Ruthenium(II)- and Copper(I)-Catalyzed C–H Functionalizations

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December 14th, 2015

Declaration

I hereby declare that the thesis:

''Ruthenium(II)- and Copper(I)-Catalyzed C–H Functionalizations''

has been written independently and with no other sources and aids than quoted.

Fanzhi Yang

October 2015, Göttingen

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I will dedicate this thesis to my family!

Fanzhi Yang

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Contents

1. Introduction

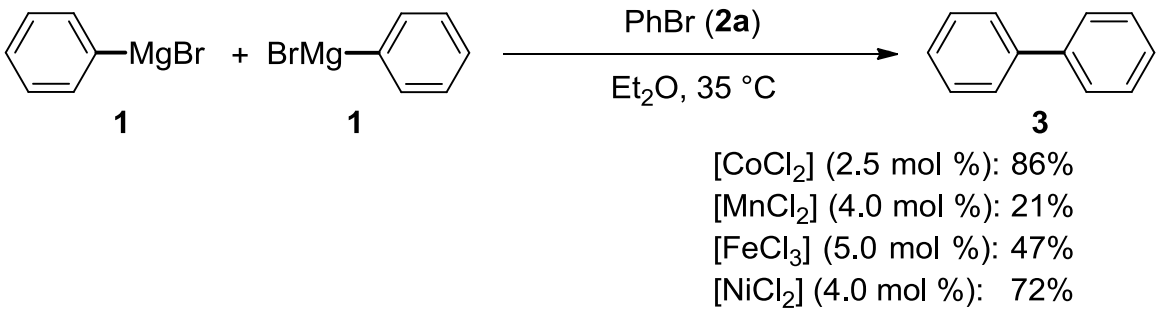
1.1 Transition Metal-Catalyzed Cross-Couplings and C–H Functionalizations

Although the concept of green chemistry—which is also known as sustainable chemistry—was introduced by Ciamician as early as the beginning of the 20th century,[1] today we have to face the global problem of environmental pollution. Chemical industries have contributed a significant proportion to the contaminants. Therefore, sustainable chemistry should not only be an urgent discipline, but more important to be the ultimate goal of all chemists.[2]

Besides the twelve principles of sustainable chemistry,[3] another two points should be especially noted: High selectivity and low cost. The first aspect will definitely reduce chemical wastes by inhibiting the generation of side products. The second aspect should be very important for industries where profits are always concerned. For example, industrial methanol synthesis commonly utilizes the inelegant syngas processes rather than the more atom economic catalytic oxidation of methane.[4] Thus, economically acceptable catalytic systems will facilitate the innovation of more environmentally-benign chemical processes.

Arenes are important in human life as key structural components of numerous natural products, pharmaceutical agents, and organic materials.[5] Therefore, it is quite reasonable and essential to study the synthesis and modification of arenes.[6] The Wurtz-Fittig reaction of aryl halides with alkyl halides and sodium provided a way to synthesize alkylated arenes.[7] At the beginning of the 20th century, Ullmann and Goldberg developed the C–C, C–N, and C–O couplings with aryl halides using stoichiometric or catalytic amounts of copper at a reaction temperature of more than 200 °C.[8-11]

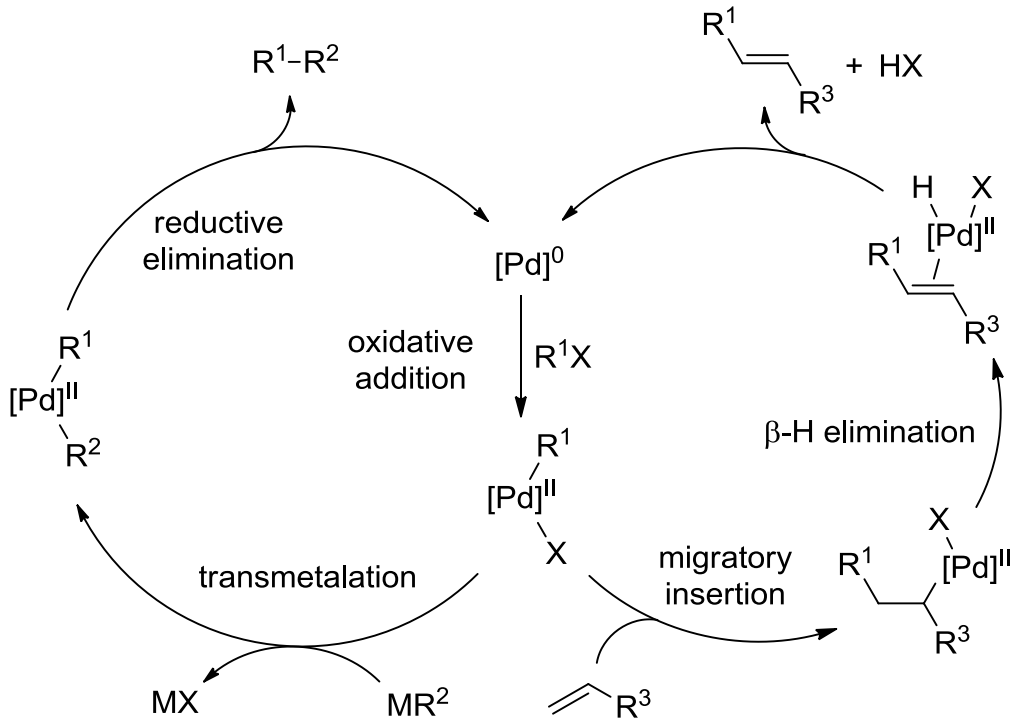
The combination of transition metal and organometallic reagents facilitated arene–arene coupling processes. During the 1940s, Kharasch et al. observed that catalytic amounts of $CoCl_2$, $MnCl_2$, $FeCl_3$ or $NiCl_2$ allowed for efficient homo-couplings of Grignard reagents **1**.[12] Organic halides **2**, such as bromo or chlorobenzene acted as terminal oxidants in these reactions.



Scheme 1.1: Transition metal-catalyzed homo-coupling of Grignard reagents **1**.

The sudden boom of transition metal-catalyzed cross-couplings started in the 1960s. In 1965, van Helden and Verberg reported the palladium-mediated intermolecular oxidative homo-coupling between arenes.[13] In the same year, Heck reported palladium-mediated oxidative arylation of alkenes employing toxic organomercury reagent.[14] In 1969, Fujiwara and Moritani discovered the oxidative coupling of alkenes with arenes using catalytic amounts of palladium complexes.[15] Mizoroki[16] and Heck[17] independently developed the palladium(0)-catalyzed arylation of alkene with iodoarene in the early 1970s. In 1972, Kumada, Tamao,[18] and Corriu[19] discovered the cross-coupling between arene halides and Grignard reagents with nickel or palladium as the catalysts. The palladium- and copper-catalyzed Sonogashira-Hagihara coupling between terminal alkynes and iodoarenes was invented in 1975.[20] The palladium-catalyzed cross-couplings between aryl and alkenyl halides and other organometallic reagents, such as organoaluminium,[21] organozinc,[22] organotin,[23] organoboron,[24] or organosilicon,[25] were developed by Negishi, Stille, Suzuki, and Hiyama, respectively.

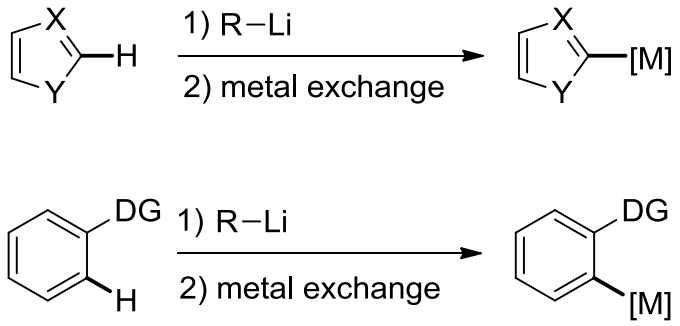
A generalized catalytic cycle of palladium-catalyzed cross-couplings is shown below (Scheme 1.2). The key steps are oxidative addition, transmetalation, and reductive elimination. The Mizoroki-Heck reaction involves oxidative addition, migratory insertion, and β-H elimination.



Scheme 1.2: Proposed mechanism for palladium-catalyzed cross-couplings (left cycle) and Mizoroki-Heck reaction (right cycle).

As one of the greatest innovations of the 20th century,[26] transition metal-catalyzed cross-coupling is not a perfect tool mainly due to the organometallic reagents which need prior preparation and careful handling. In comparison with cross-coupling reactions, C–H functionalization is definitely more atom-economic. For a long period, C–H bond has only been considered as an inert bond because of relatively high dissociation energy (methane: 439 kJ/mol; benzene: 473 kJ/mol) as well as low acidity. Therefore, it is a formidable task and was defined as one of the 'Holy Grails' in chemistry in the 1990s.[27]

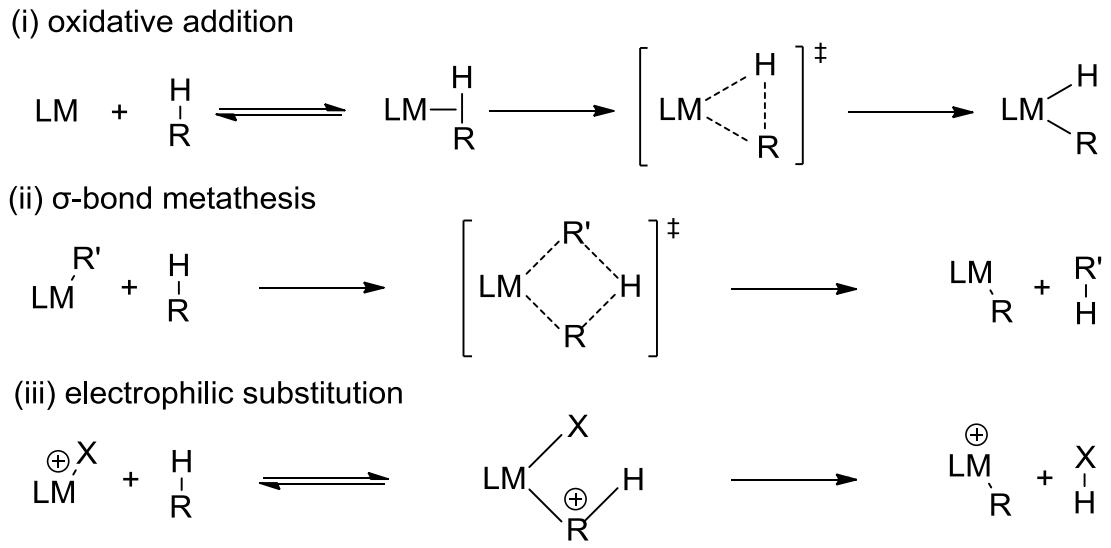
Strong bases can be utilized for the metalations of some heteroarens bearing acidic C–H bonds. Concerning the less acidic aryl C–H bonds, a coordinating group will site-selectively direct the more alkaline organometallic bases, such as organo lithium reagents, to its *ortho* position.[28] However, aryl halides maybe converted to arynes under strongly alkaline reaction conditions, which will bring about chemo- and site-selectivity problems.



Scheme 1.3: Deprotonation and metalation with strong base.

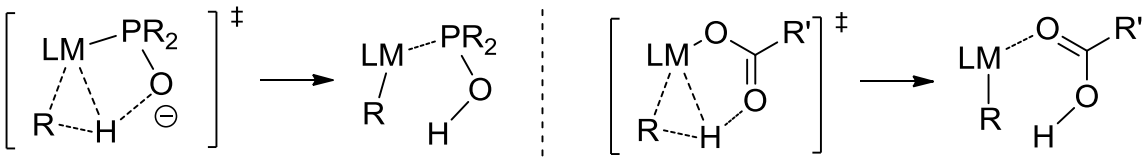
An alternative for achieving mild C–H metalations is to use catalytic amounts of transition metals. The last 20 years have witnessed the great development of C–H bond functionalizations.[29-41] As a robust synthetic tool, C–H bond functionalizations utilizing various transition metal catalysts have been applied in the synthesis of natural products, pharmaceuticals, and materials synthesis.[42-48]

It is important to understand how the C–H bond is cleaved by transition metals. There are three generally recognized categories of C–H bond metalation mechanism (Scheme 1.4):[49] (i) The most common mechanism involves oxidative addition (OA), which starts by coordination of the C–H bond to the vacant site of the metal. This mechanism is typical for electron-rich and low-valent complexes of the late transition metals. As oxidative process is not possible for early transition metals with d0 electron configuration, the predominant mechanism is (ii) *σ*-bond metathesis (SBM). (iii) A C–H bond can be cleaved by late- or post-transition metals in strong polar medium in an electrophilic activation (EA) manner.



Scheme 1.4: C–H bond metalation mechanisms.

Recent mechanistic studies indicated a base-assisted C–H bond metalation mechanism, of which the determining factor is the assistance of a bifunctional ligand bearing an additional Lewis-basic heteroatom, such as secondary phosphine oxides (SPOs) or carboxylates.[50] This mechanism will be comprehensively discussed in the next section.



Scheme 1.5: SPOs- or carboxylates-assisted C–H bond metalation.

Different pathways have been proposed for the base-assisted C–H bond metalations (Figure 1.1): Fagnou proposed a concerted-metalation-deprotonation (CMD) process.[51] DFT calculations from Davies and Macgregor were rationalized by an ambiphilic metal ligand activation process (AMLA).[52,53] Agostic interaction enhances the acidity of hydrogen which will then readily transfer to the ligand. Metals with a monodentate Lewis base ligand favor an internal electrophilic substitution pathway (IES).[54] The lone pair on ligand X forms an X–H bond, while the orbital making up the M–X bond turns into a coordinating lone pair.

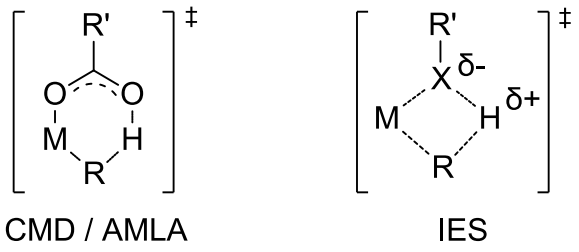
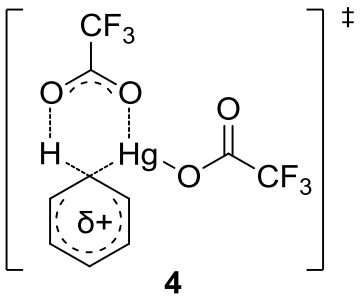


Figure 1.1: Proposed transition states of base-assisted methalation.

1.2 Carboxylate-Assisted C–H Bond Cleavage

1.2.1 Carboxylate-Assisted C–H Metalation

In 1980, Roberts and coworkers performed detailed kinetic studies on the mercuration of arenes by $Hg(O_2CCF_3)$.[55] Previous kinetic isotope effects (KIE) studies by Kresge et al. indicated the proton transfer to be the rate determining step.[56] However, Roberts doubted the formation of a discrete *σ*-complex, therefore they rationalized their observations with transition state **4** involving a synchronous bond cleavage and bond formation which was suggested by Winstein and Traylor in a study of the reverse reaction, namely protodemercuration of diphenylmercury.[57]

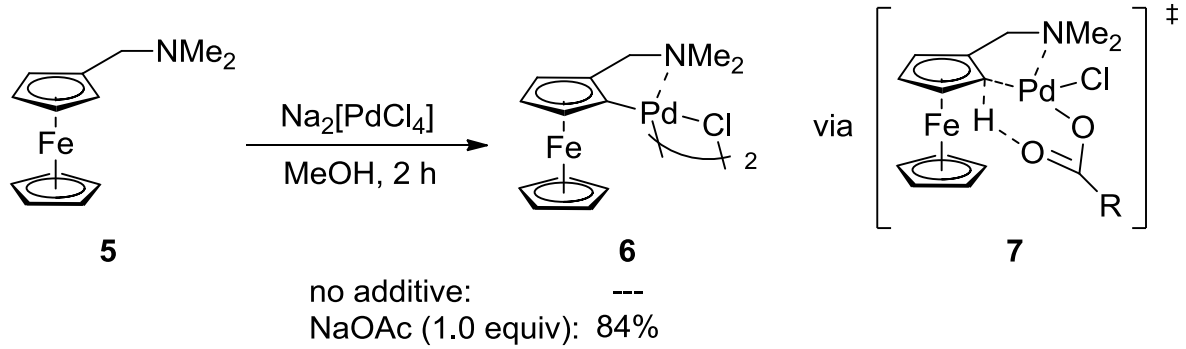


4

Figure 1.2: Proposed transition state **4** of arene mercuration.

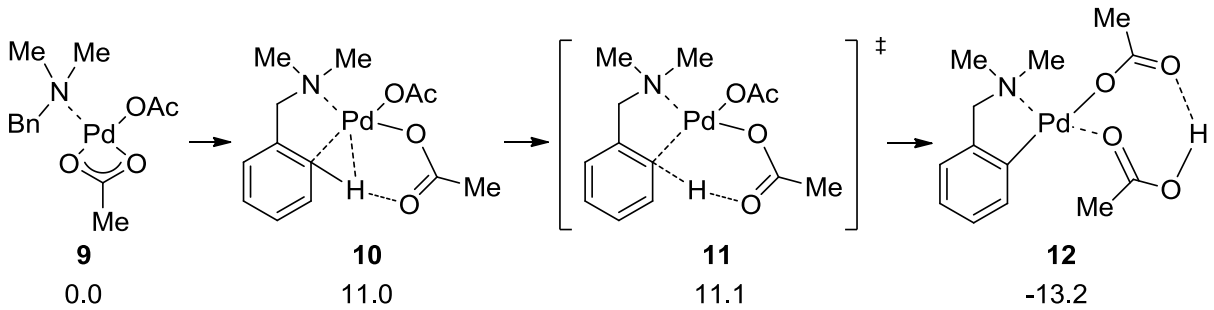
It was recognized in the 1960s that there is a strong resemblance between the palladation and mercuration of benzene.[58] Shaw and coworkers performed pioneering studies in the

synthesis of cyclometalated compounds in the early 1970s.[59] For instance, the cyclometalation with a palladium complex of *N,N*-dimethylaminomethylferrocene **5** occurred efficiently with the assistance of NaOAc (Scheme 1.6).[60] The effect of carboxylate-assisted intramolecular deprotonation was verified again in the amino acid salts-promoted palladation of amine **5** by Sokolov, Troitskaya, and Reutov in 1979.[61] It was proposed that the key C–H bond metalation occurred in a concerted fashion, as illustrated in transition-state structure **7**.



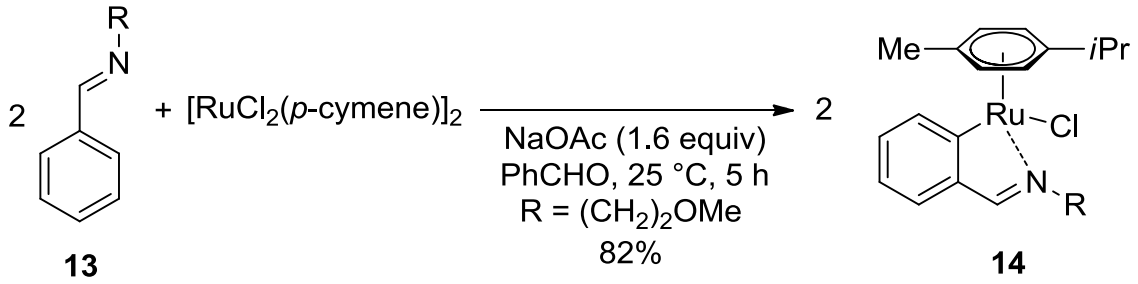
Scheme 1.6: Effect of stoichiometric NaOAc on the cyclopalladation of amine **5**.

Ryabov and coworkers investigated the mechanism of *ortho*-palladation reactions with *N,N*-dimethylbenzylamines **8** through kinetic studies. A KIE of k_H/k_D = 2.2 indicated that the C–H bond metalation is the rate-limiting step.[62,63] DFT calculations on the cyclometalation of *N,N*-dimethylbenzylamines **8** by $Pd(OAc)_2$ were later performed by Macgregor (Scheme 1.7). The AMLA mechanism was favored rather than a δ-intermediate pathway to allow for a facile proton transfer, thereby delivering cyclometalated complex **12**.[64]



Scheme 1.7: DFT calculations on the cyclometalation of *N,N*-dimethylbenzylamines. (Values in kcal/mol)

NaOAc can also facilitate C–H bond ruthenations under mild reaction conditions (Scheme 1.8). It was discovered by Davies et al. that with the assistance of NaOAc, solely *N*-alkyl-substituted imines could provide the desired ruthenacycles with $[RuCl_2(p\text{-cymene})]_2$ at ambient reaction temperature in a stoichiometric fashion.[65]

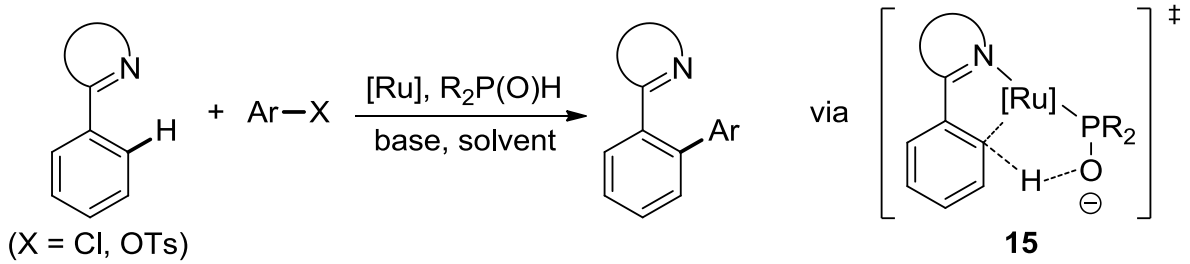


Scheme 1.8: Cycloruthenation with the assistance of NaOAc.

1.2.2 Carboxylate-Assisted Catalytic Reactions

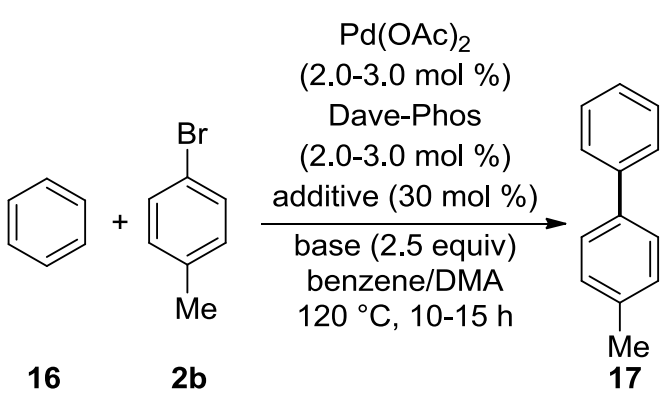
Lewis as well as Murai conducted pioneering studies in chelation-assisted ruthenium(0)-catalyzed C–H bond functionalizations.[66,67] During recent years, the Ackermann group and other groups have made stupendous contributions developing ruthenium(II) catalysis.[48, 68-72]

Primary studies from the Ackermann group highlighted a significant reaction rate acceleration applying secondary phosphine oxides (SPOs) as bifunctional preligands in ruthenium-catalyzed direct arylations (Scheme 1.9).[73-76]



Scheme 1.9: SPOs-assisted ruthenium-catalyzed C–H arylations.

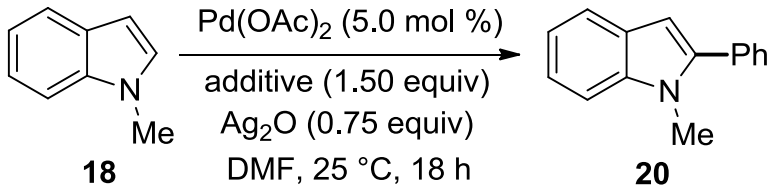
Later, Fagnou and coworkers tested different catalytic amounts of carboxylic acids in palladium-catalyzed direct arylations of unactivated arenes. The yield of the desired product was strongly affected by both the quantity and the nature of the acid (Scheme 1.10).[77] A concerted metalation-deprotonation (CMD) pathway was proposed in which pivalate served as a proton shuttle between arene and base.



base	additive	conversion (GC-MS)
K_2CO_3	—	0%
KOPiv	—	41%
K_2CO_3	AcOH	11%
K_2CO_3	*i*$PrCO_2H$	13%
K_2CO_3	PivOH	82%

Scheme 1.10: Effect of base and additive on palladium-catalyzed direct arylation.

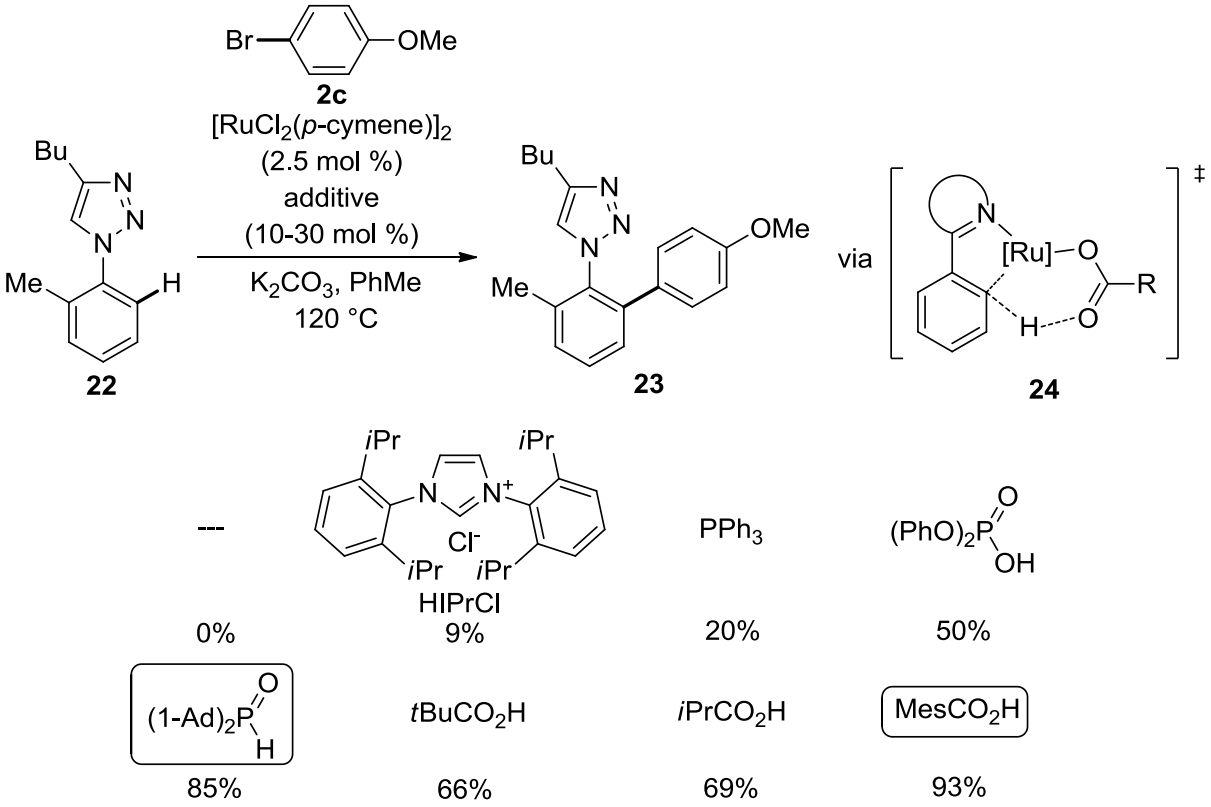
Site-selective direct C2 arylations of indoles were achieved at ambient temperature with aryl iodides as the substrates and Ag_2O as the base (Scheme 1.11). Different carboxylic acids were tested, of which electron-poor benzoic acids **21** delivered better yields than electron-rich benzoic acids.[78]



additive	conversion (GC)
—	12%
CH_3CO_2H	49%
2-$MeOC_6H_4CO_2H$	13%
4-$O_2NC_6H_4CO_2H$	81%
2-$O_2NC_6H_4CO_2H$	>99%

Scheme 1.11: Carboxylic acid-promoted palladium-catalyzed C2 arylation of indoles **18**.

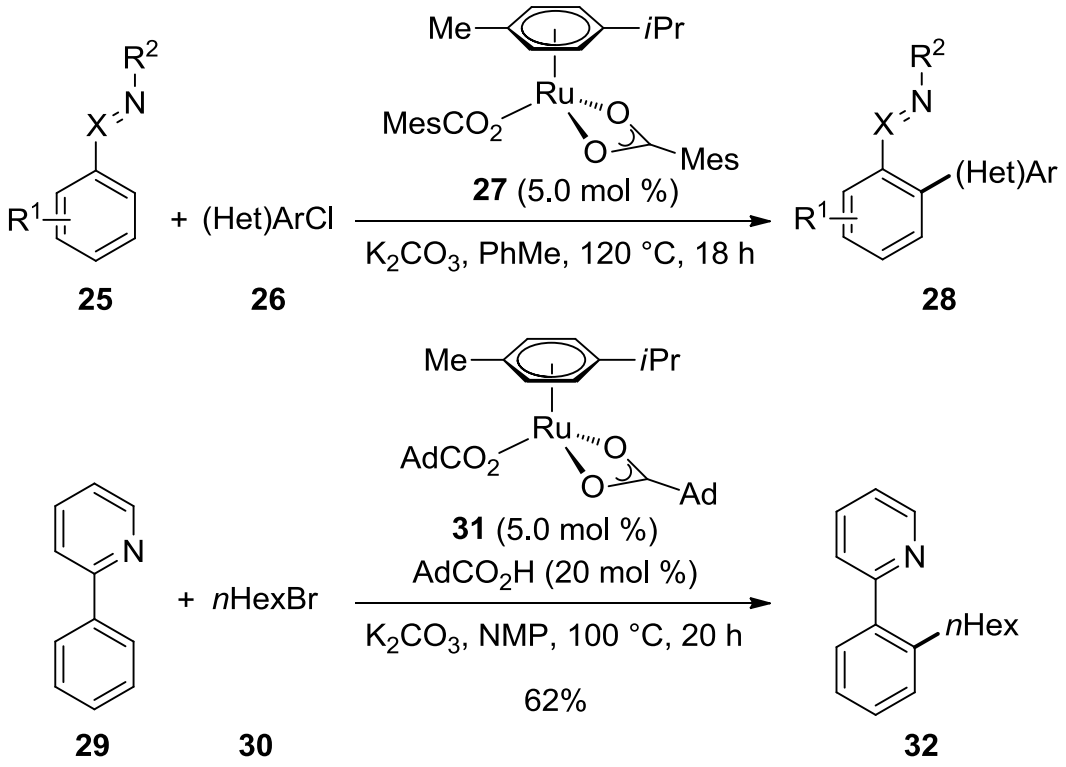
Based on the successful development of SPOs-assisted C–H functionalizations, the Ackermann group endeavored for general phosphine-free ruthenium-catalyzed direct arylations employing carboxylates as potential cocatalysts (Scheme 1.12).[79] Ligands such as tertiary phosphines or NHC precursors only performed poorly. While the sterically hindered SPO preligand $(1\text{-Ad})_2P(O)H$ derived ruthenium complex showed efficient catalytic activity. Interestingly, carboxylic acids were found to be effective cocatalysts with optimal results employing $MesCO_2H$.



Scheme 1.12: Effect of additives on ruthenium-catalyzed direct arylations.

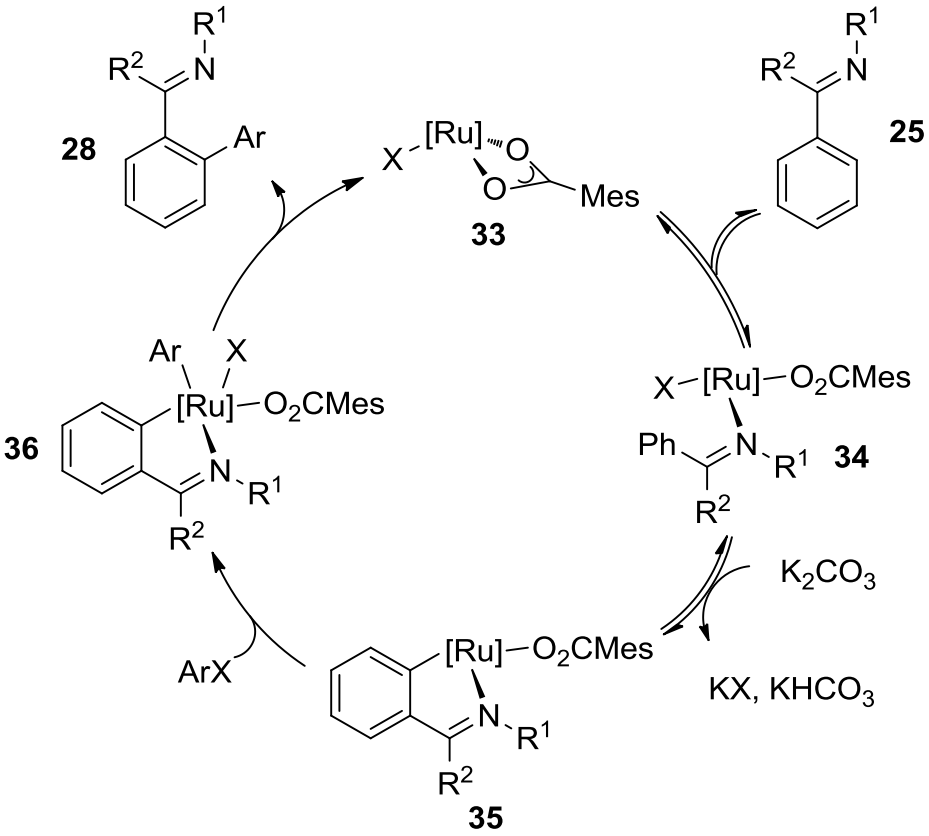
Several ruthenium(II) biscarboxylate complexes have been prepared by the Ackermann group, which turned out to be catalytically competents for C–H bond functionalizations (Scheme 1.13). Notably, well-defined ruthenium(II) complex **27** was applied in the direct arylation of various arenes with differently substituted (hetero)aryl chlorides in a highly regioselective fashion.[80] Another sterically hindered carboxylic acid $AdCO_2H$ derived

ruthenium(II) complex **31** was found to be an effective catalyst in the first direct arene alkylations with unactivated alkylhalides.[68,81]



Scheme 1.13: The application of well-defined ruthenium complex **27** and **31** in the direct arylation of arenes.

Based on experimental studies, Ackermann et al. proposed the catalytic cycle of carboxylate-assisted ruthenium(II)-catalyzed C–H arylation as shown in Scheme 1.14. First, reversible cyclometalation forms ruthenium(II) complex **35** through carboxylate-assisted deprotonation. Second, the ruthenium(II) complex **35** reacts in the rate limiting step with aryl halide to yield intermediate **36**. Third, reductive elimination releases the desired product and regenerates the active catalyst **33**.[80]



Scheme 1.14: Proposed mechanism for base-assisted ruthenium-catalyzed direct arylations, *p*-cymene was omitted, X = Cl or Br.

1.3 Transition Metal-Catalyzed Oxidative Coupling with Alkenes and Alkynes

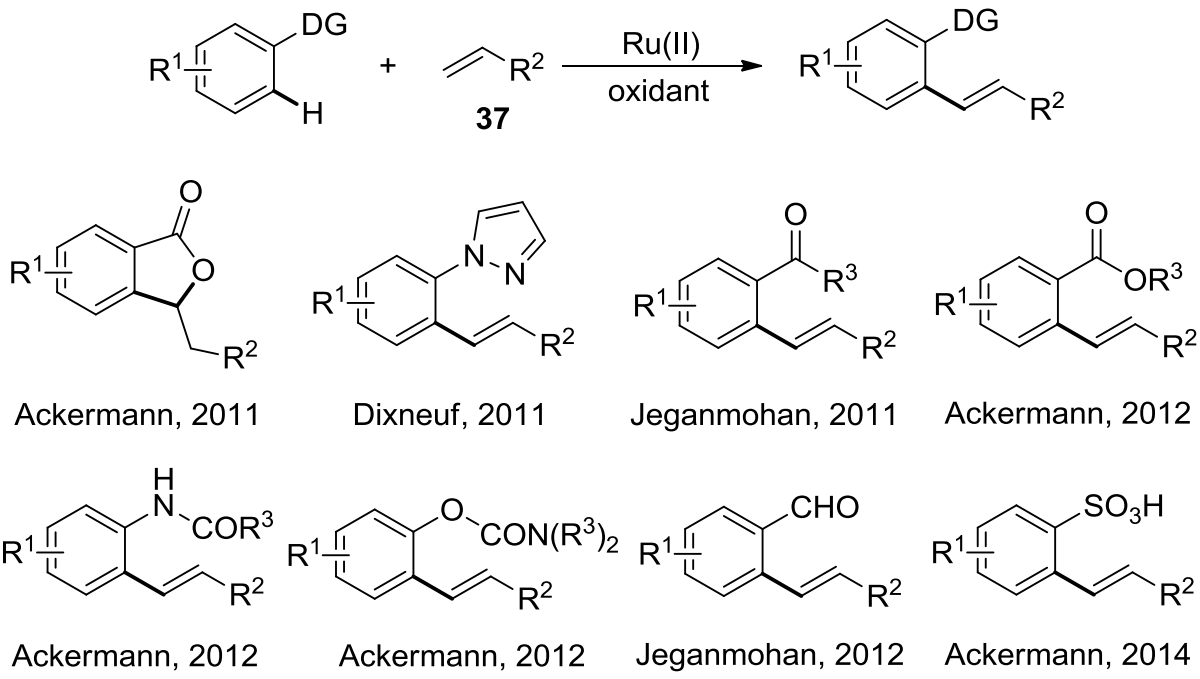
1.3.1 Transition Metal-Catalyzed Oxidative Alkenylation

Palladium-catalyzed oxidative cross-coupling reactions were discovered by Fujiwara and Moritani in the late 1960s.[82] Recent years have witnessed its wide application in the preparation of numerous synthetically and practically useful heterocycles, such as isoquinolines, isoquinolones, isocoumarins, α-pyrones and 2-pyridines.[71,83,84]

In 1979, Hong et al. reported rhodium-catalyzed styrene synthesis using simple arenes and ethylene in the presence of CO.[85] In 2007, Satoh and Miura reported the rhodium-catalyzed oxidative alkenylation of easily accessible benzoic acid employing acrylates, acryl amides or

nitriles as alkenylating reagent. The oxidant was stoichiometric amount of $Cu(OAc)_2 \cdot H_2O$ or air in the presence of catalytic $Cu(OAc)_2 \cdot H_2O$.[86] Later, Glorius and coworkers reported the rhodium-catalyzed alkenylations of acetanilides,[87] acetophenones and benzamides.[88]

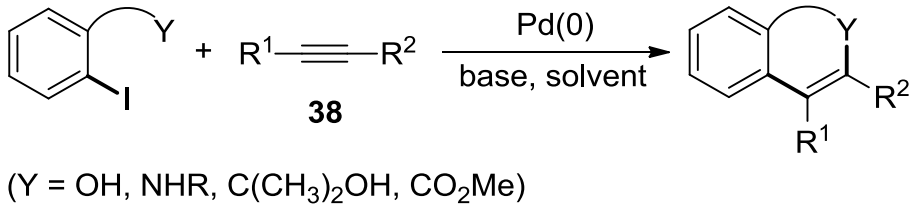
In 2001, Milstein and coworkers reported the ruthenium(0)-catalyzed oxidative alkenylation using arenes and acrylic esters.[89,90] In 2011, Ackermann et al. reported the first successful ruthenium(II)-catalyzed direct alkenylation of benzoic acids in non-toxic water.[91] Later, Ackermann and Miura independently developed the efficient ruthenium-catalyzed direct oxidative alkenylation of benzamides.[92,93] The ruthenium(II)-catalyzed alkenylation worked effectively with the chelation assistance of various directing groups, such as anilides,[92] *N*-containing hyterocycles,[94,95] carbamates,[96] esters,[97,98] phenones,[99] aldehydes,[100] or sulfonyls.[101]



Scheme 1.15: Selected recent examples of ruthenium(II)-catalyzed oxidative alkenylations.

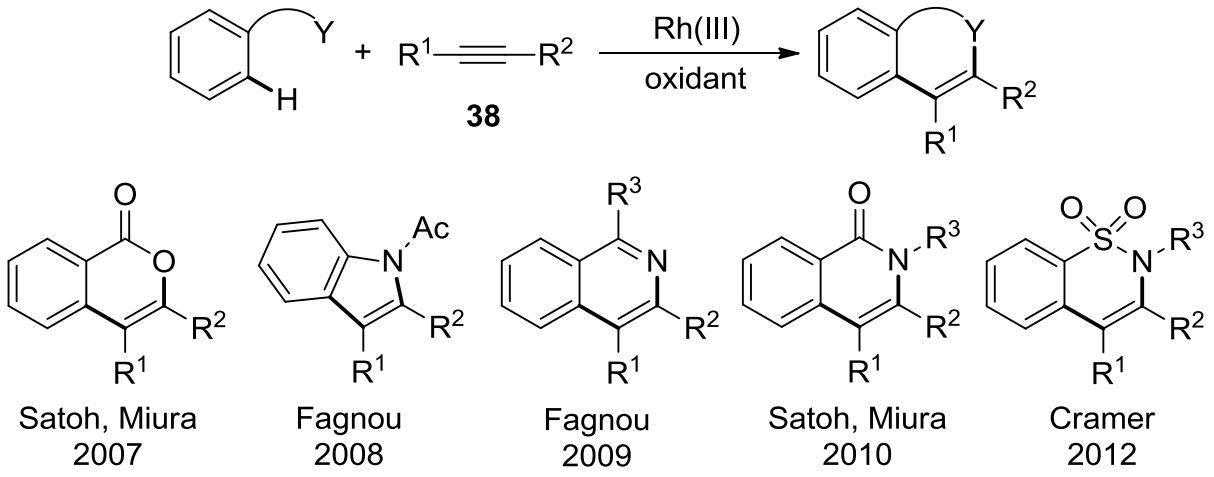
1.3.2 Transition Metal-Catalyzed Oxidative Alkyne Annulation

Larock et al. in 1991 discovered the efficient palladium-catalyzed alkyne annulation with substituted haloarenes.[102] Thus, a number of synthetically valuable protocols have been developed based on the Larock-type heterocyle synthesis.[103]



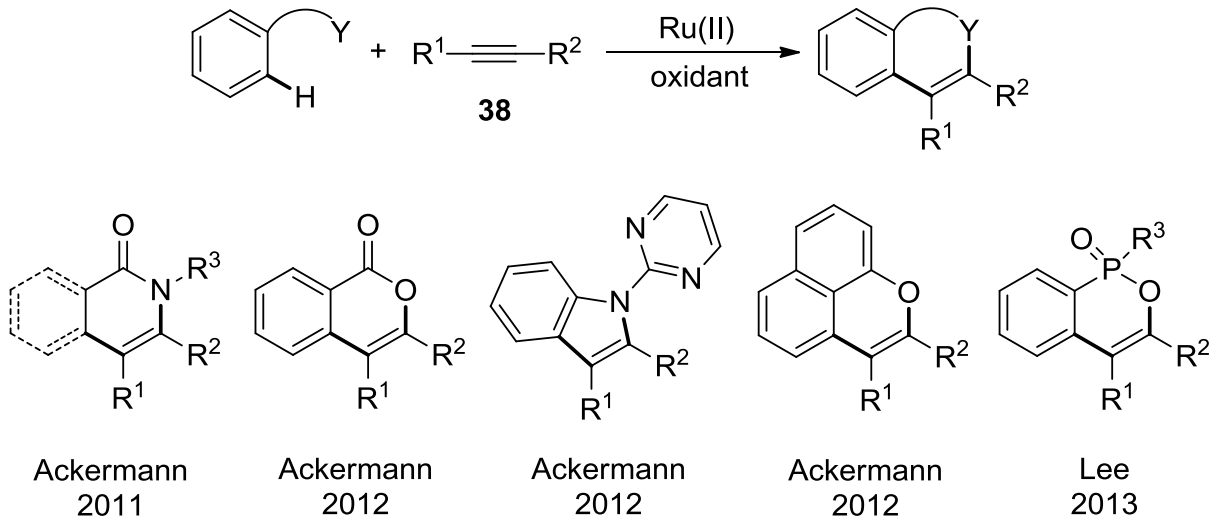
Scheme 1.16: Larock-type alkyne annulation.

It has become a challenging research target to combine transition metal-catalyzed C–H bond metalation and alkyne annulation in a one pot fashion. Various procedures have been reported with rhodium as the catalyst and $Cu(OAc)_2 \cdot H_2O$ as the oxidant (Scheme 1.17).[104]



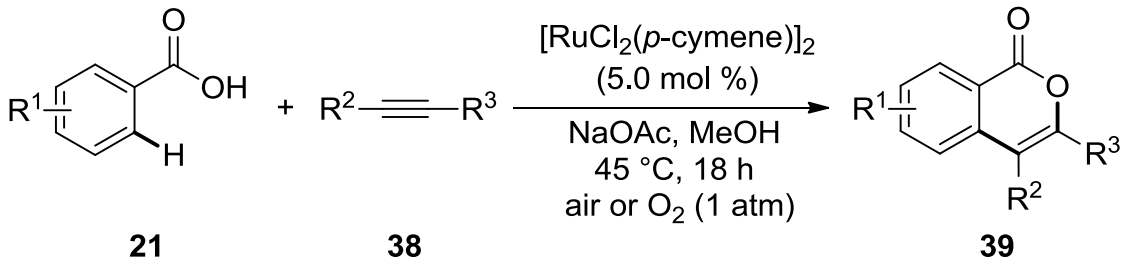
Scheme 1.17: Selected recent examples of rhodium(III)-catalyzed oxidative alkyne annulations.

Ackermann et al. in 2011 developed the first ruthenium(II)-catalyzed oxidative alkyne annulations by C–H activation.[105] Afterwards, the Ackermann group as well as other groups explored ruthenium(II)-catalyzed oxidative alkyne annulations with various directing groups (Scheme 1.18).[71]



Scheme 1.18: Selected recent examples of ruthenium(II)-catalyzed oxidative alkyne annulations.

Very recently, Ackermann and coworkers published an elegant work in which alkyne annulation with benzoic acid was performed at 45 °C employing 1 atm of O_2 or air as the sole oxidant, thus avoiding the use of any copper(II) or silver(I) salts (Scheme 1.19).[106]



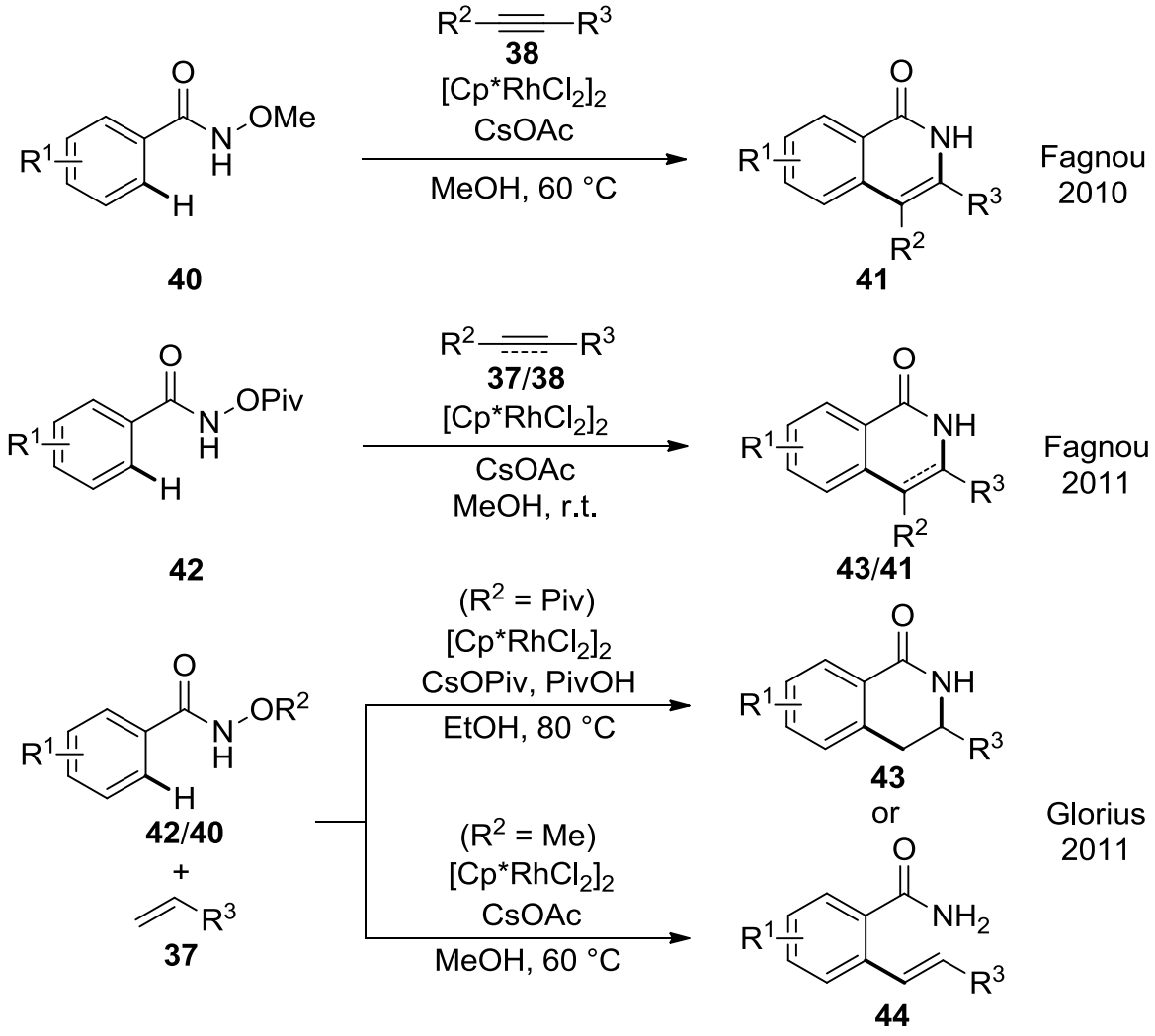
Scheme 1.19: Ruthenium(II)-catalyzed alkyne annulation using O_2 as the sole oxidant.

1.3.3 Transition Metal-Catalyzed Alkenylation and Alkyne Annulation by C–H/N–O Cleavage

Subsequent to the development of oxidative alkenylation and alkyne annulations, attempts utilized C–H/N–O bond cleavages in preceding couplings. The advantage is that the substrate

itself acts as an 'internal oxidant', thus external oxidants such as $Cu(OAc)_2 \cdot H_2O$ are no longer needed.

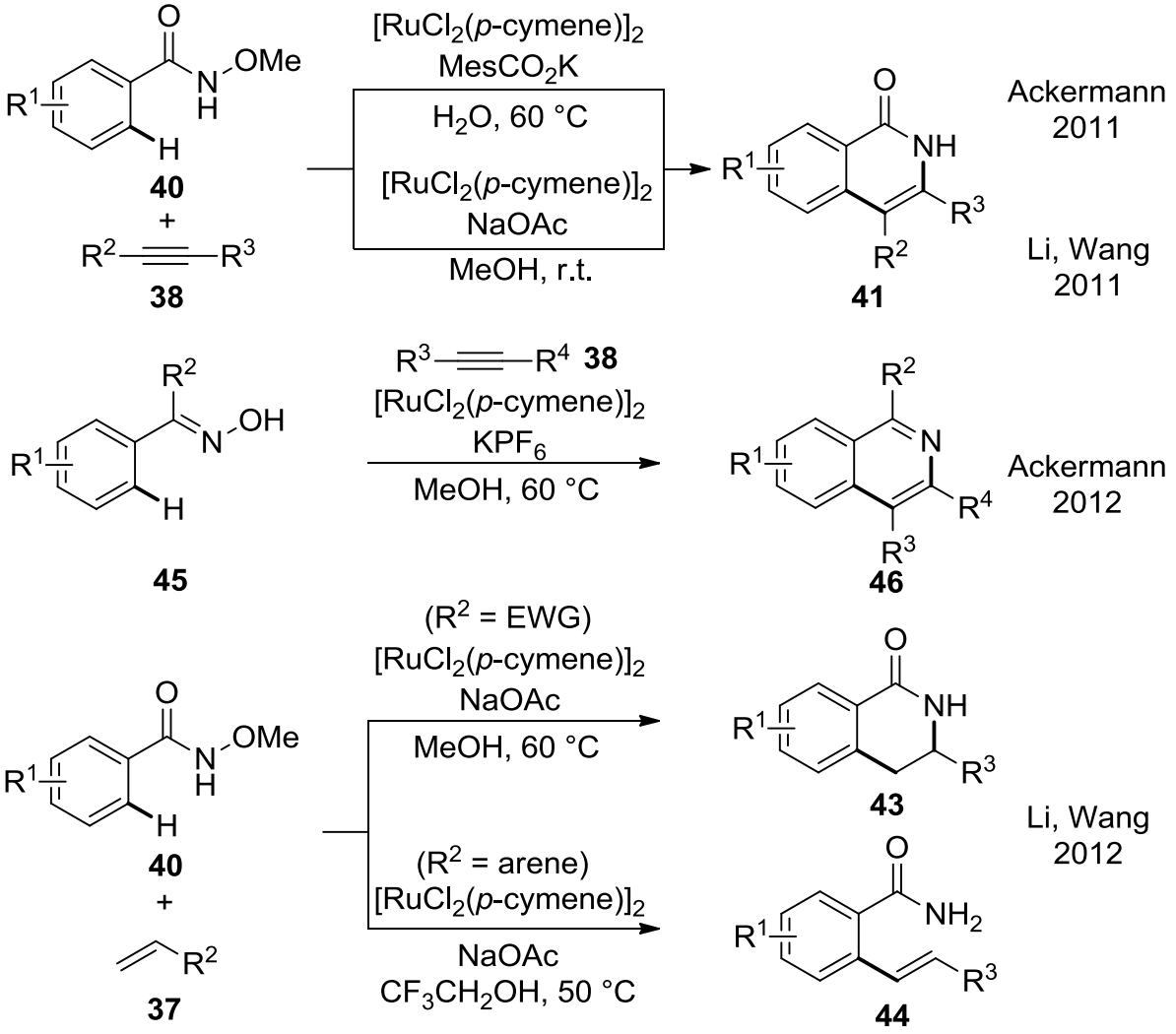
Fagnou and coworkers initiated the rhodium(III)-catalyzed C–H alkyne annulation with hydroxamic acid esters **40** and **42** as the substrates.[107,108] Later, the Fagnou group as well as the Glorius group accomplished the rhodium(III)-catalyzed direct C–H olefinations of benzhydroxamic acid esters **40** and **42** with oxidizing directing groups.[108,109]



Scheme 1.20: Rhodium(III)-catalyzed alkenylation and alkyne annulaiton by C–H/N–O bond functionalization.

Ruthenium(II)-catalyzed alkyne annulations were independently discovered by the research group of Ackermann as well as the group of Li and Wang in 2011.[110,111] Oximes **45** proved to

be effective internal oxidants. In 2012, Ackermann and coworkers reported cationic ruthenium(II) catalysts for alkyne annulations with oximes through C–H/N–O clevages.[112] Ruthenium(II)-catalyzed oxidative C–H bond alkenylation of *N*-methoxybenzamides was reported by Li and Wang employing both activated and unactivated alkenes.[113]



Scheme 1.21: Ruthenium(II)-catalyzed alkenylation and alkyne annulaiton by C–H/N–O bond functionalization.

1.4 Transition Metal-Catalyzed Arene Hydroxylations

Oxygenated aromatic molecules are key intermediates in organic synthesis and important structural components of useful pharmaceuticals, agrochemicals, polymers, and biologically active compounds.[70]

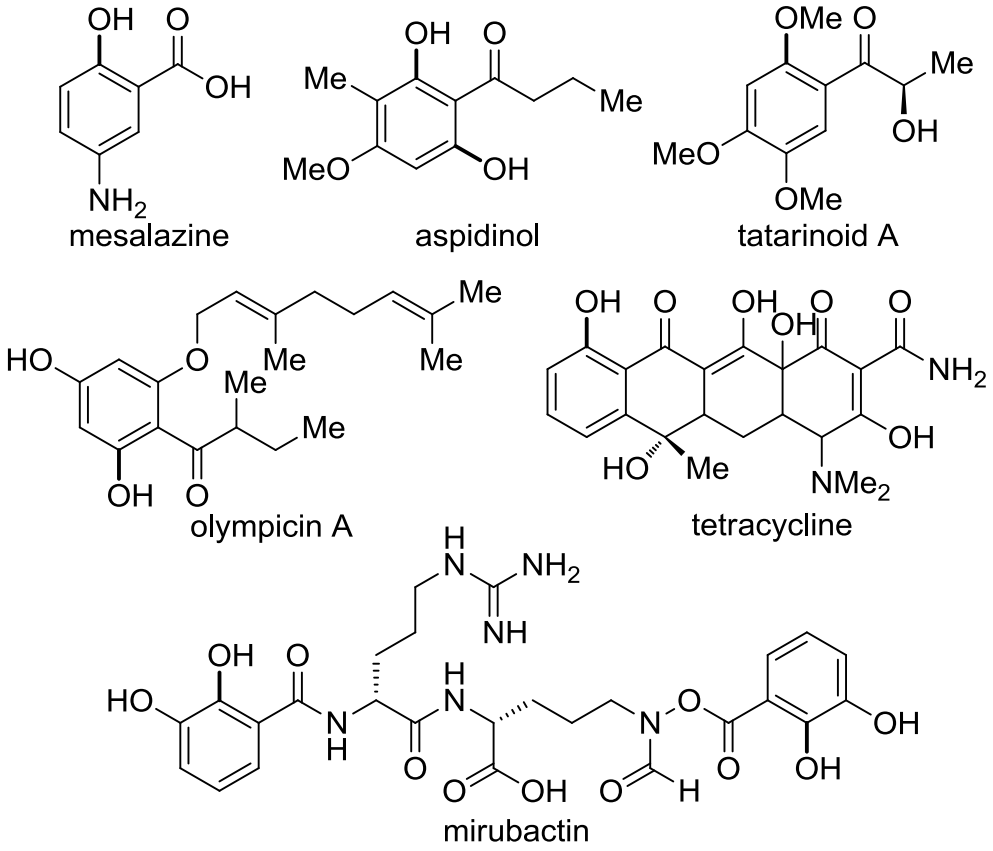
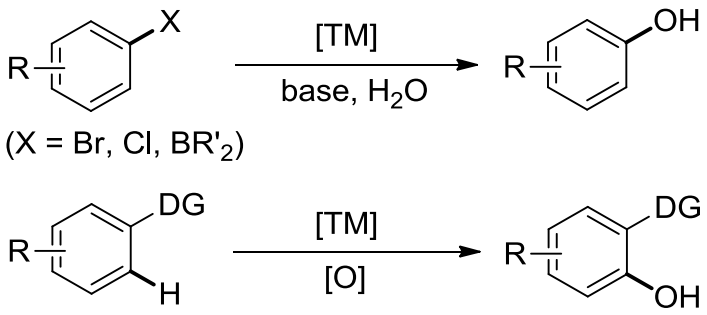


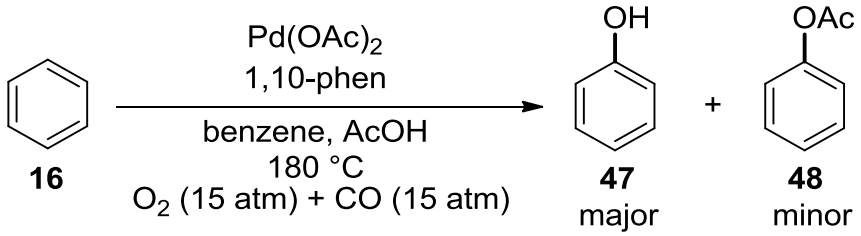
Figure 1.3: Selected bioactive compounds with phenol components.

For instance, phenol is a central commodity chemical in industry, which is produced in a three step synthesis (cumene process) starting from benzene and propylene. However, this protocol has the limitations of its high reaction temperature and low functional group tolerance. Although during recent years transition metal-catalyzed conversion of halogenated or boronated arenes to phenol has been discovered,[114-116] direct C–H oxygenation should be the optimal choice considering the atom-economy aspect.



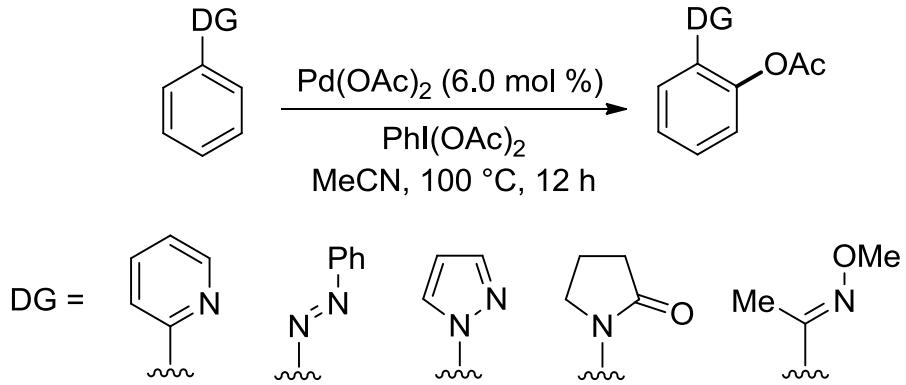
Scheme 1.22: Different routes of metal-catalyzed phenol synthesis.

In the early 1990s, Jintoku and Fujiwara reported the palladium-catalyzed transformation of benzene and molecular oxygen to phenol (Scheme1.23).[117] The palladium precursor was modified by the addition of 1,10-phenanthroline and dissolved in a mixture of benzene and acetic acid. The reaction proceeded at 180 °C under an atmosphere of oxygen (15 atm) and carbon monoxide (15 atm). The acetylated phenol **48** was monitored as a major side product.



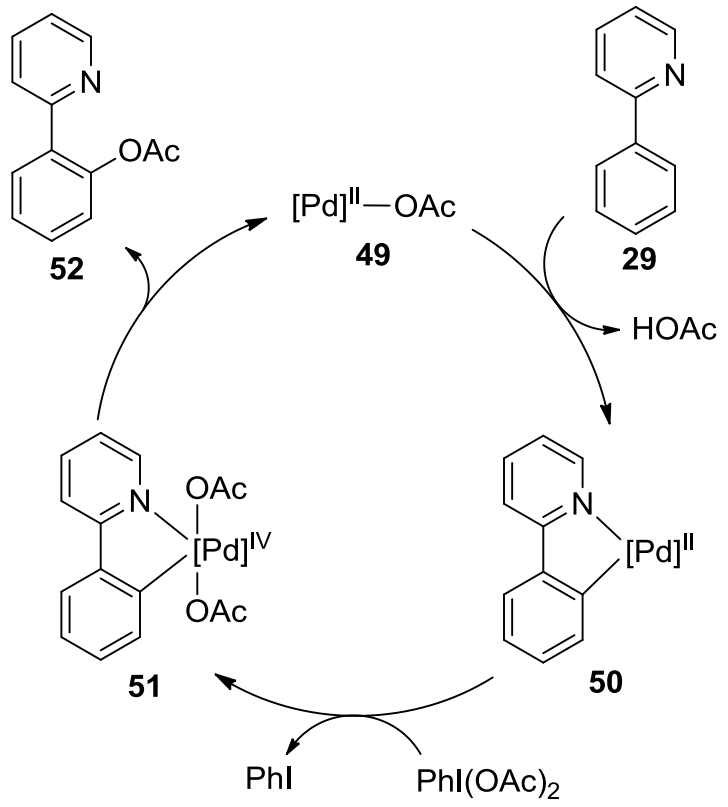
Scheme 1.23: Palladium-catalyzed phenol synthesis using O_2 as the oxidant.

Early examples of palladium-catalyzed ligand-directed C(sp^2)–H bond oxygenation were reported by Sanford and coworkers with $PhI(OAc)_2$ as the stoichiometric oxidant (Scheme 1.24).[118-122] A variety of pyridine derivatives and other nitrogen-based substituents served as excellent directing groups, delivering *ortho*-acetoxylated products in good yields. In contrast, simple ketones and aldehydes did not undergo *ortho*-acetoxylation under these conditions, presumably because these are weakly-coordinating ligands for palladium. Moreover, $PhI(OAc)_2$ could also be utilized in palladium-catalyzed ligand-directed C(sp^3)–H bond oxygenation.



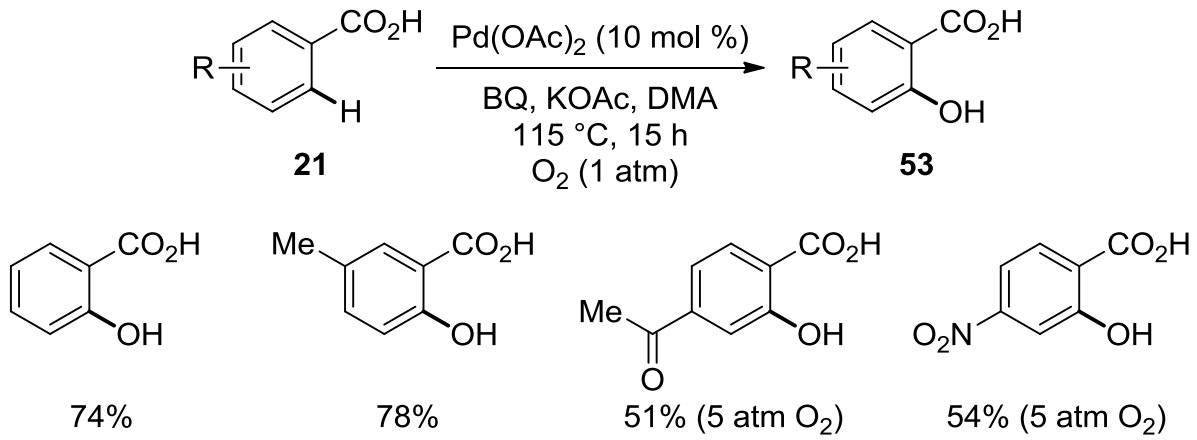
Scheme 1.24: Palladium-catalyzed ligand-directed C(sp^2)–H bond oxygenation using $PhI(OAc)_2$ as the oxidant.

Based on mechanistic studies,[123] Sanford and coworkers proposed the catalytic cycle of palladium-catalyzed *ortho*-acetoxylation as shown in Scheme 1.25: First, ligand-directed C–H activation generates a cyclopalladated intermediate **50**. Second, two-electron oxidation of the palladacycle generates a palladium(IV) species **51**. Third, reductive elimination releases the product **52** and regenerates the palladium(II) catalyst **49**.



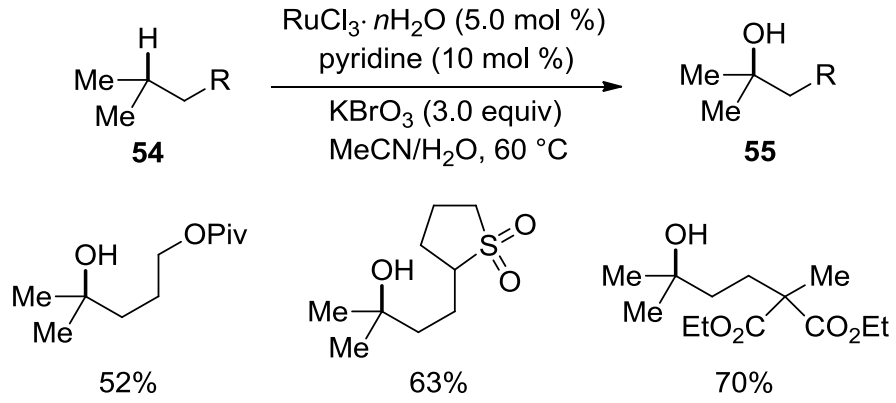
Scheme 1.25: Proposed mechanism of palladium-catalyzed *ortho*-acetoxylation.

Although other oxgenations have been investegated using inorganic peroxides, such as Oxone and $K_2S_2O_8$,[122] molecular oxygen is indubitable the optimal oxygen source considering the atom-economy aspect. Recently, the group of Yu described a palladium(II)-based catalytic system that performed the regioselective *ortho*-hydroxylation of potassium benzoates with the environmentally friendly molecular oxygen as the oxidant (Scheme 1.26).[124] The presence of stoichiometric benzoquinone (BQ) significantly increased the reaction rates and thereby converted substrates into desired *ortho*-hydroxylated product **53** in satisfying yield with 1 atm of O_2. Labeling experiments with $^{18}O_2$ confirmed that the oxygen-atom incorporated into the hydroxylated product originated from molecular oxygen.



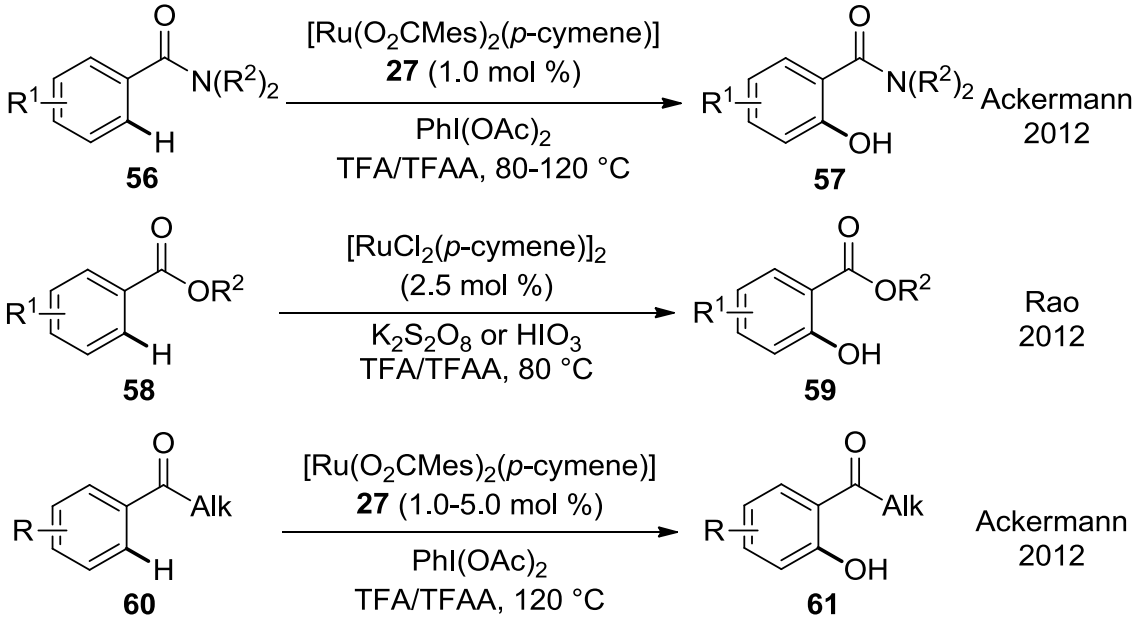
Scheme 1.26: Palladium-catalyzed chelation-assisted C(sp^2)-H bond oxygenation using O_2 as the oxidant.

Recently, ruthenium-catalyzed hydroxylations of C–H bonds have been developed. Early studies probed the RuO_4-mediated hydroxylation of unactivated tertiary C(sp^3)–H bonds in hydrocarbons.[125,126] Du Bois and coworkers disclosed the C(sp^3)–H hydroxylation with catalytic $RuCl_3 \cdot nH_2O$ employing $KBrO_3$ as the stoichiometric oxidant, allowing the oxygenation of the weakest C–H bonds (Scheme 1.27).[127] Thus, this method is largely limited to tertiary alkyl C–H bonds.



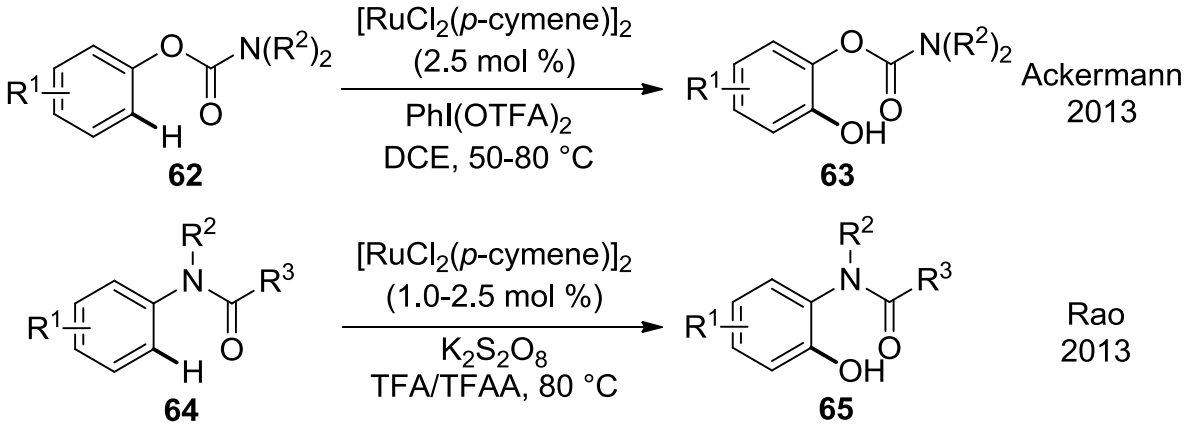
Scheme 1.27: Ruthenium-catalyzed C(sp^3)–H bond oxygenation.

The past few years have witnessed a tremendous development in the ruthenium-catalyzed direct hydroxylation of stronger C(sp^2)–H bonds in (hetro)arenes.[70] Rao and coworkers disclosed ruthenium-catalyzed *ortho*-hydroxylation with benzoic acid using $K_2S_2O_8$ or HIO_3 as the oxidant,[128] while Ackermann and coworkers employed the well-defined ruthenium(II) biscarboxylate complex [Ru(O_2CMes)$_2$(*p*-cymene)] (**27**) as well as inexpensive $RuCl_3$·*n*H_2O in the hydroxylation reactions with PhI(OAc)$_2$ as the oxidant.[129] The strong acidic reaction medium turned out to be crucial for chelation-assisted *ortho*-hydroxylations on (hetro)arenes with esters, amides, or even weakly-coordinated ketones[130,131] as the directing groups.



Scheme 1.28: Ruthenium(II)-catalyzed C(sp^2)–H bond oxygenation on arenes bearing electron-withdrawing directing groups.

Whilst previous studies had focused on the use of arenes bearing electron-withdrawing directing groups, the Ackermann group[132] and the Rao group[133] have respectively explored ruthenium-catalyzed carbamate- and aniline-directed *ortho*-hydroxylation with excellent site-selectivities.



Scheme 1.29: Ruthenium(II)-catalyzed C(sp^2)–H bond oxygenation on arenes bearing electron-donating directing groups.

1.5 Photo-Induced Transition Metal-Catalyzed C–H Functionalizations

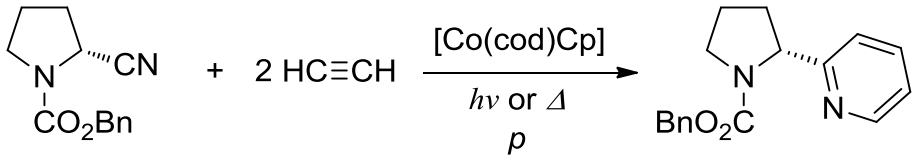
Due to the limited fossil fuels storage on this planet, it is urgent to establish new energy sources. As we know, fossil fuels together with wind energy, water energy, and biomass energy, ultimately originate from solar irradiation. Therefore, photo energy has been considered as one of the most promising alternatives for fossil fuels.[134] The discovery of the photovoltaic effect in 1839 demonstrated that people already tried to transform photo energy into other forms of energy at that time.[135]

Photo-induced synthesis was introduced into chemistry field by Ciamician who believed it was the sun light that would bring about real green synthetic pathways. Although he could not achieve his goal, because actually NADPH and ATP are the driving force in synthesis of plants, he discovered a range of interesting photochemical processes.[1]

In comparison with thermal reactions, photochemical transformations are characterized by the fact that absorbing light causes a change in electronic configuration, and consequently alters the reactivity of a chemical compound. Generally, electron transfer is facilitated under photochemical conditions, which will considerably extend the reaction spectrum of organic molecules.[136]

Recently Noyori suggested that young chemists should ''develop a 'photo-synthetic' catalyst that facilitates a thermally unachievable, energetically uphill reaction.''[137] Actually, photochemical reactions like photocyclizations, photocycloadditions, photoclevages, and photorearrangements have already become important tools in organic chemistry.[138]

The thermal reaction conditions and photo-induced reaction conditions were, for example, compared in the Vollhardt-type[139] pyridine synthesis (Scheme 1.30).[140,141] The photo-induced cyclization at 25 °C under ambient pressure proceeded faster than the thermal synthesis at 110 °C under higher pressure.

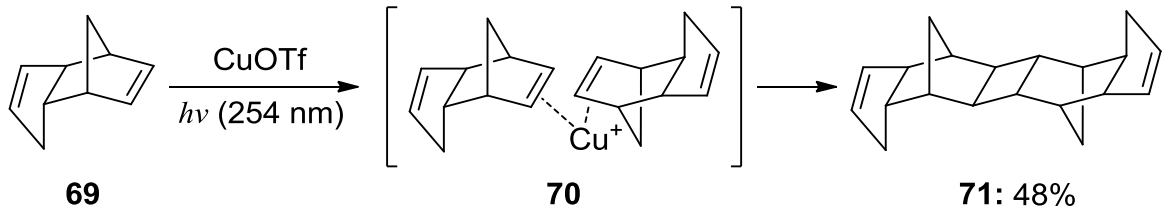


66 **67** **68**

method	[Co(cod)Cp] [mol %]	T [°C]	*p* [atm]	*t* [h]	yield [%]
hν (420 nm)	0.5	25	1	4	90
thermal	3.2	110	14	22	82

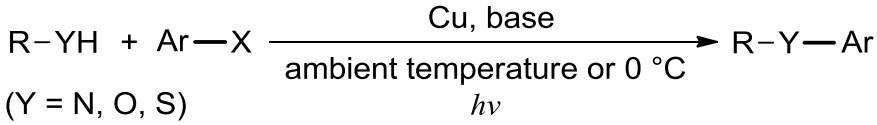
Scheme 1.30: Comparison between thermal and photochemical conditions for [2+2+2] cycloaddition of acetylene **67** to chiral pyridine **68**.

Norbornene derivate **69** underwent copper-catalyzed intermolecular [2+2] photodimerization efficiently and stereoselectively (Scheme 1.31).[142] No further functionalized alkene was obtained.



Scheme 1.31: Photo-induced copper-catalyzed [2+2] photodimerization of norbornene derivate **69**.

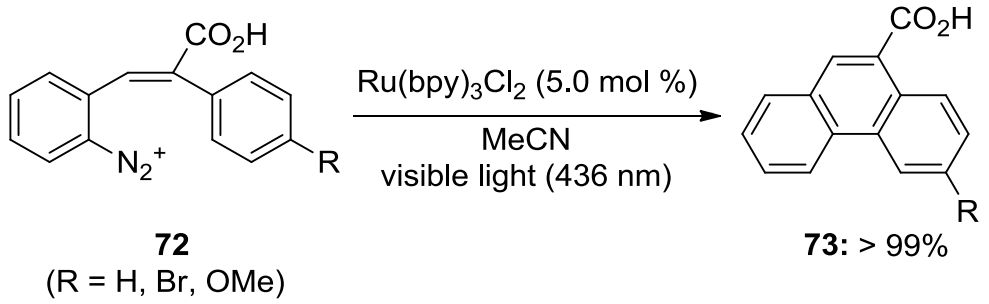
Very recently, Fu and Peters have utilized irradiation in the Ullmann-type couplings (Scheme 1.32). Thus, C–N,[143-145] C–O,[146] C–S,[147] and C–CN[148] bonds were formed at ambient temperature or 0 °C.



Scheme 1.32: Photo-induced copper-catalyzed Ullmann-type couplings.

Visible light-induced photoredox catalysis has become very attractive during recent years.[149,150] Coordination compounds such as $[Ru(bpy)_3]^{2+}$ or $[Ir(bpy)(ppy)_2]^{+}$ are among the most frequently used photocatalysts because of their relatively long excited states as well as chemically robust nature. For many transformations, organic dyes are also used as photoredox catalysts. Various light sources, such as compact fluorescent lamp (CFL), light-emitting diode (LED), and even sunlight, could be utilized in photo-induced catalytic reactions.

Despite the excellent photoredox properties, the above-mentioned transition metal complexes have until very recently attracted very little attention from synthetic organic chemists. One of the earliest examples was reported by Deronzier and coworkers in 1984,[151] demonstrating a photocatalytic Pschorr reaction[152] for the synthesis of phenanthrene and substituted phenanthrenes (Scheme 1.33).



72
(R = H, Br, OMe)

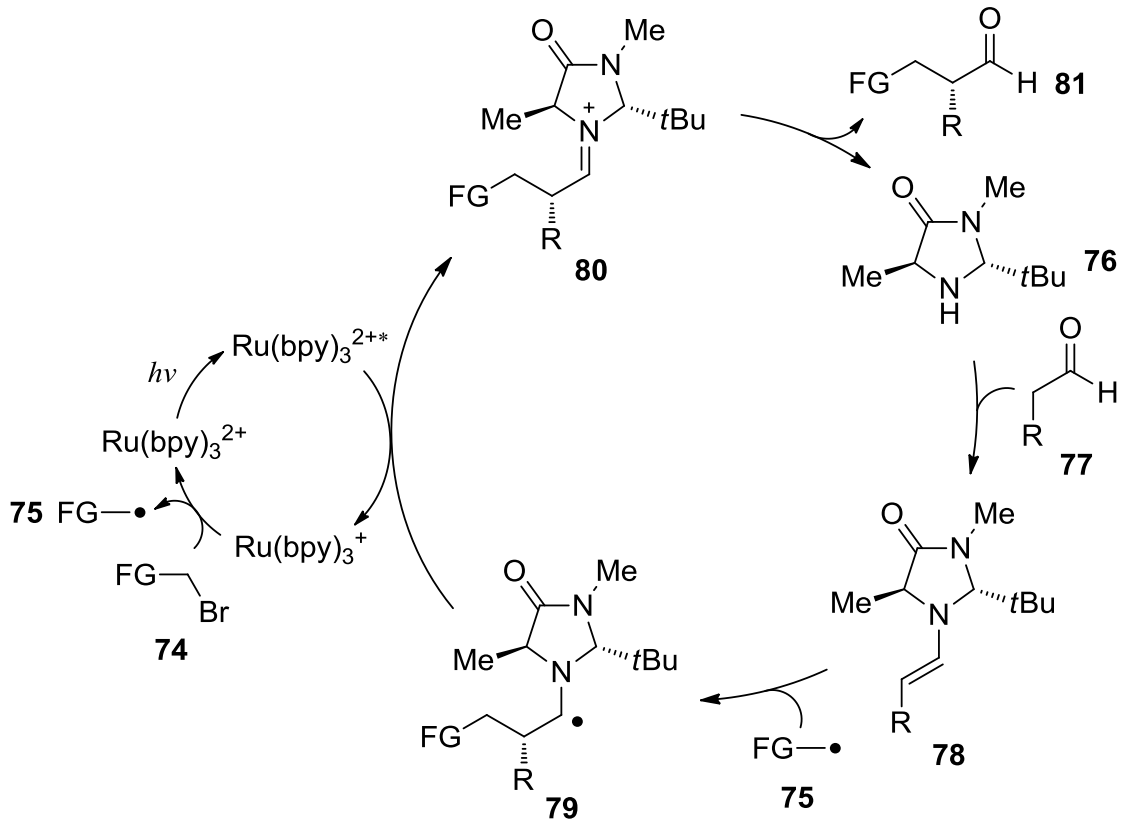
73: > 99%

Scheme 1.33: Photo catalytic Pschorr reaction for the synthesis of phenanthrenes.

Based on the success of organo-SOMO catalysis,[153] MacMillan and coworkers turned to the merging of photoredox catalysis with organocatalysis in the enantioselective alkylation of aldehydes.[154] This reaction included two catalytic cycles, namely photoredox catalytic cycle and organocatalytic cycle (Scheme 1.34).

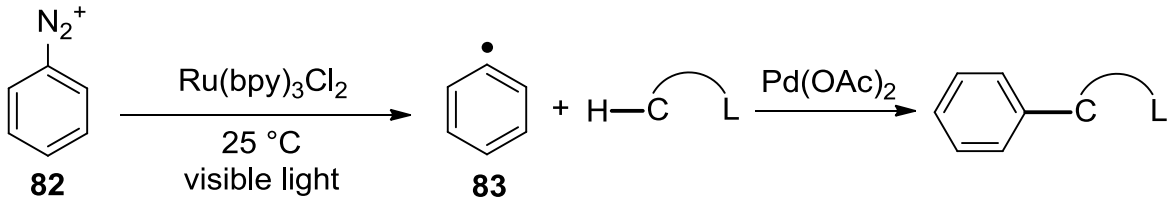
The photoredox cycle consists of the following steps: First, visible light irradiation excites $Ru(bpy)_3^{2+}$ to $Ru(bpy)_3^{2+}$*. Second, $Ru(bpy)_3^{2+}$* is reductively quenched by α-amino radical **79** to form $Ru(bpy)_3^{+}$. Third, single electron transfer from $Ru(bpy)_3^{+}$ to the α-bromocarbonyl compound **74** delivers an electron-deficient radical **75** and regenerates $Ru(bpy)_3^{2+}$.

The organo catalytic cycle consists of the following steps: First, the coupling of electron deficient radical **75** with enamine **78** forms the key C–C bond and generates the α-amino radical **79**. Second, $Ru(bpy)_3^{2+}$* oxidizes **79** to iminium cation **80**. Third, hydrolysis of the iminium cation **80** regenerates the amine catalyst **76** while delivering the desired enantioselective α-alkylated aldehyde **81**.



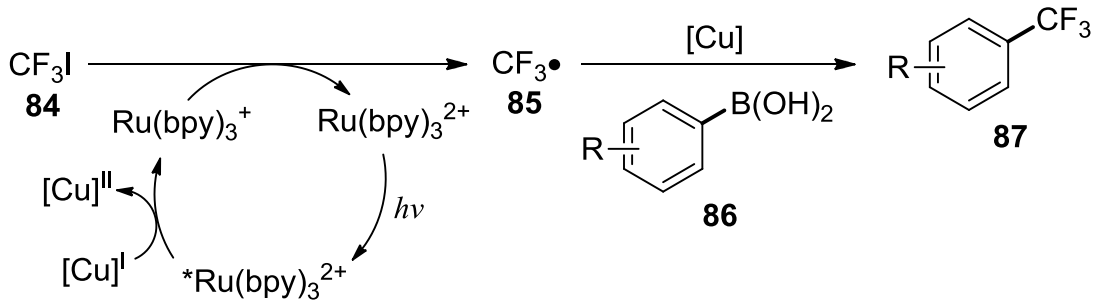
Scheme 1.34: Proposed mechanism for photoredox catalytic asymmetric α-alkylation of aldehydes.

An elegant way is to combine photoredox catalysis with transition metal-catalyzed coupling reactions. The research from Deronzier indicated that a free radical could be generated from photoredox catalysis of aryldiazonium at room temperature.[151] Thus, Sanford and coworkers successfully combined the radical generation process with palladium-catalyzed C–H metalation (Scheme 1.35).[155] In comparison with previous report of Chan,[156] this reaction occurred under milder conditions.



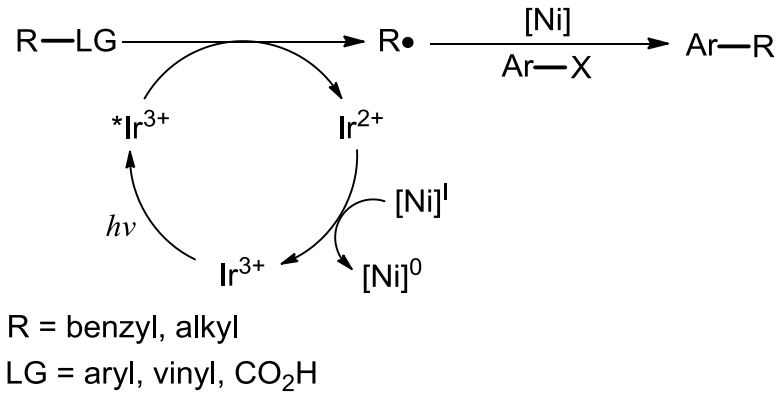
Scheme 1.35: Merging photoredox and palladium catalysis in C(sp^2)–H arylations.

More transition metal catalysis and photoredox catalysis have been emerged in cross-coupling reactions. Inspired by MacMillan´s trifluoromethalation under photoredox catalytic conditions,[157] Sanford and coworkers developed the trifluoromethylation of arylboronic acids by photo-induced copper-catalyzed Suzuki-Miyaura coupling (Scheme 1.36).[158]



Scheme 1.36: Visible light-induced copper-catalyzed trifluorometalation with boronic acids.

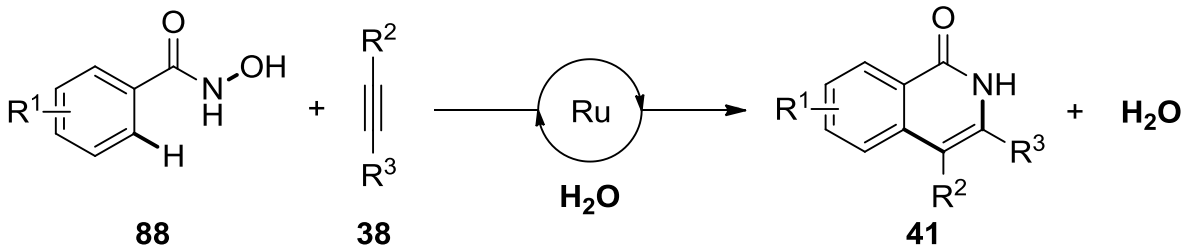
In 2014 MacMillan and coworkers reported the nickel-catalyzed decarboxylative arylation reaction,[159] meanwhile Tellis and Primer as well as Molander and coworkers independently disclosed the photo-induced nickel-catalyzed Suzuki-Miyaura cross-couplings (Scheme 1.37).[160,161] In the three reports, the organic halides were included in metal catalytic cycles, while in Schemes 1.34 and 1.36, the organic halides were included in photoredox cycles.



Scheme 1.37: Merging photoredox and nickel catalysis in cross-couplings.

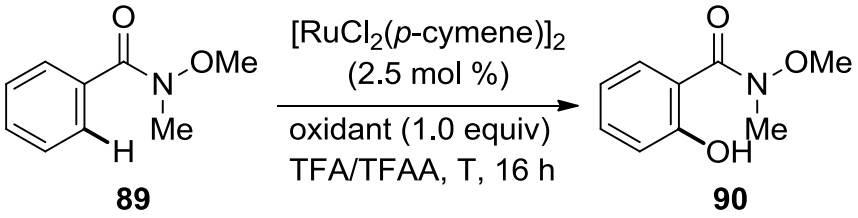
2 Objectives

Oxidative annulations of alkynes by C–H/N–H cleavages have recently emerged as a useful strategy for the sustainable preparation of *N*-heterocycles. To avoid the use of excess amount of oxidants, transition metal-catalyzed C–H/N–O bond functionalizations with *N*-substituted benzamides was reported by Fagnou and coworkers recently.[107,108] The Ackermann group have devised a green isoquinolone synthesis by ruthenium(II)-catalyzed C–H/N–O bond functionalizations.[110] Although performed in H_2O, this reaction will generate MeOH as the byproduct with *N*-methoxybenzamide as the substrate. The use of *N*-hydroxybenzamide will generate H_2O as the sole byproduct. Therefore, a real green isoquinolone synthesis by ruthenium-catalyzed C–H/N–O functionalizations should be achieved.



Scheme 2.1: Ruthenium-catalyzed C–H/N–O functionalizations towards a green isoquinolone synthesis.

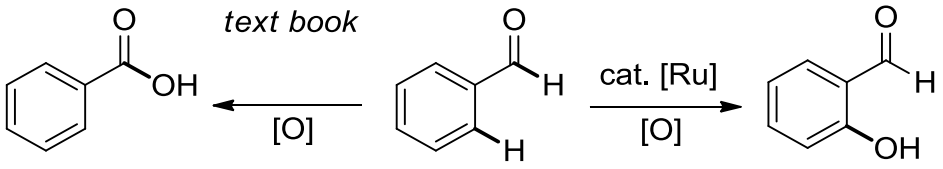
Step-economical chelation-assisted C–H oxygenations were accomplished with the aid of various directing groups utilizing transition metal catalysts. Very recently, the Ackermann group and the Rao group developed ruthenium(II)-catalyzed C–H oxygenations.[70] The easily accessible *N*-methoxy-*N*-methylamides, also known as Weinreb amides have thus far proven elusive for metal-catalyzed C–H bond functionalizations and direct oxygenations. With the additional hetero atom in the directing group, Weinreb amides have stronger coordinating ability than alkyl-substituted benzamides, and therefore should facilitate the ruthenium(II)-catalyzed C–H oxygenations.



89 **90**

Scheme 2.2: Ruthenium(II)-catalyzed C–H oxygenation on Weinreb amides **89** at a more environmentally benign temperature.

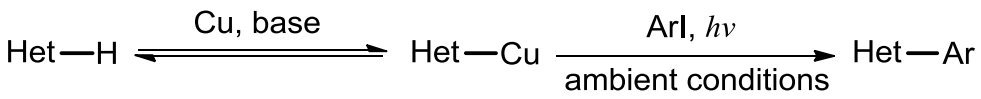
The C–H oxygenation with weakly coordinating directing groups is a challenging project.[45,72] Although the Ackermann group has developed weakly coordinated ketones for site-selective C–H oxygenations, aldehyde is doubtless much more challenging as a substrate in C–H oxygenations. Ruthenium(II)-catalyzed C–H oxygenations by formyl group assistance has proven thus far elusive. Taking advantage of the unique characteristics of ruthenium catalysis, the formyl group could possibly serve as a directing group rather than a substrate in the ruthenium-catalyzed C–H oxygenations.



21 **91** **92**

Scheme 2.3: Ruthenium(II)-catalyzed challenging C–H oxygenation on aldehydes.

The copper-catalyzed C–H arylation of heteroarenes always requires high reaction temperatures of more than 100 °C.[162] The C–H metalation is feasible for relatively more acidic HetAr–H bonds under alkaline reaction conditions. Hence, the dissociation of carbon–halogen bond should be the rate-limiting step in a number of copper-catalyzed C–H arylations. The photo irradiation could facilitate the C–I bond dissociation and therefore accelerate the copper-catalyzed heterocycle arylations.



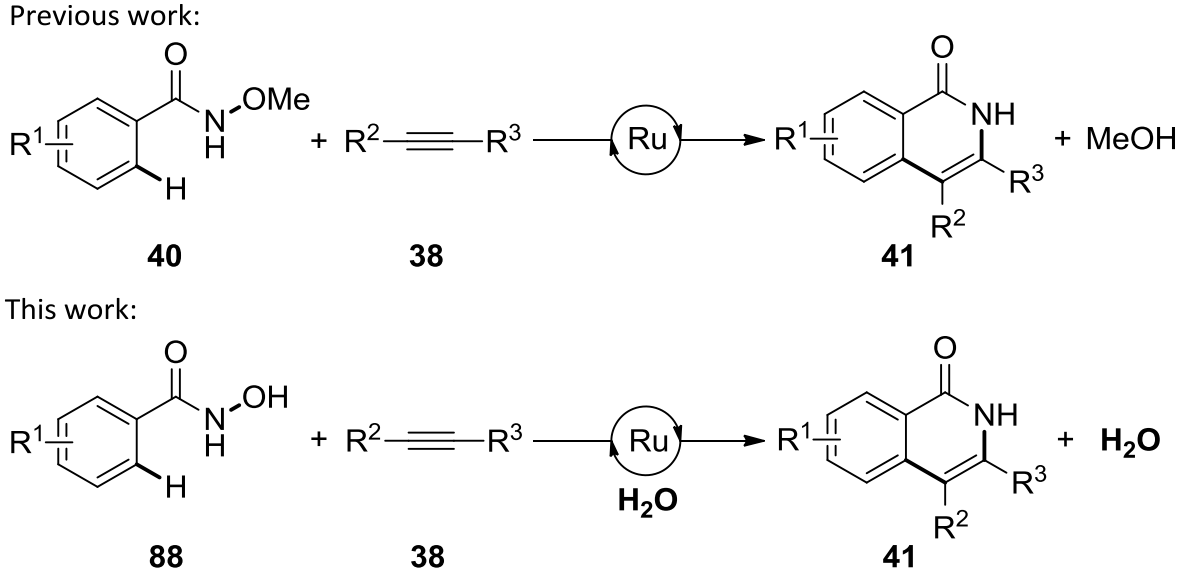
93 **94**

Scheme 2.4: Photo-induced copper-catalyzed C–H arylation.

3 Ruthenium(II)-Catalyzed C–H/N–O Functionalizations

Oxidative annulations of alkynes by C–H/N–O cleavages have recently emerged as a useful strategy for the sustainable preparation of nitrogen-containing heterocycles. The main drawback is the use of excess amount of oxidants—for example: AgOAc or $Cu(OAc)_2 \cdot H_2O$—which might bring about high costs as well as high environmental risks. However, transition metal-catalyzed C–H/N–O bond functionalizations with *N*-substituted benzamides provided the means to avoid the use of external oxidants. In 2011, Ackermann et al. devised a green isoquinolone synthesis in H_2O using ruthenium(II)-catalyzed alkyne annulations by C–H/N–O cleavages,[110] while Li and Wang independently disclosed effective ruthenium(II)-catalyzed alkyne annulations in methanol.[111]

In the previous work of the Ackermann group,[110] *N*-methoxybenzamides **40** were employed as the reactants, which generated MeOH as the byproduct. A more atom-economical and sustainable approach to the synthesis of isoquinolones was established with the use of *N*-hydroxybenzamides **88**, thereby generating H_2O as the sole byproduct.[163]



Scheme 3.1: A green isoquinolone synthesis by C–H/N–O functionalizations.

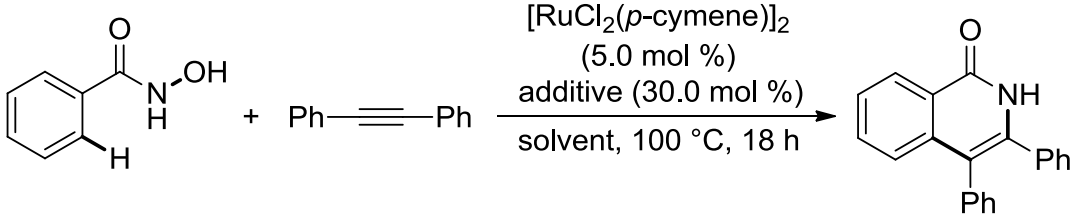
In the previous work, only few examples were listed utilizing $MesCO_2K$ as the only carboxylate ligand. Since carboxylate assisted C–H bond founctionalization has become an

important section in metal catalysis,[50,71] we decided to explore this subject further.

3.1 Optimization of Ruthenium(II)-Catalyzed C–H/N–O Functionalizations

To optimize the reaction conditions, we first tested different solvents and found H_2O to be the best reaction medium for this dehydrative transformation (Table 3.1, entry 5). Lower yield was obtained without $MesCO_2K$ (entry 6). $[RuCl_2(cod)]_n$ and $RuCl_2(PPh_3)_3$ delivered no product (entries 7 and 8), while $[RuCl_2(p\text{-cymene})]_2$ was found to be the ruthenium precatalyst of choice. Different additives were then explored (entries 9-12), such as simple base K_2CO_3, phase-transfer catalyst TBAB, or commonly used additives like KPF_6 and $AgSbF_6$. However, these additives delivered lower yields.

Table 3.1: Optimization of ruthenium(II)-catalyzed C–H/N–O functionalizations.[a]



88a **38a** **41aa**

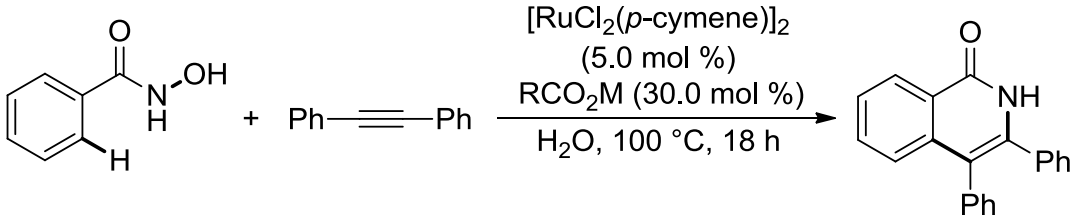
entry	additive	solvent	yield [%]	entry	additive	solvent	yield [%]
1	$MesCO_2K$	1,4-dioxane	7	7[b]	$MesCO_2K$	H_2O	trace
2	$MesCO_2K$	*t*AmOH	11	8[c]	$MesCO_2K$	H_2O	trace
3	$MesCO_2K$	DMF	12	9	K_2CO_3	H_2O	13
4	$MesCO_2K$	PhMe	6	10	TBAB	H_2O	27
5	**$MesCO_2K$**	**H_2O**	**62**	11	KPF_6	H_2O	23
6	—	H_2O	25	12	$AgSbF_6$	H_2O	38

[a] Reaction conditions: **88a** (0.5 mmol), **38a** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), additive (30.0 mol %), solvent (2.0 mL), 100 °C, 18 h, average isolated yields of two independent runs. [b] $[RuCl_2(cod)]_n$ (5.0 mol %). [c] $RuCl_2(PPh_3)_3$ (5.0 mol %).

In order to investigate carboxylate-assisted C–H bond activation in this C–H/N–O bond

functionalization, we tested various carboxylate additives (Table 3.2). Potassium acetate and potassium benzoate could not improve the yield (entries 1 and 2). Afterwards we probed different potassium benzoates with various substituents. Generally, benzoates with electron-withdrawing substituents delivered better yields than those with electron-donating substituents (entries 3-10). Among all the potassium benzoates, 3-$(F_3C)C_6H_4CO_2K$ gave the best results, delivering **41aa** in 76% yield (entry 10). We also tested sodium and caesium benzoates and obtained similar results (entries 11 and 12). Yields decreased with lower reaction temperature, lower catalyst loading, or lower amounts of the additive (entries 13-15).

Table 3.2: Optimization of ruthenium(II)-catalyzed C–H/N–O functionalization with different additives.[a]



88a **38a** **41aa**

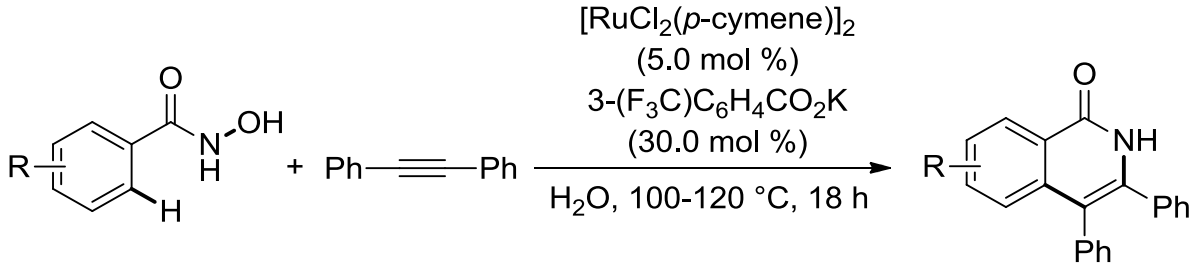
Entry	Additive	Yield [%]	Entry	Additive	Yield [%]
1	KOAc	55	9	3,4,5-$F_3C_6H_4CO_2K$	66
2	$PhCO_2K$	66	**10**	**3-$(F_3C)C_6H_4CO_2K$**	**76**
3	2-$(MeO)C_6H_4CO_2K$	59	11	3-$(F_3C)C_6H_4CO_2Na$	74
4	4-$(MeO)C_6H_4CO_2K$	61	12	3-$(F_3C)C_6H_4CO_2Cs$	74
5	4-$FC_6H_4CO_2K$	68	13[b]	3-$(F_3C)C_6H_4CO_2K$	69
6	4-$(O_2N)C_6H_4CO_2K$	71	14[c]	3-$(F_3C)C_6H_4CO_2K$	34
7	2,6-$(F_3C)_2C_6H_4CO_2K$	66	15[d]	3-$(F_3C)C_6H_4CO_2K$	60
8	3,5-$(F_3C)_2C_6H_4CO_2K$	70			

[a] Reaction conditions: **88a** (0.5 mmol), **38a** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), additive (30.0 mol %), H_2O (2.0 mL), 100 °C, 18 h, average isolated yields of two independent runs. [b] Reaction at 80 °C. [c] $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %). [d] Additive (20.0 mol %).

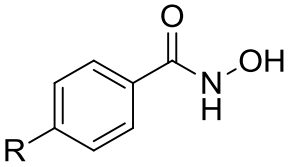
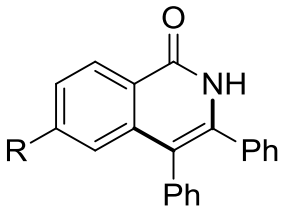
3.2 Scope of Ruthenium(II)-Catalyzed C–H/N–O Functionalizations

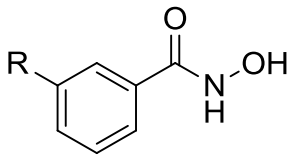
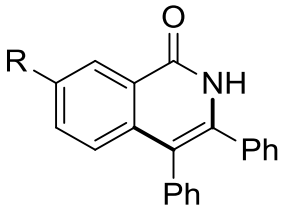
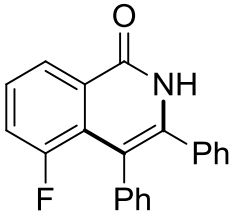
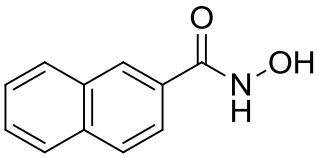
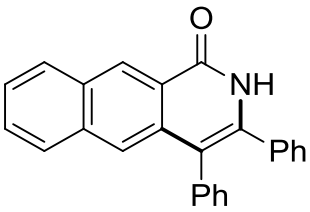
With the optimal conditions in hand, we next explored the substrate scope in the dehydrative alkyne annulation by C–H/N–O cleavages (Table 3.3). First we screened different substituted *N*-hydroxybenzamides **88**. The yields of the desired products **41** were good, and valuable functional groups, such as fluoro, chloro, bromo, iodo, and nitro substituents, were well tolerated. While the site selectivity was largely controlled by steric interactions, the inductive effect of a *meta*-fluoro substituent[49] led to the exclusive C–C bond formation at the C2 position of *N*-hydroxybenzamide **88k**.

Table 3.3: Scope of substituted *N*-hydroxybenzamides **88** with diphenylacetylene **38a**.[a]



88 **38a** **41**

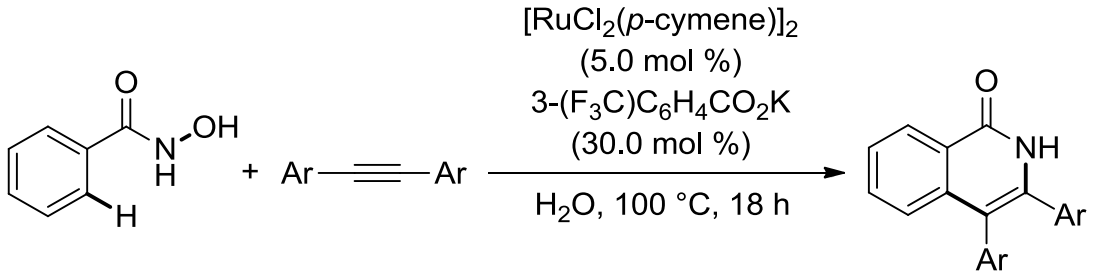
entry	**88**	**41**	yield [%]
			
1	R = H (**88a**)	**41aa**	76
2	R = Me (**88b**)	**41ba**	66
3	R = OMe (**88c**)	**41ca**	59
4	R = F (**88d**)	**41da**	81
5	R = Cl (**88e**)	**41ea**	62
6	R = Br (**88f**)	**41fa**	73
7	R = I (**88g**)	**41ga**	38
8	R = NO_2 (**88h**)	**41ha**	67

entry	**88**	**41**	yield [%]
			
9[b]	R = Me (**88i**)	**41ia**	60
10	R = CF_3 (**88j**)	**41ja**	42
11	R = F (**88k**)	 **41ka**	58
12	 **88l**	 **41la**	73

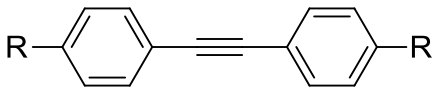
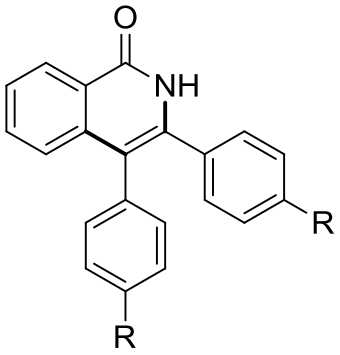
[a] Reaction conditions: **88** (0.5 mmol), **38a** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), 3-$(F_3C)C_6H_4CO_2K$ (30.0 mol %), H_2O (2.0 mL), 100 °C, 18 h. [b] 120 °C.

With water as the reaction medium, the interaction between solvent, reactant and catalyst may have a significant influence on catalytic efficacy. Therefore, sufficient stirring is essential for this reaction. As shown in Table 3.4, alkynes **38b** and **38c** could deliver moderate to good yields. However, we found the stirring was very difficult in the reactions with alkynes **38d** and **38e**. As a result, no product was generated in entries 3 and 4.

Table 3.4: Scope of *N*-hydroxybenzamide **88a** with aromatic alkynes **38**.[a]



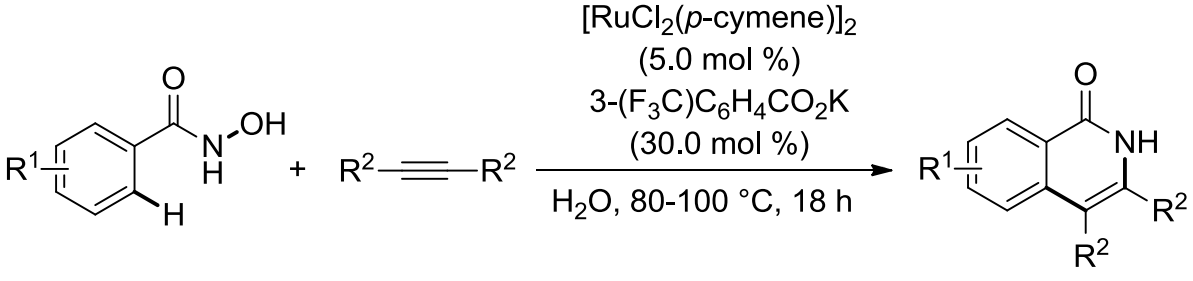
88a **38** **41**

entry	**38**	**41**	yield [%]
			
1	R = OMe (**38b**)	**41ab**	58
2	R = F (**38c**)	**41ac**	63
3	R = Cl (**38d**)	**41ad**	0
4	R = Br (**38e**)	**41ae**	0

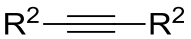
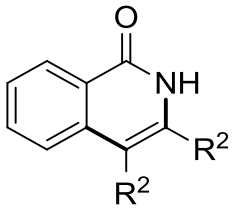
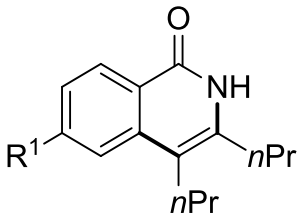
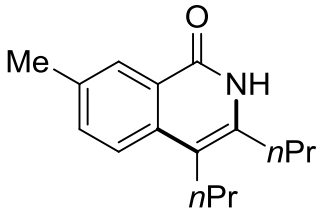
[a] Reaction conditions: **88a** (0.5 mmol), **38** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), 3-$(F_3C)C_6H_4CO_2K$ (30.0 mol %), H_2O (2.0 mL), 100 °C, 18 h.

Alkyl-substituted alkynes **38** were also converted with high catalytic efficacy (Table 3.5). With the considerable tolerance of electrophilic functional groups, it became apparent that isoquinolones **41** bearing useful functionalities could be readily prepared (entries 5 and 6).

Table 3.5: Scope of *N*-hydroxybenzamides **88** with aliphatic alkynes **38**.[a]



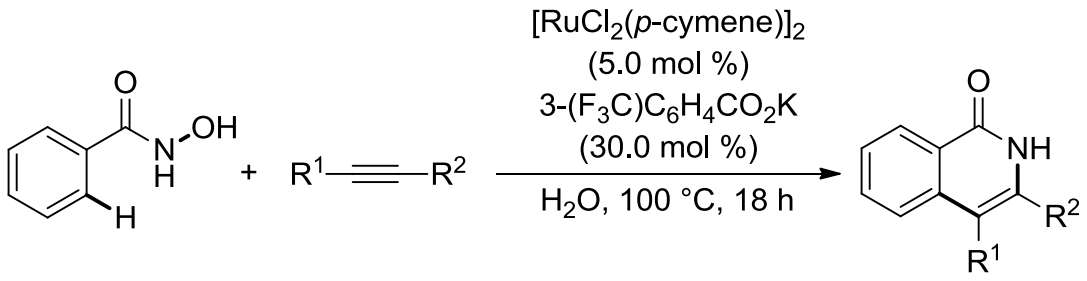
88 **38** **41**

entry	**88**	**38**	**41**	yield [%]
				
1[b]		R^2 = Et (**38f**)	**41af**	86
2	**88a**	R^2 = *n*Pr (**38g**)	**41ag**	75
3		R^2 = *n*Bu (**38h**)	**41ah**	78
				
4	**88c**		R^1 = OMe (**41cg**)	70
5	**88d**	**38g**	R^1 = F (**41dg**)	76
6	**88g**		R^1 = I (**41gg**)	69
7	**88i**	**38g**	 **41ig**	70

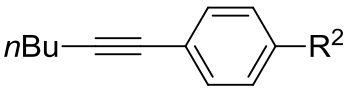
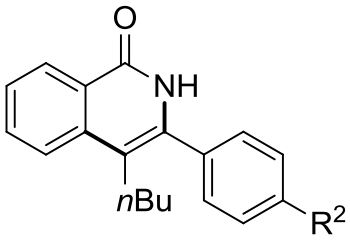
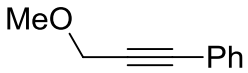
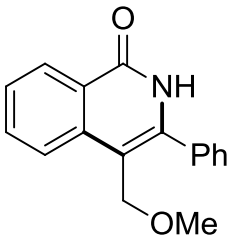
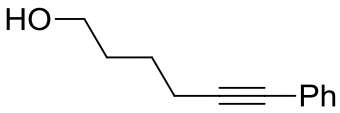
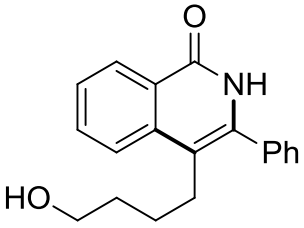
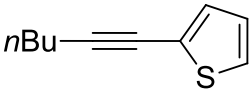
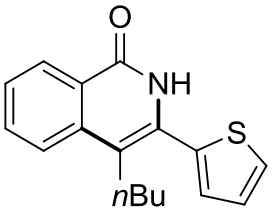
[a] Reaction conditions: **88** (0.5 mmol), **38** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), 3-$(F_3C)C_6H_4CO_2K$ (30.0 mol %), H_2O (2.0 mL), 100 °C, 18 h. [b] 80 °C.

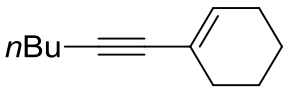
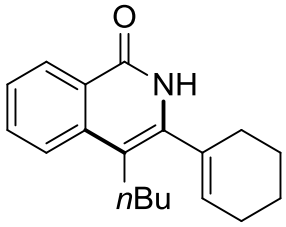
The regioselectivity of the C–H/N–O functionalization with unsymmetrically-substituted alkynes **38** was well controlled, generally placing the less steric hindered aliphatic substituent distal to nitrogen (Table 3.6). Notably, the robust ruthenium(II) catalyst proved to be tolerant of an unprotected hydroxyl group and a thiophene moiety (entries 5 and 6).

Table 3.6: Scope of *N*-hydroxybenzamide **88a** with unsymmetrically-substituted alkynes **38**.[a]



88a **38** **41**

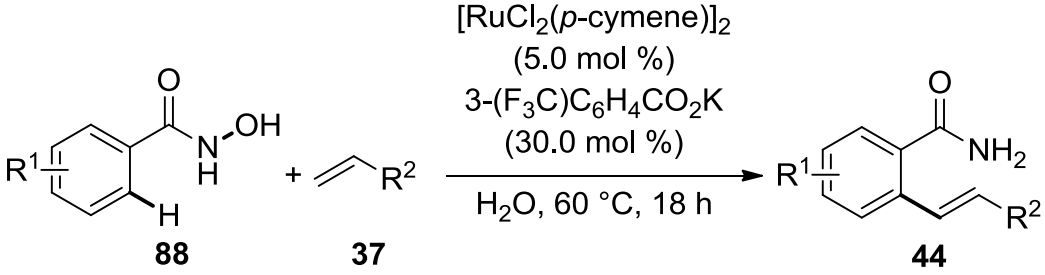
entry	**38**	**41**	yield [%]
			
1	R^2 = H (**38i**)	**41ai**	79
2	R^2 = OMe (**38j**)	**41aj**	65
3	R^2 = F (**38k**)	**41ak**	69
4	 **38l**	 **41al**	73
5	 **38m**	 **41am**	70
6	 **38n**	 **41an**	44

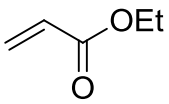
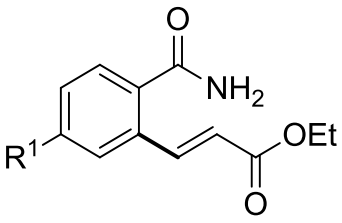
entry	**38**	**41**	yield [%]
7	 **38o**	 **41ao**	49

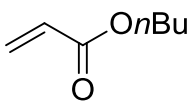
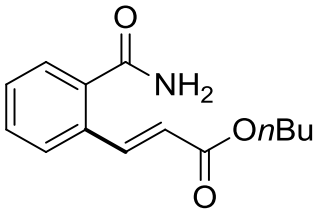
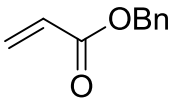
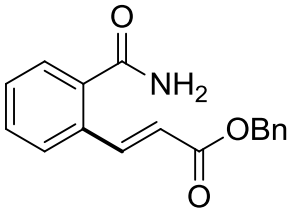
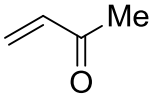
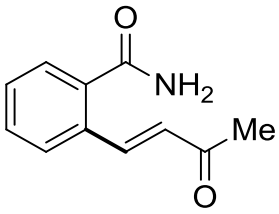
[a] Reaction conditions: **88a** (0.5 mmol), **38** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), 3-$(F_3C)C_6H_4CO_2K$ (30.0 mol %), H_2O (2.0 mL), 100 °C, 18 h.

It is noteworthy that the dehydrative C–H/N–O functionalization strategy was not restricted to transformations of alkynes. Hence, this strategy also enabled the efficient intermolecular alkenylation with *N*-hydroxybenzamides **88** to furnish the corresponding styrene derivatives **44** in an atom- and step-economical manner (Table 3.7).

Table 3.7: Scope of alkenylation by C–H/N–O functionalization.[a]



entry	**88**	**37**	**44**		yield [%]
1	**88a**	 **37a**		R^1 = H (**44aa**)	82
2	**88b**			R^1 = Me (**44ba**)	80
3	**88d**			R^1 = F (**44da**)	67

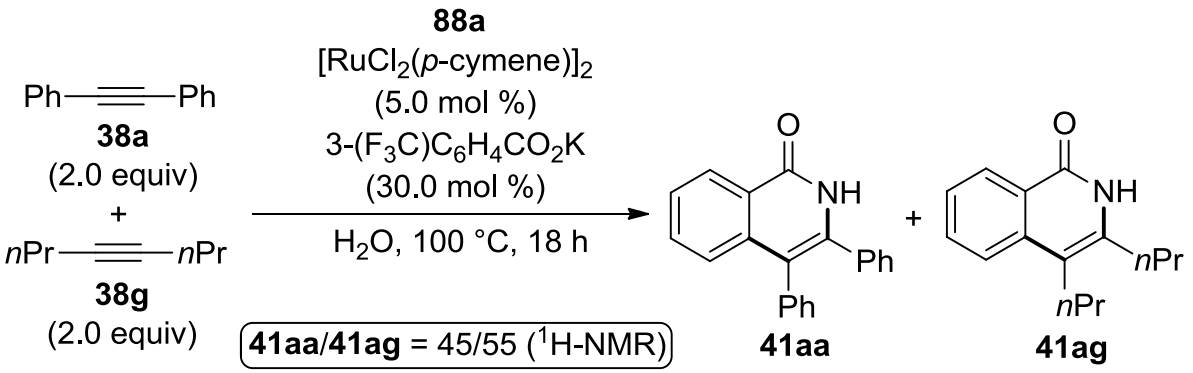
entry	**88**	**37**	**44**	yield [%]
4	**88a**	 **37b**	 **44ab**	73
5	**88a**	 **37c**	 **44ac**	82
6	**88a**	 **37d**	 **44ad**	52

[a] Reaction conditions: **88** (0.5 mmol), **37** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), 3-$(F_3C)C_6H_4CO_2K$ (30.0 mol %), H_2O (2.0 mL), 60 °C, 18 h.

3.3 Mechanistic Studies

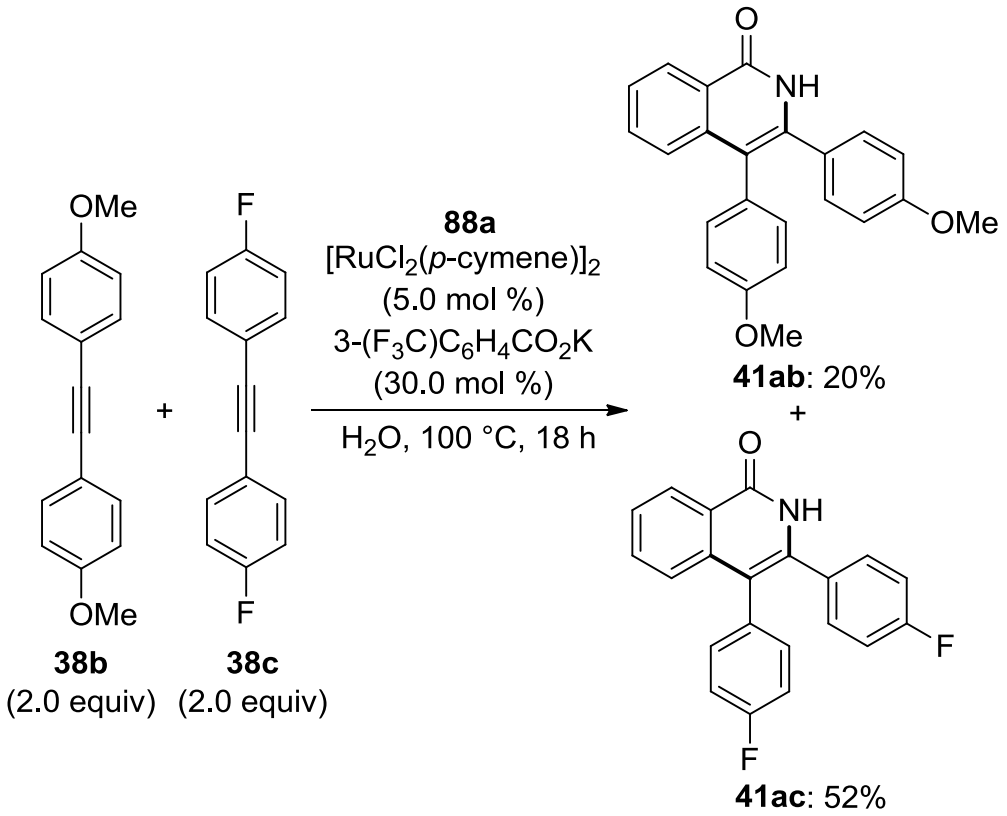
3.3.1 Competition Experiments

Within competition experiments between aryl- and alkyl-substituted alkynes, more alkyl-substituted isoquinoline was generated than aryl-substituted isoquinoline in the one-pot reaction (Scheme 3.2).



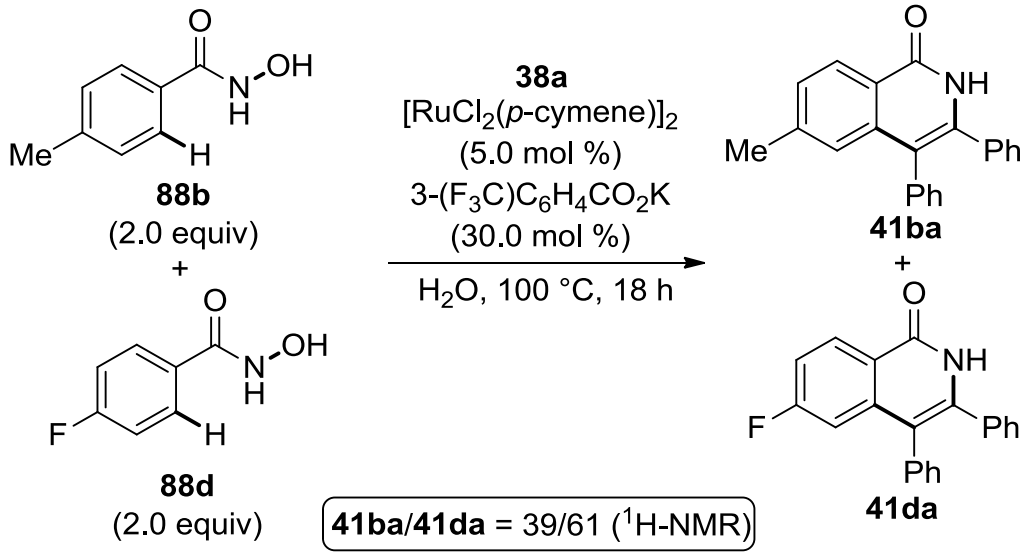
Scheme 3.2: Intermolecular competitition experiment between alkyenes **38a** and **38g**.

We compared the reactivity of alkynes bearing electron-donating or electron-withdrawing groups in a one-pot reaction (Scheme 3.3). The later one was found to be more reactive.



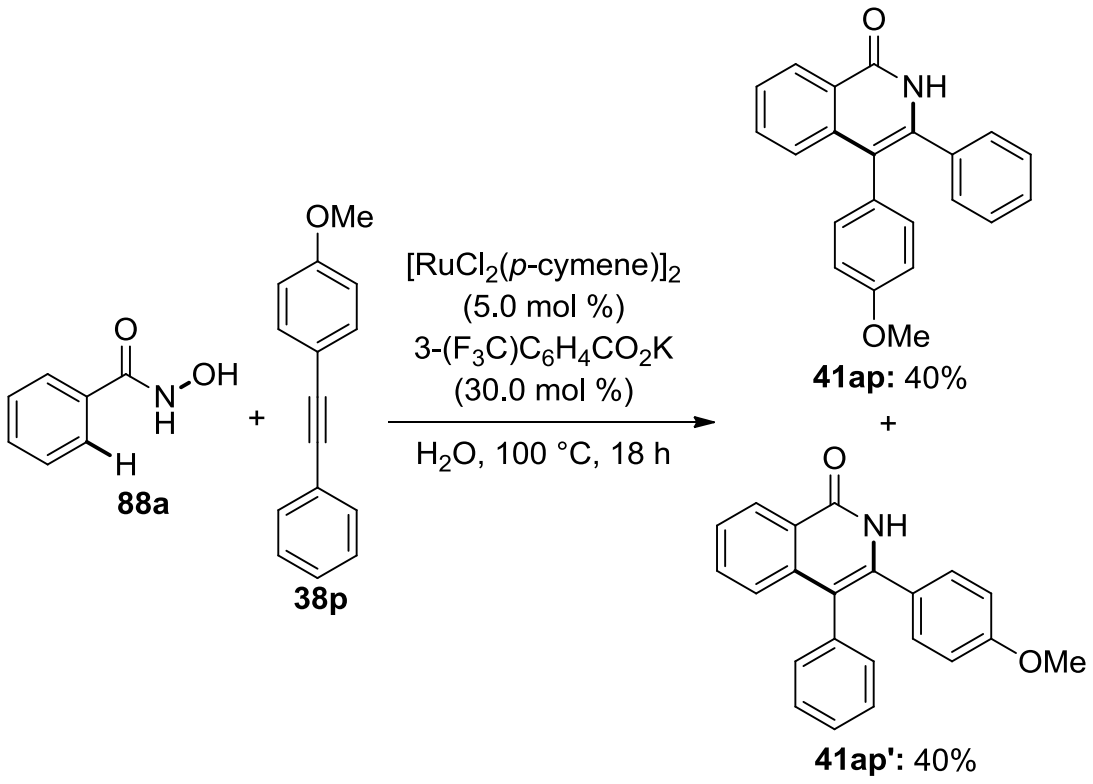
Scheme 3.3: Intermolecular competition experiment between alkynes **38b** and **38c**.

We compared the reactivity of *N*-hydroxybenzamides **88** bearing electron-donating and electron-withdrawing substituents, and found the later to be more reactive (Scheme 3.4).



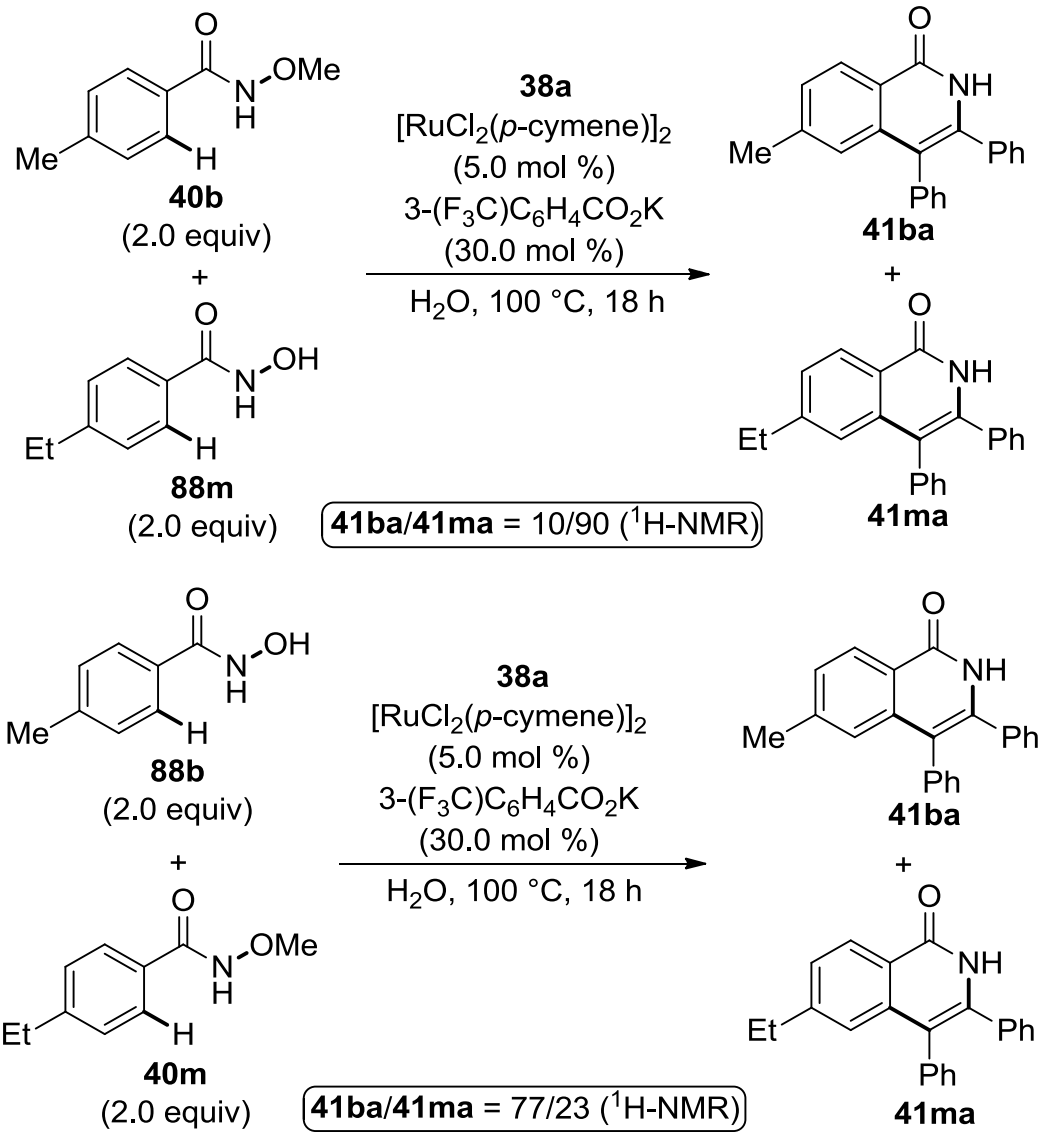
Scheme 3.4: Intermolecular competitition experiment between *N*-hydroxybenzamides **88b** and **88d**.

To investigate the influence of the tolane substituents on the regioselectivity, we performed the intramolecular competition experiment with **38p** (Scheme 3.5). The equal amount of products indicated that there is no electronic influence on regioselectivity.



Scheme 3.5: Regioselectivity of alkyne **38p** bearing ends with different electron density.

We were also eager to investigate the relative reactivity between *N*-methoxybenzamides **40** and *N*-hydroxybenzamides **88** (Scheme 3.6). The result indicated that *N*-hydroxybenzamides **88** are more reactive than *N*-methoxybenzamides **40**.

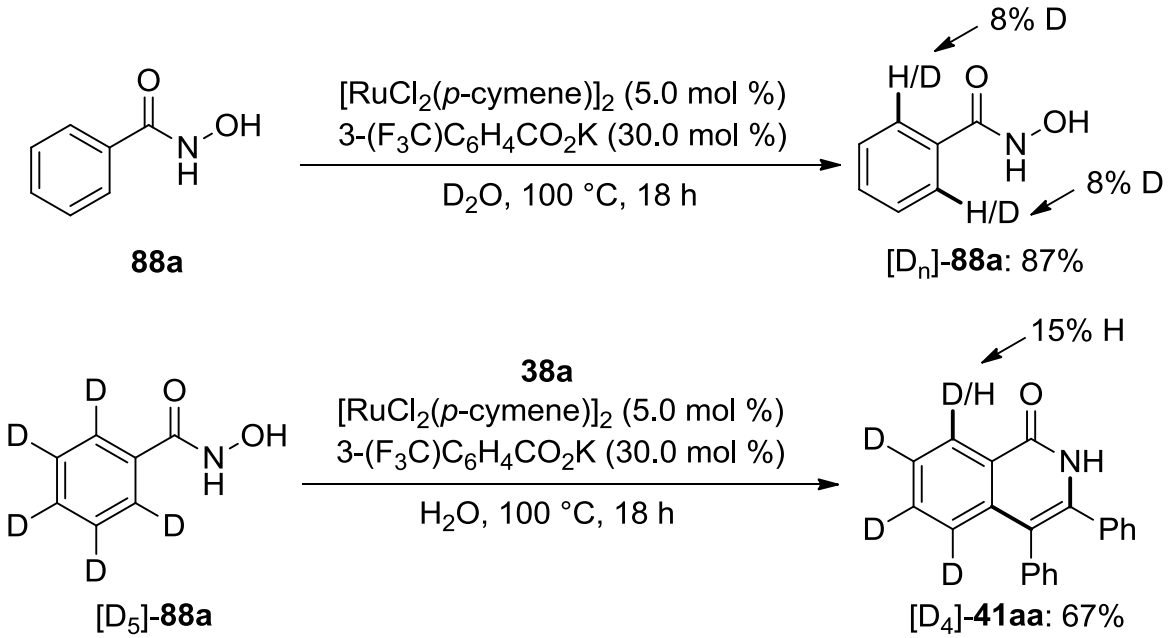


Scheme 3.6: Intermolecular competitition experiments between *N*-methoxybenzamides **40** and *N*-hydroxybenzamides **88**.

3.3.2 Studies with Isotopically Labeled Compounds

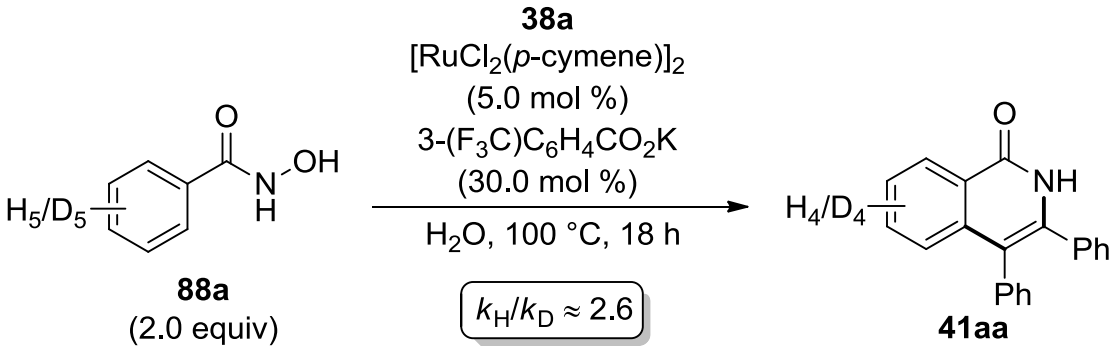
In order to gain insights into the reaction mechanism, we performed a series of isotope studies (Scheme 3.7). In the absence of an alkyne, 8% hydrogen on each *ortho* position was incorporated by deuterium, indicating an irreversible deprotonation. In another experiment

employing [D_5]-**88a**, a minor D/H scrambling in the product was observed.



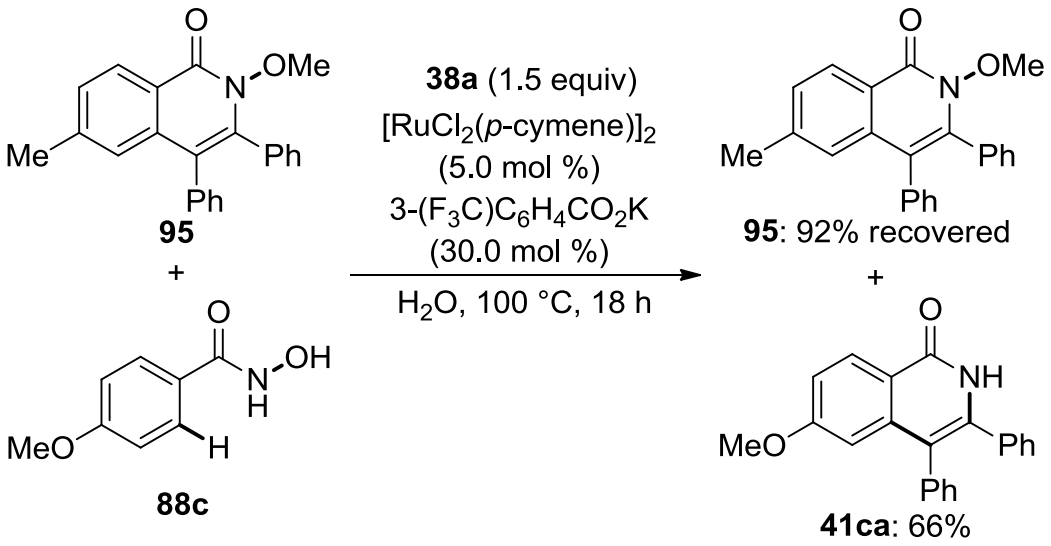
Scheme 3.7: C–H/N–O functionalization with isotopically labeled solvent and substrate [D_5]-**88a**.

The kinetic isotope effect (KIE) experiment with **88a** and [D_5]-**88a** in a one-pot reaction showed that the C–H activation should be the rate-limiting step (Scheme 3.8).



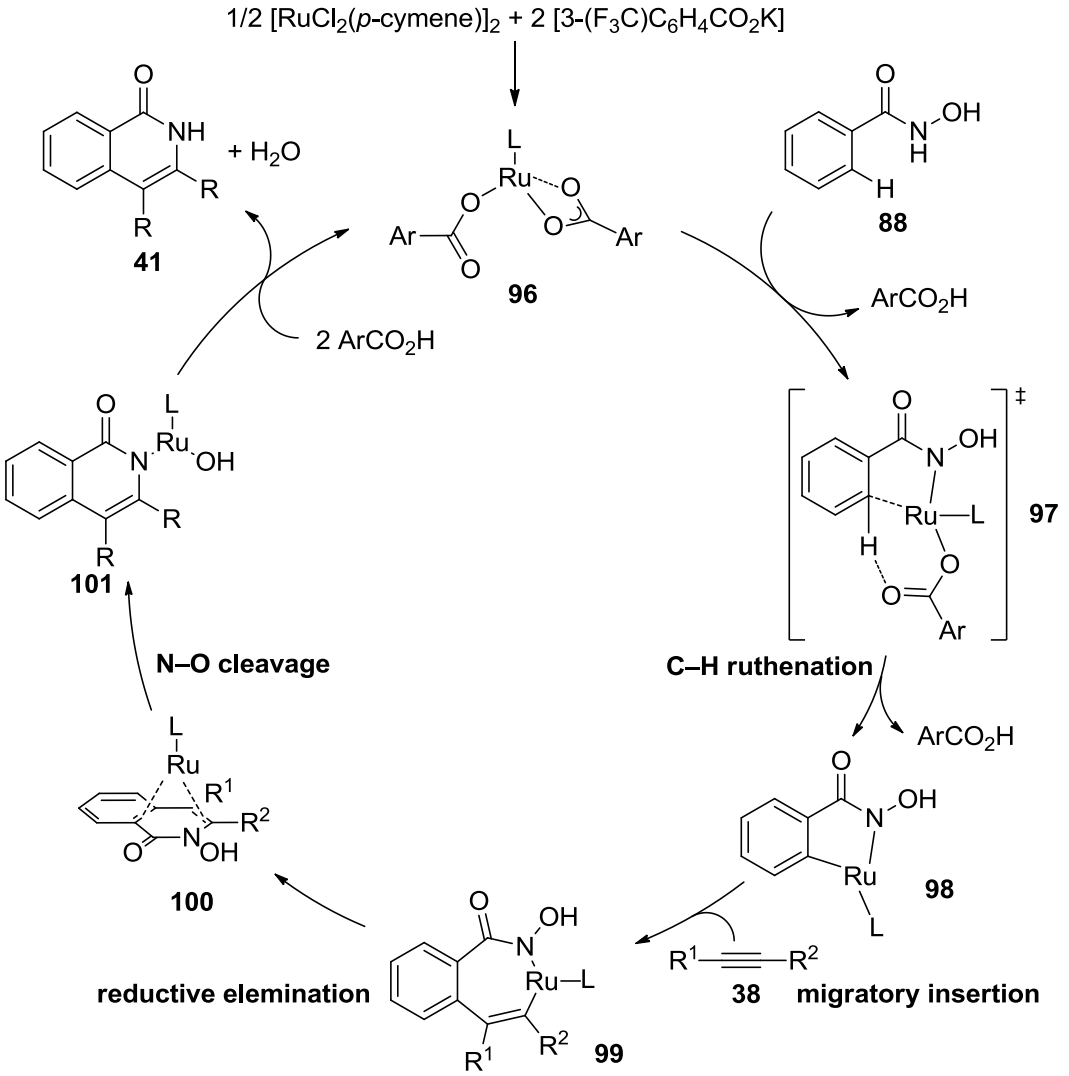
Scheme 3.8: Kinetic isotope efect of C−H/N−O functionalizations.

Furthermore, a crossover experiment was performed with substrates **95** and **88c**, indicating the re-oxidation of the ruthenium catalyst to occur in an intramolecular manner (Scheme 3.9).



Scheme 3.9: Crossover experiment.

Based on our mechanistic studies, we propose the catalytic cycle as shown in Scheme 3.10: First, the in situ-generated ruthenium(II)-carboxylate complex **96** is coordinated by *N*-hydroxybenzamide to form ruthenium(II) complex **97**. Second, carboxylate-assisted C–H ruthenation occurs to generate complex **98** and carboxylic acid. Third, migratory insertion of alkyne **38** with cyclometalated complex **98** delivers the ruthenium(II) complex **99**. Fourth, inspired by a previous report of the Ackermann group,[106] we suppose that the reductive elimination generates ruthenium(0) intermediate **100**. Fifth, oxidative addition of ruthenium(0) species onto the N–O bond in an intramolecular fashion to yield ruthenium(II) amide **101**. Finally, protodeamidation releases the desired product **41** and at the same time regenerates the catalytically active ruthenium(II) biscarboxylate catalyst **96**.



Scheme 3.10: Proposed catalytic cycle of ruthenium(II)-catalyzed C−H/N−O functionalization. (L = *p*-cymene, Ar = 3-(F_3C)C_6H_4)

4 Ruthenium(II)-Catalyzed C–H Oxygenation on Weinreb Amides

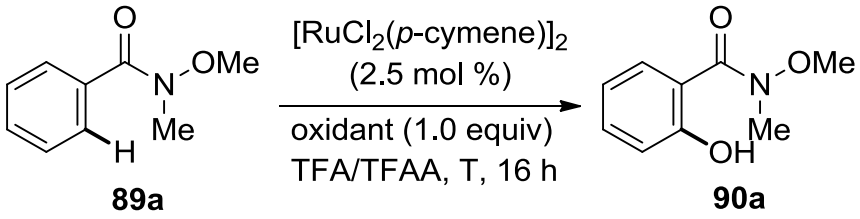
Because of their considerable importance, many synthetic procedures toward phenols have been developed. During recent years, step-economical chelation-assisted C–H oxygenations were accomplished with the aid of various directing groups utilizing transition metal catalysts. Very recently, the Ackermann group and the Rao group developed ruthenium-catalyzed C–H bond activations leading to the formation of C–O bonds.[70]

The easily accessible *N*-Methoxy-*N*-methylamides, also known as Weinreb amides, are important functional groups in organic synthesis, because they can be chemoselectively transformed into the corresponding ketones or aldehydes.[164] Therefore, Weinreb amides **89** have been widely applied in organic synthesis of naturally occurring bioactive compounds.[165] In contrast, Weinreb amides have unfortunately been less explored for metal-catalyzed C–H bond functionalizations, and direct oxygenations of aryl Weinreb amides have thus far proven elusive. Herein, we developed site-selective C(sp^2)–H bond oxygenations on aryl Weinreb amides **89** under remarkably mild reaction conditions.[166]

4.1 Optimization of Ruthenium(II)-Catalyzed C–H Oxygenation on Weinreb Amides

At the outset, we tested different oxidants, of which copper(II) or silver(I) salts were found to be ineffective, while mCPBA and $K_2S_2O_8$ proved to be promising candidates (Table 4.1, entries 2-6). The hypervalent iodine(III) reagent $PhI(OAc)_2$ was found to be the optimal oxidant at a reaction temperature of 50 °C (entry 7). It is important to note that it should be the lowest reaction temperature reported so far for ruthenium-catalyzed C(sp^2)–H oxygenations. $[RuCl_2(PPh_3)_3]$ provided a diminished yield (entry 9). With a lower catalyst loading, the well-defined ruthenium(II) biscarboxylate complex **27** delivered 80% yield (entry 10). We changed the ratio of TFA/TFAA solvents and found TFAA to be the essential component (entries 14-17). Generally, the ruthenium catalysts were found to be highly robust, as showcased by all catalytic reactions being performed without strict exclusion of moisture under an atmosphere of air. Yet, the C–H bond oxygenation also occurred readily under an inert N_2 atmosphere (entry 18).

Table 4.1: Optimization of ruthenium(II)-catalyzed C–H oxygenation on Weinreb amide **89a**.[a]



89a **90a**

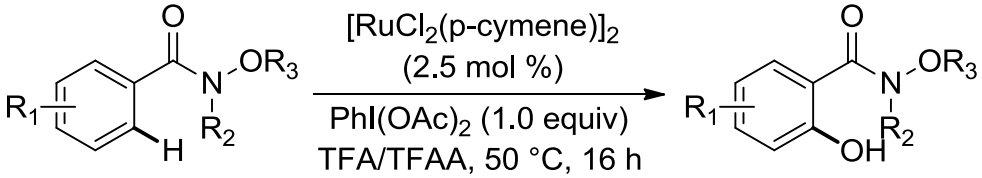
entry	oxidant	TFA/TFAA	T [°C]	yield [%]
1	—	3:1	50	—
2	$K_2S_2O_8$	3:1	50	57
3[b]	$K_2S_2O_8$	3:1	50	—
4	AgOAc	3:1	50	< 5[c]
5	$Cu(OAc)_2 \cdot H_2O$	3:1	50	—
6	mCPBA	3:1	50	39
7	**$PhI(OAc)_2$**	**3:1**	**50**	**84**
8[d]	$PhI(OAc)_2$	3:1	50	76
9[e]	$PhI(OAc)_2$	3:1	50	57
10[f]	**$PhI(OAc)_2$**	**3:1**	**50**	**80**
11	$PhI(OAc)_2$	3:1	100	54
12	$PhI(OAc)_2$	3:1	80	60
13	$PhI(OAc)_2$	3:1	30	30
14	$PhI(OAc)_2$	1:1	50	73
15	$PhI(OAc)_2$	2:1	50	74
16	$PhI(OAc)_2$	9:1	50	76
17	$PhI(OAc)_2$	1:0	50	< 5[c]
18[g]	$PhI(OAc)_2$	3:1	50	79

[a] Reaction conditions: **89a** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), oxidant (0.5 mmol), TFA/TFAA (2.0 mL); isolated yields. [b] No catalyst. [c] GC-conversion with 1,3,5-trimethoxybenzene as the internal standard. [d] $[RuCl_2(p\text{-cymene})]_2$ (1.3 mol %). [e] $RuCl_2(PPh_3)_3$ (5.0 mol %). [f] $[Ru(O_2CMes)_2(p\text{-cymene})]$ (2.5 mol %). [g] Under N_2.

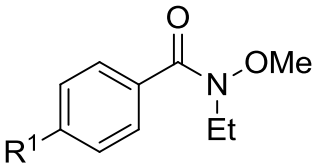
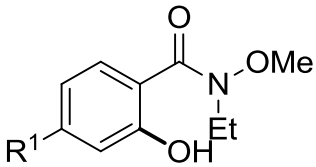
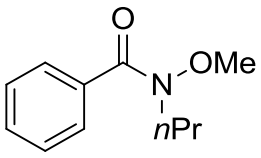
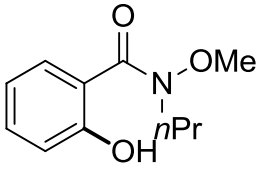
4.2 Scope of Ruthenium(II)-Catalyzed C–H Oxygenation on Weinreb Amides

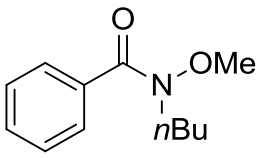
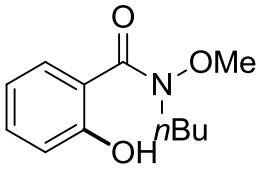
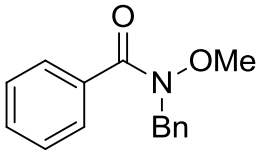
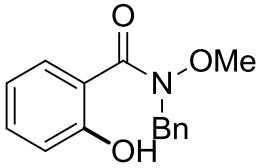
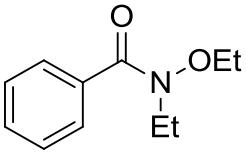
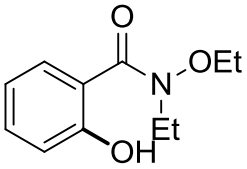
With an effective catalytic system in hand, we studied the influence of the amide *N*-substitution pattern on the efficacy of the C–H bond oxygenation (Table 4.2). Notably, a variety of functional groups on the amides were well tolerated by the catalytic system to furnish the corresponding products **90**, even when being sterically hindered (entry 7).

Table 4.2: Scope of ruthenium(II)-catalyzed C–H oxygenation on different *N*-substituted Weinreb amides **89**.[a]



89 **90**

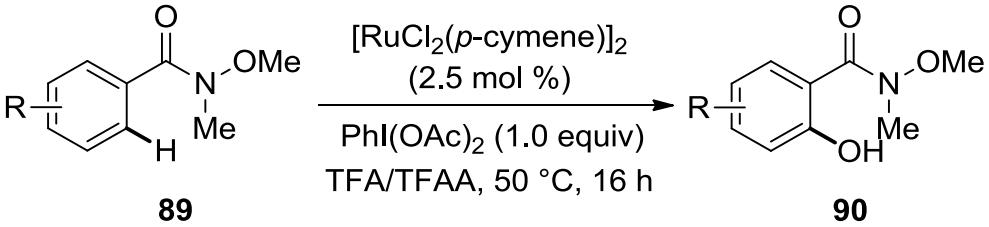
entry	**89**	**90**	yield [%]
			
1	R = H (**89b**)	**90b**	78
2	R = Me (**89c**)	**90c**	77
3	R = F (**89d**)	**90d**	75
4	 **89e**	 **90e**	74

entry	**89**	**90**	yield [%]
5	 **89f**	 **90f**	75
6	 **89g**	 **90g**	64
7	 **89h**	 **90h**	76

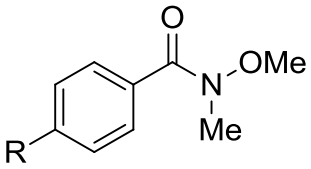
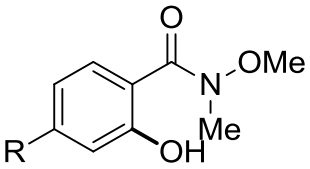
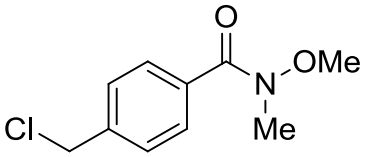
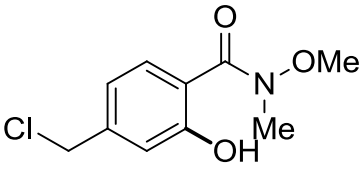
[a] Reaction conditions: **89** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $PhI(OAc)_2$ (0.5 mmol), TFA/TFAA (2.0 mL), 50 °C, 16 h.

Then we evaluated the versatility of the C–H oxygenation with *N*-methoxy-*N*-methylbenzamides **89** bearing substituents on the aromatic ring (Table 4.3). Generally, the catalytic system showed high chemoselectivity. Important electrophilic functional groups, including fluoro, chloro, iodo substituents as well as benzyl chloride were well tolerated (entries 5-8).

Table 4.3: Scope of ruthenium(II)-catalyzed C–H oxygenation on different arene-substituted Weinreb amides **89**.[a]



89 **90**

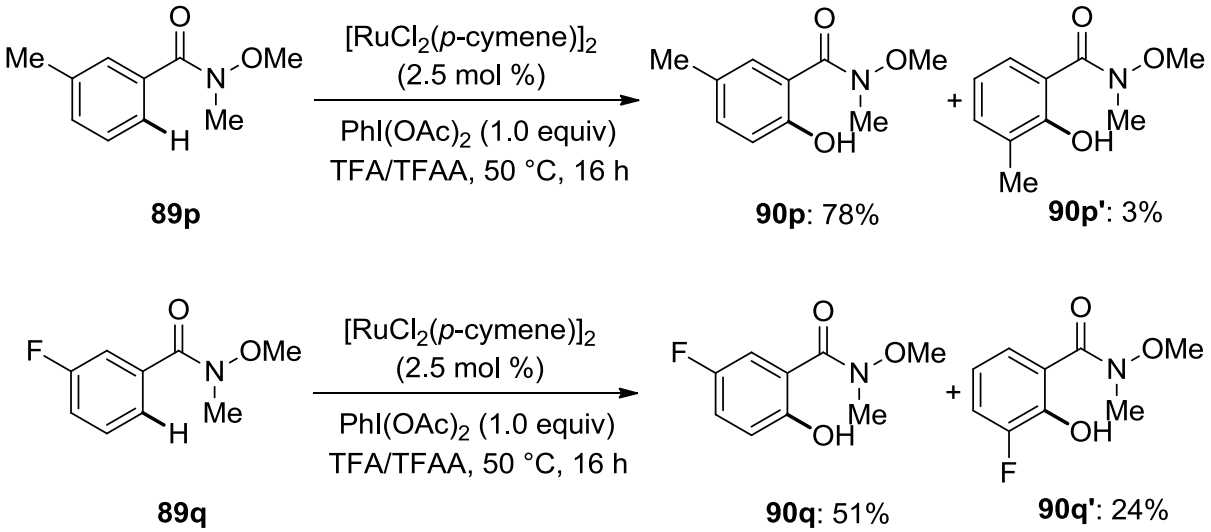
entry	**89**	**90**	yield [%]
			
1	R = H (**89a**)	**90a**	76
2	R = Me (**89i**)	**90i**	76
3	R = Et (**89j**)	**90j**	78
4	R = CF_3 (**89k**)	**90k**	73
5	R = F (**89l**)	**90l**	79
6	R = Cl (**89m**)	**90m**	85
7	R = I (**89n**)	**90n**	80
8	 **89o**	 **90o**	61

[a] Reaction conditions: **89** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $PhI(OAc)_2$ (0.5 mmol), TFA/TFAA (2.0 mL), 50 °C, 16 h.

4.3 Mechanistic Studies

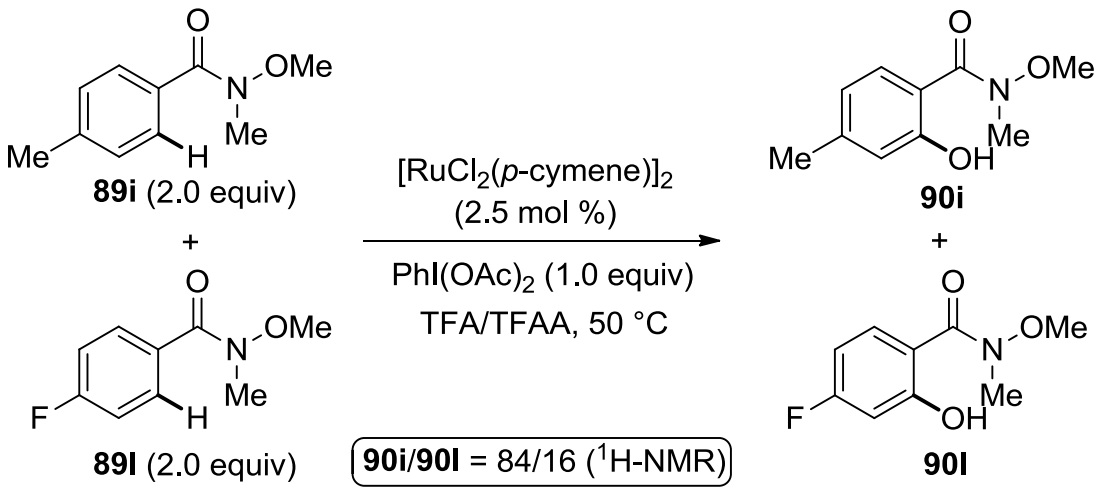
4.3.1 Competition Experiments

Intramolecular competition experiments with *meta*-methyl-substituted Weinreb amides **89p** highlighted steric effects to primarily influence on the site selectivity of the C–H bond functionalization. In contrast, *meta*-fluoro-substituted arene **89q** led to the formation of significant amounts of product **90q'** (Scheme 4.1).



Scheme 4.1: Intramolecular competition experiments with substrates **89p** and **89q**.

The intermolecular competition experiment was performed with *N*-methoxy-*N*,4-dimethylbenzamide (**89i**) and 4-fluoro-*N*-methoxy-*N*-methylbenzamide (**89l**) (Scheme 4.2). It showed electron-rich substrates to be preferentially functionalized.

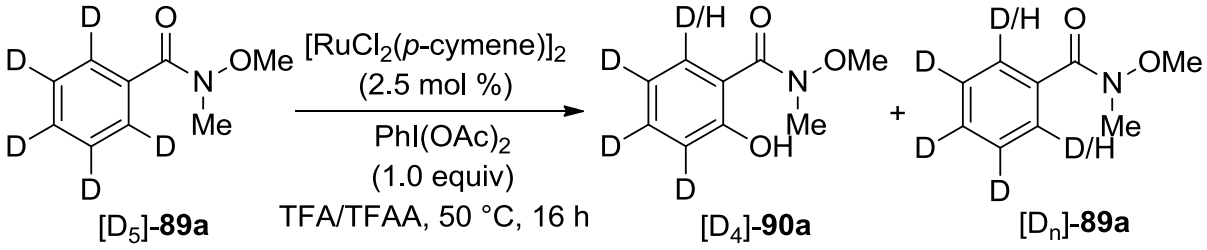


Scheme 4.2: Intermolecular competition experiment between substrates **89i** and **89l**.

4.3.2 Studies with Isotopically Labeled Compounds

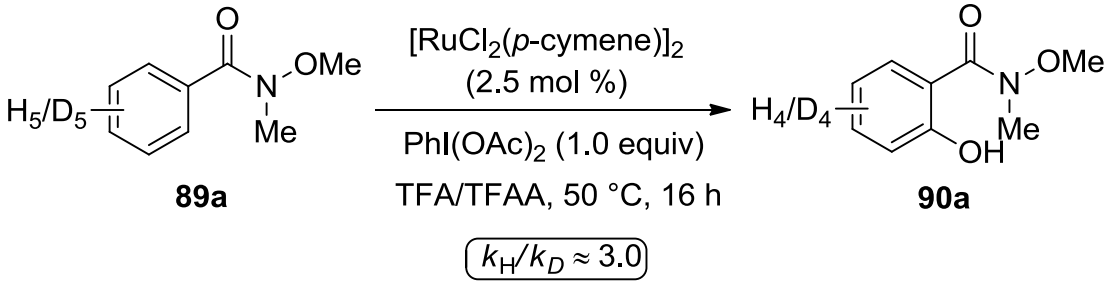
Deuterium labeled Weinreb amide [D_5]-**89a** was utilized in catalytic oxygenations (Scheme 4.3). Two parallel reactions were performed for 3 h and 16 h, respectively. Only trace hydrogen incorporation was detected on the desired product and reisolated starting material

which is in line with an irreversible C–H metalation.



Scheme 4.3: C–H oxygenation on labeled substrate [D_5]-**89a**.

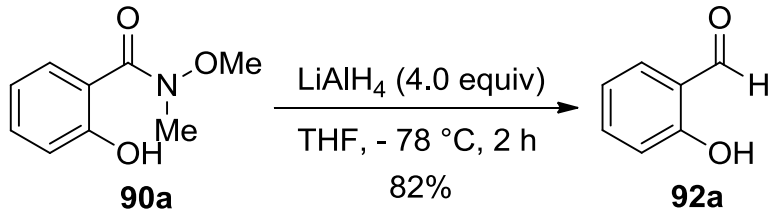
Additionally, the kinetic isotope effect (KIE) was studied with substrates **89a** and [D_5]-**89a** (Scheme 4.4). The KIE value of $k_H/k_D \approx 3.0$ provided strong support for a kinetically relevant C–H metalation step.



Scheme 4.4: Kinetic isotope effect studies with Weinreb amides **89a** and [D_5]-**89a**.

4.4 Diversification of Product

To the best of our knowledge, salicylaldehydes **92** were until recently not accessible via direct C–H bond oxygenation methods. With $LiAlH_4$ as the reducing agent, salicylaldehyde **92a** could be easily prepared from *ortho*-hydroxylated Weinreb amides **90a** (Scheme 4.5), thus illustrating the practical importance of the ruthenium(II)-catalyzed C–H bond oxygenations on Weireb amides.



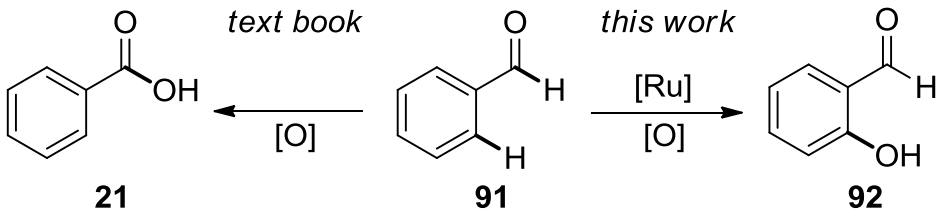
90a **92a**

Scheme 4.5: Synthesis of salicylaldehyde **92a** using *ortho*-hydroxylated Weinreb amide **90a**.

5 Ruthenium(II)-Catalyzed C–H Oxygenation on Aldehydes

It is a challenging project for C–H oxygenations with weakly coordinating directing groups.[45,72] Although the Ackermann group has made great achievements by utilizing ketones for site-selective ruthenium(II)-catalyzed C–H oxygenations, the formyl group is much more challenging as a substrate in C–H oxygenations and has unfortunately proven elusive thus far.[118] As an alternative method, protecting groups are introduced to avoid unwanted oxidation.[167] The lack of available C–H activation methods is likely due to the inherent tendency of aldehydes to undergo facile oxidation under the strongly oxidizing reaction conditions of metal-catalyzed C–H functionalizations.

Herein we disclose the first aldehyde-directed C–H oxygenation, in which the versatile ruthenium(II) catalysts overrode the inherent substrate-controlled formyl oxidation by chelation-controlled aromatic C–H activation.[168] It is noteworthy that the salicylaldehyde products can be easily converted to other useful building blocks in organic synthesis.



Scheme 5.1: Ruthenium(II)-catalyzed challenging C–H oxygenation on aldehydes.

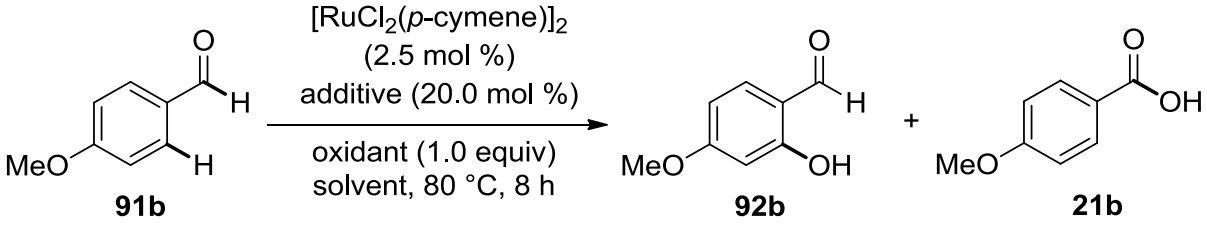
5.1 Optimization of Ruthenium(II)-Catalyzed C–H Oxygenation on Aldehydes

It is known that aldehydes are relatively volatile, thus benzaldehyde (**91a**) was not the best substrate for optimization. Therefore, we chose 4-methoxybenzaldehyde (**91b**) which has a higher boiling point of 248 °C (Table 5.1). The previously used $PhI(OAc)_2$/TFA/TFAA system delivered the acid **21b** rather than the desired phenol product **92b** (entries 1-3). Afterwards, we changed the solvent to DCE. With $Cu(OAc)_2 \cdot H_2O$, BQ, or $K_2S_2O_8$ we could get neither phenol nor acid product (entries 4-6), while $PhI(OAc)_2$ again delivered the acid **21b** as the sole product (entry 7).

The breakthrough was achieved by utilizing $PhI(OTFA)_2$ as the oxidant in DCE as the solvent at

80 °C, generating 43% of phenol **92b** and 9% of acid **21b** (entry 8). Subsequently, we tested several additives, of which KOAc significantly reversed the chemo-selectivity with the formation of 5% of phenol **92b** and 32% of acid **21b** (entry 10). Other additives showed significantly lower efficiency (entries 11 and 12).

Table 5.1: Optimization of ruthenium(II)-ctalyzed C–H oxygenation on aldehyde **91b** with different additives and oxidants.[a]

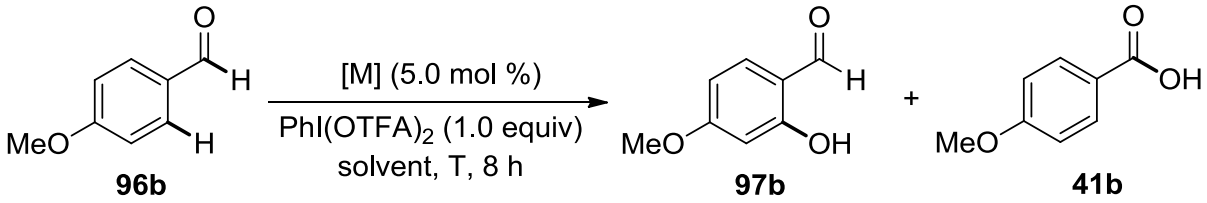


entry	additive	oxidant	solvent	yield [%]		
				91b	**92b**	**21b**
1	—	$PhI(OAc)_2$	TFA/TFAA (3:1)	33	0	41
2	—	$PhI(OTFA)_2$	TFA/TFAA (3:1)	37	0	20
3	—	$K_2S_2O_8$	TFA/TFAA (3:1)	0	0	89
4	—	$Cu(OAc)_2 \cdot H_2O$	DCE	93	0	0
5	—	BQ	DCE	91	0	0
6	—	$K_2S_2O_8$	DCE	88	0	0
7	—	$PhI(OAc)_2$	DCE	38	0	39
8	**—**	**$PhI(OTFA)_2$**	**DCE**	**32**	**43**	**9**
9[b]	—	$PhI(OTFA)_2$	DCE	69	0	5
10	KOAc	$PhI(OTFA)_2$	DCE	44	5	32
11	$AgSbF_6$	$PhI(OTFA)_2$	DCE	51	15	9
12	KPF_6	$PhI(OTFA)_2$	DCE	35	39	3

[a] Reaction conditions: **91b** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), additive (20.0 mol %), oxidant (1.0 equiv), solvent (2.0 mL), 8 h, isolated yields. [b] No catalyst.

As shown in Table 5.2, we screened other ruthenium catalysts and different solvents, but could not get any better yields. Several reaction temperatures were tested, of which 100 °C was found to be optimal. We got 72% of 2-hydroxy benzaldehyde (**92b**) and only 2% of acid **21b** by using 1.5 equivalent amount of $PhI(OTFA)_2$. This was an ideal result, concerning both yield and chemo-selectivity. It is noteworthy that under the same conditions, other metals, such as palladium, rhodium, or nickel, could only generate the acid **21b** (entries 12-14).

Table 5.2: Optimization of ruthenium(II)-ctalyzed C–H oxygenation on aldehydes with $PhI(OTFA)_2$ as the oxidant.[a]



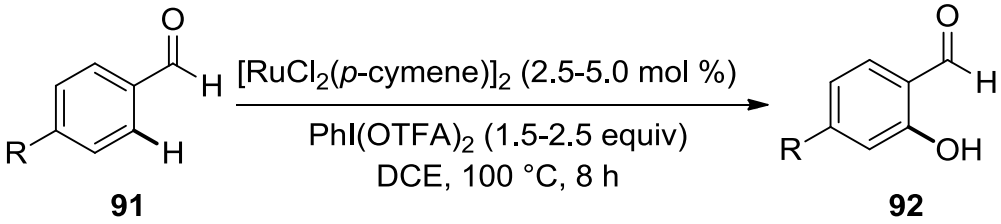
entry	[M]	solvent	T [°C]	yield [%]		
				91b	**92b**	**21b**
1	$RuCl_2(PPh_3)_3$	DCE	80	51	5	16
2	$RuCl_3$	DCE	80	51	0	34
3	$[RuCl_2(p\text{-cymene})]_2$	PhMe	80	66	21	1
4	$[RuCl_2(p\text{-cymene})]_2$	PhCl	80	62	9	3
5	$[RuCl_2(p\text{-cymene})]_2$	1,4-dioxane	80	70	3	14
6	$[RuCl_2(p\text{-cymene})]_2$	DME	80	73	0	1
7	$[RuCl_2(p\text{-cymene})]_2$	DCE	50	73	<2	9
8	$[RuCl_2(p\text{-cymene})]_2$	DCE	100	26	47	3
9	$[RuCl_2(p\text{-cymene})]_2$	DCE	120	26	40	3
10[b]	**$[RuCl_2(p\text{-cymene})]_2$**	**DCE**	**100**	**12**	**72**	**2**
11[b,c]	$[RuCl_2(p\text{-cymene})]_2$	DCE	100	16	43	13
12[b]	$Pd(OAc)_2$	DCE	100	37	0	38
13[b]	$[RhCp^*Cl_2]_2$	DCE	100	70	0	11
14[b]	$Ni(acac)_2$	DCE	100	79	0	14

[a] Reaction conditions: **91b** (0.5 mmol), [TM] (5.0 mol %), $PhI(OTFA)_2$ (1.0 equiv), solvent (2.0 mL), 8 h, isolated yields. [b] $PhI(OTFA)_2$ (1.5 equiv). [c] $[RuCl_2(p\text{-cymene})]_2$ (1.25 mol %).

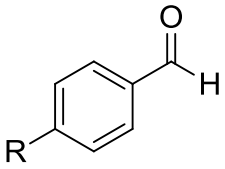
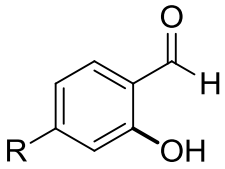
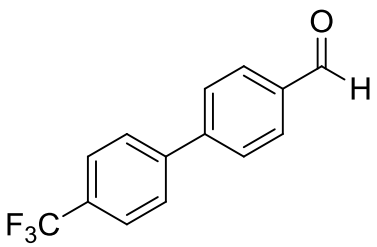
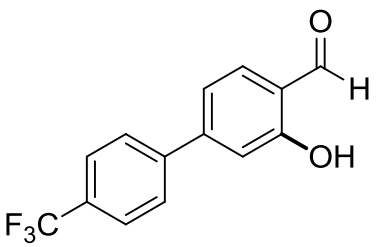
5.2 Scope of Ruthenium(II)-Catalyzed C–H Oxygenation on Aldehydes

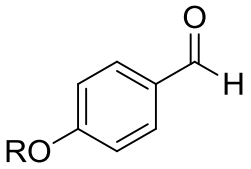
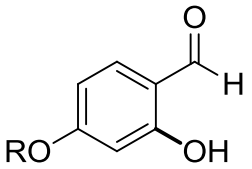
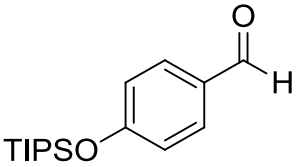
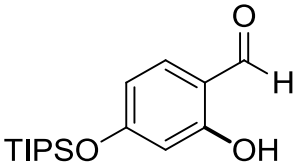
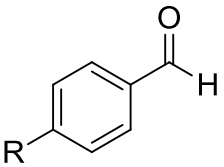
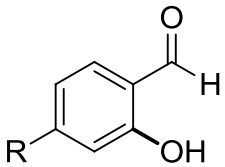
With the optimal reaction conditions in hand, we probed the scope of the aldehyde-assisted C–H oxygenation on various substituted benzaldehydes **91** (Table 5.3). Useful functional groups, such as fluoro, chloro, or silyl ether, were well tolerated by the highly chemoselective ruthenium(II) catalyst (entries 12-14). Generally, in *para*-substituted benzaldehydes, the electron-donating groups implanted positive effect to the C(sp^2)–H oxygenation, while electron-withdrawing groups led to reduced yields.

Table 5.3: Scope of ruthenium(II)-ctalyzed C–H oxygenation on *para*-substituted aldehydes **91**.[a]



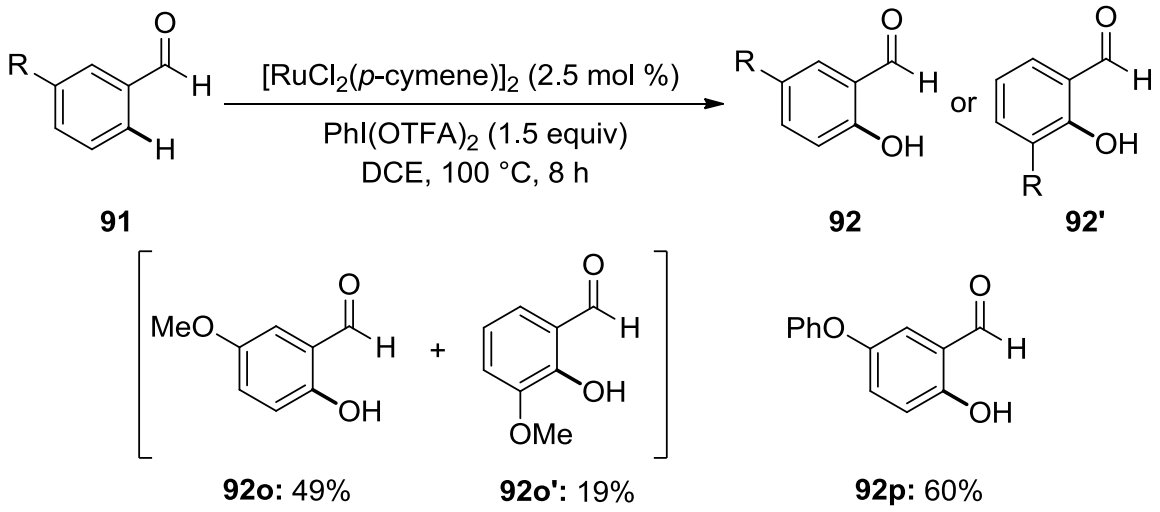
91 **92**

entry	**91**	**92**	yield [%]
			
1[b]	R = H (**91a**)	**92a**	48
2[b]	R = Me (**91c**)	**92c**	61
3[b]	R = Et (**91d**)	**92d**	57
4[b]	R = *i*Pr (**91e**)	**92e**	55
5[b]	R = *t*Bu (**91f**)	**92f**	61
6	R = Ph (**91g**)	**92g**	57
7[c]	 **91h**	 **92h**	59

entry	**91**	**92**	yield [%]
			
8	R = Me (**91b**)	**92b**	72
9	R = Et (**91i**)	**92i**	69
10	R = *n*Hex (**91j**)	**92j**	55
11	R = Ph (**91k**)	**92k**	66
12[b]	 **91l**	 **92l**	41
			
13[c]	R = F (**91m**)	**92m**	44
14[c]	R = Cl (**91n**)	**92n**	43

[a] Reaction conditions: **91** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $PhI(OTFA)_2$ (1.5 equiv), DCE (2.0 mL), 100 °C, 8 h. [b] $PhI(OTFA)_2$ (2.0 equiv). [c] $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $PhI(OTFA)_2$ (2.5 equiv).

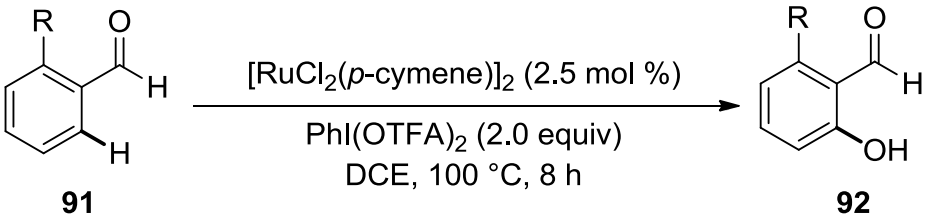
Afterwards we investigated the site-selectivity of the ruthenium(II)-catalyzed oxygenation using *meta*-substituted benzaldehydes **91** (Scheme 5.2). The steric factor was found important for controlling the site-selectivities. With the less sterically hindered methoxy group, both isomers **92o** and **92o'** were generated, while with the more congested phenoxy group, improved selectivities were obtained.

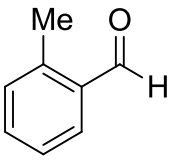
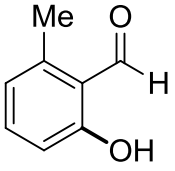


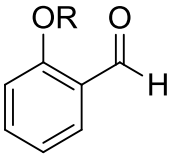
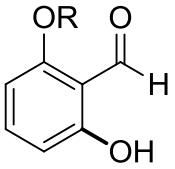
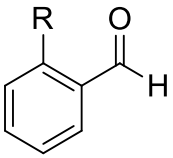
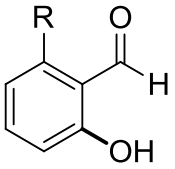
Scheme 5.2: Ruthenium(II)-ctalyzed C–H oxygenation on *meta*-substituted aldehydes **91**.

In contrast to the ruthenium(II)-catalyzed oxygenation on Weinreb amides **89**, this reaction system could efficiently convert the more sterically hindered *ortho*-substituted benzaldehydes **91** into the desired salicyaldehydes **92** (Table 5.4). It is noteworthy that the synthetically useful 2-chloro and 2-bromobenzaldehydes **91t** and **91u** delivered comparable yields (entries 4 and 5).

Table 5.4: Scope of ruthenium(II)-catalyzed C–H oxygenation on *ortho*-substituted aldehydes **91**.[a]

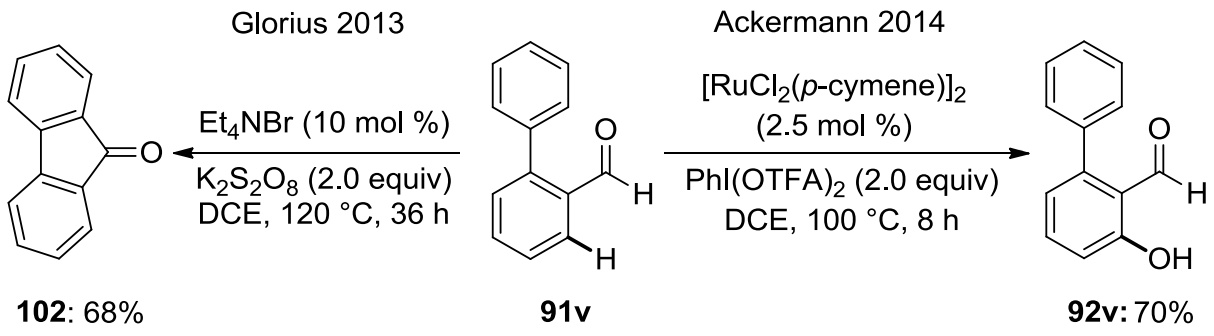


entry	**91**	**92**	yield [%]
1	 **91q**	 **92q**	53

entry	**91**	**92**	yield [%]
			
2	R = Et (**91r**)	**92r**	65
3	R = Ph (**91s**)	**92s**	63
			
4	R = Cl (**91t**)	**92t**	50
5	R = Br (**91u**)	**92u**	57

[a] Reaction conditions: **91** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $PhI(OTFA)_2$ (2.0 equiv), DCE (2.0 mL), 100 °C, 8 h.

Interestingly, 2-phenyl-benzaldehyde (**91v**) delivered the desired *ortho*-hydroxylated product **92v** with good yield (Scheme 5.3), while Glorius and coworkers reported the formation of fluorenone **102** with the substrate **91v** when employing Et_4NBr as the catalyst and $K_2S_2O_8$ as the oxidant.[169]

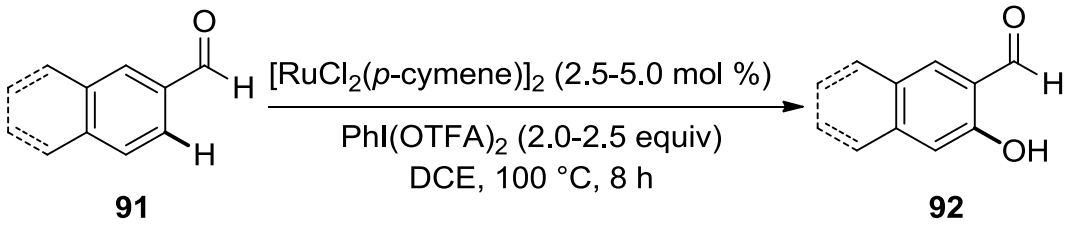


Scheme 5.3: Different chemo-selectivities in the oxidation of **91v**.

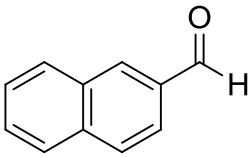
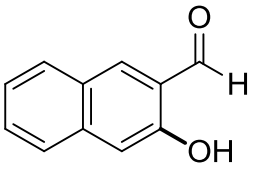
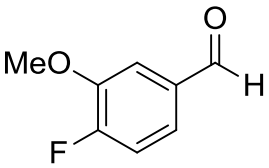
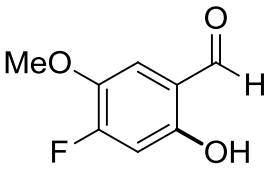
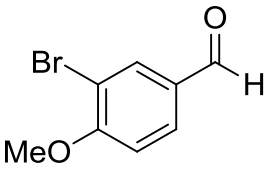
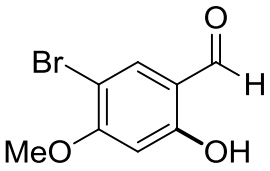
The double-substituted benzaldehydes **91** were also employed in the ruthenium(II)-catalyzed C–H oxygenation reactions with useful functional group tolerance (Table 5.5). A higher

catalyst loading was required in the synthesis of salicylaldehydes **92x** and **92y**.

Table 5.5: Scope of ruthenium(II)-ctalyzed C–H oxygenation on double-substituted aldehydes **91**.[a]



91 **92**

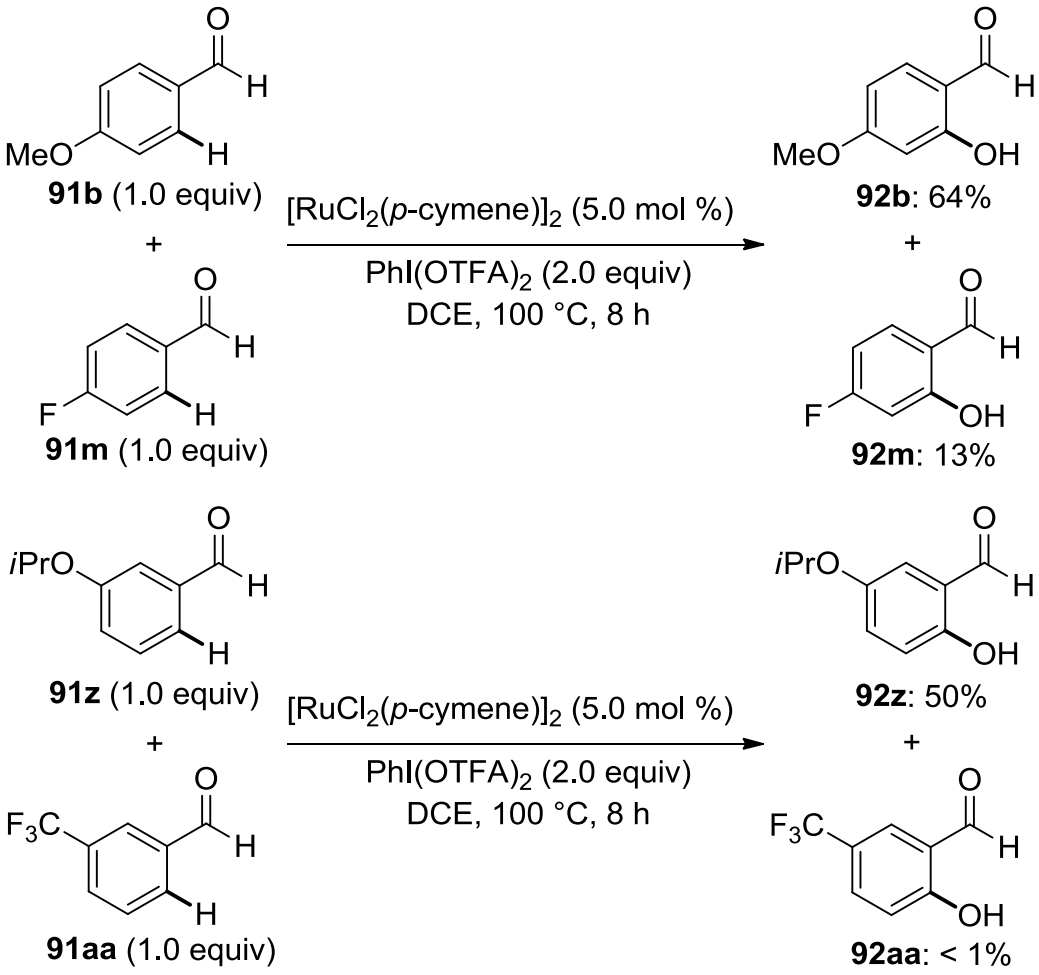
entry	**91**	**92**	yield [%]
1	 **91w**	 **92w**	52
2[b]	 **91x**	 **92x**	60
3[b]	 **91y**	 **92y**	53

[a] Reaction conditions: **91** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $PhI(OTFA)_2$ (2.0 equiv), DCE (2.0 mL), 100 °C, 8 h. [b] $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $PhI(OTFA)_2$ (2.5 equiv).

5.3 Mechanistic Studies

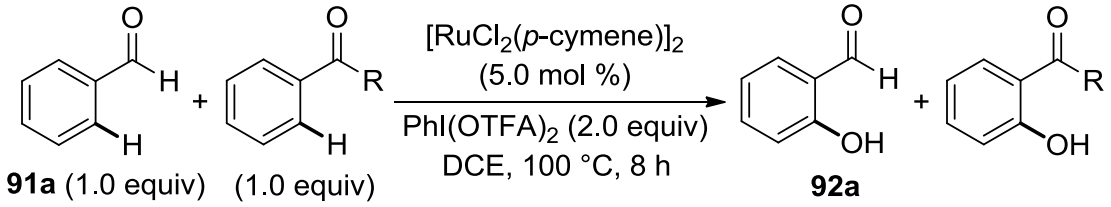
5.3.1 Competition Experiments

Competition experiments were carried out between aldehydes **91** bearing electron-donating and electron-withdrawing substituents (Scheme 5.4). In the competition experiment between 4-methoxybenzaldehyde (**91b**) and 4-fluorobenzaldehyde (**91m**), we found the 2-hydroxy-4-methoxybenzalde (**92b**) to be the major product with 64% yield. In another competition experiment between 3-isopropoxybenzaldehyde (**91z**) and 3-(trifluoromethyl)benzaldehyde (**91aa**), we isolated 50% of **92z** but could only detect trace amount of compound **92aa**. These results indicated that electron-rich arenes react preferentially.



Scheme 5.4: Intermolecular competition experiments between different aldehydes **91**.

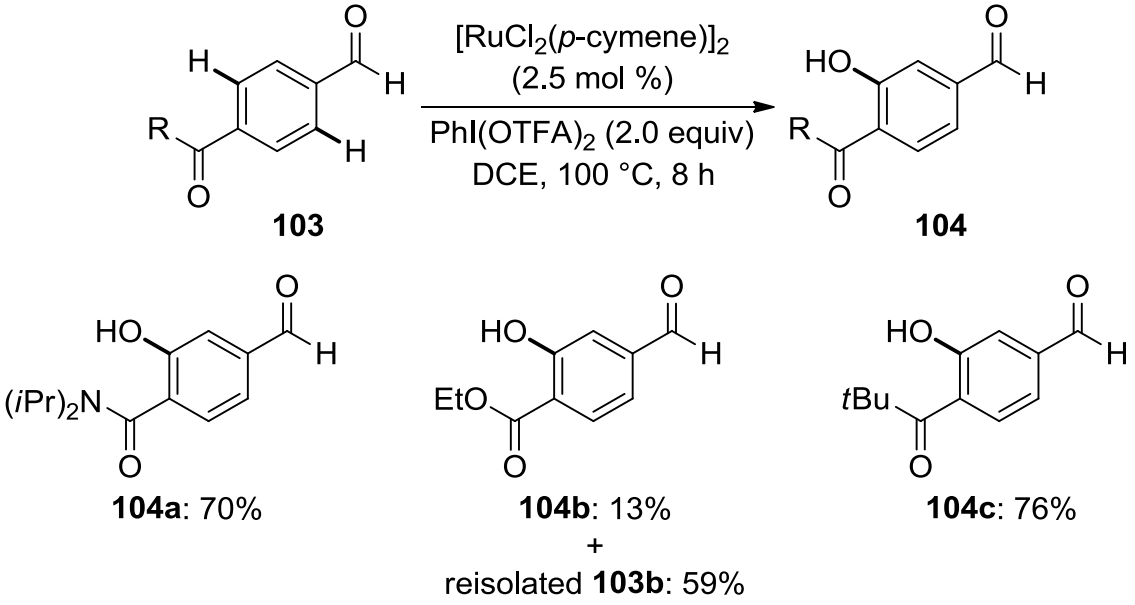
We compared the coordinating capabilities between aldehydes and other directing groups, such as amide, Weinreb amide, and ketone (Scheme 5.5). In all the intermolecular competition reactions, salicylaldehyde (**92a**) was found to be the minor product.



R = *t*Bu	(**60a**)	1	:	6.6 (**61a**)
R = N(*i*Pr)$_2$	(**56a**)	1	:	16.4 (**57a**)
R = N(Me)(OMe)	(**89a**)	1	:	17.5 (**90a**)

Scheme 5.5: Intermolecular comparison of directing group power.

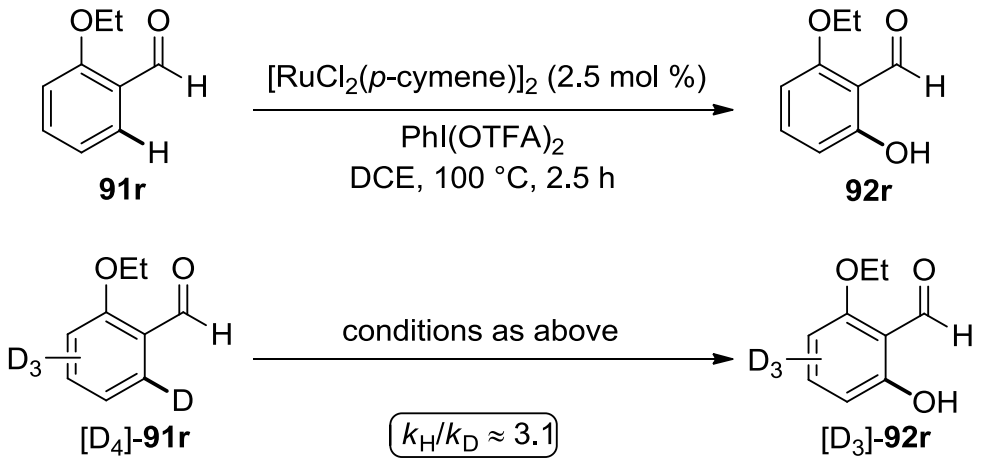
The results from intramolecular competition reactions with arenes **103** bearing two different directing groups once more confirmed the aldehyde moiety to be the weakest carbonyl coordinating group so far (Scheme 5.6).



Scheme 5.6: Intramolecular comparison of directing group power.

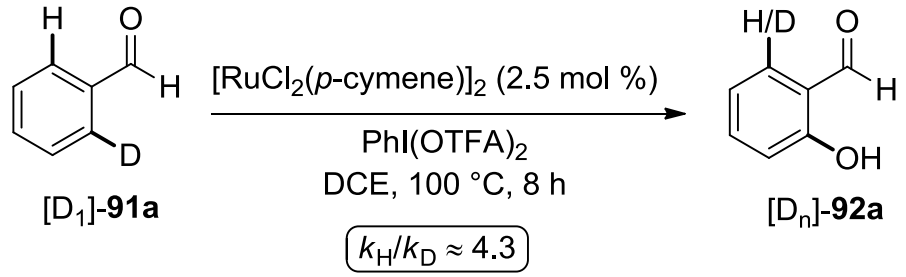
5.3.2 Studies with Isotopically Labeled Compound

The independent kinetic isotope effect (KIE) was studied with substrates **91r** and [D_4]-**91r** (Scheme 5.7). The KIE value was found to be 3.1, which indicated a kinetically relevant C–H metalation step.



Scheme 5.7: Independent kinetic isotope effect studies.

In the intramolecular kinetic isotope effect studies, we utilized mono *ortho*-deuterated benzaldehyde ([D_1]-**91a**). The KIE value was found to be 4.3 (Scheme 5.8). The considerably different inter- and intramolecular KIEs strongly suggest the formation of an intermediate in which the aldehyde carbonyl group is pre-coordinated to the active ruthenium catalyst.

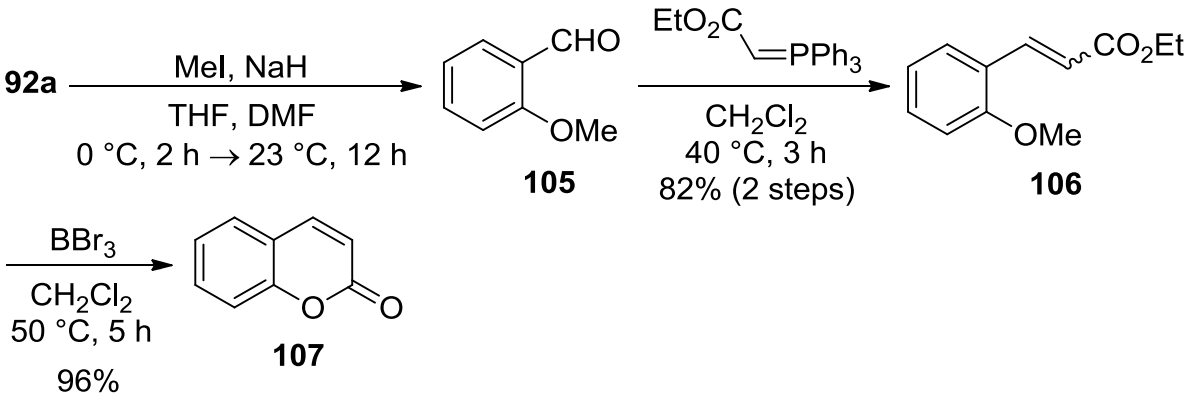


Scheme 5.8: Intramolecular kinetic isotope effect.

5.4 Diversification of Salicylaldehydes

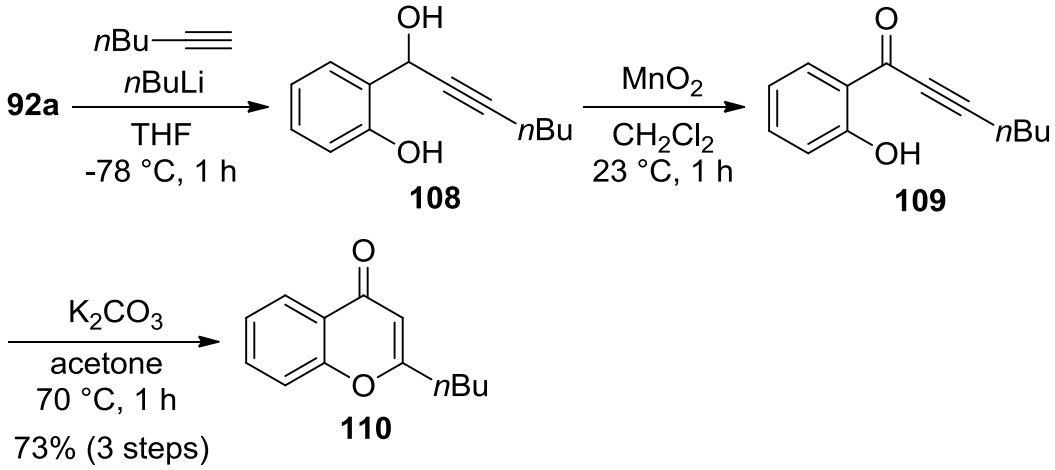
Salicylaldehyde is a useful starting material in the synthesis of many natural products. We explored the unique utility of the formyl group for the late-stage diversification (Schemes 5.9-5.12):

First, 2*H*-chromen-2-one (**107**) was synthesized in three steps with 79% overall yield.



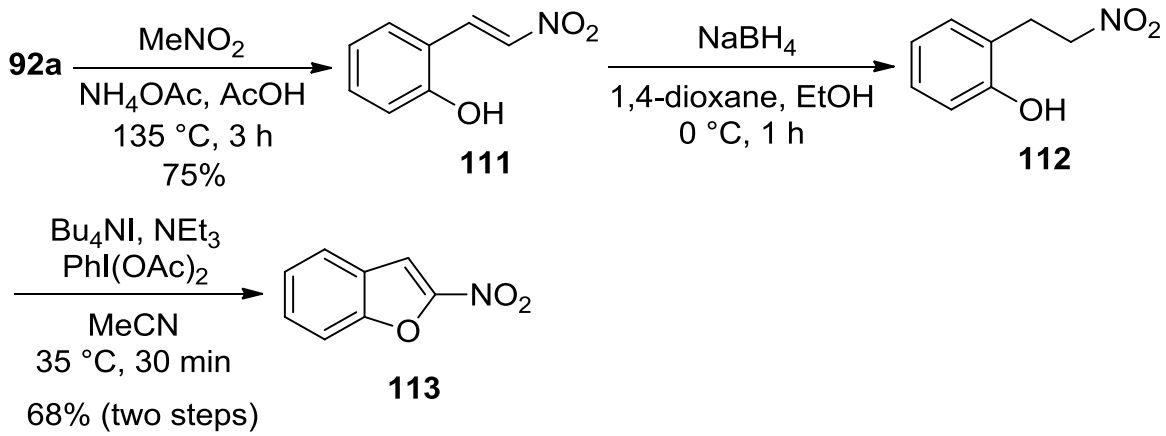
Scheme 5.9: Synthesis of 2*H*-chromen-2-one (**107**).

Second, the synthesis of 2-*n*-butyl-4*H*-chromen-4-one (**110**) required three steps with 73% overall yield. It is noteworthy that no purification was needed until the last step.



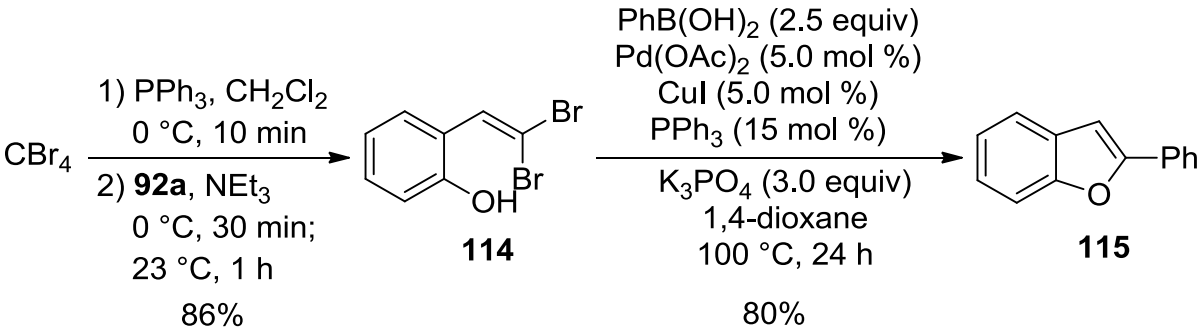
Scheme 5.10: Synthesis of 2-butyl-4*H*-chromen-4-one (**110**).

Third, 2-nitrobenzofuran (**113**) could be synthesized in three steps with 51% overall yield.



Scheme 5.11: Synthesis of 2-nitrobenzofuran (**113**).

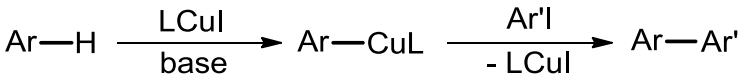
Fourth, the Lautens's method[170] was utilized for the synthesis of 2-phenylbenzofuran (**115**) which was accomplished in two steps with 69% overall yield.



Scheme 5.12: Synthesis of 2-phenylbenzofuran (**115**).

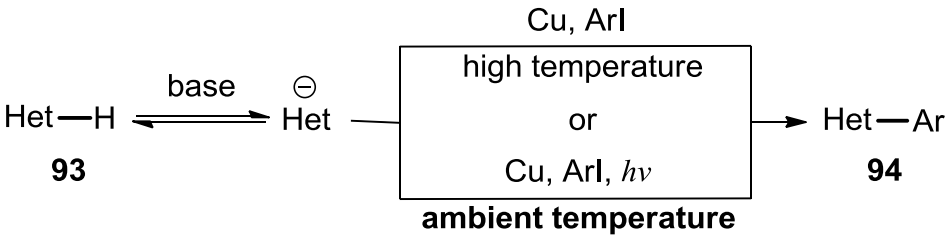
6 Photo-Induced Copper(I)-Catalyzed C(sp^2)–H Arylations

The copper-promoted biaryl synthesis was disclosed by Ullmann more than one hundred years ago.[8] Recent years have witnessed the successful application of heteroarenes in copper-catalyzed C–H arylations.[171-173] However, these reactions always required high temperatures of at least 100 °C.



Scheme 6.1: Copper(I)-catalyzed C–H arylation.

The development of transition metal-catalyzed C–H arylation at ambient temperature remains a major challenge in the field.[83] As shown in Scheme 6.1, C–H metalation is feasible for heteroarenes with relatively acidic C–H bonds, and therefore, the dissociation of carbon–halogen bond should be the rate-limiting step. In a previous study, Kim and coworkers have shown that UV irradiation of 140 nm could break the C–I bond in 2,5-diiodothiophene with the assistance of copper thus generating thienyl radicals.[174] Inspired by the above mentioned studies, we hypothesized that the rate of the copper(I)-catalyzed heteroarne arylation could be accelerated by UV light, and therefore, the reaction could perform at a more environmentally-benign temperature.



Scheme 6.2: Photo-induced copper(I)-catalyzed heterocyclic arylation.

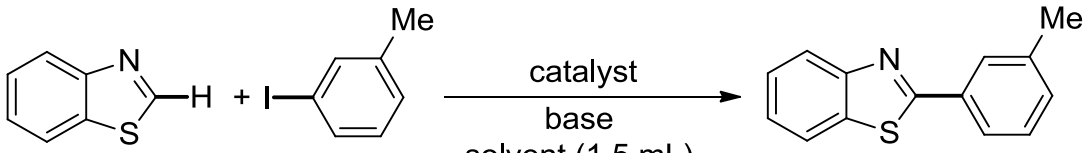
6.1 Optimization of Photo-Induced Copper(I)-Catalyzed C(sp^2)–H Arylations

We started the optimization with the commonly used solvent acetonitrile, obtaining only 10% yield (Table 6.1, entry 1). Afterwards we changed to DMF and found that the yield could reach 33% using 3-iodotoluene as the arylation reagent and LiO*t*Bu as the base (entry 3). Other bases, such as KO*t*Bu or K_3PO_4, delivered lower conversion (entries 4 and 5). Copper(I)

acetate did work as the catalyst, but with a slightly lower yield (entry 6). Later we found that the reaction proceeded better in DMA as the solvent, delivering 39% yield (entry 8). Higher reaction temperature did not increase the yield (entry 9). A second metal catalyst, such as $Pd(OAc)_2$ or AgOAc, proved powerless in the reaction (entries 10 and 11).

Thereafter we changed to etherial solvents, and obtained some inspiring results. The yield with Et_2O as solvent reached 48% (entry 14), but significantly dropped with THF or 1,4-dioxane as the solvent (entries 12 and 13). Therefore, Et_2O was identified the optimal solvent. We tried to reduce the amount of iodoarene, but the yield dropped to 39% (entry 15). A moderate yield of 57% was obtained with 20 mol % of CuI (entry 16). Higher yield was obtained with more CuI (entry 17). However, the catalyst loading and yield were not in linear correlation, indicating a catalytic reaction. Thus, the catalyst loading was set to 20 mol %. The in-situ temperature was found to be about 28 °C during the first 6 hours.

Table 6.1: Optimization of photo-induced copper(I)-catalyzed C(sp^2)–H arylations with different bases and solvents.[a]



93a **19b** **94ab**

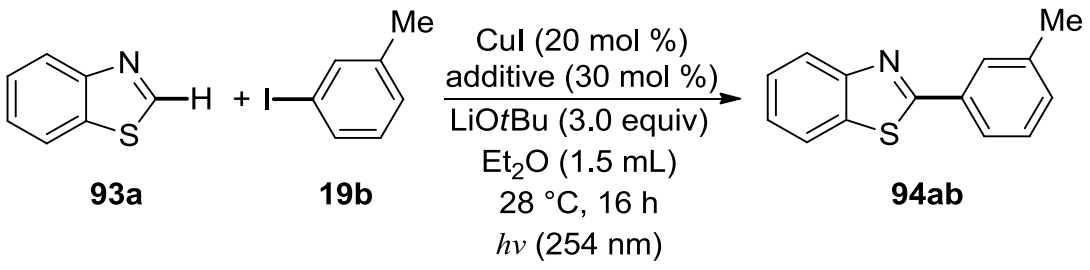
entry	**19b** [equiv]	catalyst [mol %]	base [equiv]	solvent	yield [%]
1	1.5	CuI (10)	LiO*t*Bu (1.0)	MeCN	10
2	1.5	CuI (10)	LiO*t*Bu (1.0)	DMF	21[b]
3	5.0	CuI (10)	LiO*t*Bu (3.0)	DMF	33[b]
4	5.0	CuI (10)	KO*t*Bu (3.0)	DMF	13
5	1.5	CuI (10)	K_3PO_4 (1.0)	DMF	5
6	5.0	CuOAc (10)	LiO*t*Bu (3.0)	DMF	28[b]
7	5.0	CuI (10)	LiO*t*Bu (3.0)	DMPU	< 2
8	5.0	CuI (10)	LiO*t*Bu (3.0)	DMA	39[b]
9[c]	5.0	CuI (10)	LiO*t*Bu (3.0)	DMA	37

entry	**19b** [equiv]	catalyst [mol %]	base [equiv]	solvent	yield [%]
10	5.0	$Pd(OAc)_2$ (10) + CuI (10)	LiO*t*Bu (3.0)	DMA	30
11	5.0	AgOAc (10) + CuI (10)	LiO*t*Bu (3.0)	DMA	37[b]
12	5.0	CuI (10)	LiO*t*Bu (3.0)	THF	30
13	5.0	CuI (10)	LiO*t*Bu (3.0)	1,4-dioxane	10
14	5.0	CuI (10)	LiO*t*Bu (3.0)	Et_2O	48[b]
15	2.0	CuI (10)	LiO*t*Bu (3.0)	Et_2O	39[b]
16	**5.0**	**CuI (20)**	**LiO*t*Bu (3.0)**	**Et_2O**	**57[b]**
17	5.0	CuI (50)	LiO*t*Bu (3.0)	Et_2O	80[b]

[a] Reaction conditions: **93a** (0.25 mmol), **19b** (5.0 equiv), catalyst (10 mol %), base (3.0 equiv), solvent (1.5 mL), 28 °C under 254 nm irradiation for 16 h, ^{1}H-NMR conversion with 1,3,5-trimethoxybenzene as the internal standard. [b] Isolated yield. [c] 50 °C.

Thereafter, we screened different additives (Table 6.2). DCN and fluorescein showed no or limited effect (entries 1 and 2). Nitrogen-containing ligands and carboxylate showed apparent negative impact on the reactions (entries 3-6), while picolinic acid containing both nitrogen and carboxylate showed a slightly positive effect (entry 7). Then, we tried various amino acid ligands, among which L-Alanine (L-Ala) and *N,N*-dimethylglycine (DMG) showed the best results (entry 11 and 17). Finally, we chose the *N*-protected DMG as the optimal ligand. The reaction delivered the product in 73% yield with 1.0 mL of Et_2O as the solvent (entry 20).

Table 6.2: Optimization of photo-induced copper(I)-catalyzed C(sp^2)–H arylations with different additives.[a]



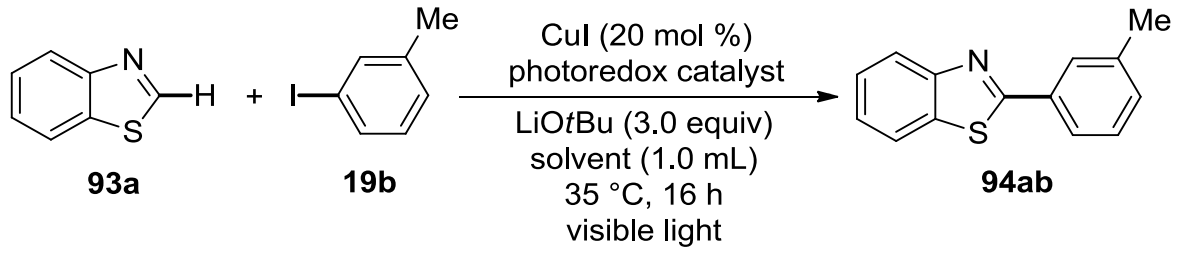
93a **19b** **94ab**

entry	additive	yield [%]	entry	additive	yield [%]
1	DCN	57	15	*N*-Ac-Gly	63
2	Fluoresein	61	16	*N*-PI-Gly	64
3	TMEDA	36	17	DMG	67[b]
4	bpy	39	18	DMG (20 mol %)	62
5	2-Ph-Pyr	32	19	DMG (50 mol %)	58
6	$AdCO_2H$	28	**20[c]**	**DMG**	**73[b]**
7	Pyr-2-CO_2H	62	21[d]	DMG	55
8	L-Pro	62[b]	22[c, e]	DMG	0
9	*N*-Boc-Pro	65	23[c, f]	DMG	0
10	Gly	64	24[c, g]	DMG	0
11	L-Ala	67[b]	25[c, h]	DMG	0
12	L-Ile	63	26[c, i]	DMG	0
13	2-Ph-Gly	61	27[c, j]	DMG	29
14	*N*-Me-Gly	63			

[a] Reaction conditions: Benzothiazole **93a** (0.25 mmol), 3-iodotoluene **19b** (5.0 equiv), CuI (20 mol %), additive (30 mol %), Li*O*tBu (3.0 equiv), Et_2O (1.5 mL), 28 °C under 254 nm irradiation for 16 h, ^{1}H-NMR conversion with 1,3,5-trimethoxybenzene as the internal standard. [b] Isolated yield. [c] Et_2O (1.0 mL). [d] Et_2O (2.5 mL). [e] No CuI. [f] No base. [g] 30 °C in dark environment. [h] Et_3N (3.0 equiv) as the base. [i] LiOAc (3.0 equiv) as the base. [j] $Ni(acac)_2$ (20 mol %) as the catalyst.

We set out to achieve copper(I)-catalyzed arylations under visible light at ambient temperature (Table 6.3). Thus, we tested different photo catalysts, including $Ir(ppy)_3$, $Ru(bpy)_3Cl_2{\cdot}6H_2O$, fluorescein, and DCN; solvents, such as Et_2O, MeCN, DMF, and DMSO; and light sources. The optimal conditions employed CuI as the C–H activation catalyst and $Ir(ppy)_3$ as the photocatalyst in DMF under blue light irradiation (entry 4). Due to the thermal radiation of blue light, the reaction temperature could reach 35 °C.

Table 6.3: Optimization of visible light-induced copper(I)-catalyzed C(sp^2)–H arylation.[a]



93a **19b** **94ab**

entry	photoredox catalyst [mol %]	solvent	light source	yield [%]
1	$Ir(ppy)_3$ (2.0)	Et_2O	blue LED	0
2	$Ir(ppy)_3$ (2.0)	MeCN	blue LED	trace
3	$Ir(ppy)_3$ (2.0)	DMSO	blue LED	38
4	**$Ir(ppy)_3$ (2.0)**	**DMF**	**blue LED**	**50[b]**
5	—	DMF	blue LED	20
6[c]	$Ir(ppy)_3$ (2.0)	DMF	blue LED	0
7	$Ir(ppy)_3$ (2.0)	DMF	18W CFL	18
8	$Ru(bpy)_3Cl_2 \cdot 6H_2O$ (2.0)	DMF	blue LED	6
9	$Ru(bpy)_3Cl_2 \cdot 6H_2O$ (2.0)	DMF	green LED	trace
10	Fluorescein (20)	DMF	blue LED	9
11	DCN (20)	DMF	blue LED	5

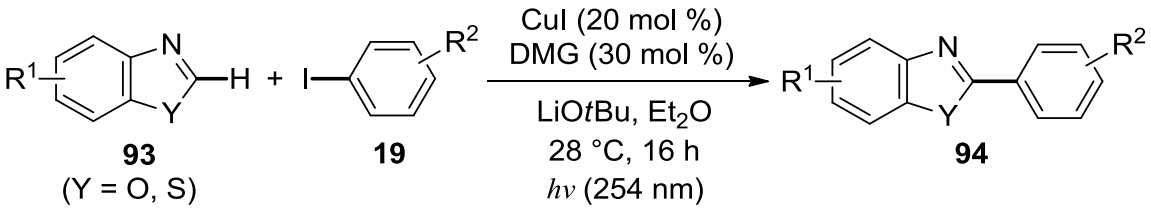
[a] Reaction conditions: **93a** (0.25 mmol), **19b** (5.0 equiv), CuI (20 mol %), photoredox catalyst, LiO*t*Bu (3.0 equiv), solvent (1.0 mL), 35 °C under visible light irradiation for 16 h, ^{1}H-NMR conversion with 1,3,5-trimethoxybenzene as the internal standard. [b] Isolated yield. [c] No CuI.

6.2 Scope of Photo-Induced Copper(I)-Catalyzed C(sp^2)–H Arylations

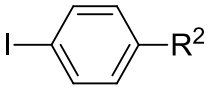
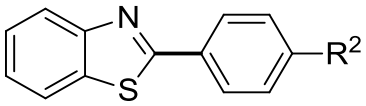
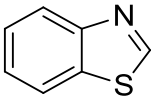
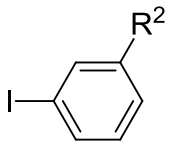
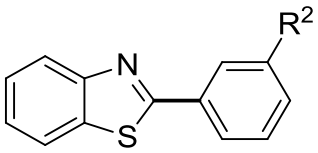
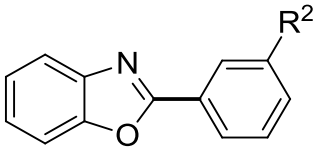
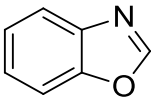
The photo-induced copper(I)-catalyzed C–H arylation on benzothiazole delivered high yields (Table 6.4). Various useful functional substituents, such as fluoro, chloro, and trifluoromethyl, were well tolerated (entries 3, 4, 7, 9, 10). The coupling between benzothiazole (**93a**) and iodo-substituted benzoic ester **19f** delivered the desired product **94af**, but in somehow lower yield (entry 5). Benzoxazole (**93b**) and 5-methylbenzoxazole (**93c**) could efficiently convert to the desired products **94ba**, **94bb**, and **94cb**, respectively. However, only 33% of desired

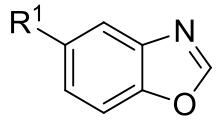
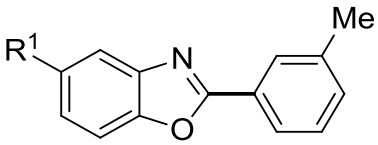
product **94db** was obtained with 5-chlorobenzoxazole (**93d**).

Table 6.4: Scope of photo-induced copper(I)-catalyzed C(sp^2)–H arylations with benzannulated heteroarenes **93**.[a]



93 (Y = O, S) **19** **94**

entry	**93**	**19**	**94**	yield [%]
				
1		R = H (**19a**)	**94aa**	70
2		R = OMe (**19c**)	**94ac**	63
3		R = CF_3 (**19d**)	**94ad**	70
4	**93a**	R = Cl (**19e**)	**94ae**	63
5		R = CO_2tBu (**19f**)	**94af**	46
				
6		R = Me (**19b**)	**94ab**	73
7		R = CF_3 (**19g**)	**94ag**	60
8	**93a**	R = OMe (**19h**)	**94ah**	70
9		R = F (**19i**)	**94ai**	79
10		R = Cl (**19j**)	**94aj**	80
				
11		**19a**	R = H (**94ba**)	64
12	**93b**	**19b**	R = Me (**94bb**)	59

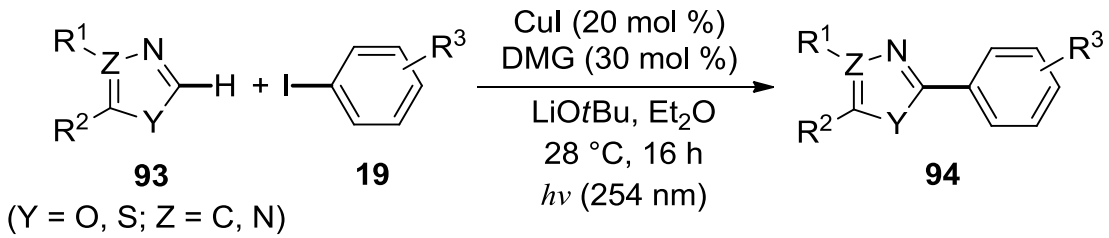
entry	**93**	**19**	**94**	yield [%]
				
13	R = Me (**93c**)	**19b**	**94cb**	72
14	R = Cl (**93d**)		**94db**	33

[a] Reaction conditions: **93** (0.25 mmol), **19** (5.0 equiv), CuI (20 mol %), DMG (30 mol %), LiO*t*Bu (3.0 equiv), Et_2O (1.0 mL), 28 °C under 254 nm irradiation for 16 h.

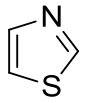
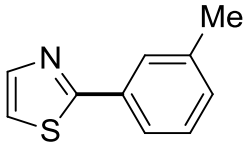
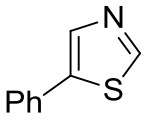
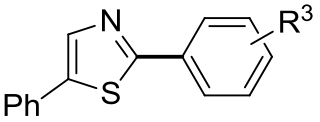
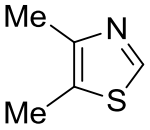
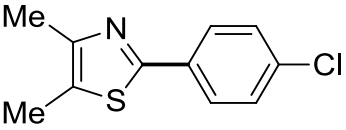
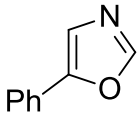
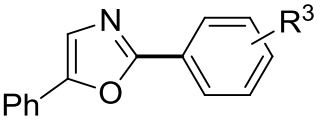
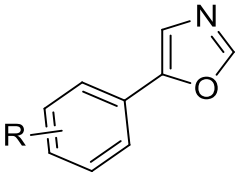
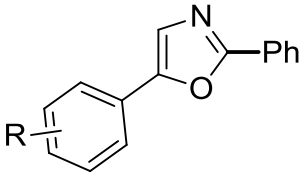
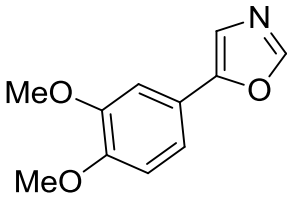
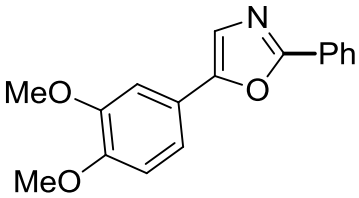
The substituted heteroarenes showed comparable efficacy in this catalytic C–H arylation, despite of higher pKa values (Table 6.5). Thiazole and oxazole with alkyl or aryl substituents all delivered moderate to good results. While oxadiazole with different substituents on two carbon atoms could be synthesized with moderate yields (entries 12 and 13).

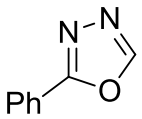
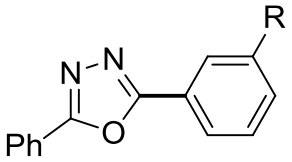
With the photo-induced copper(I)-catalyzed C–H arylation method, balsoxin (**94ka**) was synthesized in 2 steps with the total yield of 47% (entry 11). Hodgetts and coworkers required 7 steps on the synthesis of the same compound.[175] Although Greaney et al. reported a 2 step balsoxin synthesis with a higher yield, each step required a particular type of expensive palladium catalyst at higher reaction temperature.[176]

Table 6.5: Scope of photo-induced copper-catalyzed C(sp^2)–H arylations with substituted heteroarenes **93**.[a]



93 (Y = O, S; Z = C, N) **19** **94**

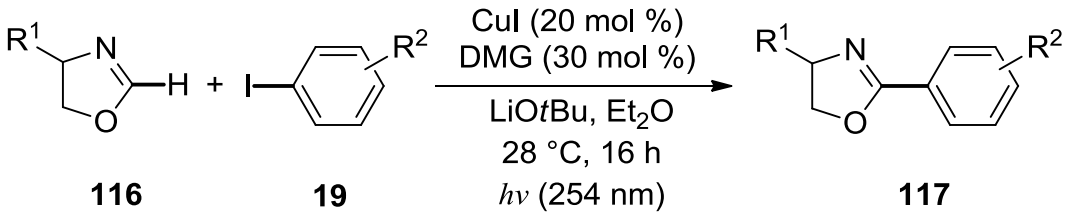
entry	**93**	**19**	**94**	yield [%]
				
1	**93e**	**19b**	**94eb**	50
				
2	**93f**	**19d**	R = 4-CF_3 (**94fd**)	64
3		**19b**	R = 3-Me (**94fb**)	78
				
4	**93g**	**19e**	**94ge**	63
				
5	**93h**	**19a**	R = H (**94ha**)	74
6		**19e**	R = 4-Cl (**94he**)	70
7		**19b**	R = 3-Me (**94hb**)	78
8		**19i**	R = 3-F (**94hi**)	70
				
9	R = 3-OMe (**93i**)	**19a**	**94ia**	68
10	R = 4-F (**93j**)	**19a**	**94ja**	62
				
11	**93k**	**19a**	Balsoxin (**94ka**)	53

entry	**93**	**19**	**94**	yield [%]
				
12	**93l**	**19b**	R = Me (**94lb**)	54
13		**19j**	R = Cl (**94lj**)	51

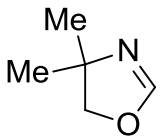
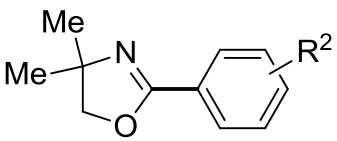
[a] Reaction conditions: **93** (0.25 mmol), **19** (5.0 equiv), CuI (20 mol %), DMG (30 mol %), LiO*t*Bu (3.0 equiv), Et_2O (1.0 mL), 28 °C under 254 nm irradiation for 16 h.

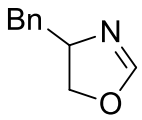
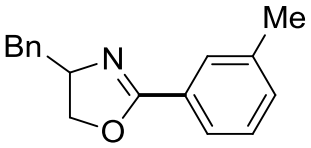
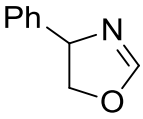
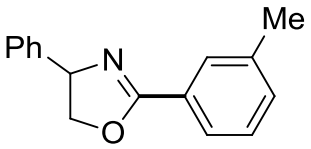
The scope is not limited to heteroarenes. Indeed, the non-aromatic oxazolines **116** could also furnish good yields with different iodo arenes **19** (Table 6.6). To the best of our knowledge, this is the first C2 arylation of oxazolines using photo catalysis.

Table 6.6: Scope of photo-induced copper-catalyzed C(sp^2)–H arylations with non-aromatic heterocycles **116**.[a]



116 **19** **117**

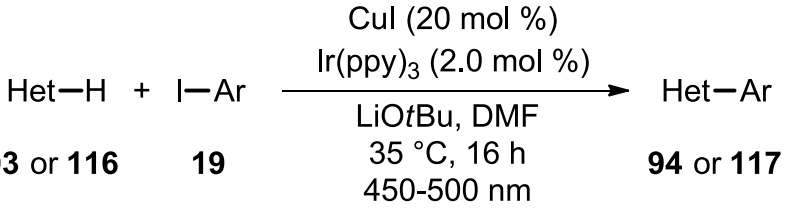
entry	**116**	**19**	**117**	yield [%]
				
1	**116a**	**19c**	R = 4-OMe (**117ac**)	51
2		**19b**	R = 3-Me (**117ab**)	74
3		**19j**	R = 3-Cl (**117aj**)	69

entry	**116**	**19**	**117**	yield [%]
4	 **116b**	**19b**	 **117bb**	72
5	 **116c**	**19b**	 **117cb**	62

[a] Reaction conditions: **116** (0.25 mmol), **19** (5.0 equiv), CuI (20 mol %), DMG (30 mol %), LiO*t*Bu (3.0 equiv), Et_2O (1.0 mL), 28 °C under 254 nm irradiation for 16 h.

We explored the substrate scope of visible light-induced copper(I)-catalyzed C–H arylation and found only **93a** could be arylated in moderate yield (Table 6.7). Other substituted heterocycles **93** as well as oxazoline **116** delivered low yields, indicating the characteristics of heterocycles are important for the visible light-induced copper(I)-catalyzed C–H arylation.

Table 6.7: Scope of visible light-induced copper(I)-catalyzed C(sp^2)–H arylation.[a]



93 or **116** **19** **94** or **117**

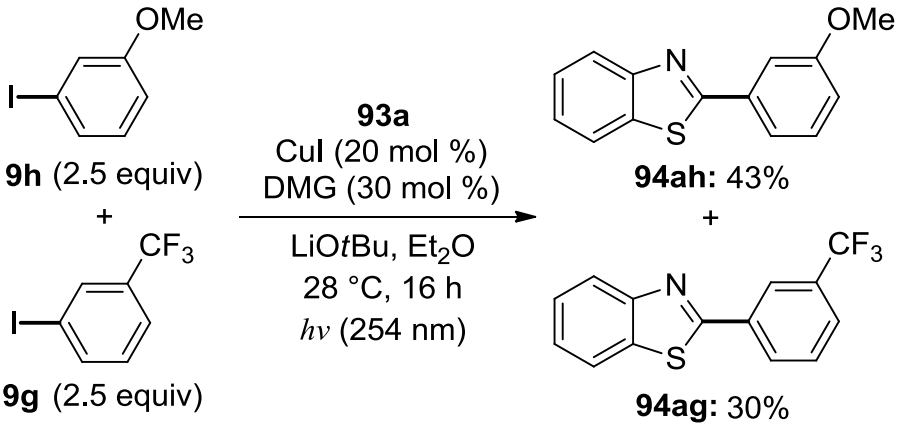
entry	**93** or **116**	**19**	**94** or **117**	yield [%]
1		**19b**	**94ab**	50
2	**93a**	**19h**	**94ah**	48
3		**19j**	**94aj**	42
4	**93c**	**19b**	**94cb**	21
5	**116a**		**117ab**	10

[a] Reaction conditions: **93** or **116** (0.25 mmol), **19** (5.0 equiv), CuI (20 mol %), $Ir(ppy)_3$ (2.0 mol %), LiO*t*Bu (3.0 equiv), DMF (1.0 mL), 35 °C under 450-500 nm irradiation for 16 h.

6.3 Mechanistic Studies

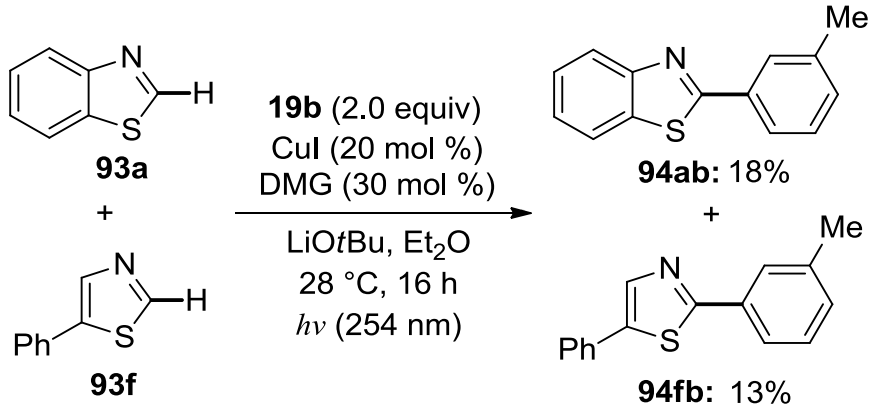
6.3.1 Competition Experiments

We performed intermolecular competition experiment between iodobenzenes **19** with electron-donating and electron-withdrawing groups (Scheme 6.3), indicating electron-rich iodoarene to be more reactive under the optimal reaction conditions.



Scheme 6.3: Competition experiment between iodoarenes **19h** and **19g**.

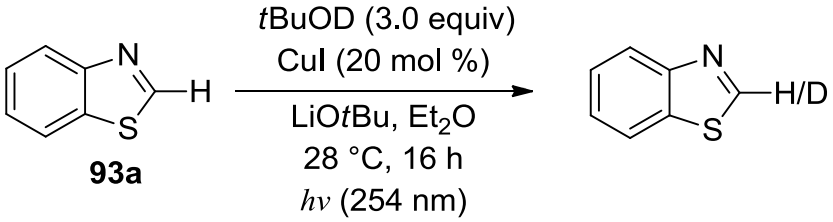
Furthermore, a competition experiment was performed between benzothiazole (**93a**) and substituted thiazole **93f**, revealing that the benzannulated heteroarene **93a** to be more reactive.



Scheme 6.4: Competition experiment between heteroarenes **93a** and **93f**.

6.3.2 Studies with Isotopically Labeled Compounds

We performed H/D exchange experiments with LiO*t*Bu as the base and *t*BuOD as the additive (Scheme 6.5). With CuI (20 mol %) the H/D ratio was determined to be 48/52 as estimated by ^{1}H-NMR, while in the absence of CuI the same H/D ratio was observed. Thus copper iodide was not essential for the H/D scrambling.



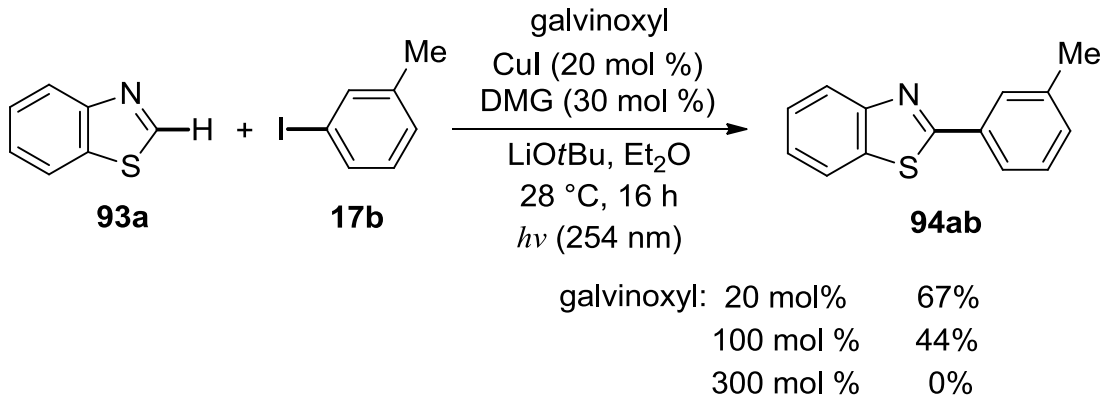
	H/D
CuI (20 mol %)	48/52
no CuI	48/52

Scheme 6.5: H/D scrambling experiment with **93a**.

6.3.3 Studies with Radical Scavenger

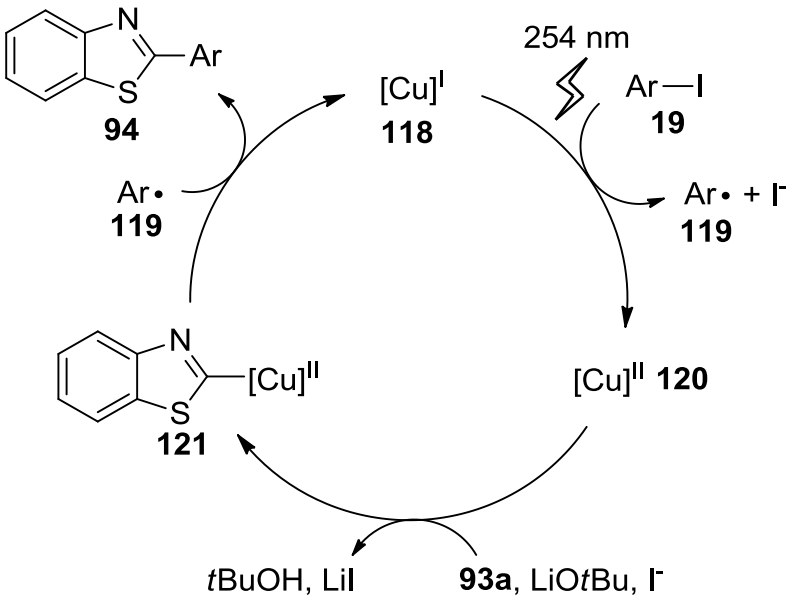
The mechanisms of copper-catalyzed reactions have been previously studied by Koyama,[177] Hartwig,[178,179] Buchwald,[180] as well as Fu and Peters[143] using different strategies.

We performed the radical trap experiment employing a radical scavenger (Scheme 6.6). We did not use TEMPO because of the potential photoreactivity of its N–O bond. Alernatively, galvinoxyl was chosen for this experiment. We obtained a slightly lower yield with 20 mol % of galvinoxyl being used. However, galvinoxyl did not capture the desired aryl radical. Instead, the hydrogenated galvinoxyl was observed. We would ascribe the fact that no galvinoxyl–aryl product generated to the steric factors of the radical scavenger. To exclude the possibility that radical scavengers may react with metal hydrido complexes,[181] we performed the reaction with 1 equivalent of galvinoxyl and isolated 44% of the arylation product **94ab**. The arylation was completely inhibited with 3 equivalent of the radical scavenger. Taken together, a radical pathway was hereby indicated.



Scheme 6.6: Mechanistic study with galvinoxyl as the radical scavenger.

Base on the mechanistic studies, we propose the catalytic cycle depicted in Scheme 6.7: First, the cycle starts from irradiation of iodoarene, the iodo–carbon bond absorbs the energy from UV light and dissociates with the assistance of copper(I) complex **118** to generate the aryl radical **119** and the iodine anion. Second, C–H activation occurs with base-assistance. Third, the intermediate **121** is attacked by the aryl radical **119** to form the arylated benzothiazole **94** and regenerate copper(I) complex **118**.

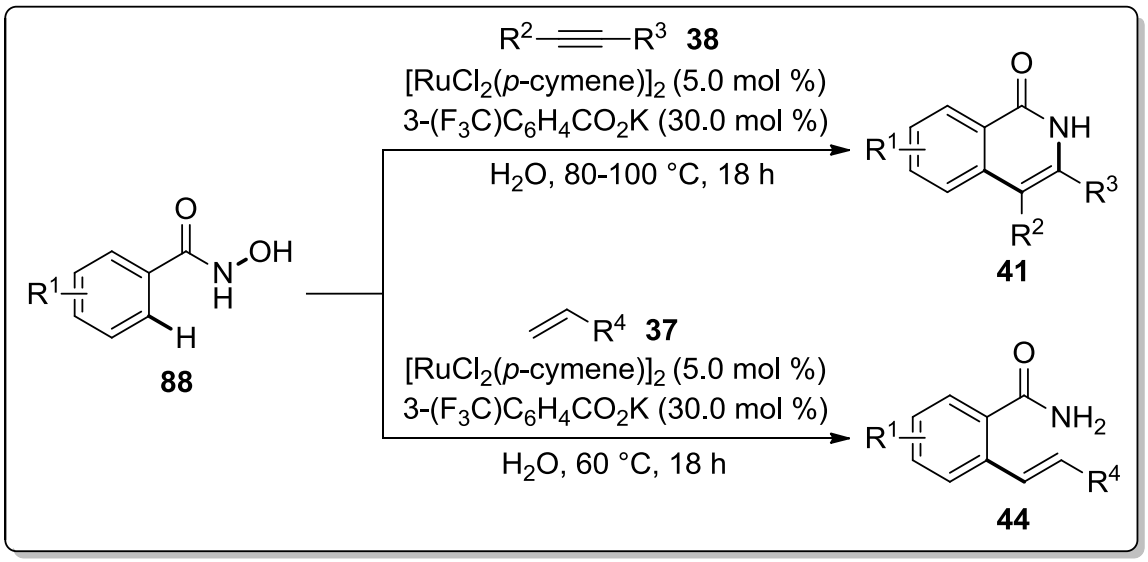


Scheme 6.7: Proposed catalytic cycle of photo-induced copper(I)-catalyzed C–H arylations.

7 Summary and Outlook

Transition metal-catalyzed cross-coupling reaction as one of the greatest chemical innovations of 20th century has to utilize stoichiometric amounts of prefunctionalized reagents. In comparison, the transition metal-catalyzed direct C–H functionalization provided a more atom- and step-economical pathway for the synthesis and modification of arenes. Within this thesis, several new synthetic methods based on transition metal-catalyzed C–H functionalization have been developed.

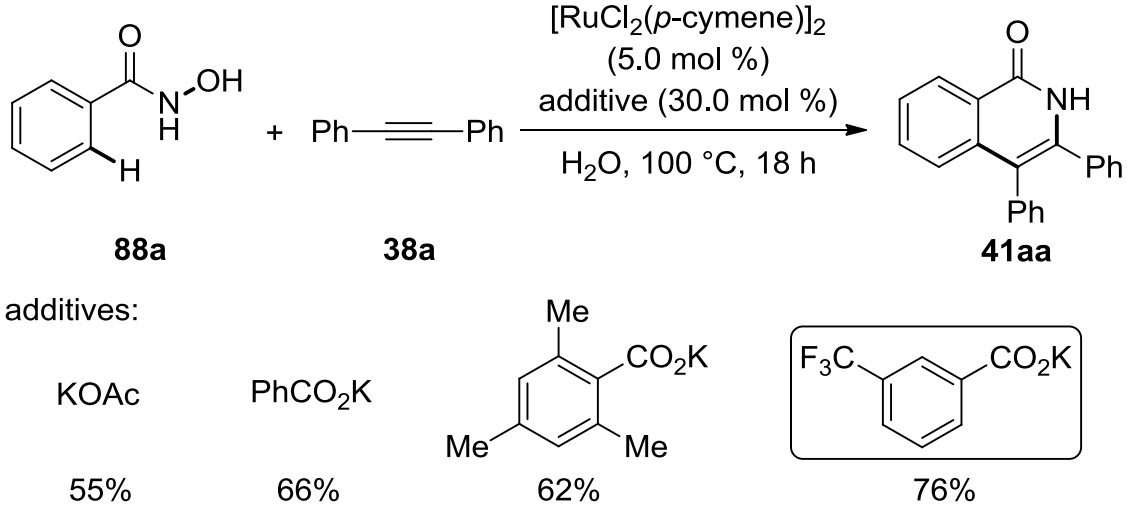
Oxidative annulations of alkynes by C–H/N–H cleavages have recently emerged as a useful strategy for the sustainable preparation of *N*-heterocycles. To avoid the use of excess amounts of sacrificial oxidants, transition metal-catalyzed C–H/N–O bond functionalizations with *N*-substituted benzamides have been investigated. In the first project, a novel isoquinolone synthesis has been achieved utilizing ruthenium(II)-catalyzed C–H/N–O functionalization (Scheme 7.1). This green approach employed H_2O as the reaction medium, and generated H_2O as the sole byproduct. The catalytic system also proved applicable for oxidative alkenylations.



Scheme 7.1: Ruthenium(II)-catalyzed C–H/N–O functionalization.

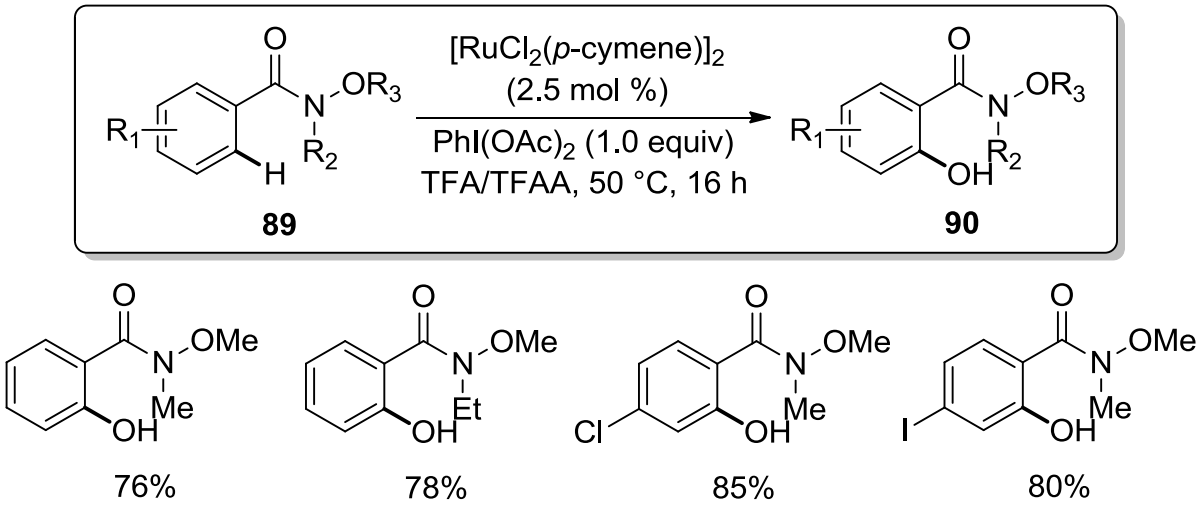
The carboxylate-assisted C–H bond founctionalization was also investigated. Various carboxylate additives were probed, of which the electron-deficient carboxylate

3-(F_3C)$C_6H_4CO_2K$ was found to be the optimal additive for the ruthenium(II)-catalyzed C–H/N–O functionalization in water. Due to the different effects of carboxylates (Scheme 7.2), next generation ruthenium(II) carboxylate catalysts should be designed and synthesized specifically for different novel transformations.



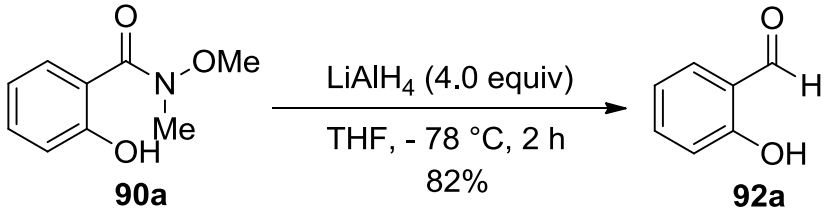
Scheme 7.2: Carboxylates as cocatalysts in ruthenium-catalyzed C–H/N–O functionalization.

The second project refers to ruthenium(II)-catalyzed C–H oxygenations on synthetically useful Weinreb amides **89**. With hypervalent iodine(III) reagent $PhI(OAc)_2$ as the oxidant, the *ortho*-selective C–O formation efficiently took place at a reaction temperature of 50 °C (Scheme 7.3), which should be the lowest reaction temperature reported thus far for ruthenium(II)-catalyzed C(sp^2)–H bond oxygenations.



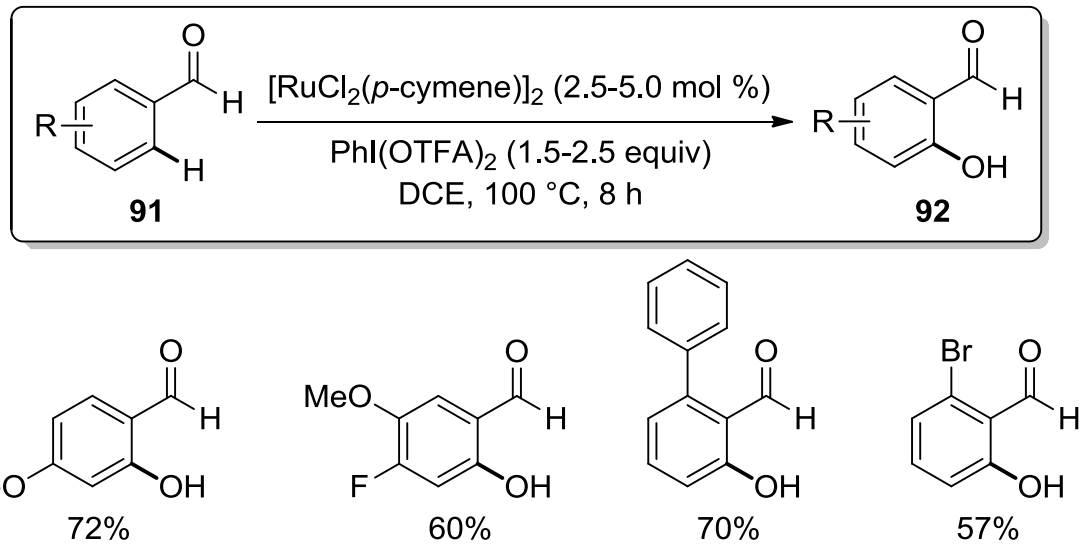
Scheme 7.3: Ruthenium(II)-catalyzed C–H oxygenation on Weinreb amides **89**.

Furthermore, the practical importance of C–H bond oxygenations on aryl Weinreb amides **89** was illustrated by the high-yielding preparation of the corresponding salicylaldehyde **92** (Scheme 7.4).



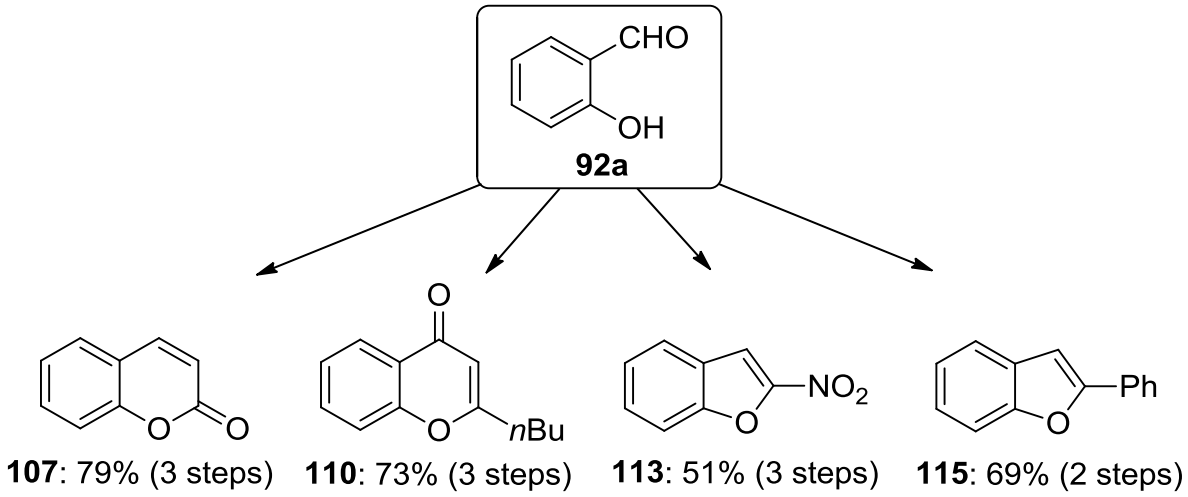
Scheme 7.4: Preparation of salicylaldehyde **92a** from *ortho*-hydroxylated Weinreb amide **90a**.

A more atom- and step-economical pathway for salicylaldehyde synthesis would directly start from benzaldehyde **91**, representing a challenging project. The intra- and intermolecular competition experiments between different carbonyl group-containing substrates showed aldehydes to be the weakest directing group so far. Meanwhile, aldehyde has the inherent tendency to be readily oxidized to the corresponding acid. Utilizing the unique catalytic activity of $[RuCl_2(p\text{-cymene})]_2$, we successfully accomplished the chelation-directed *ortho*-oxygenation on benzaldehydes with $PhI(OTFA)_2$ as the oxidant (Scheme 7.5). The use of molecular O_2 in the ruthenium-catalyzed *ortho*-oxygenation on benzaldehydes will be the 'Mount Everest' in this field.



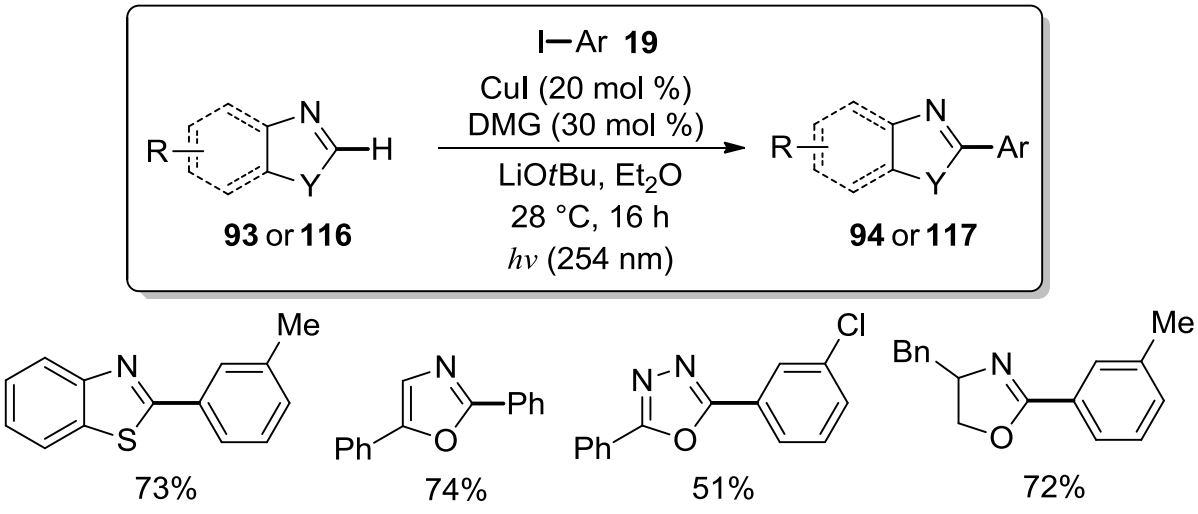
Scheme 7.5: Ruthenium (II)-catalyzed C–H oxygenation on benzaldehydes **91**.

Salicylaldehydes **92** are useful starting materials in the synthesis of many natural products. We explored the unique utility of the formyl group for the late-stage diversification (Scheme 7.6).



Scheme 7.6: Late-stage diversification of salicyaldehyde **92**.

Despite the tremendous achievements during recent years, transition metal-catalyzed direct C–H functionalizations have been somewhat limited because of the commonly used high reaction temperatures. Thus in the fourth project, we turned to photo-catalysis. Various heteroarenes as well as natural products were synthesized utilizing photo-induced copper(I)-catalyzed C–H arylations at ambient temperature (Scheme 7.7). Non-aromatic oxazolines **116** were also viable substrates in this C–H arylation reaction. Visible light catalysis was also probed with thus far somewhat limited success.



Scheme 7.7: Photo-induced copper(I)-catalyzed C(sp^2)–H arylations.

Photo-induced transition metal-catalyzed C–H functionalizations have provided a charming future for the facile synthesis of tremendous compounds and materials which cannot be achieved by thermal synthesis. I would suppose great development in this field with various transition metals, photo reagents, as well as irradiation sources.

8 Experimental Sections

8.1 General Remarks

All reactions involving moisture- or air-sensitive reagents or products were performed under a N_2 atmosphere using pre-dried glassware and standard Schlenk techniques. Syringes for handling of dry solvents were flushed with dry nitrogen threefold prior to use.

Vacuum

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

Melting Points

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

Chromatography

Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60F-plates (MACHEREY-NAGEL) with 254 nm fluorescent indicator from MERCK. Plates were visualized under UV-light and developed by treatment with a $KMnO_4$ solution followed by careful applying a heat gun.

Chromatographic purification of products was accomplished by flash column chromatography on MERCK silica gel, grade 60 (0.040–0.063 mm and 0.063–0.200 mm, 70–230 mesh astimated).

Gas Chromatograpgy

The conversion of the reactions was monitored applying coupled gas chromatography/mass spectrometry using *G1800C GCDplus* with mass detector *HP 5971*, *5890 Series II* with mass detector *HP 5972* from HEWLETT-PACKARD and *7890A GC-System* with mass detector *5975C*

(Triplex-Axis-Detector) from AGILENT TECHNOLOGIES equipped with *HP-5MS* columns (30 m × 0.25 mm × 0.25 µm) were used.

Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy was performed at 300 or 600 MHz (^{1}H-NMR), 75.5 or 125 MHz (^{13}C-NMR, APT) and 282 MHz (^{19}F-NMR) on BRUKER *AM 250*, VARIAN *Unity-300* and *Inova 500* instruments. Chemical shifts are reported as *δ*-values in ppm relative to the residual proton peak of the deuterated solvent or its carbon atom, respectively.

	^{1}H-NMR	^{13}C-NMR
$CDCl_3$:	7.26 ppm	77.0 ppm
DMSO-d_6:	2.49 ppm	49.5 ppm

For characterization of the observed resonance multiplicities the following abbrevations were applied: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet), or analogue representations. The coupling constants *J* are reported in Hertz (Hz). Analyses of the recorded spectra were carried out using *MestReNova 10.0* software.

Mass Spectrometry

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

Infrared Spectroscopy

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

Solvents

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

Solvent	Drying Method
Acetonitrile	was dried over 4Å MS, filtrated through an alumina column, and degassed using Freeze-Pump-Thaw procedure.
***tert*-Amylalcohol**	was stirred over sodium chips for 5 h at 120 °C and distilled under ambient pressure.
Chlorobenzene	was used as received.
1,2-Dichloroethane	was dried over CaH_2 for 8 h, degassed and distilled under ambient pressure.
Diethyl ether	was purified using a solvent purification system (SPS-800) from MBRAUN.
1,2-Dimethoxyethane	was distilled from sodium benzophenone ketyl.
***N,N*-Dimethylacetamide**	was dried over CaH_2 for 12 h, degassed and distilled under reduced pressure.
***N,N*-Dimethylformamide**	was dried over CaH_2 for 8 h, degassed and distilled under reduced pressure.
N,N'-Dimethylpropyleneurea	was used as received and stored under inert atmosphere.

1,4-Dioxane	was dried by distillation from sodium benzophenone ketyl.
Tetrahydrofuran	was purified using a solvent purification system (SPS-800) from MBRAUN.
Toluene	was purified using a solvent purification system (SPS-800) from MBRAUN.
Trifluoroacetic acid	was used as received and stored at 4 °C under inert atomsphere.
Trifluoroacetic anhydride	was used as received and stored at 4 °C under inert atmosphere.
Water	was degassed using Freeze-Pump-Thaw procedure.

Reagents

Chemicals obtained from commercial sources (with a purity > 95%) were used without further purification. The following compounds were synthesized according to known literature procedures and were pure by comparison with the published analytical data:

N-Hydroxybenzamides (**88**),[182] *N*-methoxybenzamides (**40**),[107] alkynes **38b-c**,[183] alkynes **38j-o**,[184] 2-methoxy-6-methyl-3,4-diphenylisoquinolin-1(2H)-one (**95**),[108] Weinreb amides **89**,[185] 4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbaldehyde (**91h**),[186] 4-[(triisopropylsilyl)oxy]benzaldehyde (**91l**),[187] *N,N*-diisopropylbenzamide (**56a**),[188] 5-phenylthiazole (**93f**),[189] 5-areneoxazoles **93i-k**,[190] 2-phenyl-1,3,4-oxadiazole (**93l**),[191] oxazolines **116b-c**,[192] *tert*-butyl 4-iodobenzoate (**19f**).[193]

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

Karsten Rauch: $[RuCl_2(p\text{-cymene})]_2$, $[Ru(O_2CMes)_2(p\text{-cymene})]$; **Dr. Marvin Schinkel:** $MesCO_2K$, $RuCl_2(PPh_3)_3$; **Dr. Christoph Kornhaaß:** 1-Phenyl-1-hexyne (**38i**); **MSc Katharina**

Kettelhoit: 4-(hexyloxy)benzaldehyde (**91j**), 4-phenoxybenzaldehyde (**91k**).

8.2 General Procedures

General Procedure A: Ruthenium(II)-Catalyzed C–H/N–O Alkyne Annulations of *N*-hydroxybenzamides 88 with Alkynes 38.

To a pre-dried 25 mL Schlenk tube were added *N*-hydroxybenzamide **88** (0.50 mmol), alkyne **38** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), potassium 3-(trifluoromethyl)benzoate (34 mg, 30.0 mol %), and H_2O (2 mL) under a N_2 atmosphere. The mixture was vigorously stirred at 100 °C for 16 h. At ambient temperature, the reaction mixture was diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic phase was washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-pentane/EtOAc) to yield the desired product **41**.

General Procedure B: Ruthenium(II)-Catalyzed C–H/N–O Alkenylations of *N*-hydroxybenzamides 88 with Alkenes 37.

To a pre-dried 25 mL Schlenk tube were added *N*-hydroxybenzamide **88** (0.50 mmol), alkene **37** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), potassium 3-(trifluoromethyl)benzoate (34 mg, 30.0 mol %), and H_2O (2 mL) under a N_2 atmosphere. The mixture was vigorously stirred at 60 °C for 16 h. At ambient temperature, the reaction mixture was diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic phase was washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc) to yield the desired product **44**.

General Procedure C: Ruthenium(II)-Catalyzed C–H Oxygenation on Weinreb Amides 89.

To a pre-dried 25 mL Schlenk tube were added Weinreb amide **89** (0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 2.5 mol %), $PhI(OAc)_2$ (161 mg, 0.50 mmol), and TFA/TFAA (2.0 mL, 3/1) under an ambient atmosphere of air. The tube was sealed tightly and the reaction mixture was stirred at 50 °C for 16 h. At ambient temperature, aqueous $NaHCO_3$ (25 mL) was slowly added to the reaction mixture and extracted with EtOAc (3 × 25 mL). The combined organic phase was washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-pentane/EtOAc) to yield the desired product **90**.

General Procedure D: Ruthenium(II)-Catalyzed C–H Oxygenation on Arylaldehydes 91.

To a pre-dried 25 mL Schlenk tube equipped with a condenser were added arylaldehyde **91** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 2.5 mol %), [bis(trifluoroacetoxy)iodo]benzene (323 mg, 0.75 mmol), and DCE (2.0 mL) under a N_2 atmosphere. The mixture was stirred at 100 °C for 8 h. At ambient temperature, HCl (1N, 0.5 mL) was added to the reaction mixture, stirred for another 0.5 h, and then purified by column chromatography on silica gel (*n*-pentane/Et_2O). The eluent was carefully removed by Vigreux distillation to yield the corresponding salicylaldehyde **92**.

General Procedure E: Photo-Induced Copper(I)-Catalyzed C–H Arylation of Hererocycles 93 or 116.

To a pre-dried 10 mL quartz tube were added heterocycle **93** or **116** (0.25 mmol), iodoarene **19** (1.25 mmol), copper(I) iodide (9.5 mg, 20 mol %), dimethylglycine (7.7 mg, 30 mol %), Li*O*t*Bu* (60 mg, 0.75 mmol), and Et_2O (1.0 mL) under a N_2 atmosphere. The tube was sealed tightly and the mixture was stirred under 254 nm irradiation in a Luzchem LZC-ICH2 photoreactor for 16 h at ambient temperature. Then, the reaction mixture was filtrated through a pad of silica gel and washed with Et_2O (20 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel

(*n*-pentane/Et_2O) to yield the desired product **94** or **117**.

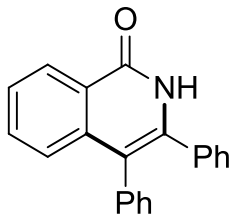
General Procedure F: Visible Light-Induced Copper(I)-Catalyzed C–H Arylation of Hererocycles 93 or 116.

To a pre-dried 25 mL Schlenk tube were added heterocycle **93** or **116** (0.25 mmol), iodoarene **19** (1.25 mmol), copper(I) iodide (9.5 mg, 20 mol %), $Ir(ppy)_3$ (3.3 mg, 2.0 mol %), LiO*t*Bu (60 mg, 0.75 mmol), and DMF (1.0 mL) under a N_2 atmosphere. The mixture was stirred under 450-500 nm irradiation with a blue LED set for 16 h at ambient temperature (35 °C). Then, to the reaction was added H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic solvents were washed with brine (5 x 10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (*n*-pentane/Et_2O) to yield the desired product **94** or **117**.

9 Analytical Data

9.1 Analytical Data for Ruthenium(II)-Catalyzed C–H/N–O Functionalizations

Synthesis of 3,4-Diphenylisoquinolin-1(2*H*)-one (41aa)



The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and diphenylacetylene (**38a**) (134 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41aa** (113 mg, 76%) as a colorless solid.

M.p. = 253–255 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.48 (s, 1H), 8.33 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.63 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H), 7.51 (ddd, *J* = 8.1, 7.2, 1.3 Hz, 1H), 7.36–7.11 (m, 11H).

^{13}C-NMR (75 MHz, DMSO-d_6): δ = 161.6 (C_q), 138.5 (C_q), 138.0 (C_q), 135.8 (C_q), 134.5 (C_q), 132.3 (CH), 131.6 (CH), 129.7 (CH), 128.1 (CH), 128.0 (CH), 127.5 (CH), 126.9 (CH), 126.7 (CH), 126.1 (CH), 124.9 (C_q), 124.8 (CH), 115.3 (C_q).

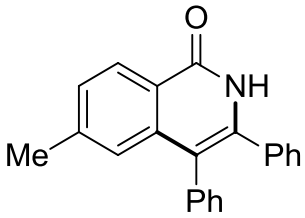
IR (neat): 3161, 3017, 2885, 1641, 1606, 1446, 1343, 693 cm^{-1}.

MS (EI) *m/z* (relative intensity): 297 ([M^+] 100), 296 (55), 278 (21), 190 (5), 165 (15), 139 (7), 77 (8).

HR-MS (EI) *m/z* calcd for $C_{21}H_{15}NO^+$ [M^+] 297.1154, found 297.1156.

The analytical data are in accordance with those reported in the literature.[108]

Synthesis of 6-Methyl-3,4-diphenylisoquinolin-1(2*H*)-one (41ba)



The general procedure **A** was followed using *N*-hydroxy-4-methylbenzamide (**88b**) (76 mg, 0.50 mmol) and diphenylacetylene (**38a**) (134 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41ba** (103 mg, 66%) as a colorless solid.

M.p. = 277–279 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.17 (s, 1H), 8.37 (d, *J* = 8.2 Hz, 1H), 7.35–7.12 (m, 12H), 2.38 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.6 (C_q), 143.3 (C_q), 138.7 (C_q), 137.1 (C_q), 135.8 (C_q), 135.2 (C_q), 131.8 (CH), 129.2 (CH), 128.5 (CH), 128.3 (CH), 128.3 (CH), 128.2 (CH), 127.5 (CH), 127.2 (CH), 125.3 (CH), 122.9 (C_q), 117.0 (C_q), 22.1 (CH_3).

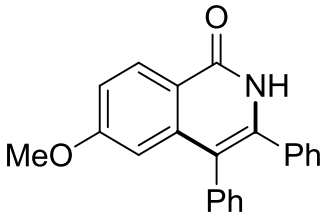
IR (neat): 3171, 3021, 2898, 1648, 1614, 1488, 1161, 698 cm^{-1}.

MS (EI) *m/z* (relative intensity): 311 ([M^+] 100), 310 (54), 292 (12), 178 (11), 104 (7), 77 (16).

HR-MS (EI) *m/z* calcd for $C_{22}H_{17}NO^+$ [M^+] 311.1310, found 311.1297.

The analytical data are in accordance with those reported in the literature.[111]

Synthesis of 6-Methoxy-3,4-diphenylisoquinolin-1(2*H*)-one (41ca)



The general procedure **A** was followed using *N*-hydroxy-4-methoxybenzamide (**88c**) (84 mg, 0.50 mmol) and diphenylacetylene (**38a**) (134 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1 → 1/1 → 1/2) yielded **41ca** (96 mg, 59%) as an off-white solid.

M.p. = 292–294 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.38 (s, 1H), 8.23 (d, J = 8.8 Hz, 1H), 7.37–7.05 (m, 11H), 6.49 (d, J = 2.5 Hz, 1H), 3.65 (s, 3H).

^{13}C-NMR (75 MHz, DMSO-d_6): δ = 162.2 (C_q), 161.2 (C_q), 140.0 (C_q), 139.1 (C_q), 135.8 (C_q), 134.6 (C_q), 131.6 (CH), 129.7 (CH), 129.0 (CH), 128.1 (CH), 128.0 (CH), 127.5 (CH), 126.9 (CH), 118.8 (C_q), 115.0 (C_q), 114.4 (CH), 107.1 (CH), 55.1 (CH_3).

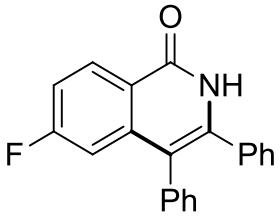
IR (neat): 3020, 2979, 2884, 1639, 1608, 1275, 1027, 694 cm^{-1}.

MS (EI) *m/z* (relative intensity): 327 ([M^+] 100), 326 (50), 283 (7), 254 (7), 152 (12), 104 (6), 77 (8).

HR-MS (EI) *m/z* calcd for $C_{22}H_{17}NO_2^+$ [M^+] 327.1259, found 327.1266.

The analytical data are in accordance with those reported in the literature.[108]

Synthesis of 6-Fluoro-3,4-diphenylisoquinolin-1(2*H*)-one (41da)



The general procedure **A** was followed using 4-fluoro-*N*-hydroxybenzamide (**88d**) (78 mg, 0.50 mmol) and diphenylacetylene (**38a**) (134 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41da** (128 mg, 81%) as a colorless solid.

M.p. = 251–253 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.58 (s, 1H), 8.37 (dd, J = 8.9, 6.1 Hz, 1H), 7.38–7.13 (m, 11H), 6.73 (dd, J = 10.9, 2.5 Hz, 1H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 164.3 (d, $J_{C\text{-}F}$ = 249.2 Hz, C_q), 160.7 (C_q), 140.5 (d, $J_{C\text{-}F}$ = 9.7 Hz, C_q), 140.0 (C_q) , 135.1 (C_q), 134.0 (C_q), 131.3 (CH), 130.3 (CH), 130.2 (CH), 129.5 (CH), 128.2 (CH), 127.5 (CH), 127.1 (CH), 121.7 (d, $J_{C\text{-}F}$ = 1.6 Hz, C_q), 114.7 (d, $J_{C\text{-}F}$ = 3.4 Hz, C_q), 114.5 (d, $J_{C\text{-}F}$ = 23.6 Hz, CH), 109.4 (d, $J_{C\text{-}F}$ = 23.2 Hz, CH).

^{19}F-NMR (283 MHz, DMSO-d_6) δ = -106.4 (ddd, J = 10.9, 8.4, 6.3 Hz).

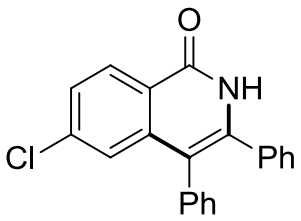
IR (neat): 3116, 3030, 2917, 1644, 1610, 1450, 1178, 695 cm^{-1}.

MS (EI) *m/z* (relative intensity): 315 ([M$^+$] 60), 314 (36), 296 (12), 183 (9), 98 (22), 57 (32), 43 (100).

HR-MS (EI) *m/z* calcd for $C_{21}H_{14}FNO^+$ [M$^+$] 315.1059, found 315.1064.

The analytical data are in accordance with those reported in the literature.[110]

Synthesis of 6-Chloro-3,4-diphenylisoquinolin-1(2*H*)-one (41ea)



The general procedure **A** was followed using 4-chloro-*N*-hydroxybenzamide (**88e**) (86 mg, 0.50 mmol) and diphenylacetylene (**38a**) (134 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41ea** (103 mg, 62%) as a colorless solid.

M.p. = 270–272 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.65 (s, 1H), 8.31 (d, J = 8.5 Hz, 1H), 7.54 (dd, J = 8.6, 2.0 Hz, 1H), 7.36–7.13 (m, 10H), 7.05 (d, J = 2.0 Hz, 1H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 160.8 (C_q), 140.1 (C_q), 139.5 (C_q), 137.4 (C_q), 134.9 (C_q), 134.0 (C_q), 131.4 (CH), 129.5 (CH), 129.1 (CH), 128.2 (CH), 128.2 (CH), 127.5 (CH), 127.1 (CH), 126.1 (CH), 123.6 (CH), 123.4 (C_q), 114.3 (C_q).

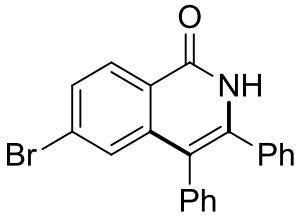
IR (neat):3155, 3022, 2882, 1644, 1594, 1442, 1080, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity): 331 ([M$^+$] 100), 330 (50), 295 (15), 267 (12), 163 (15), 77 (15).

HR-MS (EI) *m/z* calcd for $C_{21}H_{14}ClNO^+$ [M$^+$] 331.0764, found 331.0762.

The analytical data are in accordance with those reported in the literature.[110]

Synthesis of 6-Bromo-3,4-diphenylisoquinolin-1(2*H*)-one (41fa)



The general procedure **A** was followed using 4-bromo-*N*-hydroxybenzamide (**88f**) (108 mg, 0.50 mmol) and diphenylacetylene (**38a**) (134 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41fa** (138 mg, 73%) as a colorless solid.

M.p. = 285–286 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.69 (s, 1H), 8.21 (d, J = 8.6 Hz, 1H), 7.66 (dd, J = 8.6, 1.9 Hz, 1H), 7.39–7.09 (m, 11H).

^{13}C-NMR (75 MHz, DMSO-d_6): δ = 161.1 (C_q), 140.2 (C_q), 139.8 (C_q), 135.1 (C_q), 134.1 (C_q), 131.5 (CH), 129.6 (CH), 129.2 (CH), 129.0 (CH), 128.3 (CH), 127.6 (CH), 127.3 (CH), 126.8 (CH), 126.7 (C_q), 123.8 (C_q), 114.3 (C_q).

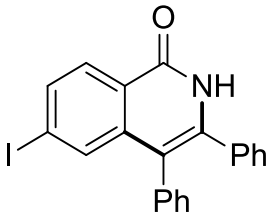
IR (neat): 3164, 3020, 2902, 1645, 1588, 1438, 1066, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity): 376 ([M^+] 95), 375 (100), 295 (28), 267 (16), 239 (13), 163 (25), 77 (20).

HR-MS (EI) *m/z* calcd for $C_{21}H_{14}{}^{79}BrNO^+$ [M^+] 375.0259, found 375.0272.

The analytical data are in accordance with those reported in the literature.[108]

Synthesis of 6-Iodo-3,4-diphenylisoquinolin-1(2*H*)-one (41ga)



The general procedure **A** was followed using *N*-hydroxy-4-iodobenzamide (**88g**) (132 mg, 0.50 mmol) and diphenylacetylene (**38a**) (134 mg, 0.75 mmol). After stirring at 100 °C for

18 h, purification by column chromatography on silica gel (*n*-pentane/CH_2Cl_2/EtOAc: 2/1/1) yielded **41ga** (81 mg, 38%) as a colorless solid.

M.p. = 311–312 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.67 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.83 (dd, J = 8.4, 1.6 Hz, 1H), 7.43 (d, J = 1.6 Hz, 1H), 7.36–7.09 (m, 10H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 161.3 (C_q), 139.9 (C_q), 139.7 (C_q), 135.1 (C_q), 134.7 (CH), 134.2 (C_q), 133.1 (CH), 131.6 (CH), 129.7 (CH), 128.7 (CH), 128.3 (CH), 128.3 (CH), 127.6 (CH), 127.2 (CH), 124.1 (C_q), 114.1 (C_q), 101.1 (C_q).

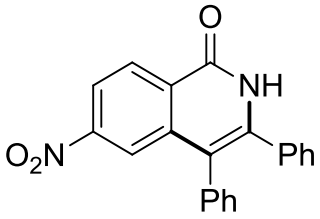
IR (neat): 3160, 3020, 2934, 1648, 1597, 1437, 1154, 697 cm^{-1}.

MS (EI) *m/z* (relative intensity): 423 ([M^+] 100), 422 (28), 295 (14), 267 (11), 239 (9), 163 (15), 77 (10).

HR-MS (EI) *m/z* calcd for $C_{21}H_{14}INO^+$ [M^+] 423.0120, found 423.0123.

The analytical data are in accordance with those reported in the literature.[111]

Synthesis of 6-Nitro-3,4-diphenylisoquinolin-1(2*H*)-one (41ha)



The general procedure **A** was followed using *N*-hydroxy-4-nitrobenzamide (**88h**) (91 mg, 0.50 mmol) and diphenylacetylene (**38a**) (134 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41ha** (114 mg, 67%) as a yellow solid.

M.p. = 260–262 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.12 (s, 1H), 8.65–8.50 (m, 1H), 8.31–8.15 (m, 2H), 7.42–7.23 (m, 8H), 7.22–7.14 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.7 (C_q), 150.6 (C_q), 139.7 (C_q), 139.5 (C_q), 134.3 (C_q), 134.1 (C_q), 131.6 (CH), 129.6 (CH), 129.2 (CH), 129.2 (CH), 128.9 (CH), 128.6 (Cq), 128.5 (CH), 128.1 (CH), 121.2 (CH), 120.1 (CH), 117.1 (Cq).

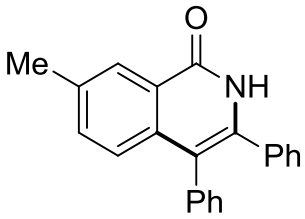
IR (neat): 3332, 3022, 1664, 1611, 1525, 1340, 701 cm^{-1}.

MS (EI) *m/z* (relative intensity): 342 ([M$^+$] 100), 341 (18), 295 (16), 268 (14), 190 (12), 165 (12), 121 (15).

HR-MS (EI) *m/z* calcd for $C_{21}H_{14}N_2O_3^+$ [M$^+$] 342.1004, found 342.1001.

The analytical data are in accordance with those reported in the literature.[108]

Synthesis of 7-Methyl-3,4-diphenylisoquinolin-1(2*H*)-one (41ia)



The general procedure **A** was followed using *N*-hydroxy-3-methylbenzamide (**88i**) (76 mg, 0.50 mmol) and diphenylacetylene (**38a**) (134 mg, 0.75 mmol). After stirring at 120 °C for 18 h, purification by column chromatography on silica gel (CH_2Cl_2/Et_2O: 5/1) yielded **41ia** (94 mg, 60%) as a colorless solid.

M.p. = 292–293 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.38 (s, 1H), 8.12 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.47 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.33–7.19 (m, 8H), 7.17–7.10 (m, 2H), 7.06 (d, *J* = 8.3 Hz, 1H), 2.45 (s, 3H).

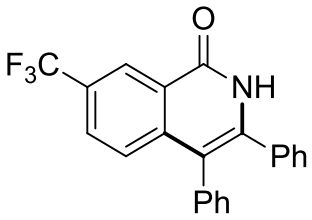
^{13}C-NMR (75 MHz, DMSO-d_6): δ = 161.0 (C_q), 138.0 (C_q), 136.5 (C_q), 136.3 (C_q), 136.3 (C_q), 135.1 (C_q), 134.2 (CH), 132.1 (CH), 130.3 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.4 (CH), 126.8 (CH), 125.5 (C_q), 125.4 (CH), 115.8 (C_q), 21.3 (CH_3).

IR (neat): 3138, 3026, 2911, 1642, 1616, 1444, 1342, 696 cm^{-1}. MS (EI) *m/z* (relative intensity): 311 ([M$^+$] 100), 310 (48), 292 (9), 178 (7), 104 (5), 77 (12).

HR-MS (EI) *m/z* calcd for $C_{22}H_{17}NO^+$ [M$^+$] 311.1310, found 311.1313.

The analytical data are in accordance with those reported in the literature.[109]

Synthesis of 7-(Trifluoromethyl)-3,4-diphenylisoquinolin-1(2*H*)-one (41ja)



The general procedure **A** was followed using *N*-hydroxy-3-(trifluoromethyl)benzamide (**88j**) (103 mg, 0.50 mmol) and diphenylacetylene (**38a**) (134 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (CH_2Cl_2/Et_2O: 10/1) yielded **41ja** (76 mg, 42%) as a colorless solid.

M.p. = 234–235 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.90 (s, 1H), 8.77–8.67 (m, 1H), 7.76 (dd, J = 8.6, 2.0 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.38–7.23 (m, 8H), 7.21–7.14 (m, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 162.1 (C_q), 141.0 (C_q), 139.5 (C_q), 134.9 (C_q), 134.3 (C_q), 131.6 (CH), 129.1 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (d, $J_{C\text{-}F}$ = 33.3 Hz, C_q), 127.6 (CH), 126.5 (CH), 125.1 (dd, $J_{C\text{-}F}$ = 8.2, 4.0 Hz, CH), 124.8 (C_q), 123.8 (d, $J_{C\text{-}F}$ = 271.7 Hz, C_q), 116.7 (C_q).

^{19}F-NMR (283 MHz, $CDCl_3$) δ = -62.4 (s).

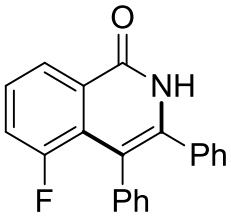
IR (neat): 3153, 3034, 2929, 1653, 1618, 1320, 1121, 697 cm^{-1}.

MS (EI) *m/z* (relative intensity): 365 ([M^+] 100), 364 (55), 346 (19), 267 (8), 239 (5), 163 (5), 77 (13).

HR-MS (EI) *m/z* calcd for $C_{22}H_{14}F_3NO^+$ [M^+] 365.1027, found 365.1024.

The analytical data are in accordance with those reported in the literature.[108]

Synthesis of 5-Fluoro-3,4-diphenylisoquinolin-1(2*H*)-one (41ka)



The general procedure **A** was followed using 3-fluoro-*N*-hydroxybenzamide (**88k**) (78 mg, 0.50 mmol) and diphenylacetylene (**38a**) (134 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (CH_2Cl_2/Et_2O: 5/1) yielded **41ka** (91 mg, 58%) as a colorless solid.

M.p. = 250–252 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.50 (s, 1H), 8.29 (dd, J = 7.9, 1.3 Hz, 1H), 7.44 (td, J = 8.0, 4.5 Hz, 1H), 7.34–7.12 (m, 11H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 161.6 (d, $J_{C\text{-}F}$ = 3.1 Hz, C_q), 158.6 (d, $J_{C\text{-}F}$ = 255.5 Hz, C_q), 138.5 (C_q), 137.4 (d, $J_{C\text{-}F}$ = 3.9 Hz, C_q), 134.8 (C_q), 131.0 (d, $J_{C\text{-}F}$ = 3.7 Hz, CH), 129.3 (CH), 128.7 (CH), 128.2 (CH), 127.5 (CH), 127.4 (d, $J_{C\text{-}F}$ = 2.5 Hz, C_q), 127.3 (d, $J_{C\text{-}F}$ = 8.4 Hz, CH), 127.3 (d, $J_{C\text{-}F}$ = 8.8 Hz, C_q), 126.9 (CH), 123.7 (d, $J_{C\text{-}F}$ = 4.0 Hz, CH), 119.8 (d, $J_{C\text{-}F}$ = 22.6 Hz, CH), 113.3 (d, $J_{C\text{-}F}$ = 2.1 Hz, C_q).

^{19}F-NMR (283 MHz, $CDCl_3$) δ = -107.3 (dd, J = 12.4, 4.5 Hz).

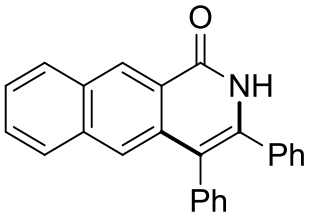
IR (neat): 3165, 3016, 2888, 1652, 1613, 1444, 1253, 697 cm^{-1}.

MS (EI) *m/z* (relative intensity): 315 ([M^+] 100), 314 (20), 296 (7), 183 (12), 104 (4), 77 (8).

HR-MS (EI) *m/z* calcd for $C_{21}H_{14}FNO^+$ [M^+] 315.1059, found 315.1071.

The analytical data are in accordance with those reported in the literature.[110]

Synthesis of 3,4-Diphenylbenzo[*g*]isoquinolin-1(2*H*)-one (41la)



The general procedure **A** was followed using *N*-hydroxy-2-naphthamide (**88l**) (94 mg, 0.50 mmol) and diphenylacetylene (**38a**) (134 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41la** (126 mg, 73%) as a pale green solid.

M.p. = 287–289 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.29 (s, 1H), 9.02 (s, 1H), 8.28–8.13 (m, 1H), 7.88–7.80 (m, 1H), 7.63 (s, 1H), 7.61–7.50 (m, 2H), 7.41–7.16 (m, 10H).

^{13}C-NMR (75 MHz, DMSO-d_6): δ = 162.1 (C_q), 137.3 (C_q), 136.0 (C_q), 134.8 (C_q), 134.7 (C_q), 134.6 (C_q), 131.7 (CH), 130.7 (C_q), 129.7 (CH), 129.0 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 128.0 (CH), 127.7 (CH), 127.6 (CH), 127.0 (CH), 126.0 (CH), 123.8 (C_q), 123.3 (CH), 115.2 (C_q).

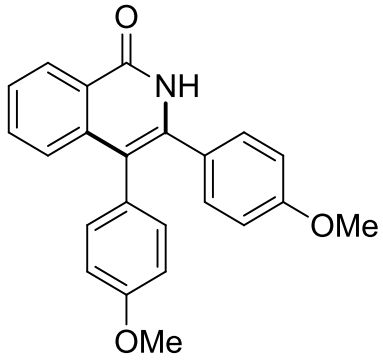
IR (neat): 3051, 3024, 2884, 1649, 1616, 1596, 1357, 697 cm^{-1}.

MS (EI) *m/z* (relative intensity): 347 ([M^+] 100), 346 (22), 328 (12), 251 (12), 158 (6), 77 (5).

HR-MS (EI) *m/z* calcd for $C_{25}H_{17}NO^+$ [M^+] 347.1310, found 347.1301.

The analytical data are in accordance with those reported in the literature.[111]

Synthesis of 3,4-Bis(4-methoxyphenyl)isoquinolin-1(2*H*)-one (41ab)



The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and 1,2-bis(4-methoxyphenyl)ethyne (**38b**) (179 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1 → 1/1 → 1/3) yielded **41ab** (103 mg, 58%) as an off-white solid.

M.p. = 265–267 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.42 (s, 1H), 8.27 (dd, J = 8.0, 1.5 Hz, 1H), 7.65–7.56 (m, 1H), 7.46–7.51 (m, 1H), 7.15–7.12 (m, 3H), 7.04 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.77 (d, J = 8.6 Hz, 2H), 3.72 (s, 3H), 3.69 (s, 3H).

^{13}C-NMR (75 MHz, DMSO-d_6): δ = 161.7 (C_q), 158.8 (C_q), 157.9 (C_q), 138.5 (C_q), 138.3 (C_q), 132.7 (CH), 132.2 (CH), 131.0 (CH), 127.9 (C_q), 126.9 (C_q), 126.6 (CH), 125.8 (CH), 124.8 (CH), 124.8 (C_q), 114.7 (C_q), 113.7 (CH), 113.0 (CH), 55.0 (CH_3), 54.9 (CH_3).

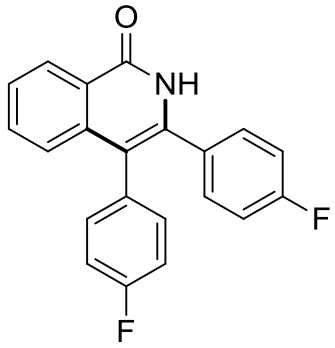
IR (neat): 3156, 3003, 2834, 1645, 1603, 1509, 1243, 1031 cm^{-1}.

MS (EI) *m/z* (relative intensity): 357 ([M^+] 100), 356 (14), 342 (11), 282 (7), 152 (7), 77 (3).

HR-MS (EI) *m/z* calcd for $C_{23}H_{19}NO_3^+$ [M^+] 357.1365, found 357.1366.

The analytical data are in accordance with those reported in the literature.[111]

Synthesis of 3,4-Bis(4-fluorophenyl)isoquinolin-1(2*H*)-one (41ac)



The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and 1,2-bis(4-fluorophenyl)ethyne (**38c**) (161 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41ac** (105 mg, 63%) as a colorless solid.

M.p. = 296–298 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.58 (s, 1H), 8.30 (dd, J = 8.0, 1.5 Hz, 1H), 7.64 (ddd, J = 8.4, 7.2, 1.6 Hz, 1H), 7.51 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.31–7.03 (m, 9H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 161.5 (d, $J_{C\text{-}F}$ = 245.4 Hz, C_q), 161.4 (C_q), 160.9 (d, $J_{C\text{-}F}$ = 243.8 Hz, C_q), 137.8 (C_q) , 137.7 (C_q), 133.4 (d, $J_{C\text{-}F}$ = 8.1 Hz, CH), 132.4 (CH), 131.9 (d, $J_{C\text{-}F}$ =

8.5 Hz, CH), 131.8 (d, J_{C-F} = 3.3 Hz, C_q), 130.7 (d, J_{C-F} = 3.3 Hz, C_q), 126.6 (CH), 126.1 (CH), 124.9 (C_q), 124.6 (CH), 114.8 (d, J_{C-F} = 21.3 Hz, CH), 114.5 (d, J_{C-F} = 21.7 Hz, CH), 114.4 (C_q).

^{19}F-NMR (283 MHz, DMSO-d_6) δ = -113.1 (tt, J = 9.0, 5.5 Hz), -115.1 (tt, J = 8.9, 5.7 Hz).

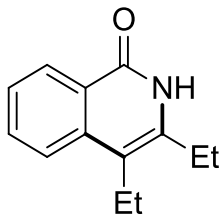
IR (neat): 3160, 3066, 2916, 1648, 1613, 1506, 1223, 773 cm^{-1}.

MS (EI) *m/z* (relative intensity): 333 ([M$^+$] 100), 332 (52), 314 (22), 183 (16), 122 (7), 95 (7).

HR-MS (EI) *m/z* calcd for $C_{21}H_{13}F_2NO^+$ [M$^+$] 333.0965, found 333.0961.

The analytical data are in accordance with those reported in the literature.[110]

Synthesis of 3,4-Diethylisoquinolin-1(2*H*)-one (41af)



The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and hex-3-yne (**38f**) (62 mg, 0.75 mmol). After stirring at 80 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41af** (87 mg, 86%) as a colorless solid .

M.p. = 178–180 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.31 (s, 1H), 8.48 (dt, J = 7.8, 1.1 Hz, 1H), 7.77–7.62 (m, 2H), 7.44 (ddd, J = 8.1, 5.8, 2.3 Hz, 1H), 2.68–2.81 (m, 4H), 1.34 (t, J = 7.6 Hz, 3H), 1.22 (t, J = 7.5 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 164.0 (C_q), 139.3 (C_q), 138.3 (C_q), 132.4 (CH), 127.8 (CH), 125.3 (CH), 125.2 (C_q), 122.9 (CH), 114.0 (C_q), 24.5 (CH_2), 19.7 (CH_2), 15.2 (CH_3), 14.3 (CH_3).

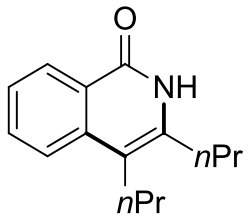
IR (neat): 3163, 2966, 2872, 1648, 1631, 1474, 1163, 769 cm^{-1}.

MS (EI) *m/z* (relative intensity): 201 ([M$^+$] 43), 187 (15), 186 (100), 168 (10), 128 (10), 115 (20), 77 (6).

HR-MS (EI) *m/z* calcd for $C_{13}H_{15}NO^+$ [M$^+$] 201.1154, found 201.1152.

The analytical data are in accordance with those reported in the literature.[111]

Synthesis of 3,4-Di-(*n*-propyl)isoquinolin-1(2*H*)-one (41ag)



The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and oct-4-yne (**38g**) (83 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41ag** (86 mg, 75%) as a colorless solid.

M.p. = 188–190 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.99 (s, 1H), 8.44 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.68–7.63 (m, 2H), 7.42 (dt, *J* = 8.1, 4.1 Hz, 1H), 2.73–2.61 (m, 4H), 1.81–1.66 (m, 2H), 1.66–1.51 (m, 2H), 1.04 (t, *J* = 7.3 Hz, 3H), 1.03 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.8 (C_q), 138.6 (C_q), 138.2 (C_q), 132.4 (CH), 127.8 (CH), 125.4 (CH), 125.3 (C_q), 123.2 (CH), 113.1 (C_q), 33.1 (CH_2), 28.8 (CH_2), 23.7 (CH_2), 22.9 (CH_2), 14.5 (CH_3), 14.1 (CH_3).

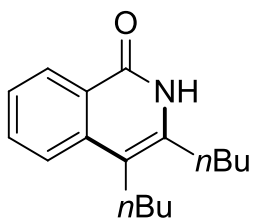
IR (neat): 3164, 3025, 2869, 1653, 1628, 1470, 1167, 774 cm^{-1}.

MS (EI) *m/z* (relative intensity): 229 ([M^+] 30), 201 (20), 200 (100), 172 (12), 115 (10), 77 (6).

HR-MS (EI) *m/z* calcd for $C_{15}H_{19}NO^+$ [M^+] 229.1467, found 229.1462.

The analytical data are in accordance with those reported in the literature.[109]

Synthesis of 3,4-Di-(*n*-butyl)isoquinolin-1(2*H*)-one (41ah)



The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and dec-5-yne (**38h**) (104 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (CH_2Cl_2/Et_2O: 4/1) yielded **41ah** (101 mg, 78%) as a colorless solid.

M.p. = 85–87 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.24 (s, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 7.66 (m, 2H), 7.41 (dt, *J* = 8.1, 4.0 Hz, 1H), 2.76–2.61 (m, 4H), 1.68 (tt, *J* = 7.9, 6.3 Hz, 2H), 1.60–1.38 (m, 6H), 0.96 (t, *J* = 7.2 Hz, 6H).

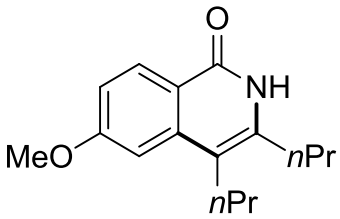
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.7 (C_q), 138.5 (C_q), 138.3 (C_q), 132.2 (CH), 127.6 (CH), 125.2 (CH), 125.1 (C_q), 122.9 (CH), 112.9 (C_q), 32.6 (CH_2), 31.6 (CH_2), 30.8 (CH_2), 26.2 (CH_2), 23.0(CH_2), 22.7 (CH_2), 14.0 (CH_3), 13.8 (CH_3).

IR (neat): 3164, 2961, 2926, 2861, 1649, 1627, 1471, 769 cm^{-1}.

MS (EI) *m/z* (relative intensity): 257 ([M^+] 58), 215 (23), 214 (100), 173 (22), 172 (83), 144 (10), 115 (12), 77 (5).

HR-MS (EI) *m/z* calcd for $C_{17}H_{23}NO^+$ [M^+] 257.1780, found 257.1788.

Synthesis of 6-Methoxy-3,4-di-(*n*-propyl)isoquinolin-1(2*H*)-one (41cg)



The general procedure **A** was followed using *N*-hydroxy-4-methoxybenzamide (**88c**) (84 mg, 0.50 mmol) and oct-4-yne (**38g**) (83 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 1/1) yielded **41cg** (91 mg, 70%) as an off-white solid.

M.p. = 158–160 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.97 (s, 1H), 8.38 (d, *J* = 9.6 Hz, 1H), 7.07–6.96 (m, 2H), 3.93 (s, 3H), 2.68–2.57 (m, 4H), 1.80–1.54 (m, 4H), 1.05 (t, *J* = 7.3 Hz, 3H), 1.04 (t, *J* = 7.3 Hz, 3H).

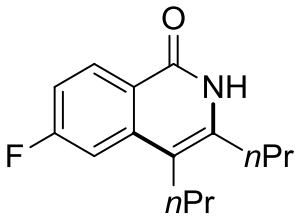
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.3 (C_q), 163.0 (C_q), 140.7 (C_q), 139.0 (C_q), 129.9 (CH), 119.2 (C_q), 114.0 (CH), 112.6 (C_q), 105.4 (CH), 55.5 (CH_3), 33.2 (CH_2), 28.9 (CH_2), 23.4 (CH_2), 22.9 (CH_2), 14.5 (CH_3), 14.1 (CH_3).

IR (neat): 3156, 2966, 2864, 1632, 1601, 1467, 1232, 833 cm^{-1}.

MS (EI) *m/z* (relative intensity): 259 ([M^+] 40), 231 (32), 230 (100), 202 (14), 189 (8), 115 (6), 77 (3).

HR-MS (EI) *m/z* calcd for $C_{16}H_{21}NO_2^+$ [M^+] 259.1572, found 259.1574.

Synthesis of 6-Fluoro-3,4-di-(*n*-propyl)isoquinolin-1(2*H*)-one (41dg)



The general procedure **A** was followed using 4-fluoro-*N*-hydroxybenzamide (**88d**) (78 mg, 0.50 mmol) and oct-4-yne (**38g**) (83 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41dg** (94 mg, 76%) as a colorless solid.

M.p. = 170–172 °C.

^{1}H-NMR (300 MHz $CDCl_3$): δ = 11.24 (s, 1H), 8.45 (ddd, *J* = 8.9, 6.2, 2.9 Hz, 1H), 7.27 (dd, *J* = 10.9, 2.7 Hz, 1H), 7.13 (td, *J* = 8.5, 2.5 Hz, 1H), 2.72–2.58 (m, 4H), 1.82–1.68 (m, 2H), 1.66–1.51 (m, 2H), 1.06 (t, *J* = 7.3 Hz, 3H), 1.04 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 165.6 (d, $J_{C\text{-}F}$ = 251.3 Hz, C_q), 163.1 (C_q), 141.1 (d, $J_{C\text{-}F}$ = 9.7 Hz, C_q), 139.8 (C_q), 130.8 (d, $J_{C\text{-}F}$ = 10.2 Hz, CH), 121.8 (d, $J_{C\text{-}F}$ = 1.5 Hz, C_q), 114.0 (d, $J_{C\text{-}F}$ = 23.6 Hz, CH), 112.7 (d, $J_{C\text{-}F}$ = 3.5 Hz, C_q), 108.4 (d, $J_{C\text{-}F}$ = 22.6 Hz, CH), 33.2 (CH_2), 28.9 (CH_2), 23.6 (CH_2), 23.0 (CH_2), 14.5 (CH_3), 14.2 (CH_3).

^{19}F-NMR (283 MHz, $CDCl_3$) δ = -106.2 (ddd, *J* = 11.1, 8.1, 6.2 Hz).

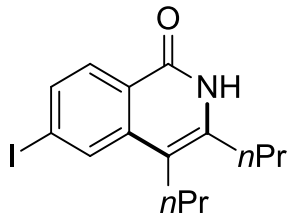
IR (neat): 3027, 2954, 2871, 1666, 1614, 1461, 1188, 863 cm^{-1}.

MS (EI) *m/z* (relative intensity): 247 ([M^+] 21), 219 (15), 218 (100), 202 (7), 190 (12), 133 (7), 43 (13).

HR-MS (EI) *m/z* calcd for $C_{15}H_{18}FNO^+$ [M^+] 247.1372, found 247.1364.

The analytical data are in accordance with those reported in the literature.[110]

Synthesis of 6-Iodo-3,4-di-(*n*-propyl)isoquinolin-1(2*H*)-one (41gg)



The general procedure **A** was followed using *N*-hydroxy-4-iodobenzamide (**88g**) (132 mg, 0.50 mmol) and oct-4-yne (**38g**) (83 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41gg** (122 mg, 69%) as an off-white solid.

M.p. = 184–186 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.19 (s, 1H), 7.98 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 2.61–2.42 (m, 4H), 1.64–1.34 (m, 4H), 1.00–0.83 (m, 6H).

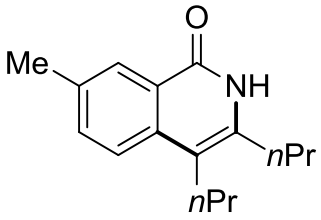
^{13}C-NMR (125 MHz, DMSO-d_6): δ = 161.3 (C_q), 140.3 (C_q), 139.4 (C_q), 133.7 (CH), 131.4 (CH), 128.8 (CH), 124.1 (C_q), 109.7 (C_q), 101.0 (C_q), 31.7 (CH_2), 27.4 (CH_2), 23.0 (CH_2), 22.4 (CH_2), 13.9 (CH_3), 13.5 (CH_3).

IR (neat): 3169, 2953, 2867, 1666, 1625, 1589, 1455, 775 cm^{-1}.

MS (EI) *m/z* (relative intensity): 355 ([M^+] 40), 327 (15), 326 (100), 298 (7), 199 (20), 184 (6), 102 (5).

HR-MS (EI) *m/z* calcd for $C_{15}H_{18}INO^+$ [M^+] 355.0433, found 355.0433.

Synthesis of 7-Methyl-3,4-di-(*n*-propyl)isoquinolin-1(2*H*)-one (41ig)



The general procedure **A** was followed using *N*-hydroxy-3-methylbenzamide (**88i**) (76 mg, 0.50 mmol) and oct-4-yne (**38g**) (83 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41ig** (85 mg, 70%) as a colorless solid.

M.p. = 176–178 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.44 (s, 1H), 8.24 (s, 1H), 7.58 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.49 (dt, *J* = 8.4, 1.9 Hz, 1H), 2.72–2.60 (m, 4H), 2.48 (s, 3H), 1.82–1.51 (m, 4H), 1.08–1.00 (m, 6H).

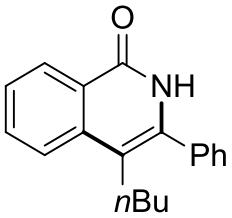
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 163.2 (C_q), 136.6 (C_q), 136.0 (C_q), 135.1 (C_q), 133.7 (CH), 127.1 (CH), 125.0 (C_q), 123.0 (CH), 112.9 (C_q), 32.9 (CH_2), 28.7 (CH_2), 23.7 (CH_2), 22.7 (CH_2), 21.2 (CH_3), 14.4 (CH_3), 14.0 (CH_3).

IR (neat): 2956, 2930, 2870, 1659, 1629, 1352, 900, 815 cm^{-1}.

MS (EI) *m/z* (relative intensity): 243 ([M^+] 32), 215 (15), 214 (100), 186 (13), 115 (12), 77 (3).

HR-MS (EI) *m/z* calcd for $C_{16}H_{21}NO^+$ [M^+] 243.1623, found 243.1629.

Synthesis of 4-(*n*-Butyl)-3-phenylisoquinolin-1(2*H*)-one (41ai)



The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and hex-1-yn-1-ylbenzene (**38i**) (119 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41ai** (110 mg, 79%) as a colorless solid.

M.p. = 154–155 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.86 (s, 1H), 8.43 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.77–7.66 (m, 2H), 7.53–7.37 (m, 6H), 2.68–2.56 (m, 2H), 1.61–1.47 (m, 2H), 1.27 (tt, *J* = 7.3, 7.3 Hz, 2H), 0.81 (t, *J* = 7.3 Hz, 3H).

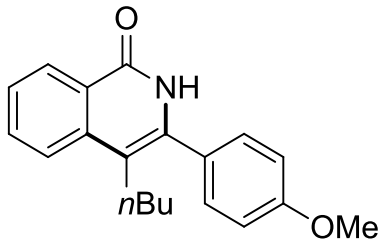
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.3 (C_q), 138.1 (C_q), 136.9 (C_q), 135.7 (C_q), 132.8 (CH), 129.3 (CH), 129.1 (CH), 128.9 (CH), 128.1 (CH), 126.4 (CH), 126.0 (C_q), 123.9 (CH), 114.5 (C_q), 32.9 (CH_2), 27.1 (CH_2), 22.9 (CH_2), 13.9 (CH_3).

IR (neat): 3160, 2950, 2869, 1646, 1615, 1469, 1157, 761 cm^{-1}.

MS (EI) *m/z* (relative intensity): 277 ([M^+] 35), 235 (15), 234 (100), 216 (19), 178 (6), 77 (11), 43 (24).

HR-MS (EI) *m/z* calcd for $C_{19}H_{19}NO^+$ [M^+] 277.1467, found 277.1461.

Synthesis of 4-(*n*-Butyl)-3-(4-methoxyphenyl)isoquinolin-1(2*H*)-one (41aj)



The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and 1-(hex-1-yn-1-yl)-4-methoxybenzene (**38j**) (141 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1 → 1/1) yielded **41aj** (100 mg, 65%) as an off-white solid.

M.p. = 167–169 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.09 (s, 1H), 8.28 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.83–7.71 (m, 2H), 7.50 (dt, *J* = 8.1, 4.1 Hz, 1H), 7.39–7.32 (m, 2H), 7.08–7.01 (m, 2H), 3.83 (s, 3H), 2.56–2.49 (m, 2H), 1.53–1.39 (m, 2H), 1.23 (tt, *J* = 7.3, 7.3 Hz, 2H), 0.77 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 161.0 (C_q), 159.1 (C_q), 137.8 (C_q), 137.2 (C_q), 132.2 (CH), 130.4 (CH), 127.1 (C_q), 126.9 (CH), 125.5 (CH), 125.5 (C_q), 123.4 (CH), 113.4 (CH), 112.0 (C_q), 55.1 (CH_3), 32.2 (CH_2), 26.2 (CH_2), 22.0 (CH_2), 13.5 (CH_3).

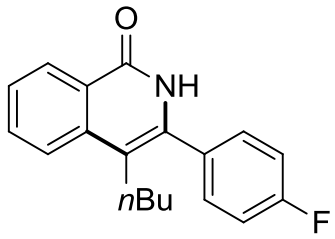
IR (neat): 2955, 2932, 2869, 1634, 1604, 1245, 1023, 532 cm^{-1}.

MS (EI) *m/z* (relative intensity): 307 ([M^+] 50), 265 (20), 264 (100), 249 (12), 233 (18), 165 (6), 102 (6), 43 (15).

HR-MS (EI) *m/z* calcd for $C_{20}H_{21}NO_2^+$ [M^+] 307.1572, found 307.1580.

The analytical data are in accordance with those reported in the literature.[110]

Synthesis of 4-(*n*-Butyl)-3-(4-fluorophenyl)isoquinolin-1(2*H*)-one (41ak)



The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and 1-fluoro-4-(hex-1-yn-1-yl)benzene (**38k**) (132 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 3/1) yielded **41ak** (102 mg, 69%) as a colorless solid.

M.p. = 182–184 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.44 (s, 1H), 8.39 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.77–7.66 (m, 2H), 7.54–7.37 (m, 3H), 7.22–7.13 (m, 2H), 2.65–2.54 (m, 2H), 1.52 (tt, *J* = 8.0, 6.3 Hz, 2H), 1.28 (tt, *J* = 7.3, 7.3 Hz, 2H), 0.82 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.2 (d, $J_{C\text{-}F}$ = 249.2 Hz, C_q), 162.5 (C_q), 138.0 (C_q), 136.1 (C_q), 132.8 (CH), 131.6 (d, $J_{C\text{-}F}$ = 3.5 Hz, C_q), 131.2 (d, $J_{C\text{-}F}$ = 8.4 Hz, CH), 128.1 (CH), 126.5 (CH), 126.0 (C_q), 123.9 (CH), 116.0 (d, $J_{C\text{-}F}$ = 21.6 Hz, CH), 114.8 (C_q), 32.9 (CH_2), 27.1 (CH_2), 22.9 (CH_2), 13.9 (CH_3).

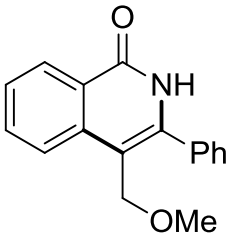
^{19}F-NMR (283 MHz, $CDCl_3$) δ = -111.6 (tt, *J* = 8.6, 5.3 Hz).

IR (neat): 3163, 2929, 2860, 1644, 1602, 1221, 840 cm^{-1}.

MS (EI) *m/z* (relative intensity): 295 ([M^+] 18), 253 (20), 252 (100), 234 (29), 196 (6), 77 (5).

HR-MS (EI) *m/z* calcd for $C_{19}H_{18}FNO^+$ [M^+] 295.1372, found 295.1368.

Synthesis of 4-(Methoxymethyl)-3-phenylisoquinolin-1(2*H*)-one (41al)



The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and (3-methoxyprop-1-yn-1-yl)benzene (**38l**) (110 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 1/1 → 1/2) yielded **41al** (97 mg, 73%) as an off-white solid.

M.p. = 236–238 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.33 (s, 1H), 8.40 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.91–7.82 (m, 1H), 7.75 (ddd, *J* = 8.3, 7.0, 1.4 Hz, 1H), 7.61–7.45 (m, 6H), 4.42 (s, 2H), 3.40 (d, *J* = 1.1 Hz, 3H).

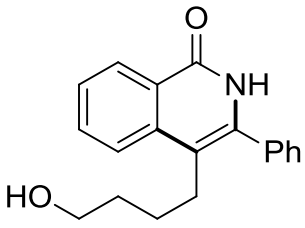
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.9 (C_q), 140.6 (C_q), 138.2 (C_q), 134.5 (C_q), 133.2 (CH), 129.9 (CH), 129.1 (CH), 129.0 (CH), 127.8 (CH), 126.8 (CH), 125.6 (C_q), 124.2 (CH), 110.4 (C_q), 68.4 (CH_2), 58.1 (CH_3).

IR (neat): 3171, 2971, 2886, 2807, 1653, 1608, 1090, 697 cm^{-1}.

MS (EI) *m/z* (relative intensity): 265 ([M^+] 40), 235 (18), 234 (100), 216 (30), 178 (8), 102 (15), 77 (22).

HR-MS (EI) *m/z* calcd for $C_{17}H_{15}NO_2^+$ [M^+] 265.1103, found 265.1102.

Synthesis of 4-(4-Hydroxy-*n*-butyl)-3-phenylisoquinolin-1(2*H*)-one (41am)



The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and 6-phenylhex-5-yn-1-ol (**38m**) (131 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 1/3) yielded **41am** (103 mg, 70%) as a colorless solid.

M.p. = 113–115 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.95 (s, 1H), 8.41 (d, *J* = 7.7 Hz, 1H), 7.77–7.65 (m, 2H), 7.52–7.34 (m, 6H), 3.51 (t, *J* = 6.4 Hz, 2H), 2.70–2.57 (m, 2H), 1.77 (s, 1H), 1.70–1.41 (m, 4H).

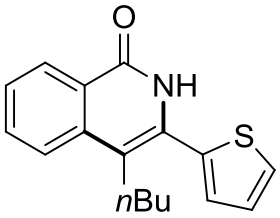
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 162.2 (C_q), 137.9 (C_q), 137.0 (C_q), 135.5 (C_q), 132.8 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 128.1 (CH), 126.4 (CH), 125.9 (C_q), 123.8 (CH), 114.1 (C_q), 62.5 (CH_2), 32.6 (CH_2), 27.1 (CH_2), 26.9 (CH_2).

IR (neat): 3167, 2931, 2860, 1647, 1606, 1359, 1053, 764 cm^{-1}.

MS (EI) *m/z* (relative intensity): 293 ([M^+] 35), 235 (17), 234 (100), 216 (25), 204 (10), 178 (8), 77 (10).

HR-MS (EI) *m/z* calcd for $C_{19}H_{19}NO_2^+$ [M^+] 293.1416, found 293.1423.

Synthesis of 4-(*n*-Butyl)-3-(thiophen-2-yl)isoquinolin-1(2*H*)-one (41an)



The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and 2-(hex-1-yn-1-yl)thiophene (**38n**) (123 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41an** (63 mg, 44%) as an off-white solid.

M.p. = 164–166 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.18 (s, 1H), 8.28 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.83–7.77 (m, 2H), 7.75 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.54 (ddd, *J* = 8.1, 5.1, 3.1 Hz, 1H), 7.31 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.19 (dd, *J* = 5.1, 3.6 Hz, 1H), 2.72–2.60 (m, 2H), 1.52 (tt, *J* = 7.9, 6.2 Hz, 2H), 1.32 (tt, *J* = 7.3, 7.3 Hz, 2H), 0.84 (t, *J* = 7.3 Hz, 3H).

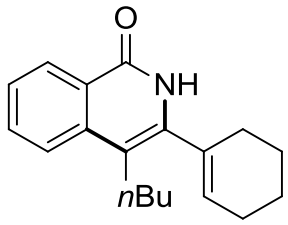
^{13}C-NMR (125 MHz, DMSO-d_6): δ = 160.9 (C_q), 136.7 (C_q), 134.6 (C_q), 132.4 (CH), 130.6 (C_q), 129.0 (CH), 127.6 (CH), 126.9 (CH), 126.9 (CH), 126.2 (CH), 125.8 (C_q), 123.7 (CH), 114.4 (C_q), 32.5 (CH_2), 26.7 (CH_2), 22.1 (CH_2), 13.5 (CH_3).

IR (neat): 3067, 2952, 2849, 1641, 1600, 1156, 764 cm^{-1}.

MS (EI) *m/z* (relative intensity): 283 ([M^+] 35), 241 (18), 240 (100), 222 (13), 184 (6), 128 (5), 77 (3).

HR-MS (EI) *m/z* calcd for $C_{17}H_{17}NOS^+$ [M^+] 283.1031, found 283.1027.

Synthesis of 4-(*n*-Butyl)-3-(cyclohex-1-en-1-yl)isoquinolin-1(2*H*)-one (41ao)



The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and 1-(hex-1-yn-1-yl)cyclohex-1-ene (**38o**) (122 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (CH_2Cl_2/Et_2O: 5/1) yielded **41ao** (69 mg, 49%) as a colorless solid.

M.p. = 152–154 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.05 (s, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 7.74–7.62 (m, 2H), 7.45 (dt, *J* = 8.2, 4.1 Hz, 1H), 5.91 (dd, *J* = 3.8, 2.1 Hz, 1H), 2.66 (dd, *J* = 9.9, 6.0 Hz, 2H), 2.31–2.14 (m, 4H), 1.87–1.65 (m, 4H), 1.63–1.35 (m, 4H), 0.96 (t, *J* = 7.2 Hz, 3H).

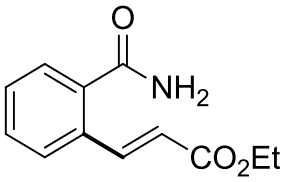
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 162.6 (C_q), 139.2 (C_q), 138.3 (C_q), 133.3 (C_q), 132.3 (CH), 130.9 (CH), 127.8 (CH), 125.7 (CH), 125.5 (C_q), 123.6 (CH), 112.9 (C_q), 33.0 (CH_2), 28.9 (CH_2), 27.1 (CH_2), 25.2 (CH_2), 23.0 (CH_2), 22.7 (CH_2), 21.8 (CH_2), 13.9 (CH_3).

IR (neat): 2958, 2922, 2856, 1650, 1622, 1460, 764 cm^{-1}.

MS (EI) *m/z* (relative intensity): 281 ([M^+] 40), 239 (20), 238 (100), 196 (23), 178 (11), 115 (9), 77 (6).

HR-MS (EI) *m/z* calcd for $C_{19}H_{23}NO^+$ [M^+] 281.1780, found 281.1770.

Synthesis of Ethyl (*E*)-3-(2-carbamoylphenyl)acrylate (44aa)



The general procedure **B** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and ethyl acrylate (**37a**) (75 mg, 0.75 mmol). After stirring at 60 °C for 18 h, purification by column chromatography on silica gel (CH_2Cl_2/EtOAc: 2/1) yielded **44aa** (90 mg, 82%) as a colorless solid.

M.p. = 161–163 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 16.0 Hz, 1H), 7.65–7.56 (m, 2H), 7.50–7.39 (m, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.12 (br s, 1H), 5.91 (br s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 170.5 (C_q), 166.4 (C_q), 141.8 (CH), 135.8 (C_q), 133.1 (C_q), 130.8 (CH), 129.7 (CH), 127.7 (CH), 127.3 (CH), 121.1 (CH), 60.6 (CH_2), 14.3 (CH_3).

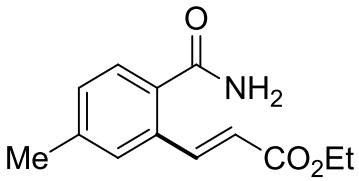
IR (neat): 3378, 3180, 2980, 1716, 1637, 1315, 1182, 634 cm^{-1}.

MS (EI) *m/z* (relative intensity): 219 ([M^+] 5), 190 (14), 174 (15), 146 (100), 131 (25), 117 (12), 103 (14), 77 (11).

HR-MS (EI) *m/z* calcd for $C_{12}H_{13}NO_3^+$ [M^+] 219.0895, found 219.0894.

The analytical data are in accordance with those reported in the literature.[113]

Synthesis of Ethyl (*E*)-3-(2-carbamoyl-5-methylphenyl)acrylate (44ba)



The general procedure **B** was followed using 4-methyl-*N*-hydroxybenzamide (**88b**) (76 mg, 0.5 mmol) and ethyl acrylate (**37a**) (75 mg, 0.75 mmol). After stirring at 60 °C for 18 h, purification by column chromatography on silica gel (CH_2Cl_2/EtOAc: 2/1) yielded **44ba** (93 mg, 80%) as a colorless solid.

M.p. = 172–174 °C.

^{1}H-NMR (300 MHz, acetone-d_6): δ = 8.22 (d, J = 16.0 Hz, 1H), 7.67 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.32–7.21 (m, 2H), 6.81 (br s, 1H), 6.46 (d, J = 16.0 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H).

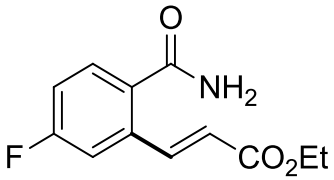
^{13}C-NMR (125 MHz, acetone-d_6): δ = 170.8 (C_q), 166.9 (C_q), 143.5 (CH), 141.0 (C_q), 135.6 (C_q), 133.7 (C_q), 131.1 (CH), 128.6 (CH), 128.2 (CH), 120.3 (CH), 60.7 (CH_2), 21.1 (CH_3), 14.6 (CH_3).

IR (neat): 3375, 3198, 1690, 1656, 1294, 1040, 643 cm^{-1}.

MS (EI) *m/z* (relative intensity): 233 ([M^+] 3), 204 (9), 188 (10), 160 (100), 145 (22), 115 (28), 77 (5).

HR-MS (EI) *m/z* calcd for $C_{13}H_{15}NO_3^+$ [M^+] 233.1052, found 233.1058.

Synthesis of Ethyl (*E*)-3-(2-carbamoyl-5-fluorophenyl)acrylate (44da)



The general procedure **B** was followed using 4-fluoro-*N*-hydroxybenzamide (**88d**) (78 mg, 0.5 mmol) and ethyl acrylate (**37a**) (75 mg, 0.75 mmol). After stirring at 60 °C for 18 h, purification by column chromatography on silica gel (CH_2Cl_2/EtOAc: 2/1) yielded **44da** (80 mg, 67%) as an off-white solid.

M.p. = 162–164 °C.

^{1}H-NMR (300 MHz, acetone-d_6): δ = 8.17 (dd, J = 16.0, 1.7 Hz, 1H), 7.70–7.59 (m, 2H), 7.38 (br s, 1H), 7.23 (td, J = 8.4, 2.6 Hz, 1H), 6.93 (br s, 1H), 6.56 (d, J = 16.0 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (125 MHz, acetone-d_6): δ = 169.9 (C_q), 166.6 (C_q), 164.1 (d, $J_{C\text{-}F}$ = 247.4 Hz), 141.9 (d, $J_{C\text{-}F}$ = 2.2 Hz), 136.5 (d, $J_{C\text{-}F}$ = 8.2 Hz), 134.9 (d, $J_{C\text{-}F}$ = 3.3 Hz), 131.0 (d, $J_{C\text{-}F}$ = 8.8 Hz), 122.0 (CH), 117.1 (d, $J_{C\text{-}F}$ = 22.0 Hz), 114.2 (d, $J_{C\text{-}F}$ = 22.9 Hz), 60.9 (CH_2), 14.6 (CH_3).

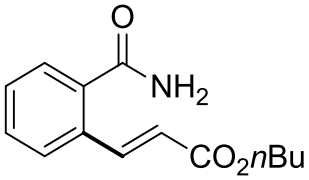
^{19}F-NMR (283 MHz, acetone-d_6): δ = -107.1 (dddd, J = 9.7, 7.7, 5.7, 1.7 Hz).

IR (neat): 3389, 3203, 3004, 1688, 1650, 1388, 1215, 978 cm^{-1}.

MS (EI) *m/z* (relative intensity): 237 ([M^+] 1), 208 (5), 192 (6), 164 (100), 149 (15), 135 (9), 120 (9).

HR-MS (EI) *m/z* calcd for $C_{12}H_{13}FNO_3^+$ [M+H^+] 238.0879, found 238.0876.

Synthesis of *n*-Butyl (*E*)-3-(2-carbamoylphenyl)acrylate (44ab)



The general procedure **B** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and butyl acrylate (**37b**) (96 mg, 0.75 mmol). After stirring at 60 °C for 18 h, purification by column chromatography on silica gel (CH_2Cl_2/EtOAc: 2/1) yielded **44ab** (90 mg, 73%) as a colorless solid.

M.p. = 140–141 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 16.0 Hz, 1H), 7.68–7.54 (m, 2H), 7.52–7.37 (m, 2H), 6.40 (d, *J* = 16.0 Hz, 1H), 6.03 (br s, 1H), 5.87 (br s, 1H), 4.19 (t, *J* = 6.7 Hz, 2H), 1.73–1.63 (m, 2H), 1.50–1.35 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 170.4 (C_q), 166.5 (C_q), 141.8 (CH), 135.7 (C_q), 133.1 (C_q), 130.8 (CH), 129.7 (CH), 127.8 (CH), 127.3 (CH), 121.2 (CH), 64.6 (CH_2), 30.7 (CH_2), 19.2 (CH_2), 13.7 (CH_3).

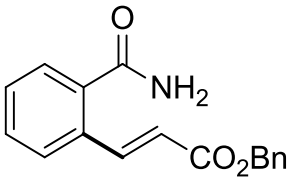
IR (neat): 3356, 3167, 2952, 1707, 1626, 1276, 974, 766 cm^{-1}.

MS (EI) *m/z* (relative intensity): 247 ([M^+] 6), 190 (15), 174 (12), 146 (100), 131 (25), 117 (11), 77 (8).

HR-MS (EI) *m/z* calcd for $C_{14}H_{18}NO_3^+$ [M+H^+] 248.1287, found 248.1282.

The analytical data are in accordance with those reported in the literature.[194]

Synthesis of Benzyl (*E*)-3-(2-carbamoylphenyl)acrylate (44ac)



The general procedure **B** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and benzyl acrylate (**37c**) (122 mg, 0.75 mmol). After stirring at 60 °C for 18 h, purification by column chromatography on silica gel (CH_2Cl_2/EtOAc: 2/1) yielded **44ac** (115 mg, 82%) as a colorless solid.

M.p. = 149–151 °C.

^{1}H-NMR (300 MHz, acetone-d_6): δ = 8.26 (d, J = 16.1 Hz, 1H), 7.90–7.83 (m, 1H), 7.59 (dd, J = 7.1, 1.9 Hz, 1H), 7.55–7.28 (m, 8H), 6.91 (br s, 1H), 6.56 (d, J = 16.1 Hz, 1H), 5.25 (s, 2H).

^{13}C-NMR (125 MHz, acetone-d_6): δ = 170.8 (C_q), 166.8 (C_q), 143.8 (CH), 138.6 (C_q), 137.5 (C_q), 133.5 (C_q), 130.8 (CH), 130.6 (CH), 129.3 (CH), 129.0 (CH), 128.8 (CH), 128.5 (CH), 127.7 (CH), 120.2 (CH), 66.5 (CH_2).

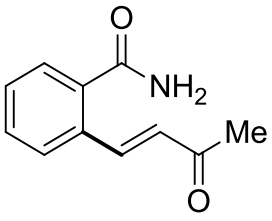
IR (neat): 3377, 3181, 1709, 1639, 1276, 1162, 765 cm^{-1}.

MS (EI) *m/z* (relative intensity): 281 ([M^+] 7), 237 (3), 190 (19), 146 (100), 131 (30), 91 (72), 77 (17).

HR-MS (EI) *m/z* calcd for $C_{17}H_{15}NO_3^+$ [M^+] 281.1052, found 281.1051.

The analytical data are in accordance with those reported in the literature.[113]

Synthesis of (*E*)-2-(3-Oxobut-1-en-1-yl)benzamide (44ad)



The general procedure **B** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and but-3-en-2-one (**37d**) (105 mg, 1.50 mmol). After stirring at 60 °C for 18 h, purification by column chromatography on silica gel (CH_2Cl_2/acetone: 2/1) yielded **44ad** (49 mg, 52%) as an off-white solid.

M.p. = 148–150 °C.

^{1}H-NMR (300 MHz, acetone-d_6): δ = 8.10 (d, J = 16.3 Hz, 1H), 7.83 (dd, J = 7.4, 1.7 Hz, 1H), 7.62 (dd, J = 7.3, 1.7 Hz, 1H), 7.54–7.43 (m, 2H), 7.36 (br s, 1H), 6.91 (br s, 1H), 6.70 (d, J = 16.3 Hz, 1H), 2.31 (s, 3H).

^{13}C-NMR (125 MHz, acetone-d_6): δ = 197.9 (C_q), 170.8 (C_q), 141.7 (CH), 138.5 (C_q), 134.0 (C_q), 130.9 (CH), 130.5 (CH), 129.4 (CH), 128.7 (CH), 127.6 (CH), 27.4 (CH_3).

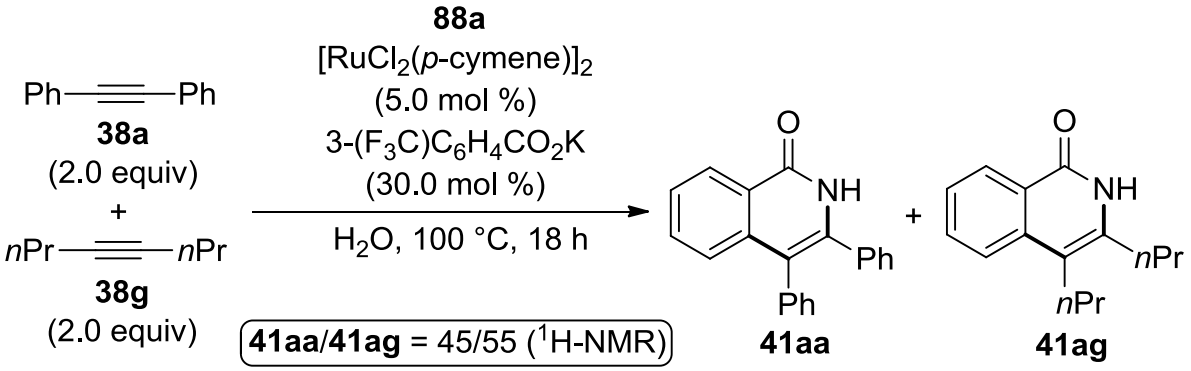
IR (neat): 3354, 3173, 1644, 1616, 1247, 971, 625 cm^{-1}.

MS (EI) *m/z* (relative intensity): 189 ([M^+] 5), 174 (3), 146 (100), 132 (24), 118 (12), 103 (16), 77 (15).

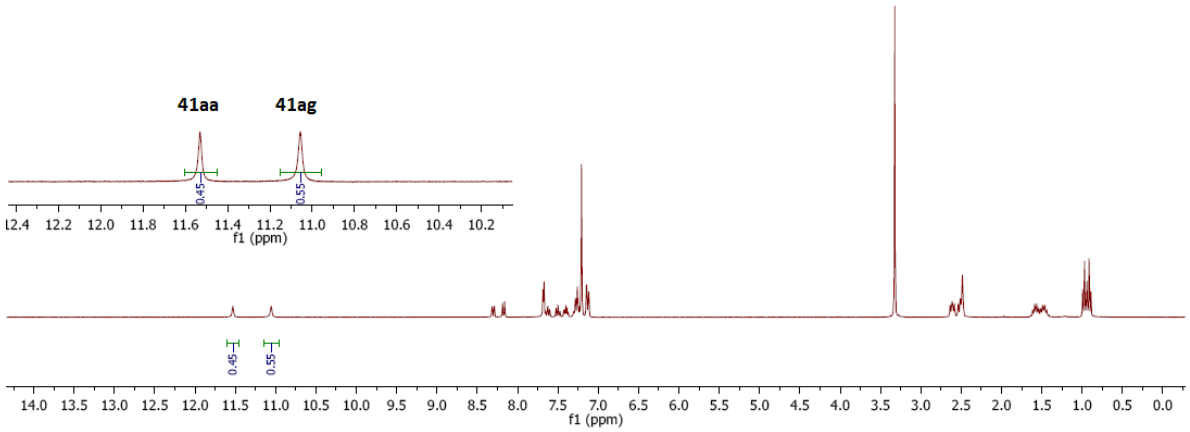
HR-MS (EI) *m/z* calcd for $C_{11}H_{11}NO_2^+$ [M^+] 189.0790, found 189.0796.

Competition Experiments

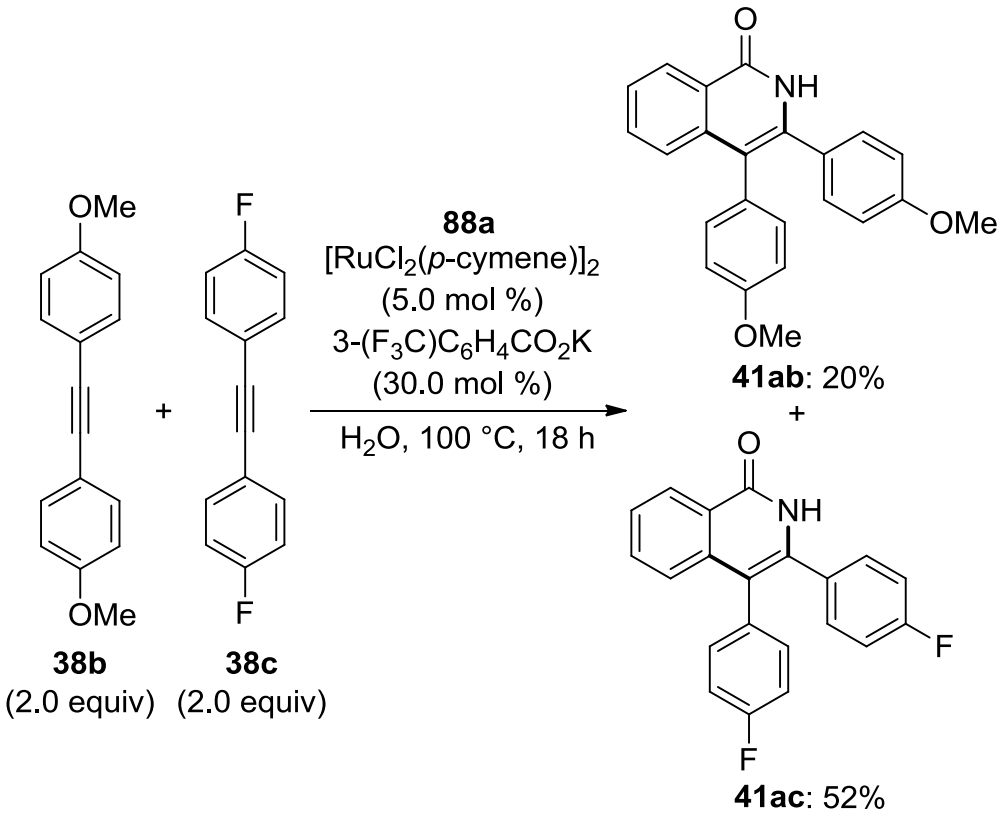
Intermolecular Competition Experiment between Alkynes 38a and 38g



The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol), and oct-4-yne (**38g**) (110 mg, 1.00 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded a mixture of **41aa** and **41ag** (94 mg), the ratio of 3a and 5b was determined to be 45/55 by ^{1}H-NMR.

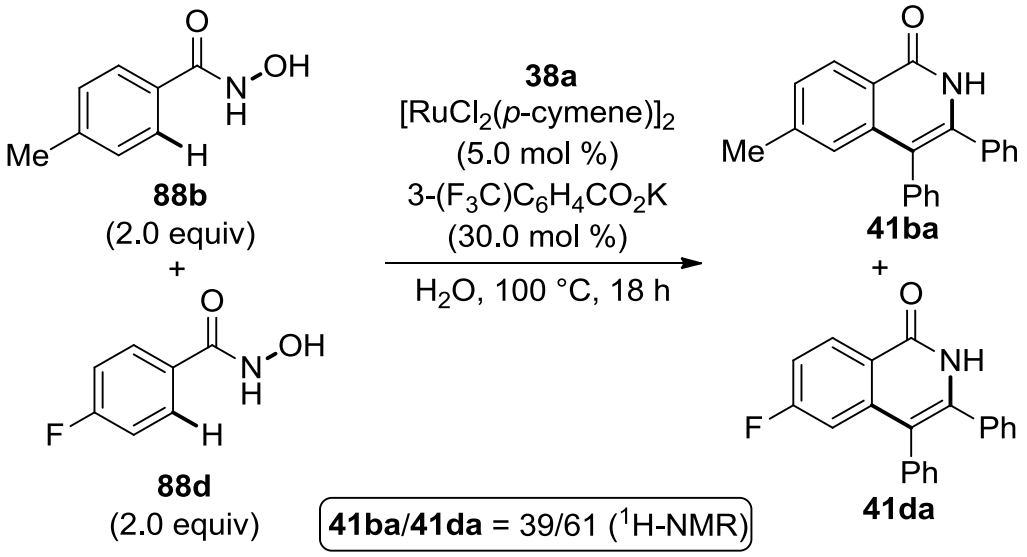


Intermolecular Competition Experiments between Alkynes 38b and 38c

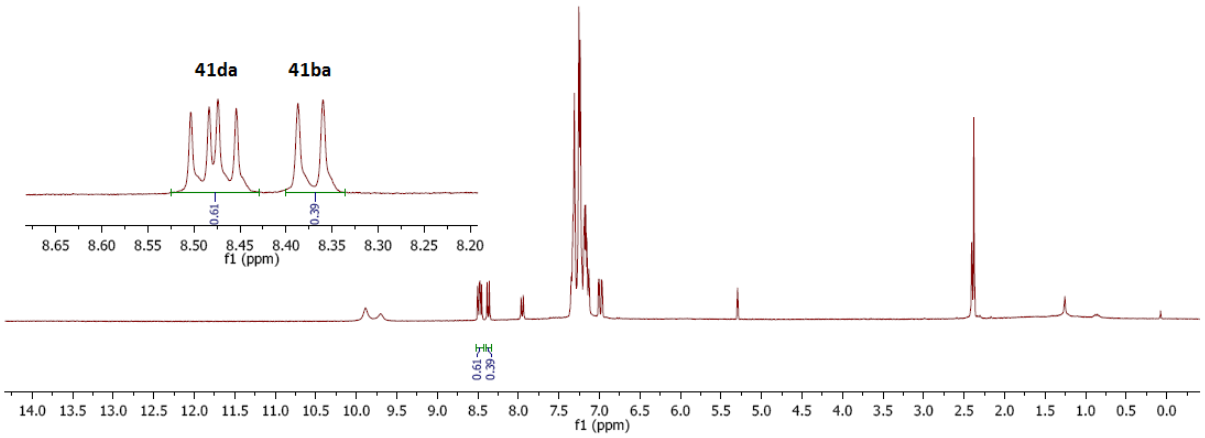


The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol), 1,2-bis(4-methoxyphenyl)ethyne (**38b**) (238 mg, 1.0 mmol) and 1,2-bis(4-fluorophenyl)ethyne (**38c**) (214 mg, 1.0 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1 → 1/1) yielded **41ab** (36 mg, 20%) and **41ac** (86 mg, 52%).

Intermolecular Competition Experiment between *N*-hydroxybenzamides 88b and 88d



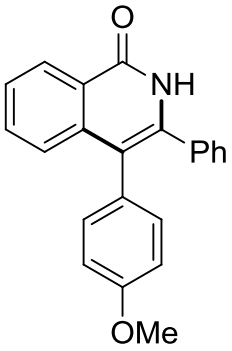
The general procedure **A** was followed using 4-methyl-*N*-hydroxybenzamide (**88b**) (151 mg, 1.0 mmol), 4-fluoro-*N*-hydroxybenzamide (**88d**) (155 mg, 1.0 mmol), and diphenylethyne (**38a**) (89 mg, 0.5 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (CH_2Cl_2/Et_2O: 3/1) yielded a mixture of **41ba** and **41da** (42 mg), the ratio of **41ba** and **41da** was determined to be 39/61 by ^{1}H-NMR spectroscopy.



Intramolecular Competition Experiment with Alkyne 38p

The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol) and 1-methoxy-4-(phenylethynyl)benzene (**38p**) (156 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41ap** (65 mg, 40%) and **41ap'** (65 mg, 40%) both as colorless solids.

4-(4-methoxyphenyl)-3-phenylisoquinolin-1(*2H*)-one (**41ap**)



M. p. = 257–259 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.41 (s, 1H), 8.29 (d, J = 7.9 Hz, 1H), 7.61 (ddd, J = 8.3, 7.1, 1.5 Hz, 1H), 7.48 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 7.22 (s, 5H), 7.18 – 7.13 (m, 1H), 7.04 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 3.71 (s, 3H).

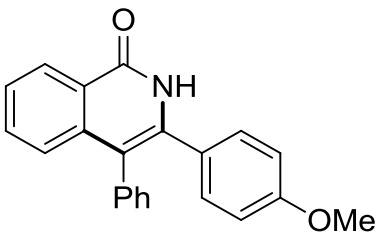
^{13}C-NMR (75 MHz, DMSO-d_6): δ = 161.6 (C_q), 158.0 (C_q), 138.5 (C_q), 138.4 (C_q), 134.7 (C_q), 132.7 (CH), 132.3 (CH), 129.7 (CH), 128.0 (CH), 127.7 (C_q), 127.6 (CH), 126.7 (CH), 126.0 (CH), 125.0(C_q), 124.9 (CH), 115.0 (C_q), 113.6 (CH), 54.9 (CH_3).

IR (neat): 3048, 3004, 2957, 1646, 1605, 1244, 1029, 695 cm^{-1}.

MS (EI) *m/z* (relative intensity): 327 ([M^+] 100), 326 (30), 284 (12), 254 (10), 152 (12), 98 (12), 77 (13).

HR-MS (EI) *m/z* calcd for $C_{22}H_{17}NO_2^+$ [M^+] 327.1259, found 327.1262.

3-(4-methoxyphenyl)-4-phenylisoquinolin-1(*2H*)-one (**41ap'**)



M. p. = 250–252 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.37 (s, 1H), 8.29 (dd, J = 8.0, 1.5 Hz, 1H), 7.60 (ddd, J = 8.4, 7.1, 1.6 Hz, 1H), 7.47 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 7.35 – 7.21 (m, 3H), 7.18 – 7.08 (m, 5H), 6.80 – 6.71 (m, 2H), 3.69 (s, 3H).

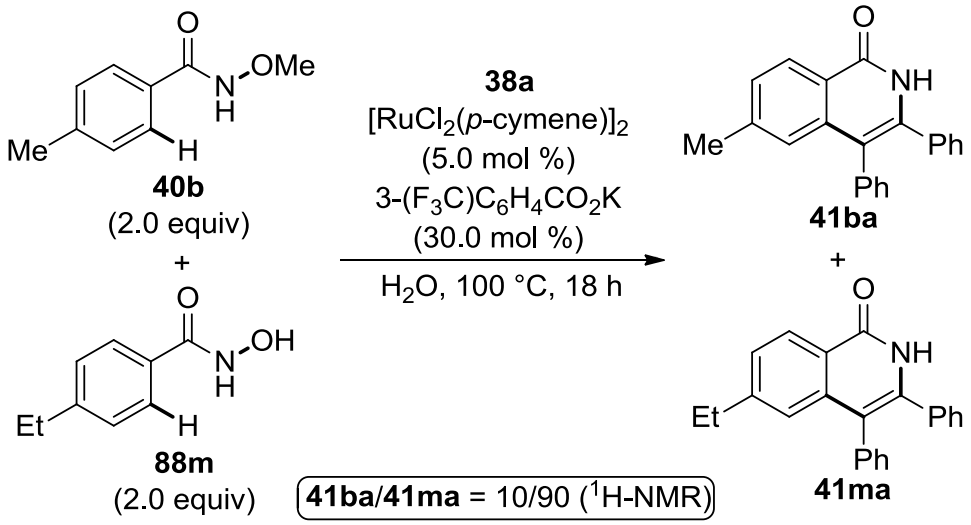
^{13}C-NMR (75 MHz, DMSO-d_6): δ = 161.7 (C_q), 158.9 (C_q), 138.3 (C_q), 138.1 (C_q), 136.0 (C_q), 132.3 (CH), 131.6 (CH), 131.1 (CH), 128.2 (CH), 126.9 (CH), 126.7 (C_q), 126.7 (CH), 125.9 (CH), 124.8 (C_q), 124.7 (CH), 115.1 (C_q), 113.0(CH), 55.0 (CH_3).

IR (neat): 3164, 3022, 2963, 1645, 1601, 1247, 1023, 775 cm^{-1}.

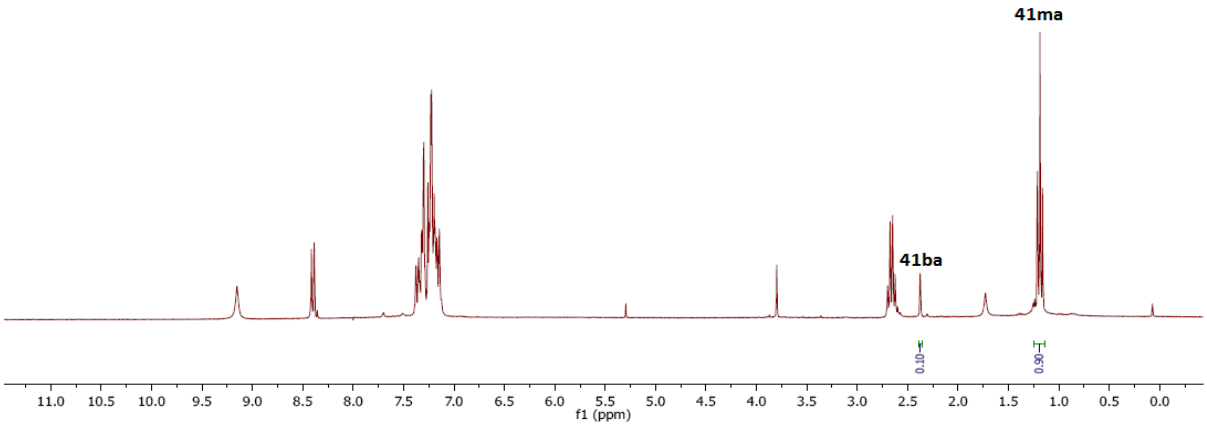
MS (EI) *m/z* (relative intensity): 327 ([M$^+$] 100), 326 (35), 283 (9), 254 (7), 165 (9), 77 (3).

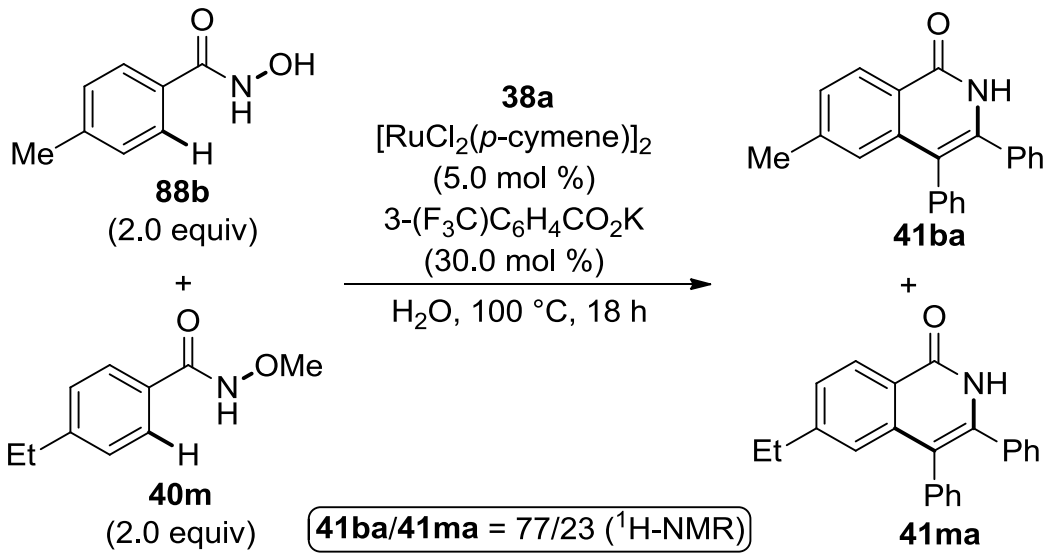
HR-MS (EI) *m/z* calcd for $C_{22}H_{17}NO_2^+$ [M$^+$] 327.1259, found 327.1246.

Relative Reactivities of *N*-Methoxybenzamides 40 and *N*-Hydroxybenzamides 88

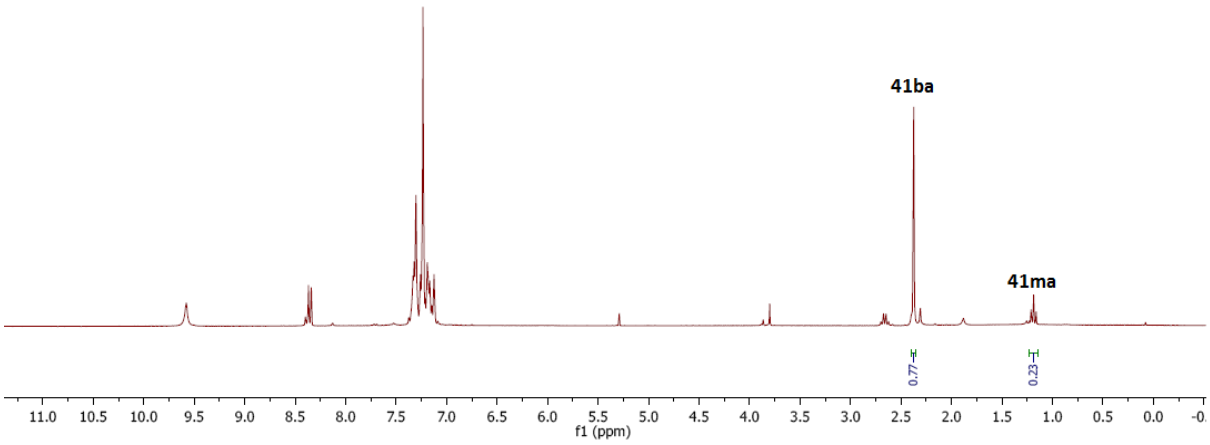


The general procedure **A** was followed using 4-methyl-*N*-methoxybenzamide (**40b**) (165 mg, 1.0 mmol), 4-ethyl-*N*-hydroxybenzamide (**88m**) (165 mg, 1.0 mmol) and diphenylethyne (**38a**) (89 mg, 0.5 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (CH_2Cl_2/Et_2O: 3/1) yielded a mixture of **41ba** and **41ma** (19 mg), the ratio of **41ba** and **41ma** was determined to be 10/90 by ^{1}H-NMR spectroscopy.

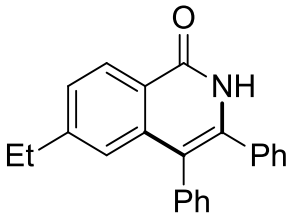




The general procedure **A** was followed using 4-methyl-*N*-hydroxybenzamide (**88b**) (151 mg, 1.0 mmol), 4-ethyl-*N*-methoxybenzamide (**40m**) (179 mg, 1.0 mmol) and diphenylethyne (**38a**) (89 mg, 0.5 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (CH_2Cl_2/Et_2O: 3/1) yielded a mixture of **41ba** and **41ma** (41 mg), the ratio of **41ba** and **41ma** was determined to be 77/23 by ^{1}H-NMR spectroscopy.



6-Ethyl-3,4-diphenylisoquinolin-1(2*H*)-one (41ma):



Off-white solid.

M.p. = 256–258 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.94 (s, 1H), 8.41 (d, *J* = 8.2 Hz, 1H), 7.48–7.06 (m, 12H), 2.66 (q, *J* = 7.6 Hz, 2H), 1.19 (t, *J* = 7.6 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 162.4 (C_q), 149.4 (C_q), 138.7 (C_q), 136.9 (C_q), 135.7 (C_q), 135.2 (C_q), 131.7 (CH), 129.0 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.5 (CH), 127.1 (CH), 127.0 (CH), 124.2 (CH), 123.1 (C_q), 117.1 (C_q), 29.4 (CH_2), 15.4 (CH_3).

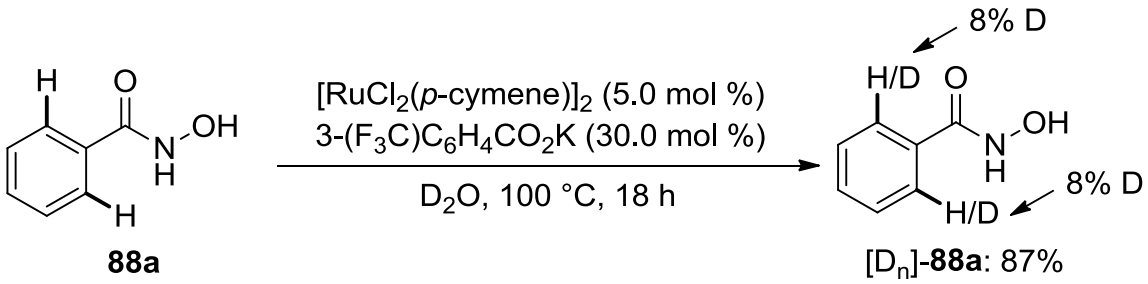
IR (neat): 3118, 3022, 2885, 1640, 1611, 1442, 1151, 695 cm^{-1}.

MS (EI) *m/z* (relative intensity): 325 ([M^+] 100), 324 (45), 295 (12), 178 (10), 104 (8), 77 (13).

HR-MS (EI) *m/z* calcd for $C_{23}H_{19}NO^+$ [M^+] 325.1467, found 325.1465.

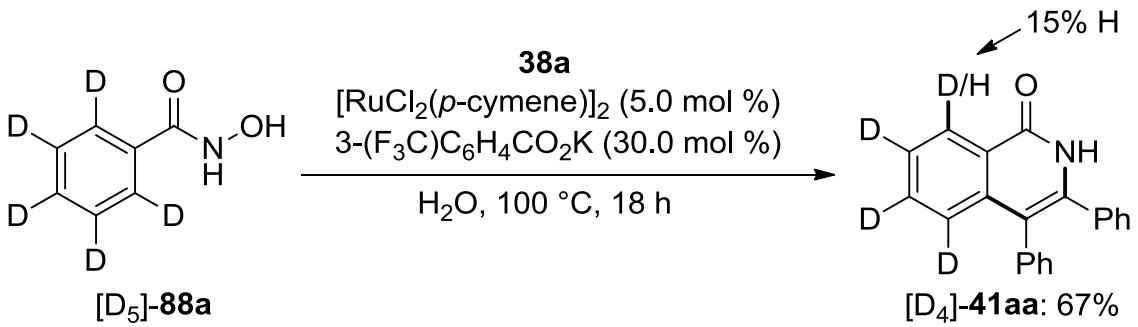
Experiments with Isotopically Labeled Compounds

C–H/N–O Functionalizations with Isotopically Labeled Solvent

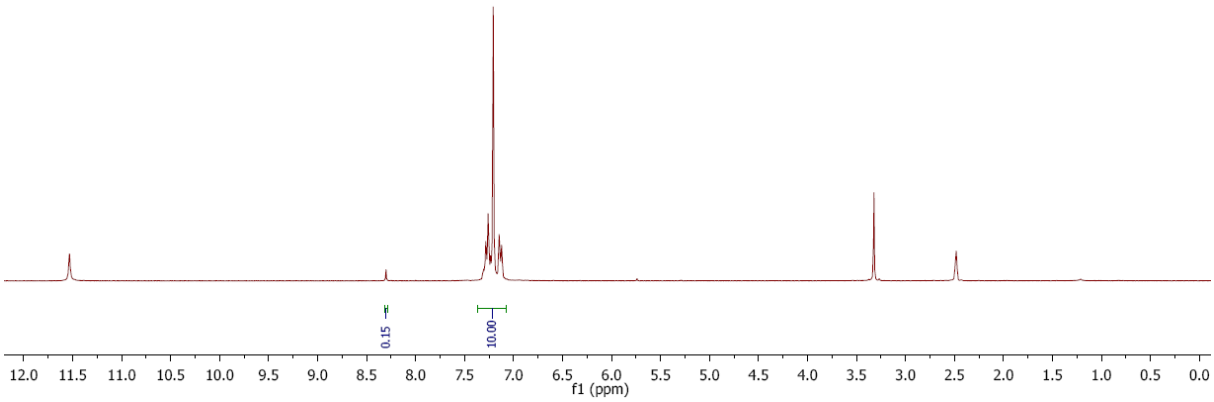


A mixture of *N*-hydroxybenzamide (**88a**) (69 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and potassium 3-(trifluoromethyl)benzoate (34 mg, 30.0 mol%) in D_2O (2 mL) was stirred at 100 °C under N_2 atmosphere for 18 h. D_2O was removed under reduced pressure. Purification by column chromatography on silica gel (CH_2Cl_2/acetone: 2/1) recovered [D_n]-**88a** (62 mg, 87%) with approximately 8% hydrogen incorporation at each *ortho*-position as estimated by ^{1}H-NMR spectroscopy.

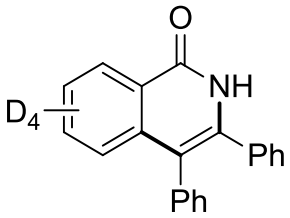
C–H/N–OH Functionalizations with Isotopically Labeled Substrate [D_5]-88a



The general procedure **A** was followed using [D_5]-**88a** (71 mg, 0.50 mmol) and diphenylacetylene (**38a**) (134 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded [D_4]-**41aa** (101 mg, 67%) with approximately 15% deuterium incorporation at the *ortho*-position as estimated by ^{1}H-NMR spectroscopy.



3,4-Diphenylisoquinolin-1(2*H*)-one-5,6,7,8-d_4 ([D_4]-41aa):



Colorless solid.

M.p. = 254–256 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.53 (s, 1H), 7.35–7.07 (m, 10H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 161.4 (C_q), 138.3 (C_q), 137.8 (C_q), 135.6 (C_q), 134.4 (C_q), 131.7 (t, J = 22.7 Hz, CD), 131.5 (CH), 129.6 (CH), 128.0 (CH), 127.9 (CH), 127.4 (CH), 126.8

(CH), 126.5 (t, *J* = 22.7 Hz, CD), 124.8 (t, *J* = 22.7 Hz, CD), 124.7 (C_q), 124.3 (t, *J* = 22.7 Hz, CD), 115.2 (C_q).

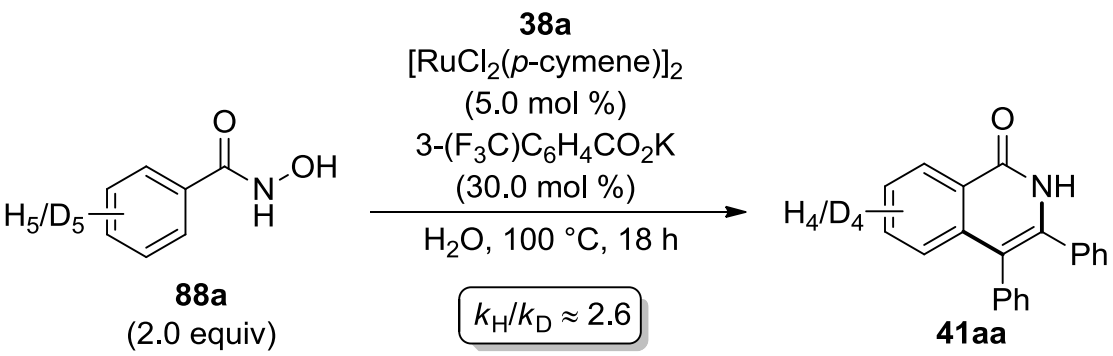
IR (neat): 3149, 3017, 2886, 1642, 1327, 902, 697 cm^{-1}.

MS (EI) *m/z* (relative intensity): 301 ([M^+] 100), 300 (80), 282 (14), 271 (9), 169 (12), 104 (5), 77 (11).

HR-MS (EI) *m/z* calcd for $C_{21}H_{11}D_4NO^+$ [M^+] 301.1405, found 301.1408.

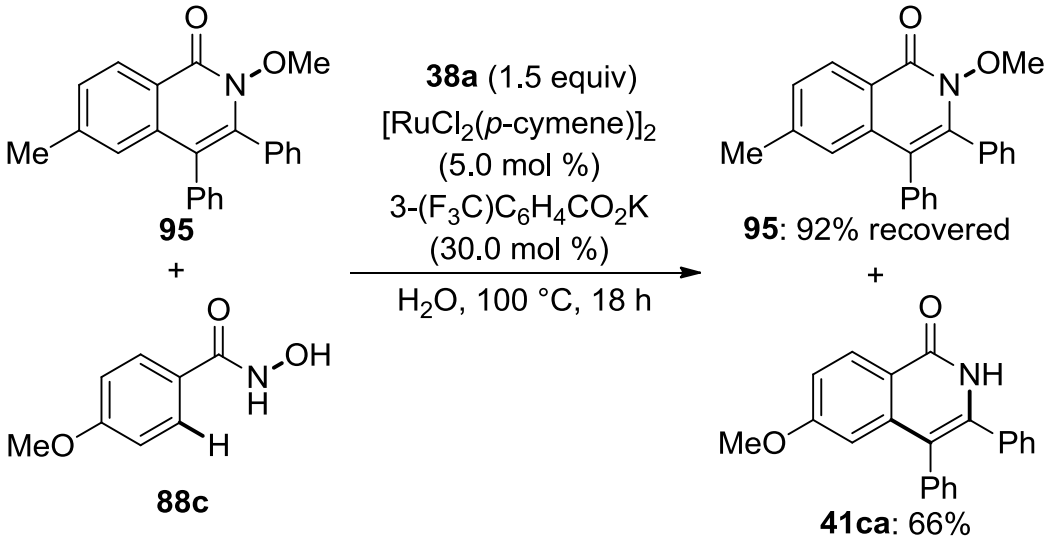
The analytical data are in accordance with those reported in the literature.[110]

Kinetic Isotope Effect Studies with 88a and [D_5]-88a



The general procedure **A** was followed using *N*-hydroxybenzamide (**88a**) (137 mg, 1.0 mmol), *N*-hydroxybenzamide-d_5 ([D_5]-**88a**) (142 mg, 1.0 mmol) and diphenylethyne (**38a**) (89 mg, 0.5 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded a mixture of [D_n]-**41aa** (15 mg), the kinetic isotope effect of this reaction was thus determined to be 2.6 as estimated by ^{1}H-NMR spectroscopy.

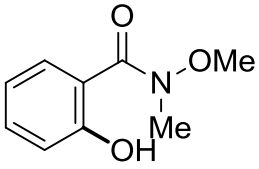
Crossover Experiment with 95 and 88c



The general procedure **A** was followed using 2-methoxy-6-methyl-3,4-diphenylisoquinolin-1(2*H*)-one (**95**) (171 mg, 0.50 mmol), *N*-hydroxy-4-methoxybenzamide (**88c**) (84 mg, 0.50 mmol) and diphenylacetylene (**38a**) (134 mg, 0.75 mmol). After stirring at 100 °C for 18 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1) yielded **41ca** (108 mg, 66%) and reisolated **95** (157 mg, 92%).

9.2 Analytical Data for Ruthenium(II)-Catalyzed C–H Oxygenation on Weinreb Amides

Synthesis of 2-Hydroxy-*N*-methoxy-*N*-methylbenzamide (90a)



The general procedure **C** was followed using *N*-methoxy-*N*-methylbenzamide (**89a**) (83 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 5/1) yielded **90a** (76 mg, 84%) as a pale green liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.17 (s, 1H), 7.95 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.36 (ddd, *J* = 8.8, 7.2, 1.7 Hz, 1H), 6.98 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.84 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 3.64 (s, 3H), 3.40 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 169.9 (C_q), 161.0 (C_q), 133.9 (CH), 129.6 (CH), 118.7 (CH), 118.1 (CH), 114.5 (C_q), 61.3 (CH_3), 34.2 (CH_3).

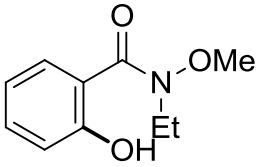
IR (neat): 2935, 1625, 1589, 1452, 755 cm^{-1}.

MS (EI) *m/z* (relative intensity): 181 ([M^+] 27), 121 (100), 93 (30), 65 (30).

HR-MS (EI) *m/z* calcd for $C_9H_{11}NO_3^+$ [M^+] 181.0739, found 181.0737.

The spectral data are in accordance with those reported in the literature.[195]

Synthesis of *N*-Ethyl-2-hydroxy-*N*-methoxybenzamide (90b)



The general procedure **C** was followed using *N*-ethyl-*N*-methoxybenzamide (**89b**) (90 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 5/1) yielded **90b** (77 mg, 78%) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.10 (s, 1H), 7.91 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.37 (ddd, *J* = 8.3, 7.3, 1.7 Hz, 1H), 7.01–6.96 (m, 1H), 6.88–6.81 (m, 1H), 3.84 (q, *J* = 7.1 Hz, 2H), 3.64 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

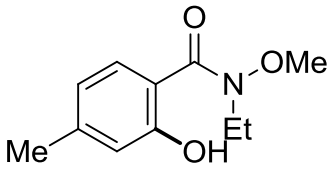
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 169.7 (C_q), 160.9 (C_q), 133.7 (CH), 129.3 (CH), 118.6 (CH), 118.0 (CH), 114.8 (C_q), 61.8 (CH_3), 42.0 (CH_2), 12.4 (CH_3).

IR (neat): 2933, 1626, 1582, 1452, 1010, 756 cm^{-1}.

MS (EI) *m/z* (relative intensity): 195([M^+] 25), 121 (100), 93 (28), 65 (28).

HR-MS (EI) *m/z* calcd for $C_{10}H_{13}NO_3^+$ [M^+] 195.0895, found 195.0900.

Synthesis of *N*-Ethyl-2-hydroxy-*N*-methoxy-4-methylbenzamide (90c)



The general procedure **C** was followed using *N*-ethyl-*N*-methoxy-4-methylbenzamide (**89c**) (97 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 10/1) yielded **90c** (81 mg, 77%) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.29 (s, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 6.81–6.78 (m, 1H), 6.65 (ddd, *J* = 8.3, 1.8, 0.5 Hz, 1H), 3.82 (q, *J* = 7.1 Hz, 2H), 3.64 (s, 3H), 2.32 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

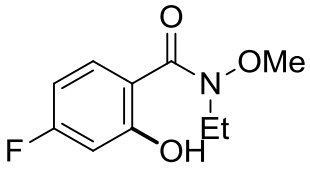
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 169.8 (C_q), 161.2 (C_q), 144.8 (C_q), 129.2 (CH), 119.7 (CH), 118.2 (CH), 111.9 (C_q), 61.7 (CH_3), 42.0 (CH_2), 21.6 (CH_3), 12.4 (CH_3).

IR (neat): 2936, 1633, 1582, 1447, 1253, 807 cm^{-1}.

MS (EI) *m/z* (relative intensity): 209 ([M^+] 9), 135 (100), 107 (12), 77 (27).

HR-MS (EI) *m/z* calcd for $C_{11}H_{15}NO_3^+$ [M^+] 209.1052, found 209.1052.

Synthesis of *N*-Ethyl-4-fluoro-2-hydroxy-*N*-methoxybenzamide (90d)



The general procedure **C** was followed using *N*-ethyl-4-fluoro-*N*-methoxybenzamide (**89d**) (99 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 10/1) yielded **90d** (80 mg, 75%) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.78 (s, 1H), 8.02 (dd, *J* = 9.1, 6.7 Hz, 1H), 6.67 (dd, *J* = 10.4, 2.7 Hz, 1H), 6.55 (ddd, *J* = 9.1, 8.0, 2.7 Hz, 1H), 3.83 (q, *J* = 7.1 Hz, 2H), 3.64 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 168.8 (C_q), 165.7 (C_q, $J_{C\text{-}F}$ = 253.1 Hz), 163.8 (C_q, $J_{C\text{-}F}$ = 13.6 Hz), 131.6 (CH, $J_{C\text{-}F}$ = 10.9 Hz), 111.0 (C_q, $J_{C\text{-}F}$ = 2.9 Hz), 106.3 (CH, $J_{C\text{-}F}$ = 22.1 Hz), 104.7 (CH, $J_{C\text{-}F}$ = 23.7 Hz), 61.7 (CH_3), 41.6 (CH_2), 12.3 (CH_3).

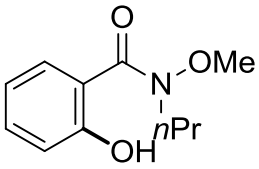
^{19}F-NMR (283 MHz, $CDCl_3$) δ = -104.1 (ddd, *J* = 10.4, 8.0, 6.8 Hz).

IR (neat): 2938, 1598, 1451, 1262, 977 cm^{-1}.

MS (EI) *m/z* (relative intensity): 213 ([M^+] 7), 139 (100), 111 (8), 83 (12).

HR-MS (EI) *m/z* calcd for $C_{10}H_{12}FNO_3^+$ [M^+] 213.0801, found 213.0804.

Synthesis of 2-Hydroxy-*N*-methoxy-*N*-*n*-propylbenzamide (90e)



The general procedure **C** was followed using *N*-methoxy-*N*-*n*-propylbenzamide (**89e**) (97 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 10/1) yielded **90e** (77 mg, 74%) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.09 (s, 1H), 7.95 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.37 (ddd, *J* = 8.4, 7.2, 1.7 Hz, 1H), 6.98 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.84 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H), 3.81–3.72 (m, 2H), 3.61 (s, 3H), 1.88–1.68 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

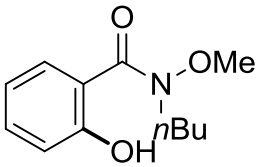
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 169.7 (C_q), 160.8 (C_q), 133.6 (CH), 129.4 (CH), 118.5 (CH), 118.0 (CH), 114.8 (C_q), 61.6 (CH_3), 48.1 (CH_2), 20.5 (CH_2), 11.2 (CH_3).

IR (neat): 2965, 2934, 1626, 1583, 1452, 756 cm^{-1}.

MS (EI) *m/z* (relative intensity): 209 ([M^+] 25), 121 (100), 93 (22), 65 (27).

HR-MS (EI) *m/z* calcd for $C_{11}H_{15}NO_3^+$ [M^+] 209.1052, found 209.1042.

Synthesis of *N*-*n*-Butyl-2-hydroxy-*N*-methoxybenzamide (90f)



The general procedure **C** was followed using *N*-*n*-butyl-*N*-methoxybenzamide (**89f**) (104 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 10/1) yielded **90f** (84 mg, 75%) as a pale yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.10 (s, 1H), 7.94 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.37 (ddd, *J* = 8.3, 7.2, 1.7 Hz, 1H), 6.98 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.84 (ddd, *J* = 8.5, 7.3, 1.3 Hz, 1H), 3.79 (t, *J* = 7.3 Hz, 2H), 3.61 (s, 3H), 1.81–1.66 (m, 2H), 1.48–1.33 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

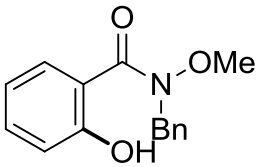
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 169.6 (C_q), 160.9 (C_q), 133.6 (CH), 129.4 (CH), 118.5 (CH), 118.0 (CH), 114.8 (C_q), 61.6 (CH_3), 46.2 (CH_2), 29.1 (CH_2), 19.9 (CH_2), 13.7 (CH_3).

IR (neat): 2958, 2933, 1627, 1584, 1454, 756 cm^{-1}.

MS (EI) *m/z* (relative intensity): 223 ([M^+] 10), 121 (100), 93 (12), 65 (11).

HR-MS (EI) *m/z* calcd for $C_{12}H_{17}NO_3^+$ [M^+] 223.1208, found 223.1211.

Synthesis of *N*-Benzyl-2-hydroxy-*N*-methoxybenzamide (90g)



The general procedure **C** was followed using *N*-benzyl-*N*-methoxybenzamide (**89g**) (121 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 10/1) yielded **90g** (83 mg, 64%) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.14 (s, 1H), 8.01 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.47–7.30 (m, 6H), 7.05–6.97 (m, 1H), 6.84 (ddd, *J* = 8.2, 7.3, 1.3 Hz, 1H), 4.99 (s, 2H), 3.58 (s, 3H).

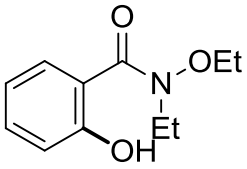
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 169.7 (C_q), 161.1 (C_q), 135.8 (C_q), 133.9 (CH), 129.4 (CH), 128.7 (CH), 128.2 (CH), 127.9 (CH), 118.7 (CH), 118.0 (CH), 114.5 (C_q), 62.2 (CH_3), 50.5 (CH_2).

IR (neat): 2926, 1626, 1582, 1447, 1249, 756 cm^{-1}.

MS (EI) *m/z* (relative intensity): 257 ([M$^+$] 13), 226 (15), 121 (100), 91 (48), 65 (35).

HR-MS (EI) *m/z* calcd for $C_{15}H_{15}NO_3^+$ [M$^+$] 257.1052, found 257.1061.

Synthesis of *N*-Ethoxy-*N*-ethyl-2-hydroxybenzamide (90h)



The general procedure **C** was followed using *N*-ethoxy-*N*-ethylbenzamide (**89h**) (97 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 10/1) yielded **90h** (80 mg, 76%) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.03 (s, 1H), 7.96 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.36 (ddd, *J* = 8.4, 7.2, 1.7 Hz, 1H), 7.03–6.92 (m, 1H), 6.83 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H), 3.82 (q, *J* = 7.1 Hz, 2H), 3.82 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H).

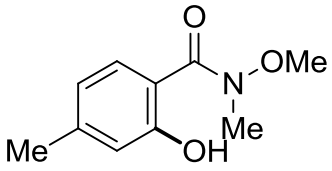
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 169.7 (C_q), 160.7 (C_q), 133.5 (CH), 129.4 (CH), 118.3 (CH), 117.9 (CH), 115.1 (C_q), 70.2 (CH_2), 42.3 (CH_2), 13.3 (CH_3), 12.5 (CH_3).

IR (neat): 2980, 2925, 1627, 1582, 1451, 1251, 1019, 756 cm^{-1}.

MS (EI) *m/z* (relative intensity): 209 ([M$^+$] 18), 121 (100), 93 (22), 65 (30).

HR-MS (EI) *m/z* calcd for $C_{11}H_{15}NO_3^+$ [M$^+$] 209.1052, found 209.1051.

Synthesis of 2-Hydroxy-*N*-methoxy-*N*,4-dimethylbenzamide (90i)



The general procedure **C** was followed using *N*-methoxy-*N*,4-dimethylbenzamide (**89i**) (90 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 10/1) yielded **90i** (74 mg, 76%) as a pale yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.36 (s, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 0.7 Hz, 1H), 6.69–6.59 (m, 1H), 3.64 (s, 3H), 3.39 (s, 3H), 2.32 (s, 3H).

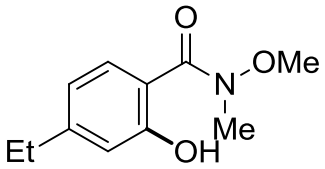
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 170.1 (C_q), 161.4 (C_q), 145.0 (C_q), 129.5 (CH), 119.9 (CH), 118.3 (CH), 111.6 (C_q), 61.2 (CH_3), 34.2 (CH_3), 21.8 (CH_3).

IR (neat): 2922, 1633, 1583, 1430, 808 cm^{-1}.

MS (EI) *m/z* (relative intensity): 195 ([M^+] 23), 169 (20), 135 (100), 107 (26), 77 (30).

HR-MS (EI) *m/z* calcd for $C_{10}H_{13}NO_3^+$ [M^+] 195.0895, found 195.0892.

Synthesis of 4-Ethyl-2-hydroxy-*N*-methoxy-*N*-methylbenzamide (90j)



The general procedure **C** was followed using 4-ethyl-*N*-methoxy-*N*-methylbenzamide (**89j**) (97 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 6/1) yielded **90j** (81 mg, 78%) as a pale yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.39 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 6.82 (d, *J* = 1.5 Hz, 1H), 6.68 (dd, *J* = 8.3, 1.5 Hz, 1H), 3.65 (s, 3H), 3.39 (s, 3H), 2.62 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H).

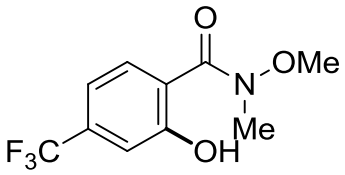
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 170.0 (C_q), 161.4 (C_q), 151.0 (C_q), 129.4 (CH), 118.5 (CH), 116.9 (CH), 111.7 (C_q), 61.1 (CH_3), 34.1 (CH_3), 28.8 (CH_2), 14.7 (CH_3).

IR (neat): 2966, 2932, 1631, 1583, 973cm^{-1}.

MS (EI) *m/z* (relative intensity): 209 ([M^+] 6), 149 (100), 91 (8), 77 (9).

HR-MS (EI) *m/z* calcd for $C_{11}H_{15}NO_3^+$ [M^+] 209.1052, found 209.1044.

Synthesis of 4-(Trifluoromethyl)-2-hydroxy-*N*-methoxy-*N*-methylbenzamide (90k)



The general procedure **C** was followed using 4-(trifluoromethyl)-*N*-methoxy-*N*-methylbenzamide (**89k**) (117 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 4/1) yielded **90k** (91 mg, 73%) as a green solid.

M. p. = 72–73 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.29 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.25–7.24 (m, 1H), 7.13–7.03 (m, 1H), 3.65 (s, 3H), 3.43 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 168.5 (C_q), 161.0 (C_q), 135.1 (C_q, $J_{C\text{-}F}$ = 32.8 Hz), 130.3 (CH), 123.3 (C_q, $J_{C\text{-}F}$ = 272.8 Hz), 117.1 (C_q), 115.3 (CH, $J_{C\text{-}F}$ = 3.9 Hz), 114.9 (CH, $J_{C\text{-}F}$ = 3.6 Hz), 61.5 (CH_3), 33.7 (CH_3).

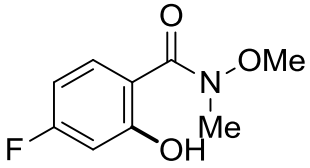
^{19}F-NMR (283 MHz, $CDCl_3$) δ = -63.8 (s).

IR (neat): 2923, 1593, 1425, 1329, 925 cm^{-1}.

MS (EI) *m/z* (relative intensity): 249 ([M^+] 27), 189 (100), 161 (40), 113 (19), 61 (19).

HR-MS (EI) *m/z* calcd for $C_{10}H_{10}F_3NO_3^+$ [M^+] 249.0613, found 249.0612.

Synthesis of 4-Fluoro-2-hydroxy-*N*-methoxy-*N*-methylbenzamide (90l)



The general procedure **C** was followed using 4-fluoro-*N*-methoxy-*N*-methylbenzamide (**89l**) (92 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 5/1) yielded **90l** (79 mg, 79%) as a pale green solid.

M. p. = 60–61 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.81 (s, 1H), 8.05 (dd, J = 9.1, 6.7 Hz, 1H), 6.67 (dd, J = 10.4, 2.7 Hz, 1H), 6.55 (ddd, J = 9.1, 8.1, 2.7 Hz, 1H), 3.65 (s, 3H), 3.40 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 169.0 (C_q), 165.7 (C_q, $J_{C\text{-}F}$ = 253.3 Hz), 163.8 (C_q, $J_{C\text{-}F}$ = 13.8 Hz), 131.7 (CH, $J_{C\text{-}F}$ = 11.0 Hz), 110.6 (C_q, $J_{C\text{-}F}$ = 2.8 Hz), 106.3 (CH, $J_{C\text{-}F}$ = 22.1 Hz), 104.7 (CH, $J_{C\text{-}F}$ = 23.8 Hz), 61.1 (CH_3), 33.8 (CH_3).

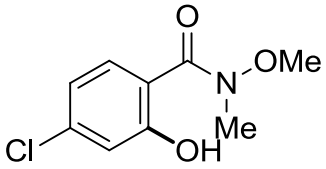
^{19}F-NMR (283 MHz, $CDCl_3$) δ = -(103.9–104.0) (m).

IR (neat): 2938, 1622, 1597, 1265, 967 cm^{-1}.

MS (EI) *m/z* (relative intensity): 199 ([M^+] 22), 139 (100), 111 (27), 83 (30), 57 (20).

HR-MS (EI) *m/z* calcd for $C_9H_{10}FNO_3^+$ [M^+] 199.0645, found 199.0645.

Synthesis of 4-Chloro-2-hydroxy-*N*-methoxy-*N*-methylbenzamide (90m)



The general procedure **C** was followed using 4-chloro-*N*-methoxy-*N*-methylbenzamide (**89m**) (100 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 5/1) yielded **90m** (92 mg, 85%) as an off-white solid.

M. p. = 94–96 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.57 (s, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.00 (d, J = 2.2 Hz, 1H), 6.82 (dd, J = 8.7, 2.2 Hz, 1H), 3.64 (s, 3H), 3.40 (s, 3H).

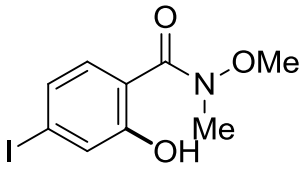
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 169.2 (C_q), 162.3 (C_q), 139.5 (C_q), 130.8 (CH), 119.2 (CH), 118.3 (CH), 112.8 (C_q), 61.4 (CH_3), 34.0 (CH_3).

IR (neat): 2934, 1621, 1572, 1458, 915 cm^{-1}.

MS (EI) *m/z* (relative intensity): 215 ([M^+] 10), 155 (100), 127 (12), 99 (15).

HR-MS (EI) *m/z* calcd for $C_9H_{10}ClNO_3^+$ [M^+] 215.0349, found 215.0352.

Synthesis of 2-Hydroxy-4-iodo-*N*-methoxy-*N*-methylbenzamide (90n)



The general procedure **C** was followed using 4-iodo-*N*-methoxy-*N*-methylbenzamide (**89n**) (146 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 5/1) yielded **90n** (123 mg, 80%) as a pale yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.40 (s, 1H), 7.69 (d, *J* = 8.6 Hz, 1H), 7.40 (d, *J* = 1.8 Hz, 1H), 7.19 (dd, *J* = 8.6, 1.8 Hz, 1H), 3.64 (s, 3H), 3.39 (s, 3H).

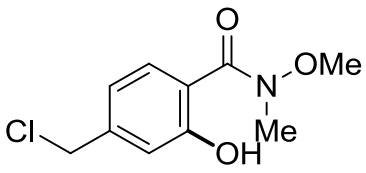
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 169.2 (C_q), 161.4 (C_q), 130.4 (CH), 127.8 (CH), 127.3 (CH), 113.6 (C_q), 100.3 (C_q), 61.3 (CH_3), 33.8 (CH_3).

IR (neat): 2925, 1617, 1570, 853 cm^{-1}.

MS (EI) *m/z* (relative intensity): 307 ([M^+] 26), 247 (100), 120 (30), 63 (21).

HR-MS (EI) *m/z* calcd for $C_9H_{10}INO_3^+$ [M^+] 306.9705, found 306.9700.

Synthesis of 4-(Chloromethyl)-2-hydroxy-*N*-methoxy-*N*-methylbenzamide (90o)



The general procedure **C** was followed using 4-(chloromethyl)-*N*-methoxy-*N*-methylbenzamide (**89o**) (107 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 4/1) yielded **90o** (70 mg, 61%) as a pale green liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.35 (s, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 7.01 (s, 1H), 6.93–6.83 (m, 1H), 4.52 (s, 2H), 3.65 (s, 3H), 3.41 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 169.3 (C_q), 161.3 (C_q), 143.1 (C_q), 130.0 (CH), 118.5 (CH), 117.8 (CH), 114.0 (C_q), 61.3 (CH_3), 45.3 (CH_2), 33.9 (CH_3).

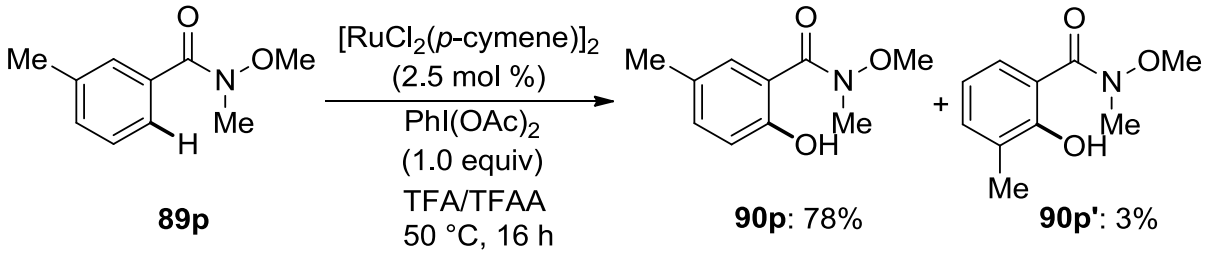
IR (neat): 2936, 1632, 1584, 1425, 714 cm^{-1}.

MS (EI) *m/z* (relative intensity): 229 ([M^+] 20), 169 (100), 134 (38), 105 (30), 77 (28).

HR-MS (EI) *m/z* calcd for $C_{10}H_{12}ClNO_3^+$ [M^+] 229.0506, found 229.0505.

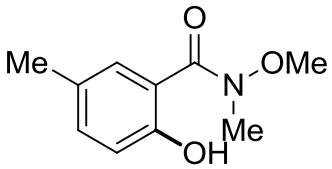
Competition Experiments

Intramolecular Competition Experiment with *meta*-Substituted Weinreb Amides 89p



The general procedure **C** was followed using *N*-methoxy-*N*,3-dimethylbenzamide (**89p**) (90 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 6/1) yielded **90p** (76 mg, 78%) and **90p'** (3 mg, 3%) both as colorless liquids.

2-Hydroxy-*N*-methoxy-*N*,5-dimethylbenzamide (90p)



^{1}H-NMR (300 MHz, $CDCl_3$) δ = 10.79 (s, 1H), 7.71 (s, 1H), 7.18 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 3.65 (s, 3H), 3.40 (s, 3H), 2.28 (s, 3H).

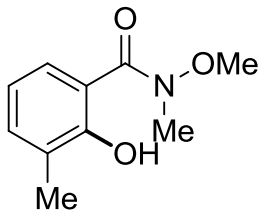
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 170.2 (C_q), 158.7 (C_q), 134.7 (CH), 129.5 (CH), 127.7 (C_q), 117.8 (CH), 114.4 (C_q), 61.3 (CH_3), 34.3 (CH_3), 20.8 (CH_3).

IR (neat): 2928, 1632, 1579, 1485, 1247, 822 cm^{-1}.

MS (EI) *m/z* (relative intensity): 195 ([M^+] 29), 135 (100), 107 (30), 77 (31).

HR-MS (EI) *m/z* calcd for $C_{10}H_{13}NO_3^+$ [M^+] 195.0895, found 195.0893.

2-Hydroxy-*N*-methoxy-*N*,3-dimethylbenzamide (90p')



^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.30 (s, 1H), 7.78 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.26–7.21 (m, 1H), 6.78–6.70 (m, 1H), 3.64 (s, 3H), 3.41 (s, 3H), 2.26 (s, 3H).

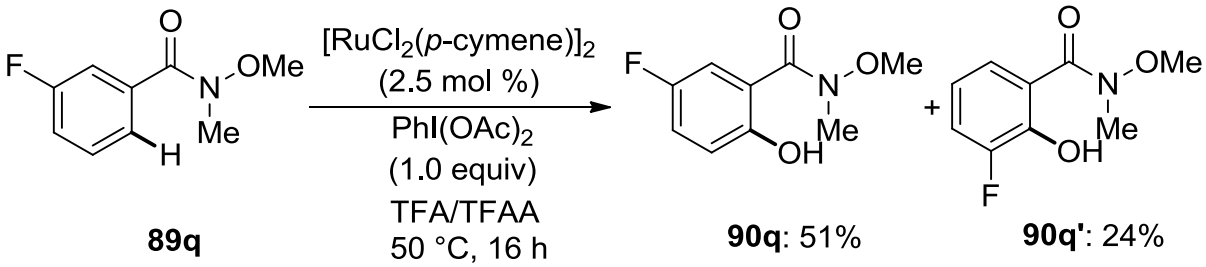
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 170.4 (C_q), 159.2 (C_q), 134.6 (CH), 127.0 (CH), 126.8 (C_q), 117.8 (CH), 113.6 (C_q), 61.2 (CH_3), 34.3 (CH_3), 16.0 (CH_3).

IR (neat): 2921, 1603, 1425, 1253, 1014, 802 cm^{-1}.

MS (EI) *m/z* (relative intensity): 195 ([M^+] 9), 135 (100), 77 (14).

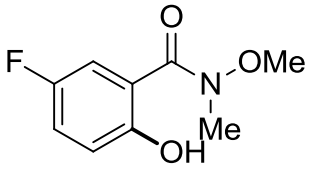
HR-MS (EI) *m/z* calcd for $C_{10}H_{13}NO_3^+$ [M^+] 195.0895, found 195.0898.

Intramolecular Competition Experiment with *meta*-Substituted Weinreb Amide 89q



The general procedure **C** was followed using 3-fluoro-*N*-methoxy-*N*-methylbenzamide (**89q**) (92 mg, 0.50 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 5/1) yielded **90q** (51 mg, 51%) and **90q'** (24 mg, 24%) both as colorless liquids.

5-Fluoro-2-hydroxy-*N*-methoxy-*N*-methylbenzamide (90q)



^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.05 (s, 1H), 7.72 (dd, J = 10.1, 3.1 Hz, 1H), 7.12 (ddd, J = 9.1, 7.7, 3.1 Hz, 1H), 6.94 (dd, J = 9.1, 4.9 Hz, 1H), 3.66 (s, 3H), 3.40 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 168.7 (C_q, $J_{C\text{-}F}$ = 2.5 Hz), 157.5 (C_q, $J_{C\text{-}F}$ = 1.7 Hz), 154.9 (C_q, $J_{C\text{-}F}$ = 236.3 Hz), 121.3 (CH, $J_{C\text{-}F}$ = 23.4 Hz), 119.1 (CH, $J_{C\text{-}F}$ = 7.7 Hz), 115.4 (CH, $J_{C\text{-}F}$ = 25.6 Hz), 114.1 (C_q, $J_{C\text{-}F}$ = 7.7 Hz), 61.5 (CH_3), 33.9 (CH_3).

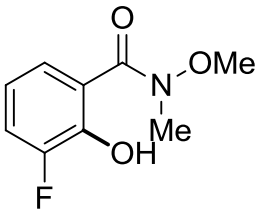
^{19}F-NMR (283 MHz, $CDCl_3$) δ = -124.7 (ddd, J = 10.0, 7.7, 4.9 Hz).

IR (neat): 2938, 1631, 1582, 1480, 1180, 789 cm^{-1}.

MS (EI) *m/z* (relative intensity): 199 ([M^+] 30), 139 (100), 111 (34), 83 (31), 57 (22).

HR-MS (EI) *m/z* calcd for $C_9H_{10}FNO_3^+$ [M^+] 199.0645, found 199.0639.

3-Fluoro-2-hydroxy-*N*-methoxy-*N*-methylbenzamide (90q')



^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.29 (s, 1H), 7.76 (dd, J = 8.3, 1.3 Hz, 1H), 7.24–7.16 (m, 1H), 6.83–6.74 (m, 1H), 3.65 (s, 3H), 3.41 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 168.9 (C_q, $J_{C\text{-}F}$ = 3.2 Hz), 151.9 (C_q, $J_{C\text{-}F}$ = 244.9 Hz), 149.8 (C_q, $J_{C\text{-}F}$ = 12.9 Hz), 124.6 (CH, $J_{C\text{-}F}$ = 3.9 Hz), 119.6 (CH, $J_{C\text{-}F}$ = 17.4 Hz), 117.8 (CH, $J_{C\text{-}F}$ = 6.8 Hz), 116.4 (C_q, $J_{C\text{-}F}$ = 3.0 Hz), 61.4 (CH_3), 33.9 (CH_3).

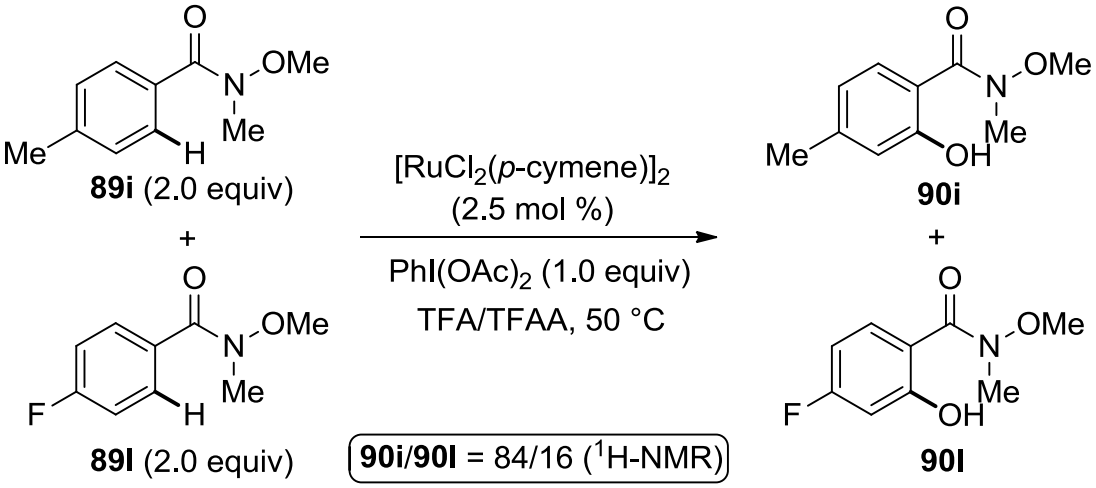
^{19}F-NMR (283 MHz, $CDCl_3$) δ = -136.0 (ddd, J = 10.5, 4.9, 1.4 Hz).

IR (neat): 2929, 1638, 1580, 1447, 1235, 743 cm^{-1}.

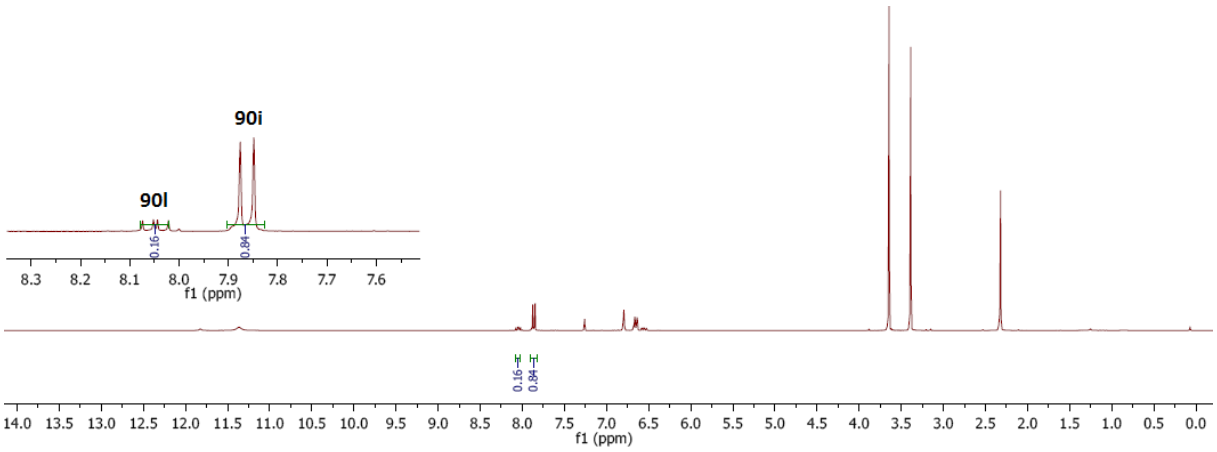
MS (EI) *m/z* (relative intensity): 199 ([M^+] 9), 139 (100), 111 (10), 83 (13), 57 (7).

HR-MS (EI) *m/z* calcd for $C_9H_{10}FNO_3^+$ [M^+] 199.0645, found 199.0646.

Intermolecular Competition Experiment between Weinreb Amides 89i and 89l

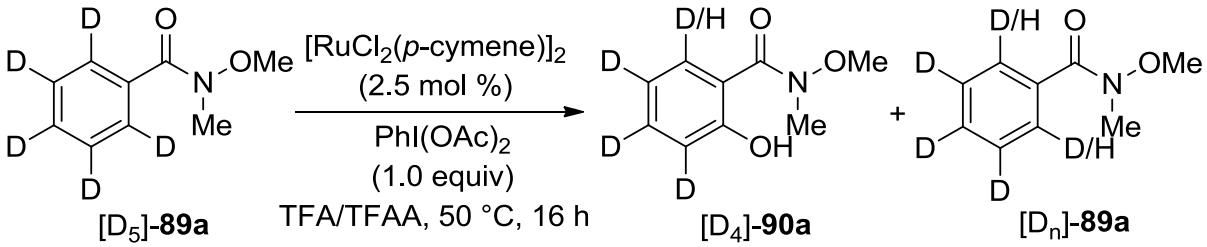


The general procedure **C** was followed using *N*-methoxy-*N*,4-dimethylbenzamide (**89i**) (179 mg, 1.00 mmol) and 4-fluoro-*N*-methoxy-*N*-methylbenzamide (**89l**) (183 mg, 1.00 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 5/1) yielded a mixture of **90i** and **90l** as a pale green liquid (90 mg), the ratio of which was found to be 84/16 by ^{1}H-NMR spectroscopy.



Experiments with Isotopically Labeled Compounds

Ruthenium(II)-Catalyzed Reaction with Labeled Substrate [D_5]-89a

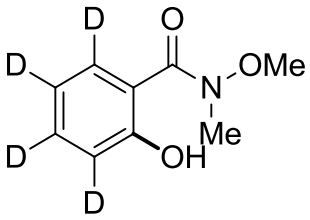


3 h:	20% (D/H > 99/1)	54% (D/H > 99/1)
16 h:	71% (D/H ≈ 95/5)	---

The general procedure **C** was followed using [D_5]-*N*-methoxy-*N*-methylbenzamide ([D_5]-**89a**) (85 mg, 0.50 mmol). After stirring at 50 °C for 3 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 5/1) yielded [D_4]-**90a** as a colorless liquid (19 mg, 20%) as a colorless liquid and reisolated [D_5]-**89a** (46 mg, 54%). The hydrogen incorporation at *ortho* position of [D_4]-**90a** or reisolated [D_5]-**89a** was less than 1% as estimated by ^{1}H-NMR spectroscopy.

An additional reaction was performed at 50 °C for 16 h and yielded [D_4]-**90a** (66 mg, 71%). The hydrogen incorporation at *ortho* position of [D_4]-**90a** was 5% as estimated by ^{1}H-NMR spectroscopy.

[D_4]-**90a**



^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.19 (s, 1H), 3.64 (s, 3H), 3.40 (s, 3H).

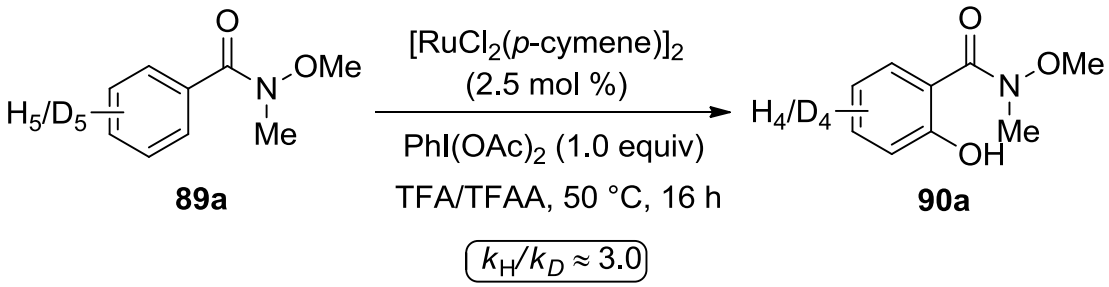
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 169.8 (C_q), 160.9 (C_q), 133.3 (t, *J* = 24.2 Hz, CD), 129.1 (t, *J* = 25.0 Hz, CD), 118.0 (t, *J* = 25.0 Hz, CD), 117.6 (t, *J* = 24.6 Hz, CD), 114.2 (C_q), 61.2 (CH_3), 34.0 (CH_3).

IR (neat): 2935, 1617, 1567, 1390, 770 cm^{-1}.

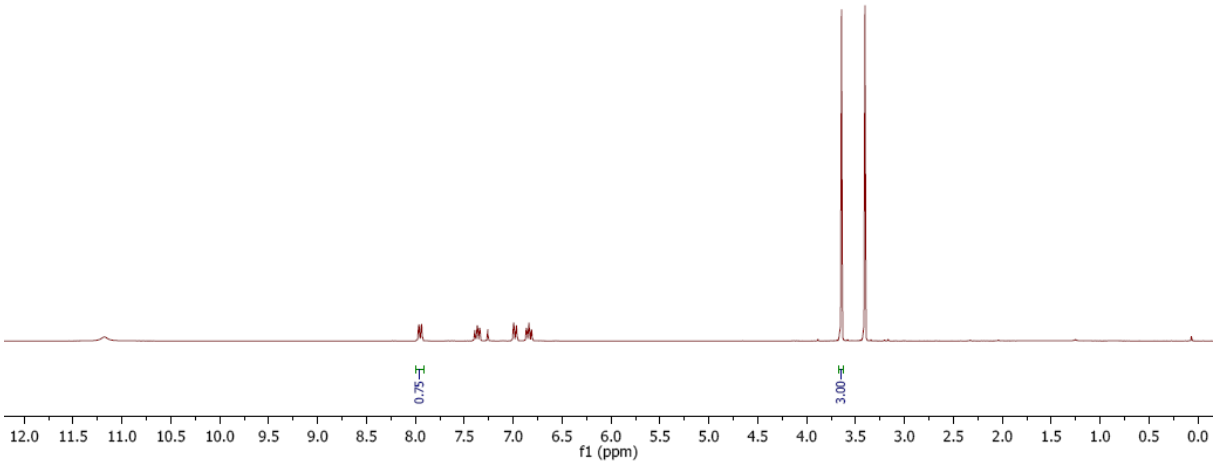
MS (EI) *m/z* (relative intensity): 185 ([M^+] 10), 125 (100), 97 (16), 69 (20), 43(18).

HR-MS (EI) *m/z* calcd for $C_9H_7D_4NO_3^+$ [M^+] 185.0990, found 185.0990.

Kinetic Isotope Effect Studies with 89a and [D_5]-89a

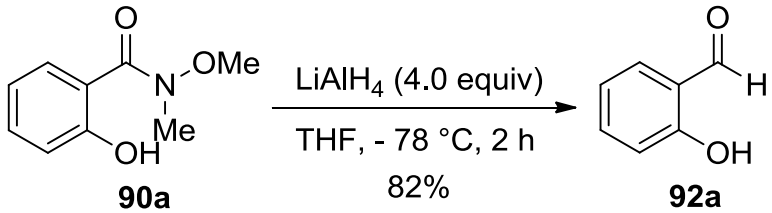


The general procedure **C** was followed using *N*-methoxy-*N*-methylbenzamide (**89a**) (165 mg, 1.00 mmol) and [D_5]-*N*-methoxy-*N*-methylbenzamide ([D_5]-**89a**) (170 mg, 1.00 mmol). After stirring at 50 °C for 16 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 5/1) yielded a mixture of **90a** and [D_4]-**90a** as a pale green liquid (81 mg, 22%). The kinetic isotope effect of this reaction was determined to be k_H/k_D ≈ 3.0 as estimated by ^{1}H-NMR spectroscopy.



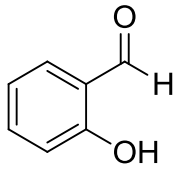
Diversification of Products

Synthesis of *ortho*-Hydroxybenzaldehyde (92a)



To a 100 mL flame dried Schlenk flask were added **90a** (181 mg, 1.0 mmol) and THF (30 mL) under N_2. At -78 °C, $LiAlH_4$ (38 mg, 1.0 mmol, 1 M in Et_2O) was added dropwise. The mixture was stirred for 15 min at -78 °C. Then, another portion of $LiAlH_4$ (114 mg, 3.0 mmol, 1 M in Et_2O) was added. The reaction mixture was afterwards allowed to warm to 0 °C in 2 h. Aqueous $NaHSO_4$ (2 mL, 10%) was carefully added, followed by HCl (20 mL, 1N). The reaction mixture was extracted with Et_2O (50 mL) and *n*-pentane (50 mL). The organic phase was washed with brine (50 mL), dried over Na_2SO_4, and evaporated under reduced pressure at ambient temperature. The crude product was purified by Kugelrohr distillation (80 ± 5 °C, 10 mbar) to yield **92a** (100 mg, 82%) as a colorless liquid.

2-Hydroxybenzaldehyde (92a)



^{1}H-NMR (300 MHz, $CDCl_3$) δ = 11.02 (s, 1H), 9.90 (s, 1H), 7.58–7.50 (m, 2H), 7.05–6.97 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ =196.6 (CH), 161.6 (C_q), 137.0 (CH), 133.7 (CH), 120.6 (C_q), 119.8 (CH), 117.6 (CH).

IR (neat): 3059, 2846, 2750, 1661, 1644, 1275, 759 cm^{-1}.

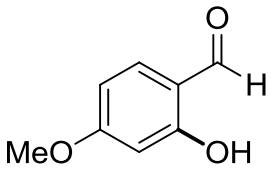
MS (EI) *m/z* (relative intensity): 122 ([M^+] 100), 121 (97), 93 (30), 65 (42).

HR-MS (EI) *m/z* calcd for $C_7H_6O_2^+$ [M^+] 122.0368, found 122.0365.

The spectral data are in accordance with those reported in the literature.[196]

9.3 Analytical Data for Ruthenium(II)-Catalyzed C–H Oxygenation on Aldehydes

Synthesis of 2-Hydroxy-4-methoxybenzaldehyde (92b)



The general procedure **D** was followed using 4-methoxybenzaldehyde (**91b**) (68 mg, 0.5 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 6/1) yielded **92b** (55 mg, 72%) as a colorless solid.

M. p. = 40–41 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.49 (s, 1H), 9.72 (s, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 6.54 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.43 (d, *J* = 2.4 Hz, 1H), 3.86 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 194.4 (CH), 166.8 (C_q), 164.5 (C_q), 135.2 (CH), 115.1 (C_q), 108.4 (CH), 100.6 (CH), 55.7 (CH_3).

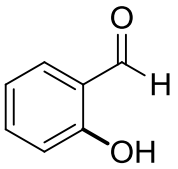
IR (neat): 3019, 2923, 2844, 1628, 1574, 1217, 797 cm^{-1}.

MS (EI) m/z (relative intensity): 152 ([M^+] 64), 151 (100), 125 (11), 111 (23), 97 (35), 71 (45).

HR-MS (ESI) m/z calcd for $C_8H_7O_3^+$ [M-H^+] 151.0395, found 151.0397.

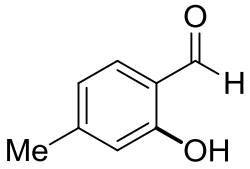
The analytical data are in accordance with those reported in the literature.[197]

Synthesis of 2-Hydroxy-4-methylbenzaldehyde (92a)



The general procedure **D** was followed using benzaldehyde (**91a**) (53 mg, 0.5 mmol) and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 50/1) yielded **92a** (29 mg, 48%) as a colorless solid.

Synthesis of 2-Hydroxy-4-methylbenzaldehyde (92c)



The general procedure **D** was followed using 4-methylbenzaldehyde (**91c**) (60 mg, 0.50 mmol) and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 50/1) yielded **92c** (41 mg, 61%) as a colorless solid.

M. p. = 59–60 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.02 (s, 1H), 9.81 (s, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.78 (s, 1H), 2.36 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 195.8 (CH), 161.7 (C_q), 148.9 (C_q), 133.5 (CH), 121.1 (CH), 118.6 (C_q), 117.6 (CH), 22.2 (CH_3).

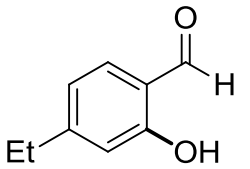
IR (neat): 3040, 2866, 2762, 1624, 1570, 1200, 715 cm^{-1}.

MS (EI) m/z (relative intensity): 136 ([M^+] 76), 135 (100), 118 (7), 107 (15), 90 (12), 77 (33).

HR-MS (ESI) m/z calcd for $C_8H_7O_2^+$ [M-H^+] 135.0446, found 135.0450.

The analytical data are in accordance with those reported in the literature.[198]

Synthesis of 4-Ethyl-2-hydroxybenzaldehyde (92d)



The general procedure **D** was followed using 4-ethylbenzaldehyde (**91d**) (67 mg, 0.50 mmol) and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 80/1) yielded **92d** (43 mg, 57%) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.05 (s, 1H), 9.83 (s, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 6.87–6.82 (m, 2H), 2.67 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 195.8 (CH), 161.9 (C_q), 155.0 (C_q), 133.7 (CH), 120.0 (CH), 118.8 (C_q), 116.7 (CH), 29.4 (CH_2), 14.7 (CH_3).

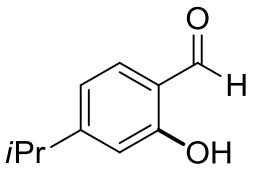
IR (neat): 2969, 2933, 2841, 1651, 1626, 1202, 809 cm^{-1}.

MS (EI) m/z (relative intensity): 150 ([M^+] 76), 149 (100), 121 (12), 107 (25), 91 (15), 77 (36).

HR-MS (ESI) m/z calcd for $C_9H_9O_2^+$ [M-H^+] 149.0603, found 149.0606.

The analytical data are in accordance with those reported in the literature.[199]

Synthesis of 2-Hydroxy-4-isopropylbenzaldehyde (92e)



The general procedure **D** was followed using 4-isopropylbenzaldehyde (**91e**) (74 mg, 0.50 mmol) and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 80/1) yielded **92e** (45 mg, 55%) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.02 (s, 1H), 9.81 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 6.87 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.83 (d, *J* = 1.6 Hz, 1H), 2.90 (hept, *J* = 6.9 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 195.8 (CH), 161.9 (C_q), 159.6 (C_q), 133.7 (CH), 119.0 (C_q), 118.7 (CH), 115.1 (CH), 34.7 (CH), 23.3 (CH_3).

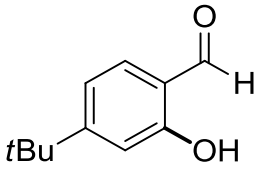
IR (neat): 2963, 2870, 2743, 1651, 1626, 1204, 720 cm^{-1}.

MS (EI) m/z (relative intensity): 164 ([M^+] 98), 163 (26), 149 (100), 135 (22), 121 (45), 103 (33), 91 (33).

HR-MS (EI) m/z calcd for $C_{10}H_{12}O_2^+$ [M^+] 164.0837, found 164.0841.

The analytical data are in accordance with those reported in the literature.[200]

Synthesis of 4-(*tert*Butyl)-2-hydroxybenzaldehyde (92f)



The general procedure **D** was followed using 4-(*tert*-butyl)benzaldehyde (**91f**) (81 mg, 0.50 mmol) and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 80/1) yielded **92f** (55 mg, 61%) as an off-white liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.00 (s, 1H), 9.84 (s, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.05 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.00 (d, *J* = 1.7 Hz, 1H), 1.32 (s, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 195.8 (CH), 161.8 (C_q), 161.6 (C_q), 133.3 (CH), 118.5 (C_q), 117.6 (CH), 114.4 (CH), 35.5 (C_q), 30.8 (CH_3).

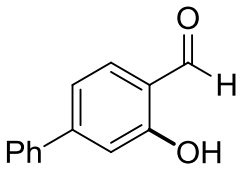
IR (neat): 2964, 2907, 2869, 1652, 1628, 1196, 705 cm^{-1}.

MS (EI) m/z (relative intensity): 178 ([M^+] 46), 163 (100), 135 (36), 107 (45), 95 (16), 77 (18).

HR-MS (EI) m/z calcd for $C_{11}H_{14}O_2^+$ [M^+] 178.0994, found 178.0990.

The analytical data are in accordance with those reported in the literature.[201]

Synthesis of 3-Hydroxy-[1,1'-biphenyl]-4-carbaldehyde (92g)



The general procedure **D** was followed using [1,1'-biphenyl]-4-carbaldehyde (**91g**) (91 mg, 0.50 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 40/1) yielded **92g** (57 mg, 57%) as a colorless solid.

M. p. = 78–79 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.10 (s, 1H), 9.90 (s, 1H), 7.64–7.57 (m, 3H), 7.50–7.39 (m, 3H), 7.25–7.19 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 196.0 (CH), 161.9 (C_q), 149.8 (C_q), 139.3 (C_q), 134.1 (CH), 129.0 (CH), 128.8 (CH), 127.3 (CH), 119.5 (C_q), 118.9 (CH), 115.8 (CH).

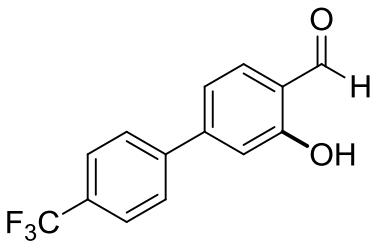
IR (neat): 3037, 2868, 1657, 1555, 1198, 694 cm^{-1}.

MS (EI) m/z (relative intensity): 198 ([M^+] 90), 197 (100), 152 (10), 141 (15), 139 (11), 115 (22).

HR-MS (EI) m/z calcd for $C_{13}H_{10}O_2^+$ [M^+] 198.0681, found 198.0679.

The analytical data are in accordance with those reported in the literature.[202]

Synthesis of 3-Hydroxy-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbaldehyde (92h)



The general procedure **D** was followed using 4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbaldehyde (**91h**) (125 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), and [bis(trifluoroacetoxy)iodo]benzene (538 mg, 1.25 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 15/1) yielded **92h** (78 mg, 59%) as colorless solid.

M. p. = 86–88 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.12 (s, 1H), 9.95 (s, 1H), 7.76–7.71 (m, 4H), 7.66 (d, J = 7.9 Hz, 1H), 7.30–7.18 (m, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 195.9 (CH), 161.8 (C_q), 148.0 (C_q), 142.8 (C_q), 134.2 (CH), 130.7 (C_q, q, $J_{C\text{-}F}$ = 33 Hz), 127.6 (CH), 125.9 (CH, q, $J_{C\text{-}F}$ = 4 Hz), 123.9 (C_q, d, $J_{C\text{-}F}$ = 273 Hz), 120.0 (C_q), 118.9 (CH), 116.2 (CH).

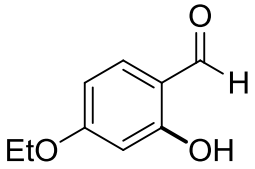
^{19}F-NMR (283 MHz, $CDCl_3$) δ = - 62.7 (s).

IR (neat): 3180, 2928, 2865, 1652, 1616, 1320, 1109 cm^{-1}.

MS (EI) m/z (relative intensity): 266 ([M^+] 83), 265 (100), 247 (9), 220 (14), 168 (11), 139 (12).

HR-MS (EI) m/z calcd for $C_{14}H_9F_3O_2^+$ [M^+] 266.0555, found 266.0549.

Synthesis of 2-Hydroxy-4-ethoxybenzaldehyde (92i)



The general procedure **D** was followed using 4-ethoxybenzaldehyde (**91i**) (75 mg, 0.50 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 10/1) yielded **92i** (57 mg, 69%) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.46 (s, 1H), 9.68 (s, 1H), 7.39 (d, *J* = 8.7 Hz, 1H), 6.50 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.39 (d, *J* = 2.4 Hz, 1H), 4.06 (q, *J* = 7.0 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 194.3 (CH), 166.2 (C_q), 164.5 (C_q), 135.2 (CH), 115.0 (C_q), 108.7 (CH), 101.0 (CH), 64.1 (CH_2), 14.5 (CH_3).

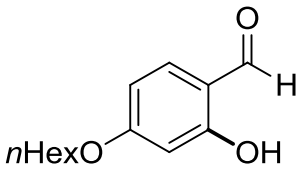
IR (neat): 2984, 2940, 2869, 1626, 1570, 1218, 1107 cm^{-1}.

MS (EI) m/z (relative intensity): 166 ([M^+] 45), 165 (7), 138 (25), 137 (100), 81 (14), 69 (12).

HR-MS (EI) m/z calcd for $C_9H_{10}O_3^+$ [M^+] 166.0630, found 166.0636.

The analytical data are in accordance with those reported in the literature.[203]

Synthesis of 4-Hexanoxy-2-hydroxybenzaldehyde (**92j**)



The general procedure **D** was followed using 4-hexanoxybenzaldehyde (**91j**) (103 mg, 0.50 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 20/1) yielded **92j** (61 mg, 55%) as an off-white liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.45 (s, 1H), 9.68 (s, 1H), 7.39 (d, *J* = 8.7 Hz, 1H), 6.50 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.39 (d, *J* = 2.3 Hz, 1H), 3.98 (t, *J* = 6.6 Hz, 2H), 1.83–1.70 (m, 2H), 1.50–1.25 (m, 6H), 0.93–0.85 (m, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 194.3 (CH), 166.4 (C_q), 164.5 (C_q), 135.2 (CH), 115.0 (C_q), 108.8 (CH), 101.0 (CH), 68.6 (CH_2), 31.5 (CH_2), 28.9 (CH_2), 25.6 (CH_2), 22.5 (CH_2), 14.0 (CH_3).

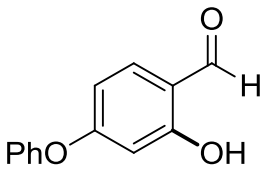
IR (neat): 2859, 2748, 1627, 1506, 1335, 1217, 1115, 803, 635 cm^{-1}.

MS (EI) m/z (relative intensity): 222 ([M^+] 52), 139 (22), 138 (100), 137 (85), 110 (10), 81 (10), 65 (12), 55 (15), 43 (49).

HR-MS (EI) m/z calcd for $C_{13}H_{18}O_3^+$ [M^+] 222.1256, found 222.1259.

The analytical data are in accordance with those reported in the literature.[204]

Synthesis of 2-Hydroxy-4-phenoxybenzaldehyde (**92k**)



The general procedure **D** was followed using 4-phenoxybenzaldehyde (**91k**) (99 mg, 0.50 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 15/1) yielded **92k** (71 mg, 66%) as an off-white liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.35 (s, 1H), 9.74 (s, 1H), 7.49–7.36 (m, 3H), 7.27–7.18 (m, 1H), 7.11–7.04 (m, 2H), 6.59 (dd, J = 8.6, 2.3 Hz, 1H), 6.39 (d, *J* = 2.3 Hz, 1H).

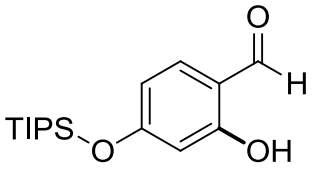
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 194.6 (CH), 165.6 (C_q), 164.1 (C_q), 154.3 (C_q), 135.6 (CH), 130.1 (CH), 125.4 (CH), 120.9 (CH), 116.2 (C_q), 109.7 (CH), 104.4 (CH).

IR (neat): 3190, 2848, 1636, 1482, 1294, 1212, 979, 499 cm^{-1}.

MS (EI) m/z (relative intensity): 214 ([M^+] 99), 213 (100), 185 (6), 128 (13), 98 (7), 77 (16), 63 (10), 57 (16), 51 (10), 43 (14).

HR-MS (EI) m/z calcd for $C_{13}H_{10}O_3^+$ [M^+] 214.0630, found 214.0619.

Synthesis of 2-Hydroxy-4-[(triisopropylsilyl)oxy]benzaldehyde (**92l**)



The general procedure **D** was followed using 4-[(triisopropylsilyl)oxy]benzaldehyde (**91l**) (139 mg, 0.50 mmol), and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 60/1) yielded **92l** (61 mg, 41%) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 11.32 (s, 1H), 9.70 (s, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 6.48 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.40 (dd, *J* = 2.2, 0.6 Hz, 1H), 1.33–1.21 (m, 3H), 1.09 (d, *J* = 7.2 Hz, 18H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 194.4 (CH), 164.2 (C_q), 164.2 (C_q), 135.4 (CH), 115.7 (C_q), 113.0 (CH), 107.5 (CH), 17.8 (CH_3), 12.7 (CH).

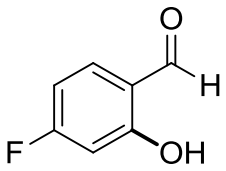
IR (neat): 2954, 2868, 1642, 1623, 1218, 683 cm^{-1}.

MS (EI) m/z (relative intensity): 294 ([M^+] 20), 251 (93), 223 (83), 195 (100), 181 (62), 75 (32).

HR-MS (EI) m/z calcd for $C_{16}H_{26}O_3Si^+$ [M^+] 294.1651, found 294.1659.

The analytical data are in accordance with those reported in the literature.[205]

Synthesis of 4-Fluoro-2-hydroxybenzaldehyde (92m)



The general procedure **D** was followed using 4-fluorobenzaldehyde (**91m**) (62 mg, 0.50 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 5 mol %), and [bis(trifluoroacetoxy)iodo]benzene (538 mg, 1.25 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 80/1 → 50/1) yielded **92m** (31 mg, 44%) as a colorless solid.

M. p. = 69–70 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.37 (s, 1H), 9.83 (s, 1H), 7.56 (dd, *J* = 8.6, 6.4 Hz, 1H), 6.79–6.63 (m, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 195.0 (CH), 167.9 (C_q, J_{C-F} = 258 Hz), 164.0 (C_q, J_{C-F} = 15 Hz), 136.0 (CH, J_{C-F} = 12 Hz), 117.8 (C_q, J_{C-F} = 2 Hz), 108.2 (CH, J_{C-F} = 23 Hz), 104.6 (CH, J_{C-F} = 25 Hz).

^{19}F-NMR (283 MHz, $CDCl_3$) δ = -97.5 (dddd, J = 10, 8, 7, 2 Hz).

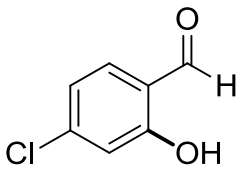
IR (neat): 3102, 2928, 2869, 1655, 1590, 1201, 802 cm^{-1}.

MS (EI) m/z (relative intensity): 140 ([M^+] 87), 139 (100), 122 (9), 111 (22), 94 (18).

HR-MS (EI) m/z calcd for $C_7H_5FO_2^+$ [M^+] 140.0274, found 140.0269.

The analytical data are in accordance with those reported in the literature.[206]

Synthesis of 4-Chloro-2-hydroxybenzaldehyde (92n)



The general procedure **D** was followed using 4-chlorobenzaldehyde (**91n**) (70 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5 mol %), and [bis(trifluoroacetoxy)iodo]benzene (538 mg, 1.25 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 80/1) yielded **92n** (34 mg, 43%) as a colorless solid.

M. p. = 48–49 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.16 (s, 1H), 9.86 (s, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.04–6.98 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 195.3 (CH), 162.1 (C_q), 143.2 (C_q), 134.5 (CH), 120.6 (CH), 119.2 (C_q), 117.9 (CH).

IR (neat): 3152, 2925, 2885, 1652, 1563, 1184, 712 cm^{-1}.

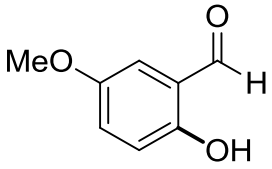
MS (EI) m/z (relative intensity): 156 ([M^+] 75), 155 (100), 138 (10), 127 (12), 111 (17), 97 (20).

HR-MS (EI) m/z calcd for $C_7H_5ClO_2^+$ [M^+] 155.9978, found 155.9978.

Synthesis of 2-Hydroxy-5-methoxybenzaldehyde (92o) and 2-Hydroxy-3-methoxybenzaldehyde (92o')

The general procedure **D** was followed using 3-methoxybenzaldehyde (**91o**) (68 mg, 0.50 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 10/1 → 3/1) yielded **92o** (37 mg, 49%) and **92o'** (14 mg, 19%).

2-Hydroxy-5-methoxybenzaldehyde (92o)



Yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.63 (s, 1H), 9.84 (s, 1H), 7.13 (dd, *J* = 9.0, 3.1 Hz, 1H), 6.98 (d, *J* = 3.1 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 3.80 (s, 3H).

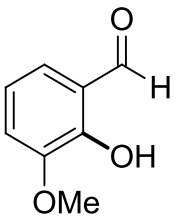
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 196.1 (CH), 156.1 (C_q), 152.7 (C_q), 125.2 (CH), 120.0 (C_q), 118.7 (CH), 115.2 (CH), 55.9 (CH).

IR (neat): 2939, 2837, 2738, 1655, 1483, 1266, 1149 cm^{-1}.

MS (EI) m/z (relative intensity): 152 ([M^+] 100), 151 (18), 137 (65), 109 (23), 81 (20), 53 (18).

HR-MS (EI) m/z calcd for $C_8H_8O_3^+$ [M^+] 152.0473, found 152.0472.

2-Hydroxy-3-methoxybenzaldehyde (92o')



Yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.12 (s, 1H), 9.92 (s, 1H), 7.18 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.12 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.97 (dt, *J* = 8.1, 7.8 Hz, 1H), 3.92 (s, 3H).

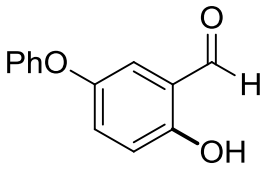
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 196.6 (CH), 151.6 (C_q), 148.3 (C_q), 124.5 (CH), 120.7 (C_q), 119.6 (CH), 117.9 (CH), 56.3 (CH).

IR (neat): 2939, 2843, 2751, 1654, 1457, 1254, 719 cm^{-1}.

MS (EI) m/z (relative intensity): 152 ([M^+] 100), 151 (14), 121 (12), 109 (30), 106 (47), 81 (28).

HR-MS (EI) m/z calcd for $C_8H_8O_3^+$ [M^+] 152.0473, found 152.0473.

Synthesis of 2-Hydroxy-5-phenoxybenzaldehyde (92p)



The general procedure **D** was followed using 3-phenoxybenzaldehyde (**91p**) (99 mg, 0.50 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 80/1) yielded **92p** (65 mg, 60%) as a yellow solid.

M. p. = 56–57 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.82 (s, 1H), 9.82 (s, 1H), 7.38–7.25 (m, 3H), 7.20 (d, *J* = 2.9 Hz, 1H), 7.14–7.08 (m, 1H), 7.02–6.95 (m, 3H).

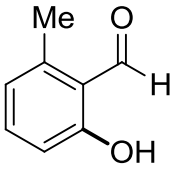
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 195.9 (CH), 157.8 (C_q), 157.6 (C_q), 149.4 (C_q), 129.9 (CH), 129.3 (CH), 123.3 (CH), 122.7 (CH), 120.5 (C_q), 119.1 (CH), 118.0 (CH).

IR (neat): 3056, 2923, 2875, 1648, 1478, 1244, 686 cm^{-1}.

MS (EI) m/z (relative intensity): 214 ([M^+] 100), 213 (25) 168 (23), 137 (9), 128 (11), 77 (17).

HR-MS (EI) m/z calcd for $C_{13}H_{10}O_3^+$ [M^+] 214.0630, found 214.0636.

Synthesis of 2-Hydroxy-6-methylbenzaldehyde (92q)



The general procedure **D** was followed using 2-methylbenzaldehyde (**91q**) (60 mg, 0.50 mmol) and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 80/1) yielded **92q** (36 mg, 53%) as an off-white liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.89 (s, 1H), 10.31 (s, 1H), 7.36 (dd, *J* = 8.4, 7.5 Hz, 1H), 6.80 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.69 (dd, *J* = 7.5, 1.2 Hz, 1H), 2.59 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 195.3 (CH), 163.2 (C_q), 142.1 (C_q), 137.4 (CH), 121.8 (CH), 118.5 (C_q), 116.1 (CH), 18.1 (CH_3).

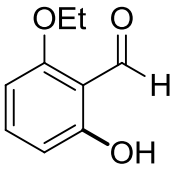
IR (neat): 3049, 2928, 2887, 1637, 1616, 718 cm^{-1}.

MS (EI) m/z (relative intensity): 136 ([M^+] 96), 135 (100), 118 (11), 107 (14), 77 (23).

HR-MS (EI) m/z calcd for $C_8H_8O_2^+$ [M^+] 136.0524, found 136.0518.

The analytical data are in accordance with those reported in the literature.[207]

Synthesis of 2-Ethoxy-6-hydroxybenzaldehyde (92r)



The general procedure **D** was followed using 2-ethoxybenzaldehyde (**91r**) (75 mg, 0.50 mmol) and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 20/1) yielded **92r** (54 mg, 65%) as an off-white liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.95 (s, 1H), 10.35 (s, 1H), 7.36 (dd, *J* = 8.4, 8.1 Hz, 1H), 6.48 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.33 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.09 (q, *J* = 7.0 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H).

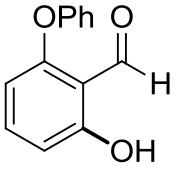
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 194.5 (CH), 163.6 (C_q), 161.9 (C_q), 138.4 (CH), 110.8 (C_q), 109.6 (CH), 101.7 (CH), 64.3 (CH_2), 14.5 (CH_3).

IR (neat): 2983, 2938, 2890, 1636, 1617, 1232, 1077 cm^{-1}.

MS (EI) m/z (relative intensity): 166 ([M^+] 50), 148 (42), 138 (30), 137 (100), 120 (24), 92 (20).

HR-MS (EI) m/z calcd for $C_9H_{10}O_3^+$ [M^+] 166.0630, found 166.0629.

Synthesis of 2-Hydroxy-6-phenoxybenzaldehyde (92s)



The general procedure **D** was followed using 2-phenoxybenzaldehyde (**91s**) (99 mg, 0.50 mmol) and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 30/1) yielded **92s** (67 mg, 63%) as a yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.85 (s, 1H), 10.42 (s, 1H), 7.44–7.28 (m, 3H), 7.25–7.17 (m, 1H), 7.12–7.05 (m, 2H), 6.63 (dt, *J* = 8.5, 0.7 Hz, 1H), 6.22 (dd, *J* = 8.3, 0.9 Hz, 1H).

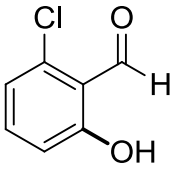
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 194.2 (CH), 163.4 (C_q), 160.8 (C_q), 155.4 (C_q), 138.0 (CH), 130.1 (CH), 124.8 (CH), 120.0 (CH), 112.2 (C_q), 111.7 (CH), 106.9 (CH).

IR (neat): 3057, 2888, 1578, 1453, 1224, 1033, 756, 691 cm^{-1}.

MS (EI) m/z (relative intensity): 214 ([M^+] 79), 213 (100), 139 (17), 137 (32), 136 (53), 128 (10), 108 (38), 77 (17), 65 (12), 51 (19).

HR-MS (EI) m/z calcd for $C_{13}H_{10}O_3^+$ [M^+] 214.0630, found 214.0620.

Synthesis of 2-Chloro-6-hydroxybenzaldehyde (92t)



The general procedure **D** was followed using 2-chlorobenzaldehyde (**91t**) (70 mg, 0.50 mmol) and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 200/1) yielded **92t** (39 mg, 50%) as a colorless solid.

M. p. = 51–52 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.89 (s, 1H), 10.40 (s, 1H), 7.39 (dd, *J* = 8.5, 8.0 Hz, 1H), 6.94 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.88 (dd, *J* = 8.5, 1.0 Hz, 1H).

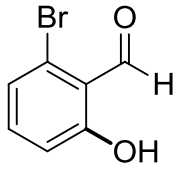
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 195.4 (CH), 163.9 (C_q), 138.1 (C_q), 137.4 (CH), 121.0 (CH), 117.1 (CH), 117.0 (C_q).

IR (neat): 3074, 2916, 1646, 1442, 1164, 698 cm^{-1}.

MS (EI) m/z (relative intensity): 156([M^+] 82), 155 (100), 138 (15), 110 (14), 99 (21), 63 (43).

HR-MS (ESI) m/z calcd for $C_7H_4ClO_2^+$ [M-H^+] 154.9900, found 154.9903.

Synthesis of 2-Bromo-6-hydroxybenzaldehyde (92u)



The general procedure **D** was followed using 2-bromobenzaldehyde (**91u**) (93 mg, 0.50 mmol) and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 100/1) yielded **92u** (57 mg, 57%) as a colorless solid.

M. p. = 55–57 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.96 (s, 1H), 10.31 (d, *J* = 0.6 Hz, 1H), 7.31 (dd, *J* = 8.5, 7.8 Hz, 1H), 7.14 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.92 (ddd, *J* = 8.4, 1.0, 0.6 Hz, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 197.6 (CH), 163.8 (C_q), 137.4 (CH), 127.3 (C_q), 124.4 (CH), 117.8 (CH), 117.7 (C_q).

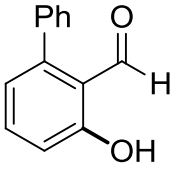
IR (neat): 3064, 2868, 1695, 1652, 1441, 1169, 1135, 901, 753 cm^{-1}.

MS (EI) m/z (relative intensity): 200 ([M^+] 61), 199 (56), 183 (47), 155 (18), 144 (12), 104 (11), 92 (21), 86 (66), 84 (100), 76 (30), 71 (19), 63 (29).

HR-MS (ESI) m/z calcd for $C_7H_5BrO_2^+$ [M^+] 199.9473, found 199.9476.

The analytical data are in accordance with those reported in the literature.[208]

Synthesis of 3-Hydroxy-[1,1'-biphenyl]-2-carbaldehyde (92v)



The general procedure **D** was followed using [1,1'-biphenyl]-2-carbaldehyde (**91v**) (91 mg, 0.50 mmol) and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-Pentane/Et_2O: 40/1) yielded **92v** (69 mg, 70%) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.90 (s, 1H), 9.82 (s, 1H), 7.56–7.40 (m, 4H), 7.38–7.32 (m, 2H), 6.98 (dd, *J* = 8.4, 0.9 Hz, 1H), 6.87 (dd, *J* = 7.5, 1.1 Hz, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 196.9 (CH), 162.7 (C_q), 147.4 (C_q), 137.3 (C_q), 136.5 (CH), 129.9 (CH), 128.3 (CH), 128.2 (CH), 121.4 (CH), 117.9 (C_q), 116.9 (CH).

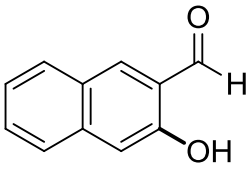
IR (neat): 3058, 2881, 1649, 1452, 1251, 1166, 700 cm^{-1}.

MS (EI) m/z (relative intensity): 198 ([M^+] 97), 197 (100), 180 (8), 169 (15), 152 (19), 141 (22), 115 (22).

HR-MS (EI) m/z calcd for $C_{13}H_{10}O_2^+$ [M^+] 198.0681, found 198.0673.

The analytical data are in accordance with those reported in the literature.[209]

Synthesis of 3-Hydroxy-2-naphthaldehyde (92w)



The general procedure **D** was followed using 2-naphthaldehyde (**91w**) (78 mg, 0.50 mmol) and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 70/1 → 50/1) yielded **92w** (45 mg, 52%) as a yellow solid.

M. p. = 95–96°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.30 (s, 1H), 10.07 (s, 1H), 8.13 (s, 1H), 7.85 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.70 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.55 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.36 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.27 (s, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 196.7 (CH), 155.8 (C_q), 138.2 (C_q), 137.8 (CH), 130.3 (CH), 129.4 (CH), 127.4 (C_q), 126.7 (CH), 124.4 (CH), 122.3 (C_q), 111.9 (CH).

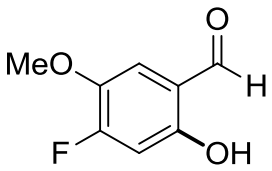
IR (neat): 3287, 3051, 2873, 1659, 1267, 742 cm^{-1}.

MS (EI) m/z (relative intensity): 172 ([M^+] 99), 171 (58), 126 (20), 115 (100), 89 (12), 63 (17).

HR-MS (ESI) m/z calcd for $C_{11}H_7O_2^+$ [M-H^+] 171.0446, found 171.0448.

The analytical data are in accordance with those reported in the literature.[210]

Synthesis of 4-Fluoro-2-hydroxy-5-methoxybenzaldehyde (92x)



The general procedure **D** was followed using 4-fluoro-3-methoxybenzaldehyde (**91x**) (77 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), and [bis(trifluoroacetoxy)iodo]benzene (538 mg, 1.25 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 10/1) yielded **92x** (51 mg, 60%) as an off-white solid.

M. p. = 85–87 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.06 (s, 1H), 9.78 (s, 1H), 7.06 (d, *J* = 9.0 Hz, 1H), 6.72 (d, *J* = 12.1 Hz, 1H), 3.87 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ =194.6 (CH), 158.4 (C_q, $J_{C\text{-}F}$ = 260 Hz), 157.8 (C_q, $J_{C\text{-}F}$ = 13 Hz), 141.8 (C_q, $J_{C\text{-}F}$ = 12 Hz), 116.6 (CH, $J_{C\text{-}F}$ = 5 Hz), 116.3 (C_q, $J_{C\text{-}F}$ = 3 Hz), 106.0 (CH, $J_{C\text{-}F}$ = 22 Hz), 57.0 (CH_3).

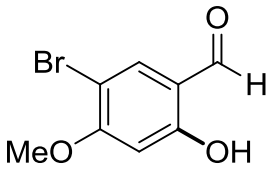
^{19}F-NMR (283 MHz, $CDCl_3$) δ = -117.9 (ddd, *J* = 12, 9, 2 Hz).

IR (neat): 3052, 2969, 2848, 1652, 1504, 1139, 695 cm^{-1}.

MS (EI) m/z (relative intensity): 170 ([M^+] 100), 169 (23), 155 (75), 127 (15), 99 (22), 71 (17).

HR-MS (EI) m/z calcd for $C_8H_7FO_3^+$ [M^+] 170.0379, found 170.0378.

Synthesis of 5-Bromo-2-hydroxy-4-methoxybenzaldehyde (92y)



The general procedure **D** was followed using 3-bromo-4-methoxybenzaldehyde (**91y**) (108 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), and [bis(trifluoroacetoxy)iodo]benzene (538 mg, 1.25 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 20/1) yielded **92y** (61 mg, 53%) as a colorless solid.

M. p. = 118–120 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.43 (s, 1H), 9.68 (s, 1H), 7.67 (s, 1H), 6.48 (s, 1H), 3.95 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 193.4 (CH), 163.6 (C_q), 162.4 (C_q), 137.1 (CH), 115.7 (C_q), 102.1 (C_q), 100.4 (CH), 56.8 (CH_3).

IR (neat): 2962, 2925, 2882, 1636, 1618, 1196, 687 cm^{-1}.

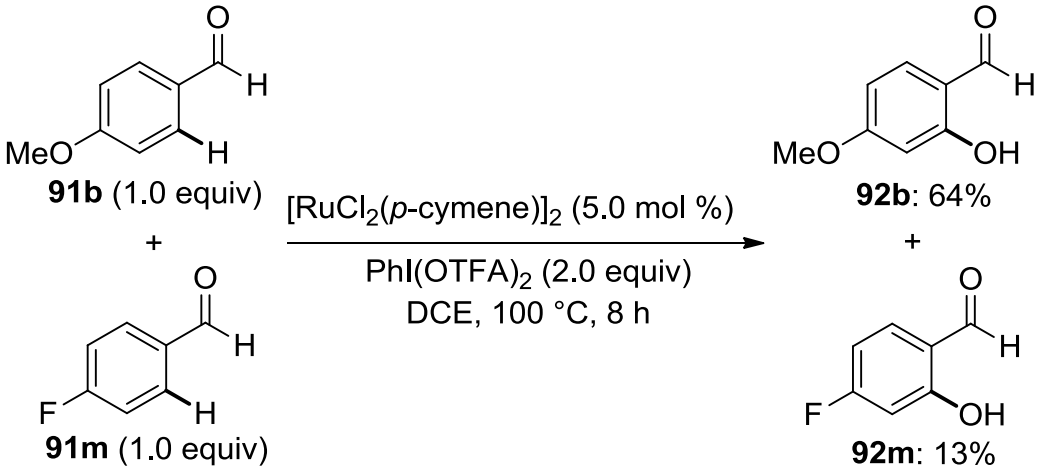
MS (EI) m/z (relative intensity): 230 ([M^+] 100), 229 (96), 186 (7), 159 (10), 111 (18), 97 (20).

HR-MS (EI) m/z calcd for $C_8H_7BrO_3^+$ [M^+] 229.9579, found 229.9579.

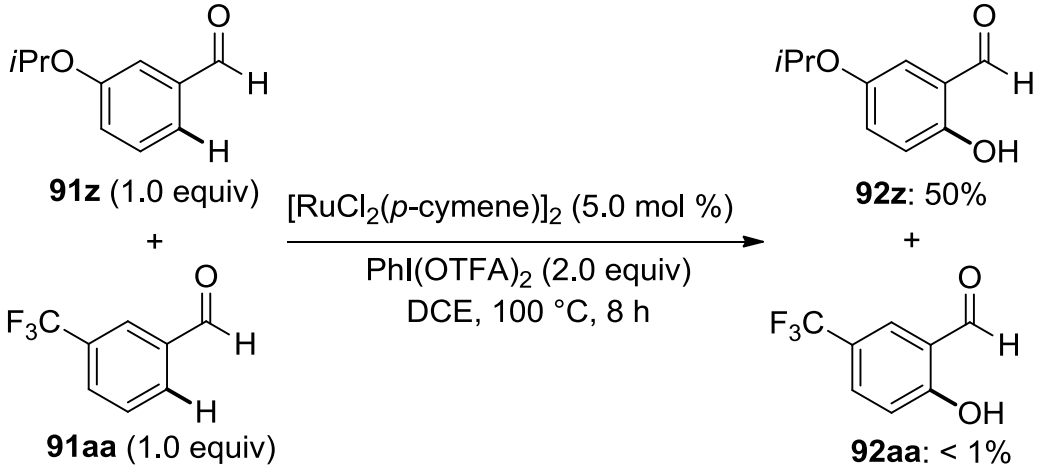
The analytical data are in accordance with those reported in the literature.[211]

Competition Experiments

Competition Experiments between Aldehydes 91

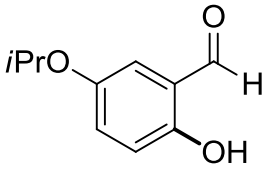


The representative procedure was followed using 4-methoxybenzaldehyde (**91b**) (68 mg, 0.50 mmol), 4-fluorobenzaldehyde (**91m**) (62 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.0 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 80/1 → 5/1) yielded **92b** (49 mg, 64%) and **92m** (9 mg, 13%).



The representative procedure was followed using 3-isopropoxybenzaldehyde (**91z**) (82 mg, 0.50 mmol), 3-(trifluoromethyl)benzaldehyde (**91aa**) (87 mg, 0.50 mmol), and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 50/1 → 30/1) yielded **92z** (45 mg, 50%) and **92aa** (< 1 mg, < 1%).

2-Hydroxy-5-isopropoxybenzaldehyde (**92z**)



^{1}H-NMR (300 MHz, CD_3OD): δ = 10.07 (s, 1H), 7.12 (d, *J* = 3.2 Hz, 1H), 7.05 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.78 (d, *J* = 9.0 Hz, 1H), 4.44 (hept, *J* = 6.0 Hz, 1H), 1.27 (d, *J* = 6.0 Hz, 6H).

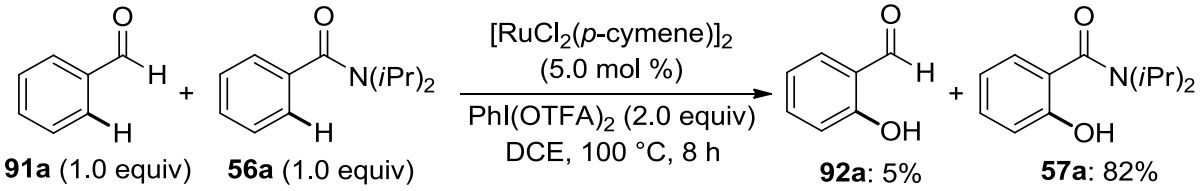
^{13}C-NMR (125 MHz, CD_3OD): δ = 195.3 (CH), 161.9 (C_q), 150.5 (C_q), 128.8 (CH), 123.2 (C_q), 121.3 (CH), 116.5 (CH), 72.3 (CH), 22.4 (CH_3).

IR (neat): 3282, 2976, 2465, 1583, 1486, 1372, 1193, 1105, 826, 768 cm^{-1}.

MS (EI) m/z (relative intensity): 180 ([M^+] 14), 139 (10), 138 (100), 137 (57), 120 (11), 92 (12), 58 (16), 41 (68).

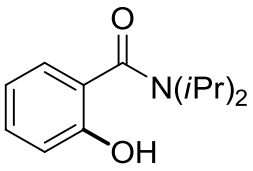
HR-MS (ESI) m/z calcd for $C_{10}H_{12}O_3Na^+$ [M+Na^+] 203.0679, found 203.0675.

Comparison between Aldehyde and Amide as Directing Groups



The representative procedure was followed using benzaldehyde (**91a**) (53 mg, 0.50 mmol), *N,N*-diisopropylbenzamide (**56a**) (103 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.0 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 60/1 → 1/2) yielded **92a** (3 mg, 5%) and **57a** (91 mg, 82%).

2-Hydroxy-*N,N*-diisopropylbenzamide (57a)



Colorless solid.

M. p. = 155–157 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.26 (ddd, J = 8.3, 6.6, 1.7 Hz, 1H), 7.15 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.97 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.81 (ddd, *J* = 7.7, 6.6, 1.2 Hz, 1H), 4.01–3.81 (m, 2H), 1.37 (d, *J* = 6.7 Hz, 12H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 170.9 (C_q), 157.9 (C_q), 131.5 (CH), 126.6 (CH), 120.2 (C_q), 118.4 (CH), 117.9 (CH), 49.0 (CH), 21.1 (CH_3).

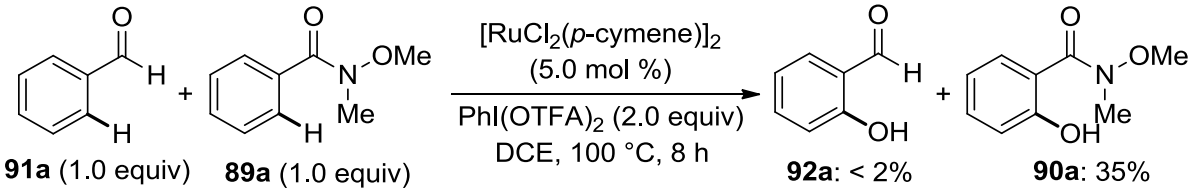
IR (neat): 3066, 2968, 2934, 1582, 1445, 1348, 750 cm^{-1}.

MS (EI) m/z (relative intensity): 221 ([M^+] 20), 178 (37), 121 (92), 86 (100), 58 (40).

HR-MS (EI) m/z calcd for $C_{13}H_{19}NO_2^+$ [M^+] 221.1416, found 221.1411.

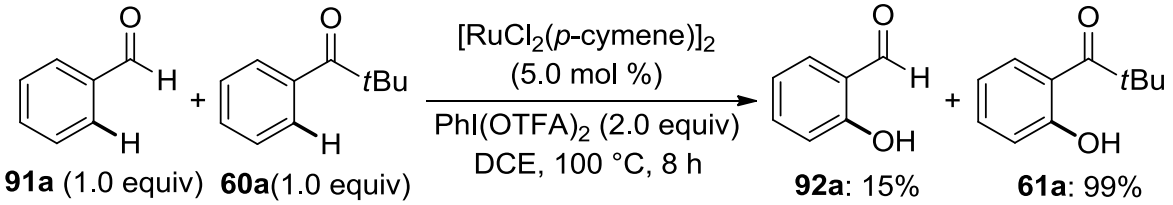
The analytical data are in accordance with those reported in the literature.[129]

Comparison between Aldehyde and Weinreb Amide as Directing Groups



The representative procedure was followed using benzaldehyde (**91a**) (53 mg, 0.50 mmol), *N*-methoxy-*N*-methylbenzamide (**89a**) (83 mg, 0.50 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %), and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.0 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 60/1 → 3/1) yielded **92a** (< 1 mg, < 2%) and **90a** (32 mg, 35%).

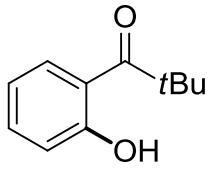
Comparison between Aldehyde and Ketone as Directing Groups



The representative procedure was followed using benzaldehyde (**91a**) (53 mg, 0.50 mmol), 2,2-dimethyl-1-phenylpropan-1-one (**60a**) (81 mg, 0.50 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %), and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.0 mmol). After stirring at

100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 60/1 → 30/1) yielded **92a** (9 mg, 15%) and **61a** (88 mg, 99%).

1-(2-Hydroxyphenyl)-2,2-dimethylpropan-1-one (**61a**)



Colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.71 (s, 1H), 8.02 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.42 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 7.01 (dd, *J* = 8.5, 1.4 Hz, 1H), 6.85 (ddd, *J* = 8.3, 7.1, 1.4 Hz, 1H), 1.46 (s, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 212.3 (C_q), 163.8 (C_q), 135.4 (CH), 130.9 (CH), 119.4 (CH), 117.8 (CH), 117.6 (C_q), 44.6 (C_q), 28.7 (CH_3).

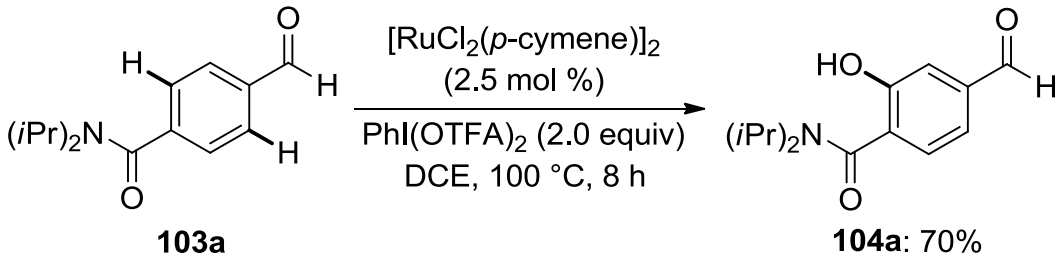
IR (neat): 2976, 2934, 2875, 1628, 1149, 754 cm^{-1}.

MS (EI) m/z (relative intensity): 178 ([M^+] 10), 155 (4), 135 (3), 122 (9), 121 (100), 93 (10), 65 (14).

HR-MS (ESI) m/z calcd for $C_{11}H_{14}O_2^+$ [M^+] 178.0994, found 178.1000.

The analytical data are in accordance with those reported in the literature.[130]

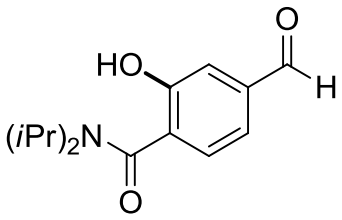
Intramolecular Competition with 103a



103a **104a**: 70%

The general procedure **D** was followed using 4-formyl-*N,N*-diisopropylbenzamide (**103a**) (117 mg, 0.50 mmol), and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/EtOAc: 2/1 → 1/1) yielded **104a** (87 mg, 70%) as a colorless solid.

4-Formyl-2-hydroxy-*N,N*-diisopropylbenzamide (104a)



M. p. = 228–230 °C.

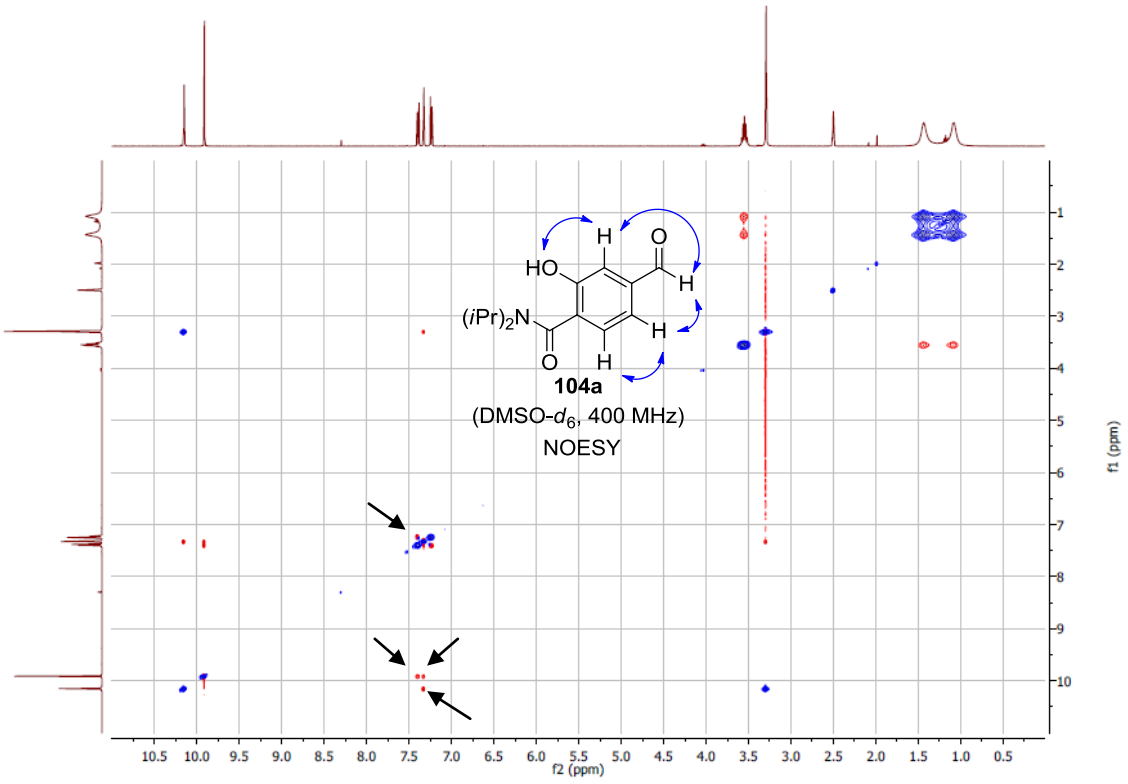
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.15 (s, 1H), 9.91 (s, 1H), 7.39 (dd, J = 7.6, 1.4 Hz, 1H), 7.32 (dd, J = 1.4, 0.4 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 3.55 (p, J = 6.7 Hz, 2H), 1.41 (br, 6H), 1.06 (br, 6H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 192.5 (CH), 166.6 (C_q), 153.4 (C_q), 136.9 (C_q), 132.6 (C_q), 127.3 (CH), 121.5 (CH), 114.7 (CH), 50.3 (CH), 20.2 (CH_3).

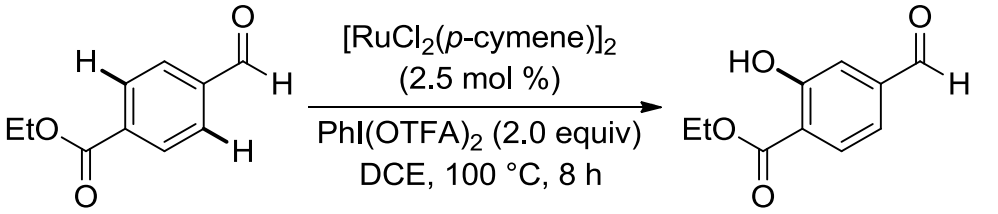
IR (neat): 2970, 2733, 1697, 1579, 1428, 1155, 817 cm^{-1}.

MS (EI) m/z (relative intensity): 249 ([M$^+$] 23), 206 (58), 149 (85), 121 (21), 86 (100), 58 (48).

HR-MS (ESI) m/z calcd for $C_{14}H_{19}NO_3^+$ [M$^+$] 249.1365, found 249.1366.



Intramoleculare Competition with 103b

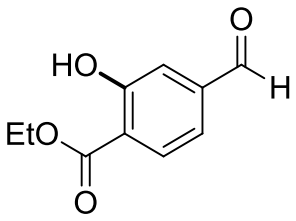


103b

104b: 13% +
reisolated **103b**: 59%

The general procedure **D** was followed using ethyl 4-formylbenzoate (**103b**) (89 mg, 0.50 mmol), and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 40/1 → 20/1) yielded **104b** (13 mg, 13%) as a pale yellow liquid and reisolated ethyl 4-formylbenzoate (53 mg, 59%).

Ethyl 4-formyl-2-hydroxybenzoate (104b)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.92 (s, 1H), 9.99 (s, 1H), 7.99 (dt, *J* = 8.1, 0.5 Hz, 1H), 7.43 (dd, *J* = 1.6, 0.5 Hz, 1H), 7.37 (dd, *J* = 8.1, 1.6 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

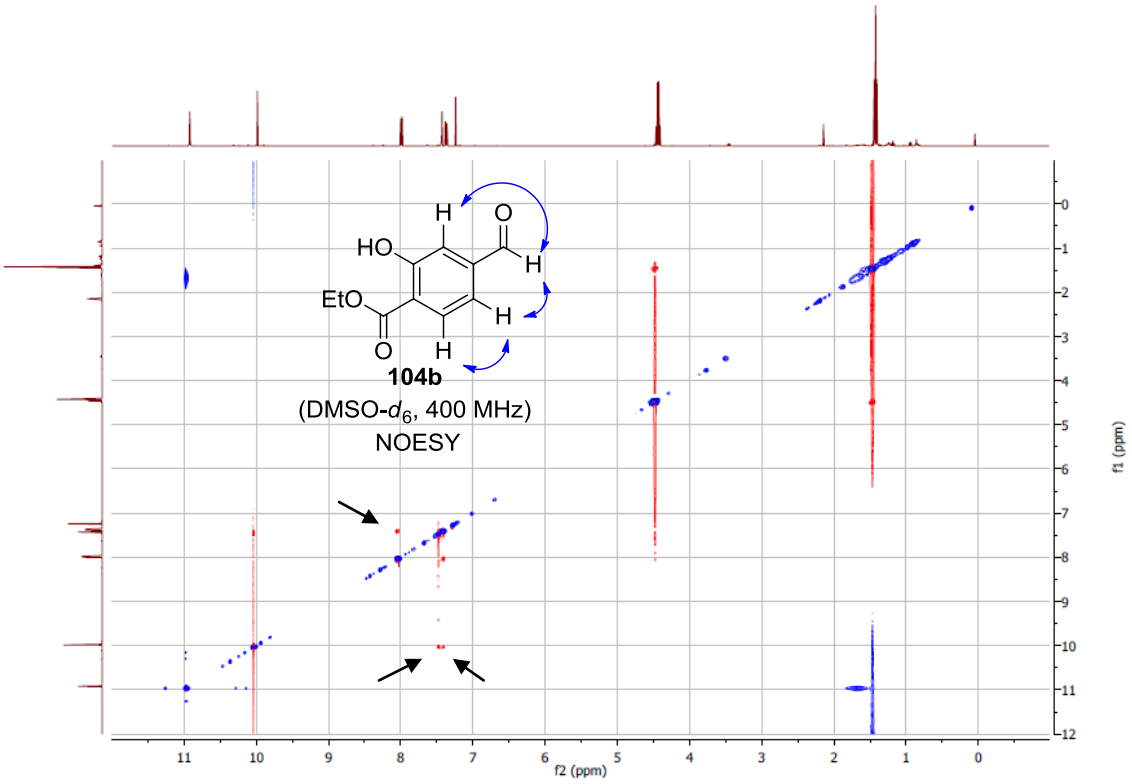
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 191.3 (CH), 169.3 (C_q), 161.8 (C_q), 141.2 (C_q), 130.7 (CH), 119.2 (CH), 118.6 (CH), 117.0 (C_q), 62.1 (CH_2), 14.2 (CH_3).

IR (neat): 3169, 2984, 1704, 1681, 1294, 783 cm^{-1}.

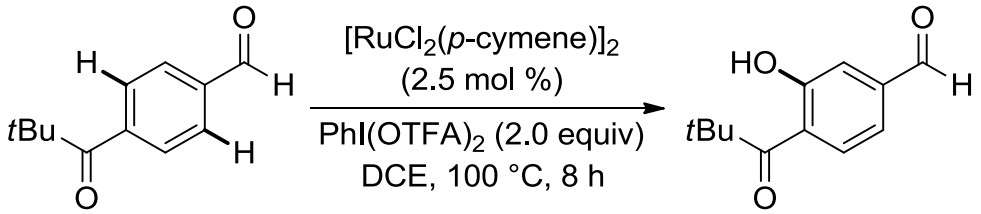
MS (EI) m/z (relative intensity): 194 ([M^+] 45), 149 (36), 148 (100), 119 (52), 65 (15).

HR-MS (ESI) m/z calcd for $C_{10}H_{10}O_4^+$ [M^+] 194.0579, found 194.0573.

The analytical data are in accordance with those reported in the literature.[212]



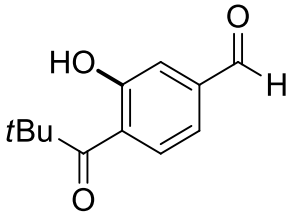
Intramoleculare Competition with 103c



103c **104c**: 76%

The general procedure **D** was followed using 4-pivaloylbenzaldehyde (**103c**) (95 mg, 0.50 mmol), and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 20/1) yielded **104c** (78 mg, 76%) as a colorless liquid.

3-Hydroxy-4-pivaloylbenzaldehyde (104c)



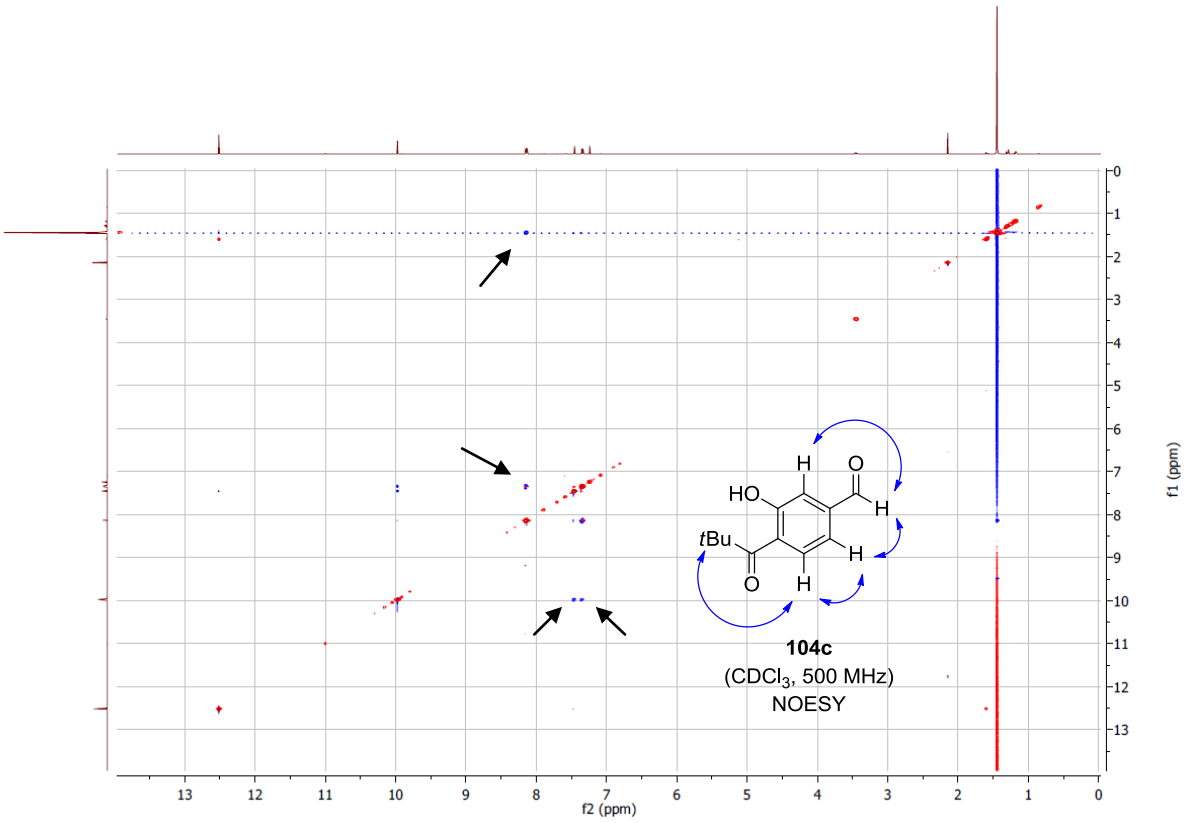
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 12.52 (s, 1H), 9.97 (s, 1H), 8.14 (dt, J = 8.4, 0.5 Hz, 1H), 7.46 (dd, J = 1.7, 0.5 Hz, 1H), 7.34 (dd, J = 8.4, 1.7 Hz, 1H), 1.44 (s, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 211.9 (C_q), 191.1 (CH), 163.6 (C_q), 140.4 (C_q), 131.3 (CH), 121.3 (CH), 121.1 (C_q), 117.0 (CH), 45.0 (C_q), 28.6 (CH_3).

IR (neat): 2975, 2935, 1698, 1635, 1294, 1146, 784 cm^{-1}.

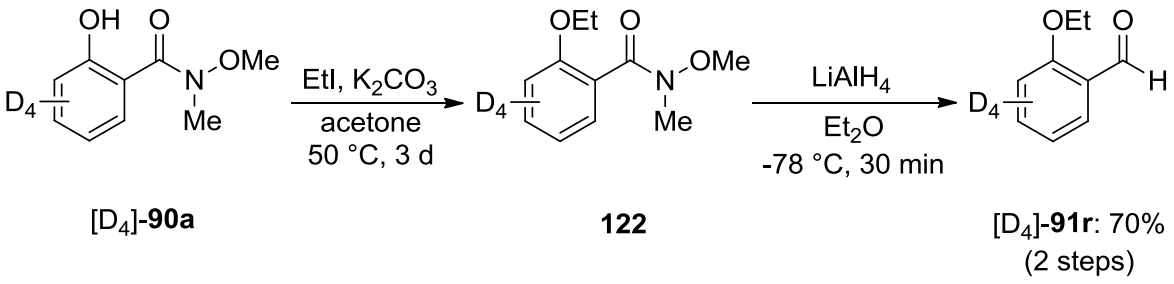
MS (EI) m/z (relative intensity): 206 ([M^+] 15), 150 (60), 149 (100), 121 (24), 65 (24), 57 (45).

HR-MS (ESI) m/z calcd for $C_{12}H_{14}O_3^+$ [M^+] 206.0943, found 206.0942.



Experiments with Isotopically Labled Compounds

Synthesis of Arene [D_4]-91r

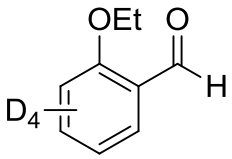


[D_4]-**90a** **122** [D_4]-**91r**: 70% (2 steps)

To a 50 mL Schlenk flask coated with aluminum foil were added [D_4]-**90a** (0.95 g, 5.0 mmol), EtI (2.34 g, 15.0 mmol), K_2CO_3 (1.04 g, 7.5 mmol), and acetone (20 mL). The mixture was stirred at 50 °C for 3 d under N_2. Acetone was removed under reduced pressure. The residue was extracted with EtOAc (50 mL), washed with brine (3 × 20 mL), and dried over Na_2SO_4. The crude product **122** was used in the next step without further purification.

To a 100 mL flame-dried Schlenk flask were added **122** and THF (50 mL) under N_2. The mixture was cooled to -78 °C. $LiAlH_4$ (0.38 g, 11.0 mmol) suspended in Et_2O (15 mL) was added dropwise. The mixture was stirred for 30 min at -78 °C, then quenched with 10% $KHSO_4$ (10 mL) and warmed up to ambient temperature. The organic phase was washed with HCl (1N, 2 × 20 mL) and brine (2 × 20 mL), dried over Na_2SO_4 and removed by rotary evaporation at ambient temperature. Purification by column chromatography on silica gel (*n*-pentane/Et_2O: 10/1) yielded [D_4]-**91r** (0.54 g, 70%) as a colorless liquid.

2-Ethoxy-3,4,5,6-*d*$_4$-benzaldehyde ([D_4]-91r)



^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.49 (s, 1H), 4.13 (q, *J* = 7.0 Hz, 2H), 1.46 (t, *J* = 7.0 Hz, 3H).

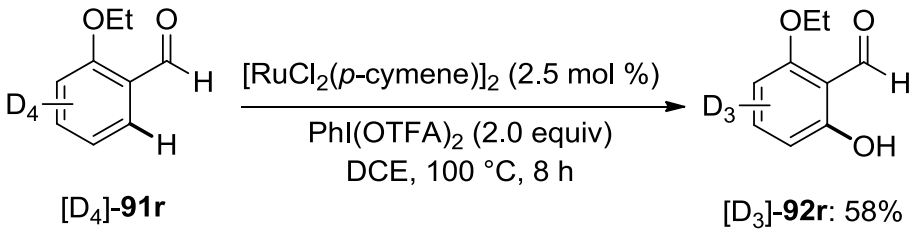
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 189.8 (CH), 161.2 (C_q), 135.3 (t, *J* = 23.8 Hz, CD), 127.8 (t, *J* = 25.0 Hz, CD), 124.7 (C_q), 119.9 (t, *J* = 25.0 Hz, CD), 112.0 (t, *J* = 25.0 Hz, CD), 64.2 (CH_2), 14.7 (CH_3).

IR (neat): 2980, 2861, 1682, 1572, 1352, 1192, 1042 cm^{-1}.

MS (EI) m/z (relative intensity): 154 ([M^+] 28), 136 (10), 125 (100), 108 (15), 97 (15), 69 (31).

HR-MS (EI) m/z calcd for $C_9H_6D_4O_2^+$ [M^+] 154.0932, found 154.0937.

Synthesis of [D_3]-92r

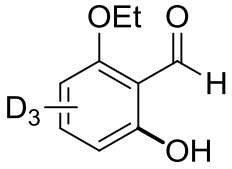


[D_4]-**91r**

[D_3]-**92r**: 58%

The representative procedure **D** was followed using [D_4]-**91r** (77 mg, 0.50 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (7.7 mg, 2.5 mol %), and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.0 mmol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 30/1) yielded [D_3]-**92r** (49 mg, 58%) as a colorless liquid.

2-Ethoxy-6-hydroxy-3,4,5-*d*$_3$-benzaldehyde ([D_3]-92r)



^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.96 (s, 1H), 10.36 (s, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 1.45 (t, *J* = 7.0 Hz, 3H).

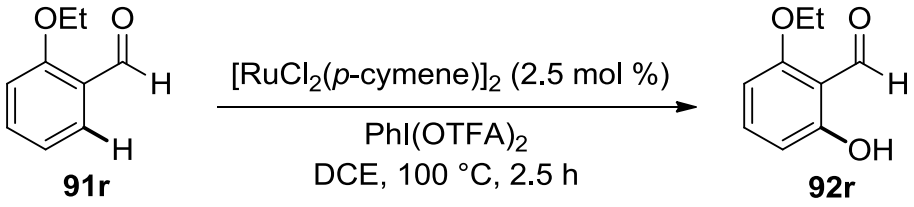
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 194.3 (CH), 163.4 (C_q), 161.7 (C_q), 137.8 (t, *J* = 24.3 Hz, CD), 110.8 (C_q), 109.1 (t, *J* = 25.1 Hz, CD), 101.3 (t, *J* = 24.7 Hz, CD), 64.3 (CH_2), 14.6 (CH_3).

IR (neat): 2983, 2936, 2889, 1636, 1610, 1280, 1114 cm^{-1}.

MS (EI) m/z (relative intensity): 169 ([M^+] 45), 151 (43), 141 (25), 140 (100), 123 (20), 95 (18).

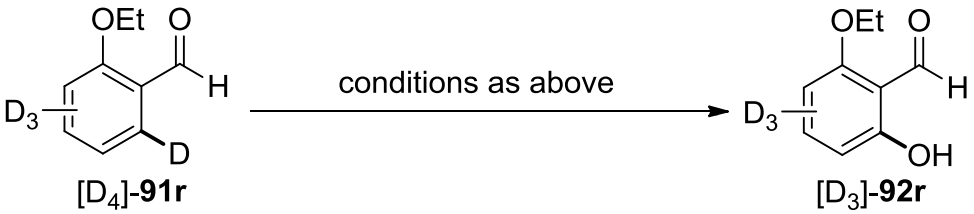
HR-MS (EI) m/z calcd for $C_9H_7D_3O_3^+$ [M^+] 169.0818, found 169.0821.

Independent KIE studies with 91r and [D_4]-91r



To a 25 mL two-necked pear-shaped flask equipped with a condenser were added 2-ethoxybenzaldehyde (**91r**) (150 mg, 1.0 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 2.5 mol %), 1,3,5-tri-*tert*butylbenzene (24.6 mg, 0.1 mmol), [bis(trifluoroacetoxy)iodo]benzene (860 mg, 2.0 mmol), and DCE (4.0 mL). The mixture was stirred at 100 °C under N_2. From the beginning to 2.5 h, an aliquot (0.1 mL) was taken out by syringe every 15 min and analyzed by ^{1}H-NMR to provide the following conversions:

Time (min)	0	15	30	45	60	75	90	105	120	135	150
91r (%)	100	94	88	75	70	63	56	50	46	41	39
92r (%)	0	5	11	17	25	31	33	40	45	49	50

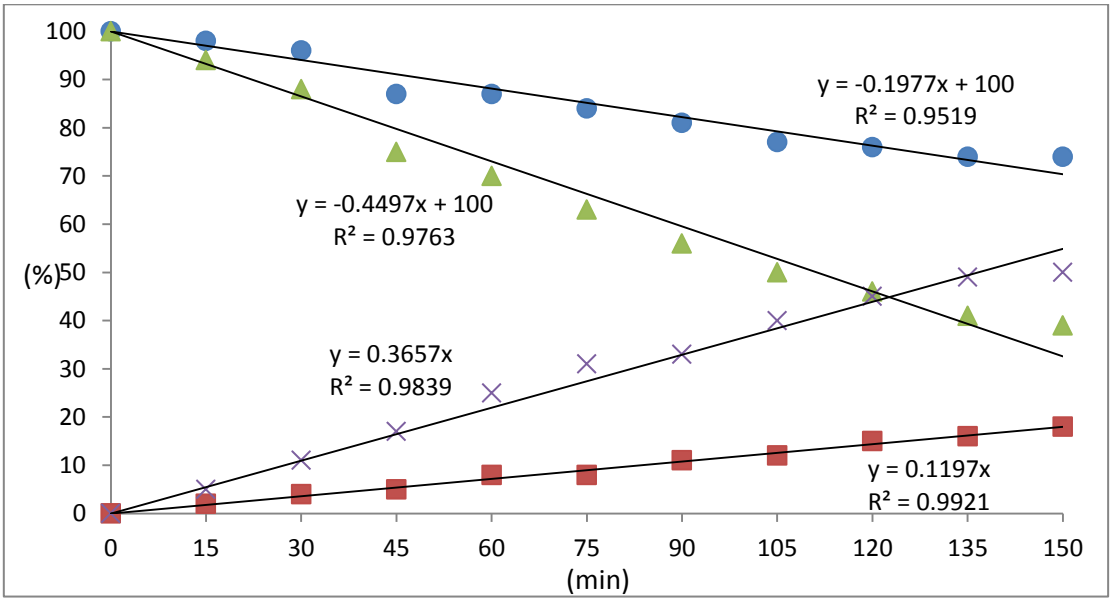


[D_4]-**91r** [D_3]-**92r**

The procedure above was followed using [D_4]-**91r** (154 mg, 1.0 mmol) to provide the following conversions:

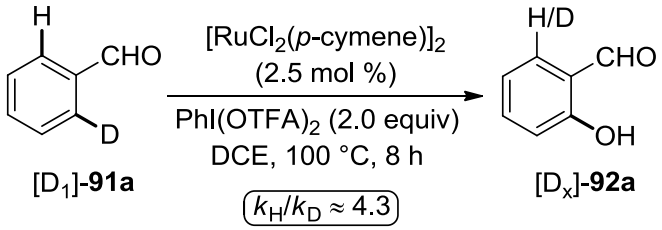
Time (min)	0	15	30	45	60	75	90	105	120	135	150
D_4-91r (%)	100	98	96	87	87	84	81	77	76	74	74
D_3-92r (%)	0	2	4	5	8	8	11	12	15	16	18

Data from independent kinetic isotope studies are collected in the scheme below and k_H/k_D was found to be 3.1.



▲: **91r**; ●: [D_4]-**91r**; ×: **92r**; ■: [D_3]-**92r**.

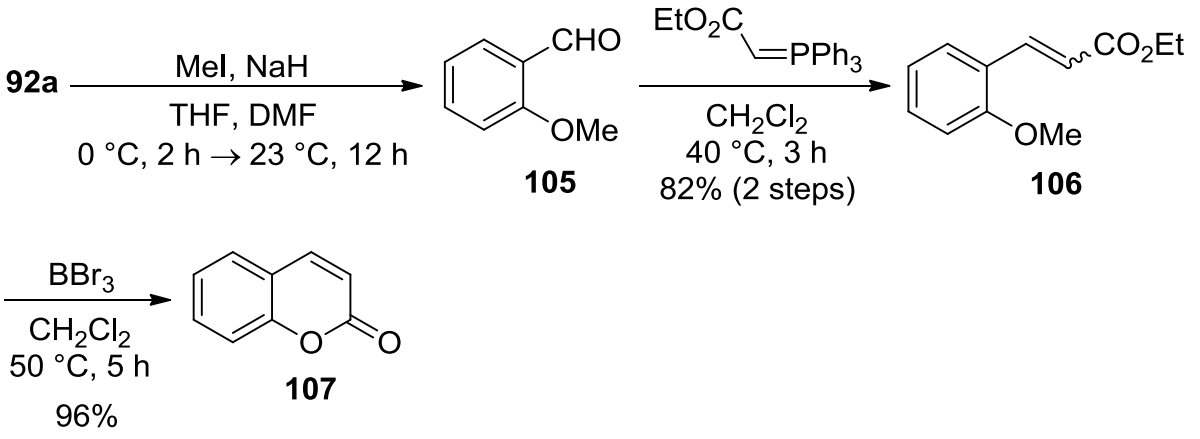
Intramolecular KIE studies



The general procedure **D** was followed using [D_1]-**91a** (54 mg, 0.50 mmol), and [bis(trifluoroacetoxy)iodo]benzene (430 mg, 1.00 mol). After stirring at 100 °C for 8 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 80/1) yielded [D_x]-**92a** (19 mg, 31%) as a colorless liquid. The intramolecular KIE was determined to be 4.3 by ^{1}H-NMR.

Diversification of Salicylaldehydes 92

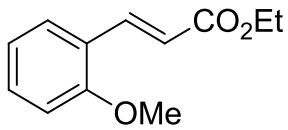
a) Synthesis of 2*H*-Chromen-2-one (107)



A literature procedure was used for the synthesis of **105**:[213] To a 25 mL flask were added NaH (0.12 g, 5.0 mmol), DMF (8.0 mL), and THF (2.0 mL), the mixture was cooled to 0 °C, followed by dropwise addition of **92a** (0.61 g, 5.0 mmol) and MeI (2.13 g, 15.0 mmol) in THF (5.0 mL). The mixture was stirred for 2 h at 0 °C, and then raised to ambient temperature to stir for another 12 h. The reaction mixture was poured into H_2O (25 mL) and extracted with Et_2O (3 × 25 mL). The combined organic phase was washed with brine (3 × 25 mL), dried over Na_2SO_4 and removed under vacuum to get the crude product **105**.

A literature procedure was used for the synthesis of **106**:[214] The crude **105** was dissolved in CH_2Cl_2 (10.0 mL), $Ph_3P{=}CHCO_2Et$ (1.92 g, 5.5 mmol) was added slowly. The mixture was stirred at 40 °C for 2 h. To the reaction was added H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). Purification by column chromatography on silica gel (*n*-pentane/EtOAc: 10/1) yielded **106** (0.85 g, 82%, *E:Z* ratio 6:1) as a colorless liquid.

Ethyl (*E*)-3-(2-methoxyphenyl)acrylate (106)



^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 16.2 Hz, 1H), 7.51 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.38–7.31 (m, 1H), 7.00–6.88 (m, 2H), 6.53 (d, *J* = 16.2 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.5 (C_q), 158.3 (C_q), 140.0 (CH), 131.4 (CH), 128.9 (CH), 123.4 (C_q), 120.7 (CH), 118.8 (CH), 111.1 (CH), 60.3 (CH_2), 55.4 (CH_3), 14.3 (CH_3).

IR (neat): 2939, 2839, 1703, 1630, 1157, 1025, 749 cm^{-1}.

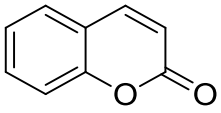
MS (EI) m/z (relative intensity): 206 ([M^+] 68), 175 (80), 161 (100), 147 (75), 131 (23), 118 (33), 105 (31).

HR-MS (ESI) m/z calcd for $C_{12}H_{14}O_3^+$ [M^+] 206.0943, found 206.0944.

The analytical data are in accordance with those reported in the literature.[214]

A literature procedure was used for the synthesis of **107**:[215] To a 25 mL two-necked flask equipped with a condenser were added **106** (0.41 , 2.0 mmol) and CH_2Cl_2 (6.0 mL). The mixture was cooled to 0 °C. BBr_3 (5.0 mmol, 1 M in CH_2Cl_2) was added dropwise. The mixture was stirred at 50 °C under N_2 for 5 h. After cooling to ambient temperature, to the reaction was added H_2O (25 mL), extracted with Et_2O (3 × 25 mL), washed with brine (50 mL), and dried over Na_2SO_4. Purification by column chromatography on silica gel (*n*-pentane/EtOAc: 5/1) yielded **107** (0.28 g, 96%) as a colorless solid.

2*H*-Chromen-2-one (107)



M.p. = 75–78 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, J = 9.6 Hz, 1H), 7.60–7.44 (m, 2H), 7.38–7.20 (m, 2H), 6.42 (d, J = 9.6 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.7 (C_q), 154.0 (C_q), 143.4 (CH), 131.8 (CH), 127.8 (CH), 124.4 (CH), 118.8 (C_q), 116.9 (CH), 116.7 (CH).

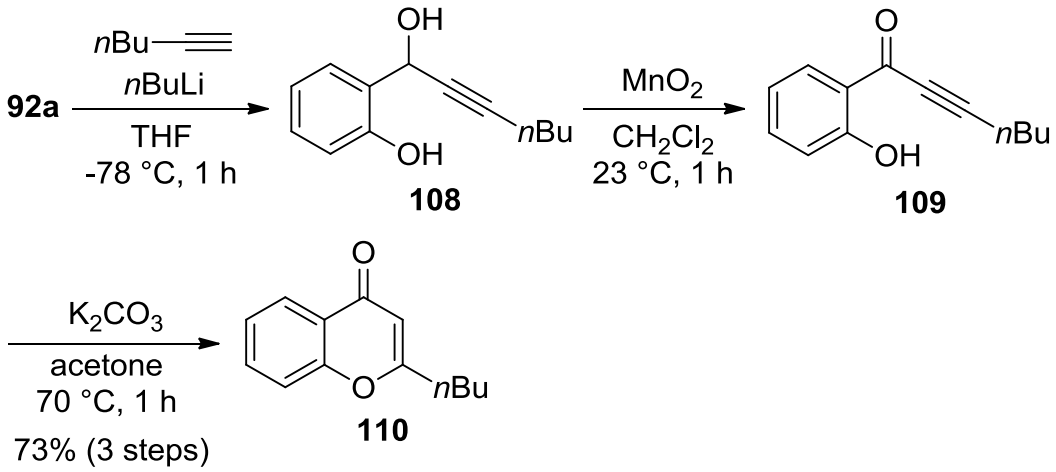
IR (neat): 3057, 1700, 1601, 1452, 1258, 1175, 753 cm^{-1}.

MS (EI) m/z (relative intensity): 146 ([M^+] 98), 118 (100), 90 (67), 89 (54), 64 (14), 63 (43), 62 (17), 51 (15).

HR-MS (EI) m/z calcd for $C_9H_6O_2^+$ [M^+] 146.0368, found 146.0372.

The analytical data are in accordance with those reported in the literature.[216]

b) Synthesis of 2-*n*-Butyl-4*H*-chromen-4-one (110)



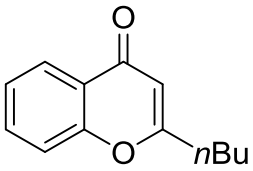
A literature procedure was used for the synthesis of **108**:[217] To a 25 mL Schlenk flask charged with N_2 were added 1-hexyne (181 mg, 2.2 mmol) and THF (5.0 mL). The mixture was cooled to -78 °C. *n*BuLi (2.1 mmol, 2.5 M in hexane) was added dropwise. The mixture was stirred for another 1 h after the addition of *n*BuLi. **92a** (122 mg, 1.0 mmol) dissolved in THF (3.0 mL) was added in dropwise, and the mixture was stirred at -78 °C for 1 h. To the reaction was added saturated aqueous NH_4Cl solution (10 mL), extracted with Et_2O (3 ×

25 mL), washed with HCl (1N, 25 mL) and brine (50 mL). The organic phase was removed under vacuum to afford crude **108**.

A literature procedure was used for the synthesis of **109**:[217] Crude **108** was dissolved in CH_2Cl_2 (10.0 mL), MnO_2 (0.87 g, 10 mmol) was added portionwise. The mixture was stirred at 23 °C for 1 h, then filtrated through a pad of silica gel. The organic phase was removed to afford crude **109**.

A literature procedure was used for the synthesis of **110**:[218] To a 25 mL flask were added crude **109**, K_2CO_3 (42 mg, 0.3 mmol), and acetone (10.0 mL). The mixture was heated at 70 °C for 1 h. The organic phase was removed under vacuum. Purification by column chromatography on silica gel (*n*-pentane/EtOAc: 5/1) yielded 2-*n*butyl-4*H*-chromen-4-one (**110**) (148 mg, 73%) as a colorless liquid.

2-*n*Butyl-4*H*-chromen-4-one (110)



^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.16 (ddd, *J* = 8.0, 1.7, 0.5 Hz, 1H), 7.62 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.44–7.30 (m, 2H), 6.16 (s, 1H), 2.60 (t, *J* = 7.5 Hz, 2H), 1.71 (tt, *J* = 7.8, 7.5 Hz, 2H), 1.42 (qt, *J* = 7.8, 7.3 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 178.2 (C_q), 169.6 (C_q), 156.4 (C_q), 133.3 (CH), 125.6 (CH), 124.8 (CH), 123.7 (C_q), 117.7 (CH), 109.7 (CH), 34.1 (CH_2), 28.9 (CH_2), 22.2 (CH_2), 13.8 (CH_3).

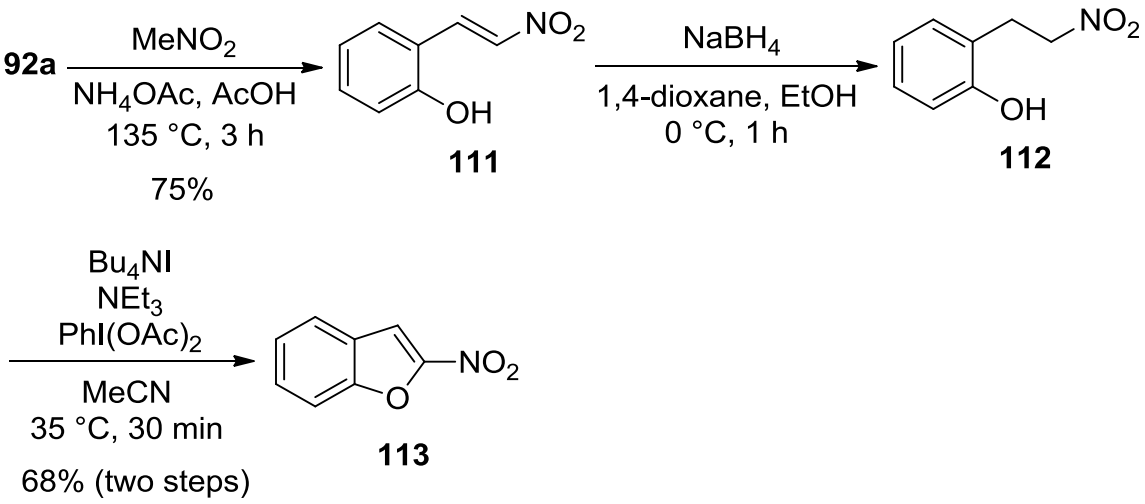
IR (neat): 2958, 2931, 2872, 1647, 1464, 1380, 758 cm^{-1}.

MS (EI) m/z (relative intensity): 202 ([M^+] 20), 173 (7), 160 (100), 131 (14), 120 (30), 92 (21).

HR-MS (EI) m/z calcd for $C_{13}H_{14}O_2^+$ [M^+] 202.0994, found 202.1000.

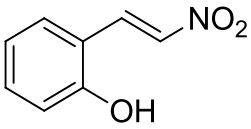
The analytical data are in accordance with those reported in the literature.[219]

c) Synthesis of 2-Nitrobenzofuran (113)



A literature procedure was used for the synthesis of **111**:[220] To a 25 mL flask were added nitromethane (5.0 mL), NH_4OAc (77 mg, 1.0 mmol), and acetic acid (2.0 mL). The mixture was stirred at 90 °C for 15 min before addition of **92a** (0.61 g, 5.0 mmol). The reaction mixture was heated at 135 °C for 3 h. After cooling to ambient temperature, to the reaction was added Et_2O (50 mL) and brine (50 mL). The organic phase was separated, dried over Na_2SO_4, removed under reduced pressure. Purification by column chromatography on silica gel (*n*-pentane/EtOAc: 5/1) yielded **111** (0.62 g, 75%) as a yellow solid.

(*E*)-2-(2-Nitrovinyl)phenol (111)



M.p. = 134–136 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 13.6 Hz, 1H), 7.97 (d, *J* = 13.6 Hz, 1H), 7.44 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.40–7.31 (m, 1H), 7.01 (ddd, *J* = 7.7, 7.5, 1.0 Hz, 1H), 6.87 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.81 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 155.9 (C_q), 138.6 (CH), 135.5 (CH), 133.2 (CH), 132.6 (CH), 121.6 (CH), 117.7 (C_q), 116.4 (CH).

IR (neat): 3343, 1621, 1492, 1320, 1241, 758 cm^{-1}.

MS (EI) m/z (relative intensity): 165 ([M^+] 20), 118 (100), 91 (28), 89 (20), 65 (25), 51 (12).

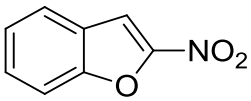
HR-MS (EI) m/z calcd for $C_8H_7NO_3^+$ [M^+] 165.0426, found 165.0421.

The analytical data are in accordance with those reported in the literature.[221]

A literature procedure was used for the synthesis of **112**:[222] $NaBH_4$ (45 mg, 1.2 mmol) was suspended in a mixture of 1,4-dioxane and EtOH (4.0 mL, 3:1). **111** (165 mg, 1 mmol) dissolved in 1,4-dioxane (3.0 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then was added saturated aqueous NH_4Cl solution (10 mL) and extracted with Et_2O (3 × 25 mL), washed with brine (50 mL), and dried over Na_2SO_4. The organic phase was removed under vacuum to afford the crude **112**.

A literature procedure was used for the synthesis of **113**:[223] To a 25 mL flask were added crude **112**, Bu_4NI (923 mg, 2.5 mmol), NEt_3 (202 mg, 2.0 mmol), $PhI(OAc)_2$ (966 mg, 3.0 mmol), and acetonitrile (10.0 mL). The mixture was stirred at 35 °C for 30 min, extracted with Et_2O (50 mL) and brine (3 × 25 mL), dried over Na_2SO_4. Purification by column chromatography on silica gel (*n*-pentane/Et_2O: 20/1) yielded 2-nitrobenzofuran (**113**) (124 mg, 76%) as an off-white solid.

2-Nitrobenzofuran (113)



M.p. = 135–137 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.8 Hz, 1H), 7.68 (s, 1H), 7.65–7.56 (m, 2H), 7.43 (ddd, *J* = 8.2, 6.0, 2.1 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 153.3 (C_q), 129.9 (CH), 125.7 (C_q), 125.2 (CH), 123.9 (CH), 112.6 (CH), 107.1 (CH).

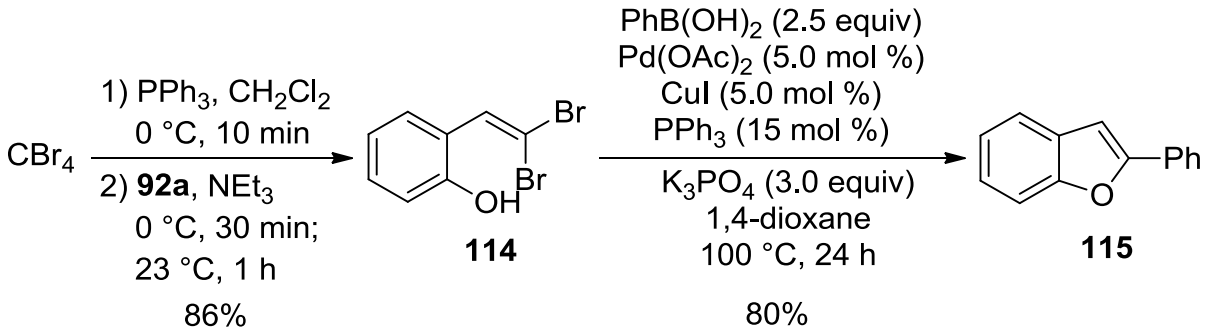
IR (neat): 3152, 2925, 1511, 1366, 1243, 751 cm^{-1}.

MS (EI) m/z (relative intensity):163 ([M^+] 80), 133 (100), 105 (50), 89 (85), 77 (45), 63 (63), 51 (25).

HR-MS (EI) m/z calcd for $C_8H_5NO_3^+$ [M^+] 163.0269, found 163.0273.

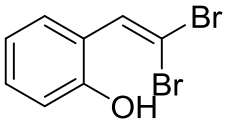
The analytical data are in accordance with those reported in the literature.[223]

d) Synthesis of 2-Phenylbenzofuran (115)



A literature procedure was used for the synthesis of **114**:[170] To a 250 mL flask were added PPh_3 (15.7 g, 60 mmol) and CH_2Cl_2 (60 mL). The mixture was cooled to 0 °C, after which CBr_4 (9.95 g, 30 mmol) dissolved in CH_2Cl_2 (30 mL) was added and stirred for 10 min. NEt_3 (6.07 g, 60 mmol) was added dropwise and stirred for an additional 5 minutes, after which **92a** (1.22 g, 10 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The mixture was stirred for an additional 30 min at 0 °C, then warmed to 23 °C and stirred for 1 h. To the reaction was added saturated aqueous NH_4Cl solution (50 mL). The phases were then separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were concentrated to approximately 10% of the original volume. The residue was dissolved in Et_2O (100 mL) and filtered over a pad of celite. The resulting solution was concentrated and purified by column chromatography on silica gel (*n*-pentane/EtOAc: 5/1) to yield **114** (2.39 g, 86%) as an off-white solid.

2-(2,2-Dibromovinyl)phenol (114)



M.p. = 65–67 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.59–7.51 (m, 2H), 7.22 (ddd, J = 7.6, 1.6, 0.5 Hz, 1H), 6.96 (ddd, *J* = 7.6, 1.2, 0.5 Hz, 1H), 6.82 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.96 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 152.4 (C_q), 132.3 (CH), 130.1 (CH), 129.2 (CH), 122.8 (C_q), 120.7 (CH), 115.7 (CH), 92.1 (C_q).

IR (neat): 3394, 3031, 1601, 1453, 1247, 759 cm^{-1}.

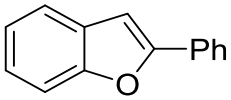
MS (EI) m/z (relative intensity): 276 ([M^+] 12), 197 (13), 169 (16), 118 (100), 89 (32), 63 (17).

HR-MS (EI) m/z calcd for $C_8H_6Br_2O^+$ [M^+] 275.8785, found 275.8790.

The analytical data are in accordance with those reported in the literature.[224]

To a 25 mL Schlenk tube were added **114** (139 mg, 0.5 mmol), $PhB(OH)_2$ (152 mg, 1.25 mmol), $Pd(OAc)_2$ (5.6 mg, 5.0 mol %), CuI (4.8 mg, 5.0 mol %), PPh_3 (20 mg, 15 mol %), K_3PO_4 (318 mg, 1.5 mmol), and 1,4-dioxane (5.0 mL) under N_2. The mixture was stirred at 100 °C for 24 h, extracted with Et_2O (50 mL) and brine (3 × 25 mL), and dried over Na_2SO_4. Purification by column chromatography on silica gel (*n*-pentane/Et_2O: 200/1) yielded 2-phenylbenzofuran (**115**) (78 mg, 80%) as a colorless solid.

2-Phenylbenzofuran (115)



M.p. = 120–121 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.94–7.85 (m, 2H), 7.63–7.58 (m, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.50–7.42 (m, 2H), 7.40–7.35 (m, 1H), 7.35–7.21 (m, 2H), 7.04 (s, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 155.8 (C_q), 154.8 (C_q), 130.4 (C_q), 129.1 (C_q), 128.7 (CH), 128.4 (CH), 124.8 (CH), 124.2 (CH), 122.8 (CH), 120.8 (CH), 111.1 (CH), 101.2 (CH).

IR (neat): 3052, 3036, 1455, 1260, 1021, 742 cm^{-1}.

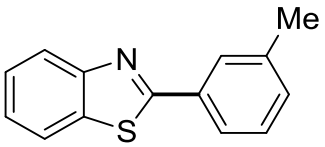
MS (EI) m/z (relative intensity): 194 ([M^+] 100), 165 (58), 139 (8), 115 (4), 97 (5).

HR-MS (EI) m/z calcd for $C_{14}H_{10}O^+$ [M^+] 194.0732, found 194.0735.

The analytical data are in accordance with those reported in the literature.[225]

9.4 Analytical Data for Photo-Induced Copper(I)-Catalyzed C(sp^2)–H Arylations

Synthesis of 2-(*m*-Tolyl)benzo[*d*]thiazole (94ab)



The general procedure **E** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol) and 1-iodo-3-methylbenzene (**19b**) (273 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 30/1 → 20/1) yielded **94ab** (41 mg, 73%) as a pale yellow liquid.

The general procedure **F** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol) and 1-iodo-3-methylbenzene (**19b**) (273 mg, 1.25 mmol). After stirring at 35 °C under 450-500 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 30/1 → 20/1) yielded **94ab** (28 mg, 50%) as a pale yellow liquid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.09 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.95 (s, 1H), 7.92–7.86 (m, 2H), 7.50 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.38 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 2H), 7.31 (dd, *J* = 7.6, 1.8 Hz, 1H), 2.45 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 168.3 (C_q), 154.1 (C_q), 138.8 (C_q), 135.0 (C_q), 133.5 (C_q), 131.8 (CH), 128.9 (CH), 127.9 (CH), 126.2 (CH), 125.1 (CH), 124.8 (CH), 123.1 (CH), 121.6 (CH), 21.3 (CH_3).

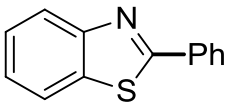
IR (neat): 3058, 2919, 2862, 1509, 1435, 1313, 1172, 757 cm^{-1}.

MS (EI) m/z (relative intensity): 225 ([M^+] 100), 210 (3), 197 (3), 165 (4), 108 (12), 82 (7), 69 (15).

HR-MS (EI) m/z calcd for $C_{14}H_{11}NS^+$ [M^+] 225.0612, found 225.0609.

The analytical data are in accordance with those reported in the literature.[226]

Synthesis of 2-Phenylbenzo[*d*]thiazole (94aa)



The general procedure **E** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol) and iodobenzene (**19a**) (255 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 30/1 → 20/1) yielded **94aa** (37 mg, 70%) as a pale yellow solid.

M. p. = 112–113 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.14–8.07 (m, 3H), 7.91 (ddd, *J* = 8.0, 1.2, 0.6 Hz, 1H), 7.53–7.47 (m, 4H), 7.39 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 168.0 (C_q), 154.1 (C_q), 135.1 (C_q), 133.6 (C_q), 130.9 (CH), 129.0 (CH), 127.5 (CH), 126.3 (CH), 125.2 (CH), 123.2 (CH), 121.6 (CH).

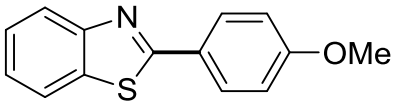
IR (neat): 3065, 3020, 1556, 1478, 1434, 1226, 963, 765 cm^{-1}.

MS (EI) m/z (relative intensity): 211 ([M^+] 100), 184 (8), 167 (3), 134 (5), 108 (30), 84 (25).

HR-MS (EI) m/z calcd for $C_{13}H_9NS^+$ [M^+] 211.0456, found 211.0461.

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

Synthesis of 2-(4-Methoxyphenyl)benzo[*d*]thiazole (94ac)



The general procedure **E** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol) and 1-iodo-4-methoxybenzene (**19c**) (293 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 15/1 → 10/1) yielded **94ac** (38 mg, 63%) as a colorless solid.

M. p. = 118–120 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.07–8.00 (m, 3H), 7.88 (ddd, *J* = 8.0, 1.2, 0.6 Hz, 1H), 7.47 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H), 7.35 (ddd, *J* = 7.9, 7.2, 1.2 Hz, 1H), 7.02–6.99 (m, 2H), 3.88 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 167.8 (C_q), 161.9 (C_q), 154.2 (C_q), 134.9 (C_q), 129.1 (CH), 126.5 (C_q), 126.2 (CH), 124.8 (CH), 122.8 (CH), 121.5 (CH), 114.4 (CH), 55.5 (CH_3).

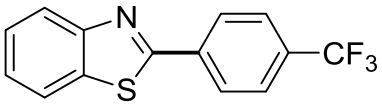
IR (neat): 3063, 2995, 2837, 1605, 1485, 1259, 832, 757 cm^{-1}.

MS (EI) m/z (relative intensity): 241 ([M^+] 100), 226 (35), 198 (33), 154 (8), 108 (6), 84 (8).

HR-MS (EI) m/z calcd for $C_{14}H_{11}NOS^+$ [M^+] 241.0561, found 241.0566.

The analytical data are in accordance with those reported in the literature.[227]

Synthesis of 2-{4-(Trifluoromethyl)phenyl}benzo[*d*]thiazole (94ad)



The general procedure **E** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol) and 1-iodo-4-(trifluoromethyl)benzene (**19d**) (340 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 40/1 → 30/1) yielded **94ad** (49 mg, 70%) as a colorless solid.

M. p. = 158–159 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.24–8.18 (m, 2H), 8.11 (ddd, *J* = 8.2, 1.2, 0.7 Hz, 1H), 7.94 (ddd, *J* = 8.0, 1.3, 0.7 Hz, 1H), 7.77–7.74 (m, 2H), 7.53 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H), 7.44 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.0 (C_q), 154.1 (C_q), 136.8 (d, $J_{C\text{-}F}$ = 2 Hz, C_q), 135.2 (C_q), 132.5 (q, $J_{C\text{-}F}$ = 33 Hz, C_q), 127.8 (CH), 126.6 (CH), 126.0 (q, $J_{C\text{-}F}$ = 4 Hz, CH), 125.8 (CH), 123.8 (d, $J_{C\text{-}F}$ = 272 Hz, C_q), 123.6 (CH), 121.7 (CH).

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -62.9 (s).

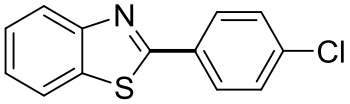
IR (neat): 3059, 1617, 1484, 1324, 1110, 1067, 759 cm^{-1}.

MS (EI) m/z (relative intensity): 279 ([M^+] 100), 260 (10), 210 (5), 170 (3), 140 (5), 108 (28), 82 (10).

HR-MS (EI) m/z calcd for $C_{14}H_8F_3NS^+$ [M^+] 279.0330, found 279.0321.

The analytical data are in accordance with those reported in the literature.[227]

Synthesis of 2-(4-Chlorophenyl)benzo[*d*]thiazole (94ae)



The general procedure **E** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol) and 1-chloro-4-iodobenzene (**19e**) (298 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 40/1 → 30/1) yielded **94ae** (39 mg, 63%) as a colorless solid.

M. p. = 113–114 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.05 (ddd, *J* = 8.2, 1.2, 0.6 Hz, 1H), 8.03–7.99 (m, 2H), 7.89 (ddd, *J* = 8.0, 1.3, 0.6 Hz, 1H), 7.51–7.43 (m, 3H), 7.38 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.6 (C_q), 154.1 (C_q), 137.0 (C_q), 135.1 (C_q), 132.1 (C_q), 129.3 (CH), 128.7 (CH), 126.5 (CH), 125.4 (CH), 123.3 (CH), 121.6 (CH).

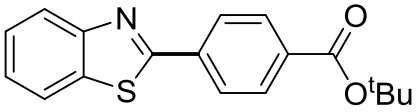
IR (neat): 3056, 3032, 1597, 1507, 1475, 1091, 829, 756 cm^{-1}.

MS (EI) m/z (relative intensity): 245 ([M^+] 100), 210 (12), 183 (5), 137 (5), 108 (25), 69 (20).

HR-MS (EI) m/z calcd for $C_{13}H_8ClNS^+$ [M^+] 245.0066, found 245.0064.

The analytical data are in accordance with those reported in the literature.[228]

Synthesis of *tert*-Butyl 4-(benzo[*d*]thiazol-2-yl)benzoate (94af)



The general procedure **E** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol) and *tert*-butyl 4-iodobenzoate (**19f**) (380 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/CH_2Cl_2/Et_2O: 1/1/0 → 1/2/0 → 10/0/1) yielded **94af** (36 mg, 46%) as a colorless solid.

M. p. = 111–112 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.17–8.07 (m, 5H), 7.93 (ddd, *J* = 8.0, 1.3, 0.7 Hz, 1H), 7.52 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H), 1.63 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.8 (C_q), 165.0 (C_q), 154.1 (C_q), 137.0 (C_q), 135.2 (C_q), 134.0 (C_q), 130.1 (CH), 127.3 (CH), 126.5 (CH), 125.6 (CH), 123.5 (CH), 121.7 (CH), 81.5 (C_q), 28.2 (CH_3).

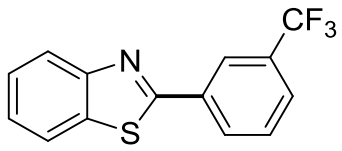
IR (neat): 3059, 2976, 2931, 1706, 1482, 1292, 1165, 1108, 755 cm^{-1}.

MS (EI) m/z (relative intensity): 311 ([M^+] 28), 255 (100), 238 (20), 210 (16), 183 (5), 139 (6), 108 (6), 57 (10).

HR-MS (EI) m/z calcd for $C_{18}H_{17}NO_2S^+$ [M^+] 311.0980, found 311.0977.

The analytical data are in accordance with those reported in the literature.[229]

Synthesis of 2-{3-(Trifluoromethyl)phenyl}benzo[*d*]thiazole (94ag)



The general procedure **E** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol) and 1-iodo-3-(trifluoromethyl)benzene (**19g**) (340 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 40/1 → 30/1) yielded **94ag** (42 mg, 60%) as a pale yellow solid.

M. p. = 91–93 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.42–8.36 (m, 1H), 8.27–8.23 (m, 1H), 8.15–8.07 (m, 1H), 7.94 (ddd, *J* = 8.0, 1.3, 0.7 Hz, 1H), 7.77–7.73 (m, 1H), 7.68–7.59 (m, 1H), 7.53 (ddd, *J* = 8.3, 7.3, 1.3 Hz, 1H), 7.43 (ddd, *J* = 8.2, 7.3, 1.3 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.1 (C_q), 154.0 (C_q), 135.1 (C_q), 134.4 (C_q), 131.6 (d, $J_{C\text{-}F}$ = 33 Hz, C_q), 130.7 (CH), 129.6 (CH), 127.3 (q, $J_{C\text{-}F}$ = 4 Hz, CH), 126.6 (CH), 125.7 (CH), 124.2 (q, $J_{C\text{-}F}$ = 4 Hz, CH), 123.8 (d, $J_{C\text{-}F}$ = 273 Hz, C_q), 123.5 (CH), 121.7 (CH).

^{19}F-NMR (283 MHz, $CDCl_3$): δ = -62.8 (s).

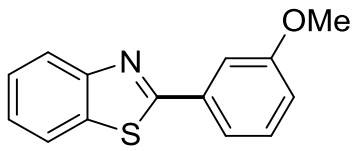
IR (neat): 3064, 2925, 2854, 1613, 1420, 1330, 1168, 1114, 757 cm^{-1}.

MS (EI) m/z (relative intensity): 279 ([M^+] 100), 258 (5), 210 (4), 159 (5), 108 (28), 69 (23).

HR-MS (ESI) m/z calcd for $C_{14}H_9F_3NS^+$ [M+H^+] 208.0408, found 208.0405.

The analytical data are in accordance with those reported in the literature.[230]

Synthesis of 2-(3-Methoxyphenyl)benzo[*d*]thiazole (94ah)



The general procedure **E** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol) and 1-iodo-3-methoxybenzene (**19h**) (293 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 10/1) yielded **94ah** (42 mg, 70%) as a pale yellow solid.

The general procedure **F** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol) and 1-iodo-3-methoxybenzene (**19h**) (293 mg, 1.25 mmol). After stirring at 35 °C under 450-500 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 10/1) yielded **94ah** (29 mg, 48%) as a pale yellow liquid.

M. p. = 82–83 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.08 (ddd, J = 8.2, 1.2, 0.6 Hz, 1H), 7.91 (ddd, J = 8.0, 1.3, 0.6 Hz, 1H), 7.70–7.62 (m, 2H), 7.50 (ddd, J = 8.2, 7.2, 1.3 Hz, 1H), 7.43–7.36 (m, 2H), 7.05 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H), 3.92 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.9 (C_q), 160.1 (C_q), 154.1 (C_q), 135.1 (C_q), 134.9 (C_q), 130.0 (CH), 126.3 (CH), 125.2 (CH), 123.2 (CH), 121.6 (CH), 120.2 (CH), 117.3 (CH), 112.0 (CH), 55.5 (CH_3).

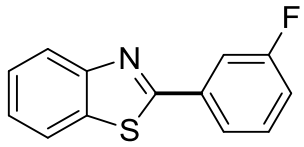
IR (neat): 3066, 2998, 2959, 2833, 1597, 1433, 1265, 1048, 758 cm^{-1}.

MS (EI) m/z (relative intensity): 241 ([M^+] 100), 211 (45), 198 (10), 154 (8), 108 (22), 69 (25).

HR-MS (ESI) m/z calcd for $C_{14}H_{12}NOS^+$ [M+H^+] 242.0640, found 242.0636.

The analytical data are in accordance with those reported in the literature.[231]

Synthesis of 2-(3-Fluorophenyl)benzo[*d*]thiazole (94ai)



The general procedure **E** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol) and 1-fluoro-3-iodobenzene (**19i**) (278 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 30/1) yielded **94ai** (45 mg, 79%) as a pale yellow solid.

M. p. = 86–87 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, J = 8.3 Hz, 1H), 7.96–7.89 (m, 1H), 7.87–7.82 (m, 2H), 7.57–7.36 (m, 3H), 7.19 (ddd, J = 8.4, 8.4, 2.5 Hz, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.4 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 163.0 (d, $J_{C\text{-}F}$ = 248 Hz, C_q), 154.0 (C_q), 135.7 (d, $J_{C\text{-}F}$ = 8 Hz, C_q), 135.1 (C_q), 130.6 (d, $J_{C\text{-}F}$ = 8 Hz, CH), 126.5 (CH), 125.5 (CH), 123.5 (CH), 123.3 (d, $J_{C\text{-}F}$ = 3 Hz, CH), 121.7 (CH), 117.8 (d, $J_{C\text{-}F}$ = 22 Hz, CH), 114.3 (d, $J_{C\text{-}F}$ = 24 Hz, CH).

^{19}F-NMR (283 MHz, $CDCl_3$): δ = -112.1 (ddd, J = 9.8, 8.5, 5.7 Hz).

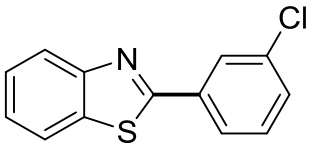
IR (neat): 3055, 3029, 1614, 1587, 1445, 1268, 755 cm^{-1}.

MS (EI) m/z (relative intensity): 229 ([M^+] 100), 202 (6), 185 (4), 108 (27), 82 (9), 69 (16).

HR-MS (EI) m/z calcd for $C_{13}H_8FNS^+$ [M^+] 229.0361, found 229.0360.

The analytical data are in accordance with those reported in the literature.[227]

Synthesis of 2-(3-Chlorophenyl)benzo[*d*]thiazole (94aj)



The general procedure **E** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol) and 1-chloro-3-iodobenzene (**19j**) (298 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 30/1) yielded **94aj** (49 mg, 80%) as a pale yellow solid.

The general procedure **F** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol) and 1-chloro-3-iodobenzene (**19j**) (298 mg, 1.25 mmol). After stirring at 35 °C under 450-500 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 30/1) yielded **94aj** (26 mg, 42%) as a pale yellow liquid.

M. p. = 95–96 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.14–8.12 (m, 1H), 8.09 (ddd, J = 8.2, 1.2, 0.7 Hz, 1H), 7.97–7.90 (m, 2H), 7.52 (ddd, J = 8.3, 7.2, 1.2 Hz, 1H), 7.48–7.39 (m, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.3 (C_q), 154.0 (C_q), 135.3 (C_q), 135.2 (C_q), 135.1 (C_q), 130.8 (CH), 130.2 (CH), 127.4 (CH), 126.5 (CH), 125.7 (CH), 125.6 (CH), 123.5 (CH), 121.7 (CH).

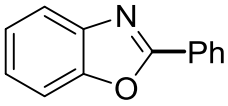
IR (neat): 3054, 1590, 1571, 1424, 1232, 759, 733 cm^{-1}.

MS (EI) m/z (relative intensity): 245 ([M^+] 100), 210 (16), 183 (5), 137 (6), 108 (25), 82 (12).

HR-MS (EI) m/z calcd for $C_{13}H_8ClNS^+$ [M^+] 245.0066, found 245.0060.

The analytical data are in accordance with those reported in the literature.[232]

Synthesis of 2-Phenylbenzo[*d*]oxazole (94ba)



The general procedure **E** was followed using benzo[*d*]oxazole (**93b**) (30 mg, 0.25 mmol) and iodobenzene (**19a**) (255 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 15/1 → 10/1) yielded **94ba** (31 mg, 64%) as a pale yellow solid.

M. p. = 101–102 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.30–8.24 (m, 2H), 7.82–7.76 (m, 1H), 7.62–7.56 (m, 1H), 7.56–7.49 (m, 3H), 7.39–7.33 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.0 (C_q), 150.8 (C_q), 142.1 (C_q), 131.5 (CH), 128.9 (CH), 127.6 (CH), 127.2 (C_q), 125.1 (CH), 124.6 (CH), 120.0 (CH), 110.6 (CH).

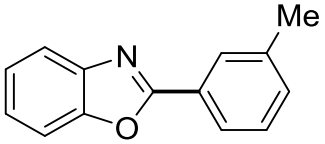
IR (neat): 3062, 3051, 2922, 1618, 1553, 1448, 1242, 1054, 743 cm^{-1}.

MS (EI) m/z (relative intensity): 195 ([M^+] 100), 167 (30), 139 (6), 92 (10), 77 (13), 63 (22).

HR-MS (EI) m/z calcd for $C_{13}H_9NO^+$ [M^+] 195.0684, found 195.0679.

The analytical data are in accordance with those reported in the literature.[233]

Synthesis of 2-(*m*-Tolyl)benzo[*d*]oxazole (94bb)



The general procedure **E** was followed using benzo[*d*]oxazole (**93b**) (30 mg, 0.25 mmol) and 1-iodo-3-methylbenzene (**19b**) (273 mg, 1.25 mmol). After stirring at 28 °C under 254 nm

irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 20/1 → 15/1) yielded **94bb** (31 mg, 59%) as a pale yellow solid.

M. p. = 80–82 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.11–8.10 (m, 1H), 8.06 (ddd, J = 7.6, 1.8, 1.3 Hz, 1H), 7.81–7.75 (m, 1H), 7.62–7.55 (m, 1H), 7.45–7.39 (m, 1H), 7.38–7.32 (m, 3H), 2.46 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.2 (C_q), 150.7 (C_q), 142.1 (C_q), 138.7 (C_q), 132.3 (CH), 128.8 (CH), 128.2 (CH), 127.0 (C_q), 125.0 (CH), 124.8 (CH), 124.5 (CH), 120.0 (CH), 110.5 (CH), 21.3 (CH_3).

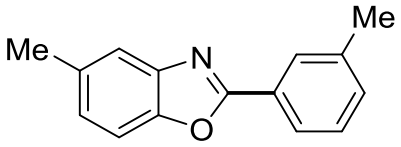
IR (neat): 3056, 2956, 2921, 1616, 1552, 1453, 1244, 744 cm^{-1}.

MS (EI) m/z (relative intensity): 209 ([M^+] 100), 180 (15), 152 (5), 116 (7), 91 (15), 63 (20).

HR-MS (EI) m/z calcd for $C_{14}H_{11}NO^+$ [M^+] 209.0841, found 209.0837.

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

Synthesis of 5-Methyl-2-(*m*-tolyl)benzo[*d*]oxazole (94cb)



The general procedure **E** was followed using 5-methylbenzo[*d*]oxazole (**93c**) (33 mg, 0.25 mmol) and 1-iodo-3-methylbenzene (**19b**) (273 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 20/1 → 15/1) yielded **94cb** (40 mg, 72%) as a yellow solid.

The general procedure **F** was followed using 5-methylbenzo[*d*]oxazole (**93c**) (33 mg, 0.25 mmol) and 1-iodo-3-methylbenzene (**19b**) (273 mg, 1.25 mmol). After stirring at 35 °C under 450-500 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 20/1 → 15/1) yielded **94cb** (12 mg, 21%) as a pale yellow liquid.

M. p. = 85–86 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.09–8.08 (m, 1H), 8.05–8.02 (m, 1H), 7.56–7.55 (m, 1H), 7.45 (ddd, *J* = 8.3, 0.3 Hz, 1H), 7.43–7.38 (m, 1H), 7.34 (ddd, *J* = 7.6, 1.9, 1.3 Hz, 1H), 7.17–7.14 (m, 1H), 2.49 (s, 3H), 2.46 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.3 (C_q), 149.0 (C_q), 142.3 (C_q), 138.7 (C_q), 134.3 (C_q), 132.2 (CH), 128.8 (CH), 128.1 (CH), 127.2 (C_q), 126.1 (CH), 124.7 (CH), 119.9 (CH), 109.9 (CH), 21.5 (CH_3), 21.3 (CH_3).

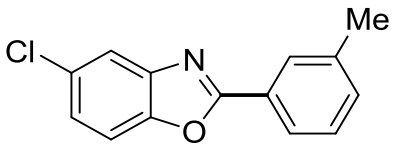
IR (neat): 3020, 2921, 2862, 1552, 1474, 1263, 1181, 1057, 791 cm^{-1}.

MS (EI) m/z (relative intensity): 223 ([M^+] 100), 194 (5), 106 (5), 91 (4), 78 (21), 51 (7).

HR-MS (ESI) m/z calcd for $C_{15}H_{14}NO^+$ [M+H^+] 224.1075, found 224.1072.

The analytical data are in accordance with those reported in the literature.[234]

Synthesis of 5-Chloro-2-(*m*-tolyl)benzo[*d*]oxazole (94db)



The general procedure **E** was followed using 5-chlorobenzo[*d*]oxazole (**93d**) (38 mg, 0.25 mmol) and 1-iodo-3-methylbenzene (**19b**) (273 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 40/1 → 30/1) yielded **94db** (20 mg, 33%) as a pale yellow solid.

M. p. = 114–115 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.08–8.06 (m, 1H), 8.04–8.01 (m, 1H), 7.73 (dd, *J* = 2.1, 0.5 Hz, 1H), 7.49 (dd, *J* = 8.6, 0.5 Hz, 1H), 7.44–7.39 (m, 1H), 7.39–7.35 (m, 1H), 7.31 (dd, *J* = 8.6, 2.1 Hz, 1H), 2.46 (s, 3H).

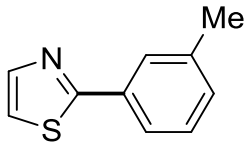
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.6 (C_q), 149.3 (C_q), 143.3 (C_q), 138.8 (C_q), 132.8 (CH), 130.0 (C_q), 128.9 (CH), 128.3 (CH), 126.6 (C_q), 125.3 (CH), 124.9 (CH), 119.9 (CH), 111.2 (CH), 21.3 (CH_3).

IR (neat): 3090, 2923, 2856, 1552, 1447, 1265, 1056, 804, 718 cm^{-1}.

MS (EI) m/z (relative intensity): 243 (M^+ 100), 215 (3), 180 (5), 152 (3), 121 (6), 91 (18), 63 (25).

HR-MS (ESI) m/z calcd for $C_{14}H_{11}ClNO^+$ [M+H^+] 244.0529, found 244.0519.

Synthesis of 2-(*m*-Tolyl)thiazole (94eb)



The general procedure **E** was followed using thiazole (**93e**) (21 mg, 0.25 mmol) and 1-iodo-3-methylbenzene (**19b**) (273 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 20/1) yielded **94eb** (22 mg, 50%) as a yellow oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 3.3 Hz, 1H), 7.82–7.81 (m, 1H), 7.75 (ddd, *J* = 7.7, 1.8, 1.2 Hz, 1H), 7.35–7.31 (m, 2H), 7.24 (ddd, *J* = 7.6, 1.8, 1.1 Hz, 1H), 2.42 (s, 3H).

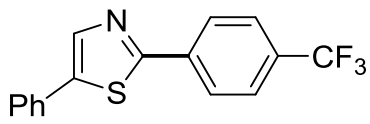
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 168.6 (C_q), 143.6 (CH), 138.7 (C_q), 133.5 (C_q), 130.8 (CH), 128.8 (CH), 127.1 (CH), 123.8 (CH), 118.7 (CH), 21.3 (CH_3).

IR (neat): 3080, 2921, 2861, 1606, 1485, 1264, 1140, 785, 692 cm^{-1}.

MS (EI) m/z (relative intensity): 175 ([M^+] 32), 131 (5), 116 (5), 104 (10), 91 (100), 58 (54).

HR-MS (ESI) m/z calcd for $C_{10}H_{10}NS^+$ [M+H^+] 176.0534, found 176.0528.

Synthesis of 5-Phenyl-2-{4-(trifluoromethyl)phenyl}thiazole (94fd)



The general procedure **E** was followed using 5-phenylthiazole (**93f**) (40 mg, 0.25 mmol) and 1-iodo-4-(trifluoromethyl)benzene (**19d**) (340 mg, 1.25 mmol). After stirring at 28 °C under

254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 15/1) yielded **94fd** (49 mg, 64%) as a pale yellow solid.

M. p. = 155–157 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.10 (s, 1H), 8.08–8.06 (m, 2H), 7.75–7.69 (m, 2H), 7.66–7.59 (m, 2H), 7.48–7.41 (m, 2H), 7.40–7.34 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.1 (C_q), 140.6 (C_q), 139.6 (CH), 136.8 (C_q), 131.5 (d, J_{C-F} = 33 Hz, C_q), 131.0 (C_q), 129.2 (CH), 128.7 (CH), 126.8 (CH), 126.5 (CH), 126.0 (q, J_{C-F} = 4 Hz, CH), 123.9 (d, J_{C-F} = 272 Hz, C_q).

^{19}F-NMR (283 MHz, $CDCl_3$): δ = -62.8 (s).

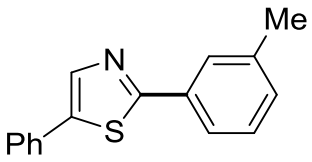
IR (neat): 3093, 3006, 2930, 1613, 1450, 1326, 1107, 757 cm^{-1}.

MS (EI) m/z (relative intensity): 305 ([M^+] 100), 286 (6), 171 (5), 134 (85), 90 (15), 77 (8).

HR-MS (ESI) m/z calcd for $C_{16}H_{11}F_3NS^+$ [M+H^+] 306.0564, found 306.0553.

The analytical data are in accordance with those reported in the literature.[46]

Synthesis of 5-Phenyl-2-(*m*-tolyl)thiazole (94fb)



The general procedure **E** was followed using 5-phenylthiazole (**93f**) (40 mg, 0.25 mmol) and 1-iodo-3-methylbenzene (**19b**) (273 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 10/1) yielded **94fb** (49 mg, 78%) as a yellow solid.

M. p. = 104–106 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.02 (s, 1H), 7.83–7.81 (m, 1H), 7.76 (ddd, *J* = 7.7, 1.8, 1.2 Hz, 1H), 7.64–7.58 (m, 2H), 7.46–7.39 (m, 2H), 7.38–7.31 (m, 2H), 7.27–7.23 (m, 1H), 2.44 (s, 3H).

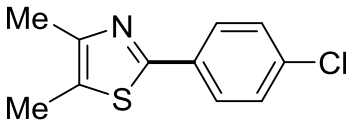
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 167.4 (C_q), 139.1 (C_q), 139.1 (CH), 138.8 (C_q), 133.6 (C_q), 131.4 (C_q), 130.8 (CH), 129.1 (CH), 128.9 (CH), 128.3 (CH), 126.9 (CH), 126.6 (CH), 123.6 (CH), 21.4 (CH_3).

IR (neat): 3065, 3029, 2916, 1599, 1447, 1143, 754, 683 cm^{-1}.

MS (EI) m/z (relative intensity): 251 ([M^+] 93), 134 (100), 108 (7), 90 (20), 77 (8).

HR-MS (EI) m/z calcd for $C_{16}H_{13}NS^+$ [M^+] 251.0769, found 251.0762.

Synthesis of 2-(4-Chlorophenyl)-4,5-dimethylthiazole (94ge)



The general procedure **E** was followed using 4,5-dimethylthiazole (**93g**) (28 mg, 0.25 mmol) and 1-chloro-4-iodobenzene (**19e**) (298 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 20/1) yielded **94ge** (35 mg, 63%) as a pale yellow solid.

M. p. = 92–93 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.82–7.78 (m, 2H), 7.39–7.35 (m, 2H), 2.39 (s, 3H), 2.38 (s, 3H).

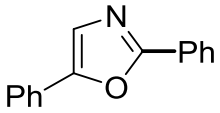
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 161.9 (C_q), 149.5 (C_q), 135.2 (C_q), 132.5 (C_q), 129.0 (CH), 127.3 (CH), 127.0 (C_q), 14.8 (CH_3), 11.5 (CH_3).

IR (neat): 2955, 2911, 2855, 1592, 1543, 1496, 1244, 1086, 839 cm^{-1}.

MS (EI) m/z (relative intensity): 223 ([M^+] 100), 190 (5), 155 (7), 137 (9), 86 (75), 71 (55).

HR-MS (EI) m/z calcd for $C_{11}H_{10}ClNS^+$ [M^+] 223.0222, found 223.0216.

Synthesis of 2,5-Diphenyloxazole (94ha)



The general procedure **E** was followed using 5-phenyloxazole (**93h**) (36 mg, 0.25 mmol) and iodobenzene (**19a**) (255 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 10/1 → 6/1) yielded **94ha** (41 mg, 74%) as a pale yellow solid.

M. p. = 70–71 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.14–8.10 (m, 2H), 7.76–7.72 (m, 2H), 7.52–7.43 (m, 6H), 7.38–7.33 (m, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 161.1 (C_q), 151.3 (C_q), 130.3 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 128.0 (C_q), 127.5 (C_q), 126.3 (CH), 124.2 (CH), 123.5 (CH).

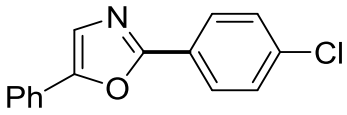
IR (neat): 3082, 3058, 3039, 588, 1480, 1134, 705, 685 cm^{-1}.

MS (EI) m/z (relative intensity): 221 ([M^+] 100), 193 (20), 165 (50), 116 (12), 105 (10), 77 (25).

HR-MS (EI) m/z calcd for $C_{15}H_{11}NO^+$ [M^+] 221.0841, found 221.0840.

The analytical data are in accordance with those reported in the literature.[235]

Synthesis of 2-(4-Chlorophenyl)-5-phenyloxazole (94he)



The general procedure **E** was followed using 5-phenyloxazole (**93h**) (36 mg, 0.25 mmol) and 1-chloro-4-iodobenzene (**19e**) (298 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 8/1 → 6/1) yielded **94he** (45 mg, 70%) as an off-white solid.

M. p. = 114–116 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.08–8.01 (m, 2H), 7.76–7.69 (m, 2H), 7.50–7.42 (m, 5H), 7.39–7.32 (m, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 160.2 (C_q), 151.5 (C_q), 136.4 (C_q), 129.1 (CH), 129.0 (CH), 128.6 (CH), 127.8 (C_q), 127.5 (CH), 125.9 (C_q), 124.2 (CH), 123.5 (CH).

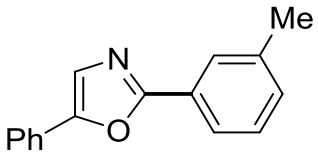
IR (neat): 3084, 3066, 3040, 1730, 1603, 1477, 1243, 1090, 833 cm^{-1}.

MS (EI) m/z (relative intensity): 255 ([M^+] 100), 227 (9), 200 (17), 165 (65), 123 (17), 105 (25), 77 (37).

HR-MS (ESI) m/z calcd for $C_{15}H_{11}ClNO^+$ [M+H^+] 256.0529, found 256.0526.

The analytical data are in accordance with those reported in the literature.[190]

Synthesis of 5-Phenyl-2-(*m*-tolyl)oxazole (94hb)



The general procedure **E** was followed using 5-phenyloxazole (**93h**) (36 mg, 0.25 mmol) and 1-iodo-3-methylbenzene (**19b**) (273 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 10/1 → 7/1) yielded **94hb** (46 mg, 78%) as a pale yellow solid.

M. p. = 88–90 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.95 –7.94 (m, 1H), 7.93–7.91 (m, 1H), 7.75–7.72 (m, 2H), 7.48–7.43 (m, 3H), 7.40–7.32 (m, 2H), 7.28 (ddd, *J* = 7.6, 1.8, 1.2 Hz, 1H), 2.45 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 161.3 (C_q), 151.1 (C_q), 138.6 (C_q), 131.1 (CH), 128.9 (CH), 128.7 (CH), 128.4 (CH), 128.1 (C_q), 127.3 (C_q), 126.8 (CH), 124.2 (CH), 123.4 (CH), 123.4 (CH), 21.4 (CH_3).

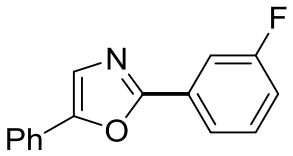
IR (neat): 3059, 3038, 2919, 1611, 1542, 1132, 725 cm^{-1}.

MS (EI) m/z (relative intensity): 235 ([M^+] 100), 207 (15), 179 (13), 165 (35), 130 (10), 77 (22).

HR-MS (ESI) m/z calcd for $C_{16}H_{13}NO^+$ [M-H$^+$] 235.0997, found 235.0995.

The analytical data are in accordance with those reported in the literature.[236]

Synthesis of 2-(3-Fluorophenyl)-5-phenyloxazole (94hi)



The general procedure **E** was followed using 5-phenyloxazole (**93h**) (36 mg, 0.25 mmol) and 1-fluoro-3-iodobenzene (**19i**) (278 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 15/1 → 10/1) yielded **94hi** (42 mg, 70%) as a pale yellow solid.

M. p. = 68–70 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.90 (ddd, J = 7.8, 1.5, 1.0 Hz, 1H), 7.80 (dddd, J = 9.6, 2.6, 1.5, 0.4 Hz, 1H), 7.75–7.70 (m, 2H), 7.50–7.42 (m, 4H), 7.40–7.32 (m, 1H), 7.16 (ddd, J = 8.4, 2.6, 1.0 Hz, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 162.9 (d, $J_{C\text{-}F}$ = 246 Hz, C_q), 160.0 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 151.7 (C_q), 130.5 (d, $J_{C\text{-}F}$ = 8 Hz, CH), 129.4 (d, $J_{C\text{-}F}$ = 9 Hz, C_q), 129.0 (CH), 128.7 (CH), 127.8 (C_q), 124.3 (CH), 123.6 (CH), 122.0 (d, $J_{C\text{-}F}$ = 3 Hz, CH), 117.2 (d, $J_{C\text{-}F}$ = 21 Hz, CH), 113.2 (d, $J_{C\text{-}F}$ = 24 Hz, CH).

^{19}F-NMR (283 MHz, $CDCl_3$): δ = -(112.1–112.2) (m).

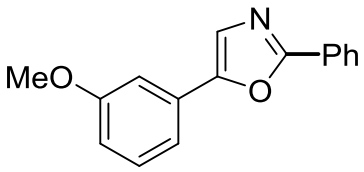
IR (neat): 3121, 3072, 3041, 1731, 1687, 1592, 1486, 1195, 728 cm^{-1}.

MS (EI) m/z (relative intensity): 239 ([M$^+$] 100), 211 (20), 183 (55), 134 (10), 105 (20), 77 (27).

HR-MS (EI) m/z calcd for $C_{15}H_{10}FNO^+$ [M$^+$] 239.0746, found 239.0739.

The analytical data are in accordance with those reported in the literature.[237]

Synthesis of 5-(3-Methoxyphenyl)-2-phenyloxazole (94ia)



The general procedure **E** was followed using 5-(3-methoxyphenyl)oxazole (**93i**) (44 mg, 0.25 mmol) and iodobenzene (**19a**) (255 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 4/1 → 3/1) yielded **94ia** (43 mg, 68%) as a colorless solid.

M. p. = 91–92 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.15–8.09 (m, 2H), 7.53–7.45 (m, 3H), 7.44 (s, 1H), 7.37 (ddd, *J* = 7.8, 7.8, 0.5 Hz, 1H), 7.32 (ddd, *J* = 7.7, 1.4, 1.4 Hz, 1H), 7.26–7.25 (m, 1H), 6.90 (ddd, *J* = 7.9, 2.6, 1.3 Hz, 1H), 3.89 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.1 (C_q), 160.0 (C_q), 151.1 (C_q), 130.3 (CH), 130.1 (CH), 129.2 (C_q), 128.8 (CH), 127.4 (C_q), 126.3 (CH), 123.8 (CH), 116.7 (CH), 114.0 (CH), 109.7 (CH), 55.4 (CH_3).

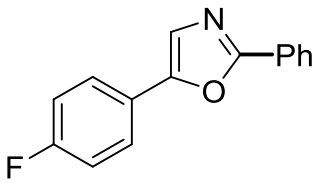
IR (neat): 3115, 3060, 3001, 2835, 1594, 1487, 1221, 1043, 711 cm^{-1}.

MS (EI) m/z (relative intensity): 251 ([M^+] 100), 208 (12), 181 (20), 165 (12), 153 (10), 116 (13), 77 (22).

HR-MS (EI) m/z calcd for $C_{16}H_{13}NO_2^+$ [M^+] 251.0946, found 251.0945.

The analytical data are in accordance with those reported in the literature.[238]

Synthesis of 5-(4-Fluorophenyl)-2-phenyloxazole (94ja)



The general procedure **E** was followed using 5-(4-fluorophenyl)oxazole (**93j**) (41 mg, 0.25 mmol) and iodobenzene (**19a**) (255 mg, 1.25 mmol). After stirring at 28 °C under

254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 7/1 → 5/1) yielded **94ja** (37 mg, 62%) as a colorless solid.

M. p. = 92–93 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.14–8.07 (m, 2H), 7.75–7.66 (m, 2H), 7.54–7.43 (m, 3H), 7.39 (s, 1H), 7.20–7.10 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.7 (d, $J_{C\text{-}F}$ = 249 Hz, C_q), 161.1 (C_q), 150.4 (C_q), 130.4 (CH), 128.8 (CH), 127.4 (C_q), 126.3 (CH), 126.1 (d, $J_{C\text{-}F}$ = 8 Hz, CH), 124.4 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 123.1 (d, $J_{C\text{-}F}$ = 2 Hz, CH), 116.1 (d, $J_{C\text{-}F}$ = 22 Hz, CH).

^{19}F-NMR (283 MHz, $CDCl_3$): δ = -112.2 (tt, J = 8.5, 5.2 Hz).

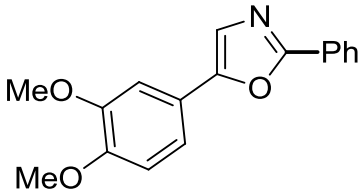
IR (neat): 3130, 3083, 3055, 1499, 1231, 1132, 952, 823 cm^{-1}.

MS (EI) m/z (relative intensity): 239 ([M^+] 100), 211 (12), 183 (50), 123 (10), 116 (11), 107 (15), 89 (16).

HR-MS (EI) m/z calcd for $C_{15}H_{10}FNO^+$ [M^+] 239.0746, found 239.0743.

The analytical data are in accordance with those reported in the literature.[238]

Synthesis of 5-(3,4-Dimethoxyphenyl)-2-phenyloxazole (94ka)



The general procedure **E** was followed using 5-(3,4-dimethoxyphenyl)oxazole (**93k**) (51 mg, 0.25 mmol) and iodobenzene (**19a**) (255 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 2/1 → 1/1) yielded **94ka** (37 mg, 53%) as a yellow solid.

M. p. = 95–96 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.13–8.07 (m, 2H), 7.52–7.42 (m, 3H), 7.34 (s, 1H), 7.31 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.20 (d, *J* = 2.0 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 3.98 (s, 3H), 3.93 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.6 (C_q), 151.3 (C_q), 149.5 (C_q), 149.4 (C_q), 130.2 (CH), 128.8 (CH), 127.5 (C_q), 126.2 (CH), 122.3 (CH), 121.1 (C_q), 117.3 (CH), 111.5 (CH), 107.5 (CH), 56.1 (CH_3), 56.0 (CH_3).

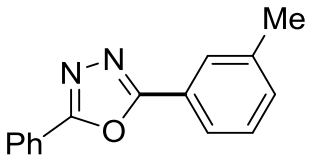
IR (neat): 3000, 2957, 2935, 2835, 1595, 1504, 1251, 1024, 710 cm^{-1}.

MS (EI) m/z (relative intensity): 281 ([M^+] 100), 266 (35), 238 (15), 195 (5), 165 (6), 107 (14), 77 (12).

HR-MS (EI) m/z calcd for $C_{17}H_{15}NO_3^+$ [M^+] 281.1052, found 281.1050.

The analytical data are in accordance with those reported in the literature.[176]

Synthesis of 2-Phenyl-5-(*m*-tolyl)-1,3,4-oxadiazole (94lb)



The general procedure **E** was followed using 2-phenyl-1,3,4-oxadiazole (**93l**) (37 mg, 0.25 mmol) and 1-iodo-3-methylbenzene (**19b**) (273 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 7/1 → 5/1) yielded **94lb** (32 mg, 54%) as a pale yellow solid.

M. p. = 112–113 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.18–8.12 (m, 2H), 7.98–7.97 (m, 1H), 7.95–7.92 (m, 1H), 7.59–7.50 (m, 3H), 7.45–7.40 (m, 1H), 7.38–7.35 (m, 1H), 2.46 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.7 (C_q), 164.5 (C_q), 138.9 (C_q), 132.5 (CH), 131.6 (CH), 129.0 (CH), 128.9 (CH), 127.4 (CH), 126.9 (CH), 124.1 (CH), 124.0 (C_q), 123.8 (C_q), 21.3 (CH_3).

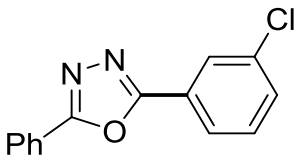
IR (neat): 3057, 2922, 2858, 1548, 1474, 1274, 1068, 724 cm^{-1}.

MS (EI) m/z (relative intensity): 236 ([M^+] 90), 178 (31), 165 (100), 119 (59), 105 (46), 91 (45), 77 (48).

HR-MS (ESI) m/z calcd for $C_{15}H_{13}N_2O^+$ [M+H^+] 237.1028, found 237.1023.

The analytical data are in accordance with those reported in the literature.[239]

Synthesis of 2-(3-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (94lj)



The general procedure **E** was followed using 2-phenyl-1,3,4-oxadiazole (**93l**) (37 mg, 0.25 mmol) and 1-chloro-3-iodobenzene (**19j**) (298 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 7/1 → 5/1) yielded **94lj** (33 mg, 51%) as a pale yellow solid.

M. p. = 119–121 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.17–8.11 (m, 3H), 8.07–8.02 (m, 1H), 7.60–7.51 (m, 4H), 7.48 (ddd, *J* = 8.1, 7.5, 0.5 Hz, 1H).

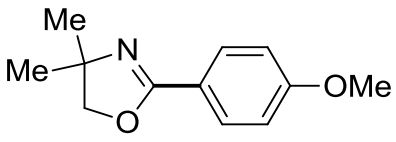
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.9 (C_q), 163.4 (C_q), 135.2 (C_q), 131.9 (CH), 131.7 (CH), 130.4 (CH), 129.1 (CH), 127.0 (CH), 126.9 (CH), 125.6 (C_q), 125.0 (CH), 123.7 (C_q).

IR (neat): 3068, 3040, 1542, 1475, 1263, 1067, 773, 723 cm^{-1}.

MS (EI) m/z (relative intensity): 256 ([M^+] 60), 200 (5), 165 (100), 139 (33), 111 (28), 105 (63), 77 (43).

HR-MS (EI) m/z calcd for $C_{14}H_9ClN_2O^+$ [M^+] 256.0403, found 256.0414.

Synthesis of 2-(4-Methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole (117ac)



The general procedure **E** was followed using 4,4-dimethyl-4,5-dihydrooxazole (**116a**) (25 mg, 0.25 mmol) and 1-iodo-4-methoxybenzene (**19c**) (293 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 3/1 → 2/1) yielded **117ac** (26 mg, 51%) as a pale yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.90–7.85 (m, 2H), 6.92–6.87 (m, 2H), 4.07 (s, 2H), 3.83 (s, 3H), 1.36 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.9 (C_q), 161.8 (C_q), 129.9 (CH), 120.6 (C_q), 113.6 (CH), 79.0 (CH_2), 67.4 (C_q), 55.3 (CH_3), 28.4 (CH_3).

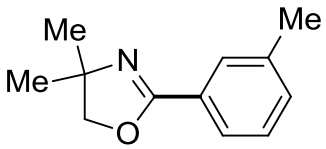
IR (neat): 2965, 2932, 2894, 2839, 1646, 1512, 1252, 1169, 840 cm^{-1}.

MS (EI) m/z (relative intensity): 205 ([M^+] 12), 190 (100), 175 (10), 162 (40), 134 (45), 119 (8), 103 (8), 77 (10).

HR-MS (EI) m/z calcd for $C_{12}H_{15}NO_2^+$ [M^+] 205.1103, found 205.1106.

The analytical data are in accordance with those reported in the literature.[240]

Synthesis of 4,4-Dimethyl-2-(*m*-tolyl)-4,5-dihydrooxazole (117ab)



The general procedure **E** was followed using 4,4-dimethyl-4,5-dihydrooxazole (**116a**) (25 mg, 0.25 mmol) and 1-iodo-3-methylbenzene (**19b**) (273 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 7/1 → 6/1) yielded **117ab** (35 mg, 74%) as a yellow liquid.

The general procedure **F** was followed using 4,4-dimethyl-4,5-dihydrooxazole (**116a**) (25 mg, 0.25 mmol) and 1-iodo-3-methylbenzene (**19b**) (273 mg, 1.25 mmol). After stirring at 35 °C under 450-500 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 7/1→6/1) yielded **117ab** (5 mg, 11%) as a pale yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80 (s, 1H), 7.73–7.69 (m, 1H), 7.31–7.27 (m, 2H), 4.10 (s, 2H), 2.37 (s, 3H), 1.38 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.2 (C_q), 138.0 (C_q), 131.9 (CH), 128.8 (CH), 128.2 (CH), 127.9 (C_q), 125.2 (CH), 79.1 (CH_2), 67.5 (C_q), 28.4 (CH_3), 21.2 (CH_3).

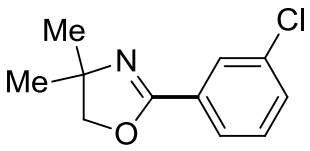
IR (neat): 2966, 2926, 2892, 1649, 1462, 1311, 1062, 716 cm^{-1}.

MS (EI) m/z (relative intensity): 189 ([M^+] 10), 174 (100), 159 (16), 146 (32), 118 (50), 101 (4), 91 (17), 77 (3).

HR-MS (EI) m/z calcd for $C_{12}H_{15}NO^+$ [M^+] 189.1154, found 189.1151.

The analytical data are in accordance with those reported in the literature.[241]

Synthesis of 2-(3-Chlorophenyl)-4,4-dimethyl-4,5-dihydrooxazole (117aj)



The general procedure **E** was followed using 4,4-dimethyl-4,5-dihydrooxazole (**116a**) (25 mg, 0.25 mmol) and 1-chloro-3-iodobenzene (**19j**) (298 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 7/1 → 6/1) yielded **117aj** (36 mg, 69%) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.95 (ddd, *J* = 2.1, 1.6, 0.5 Hz, 1H), 7.81 (ddd, *J* = 7.7, 1.6, 1.1 Hz, 1H), 7.43 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.33 (ddd, *J* = 7.9, 7.9, 0.5 Hz, 1H), 4.11 (s, 2H), 1.38 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.9 (C_q), 134.4 (C_q), 131.2 (CH), 129.8 (C_q), 129.6 (CH), 128.3 (CH), 126.3 (CH), 79.3 (CH_2), 67.8 (C_q), 28.4 (CH_3).

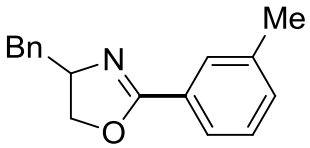
IR (neat): 3071, 2967, 2929, 2893, 1650, 1571, 1306, 1059, 715 cm^{-1}.

MS (EI) m/z (relative intensity): 209 ([M^+] 10), 194 (100), 179 (25), 166 (30), 138 (60), 111 (20), 84 (12).

HR-MS (EI) m/z calcd for $C_{11}H_{12}ClNO^+$ [M^+] 209.0607, found 209.0610.

The analytical data are in accordance with those reported in the literature.[242]

Synthesis of 4-Benzyl-2-(*m*-tolyl)-4,5-dihydrooxazole (117bb)



The general procedure **E** was followed using 4-benzyl-4,5-dihydrooxazole (**116b**) (40 mg, 0.25 mmol) and 1-iodo-3-methylbenzene (**19b**) (273 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 4/1) yielded **117bb** (45 mg, 72%) as a pale yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.79–7.77 (m, 1H), 7.74–7.70 (m, 1H), 7.34–7.18 (m, 7H), 4.56 (tdd, *J* = 9.1, 7.3, 5.0 Hz, 1H), 4.32 (dd, *J* = 9.3, 8.5 Hz, 1H), 4.16–4.08 (m, 1H), 3.25 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.71 (dd, *J* = 13.7, 9.0 Hz, 1H), 2.37 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 164.1 (C_q), 138.0 (C_q), 138.0 (C_q), 132.1 (CH), 129.2 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 127.6 (C_q), 126.5 (CH), 125.3 (CH), 71.8 (CH_2), 67.8 (CH), 41.8 (CH_2), 21.2 (CH_3).

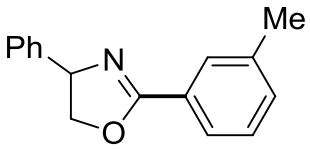
IR (neat): 3060, 3027, 2920, 2897, 1646, 1355, 1193, 971, 705 cm^{-1}.

MS (EI) m/z (relative intensity): 251 ([M^+] 3), 160 (100), 132 (35), 119 (10), 105 (45), 91 (27), 77 (6).

HR-MS (ESI) m/z calcd for $C_{17}H_{18}NO^+$ [$M+H^+$] 252.1388, found 252.1388.

The analytical data are in accordance with those reported in the literature.[226]

Synthesis of 4-Phenyl-2-(*m*-tolyl)-4,5-dihydrooxazole (117cb)



The general procedure **E** was followed using 4-phenyl-4,5-dihydrooxazole (**116c**) (37 mg, 0.25 mmol) and 1-iodo-3-methylbenzene (**19b**) (273 mg, 1.25 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 5/1) yielded **117cb** (37 mg, 62%) as a pale yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.91–7.90 (m, 1H), 7.85–7.82 (m, 1H), 7.39–7.26 (m, 7H), 5.38 (dd, *J* = 10.1, 8.1 Hz, 1H), 4.79 (dd, *J* = 10.1, 8.4 Hz, 1H), 4.28 (t, *J* = 8.3 Hz, 1H), 2.40 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.9 (C_q), 142.4 (C_q), 138.1 (C_q), 132.3 (CH), 129.1 (CH), 128.7 (CH), 128.3 (CH), 127.6 (CH), 127.4 (C_q), 126.7 (CH), 125.5 (CH), 74.8 (CH_2), 70.1 (CH), 21.2 (CH_3).

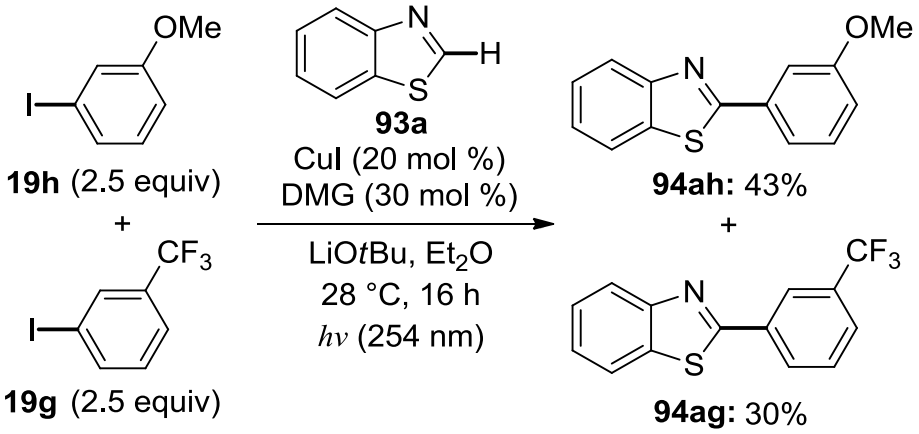
IR (neat): 3059, 3029, 2963, 2898, 1645, 1355, 1190, 1069, 699 cm^{-1}.

MS (EI) m/z (relative intensity): 237 ([M^+] 50), 207 (100), 192 (15), 179 (10), 165 (15), 119 (25), 89 (35), 77 (6).

HR-MS (EI) m/z calcd for $C_{16}H_{15}NO^+$ [M^+] 237.1154, found 237.1150.

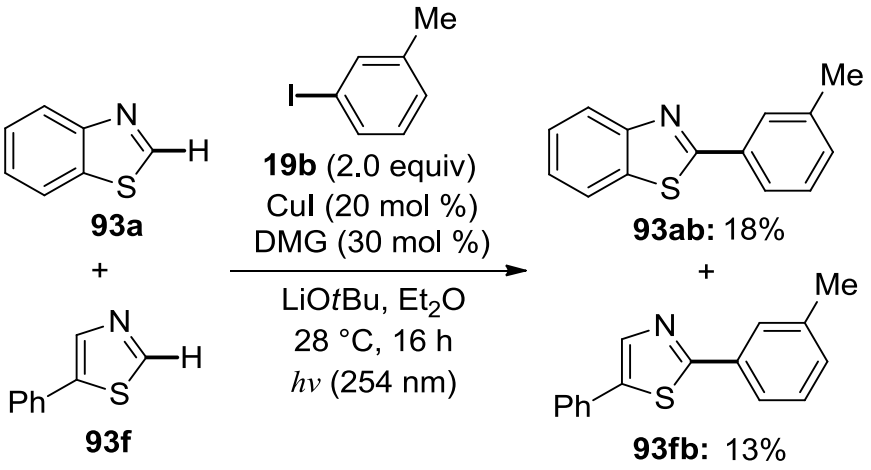
The analytical data are in accordance with those reported in the literature.[226]

Competition Experiments



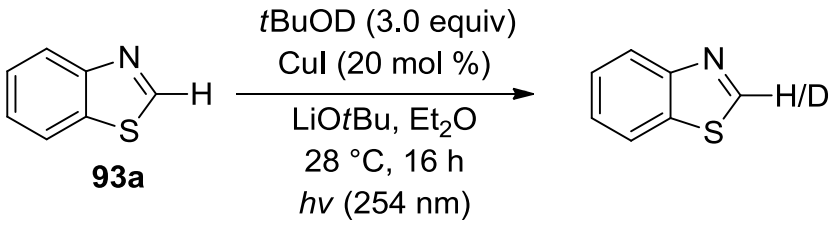
The general procedure **E** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol), 1-iodo-3-methoxybenzene (**19h**) (146 mg, 0.63 mmol) and 1-iodo-3-(trifluoromethyl)benzene (**19g**) (170 mg, 0.63 mmol). After stirring at 28 °C under

254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 40/1 → 20/1 → 10/1) yielded **93ah** (26 mg, 43%) and **93ag** (21 mg, 30%).



The general procedure **E** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol), 5-phenylthiazole (**93f**) (40 mg, 0.25 mmol) and 1-iodo-3-methylbenzene (**19b**) (109 mg, 0.50 mmol). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 30/1 → 20/1) yielded **93ab** (10 mg, 18%) and **93fb** (8 mg, 13%).

H/D Exchange Experiment

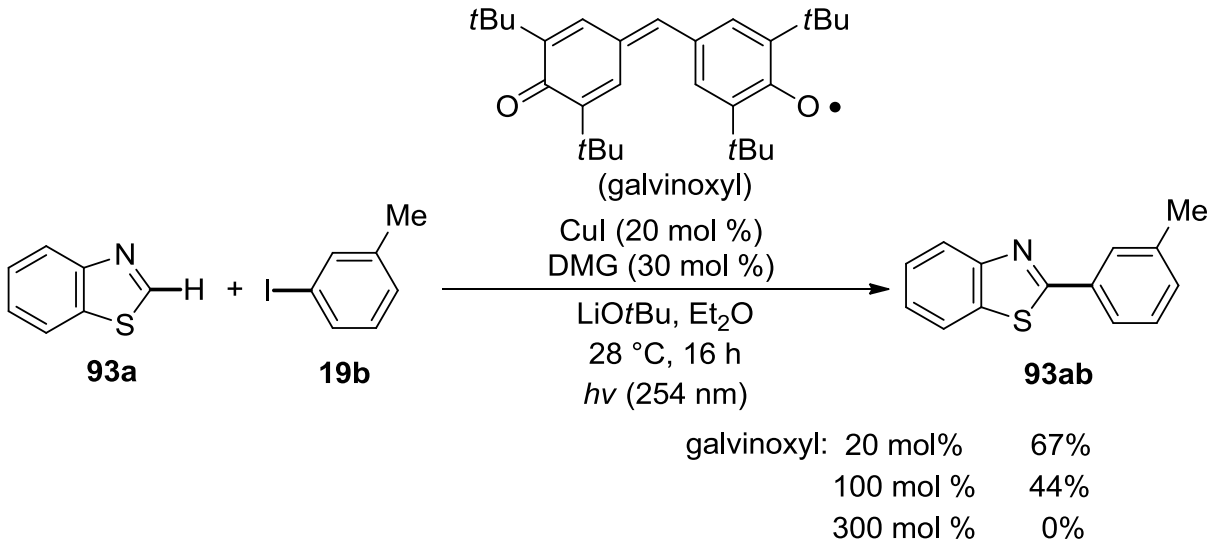


	H/D
CuI (20 mol %)	48/52
no CuI	48/52

To a pre-dried 10 mL quartz tube were added benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol), CuI (9.5 mg, 20 mol %), *tert*-butan(ol-d) (56 mg, 3.0 equiv), LiO*t*Bu (60 mg, 0.75 mmol), and Et_2O (1.0 mL) under a N_2 atmosphere. The tube was sealed tightly and stirred under 254 nm irradiation in a Luzchem LZC-ICH2 photoreactor for 16 h at ambient temperature (28 °C). Afterwards, the reaction mixture was filtrated through a pad of silica gel and washed with

Et_2O (20 mL). The solvent was removed under reduced pressure and the H/D ratio was determined to be 48/52 as estimated by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. In another reaction under aforementioned reaction conditions without copper(I) iodide the same H/D ratio was observed.

Radical Blocking Experiment



The general procedure **E** was followed using benzo[*d*]thiazole (**93a**) (34 mg, 0.25 mmol), 1-iodo-3-methylbenzene (**19b**) (273 mg, 1.25 mmol), and galvinoxyl (21 mg, 20 mol %; 105 mg, 100 mol %; and 316 mg, 300 mol %, respectively). After stirring at 28 °C under 254 nm irradiation for 16 h, purification by column chromatography on silica gel (*n*-pentane/Et_2O: 100/1 → 50/1 → 30/1) yielded **93ab** (38 mg, 67%; 25 mg, 44%; and 0 mg, 0% respectively).

10 References

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List of Abbreviations

Ac	Acetyl
acac	Acetylacetonate
Ad	Adamantyl
Ala	Alanine
Alk	Alkyl
AMLA	Ambiphilic metal-ligand activation
APT	Attached proton test
aq.	Aqueous
Ar	Aryl
atm	Atmosphere
bpy	2,2’-Bipyridine
Bn	Benzyl
Bu	Butyl
BQ	1,4-Benzoquinone
CFL	Compact fluorescent lamp
CMD	Concerted metalation-deprotonation
Cp*	1,2,3,4,5-Pentamethylcyclopentadienyl
d (NMR)	doublet
DavePhos	2-Dicyclohexylphosphino-2’-(N,N-dimethylamino)biphenyl
DCE	1,2-Dichloroethane
DCN	1,4-Naphthalenedicarbonitrile
DFT	Density functional theory
DG	Directing group
DMA	*N,N*-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMG	*N,N*-Dimethylglycine
DMSO	Dimethylsulfoxide
DMPU	*N,N´*-Dimethylpropylene urea

EI	Electron ionization
equiv	equivalent
ESI	Electronspray ionization
Et	Ethyl
GC-MS	Gas chromatography-mass spectrometry
Gly	Glycine
HASPO	Heteroatom-substituted secondary phosphine oxide
Hex	Hexyl
HRMS	High resolution mass spectrometry
IES	Internal electrophilic substitution
Ile	Isoleucine
*i*Pr	Isopropyl
IR	Infrared
KIE	Kinetic isotopic effect
LED	Light-emitting diode
m (NMR)	multiplet
m-	*meta*
mCPBA	*meta*-Chloroperoxybenzoic acid
Mes	2,4,6-trimethylphenyl
Me	Methyl
mol.	Molecular
M.p.	Melting point
NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect
NOESY	Nuclear overhauser enhancement and exchange spectroscopy
o-	*ortho*
OTFA	Trifluoroacetoxy
p-	*para*
p-cymene	4-Isopropyltoluene
phen	Phenanthroline
Ph	Phenyl

PI	Phthalimide
Piv	Pivalyl
ppm	Parts per million
ppy	2-Phenylpyridine
Pr	Propyl
Pro	Proline
pyr	Pyridyl
q (NMR)	quartet
s (NMR)	singlet
SPO	Secondary phosphine oxide
t (NMR)	triplet
*t*Bu	*tert*-Butyl
*t*Am	*tert*-Amyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofurane
TIPS	Tri-iso-propylsilyl
TMEDA	Tetramethylethylenediamine
TLC	Thin layer chromatography
TM	Transition metal
UV	Utraviolet
XPhos	2-Dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

Curriculum Vitae

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2010-2011: Visiting student at Dalian Institute of Chemical Physics, Chinese Academy of Sciences. Supervisor: Prof. Zhaoqing Xu and Prof. Zhengkun Yu.

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