CHEMICAL REVIEWS

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Review

# N-Heterocyclic Carbene Complexes in C–H Activation Reactions

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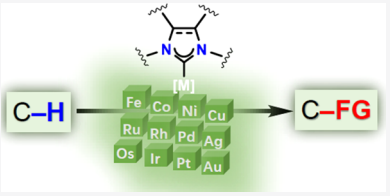
**ABSTRACT:** In this contribution, we provide a comprehensive overview of C–H activation methods promoted by NHC–transition metal complexes, covering the literature since 2002 (the year of the first report on metal–NHC-catalyzed C–H activation) through June 2019, focusing on both NHC ligands and C–H activation methods. This review covers C–H activation reactions catalyzed by group 8 to 11 NHC–metal complexes. Through discussing the role of NHC ligands in promoting challenging C–H activation methods, the reader is provided with an overview of this important area and its crucial role in forging carbon–carbon and carbon–heteroatom bonds by directly engaging ubiquitous C–H bonds.




## CONTENTS



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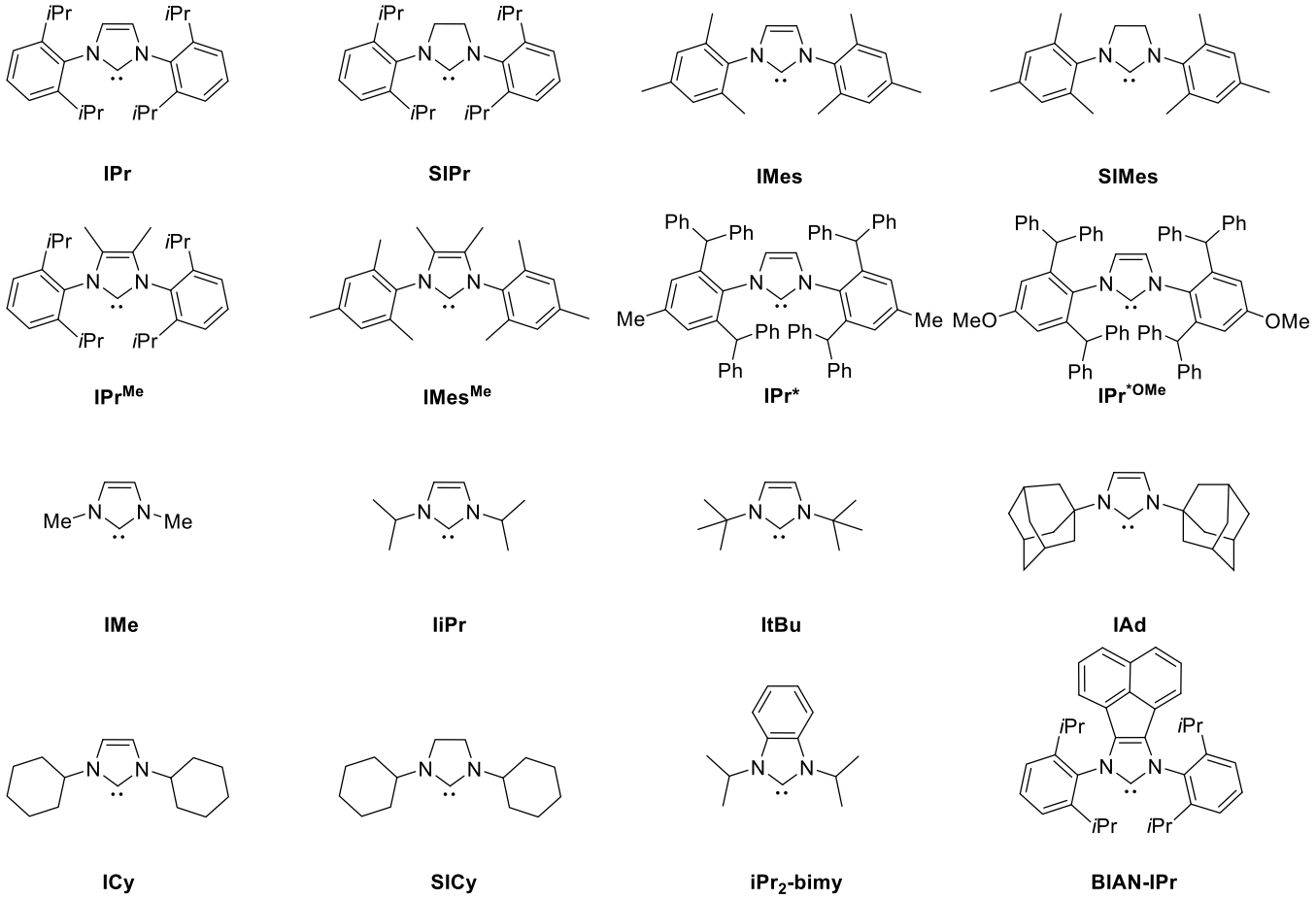


**Figure 1.** Structures of the most common NHCs used in C−H activation reactions.



## 1. INTRODUCTION

Since the seminal isolation of 1,3-diadamantylimidazol-2-ylidene by Arduengo in 1991, N-heterocyclic carbenes (NHCs) have played a central role as ligands in transition-metal catalysis.[1−59] Of particular importance is the ability of NHC ligands to enable difficult oxidative additions through strong $\sigma$-donation to various metal centers.[41−52] Furthermore, NHC ligands represent one of the most wide-ranging ways to vary the steric environment around the metal by N-wingtip substitution and backbone modifications of the ligand.[35,51,53−59] Moreover, recent studies have emphasized the importance of $\pi$-backbonding from the metal to the empty p-orbitals of the NHC, which is an important component in transition-metal catalysis employing electrophilic metals.[43] Finally, NHC ligands coordinated to metal centers are surprisingly robust to oxidative decomposition, thus enabling the use of NHC−metal complexes in oxidative transformations.[18]

In the last 20 years, tremendous advances have been achieved in C−H functionalization reactions.[60−86] At present, the synthesis of target molecules by selective activation of C−H bonds ranks among the most important objectives of modern synthetic chemistry and transition-metal catalysis.[60,61] New C−H activation methods for the direct conversion of ubiquitous C−H bonds have spurred the development of synthetic organic technologies through atom-, cost-, and step-economic installation of functional groups and functional group interconversion.[63−86] As a result, C−H functionalization methods are of broad academic and industrial importance and find widespread application in pharmaceutical, agrochemical, natural product, functional materials, polymers, and fine chemicals fields. Due to the potential important economic benefits,[85,86] the development of new and efficient C−H activation methods is a major driving methodology leading to a significantly more efficient construction of organic molecules. Despite the fact that transition-metal-catalyzed reactions exploiting NHC ligands have become invaluable in catalysis and organic synthesis in the last 20 years and significant advances have been reported, a comprehensive review on C−H activation reactions enabled by NHC ligands has not been published to date.

In this contribution, we provide a comprehensive overview of C−H activation methods promoted by NHC−transition metal complexes, covering the literature since 2002 (the year of the first report on metal−NHC-catalyzed C−H activation) through June 2019 focusing on both NHC ligands and C−H activation methods. The review covers C−H activation reactions catalyzed by group 8 to 11 NHC−metal complexes, which encompass all metals that have been used for catalytic C−H activation reactions using NHC−metal complexes to date. We believe that by discussing the role of NHC ligands in promoting challenging C−H activation methods the reader will be provided with an overview of this important area and its


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Chem. Rev. 2020, 120, 1981−2048

crucial role in forging carbon−carbon and carbon−heteroatom bonds by directly engaging ubiquitous C−H bonds.

The review is organized by metal and further by the type of C−H bonds undergoing functionalization. Unsurprisingly, the dominant metal used in C−H functionalization promoted by NHC ligands is palladium, and thus, the review starts with discussing C−H bond activation catalyzed by precious metal−NHC complexes, followed by first-row metal−NHC complexes and coinage metal−complexes. Several comprehensive reviews and monographs on NHC ligands have been published.[1−59] These publications have addressed general aspects of NHC ligands,[1−40] electronic properties of NHCs,[41−52] and steric properties of NHCs,[35,51,53−59] among other applications.

Structures of the most common NHC ligands used in C−H activation reactions together with their respective acronyms are shown in Figure 1. An important practical aspect of using metal−NHCs involves different ways of generating active complexes that could affect the outcome of C−H activation reactions.[1−5,26,34] The most common route involves the use of bench-stable NHC salts followed by an *in situ* deprotonation and metal complexation. Some C−H activation methods are sensitive to the presence of base, necessitating the use of free NHCs. Arguably, the most convenient way of applying metal−NHC complexes involves the use of well-defined metal−NHC precatalysts that are converted *in situ* into a catalytically active species.

It is further important to point out the key unique features of NHC ligands compared to other ligands used in C−H activation reactions. First, NHC ligands are strong $\sigma$-donors, which facilitates oxidative addition in nucleophilic C−H activation reactions. For example, comparison of the relative donor ability of NHCs and phosphines using the Tolman electronic parameter (TEP) of $[(L)Ir(CO)_2Cl]$ complexes demonstrates that NHCs are significantly stronger donors than commonly used tertiary phosphines (e.g., $PPh_3$, TEP = 2068.9 $cm^{-1}$; $PCy_3$, TEP = 2056.4 $cm^{-1}$; IMes, TEP = 2050.7 $cm^{-1}$; IPr, TEP = 2051.5 $cm^{-1}$; ICy, TEP = 2049.6 $cm^{-1}$; IAd, TEP = 2049.5 $cm^{-1}$), which leads to a stronger binding to the metal, improved stability to air and moisture, and more facile oxidative addition as compared with metal−phosphine counterparts.[49−51] Note that the strong $\sigma$-donation rendered possible by NHCs also allows for the high stability of metals in high oxidation states in oxidative C−H activation reactions, which are problematic with tertiary phosphines due to facile oxidation to phosphine oxides. Second, in terms of steric environment, NHCs are significantly larger than common tertiary phosphines (buried volume, $\%V_{bur}$, $[(L)AuCl]$ complexes, M−L = 2.00 Å: $PPh_3$, $\%V_{bur}$ = 27.3%; $PCy_3$, $\%V_{bur}$ = 38.8%; $PtBu_3$, $\%V_{bur}$ = 43.9%; IMes, $\%V_{bur}$ = 36.5%; IPr, $\%V_{bur}$ = 45.4%; IPr*, $\%V_{bur}$ = 50.4%).[52,53] As an illustrative example, a buried volume of common NHCs and tertiary phosphines can be correlated with bond dissociation energies (BDEs) in $[Ni(CO)_3(L)]$ complexes, wherein NHCs exhibit much higher bond dissociation energies than the corresponding tertiary phosphines with comparable steric demand (e.g., $PPh_3$: $\%V_{bur}$ = 22%; BDE = 26.7 kcal $mol^{-1}$; $PtBu_3$: $\%V_{bur}$ = 30%; BDE = 28.0 kcal $mol^{-1}$; IPr: $\%V_{bur}$ = 29%; BDE = 38.5 kcal $mol^{-1}$; ICy: $\%V_{bur}$ = 23%; BDE = 39.6 kcal $mol^{-1}$).[52,53] Third, unlike phosphines, NHCs can be more easily modified by N-wingtip substitution, backbone modification, and type of the NHC carbene, which allows for gradual tuning of the ligand for the optimum performance in catalysis.

Having pointed out the advantages of NHCs as ligands in C−H activation reactions, it is also important to note several disadvantages of this class of ligands and areas for further improvement. First, it should be considered that in general NHC ligands are more labor and cost intensive to synthesize than common tertiary phosphines. Accordingly, fewer types of NHC ligands are commercially available for rapid testing in catalysis as compared to common tertiary phosphines. Second, except for standard NHC ligands, straightforward synthetic methods that permit expeditious synthesis of diverse NHC ligands for catalyst screening and identification of active ligands are lacking. Third, NHCs are a relatively new class of ligands, and there is a lack of systematic structure−activity relationship studies that would aid the development of catalytic methods. We hope that this review will stimulate the additional use of NHC ligands in C−H activation methods by a wide range of synthetic researchers.

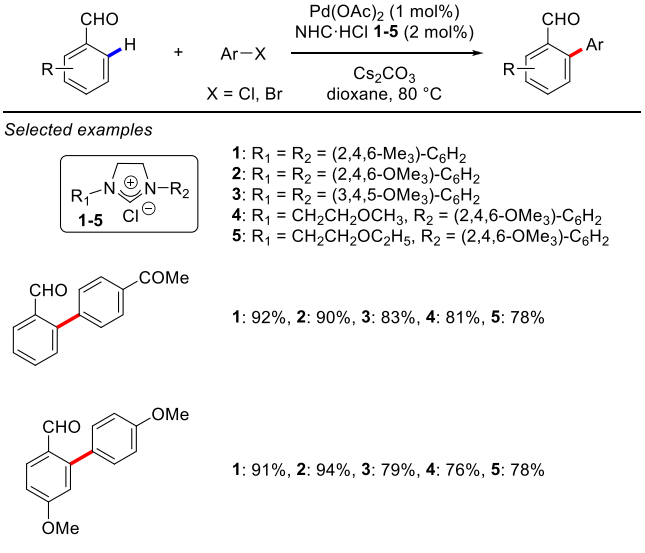
## 2. PALLADIUM−NHC COMPLEXES

In 1995, Herrmann and co-workers reported the first example of a Pd−NHC complex in cross-coupling reactions.[87] Although not optimum in terms of ligand to metal ratio and reaction conditions, this study constitutes one of the first examples of a transition-metal−NHC complex employed in catalysis. After this seminal report, the use of Pd−NHCs in cross-coupling reactions has rapidly increased in the following decades.[1−59] In particular, the vast majority of transition-metal-catalyzed cross-couplings has been significantly improved by employing NHCs instead of phosphines as ancillary ligands by taking advantage of their strong $\sigma$-donating abilities and variable steric bulk.[17,23,54] Similarly, palladium remains the most common metal used in C−H activation reactions promoted by NHC ligands.

### 2.1. C($sp^2$)−H Activation

**2.1.1. Aldehyde-Directed C($sp^2$)−H Activation.** In 2005, one of the first examples of the Pd−NHC-catalyzed C($sp^2$)−H activation was reported by Cetinkaya and co-workers (Scheme 1).[88] To our knowledge, this report represents the first comprehensive study on using metal−NHC complexes for small-molecule synthesis via directed C−

**Scheme 1. Pd−NHC-Catalyzed Aldehyde-Directed C($sp^2$)−H Arylation by Cetinkaya**



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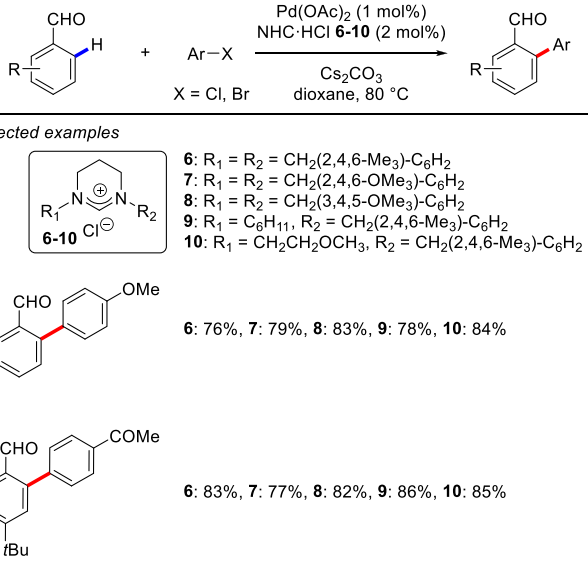
Chem. Rev. 2020, 120, 1981−2048

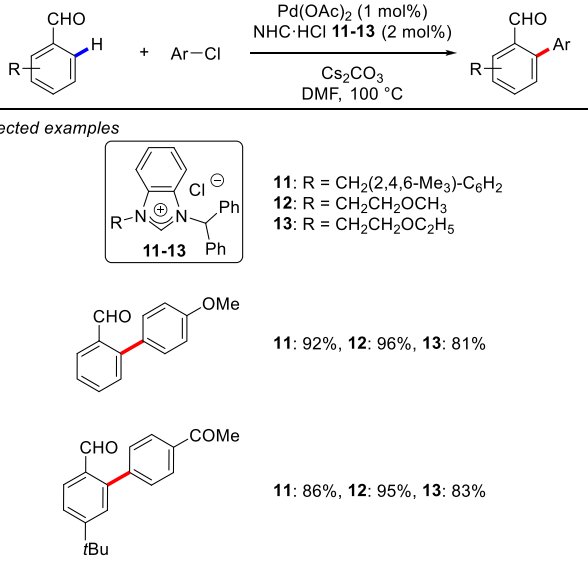
H functionalization. The direct C($sp^2$)−H arylation of benzaldehydes was achieved with the assistance of bulky, electron-rich imidazolidinylidene ligands **1**−**5**. Sterically hindered ligands **1** and **2** were shown to be particularly effective, and a variety of electronically diverse *ortho*-arylation products were obtained in high yields. In the same year, they reported a series of modified NHCs by changing the backbone from 5-membered imidazolidinylidenes to 6-membered tetrahydropyrimidinylidenes **6**−**10** (Scheme 2).[89] These new

**Scheme 2. Pd−NHC-Catalyzed Aldehyde-Directed C($sp^2$)−H Arylation Using Six-Membered NHC Ligands by Cetinkaya**



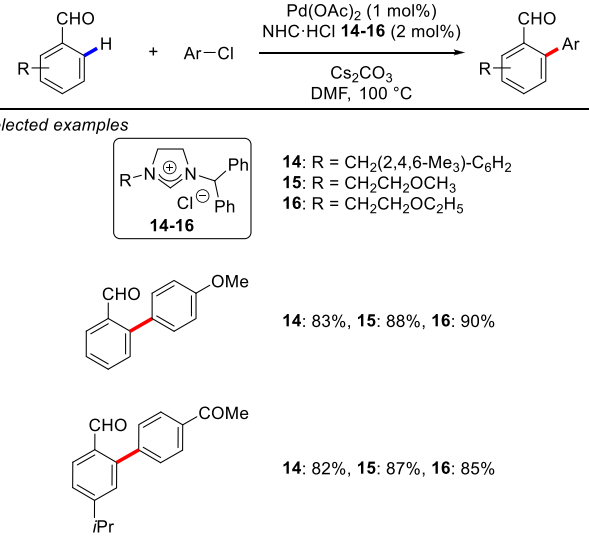

NHCs were also found to be excellent ligands for the C($sp^2$)−H arylation of benzaldehydes. In 2008, the same group described that benzimidazolylidene ligands **11**−**13** were effective for the same transformation (Scheme 3).[90] Pd−NHC complex **12** was shown to be the most efficient among

**Scheme 3. Pd−NHC-Catalyzed Aldehyde-Directed C($sp^2$)−H Arylation Using Benzimidazolium NHC Ligands by Cetinkaya**




the three complexes toward this aldehyde-directed C($sp^2$)−H arylation. In 2009, the Cetinkaya group designed three new imidazolidinylidene ligands featuring $\alpha$-branching at the N-atom that could also promote this C−H arylation reaction (Scheme 4).[91] Comparison studies showed that **15** and **16** exhibited higher reactivity than **14** in most cases.

**Scheme 4. Pd−NHC-Catalyzed Aldehyde-Directed C($sp^2$)−H Arylation Using Imidazolinium NHC Ligands by Cetinkaya**




It is interesting to note that an in situ formation of Pd−NHC complexes led to significantly better results than the direct use of preformed Pd−NHC catalysts, which might indicate a noninnocent behavior of the base (Schemes 1−4). In this example, $Cs_2CO_3$ was demonstrated as the optimal base, and 1,4-dioxane or DMF proved to be the most effective solvent.

**2.1.2. Intramolecular Nondirected C($sp^2$)−H/C−X Activation.** In 2005, Fagnou and co-workers reported an efficient intramolecular C($sp^2$)−H arylation with aryl chlorides using a hydrated [(IPr(Pd)$(OAc)_2$] catalyst bearing carboxylate ligands (Scheme 5).[92,93] The turnover number of this Pd−NHC catalyst was substantially improved through addition of IPr·HCl to the reaction. In this chemistry, deprotonation of the IPr·HCl salt in the presence of $K_2CO_3$ in DMA at 130 °C resulted in C($sp^2$)−H arylation in good to excellent yields.

A comparative study between different Pd(II)−NHC complexes in the intramolecular C($sp^2$)−H arylation with aryl chlorides was reported by Sefkow and co-workers in 2010 (Scheme 6).[94] Thus, out of four complexes investigated, namely, [(SIPr)Pd(cin)Cl] (cin = cinnamyl), [(IPr)$PdCl_2]_2$, [Pd-PEPPSI-SIPr], and [$(IPr)_2PdCl_2$], [(SIPr)Pd(cin)Cl] was the most reactive complex. In addition, the bis-NHC complex [$(IPr)_2PdCl_2$] was ineffective in promoting this C($sp^2$)−H arylation reaction. This protocol is quite effective for achieving intramolecular biaryl C−H/C−Cl coupling with easily handled Pd(II)−NHC complexes at low catalyst loadings.

**2.1.3. Intermolecular Nondirected C($sp^2$)−H/C−X Activation.** The direct C−H activation of heterocycles and acidic arene C−H bonds represents important reactions catalyzed by Pd−NHC complexes.[82,83] These reactions are classified by the type of heterocycle and bond undergoing the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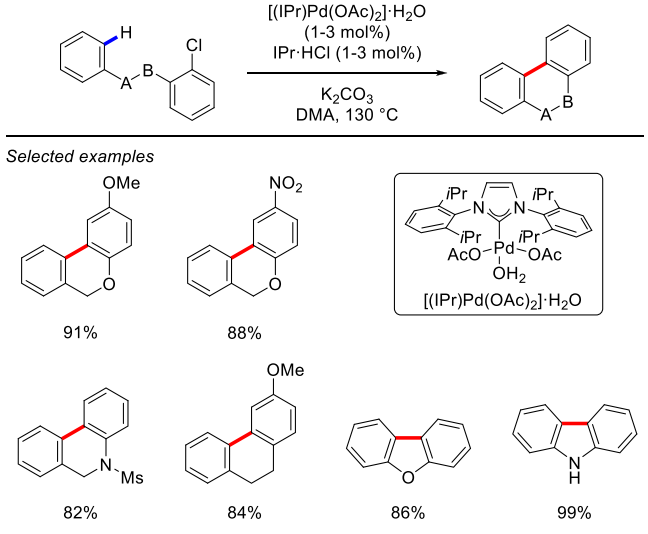
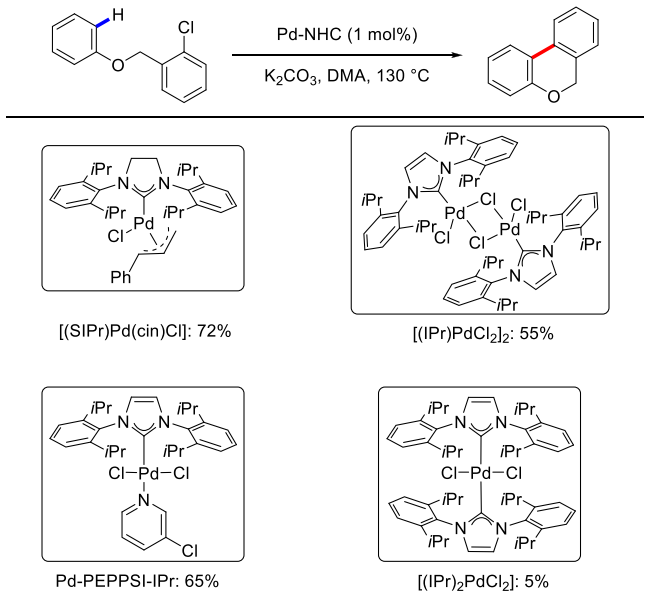
Chem. Rev. 2020, 120, 1981−2048

**Scheme 5. Pd−NHC-Catalyzed Intramolecular Nondirected C(sp²)−H/C(sp²)−X Activation by Fagnou**




**Scheme 6. Pd−NHC-Catalyzed Intramolecular Nondirected C(sp²)−H/C(sp²)−X Activation by Sefkow**

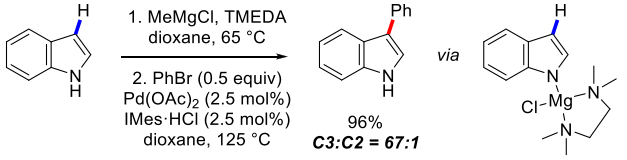



C−H activation process; however, it should be noted that several Pd−NHC complexes have been shown to be effective in activating various classes of heterocycles.

*2.1.3.1. C(sp²)−H Activation in Heteroarenes.* These reactions are categorized into 5-membered heterocycles with one heteroatom such as pyrroles, thiophenes, furans, indoles, benzofurans, and enzothiophenes and 5-membered heterocycles with two or more heteroatoms, such as imidazoles, oxazoles, thiazoles, and their benzoderivatives, among others. It is worth noting that C(sp²)−H activations in heteroarenes are among the most successful reactions developed using NHC ancillary ligands to date. Among the key advantages of Pd−NHCs in this class of C−H activation reactions are high stability to the reaction conditions, high regioselectivity, and beneficial functional group tolerance as compared to the more traditionally used tertiary phosphine ligands.

*2.1.3.1.1. 5-Membered Heterocycles with One Heteroatom.* The first example of a direct C(sp²)−H activation of heterocycles by Pd−NHC complexes was reported by Sames and co-workers in 2005 (Scheme 7).[95] These studies

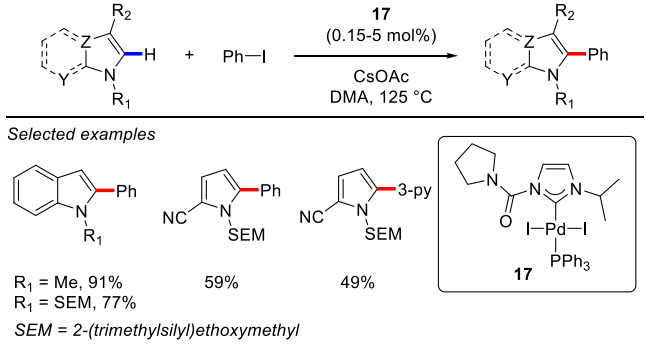
**Scheme 7. Pd−NHC-Catalyzed Direct C3−H Arylation of Indole by Sames**



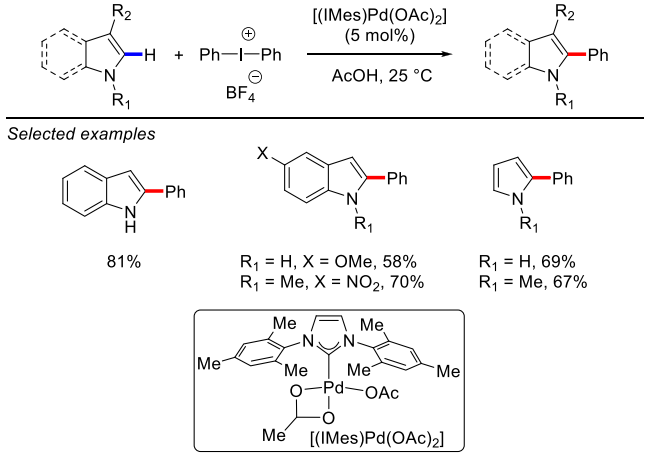

established that the C3 C−H arylation of unprotected indole after deprotonation with MeMgCl in the presence of TMEDA proceeds with 67:1 C3/C2 selectivity using the IMes ligand (cf. 14:1 C3/C2 selectivity using $PPh_3$).

In 2006, the Sames[96] and Sanford groups[97] independently reported further examples of Pd−NHC-catalyzed C(sp²)−H arylation of heterocycles (Schemes 8 and 9). Sames and co-

**Scheme 8. Pd−NHC-Catalyzed Direct C−H Arylation of Azoles by Sames**




**Scheme 9. Pd−NHC-Catalyzed Direct C−H Arylation of Indoles and Pyrroles by Sanford**




workers developed a mixed $[Pd(NHC)I_2(PPh_3)]$ complex **17** for C(sp²)−H arylation of SEM-protected (SEM = trimethylsilylethoxymethyl) azoles with aryl iodides in DMA at 125 °C (Scheme 8).[96] A wide range of azoles, including pyrroles, indoles, imidazoles, and imidazo[1,2-*a*]pyridines, were directly arylated in good to excellent yields (see also Scheme 26). The reaction was characterized by the operational simplicity and stability of the Pd(II)−NHC precatalyst **17** to air and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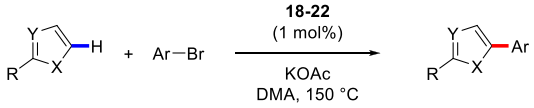
Chem. Rev. 2020, 120, 1981−2048

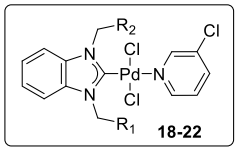
moisture. At about the same time, Sanford and co-workers reported [Pd(IMes)(OAc)$_2$], featuring carboxylate ligands, for the C(sp$^2$)−H arylation of indoles and pyrroles using aryl iodonium salts (Scheme 9).[97] A wide range of indoles and representative pyrroles were functionalized with $Ar_2I^+BF_4^-$ in AcOH at 25 °C to give 2-arylindoles and 2-arylpyrroles in high yields. It is noteworthy that this reaction could be carried out under remarkably mild room-temperature conditions and also appeared to be compatible with air and moisture.

The area of direct C(sp$^2$)−H arylation of heterocycles by Pd−NHC complexes then remained dormant until 2010 when Özdemir and co-workers synthesized a series of Pd−NHC benzimidazolylidene complexes **18**−**21** bearing different N-side chains and employed them as catalysts for the direct C(sp$^2$)−H arylation of furan, thiophene, and thiazole derivatives with aryl bromides (Scheme 10, see also Schemes 27 and 28).[98] Impressively, only 1.0 mol % of air-stable Pd(II)−NHC precatalysts was required for this transformation. This represented a major practical advantage over the procedures employing air-sensitive phosphine ligands. In addition, this procedure generates KOAc and HBr as major byproducts instead of metal salts.

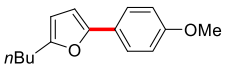
**Scheme 10. Pd−NHC-Catalyzed Direct C−H Arylation of Furans, Thiophenes, and Thiazoles by Özdemir**



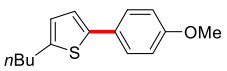

*Selected examples*



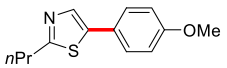

**18**: $R_1 = R_2 = CH_2$-1-Np
**19**: $R_1 = CH_2$-1-Np; $R_2 = CH_2$-Mes
**20**: $R_1 = CH_2$-1-Np; $R_2 = CH_2$-$C_6H_5$
**21**: $R_1 = R_2 = CH_2$-$C_6H_5$
**22**: $R_1 = R_2 = CH_2CH_2OCH_3$



**18**: 69%, **19**: 59%, **20**: 76%, **21**: 64%



**18**: 45%, **20**: 56%, **22**: 10%

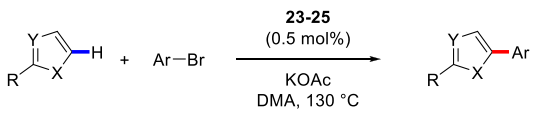


**18**: 89%, **19**: 85%, **21**: 92%

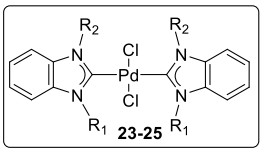
In 2014, Akkoc and co-workers reported bis-Pd−NHC benzimidazolylidene complexes **23**−**25** for the direct C(sp$^2$)−H C5 arylation of furans, thiophenes, and thiazoles (Scheme 11).[99] The procedure was compatible with both electron-deficient and electron-rich aryl halides as coupling partners. High catalytic activity was observed using 0.5 mol % of Pd−NHC complexes in DMA at 130 °C. The same group reported similar bis-Pd−NHC benzimidazolylidene complexes **26**−**30** with *N*-benzylic side chains for the direct C(sp$^2$)−H C5 arylation of furans, thiophenes, and thiazoles at the C5 position (Scheme 12).[100] Comparison of the reactivity demonstrated that Pd(II)−NHC **30** was the most efficient precatalyst.

Subsequently, Cetinkaya and co-workers reported bis-Pd−NHC tetrahydropyrimidinylidene complexes **31**−**34** as catalysts for the direct C2 or C5 arylation of furans, thiophenes, and thiazoles with aryl bromides (Scheme 13).[101] High catalytic activity was observed using KOAc in DMA at 150 °C. More recently, Akkoc and co-workers reported a series of Pd−PEPPSI-type complexes **35**−**38** based on the phthalimide-functionalized benzimidazolylidene scaffold for the direct C(sp$^2$)−H arylation reactions of furans and thiophenes (Scheme 14).[102] These complexes contain a pyridine throw-away ligand and for some of these C−H arylations displayed good catalytic activity at 110 °C.

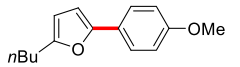
**Scheme 11. Pd−NHC-Catalyzed Direct C−H Arylation of Furans, Thiophenes, and Thiazoles by Akkoc**



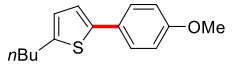

*Selected examples*



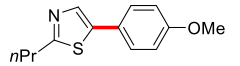

**23**: $R_1$ = Ph; $R_2 = (CH_2)_2$-N-morpholine
**24**: $R_1$ = Ph; $R_2$ = (4-$CH_2$=CH)-Bn
**25**: $R_1$ = Ph; $R_2 = CH_2$-1-Np



**23**: 92%, **24**: 54%, **25**: 70%

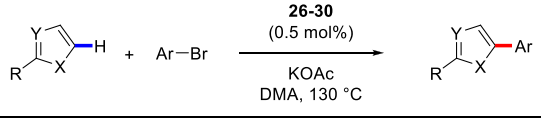


**23**: 92%, **24**: 99%, **25**: 100%

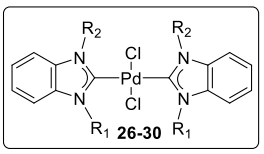


**23**: 100%, **24**: 79%, **25**: 100%

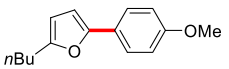
**Scheme 12. Pd−NHC-Catalyzed Direct C−H Arylation of Furans, Thiophenes, and Thiazoles by Akkoc**



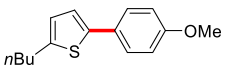

*Selected examples*



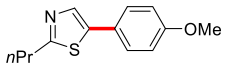

**26**: $R_1$ = Ph; $R_2$ = (2,4,6-$Me_3$)-Bn
**27**: $R_1$ = Ph; $R_2$ = (2,3,5,6-$Me_4$)-Bn
**28**: $R_1$ = Ph; $R_2$ = (2,3,4,5,6-$Me_5$)-Bn
**29**: $R_1$ = Ph; $R_2$ = (3,4,5-$OMe_3$)-Bn
**30**: $R_1 = (CH_2)_2NEt_2$; $R_2$ = (2,3,5,6-$Me_4$)-Bn



**26**: 66%, **27**: 83%, **28**: 93%, **29**: 69%, **30**: 81%



**26**: 88%, **27**: 96%, **28**: 96%, **29**: 79%, **30**: 100%



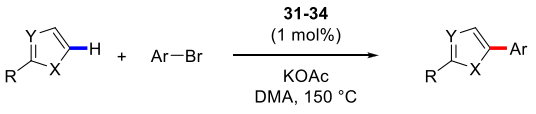
**26**: 96%, **27**: 91%, **28**: 90%, **29**: 97%, **30**: 100%

The Lee group reported that a highly electron-rich mixed [(NHC)Pd(PCy$_3$)Cl$_2$] complex **39** can be used as an efficient catalyst for the C5−H arylation of furans, thiophenes, and thiazoles with aryl chlorides (Scheme 15).[103] By using PivOH as an additive (30 mol %) and $K_2CO_3$ as a base (1.5 equiv), the desired C−H arylated products were obtained in high to excellent yields in DMA at 110 °C.

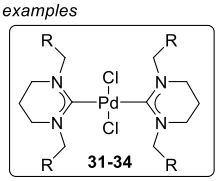
Simultaneously, the Nolan group reported the use of [(NHC)Pd(cin)Cl] complexes as catalysts for the direct C−


https://dx.doi.org/10.1021/acs.chemrev.9b00634
Chem. Rev. 2020, 120, 1981−2048

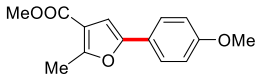
**Scheme 13. Pd−NHC-Catalyzed Direct C−H Arylation of Furans, Thiophenes, and Thiazoles Using 6-Membered NHC Ligands by Cetinkaya**



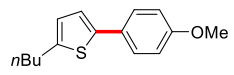

*Selected examples*



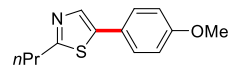

**31**: R = 4-Me-$C_6H_4$
**32**: R = 4-Et-$C_6H_4$
**33**: R = 4-$NMe_2$-$C_6H_4$
**34**: R = 3,4-$(OMe)_2$-$C_6H_3$



**31**: 78%, **32**: 85%, **33**: 81%, **34**: 75%

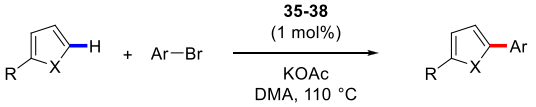


**31**: 88%, **32**: 82%, **33**: 83%, **34**: 86%

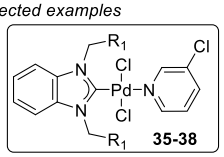


**31**: 74%, **32**: 89%, **33**: 82%, **34**: 87%

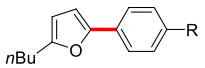
**Scheme 14. Pd−NHC-Catalyzed Direct C−H Arylation of Furans and Thiophenes by Akkoc**



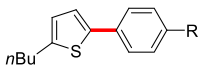

*Selected examples*




**35**: $R_1$ = phthalimide; $R_2$ = Ph
**36**: $R_1$ = phthalimide; $R_2$ = 3-Me-$C_6H_4$
**37**: $R_1$ = $R_2$ = phthalimide
**38**: $R_1$ = phthalimide; $R_2$ = $CH_2N(CH_2CH_2)_2O$



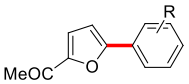
R = H, **37**: 98%
R = COMe, **35**: 14%, **36**: 49%, **37**: 83%, **38**: 89%



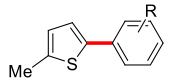
R = H, **38**: 97%
R = OMe, **35**: 79%
R = COMe, **35**: 9%, **38**: 27%

**Scheme 15. Pd−NHC-Catalyzed Direct C−H Arylation of Furans, Thiophenes, and Pyrroles by Lee**

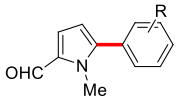

*Selected examples*



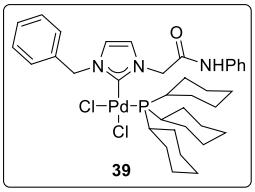
R = 4-$CF_3$, 71%
R = 4-CN, 62%
R = 3-CN, 63%
R = 3-Me, 89%

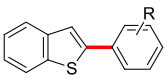


R = 4-$CF_3$, 58%
R = 4-OMe, 66%
R = 3-Me, 76%



R = 4-Me, 78%
R = 4-OMe, 74%

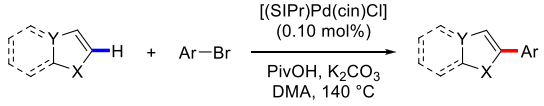


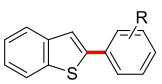
R = 4-CN, 69%
R = 4-$NO_2$, 52%

H arylation of thiophenes, benzothiophenes, and imidazo[1,2-*a*]pyridines with aryl bromides (Scheme 16).[104] The

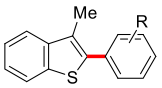
**Scheme 16. Pd−NHC-Catalyzed Direct C−H Arylation of Thiophenes and Imidazopyridines by Nolan**



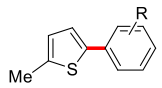

*Selected examples*



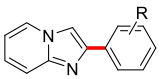
R = 4-Me, 89%
R = 3-Me, 80%
R = 2-Me, 77%
R = 4-Cl, 49%



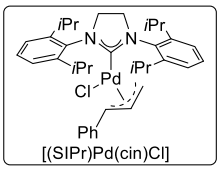
R = 4-Me, 85%
R = 2-Me, 83%
R = 4-F, 52%



R = 4-Me, 90%
R = 4-OMe, 75%
R = 4-F, 57%



R = 4-Me, 74%
R = 4-OMe, 53%
R = 4-F, 76%

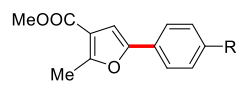



imidazolidinylidene complex [(SIPr)Pd(cin)Cl] was proved to be the most efficient catalyst for this reaction. The C−H bond functionalization was achieved at very low catalyst loadings (0.01−0.10 mol %) in DMA at 140 °C.

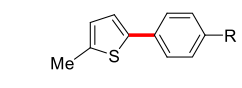
Subsequently, Grisi and co-workers reported a hydroxyl-functionalized $[(NHC)Pd(CH_3CN)Cl_2]$ complex **40** for the direct C($sp^2$)−H arylation of furan and thiophene derivatives with aryl bromides (Scheme 17).[105] The reaction afforded the C−H arylated product heterocycles in moderate to good yields and with very good functional group tolerance.

**Scheme 17. Pd−NHC-Catalyzed Direct C−H Arylation of Furans and Thiophenes by Grisi**

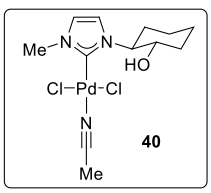

*Selected examples*



R = 4-OMe, 40%
R = 4-$NO_2$, 59%



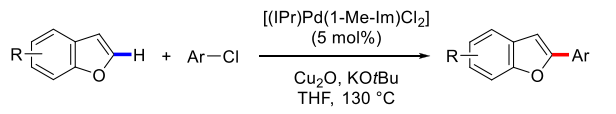
R = 4-$NMe_2$, 15%
R = 4-$NO_2$, 34%



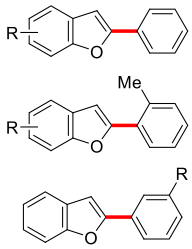

Substantial progress in the direct C−H arylation of heterocycles has been made by the Shao group using an imidazole-supported Pd−NHC complex, [(IPr)Pd(1-Me-im)-$Cl_2$] (Schemes 18and 19, see also Schemes 34 and 35 and 44 and 45). In 2015, they reported the direct C($sp^2$)−H arylation of benzofurans with aryl chlorides in the presence of $Cu_2O$ and KO*t*Bu in THF at 130 °C (Scheme 18).[106] A wide range of C2-arylated benzofurans were obtained in moderate to high yields. Subsequently, they used the same Pd(II)−NHC complex for the direct C2−H arylation of thiophenes and benzothiophenes, furnishing the arylated products in good to excellent yields (Scheme 19).[107] Thus, this work amply


https://dx.doi.org/10.1021/acs.chemrev.9b00634
*Chem. Rev.* 2020, 120, 1981−2048

**Scheme 18. Pd–NHC-Catalyzed Direct C–H Arylation of Benzo[*b*]furans by Shao**




*Selected examples*



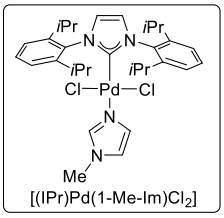
R = 5-Me, 83%
R = 7-Me, 73%
R = 5-F, 76%
R = 7-F, 62%



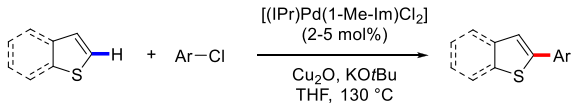
R = 5-Me, 75%
R = 7-Me, 72%



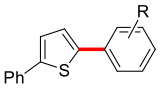
R = OMe, 78%
R = Me, 77%
R = F, 60%



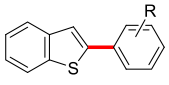

**Scheme 19. Pd–NHC-Catalyzed Direct C–H Arylation of Thiophenes by Shao**



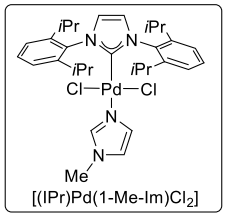

*Selected examples*



R = 4-Me, 93%
R = 4-OMe, 89%
R = 4-F, 62%



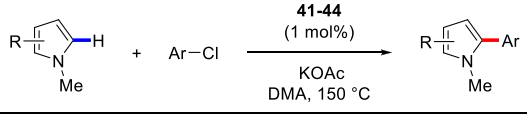
R = 4-Me, 98%
R = 2-Me, 90%
R = 4-F, 56%



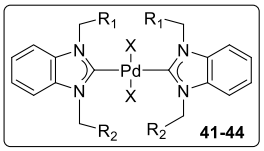

demonstrated that the class of NHC–Pd(II)-Im complexes can serve as efficient catalysts in the direct C($sp^2$)–H arylation with less reactive aryl chlorides.

The first comprehensive study on the direct C($sp^2$)–H arylation of pyrroles catalyzed by Pd–NHC complexes was reported by the Doucet group in 2013 (Scheme 20).[108] They

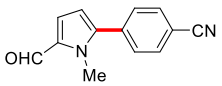
**Scheme 20. Pd–NHC-Catalyzed Direct C–H Arylation of Pyrroles by Doucet**



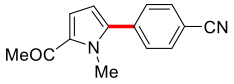

*Selected examples*



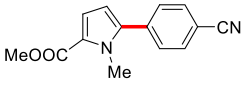
**41**: $R_1$ = $CH_2OMe$
$R_2$ = (3,5-$tBu_2$)-$C_6H_3$, X = Br
**42**: $R_1$ = (3,4,5-$OMe_3$)-$C_6H_2$
$R_2$ = (3,5-$tBu_2$)-$C_6H_3$, X = Br
**43**: $R_1$ = $R_2$ = (3,5-$tBu_2$)-$C_6H_3$, X = Br
**44**: $R_1$ = (2,3,4,5,6-$Me_5$)-$C_6$
$R_2$ = (3,5-$tBu_2$)-$C_6H_3$, X = Cl



**41**: 57%, **42**: 87%, **43**: 83%, **44**: 61%



**41**: 54%, **44**: 61%

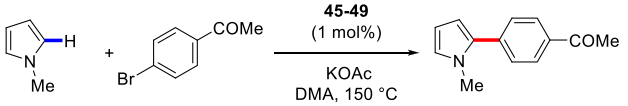


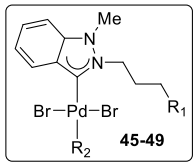
**41**: 32%, **42**: 78%, **44**: 27%

found that bis-NHC complexes **41–44** derived from the benzimidazolylidene scaffold were highly effective in the direct regioselective C2 or C5 arylation of a range of pyrrole derivatives using electron-deficient aryl chlorides. The reaction was carried out in the presence of KOAc in DMA at 150 °C. Bulky N-substituents on the NHC ligand were found to enhance the catalytic activity.

In 2014, the Huynh group reported the synthesis and application of indazolin-3-ylidene [(NHC)Pd(amine)$Br_2$] complexes **45–49** with pendant tertiary amine side chains in the direct C($sp^2$)–H arylation of *N*-methylpyrrole (Scheme 21).[109] Pd–NHC complex **46** (R = $NEt_2$) was shown to be the

**Scheme 21. Pd–NHC-Catalyzed Direct C–H Arylation of Pyrrole Using Indazolin-3-ylidene Complexes by Huynh**

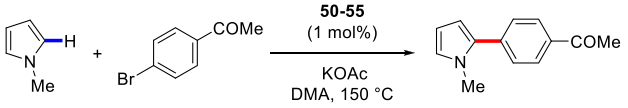


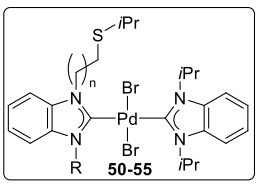




**45**: $R_1$ = Br; $R_2$ = $NCCH_3$, 85%
**46**: $R_1$ = $NEt_2$; $R_2$ = $NHEt_2$, 97%
**47**: $R_1$ = N*n*$Pr_2$; $R_2$ = NH*n*$Pr_2$, 88%
**48**: $R_1$ = N*n*$Bu_2$; $R_2$ = NH*n*$Bu_2$, 87%
**49**: $R_1$ = N*i*$Bu_2$; $R_2$ = NH*i*$Bu_2$, 84%

most effective, and the reactivity order was **46** > **45** (R = Br) ≈ **47** (R = $NPr_2$) ≈ **48** (R = $NBu_2$) ≈ **49** (R = N*i*$Bu_2$). Simultaneously, the same group reported bisbenzimidazolylidene [$(NHC)_2PdBr_2$] complexes **50–55** with an alkyl thioether side chain in the direct C($sp^2$)–H arylation of *N*-methylpyrrole (Scheme 22).[110] High catalytic activity was observed with both ethyl-thioisopropyl and propyl-thioisopropyl side chains (*n* = 1 or *n* = 2).

**Scheme 22. Pd–NHC-Catalyzed Direct C–H Arylation of Pyrrole Using Benzimidazolin-2-ylidene Complexes by Huynh**




**50**: n = 1, R = benzyl, 74%
**51**: n = 1, R = *i*Bu, 77%
**52**: n = 1, R = $CHPh_2$, 83%
**53**: n = 2, R = benzyl, 71%
**54**: n = 2, R = *i*Bu, 66%
**55**: n = 2, R = $CHPh_2$, 86%

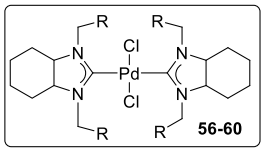
In 2017, the Yigit group investigated perhydrobenzimidazolylidene bis-Pd–NHC complexes **56–60** in the direct C($sp^2$)–H arylation of pyrroles (Scheme 23).[111] All complexes showed high catalytic activity using electronically activated aryl chlorides as the coupling partners. Reactivity comparison studies demonstrated that the reactivity order of these bis-Pd–NHC complexes depends on the substitution of both coupling partners.

Subsequently, Özdemir and co-workers reported the synthesis of benzimidazolylidene Pd–PEPPSI-type complexes **61–65** and their application in the direct C($sp^2$)–H arylation of pyrrole derivatives (Scheme 24).[112] These complexes

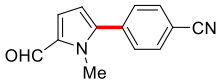

https://dx.doi.org/10.1021/acs.chemrev.9b00634
*Chem. Rev.* 2020, 120, 1981–2048

**Scheme 23. Pd–NHC-Catalyzed Direct C–H Arylation of Pyrroles by Yigit**


*Selected examples*

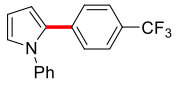



**56**: R = 4-Et-$C_6H_4$
**57**: R = 2,4-$Me_2$-$C_6H_3$
**58**: R = 3,4-$OMe_2$-$C_6H_3$
**59**: R = 2,4,5-$OMe_3$-$C_6H_2$
**60**: R = 2,3,4-$OMe_3$-$C_6H_2$



**56**: 77%, **57**: 50%, **58**: 47%, **59**: 60%, **60**: 62%

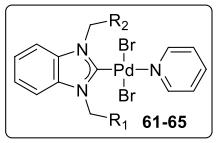
**56**: 94%, **57**: 91%, **58**: 90%, **59**: 89%, **60**: 72%



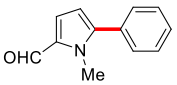
**56**: 18%, **57**: 52%, **58**: 44%, **59**: 35%, **60**: 28%

**Scheme 24. Pd–NHC-Catalyzed Direct C–H Arylation of Pyrroles by Özdemir**

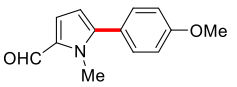

*Selected examples*



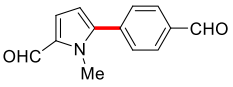

**61**: $R_1$ = $CH_2OMe$; $R_2$ = 3,5-*t*$Bu_2$-$C_6H_3$
**62**: $R_1$ = $CH(OMe)_2$; $R_2$ = 3,5-*t*$Bu_2$-$C_6H_3$
**63**: $R_1$ = 3-Me-$C_6H_4$; $R_2$ = 3,5-*t*$Bu_2$-$C_6H_3$
**64**: $R_1$ = 3-OMe-$C_6H_4$; $R_2$ = 3,5-*t*$Bu_2$-$C_6H_3$
**65**: $R_1$ = 2,4,6-$Me_3$-$C_6H_2$; $R_2$ = 3,5-*t*$Bu_2$-$C_6H_3$



X = Br
**61**: 62%, **62**: 54%, **63**: 43%, **64**: 75%, **65**: 70%
X = Cl
**61**: 70%, **62**: 65%, **63**: 51%, **64**: 67%, **65**: 63%



X = Br
**61**: 40%, **62**: 43%, **63**: 29%, **64**: 64%, **65**: 50%
X = Cl
**61**: 51%, **62**: 48%, **63**: 32%, **64**: 53%, **65**: 48%

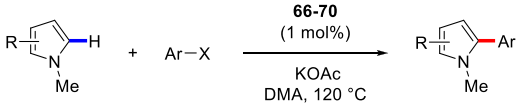


X = Br
**61**: 47%, **62**: 59%, **63**: 47%, **64**: 67%, **65**: 56%
X = Cl
**61**: 59%, **62**: 57%, **63**: 43%, **64**: 65%, **65**: 70%

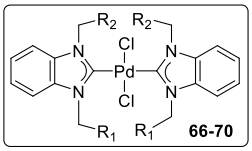
displayed high catalytic activity in that even unactivated aryl chlorides such as chlorobenzene or 4-chlorotoluene were compatible as the coupling partners in DMA at 120 °C. Pd–NHC precatalyst **64** bearing a chelating MeO group showed the highest catalytic activity. In 2018, the same group reported a series of benzimidazolylidene bis-Pd–NHC complexes **66**–**70** with chelating N-side chains as catalysts in the direct C($sp^2$)–H arylation of pyrroles (Scheme 25).[113] High catalytic performance was observed using unactivated aryl chlorides as the coupling partners. Precatalyst **67** featuring an unhindered *N*-benzyl group was found to be the most catalytically active.

*2.1.3.1.2. 5-Membered Heterocycles with Two or More Heteroatoms.* In general, the direct arylation of five-membered heterocycles with two or more heteroatoms is more facile than that of electron-rich heterocycles due to more acidic C($sp^2$)–H bonds.[82,83] In 2006, the Sames group reported the first example of a direct C($sp^2$)–H arylation of imidazoles using Pd–NHC complexes (Scheme 26).[96] The reaction was fully

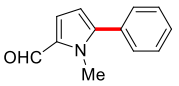
**Scheme 25. Pd–NHC-Catalyzed Direct C–H Arylation of Pyrroles by Özdemir**



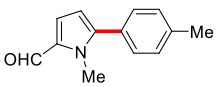

*Selected examples*



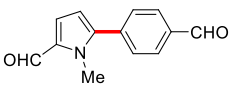

**66**: $R_1$ = $(CH_2)_2OMe$, $R_2$ = 4-Me-$C_6H_4$
**67**: $R_1$ = $(CH_2)_2OMe$, $R_2$ = 2,4,6-$Me_3$-$C_6H_2$
**68**: $R_1$ = $(CH_2)_2OMe$, $R_2$ = 2,3,5,6-$Me_4$-$C_6H$
**69**: $R_1$ = $(CH_2)_2OMe$, $R_2$ = 2,3,4,5,6-$Me_5$-C
**70**: $R_1$ = $(CH_2)_2OMe$, $R_2$ = 4-Cl-$C_6H_4$



X = Br
**66**: 59%, **67**: 77%, **68**: 41%, **69**: 79%, **70**: 58%
X = Cl
**66**: 53%, **67**: 75%, **68**: 53%, **69**: 70%, **70**: 61%

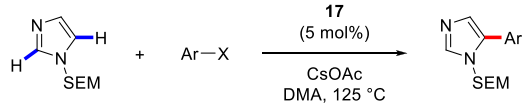


X = Br
**66**: 67%, **67**: 82%, **68**: 53%, **69**: 63%, **70**: 79%
X = Cl
**66**: 52%, **67**: 72%, **68**: 68%, **69**: 47%, **70**: 59%

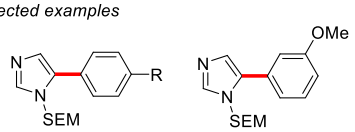


X = Br
**66**: 73%, **67**: 81%, **68**: 85%, **69**: 74%, **70**: 63%
X = Cl
**66**: 53%, **67**: 86%, **68**: 72%, **69**: 65%, **70**: 57%

**Scheme 26. Pd–NHC-Catalyzed Direct C5–H Arylation of Imidazoles by Sames**

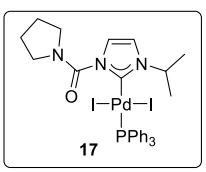



*Selected examples*



X = Br, R = $CF_3$, 64%
X = Cl, R = $CF_3$, 57%
X = Br, R = CN, 59%

X = Br, 68%
X = Cl, 56%

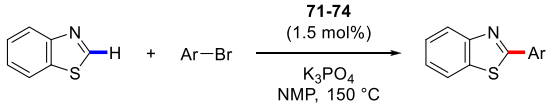



regioselective for the C5 arylation in the presence of catalytic [Pd(NHC)($PPh_3$)$I_2$] complex **17**. The authors demonstrated that the use of $Ag_2CO_3$ as a base (2.0 equiv) significantly improved the yields as compared to CsOAc used for the direct C($sp^2$)–H arylation of electron-rich heterocycles (see Scheme 8). In 2010, Sames and co-workers utilized the same conditions for the direct C($sp^2$)–H monoarylation of *N*-SEM-imidazole (SEM = trimethylsilylethoxymethyl) at the C5 position in their studies en route to complex 2,4,5-triarylimidazoles (not shown).[114]

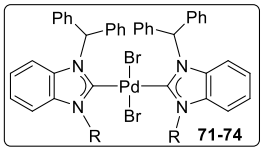
In 2009, the Özdemir group reported the synthesis and catalytic activity of benzimidazolylidene bis-Pd–NHC complexes **71**–**74** in the direct C($sp^2$)–H arylation of benzothiazole with aryl bromides (Scheme 27).[115] The optimized reaction conditions utilized $K_3PO_4$ in NMP at 150 °C. The highest activity was observed with complex **74** featuring chelating MeO groups on the *N*-benzyl ring. Around the same time, Arslan and co-workers reported a related benzimidazolylidene Pd–bis-NHC complex **75** as an efficient catalyst for the direct C($sp^2$)–H arylation of benzoxazoles and


https://dx.doi.org/10.1021/acs.chemrev.9b00634
*Chem. Rev.* 2020, 120, 1981–2048

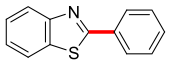
**Scheme 27. Pd−NHC-Catalyzed Direct C−H Arylation of Benzothiazole by Özdemir**



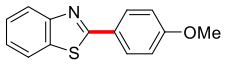

*Selected examples*



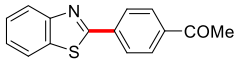

**71**: R = $CH_2CH_2OMe$
**72**: R = $CH_2CH_2OEt$
**73**: R = 2,4,6-$Me_3$-Bn
**74**: R = 3,4,5-$OMe_3$-Bn



**71**: 65%, **72**: 61%, **73**: 67%, **74**: 81%



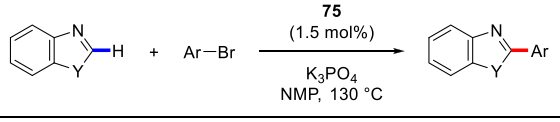
**71**: 68%, **72**: 73%, **73**: 56%, **74**: 80%



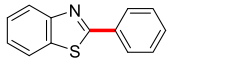
**71**: 49%, **72**: 47%, **73**: 51%, **74**: 58%

benzothiazoles with aryl bromides in the presence of $K_3PO_4$ in NMP at 130 °C (Scheme 28).[116]

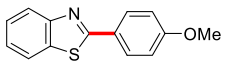
**Scheme 28. Pd−NHC-Catalyzed Direct C−H Arylation of Benzothiazole and Benzoxazole by Arslan**



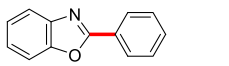

*Selected examples*



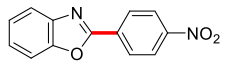
72%



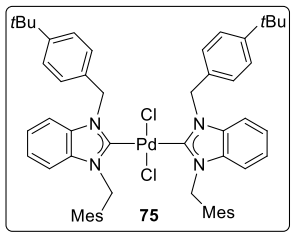
54%



65%



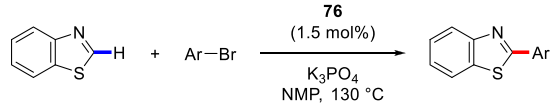
64%



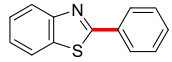

Subsequently, the Özdemir group reported the direct C($sp^2$)−H arylation of benzothiazoles with aryl bromides using a bridged benzimidazolylidene Pd−bis-NHC complex **76** bearing a linked chain (Scheme 29).[117] The arylation reactions could be accomplished in good to high yields using several functionalized aryl bromides in the presence of $K_3PO_4$ in NMP at 130 °C. The same group developed further analogues of the bridged complex **76** featuring different N-substitution of NHC ligands (Scheme 30).[118] In particular, an increase in the catalytic activity in the direct C($sp^2$)−H arylation of benzothiazoles was realized by using the more sterically hindered *N*-*i*Pr group in the NHC framework.

More recently, Özdemir and co-workers reported another series of benzimidazolylidene Pd−bis-NHC complexes **81**−**84**, which proved to be effective catalysts in the direct C($sp^2$)−H arylation of benzoxazoles and benzothiazoles with aryl bromides (Scheme 31).[119] A diverse range of aryl bromides were successfully applied in this reaction in the presence of KOAc in DMA at 150 °C. The Pd−NHC complex bearing an *N*-alkyl chain proved to be the least reactive in this catalyst

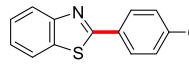
**Scheme 29. Pd−NHC-Catalyzed Direct C−H Arylation of Benzothiazole by Özdemir**



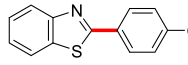

*Selected examples*



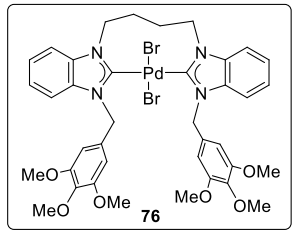
58%



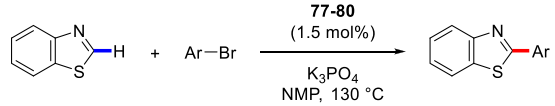
74%



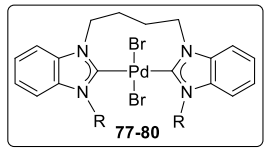
53%



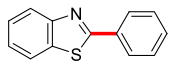

**Scheme 30. Pd−NHC-Catalyzed Direct C−H Arylation of Benzothiazole by Özdemir**



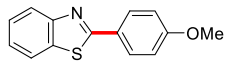

*Selected examples*



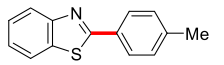

**77**: R = *i*Pr
**78**: R = $CH_2CH_2OEt$
**79**: R = 2,3,5,6-$Me_4$-Bn
**80**: R = 2,3,4,5,6-$Me_5$-Bn



**77**: 89%, **78**: 75%, **79**: 61%, **80**: 65%

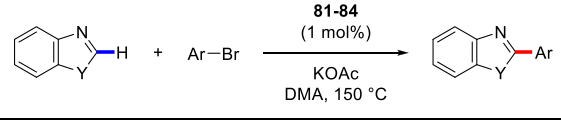


**77**: 78%, **78**: 65%, **79**: 62%, **80**: 58%

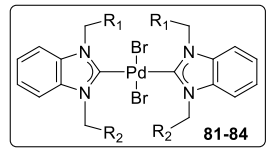


**77**: 85%, **78**: 77%, **79**: 72%, **80**: 69%

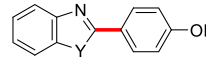
**Scheme 31. Pd−NHC-Catalyzed Direct C−H Arylation of Benzothiazole and Benzoxazole by Özdemir**



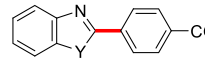

*Selected examples*




**81**: $R_1$ = $CH_2O$-2-OEt-$C_6H_4$
$R_2$ = 3,4-$Cl_2$-$C_6H_3$
**82**: $R_1$ = $CH_2O$-2-OEt-$C_6H_4$
$R_2$ = 3,4,5-$OMe_3$-$C_6H_2$
**83**: $R_1$ = $CH_2O$-2-OEt-$C_6H_4$
$R_2$ = $CH_2CH_2CH_3$
**84**: $R_1$ = $CH_2O$-2-OEt-$C_6H_4$
$R_2$ = $CH_2OMe$



Y = O, **81**: 59%, **82**: 54%, **83**: 37%, **84**: 55%
Y = S, **81**: 62%, **82**: 68%, **83**: 46%, **84**: 62%



Y = O, **81**: 70%, **82**: 73%, **83**: 64%, **84**: 75%
Y = S, **81**: 76%, **82**: 68%, **83**: 61%, **84**: 72%

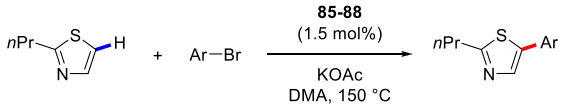
series. In 2018, Özdemir and co-workers reported similar benzimidazolylidene Pd−bis-NHC complexes **85**−**88** for the direct C($sp^2$)−H arylation of thiazoles (Scheme 32).[120] The



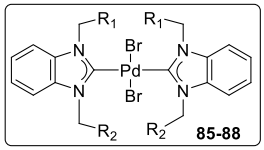
https://dx.doi.org/10.1021/acs.chemrev.9b00634
*Chem. Rev.* 2020, 120, 1981−2048

reaction was regioselective for the C5−H arylation. Both electron-deficient and electron-rich aryl bromides were shown to be excellent coupling partners.

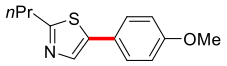
**Scheme 32. Pd−NHC-Catalyzed Direct C−H Arylation of Thiazole by Özdemir**



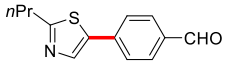

*Selected examples*




**85**: $R_1$ = 3-OMe-$C_6H_4$; $R_2$ = 4-Cl-$C_6H_4$
**86**: $R_1$ = 3-OMe-$C_6H_4$; $R_2$ = $C_3H_7$
**87**: $R_1$ = 3-OMe-$C_6H_4$; $R_2$ = $C_6H_5$
**88**: $R_1$ = 3-OMe-$C_6H_4$; $R_2$ = 4-OMe-$C_6H_4$



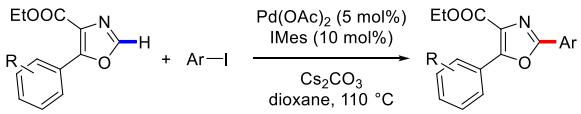
**85**: 68%, **86**: 54%, **87**: 58%, **88**: 63%



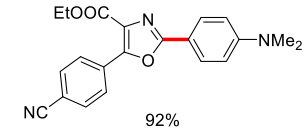
**85**: 70%, **86**: 70%, **87**: 74%, **88**: 76%

In 2011, Hoarau and co-workers disclosed the direct C($sp^2$)−H arylation of oxazoles using $Pd(OAc)_2$/IMes as an effective catalyst system (Scheme 33).[121] The reaction was

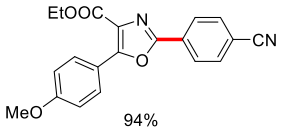
**Scheme 33. Pd−NHC-Catalyzed Direct C−H Arylation of Oxazoles by Hoarau**



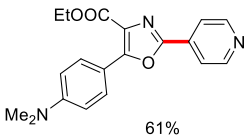

*Selected examples*



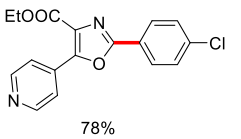
92%



94%



61%

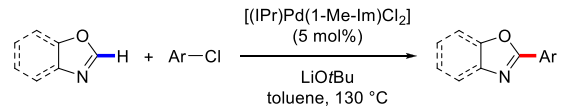


78%

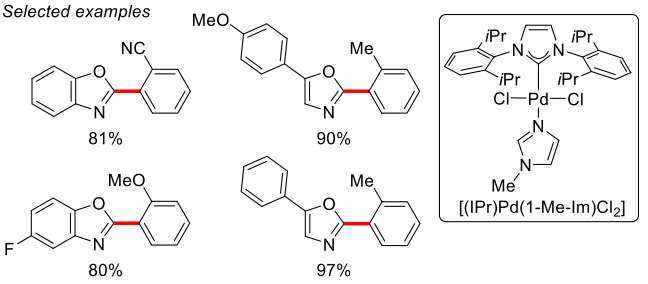
performed in the presence of $Cs_2CO_3$ in dioxane at 110 °C, giving facile access to 2,5-diaryloxazole-4-carboxylates in good to excellent yields and with high functional group tolerance. The products 2,5-diphenyloxazoles (DPO) and 1,4-bis(5-phenyloxazol-2-yl)benzenes (POPOP) constitute major components of commercial plastics and liquid scintillation mixtures. Thus, this efficient C−H arylation approach gave rapid access to novel sensors with unusual Stokes shifts.

In 2014, the Shao group reported the direct C($sp^2$)−H arylation of benzoxazoles and oxazoles with aryl chlorides using their well-defined, air- and moisture-stable [Pd(IPr)(1-Me-im)$Cl_2$] complex (Scheme 34).[122] A variety of electron-deficient and electron-rich aryl chlorides were successfully utilized as the arylating reagents in the presence of excess LiO*t*Bu (5 equiv) in toluene at 130 °C. In an interesting extension of this work, Shao and co-workers reported the direct C($sp^2$)−H benzylation of benzoxazoles and oxazoles

**Scheme 34. Pd−NHC-Catalyzed Direct C−H Arylation of Oxazoles by Shao**

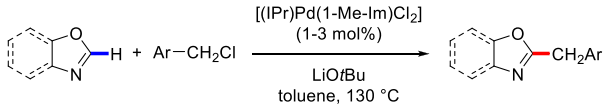



*Selected examples*

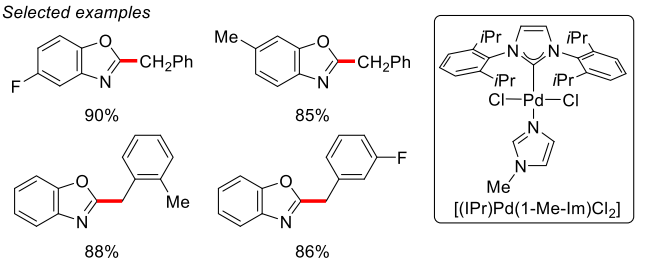



with benzyl chlorides (Scheme 35).[123] A similar catalytic protocol using lower catalyst loading of Pd− NHC was

**Scheme 35. Pd−NHC-Catalyzed Direct C−H Benzylation of Oxazoles by Shao**




*Selected examples*




employed, and a broad range of substrates gave the desired C2-benzylated products in excellent yields, highlighting the utility of [Pd(NHC)(im)$Cl_2$] complexes in the direct C($sp^2$)−H functionalization reactions.

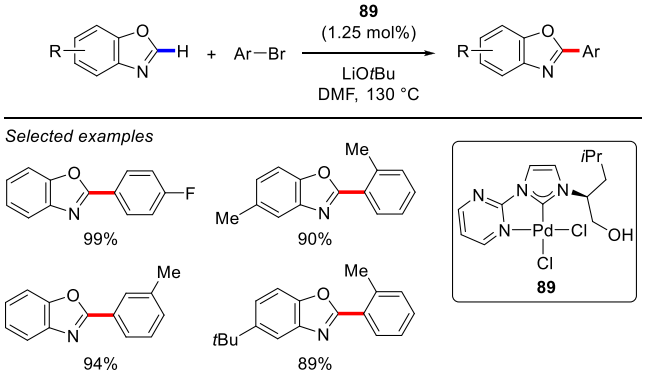
In 2015, the Yang group described a chelating [Pd(NHC)-$Cl_2$] complex **89** containing *N*-2-pyrimidine and *N*-2-hydroxyalkyl side chains as an efficient catalyst for the direct C($sp^2$)−H arylation of benzoxazoles (Scheme 36).[124] The optimized reaction conditions utilized LiO*t*Bu as a base in DMF at 130 °C. This protocol was applied to a broad range of substrates and achieved TON of 40.

In 2018, the Gandhi group developed *N*-4-dibenzofuryl-functionalized Pd−PEPPSI-type catalyst **90** for the direct C($sp^2$)−H arylation of benzoxazoles (Scheme 37).[125] The C−H arylation was achieved in DMF at 120 °C. These *N*-dibenzofuryl Pd−NHC precatalysts also showed high activity in the Suzuki−Miyaura cross-coupling of aryl bromides.

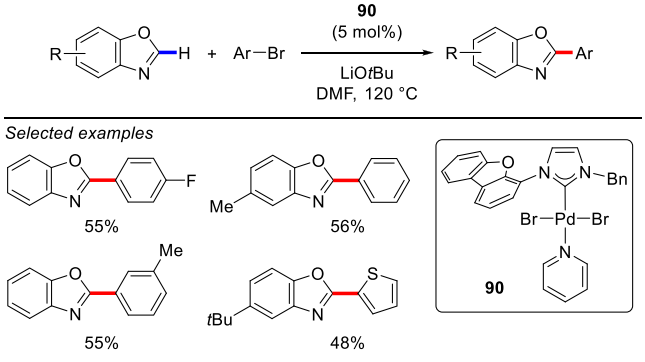
Recently, Li and co-workers reported an unsymmetrical pincer-type [Pd(NHC)($PPh_2Ar$)$Cl_2$] carbene−nitrogen−phosphine (C−N−P) complex **91** for the direct C($sp^2$)−H arylation of benzoxazoles (Scheme 38).[126] Notably, the direct C−H arylation with aryl bromides was accomplished with only 0.25−0.5 mol % catalyst loading at 90 °C. In addition, the authors showed that the $PdCl_2(\kappa^2$-CP) complex **91** is more reactive than the corresponding cationic [PdCl($\kappa^2$-CNP)]$PF_6$ complex in this direct C($sp^2$)−H arylation.


https://dx.doi.org/10.1021/acs.chemrev.9b00634
*Chem. Rev.* 2020, 120, 1981−2048

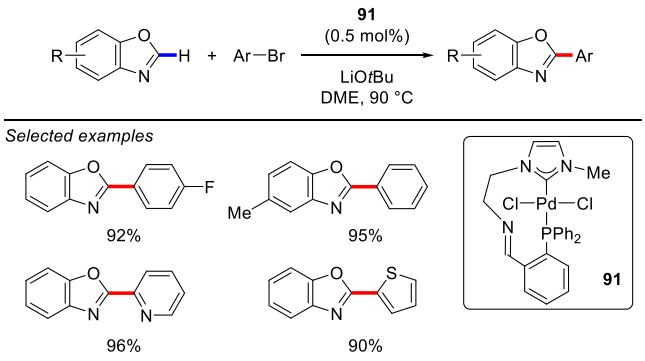
**Scheme 36. Pd−NHC-Catalyzed Direct C−H Arylation of Benzoxazoles by Yang**




**Scheme 37. Pd−NHC-Catalyzed Direct C−H Arylation of Benzoxazoles by Gandhi**

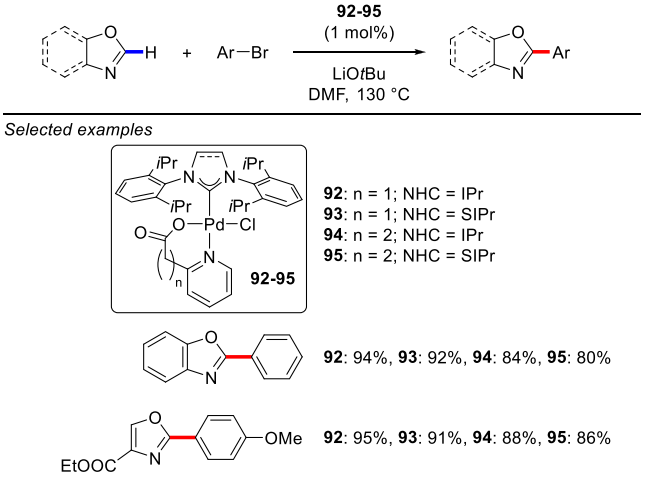



**Scheme 38. Pd−NHC-Catalyzed Direct C−H Arylation of Benzoxazoles by Li**

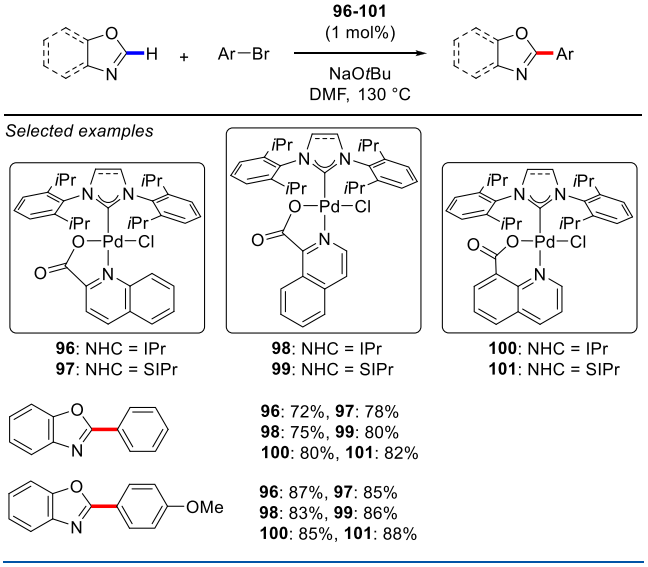



In 2018, the Yang group reported Pd−PEPPSI-type complexes featuring (2-pyridyl)alkyl carboxylate ligands **92**−**95** as catalysts for the direct C($sp^2$)−H arylation of benzoxazoles and oxazoles with aryl bromides (Scheme 39).[127] All complexes showed high activity in this transformation. Furthermore, the following order of reactivity was found: **92** ($n$ = 1, IPr) > **93** ($n$ = 1, SIPr) > **94** ($n$ = 2, IPr) > **95** ($n$ = 2, SIPr). At the same time, Yang and co-workers synthesized a series of Pd−PEPPSI complexes with (2-quinolinyl)alkyl carboxylate ligands **96**−**101** and evaluated their activity in the direct C($sp^2$)−H arylation of benzoxazoles (Scheme 40).[128] These (2-quinolinyl)alkyl carboxylate Pd−NHC complexes proved to be similarly effective in the C−H arylation to (2-pyridyl)alkyl carboxylate precatalysts **92**−**95** (Scheme 39).[127]

**Scheme 39. Pd−NHC-Catalyzed Direct C−H Arylation of Benzoxazoles by Yang**




**Scheme 40. Pd−NHC-Catalyzed Direct C−H Arylation of Benzoxazoles by Yang**

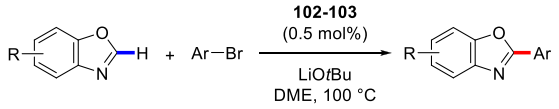



Very recently, Yang reported a series of cationic Pd−NHC complexes featuring allyl and N-heterocyclic throw-away ligands **102**−**103** (Scheme 41).[129] These catalysts showed high activity in the direct C($sp^2$)−H arylation of azoles and allowed for the C−H arylation of beznoxazoles to occur at 100 °C in DME.

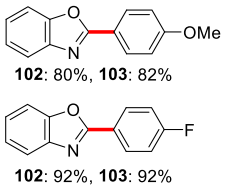
In 2011, the Lee group reported mixed [Pd(NHC)($PCy_3$)-$OAc_2$] complex **104** bearing electron-rich phosphine and carboxylate ligands for the regioselective efficient selective C5−H arylation of imidazoles at the C5 position with aryl halides (Scheme 42; cf. Scheme 15).[130] Notably, this catalytic system allowed the use of electron-deficient and electron-rich aryl chlorides as coupling partners using KOAc as a base in DMA at 140 °C. In 2016, the same group reported well-defined Pd(0)−NHC complexes **105**−**108** with N-tethered phosphine-functionalized NHC ligands, wherein Pd(0) is stabilized by maleic anhydride (Scheme 43).[131] The authors showed that complex **105**, featuring six-membered chelate, is more effective in this direct C($sp^2$)−H arylation of imidazoles than the N-sterically hindered **106** and the analogous complex

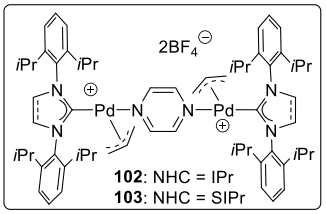

https://dx.doi.org/10.1021/acs.chemrev.9b00634
*Chem. Rev.* 2020, 120, 1981−2048

**Scheme 41. Pd–NHC-Catalyzed Direct C–H Arylation of Benzoxazoles by Yang**

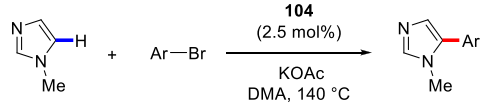



*Selected examples*

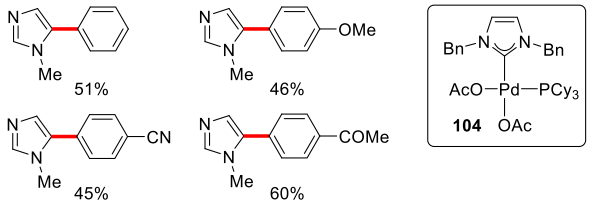


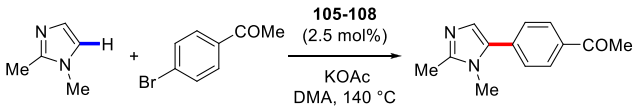

**Scheme 42. Pd–NHC-Catalyzed Direct C5–H Arylation of Imidazoles by Lee**



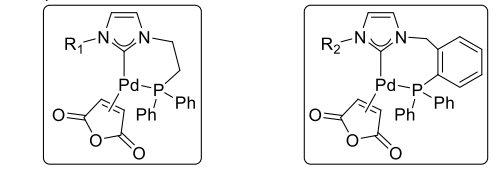

*Selected examples*




**Scheme 43. Pd–NHC-Catalyzed Direct C–H Arylation of Imidazoles by Lee**



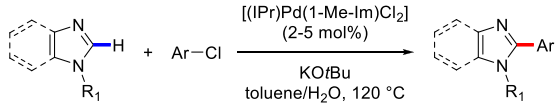

*Selected examples*



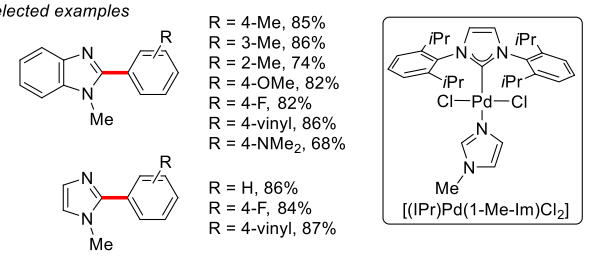

**107** featuring a conformationally restricted seven-membered chelate.

In 2014, the Shao group developed an efficient method for the C($sp^2$)–H arylation of benzimidazoles and imidazoles at the C2 position catalyzed by [Pd(IPr)(1-Me-im)$Cl_2$] (Scheme 44).[132] A variety of activated and deactivated aryl and heteroaryl chlorides were successfully coupled using KO*t*Bu as a base in toluene at 120 °C, providing access to the 2-arylbenzimidazoles and 2-arylimidazoles in good to excellent yields. Subsequently, the same Pd(II)–NHC complex was found to be successful as a catalyst in the direct C($sp^2$)–H bond arylation of imidazo[1,2-*a*]pyridines with aryl chlorides (Scheme 45).[133] These studies further demonstrate the utility of imidazole-supported Pd–NHCs in the direct C($sp^2$)–H arylation using challenging aryl chlorides.

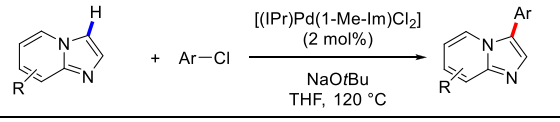
**Scheme 44. Pd–NHC-Catalyzed Direct C–H Arylation of Imidazoles by Shao**



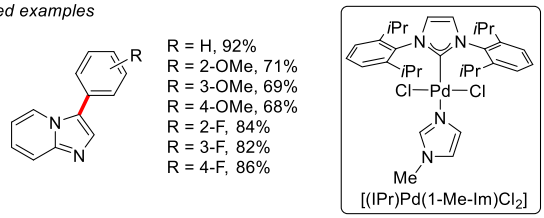

*Selected examples*




**Scheme 45. Pd–NHC-Catalyzed Direct C3–H Arylation of Imidazo[1,2-*a*]pyridines by Shao**

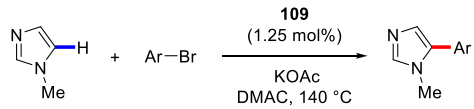



*Selected examples*

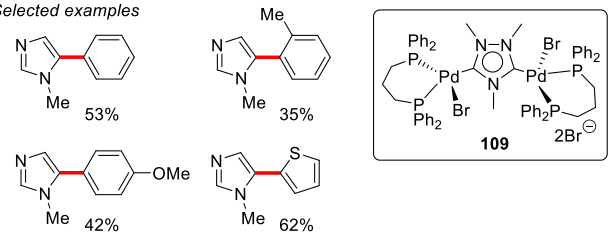



In 2014, Huynh and co-workers reported dipalladium triazolediylidene complexes such as **109** featuring phosphines as ancillary ligands (Scheme 46).[134] These Pd–triazolediyli-

**Scheme 46. Pd–NHC-Catalyzed Direct C5–H Arylation of Imidazoles by Huynh**




*Selected examples*

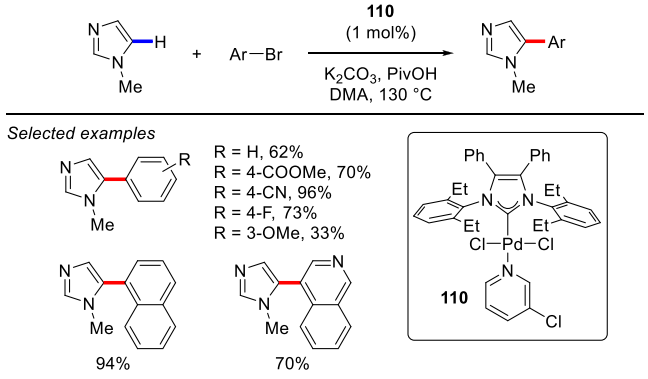



dene systems proved to be effective in the direct C5 arylation of 1-methylimidazole using aryl bromides, and the complex **109** showed the highest reactivity.

In 2016, the Liu group reported sterically hindered tetraarylimidazolylidene Pd(II)–NHC complexes as efficient precatalysts for the direct C($sp^2$)–H arylation of imidazoles at the C5 position (Scheme 47).[135] The direct arylation could be conducted under aerobic conditions in the presence of pivalic acid (30 mol %) and $K_2CO_3$ as a mild base in DMA at 130 °C. Following their initial report, Liu and co-workers identified bulky BIAN-type Pd–NHC complexes (BIAN = bis(imino)acenaphthene) for the direct C($sp^2$)–H arylation of

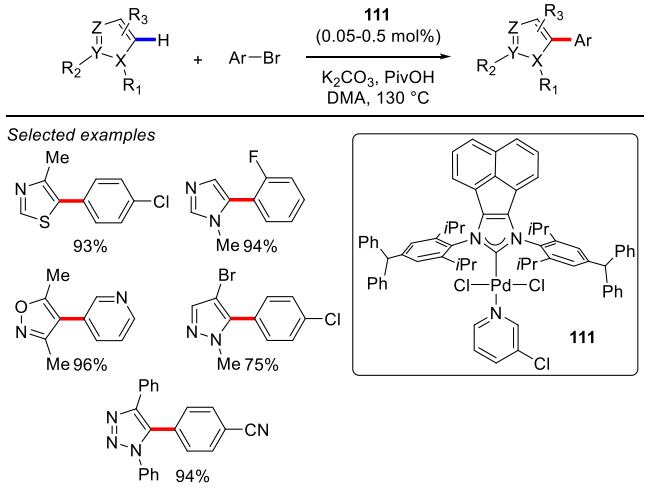

https://dx.doi.org/10.1021/acs.chemrev.9b00634
Chem. Rev. 2020, 120, 1981–2048

**Scheme 47. Pd−NHC-Catalyzed Direct C5−H Arylation of Imidazoles by Liu**




a broad range of azoles with aryl bromides (Scheme 48).[136] These impressive reactions proceed efficiently with only 0.05−

**Scheme 48. Pd−NHC-Catalyzed Direct C−H Arylation of Imidazoles, Thiazoles, Isoxazoles, Pyrazoles, and Triazoles by Liu**




0.5 mol % catalyst loading and are performed under aerobic conditions. A wide variety of heterocycles, including imidazoles, thiazoles, isoxazoles, and pyrazoles, provided the direct C−H activation products in good to excellent yields.

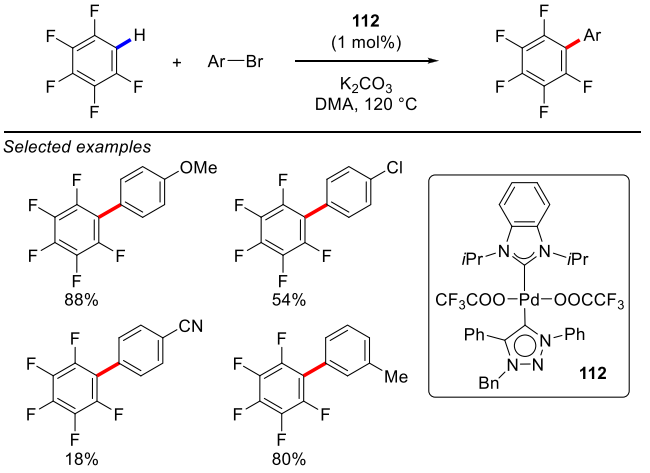
In addition, the Lee group reported decarboxylative C($sp^2$)−H arylation of electron-deficient azoles using the Pd(0)−NHC complex (not shown).[137,138] This approach offers an alternative strategy to the direct C($sp^2$)−H arylation of heterocycles using Pd−NHC catalysts.

*2.1.3.2. C($sp^2$)−H Activation in Arenes.* In contrast to the C($sp^2$)−H bond functionalization of heterocycles, the direct C($sp^2$)−H activation of acidic arenes by Pd−NHC complexes remains largely underdeveloped.

In 2012, the Huynh group reported the first example of the direct C($sp^2$)−H arylation of pentafluorobenzene catalyzed by a Pd−NHC complex (Scheme 49).[139] They found that a mixed benzimidazolylidene/triazolyldiylidene complex **112** showed high efficiency and good functional group tolerance in arylations using aryl bromides in the presence of $K_2CO_3$ in DMA at 120 °C.

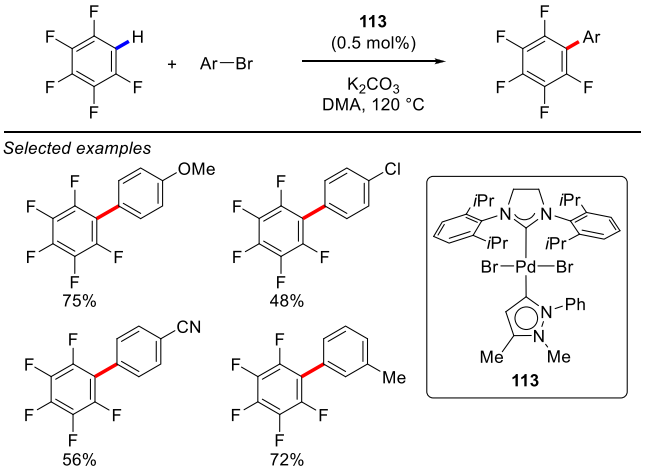
Subsequently, they reported pyrazolylidene Pd−NHC complexes for the direct C($sp^2$)−H arylation of pentafluor-

**Scheme 49. Pd−NHC-Catalyzed Direct C−H Arylation of Pentafluorobenzene by Huynh**




obenzene (Scheme 50).[140] The mixed pyrazolylidene/imidazolidinylidene complex **113**, [Pd(NHC)(SIPr)$Br_2$],

**Scheme 50. Pd−NHC-Catalyzed Direct C−H Arylation of Pentafluorobenzene by Huynh**




proved to be the best for this arylation allowing for good functional group tolerance. The high $\sigma$-donating aptitude of the pyrazolin-5-ylidene ligand, which is beneficial for the C−H arylation, was confirmed by the HEP method (HEP = Huynh's electronic parameter) using $^{13}C$ NMR spectroscopy.[41]

In addition, Huynh and co-workers reported a series of bridged Pd−NHC complexes **114**−**118** featuring two different NHC ligands (Scheme 51).[141] These complexes proved to be active in the direct C($sp^2$)−H arylation of pentafluorobenzene with 4-chlorobromobenzene. In general, it was found that Pd−NHC complexes containing more sterically hindered N-substituents showed higher catalytic activity.

**2.1.4. Hydroxyl-Directed C($sp^2$)−H Activation/Alkenylation.** The hydroxyl group has been successfully used as a directing group for the Pd−NHC-catalyzed C($sp^2$)−H functionalization (Schemes 52 and 53, cf. Schemes 1−4, Section 2.1.1).

In 2011, Liu and co-workers' group reported an oxidative phenol-directed C($sp^2$)−H activation/C−O cyclization catalyzed by the Pd($OAc)_2$/IPr system (Scheme 52).[142] After extensive optimization, it was found that the 4,5-diazafluoren-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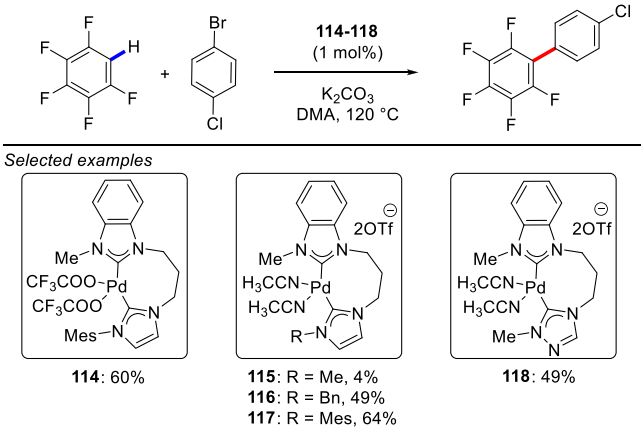
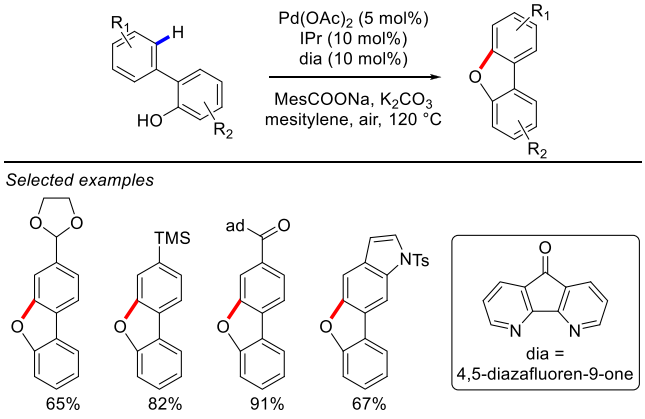
Chem. Rev. 2020, 120, 1981−2048

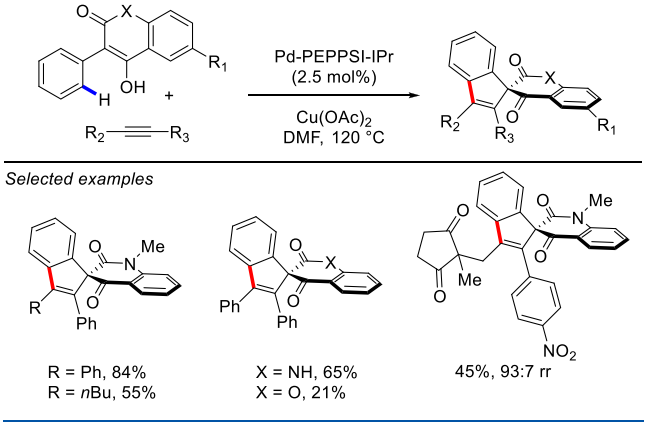
**Scheme 51. Pd–NHC-Catalyzed Direct C–H Arylation of Pentafluorobenzene by Huynh**




**Scheme 52. Pd–NHC-Catalyzed Synthesis of Benzofurans by Hydroxyl-Directed C(sp²)–H Activation by Liu**




**Scheme 53. Pd–NHC-Catalyzed Hydroxyl-Directed C(sp²)–H Oxidative Annulation by Lam**

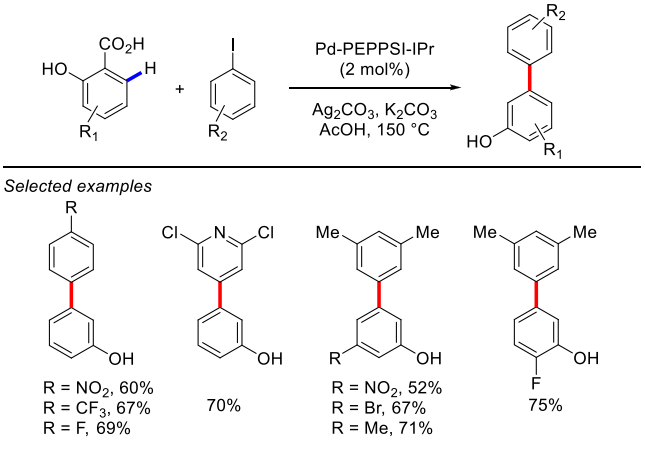



9-one additive (10 mol %) is critical in improving the reaction efficiency, presumably to facilitate regeneration of Pd(II). Based on labeling studies, the authors proposed that C–O reductive elimination is the rate-determining step in this transformation. This efficient method provides straightforward access to dibenzofurans from simple 2-arylphenols and highlights the capacity of Pd–NHC systems in oxidative C–H functionalization.

In 2013, Lam and co-workers reported a Pd–NHC-catalyzed oxidative annulation of 2-aryl-1,3-dicarbonyls with alkynes (Scheme 53).[143] Interestingly, the use of [Pd–PEPPSI–IPr] in the presence of $Cu(OAc)_2$ in DMF at 120 °C afforded the corresponding spiroindenes by the 2-aryl C(sp²)–H activation, while a catalyst system based on $[Ru(p\text{-cym})Cl_2]_2$ gave benzopyrans by the C(sp²)–H activation of the fused aromatic ring (not shown). This reaction demonstrates the capacity of Pd–NHC catalysts to promote C–H functionalization by weak coordination to enolate hydroxyl groups.

**2.1.5. Carboxyl-Directed C(sp²)–H Activation/Arylation.** The synthesis of meta-substituted biaryls with Pd–NHC systems has been achieved by Larrosa and co-workers using carboxylic acid as a transient directing group followed by decarboxylation (Scheme 54).[144] The optimized reaction

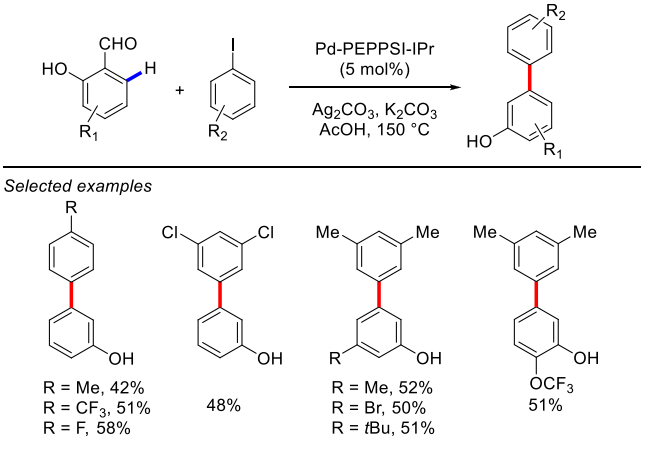
**Scheme 54. Pd–NHC-Catalyzed Carboxylate-Directed C(sp²)–H Arylation/Decarboxylation by Larrosa**




conditions use [Pd–PEPPSI–IPr] (2 mol %) in the presence of $Ag_2CO_3$ and $K_2CO_3$ in AcOH at 150 °C. Using this protocol, a variety of readily available salicylic acids could be converted into meta-substituted phenols.

In 2015, the same group reported that similar conditions could be used for the direct conversion of salicylaldehydes to meta-substituted phenols (Scheme 55).[145] The authors found that [Pd–PEPPSI–IPr] provided higher yields than $Pd(OAc)_2$ in this transformation. Mechanistically, the reaction involves the following steps: (1) aldehyde oxidation, (2) carboxylate-

**Scheme 55. Pd–NHC-Catalyzed Oxidation/Carboxylate-Directed C(sp²)–H Arylation/Decarboxylation by Larrosa**





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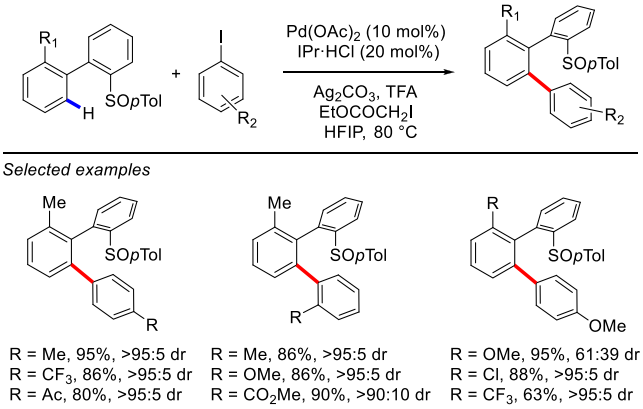
directed C(sp$^2$)−H arylation, (3) protodecarboxylation. Using the salicylaldehyde substrates resulted in decreased yields (cf. salicylic acids), which is likely due to one extra oxidation step in the sequence. This use of carboxylic acids and aldehydes as removable directing groups may facilitate future applications of Pd−NHC catalysis in regioselective C−H functionalization.

**2.1.6. Sulfoxide-Directed C(sp$^2$)−H Activation/Arylation.** Very recently, the first example of a sulfoxide-directed Pd−NHC-catalyzed C(sp$^2$)−H activation was reported by Colobert and co-workers (Scheme 56).[146] The use of chiral

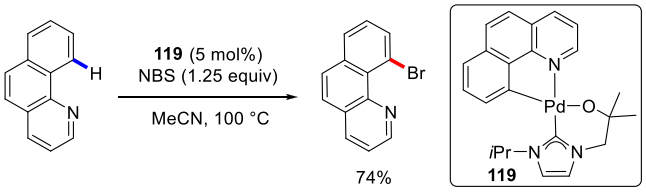
**Scheme 56. Pd−NHC-Catalyzed Sulfoxide-Directed C(sp$^2$)−H Arylation by Colobert**




sulfoxides allows for atropo-selective biaryl synthesis through weak palladium coordination in the presence of various functional groups. Interestingly, the authors found that the system based on Pd(OAc)$_2$ and IPr·HCl gave higher yields and diastereoselectivity than using IMes·HCl. Mechanistically, the authors proposed that the reaction proceeds via Pd(II)/(IV) catalysis.

**2.1.7. C(sp$^2$)−H Oxygenation/Halogenation by Pd(II)/(IV).** C−H bond functionalization via the Pd(II)/(IV) cycle has become an attractive strategy in catalysis.[77] In 2009, Arnold, Sanford, and co-workers reported that a cyclometalated Pd−NHC alkoxide complex **119** is an effective catalyst for the selective pyridine-directed C(sp$^2$)−H bromination (Scheme 57).[147] Stoichiometric studies demonstrated

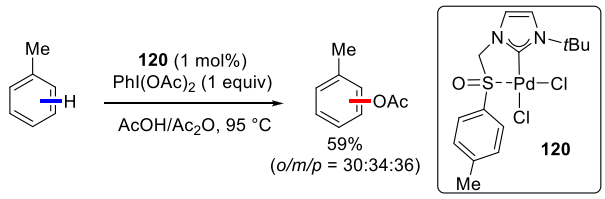
**Scheme 57. Pd−NHC-Catalyzed C(sp$^2$)−H Bromination by Arnold and Sanford**




that **119** undergoes oxidative addition of chloride ligands to give NHC-stabilized Pd(IV) alkoxide at −35 °C. Upon warming to 33 °C, this complex underwent C−Cl forming reductive elimination from Pd(IV). Thus, this elegant mechanistic study set the stage for using NHCs as supporting ligands for C−H bond functionalization via Pd(II)/(IV) catalysis.

Recently, several halogenation and oxygenation reactions using Pd−NHC systems via the Pd(II)/(IV) cycle were reported. An efficient Pd−NHC-catalyzed C(sp$^2$)−H acetoxylation of simple arenes via the Pd(II)/(IV) cycle using sulfoxide-tethered [Pd(NHC)Cl$_2$] complexes was achieved by the Cardenas group (Scheme 58).[148] These novel Pd−NHC

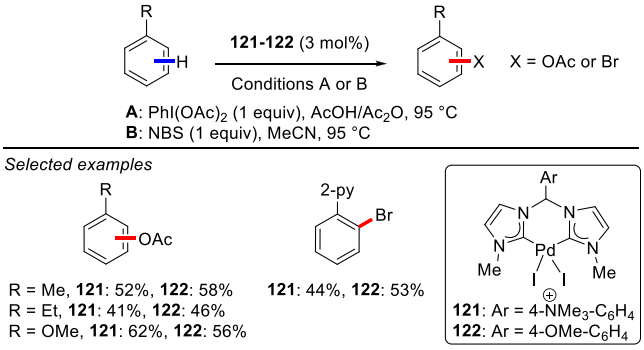
**Scheme 58. Pd−NHC-Catalyzed C(sp$^2$)−H Acetoxylation by Cardenas**




complexes feature the sulfinyl group as a hemilabile moiety. The best catalytic activity was achieved with complex **120** bearing an *N*-*t*Bu side chain. Interestingly, replacement of the *N*-*t*Bu side chain with less sterically hindered *N*-Me or by aromatic *N*-Mes or *N*-DIPP also afforded active complexes with comparable catalytic reactivity.

Subsequently, the Choudhury group demonstrated that both C(sp$^2$)−H acetoxylation and bromination can be accomplished using the same Pd−NHC complexes (Scheme 59).[149]

**Scheme 59. Pd−NHC-Catalyzed C(sp$^2$)−H Acetoxylation and Bromination by Choudhury**




They found that chelating bis-NHC−Pd complexes **121**−**122** featuring an *N*-benzylic tether display high catalytic activity in nondirected acetoxylation and pyridine-directed bromination using PhI(OAc)$_2$ and NBS as oxidants, respectively, via the Pd(II)/(IV) cycle. In 2017, the same group reported a simple PEPPSI-type [Pd(NHC)(py)I$_2$] complex **123** for efficient C(sp$^2$)−H acetoxylation, bromination, and chlorination of arenes (Scheme 60).[150] Kinetic studies suggested that a bimetallic Pd−Pd intermediate might be involved in the rate-determining C−H activation step. In 2017, in an alternative approach to C(sp$^2$)−H functionalization via Pd(II)/(IV) catalysis, Choudhury and co-workers disclosed a heterogeneous Pd−NHC complex **124** supported on the Ru(II)-terpyridine scaffold (Scheme 61).[151] This complex was successfully applied to the ortho-selective C(sp$^2$)−H bromination and chlorination of arenes using a range of directing groups. Furthermore, the complex could be recycled five times with minimal loss of catalytic activity.

The regioselective C(sp$^2$)−H acetoxylation directed by pyridines was also achieved by the Wendt group in 2016 using [Pd−PEPPSI−IPr] as the preferred catalyst (Scheme 62).[152] This complex showed better catalytic activity than Pd−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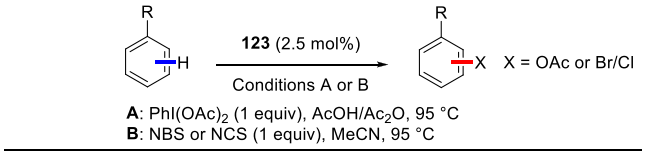
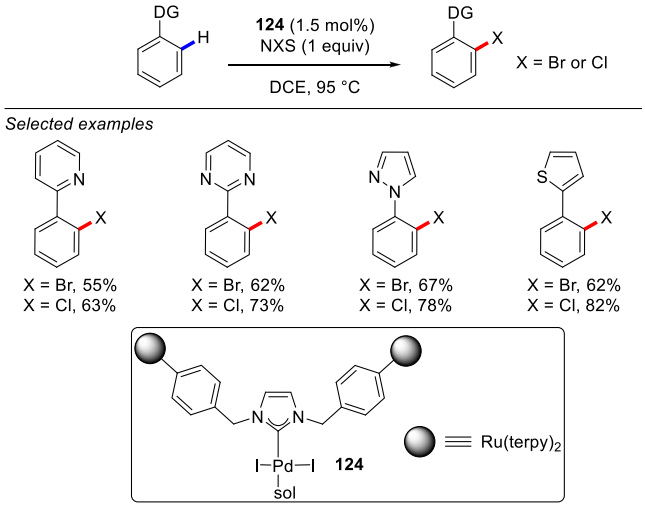
Chem. Rev. 2020, 120, 1981−2048

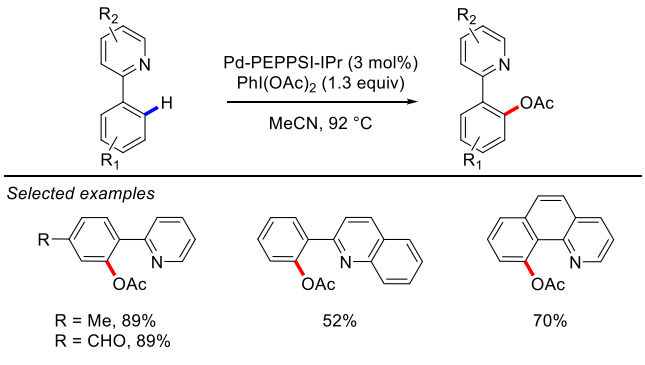
**Scheme 60. Pd–NHC-Catalyzed C($sp^2$)–H Acetoxylation and Halogenation by Choudhury**




**Scheme 61. Pd–NHC-Catalyzed C($sp^2$)–H Halogenation by Choudhury**




**Scheme 62. Pd–NHC-Catalyzed C($sp^2$)–H Acetoxylation by Wendt**

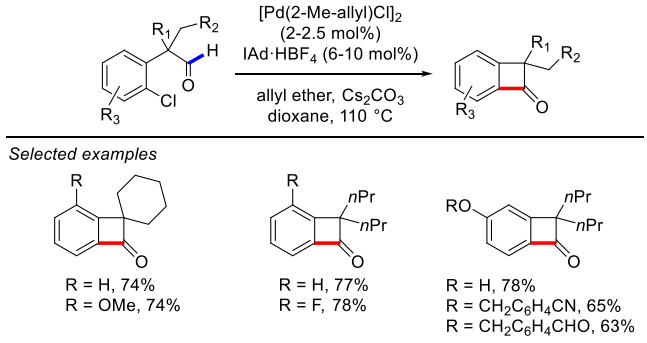



PEPPSI complexes featuring SIPr, IMes, IPent, and IAd ligands; however, it should be noted that all complexes were highly effective in the model acetoxylation of 2-phenylpyridine (77–93% yields). The scope of this reaction is broad and leads to a variety of monofunctionalized heterocycles in good to excellent yields. Several related systems for C($sp^2$)–H acetoxylation have been developed.[153−155]

It should also be mentioned that Wilton-Ely and co-workers reported a series of imidazolium-2-thiocarboxylate complexes [Pd(NHC·$CS_2$)($PR_3$)] as effective precatalysts for pyridine-directed C($sp^2$)–H chlorination via Pd(II)/(IV) catalysis.[156]

**2.1.8. C(acyl)–H Activation.** In 2012, Martin and co-workers reported an intramolecular C($sp^2$)–H acylation of aryl chlorides catalyzed by [Pd(2-Me-allyl)Cl]$_2$/IAd (Scheme 63).[157] The active Pd–NHC catalyst was prepared *in situ* by

**Scheme 63. Pd–NHC-Catalyzed Intramolecular C(Acyl)–H/C($sp^2$)–Cl Arylation by Martin**



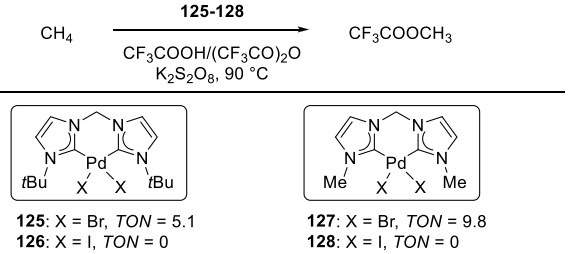

deprotonation of the IAd·$HBF_4$ salt. The reaction gave functionalized benzocyclobutenones in high yields and with excellent functional group tolerance. Interestingly, the authors found that the addition of allyl ether (50 mol %) was crucial for achieving high yields. They proposed that allyl ether might stabilize the monoligated IAd–Pd(0) species, leading to high cyclization/reduction selectivity. Several other NHCs were tested, including IPr, SIPr, SIPr, IMes, ICy, and IiPr, with IAd providing the best selectivity. This C(acyl)–H functionalization of aldehydes is related to C(acyl)–N and C(acyl)–O functionalizations of carboxylic acid derivatives by Pd–NHC complexes.[55,158−160]

## 2.2. C($sp^3$)–H Activation

Although the activation of C($sp^3$)–H bonds is significantly more challenging than that of C($sp^2$)–H bonds,[60,61] Pd–NHCs have been established as effective catalysts to perform this class of transformations. In general, the activation of C($sp^3$)–H bonds by Pd–NHCs can be categorized into the following classes: (1) oxidation of methane; (2) intramolecular C($sp^3$)–H/C–X functionalization by Pd(0)/(II) catalysis; (3) amide-directed C($sp^3$)–H functionalization using an acidic N–Ar auxiliary; (4) C($sp^3$)–H functionalization by Pd(II)/(IV) catalysis, and (5) allylic C($sp^3$)–H functionalization.

**2.2.1. Methane Oxidation.** Selective methane oxidation by Pd–NHC complexes has been pioneered by Strassner and co-workers. In 2002, they reported the first example of Pd–NHC complexes for the conversion of $CH_4$ into MeOH via a C($sp^3$)–H activation pathway isolated as trifluoroacetic acid methyl ester (Scheme 64).[161] They found that chelating Pd–

**Scheme 64. Pd–NHC-Catalyzed C–H Oxidation of Methane by Strassner**





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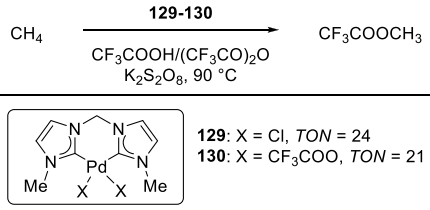
NHC complexes **125**−**128** promoted the C($sp^3$)−H activation in the presence of $K_2S_2O_8$ in $CF_3CO_2H/(CF_3CO)_2O$. In this C−H activation, the counterion had a significant impact on the activity, and the C−H activation products were not detected using iodide counterions. This interesting observation was explained by the lower basicity of iodide ligands, which could prevent opening of a free coordination site by halide protonation.

To obtain further insights into this counterion effect, the Strassner group conducted a comparative study of different counterions in the C($sp^3$)−H activation (chloride, trifluoroacetate) (Scheme 65).[162] Interestingly, all ligands except

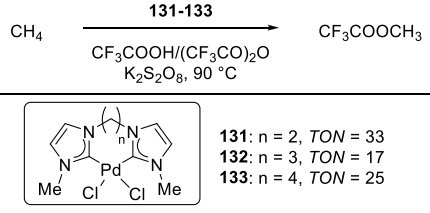
**Scheme 65. Pd−NHC-Catalyzed C−H Oxidation of Methane by Strassner**




iodide (X = Cl, $CF_3CO_2$, Br) displayed comparable activity in the C−H activation. In this case, the X-ray structures showed similarity of the ground-state geometries of these Pd−NHC complexes, while DFT computations suggested the highest energy barrier for replacing the iodide ligand with trifluoroacetic acid.

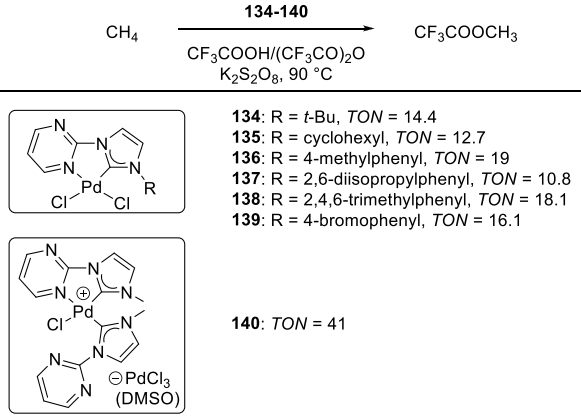
In addition, Strassner and co-workers investigated the effect of different bridge lengths in NHC ligands on methane oxidation (Scheme 66).[163] They found that the ethylene-

**Scheme 66. Pd−NHC-Catalyzed C−H Oxidation of Methane by Strassner**

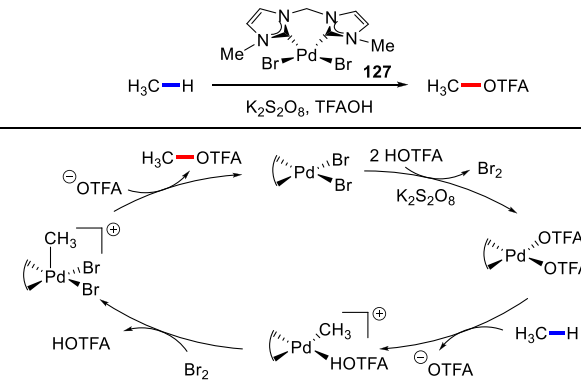



bridged Pd−NHC complex **132** was the most efficient catalyst in the C($sp^3$)−H activation of methane. The methylene-bridged complex **129** ($n$ = 1) and butylene-bridged complex **133** ($n$ = 4) showed similar reactivity, while the propylene-bridged complex **132** ($n$ = 2) was less reactive. Furthermore, the Strassner group investigated the reactivity of chelating 2-pyrimidine-functionalized Pd−NHC complexes (Scheme 67).[164] In this study, the cationic complex **140** featuring two NHC ligands coordinated to the metal center showed the highest reactivity in the C($sp^3$)−H activation of methane. On the basis of experimental and computational studies the authors proposed a mechanism involving the Pd(II)/(IV) cycle with a palladium tetrahalogenido complex as the resting state and C($sp^3$)−H activation as the rate-determining step in the catalytic cycle (Scheme 68).[165] These elegant reports from the Strassner group provide insight into the C($sp^3$)−H activation of methane and demonstrate the ability of Pd−NHC complexes in C−H activation of small molecules.[166−169]

**Scheme 67. Pd−NHC-Catalyzed C−H Oxidation of Methane Using Pyrimidine-Functionalized NHC Ligands by Strassner**



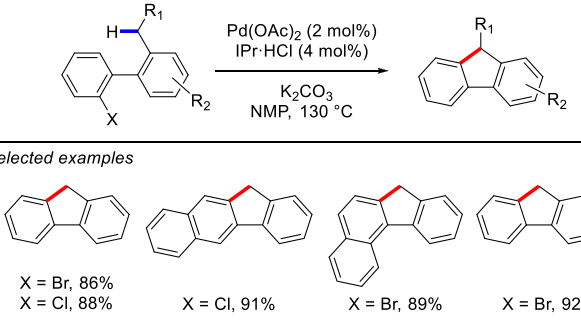

**Scheme 68. Proposed Mechanism in Pd−NHC-Catalyzed C−H Oxidation of Methane by Strassner**




In addition, Zhang reported DFT studies on related propane C−H activation.[170]

**2.2.2. Nondirected C($sp^3$)−H/C−X Activation.** *2.2.2.1. Intramolecular C($sp^3$)−H Activation.* In 2010, the Wu group reported the synthesis of methylene-bridged polyarenes using a $Pd(OAc)_2$/IPr system to effect the intramolecular benzylic C($sp^3$)−H activation (Scheme 69).[171] Interestingly, the use of IPr·HCl as a ligand precursor showed similar efficiency to a combination of $PCy_3$/pivalic acid (100 mol %), while $PCy_3$ alone was less effective. This reaction provides a general procedure for the synthesis of fluorene derivatives in excellent yields. Mechanistically, it was

**Scheme 69. Pd−NHC-Catalyzed Nondirected Benzylic C−H/C−X Arylation by Wu**



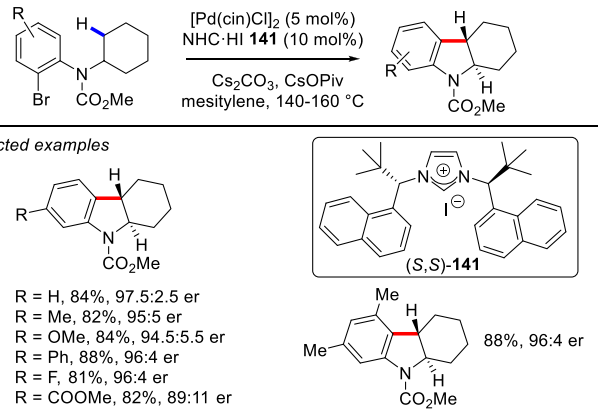


https://dx.doi.org/10.1021/acs.chemrev.9b00634
Chem. Rev. 2020, 120, 1981−2048

proposed that C(sp$^3$)−H activation is the rate-determining step.

The Kündig group has made significant contributions to the area of intramolecular C(sp$^3$)−H activation using chiral NHC ligands. In 2011, they successfully applied chiral imidazolylidene ligand **141** to the synthesis of fused indolines via intramolecular C(sp$^3$)−H activation catalyzed by Pd−NHCs (Scheme 70).[172] The active catalyst was generated *in situ* from

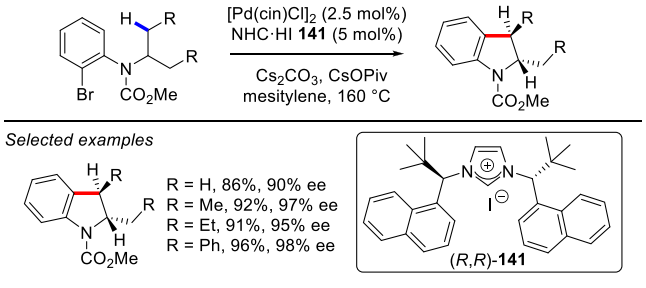
**Scheme 70. Pd−NHC-Catalyzed Asymmetric C(sp$^3$)−H/C−X Arylation by Kündig**




the NHC salt and [Pd(cin)Cl]$_2$. Examination of several related chiral ligands bearing 2-Me-benzyl and 2-MeO-benzyl N-substituents gave lower conversion and/or enantioselectivity. Despite high reaction temperature (140−160 °C), this reaction affords fused indolines with excellent enantioselectivities.

In 2012, the same group reported the synthesis of 2- and 2,3-substituted indolines using the *R*,*R* enantiomer of **141** in most cases (Scheme 71).[173,174] In this study, they also

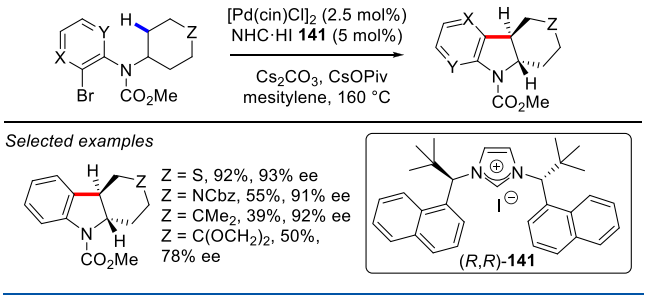
**Scheme 71. Synthesis of Indolines by Pd−NHC-Catalyzed Asymmetric C(sp$^3$)−H/C−X Arylation by Kündig**




disclosed the regiodivergent synthesis of indolines by C(sp$^3$)−H activation of either methyl or methylene groups; however, high asymmetric induction was observed only in the latter case. The reaction is distinguished by exceptionally high enantioselectivity in the synthesis of 2,3-disubstituted indolines.

In 2013, Kündig and co-workers reported an extension of the substrate scope of their asymmetric C(sp$^3$)−H functionalization, including the effects of leaving and protecting groups (Scheme 72).[175] Interestingly, these reactions are efficient with aryl bromides and iodides (77−94%), while aryl triflates and even chlorides provide promising reactivity (40−50%). Further, excellent enantioselectivities are observed in all cases

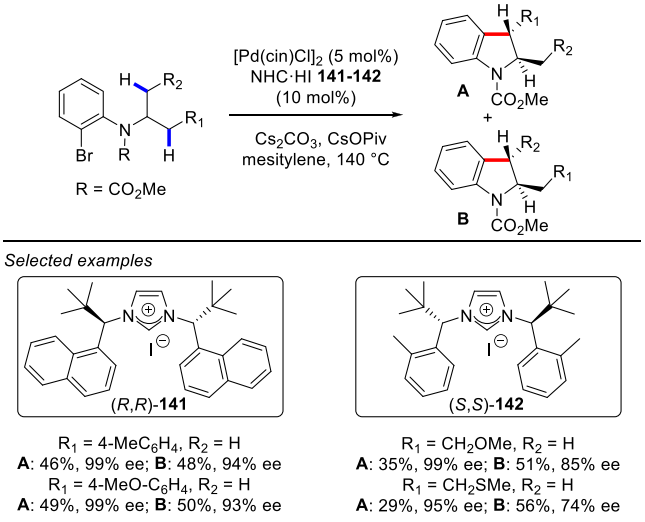
**Scheme 72. Synthesis of Functionalized Fused Indolines by Pd−NHC-Catalyzed Asymmetric C(sp$^3$)−H/C−X Arylation by Kündig**




(90−98.5% ee). In terms of the N-protecting/activating group, various carbamates ($CO_2$Me, $CO_2$Et, $CO_2$Bn) and amides (CO*i*Pr, CO*t*Bu) are well-tolerated, giving high levels of enantioinduction. On the basis of computational studies, the authors proposed that the concerted metalation deprotonation (CMD) mechanism step determines enantioselectivity, while ligand exchange from bromide to pivalate is rate-limiting.

In 2014, an efficient regiodivergent C(sp$^3$)−H activation was reported by the Kündig group (Scheme 73).[176] They

**Scheme 73. Pd−NHC-Catalyzed Regiodivergent Asymmetric C(sp$^3$)−H/C−X Arylation by Kündig**




established that using two bulky, chiral NHC ligands, namely, *R*,*R*-**141** and *S*,*S*-**142**, affords two different diastereoisomeric trans-2,3-substituted indolines. In contrast, when using enantiopure starting materials, this C−H activation reaction gives regioisomeric enantiomers depending on the catalyst structure (not shown). A comprehensive computational study provided support for the CMD mechanism in these C(sp$^3$)−H activations.

Very recently, the Baudoin group reported enantioselective synthesis of (nor)illudalane sesquiterpenes using chiral NHC ligand **141** reported by Kündig (Scheme 74).[177] In the model optimization system, they established that matching the amide chirality with the Pd−NHC catalyst is crucial to obtain high stereoselectivity in the reaction. This approach was successfully applied to the enantioselective synthesis of several natural products, demonstrating the potential of Pd−NHC-catalyzed C(sp$^3$)−H activation in complex natural product synthesis.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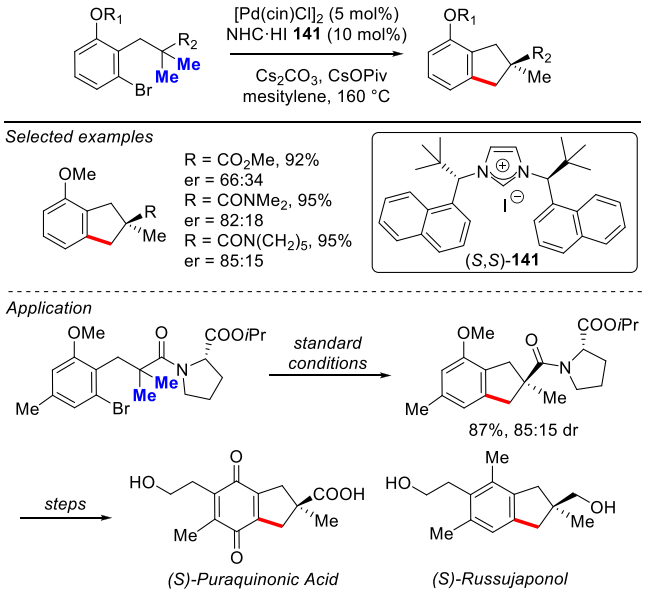
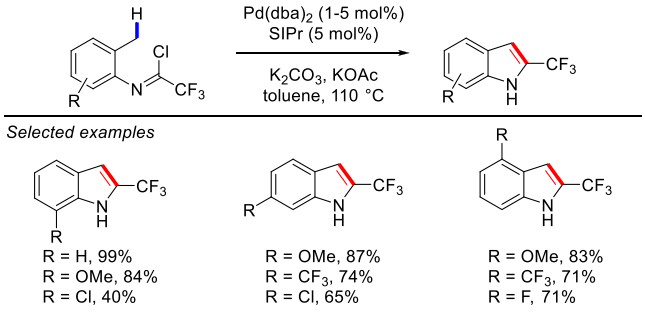
*Chem. Rev.* 2020, 120, 1981−2048

**Scheme 74. Pd–NHC-Catalyzed Asymmetric C($sp^3$)–H/C–X Arylation and Application to the Synthesis of (Nor)illudalanes by Baudoin**




A mechanistically related intramolecular benzylic C($sp^3$)–H activation was reported by Cramer and co-workers in the synthesis of 2-(trifluoromethyl)indoles from trifluoroacetimidoyl chlorides (Scheme 75).[178] Ligand screening demonstrated

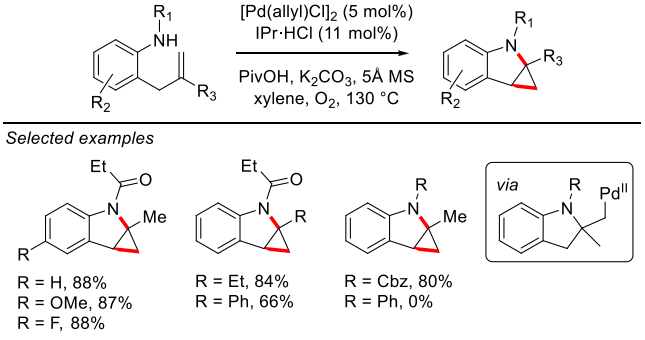
**Scheme 75. Pd–NHC-Catalyzed Benzylic C($sp^3$)–H/C–X Acylation by Cramer**




that SIPr is the preferred NHC ligand for this C–H activation, while IPr proved to be completely ineffective. Interestingly, comparable efficiency in the model system was observed using $PCy_3$; however, the Pd–NHC conditions proved to be more general in the scope investigation. Impressively, this reaction was readily performed on 2.5 g scale at 1.0 mol % catalyst loading.

In 2015, the Yang group reported Pd–NHC-catalyzed intramolecular benzylic C($sp^3$)–H activation as a part of their tandem aminoalkylation methodology (Scheme 76).[179] Mechanistically, the $\sigma$-alkyl-Pd(II) intermediate formed in the intramolecular aminopalladation step activates the benzylic C($sp^3$)–H bond to form a fused cyclopropane ring. The authors found that IPr in the presence of pivalic acid (30 mol %) and $K_2CO_3$ (1.1 equiv) in refluxing xylene under oxygen atmosphere was optimal for this tandem sequence. In contrast, with KO*t*Bu instead of $K_2CO_3$ the $\sigma$-alkyl-Pd(II) intermediate underwent amide $\alpha$-alkylation to give pyrolizidines (not shown). Non-NHC ligands, such as $PCy_3$, pyridine, or 1,10-

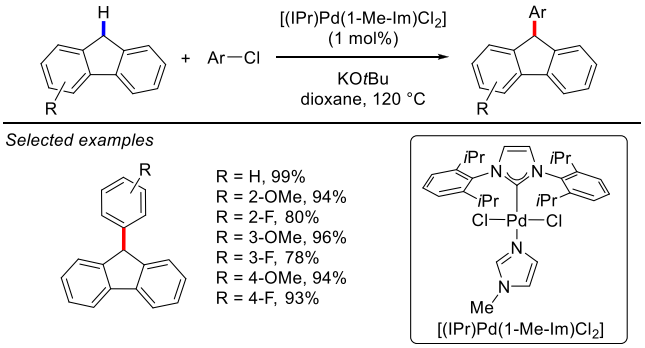
**Scheme 76. Pd–NHC-Catalyzed Tandem Aminopalladation/Benzylic C($sp^3$)–H Activation by Yang**




phenanthroline, were significantly less effective in promoting this reaction (0–45%).

*2.2.2.2. Intermolecular C($sp^3$)–H Activation.* In 2014, the Shao group reported intermolecular benzylic C($sp^3$)–H arylation of fluorenes with aryl chlorides using their [Pd(IPr)(1-Me-im)$Cl_2$] catalyst (Scheme 77).[180] KO*t*Bu is the optimal

**Scheme 77. Pd–NHC-Catalyzed Intermolecular Benzylic C($sp^3$)–H/C–X Arylation by Shao**




base in dioxane at 120 °C. The reaction is efficient for the synthesis of arylated fluorenes in typically excellent yields using electron-rich, electron-poor, and sterically hindered aryl chlorides. This reaction demonstrates the capacity of Pd–NHCs in C($sp^3$)–H activation of weakly acidic C–H bonds.

**2.2.3. Amide-Directed C($sp^3$)–H Activation.** The Yu group has made major breakthroughs in Pd-catalyzed aliphatic C($sp^3$)–H activation of weakly coordinating substrates using an acidic amide N-auxiliary.[75] This extremely useful mode of catalysis is compatible with Pd–NHC systems (Schemes 78 and 79).

In 2013, they reported the direct $\beta$-alkynylation of C($sp^3$)–H bonds in N-acidic aliphatic amides catalyzed by [Pd(allyl)Cl]$_2$ and sterically bulky IAd in the presence of $Cs_2CO_3$ (Scheme 78).[181] A library of NHC ligands was screened in the reaction optimization, and IAd·$HBF_4$ exhibited the highest reactivity. Other NHC ligands, including SIiPr, SIMes, SItBu, SIAd, and phosphines, including $PCy_3$, P*i*$Pr_3$, P*t*$Bu_2$Ph, and XPhos, were less effective. This reaction tolerates a wide range of aliphatic amides, providing the $\beta$-C($sp^3$)–H activation products in high yields. Mechanistically, the authors proposed that the reaction invovles Pd(0)/(II) catalysis.

In 2016, Yu and co-workers reported Pd–NHC-catalyzed C($sp^3$)–H arylation of piperidines directed by their weakly coordinating N-acidic amide auxiliary (Scheme 79).[182] In this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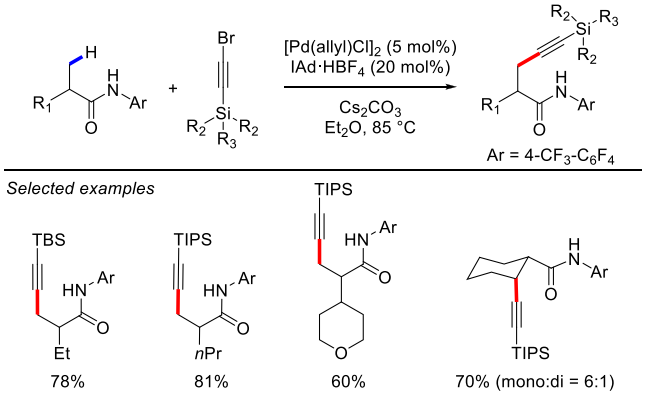
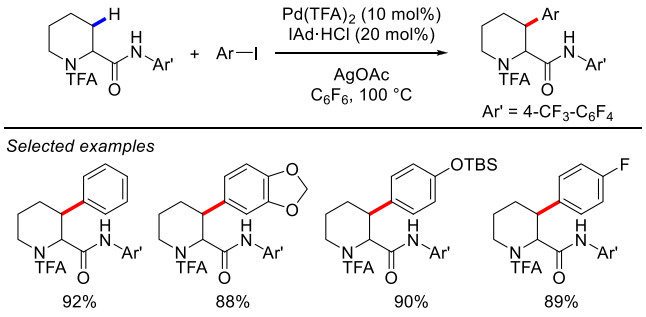
Chem. Rev. 2020, 120, 1981–2048

**Scheme 78. Pd−NHC-Catalyzed Amide-Directed C(sp$^3$)−H Alkynylation by Yu**




**Scheme 79. Pd−NHC-Catalyzed Amide-Directed C(sp$^3$)−H Arylation of Piperidines by Yu**




reaction, SIAd gave the best results, while SIMes, SIPr, and IAd were less effective. The reaction was further extended to the direct C(sp$^3$)−H arylation of tetrahydropyrans using SItBu as the preferred ligand (not shown). Based on stoichiometric experiments, the authors proposed a mechanism involving Pd(II)/(IV) catalysis. This reaction complements intramolecular C(sp$^3$)−H activation methodology via Pd(0)/(II) catalysis reported by the Kündig group (Schemes 70−73).

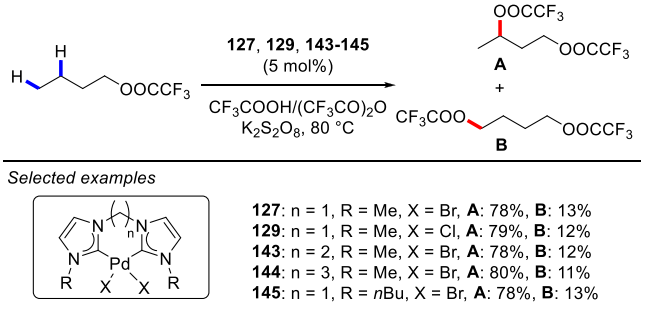
**2.2.4. C(sp$^3$)−H Oxygenation/Halogenation by Pd(II)/(IV).** In contrast to C(sp$^2$)−H activation, very few examples of the direct C(sp$^3$)−H functionalization by the Pd(II)/(IV) mechanism using Sanford's systems with Pd−NHCs have been reported.

In 2011, Hou and co-workers reported a Pd−NHC-catalyzed oxidative trifluoroacetoxylation of unactivated methylenes (Scheme 80).[183] They found that chelating bis-NHC−Pd complexes gave the monotrifluoroacetoxylation products in high yields and with good C−H activation selectivity.

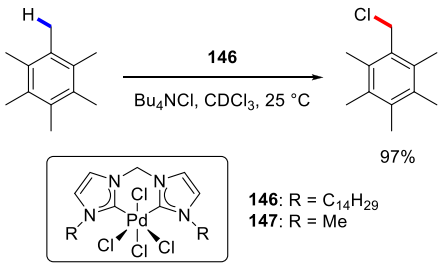
In 2010, Kraft and co-workers reported the synthesis of chelating Pd(IV)−bis-NHC complexes [Pd(NHC)-$CH_2$(NHC)$Cl_4$] **146**−**147** and their application as chlorinating reagents for C(sp$^3$)−H functionalization (Scheme 81).[184] A mechanism involving a cationic [(NHC)$CH_2$(NHC)Pd-(IV)$Cl_3$]$^+$ intermediate as a chlorinating agent was proposed.

**2.2.5. Allylic C(sp$^3$)−H Activation.** The direct C(sp$^3$)−H functionalization of allylic bonds proceeds more easily than unactivated C(sp$^3$)−H bonds due to higher bond acidity;[60,61] however, several challenges with Pd−NHC catalysis in terms of compatibility of the reaction conditions still need to be addressed.

**Scheme 80. Pd−NHC-Catalyzed C(sp$^3$)−H Acetoxylation of Unactivated Methylenes by Hou**




**Scheme 81. Pd−NHC-Catalyzed Benzylic C(sp$^3$)−H Chlorination by Kraft**




In 2017, Yang and co-workers reported the direct allylic C(sp$^3$)−H functionalization and alkylation with oxindoles using the [Pd(IPr)(cin)Cl] complex in the presence of 2,5-DMBQ (2.0 equiv) and KO*t*Bu (1.5 equiv) in $CH_2Cl_2$ at 60−80 °C (Scheme 82).[185] Interestingly, investigation of different ligands showed that the reaction was inhibited when IPr was replaced by bis(sulfoxide) or 4,5-diaza-9-fluorenone. Furthermore, phosphoramidites and $PCy_3$ instead of IPr gave the allyl activation product with lower yields and poor regioselectivity (1.1:1 to 3:2:1 vs 16:1 with IPr). Mechanistically, the active [Pd(IPr)Cl(OAc)] complex is generated in situ from IPrHCl and $Pd(OAc)_2$. The key allyl palladium intermediate [Pd-(IPr)Cl($R_3$-allyl)] is formed via allylic C−H activation. In the next step, the nucleophilic attack of an enolate and reductive elimination affords the desired C−H activation product. The active [Pd(IPr)Cl(OAc)] catalyst is regenerated by oxidation with 2,5-DMBQ. The NHC−metal complex in this C−H activation is stable to the oxidative conditions and gives high C−H allylation regioselectivity (cf. bis(sulfoxide), 4,5-diaza-9-fluorenone, phosphines). This protocol is characterized by broad scope, good to excellent yields, and exceptional regioselectivity. This direct allylic C(sp$^3$)−H method was also applied to the direct synthesis of [Pd(IPr)(cin)Cl] from IPr·HCl, $PdCl_2$, and allylbenzene.

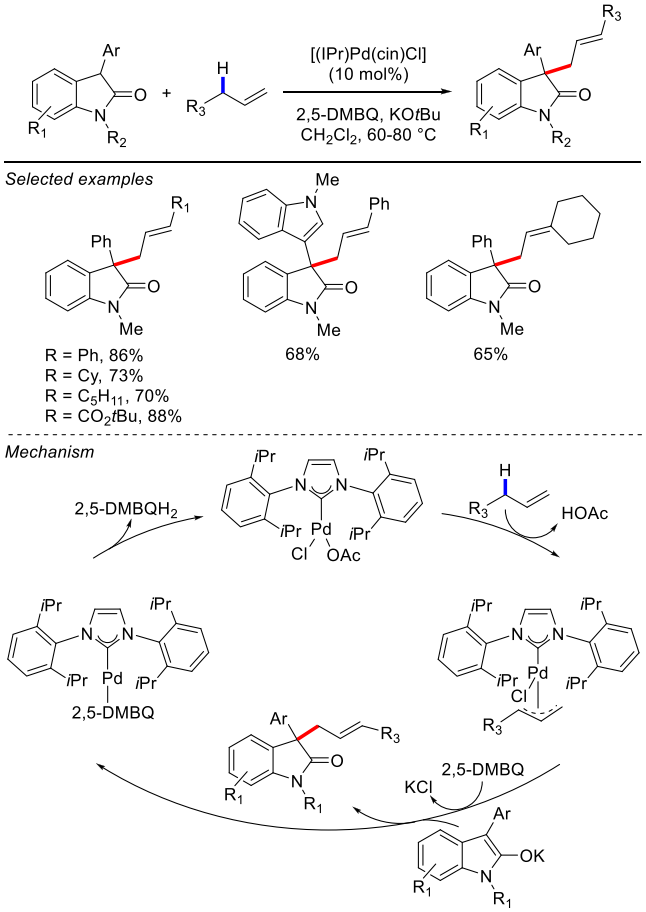
## 2.3. Miscellaneous

In 2009, Jung and co-workers reported a cationic tridentate benzimidazolylidene Pd−NHC system **148**, which showed high activity in C−H/C−D exchange in $D_2O$ (Scheme 83).[186] In this NHC template, the combined use of a strongly σ-donating NHC ligand, N-coordinating amide, and hemilabile ether linkage collectively weakens the interaction of $D_2O$ with the electrophilic Pd center, thus allowing for the high yielding C−H/C−D exchange of C(sp$^2$)−H and C(sp$^3$)−H bonds.

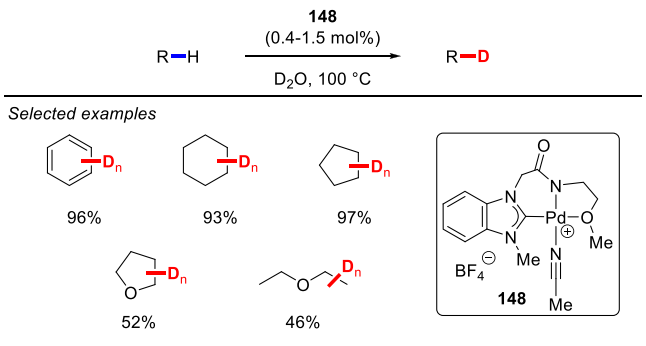
In 2015, the same group disclosed C−H/C−D exchange in $CF_3CO_2D$ catalyzed by a related neutral benzimidazolylidene Pd−NHC complex **149** (Scheme 84).[187] In the presence of


https://dx.doi.org/10.1021/acs.chemrev.9b00634
Chem. Rev. 2020, 120, 1981−2048

**Scheme 82. Pd−NHC-Catalyzed Allylic C($sp^3$)−H Activation/Allylation of Oxindoles by Yang**



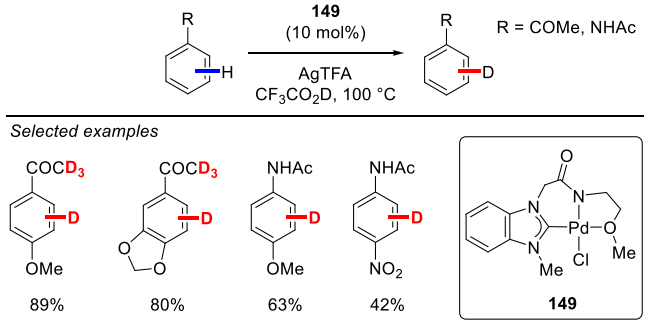

**Scheme 83. Pd−NHC-Catalyzed C−H/C−D Exchange Using $D_2O$ by Jung**



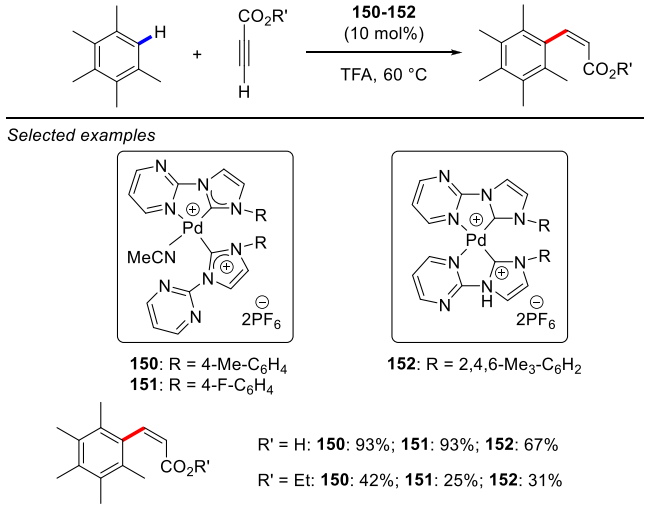

AgTFA (10 mol %), complex **149** proved to be significantly more reactive than simple Pd salts, including $PdCl_2$, $Pd(OAc)_2$, $Pd(TFA)_2$, $[Pd(MeCN)_2Cl_2]$, and $[Pd(PPh_3)_2Cl_2]$. The studies by Jung demonstrate the potential of Pd−NHC complexes in H/D exchange reactions.

In 2018, Strassner and co-workers reported chelating dicationic Pd−NHC complexes **150**−**152** featuring a hemilabile *N*-2-pyrimidyl group and two carbene ligands coordinated to the metal center (Scheme 85).[188] These complexes showed high activity in the electrophilic hydroarylation of alkynes by C($sp^2$)−H activation. Interestingly, N-steric bulk was found to disfavor the catalytic reactivity due to a slower protodemetalation step. These results are promising and

**Scheme 84. Pd−NHC-Catalyzed C−H/C−D Exchange Using $CF_3CO_2D$ by Jung**




**Scheme 85. Pd−NHC-Catalyzed Hydroarylation of Alkynes by Strassner**



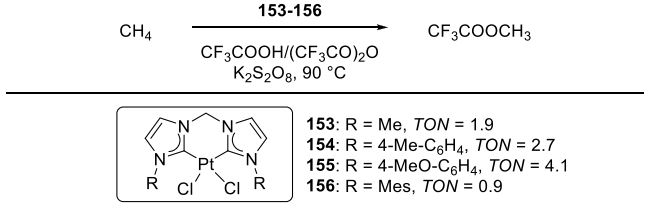

highlight the potential of Pd−NHC complexes in electrophilic C−H reactions.

## 3. PLATINUM−NHC COMPLEXES

Although the first Pt−NHC complex was reported in 1973,[189] there are few examples of Pt−NHC complexes in transition-metal catalysis. Thus far, catalytic applications of Pt−NHCs have focused almost exclusively on hydroelement addition reactions, including hydrosilylation, hydroboration, and hydroamination.[190−195] Very few examples of C−H functionalizations using Pt−NHC complexes have been reported to date.

In 2006, Strassner and co-workers reported chelating methylene-bridged Pt−bis-NHC complexes **153**−**156** in the catalytic C−H activation of methane (Scheme 86).[196] Complex **155** with electron-rich N-substituents was the most reactive; however, these Pt−NHCs showed inferior reactivity

**Scheme 86. Pt−NHC-Catalyzed C−H Activation of Methane by Strassner**





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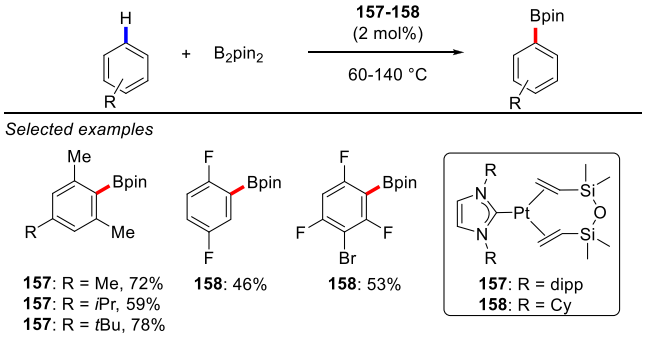
to Pd−NHCs under similar reaction conditions (cf. Schemes 64−66).

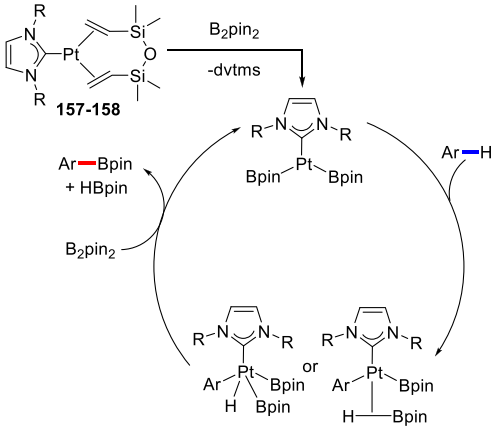
In 2015, Chatani and co-workers reported [Pt(NHC)(dvtms)] complexes (dvtms = divinyltetramethyldisiloxane) for the catalytic C($sp^2$)−H borylation of arenes with $B_2pin_2$ (Scheme 87).[197] A noteworthy feature of this protocol is

**Scheme 87. Pt-NHC-Catalyzed C($sp^2$)−H Borylation by Chatani**




selectivity for the sterically hindered positions. A variety of congested arenes were converted to 2,6-disubstituted phenylboronic esters in moderate to good yields, providing complementary outcome to the well-established iridium systems. Both IPr and ICy were found to be effective NHC ligands for this C−H borylation reaction. Furthermore, sensitive halides such as F, Cl, and Br were intact during this C−H activation. Mechanistically, the authors demonstrated that dvtms dissociates from the metal center (Scheme 88).[198]

**Scheme 88. Proposed Mechanism for the Pt-NHC-Catalyzed C($sp^2$)−H Borylation**



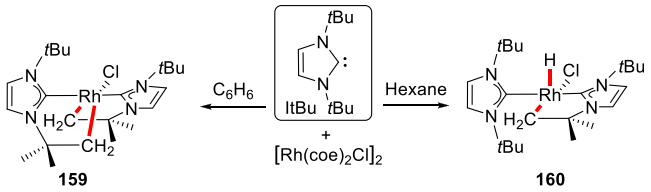

It was proposed that the coordinatively unsaturated Pt−NHC complex reacts with $B_2pin_2$ to give [Pt(NHC)(Bpin)$_2$], followed by C($sp^2$)−H activation via $\sigma$-bond metathesis or oxidative addition to give Pt(IV).

## 4. RHODIUM−NHC COMPLEXES

Following the first synthesis of a Rh−NHC complex in 1974,[199] Rh−NHCs were among the earliest metal−NHC complexes to be successfully used in catalysis.[200−203] Now, Rh−NHC complexes are routinely applied to determine the electronic properties of NHCs through the synthesis of [Rh(NHC)(CO)$_2$Cl] complexes and measurement of their CO stretching frequencies (TEP, Tolman electronic parameter).[41,42] Thus, it is not surprising that, due to their common presence and ease of synthesis, Rh−NHC complexes have featured prominently in C−H functionalization reactions.

In 2004, an early demonstration of the high activity of Rh−NHC was reported by Nolan and co-workers in the intramolecular C−H activation of the [Rh(ItBu)(coe)Cl]$_2$ complex (coe = cyclooctene) (Scheme 89).[204] It was found

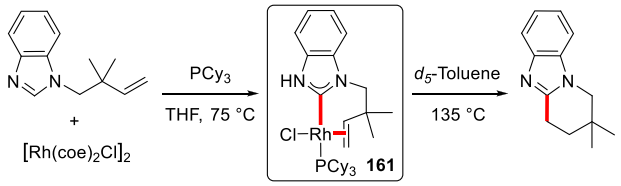
**Scheme 89. Solvent-Dependent C−H Activation in the [(ItBu)Rh(coe)Cl]$_2$ Complex by Nolan**




that this Rh(I) complex undergoes a solvent-dependent intramolecular C($sp^3$)−H bond activation process to give **159** through double C($sp^3$)−H activation in benzene or **160** through mono C($sp^3$)−H activation in hexane, respectively.

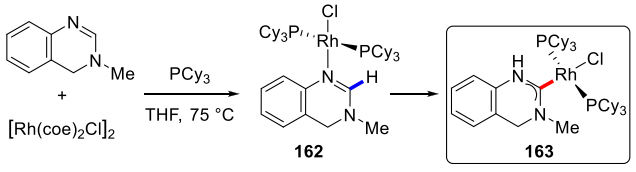
Around the same time, Bergman, Ellman, and co-workers established a novel mechanism for the intramolecular C($sp^2$)−H functionalization of heterocycles with olefins proceeding through a Rh−NHC intermediate **161** (Scheme 90).[205] The

**Scheme 90. Intramolecular C−H Activation via a Rh−NHC Complex by Bergman and Ellman**




Rh(I) complex **161** was determined to be the resting state, while the carbene insertion was found to be the rate-determining step. Later, they conducted a detailed kinetic analysis and DFT studies for the intermolecular alkylation of heterocycles with alkenes and demonstrated the intermediacy of a related Rh(I) complex **163** formed through an intramolecular C($sp^2$)−H activation (Scheme 91).[206−208]

**Scheme 91. Intermolecular C−H Activation via a Rh−NHC Complex by Bergman and Ellman**




Currently, the major applications of Rh−NHC complexes in C−H activation include the following processes: (1) pyridine-directed C($sp^2$)−H arylation and alkylation; (2) C($sp^2$)−H borylation; (3) 2-fold C−H activation via Rh−NHC intermediates; (4) C($sp^3$)−H functionalization; and (5) C−H/C−D exchange.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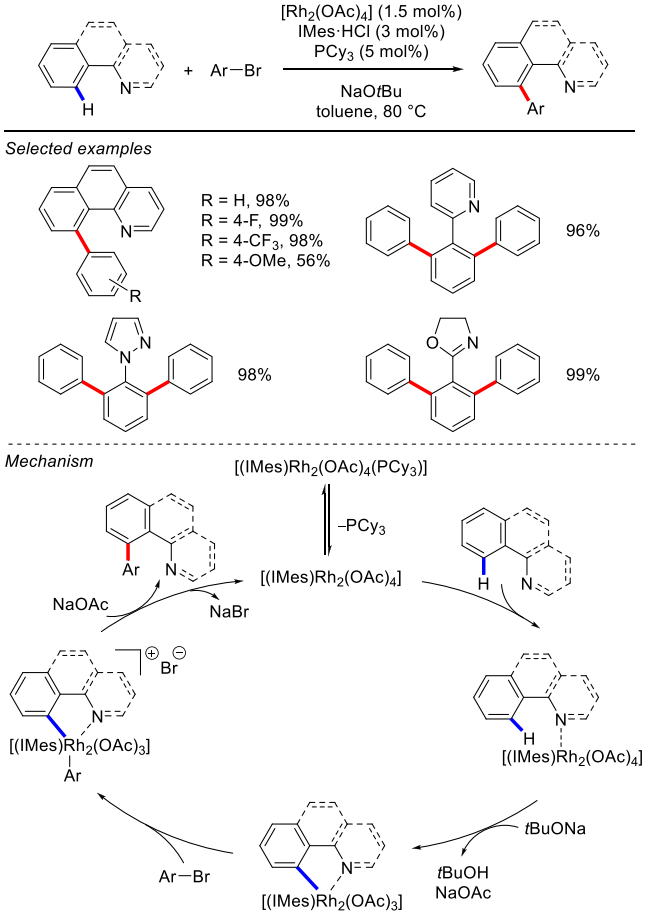
Chem. Rev. 2020, 120, 1981−2048

### 4.1. C(sp$^2$)−H Activation

**4.1.1. Directed C(sp$^2$)−H/C−X Activation.** In 2009, Chang and co-workers reported a Rh−NHC-catalyzed direct arylation of C(sp$^2$)−H bonds in pyridines with aryl bromides (Scheme 92).[209] They found that the catalytic activity was

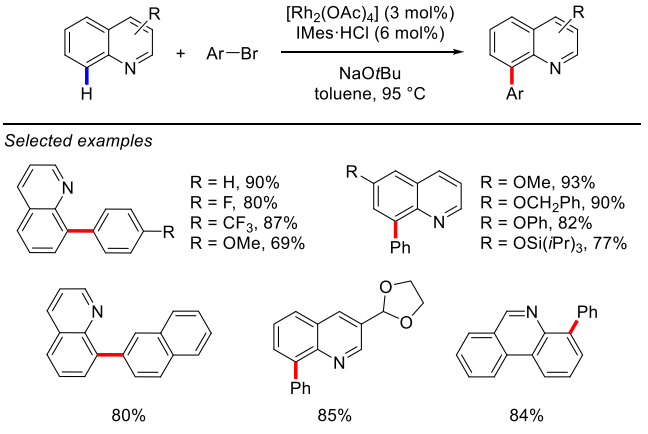
**Scheme 92. C(sp$^2$)−H/C−X Arylation Catalyzed by NHC/Phosphine Rh Complexes by Chang**




significantly increased by a combined use of IMes·HCl (3 mol %) and $PCy_3$ (5 mol %) in the presence of NaO*t*Bu as a stoichiometric base. Interestingly, when IMes·HCl was removed from the catalytic system or replaced by IPr·HCl, only traces of the C−H arylation product were formed. In contrast, $PCy_3$ had a less pronounced effect on the coupling. A mechanism involving the proton abstraction pathway by a bimetallic $[Rh_2(NHC)(OAc)_4]$ species was proposed, while phosphine was suggested to stabilize the active complex. The active NHC−dirhodium(II) complex is generated from an $[(IMes)Rh_2(OAc)_4(PCy_3)]$ complex. Coordination of the nitrogen-directing group and C−H activation assisted by *t*BuONa gives the five-membered rhodacycle intermediate. Oxidative addition to Rh(II) and reductive elimination generate the C−H arylation product and regenerate the active Rh(II) catalyst.

In 2011, the Chang group reported similar Rh−NHC conditions for the regioselective C(sp$^2$)−H arylation of quinolines with aryl bromides at the C8 position (Scheme 93).[210] NHC ligands were found to have a major effect on the C−H arylation, and IMes·HCl in combination with $[Rh_2(OAc)_4]$ and stoichiometric NaO*t*Bu gave the best results.

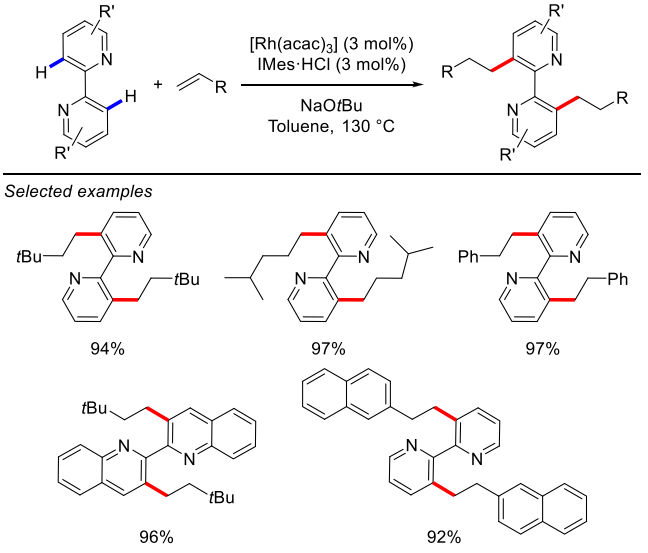
**Scheme 93. Rh−NHC-Catalyzed C(sp$^2$)−H/C−X C8-Arylation of Quinolines by Chang**




In contrast, the reaction was suppressed when IMes·HCl was replaced by other ligands, including SIMes, IPr, IiPr, IAd, and $PPh_3$. This process allows for the rare regioselective synthesis of C8-arylquinoline derivatives in high yields.

Subsequently, they described Rh−NHC-catalyzed double C(sp$^2$)−H hydroarylation of 2,2′-bipyridines by a rollover cyclometalation pathway (Scheme 94).[211] Under the opti-

**Scheme 94. Rh−NHC-Catalyzed Double C(sp$^2$)−H Activation/Hydroarylation by Chang**




mized conditions using $Rh(acac)_3$ in the presence of IMes·HCl and NaO*t*Bu, double functionalization was achieved in excellent yields with a variety of C−H activation substrates. Again, IMes was found to be significantly more effective than other ligands, including SIMes, SIPr, IPr, IiPr, ICy, IAd, and ItBu. The reaction was further extended to hydroarylation of alkynes under the same catalytic conditions (not shown). Mechanistically, it was proposed that the Rh(I) complex, [Rh(NHC)(bipy)(O*t*Bu)], re-enters the catalytic cycle after the first C−H activation step, driven by the strong trans-effect of the NHC ligand.

In 2016, Wu and co-workers reported a cationic Rh−NHC complex **164** for the C(sp$^2$)−H olefination of 4-aryl-1*H*-1,2,3-triazoles in the presence of $Cu(OAc)_2·H_2O$ and KOAc (Scheme 95).[212] A wide range of doubly C−H vinylated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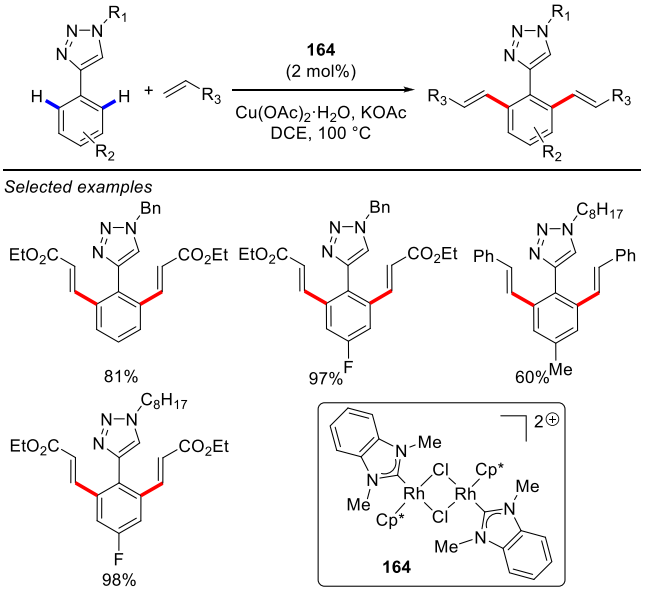
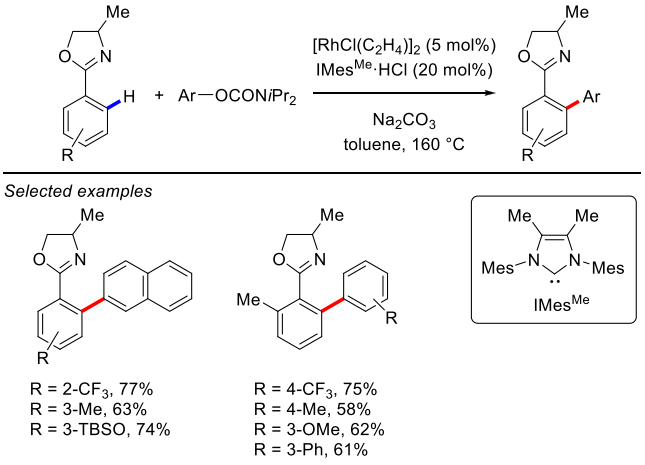
**Scheme 95. Rh−NHC-Catalyzed Double Triazole-Directed C(sp²)−H Olefination by Wu**




aryl-triazoles could be obtained in good yields in this reaction. The use of *N,N*-$Me_2$-benzimidazolylidene NHC ligand resulted in significantly improved yields for this double C−H activation compared with $[RhCp^*Cl_2]_2$. Furthermore, N-aliphatic $\alpha$-branched substituents on the NHC ligand led to a decrease in catalytic activity.

In 2017, Chatani and co-workers reported a Rh−NHC-catalyzed C(sp²)−H arylation directed by oxazoline using aryl carbamates as arylating reagents and $IMes^{Me}$ as the NHC ligand (Scheme 96).[213] The simultaneous activation of C−H

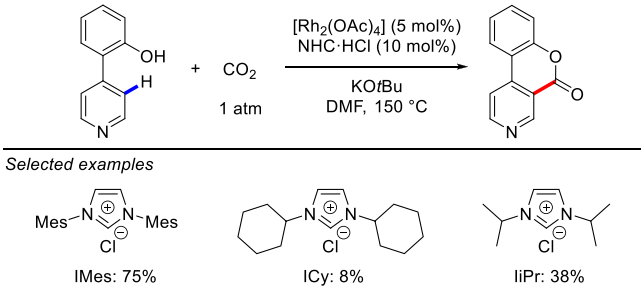
**Scheme 96. Rh−NHC-Catalyzed Oxazoline-Directed C(sp²)−H/C−O Arylation by Chatani**




and C−O bonds is very rare due to the low reactivity of these bonds. The key in this method was identification of a Rh−bis-NHC complex, while other Rh catalysts such as $[Rh(cod)Cl]_2$ and $[Rh(C_2H_4)_2Cl]_2$ were less effective. This double C−H/C−O activation was compatible with a wide range of functional groups under relatively mild reaction conditions in the presence of a carbonate base.

In 2018, the Li group reported a Rh(II)-catalyzed C(sp²)−H carboxylation of 2-pyridylphenols (Scheme 97).[214] They found

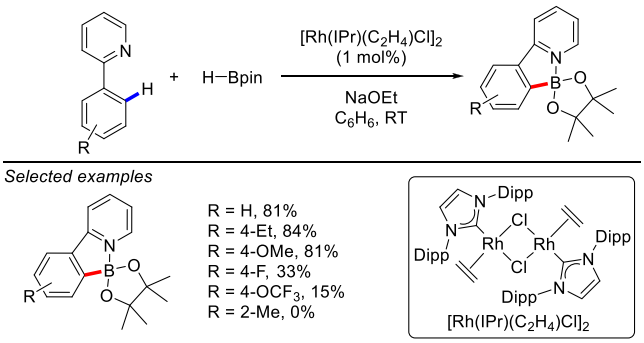
**Scheme 97. Rh−NHC-Catalyzed Hydroxyl-Directed C(sp²)−H Carboxylation by Li**



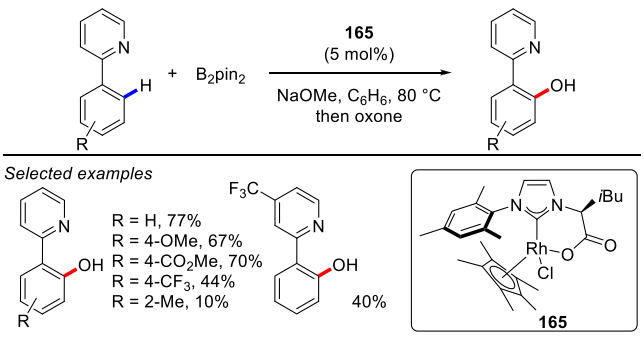

that the IMes ligand performed well during the optimization study, while ICy and IiPr were less effective. Thus, combining $[Rh_2(OAc)_4]$ and IMes·HCl in the presence of KO*t*Bu in DMF promoted the direct C(sp²)−H carboxylation in 75% yield.

Rh−NHC-catalyzed C(sp²)−H activation has been successfully employed for the synthesis of boronic acid esters (Schemes 98−100). In 2014, Crudden and co-workers

**Scheme 98. Rh−NHC-Catalyzed Pyridine-Directed C(sp²)−H Borylation by Crudden**




**Scheme 99. Rh−NHC-Catalyzed Pyridine-Directed C(sp²)−H Borylation by Basle**




reported C(sp²)−H borylation of 2-arylpyridines using the Rh(I)−NHC dimer, $[Rh(IPr)(C_2H_4)Cl]_2$, as a catalyst and pinacol borane as a boron source at room-temperature C−H borylation (Scheme 98).[215] The authors also demonstrated that sequential borylation and arylation could be efficiently performed in a one-pot fashion. However, the scope of this reaction was rather limited.

In 2018, Basle and co-workers reported a Rh(III)−NHC complex **165** featuring a pendant carboxylate group and Cp* ligand that showed high efficiency in the pyridine-directed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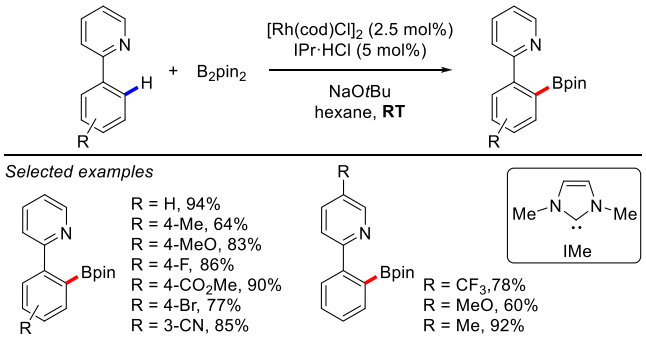
Chem. Rev. 2020, 120, 1981−2048

**Scheme 100. Rh−NHC-Catalyzed Pyridine-Directed C($sp^2$)−H Borylation by Wang**

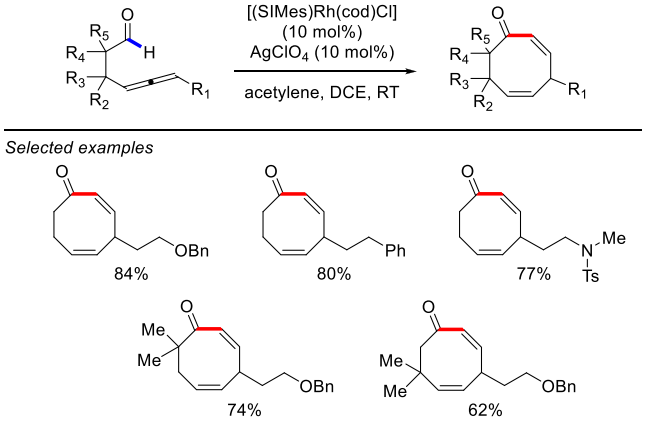



C($sp^2$)−H borylation under mild conditions (Scheme 99).[216] Interestingly, the complex **165** was more reactive than the analogous Rh(III)−NHCs with *i*Pr or Me groups in the NHC side chain. Similarly, a mixture of $[RhCp^*Cl_2]_2$ and IMes or $[Cp^*RhCl_2]_2$ alone was found to be significantly less reactive, which highlights the importance of the NHC scaffold in **165**. Importantly, the NHC ligand is readily accessible in a single step from Mes-$NH_2$, L-leucine, formaldehyde, and glyoxal according to the procedure by Mauduit and co-workers. The selective C($sp^2$)−H borylation reaction tolerated a broad range of functional groups.

Independently, Wang and co-workers developed a very mild protocol for Rh−NHC-catalyzed C($sp^2$)−H borylation of 2-arylpyridines enabled by the combination of IPr·$HBF_4$ and $[Rh(cod)Cl]_2$ in the presence of KO*t*Bu at room temperature (Scheme 100).[217] Several other NHCs showed high activity in this reaction, including SIMes, IMes, and IPr; however, the NHC ligand is critical for the reaction with no product formed in its absence. Interestingly, even the simple IMe ligand (Scheme 100, box) is effective for promoting the model reaction in 78% yield. This methodology allows for C($sp^2$)−H borylation of a variety of 2-arylpyridines in good to excellent yields and shows excellent functional group tolerance (halides, ester, cyano). This reaction could also be performed well on a gram scale at 1.0 mol % catalyst loading.

**4.1.2. C(acyl)−H Activation.** In 2012, Sato and co-workers reported Rh(I)−NHC-catalyzed intermolecular cycloaddition between 4-allenals and alkynes to construct eight-membered rings via C(acyl)−H activation (Scheme 101).[218]

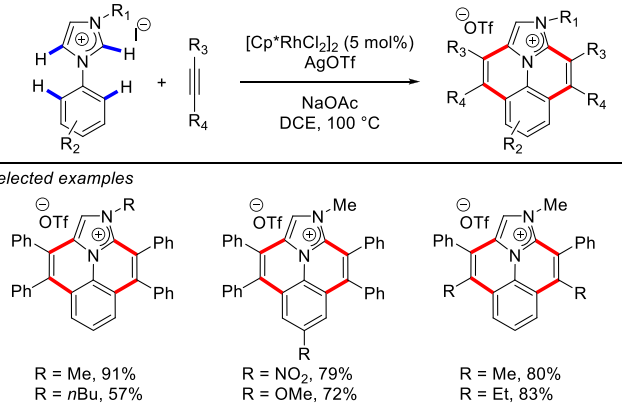
**Scheme 101. Rh−NHC-Catalyzed C(Acyl)−H Activation/Allene Addition by Sato**



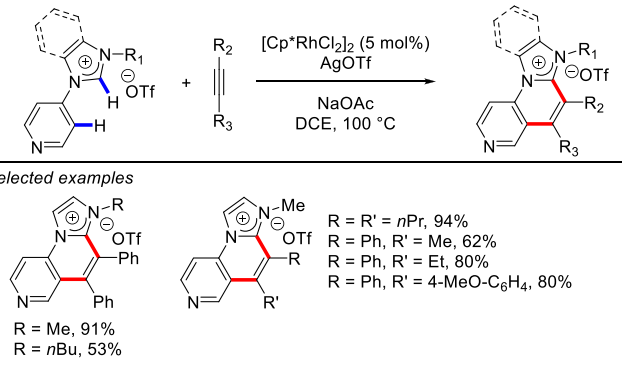

The cationic complex formed in situ from [Rh(SIMes)(cod)Cl] gave the best performance in this transformation, while related IMes-based systems were less effective. Furthermore, phosphine-based catalysts, such as $[RhCl(PPh_3)_3]$ and $[Rh(dppe)]ClO_4$, were completely inactive for this transformation. The reaction showed good functional group compatibility for the synthesis of challenging eight-membered rings. This elegant study illustrates the potential of Rh(I)−NHC systems for C(acyl)−H bond activation.

**4.1.3. Two-Fold C−H/C−H Activation.** The Choudhury group has pioneered 2-fold cascade C−H activation/C−H annulation reactions driven by the formation of Rh−NHCs (Scheme 102−109).

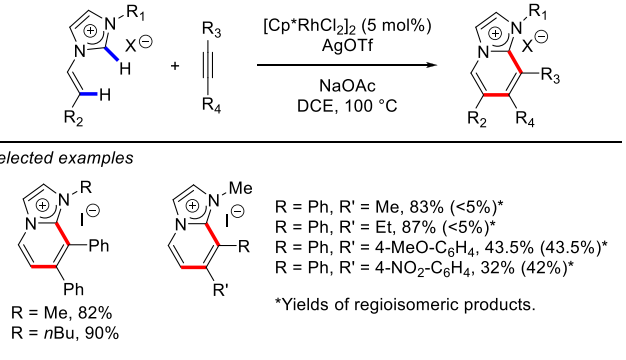
**Scheme 102. Two-Fold C($sp^2$)−H Annulation via Rh−NHCs by Choudhury**




**Scheme 103. C($sp^2$)−H Annulation of Pyridine via Rh−NHCs by Choudhury**




**Scheme 104. Vinylic C($sp^2$)−H Annulation via Rh−NHCs by Choudhury**





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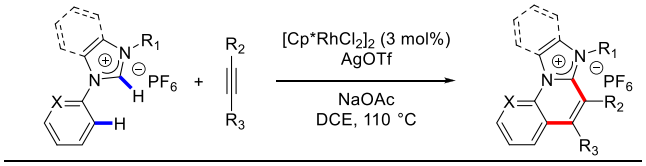
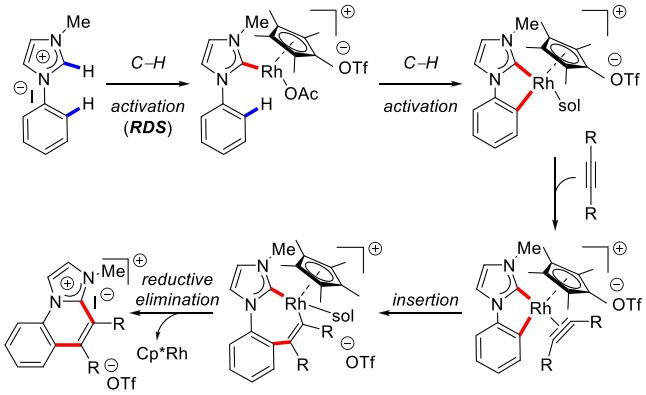
Chem. Rev. 2020, 120, 1981−2048

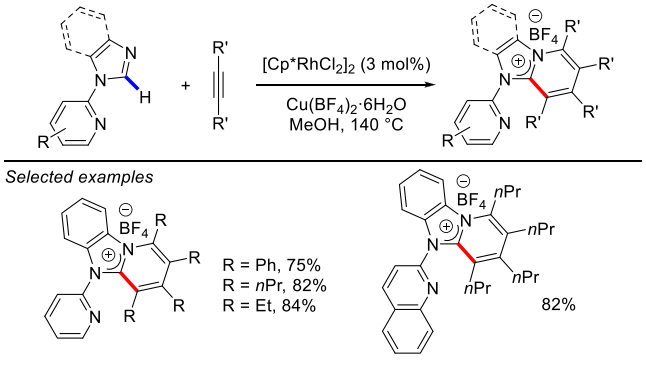
**Scheme 105. C(sp²)−H Annulation of Chelating Heterocycles via Rh−NHCs by Choudhury**




**Scheme 106. Proposed Mechanism for C(sp²)−H Annulation via Rh−NHCs by Choudhury**

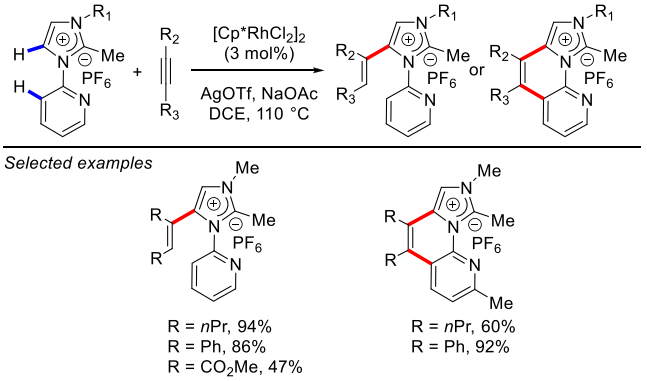



**Scheme 107. C(sp²)−H/C−N Annulation via Rh−NHCs by Choudhury**

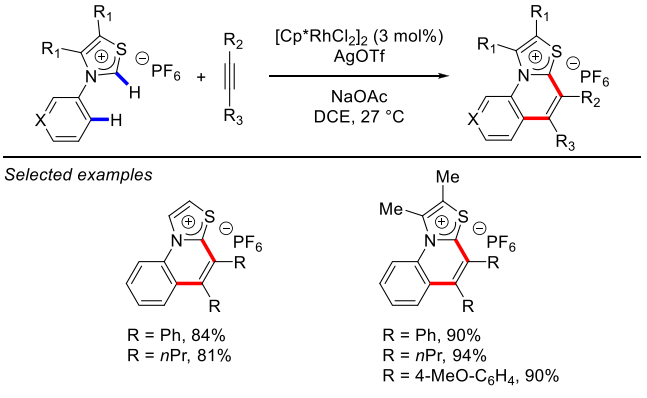



In 2014, they disclosed the first example of Rh-catalyzed annulations between *N*-arylimidazolium salts and alkynes using $[RhCp^*Cl_2]_2$ (5 mol %) in the presence of AgOTf (3 equiv) and NaOAc as a base in $CH_2Cl_2$ at room temperature, leading to the formation of imidazo[1,2-*a*]quinoliniums (not shown).[219] In 2015, the same group reported Rh-catalyzed double aromatic C(sp²)−H activation/C(sp²)−H annulation using similar reaction conditions in DCE at 100 °C (Scheme 102).[220] This method furnishes densely functionalized polycyclic heteroaromatics based on the imidazo-quinolizinium scaffold. It is worth noting that the C(sp²)−H activation proceeds through normal/abnormal NHC ligands that direct these cascade C−H activation reactions.

**Scheme 108. C(sp²)−H Annulation via Abnormal Rh−NHCs by Choudhury**




**Scheme 109. C(sp²)−H Annulation via Thiazolium Rh−NHCs by Choudhury**




At the same time, Choudhury and co-workers reported C(sp²)−H activation/C(sp²)−H annulation of electrophilic *N*-4-pyridyl-imidazolium salts (Scheme 103).[221] These less reactive precursors required higher reaction temperature and afforded imidazo-naphthyridinium heterocycles in good to excellent yields. Subsequently, this C(sp²)−H activation methodology was further extended to olefinic C(sp²)−H bond activation/C(sp²)−H annulation, leading to a variety of imidazo-pyridinium scaffolds (Scheme 104).[222] These examples demonstrate that aromatic, heteroaromatic, and olefinic C(sp²)−H bonds can be activated in the cascade Rh−NHC annulation under similar catalytic conditions.

In 2016, the Choudhury group reported C(sp²)−H activation/C(sp²)−H annulation of chelating 2-pyridylimidazolium salts catalyzed by $[RhCp^*Cl_2]_2$ (3 mol %) in the presence of AgOTf (2.5 equiv) and NaOAc as a base in DCE at 110 °C (Scheme 105).[223] In this protocol, the pyridine rollover C(sp²)−H activation was accomplished within the hemilabile $[Rh(NHC)Rh(py)X_2]^+$ complex, leading to imidazo-naphthyridinium heterocycles in good yields. In another cyclization mode, C(sp²)−H alkenylation at the abnormal Rh−NHC site produced 5-alkenylimidazoliums (not shown).[223] The selectivity was controlled by sterics of 2-pyridylimidazolium precursors.

Mechanistically, the authors proposed that the reaction involves the following steps: (1) rate-determining C−H activation of the imidazolium salt; (2) intramolecular aromatic C−H activation; (3) alkyne coordination; (4) alkyne insertion; and (5) reductive elimination (Scheme 106).[224] Both C−H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Chem. Rev. 2020, 120, 1981−2048

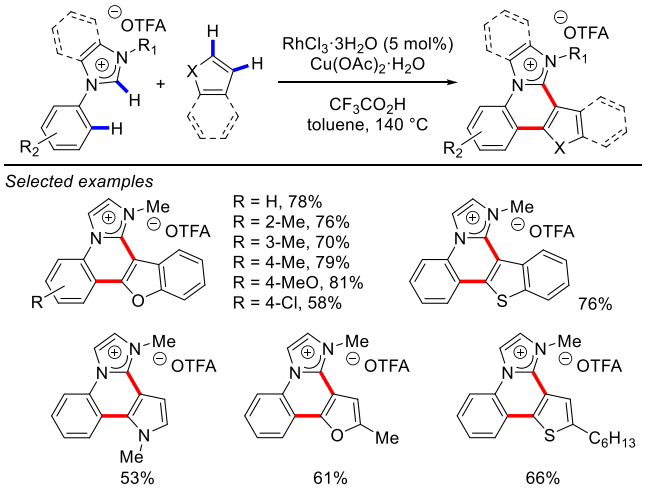
activation steps were proposed to proceed via the CMD pathway.

In 2017, yet another Rh−NHC reaction pathway via C(sp$^2$)−H activation/C−N annulation to give C−N ring expanded annulation was reported by Choudhury and co-workers (Scheme 107).[225] The reaction was promoted by $[RhCp^*Cl_2]_2$ (3 mol %) and $Cu(BF_4)_2H_2O$ (1.5 equiv) in MeOH at 140 °C. Key to this C−N annulation was the selection of an appropriate solvent/counterion combination as the use of $Cu(OAc)_2·H_2O$ in toluene at 140 °C resulted in the typical C−C annulation (see Schemes 102 and 103).

The Choudhury group also showed that the normal Rh−NHC intermediates can be efficiently switched to abnormal Rh−NHCs by blocking the C2 position of the imidazole ring (Scheme 108).[226] More recently, this C(sp$^2$)−H activation/C(sp$^2$)−H annulation was achieved with *N*-arylthiazolium substrates instead of *N*-arylimidazoliums (Scheme 109).[227,228] The reaction affords thiazolo-quinolinium heterocycles in good to excellent yields and constitutes a rare example of thiazolin-2-ylidene metal−NHCs. Furthermore, an elegant 4-fold C(sp$^2$)−H activation/C(sp$^2$)−H annulation of bisimidazolium substrates on pyridine and pyrazine backbones via rollover C−H activation with Rh−NHC intermediates has been recently reported by Choudhury and co-workers.[229] Very recently, the strategy of generating metal−NHC intermediates in C−H annulation reactions has been extended to Co catalysis by the Choudhury group.[230] The method demonstrates a potentially new approach to C(sp$^2$)−H activation/annulation using protic NHC species by metallotropism-enabled C−H activation of azoles. More importantly, the development of this reaction suggests that the expensive Rh may be replaced by more sustainable and cost-effective 3d first-row transition-metal catalysts to enable 2-fold cascade C−H activation/C−H annulation reactions by metal−NHC intermediates (see Section 8).

Independently, You and co-workers reported a 2-fold C(sp$^2$)−H activation/C(sp$^2$)−H annulation of *N*-arylimidazolium salts with electron-rich five-membered heterocycles by an overall quadruple C(sp$^2$)−H activation sequence (Scheme 110).[231] The catalytic system using $RhCl_3·H_2O$ (5 mol % in the presence of $Cu(OAc)_2·H_2O$ (2 equiv)) and $CF_3CO_2H$ (2 equiv) in toluene at 140 °C was optimal for this trans-

**Scheme 110. Two-Fold C(sp$^2$)−H/C−H Arylation via Rh−NHCs by You**



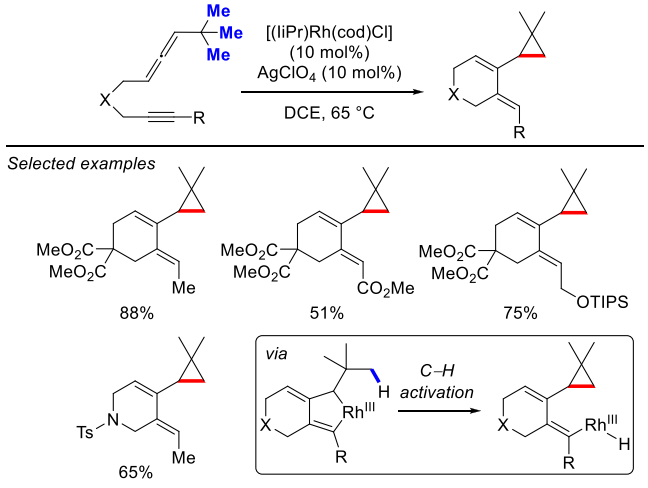

formation. The reaction showed broad substrate scope using benzofurans, thiophenes, furans, pyrroles, and indoles as the coupling partners. The mechanism was proposed to involve a Rh(III)−NHC heteroarene C−H activation via a CMD pathway, followed by a Rh(I)−Rh(III)−Rh(I) cycle with hydrogen evolution facilitated by $CF_3CO_2H$.

### 4.2. C(sp$^3$)−H Activation

Several examples of Rh−NHC-catalyzed C(sp$^3$)−H functionalization have been achieved by a number of research groups.

In 2012, Sato and co-workers reported the intramolecular C(sp$^3$)−H cyclopropanation of allenynes catalyzed by cationic $[Rh(NHC)(cod)]ClO_4$ complexes (Scheme 111).[232] The use

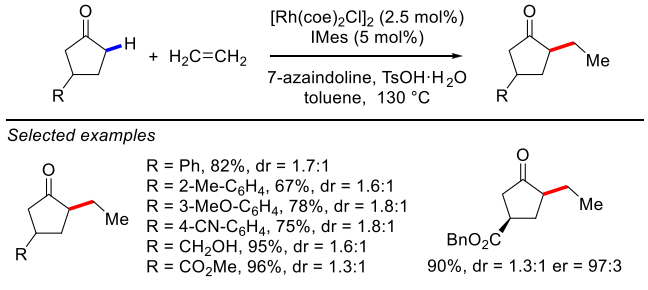
**Scheme 111. Rh−NHC-Catalyzed Intramolecular C(sp$^3$)−H Cyclopropanation by Sato**




of *N*-alkyl NHCs, such as IiPr or ICy, is crucial for this transformation as *N*-aromatic IMes resulted in inefficient cyclization, while bulky phosphines, such as *t*BuP$_3$, gave low conversion. Mechanistically, the reaction proceeds via C(sp$^3$)−H bond activation of the *tert*-butyl group by a cationic Rh(III) catalyst. On the basis of labeling studies, the authors proposed that the C(sp$^3$)−H bond activation is rate limiting. The reaction affords functionalized *gem*-dimethylcyclopropanes in high yields.

In 2014, Dong and co-workers reported *α*-ketone alkylation with olefins catalyzed by $[Rh(coe)_2Cl]_2$ (2.5 mol %) in the presence of IMes (5 mol %) and 7-azaindoline (25 mol %) (Scheme 112).[233] This strategy employs a secondary amine catalyst to generate a transient directing group in situ in a formal C(sp$^3$)−H activation via enamine intermediates. This

**Scheme 112. Rh−NHC-Catalyzed Ketone *α*-Alkylation by Dong**



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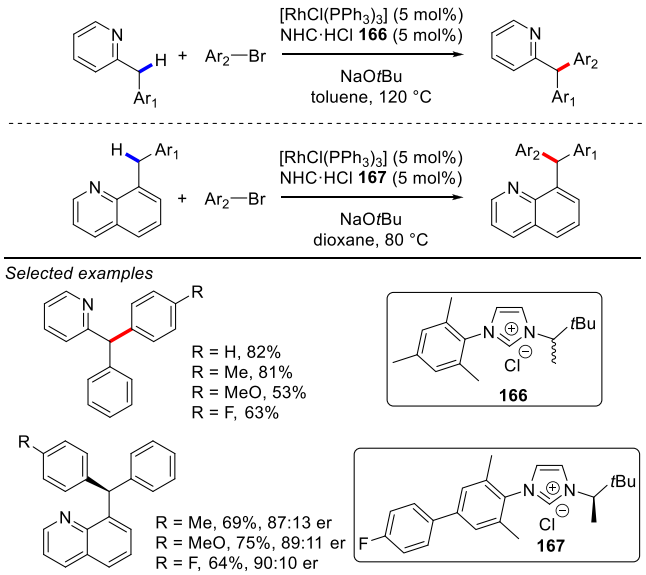
Chem. Rev. 2020, 120, 1981−2048

challenging transformation is broad in scope and could incorporate a large variety of functional groups, such as halogens, thioethers, carbonyls, and free alcohols. The reaction is fully regioselective for the less hindered $\alpha$-position. Furthermore, various cyclic, acylic, and aromatic ketones could be efficiently alkylated with simple terminal olefins, such as ethylene, propylene, or styrene. Mechanistic studies revealed that reductive elimination is the rate-determining step in the catalytic cycle.[234]

In an alternative approach to C($sp^3$)−H activation by Rh−NHC complexes, in 2016, Glorius and co-workers reported an enantioselective arylation of benzylic C($sp^3$)−H bonds with aryl bromides (Scheme 113).[235] Using [$RhCl(PPh_3)_3$] as a

**Scheme 113. Rh−NHC-Catalyzed Benzylic C($sp^3$)−H Arylation by Glorius**



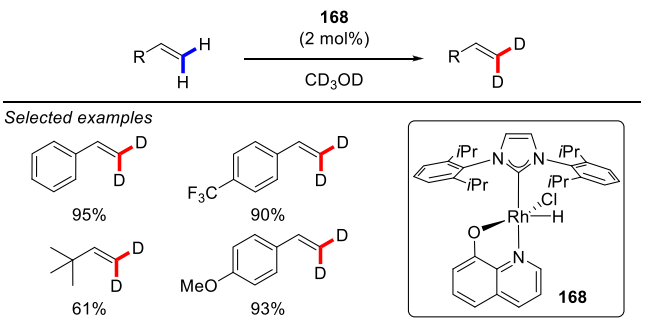

precatalyst and a chiral unsymmetrical NHC salt **167**, the reaction furnishes enantioenriched triarylmethanes in high yields and enantioselectivities. Mechanistic studies indicated that the Rh−NHC undergoes intramolecular C($sp^3$)−H activation of the *ortho*-methyl group, leading to a well-defined steric environment. This important study represents the first example of an efficient asymmetric induction by a chiral unsymmetrical NHC ligand.

### 4.3. C−H/C−D Exchange

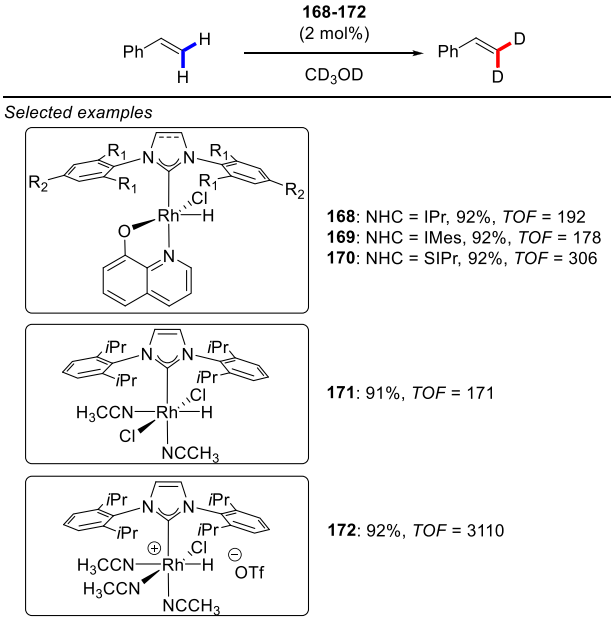
The direct C−H/C−D exchange reactions have also been demonstrated using Rh−NHC complexes. In 2011, Oro and co-workers reported selective C−H/C−D exchange at the $\beta$-position of olefins catalyzed by Rh(III)−NHC complex **168** featuring a chelating 8-quinolinate ligand (Scheme 114).[236] In this NHC scaffold, the bulky and strongly $\sigma$-donating IPr ligand controls the selective 2,1-olefin insertion. This deuteration reaction is performed in $CD_3OD$ and results in excellent selectivity for the $\beta$-deuteration in a wide range of aromatic and aliphatic olefins.

In 2014, the same group reported a detailed structure−activity study on the effect of Rh(III)−NHC catalysts on vinylic deuteration (Scheme 115).[237] In a series of Rh−NHC catalysts **168**−**172**, the bulky and electron-rich SIPr ancillary ligand provided the best reactivity in comparison with IPr and IMes. Furthermore, the cationic complex **172** catalyzed the

**Scheme 114. Rh−NHC-Catalyzed Vinylic C−H/C−D Exchange by Oro**




**Scheme 115. Rh−NHC-Catalyzed Vinylic Selective C−H/C−D Exchange by Oro**




deuteration reaction most efficiently, consistent with a more facile olefin coordination and insertion in this complex. On the other hand, removal of the chloride ligand led to catalytically inactive complexes.

## 5. IRIDIUM−NHC COMPLEXES

In general, the progress in Ir−NHC-catalyzed transformations has been slower than in using Pd−NHC and Rh−NHC complexes; however, Ir−NHC catalysts have gained significant attention in organic synthesis, and several useful reactions have been developed.[238−242] At present, the major applications of Ir−NHCs in C−H functionalization are in the following classes of transformations: (1) C($sp^2$)−H borylation; (2) C($sp^2$)−H silylation; (3) C−H/C−D exchange. In addition, the first example of a C($sp^3$)−H functionalization by Ir−NHCs has been established. These reactions together with the broad availability of Ir−NHC catalysts,[242] which along with Rh−NHCs are commonly used for the determination of the Tolman electronic parameter through [$Ir(NHC)(CO)_2Cl$] complexes,[41,42] provide a useful entry point to developing further C−H functionalizations catalyzed by Ir−NHC complexes.

In 2005, Nolan and co-workers reported an intramolecular C($sp^3$)−H activation within the [$Ir(ItBu)(coe)Cl]_2$ complex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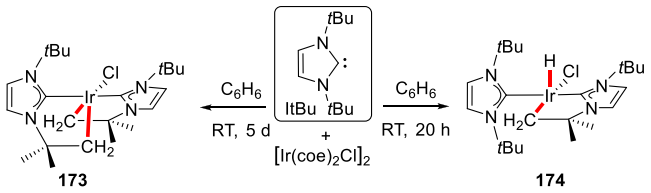
Chem. Rev. 2020, 120, 1981−2048

(Scheme 116).[243] It was found that when the bulky ItBu ligand is reacted with the Ir(I) precursor, $[Ir(coe)_2Cl]_2$, double C−H

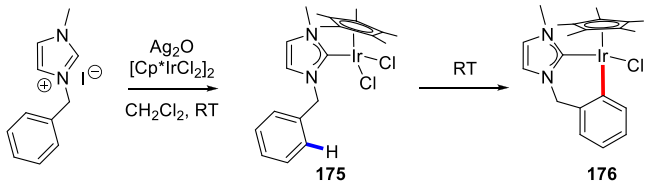
**Scheme 116. Time-Dependent C−H Activation in the $[(ItBu)Ir(coe)Cl]_2$ Complex by Nolan**




activation will take place after 5 days at room temperature in $C_6H_6$ to give **173**. The process could be stopped at the mono C−H activation by shortening the reaction time to 20 h, furnishing **174**. DFT calculations suggested that the electrophilic iridium center is stabilized by $\pi$-donation from the chelating NHC ligands. Activation of Si−H bonds with **173** has been published.[244]

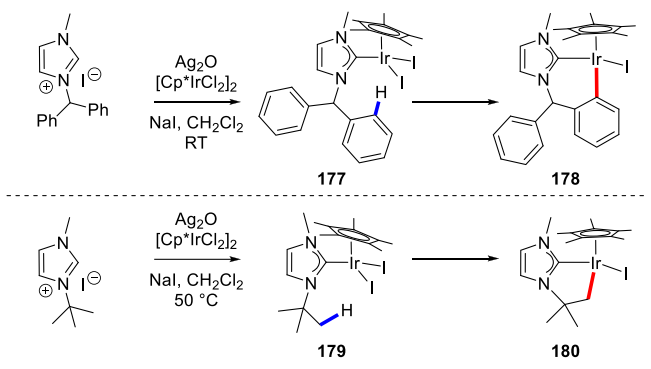
Independently, an intramolecular $C(sp^2)$−H activation within $[Ir(NHC)Cp^*Cl_2]$ complexes was observed by Peris and co-workers (Scheme 117).[245] During the attempted

**Scheme 117. Intramolecular C−H Activation in the $[(NHC)IrCp^*Cl_2]$ Complex by Peris**




synthesis of Ir−NHCs, they found that combining $[IrCp^*Cl_2]_2$ with 1-benzyl-3-methylimidazolium iodide in the presence of $Ag_2O$ afforded the expected Ir−NHC complex **175**, which underwent an intramolecular $C(sp^2)$−H activation of the ortho-aromatic hydrogen, resulting in cyclometalated complex **176**. This intramolecular C−H activation process was later extended to both intramolecular $C(sp^2)$−H and $C(sp^3)$−H activation by the Peris group (Scheme 118).[246] These reactions proceed efficiently through Ag−NHC intermediates in an in situ process using NHC salts in the presence of $Ag_2O$ and $[IrCp^*Cl_2]_2$. In both cases the C−H activation was promoted by the release of steric hindrance around the metal.

**Scheme 118. Intramolecular $C(sp^2)$−H and $C(sp^3)$−H Activation in $[(NHC)IrCp^*I_2]$ Complexes by Peris**

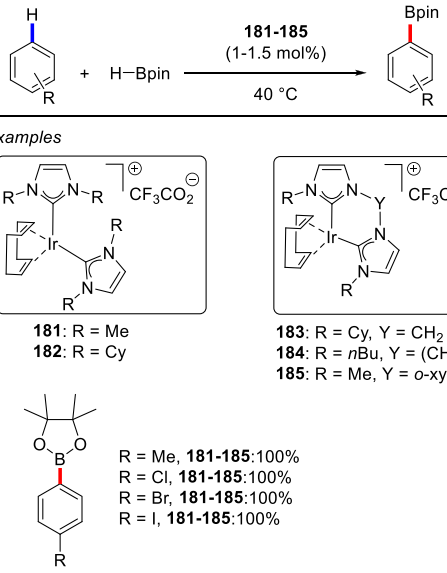



## 5.1. $C(sp^2)$−H Activation

Catalytic $C(sp^2)$−H borylation and silylation have been widely used in organic synthesis because these methods allow for the introduction of useful boron and silicon functionality directly onto simple arenes.[247]

In 2006, the Herrmann group reported the first example of a direct C−H borylation of arenes catalyzed by Ir−NHC complexes (Scheme 119).[248] The use of cationic Ir−bis-

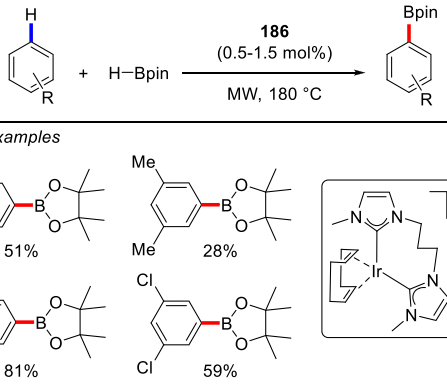
**Scheme 119. Ir−NHC-Catalyzed $C(sp^2)$−H Borylation by Herrmann**




NHC complexes **181**−**185** allowed for the $C(sp^2)$−H borylation using pinacolborane with good catalytic activity and high regioselectivity. Interestingly, even substrates containing sensitive halide groups could be functionalized in quantitative yields.

Subsequently, the same group disclosed an improved catalyst system for the $C(sp^2)$−H borylation of arenes using cationic Ir−NHC complex **186** under microwave irradiation conditions (Scheme 120).[249] The study of a counterion effect revealed that $CF_3CO_2$ was optimal for this C−H functionalization, while $BF_4$, $PF_6$, OTf, and I gave lower reactivity. Under these conditions, a variety of disubstituted benzenes could be

**Scheme 120. Ir−NHC-Catalyzed $C(sp^2)$−H Borylation of Disubstituted Benzenes by Herrmann**





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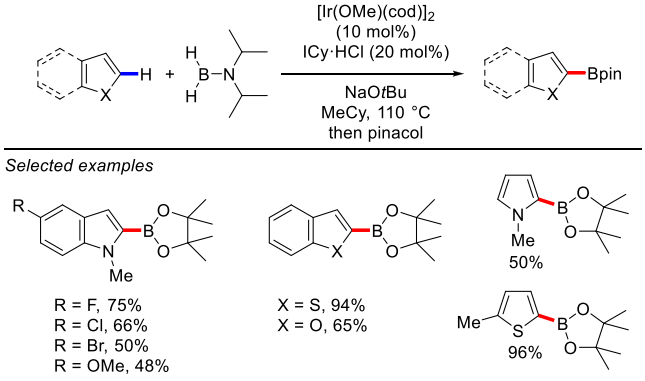
Chem. Rev. 2020, 120, 1981−2048

successfully converted into boronic esters with high regioselectivity.

In 2016, Chatani and co-workers reported an Ir−NHC system for the C(sp$^2$)−H borylation of heterocycles and arenes using ICy as the NHC ligand, [Ir(OMe)(cod)]$_2$ as the Ir precursor, and diisopropylaminoborane as the boron source (Scheme 121).[250] Optimization studies using 1-methylindole

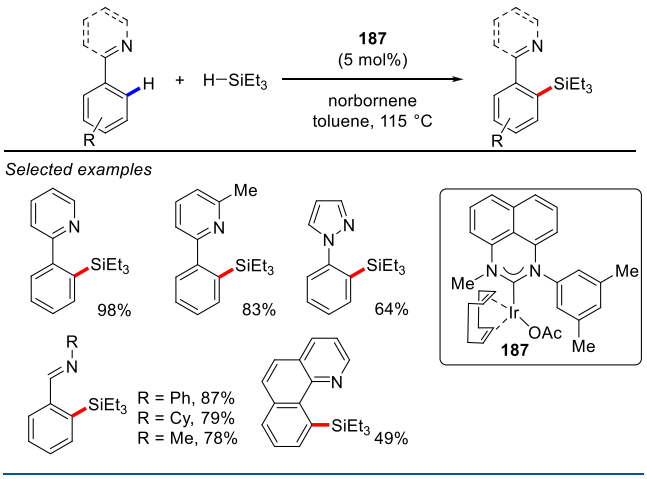
**Scheme 121. Ir−NHC-Catalyzed C(sp$^2$)−H Borylation of Heterocycles by Chatani**




demonstrated that other NHC ligands, including IPr, IMes, and ItBu, as well as phosphines, including $PPh_3$, $PCy_3$, dppe, Xantphos, and Xphos, were either ineffective or much less efficient. The developed reaction was compatible with several sensitive functional groups, providing the borylated products in good to high yields.

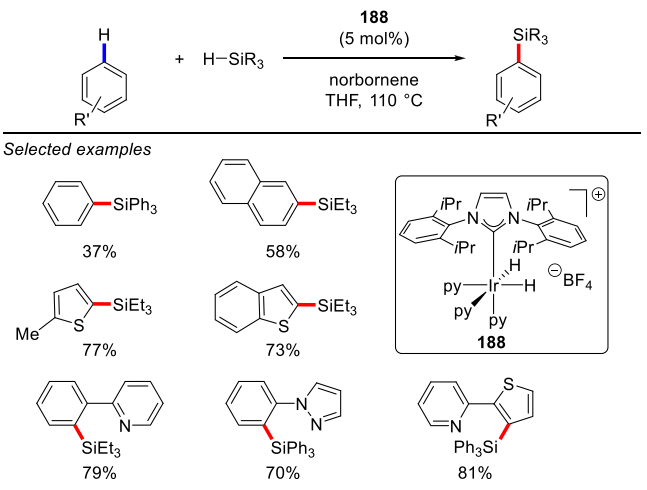
Direct C(sp$^2$)−H silylation reactions have also been achieved using Ir(I)−NHC catalysts (Schemes 122 and

**Scheme 122. Ir−NHC-Catalyzed Pyridine-Directed C(sp$^2$)−H Silylation by Mashima**




123). In 2013, Mashima and co-workers reported the direct dehydrogenative C(sp$^2$)−H silylation of 2-arylpyridines and imines with triethylsilane in the presence of norbornene as the hydrogen acceptor using a permidine-derived Ir−NHC catalyst **187** (Scheme 122).[251] Interestingly, the *N*-3,5-xylyl ring undergoes intramolecular *ortho*-C−H activation leading to a cyclometalated Ir−NHC catalyst, which increases steric hindrance around the metal and acts as a hydride acceptor. This methodology allows for the synthesis of a variety of ortho-silylated nitrogen heterocycles in good to high yields.

**Scheme 123. Ir−NHC-Catalyzed C(sp$^2$)−H Silylation of Arenes by Oro**

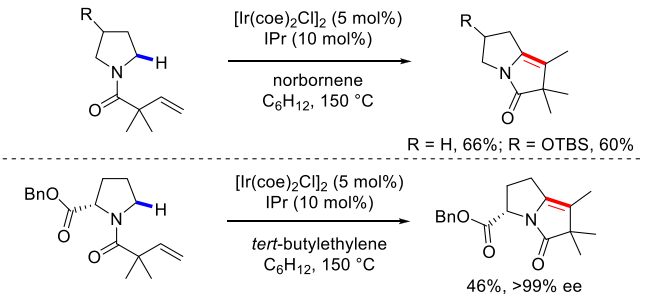



In 2017, Oro and co-workers reported dehydrogenative C(sp$^2$)−H silylation of simple arenes and 2-arylpyridines using well-defined Ir(III)−NHC catalyst **188** in the presence of norbornene as the hydrogen acceptor (Scheme 123).[252] In this catalyst scaffold, the use of labile pyridine ligands and the readily removable hydrides facilitates substrate coordination. The reaction provides access to aryl and heteroarylsilanes with good generality in high yields. Furthermore, this methodology is compatible with various silanes, including $Et_3SiH$, $Ph_2MeSiH$, $PhMe_2SiH$, $Ph_3SiH$, and $(EtO)_3SiH$, and could also be applied to the direct C−H double arylation of bishydrosilanes (not shown).

### 5.2. C(sp$^3$)−H Activation

Only one example of the direct C(sp$^3$)−H functionalization using Ir−NHC catalysts has been reported. In 2004, Sames and co-workers disclosed a catalyst system based on [Ir(cod)$_2$Cl]$_2$ and IPr in the presence of norbornene as the hydrogen acceptor for the intramolecular C(sp$^3$)−H alkylation at the $\alpha$-position of pyrrolidines (Scheme 124).[253] Interest-

**Scheme 124. Ir−NHC-Catalyzed Intramolecular C(sp$^3$)−H Activation/Cyclization by Sames**




ingly, $PCy_3$ was significantly less efficient in promoting this reaction. While only few examples were reported, the reaction was highly regioselective for the $\alpha$-C(sp$^3$)−H activation and could preserve the absolute stereochemistry of the starting pyrrolidine.

### 5.3. C−H/C−D Exchange

Major contributions to the direct C−H/C−D exchange catalyzed by Ir−NHCs have been made by Kerr and co-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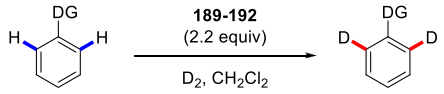
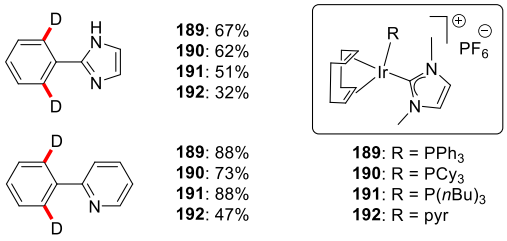
Chem. Rev. 2020, 120, 1981−2048

workers. In 2007, Powell and co-workers reported the direct C−H/C−D exchange in several aromatic substrates using Ir−NHC complexes **189**−**192** based on the IMe ligand (Scheme 125).[254] Compared with the $PCy_3$-based Crabtree catalyst, $[Ir(PCy_3)(py)cod]PF_6$, these novel Ir−NHCs showed promising reactivity; however, their activity was quite modest. Subsequently, a series of practical C−H/C−D exchange reactions catalyzed by Ir−NHC complexes have been developed. In 2008, the Kerr group reported a series of C−H/C−D exchange reactions of aromatic substrates catalyzed by Ir−NHC complexes **193**−**195**, featuring a bulky IMes ligand (Scheme 126).[255] In particular, they found that these metallacycles and gave lower levels of D-incorporation than cationic **193**.

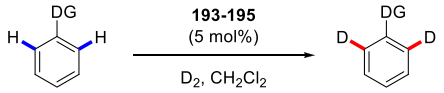
**Scheme 125. Ir−NHC-Mediated C−H/C−D Exchange by Powell**



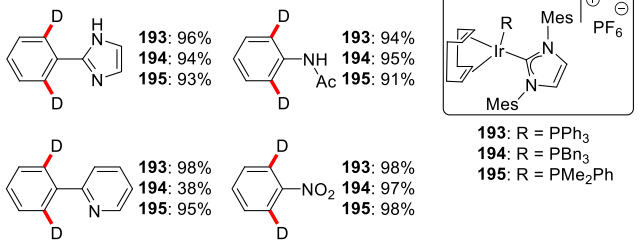

*Selected examples*




**Scheme 126. Ir−NHC-Catalyzed C−H/C−D Exchange by Kerr**




*Selected examples*

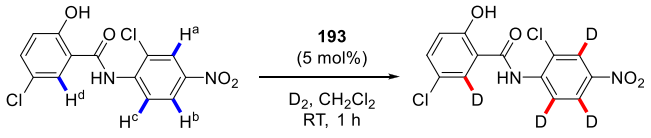



mixed NHC−phosphine complexes show significantly higher catalytic activity than Crabtree's catalyst, which has been commonly used as the standard for C−H/C−D exchange reactions.

A practical advantage of Ir−NHC complex **193** featuring a $PPh_3$/IMes combination was demonstrated in the high and regioselective C−H/C−D exchange of Niclosamide, an anilide-based antiparasite drug (Scheme 127).[256] In contrast, a lower incorporation (less than 15%) was observed using Crabtree's catalyst.

Kerr and co-workers reported a further variation in the catalyst design by replacing the phosphine ligand by chloride, resulting in neutral Ir−NHC complexes such as **196** (Scheme 128).[257] These [Ir(NHC)(cod)Cl] complexes served as effective C−H/C−D exchange catalysts for labeling of simple arenes; however, their reactivity was limited to 5-membered

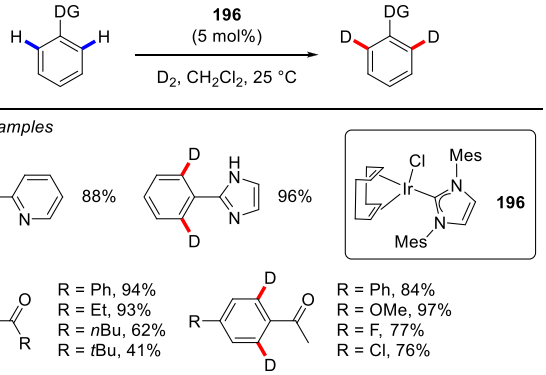
**Scheme 127. Ir−NHC-Catalyzed C−H/C−D Exchange in Niclosamide by Kerr**




*Niclosamide*

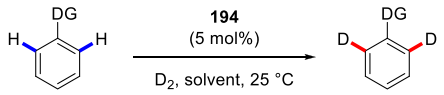
*D*% **a**: 65%, **b**:55%
**c**: 52%, **d**:62%

**Scheme 128. C−H/C−D Exchange Catalyzed by Neutral Ir−NHC Complexes by Kerr**

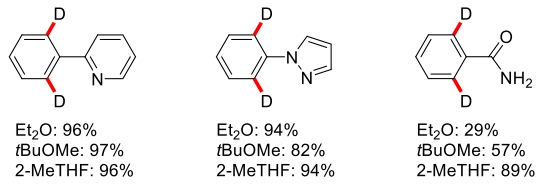



The Kerr group demonstrated that this C−H/C−D exchange methodology is also compatible with alternative solvents under mild conditions (Scheme 129).[258] Excellent levels of deuterium incorporation were observed in industrially acceptable solvents, such as *t*BuOMe and 2-MeTHF, making this Ir−NHC catalysis potentially applicable in industrial settings. Simultaneously, the Kerr group reported a facile synthesis of cationic Ir−NHC complexes $[Ir(IMes)(cod)(PR_3)]PF_6$ ($PR_3$ = $PPh_3$, $PBn_3$, $PMe_2Ph$, $PMePh_2$, $P(OiPr)_3$) (not shown).[259] Interestingly, all complexes were found to be catalytically active, allowing for deuterium exchange in good to high yields. The authors also showed that these well-defined Ir−NHC complexes are air- and moisture-stable and retain their activity over prolonged storage.

**Scheme 129. Ir−NHC-Catalyzed C−H/C−D Exchange in Benign Solvents by Kerr**



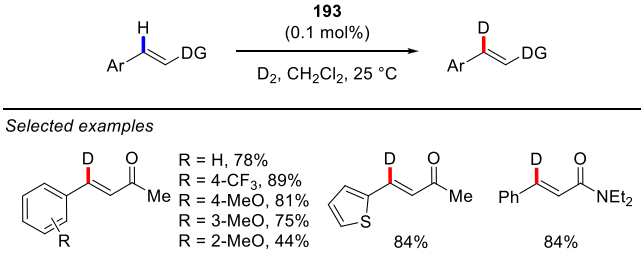

*Selected examples*




In 2014, Kerr and co-workers reported the first example of regioselective olefinic $C(sp^2)$−H/C−D exchange catalyzed by Ir−NHCs (Scheme 130).[260] Impressively, the use of $[Ir(IMes)(cod)(PPh_3)]PF_6$ catalyst **193** permitted *β*-regioselective C−H/C−D exchange of a range of Michael acceptors at


https://dx.doi.org/10.1021/acs.chemrev.9b00634
Chem. Rev. 2020, 120, 1981−2048

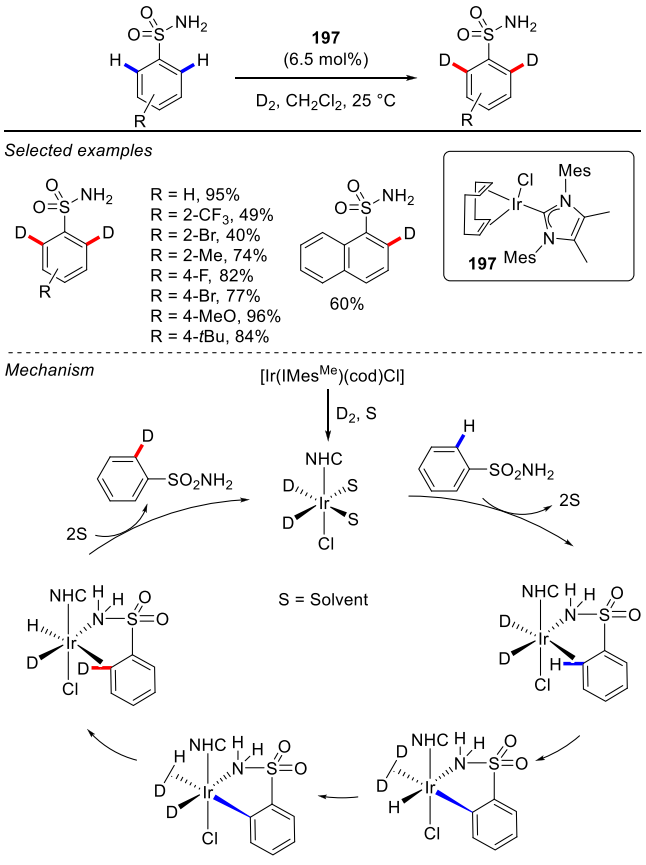
**Scheme 130. Ir–NHC-Catalyzed Vinylic C–H/C–D Exchange by Kerr**




0.10 mol % catalyst loading at room temperature. Aromatic C($sp^2$)–H bonds remain intact in this C–H/C–D exchange.

In 2015, Kerr and co-workers further expanded their Ir–NHC labeling methodology to the selective ortho-deuteration of primary benzenesulfonamides (Scheme 131).[261] This

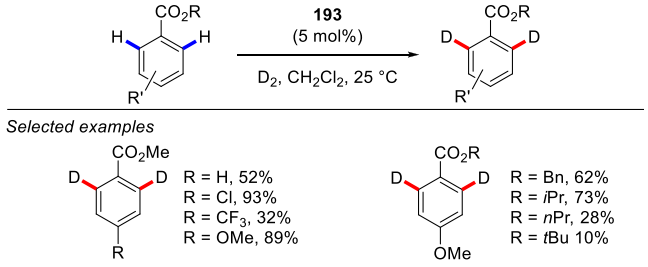
**Scheme 131. Ir–NHC-Catalyzed C–H/C–D Exchange in Aryl Sulfonamides by Kerr**




reaction was found to be most effectively catalyzed by [Ir($IMes^{Me}$)(cod)Cl] complex **197**. The $IMes^{Me}$ scaffold provided a higher degree of deuterium incorporation than IXyl, IMes, SIMes, and IPr, while the incorporation using ICy and IBn was negligible. The mechanism was proposed to involve activation of the [Ir($IMes^{Me}$)(cod)Cl] precatalyst via hydrogenative loss of cyclooctadiene to generate the active dideuteride complex [Ir($IMes^{Me}$)($D_2$)($S_2$)Cl], which is stabilized by solvent molecules. Substrate coordination and oxidative addition with a concomitant reductive elimination of deuterides afford the Ir(III) intermediate. Hydride fluxionality and the second oxidative addition/reductive elimination give the C–H/C–D exchange product and regenerate the active Ir(III) catalyst. This transformation was compatible with a broad range of functional groups to access biologically relevant deuterated sulfonamides.

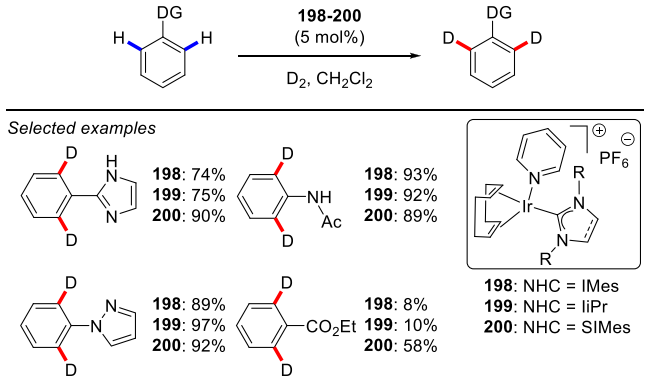
Similarly, the Kerr group conducted a comprehensive evaluation of their cationic [Ir(IMes)(cod)($PR_3$)]$PF_6$ complexes **193–195** in the C–H/C–D exchange of pharmaceutically relevant heterocycles, including arylpyrimidines, imidazoles, oxazoles, pyrazoles, isoxazoles, and thiazoles (not shown).[262] High levels of deuterium incorporation in moderate to excellent yields were observed in all examples examined. As a further extension of their studies, they reported the direct C–H/C–D exchange of aromatic esters using the cationic [Ir(IMes)(cod)(PPh)]$PF_6$ catalyst **193** (Scheme 132).[263] This reaction tolerated various alkyl benzoates, accommodating several sensitive functional groups.

**Scheme 132. Ir–NHC-Catalyzed C–H/C–D Exchange in Aryl Esters by Kerr**




Subsequently, the Kerr group reported a new class of Ir–NHC complexes **198–200** featuring a labile pyridine ligand (Scheme 133).[264] In this family of [Ir(NHC)(cod)(py)]$PF_6$

**Scheme 133. C–H/C–D Exchange Catalyzed by Cationic [(NHC)Ir(cod)(py)] Complexes by Kerr**

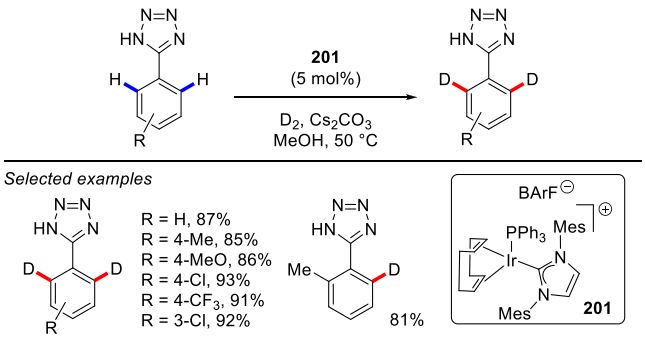



complexes, the SIMes-supported complex **200** was the most reactive. Along the same lines, they demonstrated that the more cationic Ir–NHC complexes bearing BArF counterion (cf. $PF_6$, BArF = tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate) are more reactive in promoting the C–H/C–D exchange of aromatic ketones, esters, amides, and nitrobenzenes (not shown).[265]

In 2016, the Kerr group exploited the effect of a weakly coordinating BArF counterion in the selective ortho-directed C–H/C–D exchange of N-unprotected tetrazoles under basic conditions (Scheme 134).[266] In this reaction, the cationic catalyst **201** proved to be significantly more reactive than its $PF_6$ counterpart **193**. Mechanistic investigations indicated that


https://dx.doi.org/10.1021/acs.chemrev.9b00634
Chem. Rev. 2020, 120, 1981–2048

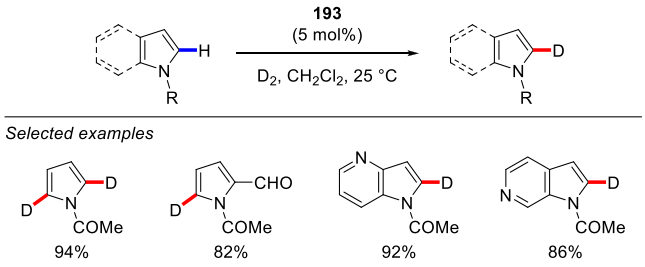
**Scheme 134. Ir–NHC-Catalyzed C–H/C–D Exchange in Aryl Tetrazoles under Basic Conditions by Kerr**




the C–H activation step involves a base-assisted CMD process. The utility of this reaction was exemplified in the direct C–H labeling of Valsartan, a top-selling angiotensin receptor blocker.

Following the C–H/C–D exchange strategy by Ir–NHC catalysis, in 2017, Kerr and co-workers disclosed the C2-selective deuteration of indoles and pyrroles directed by *N*-carbonyl groups (Scheme 135).[267] Optimization studies

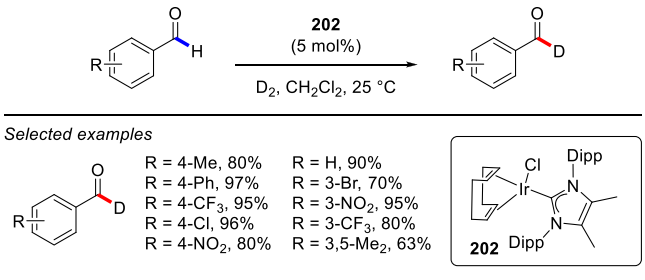
**Scheme 135. Ir–NHC-Catalyzed C–H/C–D Exchange in N-Heterocycles by Kerr**




revealed that the combination of their [Ir(IMes)(cod)($PPh_3$)]-$PF_6$ complex with the *N*-COMe directing group provided optimal results, while the use of Crabtree's catalyst was much less efficient. This method represents a practical approach to labeling of indoles and pyrroles at the C2 position, including complex pharmaceuticals, such as Sumatriptan, a best-selling antimigraine drug.

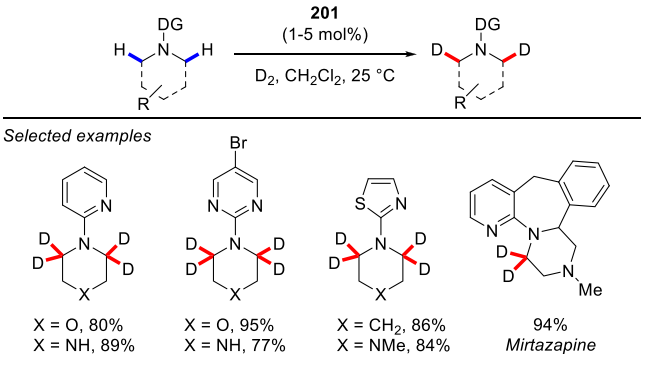
In an alternative process catalyzed by Ir–NHCs, the direct formyl C–H/C–D exchange was accomplished by the Kerr group (Scheme 136).[268] They found that using the sterically hindered [Ir($IPr^{Me}$)(cod)Cl] complex **202** allowed for the selective formyl-deuterium labeling of aromatic aldehydes. Notably, under the developed conditions, aromatic C–H/C–D exchange was not observed. The $IPr^{Me}$-based catalyst showed slightly higher reactivity than its $IMes^{Me}$ counterpart. This methodology was shown to be compatible with a broad range of functional groups (halides, nitro, hydroxyl, benzyl), providing deuterated aldehydes in good to excellent yields.

**Scheme 136. Ir–NHC-Catalyzed Formyl C–H/C–D Exchange in Aldehydes by Kerr**




More recently, Kerr and co-workers reported the direct alkyl C($sp^3$)–H/C($sp^3$)–D exchange reaction of aliphatic amines at the $\alpha$-position catalyzed by the cationic [Ir(IMes)(cod)-($PPh_3$)]BArF complex **201** (Scheme 137).[269] It was observed

**Scheme 137. Ir–NHC-Catalyzed C($sp^3$)–H/C–D Exchange in Amines by Kerr**




during the optimization studies that the cationic [Ir(IMes)-(cod)($PPh_3$)]$PF_6$ catalyst **193** gives lower deuterium incorporation, while the neutral [Ir(IMes)(cod)Cl]$PF_6$ complex **196** was completely inefficient. This reaction allows for $\alpha$-deuterium exchange in a broad range of biorelevant amines, including pharmaceuticals, such as an antidepressant, Mirtazapine, highlighting the utility of Ir–NHC complexes in various types of C–H/C–D reactions.[270]

## 6. RUTHENIUM–NHC COMPLEXES

Ru–NHC complexes are famous for their extraordinary activity in the field of olefin metathesis.[271] Furthermore, several classes of robust and stable Ru–NHC complexes have been exploited as catalysts in hydrogenation, hydrosilylation, and cyclopropanation reactions.[272,273] Ru–NHCs have also been utilized as highly effective catalysts in C–H functionalization,[71] in particular to promote the following types of transformations: (1) C($sp^2$)–H arylations; (2) redox-neutral C($sp^2$)–H annulations; and (3) oxidative C($sp^2$)–H annulations.

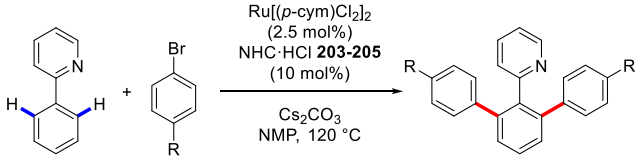
### 6.1. C($sp^2$)–H Activation

In 2008, Dixneuf and co-workers reported C($sp^2$)–H arylation of 2-arylpyridines with aryl bromides in the presence of Ru[(*p*-cym)$Cl_2$]$_2$ and tetrahydropyrimidinylidenes **203–205** (Scheme 138).[274] They found that this Ru(II)–NHC catalytic system promotes the diselective C–H arylation of 2-arylpyridines in good yields. The observed reactivity was in the following order, **203** ≈ **204** > **205**, which suggested that electron-rich N-substituents render this C–H arylation more efficient. A mechanism involving proton abstraction by a cooperative action of the Ru–NHC catalyst and carbonate base was proposed.

Subsequently, Özdemir and co-workers synthesized a series of well-defined, air- and moisture-stable Ru–NHC complexes **206–209** based on the imidazolidinylidene scaffold and evaluated their activity in ($sp^2$)–H arylation of 2-arylpyridines


https://dx.doi.org/10.1021/acs.chemrev.9b00634
Chem. Rev. 2020, 120, 1981–2048

**Scheme 138. Ru–NHC-Catalyzed Direct C($sp^2$)–H/C–Br Arylation by Dixneuf**

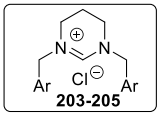



*Selected examples*

R = CN, **203**: 75%, **204**: 77%, **205**: 56%

R = OMe, **203**: 84%, **204**: 87%, **205**: 60%

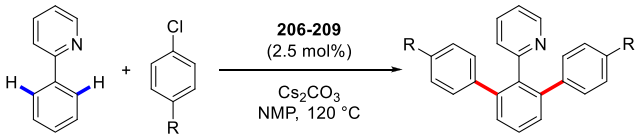
R = Me, **203**: 87%, **204**: 91%, **205**: 80%



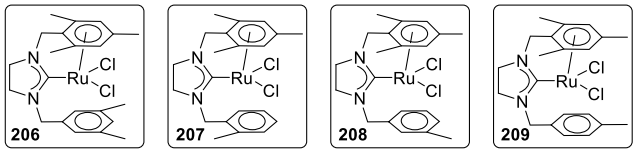

**203**: Ar = 3,4,5-$OMe_3$-$C_6H_2$
**204**: Ar = 2,4,6-$OMe_3$-$C_6H_2$
**205**: Ar = 2,4,6-$Me_3$-$C_6H_2$

with aryl chlorides (Scheme 139).[275] They found that these [Ru(NHC)$Cl_2$] complexes are highly active in the diselective

**Scheme 139. Ru–NHC-Catalyzed Direct C($sp^2$)–H/C–Cl Arylation by Özdemir**




*Selected examples*




R = COMe, **206**: 76%, **207**: 71%, **208**: 73%, **209**: 82%
R = OMe, **206**: 88%, **207**: 96%, **208**: 95%, **209**: 98%
R = Me, **206**: 98%, **207**: 94%, **208**: 97%, **209**: 98%

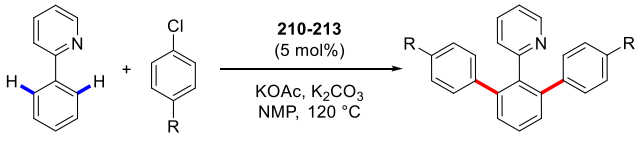
arylation of 2-arylpyridines. Catalyst comparison studies demonstrated that precatalyst **209** containing the *N*-4-methylbenzyl substituent was the most active in this series.

In 2009, Özdemir, Bruneau, and co-workers reported that *ortho*-xylyl-bridged [Ru(NHC)$_2$($PPh_3$)$Cl_2$] complexes **210–213** catalyze C($sp^2$)–H arylation of 2-arylpyridines with aryl chlorides using a combination of KOAc (5 mol %) and $K_2CO_3$ (3 equiv) in NMP at 120 °C (Scheme 140).[276] Excellent conversion was observed with all complexes, while complex **213** featuring the *N*-pentamethylbenzyl group gave the highest di-/monoarylation selectivity.

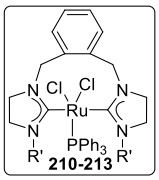
The Özdemir group also disclosed the reactivity of a slightly modified series of [Ru(NHC)$Cl_2$] complexes **214–217** based on the imidazolidinylidene ring (Scheme 141).[277] These complexes contain modified *N*-benzyl groups and showed high efficiency in the diselective C($sp^2$)–H arylation of 2-arylpyridines with aryl chlorides in the presence of $Cs_2CO_3$ (3 equiv) in NMP at 120 °C.

In 2010, the same group reported the synthesis of related benzimidazolylidene [Ru(NHC)$Cl_2$] complexes and demonstrated their reactivity in the diselective C($sp^2$)–H arylation of 2-arylpyridines with more reactive aryl bromides (not shown).[278] More recently, Özdemir and co-workers reported the monoselective C($sp^2$)–H arylation of 2-arylpyridines with aryl chlorides using benzimidazolylidene [Ru(NHC)$Cl_2$] complexes **218–221** under aqueous conditions (Scheme 142).[279]

**Scheme 140. Ru–NHC Direct Catalyzed C($sp^2$)–H/C–Cl Arylation by Bruneau**



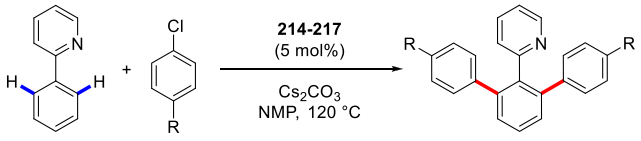

*Selected examples*



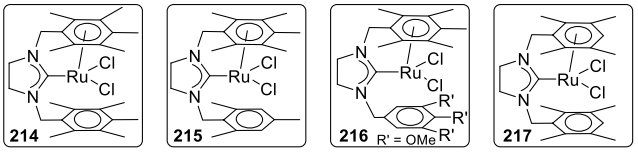

**210**: R' = $CH_2Mes$
**211**: R' = $(CH_2)_3CH_3$
**212**: R' = $CH_2$-2,3,5,6-$(CH_3)_5$-$C_6H$
**213**: R' = $CH_2$-$(CH_3)_5$-$C_6$

R = H, **210**: 88%, **211**: 73%, **212**: 91%, **213**: 95%
R = OMe, **210**: 90%, **211**: 69%, **212**: 89%, **213**: 92%

**Scheme 141. Ru–NHC-Catalyzed Direct C($sp^2$)–H/C–Cl Arylation by Özdemir**

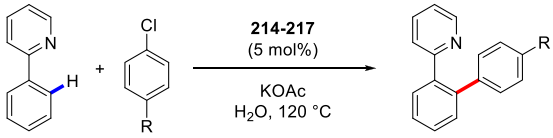



*Selected examples*

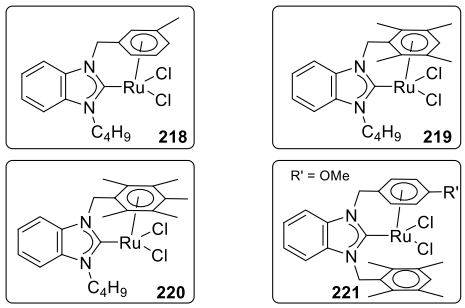



R = COMe, **214**: 75%, **215**: 70%, **216**: 83%, **217**: 88%
R = OMe, **214**: 63%, **215**: 69%, **216**: 81%, **217**: 87%

**Scheme 142. Ru–NHC-Catalyzed Monoselective C($sp^2$)–H/C–Cl Arylation by Özdemir**




*Selected examples*




R = H, **218**: 100%, **219**: 100%, **220**: 64%, **221**: 74%
R = CN, **218**: 58%, **219**: 50%, **220**: 77%, **221**: 81%

In 2010, Peris and co-workers reported [Ru(IBu)(*p*-cym)$Cl_2$] **222** as a catalyst for the direct C($sp^2$)–H arylation of 2-arylpyridines with aryl bromides and aryl chlorides (Scheme 143).[280] This catalyst together with its *N*-Me and *N*-*n*Oct analogues showed high activity for the diarylation of 2-phenylpyridine and *N*-phenylpyrazole. In addition, **222** was also an effective catalyst for the nitrogen-directed C($sp^2$)–H deuteration in $CD_3OD$. In 2014, the Peris group reported a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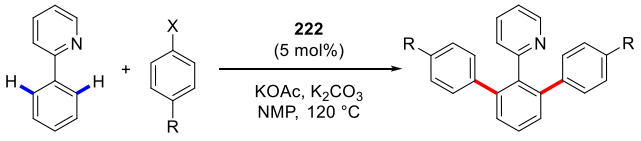
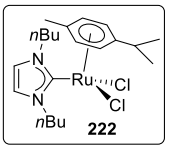
Chem. Rev. 2020, 120, 1981–2048

**Scheme 143. Ru–NHC-Catalyzed Direct C($sp^2$)–H/C–X Arylation by Peris**



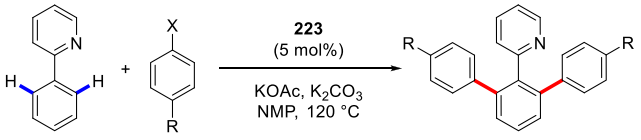

*Selected examples*

X = Cl, R = H, 92%
X = Br, R = H, 90%
X = Cl, R = Me, 90%
X = Cl, R = OMe, 60%
X = Br, R = *n*Bu, 91%



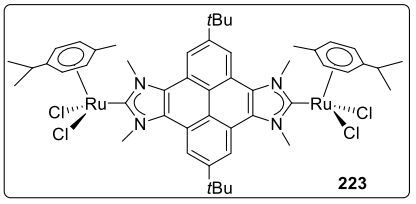

pyrene-based bis-NHC–Ru complex **223** and demonstrated its high reactivity in the diselective C($sp^2$)–H arylation and alkylation of 2-arylpyridines (Scheme 144).[281] Interestingly, **223** was more reactive than $[Ru[(p\text{-cym})Cl_2]_2$ in the sequential alkylation/arylation of 2-arylpyridines to give unsymmetrical 2-arylpyridines in good yields.

**Scheme 144. Ru–NHC-Catalyzed Direct C($sp^2$)–H/C–X Arylation Using Pyrene Ligands by Peris**




*Selected examples*

X = Cl, R = H, 98%
X = Br, R = H, 98%
X = Cl, R = Me, 99%
X = Cl, R = OMe, 99%
X = Br, R = *n*Bu, 99%

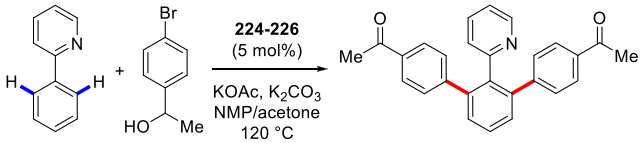



Around the same time, Peris and co-workers also reported a heterobimetallic Ru(II)–Ir(III) complex based on triazolediylidene scaffold **224** and its homobimetallic Ru(II)–Ru(II) analogue **225** (Scheme 145).[282] These complexes were applied to the tandem C($sp^2$)–H arylation/oxidation of 2-arylpyridines. Both complexes showed similar reactivity to the imidazolylidene Ru–NHC complex **222**, while the reactivity of the analogous Ir–NHC **226** was not reported.

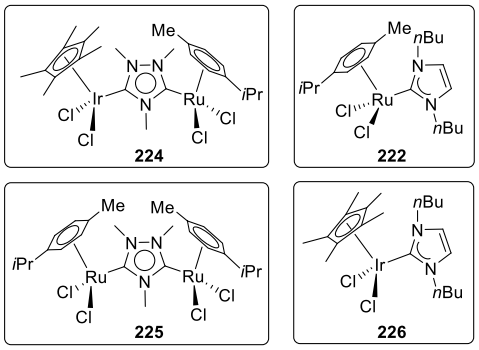
In 2016, the Ong group reported a Ru–NHC system for the C1-selective C($sp^2$)–H benzylation and alkylation of isoquinoline (Scheme 146).[283] The reaction is carried out in the presence of $[Ru(p\text{-cym})Cl_2]_2$ (2.5 mol %), IPr (10 mol %), $AdCO_2H$ (30 mol %), and $K_2CO_3$, leading to 1-substituted isoquinoline products in moderate to good yields. The alkylation mode could be switched from C($sp^2$)–H alkylation to oxidative dearomatization/N-alkylation by adding $H_2O$. The proposed mechanism involves C($sp^2$)–H activation by the CMD pathway, oxidative addition of an alkyl halide, and reductive elimination from the Ru(IV)–NHC complex.

In 2013, Zhao and co-workers reported an impressive example of Ru–NHC-catalyzed formal [3 + 2] annulation between N–H ketimines and alkynes via ortho-C($sp^2$)–H activation at room temperature (Scheme 147).[284] The key to this reaction is the use of NHCs as ancillary ligands to Ru as no reaction is observed using phosphines or in the absence of NHC. IPr is more effective than IMes in hexanes, while a

**Scheme 145. Ru–NHC-Catalyzed Direct C($sp^2$)–H/C–X Arylation/Oxidation Using Bimetallic Complexes by Peris**

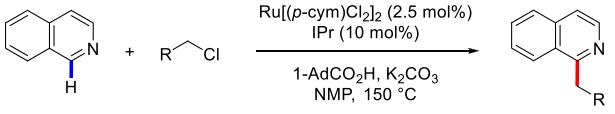



*Selected examples*

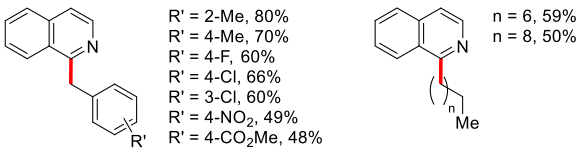



**224**: 76%, **225**: 98%, **222**: 90%

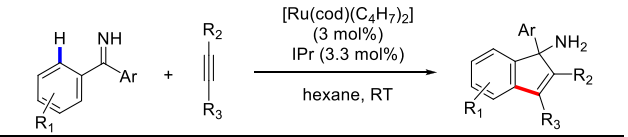
**Scheme 146. Ru–NHC-Catalyzed Direct C($sp^2$)–H/C–Cl Benzylation and Alkylation of Isoquinolione by Ong**




*Selected examples*




**Scheme 147. Ru–NHC-Catalyzed Imine-Directed C($sp^2$)–H Activation/Carbocyclization by Zhao**



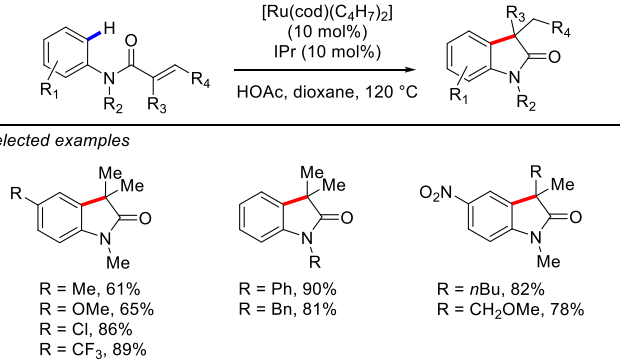

*Selected examples*


switch in the reaction efficiency was observed in toluene. SIPr and SIMes were both ineffective. This mild protocol allows for the construction of complex indenamines with excellent functional group tolerance.

In 2018, the same group reported an intramolecular amide-directed C($sp^2$)–H hydroarylation with alkenes catalyzed by a similar Ru–NHC system in the presence of acetic acid (2 equiv) in dioxane at 120 °C (Scheme 148).[285] Acetic acid likely acts as a proton source in this hydroarylation. The reaction proceeds with excellent 5-exo-trig selectivity directed


https://dx.doi.org/10.1021/acs.chemrev.9b00634
Chem. Rev. 2020, 120, 1981–2048

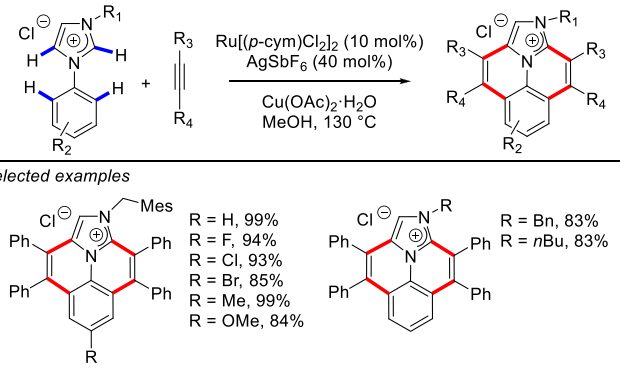
**Scheme 148. Ru−NHC-Catalyzed Amide-Directed C(sp²)−H Activation/Hydroarylation by Zhao**




by the amide group. The utility of this reaction was showcased in a rapid synthesis of a progesterone receptor antagonist featuring the oxindole ring.

In 2015, Wang and co-workers reported a Ru-catalyzed 2-fold oxidative C(sp²)−H annulation that proceeds via Ru−NHCs (Scheme 149).[286] This reaction is formally analogous to

**Scheme 149. Oxidative Two-Fold C(sp²)−H Annulation via Ru−NHCs by Wang**

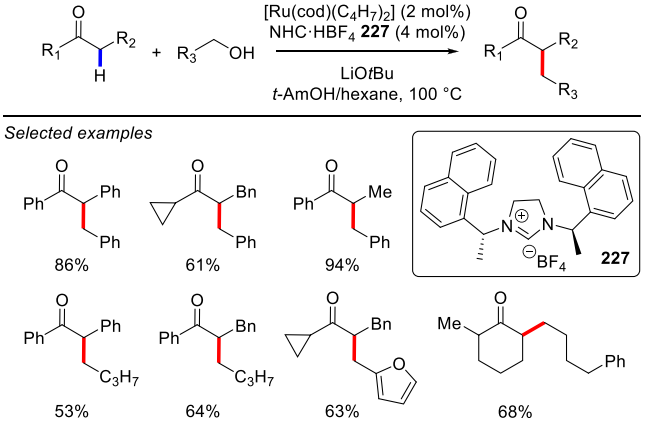



Rh-catalyzed annulations reported by Choudhury (cf. Schemes 102−110). The reaction of *N*-arylimidazolium salts with alkynes in the presence of $[Ru(p\text{-cym})Cl_2]_2$, $AgSbF_6$, and $Cu(OAc)_2$ as a terminal oxidant gave a variety of benzoimidazoquinolizinium salts in good to excellent yields through the intermediacy of normal and abnormal Ru−NHCs. The monoannulated products resulting from the cyclization of the more reactive C2−NHC could be isolated by reducing the catalyst loading. Several related reactions have been reported.[287,288]

### 6.2. C(sp³)−H Activation

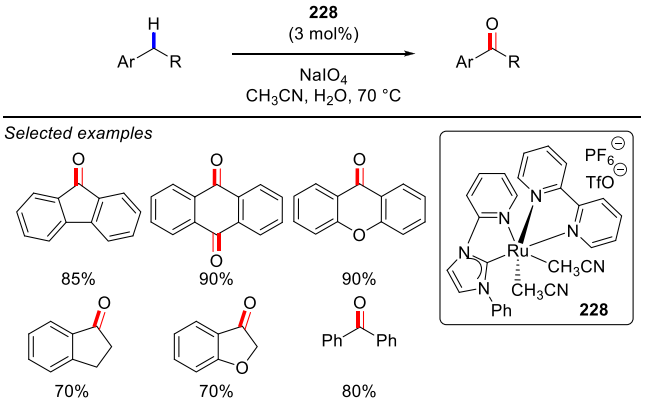
Ru−NHC-catalyzed α-alkylation of ketones was achieved by Glorius and co-workers through a borrowing hydrogen mechanism (Scheme 150).[289] This formal C(sp³)−H activation is catalyzed by a bis-NHC−Ru complex prepared in situ from the SINpEt precursor **227**, identified earlier for arene hydrogenations, while only traces of the alkylation product were observed using ICy. This protocol demonstrated high selectivity for methylene C(sp³)−H bond activation, allowing us to prepare a range of α-branched ketones, including a one-step synthesis of Donepezil, a top-selling anti-Alzeimer's drug.

**Scheme 150. Ru−NHC-Catalyzed Ketone α-Alkylation by Glorius**




In 2017, Choudhury and co-workers reported a mixed NHC/bipyridine Ru(II) complex **228** for the selective oxidation of benzylic C(sp³)−H bonds to ketones (Scheme 151).[290] The reaction was conducted using $NaIO_4$ as a mild

**Scheme 151. Ru−NHC-Catalyzed Benzylic C(sp³)−H Oxidation by Choudhury**




oxidant. The NHC ligand was found to be stable under the oxidative conditions. No reaction was observed using $[Ru(p\text{-cym})Cl_2]_2$ or $RuCl_3$ instead of **228**. In addition, several examples of an intramolecular C(sp³)−H bond activation within Ru−NHC complexes have been reported.[291−293]

## 7. IRON−NHC COMPLEXES

Due to its broad availability as the fourth most abundant element in the Earth's crust and very low toxicity, iron is an ideal metal for homogeneous catalysis.[294−296] However, despite recent important advances, the utilization of iron in homogeneous catalysis still lags behind precious metals and other earth-abundant 3d transition metals.

The first example of an Fe−NHC complex was reported quite early, in 1969, by Öfele,[297] while the first catalytic application was reported in 2000 by Grubbs and co-workers.[298] Well-defined and in situ generated Fe−NHC complexes have been utilized in homogeneous catalysis, in particular in reductions, reductive cyclizations, and polymerizations.[299−301] At present, several encouraging examples of Fe−NHC systems for C−H activation reactions exist.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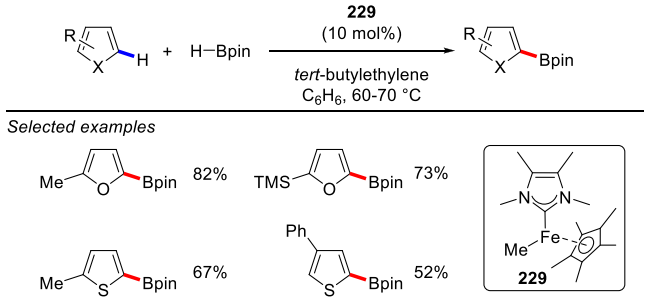
### 7.1. C(sp$^2$)−H Activation

In 2008, Tatsumi and co-workers reported intramolecular benzyl C(sp$^3$)−H activation within the [Fe(NHC)Cp*Cl] complexes (NHC = IMes, IiPr$^{Me}$) upon treatment with organolithiums (not shown).[302] The resulting cyclometalated Fe−NHC complex enabled the direct C(sp$^2$)−H activation of five-membered heterocycles, allowing their incorporation into the Fe−NHC complex to give [Fe(IiPr$^{Me}$)Cp*Het] (Het = 2-thienyl, 2-furyl). Based on this study, in 2010, Tatsumi and co-workers disclosed a dehydrogenative C(sp$^2$)−H borylation of furans and thiophenes with pinacolborane in in the presence of *tert*-butylethylene catalyzed by the Fe−NHC complex [Fe(IMe$^{Me}$)Cp*Me] **229** (Scheme 152).[303] The reactions

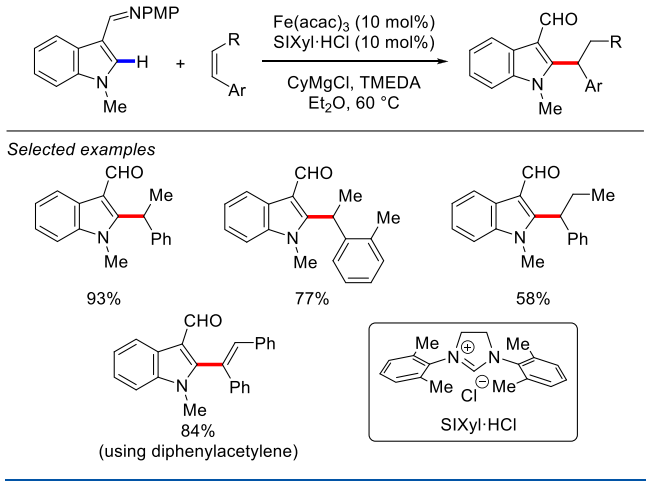
**Scheme 152. Fe−NHC-Catalyzed C(sp$^2$)−H Borylation of Furans and Thiophenes by Tatsumi**




occurred regioselectively at the C2 or C5 positions of the furan and thiophene ring and showed relatively broad substrate scope. Mechanistically, C−H activation occurs at the Fe−NHC complex **229** with a concomitant loss of methane. The reaction with pinacolborane generates the final product.

In 2015, Yoshikai and co-workers reported an imine-directed C(sp$^2$)−H alkylation of *N*-alkylindoles with vinylarenes at the C2 position catalyzed by Fe−NHCs (Scheme 153).[304] The

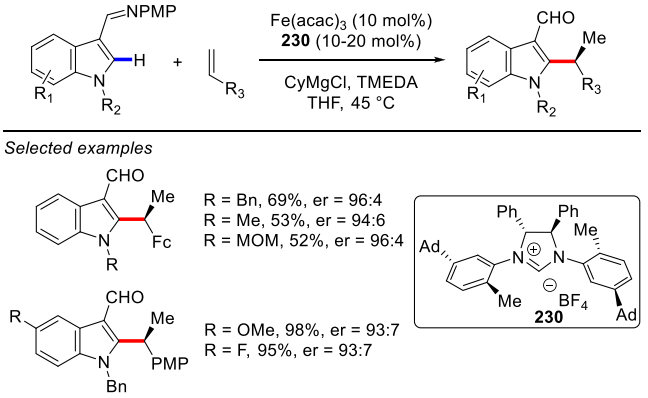
**Scheme 153. Fe−NHC-Catalyzed Imine-Directed C(sp$^2$)−H Alkylation of Indoles by Yoshikai**




active catalyst was generated in situ from Fe(acac)$_3$ and SIXyl·HCl in the presence of CyMgCl. In addition to SIXyl, several other NHC ligands were active in this reaction, including IXyl, SIMes, and SIPr; however, the use of phosphine ligands inhibited the model reaction. The reaction was also successful using internal alkynes, leading to C2-vinyl indoles. A mechanism involving oxidative addition of the C−H bond to a low-valent Fe−NHC complex, migratory insertion, and reductive elimination was proposed.

In 2017, Ackermann and co-workers disclosed an impressive example of highly enantioselective C(sp$^2$)−H alkylation of *N*-alkylindoles with vinylarenes catalyzed by a chiral Fe−NHC complex based on imidazolidinylidene **230** (Scheme 154).[305,306] The bulky group at the remote meta-position of

**Scheme 154. Asymmetric Fe−NHC-Catalyzed Imine-Directed C(sp$^2$)−H Alkylation of Indoles by Ackermann**

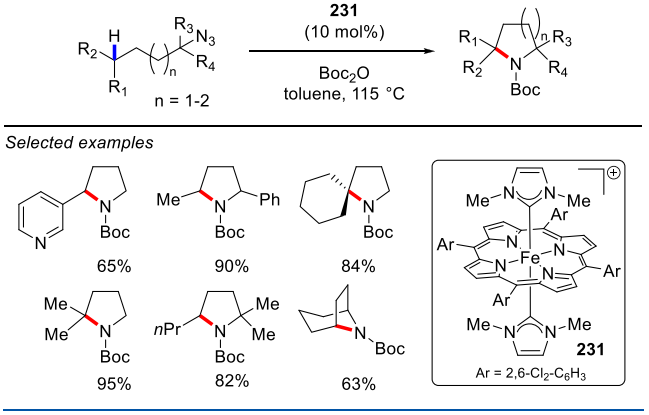



the *N*-aryl scaffold was crucial to obtain high enantioselectivity. This transformation showed broad scope and good functional group tolerance, delivering C2-alkylated products with high enantioselectivity.

### 7.2. C(sp$^3$)−H Activation

In 2018, Che and co-workers reported an iron(III) porphyrin complex [Fe(NHC)(TDCPP)] (TDCPP = tetrakis(2,6-dichlorophenyl)porphyrin) **231** for the intramolecular C-(sp$^3$)−H amination of alkyl azides, affording pyrrolidines and piperidines in good to excellent yields (Scheme 155).[307] In this

**Scheme 155. Fe−NHC Porphyrin-Catalyzed Intramolecular C(sp$^3$)−H Amination by Che**




catalyst design, the axial NHC ligand could facilitate the azide decomposition by stabilizing the iron-carbene intermediate. The authors proposed that the reaction is initiated by a thermal dissociation of one of the NHC ligands from **231**. This complex reacts with an alkyl azide to give an NHC-stabilized iron-nitrene, followed by C(sp$^3$)−H amination.

In addition, Sun and co-workers reported esterification of benzylic C(sp$^3$)−H bonds catalyzed by an iron−imidazolinium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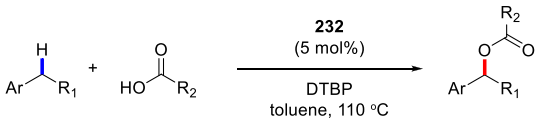
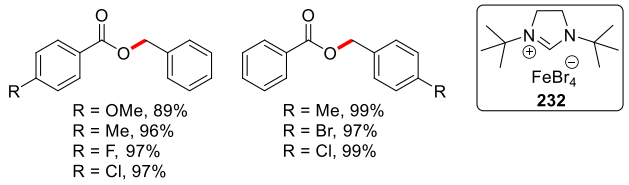
Chem. Rev. 2020, 120, 1981−2048

system (Scheme 156).[308] This reaction might proceed through Fe−NHC catalysis. This methodology showed very good

**Scheme 156. Esterification of Benzylic C(sp$^3$)−H Bonds by Sun**




*Selected examples*




tolerance, including sterically hindered substrates, providing a useful alternative for the synthesis of benzyl esters. This transformation uses DTBP (DTBP = di-*tert*-butyl peroxide) as an external oxidant and is ineffective without the imidazolium ligand. The same group reported a similar catalyst system for the allylic C(sp$^3$)−H esterification (not shown).[309] Intramolecular C(sp$^3$)−H activation within the bidentate and imido Fe(II)−NHC complexes has been reported.[310,311]

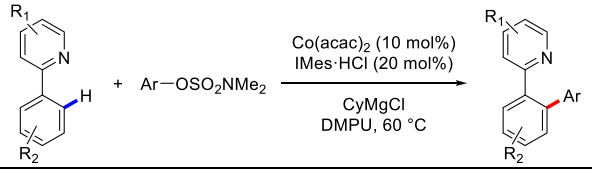
## 8. COBALT−NHC COMPLEXES

In the past few years, C−H bond activation using cost-efficient Co catalysis has emerged as a powerful tool for the synthesis of complex molecules.[312−314] In this context, Co−NHC complexes have played an important role in this emerging field. At present, the major advances in using Co−NHC complexes in C−H bond activation include the following classes of reactions: (1) pyridine-directed C(sp$^2$)−H arylation reactions with phenols and aryl chlorides; (2) pyridine-directed C(sp$^2$)−H alkenylation reactions; (3) imine-directed C(sp$^2$)−H alkylation reactions with unactivated olefins; (4) imine-directed C(sp$^2$)−H alkylation reactions with alkyl halides; (5) pyridine-directed addition of C(sp$^2$)−H bonds to imines and aziridines; (6) C(sp$^2$)−H activation reactions of pivalphenone imine; and (7) tandem C(sp$^2$)−H activation reactions via radical intermediates. In addition, the development of C(sp$^2$)−H activation/annulation via protic Co−NHC species by metallotropism-enabled C−H activation of azoles should be noted (see Section 4.1.3).[230]

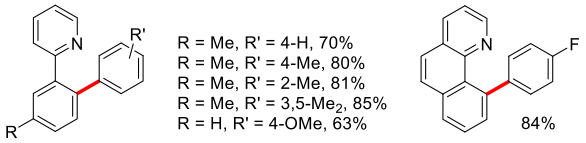
### 8.1. C(sp$^2$)−H Activation

In 2012, Ackermann and co-workers reported one of the first examples of using inexpensive Co−NHC systems for the direct C(sp$^2$)−H arylation of 2-arylpyridines with aryl sulfamates (Scheme 157).[315] Extensive optimization studies demonstrated that IMes is the preferred NHC ligand for this transformation, while IPr, SIMes, SIPr, dppe, $PCy_3$, and phenanthroline were less effective. Directing groups included 2-arylpyridines, 2-arylpyrimidines, and *N*-2-pyridylindoles. In terms of electrophiles, the C−O activation occurred efficiently with aryl sulfamates, aryl carbamates, and aryl phosphates. It was proposed that the reaction proceeds via a nonradical reaction mechanism. The mild reaction conditions and utilization of phenol derivatives as electrophiles in this methodology are noteworthy.

**Scheme 157. Co−NHC-Catalyzed Pyridine-Directed C(sp$^2$)−H/C−O Arylation by Ackermann**

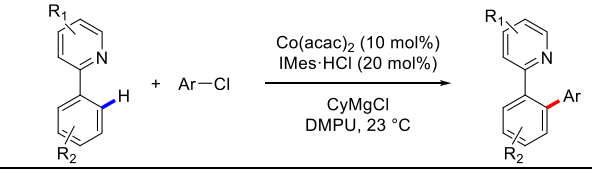



*Selected examples*

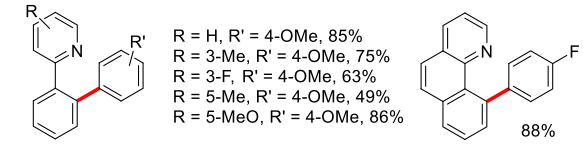



Subsequently, Ackermann and co-workers reported a similar Co−NHC catalytic systems for the direct C(sp$^2$)−H arylation of 2-arylpyridines with aryl chlorides (Scheme 158).[316] They

**Scheme 158. Co−NHC-Catalyzed Pyridine-Directed C(sp$^2$)−H/C−Cl Arylation by Ackermann**



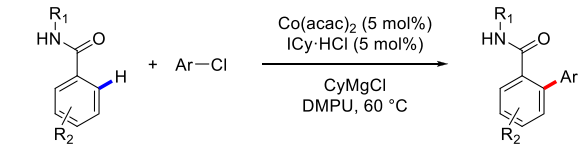

*Selected examples*



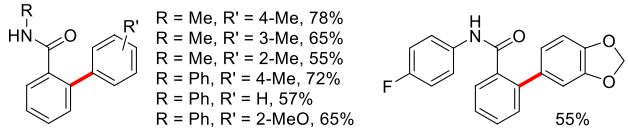

found that a combination of the inexpensive Co(acac)$_2$ and IMes·HCl as the NHC precursor in the presence of CyMgCl (1.6 equiv) in DMPU proved to be highly effective for the arylation at room temperature. Again, IMes was identified as the key ligand, while significantly lower conversion was observed using IPr, SIPr, and SIMes. A similar protocol using Co(acac)$_2$ and IPr as the NHC ligand was also reported for C(sp$^2$)−H arylation of 2-arylpyridines with alkyl chlorides (not shown).[316]

In 2015, the Ackermann group reported a further extension of their Co−NHC methodology to the direct C(sp$^2$)−H arylation of weakly coordinating secondary benzamides (Scheme 159).[317] In this study, ICy was employed as the

**Scheme 159. Co−NHC-Catalyzed Amide-Directed C(sp$^2$)−H/C−Cl Arylation by Ackermann**




*Selected examples*



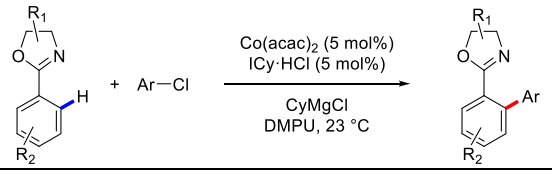


https://dx.doi.org/10.1021/acs.chemrev.9b00634
*Chem. Rev.* 2020, 120, 1981−2048

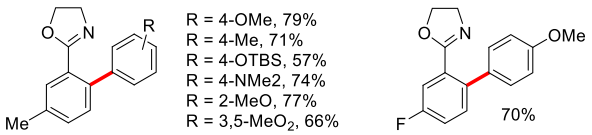
NHC ligand instead of IMes. Interestingly, replacing ICy by IPr or SIPr resulted in no reaction, while IMes, SIMes, and $PPh_3$ gave traces of the arylation product. Various benzamides were converted into biaryl products in good to high yields, including the synthesis of complex biaryls. This protocol was further extended to the direct C($sp^2$)−H arylation of 5-aryltetrazoles with aryl carbamates using IMes as the optimum NHC ligand (not shown).[317]

In 2016, the Ackermann group reported a similar reaction for the C($sp^2$)−H arylation of 2-aryloxazolines with aryl chlorides (Scheme 160).[318] This strongly chelating imidate

**Scheme 160. Co−NHC-Catalyzed Oxazoline-Directed C($sp^2$)−H/C−Cl Arylation by Ackermann**



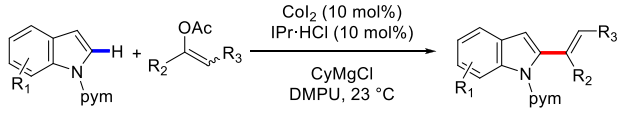

*Selected examples*



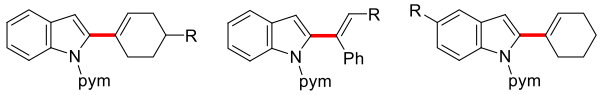

group allowed for efficient C−H arylations at room temperature. Importantly, the reaction was ineffective without the NHC ligand, while IPr, IMes, and ItBu gave lower conversion. It is worth noting that the oxazoline directing group could be readily converted into other functional groups, including alcohol, carboxylic acid, ester, and amide.

In addition to C($sp^2$)−H arylations, in 2015, the Ackermann group achieved the direct C($sp^2$)−H olefination catalyzed by Co−NHC complexes (Scheme 161).[319] A combination of

**Scheme 161. Co−NHC-Catalyzed Pyridine-Directed C($sp^2$)−H/C−O Alkenylation by Ackermann**

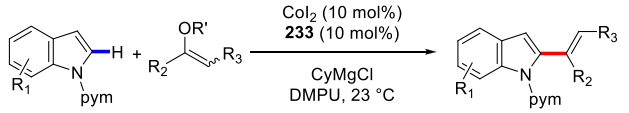



*Selected examples*

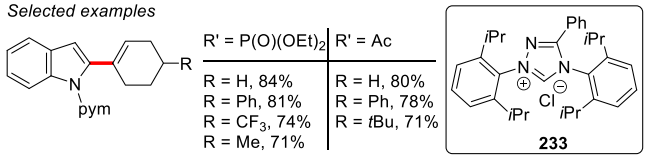



$CoI_2$ and IPr·HCl in the presence of CyMgCl in DMPU at 23 °C provided the best yields. Other ligands, including IMes, ICy, and IAd, were less effective, while phosphines $PPh_3$, $PCy_3$, and dppe completely inhibited the catalysis. A number of diverse alkenyl acetates and alkenyl phosphates proved effective as olefinating reagents, providing the C−H activation products in good to excellent yields. In 2017, Ackermann and co-workers reported triazolylidene ligands for the Co−NHC-catalyzed olefins with alkenyl acetates at room temperature (Scheme 162).[320] These NHCs offer an alternative to the typical imidazolylidene ligands in Co−NHC C($sp^2$)−H activations.

**Scheme 162. Co−NHC-Catalyzed Pyridine-Directed C($sp^2$)−H/C−O Alkenylation Using Triazolylidene Ligands by Ackermann**

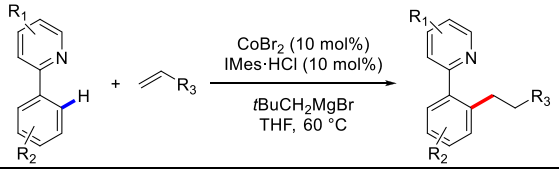



*Selected examples*

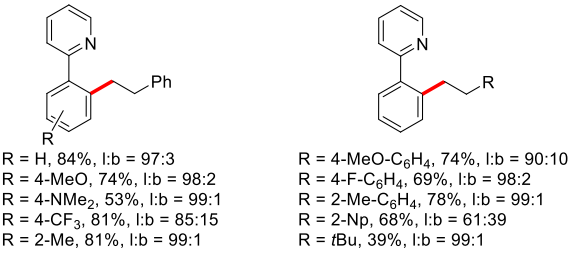



Major advances in the Co−NHC-catalyzed C($sp^2$)−H activation have been made by Yoshikai and co-workers. In 2011, they reported a linear selective C($sp^2$)−H alkylation of 2-arylpyridines with styrenes catalyzed by a combination of $CoBr_2$ and IMes·HCl in the presence of $tBuCH_2MgBr$ in THF at 60 °C (Scheme 163).[321] Interestingly, replacing IMes with

**Scheme 163. Co−NHC-Catalyzed C($sp^2$)−H Alkylation by Yoshikai**




*Selected examples*




$PCy_3$ allowed for switching the selectivity to access the branched products. High yields and excellent regioselectivities were observed for various styrenes using both catalytic systems. A mechanism involving oxidative addition of the C−H bond to a Co−NHC, styrene insertion, and reductive elimination was proposed. In this study, the first example of an imine-directed C($sp^2$)−H activation catalyzed by Co−NHCs was also reported.

Based on this study, Yoshikai and co-workers developed a Co−NHC-catalyzed intramolecular C($sp^2$)−H alkylation of indoles directed by a C3 imine group (Scheme 164).[322] The reaction affords dihydropyrroloindole **A** or tetrahydropyridoindole **B** products, controlled by the selection of the NHC ligand. Thus, SIMes favors the formation of 5-exocyclization products, while IPr leads to 6-endocyclization. Phosphines, including $PPh_3$, dppe, and DPEphos, are ineffective in this cyclization, while IMes and SIPr give the 5-exo or 6-endo selectivity, respectively, however, affording the cyclization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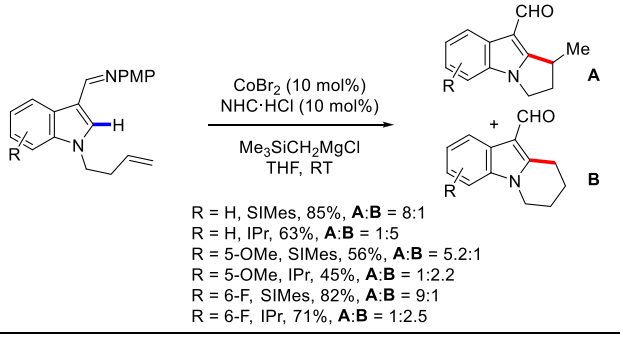
Chem. Rev. 2020, 120, 1981−2048

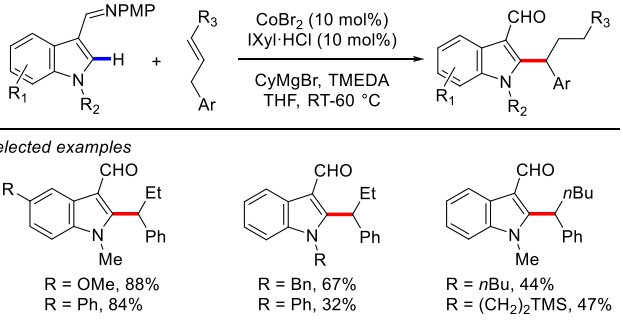
**Scheme 164. Intramolecular Co−NHC-Catalyzed C(sp²)−H Alkylation by Yoshikai**




products in lower yields. Mechanistically, the olefin insertion step determines the regioselectivity in this reaction.

Subsequently, the same group reported intermolecular C(sp²)−H alkylation of 3-iminoindoles with allyl arenes via a tandem olefin isomerization/C(sp²)−H alkylation pathway (Scheme 165).[323] The reaction provides 1,1-diarylalkanes in

**Scheme 165. Co−NHC-Catalyzed Alkene Isomerization/C(sp²)−H Alkylation by Yoshikai**

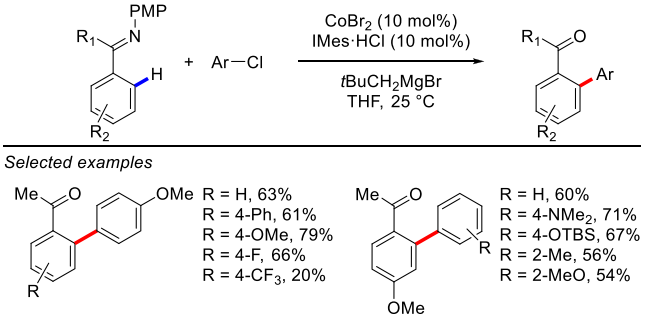



good yields. IXyl was the best ligand for this transformation, affording significantly higher yields than IMes, IPr, as well as $PPh_3$ and $PCy_3$.

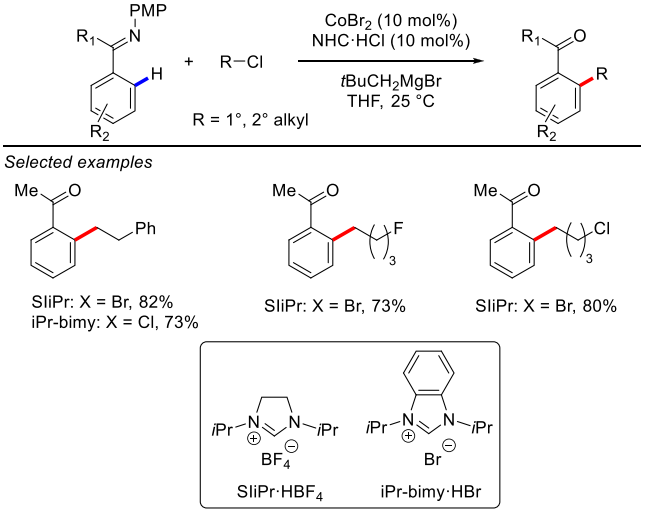
In 2012, Yoshikai and co-workers reported the direct C(sp²)−H arylation of aromatic imines with aryl chlorides using the Co−IMes catalytic system in the presence of $t$BuCH$_2$MgBr in THF at 25 °C (Scheme 166, cf. Scheme 158).[324] Optimization studies revealed that IPr, $PPh_3$, $PCy_3$, $PEt_3$, and $PMe_3$ were much less effective than IMes in this C−H arylation. This reaction affords the biaryl coupling products in good to high yields with excellent monoarylation selectivity. The imine-directing group is readily removed by acidic workup, providing a functional group equivalent to the carbonyl group.

In 2013, Yoshikai and co-workers disclosed the direct C(sp²)−H alkylation of aromatic imines with alkyl halides (Scheme 167).[325] In this reaction, $CoBr_2$ in a combination with imidazolidinylide, SIiPr, or benzimidazolylidene, iPr-bimy, provided the best yields. These C(sp²)−H alkylation reactions were accomplished in high yields and with excellent

**Scheme 166. Co−NHC-Catalyzed Imine-Directed C(sp²)−H/C−Cl Arylation by Yoshikai**



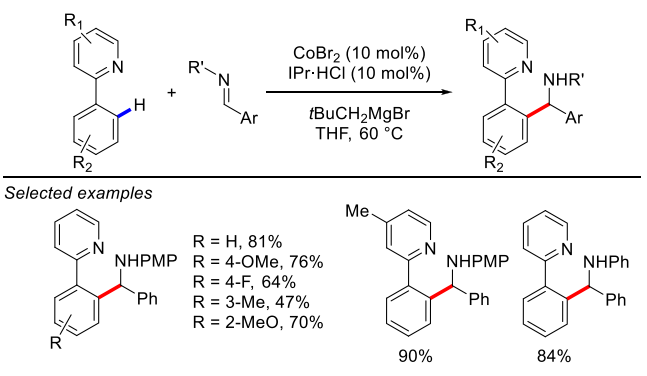

**Scheme 167. Co−NHC-Catalyzed Imine-Directed C(sp²)−H/C−X Alkylation by Yoshikai**




regioselectivity over a broad range of substrates. Linear and branched alkyl halides as well as cycloalkyl halides were shown to be effective coupling partners.[326] The authors proposed that the reaction involves a single-electron transfer from C(sp²)−H activation cobaltacycle to the alkyl halide, followed by radical coupling.

The Yoshikai group expanded their Co−NHC-catalyzed C−H activation methodology to the direct addition of 2-arylpyridines to aldimines (Scheme 168).[327] The combination of $CoBr_2$, IPr·HCl, and $t$BuCH$_2$MgBr allowed for the C(sp²)−H alkylation of 2-arylpyridines with aromatic aldimines in THF

**Scheme 168. Co−NHC-Catalyzed Pyridine-Directed C(sp²)−H Addition to Aldimines by Yoshikai**



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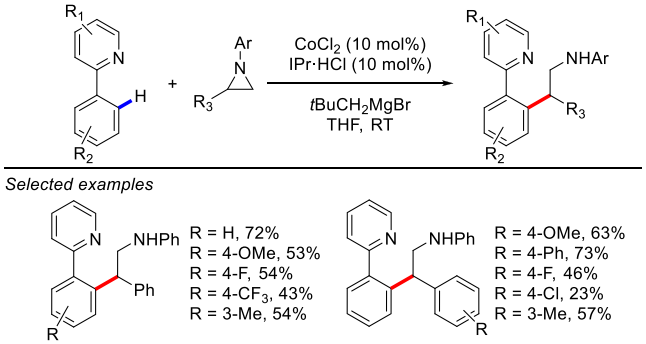
at 60 °C with good functional group tolerance. It is worth noting that IMes could also promote this reaction; however, this ligand was significantly less effective than IPr. The reaction was proposed to proceed by a mechanism involving chelation-directed C($sp^2$)−H oxidative addition, nucleophilic addition of the cobaltacycle intermediate to aldimine, and transmetalation of the cobalt amide.

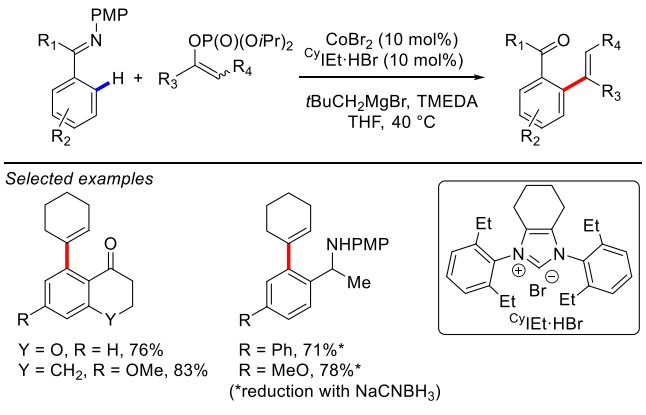
In 2014, Yoshikai and co-workers reported the direct C($sp^2$)−H alkylation of 2-arylpyridines with 2-arylaziridines (Scheme 169).[328] In this system, $CoCl_2$ is a catalyst, while IPr·HCl serves as a ligand precursor in the presence of $tBuCH_2MgBr$ in THF at room temperature. Phosphines are completely ineffective in this reaction, while IMes and SIPr gave lower yields. The reaction allows for a facile access to 1,1-diarylethanes featuring the 2-amino moiety in moderate to good yields. The mechanism was proposed to involve a nucleophilic attack of the cobaltacycle intermediate on 2-arylazirdine, resulting in an overall alkylative ring-opening process.

**Scheme 169. Co−NHC-Catalyzed Pyridine-Directed C($sp^2$)−H Addition to Aziridines by Yoshikai**



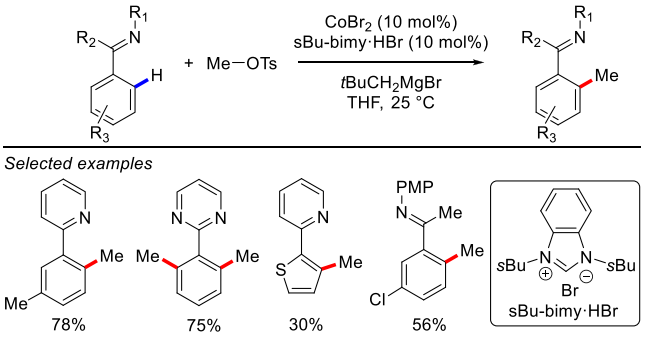

The direct C($sp^2$)−H olefination of aryl imines with vinyl phosphates catalyzed by Co−NHC complexes was also reported by Yoshikai and co-workers (Scheme 170).[329] In this reaction, they identified uncommon $^{Cy}$IEt as the best NHC ligand. Significantly lower yields were obtained with IMes, IPr, IEt, and $^{Me}$IEt. The utility of 2-alkenylacetophenones was exemplified in their conversion to benzofulvenes, indoles, and carbazoles (cf. Schemes 161 and 162).

**Scheme 170. Co−NHC-Catalyzed Imine-Directed C($sp^2$)−H/C−O Alkenylation by Yoshikai**



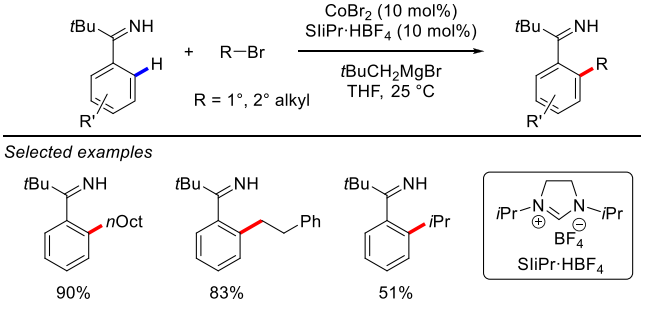

The Yoshikai group also demonstrated that MeOTs could be an effective coupling partner in the C($sp^2$)−H alkylation of 2-arylpyridines and aryl imines catalyzed by Co−NHCs (Scheme 171).[330] This methylation reaction was promoted by a benzo[*d*]imidazole-based *N*-alkyl NHC ligand, sBu-bimy. The mechanism of this apparent C−H/C−O activation involves an *in situ* conversion of MeOTs to the more active methylating reagent, MeBr.

**Scheme 171. Co−NHC-Catalyzed Pyridine- and Imine-Directed C($sp^2$)−H/C−O Methylation by Yoshikai**




The direct C($sp^2$)−H activation of pivalophenone imine represents another class of reactions that have been achieved with Co−NHC catalysis. In 2017, the Yoshikai group reported C($sp^2$)−H alkylation of pivalophenone imine using $CoBr_2$ and SIiPr as the catalyst system (Scheme 172).[331] The main advantage of this protocol is using the alkylated products of pivalphenone imine as nitrile surrogates that would be especially difficult to access by other C−H activation methods. Subsequently, Yoshikai and co-workers reported the direct C($sp^2$)−H olefination reactions using the same pivalophenone imine substrates (Scheme 173).[332] The reaction provides straightforward access to 2-alkenylated pivalophenone imines in the presence of a bulky dipp-bimy NHC ligand. This NHC gave dramatically better yields than IPr, IMes, SIPr, SIMes, and IEt, while $PPh_3$ and $PCy_3$ were completely ineffective in promoting the C−H alkenylation. A similar C($sp^2$)−H benzylation process using benzyl phosphates has been reported (not shown).[333]

**Scheme 172. Co−NHC-Catalyzed Pivalophenone Imine-Directed C($sp^2$)−H/C−Br Alkylation by Yoshikai**




C($sp^2$)−H activation catalyzed by Co−NHCs has been extended to tandem alkylations involving radical reactions. In 2018, Yoshikai and co-workers reported a tandem C($sp^2$)−H/C($sp^3$)−H coupling between aryl imines and *N*-2-bromobenzyl-protected secondary amines (Scheme 174).[334] This reaction is promoted by the combination of $CoBr_2$, SIPr·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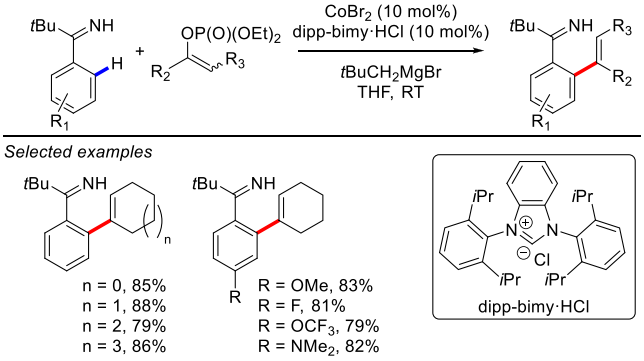
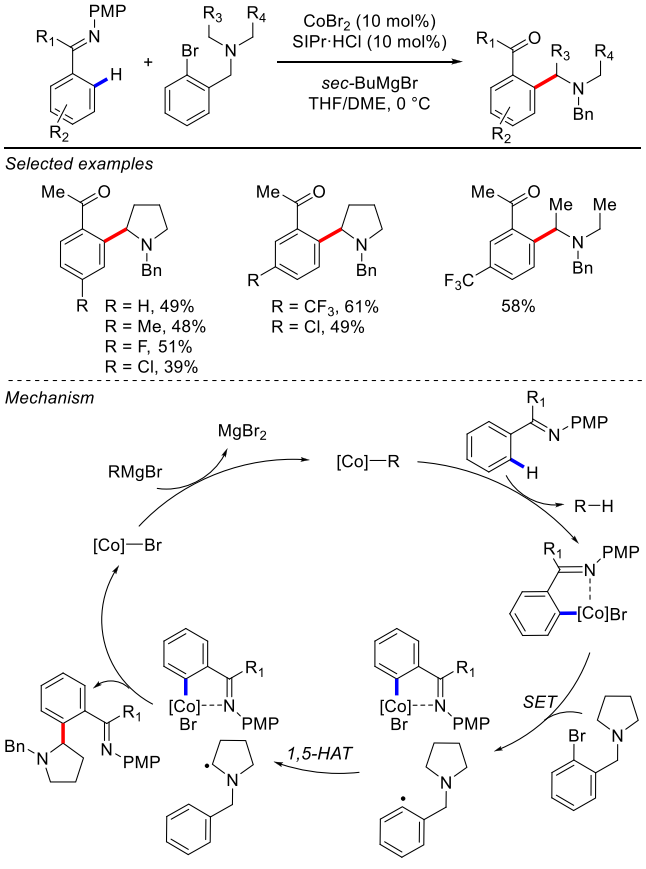
Chem. Rev. 2020, 120, 1981−2048

**Scheme 173. Co−NHC-Catalyzed Pivalophenone Imine-Directed C($sp^2$)−H/C−O Alkenylation by Yoshikai**



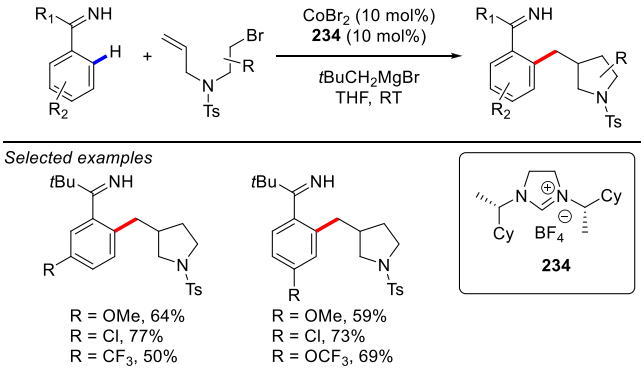

**Scheme 174. Co−NHC-Catalyzed Imine-Directed C($sp^2$)−H/C($sp^3$)−H Coupling by Yoshikai**




HCl, and *s*BuMgBr in THF/DME at 0 °C and allows for the C($sp^2$)−H alkylation with aliphatic amines at the $\alpha$ position. In this system, the cyclometalated cobalt intermediate undergoes single-electron transfer to *N*-2-bromobenzylamine, promoting 1,5-hydrogen atom transfer. The mechanism involves generation of the low-valent organocobalt catalyst, cyclometalation with an aryl imine to give the cobaltacycle intermediate, single electron transfer (SET), and 1,5-hydrogen atom transfer (HAT) steps to furnish the $\alpha$-aminoradical intermediate. Aryl−alkyl coupling gives the C−H activation product, and the catalyst is regenerated by transmetalation with a Grignard reagent. The reaction allows for $\alpha$-coupling of cyclic and alicyclic aliphatic amines with aromatic C−H bonds.

More recently, the same group disclosed a tandem C($sp^2$)−H activation/radical cyclization of bromoalkenes promoted by Co−NHC complexes (Scheme 175).[335] In this reaction, the

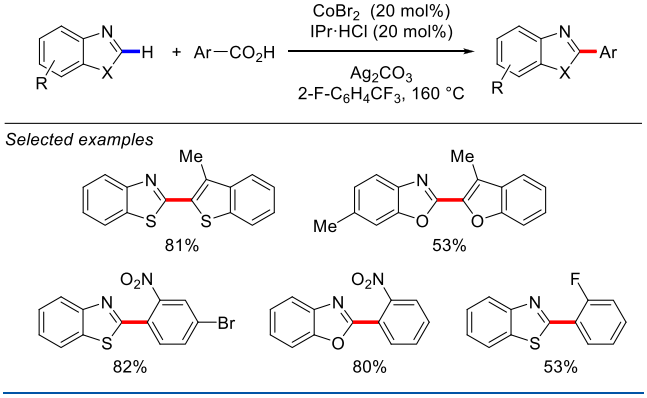
**Scheme 175. Co−NHC-Catalyzed Imine-Directed C($sp^2$)−H/Tandem C−C Coupling by Yoshikai**




cobaltacycle intermediate formed after the C($sp^2$)−H activation step undergoes single-electron transfer to bromoalkene, triggering an intramolecular radical 5-exo-trig cyclization, which is followed by radical recombination and reductive elimination to give the final product. The imidazolidinylidene-based NHC ligand **234** is the best promoter for this reaction, while SIiPr, SICy, IMes, IPr, and iPr-bimy afforded lower yields of the desired product. The reaction is compatible with various functional groups on the imine and bromoalkene coupling partner. Furthermore, imines could be directly hydrolyzed to ketones or transformed to the cyano group via radical decomposition.

In another direction utilizing Co−NHC complexes, in 2017, Li and co-workers reported a nondirected, decarboxylative C($sp^2$)−H/C($sp^2$) cross-coupling of benzothiazoles and benzoxazoles with activated carboxylic acids (Scheme 176).[336] The reaction is catalyzed by a combination of

**Scheme 176. Co−NHC-Catalyzed C($sp^2$)−H/Decarboxylative Arylation by Li**




$CoBr_2$, IPr, and $Ag_2CO_3$ in 2-fluorobenzotrifluoride at 160 °C. IPr gives higher yields than IMes, $PCy_3$, or $PPh_3$. The proposed mechanism involves a Co-catalyzed C($sp^2$)−H activation to give a Co(III)−$ArX_2$ intermediate, which then reacts with an aryl radical generated from the carboxylic acid in the presence of $Ag_2CO_3$, followed by reductive elimination. Although only highly reactive carboxylic acids capable of decarboxylation with $Ag_2CO_3$ serve as suitable substrates in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Chem. Rev. 2020, 120, 1981−2048

this process, the scope of the reaction is quite broad and accommodates various electron-withdrawing substituents on the carboxylic acid component.

### 8.2. C(sp$^3$)−H Activation

Several examples of intramolecular C(sp$^3$)−H activation within low-valent Co(0)−NHC and Co(I)−NHC complexes have been reported.[337−340] At present, these processes are limited to the synthesis of new Co−NHC complexes.

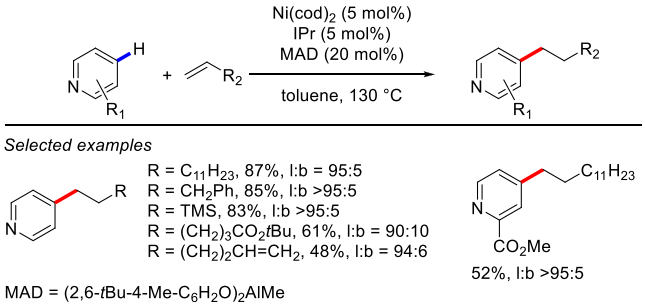
## 9. NICKEL−NHC COMPLEXES

In general, Ni-catalyzed transformations are highly attractive due to the low price and availability of nickel, while facile oxidative addition and access to various oxidation states have enabled the development of a broad variety of catalytic methods using homogeneous nickel catalysis.[341,342] In this regard, Ni−NHC complexes have found applications in numerous organic reactions, including activation of small molecules,[343,344] cleavage of C−X bonds,[345,346] and the formation of C−C and C−N bonds, among other applications.[347,348] Recently, major advances have been made in using Ni−NHCs as catalysts for C−H functionalization reactions. In particular, Ni−NHCs have emerged as an attractive class of catalysts for the following C−H functionalizations: (1) remote C(sp$^2$)−H alkylation and alkenylation reactions; (2) C(sp$^2$)−H alkylation of heterocycles; (3) intramolecular C(sp$^2$)−H annulation of nitrogen heterocycles, including enantioselective processes; (4) direct C(sp$^2$)−H arylation reactions; (5) C(sp$^2$)−H borylation; and (6) C(acyl)−H amidation and arylation reactions.

### 9.1. C(sp$^2$)−H Activation

In 2010, Nakao and co-workers reported C4-selective C(sp$^2$)−H alkylation of pyridines with olefins catalyzed by a cooperative Ni−NHC/Lewis acid catalysis (Scheme 177).[349]

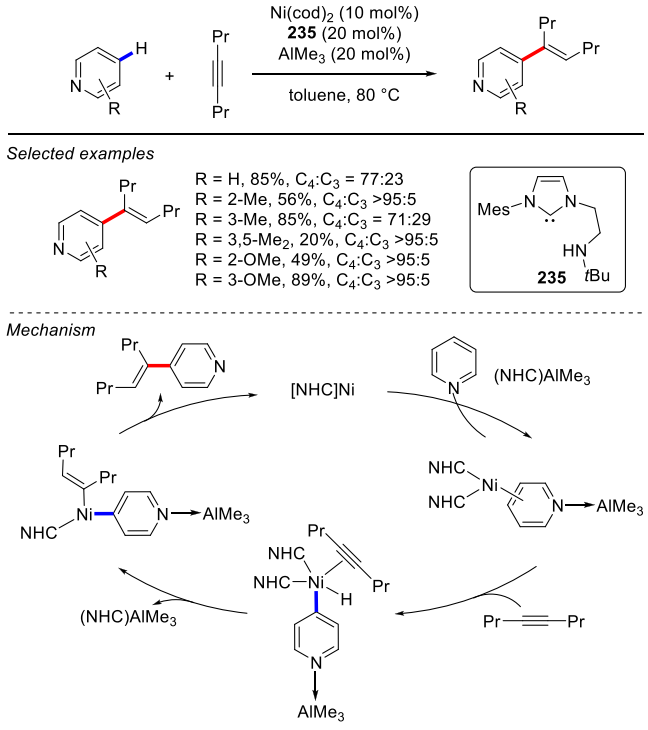
**Scheme 177. Ni−NHC-Catalyzed C4-Selective C(sp$^2$)−H Alkylation of Pyridines by Nakao**




They proposed that conventional C2−H functionalization of pyridines would be diverted into C4−H functionalization by using a combination of a bulky Lewis acid and a bulky NHC ligand that would favor oxidative addition at the remote carbon through $\eta^2$-substrate coordination to Ni(0)−NHC and $\eta^1$-*N*-coordination to the Lewis acid. They found that IPr as the NHC ligand and MAD as the Lewis acid (MAD = 2,6-*t*Bu$_2$-4-Me-C$_6$H$_2$O$_2$AlMe) in the presence of Ni(cod)$_2$ allowed for linear-selective alkylation of a wide range of pyridines with alkenes in toluene at 130 °C at the C4 position. In this system, only traces of the branched products and unselective alkylation are observed.

Independently, Ong and co-workers developed C4-selective C(sp$^2$)−H alkenylation of pyridines with alkynes using a combination of Ni(cod)$_2$, AlMe$_3$, and chelating imidazolylidene ligand **235** (Scheme 178).[350] This methodology is based

**Scheme 178. Ni−NHC-Catalyzed C4-Selective C(sp$^2$)−H Alkenylation of Pyridines by Ong**




on a similar concept to the C4-alkylation reported by Nakao and co-workers. In this case, the authors were able to directly observe and fully characterize by X-ray crystallography the $\eta^2,\eta^1$-pyridine-Ni(0)−Al(III) intermediate prior to the C4−H activation step. The authors proposed that the hemilabile amino-side chain in **235** might stabilize the Ni(0)−NHC center. In agreement with this hypothesis, other NHC ligands, including IMes, SIMes, and SIPr, proved significantly less effective in the reaction. The proposed mechanism involves the formation of the Ni−Al complex by the reaction of (NHC)Ni with pyridine and (NHC)AlMe$_3$. Oxidative addition of the C−H bond gives the Ni−H intermediate. Alkyne insertion and reductive elimination give the C−H activation product and regenerate the active catalyst. This methodology allows for the construction of C4-alkenylated pyridines with excellent C4 regioselectivity.

In 2015, Ong and co-workers reported C4-selective C(sp$^2$)−H alkylation of pyridines by a catalyst-dependent switchable isomerization of allylarenes (Scheme 179).[351] They found that the use of Ni(cod)$_2$ in the presence of IPr and MAD resulted in a linear product from the insertion of allylarene, while a similar catalyst system based on NHC ligand **236** featuring a hemilabile dimethylamino side chain promoted olefin isomerization prior to the insertion step. Interestingly, IMes was completely unselective in this reaction, while phosphines, such as PPh$_3$ and PCy$_3$, did not promote the reaction. The use of a more bulky *N*,*N*-dimethylamino ligand **236** (cf. *N*-*tert*-butyl ligand **235**) resulted in higher yields. A mechanistic study on the regioselectivity of this reaction has been published.[352]

The first example of a direct C2-selective C(sp$^2$)−H alkylation of heterocycles catalyzed by Ni−NHCs was reported by Nakao and co-workers in 2010 (Scheme 180).[353] It was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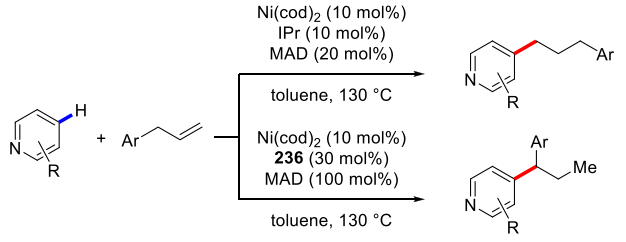
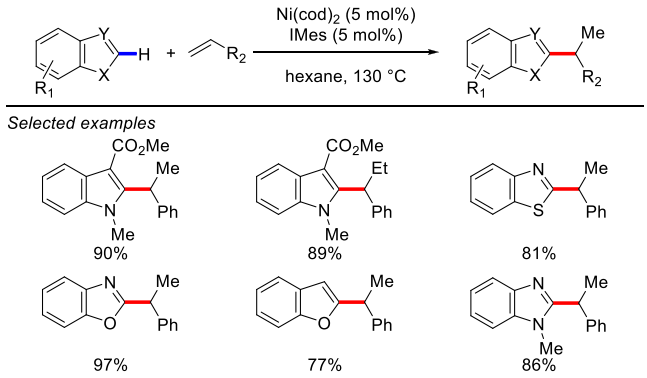
Chem. Rev. 2020, 120, 1981−2048

**Scheme 179. Ni–NHC-Catalyzed Switchable C4-Selective C(sp²)–H Alkylation of Pyridines by Ong**

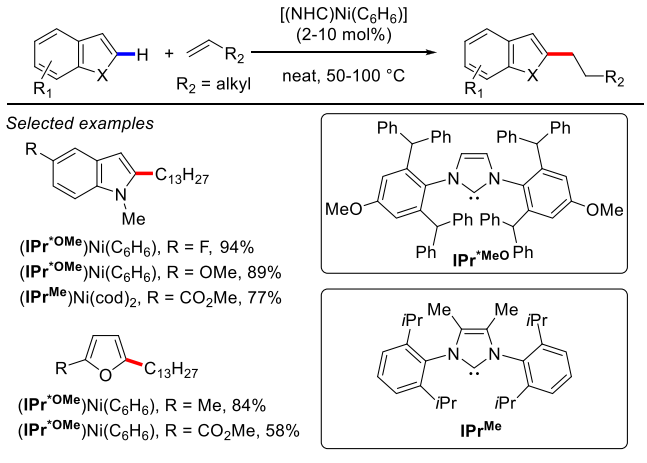



**Scheme 180. Ni–NHC-Catalyzed C2-Selective C(sp²)–H Alkylation of Heterocycles by Nakao**




found that using $Ni(cod)_2$ in the presence of IMes as a ligand in hexane at 130 °C promoted the desired C2–H alkylation of various five-membered heterocycles with olefins to give branched alkylated products in high yields. The corresponding linear alkylation products were not detected using styrenes, while an example with aliphatic olefin (cf. Scheme 181)[354] gave exclusively the linear product. Furthermore, other ligands, including IPr, $PCy_3$, and $PnBu_3$, gave only a trace amount of

**Scheme 181. Ni–NHC-Catalyzed C2 Linear Selective C(sp²)–H Alkylation of Heterocycles by Hartwig**

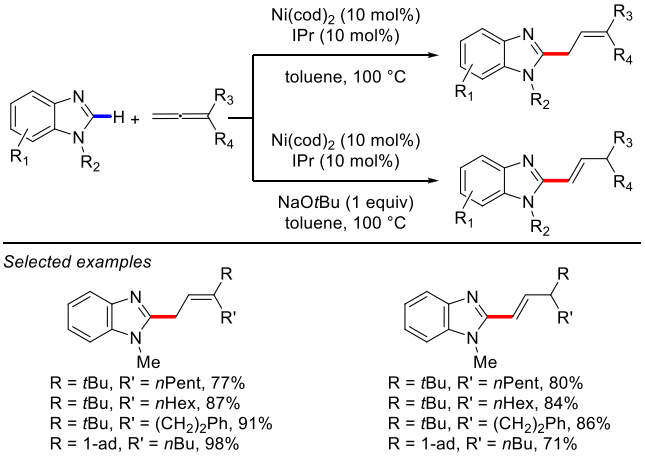



the product. The reaction was successfully applied to the alkylation of various heterocycles, including C3-activated indoles, benzimidazole, benzofuran, benzothiazole, benzoxazole, and oxazole.

Later, Nakao, Hartwig, and co-workers were able to extend this direct C2-selective C(sp²)–H alkylation of heterocycles catalyzed by Ni–NHCs to the formation of linear products using indoles, benzofurans, furans, and pyrroles as arylation substrates (Scheme 181).[354] After optimization it was observed that a catalyst system based on electron-rich, sterically demanding $IPr^{*MeO}$ or $IPr^{Me}$ NHC ligands worked best for this transformation. With these catalyst systems, various aliphatic olefins were coupled with excellent functional group tolerance and high linear:branched selectivity.

In 2017, Ackermann and co-workers reported a divergent C2-selective C(sp²)–H of five-membered heterocycles with allenes (Scheme 182).[355] Interestingly, especially from the

**Scheme 182. Ni–NHC-Catalyzed C(sp²)–H Functionalization of Heterocycles with Allenes by Ackermann**




practical point of view, this reaction leads to C2-allylated products using the catalyst system generated from $Ni(cod)_2$ and IPr in toluene at 100 °C, while the addition of NaO*t*Bu (1.0 equiv) to the same catalyst system results in the selective formation of C2-vinyl products by olefin isomerization. This bifurcated C(sp²)–H activation pathway highlights the importance of selecting appropriate conditions for generating the active Ni–NHC catalyst. The reaction represents an effective way for constructing C2-allyl and C2-vinyl purine derivatives.

In 2012, Ong and co-workers reported a switchable branched- or linear-selective C(sp²)–H alkylation of benzimidazoles with alkenes at the C2 position (Scheme 183).[356,357] They discovered that the catalytic system using $Ni(cod)_2$ in the presence of their amine-chelating NHC ligand **235** (see Scheme 178) in toluene at 100 °C furnished the branched products, while the addition of $AlMe_3$ (10 mol %) completely switched the selectivity to linear products via cooperative Ni–Al bimetallic catalysis. The structure of a Lewis pair complex with Al coordinated to the nitrogen atom of the benzimidazole ring was confirmed by X-ray crystallography. Compared with **235**, IPr and IMes also showed excellent selectivity but were less efficient. Interestingly, MAD gave much lower selectivity than $AlMe_3$.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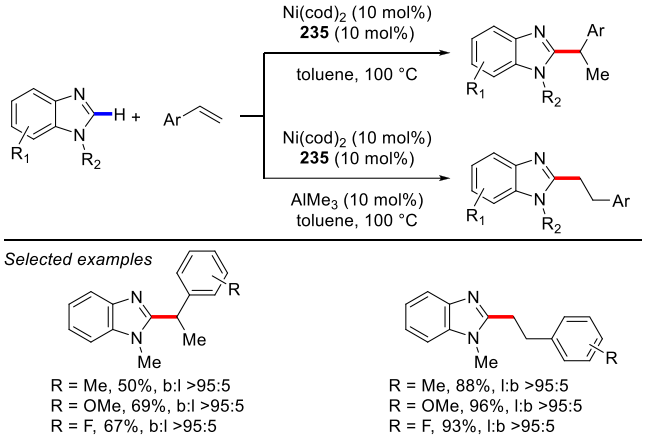
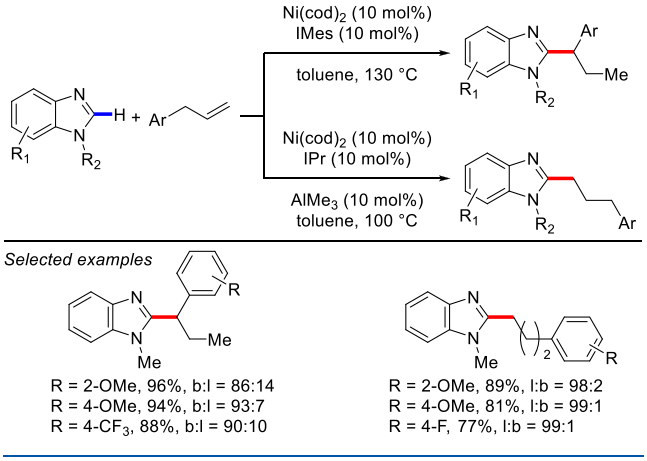
**Scheme 183. Ni−NHC-Catalyzed Switchable C2-Selective C(sp$^2$)−H Alkylation of Heterocycles by Ong**




Subsequently, the same group reported another example of a divergent C(sp$^2$)−H functionalization of imidazoles in the reactions with allylarenes using Ni−NHCs (Scheme 184).[358]

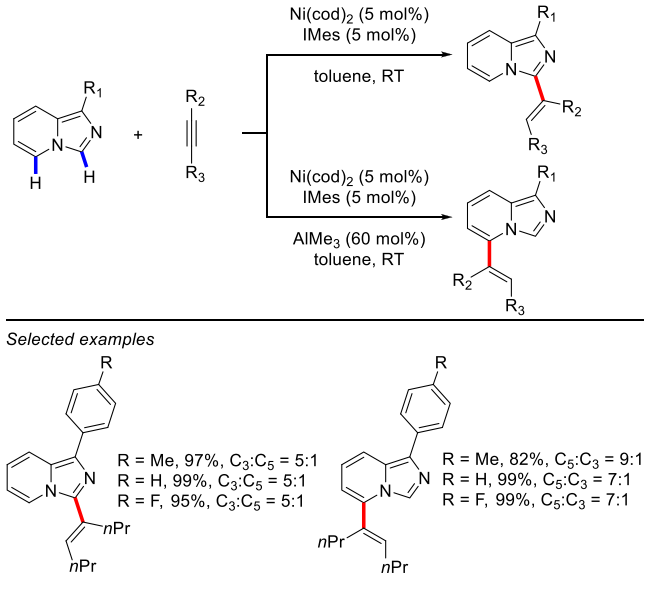
**Scheme 184. Ni−NHC-Catalyzed Switchable C2-Selective C(sp$^2$)−H Isomerization/Alkylation of Heterocycles by Ong**




Now, they found that the standard monometallic Ni−NHC catalysis protocol (Ni(cod)$_2$/IMes, toluene, 100 °C) leads to the formation of branched C2−H functionalization products by alkene isomerization, while bimetallic Ni−Al catalysis (Ni(cod)$_2$/IPr/AlMe$_3$, toluene, 100 °C) affords linear C2−H functionalization adducts through steric control of the olefin insertion.

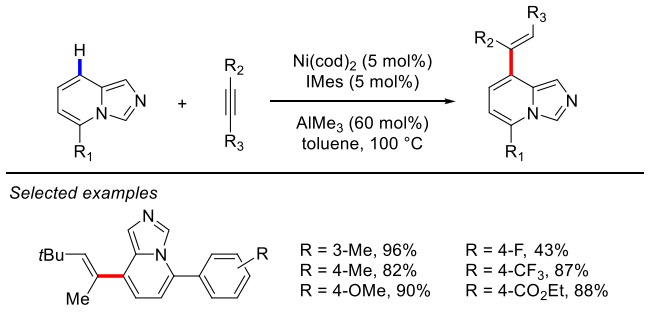
Meanwhile, Ong and co-workers established yet another regiodivergent C(sp$^2$)−H functionalization of heterocycles by switching between monometallic Ni−NHC and bimetallic Ni−NHC−Al catalysis in the direct C3 or C5 alkenylation of imidazo[1,5-*a*]pyridines with alkynes (Scheme 185).[359] In this instance, the standard Ni−NHC catalysis (Ni(cod)$_2$/IPr, toluene) results in C−H alkenylation at the most acidic C3 position, while the addition of AlMe$_3$ (60 mol %) switches the selectivity to C5−H alkenylation by Lewis acid coordination to the basic nitrogen atom. It is noteworthy that these switchable C(sp$^2$)−H activation reactions proceed under very mild room-temperature conditions, indicating a significant potential for late-stage functionalization of this class of heterocycles. The Ong group also reported that the direct C(sp$^2$)−H

**Scheme 185. Ni−NHC-Catalyzed Regiodivergent C(sp$^2$)−H Alkenylation of Imidazo[1,5-*a*]pyridine by Ong**




alkenylation of imidazo[1,5-*a*]pyridines could occur selectively at the C8 position when the C5 position is blocked (Scheme 186).[360] Interestingly, the C3 position remains intact under these cooperative Ni−NHC−Al conditions.

**Scheme 186. Ni−NHC-Catalyzed C5-Selective C(sp$^2$)−H Alkenylation of Imidazo[1,5-*a*]pyridine by Ong**




In 2015, an extension of the Ni−NHC-catalyzed C(sp$^2$)−H functionalization to the coupling with cyclic dienes was realized by Ong and co-workers (Scheme 187).[361] The catalyst system using Ni(cod)$_2$ in the presence of IMes resulted in the formation of *α*-alkenyl products at the C2 position of various azoles through olefin isomerization, while replacing IMes with PCy$_3$ fully switched the selectivity to give *β*-alkenyl C−H functionalization products. The authors demonstrated that the olefin isomerization using Ni(cod)$_2$/PCy$_3$ is much slower than with the Ni(cod)$_2$/IMes catalyst under these reaction conditions. Interestingly, IPr and their hemilabile NHC ligand **235** were found to be ineffective in this transformation.

The use of an abnormal NHC ligand in the Ni−NHC-catalyzed C(sp$^2$)−H alkylation of benzoxazoles with styrenes was reported by Mandal and co-workers (Scheme 188).[362] This reaction proceeds in the presence of Ni(cod)$_2$ and **237** in hexene at 80 °C and leads to a variety of 1,1-diarylethane products with excellent branched selectivity. Based on stoichiometric studies, the authors proposed that the mechanism involves oxidative addition of the C(sp$^2$)−H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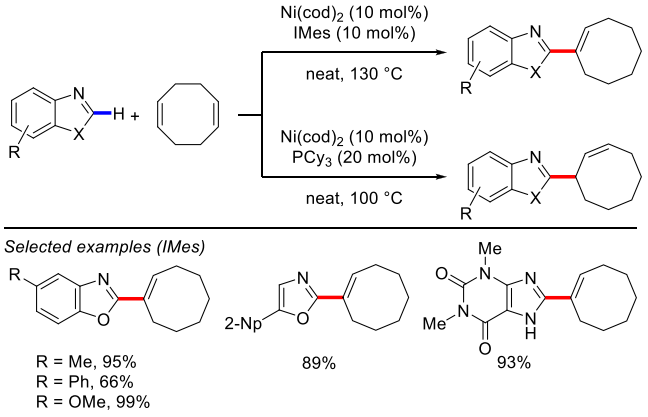
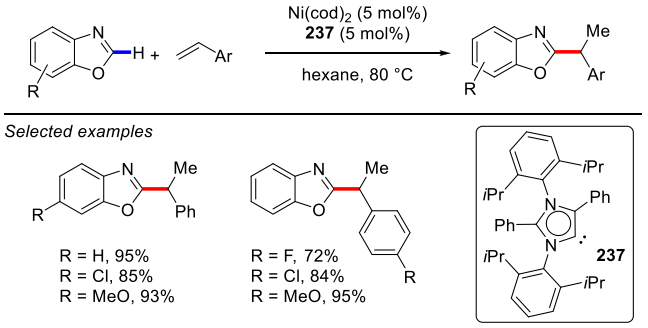
Chem. Rev. 2020, 120, 1981−2048

**Scheme 187. Ni–NHC-Catalyzed C2-Selective C($sp^2$)–H Alkenylation of Heterocycles with Cyclodienes by Ong**



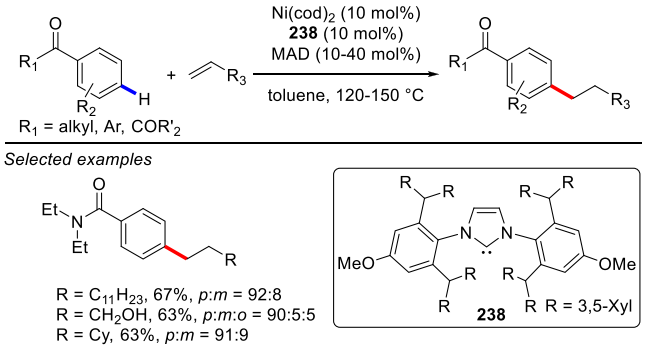

**Scheme 188. Abnormal Ni–NHC-Catalyzed C2-Selective Alkylation of Benzoxazoles by Mandal**



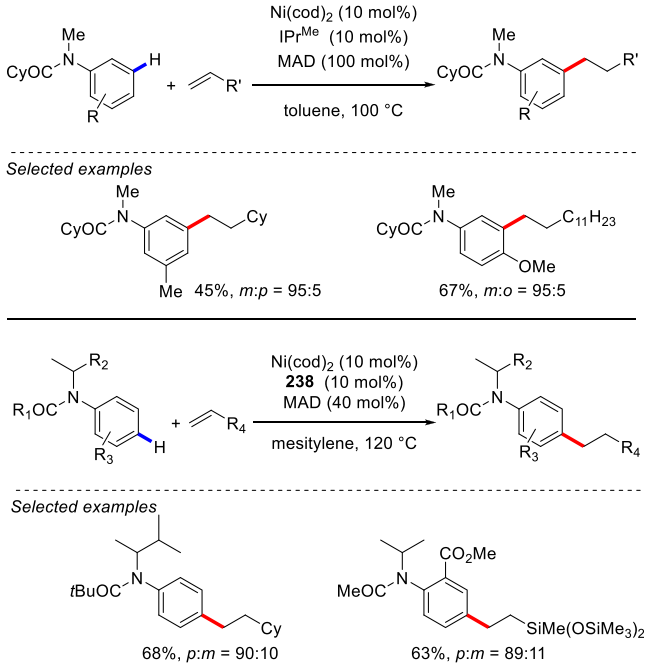

heteroarene bond to give the [Ni(NHC)(H)(Ar)] intermediate, olefin insertion, and reductive elimination. The C–H activation step is likely facilitated by the more flexible steric environment of the abnormal NHC ligand.

Following their initial report on bimetallic Ni(0)–Al(III) catalysis for the alkylation of pyridines (Scheme 177),[349] Nakao and co-workers developed several protocols for remote C($sp^2$)–H alkylation of arenes directed by the presence of a suitable Lewis basic functional group (Schemes 189–192). In 2016, the Nakao group disclosed the para-selective C($sp^2$)–H alkylation of benzamides and aromatic ketones promoted by a combination of Ni–NHC and MAD as a Lewis acid cocatalyst (Scheme 189).[363] They found that in this system the use of a sterically bulky and electron-rich NHC ligand **238** gave

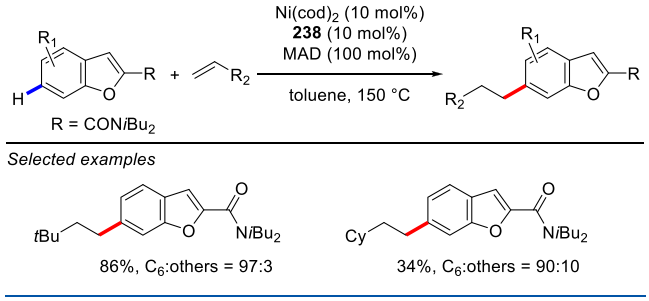
**Scheme 189. Ni–NHC-Catalyzed *p*-Selective Alkylation of Benzamides and Ketones by Nakao**



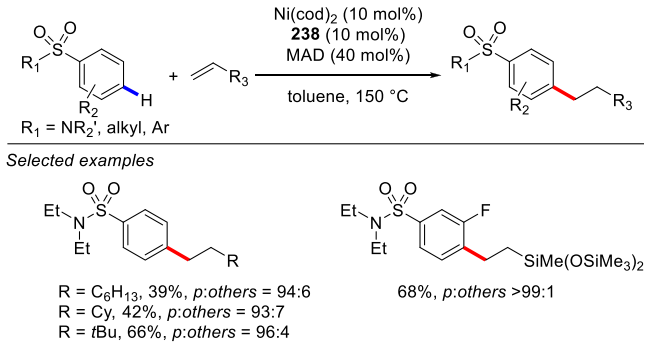

**Scheme 190. Ni–NHC-Catalyzed Remote Alkylation of Anilides by Nakao**




**Scheme 191. Ni–NHC-Catalyzed C6-Selective Alkylation of Benzofurans by Nakao**




**Scheme 192. Ni–NHC-Catalyzed *p*-Selective Alkylation of Sulfonylarenes by Nakao**




dramatically improved yields and regioselectivities than IPr or IPr*.[364] Similarly, MAD proved to be better in terms of both yield and regioselectivity than $AlMe_3$. This methodology could be used for para-selective C($sp^2$)–H alkylation of a wide range of *N*,*N*-disubstituted benzamides and aryl ketones in moderate to high yields and with excellent para-regioselectivity. Mechanistically, the reaction was proposed to involve coordination of the Lewis acid to the carbonyl group, which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Chem. Rev. 2020, 120, 1981–2048

facilitates C4-selective C−H activation by weakening the para C−H bond and sterically directing the Ni−NHC catalyst.

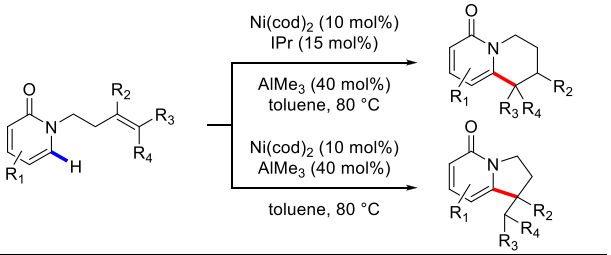
In 2018, the same group reported meta- and para-selective C(sp$^2$)−H alkylation of anilides by cooperative Ni−NHC−Al catalysis (Scheme 190).[365] In this variation, meta-selective C(sp$^2$)−H activation is achieved by the combined use of IPr$^{Me}$ (10 mol %) and MAD (100 mol %) in the presence of unhindered *N*-Me-*N*-COCy anilides, while the para-selective process exploits bulky *N*-anilide protecting groups and uses very similar reaction conditions to the alkylation of benzamides with sterically demanding NHC ligand **238** (cf. Scheme 189). This highly challenging reaction affords moderate yields and typically high regioselectivity; however, the scope appears to be limited.

In addition, Nakao and co-workers reported C6-selective C(sp$^2$)−H alkylation of benzofurans substituted with a sterically hindered 2-carbamoyl moiety (Scheme 191).[366] In this process, the bulky NHC ligand **238** (10 mol %) and MAD (100 mol %) were identified as the best combination to deliver C6-alkylated benzofurans in moderate yields and with high C6−H activation selectivity.

Furthermore, the Nakao group disclosed para-selective C(sp$^2$)−H alkylation of sulfonylarenes using the same bimetallic Ni−NHC−Al catalysis concept (Scheme 192).[367] In this case, the C−H activation occurs under very similar conditions to the para-selective alkylation of benzamides using **238** (10 mol %) and MAD (40 mol %) in toluene at 150 °C (cf. Scheme 189). The main advantage of this protocol is facile removal of the sulfonyl group to access simple arenes, which was nicely demonstrated by the authors in the synthesis of meta-substituted dialkylbenzenes.

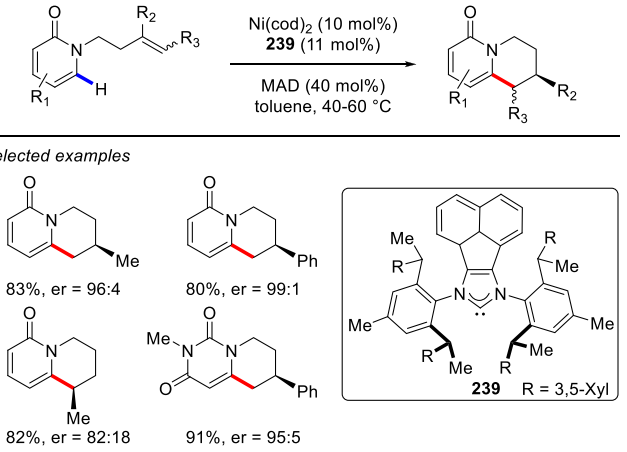
Intramolecular C(sp$^2$)−H annulations catalyzed by Ni−NHC complexes have been successfully accomplished by Cramer and co-workers (Schemes 193−195). In 2015, they

**Scheme 193. Intramolecular Ni−NHC-Catalyzed C(sp$^2$)−H Annulation of Pyridones by Cramer**

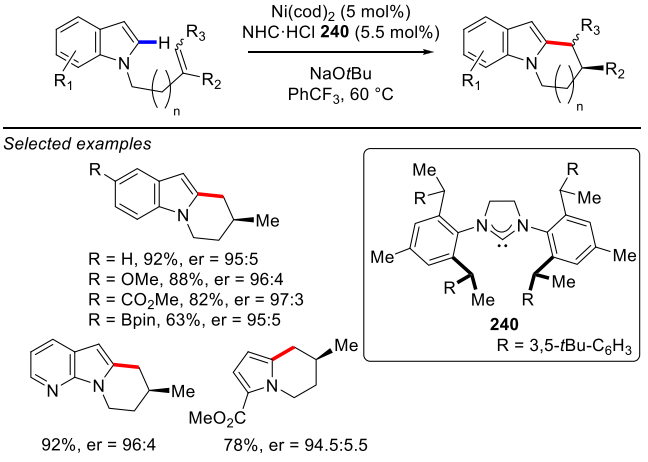



reported a regiodivergent annulation of pyridones by C(sp$^2$)−H activation at the C6 position to form 1,6-annulated products via 6-endo or 5-exo cyclization mode in good to excellent yields (Scheme 193).[368] They found that 6-endo- and 5-exocyclization regioselectivity could be switched by changing the catalyst system from Ni−NHC−Al bimetallic catalysis (Ni(cod)$_2$/IPr/AlMe$_3$) to Ni−Al catalysis (Ni(cod)$_2$/AlMe$_3$) under the same reaction conditions. A mechanism involving Ni(0)-catalyzed C−H insertion and irreversible hydroarylation was proposed. This methodology enables a straightforward

**Scheme 194. Asymmetric Ni−NHC-Catalyzed C(sp$^2$)−H Annulation of Pyridones by Cramer**




**Scheme 195. Asymmetric Ni−NHC-Catalyzed C(sp$^2$)−H Annulation of Indoles by Cramer**




way to construct medium-sized rings featuring [4.3.0] and [4.4.0] nitrogen-bridged heterocycles.

In 2018, Cramer and co-workers extended this C(sp$^2$)−H annulation methodology to the enantioselective cyclization of pyridines catalyzed by a new class of chiral Ni−NHC complexes (Scheme 194).[369] They identified a bulky BIAN-based NHC ligand **239** featuring chiral *N*-Ar wingtips as optimal for promoting this C−H annulation in terms of reactivity and enantioinduction. The X-ray analysis of a related NHC ligand in the series (R = Ph, Scheme 194) indicated % $V_{bur}$ of 43.5% for the [Au(NHC)Cl] complex ($V_{bur}$ = buried volume). This was significantly higher than the analogous [Ni(NHC)(Cp)Cl] complex (%$V_{bur}$ = 35.7%), indicating flexibility of the ligand in adjusting to the steric environment. This novel class of ligands enabled efficient 6-endoannulations under mild conditions in the presence of Ni(cod)$_2$ and MAD (40 mol %) in toluene at 40 °C.

More recently, the Cramer group achieved enantioselective C(sp$^2$)−H annulations of N-tethered indoles and pyrroles using a similar catalyst system based on Ni(cod)$_2$ and a chiral imidazolidinylidene ligand **240** (Scheme 195).[370] An intriguing feature of this design is the identification of very bulky flanking groups on the N-aromatic wingtip to enhance enantioselectivity of the process. This class of SIPr-based ligands is well poised to find further use in C−H activation reactions. The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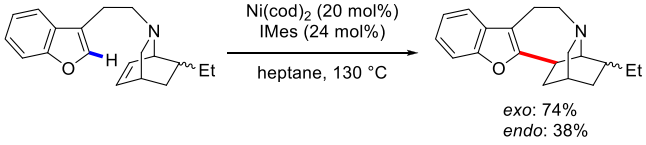
process enables access to tetrahydropyridoindoles and tetrahydroindolizines in good yields and with excellent enantioselectivities.

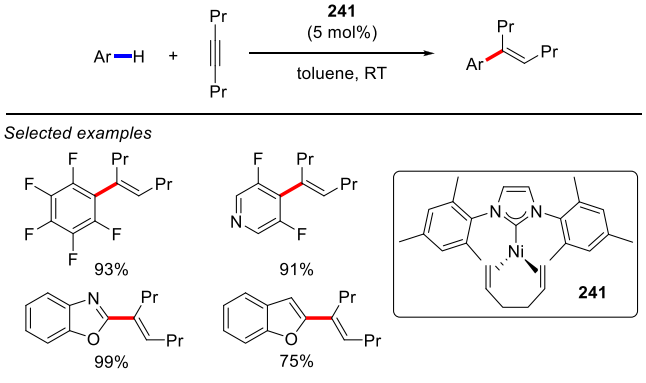
Independently, the Sames group reported the intramolecular C(sp$^2$)−H annulation of benzofurans with olefins catalyzed by Ni−NHC complexes in the context of synthetic studies on the Ibogamine alkaloids (Scheme 196).[371] By using the combination of Ni(cod)$_2$ and IMes in heptane at 130 °C, the intramolecular cyclization was achieved in moderate yields, while phosphine ligands were ineffective.

**Scheme 196. Intramolecular Ni−NHC-Catalyzed C(sp$^2$)−H Annulation by Sames**




In 2015, Montgomery and co-workers identified the IMes-based Ni−NHC complex **241** as a highly active catalyst for the C(sp$^2$)−H alkenylation of acidic C−H bonds in arenes and heteroarenes (Scheme 197).[372] Remarkably, they found that

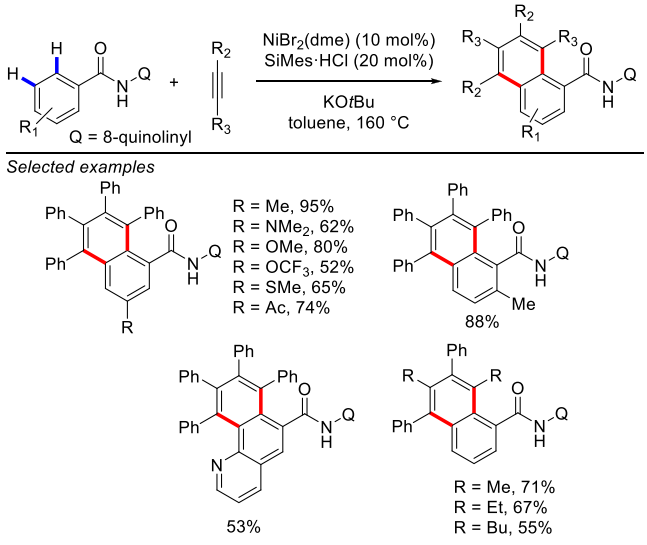
**Scheme 197. Ni−NHC-Catalyzed C(sp$^2$)−H Alkenylation of Acidic C−H Bonds by Montgomery**



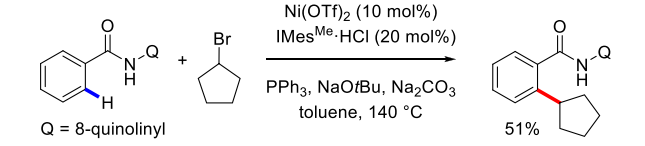

the most commonly used throw-away ligand in Ni(0)−NHC catalysis, namely, 1,5-cyclooctadiene (cod), showed a significant inhibitory effect on the catalytic activity by the formation of inactive $\pi$-allyl complexes through hydride migration to Ni-bound cod. Thus, using the cod-free Ni(0)−NHC complex, [Ni(IMes)(1,5-hexadiene)], allowed us to avoid the inactive $\pi$-allyl intermediates and resulted in high catalytic efficiency in this class of C(sp$^2$)−H activation reactions. Complex **241** is prepared in a single step from NiCl$_2$, IMes, and allylmagnesium bromide.

The Chatani group demonstrated Ni−NHC catalysis in amide-directed C(sp$^2$)−H activation reactions (Schemes 198 and 199). In 2016, they reported a NiBr$_2$(dme)/SIMes system for the oxidative intermolecular annulation of arenes and alkynes enabled by the 8-aminoquinolinyl-directing group (Scheme 198).[373] They found that other ligands, including IMes, ICy, SICy, and PCy$_3$, were capable of promoting this reaction; however, these ligands were less efficient than IMes. Mechanistically, the reaction was proposed to involve a Ni(0)/(II) cycle with the C(sp$^2$)−H activation step proceeding via a CMD pathway and the alkyne serving as the hydride acceptor. The same group also demonstrated that aromatic C(sp$^2$)−H

**Scheme 198. Ni−NHC-Catalyzed Amide-Directed C(sp$^2$)−H Oxidative Annulation by Chatani**



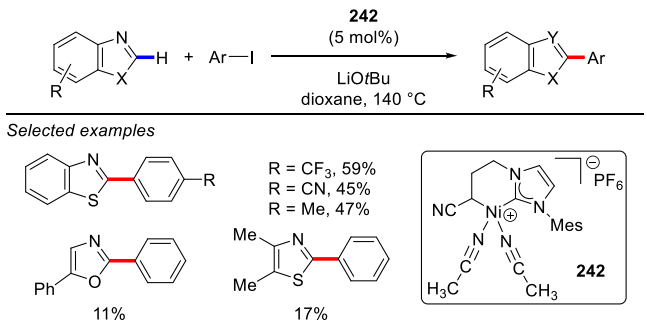

**Scheme 199. Ni−NHC-Catalyzed Amide-Directed C(sp$^2$)−H Alkylation by Chatani**




alkylation with challenging secondary alkyl halides directed by the 8-aminoquinolinyl group is facilitated by using a catalyst system based on Ni(OTf)$_2$/IMes$^{Me}$ and PPh$_3$ (Scheme 199).[374] The use of an NHC ligand is critical for the success of this reaction.

The direct C(sp$^2$)−H arylation of azoles is another class of C−H activation reactions that have been explored with Ni−NHC catalysis. In 2018, Ritleng and co-workers reported the direct C(sp$^2$)−H arylation of benzothiazoles with aryl iodides catalyzed by the cationic Ni−NHC complex **242** (Scheme 200).[375] This complex displayed modest activity in the direct

**Scheme 200. Ni−NHC-Catalyzed Direct C(sp$^2$)−H/C−I Arylation of Azoles by Ritleng**




C−H arylation. The authors proposed that the Ni(II)−NHC precatalyst is activated by the dimerization of benzothiazole. In 2018, Ong and co-workers reported Ni(cod)$_2$/IPr-catalyzed direct C(sp$^2$)−H arylation of azoles with anisoles by a dual C−H/C−O activation pathway (Scheme 201).[376] The reaction requires stoichiometric amounts of a Grignard reagent, and the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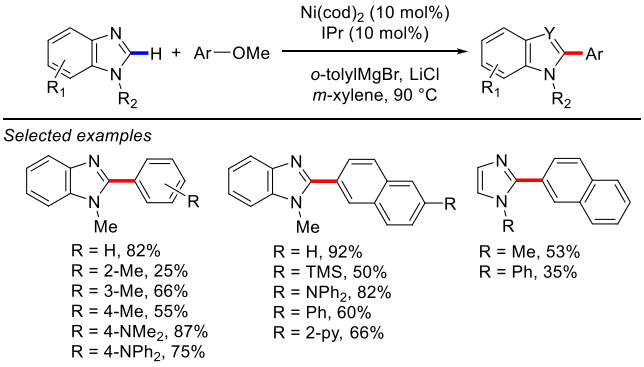
Chem. Rev. 2020, 120, 1981−2048

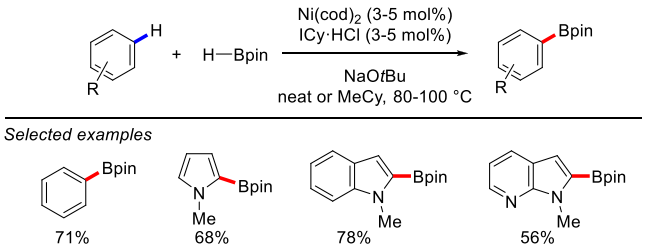
**Scheme 201. Ni–NHC-Catalyzed Direct C(sp²)–H/C–O Arylation of Azoles by Ong**




sterically demanding *o*-TolMgBr gave the best results. This process is remarkably broad in scope and includes activated conjugated arenes as well as simple arenes as coupling partners. The authors proposed that the reaction is facilitated by a synergistic action of the Ni–NHC catalyst and the Grignard reagent to deprotonate the C2–H azole bond.

In addition, a nondirected C(sp²)–H borylation of arenes and heteroarens using Ni–NHC complexes has been achieved by Chatani and co-workers (Scheme 202).[377] It was found that

**Scheme 202. Ni–NHC-Catalyzed C(sp²)–H Borylation by Chatani**



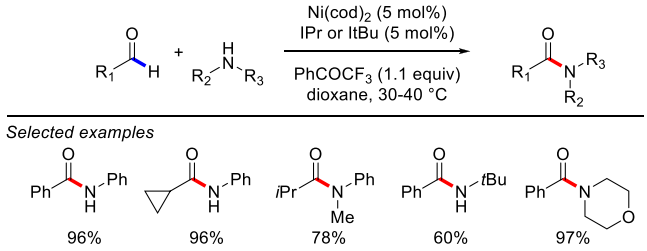

$Ni(cod)_2$ as the catalyst and ICy·HCl as the ligand precursor gave optimal results. Other NHC ligands, including SICy, IPr, IMes, IiPr, and ItBu, were less effective, while $PCy_3$ failed to deliver any product. The reaction enables the synthesis of a variety of C2-borylated indole derivatives in good yields. Furthermore, simple arenes, such as benzene, anisole, and toluene, are also suitable substrates under the reaction conditions. The reaction was proposed to involve a heterogeneous nickel catalyst. Independently, Itami and co-workers reported that a catalytic system based on $Ni(cod)_2$, IPr, and CsF promotes C(sp²)-selective C–H borylation of toluene with $B_2pin_2$ (not shown).[378]

Intramolecular ortho-N-aromatic C(sp²)–H activation within the Ni(0)–NHC complex to give a catalytically active cyclometalated Ni(II)–H for cycloisomerization of enynes has been reported by Louie and co-workers (not shown).[379]

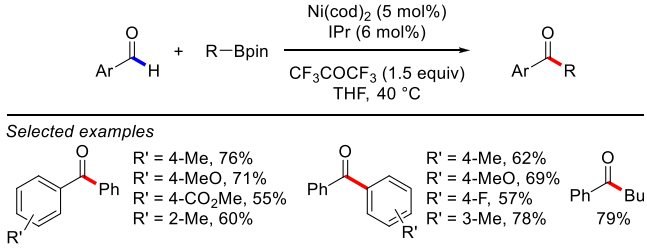
### 9.2. C(acyl)–H Activation

The synthesis of acyl derivatives by C(acyl)–H activation has been reported using Ni–NHC systems (Schemes 203 and 204). In 2015, Dong and co-workers reported the direct conversion of aldehydes to amides using a combination of $Ni(cod)_2$ (5 mol %), IPr or ItBu (5 mol %), and $PhCOCF_3$ (1.1 equiv) as a mild oxidant (Scheme 203).[380] This protocol allows for the dehydrogenative synthesis of a variety of amides

**Scheme 203. Ni–NHC-Catalyzed C(Acyl)–H Amidation by Dong**




**Scheme 204. Ni–NHC-Catalyzed C(Acyl)–H Arylation/Alkylation by Ge**




from aliphatic and aromatic aldehydes and amines. The mechanism was proposed to involve the following steps: (1) coordination of Ni–NHC to $PhCOCF_3$ and RCHO carbonyls; (2) oxidative addition of the C(acyl)–H bond; (3) hydride transfer to give Ni–alkoxide; (4) ligand exchange; and (5) reductive elimination. This methodology is also applicable to the direct coupling of aldehydes with alcohols, providing an alternative way to construct hindered esters. Independently, Gu and co-workers reported the synthesis of aryl and alkyl ketones by the direct coupling of aldehydes with aryl and alkyl boronic esters catalyzed by Ni–NHCs (Scheme 204).[381] The reaction is promoted by a very similar catalytic system using $Ni(cod)_2$ (5 mol %), IPr (6 mol %), and $CF_3COCF_3$ (1.5 equiv) as the oxidant. Other NHC ligands, including SIPr and ItBu, were less effective, while $PCy_3$ failed to produce the coupling product. The reaction is compatible with a variety of aryl aldehydes and aryl and alkyl boronic esters, affording the desired ketone products under mild conditions.

## 10. COPPER–NHC COMPLEXES

The first homoleptic Cu–NHC complex, $[Cu(IMes)_2(OTf)]$, was isolated in 1993 by Arduengo.[382] In 1994, Raubenheimer and co-workers synthesized and characterized the first monocarbene Cu–NHC complex, $[Cu(NHC)Cl]_2$ (NHC = 3,4,5-trimethylthiazole).[383] After these seminal studies, great success has been achieved in using Cu–NHC complexes as catalysts to promote organic transformations.[384−386] At present, Cu–NHCs have emerged as particularly efficient catalysts for C(sp²)–H and C(sp)–H carboxylation reactions using carbon dioxide, thus representing a very attractive method for incorporating this C1 building block into organic molecules. Further examples of C–H activation reactions promoted by Cu–NHCs include the following classes of reactions: (1) C(sp²)–H arylation reactions; (2) C(sp²)–H allylations, including enantioselective allylations; (3) C(sp²)–H amination and thiolation; and (4) enantioselective C(sp)–H allylation.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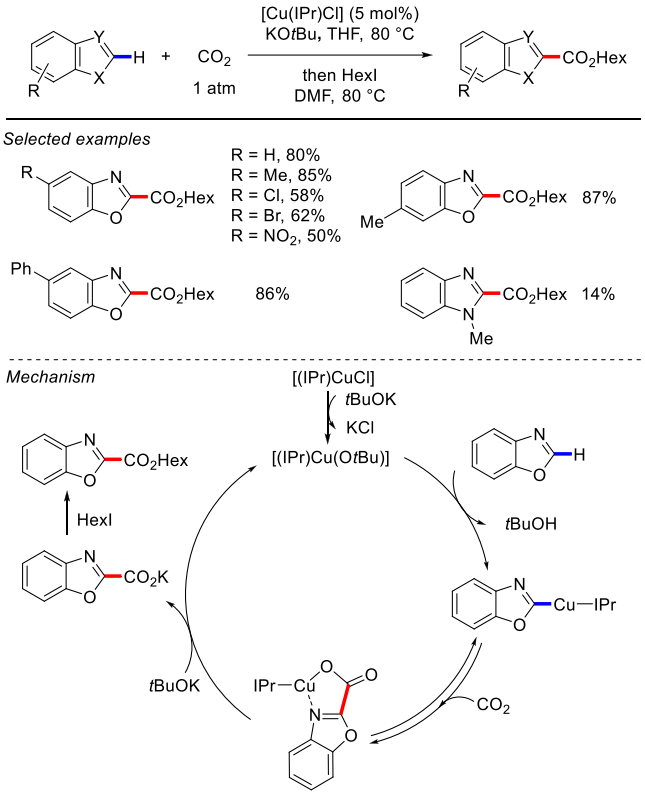
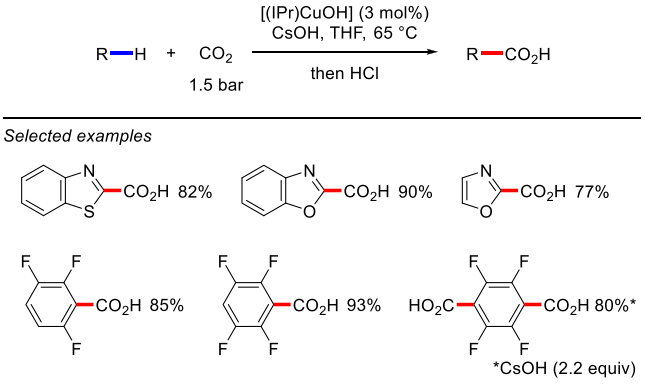
### 10.1. C(sp²)−H Activation

The first examples of C(sp²)−H carboxylation catalyzed by Cu−NHCs were reported independently by the Hou and Nolan groups in 2010 (Schemes 205 and 206).[387,388]

**Scheme 205. Cu−NHC-Catalyzed C(sp²)−H Carboxylation by Hou**




**Scheme 206. Cu−NHC-Catalyzed C(sp²)−H Carboxylation by Nolan**

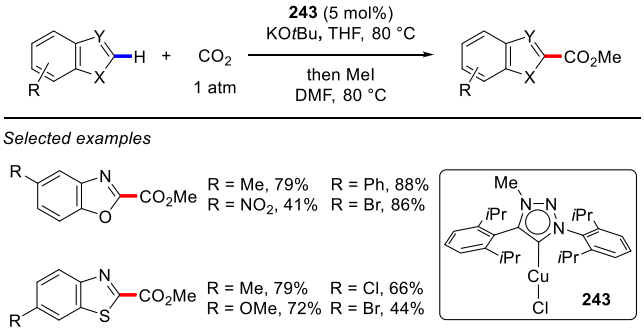



Hou and co-workers developed C(sp²)−H carboxylation of benzoxazoles with $CO_2$ at atmospheric pressure using [(IPr)CuCl] (5 mol %) in THF at 80 °C (Scheme 205).[387] The carboxylic acid products were isolated after esterification with iodohexane. Several other catalysts were tested, and SIPr, IMes, and SIMes proved to be less efficient. Importantly, the well-defined [Cu(IPr)Cl] gave higher yields than the catalyst prepared in situ from $Cu(OAc)_2$ and IPr·HCl. The reaction worked best with benzoxazole derivatives, while lower yielding examples of C(sp²)−H carboxylation of benzimidazole and 1,3,4-oxadiazole were also reported. The mechanism involving formation of the catalytically active [Cu(IPr)(O*t*Bu)] complex and deprotonation of the most acidic C−H was proposed. First, the active [(IPr)Cu(O*t*Bu)] complex reacts with the substrate to give the organocopper species [(IPr)Cu(Ar)] through Cu-mediated C−H activation. Reversible $CO_2$ insertion affords the carboxylate complex [(IPr)Cu($ArCO_2$)] stabilized by N-coordination. Ligand exchange and esterification with an alkyl halide furnish the desired product and regenerate the active [Cu(IPr)(O*t*Bu)] catalyst.

Independently, Nolan and co-workers reported C(sp²)−H carboxylation of acidic arenes and heteroarenes catalyzed by [Cu(IPr)(OH)] (Scheme 206).[388] In this system, the combination of [Cu(IPr)(OH)] (3 mol %) and CsOH in THF at 65 °C gave the optimal performance. The desired carboxylic acids were isolated directly after acidification of the reaction mixture. Furthermore, other Cu−NHC catalysts, including catalysts based on SIPr, IMes, and SIMes NHC ligands, were less effective. The reaction showed excellent selectivity and broad substrate scope, including benzoxazole, benzothiazole, oxazole, and acidic hydrocarbons.

In 2012, the Hou group expanded their C(sp²)−H carboxylation methodology to the direct carboxylation of benzoxazoles and benzothiazoles by using triazolylidene complex **243** (Scheme 207).[389] This [Cu(TPr)Cl] complex

**Scheme 207. Cu−NHC-Catalyzed C(sp²)−H Carboxylation Using Triazolylidine Complexes by Hou**




was shown to be more effective than [Cu(IPr)Cl] in the carboxylation of benzoxazole. In general, the protocol allowed for the synthesis of C2-carboxylated benzoxazoles and benzothiazoles in excellent yields. The high catalytic activity of **243** likely results from the strong $\sigma$-donation of the triazolylidene ligand.

Subsequently, several variations of the C(sp²)−H carboxylation catalyzed by Cu−NHCs have been reported (Schemes 208−210). In 2013, Li and co-workers reported morpholine-functionalized [Cu(NHC)Cl] catalyst **244** for the direct C(sp²)−H carboxylation of benzoxazoles with $CO_2$ at atmospheric pressure (Scheme 208).[390] The main advantage of this pH-responsive Cu−NHC catalyst is that the authors could recycle the catalyst four times while maintaining high activity. Independently, Hong and co-workers reported bifunctional NHC ligand **245** for the Cu−NHC-catalyzed carboxylation of benzoxazoles (Scheme 209).[391] This catalytic system gave the carboxylated products in higher yields than using [Cu(IPr)Cl] and showed excellent functional group tolerance. In an alternative approach to C(sp²)−H carboxylation, Hou and co-workers reported a tandem process relying on deprotonative alumination of arenes with $i$Bu$_3$Al(TMP)Li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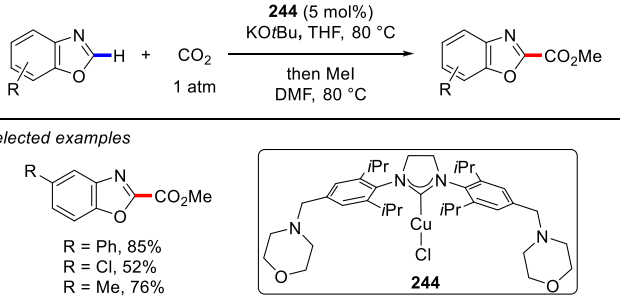
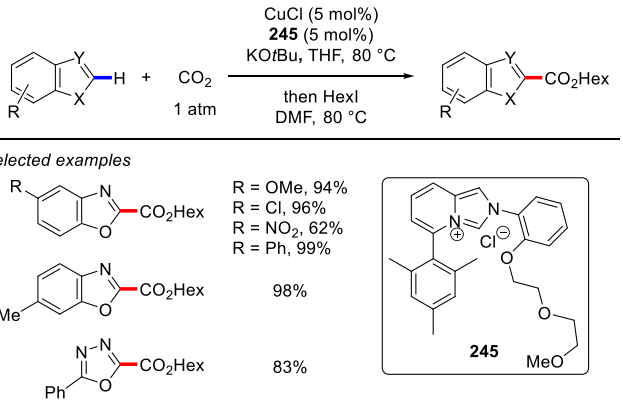
Chem. Rev. 2020, 120, 1981−2048

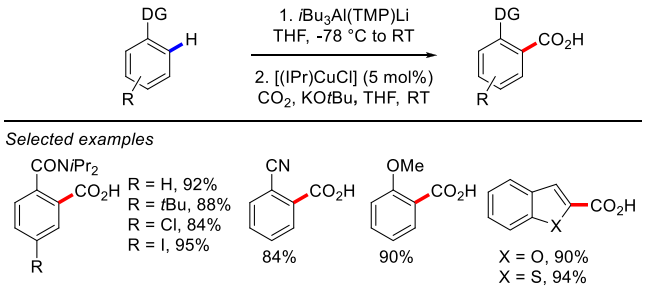
**Scheme 208. Cu−NHC-Catalyzed C($sp^2$)−H Carboxylation Using pH-Responsive Ligands by Li**




**Scheme 209. Cu−NHC-Catalyzed C($sp^2$)−H Carboxylation Using Bifunctional Ligands by Hong**



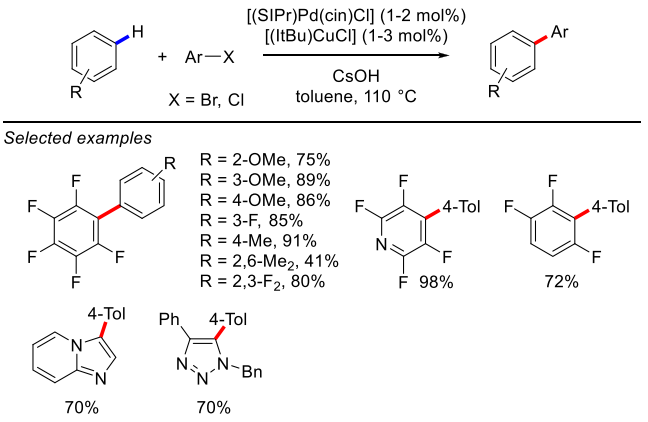

**Scheme 210. Cu−NHC-Catalyzed C($sp^2$)−H Deprotonative *ortho*-Carboxylation by Hou**




followed by carboxylation catalyzed by [Cu(IPr)Cl] (Scheme 210).[392] The reaction is characterized by excellent yields and broad functional group tolerance using benzamides, benzonitriles, anisoles, and acidic heterocycles as carboxylation substrates. A mechanism involving transmetalation of [Cu(IPr)(OtBu)] with organoaluminum to give aryl−Cu(IPr) was proposed. In addition, DFT study on the mechanism of C($sp^2$)−H carboxylation reactions promoted by Cu−NHC complexes has been published.[393] These reactions allow for the incorporation of carbon dioxide under mild conditions.[394−401]

In 2014, Cazin and co-workers reported a cooperative Cu−NHC/Pd−NHC system for the C($sp^2$)−H arylation of acidic arenes (Scheme 211).[402] In this design, [Cu(ItBu)Cl] promotes C($sp^2$)−H activation to form aryl−Cu(NHC) species after in situ conversion to the catalytically active [Cu(ItBu)(OH)]. In the cooperative cycle, Pd−NHC generates the Ar−Pd(NHC)−Cl intermediate through the standard oxidative addition to Pd(0)−NHC. Transmetalation of [Cu(ItBu)(Ar)] with [(SIPr)Pd(Ar)Cl] and reductive

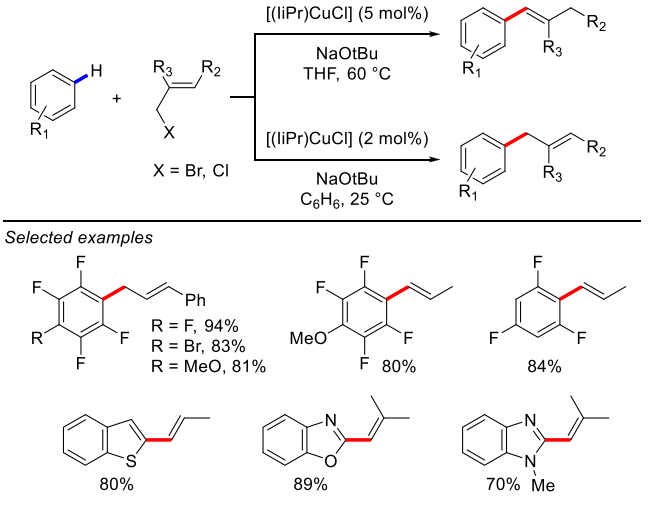
**Scheme 211. Cu−NHC/Pd−NHC-Catalyzed C($sp^2$)−H/C−X Arylation by Cazin**




elimination generates the biaryl product. This transformation shows broad scope with respect to fluorinated arenes and aryl halides and also includes examples of acidic heterocycles as the C($sp^2$)−H activation coupling partners.

In 2016, Chang and co-workers reported divergent C($sp^2$)−H alkenylation and allylation of acidic arenes and heteroarenes catalyzed by Cu−NHCs (Scheme 212).[403] Interestingly, they

**Scheme 212. Cu−NHC -Catalyzed C($sp^2$)−H Alkenylation and Allylation by Chang**

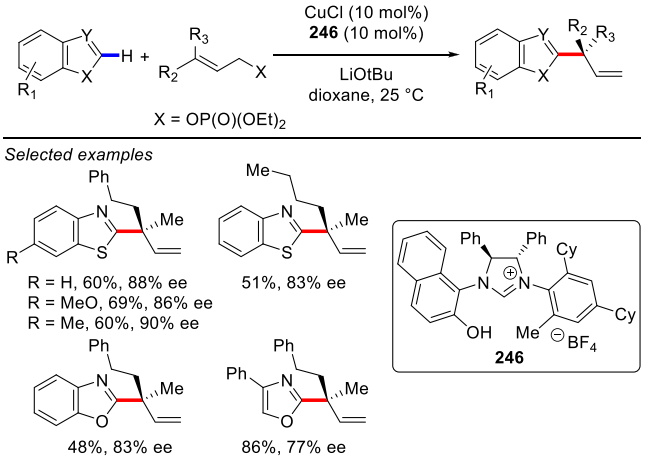



found that C($sp^2$)−H activation of arenes with allyl halides promoted by [Cu(IiPr)Cl] in the presence of NaO*t*Bu in THF at 60 °C resulted in the formation of vinyl products through the C($sp^2$)−H allylation/double bond migration pathway, while the same catalytic system in benzene at 25 °C gave C($sp^2$)−H-allylated arenes with excellent selectivity. Furthermore, this catalytic system was extended to electron-rich heteroarenes using $Me_2$EtCONa as a base. A mechanism involving the formation of Ar−Cu(NHC), oxidative addition of allyl halide to give $\pi$-allyl−Cu−Ar(NHC)(X), and reductive elimination was proposed.

Independently, Sawamura and co-workers reported enantioselective C($sp^2$)−H allylation of azoles with allyl phosphates catalyzed by Cu−NHC complexes (Scheme 213).[404] The reaction enables enantioselective construction of quaternary stereocenters with good substrate scope, excellent enantioselectivity, and branched:linear selectivity. The catalyst system


https://dx.doi.org/10.1021/acs.chemrev.9b00634
Chem. Rev. 2020, 120, 1981−2048

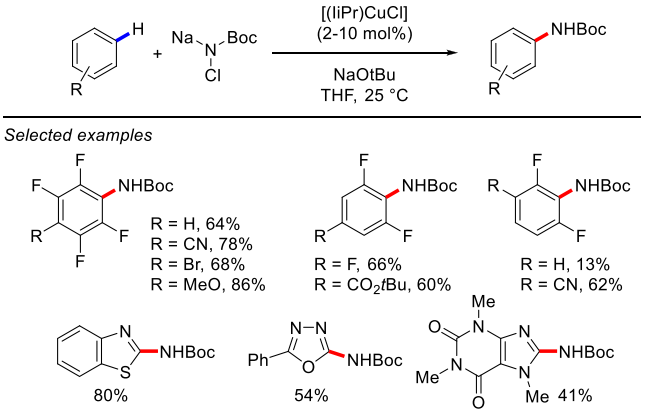
**Scheme 213. Enantioselective Cu−NHC-Catalyzed C(sp²)−H Allylation by Sawamuara**




based on a chelating *N*-2-napthol ligand **246** gave the best yield and enantioselectivity. Interestingly, a dramatic decrease in the reaction efficiency was observed when the hydroxyl group in the ligand was protected as a methyl ether, while no conversion occurred using NHC ligands without the oxygen atom, including analogues of **246**, IMes, and SIMes.

In 2016, Chang and co-workers disclosed direct C(sp²)−H amidation of acidic arenes and heteroarenes with BocNNaCl and related carbamates catalyzed by Cu−NHCs (Scheme 214).[405] This mild amidation protocol allows for the direct

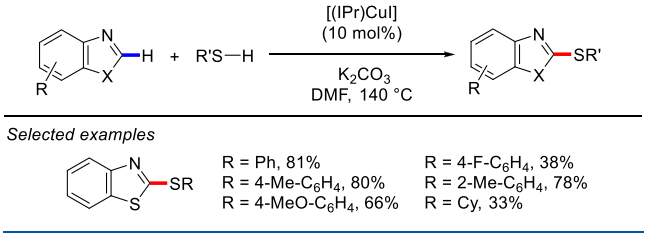
**Scheme 214. Cu−NHC-Catalyzed C(sp²)−H Amidation by Chang**




amidation of fluorobenzenes, azoles, and quinoline-*N*-oxides in the presence of [Cu(IiPr)Cl] and NaO*t*Bu in THF at 25 °C. Other NHC ligands, including SIiPr, IMes, SIMes, IPr, SIPr, and ICy, were less effective than IiPr in this transformation. A proposed mechanism involves the following steps: (1) formation of the catalytically active [Cu(IiPr)(O*t*Bu)]; (2) C(sp²)−H activation to give Ar−Cu(NHC); (3) oxidative insertion of BocNaN−Cl; (4) Ar group transfer to carbamate; and (5) ligand exchange.

In an alternative approach to forming C−heteroatom bonds by Cu−NHC catalysis, Fukuzawa and co-workers demonstrated an oxidative thiolation of azoles via direct C(sp²)−H activation (Scheme 215).[406] In the optimization study, they found that [Cu(IPr)Cl] is more catalytically active than [Cu(IMes)Cl], [Cu(TPr)Cl], and [Cu(TMes)Cl]; however,

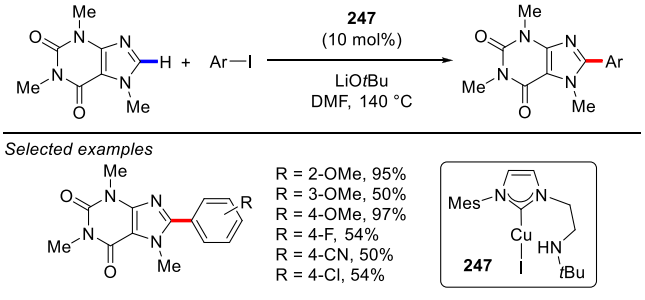
**Scheme 215. Cu−NHC-Catalyzed C(sp²)−H Oxidative Thiolation by Fukuzawa**




all complexes afforded the desired product in high yields. This methodology provides a straightforward access to diverse 2-thiobenzothiazoles.

In addition, the direct C(sp²)−H arylation of caffeine with aryl iodides catalyzed by Cu−NHC complexes was reported by Ong and co-workers (Scheme 216).[407] They found that a

**Scheme 216. Cu−NHC-Catalyzed C(sp²)−H/C−I Arylation of Caffeine by Ong**




system based on their hemilabile amino-tethered NHC scaffold **247** is an excellent catalyst for the direct arylation of a wide range of caffeine derivatives providing the C−H arylation products in good to high yields.

## 10.2. C(sp)−H Activation

Activation of terminal alkynes through copper acetylides represents another class of reactions catalyzed by Cu−NHC complexes. In general, the activation of terminal alkynes is facile due to increased C(sp)−H bond acidity. The use of copper acetylides in organic synthesis has been recently reviewed.[408]

In 2010, Zhang and co-workers reported the direct carboxylation of terminal alkynes using Cu−NHCs and carbon dioxide at atmospheric pressure (Scheme 217).[409] The main challenge associated with this transformation is the stability of the product propiolic acids to decarboxylation due to their low stability under high-temperature conditions. The authors found that a catalyst system based on poly-NHC ligand **248** and CuCl efficiently promotes this carboxylation in DMF at ambient conditions. The most significant advantage of this approach is the functional group tolerance toward a wide range of substrates, mild reaction conditions, and compatibility with deactivated alkynes.

Around the same time, Lu and co-workers reported a tandem process for the synthesis of allylic 2-alkynoates via C(sp)−H carboxylation catalyzed by Cu−NHCs as a key step (Scheme 218).[410] They identified that after the C(sp)−H carboxylation step using [Cu(IPr)Cl] under the standard conditions the resulting Cu carboxylates could be alkylated directly with allyl halides, thus providing a step-economical approach to alkynoate esters. Interestingly, CuCl and [Cu-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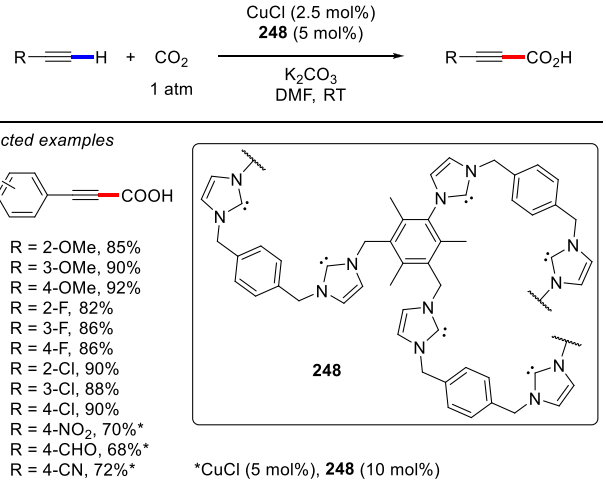
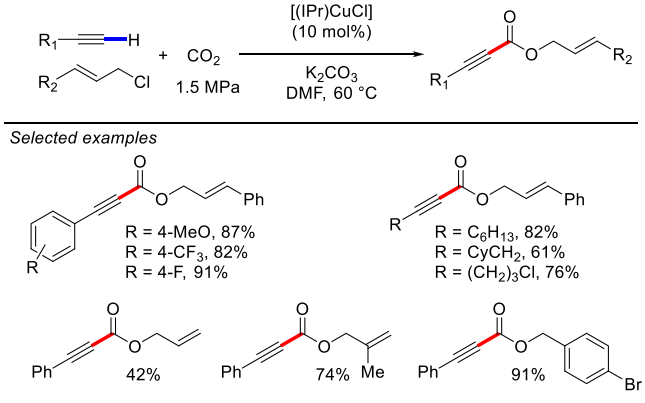
Chem. Rev. 2020, 120, 1981−2048

**Scheme 217. Cu–NHC-Catalyzed C(sp)–H Carboxylation by Zhang**




**Scheme 218. Cu–NHC-Catalyzed C(sp)–H Carboxylation/Allylation by Lu**



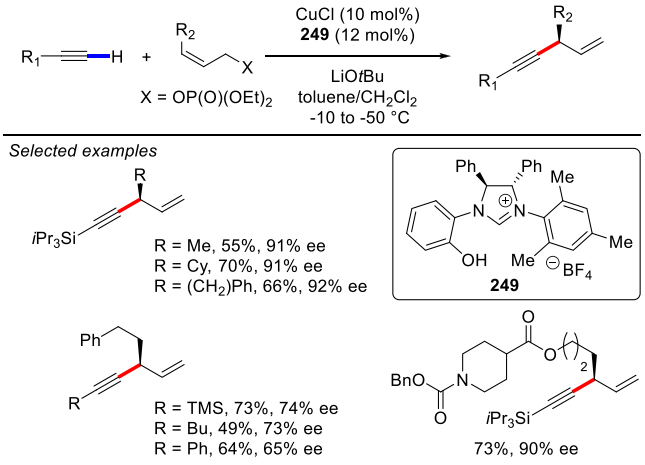

(IMes)Cl] proved to be significantly less effective in this reaction, highlighting the key importance of a well-defined and sterically hindered Cu–NHC complex.

In another illustrative example of functionalizing terminal alkynes catalyzed by Cu–NHC complexes, Sawamura and co-workers reported enantioselective C(sp)–H allylation with alkenyl phosphates (Scheme 219).[411] The success of this reaction relied on the development of a new chiral NHC ligand **249** featuring a chelating hydroxyl group on the N-aromatic side chain. Mechanistically, the authors proposed that the alkoxide coordinates to the catalytically active Cu–NHC species as an anionic ligand, leading to the formation of a well-defined chiral environment. This methodology delivers skipped enynes with excellent branched:linear selectivity and very good functional group tolerance. Additional examples of C(sp)–H functionalization via Cu–NHC acetylides have been published.[412−416]

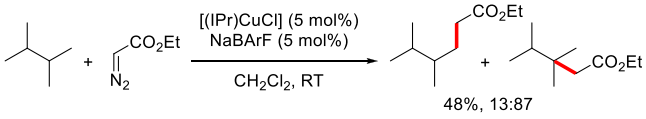
### 10.3. C(sp$^3$)–H Activation

In 2006, Perez and co-workers reported an example of C(sp$^3$)–H functionalization with ethyl diazoacetate catalyzed by [Cu(IPr)Cl] (Scheme 220).[417] This carbene insertion reaction gave a mixture of C–H activation of primary and secondary C(sp$^3$)–H bonds, favoring the branched product. Interestingly, this regioselectivity is completely reversed using Au–NHC complexes (see Scheme 225).

**Scheme 219. Enantioselective Cu–NHC-Catalyzed C(sp)–H Allylation by Sawamura**




**Scheme 220. Intermolecular Cu–NHC-Catalyzed C(sp$^3$)–H Alkylation by Perez**

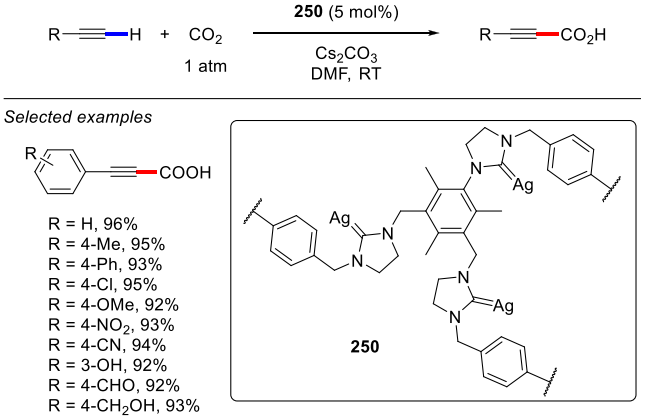



## 11. SILVER–NHC COMPLEXES

The first Ag–NHC complex, [Ag(IMes)$_2$(OTf)], was reported by Arduengo in 1993.[382] In the following years, Ag–NHC complexes have emerged as common NHC transfer reagents for the synthesis of other metal–NHC complexes by transmetalation.[418,419] Catalytic applications of Ag–NHCs remain relatively underdeveloped compared to other metals.[420−422] At present, examples of C–H bond functionalization catalyzed by Ag–NHC complexes are limited to C(sp)–H carboxylation reactions.

In 2012, Zhang and co-workers reported carboxylation of terminal alkynes catalyzed by poly-NHC–Ag complex **250** (Scheme 221).[423] This system showed high catalytic activity in C(sp)–H carboxylation under ambient conditions. The substrate scope is comparable to that observed using a related poly-NHC–Cu complex (cf. Scheme 217). The proposed mechanism involves formation of a silver acetylide inter-

**Scheme 221. Ag–NHC-Catalyzed C(sp)–H Carboxylation by Zhang**





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Chem. Rev. 2020, 120, 1981−2048

mediate. The complex could be recycled five times without a loss of catalytic activity. More recently, a related carboxylation of terminal alkynes catalyzed by *N*-benzylic Ag−NHCs was reported by Zhou and co-workers (not shown).[424] Catalytic C−H carboxylation reactions of terminal alkynes have been recently reviewed.[425]

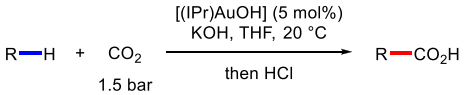
## 12. GOLD−NHC COMPLEXES

Although the first Au−NHC complex was isolated in 1973,[426] only recently Au−NHC complexes have been reported as catalysts and dynamic intermediates in organic synthesis.[427−430] Thus far, only few examples of C−H functionalizations catalyzed by Au−NHC complexes have been reported.

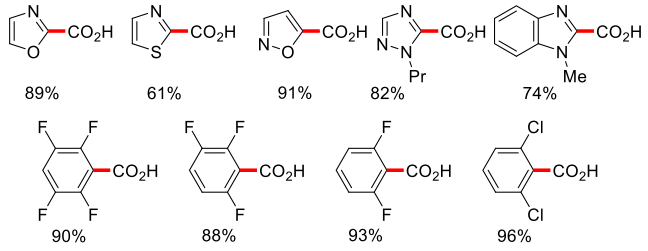
### 12.1. C(sp$^2$)−H Activation

In 2010, Nolan and co-workers reported a rare example of C(sp$^2$)−H functionalization catalyzed by Au−NHC complexes (Scheme 222).[431] They found that the direct C−H

**Scheme 222. Au−NHC-Catalyzed C(sp$^2$)−H Carboxylation by Nolan**




*Selected examples*



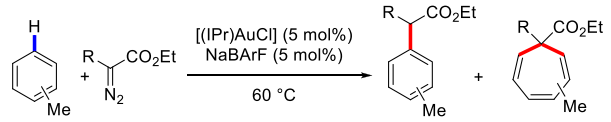

carboxylation of arenes and heteroarenes using [Au(IPr)OH] as the catalyst proceeded with high yields and excellent regioselectivity for arenes with acidic C−H bonds (p$K_a$ values of around 30 and lower). The optimized system involves catalytic Au−NHC (3 mol %), KOH (1.05 equiv), and $CO_2$ (1.5 bar) in THF at 20 °C. It is noteworthy that this methodology tolerates various five- and six-membered heterocycles, including oxazole, isoxazole, thiazole, imidazole, pyrazine, triazine, as well as chloro- and fluoroarenes, efficiently delivering the carboxylic acid products under mild conditions. A mechanism involving protonolysis of Au−NHC to give [(NHC)Au−Ar], nucleophilic addition to $CO_2$, and exchange with KOH to give arene carboxylate was proposed.

Another application of Au−NHC complexes in C(sp$^2$)−H activation was reported by the Perez group (Scheme 223). They demonstrated that [Au(IPr)Cl] catalyzes C(sp$^2$)-selective C−H carbene insertion of $\alpha$-functionalized ethyl diazoacetates to alkylbenzenes.[432] These reactions give a mixture of *o*/*m*/*p*-functionalized products; however, high selectivity for the insertion into the aromatic C−H bond (cf. aliphatic or Buchner reaction) using this catalytic system was observed.

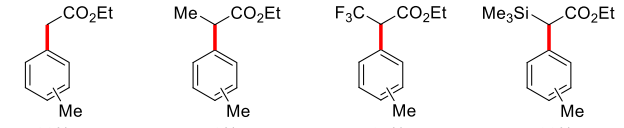
### 12.2. C(sp$^3$)−H Activation

In 2012, Che and co-workers reported oxidative C(sp$^3$)−H cyanation of *N*-aryltetrahydroisoquinolines using cationic Au(III)−NHC complex **251** under light irradiation conditions (Scheme 224).[433] In this design, the strongly $\sigma$-donating NHC

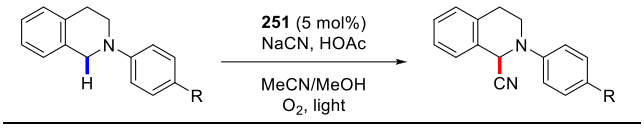
**Scheme 223. Au−NHC-Catalyzed C(sp$^2$)−H Alkylation by Perez**



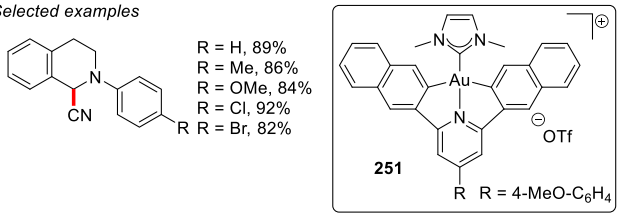

*Selected examples*




**Scheme 224. Au−NHC-Catalyzed Oxidative C(sp$^3$)−H Cyanation of Amines by Che**



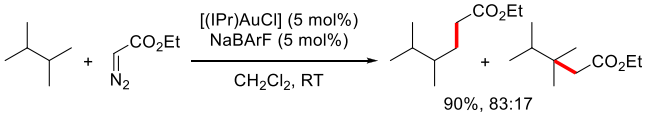

*Selected examples*




ligand increases the luminescence efficiency of Au(III). The oxidative cyanation was successful in the presence of sensitive halide functional groups, highlighting the mild conditions for oxidative generation of iminium ions by this approach.

Important studies further expanding the utility of Au−NHC complexes in aliphatic C−H functionalization by carbene insertion were published by Perez and co-workers. In their first contribution, they demonstrated the C(sp$^3$)−H alkylation of toluene catalyzed by [Au(IPr)Cl] (not shown).[434] Subsequently, they found that the same catalyst system promotes the branched-selective C−H functionalization of alkanes with ethyl diazoacetate (Scheme 225; cf. Scheme 220).[417] The mechanism and selectivity of these carbene insertion reactions have been investigated by DFT methods.[435]

**Scheme 225. Au−NHC-Catalyzed C(sp$^3$)−H Alkylation by Perez**




## 13. CONCLUSIONS AND OUTLOOK

As demonstrated in this review, tremendous advances have taken place using transition-metal−NHC complexes to promote C−H functionalization reactions. The unique electronic and steric properties of NHC ligands, in particular, their greater $\sigma$-donation than phosphine ligands and capacity to form well-defined complexes with diverse transition metals, combined with the stability to oxidative conditions have enabled the development of an array of novel C−H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Chem. Rev. 2020, 120, 1981−2048

functionalization reactions that are impossible with other ligands and resulted in significant improvements of the existing C−H functionalization methods. The progress using NHC ligands has been remarkable with both precious metals and 3d transition metals, which highlights the generality of the beneficial effect of this ligand platform. An especially exciting direction has been the development of asymmetric C−H functionalizations promoted by chiral NHC ligands, C−H activations at very low catalyst loading, C−H functionalization with typically inert electrophiles, divergent C−H functionalization, and functionalization of unreactive C($sp^3$)−H bonds.

Despite significant progress, there are numerous challenges that need to be addressed. (1) First, compared with phosphines, much fewer NHC ligands are commercially available. This needs to be addressed so that the beneficial impact of NHC ligands is available to all researchers and facilitates screening of the reaction conditions in a rapid and modular fashion. (2) Second, there is a scarcity of types of NHC ligands that have been tested in C−H activation reactions. Elegant mechanistic studies have already demonstrated that significant improvements in $\sigma$-donation and $\pi$-accepting properties of NHC ligands can be achieved by electronic and steric modification of the carbene scaffold.[24,25] The discovery of new NHC ligands is likely to facilitate further progress in the field. (3) Third, the method of generation of the active catalyst needs to be routinely explored. The most desirable is the use of well-defined NHC−metal complexes because this eliminates the complexation step and leads to the modularity of catalysis.[23,54,55] (4) Fourth, structure−activity studies between the ligand structure (%$V_{bur}$, steric maps) and electronic properties ($\sigma$-donation, $\pi$-acceptance) and catalytic activity should be routinely performed. Many of these values are already available in the literature,[41−56] and all new ligands should be identified in a similar fashion. An example should be taken from Pd-catalyzed cross-coupling reactions, which have now reached the desired level of maturity using well-defined Pd−NHC systems through NHC ligand design and further improvements in both the reaction conditions and throw-away ligand modifications. (5) Fifth, mechanistic studies that provide insight into the role of NHC ligands in C−H activation reactions should become more common. Ultimately, a better mechanistic understanding would lead to the design and discovery of improved catalyst systems that could find widespread application in various areas of organic chemistry and catalysis.

In summary, it is clear that the use of transition-metal−NHCs significantly expands the portfolio of C−H activation methods and has the potential to address the challenges in this field by designing even more efficient NHC ligands and catalytic systems. Such approaches using NHC ligands should be routinely leveraged by researchers involved in developing new C−H activation reactions.

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### Notes

The authors declare no competing financial interest.

### Biographies

Qun Zhao received his B.Sc. from Wuhan University of Technology in 2009. After a short experience in industry, he moved to Fudan University and received his M.Sc. degree in 2014. Subsequently, he joined Fluorine Team of IRCOF in France, studying C−H activation and fluorine chemistry with Professors Tatiana Besset, Thomas Poisson, Jean-Philippe Bouillon, and Xavier Pannecoucke, where he received his Ph.D. degree in 2017. In 2018, he joined the research group of Professor Michal Szostak at Rutgers University as a postdoctoral fellow. His research interests are focused on transition-metal catalysis and C−H activation reactions.

Guangrong Meng was born in Shandong Province, P.R. of China, and received his B.Sc. degree from Dalian Medical University in 2011. He received his M.Sc. from Fudan University in 2014. He completed his Ph.D. at Rutgers University in 2019 where he worked under the supervision of Professor Michal Szostak. Currently, he is a postdoctoral fellow in the group of Professor Jin-Quan Yu at The Scripps Research Institute. His research interests are focused on transition-metal catalysis and C−H activation reactions.

Steven P. Nolan received his B.Sc. in Chemistry from the University of West Florida and his Ph.D. from the University of Miami where he worked under the supervision of Professor Carl D. Hoff. After a postdoctoral stay with Professor Tobin J. Marks at Northwestern University, he joined the Department of Chemistry of the University of New Orleans in 1990. In 2006, he joined the Institute of Chemical Research of Catalonia (ICIQ). In early 2009, he joined the School of Chemistry at the University of St Andrews. In 2015 he moved to Ghent University. His research interests include organometallic chemistry and catalysis. His group has studied N-heterocyclic carbenes and their role in catalysis since 1998.

Michal Szostak received his Ph.D. from the University of Kansas with Professor Jeffrey Aubé in 2009. After postdoctoral stints at Princeton University with Prof. David MacMillan and at the University of Manchester with Prof. David Procter, in 2014, he joined the faculty at Rutgers University. His research group is focused on the development of new synthetic methodology based on transition-metal catalysis, transition-metal-mediated free-radical chemistry, and application to the synthesis of biologically active molecules.

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