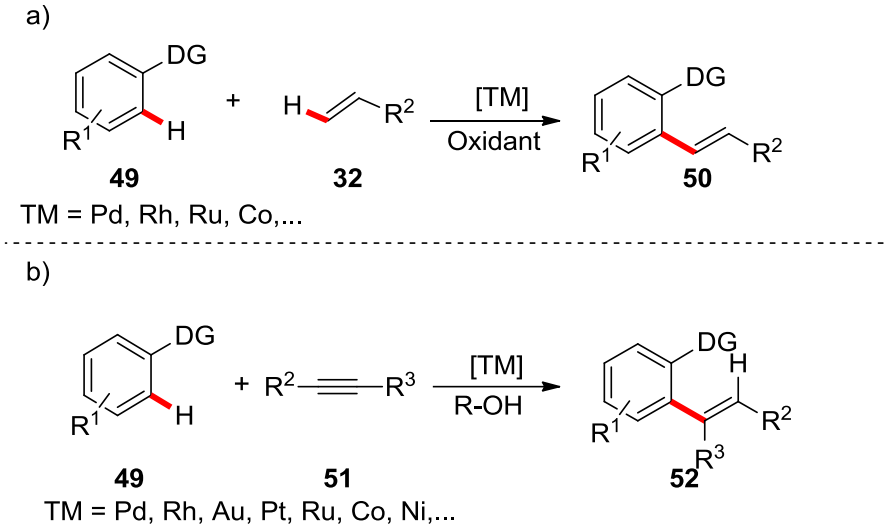
The mechanism was suggested to involve the initial formation of a Ruthenium(II)–OAc species leading to form a five-membered metallacycle intermediate **46**, then alkene insertion into aryl-metal bond to form **47** (Scheme 17).[51] Subsequently, the *β*-hydrid elimination and the intramolecular Michael addition occur.



Scheme 17. A plausible pathway for the *ortho*-alkenylation of *α*,*α*-disubstituted benzylamines **43**.

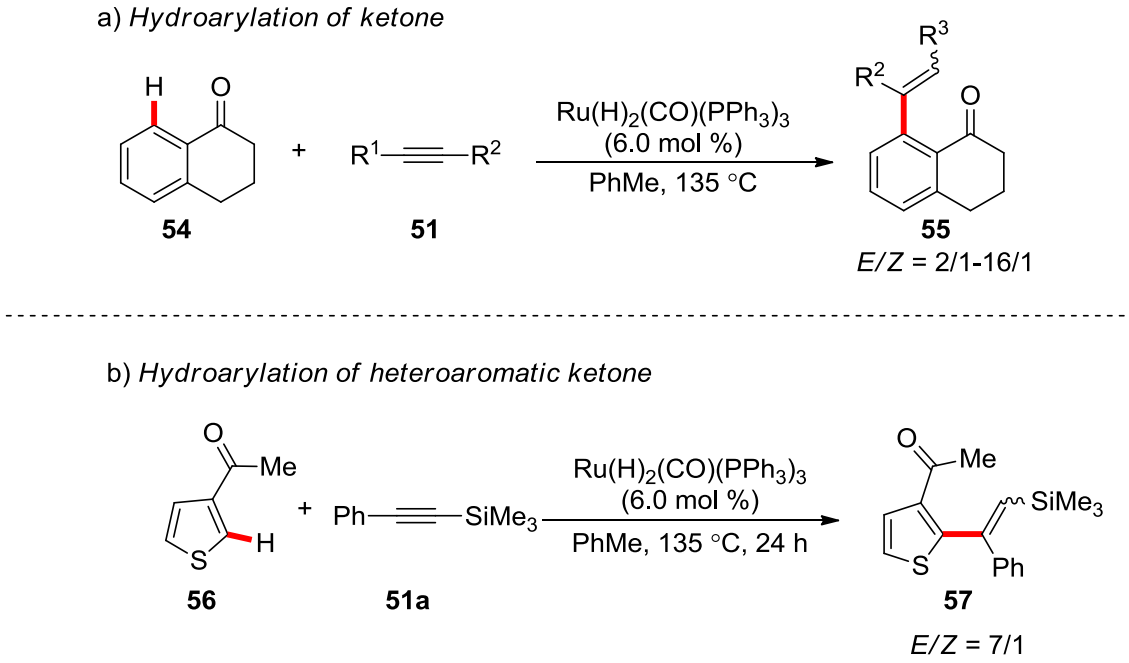
1.2.2 Ruthenium-Catalyzed Hydroarylation

Alkene derivatives are present various natural products, drug molecules and organic materials. They are also widely used in organic transformations. Based on the presented above transformation, alkene derivatives can be prepared by metal-catalyzed chelation-assisted oxidative alkenylation at the C–H bond of arenes (Scheme 18a).[35] Another efficient way to synthesize alkene derivatives is represented by metal-catalyzed hydroarylation of alkynes (Scheme 18b).[52]



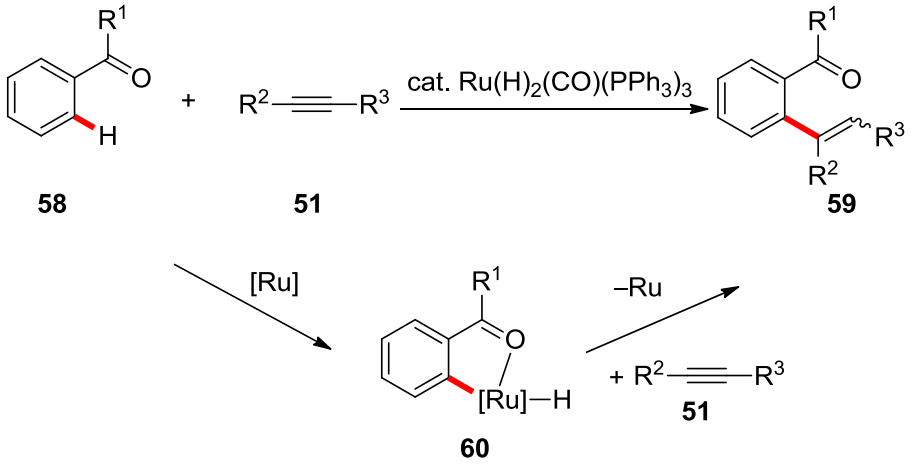
Scheme 18. Synthesis of alkene derivatives by C–H activation.

As early as 1986, Lewis and Smith demonstrated ortho-metalation of aryl phosphites under Ru-catalyzed conditions.[53] By catalytically generating the P-based directing group, they developed a hydroarylation approach to ortho-alkylated phenols. Subsequently, the Murai group reported a ruthenium-catalyzed chelation-assisted *ortho*-alkylation of aromatic ketones with alkenes via C–H bond activation in the presence of $RuH_2(CO)(PPh_3)_3$ **53**.[54] Later, under the similar reaction conditions, the Murai group demonstrated that alkynes can successfully insert to aromatic ketones *via* chelation-assisted *ortho* C–H cleavage (Scheme 19). When heating the mixure of ketone **54**, internal alkyne **51** and $RuH_2(CO)(PPh_3)_3$ in toluene under 135 °C, trisubstituted alkene **55** was achieved after 1-2 days. It is noteworthy that heteroaromatic ketons **56** were also tolerated.[55]



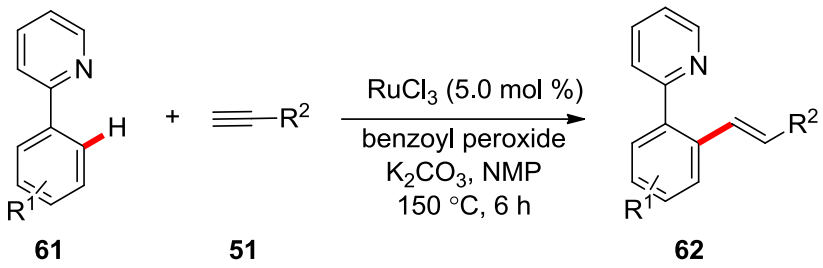
Scheme 19. Ruthenium(0)-catalyzed chelation-assisted hydroarylation of ketones **54**.

The hydroarylation of alkynes proceeds via oxidative addition parthway, which introduce a five-membered hydrometallacycle intermediate **60** (Scheme 20), then the alkyne insertion into the metal–hydride bond of intermediate **60** occurs and is followed by reductive elimination, giving the final trisubstituted alkene **59** regenerating the ruthenium(0) catalyst. However, this type of hydroarylation reaction is not completely regio- and stereoselective.



Scheme 20. Mechanism for ruthenium(0)-catalyzed chelation-assisted hydroarylation.

In recent years, it was clearly revealed that this type of regio- and stereoisomeric issues can be overcome by carrying out the hydroarylation reaction via base-assisted pathway. For instance, Zhang proposed alkenylation reactions of arylpyridines **61** with terminal alkynes **51** in the presence of benzoyl peroxide (Scheme 21).[56]

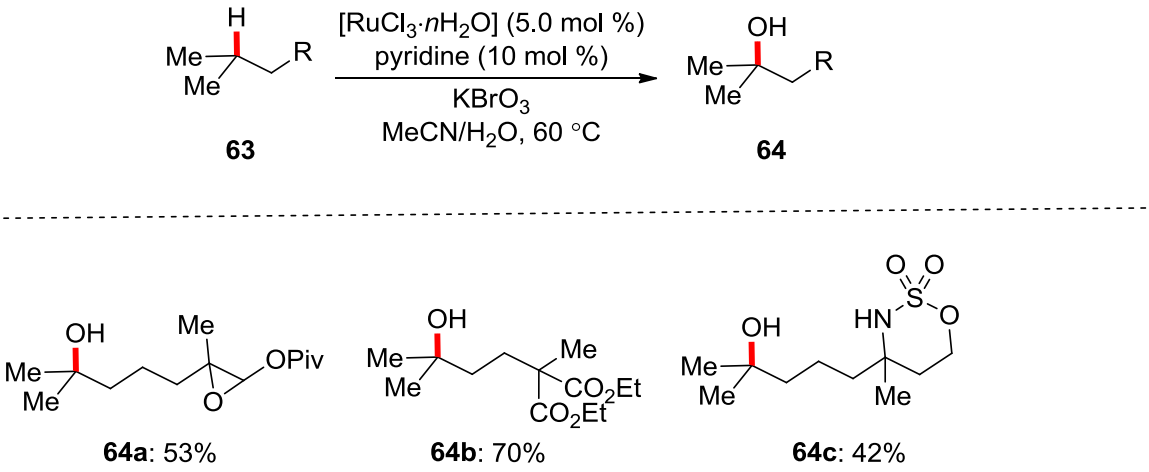


Scheme 21. Ruthenium-catalyzed hydroarylations of arylpridines **61**.

Subsequently, a significant number of ruthenium-catalyzed hydroarylation reactions *via* base-assisted C–H activation appeared in the literature, and these transformation were rapidly expanded to a variety of directing groups, including benzamides,[53b, 57] isoquinolones,[58] carbamates,[59] among others.[60] In these transformations, substituted arenes reacted with alkynes in the presence of a ruthenium catalyst, giving alkene derivatives in a regio- and stereoselective manner. It is noteworthy that the copper oxidant is inherently not necessary for the hydroarylation reaction.

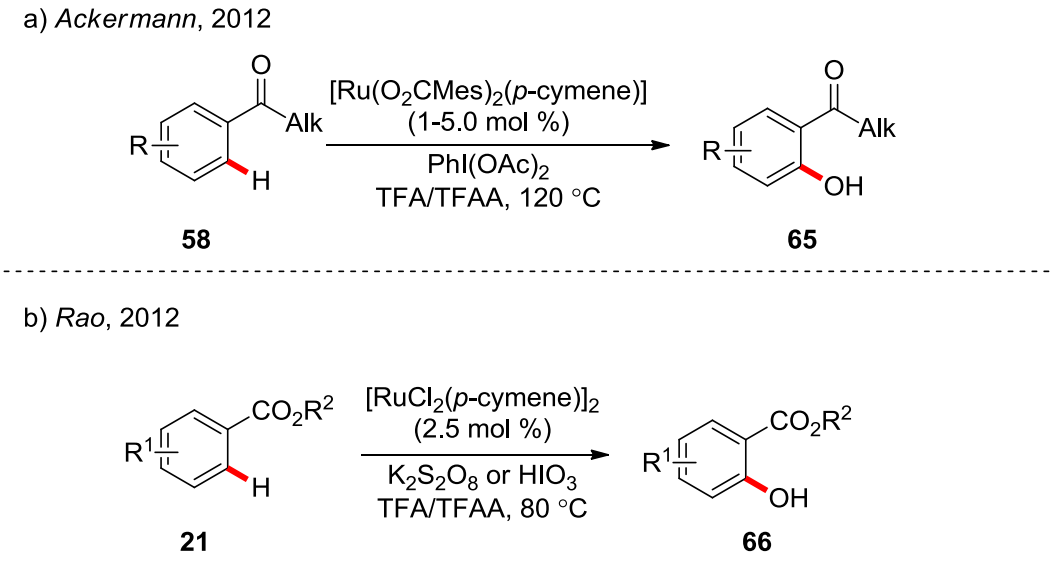
1.2.3 Ruthenium-Catalyzed C–H Oxygenation

During the past few years, ruthenium(II)-catalyzed C–H oxygenations of C–H bonds were reported by Ackermann and Rao group.[29a, 61] In contrast, DuBois and coworkers developed a protocol for the selective hydroxylation of tertiary C–H bonds that uses catalytic amounts of $RuCl_3$, an inexpensive terminal oxidant−$KBrO_3$, and pyridine as an essential additive (Scheme 22).[62] However, this reaction only has a good selectivity for tetiary C−H centers and do not proceed through C–H activation, but outer-sphere vadical processes.



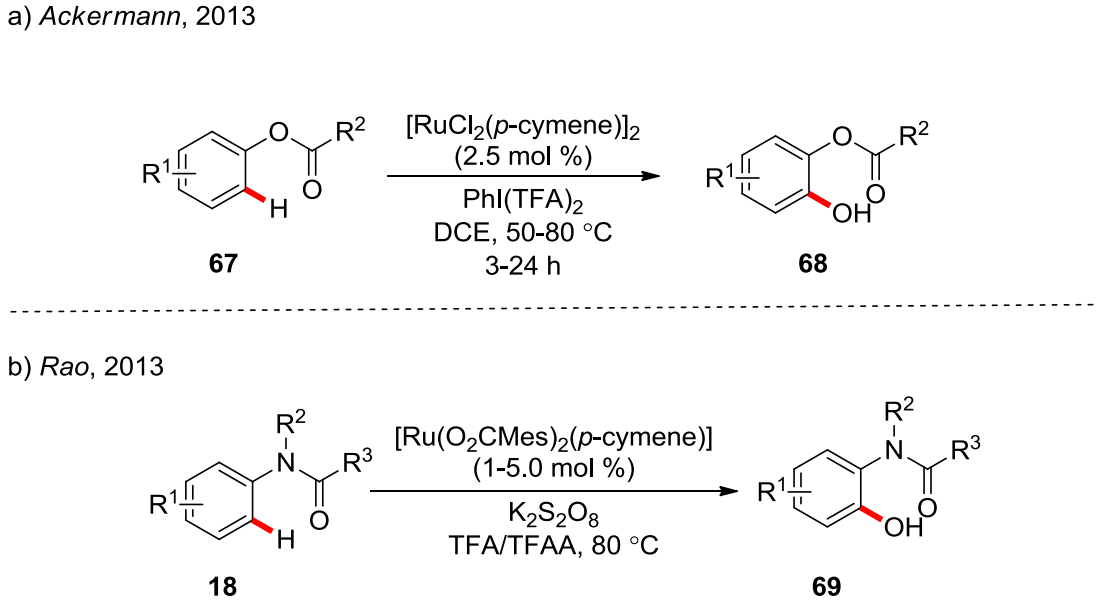
Scheme 22. Ruthenium-catalyzed outer-sphere oxygenation.

However, the Ackermann group developed ruthenium-catalyzed C−H oxygenation using $[RuCl_2(p\text{-cymene})]_2$, as well as well-defined ruthenium(II) biscarboxylate complex $[Ru(O_2CMes)_2(p\text{-cymene})]$, or even inexpensive $[RuCl_3{\cdot}nH_2O]$ as catalysts, and $PhI(OAc)_2$ as oxidant (Scheme 23a). Around the same time, Rao and co-workers used the complex $[RuCl_2(p\text{-cymene})]_2$ as the precatalyst and $K_2S_2O_8$ or HIO_3 as the oxidant in the oxygenation of C−H bonds in arenes (Scheme 23b).[63] TFA/TFAA cosolvent system and oxidants serve as the critical factors for oxygenation of arenes with esters **21**.[61b]



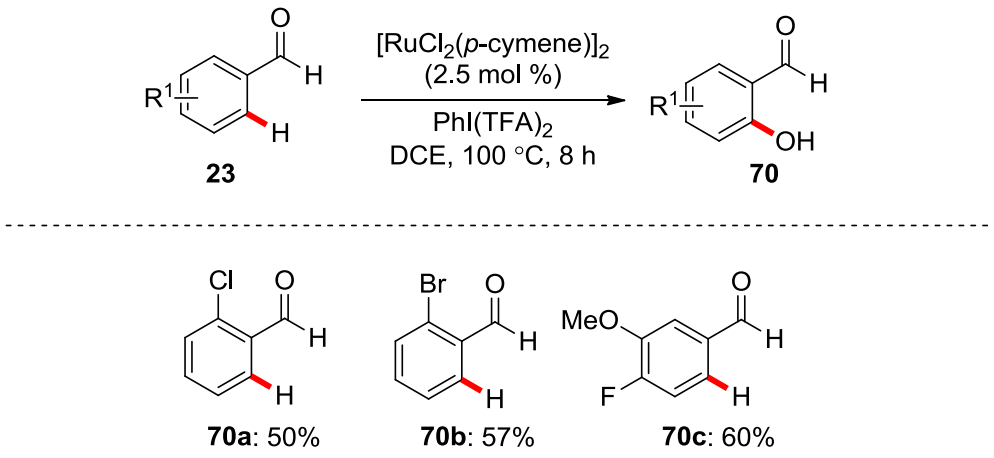
Scheme 23. Ruthenium-catalyzed C–H bond oxygenation of ketones **58** and esters **21**.

The group of Ackermann[64] and Rao[61a] further expaned the scope of ruthenium-catalyzed C−H oxygenation process to valuable aryl carbamates **67** and anilides **18** (Scheme 24).



Scheme 24. Ruthenium-catalyzed C–H bond oxygenation of aryl carbamates **67** and anilides **18**.

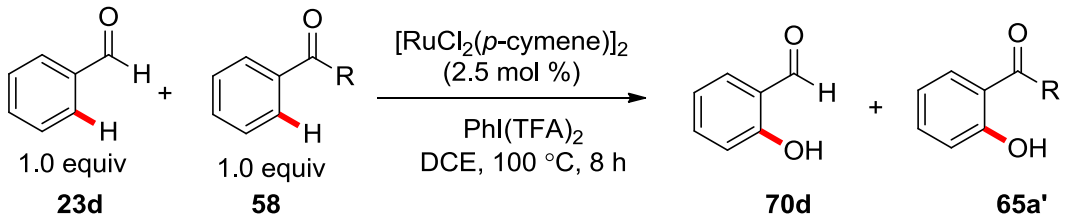
In 2014, the Ackermann group reported the first C−H oxygenation by assistance of very weakly coordinating aldehydes **23** using a ruthenium(II) complex as the catalyst (Scheme 25).[65] Under the optimal reaction conditions, electrophilic halide functional groups were well tolerated by the highly chemoselective ruthenium(II) catalyst.



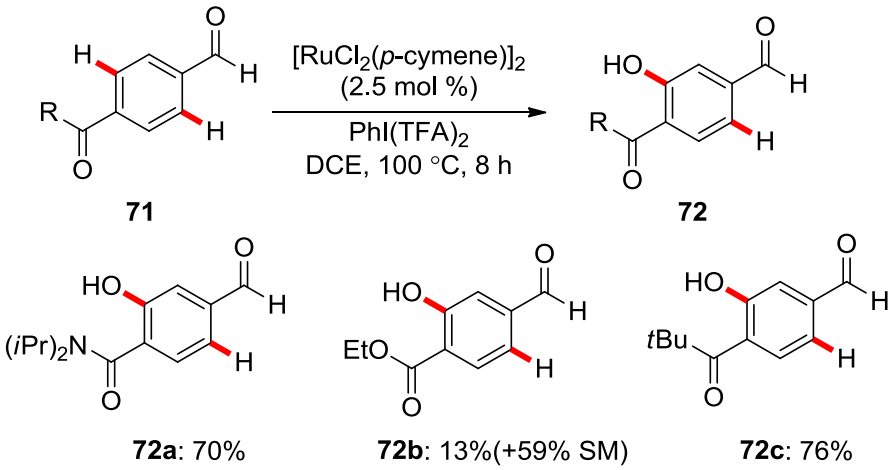
Scheme 25. Ruthenium(II)-catalyzed C−H oxygenation of aromatic aldehydes **23**.

Competition studys between arenes with different directing groups clearly showed the challenges that are associated with the use of very weakly coordinating aldehydes (Scheme 26). The success of this reaction highlighted the remarkable power of versatile and mild ruthenium(II) catalysis for the selective functionalization of unactivated C−H bonds.

a) *Intermolecular competition experiments*

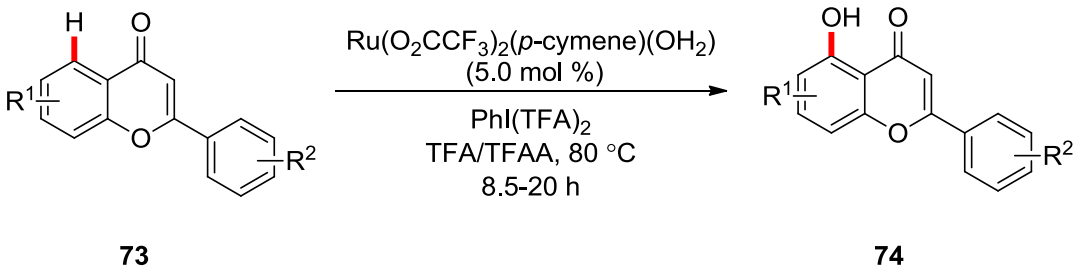


b) *Intramolecular competition experiments*



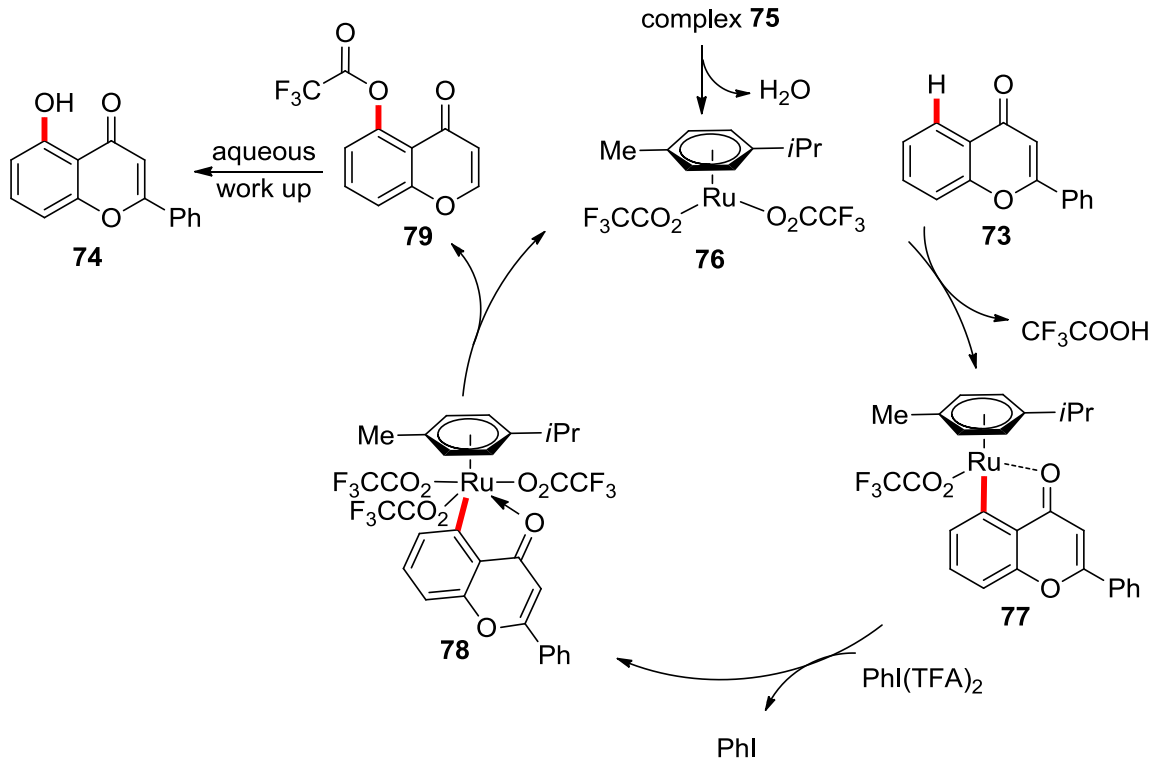
Scheme 26: Competition experiments for ruthenium(II)-catalyzed C−H oxygenations of aldehydes **23**.

Base on the above reaserch, Hong and co-workers reported ruthenium(II)-catalyzed direct C−H oxygenation of flavones and chromones **73** (Scheme 27).



Scheme 27. Ruthenium(II)-catalyzed C−H oxygenations of flavone and chromone.

A plausible catalytic cycle was proposed as depicted in Scheme 28. First, the five-membered ruthenacycle **77** can be formed via the C−H bond activation of substrate, and then the ruthenium(IV) species **78** is formed through the oxidiation by the hypervalent iodine. Subsequent reductive elimination introduce 5-(trifluoroacetyloxy)-flavone **79** and regenerate the ruthenium(II) catalyst **76**. Finally, the desired product is afforded from the trifluoroacetate **74** by aqueous work-up.



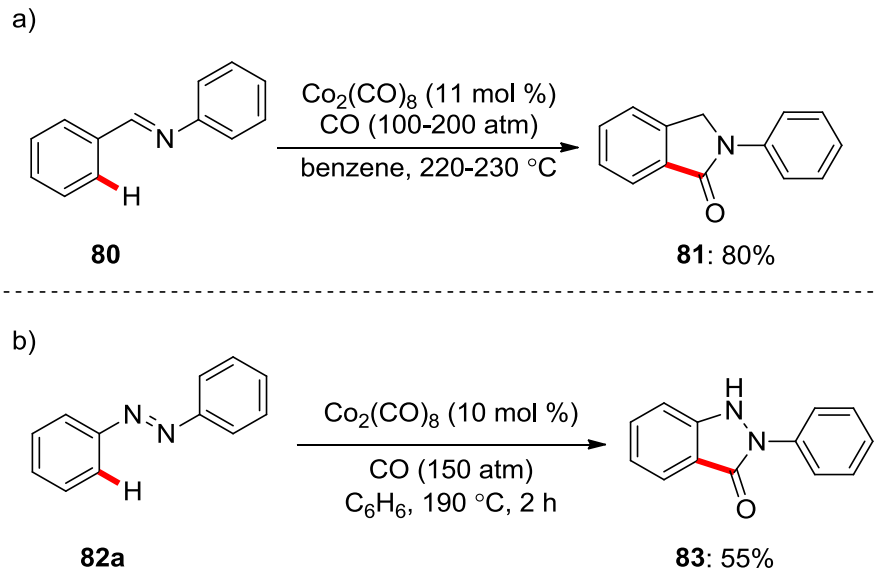
Scheme 28. A proposed mechanistic pathway for ruthenium(II)-catalyzed C−H oxygenations.

1.3 Cobalt Catalyzed C−H Activation

Transition metal-catalyzed C−H functionalizations are increasingly viable tools for sustainable syntheses. Until now, most of metal-catalyzed C−H functionalizations were achieved by second- and third-row transition metals catalyst.[7a, 13a, 16a] Thus, the second-row transition metals, such as ruthenium, palladium and rhodium, have played a major role in C−H functionalizations.[3, 7b, 8c] Despite of the great reactivity, the precious metal complexes are rather expensive and toxic. So the

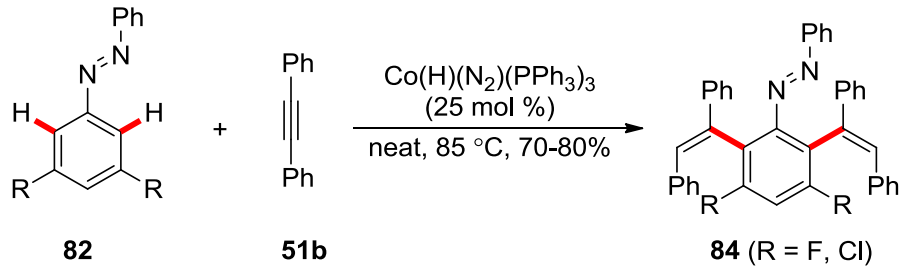
development of catalysts based on earth-abundant first-row transition metals catalysts for C−H activation reactions that allow mild reaction conditions are meaningful.

Among the first-row transition metals, inexpensive cobalt acted as powerful catalyst and has been successfully used in C−H interactive alkylations, arylations, hydroarylations, benzylations and alkenylations.[66] In 1955, Murahashi and co-workers reported an early example of cobalt used in a chelation-assisted C−H functionalization reaction.[67] The reaction of a benzaldimine **80** with carbon monoxide in the presence of $Co_2(CO)_8$ at extremely high temperature and pressure thus afforded phthalmidine **81** (scheme 29a). Later, it was found that under similar reaction conditions, azobenzene **82a** reacted with carbon monoxide at 150 atmospheres of pressure to form indazolone **83 (**Scheme 29b**)**.[68]



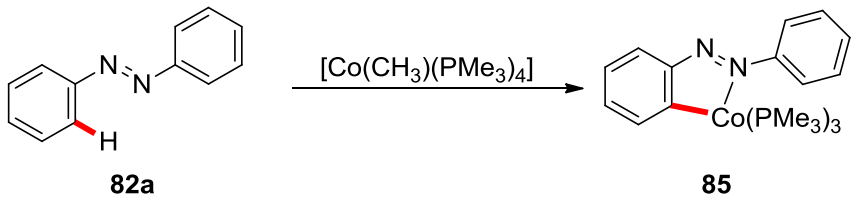
Scheme 29. Cobalt-catalyzed carbonylative cyclization.

While reports of cobalt-catalyzed C−H activation were rarely, until in 1994, Kisch and co-workers reported an *ortho*-alkenylation reaction of an azobenzene derivative **82** with alkyne **51b** using a cobalt(I) catalyst $Co(H)(N_2)(PPh_3)_3$ to afford the *anti*-addition product **84** (Scheme 30).[66c]



Scheme 30. Cobalt-catalyzed hydroarylation of alkyne **51b** with azobenzenes **82**.

Around the same time, Klein and co-workers reported an example of well-defined cyclometalation reaction using $Co(Me)(PMe_3)_4$ and azobenzene **82a** through a stoichiometric C–H activation (Scheme 31).[69] Based on these findings, their group reported the synthesis of cobaltacycles by C−H activation, directed by aromatic and olefinic substrates bearing nitrogen, oxygen, sulfur, and phosphorus directing groups. Those findings implied that cobalt have significant potential for catalytic C−H functionalization, particularly for directed *ortho* C−H functionalization of arenes.

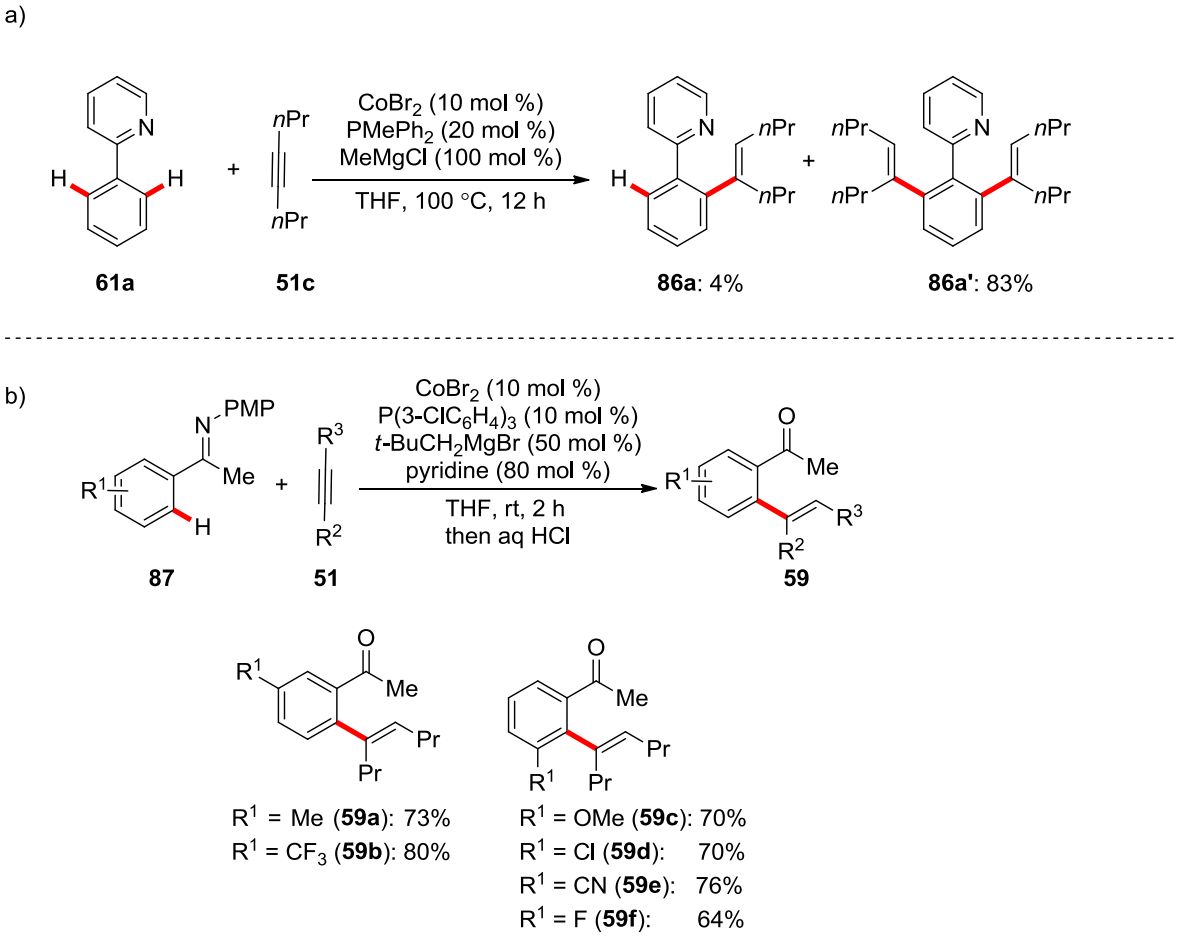


Scheme 31. Stoichiometric formation of cobaltacycle **85** through C–H activation.

1.3.1 Low-Valent Cobalt Catalyzed C−H Activation

Since the first cobalt-catalyzed hydroarylation of alkynes using cobalt(I) complex (Scheme 30),[66c] the development of cobalt-catalyzed hydroarylation of alkynes and olefins gained a significant attention during the last few years. Especially through the work of Yoshikai and co-workers, who in 2011, reported similar addition reactions of arylpyridines **61a** to internal alkynes **51c** to give trisubstituted olefins **86** in the presence of $CoBr_2$ as the catalyst, the phosphine ligand $PMePh_2$ and the stoichiometric reductant MeMgCl (Scheme 32a).[70] Furthermore, their group managed to expand

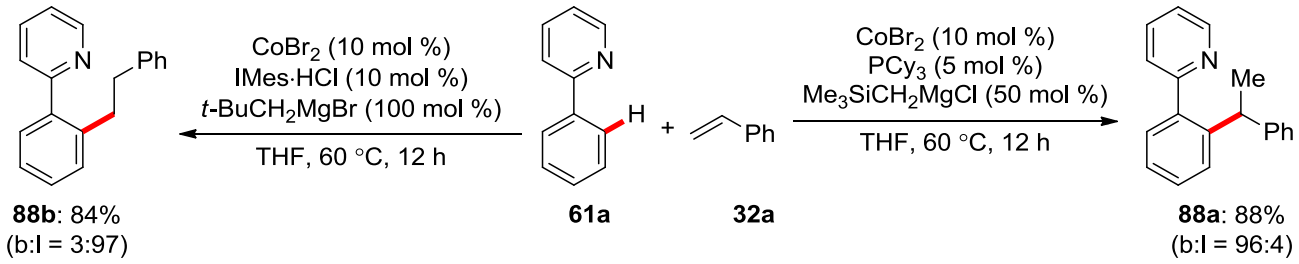
the scope of aromatic substrates to include aryl imines **87**.[71] Trisubstituted olefins **59** were hence obtained at room temperature (Scheme 32b). Potentially sensitive chloro and cyano substituents in substrates **87d** and **87e** were well tolerated. It is worth noting that the substrates bearing *m*-methoxy, *m*-chloro, *m*-cyano and *m*-fluoro substituents **87c-87f** reacted preferentially at the more sterically hindered C2-positions.



Scheme 32. Cobalt-catalyzed hydroarylation of alkynes **51**.

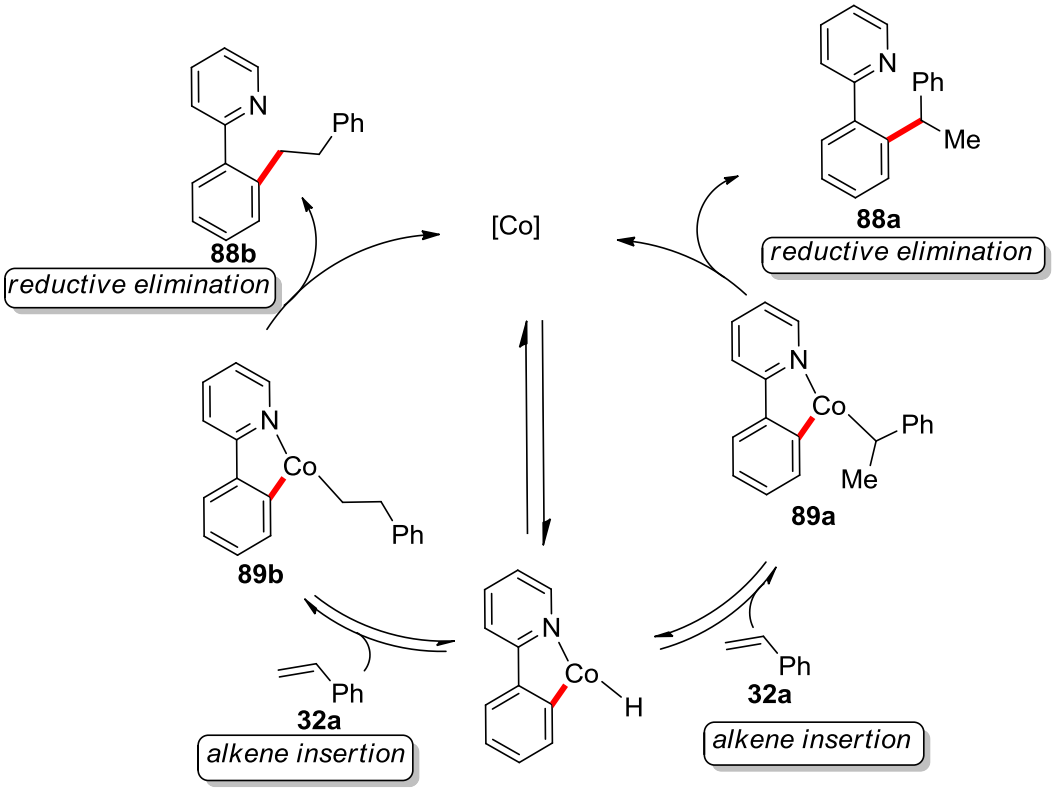
With the successful development of alkyne hydroarylation reactions, the hydroarylation of olefins also proved to be viable by low valent cobalt catalysis. Hence, Yoshikai and co-workers explored the addition reaction of 2-phenylpyridine **(61a)** to styrene (**32a**) under conditions similar to hydroarylation of alkynes. A cobalt catalyst generated from $CoBr_2$, PCy_3, and Me_3SiCH_2MgCl promoted the reaction to afford the branched adduct **88a** with high regioselectivity, while the use of

an NHC ligand instead of PCy_3 caused the reversal of the regioselectivity, leading to the formation of the linear adduct **88b** (Scheme 33).[72]



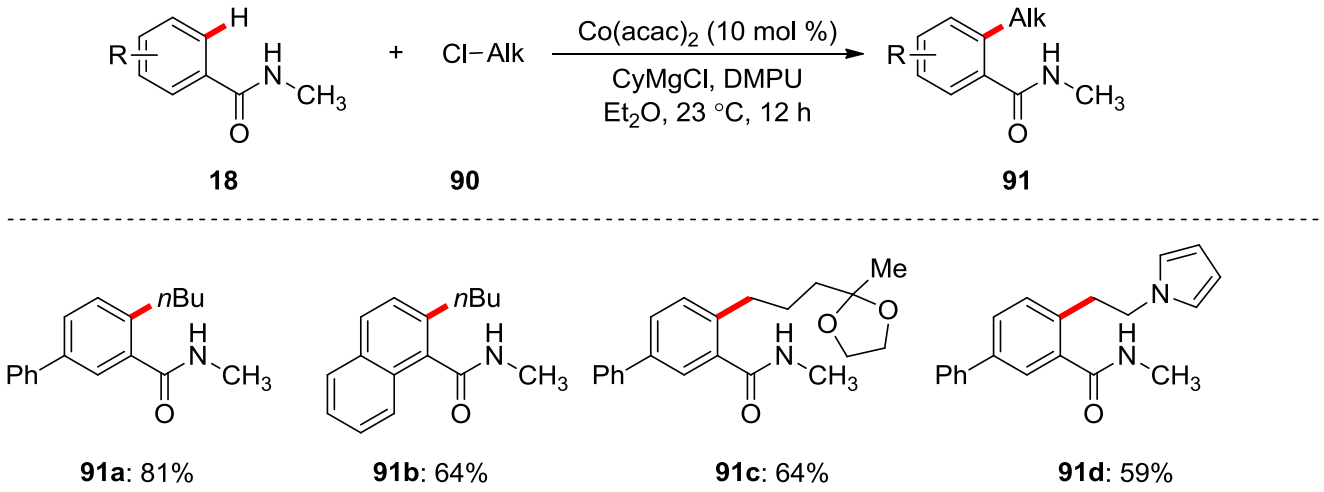
Scheme 33. Cobalt-catalyzed hydroarylation of 2-phenylpyridine **61**.

A mechanism addressing these findings was proposed (Scheme 34). First, reversible oxidative addition of the *ortho* C−H bond to cobalt takes place, then reversible insertion of styrene **32a** into the Co−H bond occurs leading to a branched or a linear intermediate **89a** or **89b**. This is followed by reductive elimination to form the 1,1- or 1,2-diarylethane **88a** or **88b** and regenerate the cobalt species.



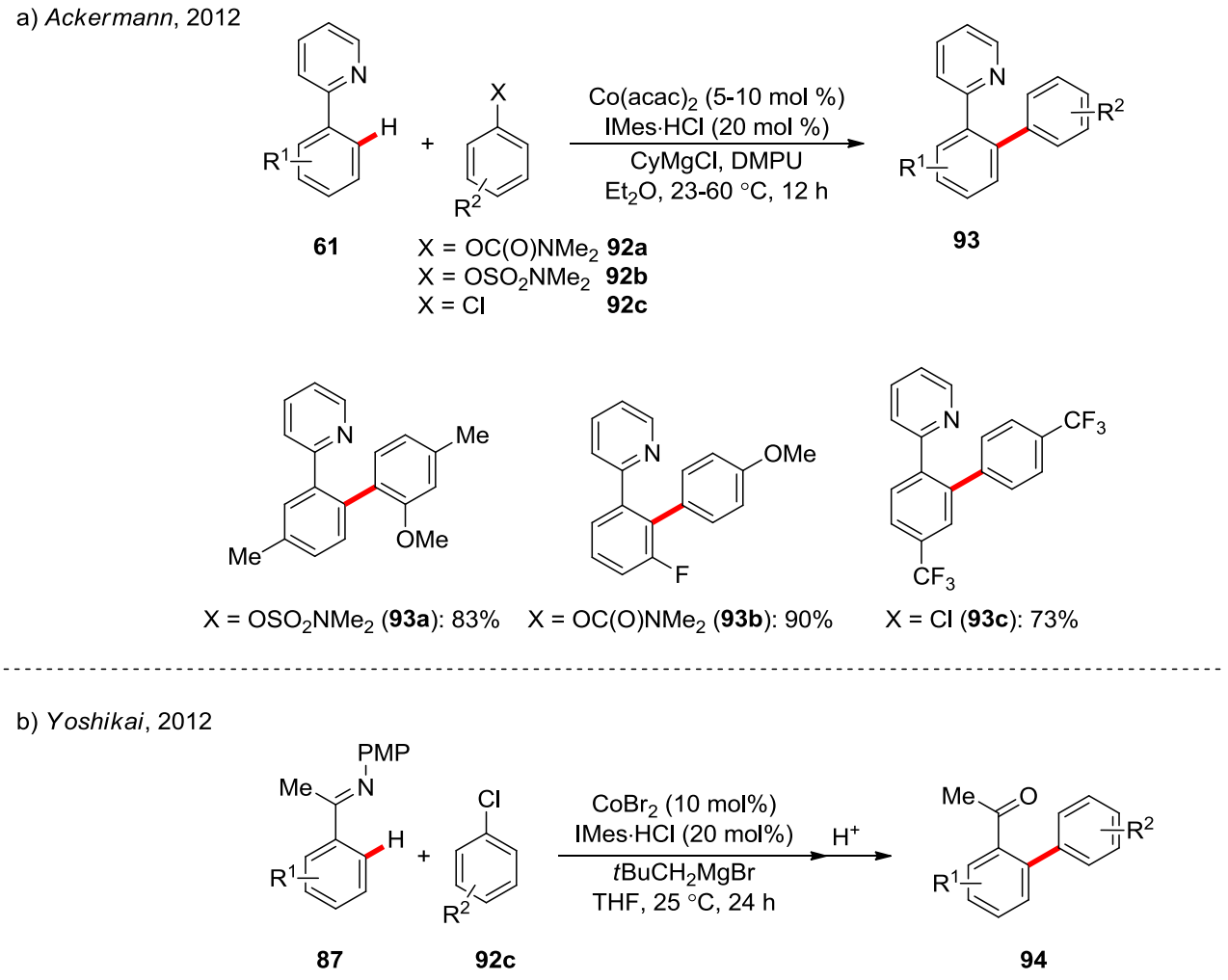
Scheme 34. Proposed catalytic cycles for cobalt-catalyzed hydroarylations of styrenes **32**.

Based on the above research, a protocol for the synthesis of alkylated arenes by cobalt catalysis was viable through hydroarylations of alkenes. Synthesis of alkylated arenes was also successful through cobalt-catalyzed C−H alkylations with organic electrophiles, such as alkyl halides.[73] In 2011, a cobalt-catalyzed *ortho*-alkylation using alkyl chlorides **90** as alkyl regent was reported. In this catalytic system, the alkylation of benzamides **91** was accomplished with various alkyl chlorides **90**, notaly without NHC or phosphine ligand (Scheme 35).[74]



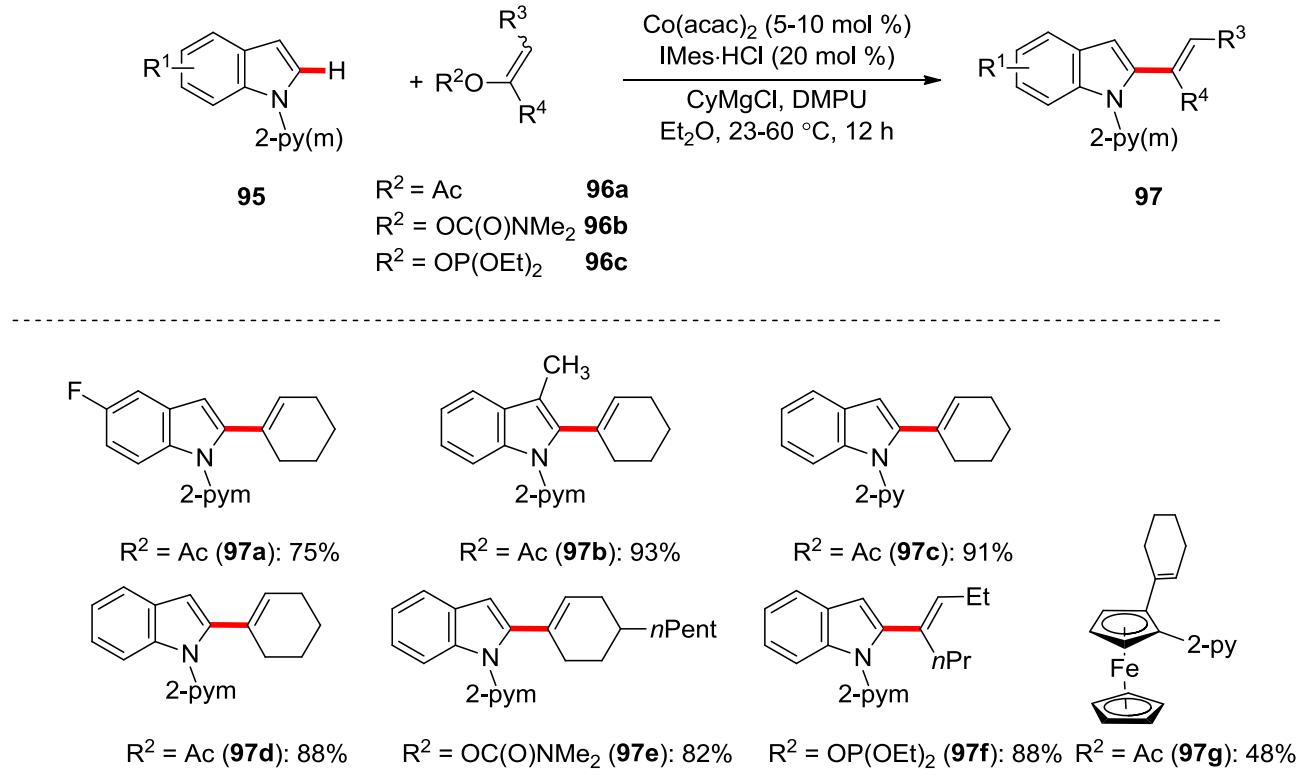
Scheme 35. Cobalt-catalyzed direct alkylation of benzamides **18**.

Later, the Ackermann group reported first C−H arylation reactions with organic electrophiles. The catalytic system consisting of $Co(acac)_2$, IMesHCl as a NHC precursor and cyclohexylmagnesium chloride allowed for the arylation of arylpyridines **61** with organic electrophiles, such as phenol derived aryl carbamates **92a**, sulfamates **92b**, as well as aryl chlorides **92c**. (Scheme 36a).[75] Furthermore, the Yoshikai group contributed to extend the scope of cobalt-catalyzed C−H arylation with organic electrophiles by using ketimines **87** as the directing groups (Scheme 36b).[76]



Scheme 36. Cobalt-catalyzed C−H arylation of arylpyridines **61** and ketimines **87**.

Apart from alkylation and arylation reactions,[74, 75] Ackermann and co-workers showed that low valent cobalt catalysis could be applied for the C−H alkenylation of arenes. In 2015, Ackermann and co-workers presented the first direct alkenylation of (hetero)arenes **95** with easily accessible enol esters **96** (Scheme 37). Under optimal reaction conditions highlighting 10 mol % CoI_2, 10 mol % preligand IPrHCl, 2.0 equivalent of base in DMPU, a varieties of differently substituted heteroarenes **95** were successfully alkenylated.[77] Pleasantly, 2-pyridylferrocene **95g** was successfully alkenylated as well, giving the alkenyl ferrocene **97g**.

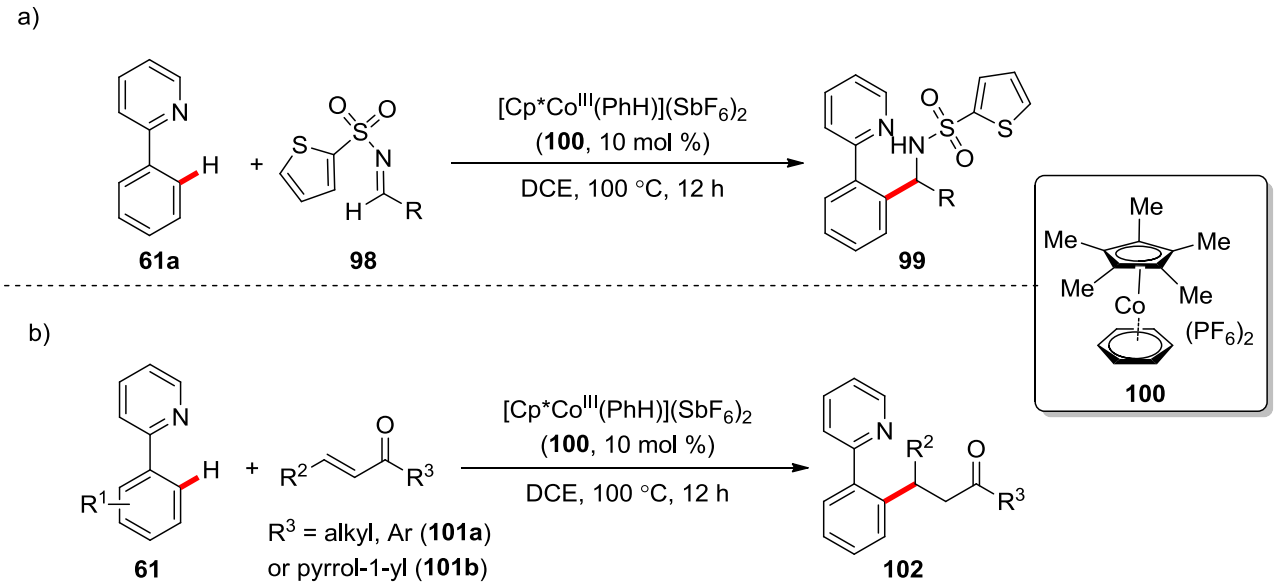


Scheme 37. Cobalt-catalyzed C−H alkenylation of heteroarenes **95**.

1.3.2 High Valent Cobalt(III)-Catalyzed C−H Activation

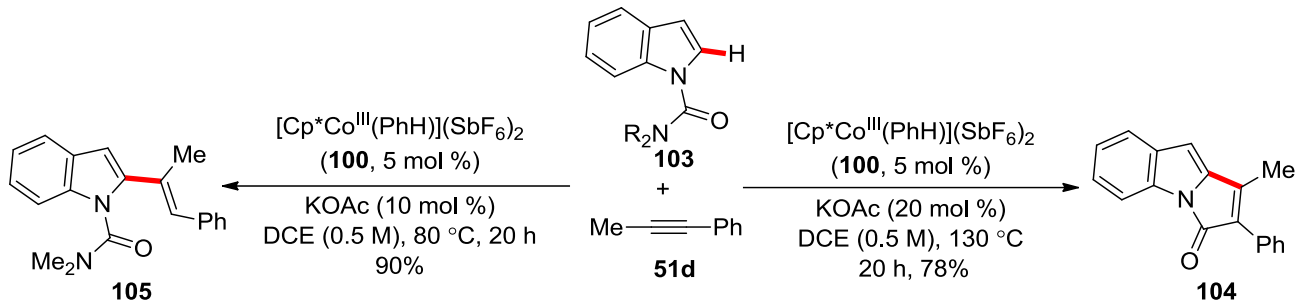
In recent years, C−H activation using Cp*Rh(III)-based catalysts has underwent a remarkable development, a variety of C–C, C–N, and C–O bond formation by means of C−H activation have been achieved under oxidative conditions.[8b, 8c] Although Cp^*Rh^{III}-catalyzed processes are useful and versatile, their high cost limites futher applications. Hence, it is necessary to search for an inexpensive base metal catalyst as an alternative to the cationic rhodium catalysis.[78, 8b, 8c] In 2013, Kanai and co-workers found that a cationic high-valent cobalt complex $[Cp^*Co^{III}(arene)](PF_6)_2$ **100** promoted the addition of 2-aryl pyridines **61** to imines **98**, enones **101a**, and *α*,*β*-unsaturated *N*-acyl pyrroles **101b** as ester and amide surrogates (Scheme 38).[79] It is worth noting that *β*-substituted *α*,*β*-unsaturated esters and amides have not been used successfully in the corresponding direct

addition of a C–H bond catalyzed by Cp*Rh^{III} complexes, which indicated the unique reactivity profile of cobalt(III)-catalysis.



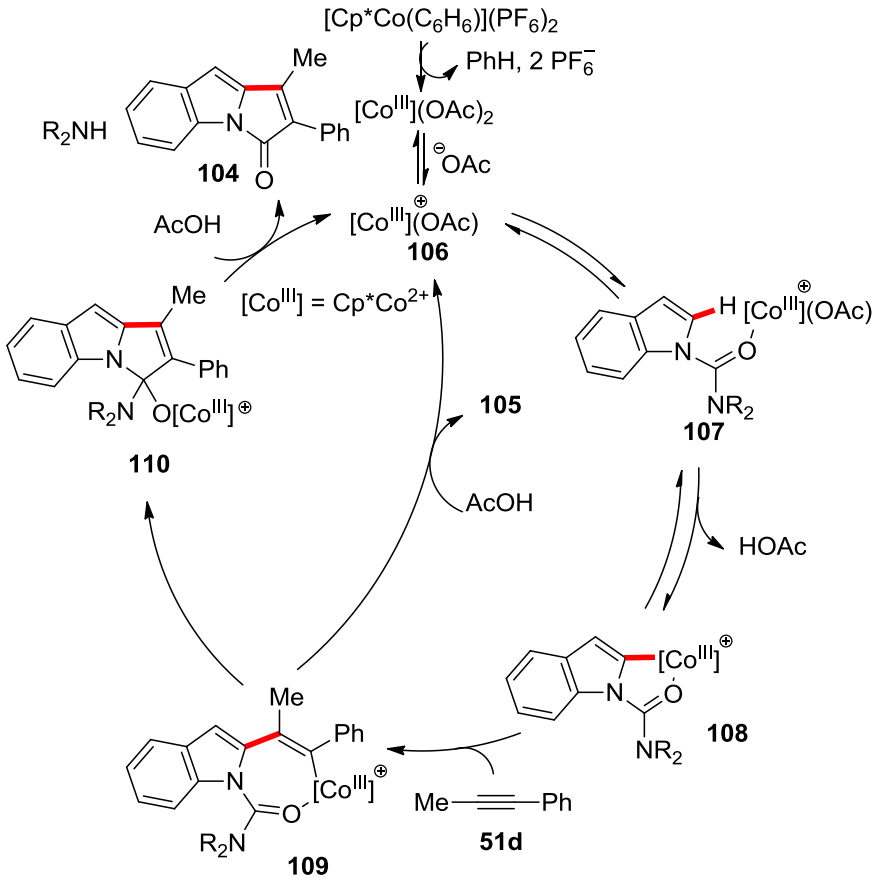
Scheme 38. Cobalt(III)-catalyzed addition reaction of 2-arylpyridines **61** to imines **98** and α,β-unsaturated ketones **101**.

Later, their group developed a C2-selective indole **103** alkenylation/annulation sequence proceeded smoothly in the presence of cobalt complex **100** and KOAc, giving pyrroloindolones **104** in 58−89% yield. By changing the directing group and reaction conditions selectivity alkenylation product **105** can be obtained (Scheme 39).[80] In contrast, Cp*Rh(III)-based catalysts did not afford annulation products under any of the investigated conditions, and only the alkenylation product was observed here. This result highlighted the unique nucleophilic activity of the organocobalt species.



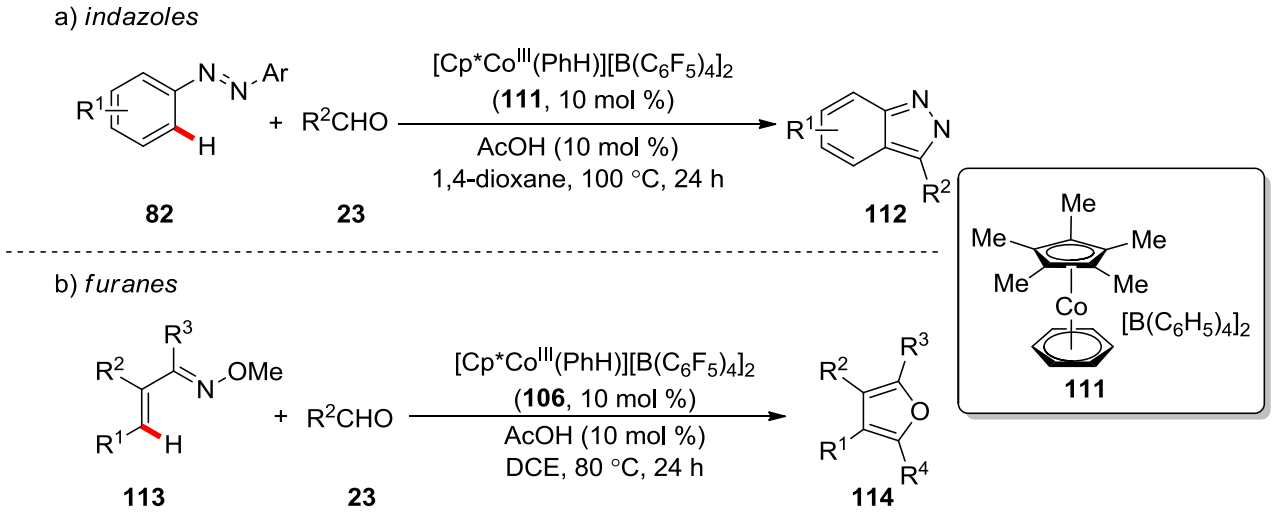
Scheme 39. Cobalt(III)-catalyzed chemoselective C–H alkenylation/annulation of indoles **103**.

Futhermore, the authors proposed a catalytic cycle (Scheme 40). The catalytically active monocationic species **106** was formed by a ligand exchange from cobalt comple **100**. Subsequently, a reversible metalation delivers the cobaltacycle **108** via an acetate-assisted C–H activation mechanism. Then by insertion of alkyne **51d** into the Co–C bond delivers the seven-membered cobaltacycle intermiedate **109**. Next, two ways are possible depending on the directing group, the annulation product **104** was formed by release of morpholine, or protodemetalation delivers the alkenylated indole **105** and regenerates the active monocationic species **106**.



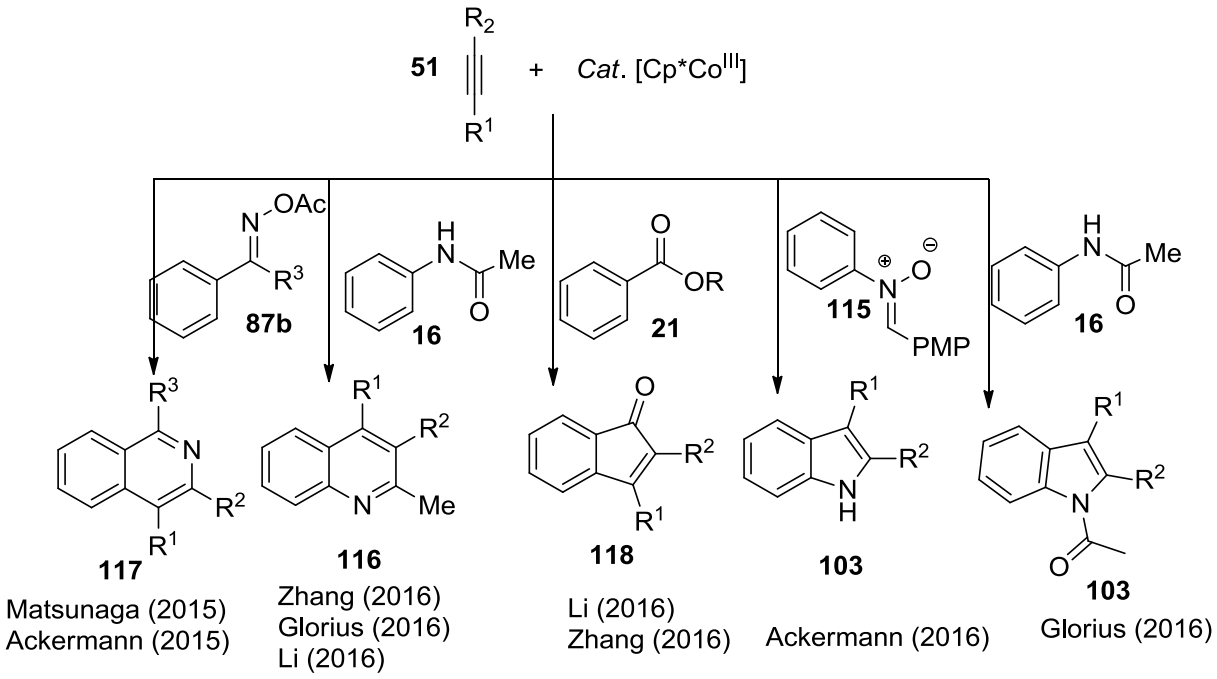
Scheme 40. Proposed catalytic cycle for cobalt(III)-catalyzed hydroarylation/annulation reaction.

Encouraged by the addition reaction of 2-aryl pyridines to amines,[79] the Ellman group reported Cp^*Co^{III}-catalyzed addition of C–H bond to aldehydes **23** to obtain heterocycles. Various indazoles **112** and furans **114** were synthesized from azobenzene **82** and *α*,*β*-unsaturated oxime ethers **113** with aldehydes **23** (Scheme 41).[81]



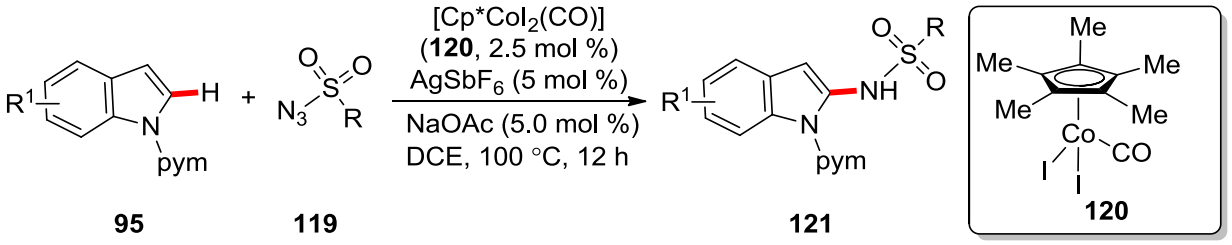
Scheme 41. Cobalt(III)-catalyzed synthesis of indazoles **112** and furans **114**.

In addition, the isohypsic synthesis of heterocyles, such as quinolines **116**,[82] isoquinolines **117**,[83] indenones **118**,[84] indoles **103**,[85, 81b] by cobalt(III)-catalyzed C–H functionalizations proved viable (Scheme 42). These transformations employed anilides **16**, oximes **87b**, benzoates **21**, nitrones **115**, as the directing groups, respectively. The synthesis of heterocyles proceeded smoothly in the presence of Cp*Co(III) complexes and silver additives in good yields. These reports demonstrated that Cp*Co(III) is a prominent catalyst for tandem alkenylation/nucleophilic addition reactions.



Scheme 42. Cobalt(III)-catalyzed synthesis of heterocyles.

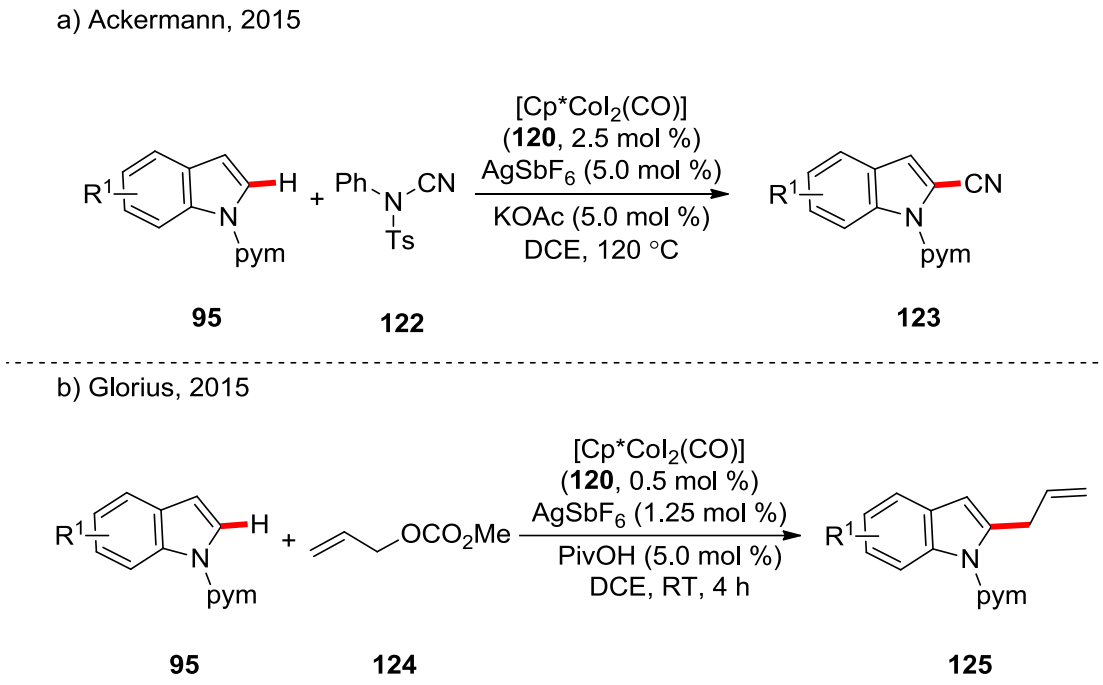
Cp*Co(III) complexes, as have been shown above, have successfully been used in C–H hydroarylation and annulation reactions. Later, the Kanai group found that the air-stable [Cp*CoI_2(CO)] complex **120**, which was first prepared by Li and Jin in 2004,[86] could be applied for C2 selective C–H amidation of indoles **95** with sulfonyl azides **119** (Scheme 43).[87]



Scheme 43. Cobalt(III)-catalyzed C2 selective amidation of indoles **95**.

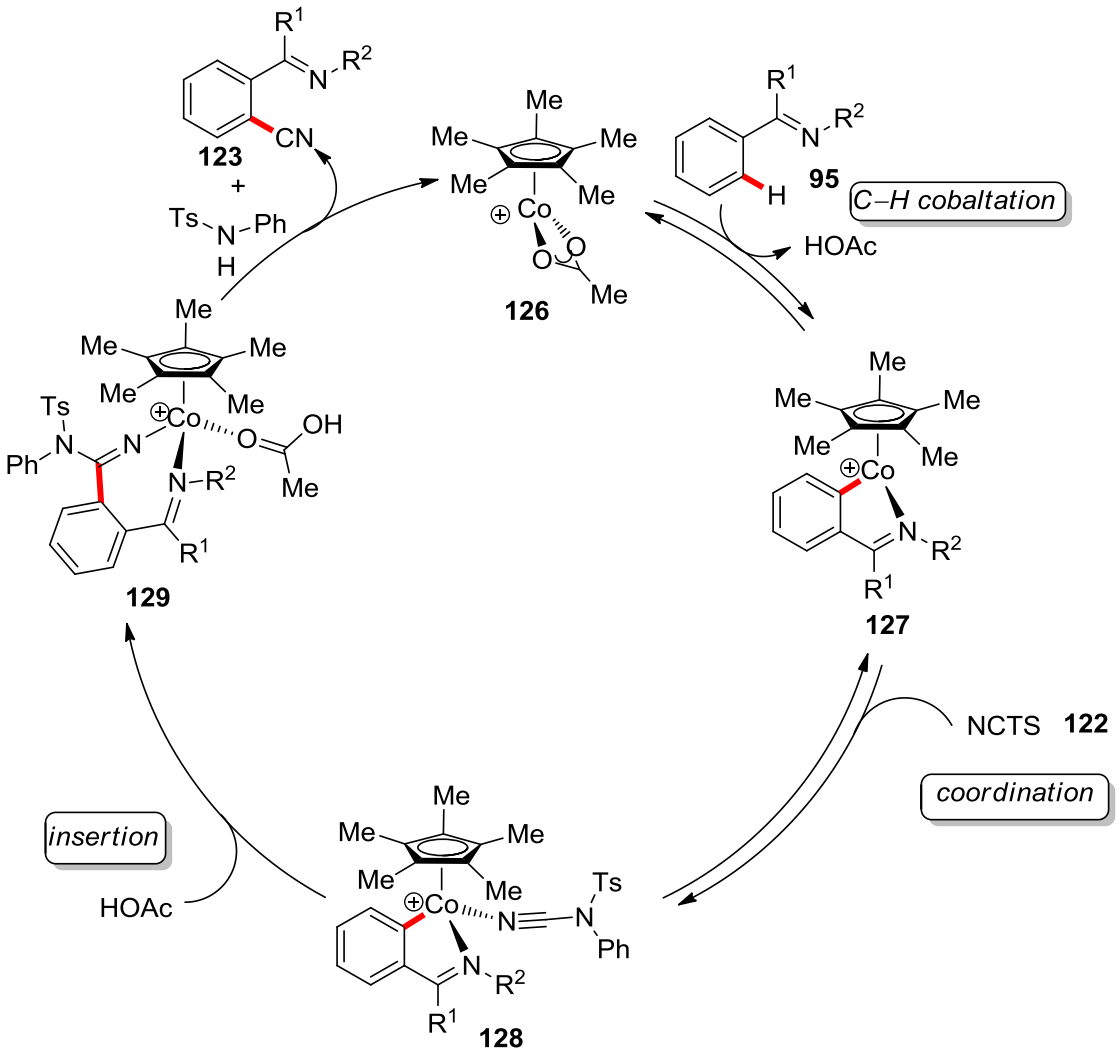
In 2015, the Ackermann group reported the Cp*Co(III)-catalyzed C–H cyanation of arenes **95** using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamid **(122)** as an easy to handle cyanating reagent (Scheme 44).

The C–H cyanation proved to be highly chemo- and regioselective in the presence of 2.5 mol % of [Cp*CoI_2(CO)], 5 mol % of $AgSbF_6$, and 5 mol % of KOAc (Scheme 44a).[88] Thereafter, the Glorius group also developed cobalt-catalyzed cyanation under similar conditions. They also achieved cobalt-catalyzed C–H allylation using pivalic acid instead of acetate salt as a key catalyst component (Scheme 44b).[89]



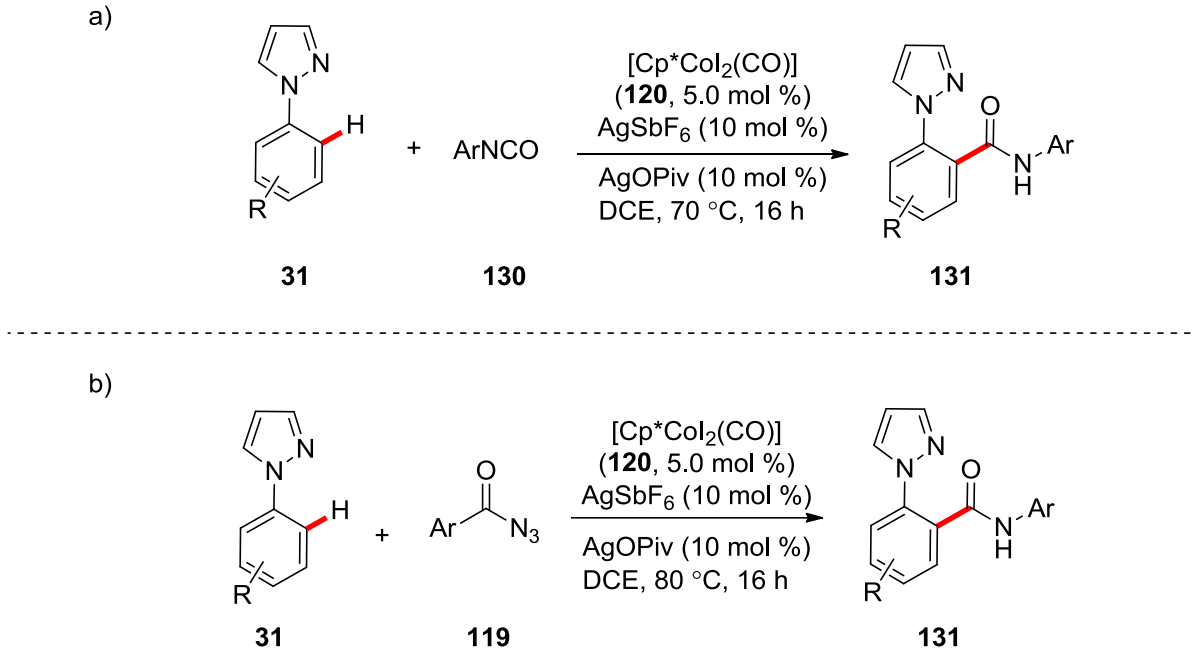
Scheme 44. Cobalt(III)-catalyzed C−H cyanation and allylation.

Based on the experimental results, the Ackermann group proposed a catalytic cycle for the cobalt(III)-catalyzed C–H cyanation (Scheme 45). The catalytic cycle is intitiated by a reversible C–H metalation, involving an acetate-assisted deprotonation pathway to form the cyclometalated complex **127**. Subsequently, coordination and insertion of the cyanation reagent **122** provide the intermideate **128** and **129**. Then proto-demetalation with the *in situ* generated acetic acid provides the desired product **123** and regenerates the catalytically active cobalt(III) catalyst **126**.



Scheme 45. Proposed catalytic cycle for cobalt(III)-catalyzed cyanation.

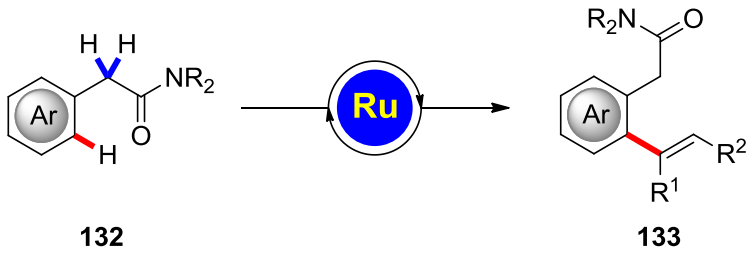
Very recently, the Ackermann group developed the cobalt(III)-catalyzed aminocarbonylation of aryl pyrazoles **31** (Scheme 46).[90] The aminocarbonylation with isocyanates **130** as the electrophiles provide high yield under the reaction conditions consist of 5 mol % of [Cp*Co(CO)I_2] **120** as the precatalyst, along with 10 mol % of $AgSbF_6$ and 10 mol % AgOPiv as the additives (Scheme 46a). As isocyanates are frequently generated in situ from acyl azides by a Curtius rearrangement, the aminocarbonylation with acyl azides **119** as the electrophiles also gave high yields with [Cp*Co(CO)I_2] **120** as the precatalyst (Scheme 46b).



Scheme 46. Cobalt-catalyzed C−H aminocarbonylations of aryl pyrazole **31**.

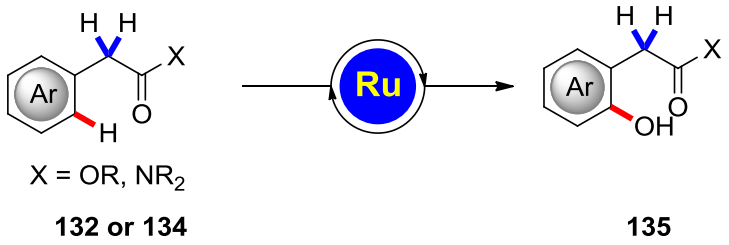
2 Objectives

Substituted arylacetamide moieties are found in many biologically active compounds, drugs and agrochemicals.[91] Ruthenium-catalyzed *ortho*-selective functionalizations of substituted benzamides *via* five-membered metallacycles have been reported.[92, 40] In contrast, contributions on *ortho*-selective functionalizations of weakly coordinating arylacetamides *via* six-membered metallacycles continue to be limited.[93] There is no report on ruthenium-catalyzed C−H functionalizations of substituted arylacetamides. Within our program on cost-effective C−H activation, we herein developed uniquely effective oxidative C−H alkenylations of weakly coordinating acetamides **132**.



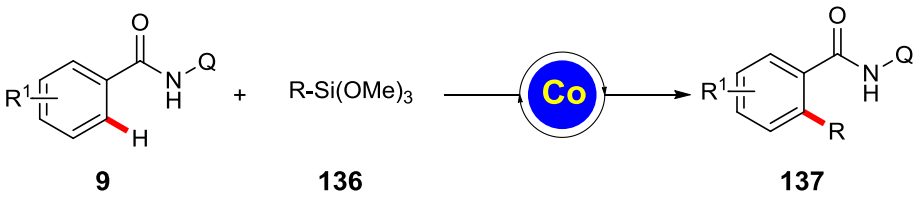
Scheme 47. Ruthenium-catalyzed C−H alkenylation of arylacetamides **132**.

While arenes bearing weakly coordinating directing groups, such as amides,[94] esters,[64] ketones,[61b] or aldehydes[65] were efficiently converted into the corresponding phenol derivatives, C−H oxygenation of distal weakly coordinating acetamides or esters *via* unfavorable six-membered metallacycles have unfortunately proven thus far elusive. Within our research program on ruthenium(II)-catalyzed C−H alkenylation of arylacetamides, we developed a ruthenium-catalyzed C−H oxygenation of weakly coordinating acetamides **132** and phenylacetyl esters **134**.



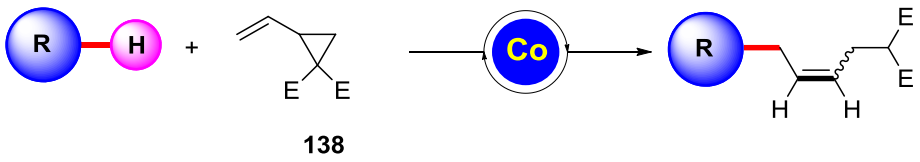
Scheme 48. Ruthenium(II)-catalyzed C–H oxygenation of acetamides **132** and esters **134**.

Organosilicon compounds are useful and ubiquitous synthetic reagents in modern organic chemistry. Among these arylsiloxanes are of particular interest due to their low toxicity and safe handling.[95] Although noble transition metals, such as palladium,[96] rhodium,[97] nickel,[98] iridium[99] and ruthenium[100] have previously been used in C–H arylation reactions with arylsilanes as the arylating reagents, cobalt(II)-catalyzed C–H arylation reactions of arylsiloxanes have not been explored yet. Therefore, we report herein a new cobalt-based catalytic system for the direct C−H arylation of various benzamides **9** using organosilanes **136**.



Scheme 49. Cobalt-catalyzed C–H arylation of benzamides **9** with organosilanes **136**.

In the past few years, high-valent Cp*Co^{III}-derivatives have been identified as increasingly viable tools for the site-selective functionalization of unactivated C–H bonds, yet almost exclusively leading to hydroarylations,[79, 101] allylations[77, 89] or alkynylations.[102] In spite of undisputed advances, cobalt(III)-catalyzed C–H/C–C activations remain highly challenging. In this regard, we developed a cobalt-catalyzed C–H/C–C activation of heteroarenes with vinylcyclopropanes **138**, for which we performed detailed mechanistic studies also.



Scheme 50. Cobalt(III)-catalyzed C–H/C–C functionalization.

3 Results and Discussion

3.1 Distal Weak Coordination of Acetamides in Ruthenium(II)-Catalyzed C–H Activation

Substituted acetamides are key structural motifs in a plethora of bioactive compounds, drugs, and crop protection agents (Figure 3).[91c, 103] C–H activation reactions of distal weakly coordinating acetamides *via* unfavorable six-membered metallacycles continue to be scarce.[91a, 104] For less expensive ruthenium catalysis,[7c, 105] C–H functionalizations of challenging arylacetamides have thus far remained elusive. Thus, we wanted to explore an efficient C–H activation of challenging arylacetamides by ruthenium(II) catalysis.

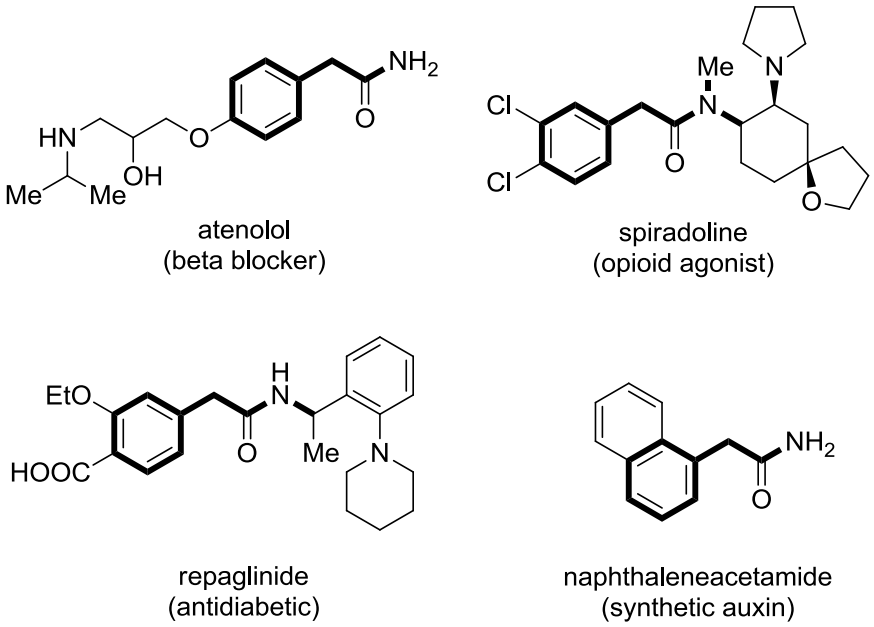


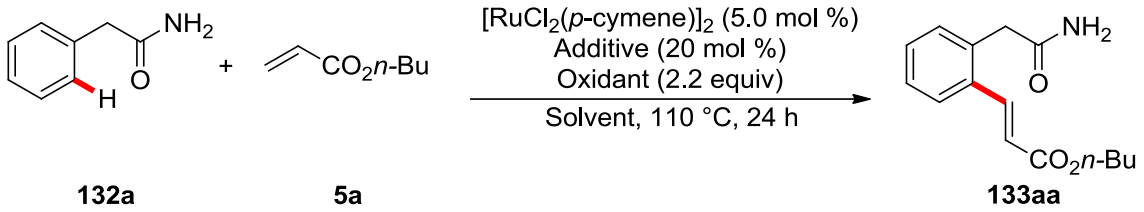
Figure 3. Selected bioactive compounds featuring arylacetamides.

3.1.1 Optimization Studies

Based on the optimized reaction conditions for the ruthenium-catalyzed C–H alkenylation of secondary arylacetamide **132i** developed by my colleague Dr. Vladislav Kotek, various reaction parameters for the envisioned oxidative C–H olefination of challenging primary arylacetamide **132a**

were explored (Table 1). The results showed that the reaction was most efficient with $AgSbF_6$ as the additive and $Cu(OAc)_2 \cdot H_2O$ as the oxidant at 110 °C for 24 h, giving the desired product **133aa** in 64% yield (entry 13). A significant solvent effect was also observed and the best yields were obtained in 1,4-dioxane (entries 1–7). Other oxidants, such as Ag_2CO_3, V_2O_5 or MnO_2, were not effective and only gave the product **133aa** in low yields (entries 10-12). We found that the same yield was obtained using $Cu(OAc)_2 \cdot H_2O$ instead of $Cu(OAc)_2$ (entries 2, 13). The use of $AgBF_4$ or $AgSO_3CF_3$ instead of $AgSbF_6$ resulted in decreased yields (entries 13-15). The crucial importance of the additive and ruthenium catalyst was verified through control experiment (entries 8 and 18).

Table 1. Development of oxidative C–H alkenylation of acetamide **132a**.[a]



132a **5a** **133aa**

Entry	Solvent	Additive	Oxidant	Yield (%)[b]
1	THF	$AgSbF_6$	$Cu(OAc)_2$	48%
2	**1,4-dioxane**	**$AgSbF_6$**	**$Cu(OAc)_2$**	**64%**
3	toluene	$AgSbF_6$	$Cu(OAc)_2$	<5%
4	H_2O	$AgSbF_6$	$Cu(OAc)_2$	--
5	MeOH	$AgSbF_6$	$Cu(OAc)_2$	<5%
6	*o*-xylene	$AgSbF_6$	$Cu(OAc)_2$	<5%
7	DCE	$AgSbF_6$	$Cu(OAc)_2$	48%
8	1,4-dioxane	--	$Cu(OAc)_2$	--
9	1,4-dioxane	$AgSbF_6$	$Cu(OTf)_2$	--
10	1,4-dioxane	$AgSbF_6$	Ag_2CO_3	--
11	1,4-dioxane	$AgSbF_6$	V_2O_5	--

12	1,4-dioxane	$AgSbF_6$	MnO_2	--

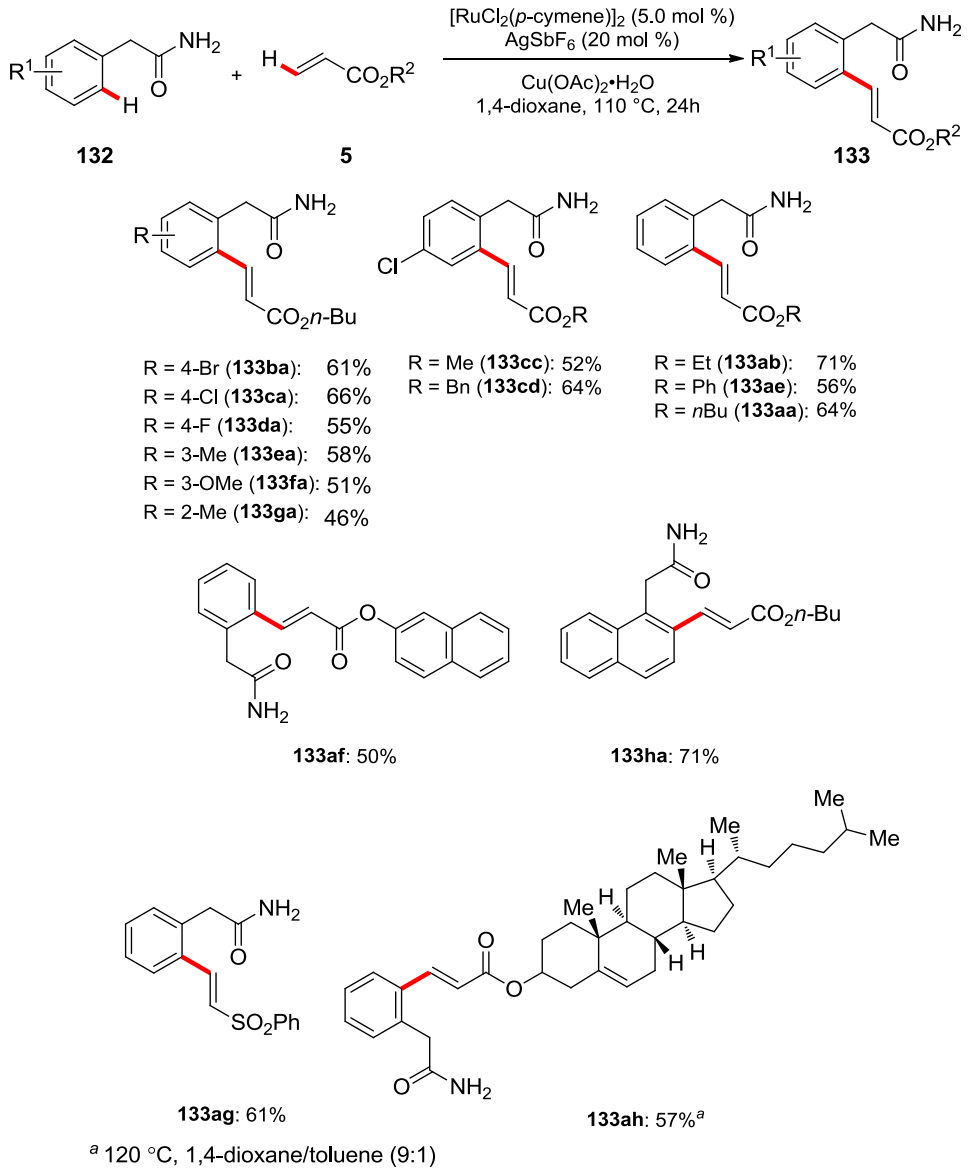
Entry	Solvent	Additive	Oxidant	Yield (%)[b]
13	**1,4-dioxane**	**$AgSbF_6$**	**$Cu(OAc)_2 \cdot H_2O$**	**64%**
14	1,4-dioxane	$AgBF_4$	$Cu(OAc)_2$	53%
15	1,4-dioxane	$AgSO_3CF_3$	$Cu(OAc)_2$	40%
16	1,4-dioxane	$AgSbF_6$	$Cu(OAc)_2$	42%[c]
17	1,4-dioxane	$AgSbF_6$	$Cu(OAc)_2$	53%[d]
18	1,4-dioxane	$AgSbF_6$	$Cu(OAc)_2$	--[e]

[a] Reaction conditions: **132a** (0.50) mmol, **5a** (1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), additive (20 mol %), oxidant (1.10 mmol), 110 °C, solvent (2.0 mL), reaction time 24 h. [b] Yields of isolated products. [c] 80 °C. [d] 120 °C. [e] Without $[RuCl_2(p\text{-cymene})]_2$.

3.1.2 Scope of Ruthenium(II)-Catalyzed C–H Alkenylation

3.1.2.1 Scope of Primary Amides

With the optimized catalytic system in hand, we explored the scope of primary amides-assisted C–H alkenylations with diversely decorated substrates **132** (Scheme 51). Pleasingly, a range of substituents at the *meta*- or *para*- positions (**132b**-**132f**) were tolerated to provide various alkenylated phenylacetamides **133ba**-**133fa** in high yields. Amides containing a napthyl moiety were also effective, providing the desired product **133**. *Ortho*-substitution **132g** slowed the reaction somewhat, but acceptable yields could be obtained nonetheless (Scheme 51). Different alkenes, such as methyl acrylate **5c**, naphthalen-2-yl acrylate **5f**, vinylsulfonylbenzene **5g**, performed very well as the alkene reaction partners. Finally, an *ortho*-alkenylated arylacetamide **133ah** containing sensitive cholesteryl moiety was synthesized in moderate yield as well.

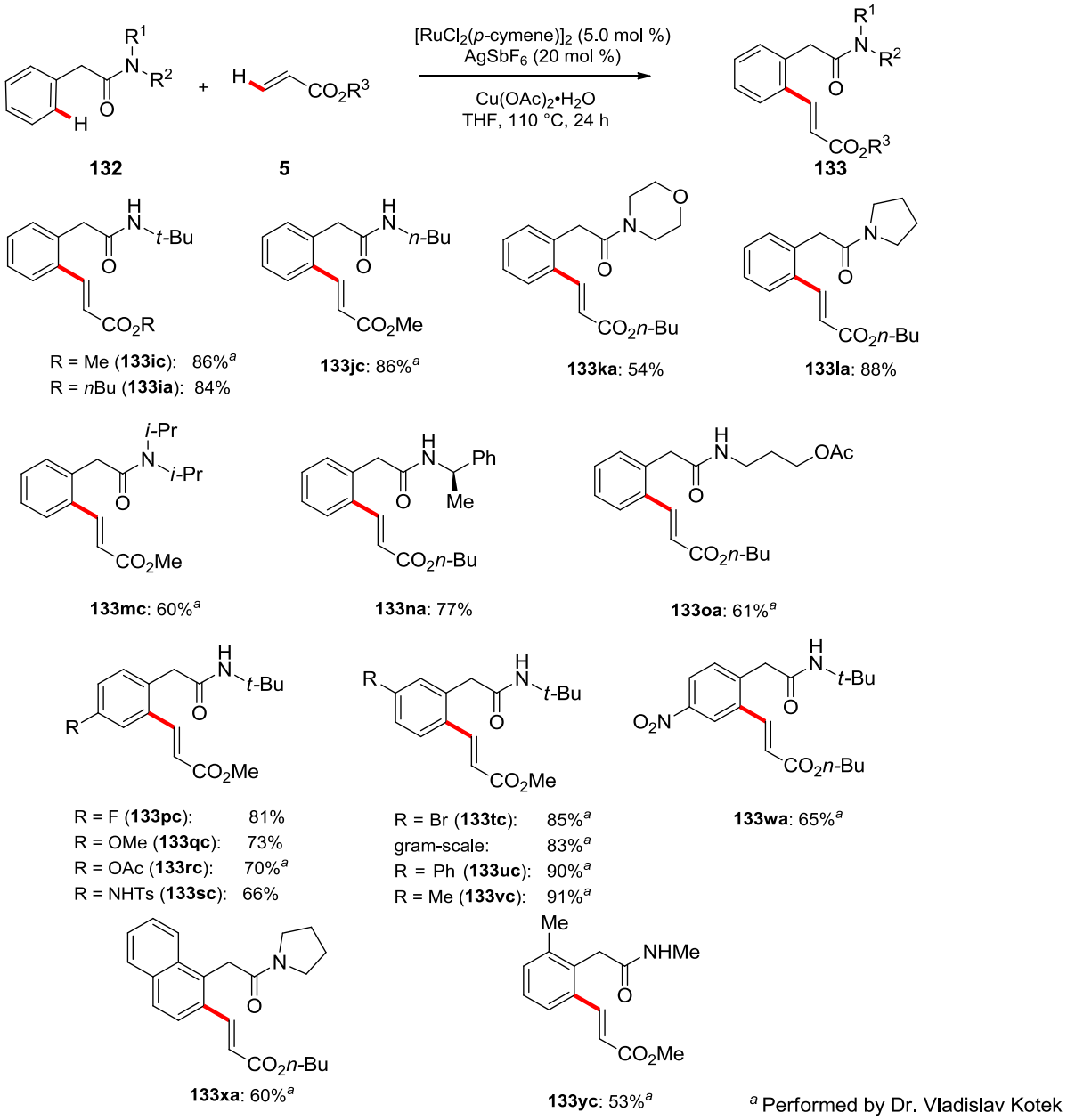


Scheme 51. Scope of primary amides group for the ruthenium(II)-catalyzed C–H alkenylation.

3.1.2.2 Scope of Secondary and Tertiary amides

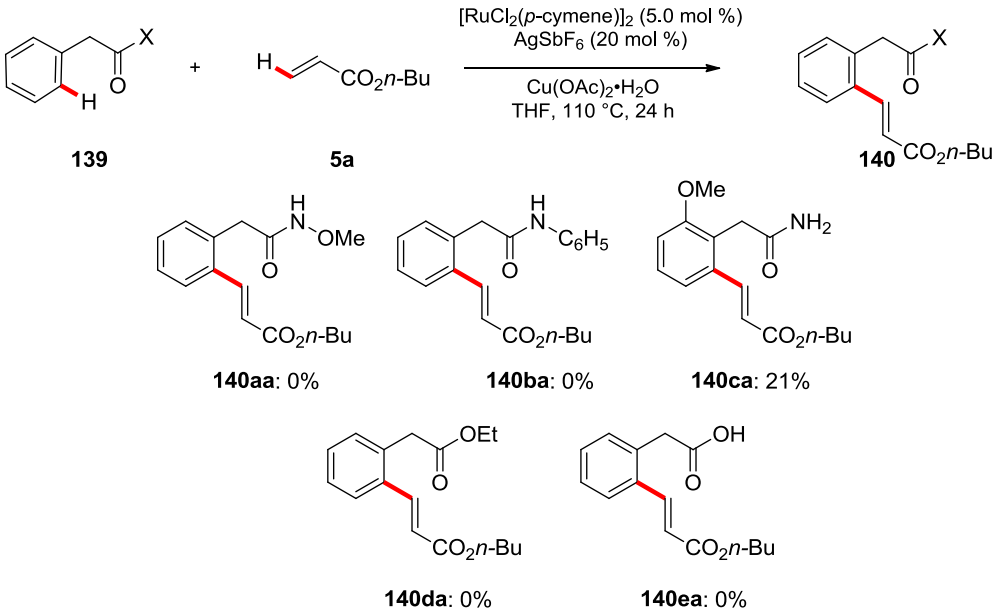
With the optimized reaction condition of C–H alkenylation of secondary amide in hand, and together with Dr. Vladislav Kotek, we explored the scope of the olefination with respect to the amide group, which was expected to have a significant effect on the reaction outcome (Scheme 52). For different substitution on the arene, both electron-donating and electron-withdrawing substituents were tolerated. Olefination of bromo-substituted amide **132t** was carried out on a gram scale and the

resulting product **133tc** could be easily isolated in very good yields by simple aqueous work-up and recrystallization. *Ortho*-substitution was also acceptabled and delivered the alkenylated product **133yc** in acceptable yield. Naphthalene derived substrate **132x** was also viable. The robustness of the ruthenium(II) catalysis was highlighted by racemization-free reaction conditions (**133na**).



Scheme 52. Scope of secondary and tertiary amides group for the ruthenium(II)-catalyzed C–H alkenylation.

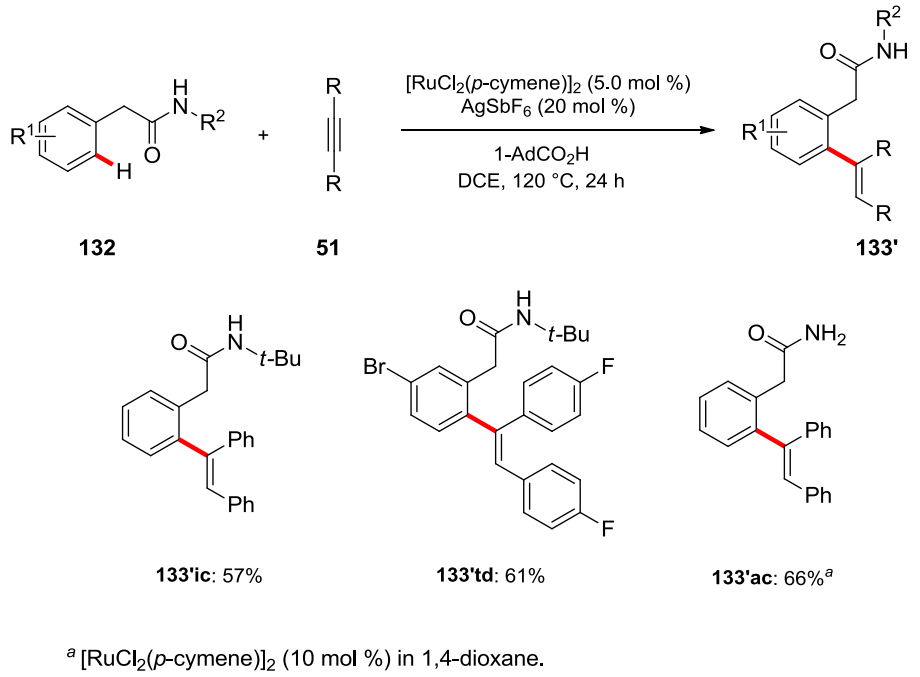
However, some substrates also turned out to be less compatible with the catalytic conditions (Scheme 53). Thus, challenging directing groups, like 2-phenylacetic acid **134e** and ethyl 2-phenylacetate **134d**, were unsuccessful under the developed reaction conditions.



Scheme 53. Limitations of the ruthenium(II)-catalyzed C–H alkenylation with different directing groups.

3.1.3 Weak *O*-Coordination for C–H Activation/Alkyne Hydroarylation

Intrigued by the versatility of the ruthenium(II)-carboxylate catalysis, we became attracted to C–H alkenylations through redox-neutral alkyne hydroarylations. By replacing $Cu(OAc)_2 \cdot H_2O$ with 1-AdCO_2H, the hydroarylation of alkynes **51** could be facilitated (Scheme 54). The ruthenium(II)-catalyzed C–H hydroarylations of acetamides **132** provided a excellent stereoselectivity in accessing trisubstituted alkenes **133'**, again with both secondary and challenging primary amides **132**, respectively.

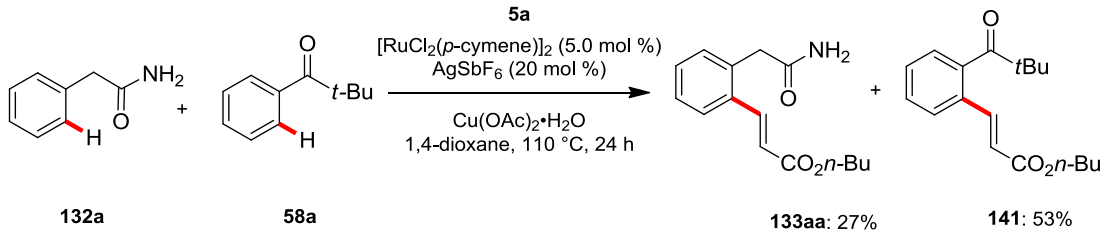


Scheme 54. Ruthenium(II)-catalyzed hydroarylation of alkynes **51**.

3.1.4 Mechanistic Studies

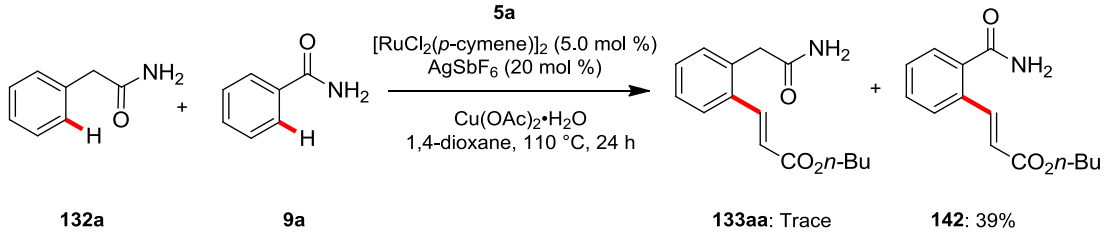
3.1.4.1 Intermolecular Competition Experiments

To gain insights into the reaction mechanism, a set of competition experiments was performed. Intermolecular competition experiment between 2-phenylacetamide **132a** and 2,2-dimethyl-1-phenylpropan-1-one **58a** revealed that although both substrates contain weakly coordinating directing groups, primary amides **132** were found to be even more difficult substrates than ketones **58** in ruthenium-catalyzed C–H functionalizations (Scheme 55).



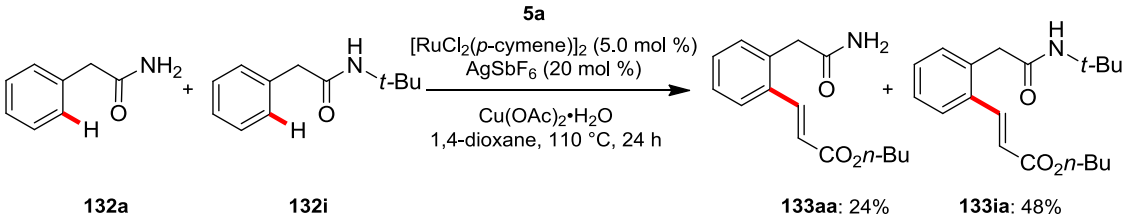
Scheme 55. Intermolecular competition experiment between acetamide **132a** and ketone **58a**.

We also performed an intermolecular competition experiment between benzamide **132a** and 2-phenylacetamide **9a** (Scheme 56). It turned out that almost exclusive functionalization of benzamide **142** was observed. Therefore, it could be concluded that formation of the five-membered ruthenacycle is preferred over formation of the six-membered metallacycle.



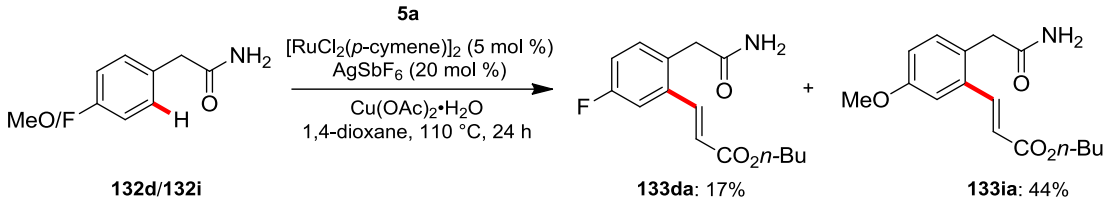
Scheme 56. Competition experiment between benzamide **132a** and 2-phenylacetamide **9a**.

Additionally, a competition experiment between primary and secondary amides showed that the secondary amide **132i** is more reactive and revealed that alkyl-subsititution on the amide nitrogen increases the reactivity (Scheme 57).



Scheme 57. Competition experiment between primary amide **132a** and secondary amide **132i**.

A competition experiment between electron-rich substrate **132i** and electron-deficient substrate **132d** revealed a preferred functionalization of **132i** (Scheme 58), which is not in agreement with a concerted metalation/deprotonation (CMD) mechanism. Instead, the observations are better rationalized by a base-assisted internal electrophilic-type substitution (BIES) process.

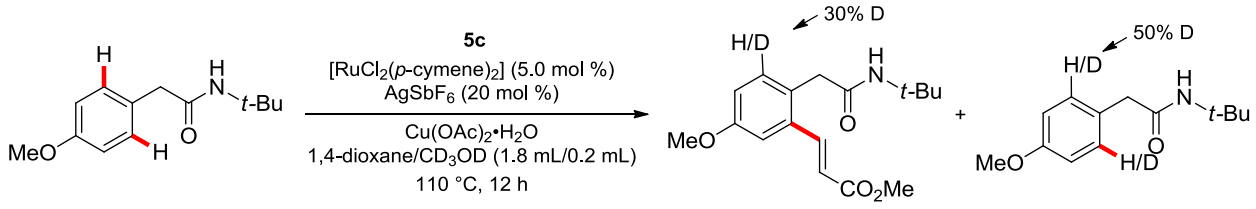


132d/132i **133da**: 17% **133ia**: 44%

Scheme 58. Competition experiment between electron-rich and electron-deficient amides **132**.

3.1.4.2 C–H Alkenylation in the Presence of Isotopically Labelled Cosolvent

To rationalize the C–H activation mechanism, the catalytic reaction was carried out in the presence of deuterated cosolvent CD_3OD under otherwise identical reaction conditions. A significant H/D exchange occurring in the *ortho*-position of the product $[D]_n$-**133qc** and reisolated starting material $[D]_n$-**132q** was observed (Scheme 59). The result suggests that the C–H metalation is reversible.



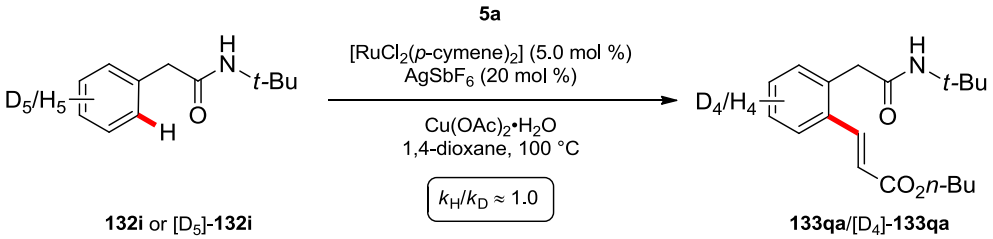
132q $[D]_n$-**133qc**: 60% $[D]_n$-**132q**: 35%

Scheme 59. H/D-exchange study of ruthenium-catalyzed C–H alkenylation.

3.1.4.3 Kinetic Isotope Effect

Kinetic isotope effect (KIE) studies using *in situ* IR spectroscopy to determine the independent reaction rates of undeuterated substrate **132i** and deuterated substrate $[D]_5$-**132i**, resulted in a minor value of $k_H/k_D \approx 1.0$ (Scheme 60). The observed KIE is in good agreement with the results obtained

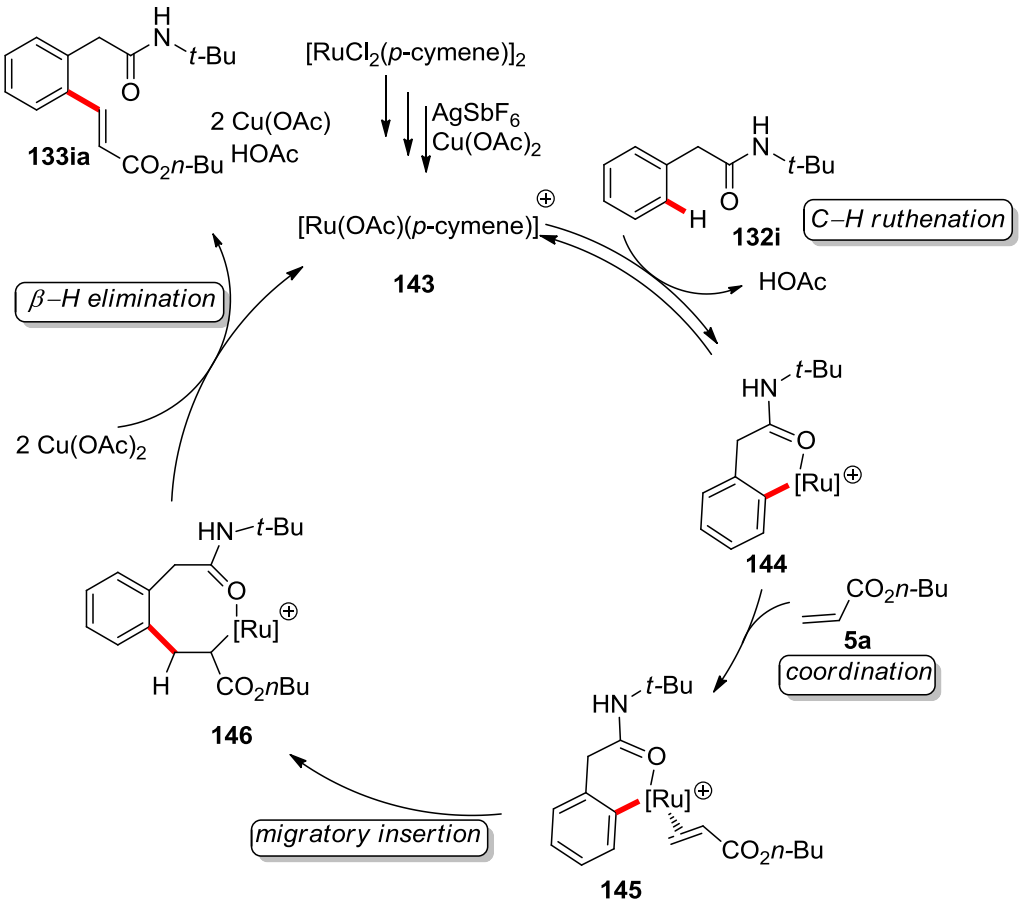
from the H/D-exchange experiments, suggesting the reaction to proceed via a reversible cycloruthenation process.



Scheme 60. KIE experiment for the ruthenium-catalyzed C–H alkenylation.

3.1.5 Proposed Catalytic Cycle

Based on our experimental studies, a plausible catalytic cycle was proposed (Scheme 61). The active catalytic species is formed by reaction of the ruthenium(II) precursor with silver hexafluoroantimonate. The key six-membered ruthenacycle **144** is then formed by a carboxylate-assisted base-assisted internal electrophilic substitution (BIES) event. Additionally, extensive computational studies by DFT calculations were performed by T. Rogge. Comparison between the corresponding five-membered analogue **144'** with the six-membered ruthenacycle **144**, found that **144** is destabilized by 6.9 kcal mol^{-1}, while the deprotonative transition state is 2.8 kcal mol^{-1} higher in energy. Therefore, these results show again that the C–H activation of arylacetamides is more challenging. Accordingly, a coordination of acrylate **5a** leads to intermediate **145**, in which a migratory insertion of the coordinated acrylate **5a** into the carbon-ruthenium bond delivers eight-membered ruthenacycle **146**. Finally, ruthenacycle **146** undergoes β-hydride elimination to form alkene-coordinated complex **143**.



Scheme 61. Plausible catalytic cycle for ruthenium-catalyzed C–H alkenylation.

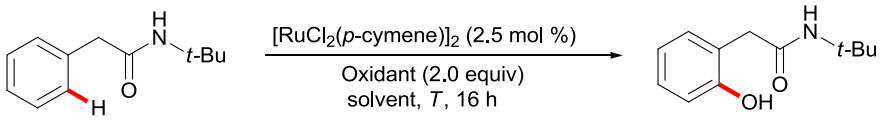
3.2 Ruthenium(II)-Catalyzed C−H Oxygenation of Weakly-Coordinating

The catalytic direct oxygenation of arene C(sp^2)–H bonds represents the most step-economical approach to substituted phenols.[106] Although significant advances have been accomplished, many challenges remain. To date, most research have been focused on metals such as palladium[107] and copper.[108] In contrast, ruthenium was rarely reported in C–H oxygenation reaction. Such kind of transformation was accomplished with versatile ruthenium(II) catalysts.[7c, 18c] Arenes bearing weakly coordinating directing groups, such as amides,[94] esters,[64] ketones,[61b] or aldehydes,[65] were efficiently converted into the corresponding phenol derivatives *via* five-membered metallacycles. While C–H oxygenation with distal weakly coordinating acetamides via unfavorable six-membered metallacycles have unfortunately thus far prove elusive.[93a, 104b] Based on the former results of ruthenium(II)-catalyzed C–H activations of weakly *O*-coordinating arylacetamides performed by our group,[109] we herein present the unique C–H oxygenation of weakly coordinating acetamides.

3.2.1 Optimization Studies for Ruthenium(II)-Catalyzed C−H Oxygenation

We commenced our studies by probing various oxidants and solvents for the envisioned oxygenation of *N*-(*tert*-butyl)-2-phenylacetamide **132i** (Table 2). At the outset, experiments identified hypervalent iodine(III) reagents as the oxidants of choice, the transformation failed to proceed in 1,4-dioxane in the presence of a ruthenium complex and an oxidant (entry 1). DCE was found to be the solvent of choice, whereas PhCl, toluene, DMF, *m*-xylene or CH_3CN gave inferior results (entries 2-6). TFA/TFAA, which acted as a good choice in a previous report of ruthenium-catalyzed C–H oxygenations, turned out to be unsuitable for this reaction (entry 7). 30% of benzofuran-2(*3H*)-one byproduct was observed when using solvent mixure of DCE/TFA (entry 8). Among a set of oxidants, such as $PhI(TFA)_2$, $K_2S_2O_8$, $(NH_4)_2S_2O_4$, $Cu(OAc)_2$ and $PhI(OAc)_2$, $PhI(TFA)_2$ gave the best results (entries 9-13). We also tried to increase or decrease the reaction temperature, but superior results were obtained at a reaction temperature of 110 °C (entries 9, 14-16). There was no conversion of the starting material **132i** in absence of the $RuCl_2$(*p*-cymene)]$_2$ catalyst (entry 17). At last, we found that 5.0 mol % of [$RuCl_2$(*p*-cymene)]$_2$ was best effective to promote the desired reaction (entry 18).

Table 2. Development of oxidative C–H oxygenation of acetamide **132i**.[a]



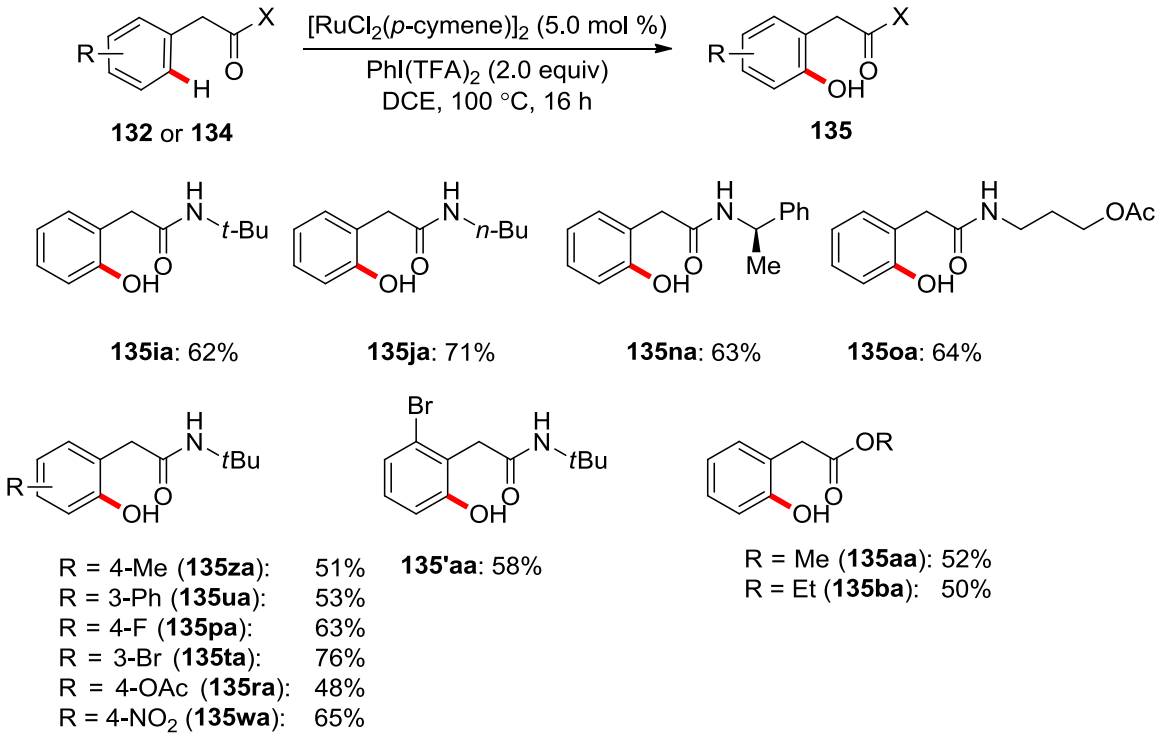
132i **135a**

Entry	Oxidant	Solvent	*T* (°C)	Yield
1	$PhI(TFA)_2$	1,4-dioxane	110	NR
2	$PhI(TFA)_2$	PhCl	110	10%
3	$PhI(TFA)_2$	toluene	110	16%
4	$PhI(TFA)_2$	DMF	110	NR
5	$PhI(TFA)_2$	*m*-xylene	110	15%
6	$PhI(TFA)_2$	CH_3CN	110	ND
7	$PhI(TFA)_2$	TFA/TFAA (3:1)	110	ND
8	$PhI(TFA)_2$	DCE/TFA (4:1)	110	30%[b]
9	$PhI(TFA)_2$	DCE	110	54%
10	$K_2S_2O_8$	DCE	100	NR
11	$(NH_4)_2S_2O_4$	DCE	100	NR
12	$Cu(OAc)_2$	DCE	100	NR
13	$PhI(OAc)_2$	DCE	100	25%
14	$PhI(TFA)_2$	DCE	120	51%
15	$PhI(TFA)_2$	DCE	80	35%
16	$PhI(TFA)_2$	DCE	rt	NR
17	$PhI(TFA)_2$	DCE	110	NR[c]
18	$PhI(TFA)_2$	DCE	100	62%[d]

[a] Reaction conditions: **132i** (0.50) mmol, oxidant (1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), solvent (2.0 mL), reaction time 16 h. [b] Yields of isolated products. [c] without $[RuCl_2(p\text{-cymene})]_2$. [d] 5 mol % of $[RuCl_2(p\text{-cymene})]_2$.

3.2.2 Scope of Acetamides in Ruthenium(II)-Catalyzed C−H Oxygenation

Having optimized the reaction condition, we next set out to explore the scope of the C–H oxygenation reaction. As displayed in Scheme 62, a variety of phenylacetamides **132** were smoothly transformed into the corresponding monohydroxylated products **135** in good yields. The reaction yields roughly correlated with the basicity of the amines incorporated in the amide moiety, and good yields were obtained with secondary amides. The *ortho*-, *meta*-, and *para*-substituted aryl group, as well as electron-withdrawing and electron-donating functional group such as halides and nitro were tolerated. Especially the substrates with eletro-withdrawing group gave the higher yields, such as fluoro and nitro (**132p** and **132w**). *meta*-bromo-substituted substarte **132t** gave the corresponding compound **135ta** as the sole product with good regioselectivity. The sterically hindered *ortho*-bromo substituted acetamide **132'a** was converted to the desired product **135'aa** in moderate yield. Next, we continued to test the feasibility of employing phenylacetyl esters as directing groups in this C–H transformation. We were pleased to find that less reactive phenylacetyl esters were also suitable for this challenging transformation.



Scheme 62. Scope of the ruthenium(II)-catalyzed C–H oxygenation.

3.3 Low-Valent Cobalt-Catalyzed C−H Arylation

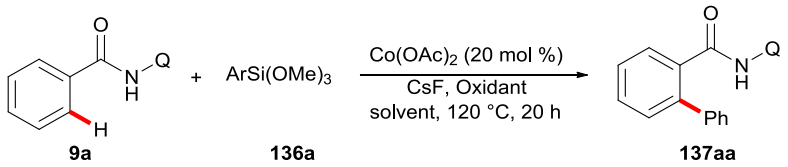
Biaryl motifs are an important class of building blocks in medicinal chemistry and biochemistry, leading to a great interest in the development of novel and efficient methods to asseable biaryl compounds.[110] Among the available methods, the formation of C–C bonds between two substrates by transition metal-catalyzed functionalization of C–H bonds presents the advantages of less synthetic steps and an overall high atom economy.[111] Hiyama cross-couplings have proven to be among the most powerful and reliable ways for C–C bond formation reactions in organic synthesis. Meanwhile, direct arylation of aromatic C–H bonds has received much attention as a potentially more efficient and complementary approach to the conventional cross-coupling methodology.[13b, 112] In 2007, the direct arylation of acetanilide with organosilanes was reported.[113] Subsequently, significant progress has been achieved using organosilanes as coupling partners in the transition-metal-catalyzed C–H arylations, with pioneering work demonstrating the utility of direct Hiyama C–H arylation based on palladium,[96a, 114] nickel,[98] rhodium,[97, 115] iridium[99] and ruthenium[100] catalysis. However, the use of organosilanes as viable cross-coupling partners in cobalt-catalyzed C–H functionalization remains unknown. Herein, we report the first cobalt-catalyzed the direct C–H arylation of benzamides with organosilanes, which notably avoids the use of stoichiometric amounts of Grignard reagents.[66b, 76, 116]

3.3.1 Optimization Studies

We began our studies by the treatment of benzamide derivative **9a** and trimethoxyphenylsilane **136a** with 20 mol % of $Co(OAc)_2$, 3.0 equivalents of CsF and 2.0 equivalents of CuF_2 in DMSO at 120 ^oC (Table 3, entry 1). The desired arylation product **137aa** was formed in 20% yield. Encouraged by this promising result, a variety of solvents were probed (entries 2-9), and NMP was found to be the reaction medium of choice with a yield of 65% (entry 8). It is worth noting that a moderate yield was obtained when the reaction was performed in green biomass-derived γ-valerolactone (GVL) (entry 7), showing the potential of the use of such green solvents in arylation reactions. Next, we investigated the effect of several oxidants in this reaction. The desired product **137aa** was obtained in 36% yield in the presence of $Cu(OAc)_2$ (entry 13), while no product was observed when replacing on CuF_2 by other oxidants, such as air, $Mn(OAc)_2$ or AgOPiv (entries 14-16). Decreasing the amount of CuF_2 to

1.0 equivalent or less gave inferior results (entries 11-12). To our delight, the desired product **137aa** could be isolated in 72% yield, when decreasing the reaction temperature to 100 °C.

Table 3. Optimization of the cobalt-catalyzed C–H arylation of benzamide **9a**.[a]

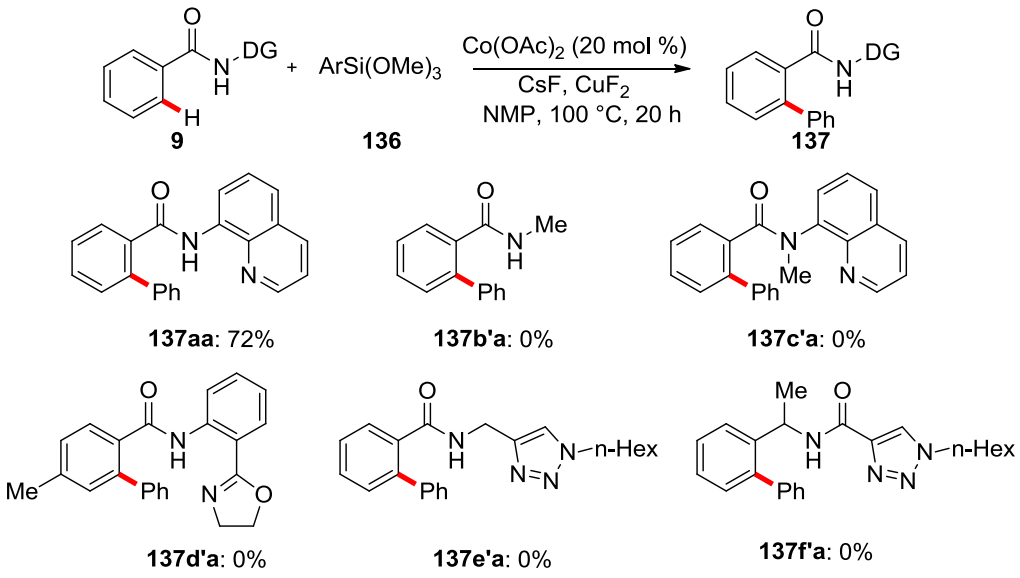


Entry	Solvent	Oxidant (equiv)	Isolated yield
1	DMSO	CuF_2 (2.0)	20%
2	DCE	CuF_2 (2.0)	18%
3	DMF	CuF_2 (2.0)	53%
4	Toluene	CuF_2 (2.0)	–
5	THF/H_2O	CuF_2 (2.0)	–
6	DMA	CuF_2 (2.0)	–
7	GVL	CuF_2 (2.0)	50%
8	NMP	CuF_2 (2.0)	65%
9	pyridine	CuF_2 (2.0)	–
10	NMP	CuF_2 (2.0)	10%[b]
11	NMP	CuF_2(1.0)	36%
12	NMP	CuF_2(0.5)	17%
13	NMP	$Cu(OAc)_2$ (2.0)	36%
14	NMP	air	–
15	NMP	$Mn(OAc)_2$ (2.0)	–
16	NMP	AgOPiv (2.0)	Trace
17	**NMP**	**CuF_2** (2.0)	**72%**[c]
18	NMP	CuF_2 (2.0)	71%[d]

[a] Reaction conditions: **9a** (0.25 mmol), **136a** (0.5 mmol), $Co(OAc)_2$ (20 mol %), CsF (3.0 equiv), oxidant (2.0 equiv), solvent (1.0 mL), under N_2. [b] without $Co(OAc)_2$. [c] 100 °C. [d] CsF (1.5 equiv).

We next examined the effect of the directing groups (Scheme 63). No phenylation took place when *N*-methyl benzamide **9b'** was used instead of substrate **9a**. Furthermore, the use of *N*-methyl amide **9c'** also failed to deliver the phenylation product, indicating that the presence of an NH-motif on the amide nitrogen is required for the reaction to proceed. The reaction appears to be more successful for

the 8-aminoquinoline motif. Directing groups, such as found in compounds **9d'**, **9e'** and **9f'** which have been extensively used in the transition-metal-catalyzed functionalization of C−H bonds,[117] were also ineffective. Therefore, the presence of an *NH* bond as well as the strougly-coordinatiy quinoline nitrogen is neccessary for the success of the reaction.

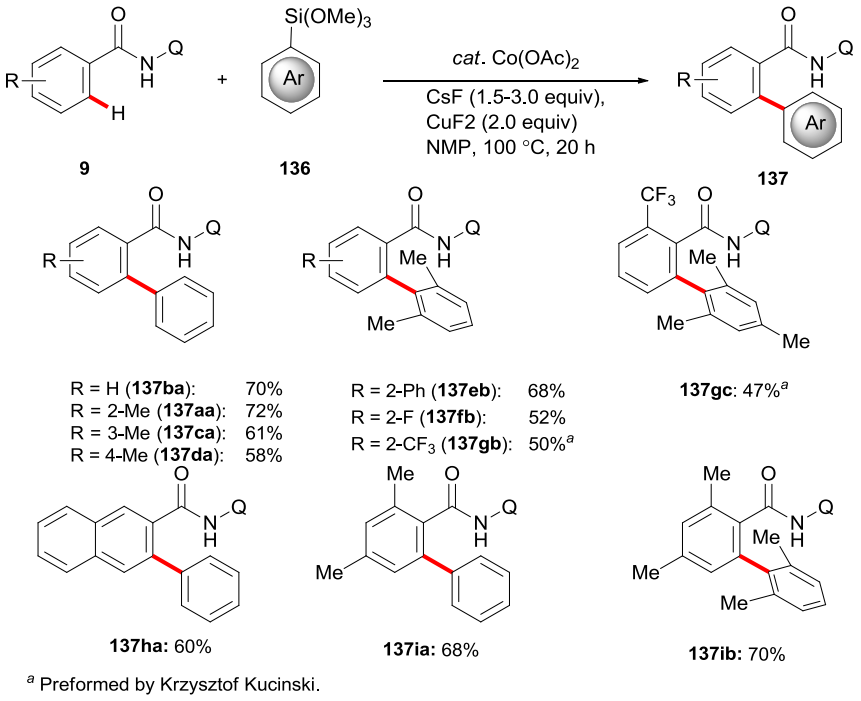


Scheme 63. Effect of *N*-substituents on cobalt-catlyzed C–H arylation.

3.3.2 Scope of Cobalt-Catalyzed C–H Arylation

3.3.2.1 Scope of benzamides

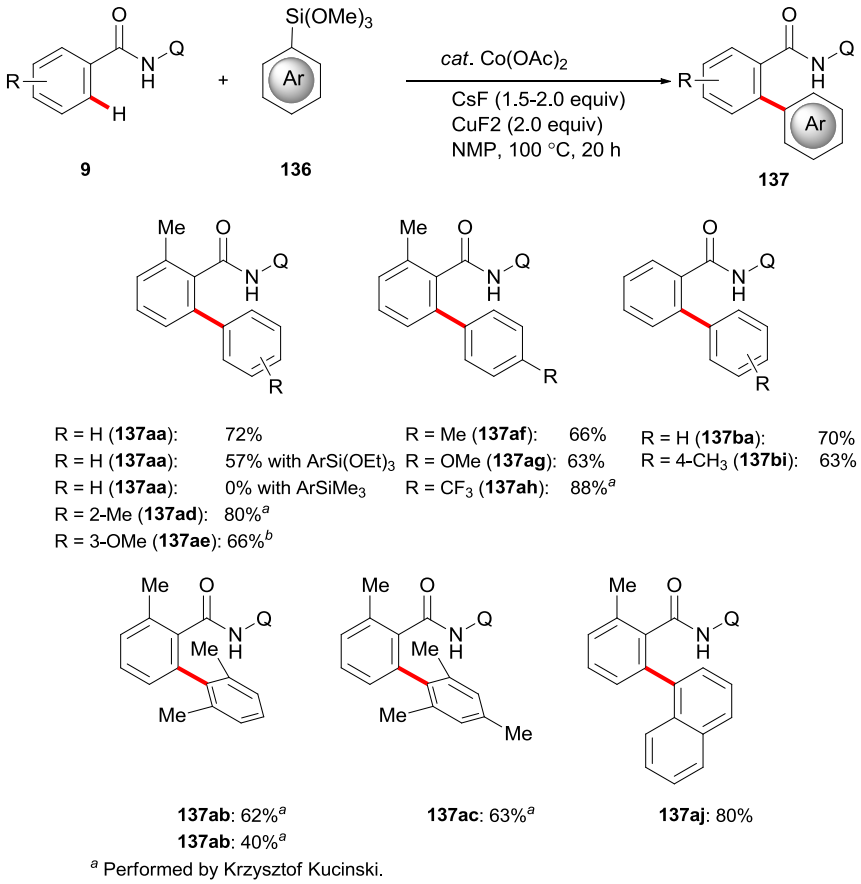
With the optimized reaction conditions in hand, we explored the scope of the cobalt(II)-catalyzed C–H arylation of arenes **9**. As shown in Scheme 64, various benzamide substrates **9** were successfully applied to the C–H arylation. Both electron-donating and electron-deficient substituents were tolerated, giving the biaryl products **137** in moderate to high yields. A broad range of functional groups, such as fluoro were compatible with the C–H activation. Naphthamide and dimethyl-substituted benzamide **9h** and **9i** were also viable substrates, giving **137ha** and **137ia** in 60% and 68% yield, respectively.



Scheme 64. Scope of cobalt-catalyzed C–H arylation of amides **9**.

3.3.2.2 Scope of Arylsilanes

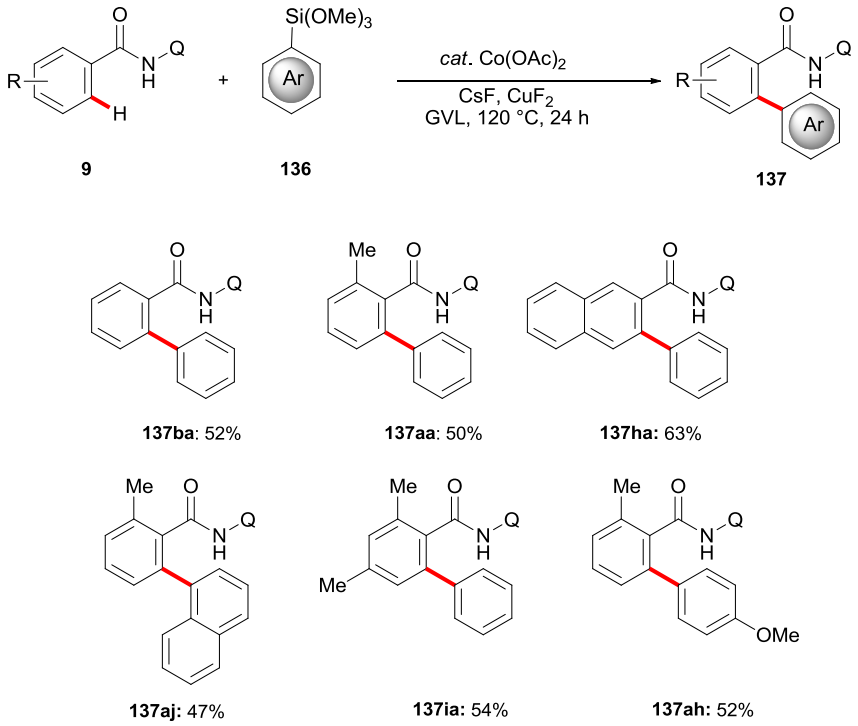
The scope of various organosilanes under the standard reaction conditions was then investigated (Scheme 65). Under the optimized reaction conditions, triethoxyarylsilane gave a lower yield, while trimethylarylsilane was not a viable arylating regent at all. Next, a range of trimthoxyarylsilanes **136** were tested. It is worth noting that triethoxyarylsilanes bearing a methyl group or dimethyl group at the *ortho*- or di*ortho*- position gave the desired arylated products **137ae** and **137ab** in 80% and 62% yields respectively, showing that the reaction is not sensitive to steric hindrance. It should be noted that *ortho*- substituted trimthoxyarylsilanes **136b** gave a higher yield with a lower amount of CsF (**137ab**). Furthermore, naphthyl organosilane **136j** could also participate in the C–H arylation, affording the desired product **137aj** in 80% yield.



Scheme 65. Scope of cobalt-catalyzed C–H arylation of amides **9** with organosilanes **136**.

3.3.2.3 Scope of the Cobalt(II)-Catalyzed C–H Arylation of benzamides in GVL

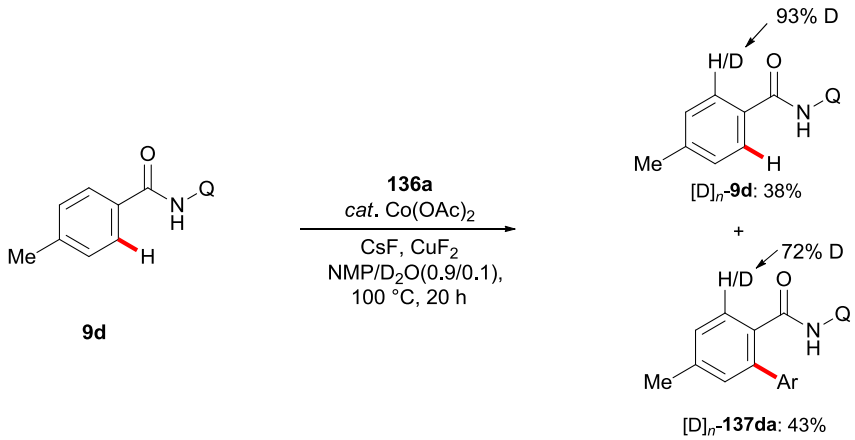
During the optimization of the reaction conditions, the reaction was found to proceed with a moderate yield when using the biomass-derived solvent GVL. We subsequently became interested to explore the scope of the C–H arylation reaction in thid green medium (Scheme 66). Surprisingly, under this reaction conditions, a minor decrease in reactivity was observed, with yields being around 10%-20% less than under the optimized reaction conditions, except for naphthyl benzamide **9h**.



Scheme 66. Scope of cobalt-catalyzed C–H arylation of amides **9** in biomass-derived GVL.

3.3.3 Mechanistic Studies – H/D-Exchange Experiment

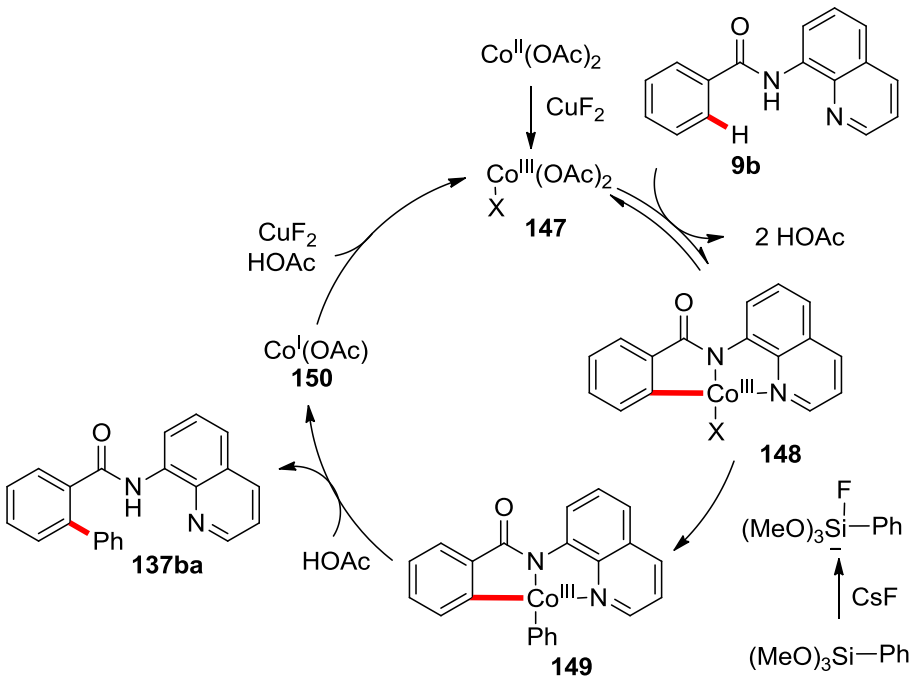
In order to gain insights into the reaction mechanism, a catalytic reaction in the presence of deuterated cosolvent D_2O was carried out under otherwise identical reaction conditions (Scheme 67). The results indicated a significant H/D scrambling in the reisolated starting material $[D]_n$-**9d** as well as in the product $[D]_n$-**137da**. This observation is indicative of a facile C–H activation by the cobalt catalyst.



Scheme 67. H/D-exchange study of cobalt-catalyzed C–H arylation.

3.3.4 Proposed Catalytic Cycle

Based on the above results, we propose a catalytic cycle to initiate by the formation of the cobalt(III) species **147** by oxidation (Scheme 68). Thereafter, a C–H activation step occurs to give the cobalt complex **148**. A fluoride-promoted transmetalation[118] then afforded the cobalt(III)−aryl intermediate **149**. Subsequent reductive elimination provide the arylated product **137ba** together with the formation of a cobalt(I) species **150**, which is reoxidized to cobalt(III) species by the action of CuF_2 to complete the catalytic cycle.



Scheme 68. Plausible catalytic cycle for the cobalt-catalyzed C–H arylation.

3.4 Cobalt(III)-Catalyzed C−H/C−C Functionalization

In recent years, the use of naturally abundant 3d transition metal catalysts for C−H functionalizations has been identified as an increasingly powerful tool for molecular syntheses.[11a, 12a, 119] Particularly, inexpensive cobalt catalysts bear high potential due to the efficient transformations catalyzed by its congeners rhodium and iridium. In early examples, low-valent cobalt catalyzed C−H functionalizations generally required a Grignard reagents as the additives.[12b] More recently, the importance of high-valent Co(III)-catalyzed chelate-assisted C−H bond functionalizations has been demonstrated by Ackermann,[102c, 120] Glorius,[82b, 89] Ellman,[121] and Chang[122] following early work by Matsunaga and Kanai.[83a, 123] High-valent [Cp*Co^{III}] complexes have been applied for the site-selective functionalization of unactivated C−H bonds.[85, 124]

Within our research program on [Cp*Co^{III}]-catalyzed C−H functionalizations,[12a, 83b] we decided to explore the distinct selectivity features of cobalt(III) catalysis. Therefore, we selected the reaction of indoles with vinylcyclopropanes as a model system to realize C−H/C−C functionalizations with high selectivity control.

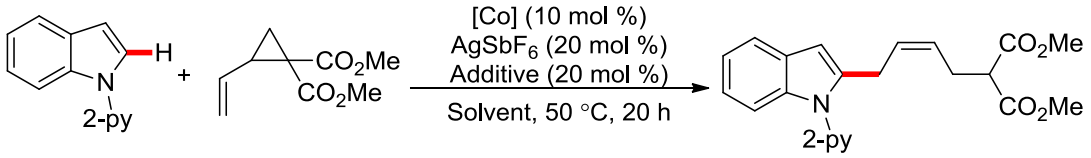
3.4.1 Optimization Studies

Optimization studies on the cobalt(III)-catalyzed C−H/C−C activation are summarized in Table 4. Solvent optimization revealed that DCE was the most efficient reaction medium. When the reaction was conducted in DCE using [Cp*Co(CO)I_2] as the catalyst and PivOH as the additive at 50 ^{o}C, the desired product **151aa** was isolated in 87% yield (entry 1). Keeping PivOH as the additive, switching the solvent to MeOH or TFE, the yield of product **151aa** significantly decreased. An even lower conversion of the starting material **95a** was observed using H_2O as the solvent (entry 3). Moreover, the additive had a significant impact on the reaction efficiency. Only trace of product **151aa** was detected when $Mg(OPiv)_2$ was used. The yield was improved when 10 mol % of [Cp*Co(CO)I_2] and NaOPiv was employed. This reaction was performed by Dr. Daniel Zell during his study on the effect of various acetate and pivalate bases, which resulted in finding that sodium pivalate was the optimal base. Furthermore, different cobalt(III) sources were tested, the results indicated that silver additives are not necessary for the reaction (entry 8) and other ligands are inferior to cyclopentadienyl group (entries 9 and 10).

Notably, all tested reaction conditions exclusively furnished the thermodynamically less favored *Z* diastereomer in very good selectivities. When treating the substrates with the related [Rh^{III}Cp*]

catalyst, a mixure of the *E/Z* diastereomers was obtained with a minor bias for the *E* diastereomer (entry 11).

Table 4. Optimization study for the Co(III)-catalyzed C–H/C–C functionalization.[a]



95a **138a** **151aa**

Entry	Solvent	Additive	Yield [%]
1	DCE	PivOH	87
2	TFE	PivOH	45
3	H_2O	PivOH	30
4	CH_3OH	PivOH	76
5	DCE	$Mg(OPiv)_2$	70[b]
6	DCE	$(t\text{BuCO})_2O$	61
7	**DCE**	**NaOPiv**	**93[c]**
8	DCE	NaOPiv	77[d]
9	DCE	NaOPiv	18[e]
10	DCE	NaOPiv	10[f]
11	DCE	NaOPiv	77[g]

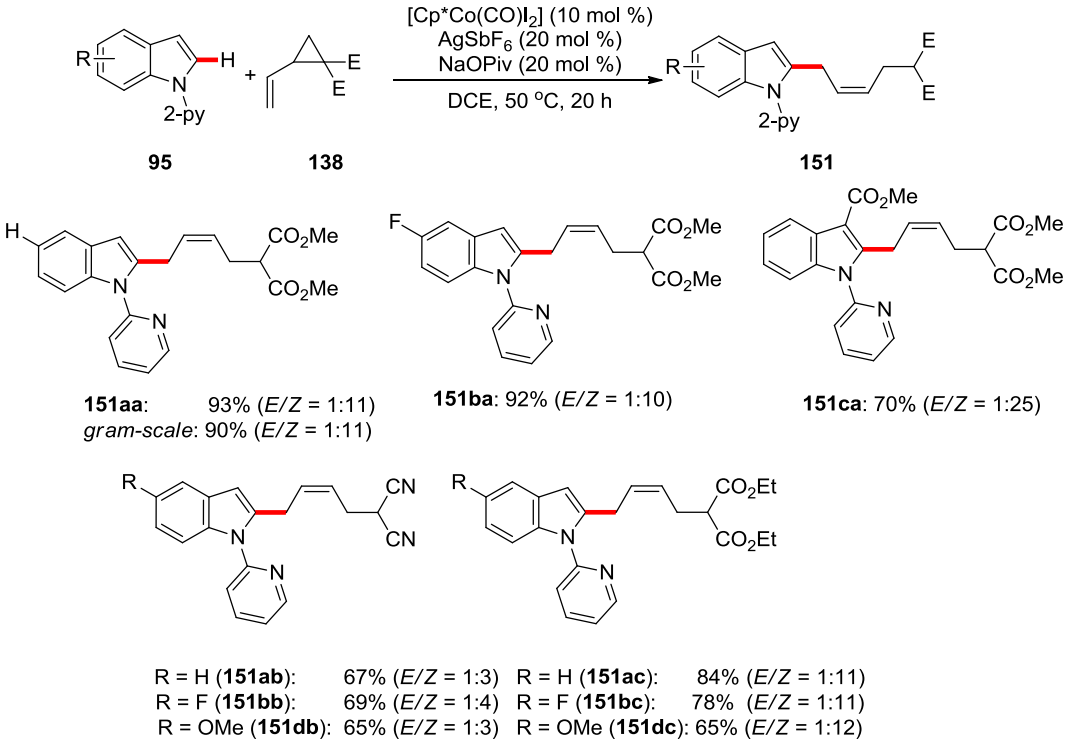
[a] Reaction conditions: **95a** (0.50 mmol), **138a** (0.60 mmol), [Cp*Co(CO)I_2] (10 mol %), $AgSbF_6$ (20 mol %), additive (20 mol %), solvent (1.0 mL), 50 °C, 20 h, isolated yield. py = pyridyl, all *E/Z* = 1:11. [b] $Mg(OPiv)_2$ (10 mol %). [c] performed by Dr. Daniel Zell. [d] $[CoCp^*(CH_3CN)_3](SbF_6)_2$.. [e] $[Co(CO)Cp^{1,3\text{-}t\text{Bu}}I_2]$. [f] $[Co(CO)CpI_2]$. [g] $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (10 mol %), *E/Z* = 2:1.

3.4.2 Scope of the Cobalt(III)-Catalyzed C–H/C–C Functionalization

With the optimized reaction conditions in hand, the scope of viable indoles **95** and cyclopropanes **133** was examined (Scheme 69). First, substituents in the C5-position of indole **95b** were tested, good yields and diastereoselectivities were achieved. Moreover, the utility of this method was further demonstrated by the 5 mmol-scale reaction, which provided the corresponding product **151aa** in 90%

yield. A sterically demanding substituent in C3-position was tested, furnishing the desired product **151ca** in good yield and excellent *E/Z* selectivity of 1:25. The observed selectivity is totally different from the one obtained in the rhodium-catalyzed C−H/C−C bond activation.[125] A reasonable explanation for this unexpected finding could be the involvement of stabilizing London dispersion interactions,[126] partly exhibited by the pyridyl-ring, which was highlighted by the DFT-calculations performed by Dr. Feldt.[127]

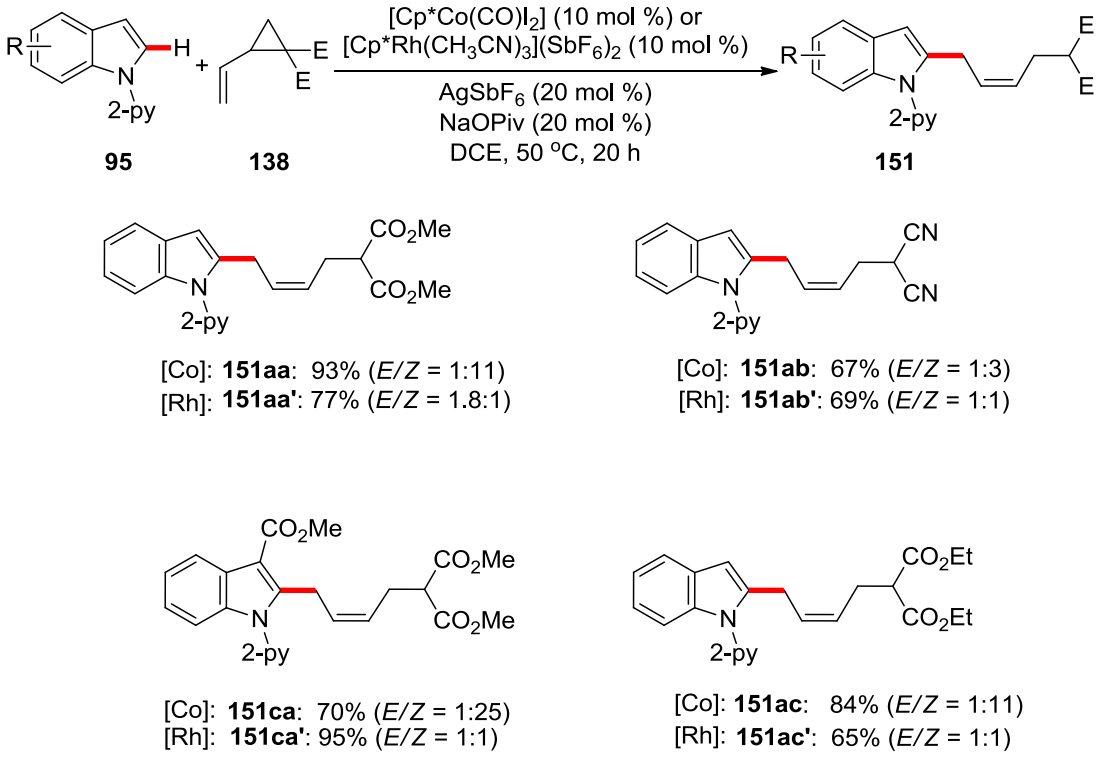
Second, various vinylcyclopropane substrates **138** were tested. Vinylcyclopropanes could easily be obtained from the corresponding activated methylene compounds and (*E*)-1,4-dibromobut-2-ene.[128] Electron-withdrawing groups such as methyl ester and ethyl ester were successfully employed in this reaction, giving the corresponding products in good to excellent yields and good *E/Z* selectivity ranging from 1:11 to 1:25. In contrast, the use of dicyano vinylcyclopropane **138c** provided the desired product in moderate yields and rather moderate *E/Z* selectivity.



Scheme 69. Scope of the cobalt(III)-catalyzed C–H/C–C functionalization of indoles **95** and vinylcyclopropanes **138**.

3.4.2.1 Comparison between Cobalt(III) and Rhodium-catalyzed C–H/C–C Functionalization

Next, under otherwise identical reaction conditions, we also probed the reactivity and selectivity of the related rhodium(III) catalyst (Scheme 70). While the less stable *Z* diastereomer was formed with high selectivity in all cases under cobalt catalysis, rhodium(III) complexes delivered difficult-to-separate mixtures of the *E/Z* diastereomers, with a minor bias for the *E* diastereomer. These findings emphasize the unique diastereo-selectivities of the cobalt(III)-catalyzed C–H/C–C activation.



Scheme 70. Cobalt/Rhodium-catalyzed C–H/C–C functionalization.

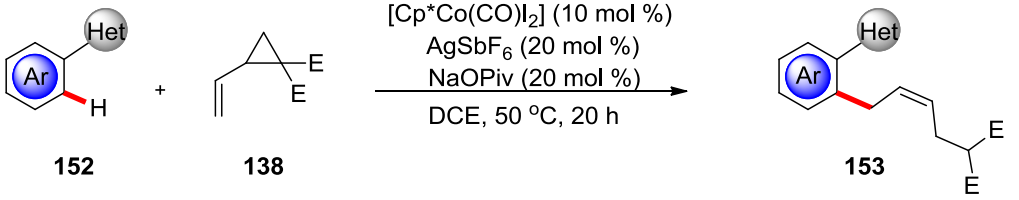
3.4.2.2 Scope of Arenes

The cobalt catalyst was not restricted to the functionalization of 1-pyridylindoles. Indeed, the heteroarene-assisted diversification of arenes **152** proved broadly applicable and proceeded with high *Z*-diastereoselectivity (Scheme 71). Phenylpyridines were successfully converted to the desired products **153** with comparable efficiency under cobalt catalysis. It is worth to note that the cobalt catalyst was characterized by excellent chemoselectivity in that the monofunctionalized arene

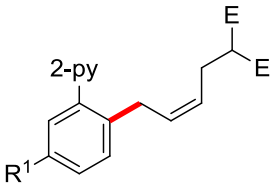
products **153ba** was formed as the sole products. In contrast, the rhodium catalyst gave difficult to separate mixtures of mono- and di-substituted arenes **153ba'** and **153ba''** with low selectivity.

In the cobalt catalysis reaction, both electron-rich and electron-deficient 2-phenylpyridines provided the desired products **153** in good yield and high *Z*-diastereoselectivity, while under the same reaction conditions, the rhodium catalyst gave lower yields and poor *E*-diastereoselectivity. These findings show the unique diastereo- and site-selectivities of the cobalt(III)-catalyzed C–H/C–C activation.

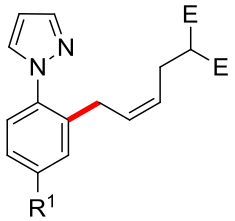
Additionaly, the reaction was found to be compatible with 1-phenyl-1*H*-pyrazole substrates **152c-152e**, giving the desired products **153ca-153ea** in higher yields and excellent diastereoselectivities compared with the rhodium catalyst. To our delight, 1-(pyridin-2-yl)-1*H*-pyrrole-2-carbaldehyde **152g** was successfully employed in this reaction, giving the corresponding product **153ga**.



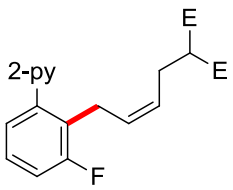
152 **138** **153**



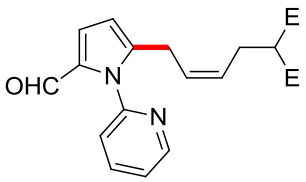
[Co]: R^1 = Me (**153aa**): 70% (*E*/*Z* = 1:3)
[Rh]: R^1 = Me (**153aa'**): 34% (*E*/*Z* = 2:1)[a]
[Co]: R^1 = OMe (**153ba**): 63% (*E*/*Z* = 1:5)
[Rh]: R^1 = OMe (**153ba'**): 24% (*E*/*Z* = 1:1) + 14% di-sub. **153ba''**[a]



R^1 = H (**153ca**): 71% (*E*/*Z* = 1:12)
[Co]: R^1 = F (**153da**): 66% (*E*/*Z* = 1:14)
[Rh]: R^1 = F (**153da'**): 48% (*E*/*Z* = 1:1)[a]
R^1 = Me (**153ea**): 69% (*E*/*Z* = 1:19)



[Co]: **153fa**: 58% (*E*/*Z* = 1:7)
[Rh]: **153fa'**: 24% (*E*/*Z* = 1:1)[a]

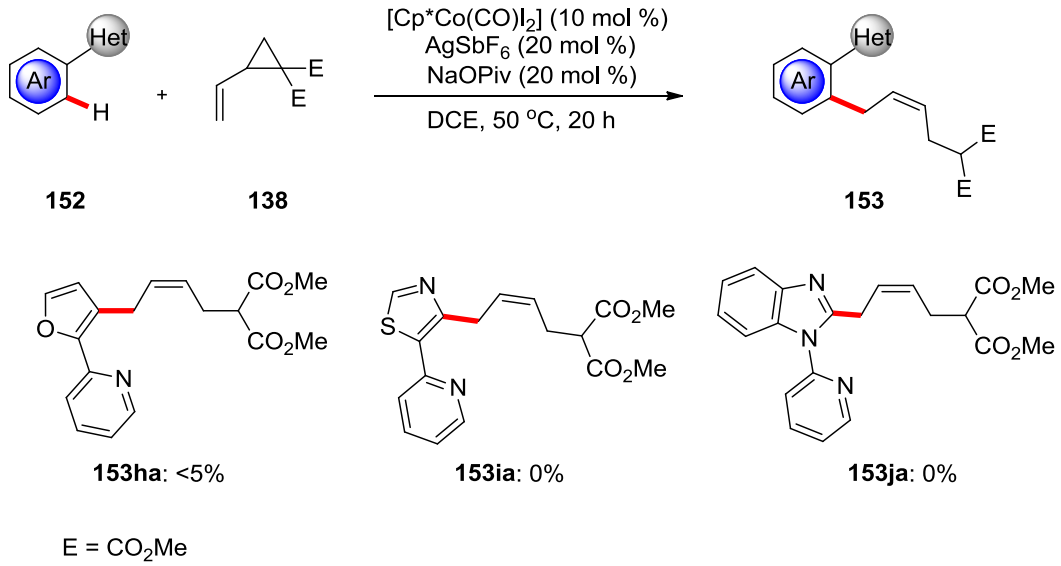


153ga: 78% (*E*/*Z* =1:1)

[a][Cp*Rh(CH3CN)3](SbF6)2 was used as the catalyst. E = CO2Me.

Scheme 71. Cobalt-catalyzed arene C–H/C–C functionalization.

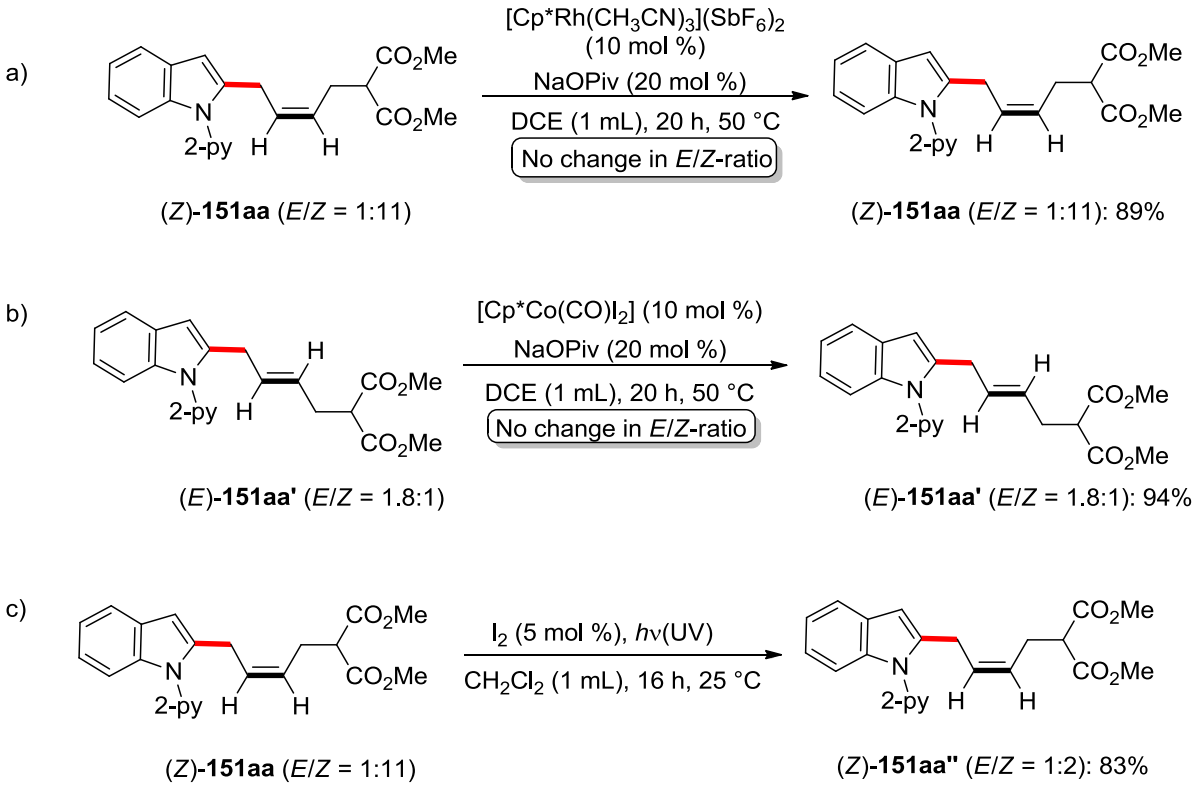
Furthermore, some limititations in the substrate scope were observed (Scheme 72). 2-(Furan-2-yl)pyridine **152h**, 5-(pyridin-2-yl)thiazole **152i** as well as 1-(pyridin-2-yl)-1*H*-benzo[*d*]imidazole **152j** unfortunately delivered no or only traces of the desired products under the optimal reaction conditions.



Scheme 72. Limitations of the cobalt(III)-catalyzed C–H/C–C functionalization.

3.4.3 Isomerization Experiments

Next, we performed several experiments to determine whether a post C–C-cleavage alkene isomerization process takes place during the catalytic reaction (Scheme 73). First, we submitted the product **151aa** isolated from the cobalt(III)-catalyzed transformation to the rhodium(III) catalysis procedure, and did not observe any post-catalytic isomerization of the double bond (Scheme 73a). Likewise, the product of the rhodium catalyzed C–H allylation did not undergo isomerization in the presence of the cobalt(III) catalyst (Scheme 73b). An *E/Z* ratio change was observed when the product from cobalt(III) catalysis was exposed to UV light in the presence of 5 mol % of I_2 in CH_2Cl_2 (Scheme 73c). All the results suggested that no catalytic isomerization of the double bond occured when the *E*-configurated product is subjected to the optimal reaction conditions, hence excluding a post C–C cleavage isomerisation process.



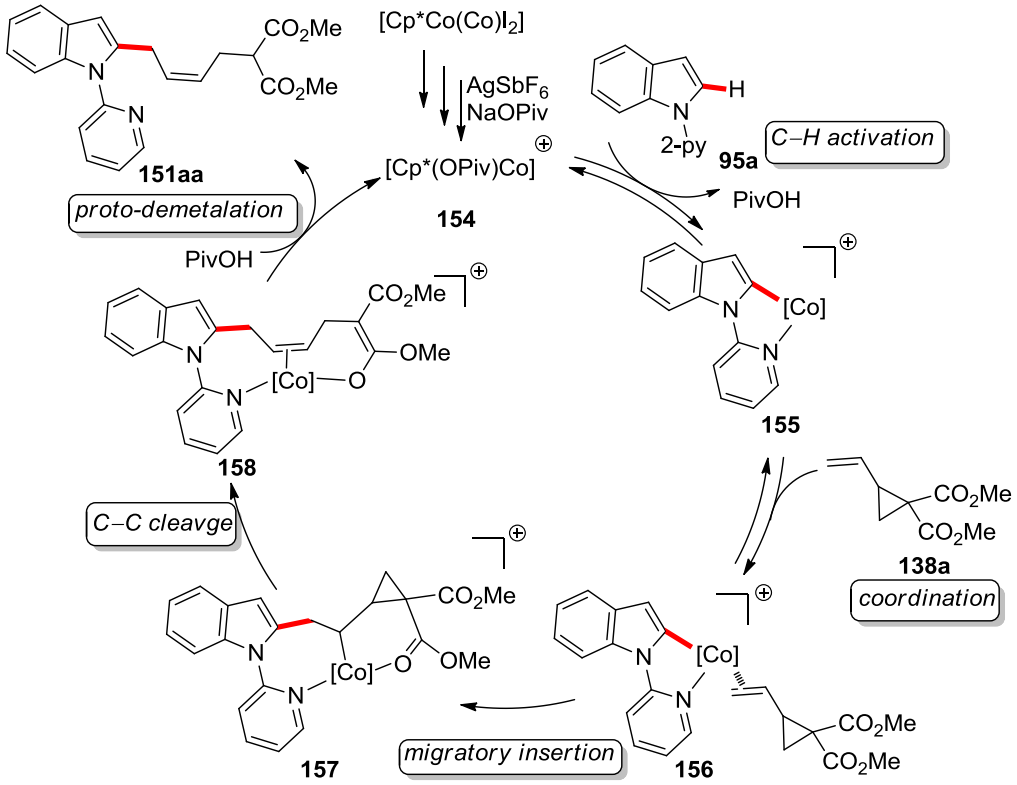
Scheme 73. Isomerization experiments.

3.4.4 Proposed Catalytic Cycle

Based on our mechanistic studies, we propose the cobalt(III)-catalyzed C–H/C–C functionalization to commence by a reversible C–H activation, which is assisted by the pivalate additive and presumably proceeds *via* a base-assisted internal electrophilic-type substitution (BIES)-type mechanistic pathway[129, 120a] to furnish the cobaltacycle **155**. Starting from the next step, computational studies by DFT calculations was performed by Dr. M. Feldt.[127] The coordination of vinylcyclopropane **138a** then delivers intermediate **156**, in which migratory insertion of the double bond of the coordinated vinylcyclopropane **138a** into the Co–C bond occurs. Thereafter, an ester group coordinates to the metal center, thereby leading to intermediate **157**. Then, the rate- and diastereoselectivity-determining C–C cleavage of vinylcyclopropane take place to form the *Z*-configurated intermediate **158** (Scheme 74).

Comparing the energetic span[130] for the vinylcyclopropane C–C cleavage step, the *Z* diastereomer is clearly preferred under cobalt(III) catalysis, with an activation barrier of 13.1 kcalmol^{-1} compared to

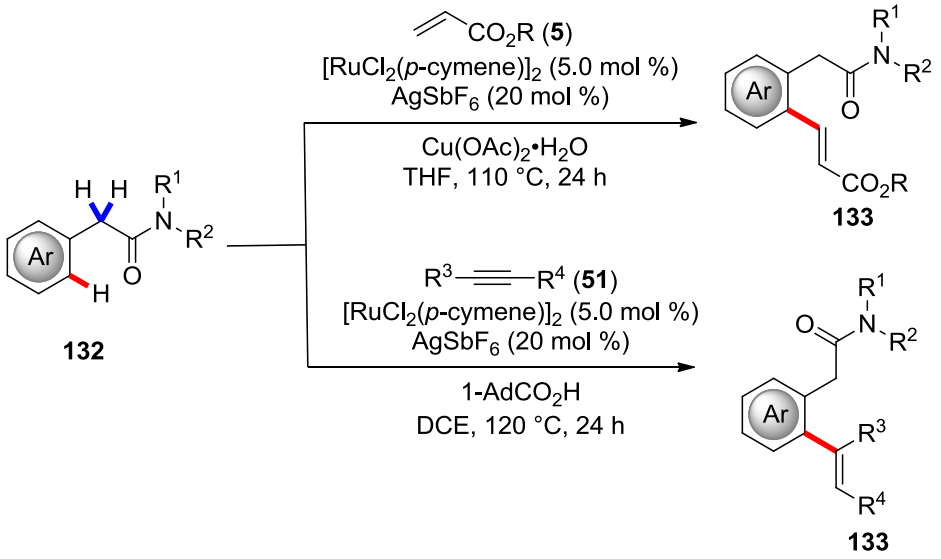
19.6 kcalmol^{-1} for the *E* diastereomer. In contrast, with the rhodium(III) catalyst, the *E* diastereomer is preferred with an energetic span of 20.9 kcalmol^{-1} compared to 23.2 kcalmol^{-1} for the *Z* diastereomer. This observation is likely due to the significantly shorter Co–C bonds translating into more compact organometallic species. Finally, the desired product **151aa** is released by a protodemetalation step, which also regenerates the active catalyst **154**.



Scheme 74. Proposed catalytic cycle for the cobalt(III)-catalyzed C–H/C–C activation. [Co] = Cp*Co^{II}

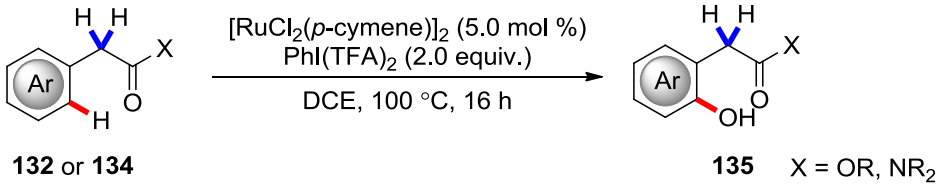
4 Summary and Outlook

In the first project, an efficient C–H alkenylation of challenging arylacetamides by ruthenium(II) catalysis through challenging six-membered ruthenacycles was developed (Scheme 75). Under the optimal reaction conditions, various acetamides **132** including tertiary, secondary, and even primary amides could be converted to the corresponding olefins with high levels of chemo-, position and stereo-selectivity. By simply switching the carboxylate source from $Cu(OAc)_2 \cdot H_2O$ to 1-$AdCO_2H$, substituted olefins **133** were also obtained by step- and atom economical alkyne hydroarylations.



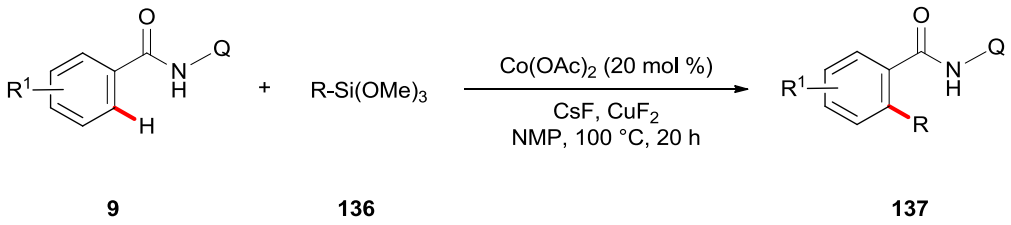
Scheme 75. Ruthenium(II)-catalyzed C–H alkenylation of weakly *O*-coordinating arylacetamides **132**.

Inspired by the above-mentioned ruthenium(II)-catalyzed C–H activations of arylacetamides, we subsequently achieved the first ruthenium-catalyzed C–H oxygenation of weakly *O*-coordinating arylacetamides (Scheme 76). This powerful synthetic tool allowed for the rapid and site-selective installation of hydroxyl groups into acetamides. Furthermore, the ruthenium(II) catalyst also allowed for the direct C–H functionalization on more challenging weakly-coordinating phenylacetyl esters.



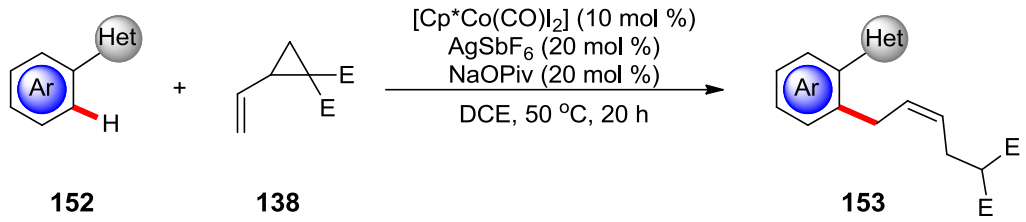
Scheme 76. Ruthenium(II)-catalyzed C–H oxygenation by weakly coordinating acetamides or esters.

In the third project, we developed an efficient cobalt catalyst for the direct Hiyama-type C–H arylation of beazamides with a variety of organosilanes (Scheme 77). The reaction tolerated a broad variety of functional groups and numerous *ortho*-arylated benzamides **137** were efficiently synthesized in good to excellent yields. The steric hindrance of the organosilanes was especially tolerated, providing arylated products **137** in good to excellent yields. Additionaly, the cost-effective cobalt catalyst was also viable in biomass-derived GVL as a green reaction medium.



Scheme 77. Cobalt-catalyzed C–H arylation.

Finally, we developed a cobalt-catalyzed C−H/C−C functionalization of valuable heteroarenes and arenes **152** with vinylcyclopropanes **138** (Scheme 78). The thermodynamically less stable *Z*-configurated diastereomer was obtained using a versatile cobalt catalyst under exceedingly mild reaction conditions with high diastereo-selectivity, ample scope and excellent functional group tolerance. The obtained selectivity was different using the related rhodium(III) complex,[125] which delivered difficult to separate mixtures of *E/Z* diastereomers, with a minor bias for the *E* diastereomer. Additionally, detailed mechanistic studies including DFT calculations provided strong support for a rate-and selectivity-determining C−C cleavage.



Scheme 78. Cobalt(III)-catalyzed C–H/C–C functionalization.

5 Experimental Section

5.1 General Remarks

Unless otherwise noted, all catalytic reactions were performed under an Ar or N_2 atmosphere using pre-dried glassware and standard Schlenk techniques.

Solvents

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

1,4-Dioxane was dried over Na, benzophenone and distilled afterwards.

Dichloromethane (DCM), ***N,N*-dimethylformamide** (DMF) and **tetrahydrofuran** (THF) were purified using a solvent purification system (SPS) from Mbraun.

Methanol (MeOH) was distilled from MgOMe.

1,2-Dichloroethane (DCE) and **1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone** (DMPU) were dried over CaH_2 for 8 h, degassed and distilled under reduced pressure.

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

***tert*-amylalcohol** (*t*-AmOH) was used as supplied by Merck or stirred over sodium chips for 5 h at 120 °C and then distilled at ambient pressure.

Water (H_2O) was degassed before its use, applying a repeated freeze-pump-thaw degassing procedure.

Toluene was pre-dried over KH followed by distillation from sodium benzophenone.

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 from Barloworldscientific. Reported values are uncorrected.

Chromatography

Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60F-plates (Merck) with 254 nm fluorescent indicator from Merck. Plates were visualized under UV-light or developed by treatment with a $KMnO_4$ solution followed by carefully heating. Chromatographic purification of products was accomplished by flash column chromatography on MERCK silica gel, grade 60 (0.040–0.063 mm and 0.063–0.200 mm).

Gas Chromatography (**GC**)

The conversion of the reactions was monitored by 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, Ø 0.25 m).

High Performance Liquid Chromatography (**HPLC**)

Preparative and analytical separations were performed on an HPLC-System from KNAUER (*Smartline Pump 100*, Dynamic Mixing Chamber, Injection-and Control-Valve, *Smartline UV Detector 2500*). Separation normal phase column (250×10 mm) from MACHEREY-NAGEL (MN) was used. Organic solvents of HPLC grade were employed. All samples were filtered through Polytetrafluoroethylene Filter from ROTH (Ø 25 mm, 0.2 µm) or VWR (Ø 13 mm, 0.2 µm) prior to separation.

Nuclear Magnetic Resonance Spectroscopy (**NMR**)

Nuclear magnetic resonance (NMR) spectroscopy was performed at 300, 400, 500 or 600 MHz (^{1}H NMR), 75, 100 or 125 MHz (^{13}C NMR, APT) and 283 MHz or 471 MHz (^{19}F NMR) on BRUKER *AM* 250, VARIAN *Unity-300* and *Inova 500* instruments. Chemical shifts were reported as δ-values in ppm relative to the residual proton peak of the deuterated solvent or its carbon atom, respectively, or the standard trimethylsilyl (TMS) peak.

Infrared Spectroscopy (**IR**)

Infrared spectra were recorded on a Bruker*Alpha-P* ATR-spectrometer. Liquid probes were measured as films between the plates of NaCl and solid probes neat applying Attenuated Total

Reflection (ATR) technique, which enabled the samples to be examined directly. Analysis of the spectral data has been done by using the *OPUS 3.1* software from Bruker, respectively *OPUS 6*. Absorption ($\tilde{\nu}$) was given in wave numbers (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* mass spectrometer. The ratios of mass to charge (*m/z*) were indicated, intensities relative to the base peak (I = 100) were written in parentheses.

Reagents

Chemicals obtained from commercial sources with purity above 95% were used without further purification. The following compounds are known and were synthesized according to previously described methods: Arylacetamides **132**,[131] $[Cp^*CoI_2(CO)]$,[132] $[Cp^*CoI_2]_2$,[133] $[Cp^*Co(MeCN)_3](SbF_6)_2$,[134] indoles **95**.[135]

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

Karsten Rauch: $[Ru(O_2CMes)_2(p\text{-cymene})]$, $[RuCl_2(p\text{-cymene})]_2$, $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$.

M. Sc. Joachim Loup: $[Co(CO)Cp^{1,3\text{-}t\text{-}Bu}I_2]$, $[Co(CO)CpI_2]$.

Dr. Vladislav Kotek: *N*-(*tert*-butyl)-2-phenylacetamide **132i**, 1-morpholino-2-phenylethanone **132k**, 2-phenyl-1-(pyrrolidin-1-yl)ethanone **132l**, *N*-(*tert*-butyl)-2-(4-fluorophenyl)acetamide **132p**, *N*-(*tert*-butyl)-2-(4-methoxyphenyl)acetamide **132q**.

M. Sc. Krzysztof Kuciński: (2,6-Dimethylphenyl)trimethoxysilane **136b**, mesityltrimethoxysilane **131c**, trimethoxy(4-methoxyphenyl)silane **136h**.

M. Sc. Yujiao Zhang: 1-(Pyridin-2-yl)-1*H*-indole **95a**, 5-fluoro-1-(pyridin-2-yl)-1*H*-indole **95b**.

5.2 General Procedures

5.2.1 General Procedure A: Ruthenium-Catalyzed Oxidative C−H Alkenylations

A suspension of arylacetamide **132** (0.5 mmol, 1.0 equiv), acrylate **5** (1.0 mmol, 2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), $AgSbF_6$ (34.4 mg, 20 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.0 mmol, 2.0 equiv) in 1,4-dioxane or THF (2.0 mL) was stirred at 110 °C for 24 h under N_2 atmosphere. At ambient temperature, the reaction mixture was diluted with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents in vacuo, the remaining residue was purified by column chromatography on silica gel (*n*-hexane/acetone).

5.2.2 General Procedure B: Ruthenium-Catalyzed Hydroarylation of Alkynes

A suspension of acetamide **132** (0.5 mmol, 1.0 equiv), alkyne **51** (1.0 mmol, 2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), $AgSbF_6$ (34.4 mg, 20 mol %), 1-$AdCO_2H$ (0.5 mmol, 1.0 equiv) in DCE (2.0 mL) was stirred at 120 °C for 24 h under N_2 atmosphere. At ambient temperature, the solvent was removed in vacuo and the remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

5.2.3 General Procedure C: Ruthenium-Catalyzed C−H Oxygenation

$[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), arylacetamide or phenylacetyl ester **132** or **134** (0.50 mmol), $PhI(TFA)_2$ (430 mg, 1.00 mmol) and DCE (2.0 mL) were placed into a 25 mL Schlenk tube equipped with a septum under N_2. The tube was then placed into an oil bath and the reaction mixture was stirred at 110 °C for 16 h. At ambient temperature, the reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layer was concentrated under reduced pressure. The crude products were purified by column chromatography (*n*-hexane/EtOAc) on silica gel to afford the desired products **135**.

5.2.4 General Procedure D: Cobalt-Catalyzed C−H Arylation

A suspension of benzamide **9** (0.25 mmol, 1.0 equiv), arylsilane **136** (0.5 mmol, 2.0 equiv), $Co(OAc)_2$ (8.9 mg, 20.0 mol %), CsF (0.75 mmol, 3.0 equiv), CuF_2 (0.5 mmol, 2.0 equiv) in NMP (1.0 mL) was stirred at 100 °C for 20 h under N_2 atmosphere. At ambient temperature, the reaction mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were

dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the remaining residue was purified by column chromatography on silica gel (*n*-hexane/acetone).

5.2.5 General Procedure E: Cobalt-Catalyzed C−H Arylation in GVL

A suspension of benzamide **9** (0.25 mmol, 1.0 equiv), arylsilane **136** (0.5 mmol, 2.0 equiv), $Co(OAc)_2$ (8.9 mg, 20.0 mol %), CsF (0.375 mmol, 1.5 equiv), CuF_2 (0.5 mmol, 2.0 equiv) in GVL (1.0 mL) was stirred at 120 °C for 20 h under N_2 atmosphere. At ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with NaOH (2 M, 10 mL) and H_2O (2 x 20 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the remaining residue was purified by column chromatography on silica gel (*n*-hexane/acetone).

5.2.6 General Procedure F: Cobalt(III)-Catalyzed C−H/C−C Functionalization

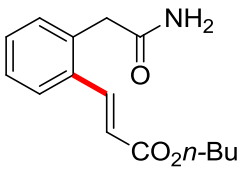
A suspension of indole **95** or heteroarene **152** (0.50 mmol, 1.0 equiv), vinylcyclopropanes **138** (0.60 mmol, 1.2 equiv), [Cp*Co(CO)I_2] (23.8 mg, 50.0 µmol, 10 mol %), $AgSbF_6$ (34.4 mg, 100 µmol, 20 mol %) and NaOPiv (12.4 mg, 100 µmol, 20 mol %) in DCE (1.0 mL, 0.50 M) was stirred at 50 °C for 20 h. At ambient temperature, the solvent was removed *in vacuo* and the remaining residue was purified by column chromatography on silica gel to afford the desired products **146** or **148**.

5.2.7 General Procedure G: Rhodium(III)-Catalyzed C−H/C−C Functionalization

A suspension of indole **95** or heteroarene **147** (0.25 mmol, 1.0 equiv), vinylcyclopropane **133** (0.30 mmol, 1.2 equiv), [Cp*Rh(CH_3CN)$_3$](SbF_6)$_2$ (19.7 mg, 25.0 µmol, 10 mol %) and NaOPiv (6.2 mg, 50.0 µmol, 20 mol %) in DCE (1.0 mL, 0.25 M) was stirred at 50 °C for 20 h. At ambient temperature, the solvent was removed *in vacuo* and the remaining residue was purified by column chromatography on silica gel to afford the desired products **151** or **153**.

5.3 Experimental Procedures and Analytical Data

5.3.1 Ruthenium-Catalyzed Oxidative C−H Alkenylations of Arylactamides



(*E*)-*n*-Butyl 3-[2-(2-amino-2-oxoethyl)phenyl]acrylate (133aa):

The general procedure **A** was followed using 2-phenylacetamide (**132a**) (67.5 mg, 0.50 mmol) and *n*-butyl acrylate (**5a**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/acetone: 3/1) yielded **133aa** (84 mg, 64%) as a white solid.

M. p. = 118–119 °C.

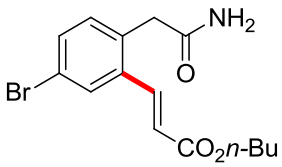
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 15.8 Hz, 1H), 7.63–7.60 (m, 1H), 7.39–7.28 (m, 3H), 6.38 (d, J = 15.8 Hz, 1H), 5.74 (s_{br}, 1H), 5.46 (s_{br}, 1H), 4.19 (t, J = 6.7 Hz, 2H), 3.72 (s, 2H), 1.68 (dt, J = 14.6, 6.8 Hz, 2H), 1.42 (dd, J = 14.6, 7.5 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (C_q), 166.6 (C_q), 141.0 (CH), 134.2 (C_q), 134.1 (C_q), 131.3 (CH), 130.4 (CH), 128.1 (CH), 127.2 (CH), 121.1 (CH), 64.6 (CH_2), 40.6 (CH_2), 30.7 (CH_2), 19.2 (CH_2), 13.7 (CH_3).

IR (ATR): 2959, 1710, 1660, 1626, 1310, 1165, 766 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 545 (100) $[2M+Na]^+$, 284 (45) $[M+Na]^+$, 262 (27) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1438, found: 262.1435.



(*E*)-*n*-Butyl 3-[2-(2-amino-2-oxoethyl)-5-bromophenyl]acrylate (133ba):

The general procedure **A** was followed using 2-(4-bromophenyl)acetamide (**132b**) (106 mg, 0.50 mmol) and *n*-butyl acrylate (**5a**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/acetone: 3/1) yielded **133ba** (104 mg, 61%) as a white solid.

M. p. = 165–166 °C.

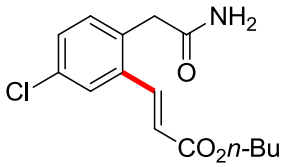
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 15.8 Hz, 1H), 7.72 (d, *J* = 2.1 Hz, 1H), 7.46 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.36 (d, *J* = 15.8 Hz, 1H), 5.58 (s_{br}, 1H), 5.44 (s_{br}, 1H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.64 (s, 2H), 1.74–1.60 (m, 2H), 1.48–1.33 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6 (C_q), 165.4 (C_q), 138.8 (CH), 135.3 (C_q), 132.3 (CH), 132.1 (C_q), 131.9 (CH), 129.2 (CH), 121.5 (CH), 121.2 (C_q), 64.0 (CH_2), 39.2 (CH_2), 30.0 (CH_2), 18.4 (CH_2), 13.1 (CH_3).

IR (ATR): 2957, 1712, 1657, 1312, 1173, 975, 806 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 362 (100) ($[M+Na]^+$, ^{79}Br), 342 (23) ($[M+H]^+$, ^{81}Br).

HR-MS (ESI) *m/z* calcd for $C_{15}H_{19}{}^{79}BrNO_3$ $[M+H]^+$: 340.0543, found: 340.0540.



(*E*)-*n*-Butyl 3-[2-(2-amino-2-oxoethyl)-5-chlorophenyl]acrylate (133ca):

The general procedure **A** was followed using 2-(4-chlorophenyl)acetamide (**132c**) (84.5 mg, 0.50 mmol) and *n*-butyl acrylate (**5a**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/acetone: 3/1) yielded **133ca** (97 mg, 66%) as a white solid.

M. p. = 153–154 °C.

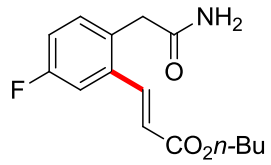
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 15.8 Hz, 1H), 7.57 (d, *J* = 2.2 Hz, 1H), 7.32 (dd, *J* = 7.6, 2.2 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 6.37 (d, *J* = 15.8 Hz, 1H), 5.50 (s_{br}, 1H), 5.42 (s_{br}, 1H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.66 (s, 2H), 1.70–1.61 (m, 2H), 1.46–1.35 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.5 (C_q), 166.2 (C_q), 139.7 (CH), 135.7 (C_q), 134.1 (C_q), 132.6 (CH), 132.4 (C_q), 130.2 (CH), 127.0 (CH), 122.3 (CH), 64.8 (CH_2), 39.8 (CH_2), 30.7 (CH_2), 19.0 (CH_2), 13.6 (CH_3).

IR (ATR): 2958, 1711, 1657, 1635, 1313, 1171, 976 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 613 (100) $[2M+Na]^+$, 318 (75) $[M+Na]^+$, 296 (20) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{15}H_{19}ClNO_3$ $[M+H]^+$: 296.1048, found: 296.1045.



(*E*)-*n*-Butyl 3-[2-(2-amino-2-oxoethyl)-5-fluorophenyl]acrylate (133da):

The general procedure **A** was followed using 2-(4-fluorophenyl)acetamide (**132d**) (76.5 mg, 0.50 mmol) and *n*-butyl acrylate (**5a**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/acetone: 3/1) yielded **133da** (76.7 mg, 55%) as a white solid.

M. p. = 127–128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 15.8, 1H), 7.30–7.25 (m, 2H), 7.06 (td, J = 8.2, 2.7 Hz, 1H), 6.35 (d, J = 15.8 Hz, 1H), 5.62 (s_{br}, 1H), 5.44 (s_{br}, 1H), 4.18 (t, J = 6.7 Hz, 2H), 3.66 (s, 2H), 1.70–1.62 (m, 2H), 1.45–1.35 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).

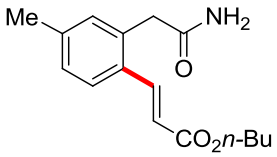
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9 (C_q), 166.3 (C_q), 162.2 (C_q, $^{1}J_{C-F}$ = 247.3 Hz), 139.9 (CH, $^{4}J_{C-F}$ = 2.3 Hz), 136.0 (C_q, $^{3}J_{C-F}$ = 7.6 Hz), 133.0 (CH, $^{3}J_{C-F}$ = 8.2 Hz), 130.0 (C_q, $^{4}J_{C-F}$ = 3.2 Hz), 122.2 (CH), 117.3 (CH, $^{2}J_{C-F}$ = 21.5 Hz), 113.7 (CH, $^{2}J_{C-F}$ = 22.4 Hz), 64.7 (CH_2), 39.7 (CH_2), 30.7 (CH_2), 19.1 (CH_2), 13.7 (CH_3).

^{19}F NMR (376 Hz, $CDCl_3$): δ = –113.8.

IR (ATR): 2956, 1703, 1674, 1492, 1268, 1175, 730 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 581 (100) $[2M+Na]^+$, 302 (40) $[M+Na]^+$, 280 (25) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{15}H_{19}FNO_3$ $[M+H]^+$: 280.1343, found: 280.1341.



(*E*)-*n*-Butyl 3-[2-(2-amino-2-oxoethyl)-4-methylphenyl]acrylate (133ea):

The general procedure **A** was followed using 2-(*m*-tolyl)acetamide (**132e**) (74.5 mg, 0.50 mmol) and *n*-butyl acrylate (**5a**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/acetone: 3/1) yielded **133ea** (78 mg, 58%) as a white solid.

M. p. = 133–134 °C.

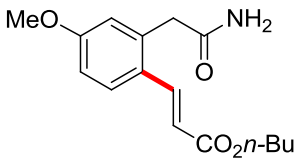
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 15.7 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.15–7.06 (m, 2H), 6.34 (d, *J* = 15.7 Hz, 1H), 5.47 (s_{br}, 1H), 5.35 (s_{br}, 1H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.68 (s, 2H), 2.34 (s , 3H), 1.71–1.61 (m, 2H), 1.47–1.34 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3 (C_q), 165.9 (C_q), 140.1 (C_q), 139.9 (CH), 133.3 (C_q), 131.2 (CH), 130.3 (C_q), 128.2 (CH), 126.4 (CH), 119.3 (CH), 63.8 (CH_2), 39.9 (CH_2), 30.1 (CH_2), 20.6 (CH_3), 18.5 (CH_2), 13.1 (CH_3).

IR (ATR): 2959, 1700, 1666, 1313, 1176, 906, 729 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 573 (100) $[2M+Na]^+$, 298 (23) $[M+Na]^+$, 276 (17) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{16}H_{22}NO_3$ $[M+H]^+$: 276.1594, found: 276.1592.



(*E*)-*n*-Butyl 3-[2-(2-amino-2-oxoethyl)-4-methoxyphenyl]acrylate (133fa):

The general procedure **A** was followed using 2-(3-methoxyphenyl)acetamide (**132f**) (82.5 mg, 0.50 mmol) and *n*-butyl acrylate (**5a**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/acetone: 3/1) yielded **133fa** (74 mg, 51%) as a white solid.

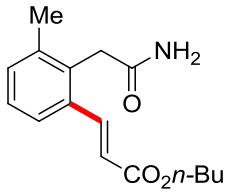
M. p. = 123–124 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 15.7 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 6.89–6.80 (m, 2H), 6.30 (d, *J* = 15.7 Hz, 1H), 5.50 (s_{br}, 1H), 5.45 (s_{br}, 1H), 4.19 (t, *J* = 6.7 Hz, 2H), 3.83 (s, 3H), 3.71 (s, 2H), 1.73–1.63 (m, 2H), 1.47–1.43 (m, 2H), 0.96 (t, *J* = 8.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1 (C_q), 166.1 (C_q), 160.4 (C_q), 139.5 (CH), 135.2 (C_q), 127.9 (CH), 125.5 (C_q), 117.7 (CH), 115.5 (CH), 113.2 (CH), 63.7 (CH_2), 54.7 (CH_3), 40.1 (CH_2), 30.1 (CH_2), 18.5 (CH_2), 13.1 (CH_3).

MS (ESI) *m/z* (relative intensity): 314 (100) $[M+Na]^+$, 292 (15) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{16}H_{22}NO_4$ $[M+H]^+$: 292.1543, found: 292.1541.



(*E*)-Butyl 3-(2-(2-amino-2-oxoethyl)-3-methylphenyl)acrylate (133ga):

The general procedure **A** was followed using 2-(3-methoxyphenyl)acetamide (**132g**) (82.5 mg, 0.50 mmol) and *n*-butyl acrylate (**5a**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/acetone: 3/1) yielded **133ga** (74 mg, 51%) as a white solid.

M. p. = 120–121 °C.

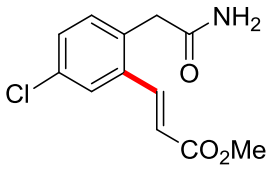
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 15.7 Hz, 1H), 7.43 (dd, *J* = 6.7, 2.4 Hz, 1H), 7.25–7.18 (m, 2H), 6.33 (d, *J* = 15.7 Hz, 1H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.73 (s, 2H), 2.34 (s, 3H), 1.72–1.62 (m, 2H), 1.48–1.34 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.8 (C_q), 166.4 (C_q), 141.7 (CH), 138.2 (C_q), 134.6 (C_q), 132.6 (C_q), 132.2 (CH), 127.8 (CH), 125.2 (CH), 121.6 (CH), 64.6 (CH_2), 36.9 (CH_2), 30.8 (CH_2), 20.3 (CH_3), 19.3 (CH_2), 13.8 (CH_3).

IR (ATR): 2960, 1709, 1656, 1276, 1180, 909, 731 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 573 (100) $[2M+Na]^+$,298 (50) $[M+Na]^+$, 276 (20) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{16}H_{22}NO_3$[M+H]+: 276.1594, found: 276.1592.



(*E*)-Methyl 3-[2-(2-amino-2-oxoethyl)-5-chlorophenyl]acrylate (133cc):

The general procedure **A** was followed using 2-(4-chlorophenyl)acetamide (**132c**) (84.5 mg, 0.50 mmol) and methyl acrylate (**5c**) (86 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/acetone: 3/1) yielded **133cc** (66 mg, 52%) as a white solid.

M. p. = 133–134 °C.

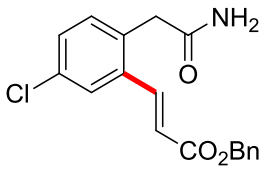
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 15.8 Hz, 1H), 7.56 (d, *J* = 2.1 Hz, 1H), 7.33 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 6.36 (d, *J* = 15.8 Hz, 1H), 5.51 (s_{br}, 1H), 5.40 (s_{br}, 1H), 3.79 (s, 3H), 3.66 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0 (C_q), 166.0 (C_q), 139.4 (CH), 135.1 (C_q), 133.5 (C_q), 132.0 (CH), 131.9 (C_q), 129.7 (CH), 126.5 (CH), 121.3 (CH), 51.4 (CH_3), 39.3 (CH_2).

IR (ATR): 2953, 1712, 1669, 1312, 1169, 973, 697 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 529 (100) $[2M+Na]^+$,276 (50) $[M+Na]^+$, 254 (20) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{12}H_{13}ClNO_3$ $[M+H]^+$: 254.0516, found: 254.0519.



(*E*)-Benzyl 3-[2-(2-amino-2-oxoethyl)-5-chlorophenyl]acrylate (133cd):

The general procedure **A** was followed using 2-(4-chlorophenyl)acetamide (**132c**) (84.5 mg, 0.50 mmol) and benzyl acrylate (**5d**) (162 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/acetone: 3/1) yielded **133cd** (105 mg, 64%) as a white solid.

M. p. = 165–166 °C.

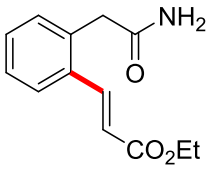
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 15.8 Hz, 1H), 7.56 (d, *J* = 2.2 Hz, 1H), 7.40–7.35 (m, 3H), 7.35–7.30 (m, 2H), 7.24–7.20 (m, 2H), 6.41 (d, *J* = 15.8 Hz, 1H), 5.46 (s_{br}, 1H), 5.40 (s_{br}, 1H), 5.23 (s, 2H), 3.65 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3 (C_q), 165.9 (C_q), 140.2 (CH), 135.7 (C_q), 135.5 (C_q), 134.0 (C_q), 132.5 (CH), 132.4 (C_q), 130.2 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.0 (CH), 121.8 (CH), 66.7 (CH_2), 39.8 (CH_2).

IR (ATR): 2940, 1710, 1669, 1635, 1312, 1168, 697 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 352 (100) $[M+Na]^+$, 330 (20) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{18}H_{17}ClNO_3$ $[M+H]^+$: 330.0891, found: 330.0888.



(*E*)-Ethyl 3-[2-(2-amino-2-oxoethyl)phenyl]acrylate (133ab):

The general procedure **A** was followed using 2-phenylacetamide (**132a**) (67.5 mg, 0.50 mmol) and ethyl acrylate (**5b**) (100 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/acetone: 3/1) yielded **133ab** (83 mg, 71%) as a white solid.

M. p. = 101–103 °C.

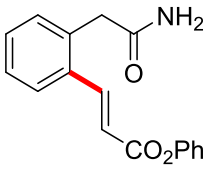
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 15.7 Hz, 1H), 7.62 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.40–7.28 (m, 3H), 6.38 (d, *J* = 15.7 Hz, 1H), 5.53 (s_{br}, 1H), 5.40 (s_{br}, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2 (C_q), 165.6 (C_q), 139.9 (CH), 133.1 (C_q), 133.1 (C_q), 130.3 (CH), 129.5 (CH), 127.2 (CH), 126.3 (CH), 120.2 (CH), 59.7 (CH_2), 39.6 (CH_2), 13.3 (CH_3).

IR (ATR): 2934, 1714, 1667, 1633, 1315, 1179, 766 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 489 (100) $[2M+Na]^+$,256 (65) $[M+Na]^+$, 234 (25) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{16}NO_3$ $[M+H]^+$: 234.1125, found: 234.1123.



(*E*)-Phenyl 3-[2-(2-amino-2-oxoethyl)phenyl]acrylate (133ae):

The general procedure **A** was followed using 2-phenylacetamide (**132a**) (67.5 mg, 0.50 mmol) and phenyl acrylate (**5e**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/acetone: 3/1) yielded **133ae** (79 mg, 56%) as a white solid.

M. p. = 153–154 °C.

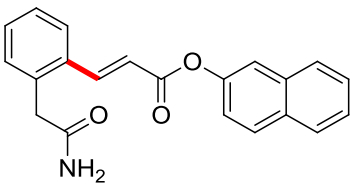
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 15.7 Hz, 1H), 7.68 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.44–7.29 (m, 5H), 7.24–7.20 (m, 1H), 7.18–7.12 (m, 2H), 6.57 (d, *J* = 15.7 Hz, 1H), 5.56 (s_{br}, 1H), 5.44 (s_{br}, 1H), 3.74 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9 (C_q), 164.8 (C_q), 150.6 (C_q), 142.8 (CH), 134.4 (C_q), 133.7 (C_q), 131.3 (CH), 130.8 (CH), 129.3 (CH), 128.4 (CH), 127.3 (CH), 125.8 (CH), 121.5 (CH), 120.0 (CH), 40.6 (CH_2).

IR (ATR): 3182, 1722, 1661, 1631, 1483, 1142, 975 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 585 (100) $[2M+Na]^+$, 304 (55) $[M+Na]^+$, 282 (4) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{17}H_{16}NO_3$ $[M+H]^+$: 282.1125, found: 282.1123.



(*E*)-naphthalen-2-yl 3-(2-(2-amino-2-oxoethyl)phenyl)acrylate (133af):

The general procedure **A** was followed using 2-phenylacetamide (**132a**) (67.5 mg, 0.50 mmol) and phenyl acrylate (**5f**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/acetone: 3/1) yielded **133af** (79 mg, 56%) as a white solid.

M. p. = 158–159 °C.

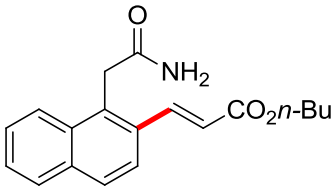
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 15.7 Hz, 1H), 7.89–7.78 (m, 3H), 7.73–7.68 (m, 1H), 7.63 (d, *J* = 2.3 Hz, 1H), 7.52–7.44 (m, 2H), 7.44–7.36 (m, 2H), 7.34–7.27 (m, 2H), 6.62 (d, *J* = 15.7 Hz, 1H), 3.75 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8 (C_q), 164.0 (C_q), 147.3 (C_q), 142.0 (CH), 133.4 (C_q), 132.7 (C_q), 132.7 (C_q), 130.4 (C_q), 130.3 (CH), 129.8 (CH), 128.3 (CH), 127.2 (CH), 126.7 (CH), 126.6 (CH), 126.3 (CH), 125.5 (CH), 124.6 (CH), 120.1 (CH), 119.0 (CH), 117.5 (CH), 39.7 (CH_2).

IR (ATR): 2924, 1724, 1667, 1598, 1214, 1142, 760 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 685 (100) $[2M+Na]^+$,354 (52) $[M+Na]^+$, 332 (6) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{21}H_{18}NO_3[M+H]^+$: 332.1281, found: 332.1278.



(*E*)-*n*-Butyl 3-[1-(2-amino-2-oxoethyl)naphthalen-2-yl]acrylate (133ha):

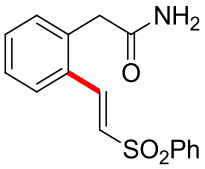
The general procedure **A** was followed using 2-(naphthalen-1-yl)acetamide (**132h**) (92.5 mg, 0.50 mmol) and *n*-butyl acrylate (**5a**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/aceton: 3/1) yielded **133ha** (110 mg, 71%) as a white solid.

M. p. = 156–157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 15.7 Hz, 1H), 8.08 (d, *J* = 8.3 Hz, 1H), 7.85 (t, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.65–7.50 (m, 2H), 6.52 (d, *J* = 15.7 Hz, 1H), 5.42 (s_{br}, 1H), 5.24 (s_{br}, 1H), 4.27–4.22 (m, 4H), 1.76–1.66 (m, 2H), 1.44 (dt, *J* = 13.6, 6.8 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (C_q), 165.6 (C_q), 140.2 (CH), 133.3 (C_q), 131.5 (C_q), 130.7 (C_q), 129.8 (C_q), 127.9 (CH), 127.8 (CH), 126.7 (CH), 126.2 (CH), 123.5 (CH), 122.9 (CH), 121.2 (CH), 63.8 (CH_2), 35.3 (CH_2), 29.7 (CH_2), 18.2 (CH_2), 12.7 (CH_3).

IR (ATR): 2957, 1644, 1626, 1380, 1259, 1175, 1164, 792 cm^{-1}. MS (ESI) *m/z* (relative intensity): 645 (68) $[2M+Na]^+$, 334 (100) $[M+Na]^+$, 312 (24) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.1594, found: 312.1590.



(*E*)-2-{2-[2-(Phenylsulfonyl)vinyl]phenyl}acetamide (133ag):

The general procedure **A** was followed using 2-phenylacetamide (**132a**) (67.5 mg, 0.50 mmol) and (vinylsulfonyl)benzene (**5g**) (168 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/acetone: 3/1) yielded **133ag** (95 mg, 61%) as a yellow solid.

M. p. = 135–136 °C.

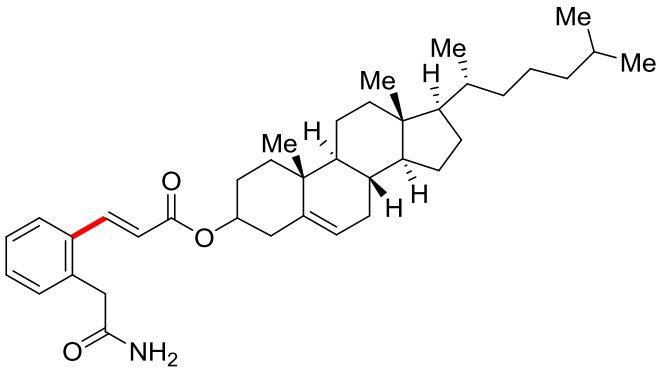
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96–7.87 (m, 3H), 7.63–7.47 (m, 4H), 7.42–7.26 (m, 3H), 6.80 (d, *J* = 15.2 Hz, 1H), 5.44 (s_{br}, 2H), 3.72 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.4 (C_q), 140.3 (C_q), 139.3 (CH), 134.6 (C_q), 133.4 (CH), 132.0 (C_q), 131.4 (CH), 131.2 (CH), 129.7 (CH), 129.3 (CH), 128.2 (CH), 127.7 (CH), 127.5 (CH), 40.6 (CH_2).

IR (ATR): 1670, 1303, 1144, 1084, 752, 687, 541 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 625 (100) $[2M+Na]^+$, 324 (73) $[M+Na]^+$, 302 (13) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{16}H_{16}NO_3S$ $[M+H]^+$: 302.0845, found: 302.0841.



(*E*)-Cholesteryl [2-(2-amino-2-oxoethyl)phenyl]acrylate (133ah):

The general procedure **A** was followed using 2-phenylacetamide (**132a**) (67.5 mg, 0.50 mmol) and cholesteryl acrylate (**5h**) (440 mg, 1.00 mmol) in 1,4-dioxane (1.8 mL) and PhMe (0.2 mL) at 120 °C.

Isolation by column chromatography (*n*-hexane/acetone: 3/1) yielded **133ah** (163 mg, 57%) as a white solid.

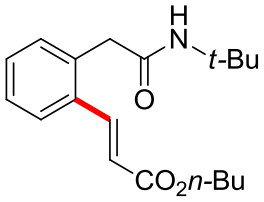
M. p. = 127–128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 15.8 Hz, 1H), 7.59 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.38–7.25 (m, 3H), 6.35 (d, *J* = 15.8 Hz, 1H), 5.64 (s_{br}, 1H), 5.45 (s_{br}, 1H), 5.40–5.34 (m, 1H), 4.78–4.64 (m, 1H), 3.69 (s, 2H), 2.37 (d, *J* = 7.8 Hz, 2H), 2.08–0.94 (m, 29H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.85 (dd, *J* = 6.6, 1.3 Hz, 6H), 0.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5 (C_q), 166.0 (C_q), 140.9 (CH), 139.6 (C_q), 134.2 (C_q), 134.1 (C_q), 131.3 (CH), 130.4 (CH), 128.1 (CH), 127.2 (CH), 122.7 (CH), 121.4 (CH), 74.3 (CH), 56.7 (CH), 56.1 (CH), 50.0 (CH), 42.3 (C_q), 40.5 (CH_2), 39.7 (CH_2), 39.5 (CH_2), 38.2 (CH_2), 37.0 (CH_2), 36.6 (C_q), 36.2 (CH_2), 35.8 (CH), 31.9 (CH_2), 31.8 (CH), 28.2 (CH_2), 28.0 (CH), 27.8 (CH_2), 24.3 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.0 (CH_2), 19.3 (CH_3), 18.7 (CH_3), 11.8 (CH_3).

IR (ATR): 2936, 1667, 1320, 1171, 907, 765, 731, 593 cm^{-1}. MS (ESI) *m/z* (relative intensity): 1169 (100) $[2M+Na]^+$, 596 (70) $[M+Na]^+$, 574 (12) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{38}H_{56}NO_3$ $[M+H]^+$: 574.4255, found: 574.4249.



(*E*)-*n*-Butyl 3-{2-[2-(*tert*-butylamino)-2-oxoethyl]phenyl}acrylate (133ia):

The general procedure **A** was followed using *N*-(*tert*-butyl)-2-phenylacetamide (**132i**) (95.5 mg, 0.50 mmol) and *n*-butyl acrylate (**5a**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133ia** (133 mg, 84%) as a white solid.

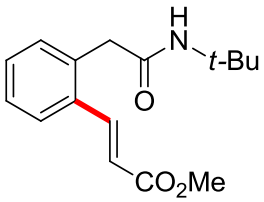
M. p. = 142–143 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 15.8 Hz, 1H), 7.58 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.37–7.23 (m, 3H), 6.35 (d, *J* = 15.8 Hz, 1H), 5.15 (s_{br}, 1H), 4.19 (t, *J* = 6.7 Hz, 2H), 3.60 (s, 2H), 1.71–1.61 (m, 2H), 1.47–1.36 (m, 2H), 1.25 (s, 9H), 0.94 (t, *J* = 8.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8 (C_q), 166.4 (C_q), 141.2 (CH), 134.7 (C_q), 133.9 (C_q), 131.2 (CH), 130.3 (CH), 127.8 (CH), 127.0 (CH), 120.8 (CH), 64.5 (CH_2), 51.4 (C_q), 42.4 (CH_2), 30.8 (CH_2), 28.7 (CH_2), 19.3 (CH_3), 13.8 (CH_3).

IR (ATR): 2961, 1710, 1636, 1547, 1358, 1167, 762 cm^{-1}. MS (ESI) *m/z* (relative intensity): 340 (60) $[M+Na]^+$, 318 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{19}H_{28}NO_3$ $[M+H]^+$: 318.2064, found: 318.2063.



(*E*)-Methyl 3-{2[2-(*tert*-butylamino)-2-oxoethyl]phenyl}acrylate (133ic):

The general procedure **A** was followed using *N*-(*tert*-butyl)-2-phenylacetamide (**132i**) (95.5 mg, 0.50 mmol) and methyl acrylate (**5c**) (86 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133ic** (118 mg, 86%) as a white solid.

M. p. = 135–136 °C.

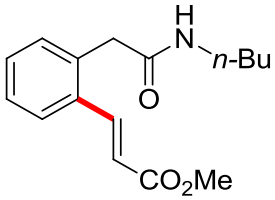
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 15.8 Hz, 1H), 7.58 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.37–7.24 (m, 3H), 6.35 (d, *J* = 15.8 Hz, 1H), 5.17 (s_{br}, 1H), 3.78 (s, 3H), 3.60 (s, 2H), 1.25 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1 (C_q), 166.0 (C_q), 140.6 (CH), 133.8 (C_q), 132.9 (C_q), 130.3 (CH), 129.4 (CH), 126.9 (CH), 126.1 (CH), 119.3 (CH), 50.8 (CH_3), 50.5 (C_q), 41.4 (CH_2), 27.6 (CH_3).

IR (ATR): 2925, 1711, 1646, 1545, 1318, 1170, 765 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 298 (100) $[M+Na]^+$, 276 (30) $[M+H]^+$, 244 (20).

HR-MS (ESI) *m/z* calcd for $C_{16}H_{22}NO_3$ $[M+H]^+$: 276.1594, found: 276.1596.



(*E*)-Methyl 3-{2-[2-(*n*-butylamino)-2-oxoethyl]phenyl}acrylate (133jc):

The general procedure **A** was followed using *N*-*n*-butyl-2-phenylacetamide (**132j**) (95.5 mg, 0.50 mmol) and methyl acrylate (**5c**) (86 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133jc** (118 mg, 86%) as a white solid.

M. p. = 142–143 °C.

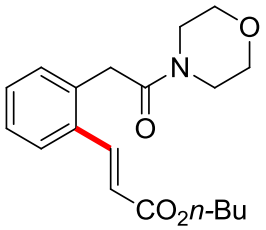
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 15.8 Hz, 1H), 7.59 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.38–7.23 (m, 3H), 6.35 (d, *J* = 15.8 Hz, 1H), 5.32 (s_{br}, 1H), 3.77 (s, 3H), 3.67 (s, 2H), 3.21–3.12 (m, 2H), 1.42–1.28 (m, 2H), 1.27–1.13 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5 (C_q), 166.7 (C_q), 141.2 (CH), 134.3 (C_q), 133.9 (C_q), 31.3 (CH), 130.4 (CH), 128.0 (CH), 127.1 (CH), 120.5 (CH), 51.8 (CH_3), 41.3 (CH_2), 39.5 (CH_2), 31.6 (CH_2), 20.0 (CH_2), 13.7 (CH_3).

IR (ATR): 2955, 1713, 1637, 1546, 1315, 1167, 762 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 298 (100) $[M+Na]^+$, 276 (45) $[M+H]^+$, 244 (70).

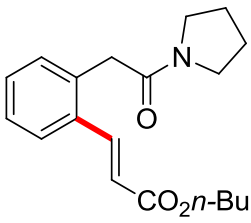
HR-MS (ESI) *m/z* calcd for $C_{16}H_{21}NO_3$ $[M+H]^+$: 276.1594, found: 276.1596.



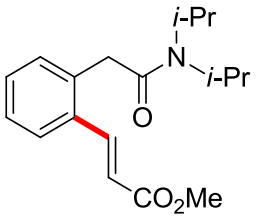
(*E*)-*n*-Butyl 3-[2-(2-morpholino-2-oxoethyl)phenyl]acrylate (133ka):

The general procedure **A** was followed using 1-morpholino-2-phenylethanone (**132k**) (103 mg, 0.50 mmol) and *n*-butyl acrylate (**5a**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133ka** (89 mg, 54%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 15.8 Hz, 1H), 7.57 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.35–7.25 (m, 2H), 7.20 (dd, *J* = 7.4, 1.5 Hz, 1H), 6.34 (d, *J* = 15.8 Hz, 1H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.79 (s, 2H), 3.66–3.56 (m, 6H), 3.47–3.41 (m, 2H), 1.71–1.61 (m, 2H), 1.49–1.32 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0 (C_q), 166.8 (C_q), 141.3 (CH), 134.5 (C_q), 133.6 (C_q), 130.2 (CH), 130.1 (CH), 127.6 (CH), 127.0 (CH), 120.5 (CH), 66.8 (CH_2), 66.5 (CH_2), 64.5 (CH_2), 46.4 (CH_2), 42.3 (CH_2), 37.5 (CH_2), 30.8 (CH_2), 19.2 (CH_2), 13.7 (CH_3).
IR (ATR): 2958, 1708, 1633, 1433, 1169, 1113, 763 cm^{-1}. MS (ESI) *m/z* (relative intensity): 354 (100) $[M+Na]^+$, 332 (70) $[M+H]^+$, 258 (40).
HR-MS (ESI) *m/z* calcd for $C_{19}H_{26}NO_4$ $[M+H]^+$: 332.1856, found: 332.1854.



(*E*)-*n*-Butyl 3-{2-[2-oxo-2-(pyrrolidin-1-yl)ethyl]phenyl}acrylate (133la):
The general procedure **A** was followed using 2-phenyl-1-(pyrrolidin-1-yl)ethanone (**132l**) (94.5 mg, 0.50 mmol) and *n*-butyl acrylate (**5a**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133la** (139 mg, 88%) as a white oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 15.5, 1H), 7.55 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.33–7.19 (m, 3H), 6.33 (d, *J* = 15.5 Hz, 1H), 4.16 (dd, *J* = 8.4, 4.9 Hz, 2H), 3.73 (s, 2H), 3.43–3.49 (m, 4H), 1.98–1.89 (m, 2H), 1.87–1.80 (m, 2H), 1.70–1.58 (m, 2H), 1.47–1.34 (m, 2H), 0.93 (t, *J* = 8.6 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6 (C_q), 165.9 (C_q), 140.8 (CH), 133.8 (C_q), 132.8 (C_q), 129.4 (CH), 129.0 (CH), 126.3 (CH), 125.7 (CH), 119.1 (CH), 63.3 (CH_2), 45.8 (CH_2), 44.9 (CH_2), 38.1 (CH_2), 29.7 (CH_2), 25.1 (CH_2), 23.3 (CH_2), 18.1 (CH_2), 12.7 (CH_3).
IR (ATR): 2958, 1707, 1632, 1431, 1311, 1216, 730 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 338 (65) $[M+Na]^+$, 316 (100) $[M+H]^+$.
HR-MS (ESI) *m/z* calcd for $C_{19}H_{26}NO_3$ $[M+H]^+$: 316.1907, found: 316.1912.



(*E*)-Methyl 3-{2-[2-(diisopropylamino)-2-oxoethyl]phenyl}xacrylate (133mc):

The general procedure **A** was followed using *N*,*N*-diisopropyl-2-phenylacetamide (**132m**) (110 mg, 0.50 mmol) and methyl acrylate (**5c**) (86 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133ma** (91 mg, 60%) as a white solid.

M. p. = 136–137 °C.

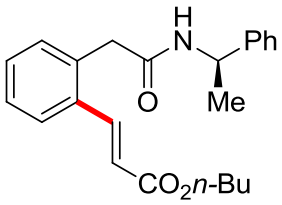
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 15.8 Hz, 1H), 7.55 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.34–7.18 (m, 3H), 6.32 (d, *J* = 15.8 Hz, 1H), 3.93 (dt, *J* = 13.3, 6.7 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 2H), 3.43 (dt, *J* = 13.0, 6.3 Hz, 1H), 1.38 (d, *J* = 6.8 Hz, 6H), 1.15 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8 (C_q), 167.0 (C_q), 141.9 (CH), 135.5 (C_q), 133.4 (C_q), 130.2 (CH), 130.0 (CH), 127.1 (CH), 126.7 (CH), 119.6 (CH), 51.6 (CH_3), 49.2 (CH), 46.0 (CH), 40.1 (CH_2), 20.8 (CH_3), 20.5 (CH_3).

IR (ATR): 2964, 1712, 1631, 1435, 1336, 1169, 729 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 326 (33) $[M+Na]^+$, 304 (100) $[M+H]^+$, 272 (45).

HR-MS (ESI) *m/z* calcd for $C_{18}H_{26}NO_3$ $[M+H]^+$: 304.1907, found: 304.1913.



(*E*)-*n*-Butyl 3-{2-{2-oxo-2-[((*R*)-1-phenylethyl)amino]ethyl}phenyl}acrylate (133na):

The general procedure **A** was followed using 2-phenyl-*N*-{(*R*)-1-phenylethyl}acetamide (**132n**) (120 mg, 0.50 mmol) and *n*-butyl acrylate (**5a**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133na** (141 mg, 77%) as a white solid.

M. p. = 77–78 °C.

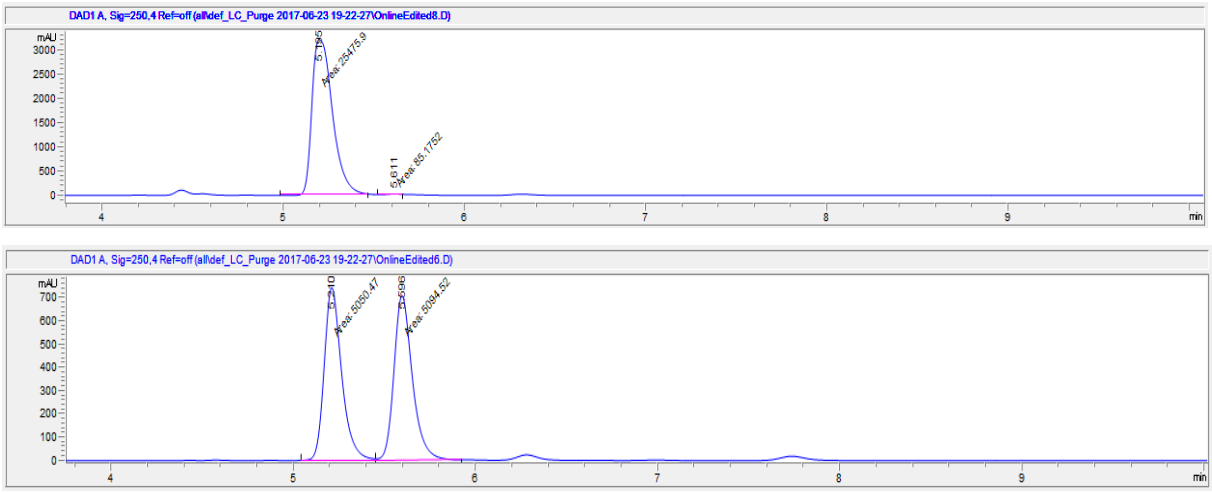
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 15.8 Hz, 1H), 7.58 (dd, J = 7.5, 1.7 Hz, 1H), 7.36–7.29 (m, 2H), 7.26-7.23 (m, 3H), 7.22–7.19 (m, 1H), 7.18–7.15 (m, 2H), 6.34 (d, J = 15.8 Hz, 1H), 5.06-5.11 (m, 1H), 5.62 (s_{br}, 1H), 4.21–4.15 (m, 2H), 3.68 (s, 2H), 1.66 (dq, J = 12.3, 6.9 Hz, 2H), 1.47–1.38 (m, 2H), 1.37 (d, J = 7.0 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H).

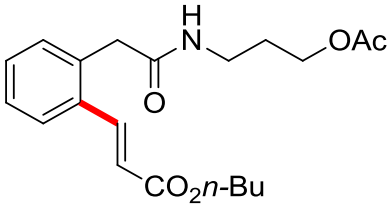
^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9 (C_q), 166.5 (C_q), 142.8 (C_q), 141.0 (CH), 131.3 (C_q), 130.4 (C_q), 129.3 (CH), 129.0 (CH), 128.5 (CH), 128.1 (CH), 127.2 (CH), 127.1 (CH), 126.0 (CH), 121.0 (CH), 64.5 (CH_2), 48.8 (CH), 41.3 (CH_2), 30.7 (CH_2), 21.4 (CH_3), 19.1 (CH_2), 13.6 (CH_3).

IR (ATR): 2960, 1712, 1641, 1541, 1312, 1171, 699 cm^{-1}. MS (ESI) *m/z* (relative intensity): 388 (100) $[M+Na]^+$, 366 (57) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{23}H_{28}NO_3$ $[M+H]^+$: 366.2064, found: 366.2064.

HPLC (*n*-hexane/*i*PrOH: 70/30): t = 5.20 min.





(*E*)-*n*-Butyl 3-{2-{2-[(3-acetoxypropyl)amino]-2-oxoethyl}phenyl}acrylate (133oa):

The general procedure **A** was followed using 3-(2-phenylacetamido)propyl acetate (**132o**) (118 mg, 0.50 mmol) and *n*-butyl acrylate (**5a**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133oa** (110 mg, 61%) as a colorless oil.

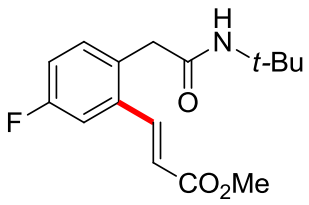
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 15.8 Hz, 1H), 7.57 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.35–7.22 (m, 3H), 6.34 (d, *J* = 15.8 Hz, 1H), 5.81 (s_{br}, 1H), 4.15 (t, *J* = 6.7 Hz, 2H), 3.98 (t, *J* = 6.0, 2H), 3.65 (s, 2H), 3.22 (dd, *J* = 12.8, 6.7 Hz, 2H), 1.94 (s, 3H), 1.77–1.68 (m, 2H), 1.67–1.59 (m, 2H), 1.34–1.32 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9 (C_q), 169.8 (C_q), 166.4 (C_q), 140.9 (CH), 134.1 (C_q), 133.9 (C_q), 131.1 (CH), 130.2 (CH), 127.9 (CH), 127.0 (CH), 120.7 (CH), 64.4 (CH_2), 61.7 (CH_2), 41.1 (CH_2), 36.5 (CH_2), 30.7 (CH_2), 28.6 (CH_2), 20.8 (CH_3), 19.2 (CH_2), 13.7 (CH_3).

IR (ATR): 2961, 1710, 1649, 1239, 1174, 907, 726 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 384 (100) $[M+Na]^+$, 362 (70) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{20}H_{28}NO_5$ $[M+H]^+$: 362.1962, found: 362.1961.



(*E*)-Methyl 3-{2-[2-(*tert*-butylamino)-2-oxoethyl]-5-fluorophenyl}acrylate (133pc):

The general procedure **A** was followed using *N*-(*tert*-butyl)-2-(4-fluorophenyl)acetamide (**132p**) (105 mg, 0.50 mmol) and methyl acrylate (**5c**) (86 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133pc** (119 mg, 81%) as a white solid.

M. p. = 147–148 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (dd, *J* = 15.8, 1.5 Hz, 1H), 7.26–7.19 (m, 2H), 7.02 (td, *J* = 8.2, 2.7 Hz, 1H), 6.32 (d, *J* = 15.8 Hz, 1H), 5.28 (s_{br}, 1H), 3.77 (s, 3H), 3.53 (s, 2H), 1.26 (s, 9H).

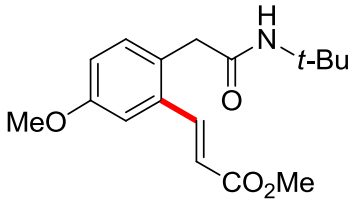
^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9 (C_q), 166.6 (C_q), 162.0 (C_q, $^{1}J_{C-F}$ = 246.7 Hz), 140.6 (CH, $^{4}J_{C-F}$ = 2.3 Hz), 135.7 (C_q, $^{3}J_{C-F}$ = 7.7 Hz), 132.9 (CH, $^{3}J_{C-F}$ = 8.2 Hz), 130.7 (C_q, $^{4}J_{C-F}$ = 3.2 Hz), 121.2 (CH), 117.2 (CH, $^{2}J_{C-F}$ = 21.4 Hz), 113.4 (CH, $^{2}J_{C-F}$ = 22.4 Hz), 51.8 (CH_3), 51.5 (C_q), 41.4 (CH_2), 28.6 (CH_3).

^{19}F NMR (376 Hz, $CDCl_3$): δ = –114.3.

IR (ATR): 2967, 1718, 1645, 1491, 1266, 1171, 977 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 316 (90) $[M+Na]^+$, 294 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{16}H_{21}FNO_3$ $[M+H]^+$: 294.1500, found: 294.1502.



(*E*)-Methyl 3-{2-[2-(*tert*-butylamino)-2-oxoethyl]-5-methoxyphenyl}acrylate (133qc):

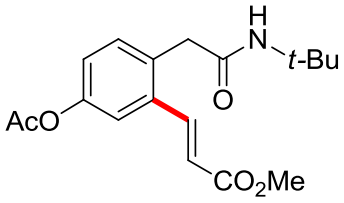
The general procedure **A** was followed using *N*-(*tert*-butyl)-2-(4-methoxyphenyl)acetamide (**132q**) (111 mg, 0.50 mmol) and methyl acrylate (**5c**) (86 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133qc** (111 mg, 73%) as a white solid.

M. p. = 142–143 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 15.7 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.10 (d, *J* = 2.1 Hz, 1H), 6.95–6.89 (m, 1H), 6.35 (d, *J* = 15.7 Hz, 1H), 5.16 (s_{br}, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.55 (s, 2H), 1.26 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.0 (C_q), 166.9 (C_q), 159.0 (C_q), 141.6 (CH), 134.9 (C_q), 132.5 (CH), 127.1 (C_q), 120.3 (CH), 116.4 (CH), 111.9 (CH), 55.4 (CH_3), 51.8 (CH_3), 51.3 (C_q), 41.6 (CH_2), 28.6 (CH_3). **IR (ATR)**: 2965, 1715, 1645, 1496, 1228, 1194, 978 cm^{-1}. MS (ESI) *m/z* (relative intensity): 328 (33) $[M+Na]^+$, 306 (40) $[M+H]^+$, 274 (20).

HR-MS (ESI) *m/z* calcd for $C_{17}H_{24}NO_4$ $[M+H]^+$: 306.1700, found: 306.1703.



(*E*)-Methyl 3-{5-acetoxy-2-[2-(*tert*-butylamino)-2-oxoethyl]phenyl}acrylate (133rc):

The general procedure **A** was followed using 4-[2-(*tert*-butylamino)-2-oxoethyl]phenyl acetate (**132r**) (125 mg, 0.50 mmol) and methyl acrylate (**5c**) (86 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133rc** (117 mg, 70%) as a white solid.

M. p. = 128–129 °C.

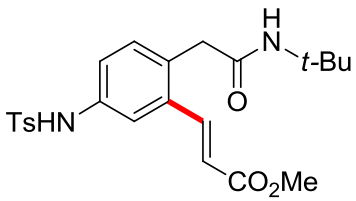
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 15.8 Hz, 1H), 7.25 (d, *J* = 2.1 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 1H), 7.06–7.01 (m, 1H), 6.28 (d, *J* = 15.8 Hz, 1H), 5.16 (s_{br}, 1H), 3.73 (s, 3H), 3.51 (s, 2H), 2.24 (s, 3H), 1.22 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0 (C_q), 168.6 (C_q), 166.6 (C_q), 150.0 (C_q), 140.7 (CH), 135.1 (C_q), 132.3 (C_q), 132.2 (CH), 123.4 (CH), 121.0 (CH), 119.8 (CH), 51.8 (CH_3), 51.6 (C_q), 41.7 (CH_2), 28.7 (CH_3), 21.2 (CH_3).

IR (ATR): 2967, 1762, 1716, 1648, 1203, 1171, 731 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 356 (50) $[M+Na]^+$, 334 (100) $[M+H]^+$, 302 (45).

HR-MS (ESI) *m/z* calcd for $C_{18}H_{24}NO_5$ $[M+H]^+$: 334.1649, found: 334.1646.



(*E*)-Methyl 3-{2-[2-(*tert*-butylamino)-2-oxoethyl]-5-(4-methylphenylsulfonamido)-phenyl}acrylate (133sc):

The general procedure **A** was followed using *N*-(*tert*-butyl)-2-[4-(4-methylphenylsulfonamido)-phenyl]acetamide (**132s**) (180 mg, 0.50 mmol) and methyl acrylate (**5c**) (86 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133sc** (147 mg, 66%) as a white solid.

M. p. = 152–153 °C.

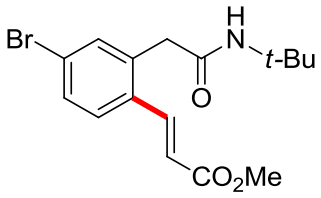
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 15.8 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.43 (s_{br}, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 2.2 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.97 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.17 (d, *J* = 15.8 Hz, 1H), 5.30 (s_{br}, 1H), 3.79 (s, 3H), 3.51 (s, 2H), 2.36 (s, 3H), 1.30 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.4 (C_q), 165.9 (C_q), 142.9 (C_q), 140.0 (CH), 135.5 (C_q), 135.2 (C_q), 133.6 (C_q), 131.3 (CH), 130.4 (C_q), 128.6 (CH), 126.2 (CH), 122.5 (CH), 119.8 (CH), 118.7 (CH), 50.8 (CH_3), 50.7 (C_q), 40.5 (CH_2), 27.5 (CH_3), 20.5 (CH_3).

IR (ATR): 2966, 1718, 1649, 1321, 1159, 1092, 543 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 467 (100) $[M+Na]^+$, 445 (70) $[M+H]^+$, 413 (20).

HR-MS (ESI) *m/z* calcd for $C_{23}H_{29}N_2O_5S$ $[M+H]^+$: 445.1792, found: 445.1791.



(*E*)-Methyl 3-{4-bromo-2-[2-(*tert*-butylamino)-2-oxoethyl]phenyl}acrylate (133tc):

The general procedure **A** was followed using 2-(3-bromophenyl)-*N*-(*tert*-butyl)acetamide (**132t**) (135 mg, 0.50 mmol) and methyl acrylate (**5c**) (86 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133tc** (150 mg, 85%) as a white solid.

Gram-scale reaction: The general procedure **A** was followed using 2-(3-bromophenyl)-*N*-(*tert*-butyl)acetamide (**132t**) (1.08 g, 4.00 mmol) and methyl acrylate (**5c**) (0.69 g, 8.00 mmol) in THF (16 mL). Recrystallization from PhMe yielded **133tc** (1.17 g, 83%) as a white solid.

M. p. = 143–144 °C.

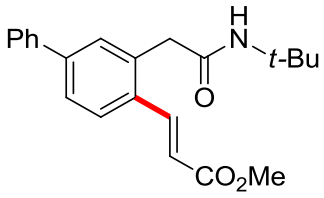
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 15.8 Hz, 1H), 7.47–7.45 (m, 2H), 7.45–7.44 (m, 1H), 6.36 (d, J = 15.8 Hz, 1H), 5.30 (s_{br}, 1H), 3.80 (s, 3H), 3.56 (s, 2H), 1.30 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3 (C_q), 166.8 (C_q), 140.6 (CH), 136.7 (C_q), 134.2 (CH), 132.9 (C_q), 131.0 (CH), 128.4 (CH), 124.4 (C_q), 120.6 (CH), 51.8 (CH_3), 51.7 (C_q), 41.9 (CH_2), 28.6 (CH_3).

IR (ATR): 2970, 1713, 1644, 1586, 1315, 1172, 821 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 376 (95) ($[M+Na]^+$, ^{79}Br), 356 (100) ($[M+H]^+$, ^{81}Br).

HR-MS (ESI) *m/z* calcd for $C_{16}H_{21}{}^{79}BrNO_3$ $[M+H]^+$: 354.0699, found: 354.0699.



(*E*)-Methyl 3-{3-[2-(*tert*-butylamino)-2-oxoethyl]-[1,1'-biphenyl]-4-yl}acrylate (133uc):

The general procedure **A** was followed using 2-([1,1'-biphenyl]-3-yl)-*N*-(*tert*-butyl)acetamide (**132u**) (134 mg, 0.50 mmol) and methyl acrylate (**5c**) (86 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133uc** (158 mg, 90%) as a white solid.

M. p. = 182–183 °C.

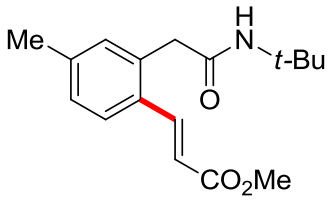
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 15.8 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.61–7.57 (m, 2H), 7.56 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.51 (d, *J* = 1.7 Hz, 1H), 7.48–7.43 (m, 2H), 7.40–7.35 (m, 1H), 6.42 (d, *J* = 15.8 Hz, 1H), 5.25 (s_{br}, 1H), 3.81 (s, 3H), 3.69 (s, 2H), 1.30 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0 (C_q), 167.0 (C_q), 143.2 (C_q), 141.2 (CH), 139.8 (C_q), 135.4 (C_q), 132.7 (C_q), 129.9 (CH), 128.9 (CH), 128.0 (CH), 127.5 (CH), 127.0 (CH), 126.5 (CH), 119.9 (CH), 51.8 (C_q), 51.5 (CH_2), 42.6 (CH_3), 28.6 (CH_3).

IR (ATR): 2966, 1716, 1645, 1543, 1167, 763, 697 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 374 (50) $[M+Na]^+$, 352 (100) $[M+H]^+$, 320 (45).

HR-MS (ESI) *m/z* calcd for $C_{22}H_{26}NO_3$ $[M+H]^+$: 352.1907, found: 352.1905.



(*E*)-Methyl 3-{2-[2-(*tert*-butylamino)-2-oxoethyl]-4-methylphenyl}acrylate (133vc):

The general procedure **A** was followed using *N*-(*tert*-butyl)-2-(*m*-tolyl)acetamide (**132v**) (103 mg, 0.50 mmol) and methyl acrylate (**5c**) (86 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133vc** (132 mg, 91%) as a white solid.

M. p. = 140–141 °C.

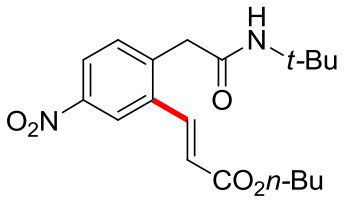
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 15.8 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 1H), 7.08 (s, 1H), 6.34 (d, *J* = 15.8 Hz, 1H), 5.10 (s_{br}, 1H), 3.79 (s, 3H), 3.58 (s, 2H), 2.36 (s, 3H), 1.27 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2 (C_q), 167.2 (C_q), 141.5 (CH), 140.9 (C_q), 134.8 (C_q), 132.1 (CH), 131.0 (C_q), 128.8 (CH), 127.0 (CH), 119.1 (CH), 51.7 (CH_3), 51.4 (C_q), 42.4 (CH_2), 28.6 (CH_3), 21.3 (CH_3).

IR (ATR): 2967, 1717, 1646, 1543, 1173, 1159, 816 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 312 (100) $[M+Na]^+$, 290 (60) $[M+H]^+$, 258 (40).

HR-MS (ESI) *m/z* calcd for $C_{17}H_{24}NO_3$ $[M+H]^+$: 290.1751, found: 290.1754.



(*E*)-*n*-Butyl 3-{2-[2-(*tert*-butylamino)-2-oxoethyl]-5-nitrophenyl}acrylate (133wa):

The general procedure **A** was followed using *N*-(*tert*-butyl)-2-(4-nitrophenyl)acetamide (**132w**) (118 mg, 0.50 mmol) and *n*-butyl acrylate (**5a**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133wa** (104 mg, 65%) as a white solid.

M. p. = 159–160 °C.

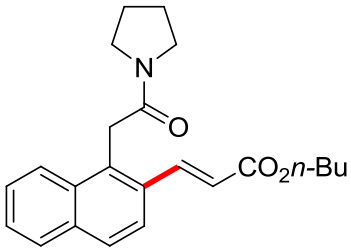
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 2.3 Hz, 1H), 8.17 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.86 (d, *J* = 15.8 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 15.8 Hz, 1H), 5.37 (s_{br}, 1H), 4.22 (t, *J* = 6.7 Hz, 2H), 3.67 (s, 2H), 1.71–1.65 (m, 2H), 1.48–1.40 (m, 2H), 1.32 (s, 9H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.4 (C_q), 165.1 (C_q), 146.4 (C_q), 140.6 (C_q), 138.3 (CH), 134.6 (C_q), 131.3 (CH), 123.2 (CH), 122.4 (CH), 120.8 (CH), 63.9 (CH_2), 50.9 (C_q), 40.8 (CH_2), 29.7 (CH_2), 27.6 (CH_3), 18.1 (CH_2), 12.7 (CH_3).

IR (ATR): 2962, 1714, 1648, 1547, 1176, 821, 739 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 385 (100) $[M+Na]^+$, 363 (55) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{29}H_{27}N_2O_5$ $[M+H]^+$: 363.1914, found: 363.1911.



(*E*)-*n*-Butyl 3-{1-[2-oxo-2-(pyrrolidin-1-yl)ethyl]naphthalen-2-yl}acrylate (133xa):

The general procedure **A** was followed using 2-(naphthalen-1-yl)-1-(pyrrolidin-1-yl)ethanone (**132x**) (120 mg, 0.50 mmol) and *n*-butyl acrylate (**5a**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133xa** (110 mg, 60%) as a white solid.

M. p. = 149–150 °C.

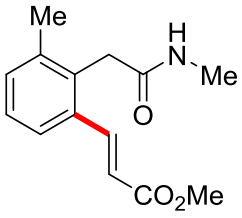
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 15.7 Hz, 1H), 7.98–7.94 (m, 1H), 7.84–7.74 (m, 2H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.56–7.45 (m, 2H), 6.47 (d, *J* = 15.7 Hz, 1H), 4.22 (m, 4H), 3.68 (t, *J* = 6.8 Hz, 2H), 3.52 (t, *J* = 6.9 Hz, 2H), 2.15–2.00 (m, 2H), 1.91 (m, 2H), 1.71 (ddd, *J* = 14.5, 9.6, 6.6 Hz, 2H), 1.46 (tdd, *J* = 14.4, 8.4, 6.4 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0 (C_q), 166.9 (C_q), 142.4 (CH), 134.2 (C_q), 132.9 (C_q), 132.1 (C_q), 131.4 (C_q), 128.5 (CH), 127.8 (CH), 126.8 (CH), 126.4 (CH), 124.7 (CH), 123.6 (CH), 120.7 (CH), 64.3 (CH_2), 46.9 (CH_2), 46.1 (CH_2), 34.5 (CH_2), 30.8 (CH_2), 26.4 (CH_2), 24.4 (CH_2), 19.3 (CH_2), 13.8 (CH_3).

IR (ATR): 2957, 1705, 1628, 1418, 1172, 912, 727 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 388 (30) $[M+Na]^+$, 366 (100) $[M+H]^+$, 292 (25).

HR-MS (ESI) *m/z* calcd for $C_{23}H_{28}NO_3$ $[M+H]^+$: 366.2064, found: 366.2065.



(*E*)-Methyl 3-{3-methyl-2-[2-(methylamino)-2-oxoethyl]phenyl}acrylate (133yc):

The general procedure **A** was followed using *N*-methyl-2-(*o*-tolyl)acetamide (**132y**) (81.5 mg, 0.50 mmol) and methyl acrylate (**5c**) (86 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133yc** (65 mg, 53%) as a white solid.

M. p. = 112–113 °C.

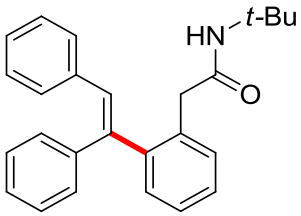
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 15.7 Hz, 1H), 7.43 (dd, *J* = 6.3, 2.9 Hz, 1H), 7.25–7.22 (m, 2H), 6.32 (d, *J* = 15.7 Hz, 1H), 5.20 (s_{br}, 1H), 3.78 (s, 3H), 3.72 (s, 2H), 2.72 (d, *J* = 4.8 Hz, 3H), 2.30 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0 (C_q), 166.7 (C_q), 141.9 (CH), 138.4 (C_q), 134.7 (C_q), 132.5 (C_q), 132.3 (CH), 127.8 (CH), 125.2 (CH), 121.1 (CH), 51.8 (CH_3), 37.3 (CH_2), 26.6 (CH_3), 20.3 (CH_3).

IR (ATR): 2950, 1718, 1644, 1599, 1316, 1164, 790 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 270 (100) $[M+Na]^+$, 248 (15) $[M+H]^+$, 216 (20).

HR-MS (ESI) *m/z* calcd for $C_{14}H_{18}NO_3$ $[M+H]^+$: 248.1281, found: 248.1280.



(*E*)-*N*-(*tert*-butyl)-2-[2-(1,2-diphenylvinyl)phenyl]acetamide (133'ic):

The general procedure **B** was followed using *N*-(*tert*-butyl)-2-phenylacetamide (**132i**) (95.5 mg, 0.50 mmol) and 1,2-diphenylethyne (**51b**) (106 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133'ic** (105 mg, 57%) as a white solid.

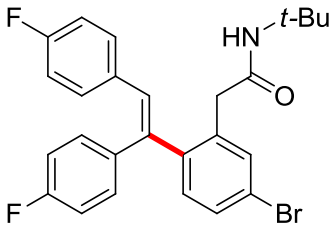
M. p. = 135–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 4H), 7.20 (ddd, J = 5.8, 2.4, 1.2 Hz, 3H), 7.17–7.12 (m, 5H), 7.10–7.07 (m, 2H), 6.59 (s, 1H), 4.85 (s_{br}, 1H), 3.35 (s, 2H), 1.16 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1 (C_q), 144.1 (C_q), 142.0 (C_q), 139.9 (C_q), 136.9 (C_q), 133.7 (C_q), 131.1 (CH), 130.9 (CH), 130.9 (CH), 129.7 (CH), 129.4 (CH), 128.5 (CH), 128.1 (CH), 128.1 (CH), 127.6 (CH), 127.1 (CH), 127.0 (CH), 51.0 (CH_2), 42.3 (C_q), 28.56 (CH_3).

IR (ATR): 2914, 1694, 1656, 1444, 1221, 747, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity): 369 (70) $[M]^+$, 278 (75), 222 (55).

HR-MS (ESI) *m/z* calcd for $C_{26}H_{28}NO$ $[M+H]^+$: 370.2145, found: 370.2141.



(*E*)-2-{2-[1,2-Bis(4-fluorophenyl)vinyl]-5-bromophenyl}-*N*-(*tert*-butyl)acetamide (133'td):

The general procedure **B** was followed using 2-(3-bromophenyl)-*N*-(*tert*-butyl)acetamide (**132t**) (134.5 mg, 0.50 mmol) and 1,2-bis(4-fluorophenyl)ethyne (**51d**) (128 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133'td** (148 mg, 61%) as a white solid.

M. p. = 135–136 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 2.0 Hz, 1H), 7.40 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.10–7.01 (m, 4H), 6.94–6.83 (m, 4H), 6.53 (s, 1H), 4.85 (s_{br}, 1H), 3.25 (s, 2H), 1.19 (s, 9H).

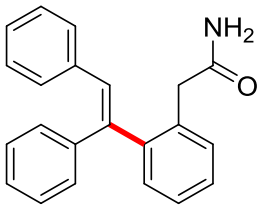
^{13}C NMR (125 MHz, CDC_3): δ = 168.7 (C_q), 162.1 (C_q, $^{1}J_{C–F}$ = 248.8 Hz), 161.7 (C_q, $^{1}J_{C–F}$ = 247.6 Hz), 142.4 (C_q), 139.6 (C_q,), 135.6 (C_q), 135.1 (C_q, $^{4}J_{C–F}$ = 3.8 Hz), 133.8 (CH), 132.4 (C_q, $^{4}J_{C–F}$ = 3.8 Hz), 132.2 (CH), 131.4 (CH, $^{3}J_{C–F}$ = 8.2 Hz), 130.8 (CH, $^{3}J_{C–F}$ = 8.2 Hz), 130.3 (CH), 130.2 (CH), 121.9 (C_q), 115.7 (CH, $^{2}J_{C–F}$ = 21.5 Hz), 115.2 (CH, $^{2}J_{C–F}$ = 21.5 Hz), 51.3 (CH_2), 41.9 (C_q), 28.7 (CH_3).

^{19}F NMR (282 Hz, $CDCl_3$): δ = –113.81, –113.7.

IR (ATR): 1639, 1544, 1506, 1228, 823, 548 cm^{-1}.

MS (EI) *m/z* (relative intensity): 485 (25) [M, $^{81}Br]^+$, 374 (20), 304 (30).

HR-MS (ESI) *m/z* calcd for $C_{26}H_{25}{}^{81}BrF_2NO$ $[M+H]^+$: 485.1013, found: 485.1010.



(*E*)-2-[2-(1,2-diphenylvinyl)phenyl]acetamide (133'ac):

The general procedure **B** was followed using 2-phenylacetamide (**132a**) (67.5 mg, 0.50 mmol), 1,2-diphenylethyne (**51b**) (106 mg, 1.00 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (30.6 mg, 10.0 mol %) in 1,4-dioxane (2.0 mL). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **133'ab** (103 mg, 66%) as a white solid.

M. p. = 123–124 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.34 (m, 1H), 7.33-7.29 (m, 3H), 7.22–7.18 (m, 3H), 7.18–7.13 (m, 5H), 7.12-7.08 (m, 2H), 6.63 (s, 1H), 4.91 (s_{br}, 1H), 3.46 (s, 2H).

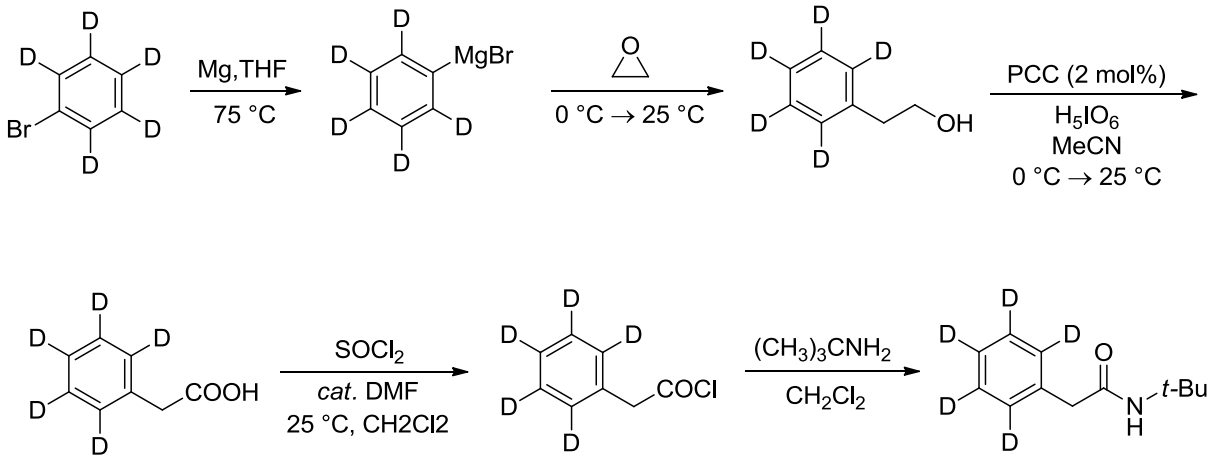
^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1 (C_q), 144.3 (C_q), 141.8 (C_q), 140.0 (C_q), 136.8 (C_q), 133.1 (C_q), 131.3 (CH), 131.1 (CH), 130.9 (CH), 129.9 (CH), 129.4 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 127.1 (CH), 40.6 (CH_2).

IR (ATR): 1666, 1606, 1490, 1441, 1373, 769, 698 cm^{-1}.

MS (EI) *m/z* (relative intensity): 313 (50) $[M]^+$, 268 (30), 222 (65).

HR-MS (ESI) *m/z* calcd for $C_{22}H_{20}NO$ $[M+H]^+$: 313.1462, found: 313.1465.

Sythesis of [D_5]-132i

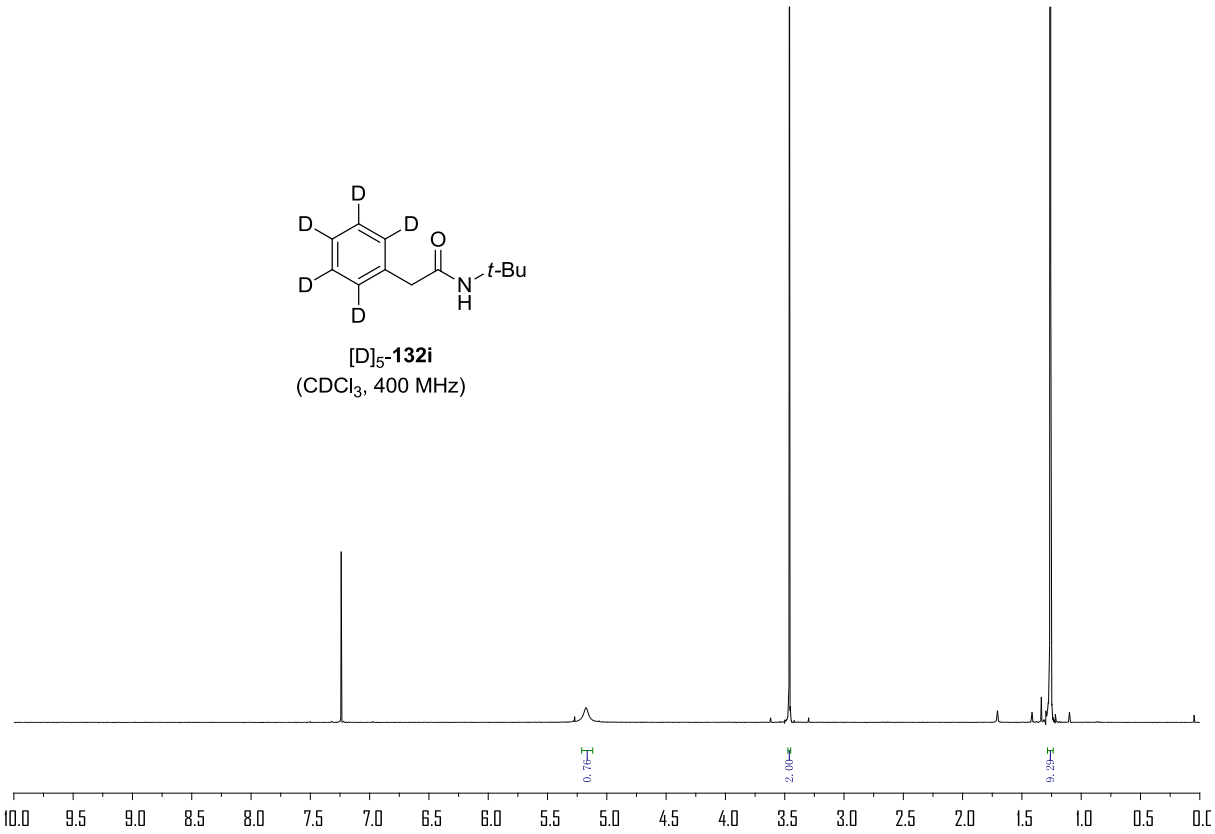


A solution of the [D]$_5$-PhMgBr in THF (30 mL) was prepared from bromobenzene-d_5 (1.62 g, 10 mmol) and magnesium (0.25 g, 10 mmol). Then, the reaction mixture was cooled to 0 °C and at –78 °C cold ethylene oxide (approx. 15 mmol) was added. The resulting mixture was allowed to warm to 25 °C and then stirred for an additional 6 h. The reaction was stopped by the addition of aq. HCl (2N, 10 mL), the solution was extracted with Et_2O (3 x 20 mL) and washed with brine (20 mL). The combined organic extracts were dried over $NaSO_4$ and concentrated. Purification of the crude product by flash chromatography on silica gel (*n*-hexane/EtOAc 10/1→0/1) yielded 2-phenylethanol-d_5 (0.43 g, 34%).[136]

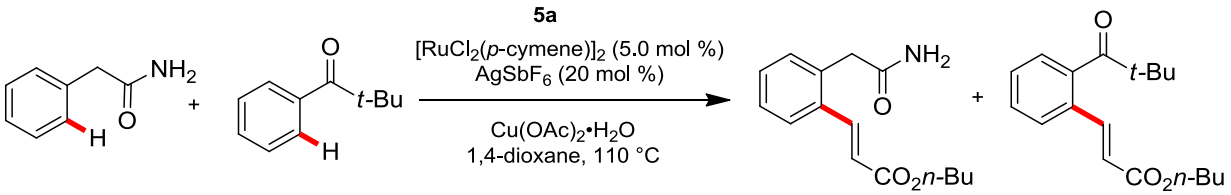
H_5IO_6 (1.37 g, 6 mmol) was dissolved in MeCN (20 mL) and the mixture was stirred vigorously at 25 °C for 15 min and 2-phenylethanol-d_5 (0.38g, 3.0 mmol) was added. A solution of PCC (13 mg, 2 mol %) in MeCN (6 mL) was then added in two portions at 0 °C and the reaction mixture was stirred at 25 °C for 3 h. The reaction mixture was then diluted with EtOAc (30 mL) and washed with a mixture of brine and water (1:1, 30 mL), sat. aq. $NaHSO_3$ solution (30 mL) and brine (30 mL). The solution was dried over Na_2SO_4 and concentrated to give 2-phenyl acetic acid-d_5 (80%).

2-Phenyl acetic acid-d_5 was converted to [D_5]-**132i** following previously reported procedures.[137]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.18 (s_{br}, 1H), 3.46 (s, 2H), 1.26 (s, 9H).

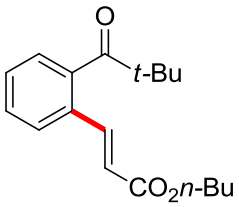


Intermolecular competition experiment between amide and ketone



132a **58a** **133aa**: 27% **141**: 53%

A suspension of 2-phenylacetamide (**132a**) (67.5 mg, 0.50 mmol), 2,2-dimethyl-1phenylpropan-1-one (**58a**) (81.0 mg, 0.50 mmol), *n*-butyl acrylate (**5a**) (64 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), $AgSbF_6$ (35.5 mg, 20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (200 mg, 1.00 mmol) in 1,4-dioxane (2.0 mL) was stirred at 110 °C for 24 h under N_2 atomsphere. Afterwards, the solvent was removed *in vacuo* and purification of the remaining residue by column chromatography (*n*-hexane/EtOAc) yieled **133aa** (35 mg, 27%) and **141** (76 mg, 53%).



^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.61 (m, 1H), 7.49 (d, J = 15.9 Hz, 1H), 7.40–7.32 (m, 2H), 7.20–7.15 (m, 1H), 6.35 (d, J = 15.9 Hz, 1H), 4.19–4.10 (m, 2H), 1.71–1.56 (m, 2H), 1.45–1.34 (m, 2H), 1.23–1.20 (m, 9H), 0.92 (t, J = 7.4 Hz, 3H).

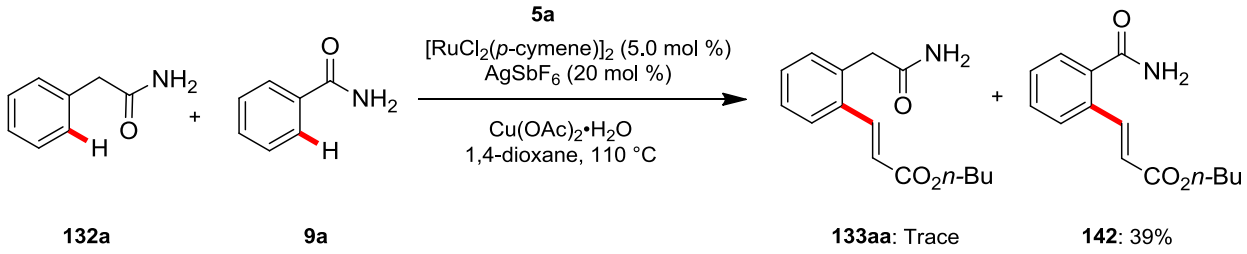
^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.1 (C_q), 166.3 (C_q), 142.0 (C_q), 141.5 (CH), 131.1 (C_q), 129.1 (CH), 129.0 (CH), 126.6 (CH), 125.3 (CH), 120.5 (CH), 64.5 (CH_2), 45.2 (CH_2), 30.7 (CH_2), 27.2 (CH_3), 19.1 (CH_2), 13.7 (CH_3).

IR (ATR): 2961, 1710, 1688, 1463, 1307, 1267, 1177, 962, 758 cm^{-1}.

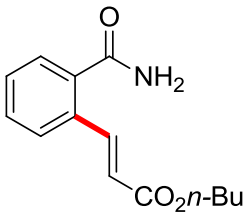
MS (EI) *m*/*z* (relative intensity): 288 (45) $[M]^+$, 231 (50), 174 (25).

HR-MS (ESI) m/z calcd for $C_{18}H_{25}O_3$ $[M+H]^+$: 289.1324, found: 289.1327.

Intermolecular competition experiment between arylacetamide and benzamide



A suspension of 2-phenylacetamide (**132a**) (67.5 mg, 0.50 mmol), benzamide (**9a**) (60.5 mg, 0.50 mmol), *n*-butyl acrylate (**5a**) (64 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), $AgSbF_6$ (35.5 mg, 20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (200 mg, 1.00 mmol) in 1,4-dioxane (2.0 mL) was stirred at 110 °C for 24 h under N_2 atomsphere. Afterwards, the solvent was removed *in vacuo* and purification of the remaining residue by column chromatography (*n*-hexane/EtOAc) yieled **142** (48 mg, 39%).

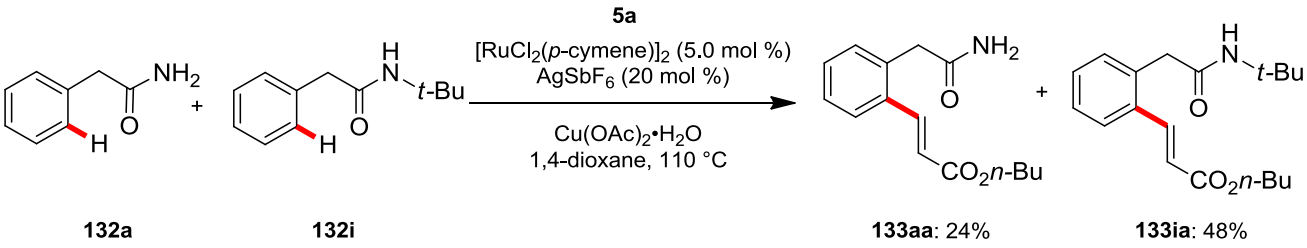


^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 16.0 Hz, 1H), 7.64–7.61 (m, 1H), 7.58–7.54 (m, 1H), 7.48–7.43 (m, 1H), 7.40 (td, J = 7.5, 1.4 Hz, 1H), 6.39 (d, J = 16.0 Hz, 1H), 5.89 (s_{br}, 1H), 5.80 (s_{br}, 1H), 4.18 (t, J = 6.7 Hz, 2H), 1.66 (dq, J = 12.2, 6.9 Hz, 2H), 1.46–1.35 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3 (C_q), 166.5 (C_q), 141.8 (CH), 135.8 (C_q), 133.1 (C_q), 130.8 (CH), 129.8 (CH), 127.8 (CH), 127.3 (CH), 121.1 (CH), 64.6 (CH_2), 30.7 (CH_2), 19.2 (CH_2), 13.7 (CH_3).

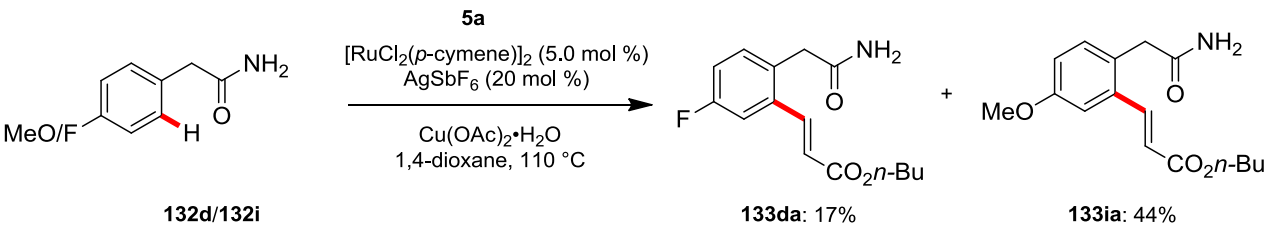
The analytical data are in accordance with previously reported data.[138]

Intermolecular competition experiment between primary and secondary amide



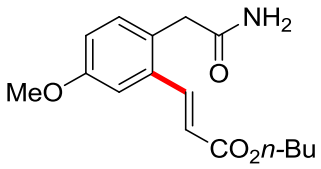
A suspension of 2-phenylacetamide (**132a**) (67.5 mg, 0.50 mmol), *N*-(*tert*-butyl)-2-phenylacetamide (**132i**) (95.5 mg, 0.50 mmol), *n*-butyl acrylate (**5a**) (64 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), $AgSbF_6$ (35.5 mg, 20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (200 mg, 1.00 mmol) in 1,4-dioxane (2.0 mL) was stirred at 110 °C for 24 h under N_2 atomsphere. Afterwards, the solvent was removed *in vacuo* and purification of the remaining residue by column chromatography (*n*-hexane/EtOAc) yieled **133aa** (31 mg, 24%) and **133ia** (76 mg, 48%).

Intermolecular competition experiment between electron-rich and electron-deficient amide



132d/132i **133da**: 17% **133ia**: 44%

A suspension of 2-(4-fluorophenyl)acetamide (**132d**) (76.5 mg, 0.50 mmol), 2-(4-methoxyphenyl)acetamide (**132i**) (82.5 mg, 0.50 mmol), *n*-butyl acrylate (**5a**) (64 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), $AgSbF_6$ (35.5 mg, 20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (200 mg, 1.00 mmol) in 1,4-dioxane (2.0 mL) was stirred at 110 °C for 24 h under N_2 atomsphere. Afterwards, the solvent was removed *in vacuo* and purification of the remaining residue by column chromatography (*n*-hexane/EtOAc) yieled **133da** (24 mg, 17%) and **133ia** (64 mg, 44%).



M. p. = 129–130 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 15.7 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 2.6 Hz, 1H), 6.88 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.37 – 6.28 (m, 1H), 5.96 (d, *J* = 15.9 Hz, 1H), 5.57 (s, 1H), 4.16 (t, *J* = 6.7 Hz, 2H), 3.79 (s, 3H), 3.61 (s, 2H), 1.65 (dt, *J* = 14.7, 6.8 Hz, 2H), 1.39 (dq, *J* = 14.4, 7.3 Hz, 2H), 0.98 – 0.88 (m, 3H).

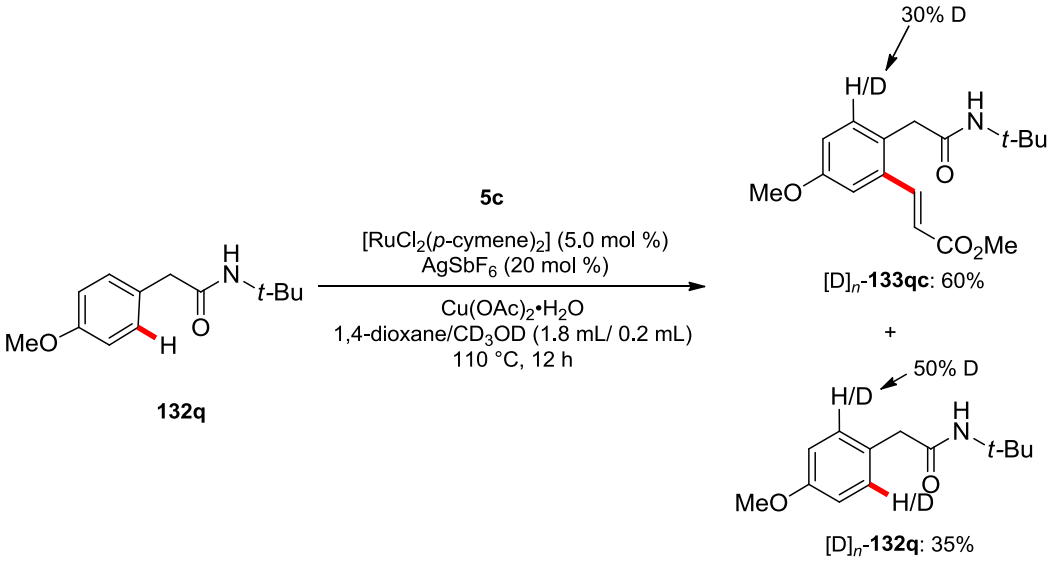
^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.8 (C_q), 166.5 (C_q), 159.0 (C_q), 141.1 (CH), 134.9 (C_q), 132.3 (CH), 126.5 (C_q), 121.0 (CH), 116.4 (CH), 111.8 (CH), 64.6 (CH_2), 55.4 (CH_3) , 34.0 (CH_2), 30.8 (CH_2), 19.2 (CH_2), 13.8 (CH_3).

IR (ATR): 2965, 1705, 1654, 1312, 1264, 1176, 728 cm^{-1}.

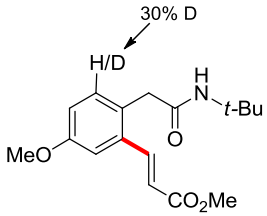
MS (ESI) *m/z* (relative intensity): 314 (100) $[M+Na]^+$, 292 (20) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{16}H_{22}NO_4$ $[M+H]^+$: 292.1545, found: 292.1542.

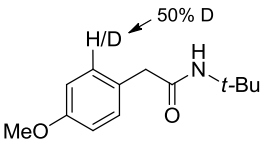
H/D Exchange Experiments



The representative procedure B was followed using **132q** (111 mg, 0.50 mmol), **5c** (86 mg, 1.0 mmol), [$RuCl_2$(*p*-cymene)] (15.3 mg, 5.0 mol %), $AgSbF_6$ (35.5 mg, 20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (200 mg, 1.0 mmol) in 1,4-dioxane (1.8 mL) and CD_3OD (0.2 mL). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded [D]$_n$-**133qc** (91.5 mg, 60%) as a colorless solid and reisolated starting material [D]$_n$-**132q** (38.9 mg, 35%). The deuterium content was determinded by NMR spectroscopy.



[D]$_n$-**133qc**
(CDCl$_3$, 600 MHz)

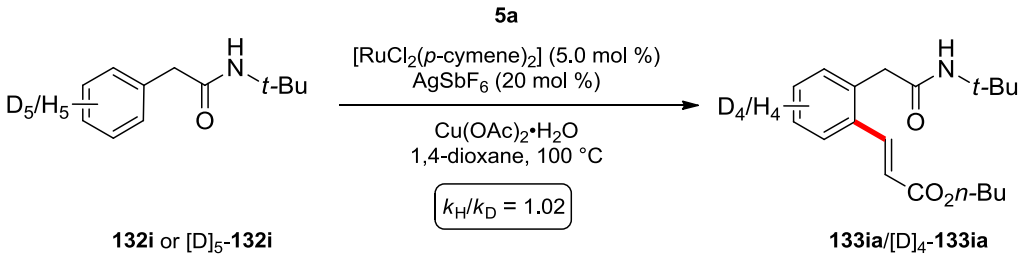


[D]$_n$-**132q**
(CDCl$_3$, 600 MHz)

Kinetic Isotope Effect (KIE) Studies

Under an atmosphere of nitrogen **132i** (143 mg, 0.75 mmol) or $[D]_5$-**132i** (147 mg, 0.75 mmol), **5a** (192 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (23 mg, 5.0 mol %), $AgSbF_6$ (52 mg, 20 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (299 mg, 1.50 mmol) were dissolved in 1,4-dioxane (3.0 mL) and stirred at 100 °C. For the first 2 h an *in situ* IR spectrum was acquired every 30 s, for the following 4 h one spectrum was acquired every 1 min and for the remaining 16 h one spectrum was acquired every 2 min.

The KIE was determined by measuring initial rates from the increase of the peak at 1726 cm^{-1}, which corresponds to a C=O vibration of product **133ia**. The absolute peak area was measured from 1744 to 1701 cm^{-1} with a one-point baseline at 871 cm^{-1}. A linear fit was employed to derive the initial rates.



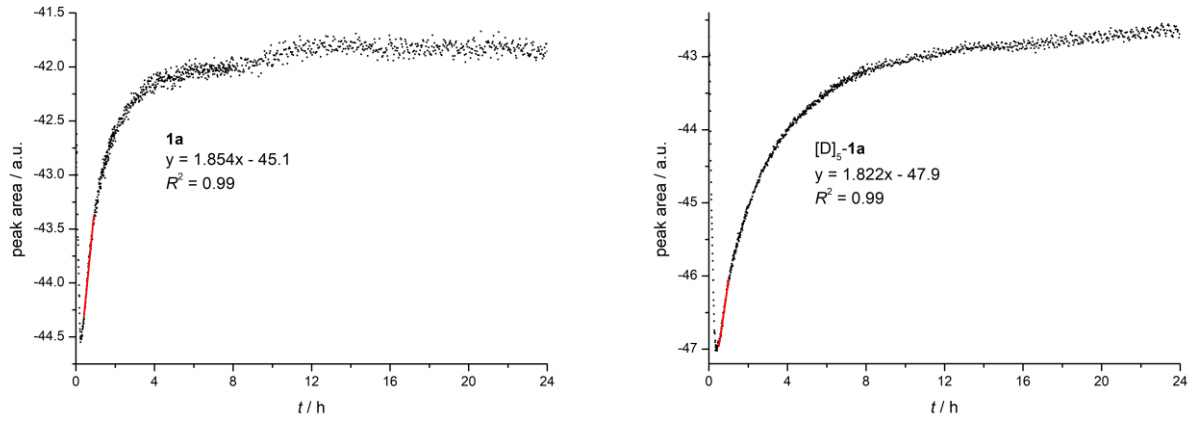
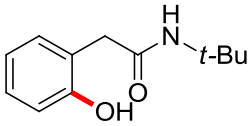


Figure xx. Plot of peak area at 1726 cm^{-1} vs reaction time for **132i** (left) and $[D]_5$-**132i** (right).

5.3.2 Ruthenium-Catalyzed C−H Oxygenation

Analytical Data



***N*-(*tert*-butyl)-2-(2-hydroxyphenyl)acetamide (135ia):**

The general procedure **C** was followed using *N*-(*tert*-butyl)-2-phenylacetamide (**132i**) (95.5 mg, 0.50 mmol), $PhI(TFA)_2$ (430 mg, 1.00 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) in DCE (2.0 mL). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **135ia** (64.2 mg, 62%) as a white solid.

M.p. = 125–126 °C.

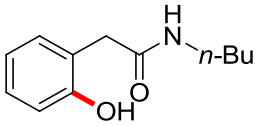
^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.25 (s_{br}, 1H), 7.20 (m, 1H), 7.03–6.97 (m, 2H), 6.84 (t, J = 7.4 Hz, 1H), 5.89 (s_{br}, 1H), 3.51 (s, 2H), 1.37 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1 (C_q), 156.6 (C_q), 130.4 (CH), 129.0 (CH), 121.9 (C_q), 120.1 (CH), 118.1 (CH), 52.2 (C_q), 42.4 (CH_2), 28.6 (CH_3).

IR (ATR): 1632, 1555, 1492, 1355, 1057, 942, 797 cm^{-1}.

MS (EI) *m/z* (relative intensity): 207 (40) $[M]^+$, 134 (65), 108 (70).

HR-MS (EI) *m/z* calcd for $C_{12}H_{17}NO_2^+$ $[M]^+$: 207.1259, found: 207.1261.



***n*-Butyl-2-(2-hydroxyphenyl)acetamide (135ja):**

The general procedure **C** was followed using *n*-butyl-2-phenylacetamide (**132j**) (95.5 mg, 0.50 mmol), $PhI(TFA)_2$ (430 mg, 1.00 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) in DCE (2.0 mL). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **135ja** (73.5 mg, 71%) as a white solid.

M.p. = 130–131 °C.

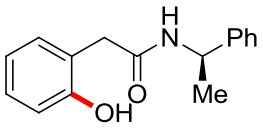
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.98 (s_{br}, 1H), 7.19 (td, J = 7.9, 1.7 Hz, 1H), 7.05–6.97 (m, 2H), 6.84 (td, J = 7.4, 1.2 Hz, 1H), 6.24 (s_{br}, 1H), 3.58 (s, 2H), 3.26 (td, J = 7.1, 5.9 Hz, 2H), 1.57–1.44 (m, 2H), 1.41–1.26 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4 (C_q), 156.2 (C_q), 130.5 (CH), 129.1 (CH), 121.6 (C_q), 120.3 (CH), 117.9 (CH), 41.1 (CH_2), 39.9 (CH_2), 31.3 (CH_2), 20.0 (CH_2), 13.7 (CH_3).

IR (ATR): 1630, 1542, 1488, 1299, 1057, 966 cm^{-1}.

MS (EI) *m/z* (relative intensity): 207 (70) $[M]^+$, 134 (50), 108 (100).

HR-MS (EI) *m/z* calcd for $C_{12}H_{17}NO_2^+$ $[M]^+$: 207.1259, found: 207.1258.



(*R*)-2-(2-hydroxyphenyl)-*N*-(1-phenylethyl)acetamide (135na):

The general procedure **C** was followed using (*R*)-2-phenyl-*N*-(1-phenylethyl)acetamide (**132n**) (119.5 mg, 0.50 mmol), $PhI(TFA)_2$ (430 mg, 1.00 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) in DCE (2.0 mL). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **135na** (80.3 mg, 63%) as a white solid.

M.p. = 140–141 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.77 (s_{br}, 1H), 7.31 (m, 2H), 7.28–7.24 (m, 3H), 7.20–7.11 (m, 1H), 6.96 (m, 2H), 6.83–6.77 (m, 1H), 6.27 (s_{br}, 1H), 5.06 (m, 1H), 3.61–3.46 (m, 2H), 1.47 (d, J = 6.9 Hz, 3H).

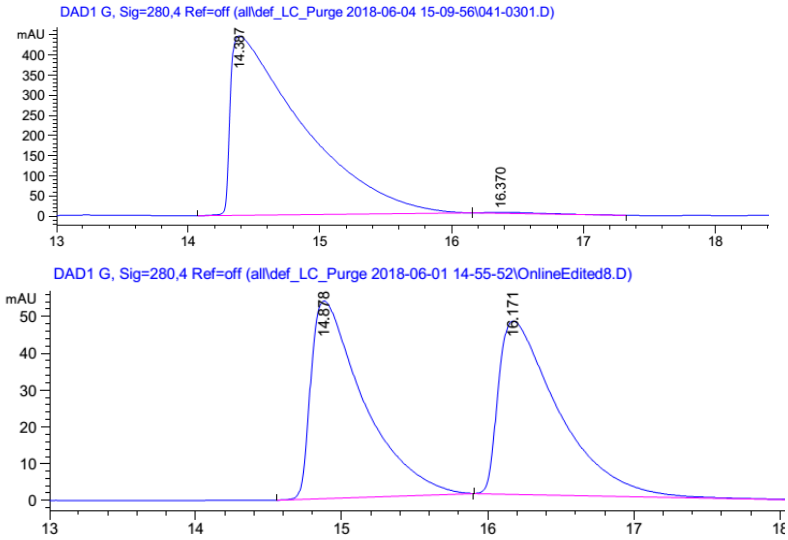
^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5 (C_q), 156.2 (C_q), 142.2 (C_q), 130.4 (CH), 129.2 (CH), 128.8 (CH), 127.7 (CH), 126.1 (CH), 121.4 (C_q), 120.2 (CH), 118.1 (CH), 49.5 (CH), 41.2 (CH_2), 21.4 (CH_3).

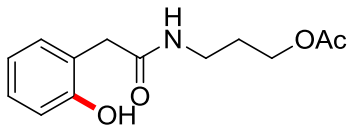
IR (ATR): 1635, 1521, 1438, 1219, 1059, 734 cm^{-1}.

MS (EI) *m/z* (relative intensity): 255 (30) $[M]^+$, 178 (45), 108 (70).

HR-MS (EI) *m/z* calcd for $C_{16}H_{17}NO_2^+$ $[M]^+$: 255.1259, found: 255.1257.

HPLC (*n*-hexane/EtOAc: 80/20): t = 14.39 min.





3-{2-(2-hydroxyphenyl)acetamido}propyl acetate (135oa):

The general procedure **C** was followed using 3-(2-phenylacetamido)propyl acetate (**132o**) (117.5 mg, 0.50 mmol), $PhI(TFA)_2$ (430 mg, 1.00 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) in DCE (2.0 mL). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **135oa** (80.3 mg, 64%) as a colorless oil.

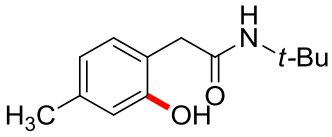
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.66 (s_{br}, 1H), 7.18–7.12 (m, 1H), 7.02–6.91 (m, 2H), 6.83–6.77 (m, 1H), 5.66 (s_{br}, 1H), 4.13–4.06 (m, 2H), 3.53 (s, 2H), 3.31–3.24 (m, 2H), 2.06–2.01 (m, 2H), 1.84–1.76 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.2 (C_q), 171.3 (C_q), 156.0 (C_q), 130.3 (CH), 129.1 (CH), 121.4 (C_q), 120.2 (CH), 117.9 (CH), 61.7 (CH_2), 41.1 (CH_2), 36.7 (CH_2), 28.4 (CH_2), 21.0 (CH_3).

IR (ATR): 1637, 1541, 1366, 1236, 1041, 754 cm^{-1}.

MS (EI) *m/z* (relative intensity): 251 (30) $[M]^+$, 191 (25), 134 (40).

HR-MS (EI) *m/z* calcd for $C_{13}H_{17}NO_4^+$ $[M]^+$: 251.1158, found: 251.1158.



***N*-(*tert*-butyl)-2-(2-hydroxy-4-methylphenyl)acetamide (135za):**

The general procedure **C** was followed using *N*-(*tert*-butyl)-2-(p-tolyl)acetamide (**132z**) (102.5 mg, 0.50 mmol), $PhI(TFA)_2$ (430 mg, 1.00 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) in DCE (2.0 mL). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **135za** (56.4 mg, 51%) as a white solid.

M.p. = 118–119 °C.

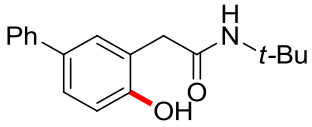
^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.04 (s_{br}, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.78 (d, J = 0.8 Hz, 1H), 6.61 (ddd, J = 7.6, 1.7, 0.8 Hz, 1H), 5.64 (s_{br}, 1H), 3.41 (s, 2H), 2.26 (s, 3H), 1.33 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.0 (C_q), 156.3 (C_q), 139.0 (C_q), 129.9 (CH), 120.6 (CH), 118.8 (CH), 118.6 (C_q), 52.2 (C_q), 42.3 (CH_2), 28.6 (CH_3), 21.2 (CH_3).

IR (ATR): 1641, 1548, 1364, 1222, 909, 733 cm^{-1}.

MS (EI) *m/z* (relative intensity): 221 (25) $[M]^+$, 148 (50), 120 (70).

HR-MS (EI) *m/z* calcd for $C_{13}H_{19}NO_2^+$ $[M]^+$: 221.1416, found: 221.1413.



***N*-(*tert*-Butyl)-2-(4-hydroxy-[1,1'-biphenyl]-3-yl)acetamide (135ua):**

The general procedure **C** was followed using 2-([1,1'-biphenyl]-3-yl)-*N*-(*tert*-butyl)acetamide (**132u**) (133.5 mg, 0.50 mmol), $PhI(TFA)_2$ (430 mg, 1.00 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) in DCE (2.0 mL). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **135ua** (75 mg, 53%) as a white solid.

M.p. = 145–146 °C.

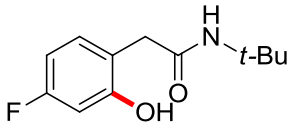
^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.45 (s_{br}, 1H), 7.55 (d, J = 1.6 Hz, 1H), 7.53 (dd, J = 3.0, 1.6 Hz, 1H), 7.44 (m, 3H), 7.34–7.27 (m, 1H), 7.25 (d, J = 2.6 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 5.92 (s_{br}, H), 3.58 (s, 2H), 1.39 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0 (C_q), 156.2 (C_q), 140.8 (C_q), 133.2 (C_q), 129.2 (CH), 128.7 (CH), 127.7 (CH), 126.7 (CH), 126.6 (CH), 122.1 (C_q), 118.5 (CH), 52.2 (C_q), 42.7 (CH_2), 28.6 (CH_3).

IR (ATR): 1643, 1556, 1483, 1357, 1054, 964, 826 cm^{-1}.

MS (EI) *m/z* (relative intensity): 283 (20) $[M]^+$, 210 (100), 182 (70).

HR-MS (EI) *m/z* calcd for $C_{18}H_{21}NO_2^+$ $[M]^+$: 283.1572, found: 283.1569.



***N*-(*tert*-Butyl)-2-(4-fluoro-2-hydroxyphenyl)acetamide (135pa):**

The general procedure **C** was followed using *N*-(*tert*-butyl)-2-(4-fluorophenyl)acetamide (**132p**) (104.5 mg, 0.50 mmol), $PhI(TFA)_2$ (430 mg, 1.00 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) in DCE (2.0 mL). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **135pa** (70.9 mg, 63%) as a white solid.

M.p. = 115–116 °C.

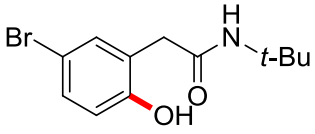
^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.71 (s_{br}, 1H), 6.93 (t, J = 8.3, 1H), 6.70 (dd, J = 10.4, 2.6 Hz, 1H), 6.53 (td, J = 8.3, 2.6 Hz, 1H), 5.83 (s_{br}, 1H), 3.46 (s, 2H), 1.38 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9 (C_q), 164.8 (C_q, $^1J_{C–F}$ = 245.2 Hz), 158.0 (C_q, $^3J_{C–F}$ = 12.4 Hz), 130.8 (CH, $^3J_{C–F}$ = 10.5 Hz), 117.6 (C_q, $^4J_{C–F}$ = 2.8 Hz), 106.5 (CH, $^2J_{C–F}$ = 21.4 Hz), 105.4 (CH, $^2J_{C–F}$ = 24.1 Hz), 52.2 (C_q), 41.6 (CH_2), 28.4 (CH_3).

IR (ATR): 1643, 1604, 1517, 1264, 906, 729, 650 cm^{-1}.

MS (EI) *m/z* (relative intensity): 225 (30) $[M]^+$, 152 (40), 126 (60).

HR-MS (EI) *m/z* calcd for $C_{12}H_{16}FNO_2^+$ $[M]^+$: 225.1165, found: 225.1161.



2-(5-Bromo-2-hydroxyphenyl)-*N*-(*tert*-butyl)acetamide (135ta):

The general procedure **C** was followed using 2-(3-bromophenyl)-*N*-(*tert*-butyl)acetamide (**132t**) (135 mg, 0.50 mmol), $PhI(TFA)_2$ (430 mg, 1.00 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) in

DCE (2.0 mL). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **135ta** (108.7 mg, 76%) as a white solid.

M.p. = 132–133 °C.

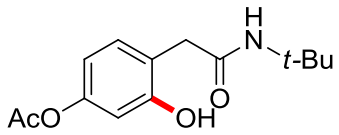
^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.40 (s_{br}, 1H), 7.25–7.20 (m, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 5.77 (s_{br}, 1H), 3.41 (s, 2H), 1.33 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.3 (C_q), 155.9 (C_q), 132.6 (CH), 131.7 (CH), 123.8 (C_q), 120.0 (CH), 111.5 (C_q), 52.5 (C_q), 42.2 (CH_2), 28.6 (CH_3).

IR (ATR): 1634, 1566, 1412, 1268, 1151, 817, 628 cm^{-1}.

MS (EI) *m/z* (relative intensity): 285 (15) [M, ^{79}Br]$^+$, 211 (45), 186 (40).

HR-MS (EI) *m/z* calcd for $C_{12}H_{16}{}^{79}BrNO_2^+$ [M]$^+$: 285.0364, found: 285.0363.



4-(2-(*tert*-Butylamino)-2-oxoethyl)-3-hydroxyphenyl acetate (135ra):

The general procedure **C** was followed using 4-(2-(*tert*-butylamino)-2-oxoethyl)phenyl acetate (**132r**) (124.5 mg, 0.50 mmol), $PhI(TFA)_2$ (430 mg, 1.00 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) in DCE (2.0 mL). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **135ra** (63.6 mg, 48%) as a colorless oil.

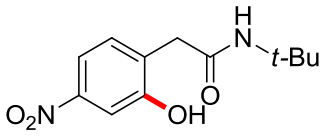
^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.57 (s_{br}, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 6.54 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.71 (s_{br}, 1H), 3.42 (s, 2H), 2.25 (s, 3H), 1.32 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.7 (C_q), 169.3 (C_q), 157.6 (C_q), 151.0 (C_q), 130.5 (CH), 121.9 (C_q), 112.9 (CH), 111.6 (CH), 52.4 (C_q), 42.2 (CH_2), 28.6 (CH_3), 21.2 (CH_3).

IR (ATR): 1640, 1552, 1392, 1205, 1145, 731 cm^{-1}.

MS (EI) *m/z* (relative intensity): 265 (20) [M]$^+$, 193 (30), 165 (60).

HR-MS (EI) *m/z* calcd for $C_{14}H_{19}NO_4^+$ [M]$^+$: 265.1314, found: 265.1312.



***N*-(*tert*-butyl)-2-(2-hydroxy-4-nitrophenyl)acetamide (135wa):**

The general procedure **C** was followed using *N*-(*tert*-butyl)-2-(4-nitrophenyl)acetamide (**132w**) (118 mg, 0.50 mmol), $PhI(TFA)_2$ (430 mg, 1.00 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) in DCE (2.0 mL). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **135wa** (81.9 mg, 65%) as a white solid.

M.p. = 128–129 °C.

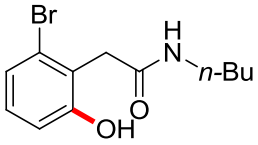
^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.06 (s_{br}, 1H), 7.81 (d, *J* = 2.3 Hz, 1H), 7.69 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 5.81 (s_{br}, 1H), 3.60 (s, 2H), 1.39 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1 (C_q), 157.7 (C_q), 148. 7 (C_q), 130.0 (CH), 127.7 (C_q), 114.6 (CH), 113.2 (CH), 51.7 (C_q), 42.1 (CH_2), 27.8 (CH_3).

IR (ATR): 1643, 1520, 1426, 1318, 899, 730 cm^{-1}.

MS (EI) *m/z* (relative intensity): 252 (20) $[M]^+$, 179 (50), 153 (90).

HR-MS (EI) *m/z* calcd for $C_{12}H_{16}N_2O_4^+$ $[M]^+$: 252.1110, found: 252.1109.



2-(2-Bromo-6-hydroxyphenyl)-*n*-butylacetamide (135'aa) :

The general procedure **C** was followed using 2-(2-bromophenyl)-*n*-butylacetamide (**132'a**) (134.5 mg, 0.50 mmol), $PhI(TFA)_2$ (430 mg, 1.00 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) in DCE (2.0 mL). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **135'aa** (82.6 mg, 58%) as a white solid.

M.p. = 133–134 °C.

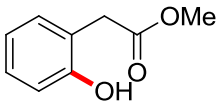
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.99 (s_{br}, 1H), 7.13 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.04 (dd, *J* = 8.0, 7.8 Hz, 1H), 6.96 (dd, *J* = 8.0, 1.4 Hz, 1H), 5.99 (s_{br}, 1H), 3.83 (s, 2H), 3.29 (m, 2H), 1.59–1.47 (m, 2H), 1.42–1.30 (m, 2H), 0.93 (t, *J* = 9.1, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5 (C_q), 157.3 (C_q), 129.6 (CH), 124.3 (CH), 124.2 (C_q), 122.1 (C_q), 117.7 (CH), 39.9 (CH_2), 39.7 (CH_2), 31.2 (CH_2), 19.9 (CH_2), 13.6 (CH_3).

IR (ATR): 1643, 1538, 1484, 1361, 1063, 963, 866 cm^{-1}.

MS (EI) *m/z* (relative intensity): 285 (40) [M, ^{79}Br]$^+$, 206 (90), 186 (70).

HR-MS (EI) *m/z* calcd for $C_{12}H_{16}{}^{79}BrNO_2{}^+$ [M]$^+$: 285.0364, found: 285.0360.



Methyl 2-(2-hydroxyphenyl)acetate (135aa):

The general procedure **C** was followed using methyl 2-phenylacetate (**134a**) (75 mg, 0.50 mmol), $PhI(TFA)_2$ (430 mg, 1.00 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) in DCE (2.0 mL). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **135aa** (41.5 mg, 50%) as a colorless liquid.

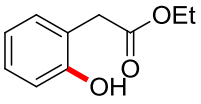
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (s_{br}, 1H), 7.21–7.15 (m, 1H), 7.10–7.06 (m, 1H), 6.93 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.87 (td, *J* = 7.4, 1.2 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3 (C_q), 155.2 (C_q), 131.0 (CH), 129.3 (CH), 121.0 (CH), 120.5 (C_q), 117.7 (CH), 52.8 (CH_3), 37.8 (CH_2).

IR (ATR): 1642, 1535, 1412, 1228, 1058, 914, 730 cm^{-1}.

MS (EI) *m/z* (relative intensity): 166 (20) [M]$^+$, 134 (90), 106 (80).

HR-MS (EI) *m/z* calcd for $C_9H_{10}O_3{}^+$ [M]$^+$: 166.0630, found: 166.0627.



Ethyl 2-(2-hydroxyphenyl)acetate (135ba):

The general procedure **C** was followed using ethyl 2-phenylacetate (**134b**) (82 mg, 0.50 mmol), $PhI(TFA)_2$ (430 mg, 1.00 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) in DCE (2.0 mL). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **135ba** (45 mg, 50%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (s_{br}, 1H), 7.26–7.19 (m, 1H), 7.12 (d, *J* = 6.3 Hz, 1H), 7.00–6.87 (m, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.70 (s, 2H), 1.31 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7 (C_q), 144.4 (C_q), 131.0 (CH), 129.2 (CH), 120.9 (CH), 117.9 (C_q), 100.0 (CH), 62.0 (CH_2), 38.2 (CH_2), 14.0 (CH_3).

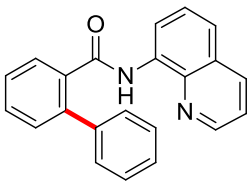
IR (ATR): 1703, 1642, 1422, 1359, 1110, 964, 732 cm^{-1}.

MS (EI) *m/z* (relative intensity): 180 (20) $[M]^+$, 134 (90), 106 (85).

HR-MS (EI) *m/z* calcd for $C_{10}H_{12}O_3^+$ $[M]^+$: 180.0786, found: 180.0789.

5.3.3 Cobalt-Catalyzed C−H Arylation

Analytical Data



***N*-(Quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (137ba):**

The general procedure **D** was followed using *N*-(quinolin-8-yl)benzamide **9b** (62 mg, 0.25 mmol) and trimethoxy(phenyl)silane **136a** (99 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137ba** (56.7 mg, 70%) as a white solid.

M. p. = 125–126 °C.

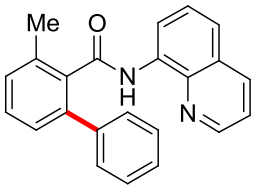
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.77 (s_{br}, 1H), 8.80 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.51 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.05 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.90 (dd, *J* = 3.1, 1.9 Hz, 1H), 7.60–7.39 (m, 7H), 7.36–7.24 (m, 3H), 7.18–7.11 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.6 (C_q), 147.6 (CH), 140.2 (C_q), 139.9 (C_q), 138.3 (C_q), 136.0 (C_q), 135.9 (CH), 134.5 (C_q), 130.6 (CH), 130.4 (CH), 129.1 (CH), 128.9 (CH), 128.3 (C_q), 127.6 (CH), 127.5 (CH), 127.5 (CH), 127.2 (CH), 121.4 (CH), 121.3 (CH), 116.2 (CH).

IR (ATR): 1669, 1523, 1483, 1326, 826, 765 cm^{-1}.

MS (EI) *m/z* (relative intensity): 324 (40) $[M]^+$, 181 (100), 152 (55).

HR-MS (EI) *m/z* calcd for $C_{22}H_{16}N_2O^+$ $[M]^+$: 380.1263, found: 324.1257.



3-Methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (137aa):

The general procedure **D** was followed using 2-methyl-*N*-(quinolin-8-yl)benzamide **9a** (65.5 mg, 0.25 mmol) and trimethoxy(phenyl)silane **136a** (99 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137aa** (60.8 mg, 72%) as a pale yellow solid.

M. p. = 120–121 °C.

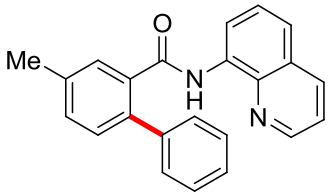
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.61 (s_{br}, 1H), 8.75 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.59 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.06 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.51 (dd, *J* = 3.4, 1.3 Hz, 1H), 7.50–7.49 (m, 1H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.45–7.41 (m, 1H), 7.40–7.37 (m, 1H), 7.34 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.30 (dd, *J* = 1.6, 0.6 Hz, 1H), 7.28 (ddd, *J* = 2.0, 1.3, 0.7 Hz, 1H), 7.22–7.17 (m, 2H), 7.10–7.05 (m, 1H), 2.52 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3 (C_q), 148.0 (CH), 140.4 (C_q), 139.7 (C_q), 138.4 (C_q), 136.9 (C_q), 136.1 (CH), 135.8 (C_q), 134.4 (C_q), 129.5 (CH), 129.2 (CH), 128.6 (CH), 128.1 (CH), 127.8 (C_q), 127.6 (CH), 127.2 (CH), 127.2 (CH), 121.6 (CH), 121.4 (CH), 116.4 (CH), 19.8 (CH_3).

IR (ATR): 1671, 1483, 1424, 1328, 791, 698 cm^{-1}.

MS (EI) *m/z* (relative intensity): 338 (25) $[M]^+$, 195 (30).

HR-MS (ESI) *m/z* calcd for $C_{23}H_{18}N_2O^+$ $[M]^+$: 338.1419, found: 338.1419.



4-Methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (137ca):

The general procedure **D** was followed using 3-methyl-*N*-(quinolin-8-yl)benzamide **9c** (65.5 mg, 0.25 mmol) and trimethoxy(phenyl)silane **136a** (98 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137ca** (51.5 mg, 61%) as a white solid.

M. p. = 136–137 °C.

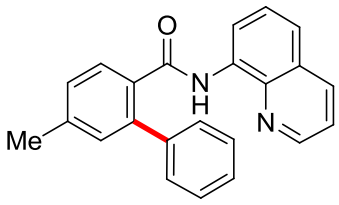
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (s_{br}, 1H), 8.79 (dd, *J* = 7.6, 1.3 Hz, 1H), 8.49 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.05 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.71 (d, *J* = 0.8 Hz, 1H), 7.49 (dd, *J* = 8.4, 7.4 Hz, 3H), 7.43 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.36 (d, *J* = 0.9 Hz, 2H), 7.32 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.27–7.23 (m, 2H), 7.12 (ddd, *J* = 8.7, 2.5, 1.3 Hz, 1H), 2.46 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0 (C_q), 147.7 (CH), 134.0 (C_q), 138.4 (C_q), 137.5 (C_q), 137.4 (C_q), 136.0 (C_q), 135.9 (CH), 134.6 (C_q), 131.2 (CH), 130.6 (CH), 129.8 (CH), 129.0 (CH), 128.3 (CH), 127.7 (C_q), 127.4 (CH), 127.3 (CH), 121.4 (CH), 121.3 (CH), 116.2 (CH), 21.0 (CH_3).

IR (ATR): 1659, 1519, 1482, 1279, 766, 665 cm^{-1}.

MS (EI) *m/z* (relative intensity): 338 (35) $[M]^+$, 195 (100), 152 (30).

HR-MS (EI) *m/z* calcd for $C_{23}H_{18}N_2O^+$ $[M]^+$: 338.1419, found: 338.1420.



5-Methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (137da):

The general procedure **D** was followed using 4-methyl-*N*-(quinolin-8-yl)benzamide **9d** (65.5 mg, 0.25 mmol) and trimethoxy(phenyl)silane **136a** (99 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137da** (49 mg, 58%) as a white solid.

M. p. = 118–119 °C.

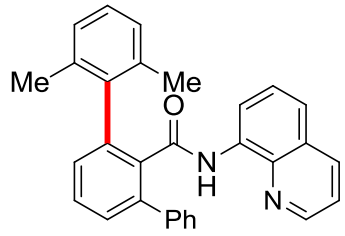
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.74 (S_{br}, 1H), 8.79 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.49 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.04 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.50 (dd, *J* = 3.5, 2.1 Hz, 1H), 7.49–7.46 (m, 2H), 7.44–7.40 (m, 1H), 7.34–7.29 (m, 2H), 7.29–7.25 (m, 3H), 7.17–7.11 (m, 1H), 2.45 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.6 (C_q), 147.5 (CH), 140.6 (C_q), 140.2 (C_q), 140.1 (C_q), 138.3 (C_q), 135.8 (CH), 134.6 (C_q), 133.3 (C_q), 131.3 (CH), 129.3 (CH), 128.9 (CH), 128.2 (CH), 128.2 (CH), 127.6 (C_q), 127.4 (CH), 127.2 (CH), 121.2 (CH), 121.2 (CH), 116.1 (CH), 21.5 (CH_3).

IR (ATR): 1661, 1520, 1482, 1263, 853, 765 cm^{-1}.

MS (EI) *m/z* (relative intensity): 338 (30) $[M]^+$, 195 (90), 165 (30).

HR-MS (EI) *m/z* calcd for $C_{23}H_{18}N_2O^+$ $[M]^+$: 338.1419, found: 338.1423.



2,6-Dimethyl-*N*-(quinolin-8-yl)-[1,1':3',1''-terphenyl]-2'-carboxamide (137eb):

The general procedure **D** was followed using *N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide **9e** (81 mg, 0.25 mmol) and (2,6-dimethylphenyl)trimethoxysilane **136b** (113 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137eb** (70 mg, 68%) as a white solid.

M. p. = 210–211 °C.

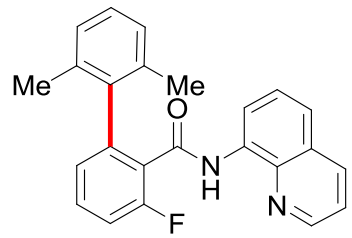
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.48 (s_{br}, 1H), 8.59 (dd, J = 4.2, 1.7 Hz, 1H), 8.39 (dd, J = 6.1, 2.9 Hz, 1H), 8.03–7.99 (m, 1H), 7.59–7.54 (m, 3H), 7.50–7.47 (m, 1H), 7.37–7.28 (m, 4H), 7.23–7.17 (m, 3H), 7.15–7.08 (m, 1H), 6.95 (d, J = 1.7 Hz, 2H), 2.20 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.8 (C_q), 147.5 (CH), 140.4 (C_q), 140.3 (C_q), 139.5 (C_q), 139.4 (C_q), 138.1 (C_q), 136.3 (C_q), 136.3 (C_q), 135.8 (CH), 134.2 (C_q), 129.4 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.1 (CH), 127.5 (C_q), 127.2 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 121.2 (CH), 121.0 (CH), 116.1 (CH), 21.0 (CH_3).

IR (ATR): 1673, 1517, 1480, 1324, 824, 698 cm^{-1}.

MS (EI) *m/z* (relative intensity): 428 (30) $[M]^+$, 285 (100), 241 (30), 144 (80).

HR-MS (EI) *m/z* calcd for $C_{30}H_{24}N_2O^+$ $[M]^+$: 428.1889, found: 428.1888.



3-Fluoro-2',6'-dimethyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (137fb):

The general procedure **D** was followed using 2-fluoro-*N*-(quinolin-8-yl)benzamide **9f** (66.5 mg, 0.25 mmol) and (2,6-dimethylphenyl)trimethoxysilane **136b** (113 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137fb** (48 mg, 52%) as a white solid.

M. p. = 160–161 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.87 (s_{br}, 1H), 8.72 (dd, J = 4.2, 1.7 Hz, 1H), 8.66 (dd, J = 6.2, 2.9 Hz, 1H), 8.09 (dd, J = 8.4, 1.7 Hz, 1H), 7.53–7.46 (m, 1H), 7.44–7.37 (m, 3H), 7.21 (ddd, J = 9.4, 8.4, 1.1 Hz, 1H), 7.02–6.99 (m, 1H), 6.99–6.94 (m, 3H), 2.16 (s, 6H).

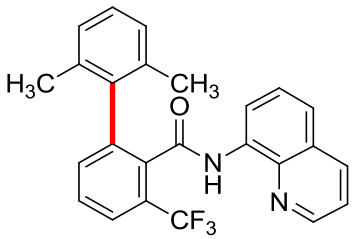
^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5 (C_q), 159.9 (C_q, $^{1}J_{C\text{-}F}$ = 250.1 Hz), 147.9 (CH), 141.6 (C_q, $^{3}J_{C\text{-}F}$ = 11.0 Hz), 138.3 (C_q), 138.2 (C_q, $^{4}J_{C\text{-}F}$ = 2.0 Hz), 136.1 (C_q), 134.2 (C_q), 131.2 (CH, $^{3}J_{C\text{-}F}$ = 9.0 Hz), 128.4 (CH), 127.8 (C_q), 127.6 (CH), 127.3 (CH), 125.9 (CH, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 125.4 (C_q, $^{2}J_{C\text{-}F}$ = 16.3 Hz), 121.7 (CH), 121.5 (CH), 116.6 (CH), 114.9 (CH), 114.8 (CH, $^{2}J_{C\text{-}F}$ = 22.0 Hz), 20.7 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –114.6.

IR (ATR): 1677, 1520, 1483, 1423, 905, 757 cm^{-1}.

MS (EI) *m/z* (relative intensity): 370 (20) $[M]^+$, 227 (20), 183 (35), 144 (100).

HR-MS (EI) *m/z* calcd for $C_{24}H_{19}FN_2O^+$ $[M]^+$: 370.1481, found: 370.1484.



2',6'-Dimethyl-*N*-(quinolin-8-yl)-3-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxamide (137gb):

The general procedure **D** was followed using *N*-(quinolin-8-yl)-2-(trifluoromethyl)benzamide **9g** (65.5 mg, 0.25 mmol) and (2,6-dimethylphenyl)trimethoxysilane **136b** (113 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137gb** (53 mg, 50%) as a white solid.

M. p. = 145–146 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (s_{br}, 1H), 8.69 (dd, J = 4.2, 1.7 Hz, 1H), 8.56 (dd, J = 6.6, 2.4 Hz, 1H), 8.08 (dd, J = 8.3, 1.7 Hz, 1H), 7.79 (dd, J = 7.8, 0.6 Hz, 1H), 7.64 (td, J = 7.8, 0.8 Hz, 1H), 7.44–7.36 (m, 4H), 6.95 (dd, J = 9.0, 5.5 Hz, 1H), 6.92–6.88 (m, 2H), 2.15 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5 (C_q), 147.9 (CH), 140.4 (C_q), 138.2 (C_q), 137.7 (C_q), 136.3 (C_q), 136.1 (CH), 135.3 (C_q, $^{3}J_{C\text{-}F}$= 2.0 Hz), 134.0 (C_q), 133.7 (CH), 129.6 (CH), 128.1 (C_q, $^{2}J_{C\text{-}F}$=

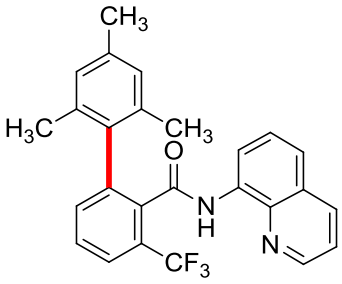
31.0 Hz), 127.9 (CH), 127.7 (C_q), 127.3 (CH), 127.3 (CH), 125.3 (CH, ^3J = 4.9 Hz), 123.8 (C_q, ^1J = 272.0 Hz), 121.7 (CH), 121.5 (CH), 116.5 (CH), 20.8 (CH_3).

^{19}F NMR (376 Hz, $CDCl_3$): δ = –58.9.

IR (ATR): 1680, 1526, 1322, 1127, 822, 789 cm^{-1}.

MS (EI) *m/z* (relative intensity): 420 (20) $[M]^+$, 276 (80), 248 (30).

HR-MS (EI) *m/z* calcd for $C_{25}H_{19}F_3N_2O^+$ $[M]^+$: 420.1443, found: 420.1446.



2',4',6'-Trimethyl-*N*-(quinolin-8-yl)-3-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxamide (137gc): The general procedure **D** was followed using *N*-(quinolin-8-yl)-2-(trifluoromethyl)benzamide **9g** (65.5 mg, 0.25 mmol) and mesityltrimethoxysilane **136c** (120 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137gc** (51 mg, 47%) as a white solid.

M. p. = 158–159 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (s_{br}, 1H), 8.69 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.58 (dd, *J* = 6.1, 2.9 Hz, 1H), 8.08 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.79–7.76 (m, 1H), 7.62 (td, *J* = 7.8, 0.8 Hz, 1H), 7.44–7.37 (m, 4H), 6.73 (d, *J* = 0.6 Hz, 2H), 2.10 (s, 9H).

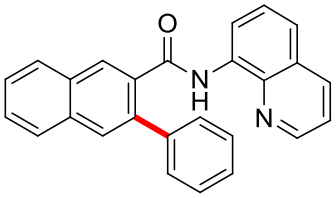
^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7 (C_q), 147.9 (CH), 140.6 (C_q), 138.2 (C_q), 137.3 (C_q), 136.1 (CH), 135.5 (CH, $^3J_{C–F}$ = 5.0 Hz), 134.9 (C_q), 134.1 (C_q), 134.0 (C_q), 129.5 (CH), 128.0 (C_q, $^2J_{C–F}$ = 31.3 Hz), 128.1 (CH), 127.7 (C_q), 127.3 (CH), 125.2 (CH, $^3J_{C–F}$ = 11.2 Hz), 121.9 (C_q, $^3J_{C–F}$ = 5.3 Hz), 121.7 (CH), 121.5 (CH), 118.3 (C_q, $^1J_{C–F}$ = 279.3 Hz), 116.5 (CH), 20.9 (CH_3), 20.7 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –58.9.

IR (ATR): 1682, 1528, 1485, 1117, 822, 693 cm^{-1}.

MS (EI) *m/z* (relative intensity): 434 (30) $[M]^+$, 291 (20), 144 (100).

HR-MS (EI) *m/z* calcd for $C_{26}H_{24}N_2O^+$ $[M]^+$: 434.1606, found: 434.1606.



3-Phenyl-*N*-(quinolin-8-yl)-2-naphthamide (137ha):

The general procedure **D** was followed using *N*-(quinolin-8-yl)-2-naphthamide **9h** (74.5 mg, 0.25 mmol) and trimethoxy(phenyl)silane **136a** (99 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137ha** (56 mg, 60%) as a white solid.

M. p. = 200–201 °C.

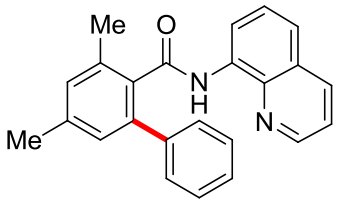
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (s_{br}, 1H), 8.90 (dd, *J* = 7.6, 1.3 Hz, 1H), 8.52 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.24–8.19 (m, 1H), 8.06 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.92 (td, *J* = 5.6, 2.6 Hz, 1H), 7.65–7.62 (m, 2H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.56–7.51 (m, 3H), 7.47 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.32 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.26 (dd, *J* = 8.5, 2.9 Hz, 2H), 7.14–7.09 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8 (C_q), 148.0 (CH), 140.3 (C_q), 138.4 (C_q), 137.0 (C_q), 136.0 (CH), 134.5 (C_q), 134.2 (C_q), 133.8 (C_q), 132.6 (C_q), 130.5 (C_q), 129.7 (CH), 128.9 (CH), 128.3 (CH), 128.0 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 126.4 (CH), 125.7 (CH), 121.8 (CH), 121.4 (CH), 116.6 (CH).

IR (ATR): 1667, 1518, 1482, 1325, 825, 790 cm^{-1}.

MS (EI) *m/z* (relative intensity): 374 (10) $[M]^+$, 231 (60), 202 (30).

HR-MS (EI) *m/z* calcd for $C_{26}H_{18}N_2O^+$ $[M]^+$: 374.1419, found: 374.1417.



3,5-Dimethyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (137ia):

The general procedure **D** was followed using 2,4-dimethyl-*N*-(quinolin-8-yl)benzamide **9i** (69 g, 0.25 mmol) and trimethoxy(phenyl)silane **136a** (99 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/Actone: 10/1) yielded **137ia** (60 mg, 68%) as a white solid.

M. p. = 123–124 °C.

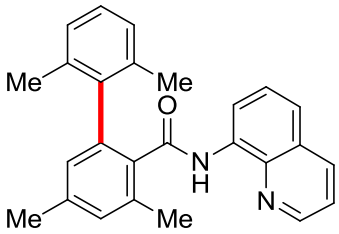
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.59 (s_{br}, 1H), 8.74 (dd, J = 7.3, 1.7 Hz, 1H), 8.57 (dd, J = 4.2, 1.7 Hz, 1H), 8.05 (dd, J = 8.3, 1.7 Hz, 1H), 7.50 (t, J = 1.7 Hz, 1H), 7.49–7.45 (m, 2H), 7.42 (dd, J = 8.3, 1.7 Hz, 1H), 7.33 (dd, J = 8.3, 4.2 Hz, 1H), 7.22–7.14 (m, 2H), 7.10 (s, 2H), 7.08–7.02 (m, 1H), 2.48 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3 (C_q), 147.8 (CH), 140.4 (C_q), 139.6 (C_q), 138.92 (C_q), 138.3 (C_q), 135.9 (CH), 135.8 (C_q), 134.4 (C_q), 134.1 (C_q), 130.1 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 127.7 (C_q), 127.2 (CH), 127.1 (CH), 121.4 (CH), 121.3 (CH), 116.3 (CH), 21.3 (CH_3), 19.8 (CH_3).

IR (ATR): 1671, 1519, 1482, 1325, 826, 700 cm^{-1}.

MS (EI) *m/z* (relative intensity): 352 (25) $[M]^+$, 209 (100), 165 (35).

HR-MS (EI) *m/z* calcd for $C_{24}H_{20}N_2O^+$ $[M]^+$: 352.1576, found: 352.1569.



2',3,5,6'-Tetramethyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (137ib):

The general procedure **D** was followed using 2,4-dimethyl-*N*-(quinolin-8-yl)benzamide **9i** (69 g, 0.25 mmol) and (2,6-dimethylphenyl)trimethoxysilane **136b** (113 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137ib** (66.5, 70%) as a white solid.

M. p. = 137–138 °C.

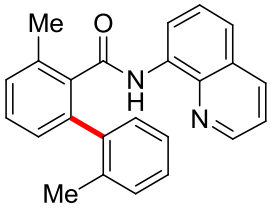
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (s_{br}, 1H), 8.69 (dd, J = 4.2, 1.7 Hz, 1H), 8.65 (dd, J = 6.2, 2.8 Hz, 1H), 8.06 (dd, J = 8.3, 1.7 Hz, 1H), 7.42–7.39 (m, 2H), 7.37 (dd, J = 8.3, 4.2 Hz, 1H), 7.12–7.09 (m, 1H), 6.90 (s, 3H), 6.84 (dd, J = 1.0, 0.6 Hz, 1H), 2.47 (s, 3H), 2.39 (s, 3H), 2.19 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0 (C_q), 147.7 (CH), 139.5 (C_q), 139.0 (C_q), 138.4 (C_q), 138.3 (C_q), 136.2 (C_q), 136.1 (CH), 135.6 (C_q), 134.7 (C_q), 134.4 (C_q), 130.0 (CH), 127.7 (C_q), 127.6 (CH), 127.3 (CH), 127.1 (CH), 127.1 (CH), 121.4 (CH), 121.3 (CH), 116.2 (CH), 21.3 (CH_3), 20.8 (CH_3), 19.8 (CH_3).

IR (ATR): 1671, 1518, 1482, 1325, 858, 770 cm^{-1}.

MS (EI) *m/z* (relative intensity): 380 (20) $[M]^+$, 237 (80), 179 (35), 144 (40).

HR-MS (EI) *m/z* calcd for $C_{26}H_{24}N_2O^+$ $[M]^+$: 380.1889, found: 380.1894.



2',3-Dimethyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (137ad):

The general procedure **D** was followed using 2-methyl-*N*-(quinolin-8-yl)benzamide **9a** (65.5 mg, 0.25 mmol) and trimethoxy(*o-tolyl*)silane **136d** (106 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137ad** (70.4 mg, 80%) as a white solid.

M. p. = 115–116 °C.

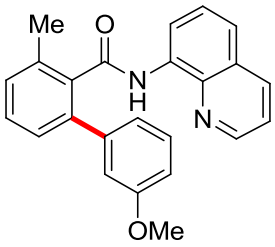
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.61 (s_{br}, 1H), 8.67 (dt, *J* = 2.9, 1.4 Hz, 1H), 8.65 (dd, *J* = 6.3, 2.7 Hz, 1H), 8.07 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.43–7.41 (m, 2H), 7.40–7.34 (m, 2H), 7.30–7.28 (m, 1H), 7.28–7.25 (m, 1H), 7.14 (ddd, *J* = 7.6, 1.2, 0.6 Hz, 1H), 7.06–7.02 (m, 1H), 6.99–6.95 (m, 2H), 2.52 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8 (C_q), 147.8 (CH), 139.7 (C_q), 139.3 (C_q), 138.3 (C_q), 137.5 (C_q), 136.1 (CH), 135.9 (C_q), 135.6 (C_q), 134.3 (C_q), 129.9 (CH), 129.6 (CH), 129.3 (CH), 128.7 (CH), 127.7 (C_q), 127.6 (CH), 127.4 (CH), 127.3 (CH), 125.2 (CH), 121.4 (CH), 121.4 (CH), 116.2 (CH), 20.3 (CH_3), 19.8 (CH_3).

IR (ATR): 1673, 1519, 1482, 1325, 899, 790 cm^{-1}.

MS (EI) *m/z* (relative intensity): 352 (15) $[M]^+$, 209 (100), 165 (55), 144 (70).

HR-MS (EI) *m/z* calcd for $C_{24}H_{20}N_2O^+$ $[M]^+$: 353.1576, found: 352.1586.



3'-Methoxy-3-methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (137ae):

The general procedure **D** was followed using 2-methyl-*N*-(quinolin-8-yl)benzamide **9a** (65.5 mg, 0.25 mmol) and trimethoxy(3-methoxyphenyl)silane **136e** (114 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137ae** (61 mg, 66%) as a white solid.

M. p. = 102–103 °C.

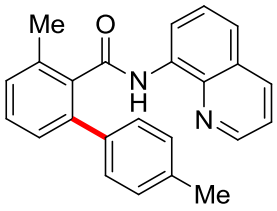
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.66 (s_{br}, 1H), 8.80–8.76 (m, 1H), 8.59 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.05 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.52–7.45 (m, 2H), 7.41 (dd, *J* = 6.1, 3.1 Hz, 1H), 7.38–7.34 (m, 1H), 7.32 (t, *J* = 3.1 Hz, 1H), 7.31–7.26 (m, 1H), 7.11–7.06 (m, 3H), 6.62 (ddd, *J* = 5.1, 4.0, 2.1 Hz, 1H), 3.63 (s, 3H), 2.52 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2 (C_q), 159.2 (C_q), 147.8 (CH), 141.6 (C_q), 139.5 (C_q), 138.3 (C_q), 136.7 (C_q), 136.0 (CH), 135.8 (C_q), 134.3 (C_q), 129.5 (CH), 129.1 (CH), 129.1 (CH), 127.7 (C_q), 127.4 (CH), 127.1 (CH), 121.6 (CH), 121.3 (CH), 121.1 (CH), 116.3 (CH), 113.6 (CH), 107.8 (CH), 55.1 (CH_3), 19.8 (CH_3).

IR (ATR): 1671, 1520, 1482, 1264, 730, 700 cm^{-1}.

MS (EI) *m/z* (relative intensity): 368 (40) $[M]^+$, 225 (100), 144 (60).

HR-MS (EI) *m/z* calcd for $C_{24}H_{20}N_2O_2^+$ $[M]^+$: 368.1525, found: 368.1526.



3,4'-Dimethyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (137af):

The general procedure **D** was followed using 2-methyl-*N*-(quinolin-8-yl)benzamide **9a** (65.5 mg, 0.25 mmol) and trimethoxy(*p-tolyl*)silane **136f** (106 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137af** (55 mg, 62%) as a white solid.

M. p. = 118–119 °C.

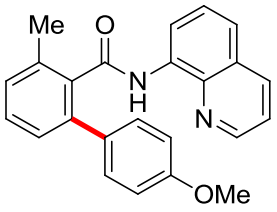
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (s_{br}, 1H), 8.78 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.60 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.07 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.52–7.47 (m, 1H), 7.46–7.43 (m, 3H), 7.39–7.32 (m, 2H), 7.29–7.24 (m, 2H), 6.75–6.72 (m, 2H), 3.61 (s, 3H), 2.51 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5 (C_q), 158.9 (C_q), 148.0 (CH), 139.3 (C_q), 138.4 (C_q), 136.8 (C_q), 136.1 (CH), 135.8 (C_q), 134.5 (C_q), 132.8 (C_q), 129.8 (CH), 129.1 (CH), 129.1 (CH), 127.8 (C_q), 127.6 (CH), 127.2 (CH), 121.6 (CH), 121.4 (CH), 116.5 (CH), 113.7 (CH), 55.1 (CH_3), 19.8 (CH_3).

IR (ATR): 1666, 1514, 1244, 1176, 786, 569 cm^{-1}.

MS (EI) *m/z* (relative intensity): 352 (20) $[M]^+$, 208 (80), 180 (40).

HR-MS (ESI) *m/z* calcd for $C_{24}H_{20}N_2O^+$ $[M]^+$: 352.1576, found: 352.1574.



4'-Methoxy-3-methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (137ag):

The general procedure **D** was followed using 2-methyl-*N*-(quinolin-8-yl)benzamide **9a** (65.5 mg, 0.25 mmol) and trimethoxy(4-methoxyphenyl)silane **136g** (114 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137ag** (58 mg, 63%) as a white solid.

M. p. = 150–151 °C.

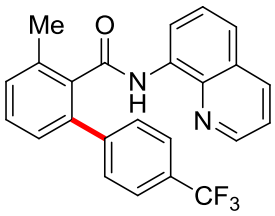
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.63 (s_{br}, 1H), 8.78 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.60 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.06 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.52–7.47 (m, 1H), 7.46–7.42 (m, 3H), 7.39–7.32 (m, 2H), 7.28–7.25 (m, 2H), 6.76–6.74 (m, 1H), 6.73–6.72 (m, 1H), 3.61 (s, 3H), 2.51 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5 (C_q), 158.9 (C_q), 148.0 (CH), 139.2 (C_q), 138.4 (C_q), 136.8 (C_q), 136.1 (CH), 135.7 (C_q), 134.4 (C_q), 132.8 (C_q), 129.8 (CH), 129.12 (CH), 129.13 (CH), 127.8 (C_q), 127.6 (CH), 127.2 (CH), 121.6 (CH), 121.4 (CH), 116.5 (CH), 113.7 (CH), 55.1 (CH_3), 19.8 (CH_3).

IR (ATR): 1673, 1519, 1482, 1245, 791, 665 cm^{-1}.

MS (EI) *m/z* (relative intensity): 368 (30) $[M]^+$, 225 (100).

HR-MS (EI) *m/z* calcd for $C_{24}H_{20}N_2O_2^+$ $[M]^+$: 368.1525, found: 368.1528.



3-Methyl-*N*-(quinolin-8-yl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxamide (132ah):

The general procedure **D** was followed using 2-methyl-*N*-(quinolin-8-yl)benzamide **9a** (65.5 mg, 0.25 mmol) and trimethoxy(4-(trifluoromethyl)phenyl)silane **136h** (133 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/Actone: 10/1) yielded **137ah** (89 mg, 88%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.62 (s_{br}, 1H), 8.72 (dd, *J* = 6.7, 2.3 Hz, 1H), 8.58 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.10–8.06 (m, 1H), 7.62 (dd, *J* = 8.7, 0.7 Hz, 2H), 7.49 (dd, *J* = 4.5, 3.4 Hz, 2H), 7.43 (m, 3H), 7.38 (dd, *J* = 8.5, 3.8 Hz, 1H), 7.34 (dd, *J* = 2.5, 1.7 Hz, 1H), 7.30–7.26 (m, 1H), 2.54 (s, 3H).

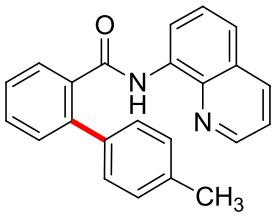
^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.8 (C_q), 148.0 (CH), 144.0 (C_q), 138.2 (C_q), 136.7 (C_q), 136.3 (C_q), 136.1 (CH), 134.0 (C_q), 130.3 (CH), 129.4 (CH), 129.2 (C_q, $^{2}J_{C–F}$ = 32.5 Hz), 129.0 (CH), 127.8 (C_q), 127.5 (CH), 127.2 (CH), 125.1 (CH, $^{3}J_{C–F}$ = 7.9 Hz), 123.9 (C_q, $^{1}J_{C–F}$ = 270.3 Hz), 122.9 (C_q), 122.0 (CH), 121.5 (CH), 116.8 (CH), 19.8 (CH_3).

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

IR (ATR): 1671, 1518, 1481, 1321, 1061, 825, 606 cm^{-1}.

MS (EI) *m/z* (relative intensity): 406 (30) $[M]^+$, 263 (70), 165 (20).

HR-MS (EI) *m/z* calcd for $C_{24}H_{17}F_3N_2O^+$ $[M]^+$: 406.1293, found: 406.1294.



4'-Methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (137bi):

The general procedure **D** was followed using *N*-(quinolin-8-yl)benzamide **9b** (62 mg, 0.25 mmol) and trimethoxy(*p*-tolyl)silane **136i** (100 µL, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137bi** (46 mg, 54%) as a white solid.

M. p. = 115–116 °C.

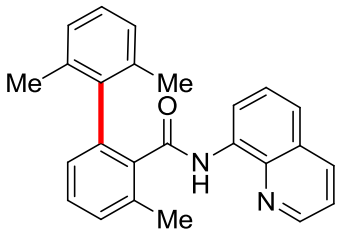
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.79 (s_{br}, 1H), 8.80 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.51 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.07 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.90–7.85 (m, 1H), 7.53 (m, 2H), 7.49–7.43 (m, 4H), 7.42–7.40 (m, 1H), 7.34 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.83–6.77 (m, 2H), 3.64 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.1 (C_q), 159.3 (C_q), 147.7 (CH), 139.9 (C_q), 138.5 (C_q), 136.0 (CH), 135.9 (C_q), 134.6 (C_q), 132.4 (C_q), 130.6 (CH), 130.5 (CH), 130.1 (CH), 129.3 (CH), 127.7 (C_q), 127.3 (CH), 127.2 (CH), 121.5 (CH), 121.4 (CH), 116.3 (CH), 113.9 (CH), 55.1 (CH_3).

IR (ATR): 1663, 1517, 1481, 1245, 826, 762 cm^{-1}.

MS (EI) *m/z* (relative intensity): 338 (30) $[M]^+$, 195 (80), 165 (30).

HR-MS (EI) *m/z* calcd for $C_{23}H_{18}N_2O^+$ $[M]^+$: 338.1419, found: 338.1416.



2',3,6'-Trimethyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (137ab):

The general procedure **D** was followed using 2-methyl-*N*-(quinolin-8-yl)benzamide **9a** (65.5 mg, 0.25 mmol) and (2,6-dimethylphenyl)trimethoxysilane **136b** (113 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137ab** (57 mg, 62%) as a white solid.

M. p. = 128–129 °C.

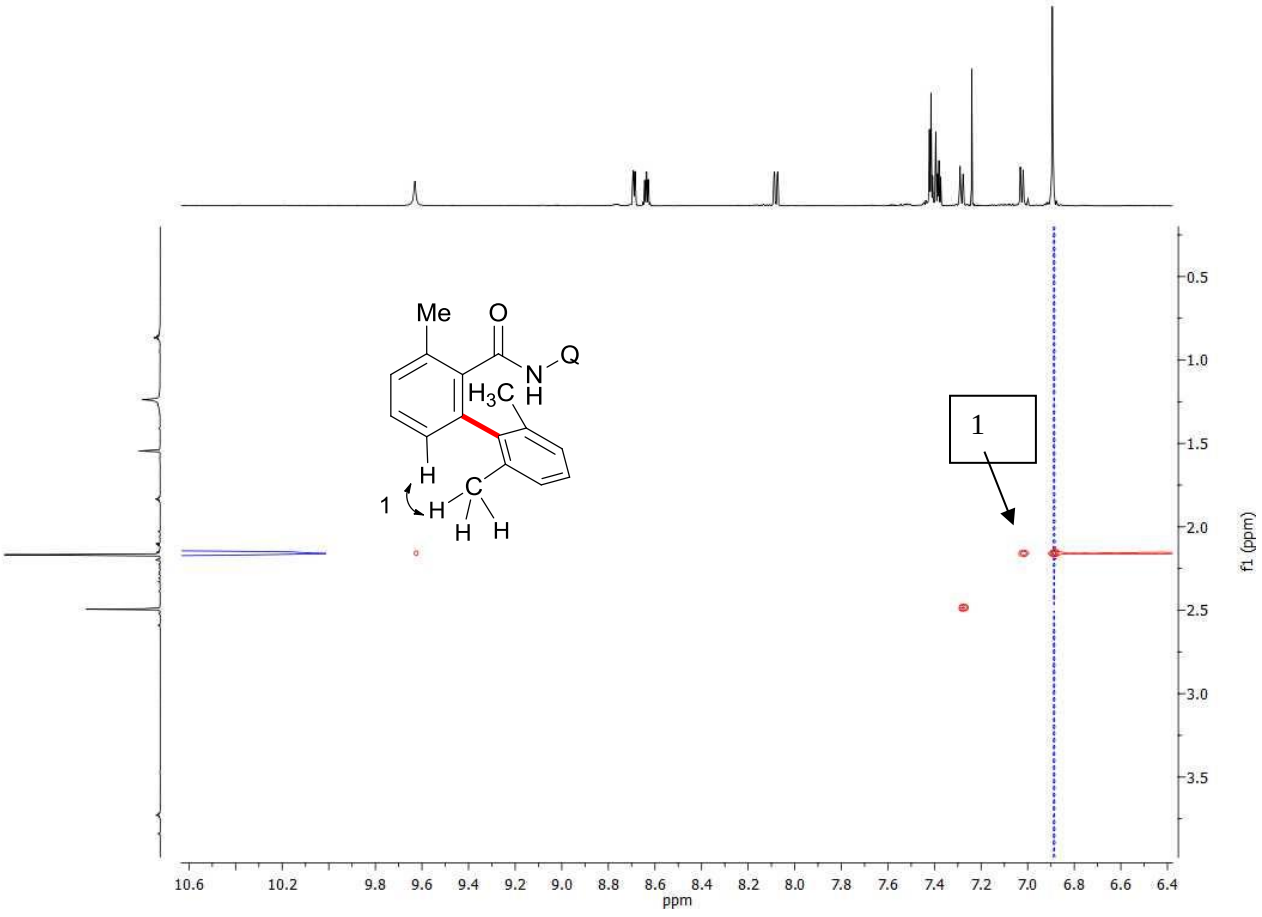
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.63 (s_{br}, 1H), 8.69 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.66–8.62 (m, 1H), 8.08 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.43 (d, *J* = 0.9 Hz, 1H), 7.41 (s, 1H), 7.41–7.36 (m, 2H), 7.28 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.05–7.01 (m, 1H), 6.90 (s, 3H), 2.50 (s, 3H), 2.17 (s, 6H).

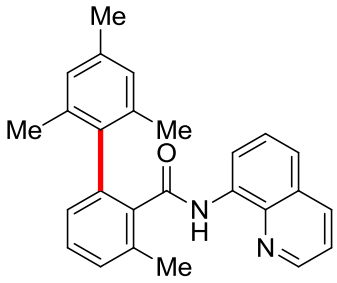
^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.6 (C_q), 147.5 (CH), 139.3 (C_q), 138.3 (C_q), 138.2 (C_q), 137.3 (C_q), 136.2 (C_q), 136.0 (CH), 135.5 (C_q), 134.3 (C_q), 129.2 (CH), 129.1 (CH), 127.7 (C_q), 127.2 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 121.4 (CH), 121.3 (CH), 116.2 (CH), 20.9 (CH_3), 19.9 (CH_3).

IR (ATR): 1665, 1523, 1481, 1384, 825, 762 cm^{-1}.

MS (EI) *m/z* (relative intensity): 366 (35) $[M]^+$, 223 (100), 165 (50).

HR-MS (EI) *m/z* calcd for $C_{25}H_{22}N_2O^+$ $[M]^+$: 366.1732, found: 366.1737.





2',3,4',6'-Tetramethyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (137ac):

The general procedure **D** was followed using 2-methyl-*N*-(quinolin-8-yl)benzamide **9a** (65.5 mg, 0.25 mmol) and mesityltrimethoxysilane **136c** (120 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **137ac** (60 mg, 63%) as a white solid.

M. p. = 156–157 °C.

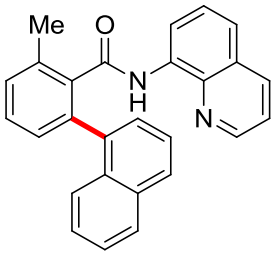
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (s_{br}, 1H), 8.69 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.67 (dd, *J* = 5.7, 3.3 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.44–7.42 (m, 2H), 7.41–7.36 (m, 2H), 7.27 (ddd, *J* = 7.6, 1.2, 0.7 Hz, 1H), 7.01 (dd, *J* = 7.6, 1.2, 0.6 Hz, 1H), 6.72 (d, *J* = 0.6 Hz, 2H), 2.49 (s, 3H), 2.13 (s, 6H), 2.09 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9 (C_q), 147.8 (CH), 138.5 (C_q), 138.3 (C_q), 137.7 (C_q), 136.6 (C_q), 136.5 (C_q), 136.12 (C_q), 136.11 (CH), 135.5 (C_q), 134.4 (C_q), 129.2 (CH), 129.1 (CH), 127.9 (CH), 127.8 (C_q), 127.5 (CH), 127.3 (CH), 121.5 (CH), 121.4 (CH), 116.3 (CH), 20.9 (CH_3), 20.7 (CH_3), 19.8 (CH_3).

IR (ATR): 1672, 1518, 1481, 1325, 790, 729 cm^{-1}.

MS (EI) *m/z* (relative intensity): 380 (30) $[M]^+$, 237 (90), 179 (45), 144 (100).

HR-MS (ESI) *m/z* calcd for $C_{26}H_{24}N_2O^+$ $[M]^+$: 380.1883, found: 380.1875.



2-Methyl-6-(naphthalen-1-yl)-*N*-(quinolin-8-yl)benzamide (137aj):

The general procedure **D** was followed using 2-methyl-*N*-(quinolin-8-yl)benzamide **9a** (65.5 mg, 0.25 mmol) and trimethoxy(naphthalen-1-yl)silane **131j** (124 mg, 0.50 mmol). Isolation by column chromatography (*n*-hexane/acetone: 10/1) yielded **132aj** (78 mg, 80%) as a white solid.

M. p. = 215–216 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.52 (s_{br}, 1H), 8.51 (dd, *J* = 6.8, 2.1 Hz, 1H), 8.29 (dd, *J* = 4.2, 1.6 Hz, 1H), 7.93 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.50 (d, *J* = 7.1 Hz, 1H), 7.47–7.45 (m, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.40–7.32 (m, 3H), 7.31 (d, *J* = 1.9 Hz, 2H), 7.29–7.26 (m, 1H), 7.22 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.57 (s, 3H).

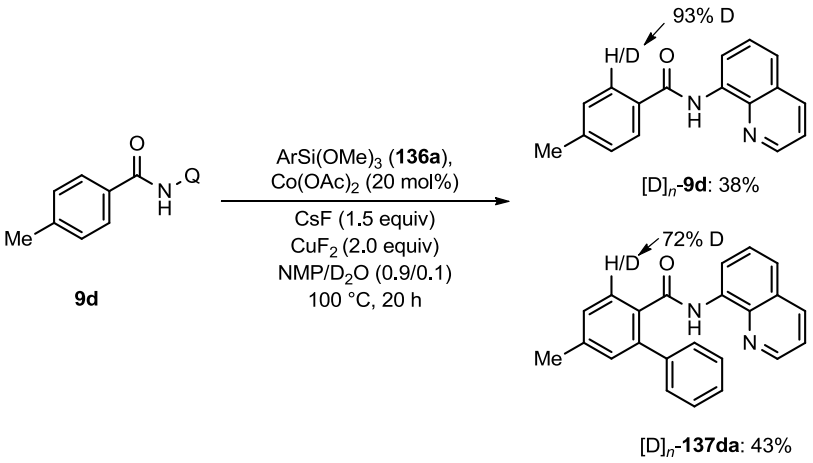
^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6 (C_q), 147.5 (CH), 138.2 (C_q), 138.0 (C_q), 137.8 (C_q), 137.7 (C_q), 136.2 (C_q), 135.8 (CH), 134.1 (C_q), 133.5 (C_q), 132.2 (C_q), 129.8 (CH), 128.8 (CH), 128.6 (CH), 128.0 (CH), 127.7 (CH), 127.5 (C_q), 127.1 (CH), 127.0 (CH), 126.3 (CH), 126.0 (CH), 125.6 (CH), 124.9 (CH), 121.3 (CH), 121.1 (CH), 116.0 (CH), 19.9 (CH_3).

IR (ATR): 1674, 1521, 1479, 1261, 798, 609 cm^{-1}.

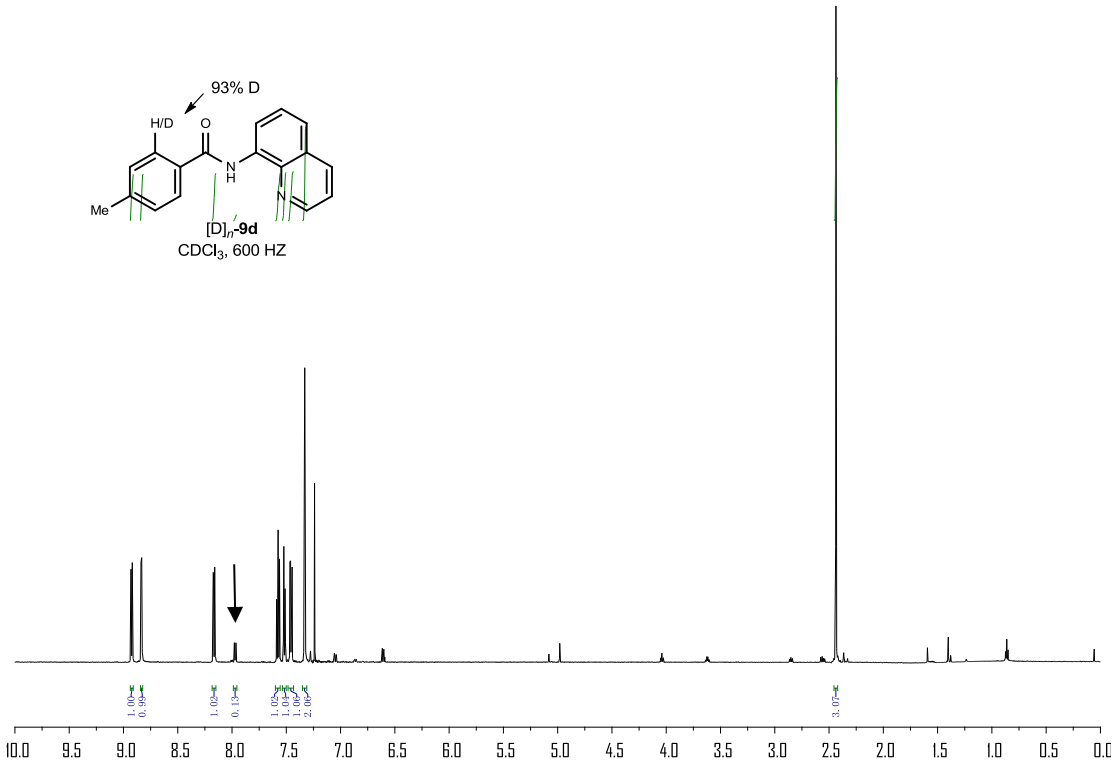
MS (EI) *m/z* (relative intensity): 388 (35) $[M]^+$, 245 (100), 202 (35).

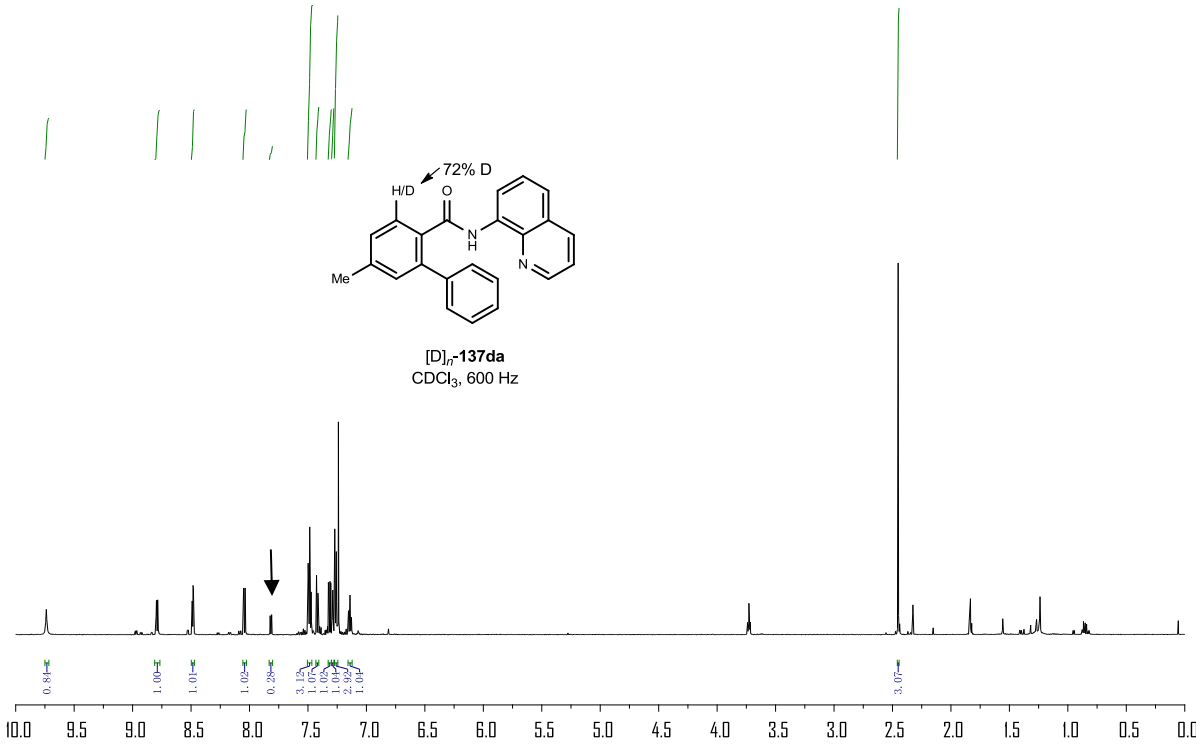
HR-MS (EI) *m/z* calcd for $C_{27}H_{20}N_2O^+$ $[M]^+$: 388.1576, found: 388.1579.

H/D-Exchange Experiment



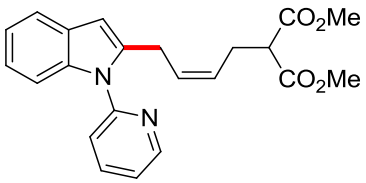
The representative procedure **D** was followed using **9d** (65.5 mg, 0.25 mmol, 1.0 equiv), **136a** (37.1 mg, 0.375 mmol, 1.5 equiv), $Co(OAc)_2$ (8.9 mg, 20 mol %), CsF (114 mg, 0.75 mmol, 3.0 equiv) and CuF_2 (51.0 mg, 0.5 mmol, 2.0 equiv) in NMP (0.9 mL) and D_2O (0.1 mL). At ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with NaOH (2 M, 10 mL) and H_2O (2 x 20 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the remaining residue was purified by column chromatography on silica gel (*n*-hexane/Aceton) to yield $[D]_n$-**9d** (25.1 mg, 38 %,) and $[D]_n$-**137da** (36.6 mg, 43 %) as white solids.


93% D
H/D
O
N
H
N
Me
[D]n-9d
CDCl3, 600 HZ


72% D
H/D
O
N
H
N
Me
[D]n-137da
CDCl3, 600 Hz

5.3.4 Cobalt-Catalyzed C−H/C-C Functionalizations

Analytical Data



(*Z*)-Dimethyl 2-{4-[1-(pyridin-2-yl)-1*H*-indol-2-yl]but-2-en-1-yl}malonate [(*Z*)-151aa]:

The general procedure **F** was followed using 1-(pyridin-2-yl)-1*H*-indole (**95a**) (97.1 mg, 0.50 mmol) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (110 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*Z*)-**151aa** (176 mg, 93%, *E*/*Z* = 1:11) as a yellow oil.

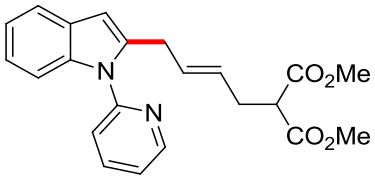
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 4.9, 1.9, 0.8 Hz, 1H), 7.86 (ddd, *J* = 8.0, 7.6, 1.9 Hz, 1H), 7.59–7.53 (m, 1H), 7.46–7.41 (m, 1H), 7.36–7.27 (m, 2H), 7.15–7.09 (m, 2H), 6.43 (d, *J* = 0.7 Hz, 1H), 5.64 (dtt, *J* = 10.8, 7.2, 1.0 Hz, 1H), 5.40 (dtt, *J* = 10.8, 7.6, 1.0 Hz, 1H), 3.69 (s, 6H), 3.65 (d, *J* = 7.2 Hz, 2H), 3.35 (t, *J* = 7.7 Hz, 1H), 2.62 (ddd, *J* = 7.7, 7.6, 1.0 Hz, 1.83H, *Z*), 2.54 (ddd, *J* = 7.7, 7.6, 1.0 Hz, 0.17H, *E*).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.0 (C_q), 151.1 (C_q), 149.5 (CH), 139.2 (C_q), 138.1 (CH), 137.2 (C_q), 128.8 (CH), 128.4 (C_q), 126.2 (CH), 121.9 (CH), 121.7 (CH), 120.8 (CH), 120.5 (CH), 119.9 (CH), 109.9 (CH), 102.7 (CH), 52.5 (CH_3), 51.5 (CH), 31.7 (CH_2, *E*), 30.9 (CH_2, *E*), 26.7 (CH_2, *Z*), 25.9 (CH_2, *Z*).

IR (ATR): 1732, 1586, 1469, 1436, 1150, 745 cm^{-1}.

MS (EI) *m*/*z* (relative intensity): 378 (30) $[M]^+$, 247 (100), 219 (90), 206 (70).

HR-MS (EI): *m*/*z* calcd. for $[C_{22}H_{22}N_2O_4]^+$ $[M]^+$ 378.1574, found 378.1578.



(*E*)-Dimethyl 2-{4-[1-(pyridin-2-yl)-1*H*-indol-2-yl]but-2-en-1-yl}malonate [(*E*)-151aa']:

The general procedure **G** was followed using 1-(pyridin-2-yl)-1*H*-indole (**95a**) (48.5 mg, 0.25 mmol) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (55.2 mg, 0.30 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*E*)-**151aa'** (72.8 mg, 77%, *E*/*Z* = 2:1) as a yellow oil.

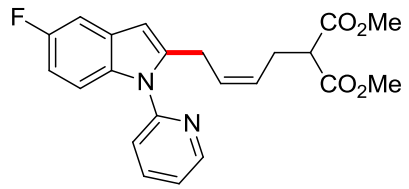
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.65–8.60 (m, 1H), 7.85 (ddd, *J* = 8.0, 7.6, 2.0 Hz, 1H), 7.55 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.46–7.38 (m, 1H), 7.35–7.26 (m, 2H), 7.14–7.08 (m, 2H), 6.41 (d, *J* = 0.7 Hz, 1H), 5.69–5.56 (m, 1H), 5.40 (dtt, *J* = 10.8, 7.6, 1.0 Hz, 0.33H, *Z*), 5.32 (dtt, *J* = 15.7, 7.6, 1.0 Hz, 0.67H, *E*), 3.69 (s, 6H), 3.55 (d, *J* = 6.6 Hz, 2H), 3.33 (t, *J* = 7.7 Hz, 1H), 2.62 (ddd, *J* = 7.7, 7.6, 1.4 Hz, 0.73H, *Z*), 2.53 (ddd, *J* = 7.7, 7.6, 1.4 Hz, 1.27H, *E*).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.0 (C_q), 151.1 (C_q), 149.3 (CH), 139.1 (C_q), 138.0 (CH), 137.1 (C_q), 129.6 (CH), 127.5 (C_q), 126.2 (CH), 121.8 (CH), 121.7 (CH), 120.8 (CH), 120.5 (CH), 119.9 (CH), 110.0 (CH), 102.9 (CH), 52.4 (CH_3), 51.6 (CH), 31.7 (CH_2, *E*), 30.9 (CH_2, *E*), 26.7 (CH_2, *Z*), 25.9 (CH_2, *Z*).

IR (ATR): 1732, 1586, 1469, 1436, 1150, 745 cm^{-1}.

MS (EI) *m*/*z* (relative intensity): 378 (30) $[M]^+$, 247 (100), 219 (90), 206 (70).

HR-MS (EI): *m*/*z* calcd. for $[C_{22}H_{22}N_2O_4]^+$ $[M]^+$ 378.1574, found 378.1578.



(*Z*)-Dimethyl 2-{4-[5-fluoro-1-(pyridin-2-yl)-1*H*-indol-2-yl]but-2-en-1-yl}malonate [(*Z*)-151ba]:

The general procedure **F** was followed using 5-fluoro-1-(pyridin-2-yl)-1*H*-indole (**95b**) (106 mg, 0.50 mmol) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (110 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*Z*)-**151ba** (182 mg, 92%, *E*/*Z* = 1:10) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 7.90 (ddd, *J* = 8.0, 7.5, 2.0 Hz, 1H), 7.42 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.36–7.30 (m, 1H), 7.23–7.15 (m, 2H), 6.85 (td, *J* = 9.1, 2.6 Hz, 1H), 6.38 (d, *J* = 0.8 Hz, 1H), 5.60 (dtt, *J* = 10.8, 7.4, 1.4 Hz, 1H), 5.39 (dtt, *J* = 10.8, 7.6, 1.0 Hz, 1H), 3.68 (s, 6H), 3.61 (d, *J* = 7.4 Hz, 2H), 3.36 (t, *J* = 7.6, 1H), 2.59 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 1.82H, *Z*), 2.53 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 0.18H, *E*).

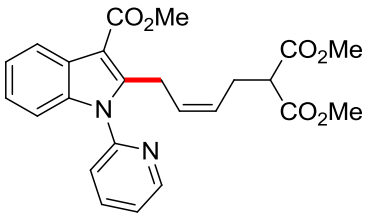
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.1 (C_q), 158.3 (C_q, $^{1}J_{C-F}$ = 234.0 Hz), 151.0 (C_q), 149.6 (CH), 140.8 (C_q), 138.3 (CH), 133.8 (C_q), 128.8 (C_q, $^{3}J_{C-F}$ = 10.3 Hz), 128.5 (CH), 126.5 (CH), 122.1 (CH), 120.8 (CH), 110.7 (CH, $^{3}J_{C-F}$ = 9.7 Hz), 109.7 (CH, $^{2}J_{C-F}$ = 25.9 Hz), 104.9 (CH, $^{2}J_{C-F}$ = 23.6 Hz), 102.6 (CH, $^{4}J_{C-F}$ = 4.5 Hz), 52.5 (CH_3), 51.5 (CH), 31.7 (CH_2, *E*), 31.0 (CH_2, *E*), 26.7 (CH_2, *Z*), 26.0 (CH_2, *Z*).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = –123.9 (*E*), –124.0 (*Z*).

IR (ATR): 1732, 1585, 1470, 1436, 1265, 1230, 1151, 730, 701 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 419 (80) $[M+Na]^+$, 397 (100) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{22}H_{22}FN_2O_4^+$ $[M+H]^+$ 397.1558, found 397.1557.



(*Z*)-Dimethyl 2-{4-[6-(methoxycarbonyl)-1-(pyridin-2-yl)-1*H*-indol-2-yl]but-2-en-1-yl}malonate [(*Z*)-151ca]:

The general procedure **F** was followed using 3-methoxycabonyl-1-(pyridin-2-yl)-1*H*-indole (**95c**) (126 mg, 0.50 mmol) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (110 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*Z*)-**151ca** (153 mg, 70%, *E*/*Z* = 1:25) as a yellow oil.

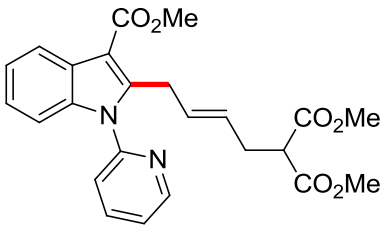
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.71–8.66 (m, 1H), 8.18–8.14 (m, 1H), 7.92 (td, *J* = 7.7, 2.0 Hz, 1H), 7.44–7.36 (m, 2H), 7.24 (ddd, *J* = 8.0, 6.2, 2.0 Hz, 1H). 7.19–7.11 (m, 2H), 5.40 (dtt, *J* = 10.8, 7.6, 0.8 Hz, 1H), 5.16 (dtt, *J* = 10.8, 7.5, 1.2 Hz, 1H), 4.06 (dd, *J* = 6.8, 1.4 Hz, 2H), 3.94 (s, 3H), 3.69 (s, 5.78H, *Z*), 3.61 (s, 0.22H, *E*), 3.24 (t, *J* = 7.6 Hz, 1H), 2.37 (ddd, *J* = 7.6, 7.5, 0.8 Hz, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.0 (C_q), 165.8 (C_q), 150.0 (C_q), 149.9 (CH), 146.5 (CH), 138.6 (C_q), 136.7 (CH), 128.7 (CH), 128.5 (C_q), 126.4 (CH), 125.7 (C_q), 123.4 (CH), 122.9 (CH), 122.3 (CH), 121.6 (C_q), 110.2 (CH), 105.8 (CH), 52.4 (CH), 51.2 (CH_3), 50.9 (CH_3), 26.6 (CH_2), 24.6 (CH_2).

IR (ATR): 1735, 1698, 1588, 1538, 1469, 1436, 1194, 788, 749 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 459 (100) $[M+Na]^+$, 437 (100) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{24}H_{25}N_2O_6^+$ $[M+H]^+$ 437.1707, found 437.1709.



(*E*,*Z*)-Dimethyl 2-{4-[6-(methoxycarbonyl)-1-(pyridin-2-yl)-1*H*-indol-2-yl]but-2-en-1-yl}-malonate [(*E*,*Z*)-151ca']:

The general procedure **G** was followed using 3-methoxycabonyl-1-(pyridin-2-yl)-1*H*-indole (**95c**) (63.0 mg, 0.25 mmol) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (55.2 mg, 0.30 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*E*,*Z*)**-151ca'** (104 mg, 95%, *E*/*Z* = 1:1) as a yellow oil.

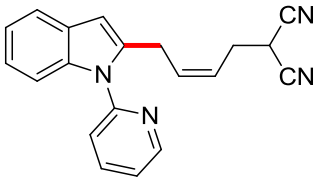
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.72–8.67 (m, 1H), 8.19–8.13 (m, 1H), 7.96–7.89 (m, 1H), 7.43–7.37 (m, 2H), 7.27–7.22 (m, 1H), 7.19–7.12 (m, 2H), 5.53 (dtt, *J* = 15.4, 7.5, 1.4 Hz, 0.50H, *E*), 5.40 (dtt, *J* = 10.7, 7.5, 1.4 Hz, 0.50H, *Z*), 5.19 (dtt, *J* = 10.7, 7.5, 1.1 Hz, 0.50H, *Z*), 5.09 (dtt, *J* = 15.4, 7.5, 1.1 Hz, 0.50H, *E*), 4.06 (d, *J* = 7.0 Hz, 0.96H, *E*), 3.95 (s, 3H), 3.93 (d, *J* = 7.0 Hz, 1.04H, *Z*), 3.69 (s, 3.17H, *Z*), 3.62 (s, 2.83H, *E*), 3.23–3.21 (m, 1H), 2.42 (d, *J* = 7.6, 7.5, 1.4 Hz, 0.94H, *E*), 2.37 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 1.06H, *Z*).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.3 (C_q), 166.1 (C_q), 150.2 (C_q), 146.7 (C_q), 138.8 (CH), 136.8 (C_q), 129.3 (CH), 128.7 (CH), 127.2 (CH), 126.6 (C_q), 125.8 (CH), 123.6 (CH), 123.1 (CH), 122.5 (CH), 121.7 (CH), 110.4 (CH), 106.0 (C_q), 52.6 (CH_3), 51.3 (CH), 51.0 (CH_3), 31.6 (CH_2, *E*), 29.1 (CH_2, *E*), 26.6 (CH_2, *Z*), 24.6 (CH_2, *Z*).

IR (ATR): 1732, 1695, 1587, 1468, 1434, 1190, 1152, 1077, 788, 732 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 459 (100) $[M+Na]^+$, 437 (100) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{24}H_{24}N_2NaO_6^+$ $[M+Na^+]$ 459.1527, found 459.1527.



(*Z*)-2-{4-[1-(Pyridin-2-yl)-1*H*-indol-2-yl]but-2-en-1-yl}malonitrile [(*Z*)-151ab]:

The general procedure **F** was followed using 1-(pyridin-2-yl)-1*H*-indole (**95a**) (97.1 mg, 0.50 mmol) and 2-vinylcyclopropane-1,1-dicarbonitrile (**138b**) (70.9 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*Z*)-**151ab** (105 mg, 67%, *E*/*Z* = 1:3) as a pale yellow oil.

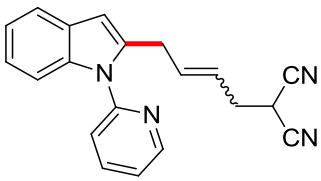
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.66–8.63 (m, 1H), 7.90 (ddd, *J* = 7.9, 4.9, 2.0 Hz, 1H), 7.58–7.54 (m, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.36–7.30 (m, 2H), 7.16–7.11 (m, 2H), 6.44 (d, *J* = 0.7 Hz, 1H), 5.98–5.88 (m, 1H), 5.50 (dtt, *J* = 10.4, 7.5, 1.1 Hz, 0.77H, *Z*), 5.37 (dtt, *J* = 15.4, 7.5, 1.0 Hz, 0.23H, *E*), 3.70 (d, *J* = 7.5 Hz, 2H), 3.60 (t, *J* = 7.2 Hz, 0.77H, *Z*), 3.60 (t, *J* = 7.2 Hz, 0.23H, *E*), 2.71 (ddd, *J* = 7.3, 7.2, 1.1 Hz, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 151.1 (C_q), 149.6 (CH), 138.4 (CH), 137.9 (C_q), 137.2 (C_q), 135.0 (CH), 133.2 (CH), 128.3 (C_q), 122.6 (CH), 122.1 (CH), 122.0 (CH), 120.9 (CH), 120.2 (CH), 112.1 (C_q), 110.0 (CH), 103.2 (CH), 33.8 (CH_2, *E*), 30.9 (CH_2, *E*), 28.6 (CH_2, *Z*), 26.3 (CH_2, *Z*), 22.8 (CH).

IR (ATR): 2257, 1586, 1469, 1456, 1437, 1211, 1149, 782, 745 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 335 (100) $[M+Na]^+$, 313 (80) $[M+H]^+$, 197 (80).

HR-MS (ESI) *m*/*z* calcd. for $C_{20}H_{17}N_4^+$ $[M+H]^+$ 313.1448, found 313.1442.



(*E*,*Z*)-2-{4-[1-(Pyridin-2-yl)-1*H*-indol-2-yl]but-2-en-1-yl}malonitrile [(*E*,*Z*)-151ab']:

The general procedure **G** was followed using 1-(pyridin-2-yl)-1*H*-indole (**95a**) (48.5 mg, 0.25 mmol) and 2-vinylcyclopropane-1,1-dicarbonitrile (**138b**) (35.5 mg, 0.30 mmol). Isolation by column

chromatography (*n*-hexane/EtOAc: 3/1) yielded (*E*,*Z*)-**151ab'** (54.2 mg, 69%, *E*/*Z* = 1:1) as a pale yellow oil.

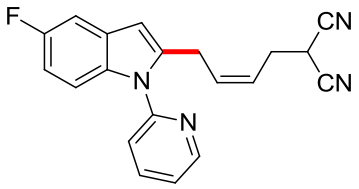
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.68–8.64 (m, 1H), 7.92 (ddd, *J* = 7.9, 4.9, 2.0 Hz, 1H), 7.58 (dd, *J* = 8.1, 3.9 Hz, 1H), 7.48 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.37–7.32 (m, 2H), 7.18–7.14 (m, 2H), 6.49 (d, 0.7 Hz, 0.47H, *E*), 6.46 (d, 0.7 Hz, 0.53H, *Z*), 5.98–5.88 (m, 1H), 5.50 (dtt, *J* = 10.4, 7.5, 1.1 Hz, 0.47H, *Z*), 5.37 (dtt, *J* = 15.4, 7.5, 1.0 Hz, 0.53H, *E*), 3.72 (d, *J* = 7.6 Hz, 2H), 3.67 (t, *J* = 7.5 Hz, 0.53H, *Z*), 3.58 (t, *J* = 7.5 Hz, 0.47H, *E*), 2.73 (ddd, *J* = 7.5, 7.4, 1.1 Hz, 1.06H), 2.62 (ddd, *J* = 7.5, 7.4, 1.1 Hz, 0.94H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 151.1 (C_q), 149.7 (CH), 138.5 (CH), 138.0 (C_q), 137.2 (C_q), 135.1 (CH), 133.3 (CH), 128.3 (C_q), 122.6 (CH), 122.2 (CH), 120.9 (CH), 120.3 (CH), 112.2 (C_q), 110.0 (CH), 103.5 (CH), 103.2 (CH), 33.7 (CH_2, *E*), 30.9 (CH_2, *E*), 28.5 (CH_2, *Z*), 26.2 (CH_2, *Z*), 23.7 (CH, *E*), 22.1 (CH, *Z*).

IR (ATR): 2257, 1586, 1468, 1455, 1436, 1211, 908, 738, 737 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 335 (100) $[M+Na]^+$, 313 (80) $[M+H]^+$, 197 (80).

HR-MS (ESI) *m*/*z* calcd. for $C_{20}H_{16}N_4Na^+$ $[M+Na]^+$ 335.1267, found 335.1270.



(*Z*)-2-{4-[5-Fluoro-1-(pyridin-2-yl)-1*H*-indol-2-yl]but-2-en-1-yl}malonitrile [(*Z*)-151bb]:

The general procedure **F** was followed using 5-fluoro-1-(pyridin-2-yl)-1*H*-indole (**95b**) (106 mg, 0.50 mmol) and 2-vinylcyclopropane-1,1-dicarbonitrile (**138b**) (70.9 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*Z*)-**151bb** (114 mg, 69%, *E*/*Z* = 1:4) as a yellow oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.66–8.63 (m, 1H), 7.91 (ddd, *J* = 7.9, 5.0, 2.0 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.37–7.30 (m, 1H), 7.25–7.17 (m, 2H), 6.91–6.82 (m, 1H), 6.42 (s, 0.20H, *E*), 6.40 (s, 0.80H, *Z*), 5.98–5.83 (m, 1H), 5.53 (dtt, *J* = 10.8, 7.5, 1.0 Hz, 0.80H, *Z*), 5.39 (dtt, *J* = 15.4, 7.5, 1.0 Hz, 0.20H, *E*), 3.75–3.56 (m, 2H), 3.63 (t, *J* = 7.5 Hz, 0.80H, *Z*), 3.63 (t, *J* = 7.5 Hz, 0.20H, *E*), 2.72 (ddd, *J* = 7.5, 7.4, 1.0 Hz, 1.60H, *Z*), 2.62 (ddd, *J* = 7.5, 7.4, 1.0 Hz, 0.40H, *E*).

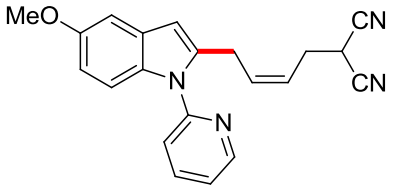
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 158.4 (C_q, $^1J_{C-F}$ = 235.5 Hz), 150.8 (C_q), 149.6 (CH), 139.5 (C_q), 138.6 (CH), 133.7 (C_q), 132.9 (CH), 128.7 (C_q, $^3J_{C-F}$ = 10.5 Hz), 122.4 (CH), 122.1 (CH), 120.8 (CH), 112.1 (C_q), 110.7 (CH, $^3J_{C-F}$ = 9.7 Hz), 110.1 (CH, $^2J_{C-F}$ = 26.4 Hz), 105.1 (CH, $^2J_{C-F}$ = 23.9 Hz), 103.1 (CH, $^4J_{C-F}$ = 4.6 Hz), 33.7 (CH_2, *E*), 31.0 (CH_2, *E*), 28.6 (CH_2, *Z*), 26.3 (CH_2, *Z*), 23.2 (CH, *E*), 22.8 (CH, *Z*).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = –123.5.

IR (ATR): 2255, 1617, 1470, 1438, 1385, 1175, 785, 735 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 353 (100) $[M+Na]^+$, 331 (80) $[M+H]^+$, 215 (100).

HR-MS (ESI) *m*/*z* calcd. for $C_{20}H_{16}FN_4^+$ $[M+H]^+$ 331.1354, found 331.1342.



(*Z*)-2-{4-[5-Methoxy-1-(pyridin-2-yl)-1*H*-indol-2-yl]but-2-en-1-yl}malonitrile [(*Z*)-151db]:

The general procedure **F** was followed using 5-methoxy-1-(pyridin-2-yl)-1*H*-indole (**95d**) (112 mg, 0.50 mmol) and 2-vinylcyclopropane-1,1-dicarbonitrile (**138b**) (70.9 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*Z*)-**151db** (118 mg, 65%, *E*/*Z* = 1:3) as a pale yellow oil.

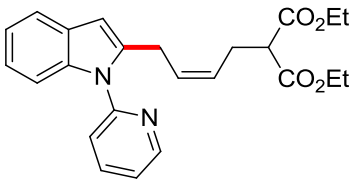
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.63−8.60 (m, 1H), 7.87 (ddd, *J* = 7.9, 5.0, 2.0 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.32–7.26 (m, 2H), 7.03 (d, *J* = 2.5 Hz, 1H), 6.78 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.39 (s, 0.23H, *Z*), 6.37 (s, 0.77H, *E*), 5.91–5.84 (m, 1H), 5.49 (dtt, *J* = 10.8, 7.5, 1.1 Hz, 0.23H, *Z*), 5.34 (dtt, *J* = 15.4, 7.5, 1.1 Hz, 0.77H, *E*), 3.83 (s, 3H), 3.72–3.68 (m, 2H), 3.63 (t, *J* = 7.5 Hz, 1H), 2.69 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1.54H, *Z*), 2.57 (ddd, *J* = 7.5, 7.4, 1.1 Hz, 0.46H, *E*).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 154.8 (C_q), 151.1 (C_q), 149.5 (CH), 138.4 (C_q), 138.4 (CH), 134.9 (CH), 133.2 (CH), 132.2 (C_q), 128.8 (C_q), 121.9 (CH), 120.5 (CH), 112.2 (C_q), 111.7 (CH), 110.8 (CH), 103.0 (CH), 102.3 (CH), 55.8 (CH_3), 33.6 (CH_2, *E*), 31.0 (CH_2, *E*), 28.6 (CH_2, *Z*), 26.3 (CH_2, *Z*), 23.1 (CH, *E*), 22.7 (CH, *Z*).

IR (ATR): 2254, 1616, 1582, 1470, 1436, 1203, 1172, 729 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 365 (100) $[M+H]^+$, 343 (40), 227 (80).

HR-MS (ESI) *m*/*z* calcd. for $C_{21}H_{19}N_4O^+$ $[M+H]^+$ 365.1373, found 365.1365.



(*Z*)-Diethyl 2-{4-[1-(Pyridin-2-yl)-1*H*-indol-2-yl]but-2-en-1-yl}malonate [(*Z*)-151ac]:

The general procedure **F** was followed using (pyridin-2-yl)-1*H*-indole (**95a**) (97.1 mg, 0.50 mmol) and diethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138c**) (127 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*Z*)-**151ac** (171 mg, 84%, *E*/*Z* =1:12) as a yellow oil.

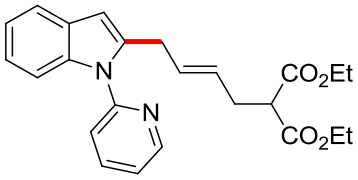
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 7.90–7.83 (m, 1H), 7.56–7.53 (m, 1H), 7.42 (dt, *J* = 8.0, 8.0, 1.0 Hz, 1H), 7.33–7.25 (m, 2H), 7.13–7.08 (m, 2H), 6.44 (d, *J* = 0.9 Hz, 1H), 5.62 (dtt, *J* = 10.8, 7.4, 1.4 Hz, 1H), 5.41 (dtt, *J* = 10.8, 7.6, 1.0 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 4H), 3.64 (d, *J* = 7.4 Hz, 1.84H, *Z*), 3.55 (d, *J* = 7.4 Hz, 0.16H, *E*), 3.33 (t, *J* = 7.6 Hz, 1H), 2.60 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.7 (C_q), 151.1 (C_q), 149.5 (CH), 139.2 (C_q), 138.1 (CH), 137.1 (C_q), 128.6 (CH), 128.4 (CH), 126.4 (C_q), 121.8 (CH), 121.6 (CH), 120.8 (CH), 120.5 (CH), 119.8 (CH), 109.9 (CH), 102.6 (CH), 61.2 (CH_2), 51.7 (CH), 31.4 (CH_2, *E*), 30.7 (CH_2, *E*), 26.4 (CH_2, *Z*), 25.8 (CH_2, *Z*), 13.9 (CH_3).

IR (ATR): 1727, 1585, 1468, 1455, 1436, 1149, 1025, 783, 745 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 429 (60) $[M+Na]^+$, 407 (100) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{24}H_{27}N_2O_4^+$ $[M+H]^+$ 407.1965, found 407.1960.



(*E*)-Diethyl 2-{4-[1-(Pyridin-2-yl)-1*H*-indol-2-yl]but-2-en-1-yl}malonate [(*E*)-151ac']:

The general procedure **G** was followed using (pyridin-2-yl)-1*H*-indole (**95a**) (48.5 mg, 0.25 mmol) and diethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138c**) (63.5 mg, 0.30 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*E*)-**151ac'** (66.1 mg, 65%, *E*/*Z* =1.3:1) as a yellow oil.

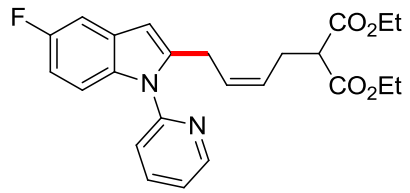
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.67–8.60 (m, 1H), 7.90–7.82 (m, 1H), 7.57–7.51 (m, 1H), 7.46–7.38 (m, 1H), 7.34–7.26 (m, 2H), 7.14–7.07 (m, 2H), 6.41 (d, *J* = 0.8 Hz, 1H), 5.67–5.55 (m, 1H), 5.41 (dtt, *J* = 10.8, 7.6, 1.0 Hz, 0.43H, *Z*), 5.32 (dtt, *J* = 15.3, 7.6, 1.0 Hz, 0.57H, *E*), 4.15 (q, *J* = 7.2 Hz, 4H), 3.65 (d, *J* = 7.4 Hz, 0.86H, *Z*), 3.54 (d, *J* = 7.4 Hz, 1.14H, *E*), 3.29 (t, *J* = 7.6 Hz, 1H), 2.60 (ddd, *J* = 7.6, 7.6, 1.5 Hz, 0.86H, *Z*), 2.52 (ddd, *J* = 7.6, 7.6, 1.5 Hz, 1.14H, *E*), 1.23 (t, *J* = 7.2 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.9 (C_q), 151.4 (C_q), 149.5 (CH), 139.3 (C_q), 138.2 (CH), 137.3 (C_q), 129.6 (CH), 128.8 (CH), 128.5 (C_q), 127.8 (CH), 126.6 (CH), 121.8 (CH), 121.0 (CH), 120.0 (CH), 110.1 (CH), 103.0 (CH), 61.3 (CH_2), 51.9 (CH), 31.5 (CH_2, *E*), 30.6 (CH_2, *E*), 26.7 (CH_2, *Z*), 25.9 (CH_2, *Z*), 14.0 (CH_3).

IR (ATR): 1728, 1585, 1469, 1436, 1149, 782, 746 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 429 (100) $[M+Na]^+$, 407 (20) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{24}H_{27}N_2O_4^+$ $[M+H]^+$ 407.1965, found 407.1966.



(*Z*)-Diethyl 2-{4-[5-Fluoro-1-(pyridin-2-yl)-1*H*-indol-2-yl]but-2-en-1-yl}malonate [(*Z*)-151bc]:

The general procedure **F** was followed using 5-fluoro-1-(pyridin-2-yl)-1*H*-indole (**95b**) (106 mg, 0.50 mmol) and diethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138c**) (127 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*Z*)-**151bc** (166 mg, 78%, *E*/*Z* = 1:11) as a yellow oil.

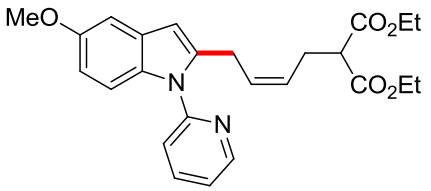
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.64–8.60 (m, 1H), 7.89–7.82 (m, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.32–7.26 (m, 1H), 7.22–7.14 (m, 2H), 6.82 (td, *J* = 9.1, 2.6 Hz, 1H), 6.37 (s, 1H), 5.59 (dtt, *J* = 10.8, 7.5, 1.4 Hz, 1H), 5.40 (dtt, *J* = 10.8, 7.6, 1.2 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 4H), 3.61 (d, *J* = 7.5 Hz, 1.83H, *Z*), 3.50 (d, *J* = 7.5 Hz, 0.17H, *E*), 3.29 (t, *J* = 7.5 Hz, 1H), 2.58 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.8 (C_q), 158.3 (C_q, $^{1}J_{C-F}$ = 234.2 Hz), 151.0 (C_q), 149.6 (CH), 140.9 (C_q), 138.4 (CH), 133.8 (C_q), 128.8 (C_q, $^{3}J_{C-F}$ = 9.7 Hz), 128.2 (CH), 126.8 (CH), 122.1 (CH), 120.8 (CH), 110.7 (CH, $^{3}J_{C-F}$ = 9.6 Hz), 109.6 (CH, $^{2}J_{C-F}$ = 25.8 Hz), 104.3 (CH, $^{2}J_{C-F}$ = 25.5 Hz), 102.6 (CH, $^{4}J_{C-F}$ = 4.2 Hz), 61.3 (CH_2), 51.7 (CH), 31.5 (CH_2, *E*), 30.9 (CH_2, *E*), 26.5 (CH_2, *Z*), 25.9 (CH_2, *Z*), 13.9 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = –124.0. IR (ATR): 1727, 1584, 1469, 1437, 1173, 1151, 1031, 855, 785 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 447 (90) $[M+Na]^+$, 425 (100) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{24}H_{26}FN_2O_4^+$ $[M+H]^+$ 425.1871, found 425.1875.



(*Z*)-Diethyl 2-{4-[5-Methoxy-1-(pyridin-2-yl)-1*H*-indol-2-yl]but-2-en-1-yl}malonate [(*Z*)-151dc]: The general procedure **F** was followed using 5-methoxy-1-(pyridin-2-yl)-1*H*-indole (**95d**) (112 mg, 0.50 mmol) and diethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138c**) (127 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*Z*)-**151dc** (142 mg, 65%, *E*/*Z* = 1:12) as a yellow oil.

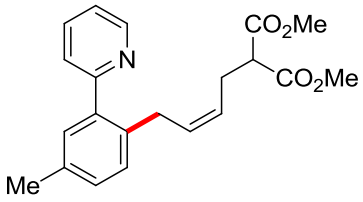
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.60 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 7.83 (ddd, *J* = 8.0, 7.5, 2.0 Hz, 1H), 7.39 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.25 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.24−7.21 (m, 1H), 7.01 (d, *J* = 2.5 Hz, 1H), 6.75 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.34 (d, *J* = 0.9 Hz, 1H), 5.60 (dtt, *J* = 10.8, 7.3, 1.2 Hz, 1H), 5.39 (dtt, *J* = 10.8, 7.5, 1.2 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 4H), 3.81 (s, 3H), 3.63 (d, *J* = 7.3 Hz, 1.84H, *Z*), 3.53 (d, *J* = 7.3 Hz, 0.16H, *E*), 3.30 (t, *J* = 7.6 Hz, 1H), 2.59 (ddd, *J* = 7.6, 7.5, 1.2 Hz, 1.84H, *Z*), 2.51 (ddd, *J* = 7.6, 7.5, 1.2 Hz, 0.16H, *E*), 1.20 (t, *J* = 7.2 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.8 (C_q), 154.7 (C_q), 151.3 (C_q), 149.5 (CH), 139.8 (C_q), 138.2 (CH), 132.3 (C_q), 129.0 (C_q), 128.7 (CH), 126.4 (CH), 121.7 (CH), 120.6 (CH), 111.2 (CH), 110.8 (CH), 102.6 (CH), 102.2 (CH), 61.3 (CH_2), 55.7 (CH_3), 51.8 (CH), 31.5 (CH_2, *E*), 30.6 (CH_2, *E*), 26.7 (CH_2, *Z*), 26.0 (CH_2, *Z*), 14.0 (CH_3).

IR (ATR): 1727, 1581, 1470, 1436, 1203, 1171, 1151, 1031, 770, 712 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 459 (100) $[M+Na]^+$, 437 (90) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{25}H_{29}N_2O_5^+$ $[M+H]^+$ 437.2071, found 437.2071.



(*Z*)-Dimethyl 2-{4-[4-methyl-2-(pyridin-2-yl)phenyl]but-2-en-1-yl}malonate [(*Z*)-153aa]:

The general procedure **F** was followed using 2-(*m*-tolyl)pyridine (**152a**) (42.3 mg, 0.25 mmol) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (55.2 mg, 0.30 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*Z*)-**153aa** (61.8 mg, 70%, *E*/*Z* = 1:3).

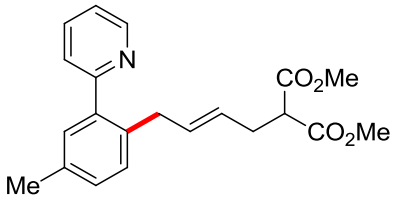
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.67–8.65 (m, 1H), 7.73–7.67 (m, 1H), 7.37–7.32 (m, 1H), 7.17 (s, 1H), 7.16–7.11 (m, 3H), 5.55 (dtt, *J* = 15.1, 7.6, 1.4 Hz, 0.25H, *E*), 5.49 (dtt, *J* = 10.8, 7.6, 1.4 Hz, 0.75H, *Z*), 5.29–5.18 (m, 1H), 3.68 (s, 4.62H, *Z*), 3.66 (s, 1.38H, *E*), 3.45 (d, *J* = 7.2 Hz, 2H), 3.34–3.29 (m, 1H), 2.55 (ddd, *J* = 7.7, 7.6, 1.3 Hz, 1.54H, *Z*), 2.51 (ddd, *J* = 7.7, 7.6, 1.3 Hz, 0.46H, *E*), 2.33 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.3 (C_q), 159.9 (C_q), 149.2 (CH), 140.1 (C_q), 136.1 (CH), 135.7 (C_q), 135.1 (C_q), 132.1 (CH), 130.4 (CH), 129.6 (CH), 129.2 (CH), 124.7 (CH), 124.1 (CH), 121.6 (CH), 52.5 (CH_3, *E*), 52.4 (CH_3, *Z*), 51.7 (CH, *Z*), 51.5 (CH, *E*), 35.7 (CH_2, *E*), 31.8 (CH_2, *E*), 30.5 (CH_2, *Z*), 26.6 (CH_2, *Z*), 20.9 (CH_3).

IR (ATR): 1734, 1586, 1433, 1339, 1271, 1231, 1196, 1152, 749 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 376 (70) $[M+Na]^+$, 354 (100) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{21}H_{24}NO_4^+$ $[M+H]^+$ 354.1700, found 354.1702.



(*E*)-Dimethyl 2-{4-[4-methyl-2-(pyridin-2-yl)phenyl]but-2-en-1-yl}malonate [(*E*)-153aa']:

The general procedure **G** was followed using 2-(*m*-tolyl)pyridine (**152a**) (42.3 mg, 0.25 mmol) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (55.2 mg, 0.30 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*E*)-**153aa'** (30.1 mg, 34%, *E*/*Z* = 2:1).

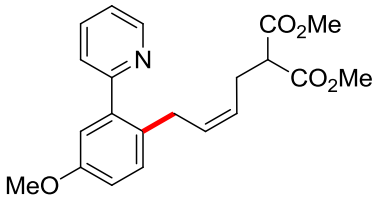
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.73–7.68 (m, 1H), 7.37–7.32 (m, 1H), 7.17 (s, 1H), 7.16–7.11 (m, 3H), 5.55 (dtt, *J* = 15.1, 7.6, 1.4 Hz, 0.67H, *E*), 5.49 (dtt, *J* = 10.8, 7.6, 1.4 Hz, 0.33H, *Z*), 5.27–5.18 (m, 1H), 3.68 (s, 2.00H, *Z*), 3.66 (s, 4.00H, *E*), 3.46–3.29 (m, 3H), 2.55 (ddd, *J* = 7.7, 7.6, 1.3 Hz, 0.66H, *Z*), 2.51 (ddd, *J* = 7.7, 7.6, 1.3 Hz, 1.34H, *E*), 2.33 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.3 (C_q), 159.8 (C_q), 149.1 (CH), 140.1 (C_q), 136.0 (CH), 135.7 (C_q), 134.7 (C_q), 132.9 (CH), 130.4 (CH), 129.8 (CH), 129.1 (CH), 126.2 (CH), 124.1 (CH), 121.6 (CH), 52.5 (CH_3), 52.4 (CH_3), 51.7 (CH, *Z*), 51.5 (CH, *E*), 35.7 (CH_2, *E*), 31.8 (CH_2, *E*), 30.5 (CH_2, *Z*), 26.6 (CH_2, *Z*), 20.9 (CH_3).

IR (ATR): 1732, 1599, 1434, 1230, 1151, 829, 972, 773, 752 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 376 (80) $[M+Na]^+$, 354 (100) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{21}H_{24}NO_4^+$ $[M+H]^+$ 354.1700, found 354.1701.



(*Z*)-Dimethyl 2-{4-[4-methoxy-2-(pyridin-2-yl)phenyl]but-2-en-1-yl} malonate [(*Z*)-153ba]:

The general procedure **F** was followed using 2-(3-methoxyphenyl)pyridine (**152b**) (46.3 mg, 0.25 mmol) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (55.2 mg, 0.30 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*Z*)-**153ba** (58.1 mg, 63%, *E*/*Z* = 1:5).

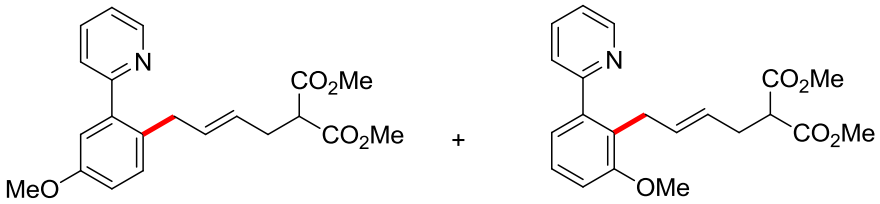
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.68–8.64 (m, 1H), 7.72 (ddd, *J* = 6.7, 4.8, 1.8 Hz, 1H), 7.37–7.33 (m, 1H), 7.24–7.20 (m, 1H), 7.19–7.14 (m, 1H), 6.89 (s, 1H), 6.87–6.85 (m, 1H), 5.56 (dtt, *J* = 15.3, 7.6, 1.4 Hz, 0.17H, *E*), 5.47 (dtt, *J* = 10.8, 7.6, 1.4 Hz, 0.83H, *Z*), 5.30–5.14 (m, 1H), 3.79 (s, 3H), 3.69 (s, 5.00H, *Z*), 3.67 (s, 1.00H, *E*), 3.41 (d, *J* = 7.2 Hz, 2H), 3.34–3.28 (m, 1H), 2.55 (ddd, *J* = 7.6, 7.5, 1.3 Hz, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.2 (C_q), 159.6 (C_q), 157.7 (C_q), 149.1 (CH), 141.1 (C_q), 136.1 (CH), 132.1 (CH), 130.6 (CH), 130.3 (C_q), 124.6 (CH), 124.0 (CH), 121.7 (CH), 114.9 (CH), 114.4 (CH), 55.4 (CH_3), 52.5 (CH), 51.6 (CH_3), 35.3 (CH_2, *E*), 31.8 (CH_2, *E*), 30.2 (CH_2, *Z*), 26.7 (CH_2, *Z*).

IR (ATR): 1732, 1607, 1586, 1499, 1469, 1224, 1230, 1150, 750, 611 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 392 (100) $[M+Na]^+$, 369 (90) $[M]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{21}H_{24}NO_5^+$ $[M+H]^+$ 370.1649, found 370.1652.



(*E*,*Z*)-Dimethyl 2-{4-[4-methoxy-2-(pyridin-2-yl)phenyl]but-2-en-1-yl}malonate [(*E*,*Z*)-153ba] and (*E*,*Z*)Dimethyl 2{4-[2-methoxy-6-(pyridin-2-yl)phenyl}but-2-en-1-yl}malonate [(*E*,*Z*)-153ba']:

The general procedure **G** was followed using 2-(3-methoxyphenyl)pyridine (**152b**) (46.3 mg, 0.25 mmol) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (55.2 mg, 0.30 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1->3/1->2/1) yielded (*E*,*Z*)**-153ba** and (*E*,*Z*)**-ba'** as inseparable mixture (22.2 mg, 24%, *E*/*Z* = 1:1) and (*E*,*Z*)**-153ba''** (19.4 mg, 14%, *E*/*Z* = 1:1).

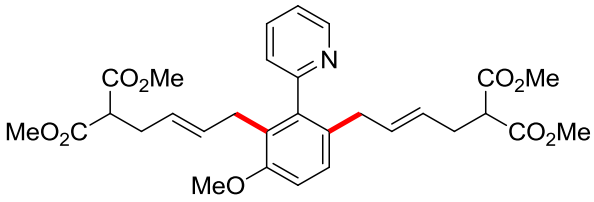
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.68–8.63 (m, 1H), 7.76–7.66 (m, 1H), 7.34 (ddd, *J* = 4.1, 2.0, 1.0 Hz, 1H), 7.24–7.20 (m, 1H), 7.19–7.14 (m, 1H), 6.89 (s, 1H), 6.87–6.85 (m, 1H), 5.56 (dtt, *J* = 15.3, 7.6, 1.4 Hz, 0.50H, *E*), 5.47 (dtt, *J* = 10.8, 7.6, 1.4 Hz, 0.50H, *Z*), 5.28–5.02 (m, 1H), 3.85–3.79 (s, 3H), 3.70–3.62 (s, 6H), 3.47–3.22 (m, 3H), 2.57–2.51 (m, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.2 (C_q), 159.5 (C_q), 157.7 (C_q), 149.1 (CH), 141.2 (C_q), 136.0 (CH), 135.4 (CH), 132.9 (CH), 130.9 (C_q), 126.1 (CH), 124.2 (CH), 121.7 (CH), 114.4 (CH), 110.4 (CH), 55.4 (CH_3), 52.4 (CH_3), 51.9 (CH), 35.4 (CH_2, *E*), 31.8 (CH_2, *E*), 26.6 (CH_2, *Z*), 25.1 (CH_2, *Z*).

IR (ATR): 1732, 1607, 1586, 1499, 1469, 1224, 1230, 1150, 750, 611 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 392 (100) $[M+Na]^+$, 369 (90) $[M]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{21}H_{24}NO_5^+$ $[M+H]^+$ 370.1649, found 370.1652.



(2*E*,*Z*,2'*E*,*Z*)-Tetramethyl [4-methoxy-2-(pyridin-2-yl)-1,3-phenylenebis(but-2-ene-4,1-diyl)]dimalonate [(*E*,*Z*)-153ba'']:

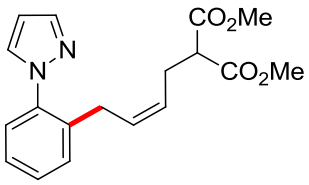
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.72–7.65 (m, 1H), 7.23–7.17 (m, 1H), 7.14 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.04–7.00 (m, 1H), 6.83 (d, *J* = 1.6 Hz, 1H), 5.51–5.39 (m, 2H), 5.15–4.88 (m, 2H), 3.79 (s, 3H), 3.66 (s, 12H), 3.31 (t, *J* = 6.2 Hz, 2H), 3.11–2.80 (m, 4H), 2.53–2.39 (m, 4H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.2 (C_q), 158.7 (C_q), 155.8 (C_q), 149.2 (CH), 141.0 (C_q), 135.5 (CH), 132.5 (CH), 131.7 (CH), 130.2 (C_q), 127.6 (CH), 126.6 (C_q), 125.9 (CH), 125.1 (CH), 121.7 (CH), 110.4 (CH), 55.7 (CH_3), 52.4 (CH_3), 52.0 (CH), 36.1 (CH_2, *E*), 31.9 (CH_2, *E*), 30.6 (CH_2, *Z*), 26.6 (CH_2, *Z*).

IR (ATR): 1732, 1584, 1466, 1434, 1257, 1151, 1033, 972, 731 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 554 (80) $[M+H]^+$, 553 (100) $[M]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{30}H_{36}NO_9^+$ $[M+H]^+$ 554.2385, found 554.2389.



(*Z*)-Dimethyl 2-{4-[2-(1*H*-pyrazol-1-yl)phenyl]but-2-en-1-yl}malonate [(*Z*)-153ca]:

The general procedure **F** was followed using 1-phenyl-1*H*-pyrazole (**152c**) (72.1 mg, 0.50 mmol) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (110 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*Z*)-**153ca** (117 mg, 71%, *E*/*Z* = 1:12) as a yellow oil.

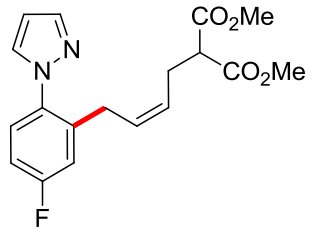
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.66 (dd, *J* = 2.4, 0.7 Hz, 1H), 7.55 (dd, *J* = 2.4, 0.7 Hz, 1H), 7.32–7.28 (m, 2H), 7.25–7.24 (m, 2H), 6.39–6.37 (m, 1H), 5.43 (dtt, *J* = 10.7, 7.5, 1.0 Hz, 1H), 5.32 (dtt, *J* = 10.7, 7.5, 1.4 Hz, 1H), 3.66 (s, 6H), 3.34–3.31 (m, 3H), 2.59 (ddd, *J* = 7.6, 7.5, 1.0 Hz, 1.84H), 2.53 (ddd, *J* = 7.6, 7.5, 1.0 Hz, 0.16H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.1 (C_q), 140.3 (CH), 139.5 (C_q), 136.3 (C_q), 130.6 (CH), 130.4 (CH), 130.1 (CH), 128.6 (CH), 126.8 (CH), 126.4 (CH), 125.8 (CH), 106.2 (CH), 52.4 (CH_3), 51.3 (CH), 34.1 (CH_2, *E*), 31.1 (CH_2, *E*), 29.0 (CH_2, *Z*), 26.5 (CH_2, *Z*).

IR (ATR): 1731, 1517, 1435, 1394, 1233, 1153, 911, 759, 730 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 351 (20) $[M+Na]^+$, 329 (100) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{18}H_{21}N_2O_4^+$ $[M+H]^+$ 329.1496, found 329.1497.



(*Z*)-Dimethyl 2-{4-[5-fluoro-2-(1*H*-pyrazol-1-yl)phenyl]but-2-en-1-yl}malonate [(*Z*)-153da]:

The general procedure **F** was followed using 1-(4-fluorophenyl)-1*H*-pyrazole (**152d**) (81.2 mg, 0.50 mmol) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (110 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*Z*)-**153da** (114 mg, 66%, *E*/*Z* = 1:17) as a yellow oil.

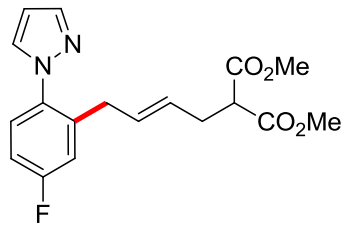
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.66–7.63 (m, 1H), 7.52–7.48 (m, 1H), 7.24–7.19 (m, 1H), 6.97 (m, 2H), 6.38 (m, 1H), 5.45–5.32 (m, 2H), 3.66 (s, 6H), 3.32 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 1H), 3.26 (d, *J* = 6.4 Hz, 1.89H, *Z*), 3.14 (d, *J* = 6.4 Hz, 0.11H, *E*), 2.57–2.52 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.0 (C_q), 162.2 (C_q, $^{1}J_{C-F}$ = 248.2 Hz), 140.4 (CH), 139.2 (C_q, $^{3}J_{C-F}$ = 8.0 Hz), 135.6 (C_q, $^{4}J_{C-F}$ = 3.1 Hz), 130.8 (CH), 129.4 (CH), 128.1 (CH, $^{3}J_{C-F}$ = 9.0 Hz), 126.7 (CH), 116.5 (CH, $^{2}J_{C-F}$ = 23.0 Hz), 113.5 (CH, $^{2}J_{C-F}$ = 22.7 Hz), 106.3 (CH), 52.4 (CH_3), 51.2 (CH), 34.0 (CH_2, $^{4}J_{C-F}$ = 1.5 Hz, *E*), 31.3 (CH_2, *E*), 28.8 (CH_2, $^{4}J_{C-F}$ = 1.5 Hz, *Z*), 26.5 (CH_2, *Z*).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = –112.7 (*E*), –112.5 (*Z*). IR (ATR): 1731, 1518, 1497, 1434, 1267, 1230, 1150, 1024, 755 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 369 (30) $[M+Na]^+$, 347 (100) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{18}H_{20}FN_2O_4^+$ $[M+H]^+$ 347.1402, found 347.1402.



(*E*)-Dimethyl 2-{4-[5-fluoro-2-(1*H*-pyrazol-1-yl)phenyl]but-2-en-1-yl}malonate [(*E*)-153da']:

The general procedure **G** was followed using 1-(4-fluorophenyl)-1*H*-pyrazole (**152d**) (41 mg, 0.25 mmol) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (55.2 mg, 0.30 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*E*)-**153da'** (44.2 mg, 48%, *E*/*Z* = 1:2) as a yellow oil.

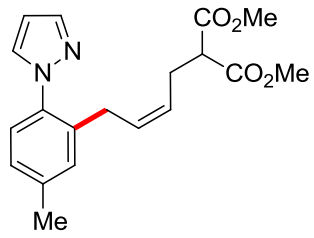
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.69–7.66 (m, 1H), 7.55–7.50 (m, 1H), 7.33–7.24 (m, 1H), 7.02–6.92 (m, 2H), 6.45–6.38 (m, 1H), 5.55–5.23 (m, 2H), 3.70 (s, 6H), 3.41–3.32 (m, 1H), 3.28 (d, *J* = 6.4 Hz, 1.20H, *Z*), 3.17 (d, *J* = 6.4 Hz, 0.80H, *E*), 2.62–2.52 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.0 (C_q), 162.8 (C_q, $^1J_{C-F}$ = 248.1 Hz), 140.4 (CH), 138.9 (C_q, $^3J_{C-F}$ = 8.0 Hz), 135.6 (C_q, $^4J_{C—F}$ = 3.1 Hz), 130.8 (CH), 129.4 (CH), 128.2 (CH, $^3J_{C-F}$ = 9.0 Hz), 126.7 (CH), 116.8 (CH, $^2J_{C-F}$ = 23.0 Hz), 113.7 (CH, $^2J_{C-F}$ = 22.7 Hz), 106.5 (CH), 52.5 (CH_3), 51.4 (CH), 34.4 (CH_2, $^4J_{C-F}$ = 1.5 Hz, *E*), 31.2 (CH_2, *E*), 29.0 (CH_2, $^4J_{C-F}$ = 1.5 Hz, *Z*), 26.5 (CH_2, *Z*).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = –112.7 (*E*), –112.5 (*Z*). IR (ATR): 1732, 1518, 1497, 1435, 1334, 1268, 1151, 755 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 369 (20) $[M+Na]^+$, 347 (100) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{18}H_{19}FNaN_2O_4^+$ $[M+Na]^+$ 369.1221, found 369.1221.



(*Z*)-Dimethyl 2-{4-[5-methyl-2-(1*H*-pyrazol-1-yl)phenyl]but-2-en-1-yl}malonat [(*Z*)-153ea]:

The general procedure **F** was followed using 1-(*p*-tolyl)-1*H*-pyrazole (**152e**) (79.3 mg, 0.50 mmol) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (110 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded (*Z*)-**153ea** (118 mg, 69%, *E*/*Z* = 1:19) as a yellow oil.

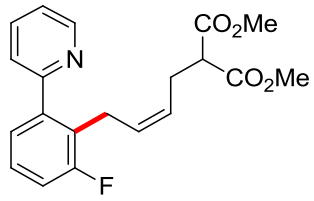
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.66–7.63 (m, 1H), 7.52–7.48 (m, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 7.08–7.02 (m, 2H), 6.37 (m, 1H), 5.43 (dtt, *J* = 10.7, 7.4, 1.4 Hz, 1H), 5.32 (dtt, *J* = 10.7, 7.6, 1.4 Hz, 1H), 3.66 (s, 6H), 3.32 (t, *J* = 7.8 Hz, 1H), 3.27 (d, *J* = 7.4 Hz, 1.90H, *Z*), 3.15 (d, *J* = 7.3 Hz, 0.10H, *E*), 2.57 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 2H), 2.33 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.1 (C_q), 140.1 (CH), 138.5 (C_q), 137.1 (C_q), 136.0 (C_q), 130.7 (CH), 130.6 (CH), 130.5 (CH), 127.3 (CH), 126.2 (CH), 125.6 (CH), 106.0 (CH), 52.3 (CH_3), 51.3 (CH), 34.1 (CH_2, *E*), 31.1 (CH_2, *E*), 29.0 (CH_2, *Z*), 26.5 (CH_2, *Z*), 21.0 (CH_3).

IR (ATR): 1732, 1518, 1434, 1495, 1231, 1152, 1023, 916, 753, 624 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 365 (10) $[M+Na]^+$, 343 (100) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{19}H_{23}N_2O_4^+$ $[M+H]^+$ 343.1652, found 343.1655.



(*Z*)-Dimethyl 2-{4-[2-fluoro-6-(pyridin-2-yl)phenyl]but-2-en-1-yl}malonate [(*Z*)-153fa]:

The general procedure **F** was followed using 2-(3-fluorophenyl)pyridine (**152f**) (42.5 mg, 0.25 mmol) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (55.2 mg, 0.30 mmol). Isolation by

column chromatography (*n*-hexane/EtOAc: 10/1->7/1->5/1) yielded (*Z*)-**153fa** (51.8 mg, 58%, *E*/*Z* = 1:7) and (*Z*)-**153fa'** (12.5 mg, 14%, *E*/*Z* = 1:5) as yellow oils.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.69 (ddd, *J* = 4.3, 1.6, 0.8 Hz, 1H), 7.79–7.72 (m, 1H), 7.38–7.26 (m, 2H), 7.09–6.95 (m, 3H), 5.57 (dtt, *J* = 15.2, 7.2, 1.4, 0.13H, *E*), 5.46 (dtt, *J* = 10.8, 7.2, 1.4, 0.87H, *Z*), 5.34–5.16 (m, 1H), 3.69 (s, 5.20H, *Z*), 3.64 (s, 0.80H, *E*), 3.51 (d, *J* = 7.2 Hz, 1.74H, *Z*), 3.38 (d, *J* = 7.2 Hz, 0.26H, *E*), 3.28 (t, *J* = 7.7 Hz, 1H), 2.49 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 2H).

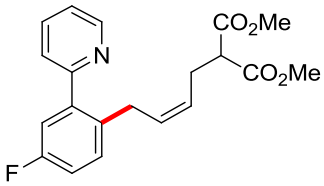
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.3 (C_q), 161.5 (C_q, $^{1}J_{C-F}$ = 245.1 Hz), 158.6 (C_q, $^{4}J_{C-F}$ = 3.0 Hz), 149.3 (CH), 142.4 (C_q, $^{3}J_{C-F}$ = 3.8 Hz), 136.5 (CH), 130.5 (CH), 127.4 (CH, $^{3}J_{C-F}$ = 9.2 Hz), 126.0 (C_q, $^{2}J_{C-F}$ = 17.0 Hz), 125.5 (CH, $^{4}J_{C-F}$ = 3.2 Hz), 124.8 (CH), 124.2 (CH), 122.1 (CH), 115.3 (CH, $^{2}J_{C-F}$ = 22.5 Hz), 52.5 (CH_3), 51.4 (CH), 31.6 (CH_2, *E*), 29.0 (CH_2, *E*), 26.5 (CH_2, *Z*), 24.2 (CH_2, *Z*).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = –116.4 (*Z*), –116.7 (*E*).

IR (ATR): 1732, 1585, 1565, 1471, 1434, 1232, 1194, 1150, 749 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 380 (60) $[M+Na]^+$, 358 (100) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{20}H_{21}FNO_4^+$ $[M+H]^+$ 358.1449, found 358.1450.



(*Z*)-Dimethyl 2-{4-[4-fluoro-2-(pyridin-2-yl)phenyl]but-2-en-1-yl}malonate [(*Z*)-153'fa]:

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.67 (ddd, *J* = 4.3, 1.6, 0.8 Hz, 1H), 7.77–7.71 (m, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.26 (ddd, *J* = 4.2, 2.4, 1.4 Hz, 1H), 7.22 (dd, *J* = 6.2, 3.8 Hz, 1H), 7.16–7.02 (m, 2H), 5.57 (dtt, *J* = 15.3, 7.0, 1.2, 0.16H, *E*), 5.45 (dtt, *J* = 10.8, 7.0, 1.2, 0.84H, *Z*), 5.27–5.08 (m, 1H), 3.70 (s, 5.17, *Z*), 3.65 (s, 0.83H, *E*), 3.51 (d, *J* = 7.0 Hz, 2H), 3.29 (dd, *J* = 7.6 Hz, 1H), 2.48 (ddd, *J* = 7.3, 7.2, 1.2 Hz, 2H).

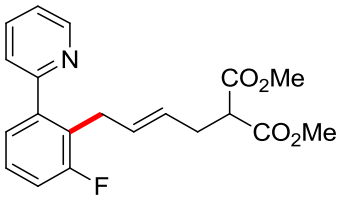
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.3 (C_q), 161.1 (C_q, $^{1}J_{C-F}$ = 245.1 Hz), 158.6 (C_q, $^{4}J_{C-F}$ = 4.4 Hz), 149.3 (CH), 141.6 (C_q, $^{3}J_{C-F}$ = 4.6 Hz), 136.6 (CH), 134.0 (CH), 131.6 (CH), 131.2 (C_q, $^{4}J_{C-F}$ =

7.7 Hz), 125.2 (CH), 124.1 (CH), 122.2 (CH), 116.4 (CH, $^{2}J_{C–F}$ = 22.3 Hz), 115.3 (CH, $^{2}J_{C–F}$ = 22.3 Hz), 52.5 (CH_3), 51.5 (CH), 35.5 (CH_2, *E*), 31.7 (CH_2, *E*), 30.2 (CH_2, *Z*), 26.6 (CH_2, *Z*).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = –117.3 (*Z*), –117.2 (*E*).

IR (ATR): 1735, 1452, 1436, 1372, 1237, 1154, 1045, 778 cm^{-1}.

HR-MS (ESI) *m*/*z* calcd. for $C_{20}H_{21}FNO_4^+$ [M+H$^+$] 358.1449, found 358.1456.



(*E*,*Z*)-Dimethyl 2-{4-[2-fluoro-6-(pyridin-2-yl)phenyl]but-2-en-1-yl}malonate [(*E*,*Z*)-153fa']:

The general procedure **G** was followed using 2-(3-fluorophenyl)pyridine (**152f**) (42.5 mg, 0.25 mmol) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (55.2 mg, 0.30 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1->7/1->5/1) yielded (*E*,*Z*)-**153fa'** (21.4 mg, 24%, *E*/*Z* = 1:1) and (*E*,*Z*)-**153fa"** (5.4 mg, 6%, *E*/*Z* = 1:1).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.67 (ddd, *J* = 4.3, 1.6, 0.8 Hz, 1H), 7.77–7.71 (m, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.26 (ddd, *J* = 4.2, 2.4, 1.4 Hz, 1H), 7.22 (dd, *J* = 6.2, 4.2 Hz, 1H), 7.16–7.02 (m, 2H), 5.57 (dtt, *J* = 15.2, 7.2, 1.4, 0.53H, *E*), 5.46 (dtt, *J* = 10.8, 7.2, 1.4, 0.47H, *Z*), 5.27–5.08 (m, 1H), 3.70 (s, 2.66H, *Z*), 3.64 (s, 3.34H, *E*), 3.50 (d, *J* = 7.0 Hz, 0.84H, *Z*), 3.38 (d, *J* = 7.0 Hz, 1.16H, *E*), 3.33−3.25 (m, 1H), 2.48 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 2H).

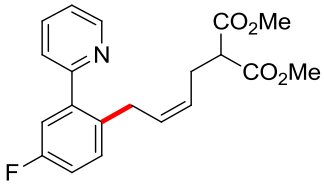
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.3 (C_q), 161.4 (C_q, $^{1}J_{C–F}$ = 245 Hz), 158.5 (C_q, $^{4}J_{C–F}$ = 3.3 Hz), 149.3 (CH), 142.5 (C_q, $^{3}J_{C–F}$ = 3.8 Hz), 136.5 (CH), 130.5 (CH), 127.4 (CH, $^{3}J_{C–F}$ = 9.2 Hz), 126.0 (C_q, $^{2}J_{C–F}$ = 17.2 Hz), 125.5 (CH, $^{4}J_{C–F}$ = 3.2 Hz), 124.8 (CH), 124.2 (CH), 122.1 (CH), 115.3 (CH, $^{2}J_{C–F}$ = 22.8 Hz), 52.5 (CH_3, *Z*), 52.4 (CH_3, *E*), 51.8 (CH, *E*), 51.5 (CH, *Z*), 31.8 (CH_2, *E*), 29.0 (CH_2, *E*), 26.5 (CH_2, *Z*), 24.2 (CH_2, *Z*).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = –116.4 (*Z*), –116.7 (*E*).

IR (ATR): 1735, 1452, 1436, 1372, 1237, 1154, 1045, 778 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 380 (60) [M+Na]$^+$, 358 (100) [M+H]$^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{20}H_{21}FNO_4^+$ [M+H$^+$] 358.1449, found 358.1456.



(*E*,*Z*)-Dimethyl 2-{4-[4-fluoro-2-(pyridin-2-yl)phenyl]but-2-en-1-yl}malonate [(*E*,*Z*)-153fa'']:

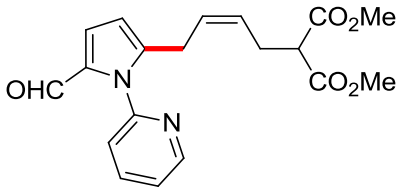
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.67 (ddd, *J* = 4.3, 1.6, 0.8 Hz, 1H), 7.77–7.71 (m, 1H), 7.39–7.32 (m, 1H), 7.31–7.27 (m, 1H), 7.25–7.19 (m, 1H), 7.12–6.98 (m, 2H), 5.57 (dtt, *J* = 15.2, 7.2, 1.4, 0.50H, *E*), 5.46 (dtt, *J* = 10.8, 7.2, 1.4, 0.50H, *Z*), 5.34–5.21 (m, 1H), 3.71 (s, 3.00H, *Z*), 3.68 (s, 3.00H, *E*), 3.47 (d, *J* = 7.0 Hz, 1H), 3.38–3.33 (m, 2H), 2.60–2.49 (m, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.3 (C_q), 161.1 (C_q, $^{1}J_{C-F}$ = 245.4 Hz), 158.6 (C_q, $^{4}J_{C-F}$ = 4.4 Hz), 149.3 (CH), 141.6 (C_q, $^{3}J_{C-F}$ = 4.6 Hz), 136.6 (CH), 134.0 (CH), 131.6 (CH), 131.2 (C_q, $^{4}J_{C-F}$ = 7.7 Hz), 125.2 (CH), 124.1 (CH), 122.2 (CH), 116.4 (CH, $^{2}J_{C-F}$ = 22.3 Hz), 115.3 (CH, $^{2}J_{C-F}$ = 22.3 Hz), 52.5 (CH_3), 51.5 (CH), 35.5 (CH_2, *E*), 31.7 (CH_2, *E*), 30.2 (CH_2, *Z*), 26.6 (CH_2, *Z*).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = –117.3 (*Z*), –117.2 (*E*).

IR (ATR): 1735, 1452, 1436, 1372, 1237, 1154, 1045, 778 cm^{-1}.

HR-MS (ESI) *m*/*z* calcd. for $C_{20}H_{21}FNO_4^+$ [M+H$^+$] 358.1449, found 358.1456.



(*Z*)-dimethyl 2-(4-(5-formyl-1-(pyridin-2-yl)-*1H*-pyrrol-2-yl)but-2-en-1-yl)malonate (153ga):

The representative procedure **F** was followed using 1-phenyl-*1H*-pyrrole-2-carbaldehyde (**152g**) and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**138a**) (55.2 mg, 0.30 mmol). (85 mg, 0.50 mmol), Isolation by column chromatography(n-hexane/EtOAc: 10/1->7/1->5/1) yielded (*E*,*Z*)-**153ga** (138 mg, 78%, *Z*/*E* = 1:1) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.39 (s, 1H), 8.60–8.53 (m, 1H), 7.82 (tdd, *J* = 7.6, 5.6, 1.9 Hz, 1H), 7.40–7.33 (m, 1H), 7.32–7.24 (m, 1H), 7.01 (d, *J* = 3.9 Hz, 1H), 6.15 (dd, *J* = 6.9, 3.9 Hz, 1H), 5.55–

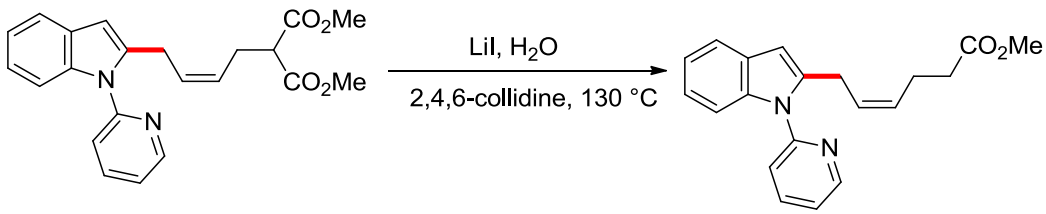
5.43 (m, 1H), 5.40–5.30 (m, 1H), 3.67 (s, 6H), 3.39–3.25 (m, 1H), 3.28-3.18 (m, 2H), 2.49 (dd, *J* = 12.5, 7.0 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 177.7 (CHO), 168.9 (C_q), 150.6 (C_q), 149.0 (CH), 142.4 (C_q), 138.0 (CH), 132.9 (C_q), 128.4 (CH), 127.6 (CH), 126.9 (CH), 123.6 (CH), 122.8 (CH), 109.8 (CH), 52.5 (CH_3), 51.5 (CH), 30.0 (CH_2), 25.0 (CH_2).

IR (ATR): 1731, 1517, 1434, 1394, 1271, 1022, 760, 623 cm^{-1}.

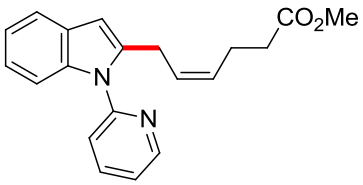
HR-MS (ESI) m/z calcd for $C_{19}H_{21}N_2O_5^+$ [M+H$^+$] 357.1445, found 357.1443.

Decarboxylation



(*Z*)-**151aa** (*Z*)-**S-1**

A mixture of dimethyl (*Z*)-2-{4-[1-(pyridin-2-yl)-1*H*-indol-2-yl]but-2-en-1-yl}malonate (**151aa**) (113 mg, 300 µmol, 1.0 equiv), LiI (60.2 mg, 450 µmol, 1.5 equiv) and H_2O (10.8 µl, 600 µmol, 2.0 equiv) in 2,4,6-collidine (2.0 mL, 0.15 M) was stirred at 140 °C for 24 h. At ambient temperature, the mixture was diluted with EtOAc (5.0 mL), washed four times successively with 1 M HCl (5.0 mL) and *sat*. $NaHCO_3$/brine (1:3, 5.0 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the product **S-1** as a pale yellow liquid (72.0 mg, 75%).



(*Z*)-Methyl 6-[1-(pyridin-2-yl)-1*H*-indol-2-yl]hex-4-enoate (S-1):

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.91–7.83 (m, 1H), 7.55 (ddd, *J* = 6.0, 3.1, 0.7 Hz, 1H), 7.43 (ddd, *J* = 3.9, 2.0, 1.0 Hz, 1H), 7.34–7.27 (m, 2H), 7.12–7.07 (m, 2H), 6.42 (d, *J* = 1.0 Hz, 1H), 5.59–5.49 (m, 1H), 5.46–5.34 (m, 1H), 3.65 (s, 3H), 3.64–3.61 (m, 2H), 2.34–2.29 (m, 4H).

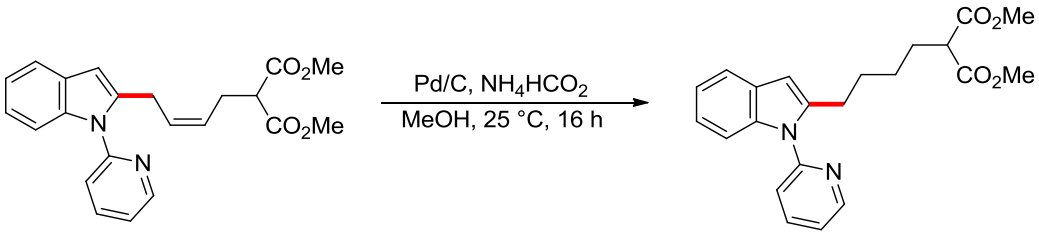
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 173.3 (C_q), 151.3 (C_q), 149.6 (CH), 139.5 (CH), 138.1 (C_q), 137.3 (CH), 129.2 (CH), 128.5 (C_q), 127.1 (CH), 121.9 (CH), 121.7 (CH), 121.0 (CH), 120.6 (CH), 119.9 (CH), 110.0 (C_q), 102.7 (CH), 51.6 (CH_2), 34.0 (CH_2), 26.0 (CH_3), 22.8 (CH_2).

IR (ATR): 1733, 1586, 1469, 1455, 1435, 1151, 1024, 972, 747 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 321 (20) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{20}H_{21}N_2O_2^+$ $[M+H]^+$ 321.1598, found 321.1598.

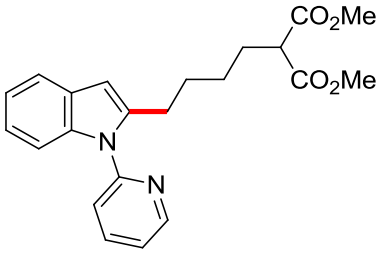
Hydrogenation



(Z)-**151aa** **S-2**

To a solution of dimethyl (*Z*)-2-{4-[1-(pyridin-2-yl)-1*H*-indol-2-yl]but-2-en-1-yl}malonate [(*Z*)-**151aa**] (94.5 mg, 0.25 mmol) in MeOH (1.0 mL) was added Pd/C (9.5 mg, 10 wt.-%) and ammonium formate (79.0 mg, 5.0 equiv). The mixture was stirred at 25 °C for 20 h and then filtered through a short pad of celite. The residue was washed with EtOAc (10 mL), filtered and the combined

filtrate was concentrated *in vacuo*. The crude mixture was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc: 5/1) to yield **S-2** (88.4 mg, 93%) as a yellow oil.



Dimethyl 2-{4-[1-(pyridin-2-yl)-1*H*-indol-2-yl]butyl}malonate (S-2):

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.9, 1.9, 0.7 Hz, 1H), 7.89 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.58–7.56 (m, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.34–7.31 (m, 2H), 7.14–7.11 (m, 2H), 6.44 (d, *J* = 0.6 Hz, 1H), 3.71 (s, 6H), 3.31 (t, *J* = 7.7 Hz, 1H), 2.85 (ddd, *J* = 7.6,7.5, 1.0 Hz, 2H), 1.91–1.84 (m, 2H), 1.64–1.57 (m, 2H), 1.37–1.30 (m, 2H).

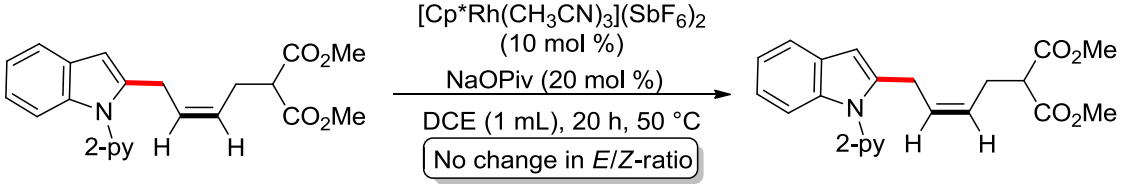
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.9 (C_q), 151.5 (C_q), 149.7 (CH), 141.1 (C_q), 138.3 (CH), 137.3 (C_q), 128.6 (C_q), 122.1 (CH), 121.7 (CH), 121.1 (CH), 120.6 (CH), 119.9 (CH), 110.1 (CH), 102.2 (CH), 52.5 (CH_3), 51.6 (CH), 28.6 (CH_2), 28.1 (CH_2), 27.2 (CH_2), 26.9 (CH_2).

IR (ATR): 1731, 1570, 1469, 1435, 1148, 909, 781, 731 cm^{-1}.

MS (ESI) *m*/*z* (relative intensity): 403 (100) $[M+Na]^+$, 381 (20) $[M+H]^+$.

HR-MS (ESI) *m*/*z* calcd. for $C_{22}H_{25}N_2O_4^+$ $[M+H]^+$ 381.1809, found 381.1810.

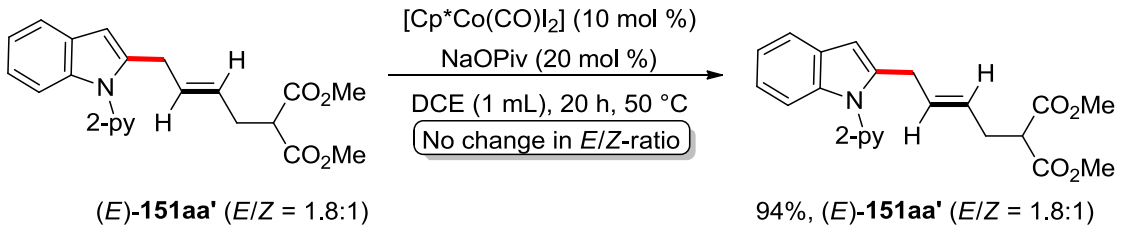
Isomerization Experiments



(*Z*)-**151aa** (*E*/*Z* = 1:11) (*Z*)-**151aa** (*E*/*Z* = 1:11): 89%

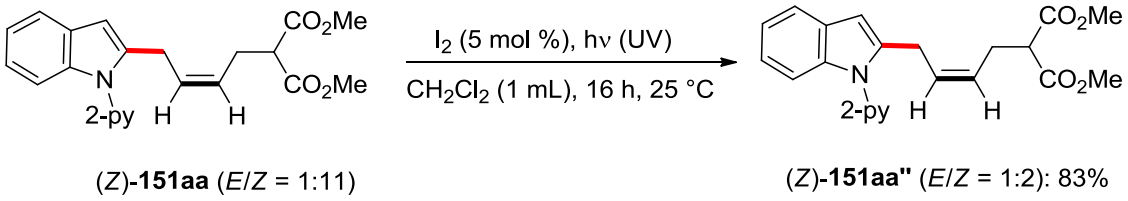
A solution of (*Z*)-**151aa** (94.5 mg, 0.25 mmol, 1.0 equiv), $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (20.0 mg, 10 mol %) and NaOPiv (6.2 mg, 20 mol %) in DCE (1 mL, 0.25 M) was stirred at 50 °C for 20 h. At

ambient temperature, the solvent was removed and the crude mixture was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc: 3/1) to yield (*Z*)-**151aa** (84.1 mg, 89%, *E*/*Z* = 1:11) as a pale yellow oil.



(*E*)-**151aa'** (*E*/*Z* = 1.8:1) 94%, (*E*)-**151aa'** (*E*/*Z* = 1.8:1)

A solution of (*E*)-**151aa'** (94.5 mg, 0.25 mmol, 1.0 equiv), [Cp*Co(CO)I_2] (11.9 mg, 10 mol %) and NaOPiv (6.2 mg, 20 mol %) in DCE (1 mL, 0.25 M) was stirred at 50 °C for 20 h. At ambient temperature, the solvent was removed and the crude mixture was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc: 3/1), yielding (*E*)-**151aa'** (88.9 mg, 94%, *E*/*Z* = 1.8:1) as a yellow oil.



(*Z*)-**151aa** (*E*/*Z* = 1:11) (*Z*)-**151aa''** (*E*/*Z* = 1:2): 83%

A solution of (*Z*)-**151aa** (94.5 mg, 0.25 mmol, 1.0 equiv) and I_2 (1.6 mg, 5 mol %) in CH_2Cl_2 (1 mL, 0.25 M) was irradiated by UV-light (254 nm) at 25 °C for 16 h. The solvent was removed and the crude mixture was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1) to yield (*Z*)-**151aa''** (78.4 mg, 83%, *E*/*Z* = 1:2) as a yellow oil.

6 References

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I will dedicate this thesis to my family!

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3. Publication

1) **Q. Bu**,' T. Rogge,' V. Kotek, L. Ackermann, *"Distal Weak Coordination of Acetamides in Ruthenium(II)-Catalyzed C–H Activation Processes" Angew. Chem. Int. Ed.* **2018**, 57, 765-768. 'Both authors contributed equally.
2) D. Zell,' **Q. Bu**,' M. Feldt, L. Ackermann, *"Mild C-H/C-C Activation by (Z)-Selective Cobalt-Catalysis" Angew. Chem. Int. Ed.* **2016**, 55, 7408-7412. 'Both authors contributed equally.
3) Cobalt-catalyzed C–H arylations. *Manuscript is in preparation.*
4) Ruthenium–catalyzed C–H oxygenations. *Manuscript is in preparation.*
5) A conference paper (accepted by The 13th National homogeneous catalysis symposium, 09. 2013, Suzhou).
6) A patent Applications has been granted, Chinese Patent Application No: CN103613479A.

Erklärung

Ich versichere, dass ich die vorliegende Dissertation in dem Zeitraum von Oktober 2014 bis Oktober 2018 am Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen

auf Anregung und unter Anleitung von

Herrn Prof. Dr. Lutz Ackermann

selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel und Quellen verwendet habe.

Göttingen, den 20.09.2018