HHS Public Access

Author manuscript

Tetrahedron. Author manuscript; available in PMC 2016 November 18.

Published in final edited form as:

Tetrahedron. 2015 November 18; 71(46): 8683–8716. doi:10.1016/j.tet.2015.08.034.

Recent Advances in the C–H-Functionalization of the Distal Positions in Pyridines and Quinolines

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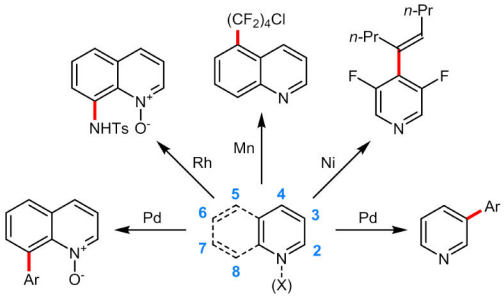
Abstract

This review summarizes recent developments in the C–H-functionalization of the distal positions of pyridines, quinolines and related azaheterocycles. While the functionalization of the C2 position has been known for a long time and is facilitated by the proximity to N1, regioselective reactions in the distal positions are more difficult to achieve and have only emerged in the last decade. Recent advances in the transition metal-catalyzed distal C–H-functionalization of these synthetically-important azaheterocycles are discussed in detail, with the focus on the scope, site-selectivity and mechanistic aspects of the reactions.

Graphical Abstract



Keywords

C–C Bond formation; Borylation; C–H-Functionalization; *N*-Heterocycles; Pyridines; Quinolines; Transition metal catalysis; Site-selectivity

1. Introduction

C–H-functionalization has emerged as a powerful tool for the synthesis of heterocyclic compounds.[1] However, with numerous C–H-bonds simultaneously available for activation, site-selective functionalization of complex molecules remains a significant challenge.[2] In

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pyridines, quinolines, and other structurally-related *N*-heterocycles, the C2 position can be readily functionalized using a variety of transition metal-catalyzed reactions with Pd,[3,4] Cu,[5] Ni,[6] Rh,[7] Ru,[8] Fe,[9] and Ag[10] as catalysts, as well as by means of non-catalytic approaches.[11] The facility of the C2–H-functionalization is due to the favourable electronic factors, e.g. increased acidity of the C2–H bond and increased electrophilic character of the C2=N moiety; and due to the proximity of the nitrogen atom (or oxygen in the *N*-oxides) that can serve as a directing group.[12] Other positions in pyridines (C3, C4) and quinolines (C3–C8) have been less readily accessible, with far fewer reports of regioselective C–H-functionalization reactions. Recently, significant progress has been made in the area of the distal C–H-functionalization of azines. While some positions, e.g. C5, C6 and C7 in quinolines, have by and large remained inaccessible by means of catalytic techniques based on C–H-activation, other positions, e.g. C3, C4 and C8 have become a focal point of intense research. In the past several years a number of efficient synthetic techniques that exploit combinations of intrinsic (steric and electronic), proximal (directing groups) and extrinsic (influence of ligands and solvents) regioselectivity factors have been reported for these positions.

Pyridines, quinolines and related azines are important structural motifs of natural products,[13] pharmaceuticals,[14] advanced materials,[15] catalysts[16] and ligands.[17] Catalytic C–H-functionalization in the distal positions of azines can significantly simplify access to these compounds and their structural analogues. Examples will be presented in such a way, as to allow the reader to view the progression of the area of regioselective C–H functionalization of azines through the course of time. This review focuses on the recent advances in the C–H-functionalization of the distal positions of pyridines and quinolines and related azines. Both directed, as well as sterically- and electronically-controlled catalytic processes are discussed from the mechanistic and synthetic perspectives. In those cases, where the synthetic scope of a particular method includes other classes of (hetero)aromatic compounds, these details are briefly discussed as well.

2. C3–H-Functionalization

In 2002, Ishiyama, Miyaura and co-workers disclosed two examples of borylation of heteroarenes catalyzed by $[IrCl(cod)]_2$/4,4’-di-*tert*-butyl-2,2’-bipyridine (dtbpy) in octane at 100 °C.[18] The borylation of quinoline (**1**) and pyridine (**3**) in octane was sluggish at 80 °C, but proceeded smoothly at 100 °C. Excess quinoline (10 equiv.) was required to provide 3-borylated product **2** in 84 % yield with >99 % regioselectivity. This report of monoborylation stands out, as a number of other reported techniques provide the bis-borylation product as 3,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline and 3,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline.[19,20] Pyridine (**3**) (2 equiv.) gave a mixture of 3- and 4-regioisomers in a ratio of 67 : 33, respectively with an overall yield of 42 %. 2 examples are given of the boronate esters in 42 and 84 % yield (Scheme 1).

In 2005, in the course of studies of the sterically-directed borylation of cyanoarenes, Smith and co-workers provided an example of borylation of the cyano-substituted pyridine **5**.[21] The ortho-selective borylation proceeded with $[Ir(cod)(OMe)]_2$/dtbpy as a catalyst in THF at 25 °C. Unlike directed lithiation methods that are regioselective due to electronic or

directing properties of pendant functional groups, the Ir-catalyzed borylation is sterically-controlled. In the case of 5-bromo-2-cyanopyridine (**5**) the reaction yielded a 67:33 ratio of C3/C4 borylation products **6** and **7** in an overall 81% yield (Scheme 2). When the same reaction was attempted with 2-bromo-5-cyanopyridine (**8**), no borylated product was observed (Scheme 2).

In 2007, Hartwig presented a one-pot, two-step synthesis of 3- and 4-haloarenes and 3- and 4-halopyridines that utilized a C3-selective borylation catalyzed by $[Ir(cod)(OMe)]_2$/dtbpy.[22] As this is a sterically-driven reaction, C3/C4 selectivity was very high with 2,6-dimethylpyridine and 3-methylpyridine (**9**). The borylation occurred meta to the bulky group (Scheme 3). Copper(II) chloride and bromide (3–3.5 equiv.) were then added to effect the halodeboronation.

The method affords *meta*- and *para*-haloheteroarenes. Hartwig applied the Ir-catalyzed arene borylation to the synthesis of an intermediate en route to altinicline,[23] a selective nicotinic acetylcholine receptor agonist, previously prepared in the enantiomerically pure form in 5 steps in an overall yield of 32 %.[24] The improved synthesis begins with the Ir-catalyzed C3-borylation of the pyridine core that is followed by the halogenation with copper(II) bromide to give the drug candidate in four steps with an overall yield of 75% by intermediate **12** (Scheme 3).[22] Advantageously, the *meta*-borylation/halodeboronation procedure allows for a streamlined and directing group-free synthesis of highly functionalized (hetero)arenes.

Although steric considerations are often invoked to explain C3-selectivity of C–H-borylation of azines, recent mechanistic and computational studies by Hartwig and Larsen suggest that the C2-pathway is disfavored due to the combination of the instability of the 2-borylazines under the reaction conditions, and the higher energy of the C2-pathway.[25]

In 2010 Yu and co-workers reported a Pd-catalyzed C3/C4 arylation of a number of nicotinic and isonicotinic acid derivatives using an amide directing group.[26] No reaction was observed for the substrates that did not have the directing amide groups, e.g. isonicotinic acid. *N*-Phenyl isonicotinamide (**13**) gave an excellent overall yield, with low selectivity for monoarylated product **14**. Conversely, *N*-3,5-dimethylphenyl amide increased the ratio of mono- and bisarylated products, but lowered the overall yield.[26] The divergent outcomes observed with the two directing groups can be exploited in the context of synthesis, e.g. the sterically hindered amide can be used for the monoarylation, whereas the less bulkier directing group can be used, when bis-arylation is desired.

Ortho substituents in the *N*-aryl amide moiety proved detrimental and led to substantially lower yields and poor selectivity for the monoarylation product. *N*-Phenyl isonicotinamide was chosen for the arylation of isonicotinic derivatives. Subsequent screening of phosphine ligands identified PCy_2t-Bu as the most effective ligand with cesium carbonate as a base at 130 °C. Various substituted *N*-phenyl 4-quinolinecarboxamides and *N*-phenyl isonicotinamides reacted with a variety of bromoarenes, giving rise to the C3-monoarylation products in up to 94% yields (Scheme 4). Isonicotinamide **13**, in addition to monoarylation products, also afforded diarylation products in up to 51% yield. *N*-Phenyl nicotinamide was

also successfully arylated, predominantly in C4 position, although C2-arylation products were also observed in up to 9% yield for several bromoarenes. It was noted that only one of the *ortho*-C–H bonds underwent the arylation, possibly due to the differences in the reactivities of the *ortho*-C–H bonds.[26]

In 2010, Snieckus and co-workers disclosed the meta-borylation of *N*,*N*-diethyl amides of (hetero)aromatic acids, and *N*,*N*-diethyl (hetero)aryl *O*-carbamates.[27] The amide groups in these substrates were found to provide steric shielding for the C–H bonds in the adjacent positions under the conditions of the Ir-catalyzed borylation. Thus, regioselectivity of this method is complimentary to that of the directed ortho metalation (DoM).[28] Four pyridine substrates were subjected to the borylation (Scheme 5). It was found that presence of a trimethylsilyl group as a latent regiodirective moiety in the *meta*-position of *N*,*N*-diethyl picolinamide improved the yield of the borylation product from 47% for **18** to 71% for **19**.

A high-yielding *meta*-borylation of *N*,*N*-diethyl 2-bromonicotinamide was also accomplished to obtain **21**. The yields of the borylation products **18–21** were 47–84% (Scheme 5). As a proof of concept two heteroarenes (**22** and **24**) were subjected to borylation that was followed by a Suzuki-Miyaura cross-coupling reaction to give **23** and **25** in 90 and 71% yields (Scheme 6).[27]

In 2010, Sarpong and co-workers reported the total synthesis of (+)-complanadine A using the Ir-catalyzed borylation reaction for the selective C3-borylation of the pyridine ring (Scheme 7).[30] The resulting boronate **27** was then subjected to a Suzuki-Miyaura cross-coupling to give the C2–C3’ bipyridine motif found in the natural product.

In 2011 Shi and co-workers described a C3-selective iridium-catalyzed nucleophilic addition of pyridines to aromatic aldehydes (Scheme 8).[31] Much like the sterically-controlled *meta*-borylation reported by Hartwig and Ishiyama,[18,22,27] the site-selectivity is determined by the steric factors. Ir complexes were uniquely active, while Mn, Re, Ru, and Rh showed no catalytic activity.

$Ir_4(CO)_{12}$ proved to be superior to other Ir sources. Bidentate aromatic nitrogenous ligands significantly improved the yield, with 1,10-phenanthroline (phen) emerging as a ligand of choice. The reaction was carried out in benzene in the presence of triethylsilane at 135 °C with a variety of substituted aromatic aldehydes. Halogen-substituted benzaldehydes, heteroaromatic aldehydes, and electron-deficient aromatic aldehydes gave good yields. Electron-rich aromatic aldehydes afforded addition products in slightly lower yields, while <10% product was formed from *n*-hexanal. Various *meta*-substituted pyridines were found suitable, as well as isoquinoline (C4-addition) and quinoline (C3-addition). A detailed study was carried out to elucidate the reaction mechanism (Schemes 9). No reaction occurred in the absence of trialkylsilanes, whereas in the absence of benzaldehyde C–H-silylation was observed in low yields. In an attempt to increase the yield of the C–H-silylation, norbornene and *tert*-butylethylene were added, however, these hydrogen acceptors did not increase the yield of silylated product **30**.

3-Phenyl-5-(triethylsilyl)pyridine (**31**) did not undergo the nucleophilic addition to benzaldehyde either directly or in the presence of the iridium catalyst. Upon subjecting 3-

(triethylsilyl)pyridine (**32**) to the reaction under the optimized conditions the desired coupling product **33** was obtained, however, no desilylation or displacement of the silyl group by the aldehyde occurred, as evidenced by the absence of silyl ethers **34** and **35** in the mixture of products. These results indicated that a two-step mechanism involving C–H-silylation followed by the addition to the aldehyde is unlikely. No D/H scrambling was observed for 2-deuterated 3-phenylpyridne (D_1-**29**), suggesting that the migration of iridium from C2 to C3 is unlikely as well (Scheme 9). Additional experiments suggested that a silyl iridium complex could be an intermediate in the catalytic cycle (Scheme 10). Thus, the following mechanism was proposed: silyl iridium complex **36** oxidatively adds to the pyridine C3–H bond to produce intermediate **38**. This step is then followed by an aldehyde C=O insertion into the Ir–Si bond to produce **39**.

Subsequent reductive elimination yields product **40** and iridium hydride intermediate **41** that regenerates the catalyst upon reaction with triethylsilane. 25 examples were reported with yields up to 78%. A potential extension of this work, which has yet to be explored, is an asymmetric variant of this reaction, possibly using chiral chelating *N*-ligands.

In 2011, Yu and co-workers described a palladium-catalyzed C3-selective olefination of pyridine.[32] It was envisioned that, a bidentate N,N-ligand can enhance the rate of the ligand exchange on Pd due to the *trans*-effect (Scheme 12).[33] While the equilibrium between π-complex **43**, and σ-complex **44** is shifted to the right, fast ligand exchange can be beneficial for the turnover even if the concentration of the reactive π-complex **43** is low. It can then react with the available olefin to produce the desired product **42** (Scheme 11). The equilibrium between **43** and **44** was also envisioned to be influenced by the solvent, as well as the ligands and counterions.

In order to improve the reactivity, and shift the equilibrium in favour of the desired π-coordination of pyridine to the Pd, a number of bidentate ligands were screened with 1,10-phenanthroline (phen) giving the best results. $Pd(OAc)_2$ proved to be the Pd source of choice. Under the optimized conditions, the reaction was carried out with silver carbonate as a base in DMF at 140 °C. The C3-alkenylation is applicable to substituted pyridines, as well as quinoline and pyrimidine.

Both electron-withdrawing and electron-donating groups in the pyridine, e.g. halogens, methoxy, methyl, and trifluoromethyl groups, are well-tolerated under the reaction conditions. While C2/C6 substituents retarded the addition of the olefin to the C3 position, higher yields were not always accompanied by higher site-selectivity. C4 substitution of the pyridyl unit also decreased the yields, presumably due to the steric hindrance around the C3 position.

The reaction is primarily selective for the C3 position, although some concomitant C2/C4-alkenylation was observed in up to 33% yield. Monosubstituted olefin coupling partners containing ester, amide, acetyl, and aryl groups gave acceptable yields, while internal olefins gave poor yields (<15%). The yields of the C3- and C4-alkenylpyridines were typically in the range of 27–73%. A kinetic isotope study was performed with D_5-pyridine (D_5-**3**) and pyridine (**3**). The resulting product showed a k_H/k_D value of 4.0. The authors postulate that

the mechanism involves a Pd-mediated C–H bond cleavage, rather than a Lewis acid mediated Friedel-Crafts type reaction (Scheme 13).

In 2011 Sames and co-workers disclosed a Pd-catalyzed regioselective arylation of electron-deficient pyridines (Scheme 14).[34] After optimization of the reaction conditions it was found that $Pd(OAc)_2$/*n*-$BuAd_2P$, Cs_2CO_3, Ag_2CO_3, and pivalic acid in toluene at 120 °C provided the highest selectivity and yield. Addition of Ag_2CO_3 was necessary to achieve high regioselectivity. Studies performed with sub- and superstoichiometric amounts of the silver salt found that 1 equiv. of Ag_2CO_3 was optimal for the yield and site-selectivity. With substoichiometric Ag_2CO_3 the regioselectivity eroded, while superstoichiometric amounts of Ag_2CO_3 did not improve the reaction performance. Cs_2CO_3 was also required as a base, with lower yields observed for K_2CO_3. Both bromo- and iodoarenes were suitable electrophiles under the cross-coupling conditions. No reaction was observed with chloroarenes suggesting that the chloro group can be further modified at a later stage of synthesis. Both electron-rich and electron-deficient haloarenes afforded coupling products in good yields. It was shown that the structure of the carboxylic acid additive should be further optimized depending on the electron-withdrawing group (EWG) used.

Bulkier, more soluble acids tend to provide higher selectivity and improved yields. In general, an electron-withdrawing group in the C4 position favours a smooth C3-addition, while an EWG in the C3 position directs the reaction in the C4 position. Most substrates had either a bulky group to prevent bis-addition in the C3 and C5 position, or employed haloarene as a limiting reagent. 4-Cyanopyridines were not compatible with silver carbonate, presumably, due to coordination of the cyano group with the silver salts.

This limitation was overcome by excluding Ag_2CO_3 from the reaction mixture. Similarly, fluorinated and chlorinated heteroarenes were arylated in good to moderate yields, with 2,2-dimethylhexanoic acid used in place of pivalic acid. While the mechanism of the reaction awaits further investigation, H/D exchange experiments hint to the role of Ag_2CO_3 as a Lewis base. 33 examples were reported with yields in the range of 15–88% (Scheme 14).

In 2011, Yu and co-workers published a study of non-directed C3-arylation[35] (Scheme 15) based on the Pd^{II}/phen catalytic system that they disclosed earlier that year. By adapting their previously reported C–H alkenylation conditions,[32] formation of the C3-arylated pyridine was observed in an 11% yield. Further optimization identified Cs_2CO_3 as a base of choice that provided a 74% yield and an outstanding C3 selectivity (C3/C4/C2 ratio 25/1/1).

The optimal catalytic system was found to be formed with 15 mol% of 1,10-phenanthroline as a bidentate ligand and 5 mol% of $Pd(OAc)_2$. It was noted that a 3:1 ratio of ligand to palladium increased the yield by 19%. Excess pyridine substrate (up to 75 equiv.) was required to achieve high yields.

A decrease in the amount of pyridine from the optimal 75 equiv. to 6 equiv. resulted in significantly lower yields (a drop from 92% to 18%, respectively). Iodo- and bromoarenes were found to be suitable electrophiles, while aryl chlorides were unreactive. The reaction tolerated both electron-withdrawing and electron-donating substituents in the haloarene in the para, meta, and ortho positions, including a redox-active thiomethoxy group. The

pyridine core can accommodate substituents in the ortho and meta positions. Quinoline was found to provide the arylated product in a 65% yield and a 3:0:1 (C3/C4/C2) selectivity. A primary kinetic isotope effect of 4.2 was obtained. This is higher than that for a typical Fujiwara-type electrophilic palladation (Scheme 16), pointing to a metalation/deprotonation reaction en route to C3-Pd species (Martinez pathway).[36] This suggests that an S_EAr mechanism involving a rate-limiting deprotonation cannot be ruled out (Scheme 16). A competition reaction between pyridine (**3**) and benzene (**52**) showed that pyridine is 3.26 times more reactive than benzene (Scheme 16).

The authors postulate that the coordination of the pyridine to the Pd center allows it to have an effectively higher molarity near Pd. In order to show the utility of the methodology a 4-step synthesis of the preclinical drug preclamol (**63**) from pyridine was carried out (Scheme 17).[37] Under the optimized conditions, a 70% yield of the C3-arylated pyridine **60** was obtained with a 19:1:1 C3/C2/C4 selectivity.

Propylation of the pyridine ring afforded pyridinium salt **61** that was further reduced to piperidine **62**. Finally, demethylation gave rise to racemic preclamol (**63**) in 4 steps and in 69% overall yield.

In 2013, Chatani and Aihara reported the Ru-catalyzed direct arylation of C–H bonds in aromatic amides.[38] Only one example is pertinent to this review, that of arylation of *N*-(quinolin-8-yl)quinoline-4-carboxamide (**64**) in 86% yield (Scheme 18). The method called for use of $[RuCl_2(p\text{-cymene})]_2$ or $[Ru(OAc)_2(p\text{-cymene})]_2$ (5–10 mol%) as a catalyst and PPh_3 (40 mol%) as a ligand, in the presence of Na_2CO_3 (2 equiv.), and PhBr (1.2 equiv.) in PhMe at 140 °C. Aryl bromides and iodides proved to be suitable electrophilic coupling partners under the optimized reaction conditions.

In 2013, Shi and co-workers reported the Rh-catalyzed olefination of azines assisted by an amide directing group (Scheme 19).[39] The study began with evaluation of the reaction conditions reported by Glorius for the Rh(III)-catalyzed oxidative Heck reaction of acetanilide with styrene.[40] While no product was obtained with *N*-(pyridin-2-yl)acetamide (**66**) and styrene, a reaction of **66** with ethyl acrylate (1.5 equiv.) afforded product **67** in a 6% yield under the same conditions.

Further optimization of the reaction conditions (DCE, $Cu(OAc)_2$, $[RhCp^*Cl_2]_2$ (5 mol%) and $AgSbF_6$ (20 mol%) at 120 °C) led to a complete conversion of **66** to **67**. Other additives such as Ag_2CO_3 or $Zn(OAc)_2$ were less effective. Acrylates were found to provide the corresponding olefinated products in good yields. Substituted 2-aminopyridines are compatible with a number of functional groups, e.g. halides, methoxy, ester, and trifluoromethyl, in the C4/C5/C6 positions.

The functionalization generally occurred in the C3 position, except for 2,6-*N*-(pyridin-2-yl)bisacetamide that provided a C3/C5 bis-substituted product **68** in a 98% yield with ethyl acrylate. A total of 38 examples were reported in up to 100% yield. The alkenylation products were then transformed to a number of analogues. For example, acidic cleavage of the pivalamide in **69** was followed by the diazotization and subsequent nucleophilic

displacement to give the fluorinated pyridine **70**. The methodology was then applied to the formal synthesis of pharmaceutically important compounds **71** and **72** (Scheme 20). Thus, a multigram-scale synthesis of 7-methoxy-3,4-dihydro-1,8-naphthyridin-2(1*H*)-one (**73**), – a precursor to the antibacterial agent **71**, – can be achieved in three steps in 76% overall yield from pivalamide **74**. The alkenylation of **74** was successfully carried out with 0.1 mol % catalyst resulting in a turnover number (TON) of 840. The intermediate **75** was then converted to **76** that produced dihydronaphthyridinone **73** upon exposure to HCl, thus completing the formal synthesis of the antibacterial agent **71**.[41]

The next synthetic target, – indole naphthyridinone **72**, – has shown significant activity in animal studies of the reduction in bacteria fatty acids production through inhibition of bacterial enoyl-ACP reductase (FabI). This interruption halts bacterial biosynthesis and is a promising target for novel antibacterial agents. Thus, alkenylation product **77** was hydrolyzed under acidic conditions to give aminopyridine **78** in 80% yield. Ni-mediated conjugate reduction afforded saturated ester **79** that underwent a base-mediated cyclization to give lactam **80** that can be further converted to indole naphthyridinone **72**.[42]

In 2013, Miura, Hirano, and co-workers disclosed the 8-aminoquinoline-directed dehydrogenative cross-coupling of (hetero)arenes and 1,3-azoles.[43] The scope of the method includes arenes and heteroarenes that are not covered by this review, as well as an example of isonicotinamide derivative **82** that was obtained in 34% yield (Scheme 21).

To gain insights into the mechanism, experiments involving deuterium-labeled benzamide and benzoxazole were performed. When a mixture of benzoxazole (**83**) with the C2-deuteromer (D_1-**83**) was reacted with benzamide **85**, under the standard conditions, a primary KIE value of 1.0 was obtained. On the other hand, a KIE value of 2.0 was observed for the ortho positions in benzamide **85**. This KIE data may suggest that the rate-limiting step is the C–H bond cleavage in benzamide **85** (Scheme 22).[44]

H/D exchange experiments were performed with D_5-benzamide (D_5-**85**) and D_1-benzoxazole (D_1-**83**) independently and together (Scheme 23). 57% H/D exchange in D_1-benzoxazole (D_1-**83**) in the absence of benzamide **85** was observed, while addition of **85** led to a 35% H incorporation (with 43% of the coupling product formed) in 10 min. Based on these results, the C–H activation of the benzoxazole was proposed to be reversible. When benzamide D_5-**85** was subjected to the reaction under the standard conditions in the absence of benzoxazole **83** a 14% H incorporation was observed, while addition of benzoxazole **83** led to a 2% H incorporation (with 23% of the coupling product formed) in 10 min. These results suggest that the C–H-activation is irreversible. These two data sets show that benzoxazole should undergo C–H-activation first, followed by the C–H-activation of the benzamide (Scheme 24). The proposed mechanism begins with an acetate ligand-assisted cupration to generate azolylcopper intermediate **86**. Subsequent ligand exchange forms complex **87**.

A $Cu(OAc)_2$-promoted disproportionation induces the C–H cupration of the benzene ring (complex **89**), followed by the reductive elimination of Cu(I) to give the desired product **84** (Scheme 24).[45]

In 2013, Daugulis and co-workers disclosed the 8-aminoquinoline-directed, copper-catalyzed fluorination of (hetero)arene C–H bonds.[46] The optimal conditions for monofluorination involve CuI as a catalyst, *N*-methylmorpholine *N*-oxide (NMO) as an oxidant, and DMF as solvent, with AgF as the fluoride source at 50–125°C for 30–120 min.

Di-fluorination can be achieved if the amounts of the reagents are doubled at 75–105 °C. Two heterocycles pertinent to this review are reported in 62% and 61% yields for di- and mono-fluorinated products **90** and **91**, respectively (Scheme 5).

Daugulis and Roane subsequently disclosed the copper-catalyzed etherification of arene C–H bonds (Scheme 26).[47] Previously reported amination conditions[48] were used first to give a 21% yield observed of the reaction between 8-aminoquinoline 3-trifluoromethylbenzamide with 4-*tert*-butylphenol. Upon changing the oxidant to NMO/O_2 a yield of 67% was obtained, with an 88% yield reported using $(CuOH)_2CO_3$ as a catalyst, K_2CO_3 as base, and air as oxidant.

The method can be used with a number of aliphatic alcohols in addition to substituted phenols. Mono- and bis-substitution with 4-*tert*-butylphenol at C3 and C5 positions in isonicotinamide **81** was reported (Scheme 26). The yields of the mono- and bis-addition products **92** and **93** were 51 and 47%, respectively.

In 2013, Su and co-workers disclosed the Rh(III)-catalyzed amide-directed cross coupling of pyridines with other heteroarenes (Scheme 27).[49] Initial screening began by evaluating the reaction between *N*-phenyl isonicotinamide (**94**) and 2-methylthiophene. $[RhCp^*Cl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), CsOPiv (1.5 equiv.) and $Cu(OAc)_2$ (2 equiv.) in 1,4-dioxane at 130 °C furnished product **95** in a 6% yield. Under the optimized conditions with K_2HPO_4 (1.5 equiv.) as a base and with 1.5 mol% of the catalyst, coupling product **95** was obtained in 70 % yield.

The influence of the directing group of the amide was studied in an attempt to increase the yield. Sterically-hindered or electron-withdrawing *N*-polyfluorophenyl amides, *N*-4-methoxyphenyl amide, and alkyl amides afforded trace amounts of the cross-coupling product. Other aryl amides, e.g. *N*-4-fluorophenyl amide, *N*-4-methoxyphenyl amide, *N*-3,5-dimethylphenyl amide, furnished the target compounds in moderate yields. The role of the substituents in the directing group may be complex and remains to be clarified in the future.

A variety of thiophenes bearing both electron-donating and withdrawing substituents, including alkyl, aryl, halo, cyano, and ester groups, can be employed as coupling partners, as well as benzothiophene, benzofuran and 2-methylthiazole. Disubstituted pyridines were also used (Scheme 28).

A variety of substituted *N*-phenyl pyridinecarboxamides, as well as *N*-phenylquinoline-3-carboxamide were successfully reacted with substituted thiophenes to give the C3-heteroarylation products (e.g. **100**–**104**) in up to 73% yield and with exclusive C3-regioselectivity. A notable practical feature of this method is that the formation of the monoarylation products is not accompanied by concomitant diarylation. Based on the previous studies by Fagnou[50] and Ellman,[51] the following mechanism was proposed:

coordination of the Rh(III) species with *N*-phenylamide is followed by formation of arylrhodium(III) intermediate **106**, which, upon reaction with 2-methylthiophene, gives rise to complex **107**. Subsequent reductive elimination produces rhodium(I) species **108** and cross-coupling product **95**. Finally, oxidation of rhodium(I) species **108** by copper (II) regenerates the rhodium(III) catalyst **105** (Scheme 29). [49]

Later in 2014, Shi and co-workers reported the Rh(III)-catalyzed hydroarylation of alkynes via a directed C–H-functionalization of pyridines.[52] Previous reports of the C2/C4/C6 alkenylation through the use of Ni(0) catalysts with and without Lewis acids were reported, but are not covered in this review.[53] For optimization, Shi and co-workers started with the reaction conditions reported for the oxidative olefination of *N*-(2-pyridyl)pivalamides (Scheme 19).[39] Under these conditions the coupling of *N*,*N*-diethyl 5-bromopicolinamide and diphenylacetylene afforded the product of type **111** in 74% yield. Upon addition of 4 equiv. of AcOH the yield increased to 92%. Stoichiometric $Cu(OAc)_2$ as an additive proved to be important, as its exclusion or use in catalytic amounts resulted in poor yields. Other copper salts (e.g. $CuBr_2$ or $CuSO_4$) were less effective. $Mn(OAc)_2$ and $Co(OAc)_2$ demonstrated comparable to $Cu(OAc)_2$ activity, suggesting that they act as Lewis acids.

The method tolerates various substituents in the C4, C5 and C6 positions including halides, methoxycarbonyl, *p*-methoxyphenyl and acetoxy groups. Electron-withdrawing substituents typically increased the yield, with the opposite result for electron-donating substituents. The alkyne scope was also briefly studied. Both symmetric and unsymmetric alkynes emerged as suitable reaction partners. While, di(*p*-methoxyphenyl)acetylene yielded alkenylation product **112** as a 1.7:1 mixture of *Z* and *E* isomers, most of the other alkynes tested, (e.g. 4-octyne, 1-phenyl-1-butyne, 1-phenyl-1-propyne, and *p*-diarylacetylenes bearing F, Cl, Me, *t*-Bu substituents) produced *E* isomers as major products. 26 examples were reported with overall yields in the range of 30–99% (Scheme 30).

To probe the mechanism of the hydroarylation a number of experiments were performed. When 3-bromo-*N*,*N*-diethylpicolinamide was reacted under the optimized reaction conditions in the absence of the alkyne and with 4 equiv. of AcOD, for 20 min and for 4 h, 5% and 30% deuteration at C3 was observed, respectively. This result suggests a reversible Rh insertion into the C3 position, although a concomitant C6-deuteration (3–6%) was also noted. Primary KIE of 3.1 (k_H/k_D) indicates that the C–H bond cleavage could occur in the rate-limiting step. When 3-deuterated-*N*,*N*-diethyl 5-bromopicolinamide (80% D) was reacted with diphenylacetylene, no deuterium incorporation was observed in the product. This result suggests that oxidative addition of the *ortho*-C–H bond under reported conditions is unlikely. Alkyne activation by a cationic catalyst was eliminated due to the high *E*-stereoselectivity and the primary KIE data.

The following mechanism was proposed: initial Rh insertion in C3–H to form the five-membered rhodacycle **116** is then followed by the migratory insertion of the alkyne to form the seven-membered rhodacycle **117**. Subsequent protodemetalation completes the catalytic cycle (Scheme 31).

Later in 2014, Shi and co-workers reported the oxidative C3–H-olefination of picolinamides with the amide functionality acting as a directing group.[54] Near-quantitative yields of the coupled products were achieved with *N*,*N*-dialkyl-substituted picolinamides. A variety of alkylamide groups (e.g. ethyl, isopropyl, cyclohexyl, benzyl, *n*-pentyl, and *n*-butyl) proved to be effective directing groups. In contrast, no reaction was observed with the *N*-phenylamide and Weinreb amide.

A number of activated alkenes were successfully employed as coupling partners, including acrylate esters, styrene and diethyl vinylphosphonate (Scheme 32). The method tolerates both electron-donating and electron-withdrawing groups in the pyridine ring. Quinoline- and pyrimidinecarboxamides were also found to be suitable substrates, and dual alkenylation can be achieved with a 2,6-pyridinediamide (Scheme 33). The catalyst loading can be further reduced to 0.5 mol%. 31 examples were provided with yields in the range of 20–100%.

Mechanistic studies were carried out to clarify the catalytic cycle. A competition reaction between *N*,*N*-diethyl 4-methylpicolinamide (**130**) and *N*,*N*-diethyl picolinamide (**123**) afforded a 4.8:1 mixture of 4-H and 4-Me products **131** and **132** pointing to the importance of the steric interactions. On the other hand, a competition experiment with 6-methoxypicolinamide (**133**) and *N*,*N*-diethyl 6-fluoropicolinamide (**134**) produced a 3.5:1 mixture of 6-MeO and 6-F products **135** and **136**, indicating that the reaction favors more electron-rich substrates. Further, the H/D-exchange was not observed under the standard reaction conditions in the presence of MeOD.

The reaction has a primary KIE (k_H/k_D) of 2.5, indicating that C–H-cleavage could be the rate-determining step (Scheme 34). Based on the above mechanistic studies a catalytic pathway was proposed (Scheme 35). According to the mechanism, initial cyclometalation of the substrate by catalyst **139** is followed by the olefin insertion into the C–Rh bond of five-membered rhodacycle **140**. Subsequent β-hydride elimination in the seven-membered intermediate **141** affords intermediate **142**, that, upon protodemetalation and oxidation of Rh(I) by Cu(II), releases the coupling product **131** and catalyst **139**.

In 2014, Hartwig and Cheng disclosed a Rh/bisphosphine system that efficiently catalyzed silylation of arene C–H bonds, however, a number of functional groups, e.g. heavy halogens and basic heterocyclic moieties, were not compatible with the catalytic system.[55] A year later the authors reported on a Ir-based catalytic system with broad functional group compatibility and tolerance for basic heterocycles.[56] The reactions were performed with $HSiMe(OSiMe_3)_2$ as an inexpensive and uniquely active silylating reagent.

Optimization studies conducted with $[Ir(cod)(OMe)]_2$ identified 2,4,7-trimethyl-1,10-phenanthroline (tmphen) as a ligand of choice that provided a high yield and high regioselectivity of the silylation. The reactions were carried out at 80–100 °C in THF with cyclohexene (1 equiv.) as a hydrogen acceptor. The Ir-catalyzed silylation procedure showed broad functional group tolerance (e.g. ester, ketone, bromide, iodide, nitrile, and sulfones). Several examples of the silylation of pyridines are reported with yields between 46 and 94%. (Scheme 36). 3-Methylpyridine was silylated in a 59% yield. Mirtazapine, an antidepressant, was also silylated in the *meta*-position of the pyridine ring in a 46% yield.

Concomitant silylation of the benzene ring (14% yield) was also observed. In addition, 6-methoxyquinoline afforded C3-silyl derivative **145** that was further converted to 3-bromo-6-methoxyquinoline in a 64% yield.

In 2014, Song, Niu and co-workers reported the Cu-mediated alkoxylation of arenes using an *N*,*O*-bidentate directing system.[57] The authors sought to optimize the reaction of 2-benzamidopyridine 1-oxide (**149**) with ethanol.

This *N*,*O*-bidentate directing group was previously used by the same group in aryloxylation using stoichiometric amounts of copper.[58] Stoichiometric amounts of $Cu(OAc)_2$ in ethanol provided product **150** in a 21% yield. Inorganic bases were tested (e.g. KO*t*-Bu, NaOEt, KOH, Cs_2CO_3), with K_2CO_3 emerging as the base of choice. Under the optimized conditions with CuCl (1 equiv.) in a 1:1 mixture of ethanol and pyridine at 130 °C the reaction afforded **150** in an 84% yield. Catalytic amounts of CuCl provided the product in lower yields. The reaction tolerates aliphatic alcohols, and a number of substituents in the arene ring, including iodo, methyl, and chloro groups. In one example, isonicotinamide was reacted with hexafluoroisopropanol (HFIP) to give the C3/C5-ether in 75% combined yield with a 2.6:1 ratio of mono- and bis-etherification products (Scheme 37).

In 2014, Yu, Dai, and co-workers reported the use of an amide-tethered oxazoline directing group for the Cu(II)-mediated amination of arenes (Scheme 38).[59]

Unlike Daugulis's[60] 8-quinolinamide directing group that forms a five-membered ring incorporating N–M–N, Yu's directing group forms a six-membered bidentate complex.[61]

During the optimization stage a reaction between *N*-(2-(4,5-dihydrooxazol-2-yl)phenyl)benzamide (**155**) and tosylamide in the presence of a stoichiometric amount of $Cu(OAc)_2$ and K_2CO_3 (2 equiv.) in DMSO at room temperature afforded the product in 8% yield. The yield was increased to 70% at 80 °C and with Na_2CO_3 as a base. Several isonicotinamide examples are reported with yields in the range of 31–70% (Scheme 38). After completion of the reaction, the amide-tethered oxazoline directing group can be removed with KOH in EtOH at 80 °C.

In 2014, Yu, Dai, and co-workers disclosed the Cu(II)-mediated *ortho*-C–H-alkynylation of (hetero)arenes with terminal alkynes using the same amide-tethered oxazoline directing group.[62] The conditions[59] previously-reported for the amination (Scheme 38) yielded product **157** arising from a reaction of benzamide **155** with (4-methylphenyl)acetylene in 52% yield. Various bases were tested, with NaOAc (1 equiv.) providing coupling product **157** in 85% yield at 60 °C. Excess acetylene (typically 3 equiv.) is used, due to concurrent homocoupling, and stoichiometric amounts of $Cu(OAc)_2$ were used to achieve good yields. The method tolerates a variety of aliphatic alkynes, a conjugated enyne, and heteroarenes. 4-Pyridine- and quinolinecarboxamides were reported to give the alkynylation products **158**–**160** in moderate yields (Scheme 39).

In 2014, Yu, Dai, and co-workers reported the Cu(II)-catalyzed *ortho*-C–H-trifluoromethylation of arenes using the Ruppert-Prakash reagent (CF_3TMS).[63] Using their previously reported amide-tethered oxazoline directing group,[59] the authors set out to

optimize the trifluoromethylation reaction. Treatment of benzamide **155** with 30 mol% of $Cu(OAc)_2$, 5 equiv. of $TMSCF_3$, 1 equiv. of Ag_2CO_3, and 4 equiv. of KF in DMSO at 100 °C gave the coupling product **161** in 37% yield. NaF and CsF provided no increase in yield, however increasing the amounts of $Cu(OAc)_2$ and Ag_2CO_3 to 1 and 1.5 equiv., respectively, raised the yield to 80% of mono/bis-trifluoromethylation products. Reducing the reaction time from 5 h to 30 min increased the ratio of mono- and bis-trifluoromethylation products to 3.8:1. The method was applied to a number of substituted heteroarenes. 4-Pyridine- and quinolinecarboxamides were reported to give the alkynylation products **162**–**164** in 40–62% (Scheme 40).

3-Fluoroisonicotinamide and 4-quinolinecarboxamide afforded the mono-trifluoromethylation product exclusively, while the unsubstituted isonicotinamide gave rise to a ratio of 27:25 mono-/bis-functionalization products. To probe the mechanism, intra- and intermolecular kinetic isotope effects were measured. An intermolecular competition experiment gave a KIE of 3.2, while an intramolecular competition experiment produced a KIE of 3.5 (Scheme 41).

No discernible effect was observed with the addition of a radical quencher (TEMPO), ruling out a possible radical pathway.

The reaction is believed to proceed through organocopper intermediate **165** that is oxidized to copper(III) species **166**. Subsequent transmetalation with $TMSCF_3$ affords organocopper(III) intermediate **167** that undergoes reductive elimination to yield the desired product **161** and Cu(I).

In 2014, Yu, Dai, and co-workers reported the Cu(II)-catalyzed coupling of aromatic C–H bonds with arylboronates using the same oxazoline directing group.[64] One pyridine, *N*- 2-(4,5-dihydrooxazol-2-yl)phenyl isonicotinamide (**153**), was arylated in the C3 position (*meta* to the pyridine nitrogen) with PhBpin (**168**), $Cu(OAc)_2$, Ag_2O, Na_2CO_3, and KOAc in DMSO at 70 °C, giving rise to product **169** in 26% yield (Scheme 42).

A possible mechanism may involve initial copper acetate-mediated C–H-activation en route to **170**, followed by disproportionation to yield Cu(III) intermediate **171**. Transmetalation with **168** affords intermediate **172** that undergoes reductive elimination to give Cu(I) complex **173**. Subsequent protonolysis yields CuOAc and product **169**. Finally, oxidation of the Cu(I) species leads to regeneration of the catalyst (Scheme 43).

In 2014, Gooßen and co-workers reported the Cu(II)-catalyzed *ortho*-nitration of arenes and heteroarenes with 8-amidoquinoline as a directing group.[65] A number of directing groups were tested, with Daugulis's[66] 8-aminoquinoline bidentate directing group providing the highest yield and selectivity. The reaction conditions included $Cu(NO_3)_2$ and $AgNO_3$ in propylene carbonate with *N*-methylmorpholine *N*-oxide (NMO) as the oxidant at 50 °C to yield 30% of 2-nitrobenzamide **174**. Addition of phosphine ligands improved the yield, with triphenylphosphine emerging as a ligand of choice. The preformed $Cu(PPh_3)_2NO_3$[67] provided product **174** in 78% yield. Two *N*-heterocyclic C3-nitration products **175** and **176** were obtained in 76 and 52% yields (Scheme 44). The kinetic isotope effect of 2.7 was

observed, confirming that the C–H bond activation could the rate-determining step. The reaction was also performed with radical scavengers (*p*-benzoquinone or TEMPO), with an insignificant decrease in yields, suggesting that a radical pathway is unlikely.[68]

The following mechanism was proposed, based on the aforementioned experimental data: initial cyclometalation by copper(II) to give organocopper species **177** is followed by oxidation to Cu(III) intermediate **178** and transmetalation to nitrate **179**; lastly, reductive elimination furnishes product **175** (Scheme 45).[69]

In 2014, Shi and co-workers reported the Cu(II)-mediated C–H-hydroxylation of arenes and heteroarenes with a 2'-(pyridine-2-yl)isopropylamine (PIP) directing group (Scheme 46).[70] The initial experiment was carried out with *N*-(2-(pyridin-2-yl-propan-2-yl)benzamide (**180**), $Cu(OAc)_2$ (1 equiv.), Ag_2CO_3 (2 equiv.), and $NaHCO_3$ (1 equiv.) in DMF at 100 °C to give the hydroxylation product **181** in 51% yield. Among the additives tested (e.g. $NaHCO_3$, KOAc, $PhCO_2Na$) tetrabutylammonium iodide (TBAI, 2 equiv.) provided the highest yield (90%) within 1 h. The reaction tolerates both arenes and heteroarenes bearing a variety of functional groups (e.g. fluoro, chloro, trifluoromethyl, methoxy, and methyl). Substituted isonicotinamides of type **182** were successfully converted to the hydroxylated products **183** in 53–65% yields (Scheme 46). When 2-chloro- or 2-fluoroisonicotinamides were employed, a mixture of C3- and C5-oxidation products **184** and **185** was obtained, with 3-hydroxy amide **183** being the major product. On the other hand, *N*-PIP 2-methoxyisonicotinamide afforded 5-hydroxy amide **186** as a sole product.

Interestingly when the *N*-PIP picolinamide was subjected to the oxidation with the aim of obtaining a C3-oxidation product, no reaction occurred. In addition, C2-oxidation was not observed under the reaction conditions. The authors carried out a number of experiments to gain insight into the mechanism. Addition of radical scavengers (1,4-dinitrobenzene, TEMPO, or 1,1-diphenylethylene) had no influence on the yield, eliminating a radical pathway. A KIE of 5.3 was observed, indicating that the C–H bond cleavage is the rate-determining step.

No deuterium incorporation was observed under standard conditions in the presence of D_2O or AcOD. This result eliminates a reversible C–H activation step. The following mechanism was, therefore, put forward: complexation of Cu^{II} produces chelate **187** that gives rise to organocopper(II) species **188** via a concerted metalation deprotonation pathway. Subsequent oxidation with CuX_2 delivers Cu(III) intermediate **189** that undergoes reductive elimination to give acetate **190**. Rapid hydrolysis of the acetate produces *ortho*-hydroxy amide **181**. Alternatively, a disproportionative C–H-activation[71] may yield Cu(III) intermediate **189** directly from chelate **187**.

In 2015, Shi and co-workers utilized the PIP directing group in the copper- and silver-mediated *ortho*-ethynylation of (hetero)aryl C–H bonds with triisopropylsilylacetylene.[72] Initial experiments with benzamide **180** in the presence of Na_2CO_3 (2 equiv.) and Ag_2CO_3 (1 equiv.) with 50 mol% $Cu(OAc)_2$ gave alkynylation product **191** in 55% yield. Adding triethylamine (0.8 equiv.) and increasing the amount of Ag_2CO_3 to 1.5 equiv. with 1 equiv. of Na_2CO_3 improved the yield to 80% with only 30 mol% of $Cu(OAc)_2$. The reaction

tolerates a number of functional groups (e.g. chloro, fluoro, methyl, phenyl, and nitro). Isonicotinamides **182** underwent C3-alkynylation (Scheme 47) producing monoacetylenes **192** along with substantial amounts of the C3,C5-dialkynylation products in 50–82% combined yields. The ratio of mono- and dialkynylation products varied from 4 : 1 for isonicotinamide **193** to 0.7 : 1 for 2-chloroisonicotinamide **194**.

In a series of competition experiments electron-deficient substrates were found to be more reactive than electron-rich substrates, ruling out a simple electrophilic aromatic substitution (S_EAr). The reaction proceeded smoothly in the presence of radical scavengers, suggesting that a radical mechanism is unlikely. This data, together with the high values of the intermolecular KIE (k_H/k_D = 3.6) and the intramolecular KIE (k_H/k_D = 7.5), led to the following mechanistic proposal: initial C–H-activation by concerted metalation deprotonation (CMD) is followed by oxidation and transmetalation to generate Cu(III). Lastly, reductive elimination furnishes the desired product.

In 2015, Shi and co-workers reported the Cu(II)-catalyzed methoxylation of (hetero)arenes[73] using their bidentate (pyridin-2-yl)isopropylamine (PIP-amine) directing group (Scheme 49). The reaction proceeds with 5 mol% of $Cu_2(OH)_2CO_3$, with KOCN as base in MeOH at 120 °C, and with air as an oxidant. Other copper salts (e.g. $Cu(OAc)_2$, $CuBr_2$ and $Cu(OTf)_2$) were less efficient even at higher catalyst loadings. Methoxylation of PIP-isonicotinamide **195** afforded a 4:1 mixture of C3-monomethoxylation product **196** and the C3/C5-bismethoxylation product in a 95% yield. The catalytic system tolerates methyl, chloro, and methoxy groups in C2. The 2-methoxy amide **197** afforded a mixture of regioisomers **198** and **199**. *N*-PIP-nicotinamides afforded the corresponding C4-methoxylated products.

3 C4–H-Functionalization

In 1997, Grigg and Savic published a method of C3/C4-directed Ru-catalyzed addition of heteroarenes to alkenes (Scheme 50).[74] They surmised that an acetyl group could direct the substitution at either C3 or C4 faster than at the C2 position.

Reactions were carried out with $RuH_2CO(PPh_3)_3$ (5 mol%) as a catalyst and with a 1:3–4 ratio of heteroarene to alkene. The initial experiment with 3-acetylpyridine (**200**) and 1-octene gave rise to the desired product **201** in an 11% yield. No C2- or bis-C3/C5-alkenylation products were observed. The low yield was attributed to the competitive double bond isomerization.

This side-reaction was avoided by using alkenes that lack C–H bonds in the allylic positions, e.g. 3,3-dimethylbutane that yielded 50% of the desired product. A number of silylalkenes were also used. With trimethyl(vinyl)silane, addition to both the C4 and C2 was observed. 3-Benzoylpyridine **202** was also reacted with triethoxy(vinyl)silane to give a C4-addition product **203** in 48% yield.

In 2000, Smith and co-workers reported a sterically controlled C4-borylation of 2,6-dimethylpyridine (**204**) with pinacolborane by dual C–H-activation.[75] The method was developed for *meta*-borylation (meta to the two methyl groups) of disubstituted arenes. The reaction with 2,6-dimethylpyridine produced boronate **205** in 41% yield (Scheme 51).

Another example was reported in 2002 with 2,6-dichloropyridine (**206**).[76] The catalyst used was (Ind)Ir(cod) with bis-1,2-bis(diphenylphosphino)ethane (dppe) as a ligand. The reaction afforded boronate **207** in 69 % yield at 100 °C in cyclohexane under solvent-free conditions (Scheme 52). The methodology subsequently was further expanded to a one-pot borylation/ oxidation protocol.[77]

Using the previously reported borylation conditions[76] **206** was successfully borylated at C4 position. Subsequent oxidation by Oxone in acetone afforded the corresponding 4-hydroxypyridine **208** in 64% yield (Scheme 53).

In 2004, Nishida and Tagata disclosed an Ir-catalyzed C4-selective-borylation of 2,6-dichloropyridine with two different ligands (**209** and **210**, Scheme 54) and two boronate esters.[78]

The isopropyl groups in the ligands **209** and **210** were important for obtaining high yields. Pinacolborane gave higher yields than bis(pinacolato)diboron by ~20%. The yields for C4-borylation of 2,6-dichloropyridine were in the range of 71–93% (Scheme 55).

In 2009, Marder, Steel, and co-workers developed a one-pot borylation/Suzuki-Miyaura cross-coupling procedure based on the group's prior work in this area.[73,19]

The key to the success of the one-pot procedure was the discovery of a solvent (MTBE) that was suitable for both the borylation and the cross-coupling reaction. The compatibility of the Ir/dtbpy with MTBE was explained by the steric hindrance that prevents coordination of MTBE to the Ir catalyst. This result allowed for replacement of hexane that is not suitable for the Suzuki-Miyaura reaction. Using this one-pot method, 2,6-dichloropyridine (**206**) was transformed to methyl 4’-(2,6-dichloropyridin-4-yl)benzoate (**211**) in a 94% yield (Scheme 56).

Marder, Steel, and co-workers reported the microwave-assisted borylation of a number of heteroarenes, as a continuation of their sterically directed borylation.[79] The use of microwave irradiation allowed for the reduction in reaction time from 2 h to as little as 3 min (Scheme 57).

Marder and co-workers also reported a sterically-controlled Ir-catalyzed C4-borylation of 2-phenylpyridine (**212**) that produced a mixture of C3- and C4-pyridineboronates. The boronates were coupled with 1-iodonapthalene and a Pd catalyst to yield the C3/C4 products **213** in 61% yield over two steps (Scheme 58).[80]

In 2013, Krska, Maleczka, Smith and co-workers reported a Ir-catalyzed C–H borylation of aminopyridines **214** guided by a traceless directing group (Scheme 59).[81] HBpin first engages the amino group to give aminoboronate **215** that undergoes a selective meta- or para-borylation. The resulting aminoboronate **216** is then cleaved hydrolytically to give amine **217**, thus acting as a traceless directing group.

The reaction was conducted with 1.2 equiv. of HBpin, 0.5 equiv. of B_2pin_2, 1.5 mol% of $[Ir(cod)(OMe)]_2$ and 3 mol% of 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen) in THF at

80 °C. All aminopyridines had at least one C2-substituent, e.g. a methoxy, chloro, trifluoromethyl, or methyl group. C4-Borylation occurred both with 2- and 3-aminopyridines. With 2-aminopyridines the reaction was not directed by the NHBpin group, but instead took place at the least sterically hindered C4 position. Several substituted 4-pyridineboronates (**218**–**221**) were produced in good to excellent yields (Scheme 60). In order to better understand the mechanism, ^{1}H and ^{11}B NMR studies were performed.

The spectroscopic data indicated that ArNHBpin species was formed. This intermediate did not react further with HBpin to $ArN(Bpin)_2$ even at elevated temperatures. Previous computational work on the borylation of *N*-Boc-protected anilines showed that *ortho*-borylation was favored due to the hydrogen bonding between the NH moiety of the aniline and an oxygen atom of the Bpin reagent in the transition state.[82] No C- or N-borylation was observed, when HBpin was omitted, supporting the proposed mechanism.

In 2006, Fagnou and co-workers published a general method for a cross coupling reaction of aryl halides with perfluoroaromatics, e.g. 2-chlorotoluene with 2,3,5,6-tetrafluoropyridine (**222**).[83] The cross-coupling was carried out with $Pd(OAc)_2$, *S*-Phos, K_2CO_3 as a base, in isopropyl acetate at 80 °C. The reaction afforded product **223** in 97% yield (Scheme 61).

Later in the year the same group published a follow-up study, where **222** was coupled with 4-bromotoluene to give the biaryl product **223** in 86% yield.[84] $Pd(OAc)_2$ was used as a catalyst with P*t*-Bu_2Me as a ligand.

In 2008, Daugulis and Do reported the copper catalyzed arylation of fluoropyridines **222** and **224**.[85] The reactions were carried out with catalytic amounts of CuI and phen, with K_3PO_4 as a base in DMF at 130–140 °C. It is believed that the reaction proceeds first through deprotonation of the fluoropyridines, followed by a Li/Cu transmetalation. The intermediate organocopper species then reacts with the aryl iodide. This reaction requires 3 equiv. of the heteroarene. Lithium *tert*-butoxide was used as a stronger base in the case of the less acidic 3-fluoropyridine (**224**). The coupling products **223** and **225** were formed in 91 and 40% yields, respectively (Scheme 62).

In 2009, Su and co-workers reported the Pd-catalyzed cross-coupling of arylboronic acids with electron-deficient polyfluoro(hetero)arenes.[86] The reaction was carried out under basic conditions to effect the cleavage of the C–H bond in the polyfluoro(hetero)arene. However, these conditions also accelerated the transmetalation of the arylboronic acid, which in turn promoted the undesired homocoupling of the phenylboronic acid to biphenyl.

In order to avoid the homocoupling, a combination of a weak base and a weak acid, – *p*-$MeC_6H_4CO_2K$ and *t*-$BuCO_2H$, – was employed. Under these conditions, with Ag_2CO_3 as an oxidant and $Pd(OAc)_2$ as a catalyst, the coupling of 2,3,5,6-terafluoropyridine (**222**, 3 equiv.) and phenylboronic acid proceeded in 71% yield (**226**, Scheme 63).

In 2010, Zhang and co-workers reported the Pd-catalyzed C–H-olefination of perfluoroarenes.[87] The authors optimized reaction conditions included $Pd(OAc)_2$ (10–20 mol%), Ag_2CO_3 (2 equiv.) in DMF/DMSO at 120 °C. Internal and branched olefins were successfully cross-coupled with both electron-poor and electron-rich (hetero)arenes. For

example, 2,3,5,6-tetrafluoropyridine (**222**) was reacted with *tert*-butyl acrylate and styrene to give products **227** and **228** in 69 and 72% yields (Scheme 64).

Subsequently, Zhang and co-workers reported the Pd-catalyzed cross-coupling of polyfluoroarenes with aromatic heterocycles.[88] A 72% yield of thiophene **229** was obtained in the reaction between pentafluorobenzene (**230**) and 2-acetylthiophene with $Pd(OAc)_2$ as a catalyst and Ag_2CO_3 as an oxidant in DMF/DMSO at 120 °C. The yield dropped substantially upon removal of DMSO or switching to other polar solvents (e.g. DMF, NMP, 1,4-dioxane). The authors surmised that DMSO acts as a ligand to the Pd, preventing the formation of Pd black. A 1:1 mixture of Ag_2CO_3 and AgOAc afforded a higher yield. Use of an excess of Ag_2CO_3 (1.5 equiv.) with AcOH (1 equiv.) afforded **229** in 77%. For the reaction involving pyridine **222** the thiophene was used as the limiting reagent. Pyridine **222** was reacted with three 2-substituted thiophenes to give the coupling products **231**–**233** in high yields (Scheme 65).

In 2010, Su and co-workers reported the Cu-catalyzed alkynylation of electron-deficient polyfluoroarenes.[89] A coupling reaction between pentafluorobenzene (**230**) and phenylacetylene in the presence of $CuCl_2$ (30 mol%), LiO*t*-Bu (3 equiv.), DDQ (30 mol%), and phen (30 mol%) in the atmosphere of O_2 (1 atm) proceeded in 72% yield. A five-fold excess of the electron-deficient arene was used. 2,3,5,6-Tetrachloropyridine (**234**) was successfully coupled with phenylacetylene to yield acetylene **235** in 41% yield (Scheme 66).

In 2010, Su and Wei reported the Pd-catalyzed dehydrogenative C–H-cross-coupling of electron-deficient polyfluoroarenes with simple arenes.[90] The majority of the substrates studied were substituted polyfluoroarenes that were reacting with benzene or substituted benzenes. In one case, 2,3,5,6-tetrafluoropyridine (**222**) underwent a cross-coupling reaction with benzene by way of dual C–H-activation.

Under the optimized reaction conditions with 45 equiv. of benzene, $Pd(OAc)_2$ (20 mol%) as a catalyst, $Cu(OAc)_2$ (2 equiv.) as an oxidant, Na_2CO_3 (0.75 equiv.) as a base, and pivalic acid (1.5 equiv.) as an acidic additive in dimethylacetamide at 110 °C, 2,3,5,6-tetrafluoro-4-phenylpyridine (**226**) was produced in 70% yield (Scheme 67). In order to determine, which of the two C–H bond-cleavage processes occurred first, the authors measured the KIE for both coupling partners. A KIE of 1.3 was observed for the C4–H bond in **236**. This result showed that the rate-limiting step did not involve the C–H cleavage in the fluorobenzene substrate. On the other hand, KIEs of 6.5 and 4.8 were obtained for benzene and 1,2-dichlorobenzene. These high KIEs suggested that the C–H cleavage in the arene component was the rate-determining step. This assessment was supported by lower yields, when electron-poor arenes were employed as coupling partners with polyfluoroarenes.

In 2011, Daugulis and Do reported the cross dimerization of electron-rich and electron-deficient arenes.[91] The reaction is believed to be a two-step process. In the first, fast step, one of the coupling partners undergoes iodination.

In the second step, the regioselective copper-catalyzed arylation of a C–H bond ensues, as reported by Daugulis earlier.[47] The iodination proceeds with iodine, in the presence of the copper iodide/phenanthroline catalyst.

The reaction was performed with K_3PO_4 or K_3PO_4/LiO*t*-Bu as a base in either 1,4-dioxane or 1,2-dichlorobenzene, with pyridine as an additive (Scheme 68). A number of 4-(hetero)arylpyridines were prepared using this method (for example, **244–251** in Scheme 69). The notable features of the method are low ratios of coupling partners (1.5–3 equiv.), low rates of homocoupling side product formation and excellent functional group tolerance.

In 2011, Ohmura, Suginome, and Oshima reported the palladium-catalyzed C4/N-silaboration of 2- and 3-disubstituted pyridines **252** to dihydropyridines **253** under mild conditions (Scheme 70).[92] The initial experiment that was carried out with pyridine (10 equiv.), Me_2PhSi-Bpin (1 equiv.), in D_6-benzene with (η^3-C_3H_5)PdCl(PPh_3) (2 mol%) at 50 °C yielded no product. Upon replacement of PPh_3 with $PCyPh_3$ the silaboration product **254** was obtained in 36% yield, while a reaction with PCy_3 as a ligand furnished **254** in 79% yield after 96 h. Changing the palladium source to $Pd(dba)_2$ with PCy_3 as a ligand gave product **254** in 85% yield. The reaction was then carried out with several 2- and 3-disubstituted pyridines. A number of functional groups, e.g. methyl, phenyl methoxy, and methyl ester, were found to be compatible with the catalytic system. Quinoline was also subjected to the silaboration reaction, yielding the 1,4-adduct **255** as the major product in 81% yield (by NMR).

Surprisingly, no reaction was observed with 2-methylpyridine. All reactions were carried out with either Me_2PhSi–Bpin or Me_2ClSi–Bpin. The silaboration adducts **253** can be isolated, if stable, or easily converted to 4-silylpyridines **256** upon heating with benzaldehyde in a single-flask fashion. For example, silylpyridines **257** and **258** were prepared using this method in 86 and 62% yields, respectively.

The following mechanism was proposed for the silaboration reaction (Scheme 71).[93] Oxidative addition of the silylboronic ester **259** to Pd(0) and coordination to the pyridine produce complex **260**. The regioselective insertion of pyridine into the Pd–B bond with the introduction of the boryl group onto the nitrogen atom produces the π-allylpalladium complex **261**. Lastly, reductive elimination gives rise to dihydropyridines **262** and **263** and regenerates the Pd(0) catalyst.[92] Involvement of Pd(0) is supported by the experiments with $Pd(dba)_2$ as a catalyst that gave the product in yields similar to those obtained under the standard conditions.

In 2012, Daugulis and co-workers reported the copper catalyzed bis-trifluoromethylsulfenylation of *N*-(8-quinolinyl)nicotinamide (**264**) to give disulfide **265** in 43% yield (Scheme 72).[94] The bulk of the paper is devoted to the sulfenylation of benzamide derivatives catalyzed by copper(II) acetate. The optimal conditions include $Cu(OAc)_2$ (50 mol%), and bis(trifluoromethyl) disulfide (1.8–2.5 equiv.) at 90–110 °C in DMSO.

A control experiment with 99.999% $Cu(OAc)_2$ verified that the reaction is catalyzed by copper. No reaction occurred in the absence of copper.

In 2013, Daugulis and co-workers reported the directed amination of arene C–H bonds by copper(II).[48] Initial studies focused on the reaction between 8-aminoquinoline *p*-methoxybenzamide (**266**) and morpholine with $Cu(OAc)_2$ as a catalyst in *N*-methylpyrrolidinone at 110 °C. Under these conditions coupling product **267** was obtained in 39% yield. Use of *N*-methylmorpholine *N*-oxide (NMO) as an oxidant and Ag_2CO_3 (0.13 equiv.) with 10 mol% $Cu(OAc)_2$ afforded **267** in 87% yield. K_2CO_3 and O_2 gave lower yields. Arenes featuring fluoro, methyl, methyl ester, methoxy, trifluoromethyl, and *tert*-butyl groups were suitable substrates for the reaction conditions.

The C4-amination of isonicotinamide **268** furnished the amination product **269** in 56% yield (Scheme 73). A mechanism was proposed that involves activation of the aryl C–H bond by Cu(II), followed by oxidation to a Cu(III) species, coordination of the morpholine, and subsequent reductive elimination that gives rise to the Cu(I) species.[95]

In 2013, Yu and co-workers reported the Pd(II)-catalyzed iodination of (hetero)arenes with elemental iodine (Scheme 74).[96]

It was found that $CsOAc/NaHCO_3$ facilitated iodine abstraction for the catalytic cycle. A mixture of DMF/*t*-AmylOH solubilized the PdI_2 sufficiently well with catalyst loading as low as 2 mol%. The reactions were run with 4Å molecular sieves at 80 °C. Ortho-substitution to the amide directing group is observed in all cases. Using this method, nicotinamide **270** was converted to 4-iodopyridine **271** in 54% yield (Scheme 74).

$K_2S_2O_8$ (20 mol %) was used in place of $NaHCO_3$, to prevent dimerization, and DMSO as the solvent at 65–80°C. The *ortho*-selectivity of the iodination was explained by a strong trans-effect and the steric effects that favor structure **272** over bispyridine complex **273** (Scheme 75).

In 2013, Cui, Wu, and co-workers reported a method that allows for a regioselective synthesis of various 2-arylsulfonylquinoline *N*-oxides.[97] The reaction was carried out with arylsulfonyl chloride (4 equiv.), CuI (10 mol%), K_2CO_3 (2 equiv.) in 1,2-dichloroethane at 100 °C. Most of the examples are provided for 2-arylsulfonylquinoline *N*-oxides, with one example for isoquinoline *N*-oxide (**274**) that produced sulfone **275** in 88% yield (Scheme 76). The unusual C4-substitution pattern that was observed with isoquinoline *N*-oxide remains to be explained.

In 2008, Hiyama, Nakao, and co-workers reported the alkenylation and alkylation of fluoroarenes using $Ni(cod)_2$ as a catalyst.[98] The electron-deficient pyridines **222** and **239** underwent alkenylation with 4-octyne in C4 position to give 4-vinylpyridines **276** and **277** in 85 and 99% yields, respectively (Scheme 77).

In 2010, Ong and co-workers reported a Ni-catalyzed conversion of substituted pyridines **16** to 4-vinylpyridines **278** (Scheme 78).[99] Concomitant formation of 3-vinylpyridines **279**, typically as minor products, was also observed. In the optimization screening, a reaction of

pyridine with 4-octyne in the presence of a complex of $AlMe_3$with amino-NHC ligand **280** (20 mol%), and $Ni(cod)_2$ (10 mol%) at 80 °C afforded the desired product **281** in 83% yield.

Other Lewis acids such as $ZnMe_2$ or BH_3 proved detrimental to the reaction (7% and 5%, respectively). Good yields were reported for monosubstituted pyridines containing phenyl, methyl, and methoxy groups. Quinoline and 6-methyl quinoline were also studied. 3-Methylpyridine gave rise to product **282** along with the 3-isomer in a 5:2 C4/C3 ratio. Quinoline afforded product **283** with a 10 : 1 C4/C3 ratio.

In order to understand factors influencing the regioselectivity, $Ni(cod)_2$ was treated with stoichiometric amounts of ligand **280** and pyridine (Scheme 79). After a few hours all of ligand **280** had been consumed and complex **284** formed. A crystal structure unambiguously confirmed a three-coordinate nickel(0) center bound to two **243** units and one pyridine unit. The Lewis acid, $AlMe_3$ is coordinated to the nitrogen of the pyridine ring, providing a plausible explanation of the C4/C3-selectivity.[53]

Competition experiments yielded a small kinetic isotope effect of 1.25. This result shows that the C–H bond cleavage is not the rate-limiting step. The proposed mechanism is shown in Scheme 80. Formation of **285** is followed by the oxidative addition of the alkyne to produce Ni hydride **286**. Subsequent alkyne insertion into the Ni–H bond gives rise to intermediate **287**. Finally, reductive elimination yields product **278** and the catalytically-active Ni(0) complex.

In 2010, Hiyama, Nakao, and co-workers reported the C4-selective Ni-catalyzed alkylation of pyridines (Scheme 81).[100] After developing a C2-selective alkylation of pyridine using a nickel-based catalytic system with electron-rich phosphine ligands,[101] the authors used a Lewis acid to coordinate to the N1-nitrogen, allowing for the steric and electronic factors to dictate the selectivity away from C2. For their optimization study the research team used pyridine, 1-tridecene, $Ni(cod)_2$, 1,3-2,6-diisoprpylphenyl)imidazole-2-ylide (IPr, **288**) and $AlMe_3$ in toluene at 130 °C. This reaction yielded 4-tridecylpyridine (**289**) in 70% yield. No product was observed upon replacement of the NHC with various phosphine ligands. A number of Lewis acids were screened, with $AlMe_3$ and MAD (**290**) providing the highest yields and C4 selectivity. On the other hand, diorganozinc reagents were inefficient Lewis acids, with no product obtained. 30 mol% of the Lewis acid was optimal with higher loadings providing no benefit, and lower loadings providing lowered yields. IMes (**291**) and IPr (**288**) gave the optimal yields of alkylpyridines **292** and **293**. High selectivity of the linear C4-alkylated product **292** was observed, with the branched product **293** as a minor contaminant with aliphatic 1-alkenes. With styrene, however, the branched addition product **294** was obtained in 95% yield.

The reaction proceeds with a number of substrates in 12–95% yields. Aliphatic 1-alkenes having a phenylsilyl- or pivaloyl-protected hydroxyl group and a terminal or internal double bond as well as vinylsilanes were suitable substrates for the alkylation reaction.

One reaction was also carried out with 4-octyne under standard conditions. The reaction produced a *Z*-alkenylated pyridine **281** in 53% yield, along with the corresponding C3-

isomer in 15% yield. In order to better understand the mechanism, a reaction with D_5-pyridine and 1-tridecene (1.5 equiv.) was performed under the standard conditions. While some loss of deuterium at C2 and C3 was observed after 9 h, no D/H exchange was detected after 3 min (value in parentheses) (Scheme 82).

While there is an H/D exchange at the C2 and C3 positions, lack of a large amount of these alkylated products implies that the coordination of Ni to these sites is reversible, in contrast to the irreversible reaction at the C4 position (Scheme 82). This result also implies a catalytic cycle initiated by the oxidative addition of the C4–H bond of the pyridine in the Ni/pyridine-MAD complex **295** The resulting intermediate **296** engages the alkene to give complex **297**. Subsequent migratory insertion of the alkene into the Ni–H bond produces alkyl nickel species **298**. Finally, reductive elimination from **298** gives rise to alkylpyridine **299** and, after complexation with pyridine and MAD, the Ni(0) complex **295**.

4 C5/C6/C7–H-Functionalization

In 1995, Huang and co-workers reported the perfluoroalkylation of pyridine, quinoline, and isoquinoline.[102] Based on the previous research by the group,[103] sodium perfluoroalkanesulfinates were reacted with heteroarenes and $Mn(OAc)_3$ in MeCN/AcOH/Ac_2O at 80–85 °C. The reaction generates perfluoroalkyl radicals by oxidation with $Mn(OAc)_3$. The radicals add at C2 in substituted pyridines with some C3/C4 addition as well. Quinoline (**1**), 4-methylquinoline (**300**), and isoquinoline (**301**) were also reacted under the standard conditions, with all three giving mixtures of C6-isomers **302**–**304** and C8-isomers **305**–**307** in 45–61% yields and with a 1.3:1 average C6/C8 selectivity (Scheme 83).

In 2010, Yamakawa and co-workers reported the trifluoromethylation of arenes and heteroarenes with trifluoroiodomethane and Fe(II).[104] Previous work performed by the same group described the radical trifluoromethylation of a number of nucleobases.[105] The method uses CF_3I, $FeSO_4$ or Cp_2Fe, H_2O_2, DMSO as a radical promoter, and H_2SO_4.

A number of arenes, heterocycles, and pyridine derivatives were converted to the corresponding trifluoromethylated derivatives by this procedure. When quinoline was reacted under these conditions, the C5-trifluromethylated product **308** was obtained in 10% yield. With 8-aminoquinoline (**309**), a mixture of C5-mono-, C7-mono-, and C5/C7-bistrifluoromethylation products **310**–**312** were obtained in a 2:1:5.8 ratio with an overall 79% yield. The reaction is postulated to proceed via an initial formation of a hydroxyl radical through the reduction of H_2O_2 by Fe(II) that is followed by the interception of the OH radical by DMSO to form a methyl radical. The methyl radical reacts with CF_3I to give the trifluoromethyl radical.[106]

In 2013, Ertem, Stahl, and co-workers reported the radical chlorination of 8-amidoquinolines under acidic conditions.[107] The work focused on the reactivity of the *N*-(quinolin-8-yl)benzamide **85**. Previous work on the Cu(II)-catalyzed aerobic C–H-oxidation had been studied on electron-rich arenes, but not on substituted azines. The optimization study began with conditions similar to the oxidative chlorination of electron-rich arenes: 1

atm O_2, 2 equiv. LiCl in AcOH at 100 °C with CuCl or $CuCl_2$. Surprisingly, instead of the chlorination of the aryl ring of the benzamide they observed formation of the C5-chlorination product **313** in 34% and 81% yields with $CuCl_2$ and CuCl, respectively. Upon addition of 20 mol% LiOAc with $CuCl_2$ the yield was increased to 88% with exclusive C5-chlorination. Lithium acetate was proposed to act as a Brønsted base that promotes substrate binding to the Cu center.[108] Mechanistic studies were performed to better understand chlorination of the quinoline ring. No deuterium incorporation was observed in CD_3CO_2D in place of AcOH, indicating that the C–H bond cleavage is irreversible. Based on the KIE studies a single electron transfer (SET) C–H-functionalization pathway was proposed for the quinoline chlorination. A calculated mechanism for the Cu(II) mediated chlorination is shown in Scheme 85. Cu(II) complex **314** undergoes an SET oxidation of the quinoline system to give radical cation **315**.

A chlorine atom is then transferred from $CuCl_2$ to C5 position with the C5–H of the azine activated by a chloride and acetic acid via a transition state **316** to give the cationic species **317**. Further deprotonation proceeding via transition state **318** furnishes the C5-chlorinated quinoline complex **319**.

In 2014, Zeng and Cong described a chelation-induced C5-allylation of 8-amidoquinolines **320** (Scheme 86).[109] The reaction was catalyzed by iron(III) chloride. Preliminary mechanistic analysis pointed to the activation of the substrates **320** via chelation of the Fe catalyst, and the activation of the allylic alcohol by Fe(III). The products **322** were obtained in good to excellent yields and with an excellent C5-regioselectivity.

In 2013, Dong and Dong reported the Pd and norbornene catalyzed C–H amination using aryl halides (Scheme 87).[110] The authors utilized a reductive Catellani reaction pathway to install an amino group ortho to the position previously occupied by the halogen. Numerous (hetero)arene examples are provided, including three quinolines. Under the optimized conditions 5-iodoquinoline (**322**) was reacted with *N*-benzoyloxymorpholine (**323**) to give aminoquinoline **324** in 88% yield. Substituted 6-aminoquinolines **325** and **326** were also produced in 50 and 99% yields, respectively.

5 C8–H-Functionalization

In 2011, Chang and co-workers reported the Rh(NHC)-catalyzed regioselective synthesis of 8-arylquinolines **327** from quinolines **328**.[111] Prior work by the group[112] led them to postulate the possibility of a Rh-NHC catalytic system for direct regioselective C8-arylation of quinoline.

Quinoline, 4-bromotoluene, and $Rh_2(OAc)_4$ with and without IMes ligand **291** were reacted at 95 °C. C8-arylation product **329** was obtained in 3% yield in the absence of the ligand **291**. With the ligand added, product **329** was obtained in 58% yield with >99:1 C8/C2 regioselectivity. With other bulkier NHC ligands, e.g. IAd (**330**) or IPr (**288**), the selectivity decreased to 2:1 and 10:1, respectively. Phosphine ligands proved ineffective, providing low yields and site-selectivity. For example, the yield of **329** was only 5% and the C8:C2 ratio was 5:1 with PCy_3. The method tolerates a number of *para*-substituents in the aryl bromides

(e.g. Me, MeO, F, CF_3). *ortho*-Substituted aryl bromides were not reactive, while aryl chlorides were as active as aryl bromides. Quinolines bearing a number of functional groups (e.g. methyl, benzyl, phenyl, methoxymethyl ethers, alkyl, aryl) in C3, C4, and C6 positions provided C8-arylation products **327** in 64–93% yields (Scheme 88). Quinolines **331** and **332** containing a tertiary amino group and an acetal were also prepared in good yields.

In order to better understand the mechanism primary kinetic isotope effect was measured. A KIE of 2.76 was observed for the C8-arylation of quinoline. Chang and co-workers attribute this result to a base-assisted concerted proton abstraction and metalation in the C8-position of quinoline. Both bimetallic **333** and monomeric **334** are plausible intermediates, and more studies are needed to clarify the mechanism (Scheme 88).[113]

In 2014, Marder, Sawamura and co-workers reported the C8-selective borylation of quinolines catalyzed by a silica-supported Ir/phosphine system (Scheme 89).[114] 8-Borylquinolines **335** had previously been prepared by multistep sequences via borylation of 8-haloquinolines.[115] As discussed earlier in this review, prior to this work borylation of pyridines and quinolines under Ir or Rh catalysis occurred preferentially at the C3 or C4 positions with bidentate *N*-containing ligands (e.g. dtbpy). The authors began their study by reacting quinoline and B_2pin_2 in MTBE at 60 °C in the presence of an immobilized Ir-catalyst precursor prepared from silica-SMAP ligand **336** and $[Ir(cod)(OMe)]_2$. The C8-borylated quinoline **337** was formed in an 81% yield, with 13% of the 1,2,3,4-tetrahydroquinoline (**338**) as a side product. HBpin was also tested as a boronic ester source, however, product **337** was obtained in only 17% yield. In addition, side product **338** was also formed in 30% yield. A similar immobilized Rh-catalyst afforded no C8-borylation product. Other phosphine ligands or silica supported ligands yielded only trace amounts of products (Scheme 90). The method is applicable to a number of mono- and di-substituted quinolines bearing alkyl, chloro, methoxy, and aryl groups. For example, the 2-substituted 8-borylquinolines **339** and **340** were readily prepared in 91 and 74% yields. It was noted that with 2-methylquinoline and Ir-dtbpy catalyst, in place of **336**, a mixture of C4/C6/C7 borylated products was obtained in 16%, 27%, and 20% yields, respectively.

A number of 8-borylquinolines **335** were too unstable to be isolated, hence the crude product was subjected to the oxidation with $NaBO_3$, followed by treatment with Boc_2O (Boc = *tert*-butoxycarbonyl). This sequence furnished four 8-*tert*-butoxycarboxyquinolines **341** in 60–71% yields (Scheme 91). To further demonstrate the utility of this method, the corticotropin-releasing $factor_1$ (CRF_1) receptor antagonist **342** was synthesized from quinoline **343** using the C8-borylation that was followed by a Suzuki-Miyaura reaction of the intermediate boronate **344** in the late stage of the synthesis (Scheme 92).[116]

In 2014, Shibata and Matsuo reported the Rh-catalyzed regioselective C8-alkenylation of quinoline *N*-oxides **345** (Scheme 93) that produced 8-vinyl derivatives **346**.[117] This method uses the *N*-oxide moiety as a directing group that is presumed to facilitate formation of a five-membered rhodacycle. Initial experiment with quinoline *N*-oxide (**347**), diphenylacetylene, $[Rh(cod)_2BF_4]$ (10 mol%), BINAP (10 mol%), in chlorobenzene at 135 °C afforded product **348** in 34% yield.

It was found that shorter reaction times were key, as prolonged reaction times led to extensive decomposition. By changing the Rh-counterion to triflate and the ligand to 3,5-xylyl-BINAP, and shortening the reaction time to 1 h, **348** was obtained in >95% yield.

Heating at 135 °C was necessary to achieve a high yield in chlorobenzene. On the contrary, in cyclopentyl methyl ether (CPME) the reaction gave comparable results already at 110 °C. A number of *para*-diarylacetylenes afforded products **346** in 41–89% yields. The best *E/Z* ratio of the addition product was >20:1 with the trifluoromethyl- (in chlorobenzene at 135 °C), and chloro-substituted diarylacetylenes (in CPME at 110 °C).

A 1/1 *E/Z* ratio was obtained with bis(4-methoxyphenyl)acetylene. C2-, C3-, C4-, C6- and C2/C6-substituted quinolines bearing methyl, methoxy, chloro, and nitro groups afforded corresponding products **346** (e.g. **348**–**351**) in 50–89% yields. *E/Z* ratio was highest (>20:1) for the products **349** and **350** that arouse from 3- and 4-methylquinolines, while quinoline **351** was formed with the 5 : 1 *E/Z* ratio.

In order to shed light on the mechanism of the reaction, quinoline *N*-oxide (**347**) was reacted in the presence of D_2O and in the absence of the alkyne under the standard reaction conditions. 69% of H/D exchange was observed in C2- and C8-positions. With pyridine *N*-oxide (**352**) 50–60% of C2-deuteration was observed under the same conditions (Scheme 94). These results suggested that the C–H-activation by Rh occurs in both positions and produces intermediates **353** and **354** (Scheme 95). However, alkyne insertion only occurs in C8 position due to the stability of the five-membered metalacycle **353**. Subsequent reductive elimination from intermediate **355** affords *N*-oxide **348**.

In 2014, Chang and co-workers reported the C8-selective Rh-catalyzed iodination and amidation of quinoline *N*-oxides.[118] After initial screening of the reaction conditions it was found that a Rh(III) catalytic system enabled the iodination of substituted quinoline *N*-oxides **345**.

Bromination and chlorination reactions were not synthetically useful providing corresponding C8-halogenated products in less than 20% yields. The optimized reaction conditions include $[RhCp^*Cl_2]_2$ (4 mol%), *N*-iodosuccinimide (NIS, 1.5 equiv.), $AgNTf_2$ (16 mol%) in DCE at 50 °C. Products **356** were formed in 32–93% yields (Scheme 96). A number of functional groups were compatible with the catalytic system.

For example, nitro- and formyl-substituted 8-iodoquinoline *N*-oxides **357** and **358** were produced in 77 and 93% yields. 8-Iodoquinoline *N*-oxides are valuable synthetic intermediates that can be used for further functionalization of the C8-position.[119] Attention was further turned to the catalytic synthesis of 8-amidoquinoline *N*-oxides **359** (Scheme 97). Using conditions reported in their previous work[111] with *p*-toluenesulfonyl azide, $[IrCp^*Cl_2]_2/AgNTf_2$ in DCE at 80 °C 8-tosylamide **360** was obtained in 24% yield. While addition of sodium acetate did not improve the catalytic performance, addition of acetic acid (30 mol%) at a lower temperature (50 °C) resulted in an improved yield (92%).

No C2-amidation was observed under the reaction conditions. Other acids were tested as additives (e.g. trifluoroacetic acid, camphorsulfonic acid, pivalic acid and benzoic acid),

with acetic acid emerging as an additive of choice, due to the ease of handling and the ease of removal for purification. It was also noted that rhodium-, ruthenium-, and palladium-based catalytic systems, were ineffective at 50 °C.

Various functional groups were tolerated under the reaction conditions, e.g. nitro, esters, acetal, alkoxy, siloxy, carbamate, and aldehyde in the quinoline core (**361**-**366**). Alkanesulfonyl, benzenesulfonyl, naphthalene, and acyl azides were suitable, giving rise to products **367**–**369**, whereas aryl and alkyl azides did not react under these conditions (Scheme 97). The reaction proceeds with a small kinetic isotope effect (k_H/k_D = 1.23 with acetic acid, k_H/k_D = 1.14 without acetic acid) (Scheme 98). Due to the small observed KIE the C–H bond cleavage is the rate-limiting step.[120] Crystalline C8-Ir complex **370** was isolated and was subjected to the reaction conditions as a catalyst. The reaction gave rise to the desired product in a 62% yield, suggesting that complex **370** could be an intermediate in the catalytic cycle, although it could also be an off-cycle intermediate. Based on the aforementioned information the following mechanism was proposed (Scheme 99). The silver salt converts the dimeric Ir to a cationic species that reacts with the *N*-oxide substrate to give the five-membered iridacycle **370**.

Subsequent coordination of azide **371** produces intermediate **372**. Insertion of the amido group into the C–Ir bond affords complex **373** that subsequently undergoes protodemetalation, as shown in structure **374**, to give complex **375**. Acid-assisted release of the cationic Ir catalyst completes the catalytic cycle. The synthetic utility of the method was demonstrated by the synthesis of zinquin ethyl ester **376**. The ester is a derivative of an important fluorescent sensor for Zn(II) in cells.[121] The starting material **377** was synthesized from 6-hydroxy-2-methylquinoline (**378**) in two steps. The C8–H-amidation furnished sulfonamide **379** in a 76% yield and with high C8-selectivity. Subsequent reduction with zinc produced zinquin ethyl ester **376** in a 54% overall yield (Scheme 100).

Later that year Chang and co-workers reported new examples of C8–H-functionalization catalyzed by Rh(III) at room temperature with hypervalent iodoalkynes and diazoesters (Scheme 101).[122] The reaction optimization was performed for the reaction of 6-methylquinoline *N*-oxide with methyl diazomalonate catalyzed by $[RhCp^*Cl_2]_2$ and $AgSbF_6$ at various temperatures in DCE. Addition of 20 mol% pivalic acid at 25 °C provided *N*-oxide **380** in 94% yield. Solvents other than DCE retarded the reaction.

Changing the catalyst to $[IrCp^*Cl_2]_2$ or $[Ru(p\text{-cymene})Cl_2]_2$ severely reduced the yield (<5%). For the alkylation of quinoline *N*-oxides with diazo compounds it was found that alkyl, nitro, halogen, carbamate, siloxy (**381**), acetoxy, acetal (**382**), aldehyde, keto, and ester groups in the quinoline *N*-oxides were well-tolerated. The diazoesters bearing phenylsulfonyl and benzoyl groups, as well as diethyl diazomalonate were suitable for the reaction, while phosphoryl-, cyano- and nitro-substituted diazoesters did not provide the desired products. 8-Alkylquinoline *N*-oxides **383** were typically formed in 40–96% yields.

In addition to C8–H-alkylation, Chang and co-workers developed alkynylation with *I*-alkynyl-substituted hypervalent iodine reagents previously reported by Loh, Li and Glorius groups independently: 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-

EBX, **384**) (Scheme 102).[123] A variety of 8-alkynylquinoline *N*-oxides **385** were prepared in 62–95% yields.

The optimal catalyst for this reaction was found to be $[RhCp^*(MeCN)_3](SbF_6)_2$. Addition of 4Å molecular sieves improved the yield dramatically. Quinoline *N*-oxides bearing halogen, alkyl, as well as ester, carbamate, siloxy, acetoxy, acetal, aldehyde and ketone groups proved to be viable substrates (see, for example, products **386**–**390** in Scheme 102). To gain insights into the mechanism, isotope-labeling experiments were carried out for both reactions under the standard conditions (Scheme 103). For the alkylation a k_H/k_D value of 5.0 was obtained, while a somewhat smaller but significant KIE (k_H/k_D = 2.7) was observed for the alkynylation. It was, therefore, proposed that the C–H-bond cleavage was involved in the rate-limiting step. Based on the KIE data, the following mechanism was proposed: initial formation of the five-membered rhodacycle **393** is followed by coordination of the diazo species to give intermediate **394** that, upon elimination of N_2, produces the metal carbenoid species **395** (pathway A, Scheme 104). Subsequent migratory insertion gives rise to a 6-memebered rhodacycle **396** that undergoes protodemetalation to give the desired product **397** and the catalyst. In addition, a pathway that does not involve a discrete carbenoid intermediate en route to the 6-membered rhodacycle cannot be ruled out (pathway B, Scheme 104).[122]

In 2014, Li and co-workers reported the Rh(III)-catalyzed C8–H-alkylation of quinoline *N*-oxides followed by O-atom transfer, resulting in ketone products **398** (Scheme 105).[124] The initial experiment with quinoline *N*-oxide (**347**), diphenylacetylene and $[RhCp^*Cl_2]_2$ in DCE at 110 °C afforded no product. Addition of $AgSbF_6$, to cleave the Rh-dimer, led to formation of product **399** in 32% yield. A number of additives were tested including acetic and pivalic acids, as well as $Zn(OTf)_2$. Under the optimal conditions in 1,4-dioxane, with AcOH (2 equiv.), and $Zn(OTf)_2$ (20 mol%) as additives product **399** was formed in 90% yield. Several symmetric *para*-substituted diarylacetylenes were tested, and the corresponding products containing halogen (**400**, **401**), alkyl (**402**, **403**), trifluoromethyl (**404**), methoxy (**405**), and other groups were isolated in good yields. No reduction of yields was observed with C2-substituted *N*-oxides (e.g. products **406** and **407**).

On the other hand, 7-chloroquinoline *N*-oxide afforded the corresponding product **408** in a lower yield (38%), indicating that steric hindrance close to the addition position is detrimental to the reaction. Symmetric *para*- and *meta*-substituted diarylacetylenes proved to be suitable substrates. An electronically-biased alkyne, (*p*-methoxyphenyl)(*p*-trifluoromethylphenyl)-acetylene afforded a mixture of isomers **406** and **407** with a 1.5 : 1 **406**/**407** ratio (Scheme 105).

Acetylenes bearing a phenyl and an alkyl group also proved to be suitable coupling partners, giving rise to aromatic ketones, e.g. **409** and **410**. In contrast, dialkyl-substituted acetylenes and 1-phenyl-2-trimethylsilylacetylene did not give the expected products. Extensive mechanistic studies were performed in order to elucidate the mechanism of the C–H-activation, and O-atom transfer process. The reaction was run under standard conditions with di(*p*-tolyl)acetylene in the presence of 4 equiv. of D_4-acetic acid. Low deuterium incorporation (5%) at C8 was observed (at 20% conversion), suggesting an irreversible C8–

H activation. A competition reaction between quinoline *N*-oxide (**347** and its D_7-isotopomer (D_7-**347**) with di(*p*-tolyl)acetylene under standard conditions at 20% conversion afforded a KIE value of 3.6–4.0, indicating that the C–H-activation may be involved in the rate-determining step.

In order to gain insights into the O-atom transfer (OAT) process, quinoline *N*-oxide (**347**) was reacted with diphenylacetylene under standard conditions with 6 equiv. of $H_2{}^{18}O$. No ^{18}O incorporation was observed in the isolated product, indicating that water is not involved, and that the OAT is an intramolecular process. Furthermore, the reaction was carried out in the presence of 3-bromoquinoline (**411**). Bromide **411** is expected to compete with the quinoline, if the oxygen transfer occurs prior to C8–H-activation. Formation of a product arising from 3-bromoquinoline was not observed, suggesting that a direct O-atom transfer to alkynes that produces quinoline and a rhodium α-oxocarbene species is unlikely. The possibility of an unassisted insertion of a rhodium(III)/α-oxocarbene intermediate into the C8–H bond of quinoline was also excluded. It was, therefore, proposed that the C–H-activation occurs prior to the O-atom transfer. When 8-(1,2-diphenylvinyl)quinoline *N*-oxide (**412**) was subjected to the reaction, no O-atom transfer was observed. This result suggests that an intermediate, such as olefin **412**, is not plausible. Rhodium(III) η^3-benzyl complex **413** was isolated, that produced ketone **399** when treated with **347** (Scheme 107). Metalacycle **414** was detected by HRMS during in the reaction mixture. These results suggest that **413** is a resting state of the catalyst in the absence of AcOH, and that the release of the catalyst, likely through participation of quinoline *N*-oxide may be the rate-determining step.

Two possible mechanisms were proposed (Scheme 108), – path A and path B. In path A, the cyclometalation followed by alkyne coordination and the migratory insertion produces the seven membered rhodacycle **415**. Subsequent reductive elimination generates a rhodium(I) species and intermediate **416**. Oxidative addition of **416** to the rhodium species generates an O- or C-bound enolate (**417** or **418**). Tautomerization produces rhodium(III) η^3-benzyl complex **413** that liberates the product upon reaction with quinoline *N*-oxide. In path B formation of the five-membered rhodacycle **419** is followed by the alkyne insertion to give the seven membered rhodacycle **420**. Cleavage of the N–O bond affords a metal α-oxocarbene species **421** that undergoes migratory insertion to yield rhodium(III) η^3-benzyl complex **418**, which then follows path A.

In 2015 Lan, Li, and co-workers reported a computation study of this Rh-catalyzed reaction,[125] using the M11L DFT method.[126] While four different pathways were ultimately evaluated, the path A in Scheme 108 was found to be the most energetically favorable one.

Later that year Chang and co-workers reported a similar Rh(III)-catalyzed C8-alkylation/O-atom transfer cascade for quinoline *N*-oxides (Scheme 109).[127] Under the optimal conditions for Chang's method, an excess of quinoline *N*-oxide is reacted with the alkyne in the presence of $[RhCp^*Cl_2]_2$ (2.5 mol%) and $Cu(OAc)_2$ (5 mol%) in DMF at 110 °C. Kinetic isotope studies produced a KIE of 2.1, – almost half of that reported by Li.

Further, 8-(1,2-diphenylvinyl)quinoline *N*-oxide (**412**) was synthesized and subjected to the reaction. Less than 5% yield of the OAT product was formed in this case. The ^{18}O-isotopomer of 3-methylquinoline *N*-oxide (^{18}O-**422**) was also reacted with diphenylacetylene. Complete incorporation of the ^{18}O in the ketone moiety of the product **423** was observed. The products **398** were typically isolated in 17–93% yields.

In 2015, Larionov and co-workers reported the Pd-catalyzed site-selective C8-arylation of quinoline *N*-oxides (Scheme 110).[128] In a departure from the previously reported Rh- and Ir-based methodology, the authors focused their efforts on catalysis with palladium. Initial screening with quinoline *N*-oxide, 4-iodobenzotrifluoride, $Pd(OAc)_2$ and acetic acid (10 equiv.) at 120 °C gave product **424** in 8% yield. With the addition of AgOAc (3 equiv.) the yield improved to 39%. Use of Ag_3PO_4 (0.5 equiv.) and $AcOH/H_2O$ (30/5.5 equiv.) raised the yield to 95% and the C8/C2 selectivity to 23:1. Microwave conditions were also developed that allowed for sub-hour reaction times. The reactions were generally complete within 50 min at 180 °C under the microwave irradiation, while under thermal conditions at 120 °C the reaction required ~16 h.

A one-pot synthesis of 8-(4-bromophenyl)quinoline (**426**) can be accomplished under the microwave irradiation within 3 h. In this case, the N-oxidation of quinoline with hydrogen peroxide in acetic acid to give *N*-oxide **347** that was subjected to the C8–H-coupling with 4-bromoiodobenzene. Reduction of the *N*-oxide with hypophosphorous acid produced **426** in 67% overall yield. A number of 8-arylquinoline *N*-oxides **425** bearing diverse substituents (e.g. aryl, nitro, halogen, ester, methoxy, and alkyl groups) at C2/C3/C4/C5/C6 in the quinoline core were synthesized in 54–93% for the thermal conditions, and in 69–94% for the microwave-assisted reactions (Scheme 110). The synthesis of 8-phenylquinoline *N*-oxide (**427**) was carried out on a 2 gram scale with 82% yield.

A mechanistic study was undertaken to clarify the origin of the site-selectivity. The H/D exchange occurred in the C8 position, but not in C2 position of quinoline *N*-oxide under standard conditions in deuterated solvents. A primary KIE of 2.0 was observed for the C8-arylation. These results, together with the data on the substituent effects obtained from the Hammett studies suggest that the C8-cyclometalation may be the rate-determining step. With this information in hand, a computational study was performed to determine the factors that influence the site-selectivity of the cyclopalladation of quinoline *N*-oxides. It was found that acetic acid plays a crucial role as a ligand that makes Pd more electrophilic and diverts the reaction in the more electron-rich C8 position.

On the other hand, Fagnou's Pd/phosphine systems react predominantly in the C2 position due to the higher acidity and strength of the C2–H bond.[12] (Scheme 111).

C8–H-Arylation of quinoline *N*-oxides **345** was also recently accomplished by Chang and co-workers, with arenediazonium salts as the electrophilic coupling partners (Scheme 112).[129] The reaction was catalyzed by $[IrCp^*Cl_2]_2$ (5 mol%)/$AgNTf_2$ (20 mol%) at 45 °C in trifluoroethanol. Eight 8-arylquinoline *N*-oxides **425** were prepared in 49–89% yields.

In addition to the C8–H-arylation of *N*-oxides **345**, efficient ortho-C–H-arylation of benzamides and C3–H-arylation of acrylamides were also described.

In 2015, Larionov and co-workers added another example of a Pd-catalyzed C8–H-functionalization, – the C–H homocoupling of quinoline *N*-oxides (Scheme 113).[130] During optimization of their Pd-catalyzed C8-site-selective arylation,[128] a formation of a side product was observed in some instances. Upon removal of the iodoarene from the reaction mixture, the yield of the side product increased to almost 50%.

Single crystal X-ray crystallographic analysis of the side product confirmed that it was 8,8'-biquinolyl *N*,*N*′-dioxide (**428**) that was formed by way of oxidative C8–H-homocoupling of quinoline *N*-oxide. The dimerization products were obtained in 42–83% yields in the presence of $Pd(OAc)_2$ (10 mol%), AgOAc (4 equiv.), AcOH (5 equiv.) and H_2O (1.5 equiv.) at 120 °C. In line with earlier observations, the addition of water significantly increased the yield. It was suggested that water assists the breakdown of trimetric $Pd(OAc)_2$.[131]

In order to gain insights into the mechanism of the reaction, a Hammett substituents effect and kinetic isotope effect studies were undertaken. A ρ value of −1.28 was obtained that was significantly smaller then for the H/D exchange and for the C8–H-arylation. No primary KIE (k_H/k_D = 1) was observed for the homocoupling, showing that formation of palladacycles **429** and **430** was not a turnover-limiting step, in contrast to the Pd-catalyzed C8–H-arylation. It was, therefore, proposed that the reaction involved higher oxidation state Pd intermediates **431** (Scheme 113).

In 2015, Li, Wan and Yu reported the Rh(III)-catalyzed regioselective C–H-selenation of (hetero)arenes (Scheme 114).[132] The reaction was carried out with $[RhCp^*Cl_2]_2$ as a catalyst in the presence of $AgSbF_6$ (1.5 equiv.), NaOAc (1.2 equiv.), and phenylselenyl chloride (1.2 equiv.) in THF at 80 °C. Low yields of 8-selenylquinoline *N*-oxides **432** were observed with other silver salts or other acetate salts. Products **433**–**437** were isolated in 45–67% yields. The reaction is believed to proceed through the initial formation of rhodacycle **438** that engages phenylselenyl chloride to give the cationic species **439**. In the next step, silver salt-assisted electrophilic selenylation of the C–Rh bond affords complex **440**. Subsequent reaction of complex **440** with substrate **441** affords selenation product **442** and rhodacycle **438**, thus completing the catalytic cycle. A Rh(III)/Rh(V) pathway, where the Se–Cl bond oxidatively adds to a Rh(III) species may also be operative.[133]

6 Summary and Outlook

The reactions discussed in this review attest to the significant progress that has been achieved in the area of distal C–H-functionalization of pyridines and quinolines in the past decade. A number of site-selective transformations have been developed for C3 and C4 positions, as well as C8 position in quinolines. On the other hand, C5, C6 and C7 positions in quinolines have generally only been functionalized by using a directing group in an adjacent position. Hence, methods of non-directed C–H-functionalization in these positions have yet to be established. In addition, diversification of functional groups that can be installed by means of C–H-functionalization is an important area of the future systematic

mechanism-driven studies. Site-selective C–X (e.g. F and Cl), C–O, C–N and C–C bond-forming reactions (e.g. trifluoromethylation and alkylation) will also likely become the focus of the future work. New catalytic systems based on other metals, – in particular the more abundant Mn, Co, Ni, Fe, and Cu, – should also become a focal point for future research. Together, these developments are expected to significantly simplify access to the important class of azaheterocycles.

Acknowledgments

Financial support by the Welch Foundation (AX-1788), NIGMS (SC3GM105579), the Max and Minnie Tomerlin Voelcker Fund and the University of Texas at San Antonio is gratefully acknowledged.

Biography

Oleg Larionov graduated with a Master's degree in Chemistry from the Higher Chemical College of the Russian Academy of Sciences. After the doctoral studies under the supervision of Prof. Armin de Meijere at Georg-August-University in Göttingen, Germany, he moved to Mülheim an der Ruhr, Germany to work with Prof. Alois Fürstner at Max-Planck Institut für Kohlenforschung. In 2007 he joined the group of Prof. E. J. Corey at Harvard University to work on the synthesis of caryophylloid natural products. Since 2010 he has been an Assistant Professor at the University of Texas at San Antonio. His research is focused on the development of catalytic methods of synthesis of *N*- and *N*,*O*-heterocycles, and the total synthesis of bioactive heterocyclic natural products.

David Stephens graduated with a B.S. degree in Chemistry from St. Edward's University in Austin, TX. Since 2011 he has been conducting his doctoral studies under the guidance of Prof. Oleg Larionov at the University of Texas at San Antonio. His current work is focused on the catalytic methods of synthesis of *N*- and *N*,*O*-heterocycles and their applications in medicinal chemistry.

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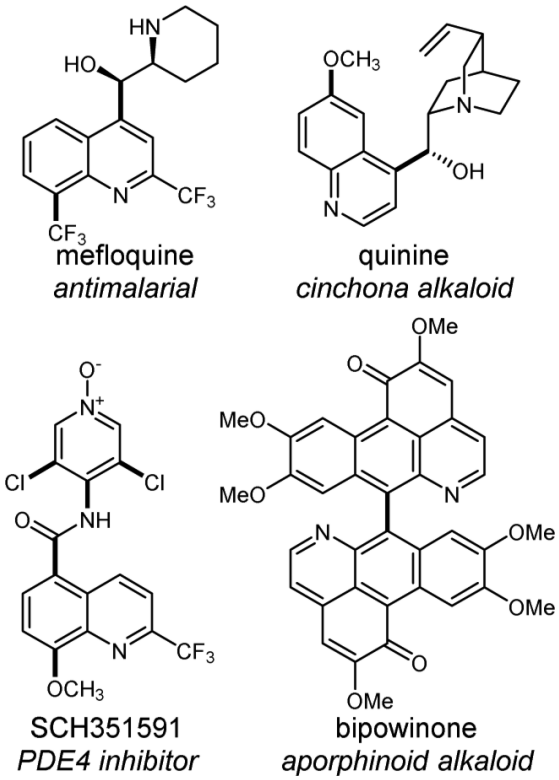
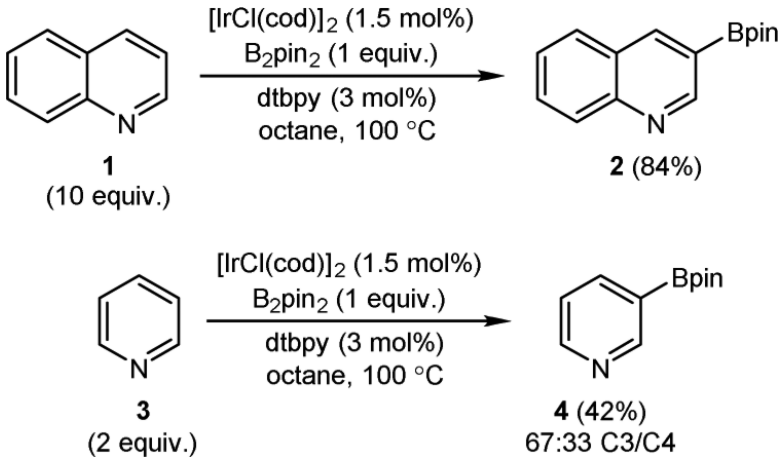
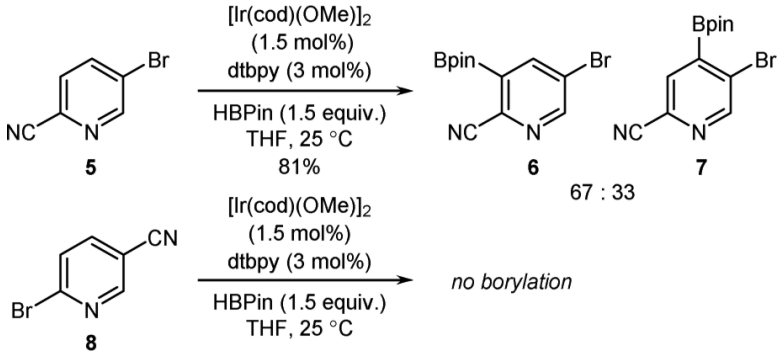


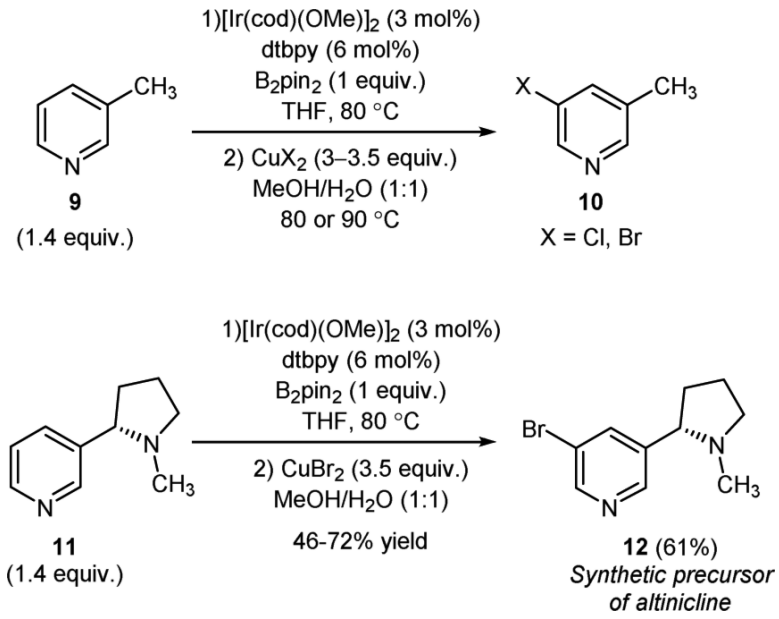
Figure 1.
Examples of important distally-substituted pyridines and quinolines.



Scheme 1.
Ir-catalyzed C3-borylation of quinoline and pyridine.

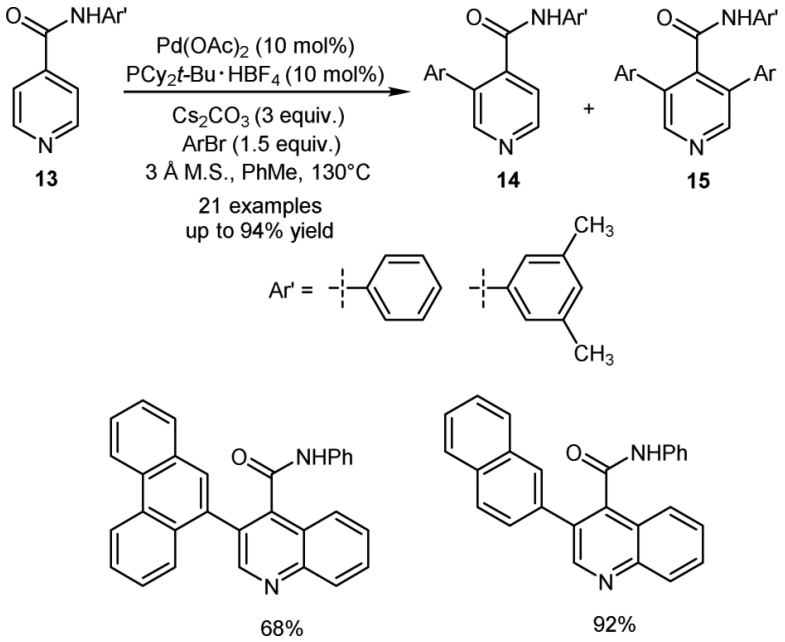


Scheme 2.
Sterically controlled C3/C4-borylation.



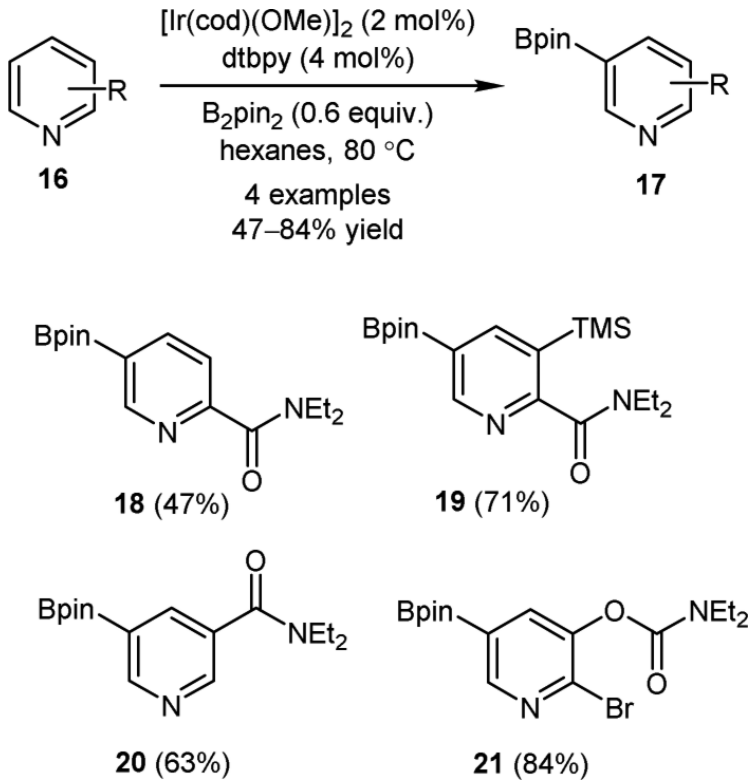
Scheme 3.

C3-Halogenation of pyridines and the synthesis of altinicline precursor **12**.



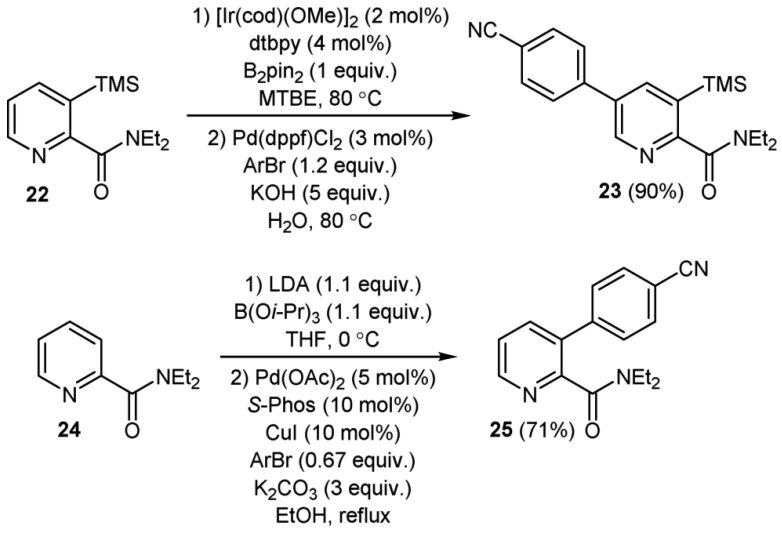
Scheme 4.

Pd-catalyzed C3/C4-selective C–H-arylation of isonicotinamides.

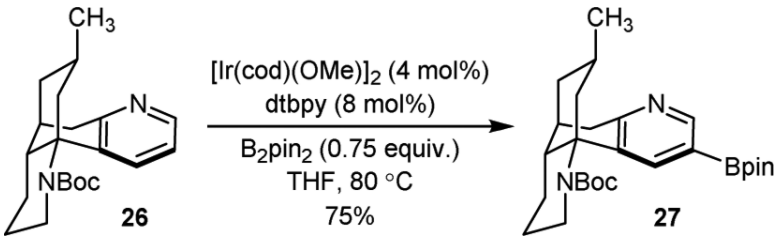


Scheme 5.

Sterically-controlled *meta*-borylation of *N*,*N*-diethyl pyridinecarboxamides and *N*,*N*-diethyl 3-pyridyl carbamate.

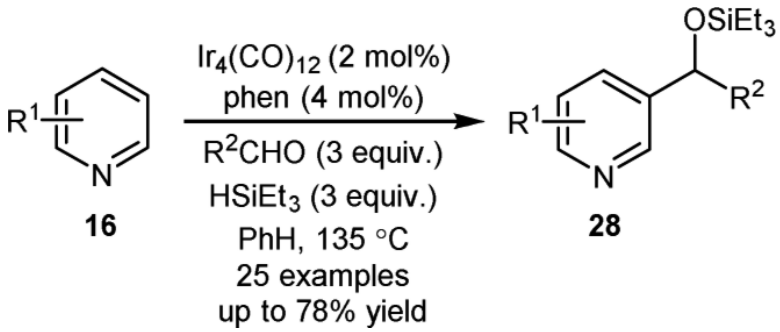


Scheme 6.
Suzuki-Miyaura cross-coupling products.[29]

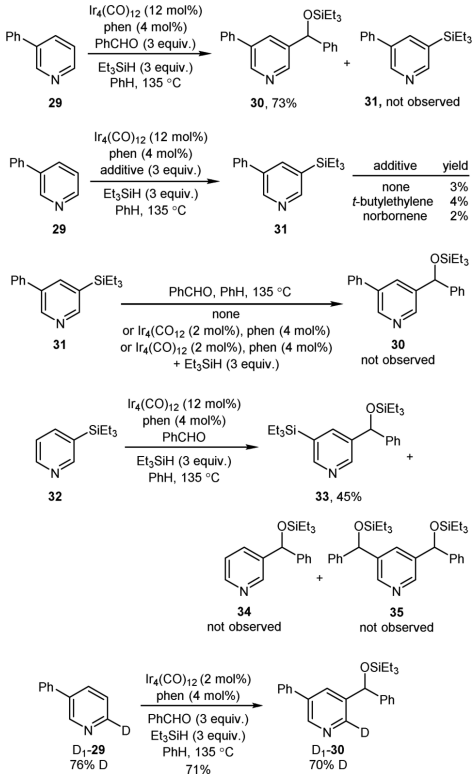


Scheme 7.

Ir-catalyzed C3-borylation in the total synthesis of (+)-complanadine A.

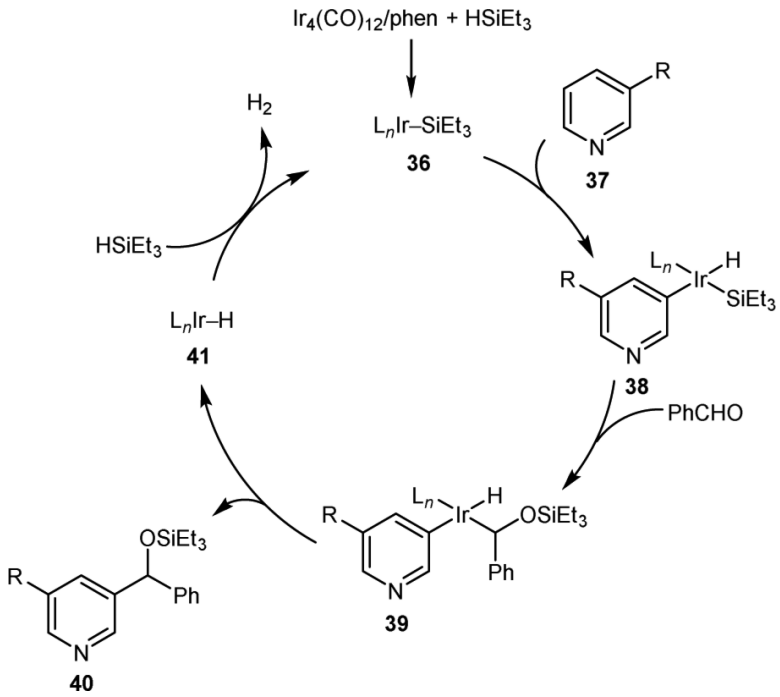


Scheme 8.
$Ir_4(CO)_{12}$-catalyzed C3-addition of pyridines to aldehydes.

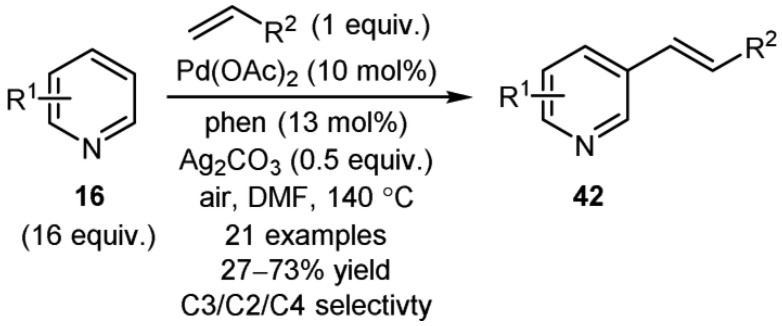


Scheme 9.

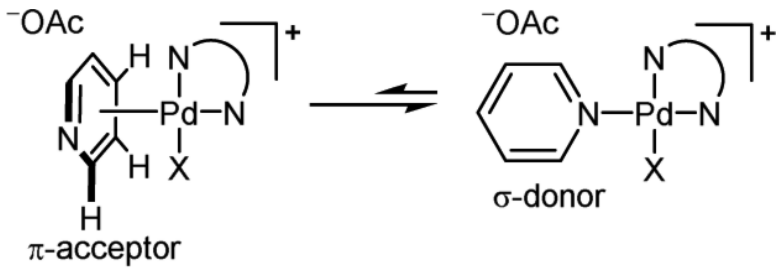
Mechanistic studies of the $Ir_4(CO)_{12}$-catalyzed C3-addition of pyridines to aldehydes.



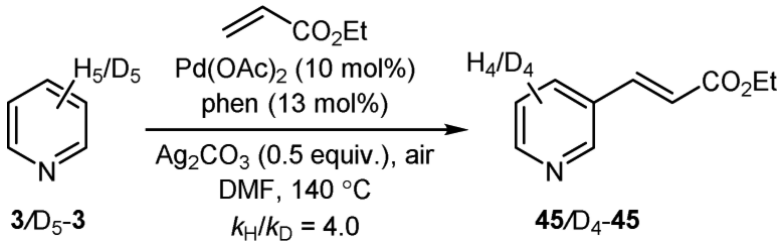
Scheme 10.
Proposed mechanism.



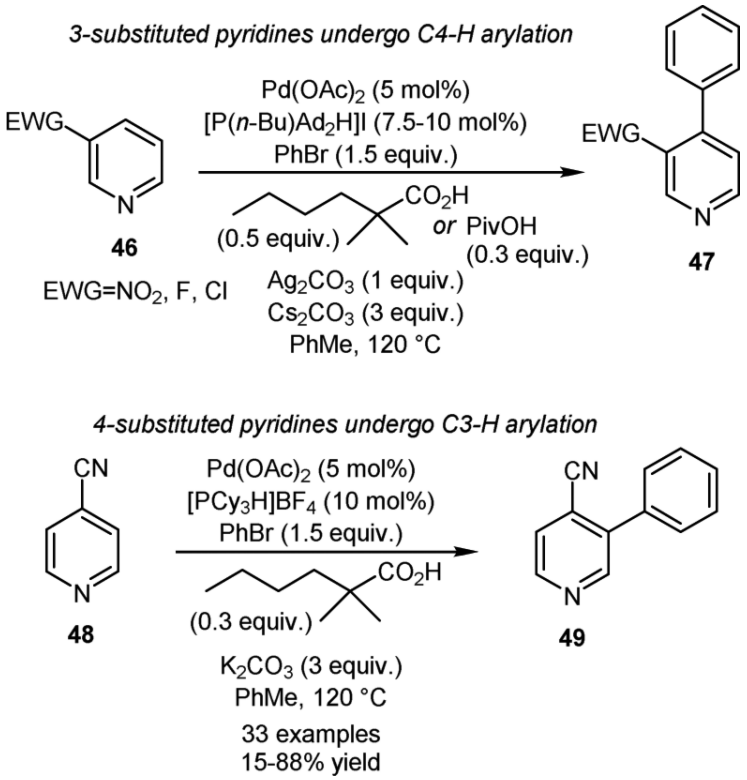
Scheme 11.
Pd-catalyzed C3-alkenylation of azines.



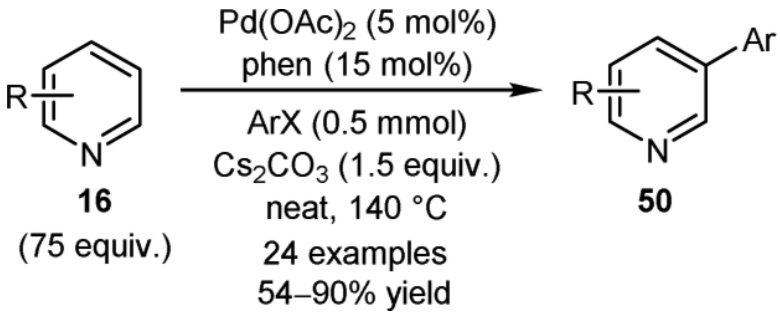
Scheme 12.
Equilibrium between σ- and π-complexes of Pd with pyridine.



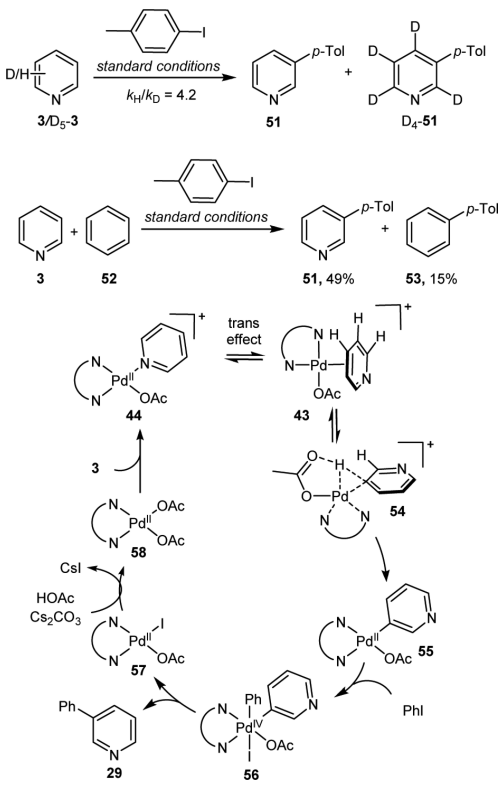
Scheme 13.
Kinetic isotope effect study.



Scheme 14.
Pd-catalyzed C3/C4-arylation of electron poor-pyridines.

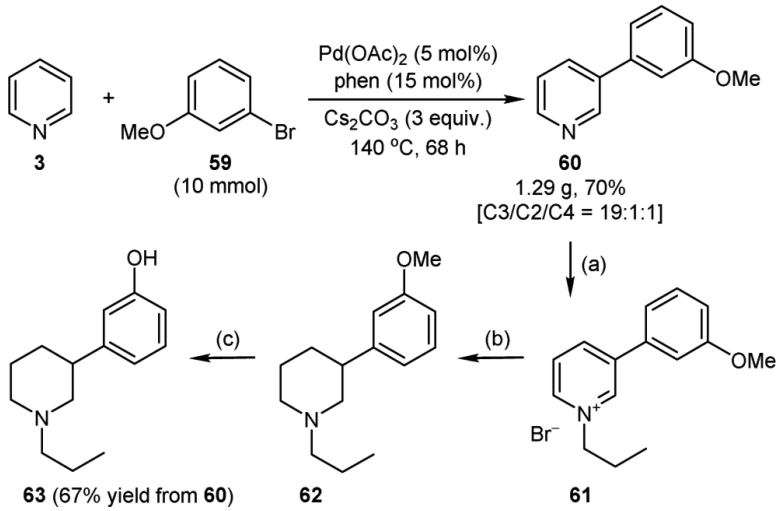


Scheme 15.
Non-directed Pd/phen-catalyzed C3–H-arylation of pyridines.



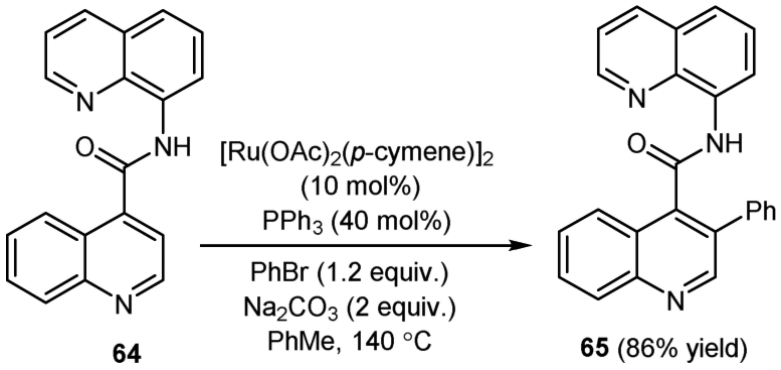
Scheme 16.

KIE studies and the plausible mechanism of the Pd-catalyzed C3–H-arylation of pyridines.

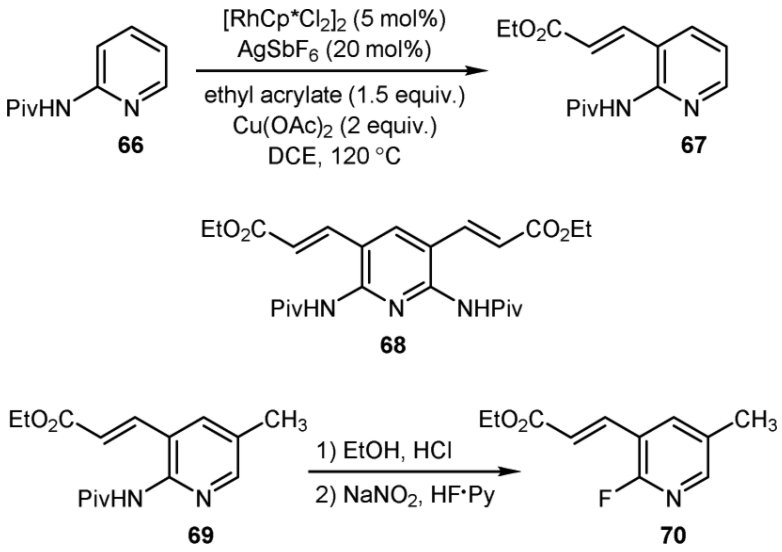


Scheme 17.

Synthesis of *rac*-preclamol. Reagents and conditions: (a) 1-bromopropane, CH_3CN, 110 °C; (b) PtO_2, MeOH, H_2 (60 psi), r.t.; (c) HBr in AcOH, reflux.

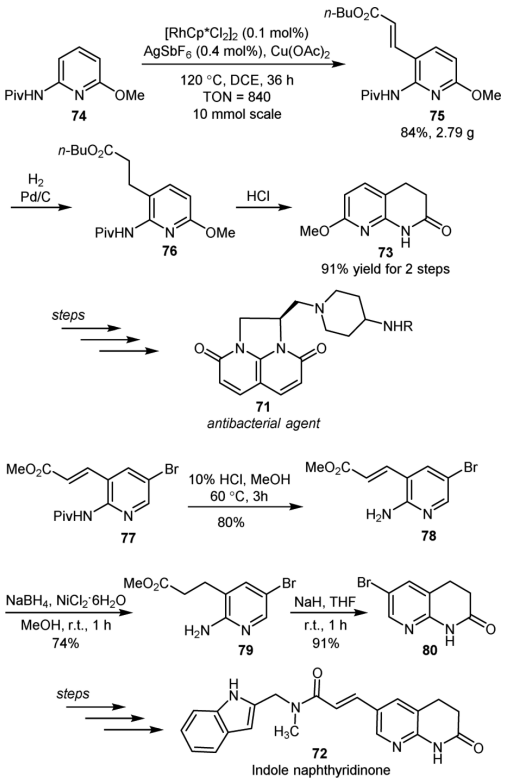


Scheme 18.
Ru-catalyzed arylation of C4-substituted quinoline.



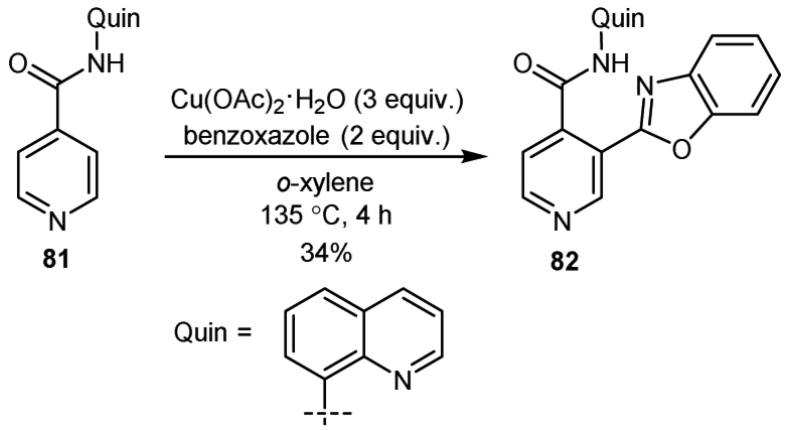
Scheme 19.

Rh(III)-catalyzed olefination of azines.



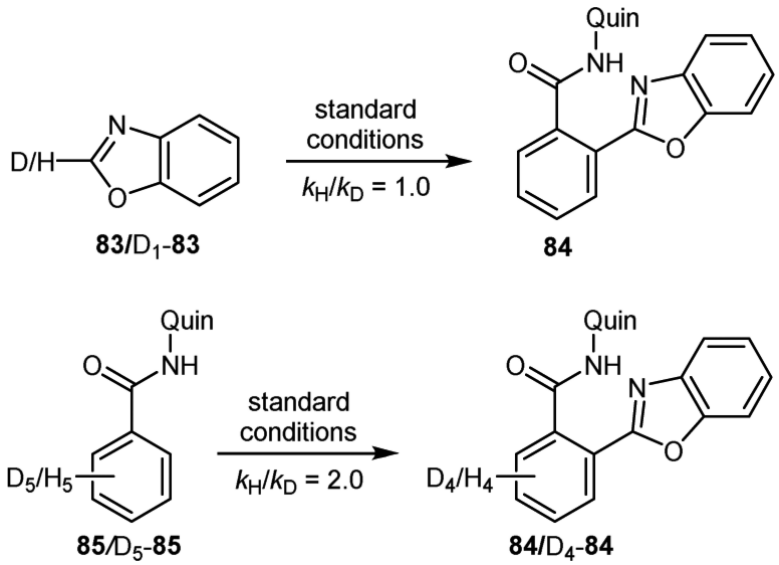
Scheme 20.

Application of the amide-directed dehydrogenative C3–H-alkenylation of pyridines to the synthesis of intermediates en route to medicinally important compounds **71** and **72**.



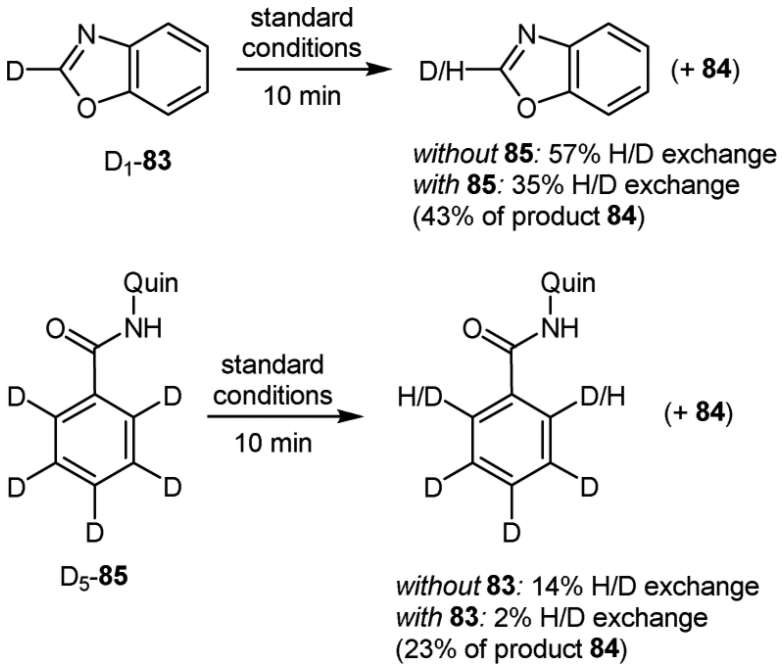
Scheme 21.

Copper-mediated dehydrogenative cross-coupling of isonicotinamide **81** with benzoxazole.



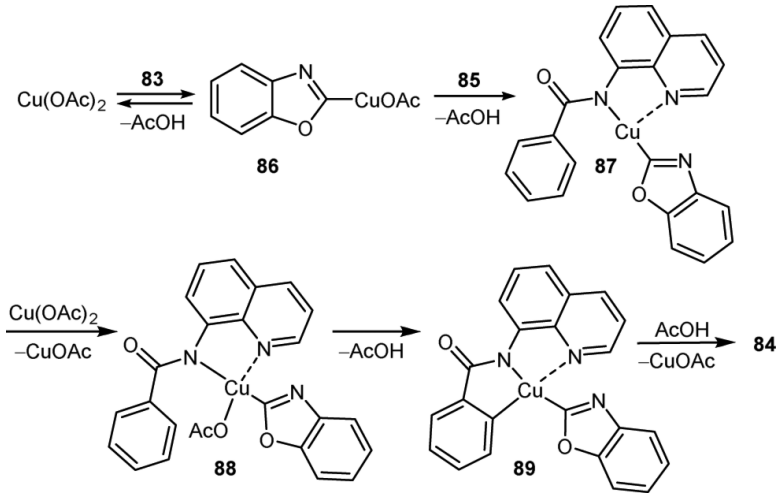
83/D_1-**83** **84** **85**/D_5-**85** **84**/D_4-**84**

Scheme 22.
Primary kinetic isotope effect studies.



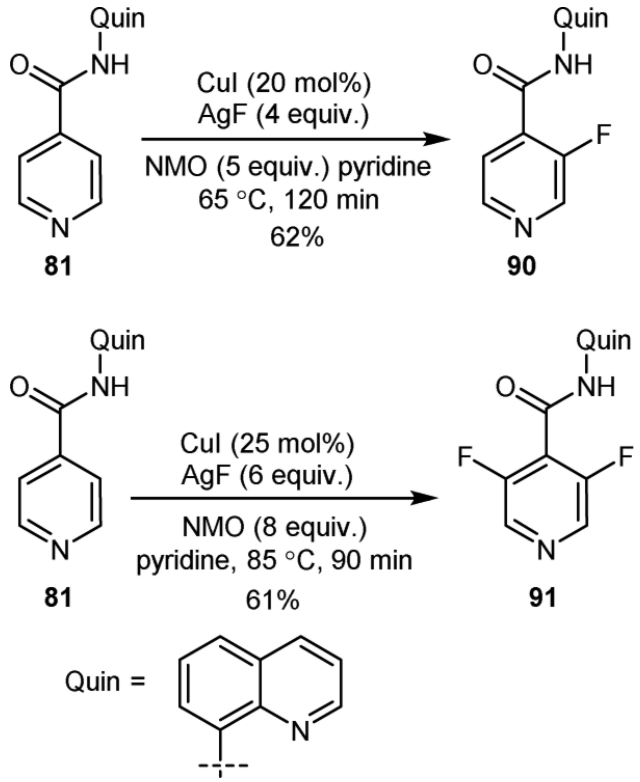
Scheme 23.

H/D exchange experiments with benzamide D_5-**85** and D_1-benzoaxazole (D_1-**83**).

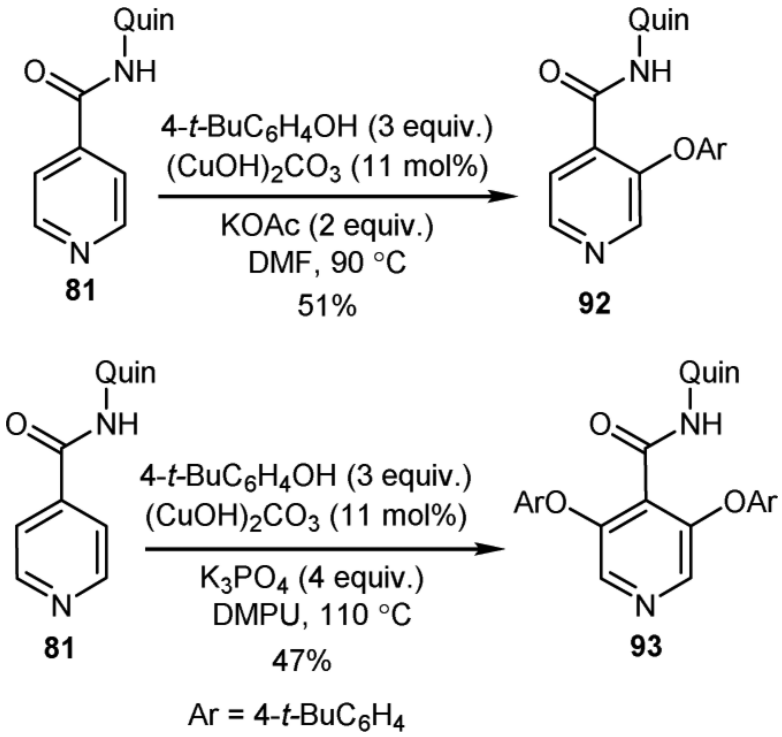


Scheme 24.

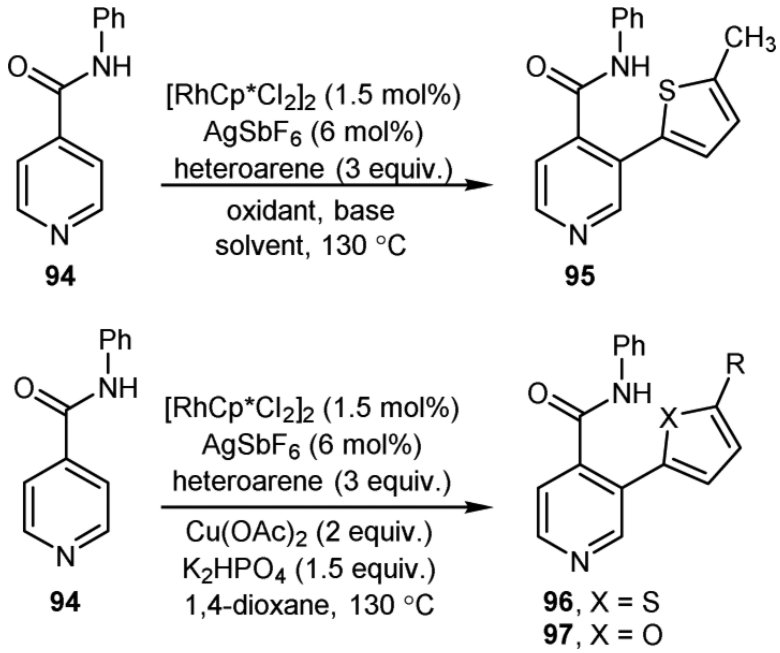
Plausible mechanism of the Cu-mediated dehydrogenative cross-coupling.



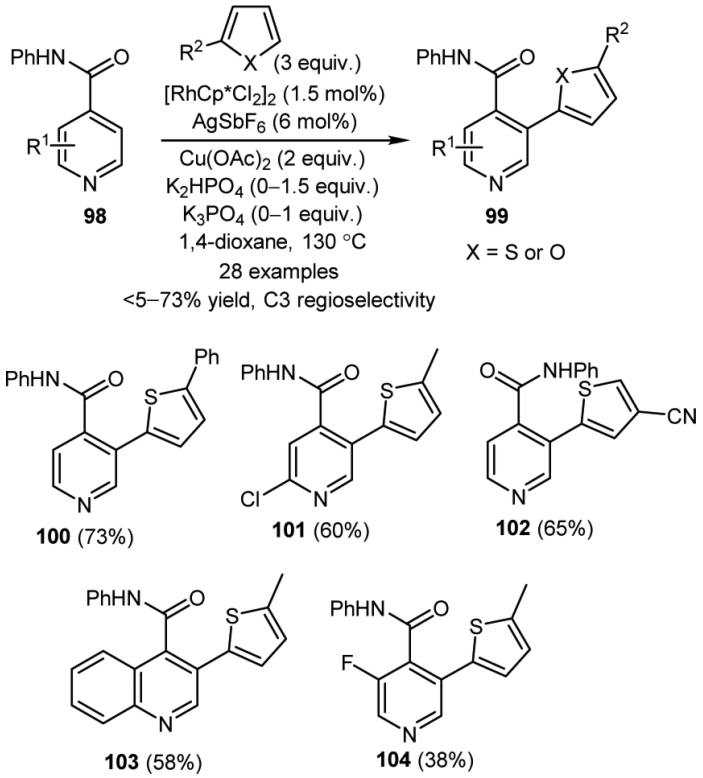
Scheme 25.
8-Quinolylamide-directed fluorination.



Scheme 26.
Cu-catalyzed C–H-etherification of isonicotinamides.

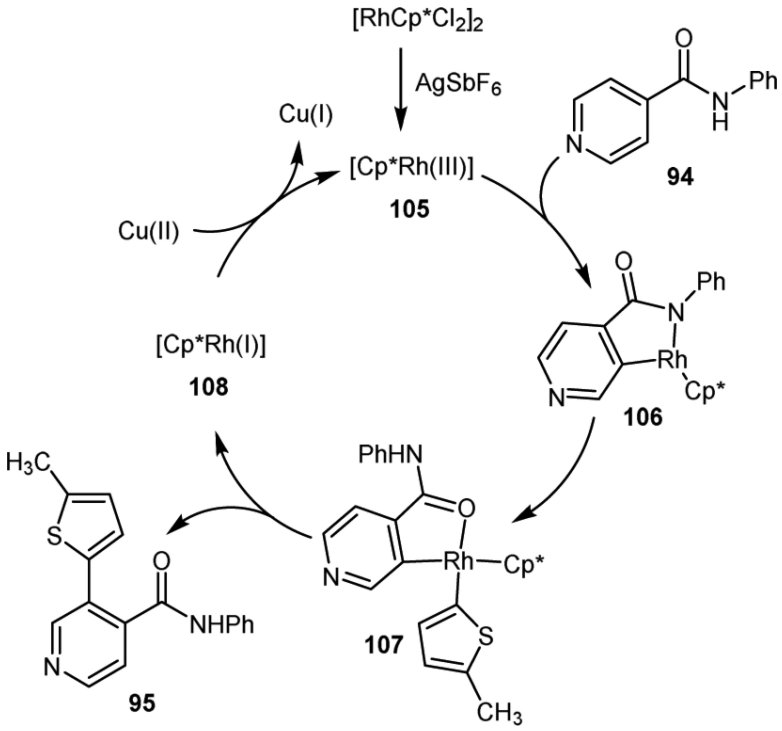


Scheme 27.
C3-selective heteroarylation of disubstituted pyridines.

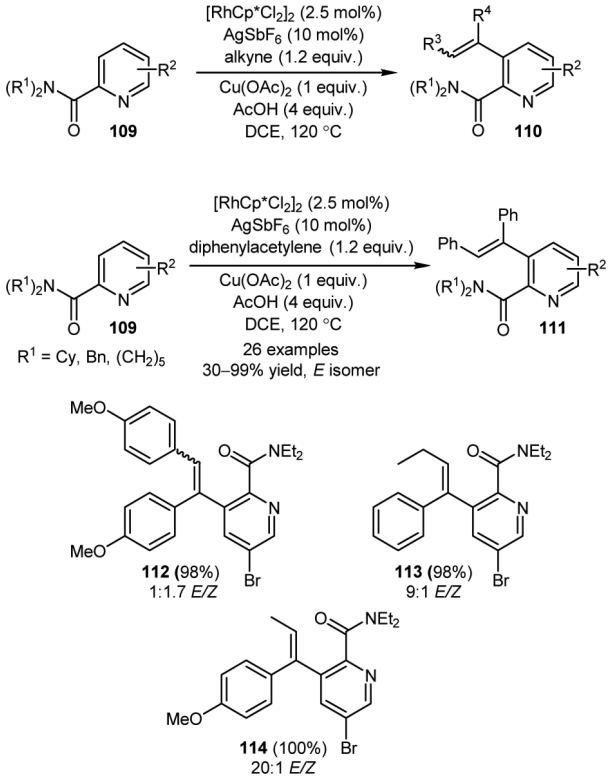


Scheme 28.

Rh(III)-catalyzed dehydrogenative C2/C3-heteroarylation.

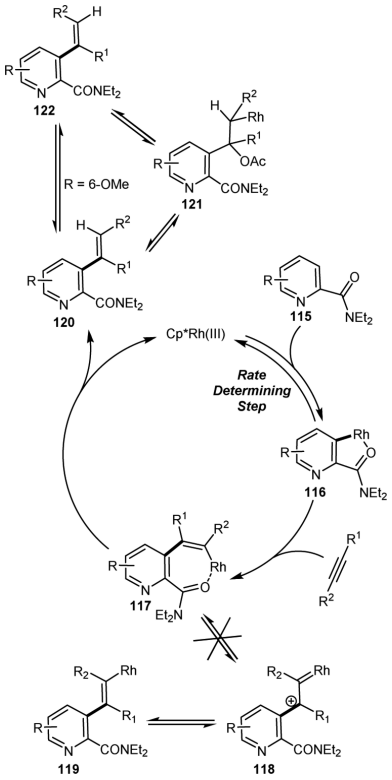


Scheme 29.
Proposed catalytic cycle.

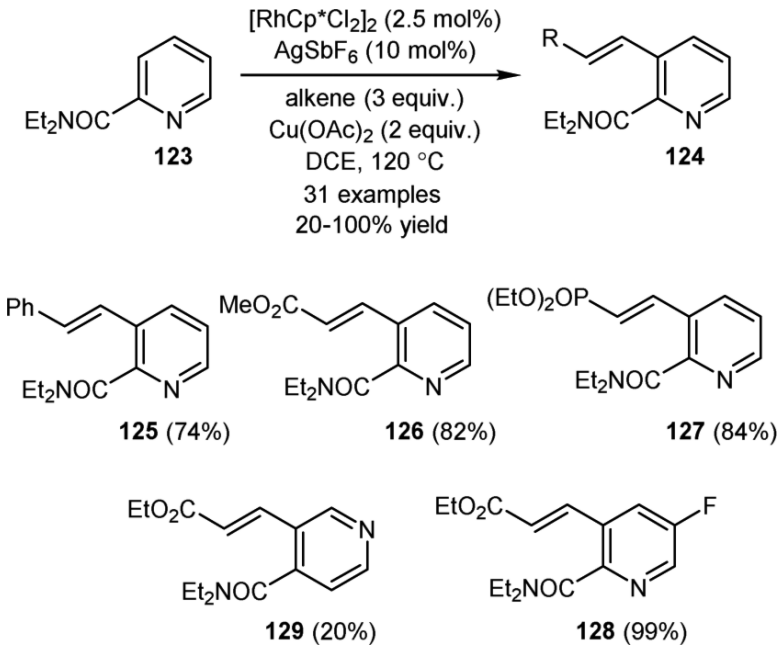


Scheme 30.

Rh(III)-catalyzed alkenylation of picolinamide derivatives.

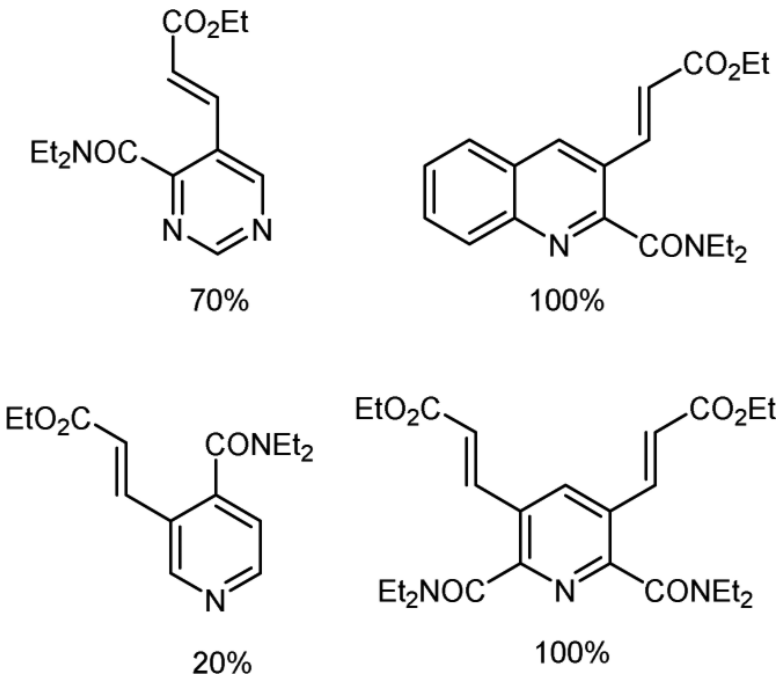


Scheme 31.
Plausible mechanism for Rh(III)-catalyzed alkynylation.

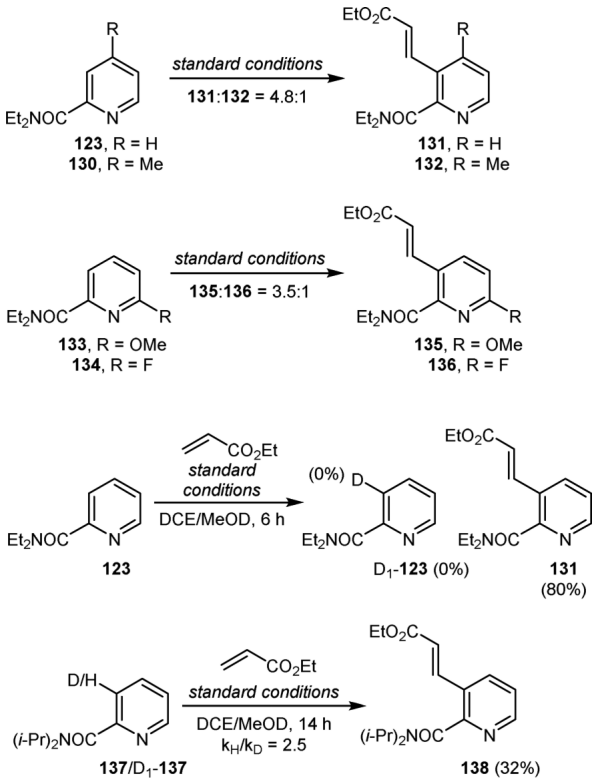


Scheme 32.

Rh(III)-catalyzed alkenylation of picolinamides.

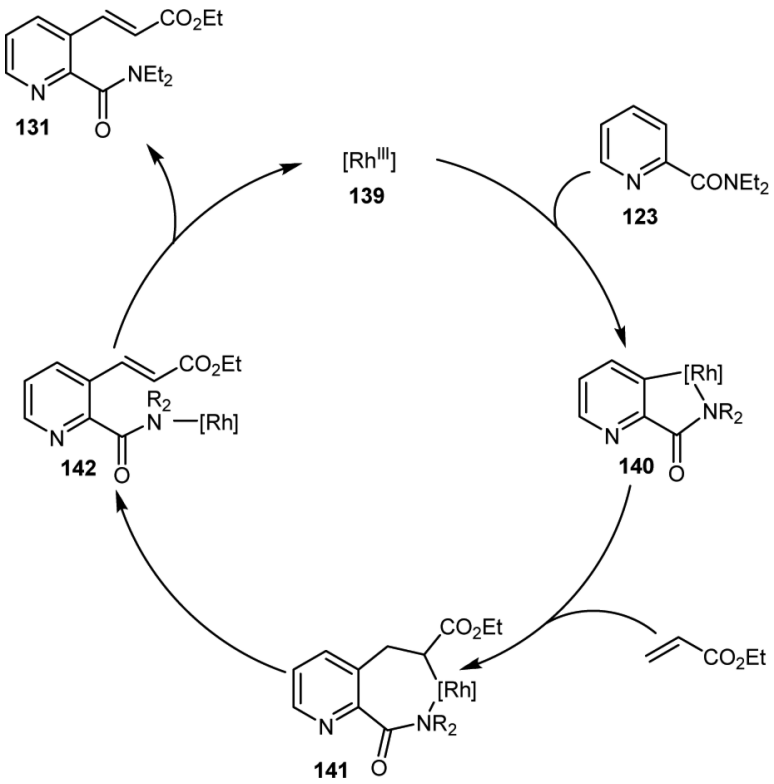


Scheme 33.
Products of C3-olefination of various azinecarboxamides.

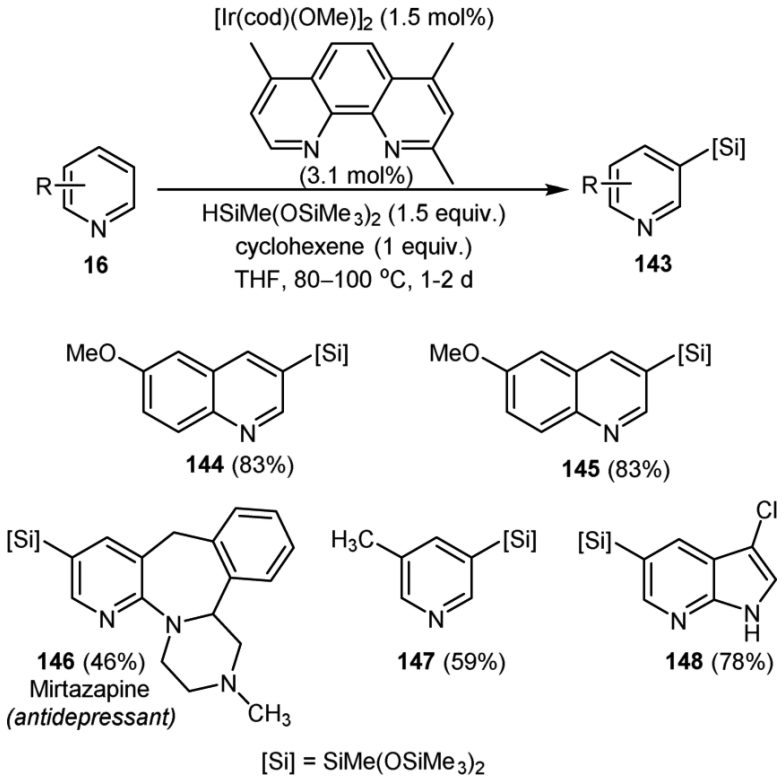


Scheme 34.

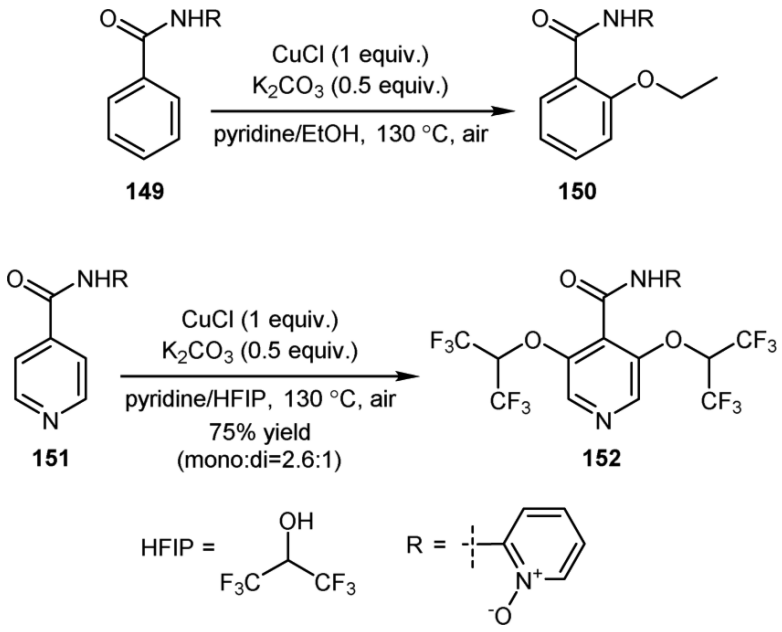
Mechanistic studies for the Rh-catalyzed C3-olefination of picolinamides.



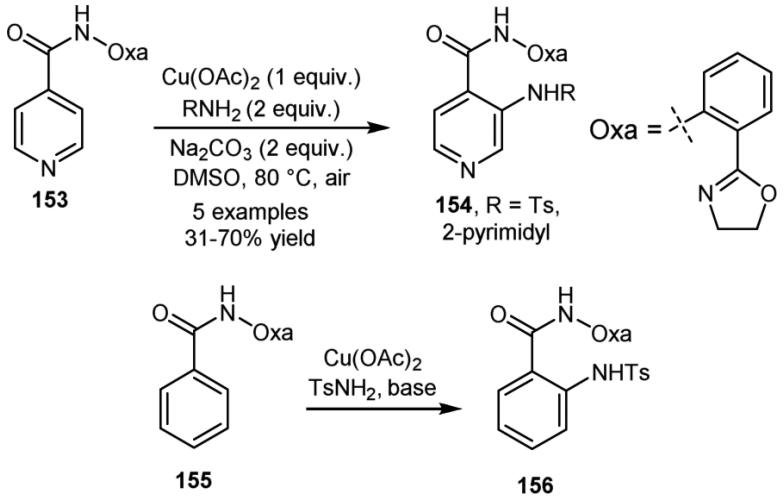
Scheme 35.
Proposed mechanism of Rh(III)-catalyzed C3-olefination.



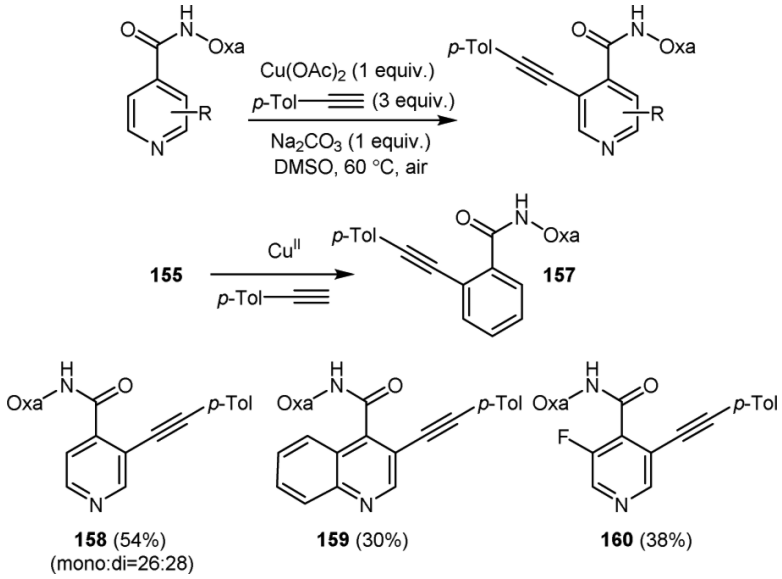
Scheme 36.
Ir-catalyzed C3–H-silylation.



Scheme 37.
Cu-catalyzed C–H-etherification.

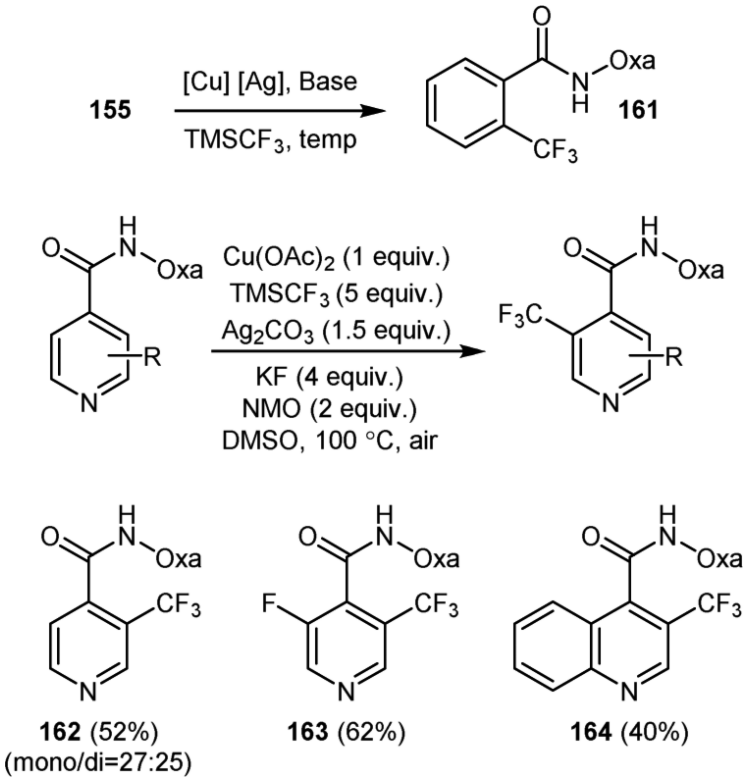


Scheme 38.
Cu(II)-mediated amination.

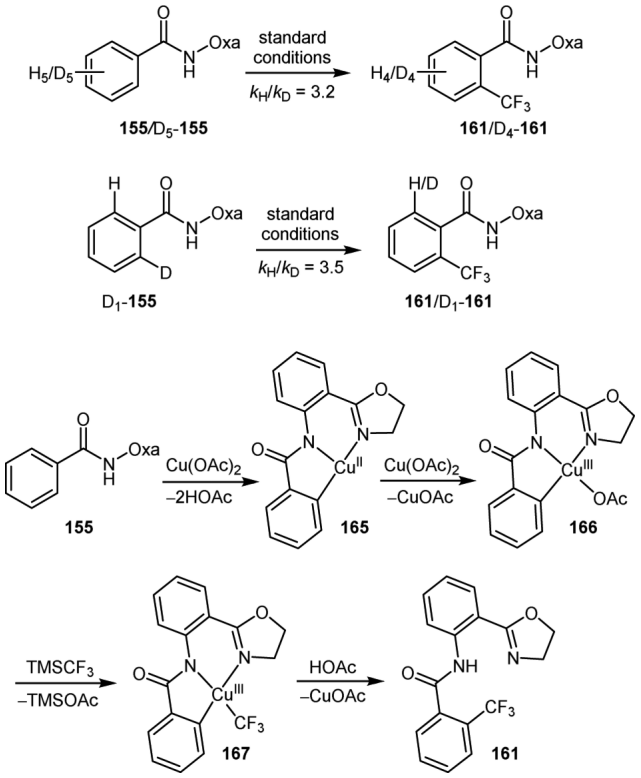


Scheme 39.

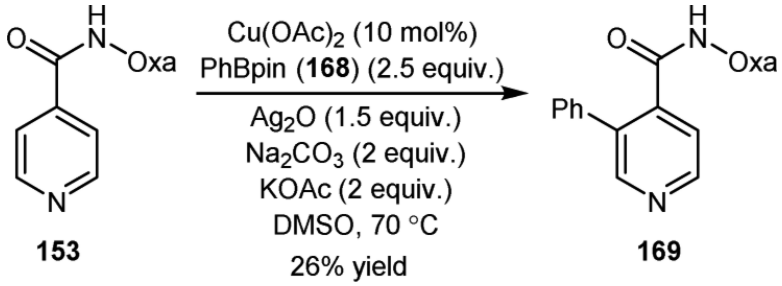
Cu(II) catalyzed alkynylation with amide-tethered oxazoline directing group.



Scheme 40.
Cu(II)-promoted trifluoromethylation.

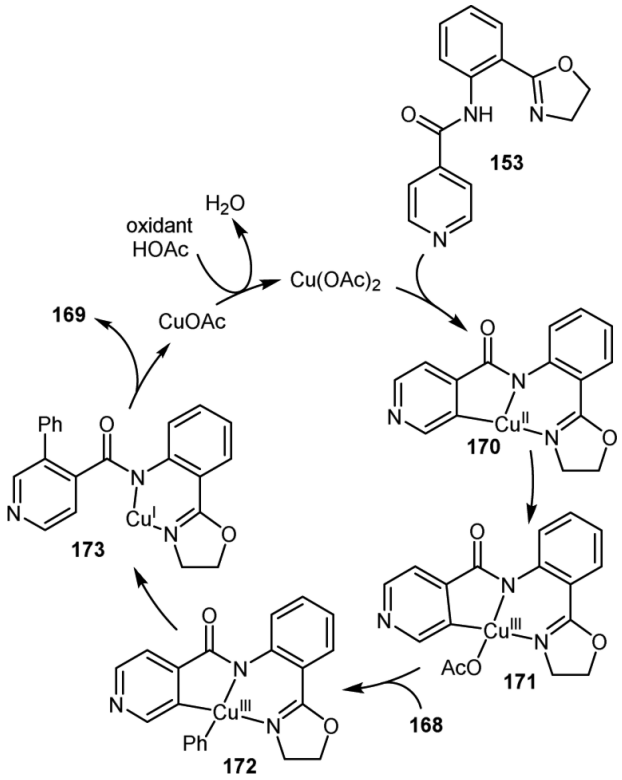


Scheme 41.
Cu(II)-promoted trifluoromethylation.

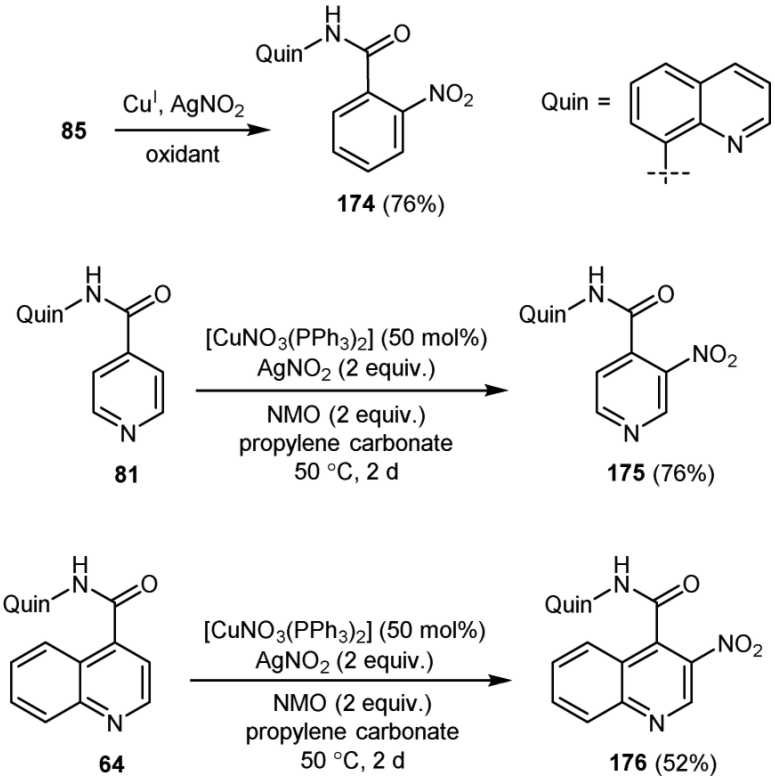


Scheme 42.

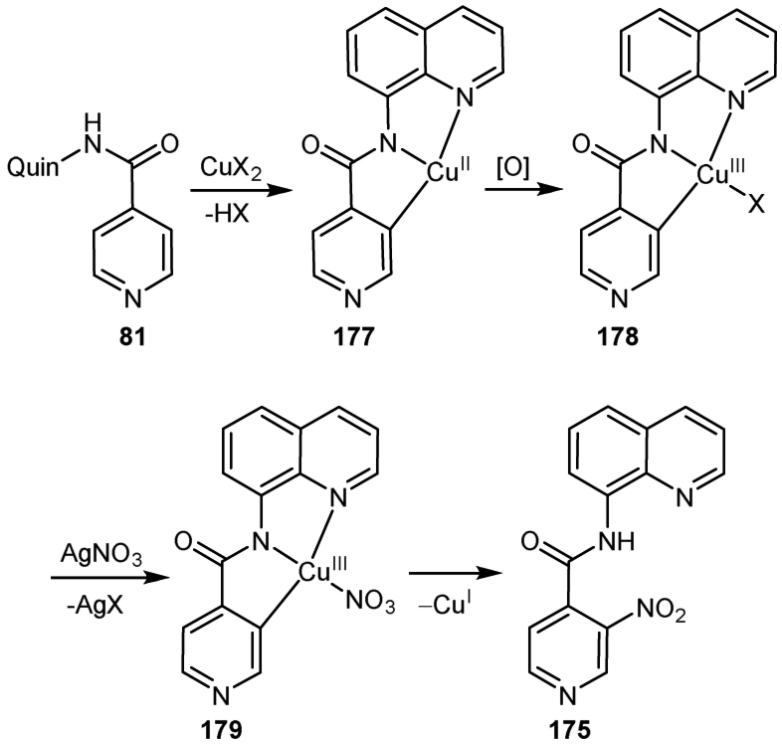
Cu-catalyzed arylation of isonicotinamide derivative **153**.



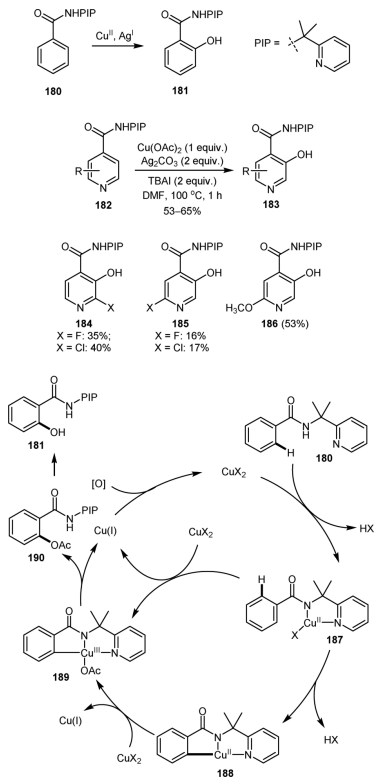
Scheme 43.
Cu-catalyzed arylation with amide-oxa directing group.



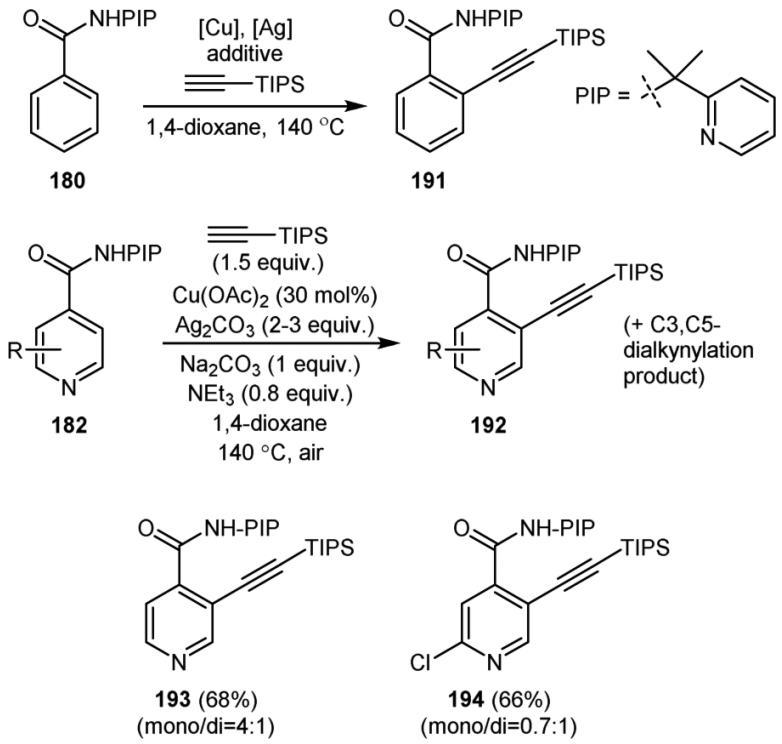
Scheme 44.
Cu(II)-mediated nitration.



Scheme 45.
Plausible mechanism of directed C3–H-nitration.

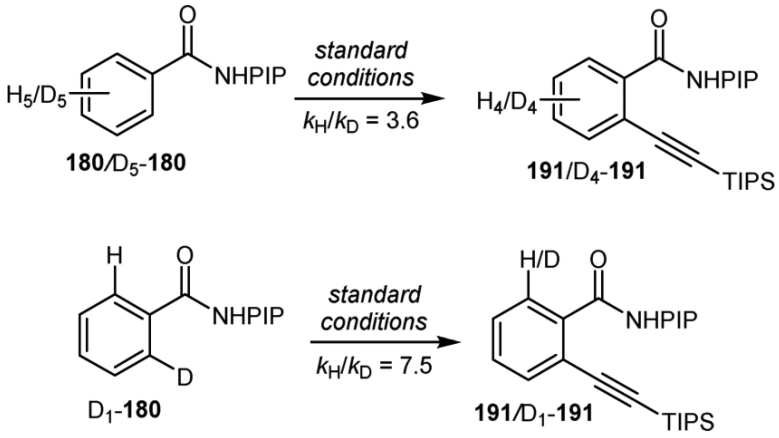


Scheme 46.
Cu(II)-mediated hydroxylation.

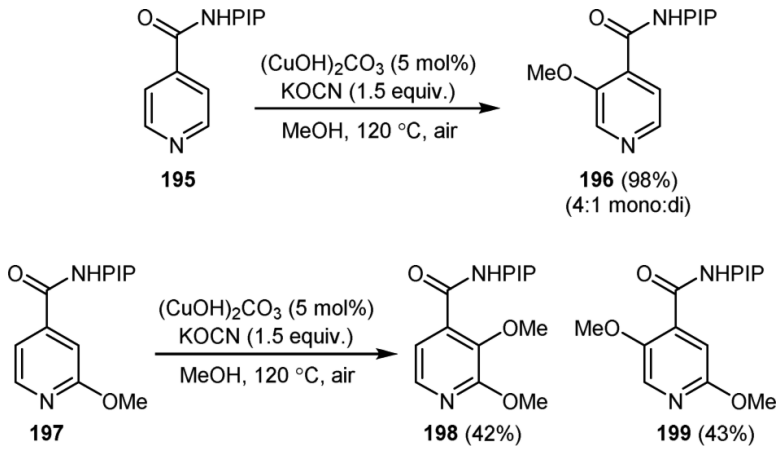


Scheme 47.

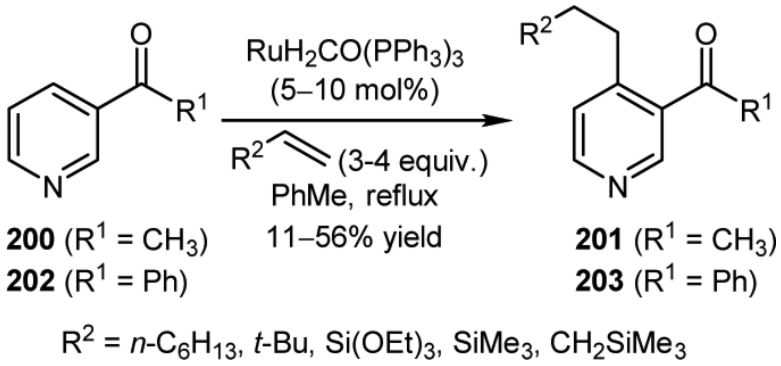
Cu-catalyzed directed alkynylation of isonicotinamides.



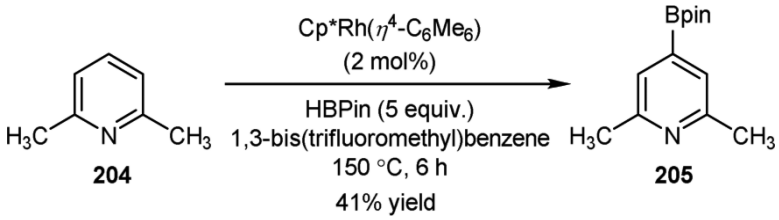
Scheme 48.
Kinetic isotope effect studies.



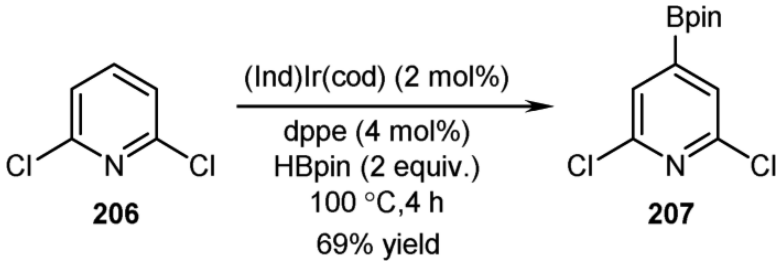
Scheme 49.
PIP-amide-directed methoxylation.



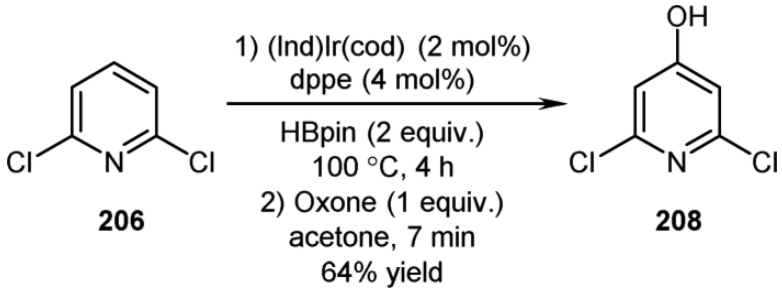
Scheme 50.
Ru-catalyzed addition of pyridines to alkenes.



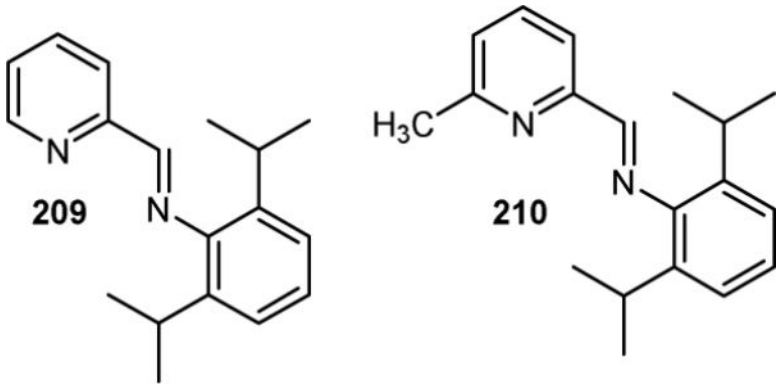
Scheme 51.
Ir-catalyzed C4-selective borylation of 2,6-dimethylpyridine.



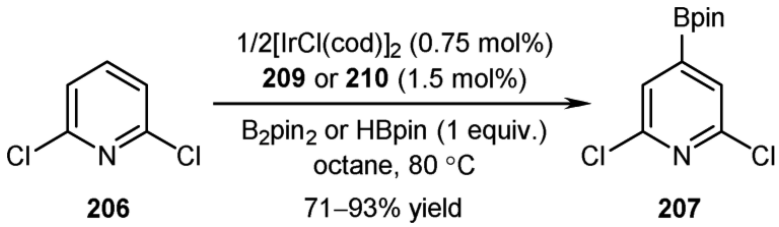
Scheme 52.
Ir-catalyzed C4-selective borylation of 2,6-dimethylpyridine.



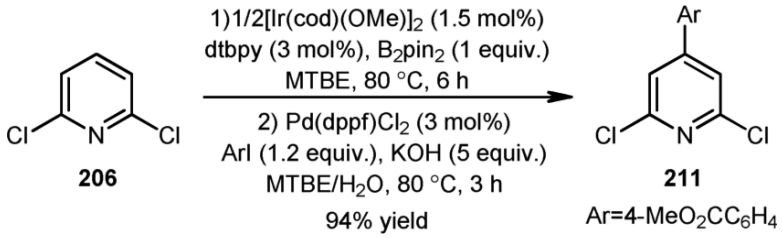
Scheme 53.
Sequential Ir-catalyzed C4–H-borylation and oxidation.



Scheme 54.
Ligands used for selective borylation.

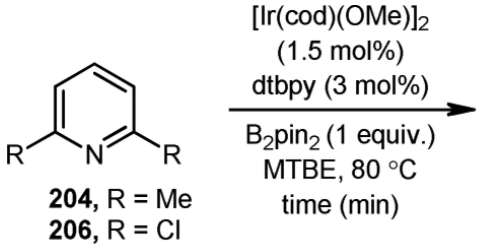


Scheme 55.
C4-selective-borylation of pyridines.



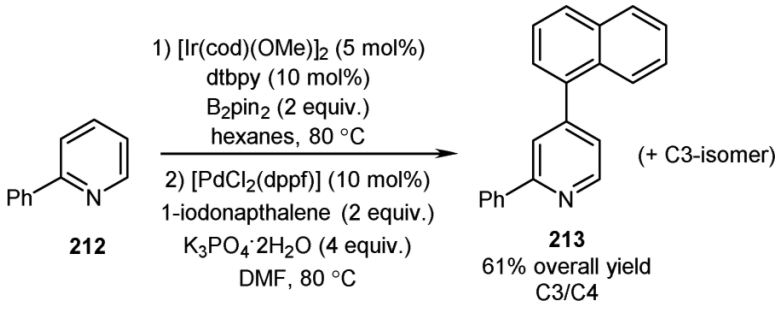
Scheme 56.

One-pot reaction with 2,6-dichloropyridine and methyl 4-iodobenzoate.



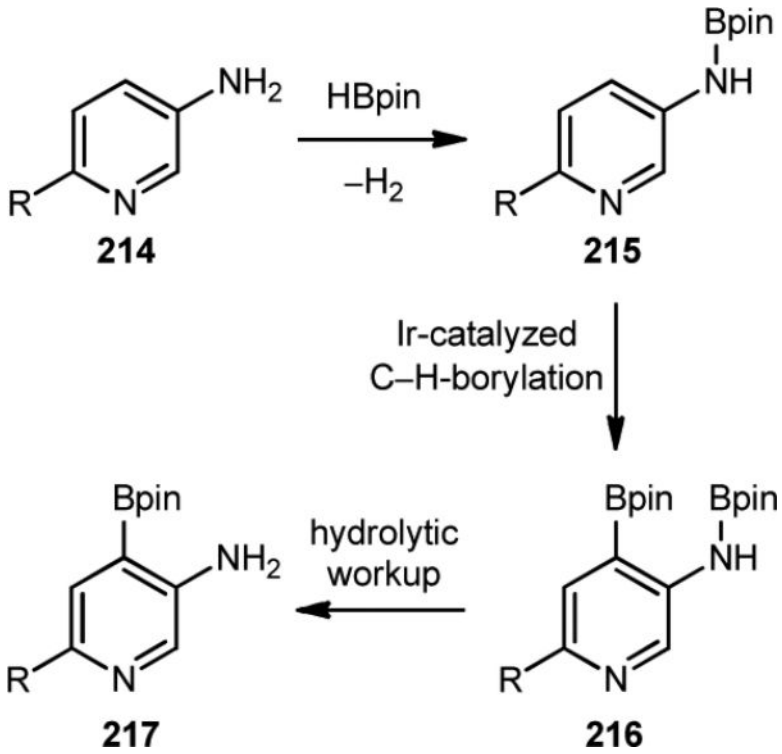
	microwave		thermal	
product	time	yield	time	yield
205, R = Me	5	98%	30	95%
207, R = Cl	3	98%	20	96%

Scheme 57.
Microwave-assisted Ir-catalyzed C4–H-borylation.

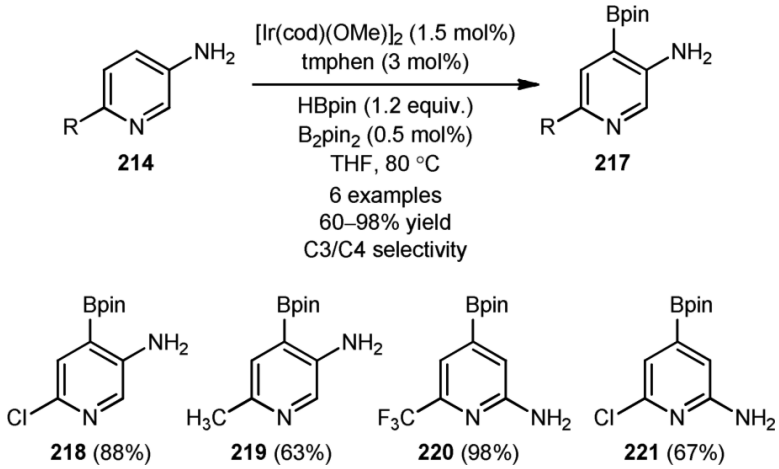


Scheme 58.

Ir-catalyzed borylation/Suzuki-Miyaura coupling of 2-phenylpyridine.

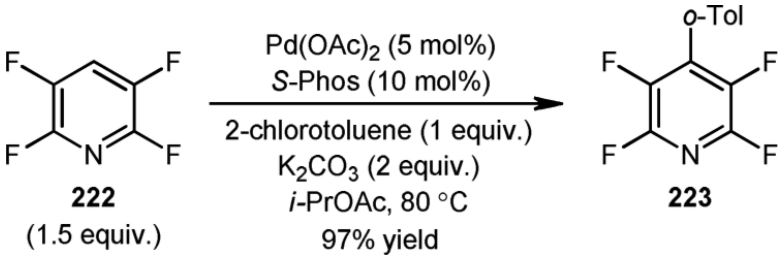


Scheme 59.
Intermediates in the Bpin-directed borylation.

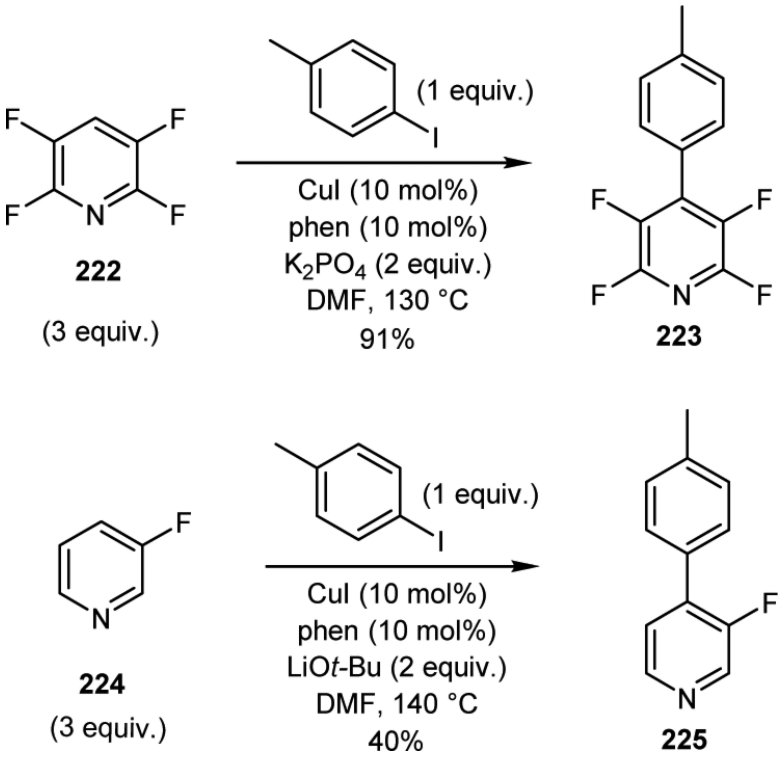


Scheme 60.

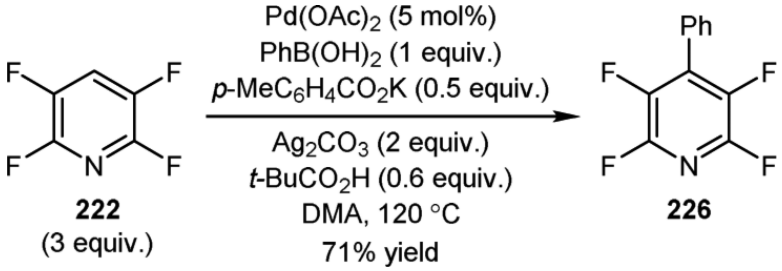
Traceless borylation of aminopyridines.



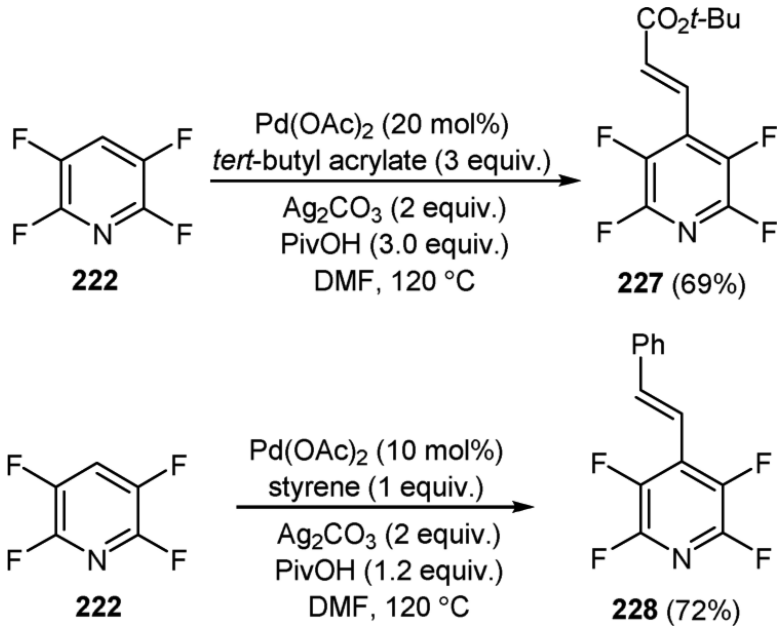
Scheme 61.
C4-Arylation of tetrafluoropyridine.



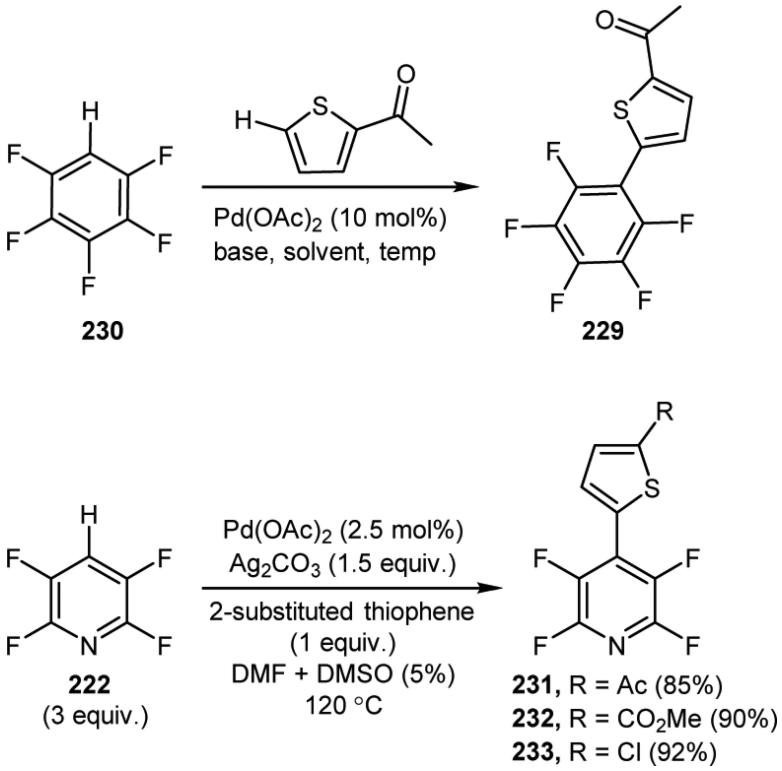
Scheme 62.
Cu-catalyzed arylation of polyfluoropyridines.



Scheme 63.
Pd-catalyzed arylation of 2,3,5,6-tetrafluoropyridine (**222**).

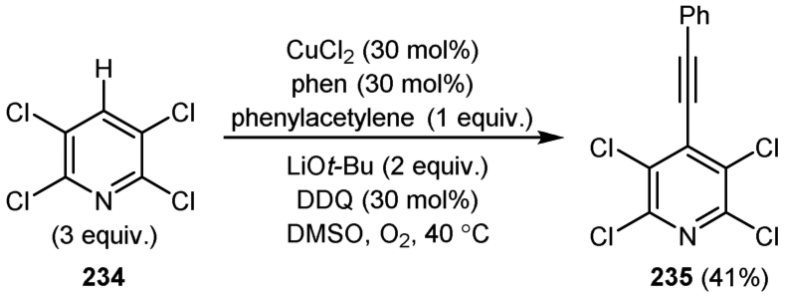


Scheme 64.
Pd-catalyzed olefination of electron-deficient heteroarenes.

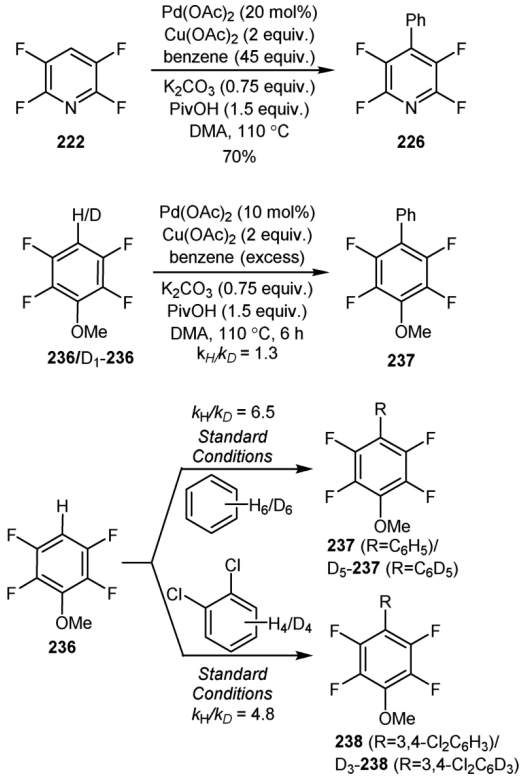


Scheme 65.

Cross coupling of 2,3,5,6-tetrafluoropyridine (**222**) with substituted thiophenes.

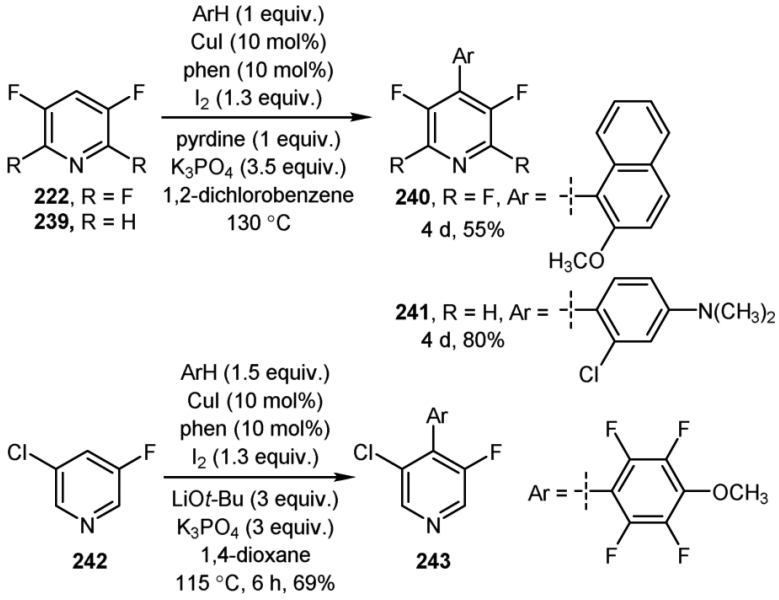


Scheme 66.
Alkynylation of 2,3,5,6-tetrachloropyridine (**234**).



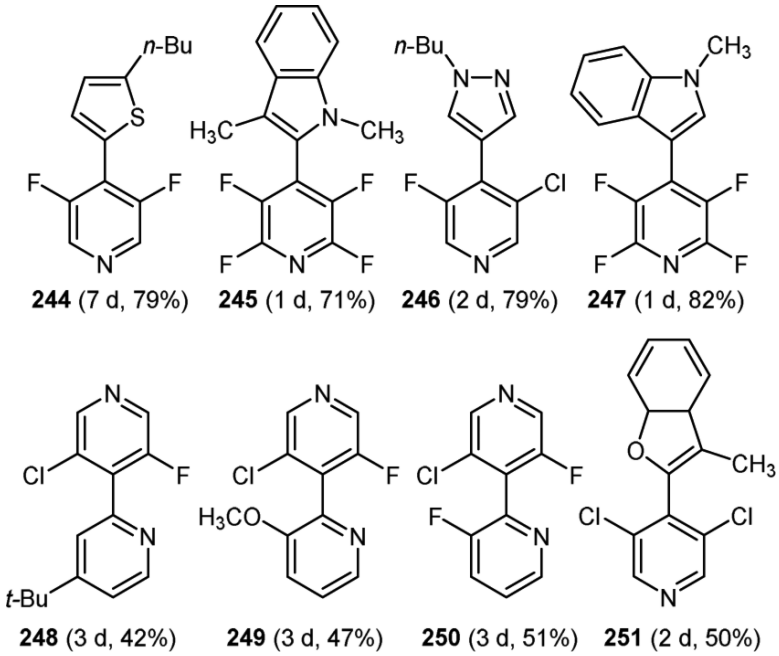
Scheme 67.

Pd-catalyzed dehydrogenative C–H-cross-coupling reaction of 2,3,5,6-tetrafluoropyridine (**222**) and the reaction kinetic data.



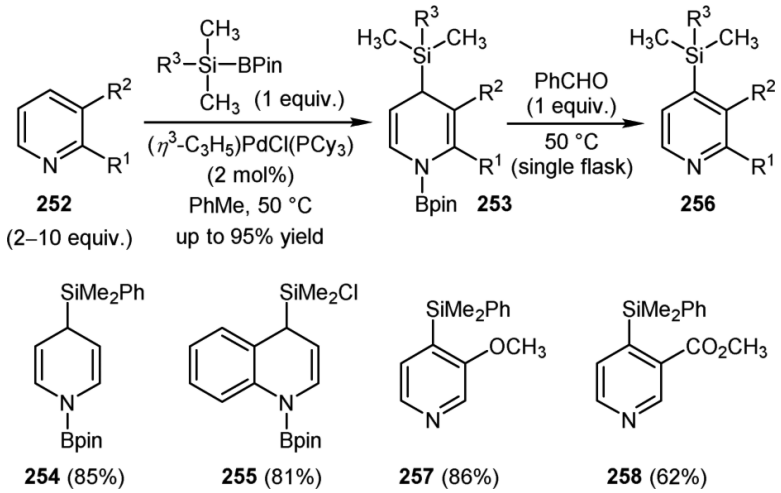
Scheme 68.

Dehydrogenative cross-coupling reaction of electron-rich arenes and electron-deficient pyridines.



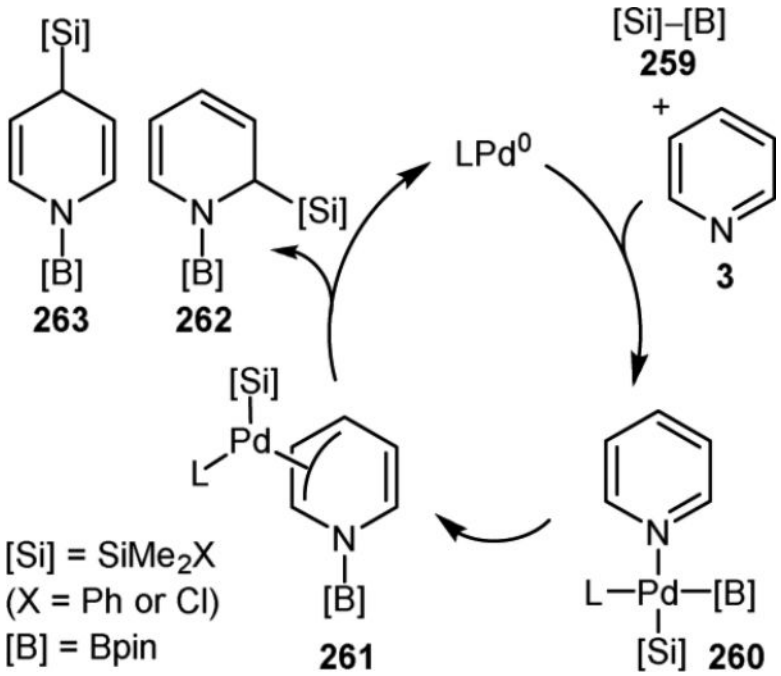
Scheme 69.

Cu-catalyzed cross-coupling of heteroarenes.

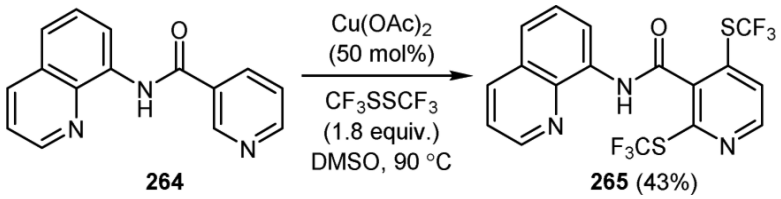


Scheme 70.

Pd-catalyzed silaboration of 2,3-substituted azines.

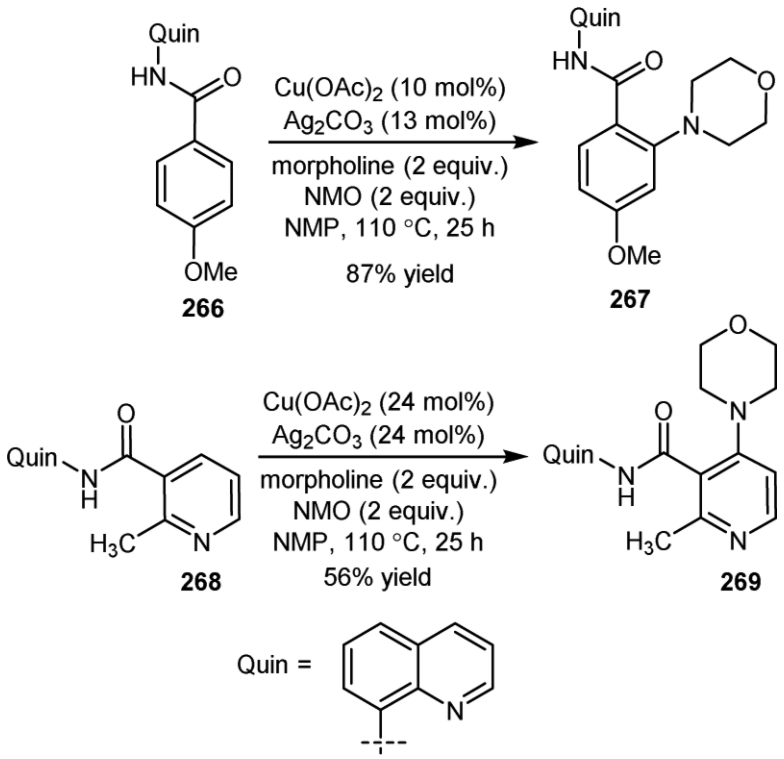


Scheme 71.
Proposed mechanism of the Pd-catalyzed silylboration.

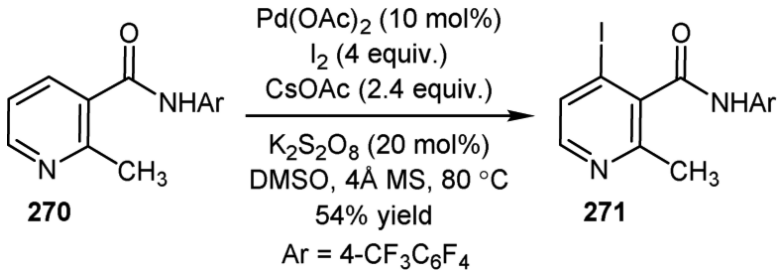


Scheme 72.

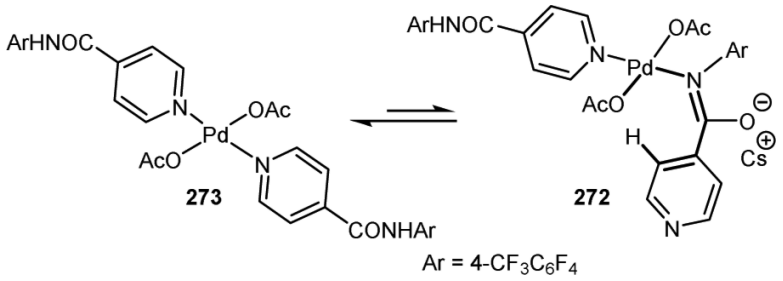
Cu-catalyzed trifluoromethylsulfenylation of nicotinamide **264**.



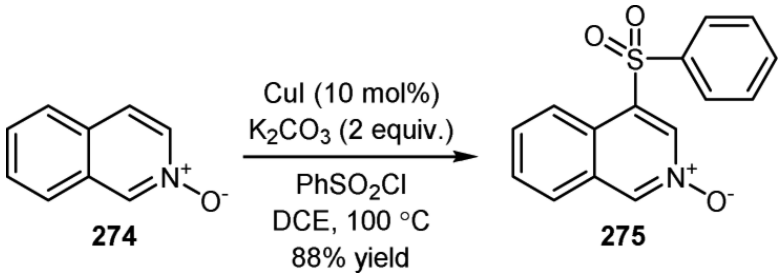
Scheme 73.
Cu-catalyzed amination of isonicotinamide **268**.



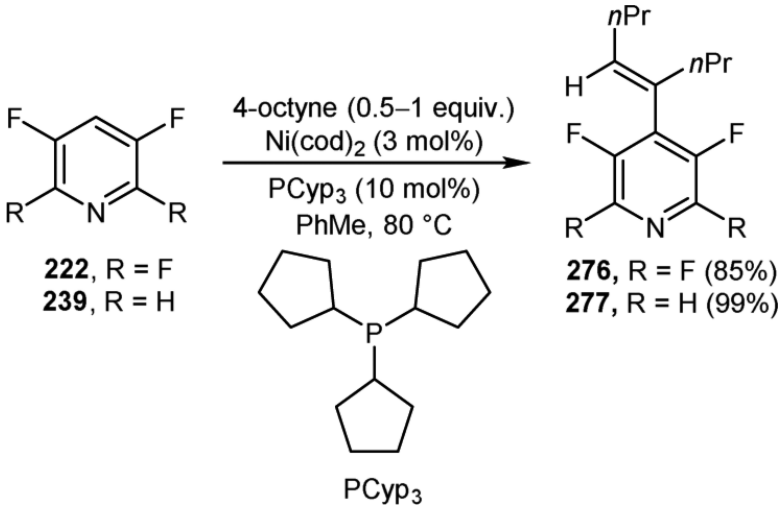
Scheme 74.
Pd(II)-catalyzed iodination.



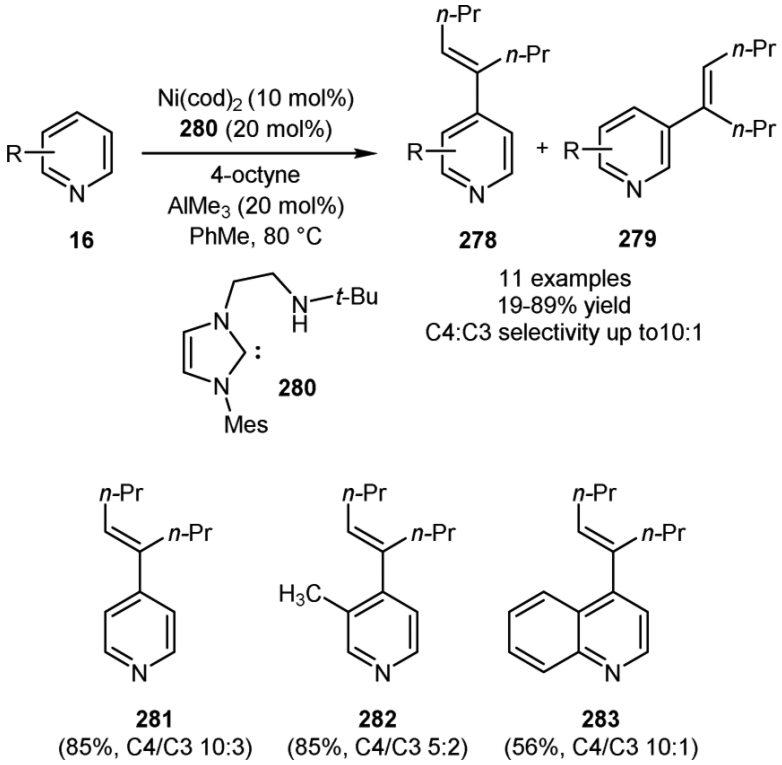
Scheme 75.
Assembly of the reactive precursor.



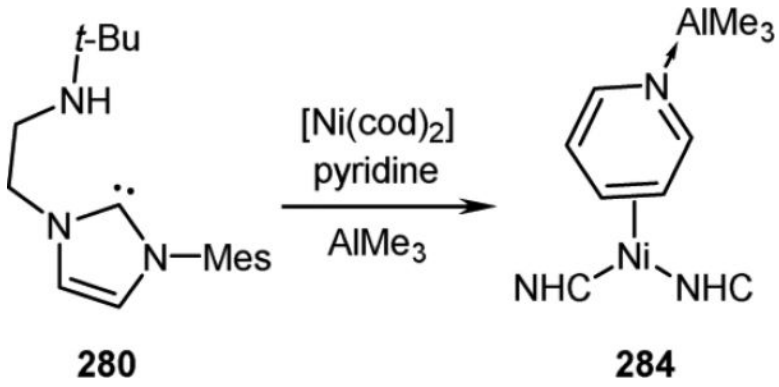
Scheme 76.
Cu-catalyzed C4-phenylsulfonylation of isoquinoline *N*-oxide.



Scheme 77.
Ni-catalyzed alkenylation of electron-deficient pyridines.

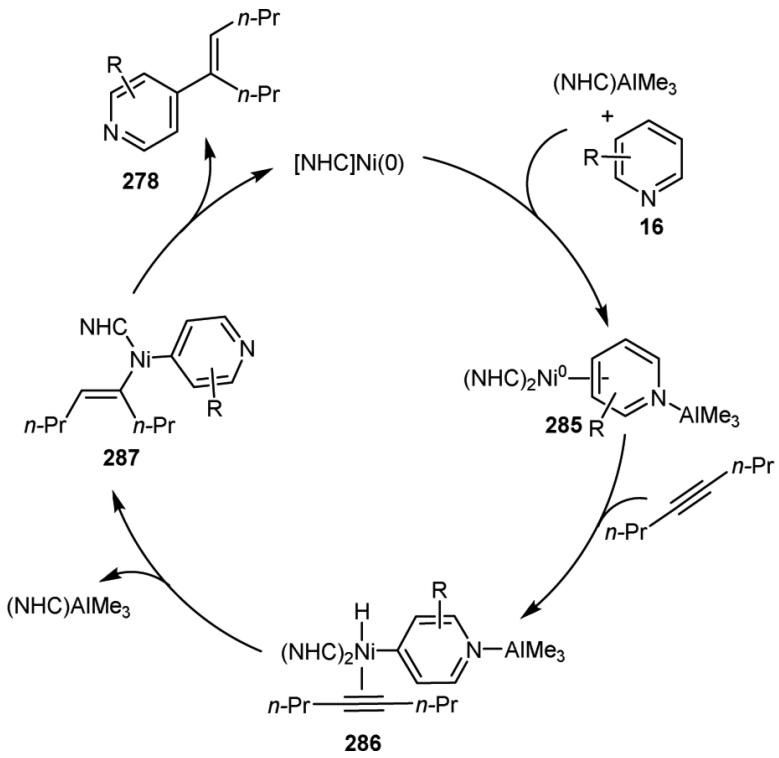


Scheme 78.
Ni-catalyzed C4-alkenylation of pyridines.



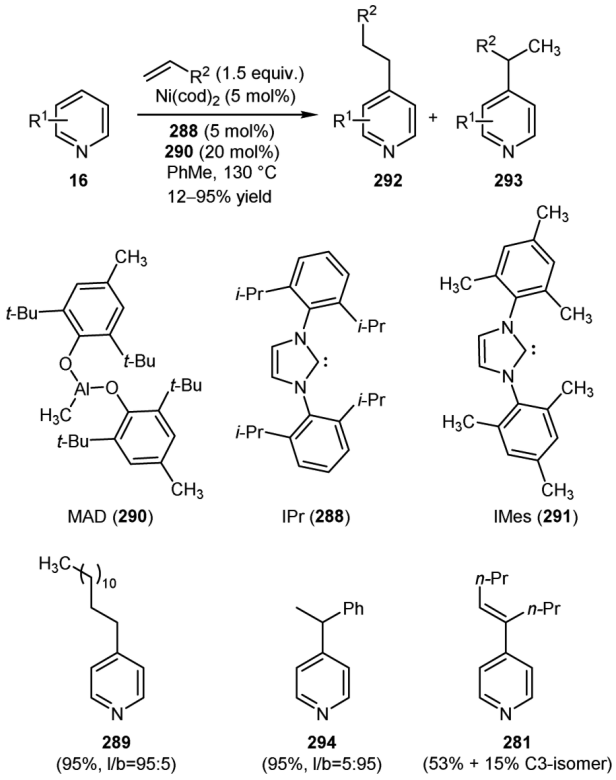
280 **284**

Scheme 79.
Complexation of Ni^0 with NHC and pyridine.

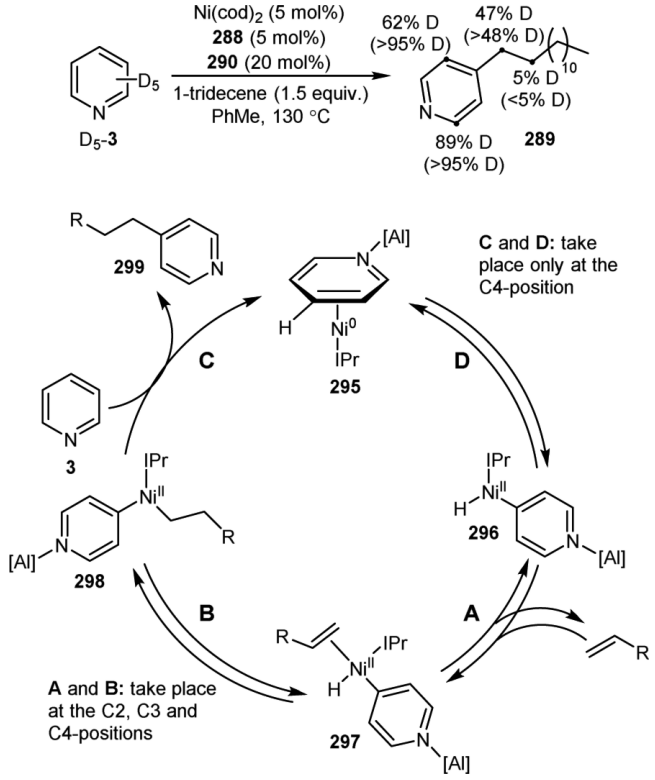


Scheme 80.

Plausible mechanism of the Ni-catalyzed C4-alkenylation of pyridines.

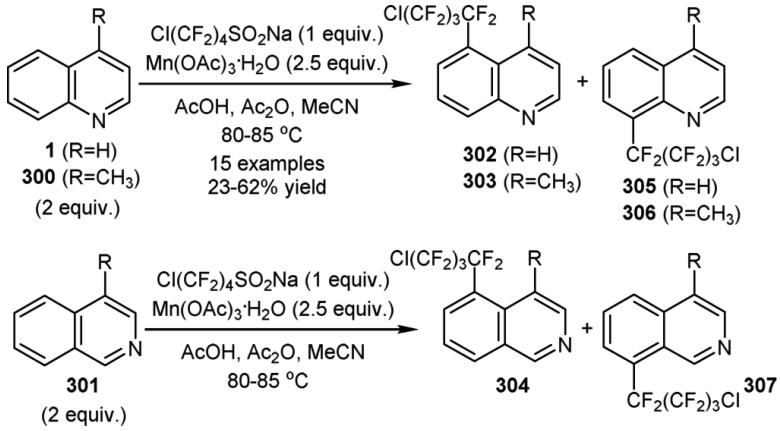


Scheme 81.
Ni-catalyzed C4-alkylation of pyridines.



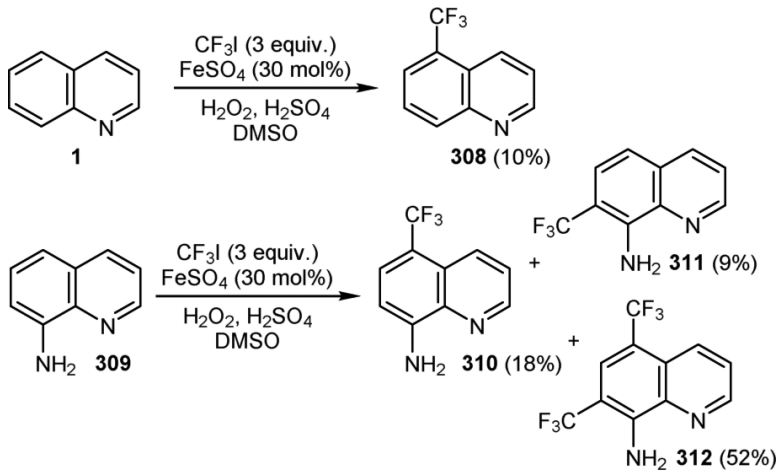
Scheme 82.

H/D exchange in the Ni-catalyzed C4-alkylation of pyridines and plausible mechanism.

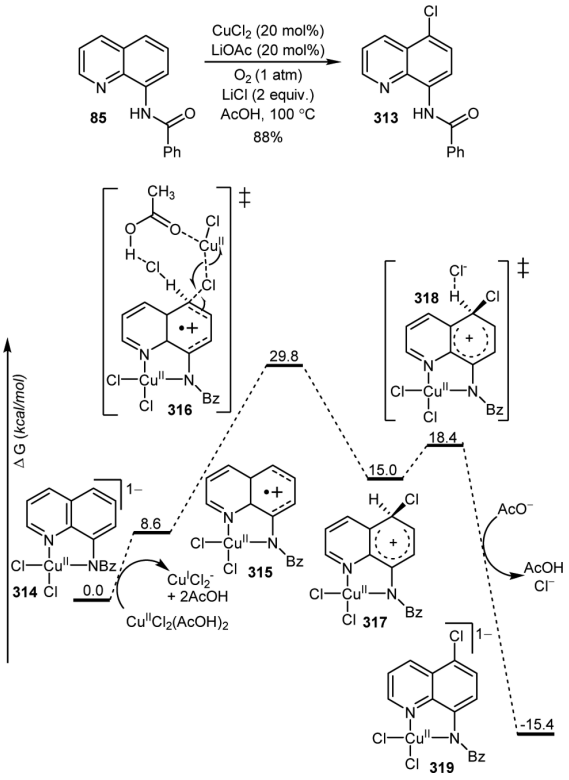


Scheme 83.

Radical perfluoroalkylation of heteroarenes.

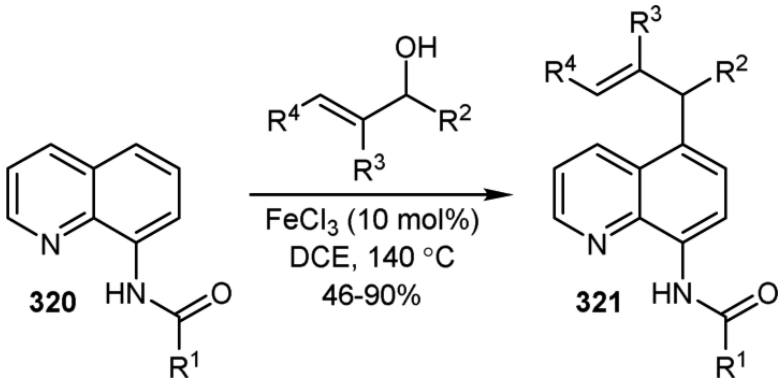


Scheme 84.
Radical trifluoromethylation of azines.

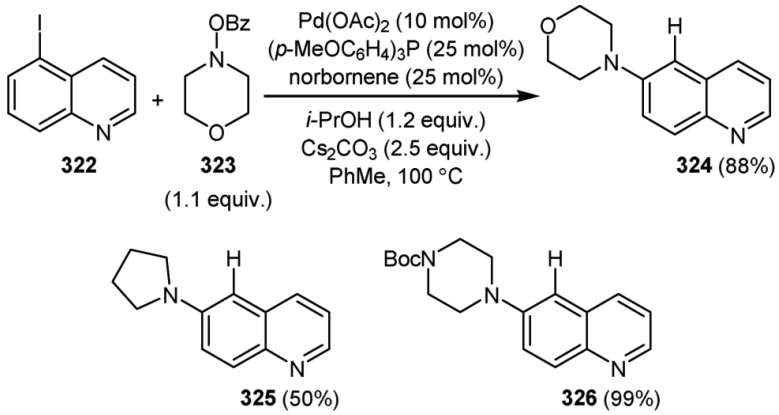


Scheme 85.

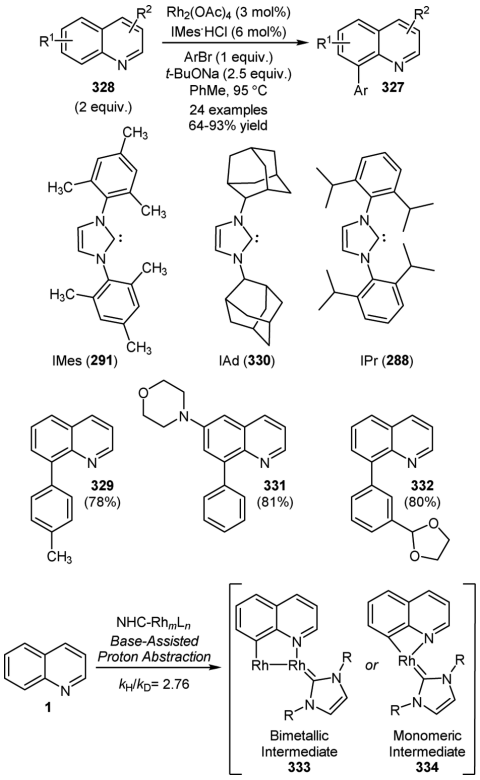
Calculated mechanism for the copper-mediated C5-chlorination.



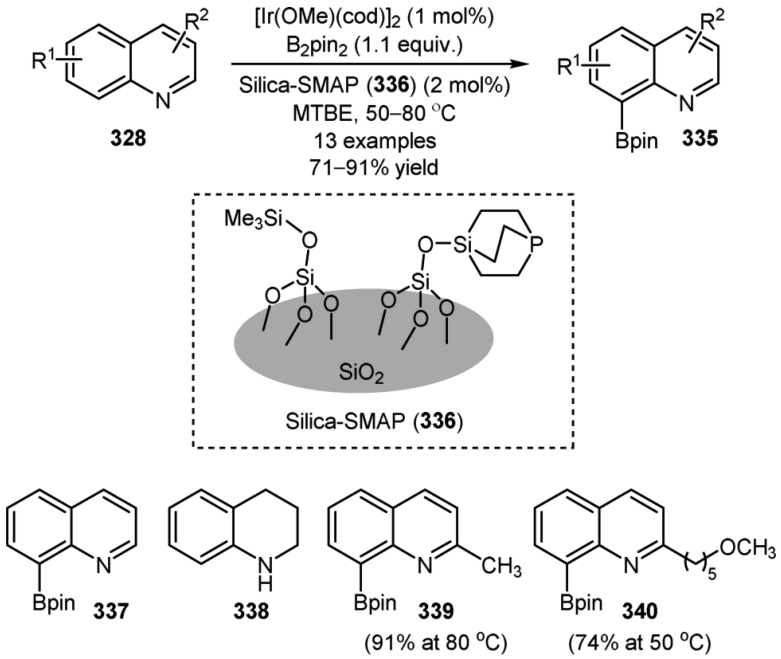
Scheme 86.
Fe(III)-catalyzed C5-allylation of 8-amidoquinolines.



Scheme 87.
Pd- and norbornene-catalyzed *ortho*-amination.

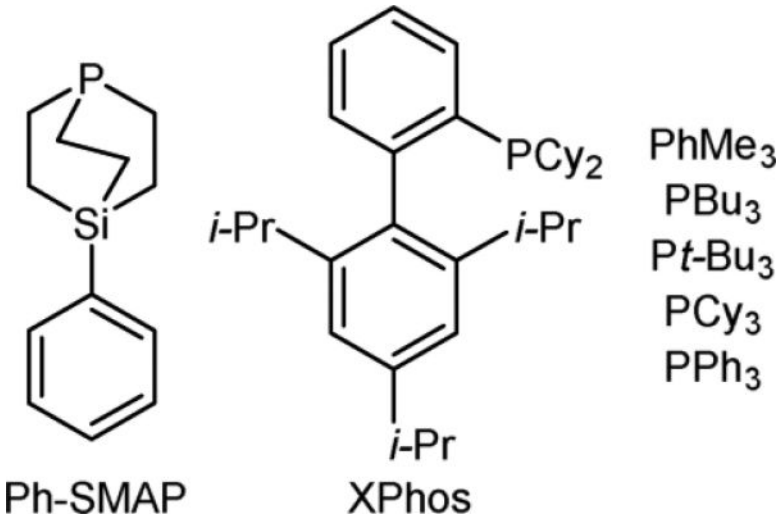


Scheme 88.
Rh(NHC)-catalyzed C8–H-arylation of quinolines.

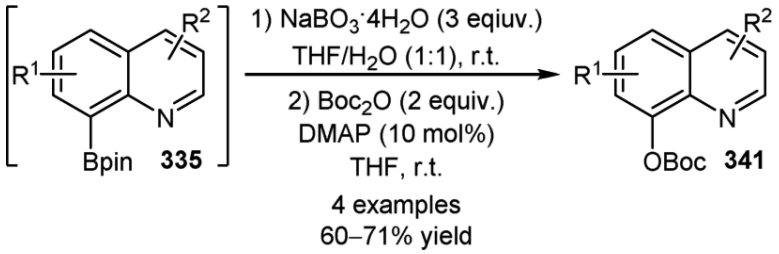


Scheme 89.

Ir-catalyzed C8–H-borylation of quinolines.

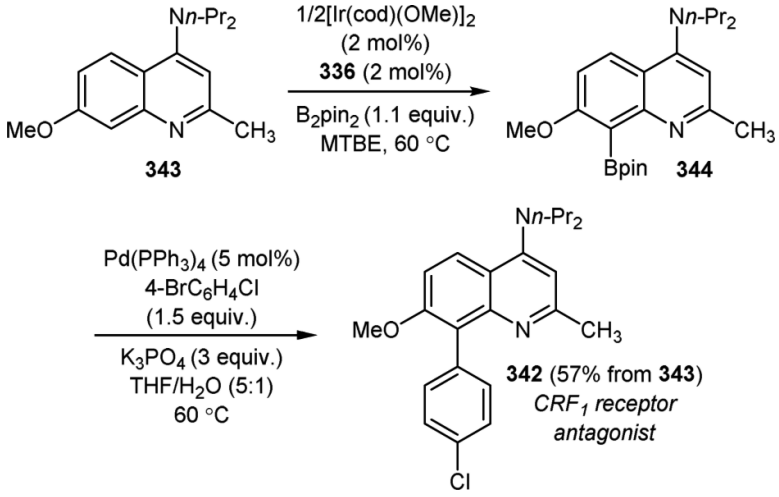


Scheme 90.
Phosphines providing trace C8–H-borylation product.



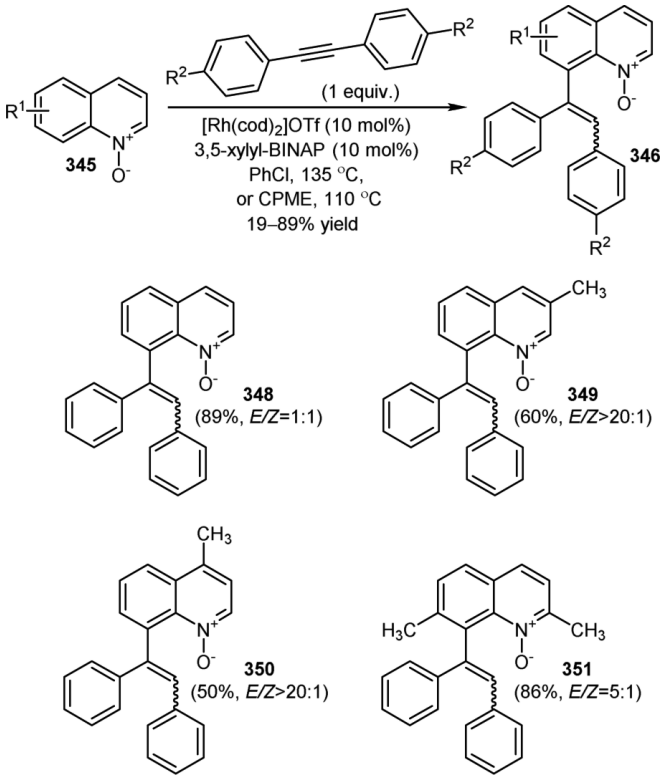
Scheme 91.

8-*tert*-butoxycarboxy-substituted quinolines prepared using the Ir/**336**-catalyzed C8-borylation of quinolines.



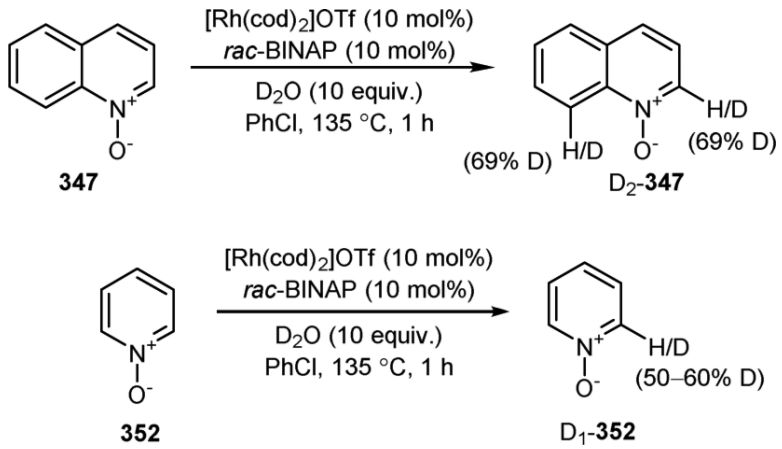
Scheme 92.

Synthesis of the CRF_1 receptor antagonist **342** using a late-stage C8–H borylation strategy.



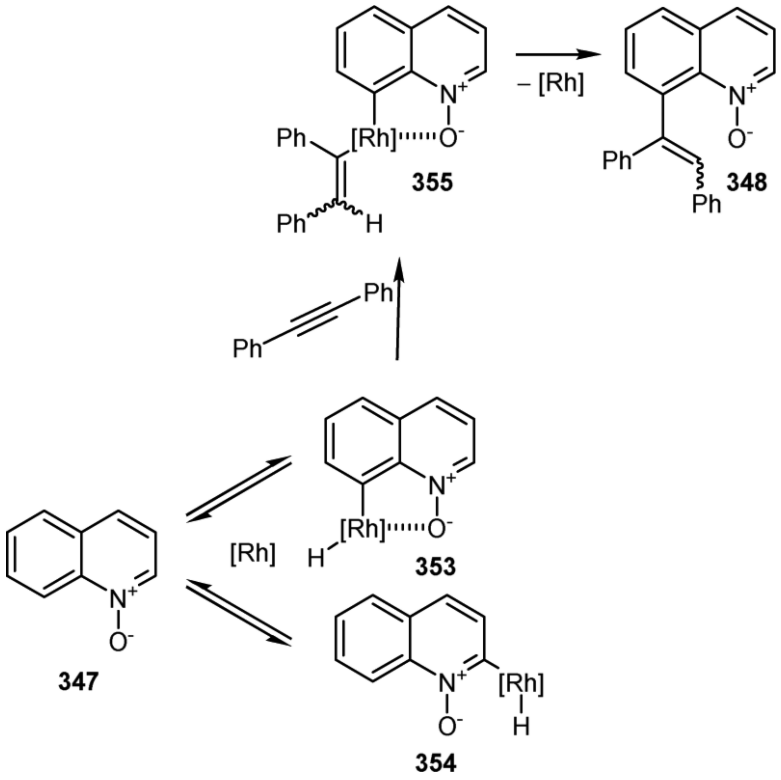
Scheme 93.

Rh-catalyzed C8-selective alkenylation of quinoline *N*-oxide.

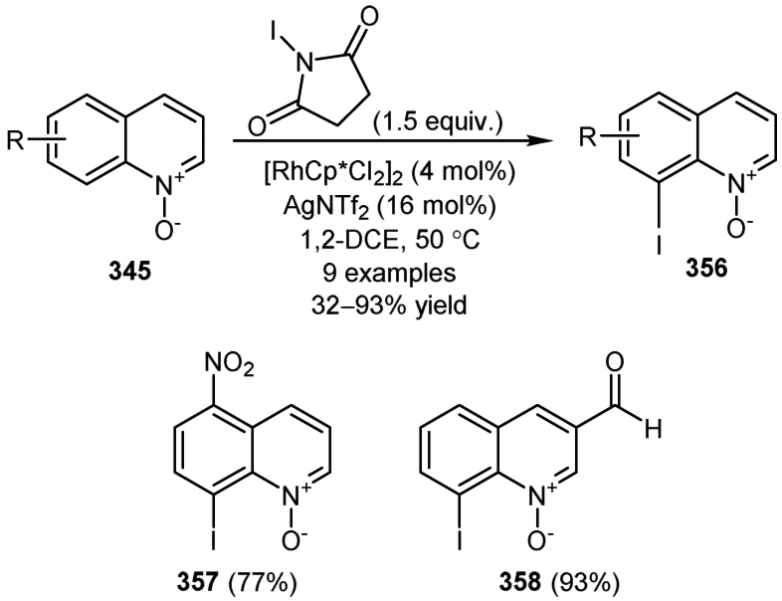


Scheme 94.

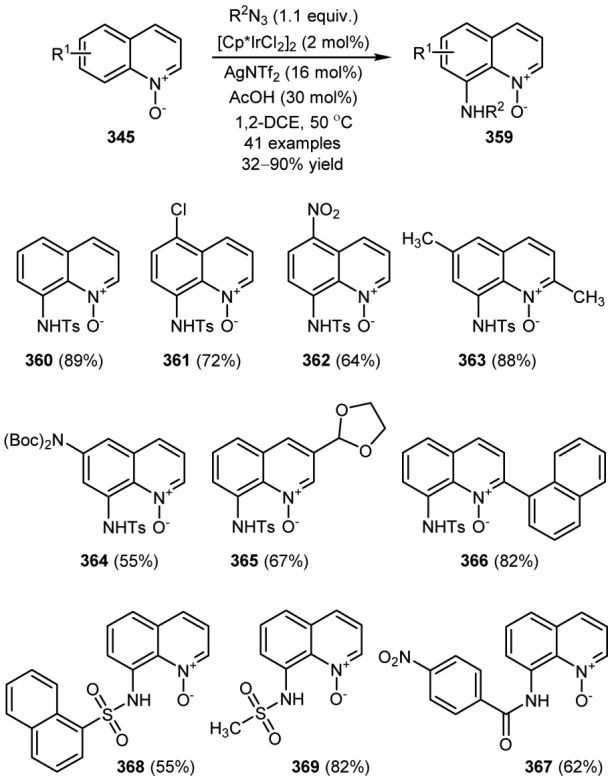
Rh-catalyzed C2- and C8-H/D exchange in azine *N*-oxides.



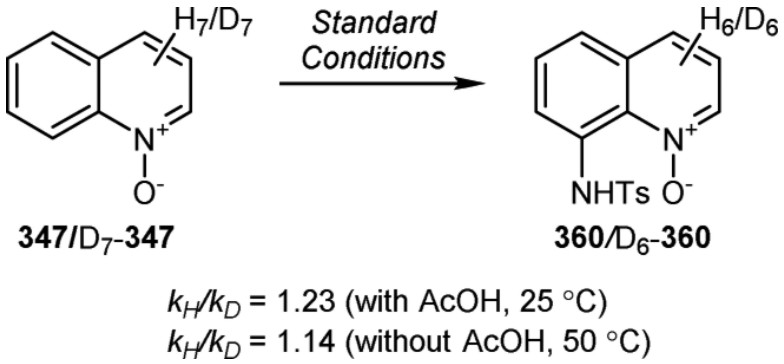
Scheme 95.
Plausible mechanism of the C8-selective alkenylation.



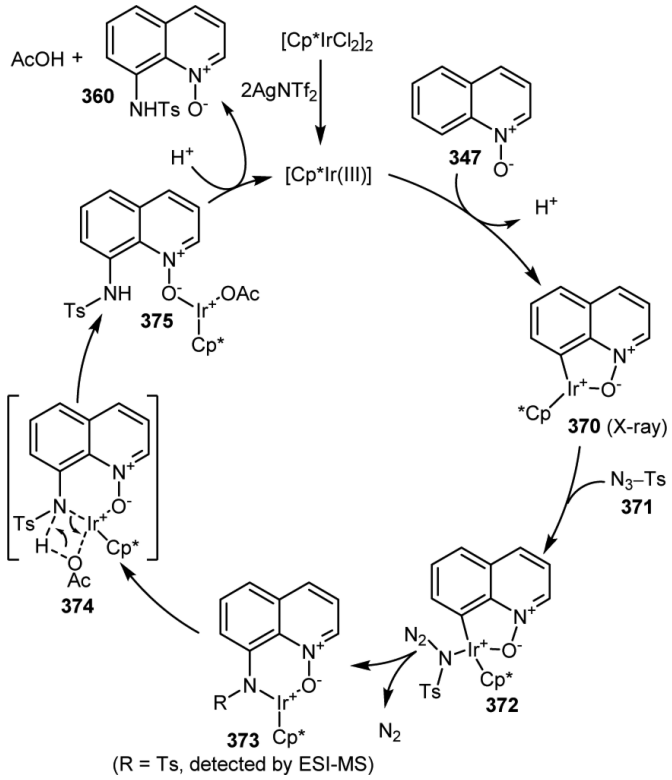
Scheme 96.
Rh-catalyzed C8–H-iodination.



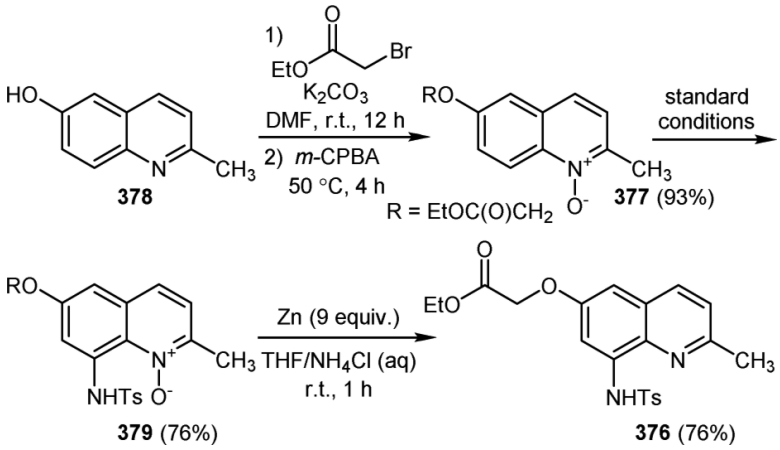
Scheme 97.
Ir-catalyzed C8–H-amidation of quinoline *N*-oxides.



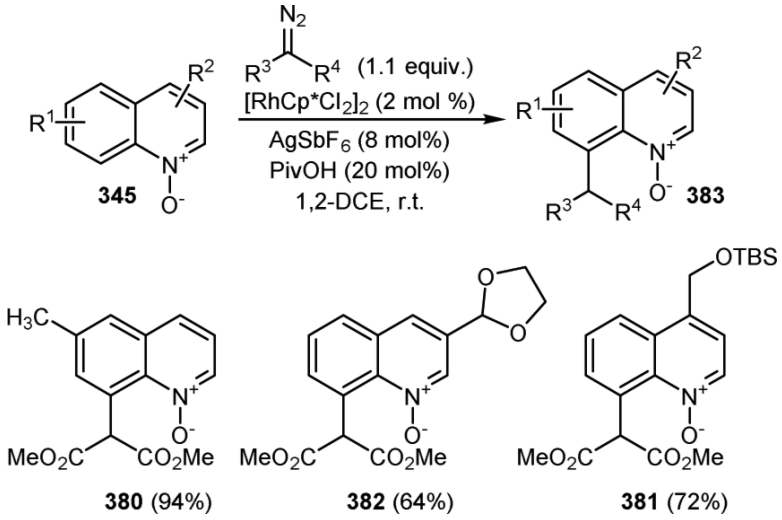
Scheme 98.
Study of the primary kinetic isotope effect.



Scheme 99.
Proposed mechanism for the Ir-catalyzed C8–H-amidation.

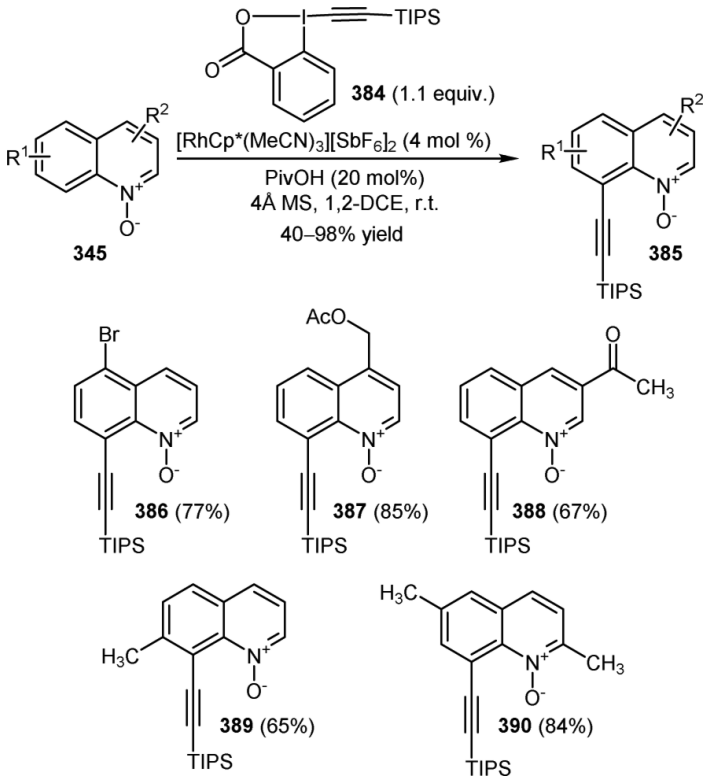


Scheme 100.
Synthesis of zinquin ethyl ester.

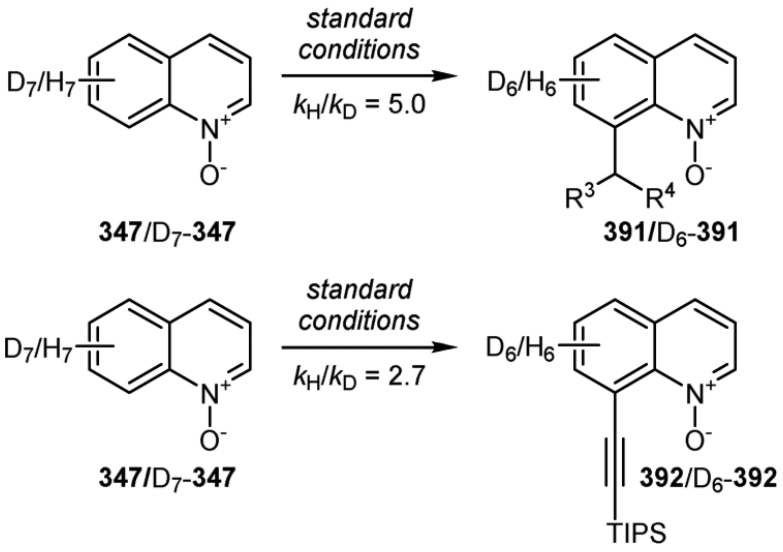


Scheme 101.

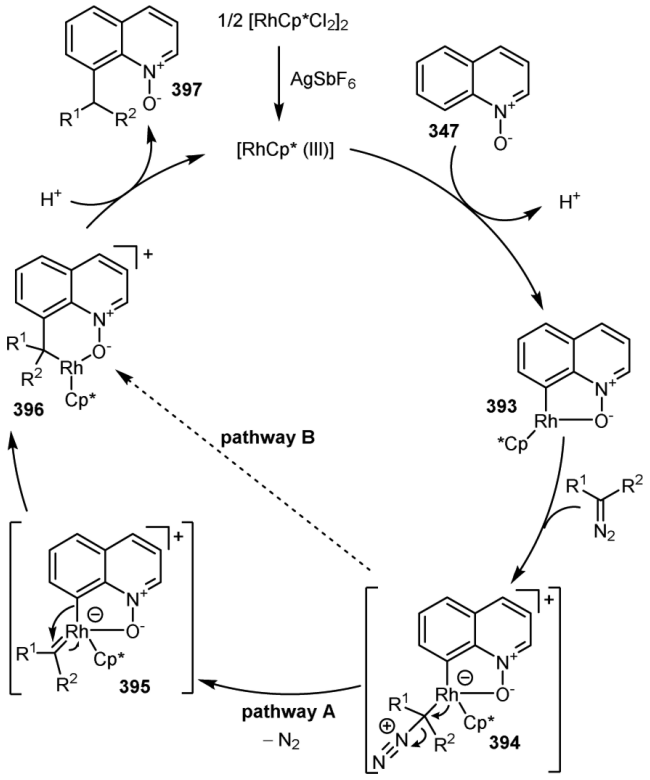
Rh-catalyzed C8–H-alkylation of quinoline *N*-oxides.



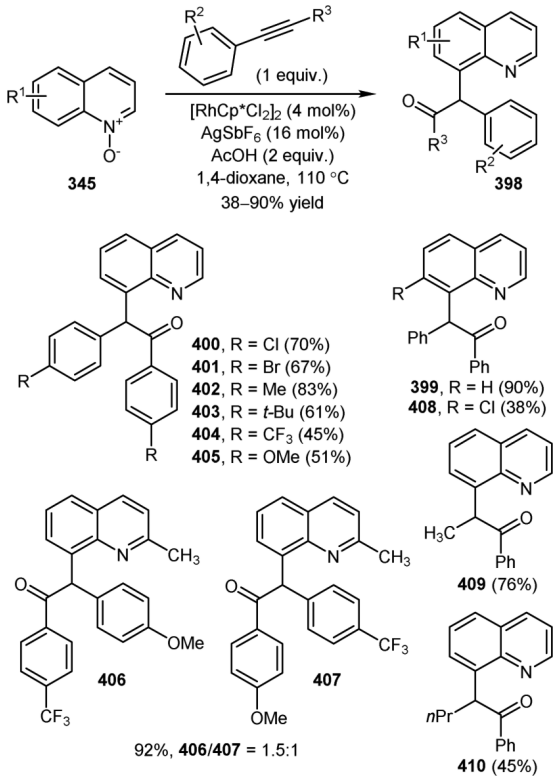
Scheme 102.
Rh-catalyzed C8–H-alkynylation of azine *N*-oxides.



Scheme 103.
Kinetic isotope effect experiments.

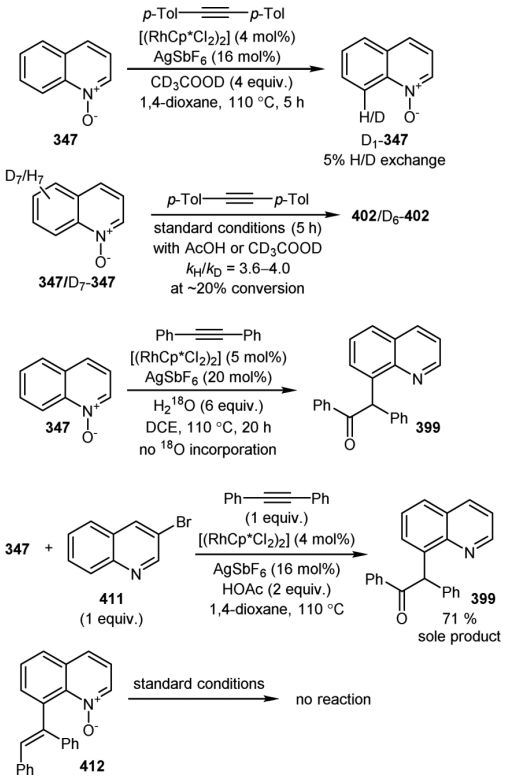


Scheme 104.
Proposed mechanism of the C8–H-alkylation of quinoline *N*-oxides.

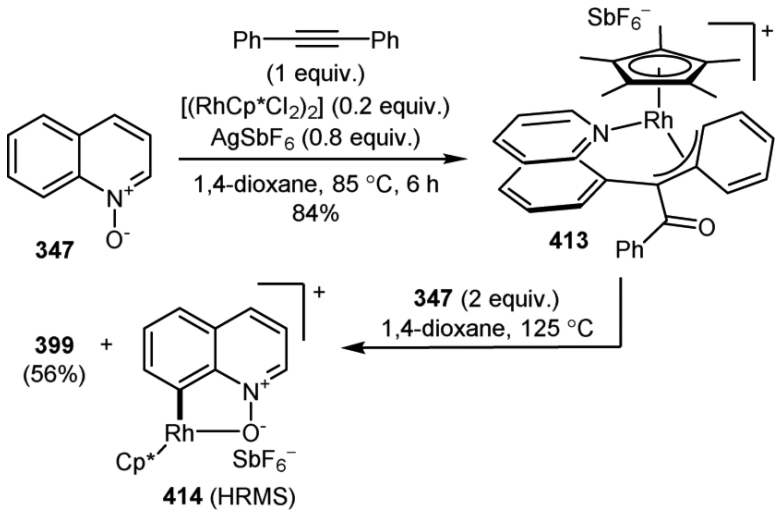


Scheme 105.

Cascade C8–H-alkynylation/O-transfer reaction of quinoline *N*-oxides.

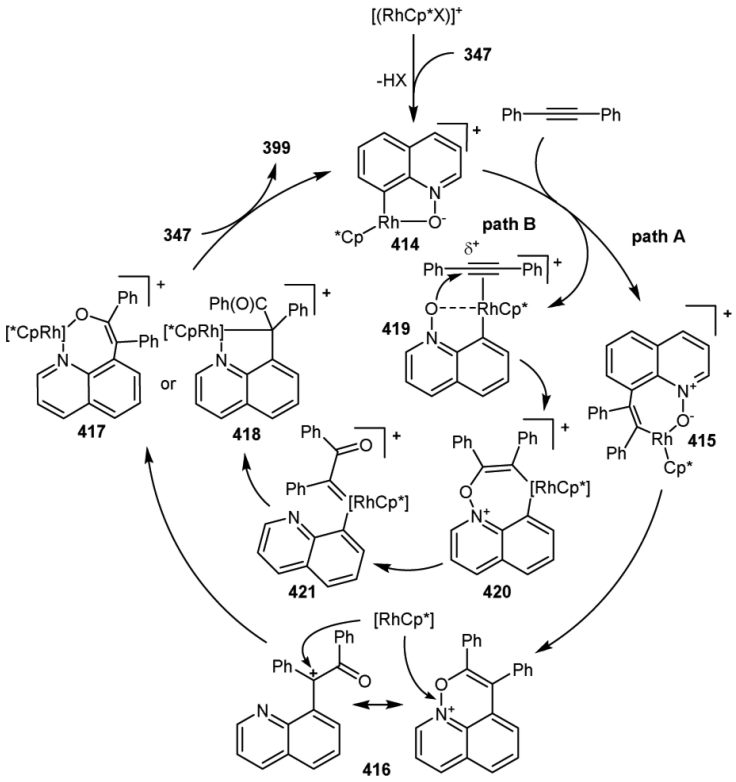


Scheme 106.
Studies performed to elucidate the mechanism.

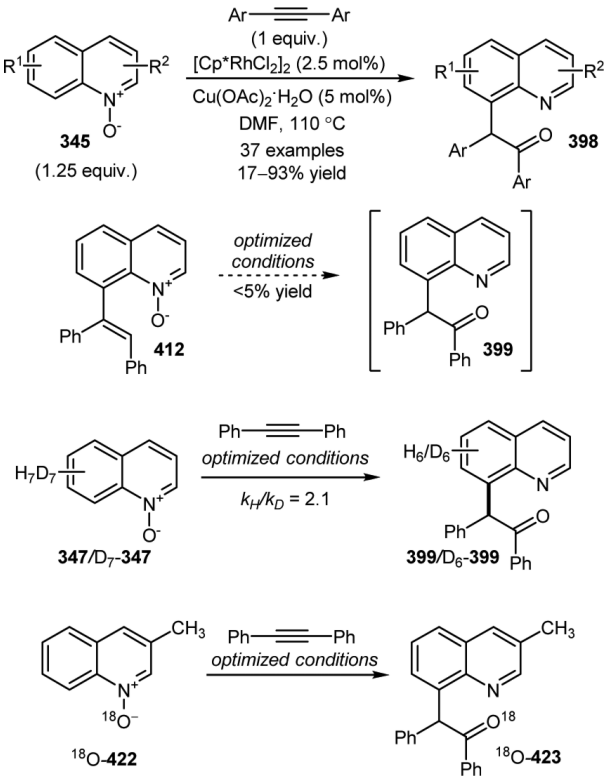


Scheme 107.

Isolation of rhodium(III) η^3-benzyl complex **413** and further mechanistic studies.

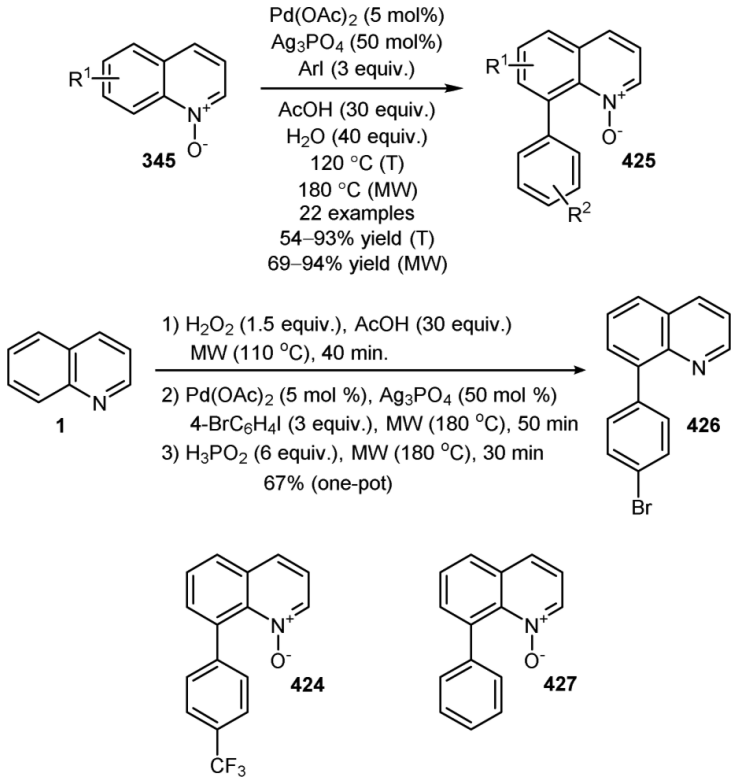


Scheme 108.
Two possible mechanistic pathways.



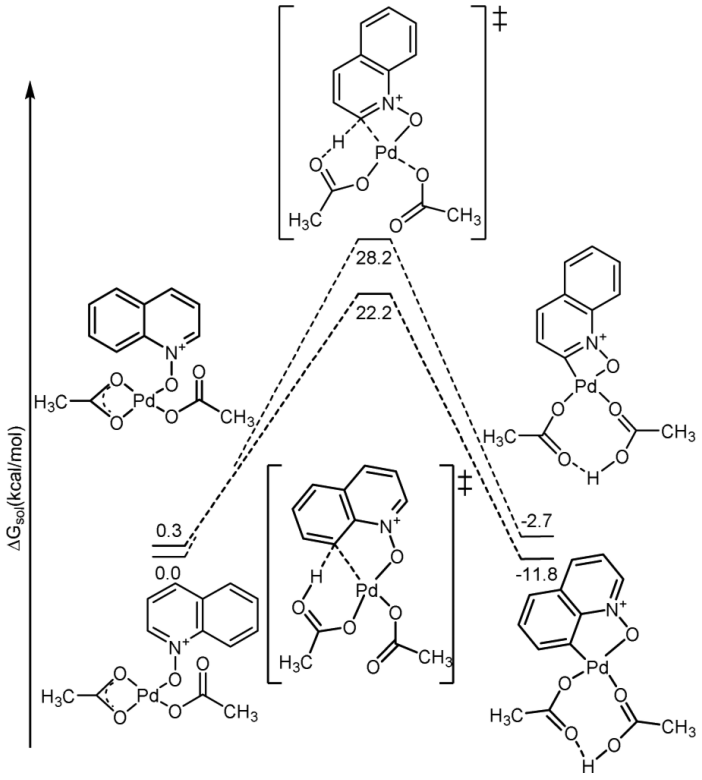
Scheme 109.

Kinetic isotope effect studies and the scope of the Rh-catalyzed C8-alkylation/O-atom transfer.



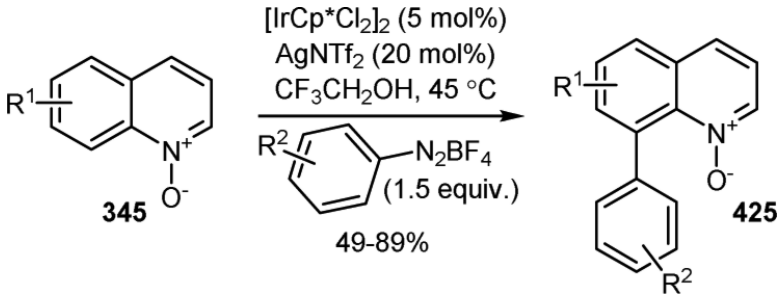
Scheme 110.

Pd-catalyzed C8-arylation of quinoline *N*-oxides.

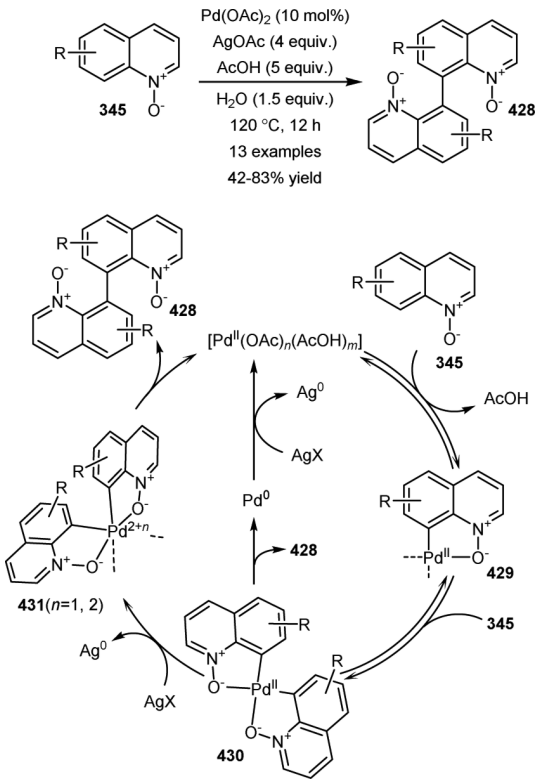


Scheme 111.

Computational study of the Pd-catalyzed C8-arylation of quinoline *N*-oxides.

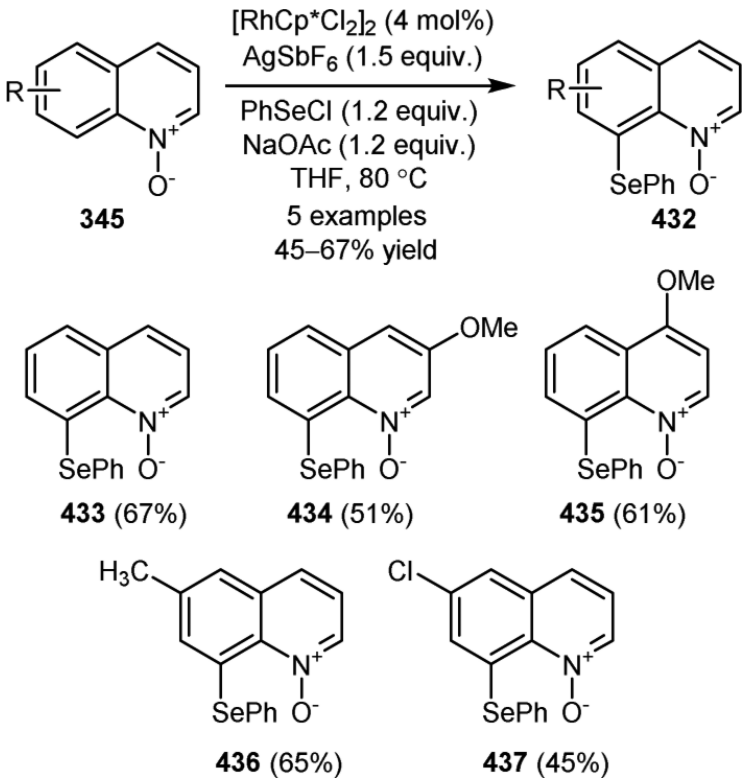


Scheme 112.
Pd-catalyzed C8-arylation of quinoline *N*-oxides.

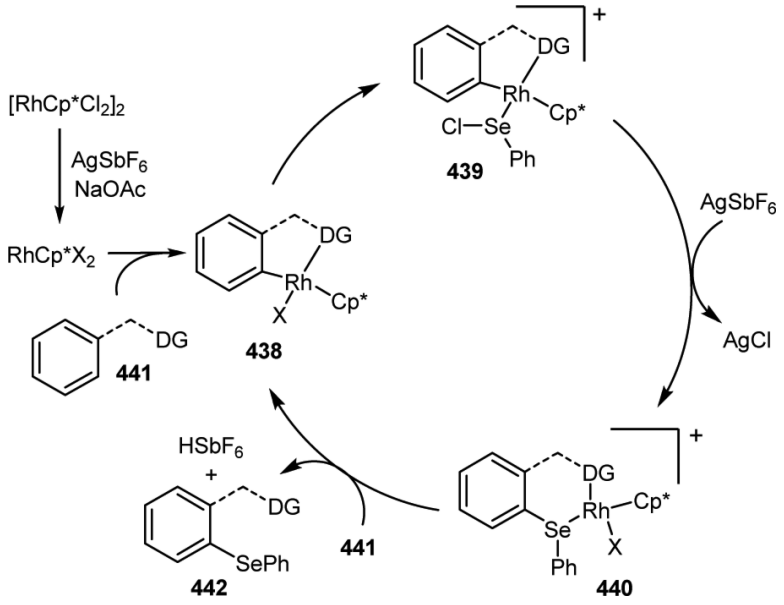


Scheme 113.

Pd-catalyzed oxidative C8–H-homocoupling of quinoline *N*-oxides and proposed mechanism.



Scheme 114.
Rh(III)-catalyzed selenation.



Scheme 115.

Plausible mechanism for the Rh(III)-catalyzed selenation.