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Transition-Metal-Catalyzed Direct C–H Alkenylation, Alkynylation, Benzylation, and Alkylation of (Hetero)arenes

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Direct functionalization of (hetero)aromatic C–H bonds has recently emerged as a powerful tool for the functionalization of organic molecules. In the past decade, while many efforts have focused on the direct arylation of (hetero)arenes, much less attention has been devoted to the direct alkenylation, alkynylation, and benzylation of (hetero)arenes. This microreview summarizes the development in this area to date, with the focus on how the substrate scope has been expanded through selection of more appropriate synthetic methods, such as the careful choice of catalysts, ligands, bases and reaction conditions.

Introduction

The complexity of organic target molecules is constantly increasing and novel strategies allowing the efficient formation of new carbon-carbon bonds between functionalized moieties are needed. The discovery in 1972 and subsequent systematic investigations of the Ni-catalyzed cross-coupling reactions of Grignard reagents by Kumada, Tamao, Corriu, and Masse represent in many respects the birth of modern transition-metal-catalyzed cross-coupling. Over the last 30 years, metal-catalyzed cross-couplings of (hetero)aryl halides and (hetero)arylmetal derivatives (path 1, Scheme 1) – including boronic acids (Suzuki), organostannanes (Stille), organosiloxanes (Hiyama), organozinc compounds (Negi-

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Samir Messaoudi was born in 1976 (Mechtras, Algeria) and studied chemistry at the Blaise Pascal University (Clermont Ferrand). He received his PhD in 2004 under the supervision of Prof. Michelle Prudhomme, working on the synthesis of rebeccamycin, granulatimide, and staurosporin analogues as anticancer agents. In 2004 he moved to Prof. D.-J. Aitken's group as a temporary lecturer. Then in 2005 he joined the group of Prof. J.-D. Brion and Dr. M. Alami at Paris XI University as a postdoctoral researcher, working on the field of the synthesis of aromatase inhibitors. Since 2006 he has been a CNRS permanent junior research scientist in the same laboratory. His research interests focus on the use of transition metal complexes as catalysts in the development of new chemical reactions. Much of the research is directed towards the establishment of more chemically and economically efficient processes for potential application in the preparation of hsp90 inhibitors and vascular disrupting agents (VDAs).

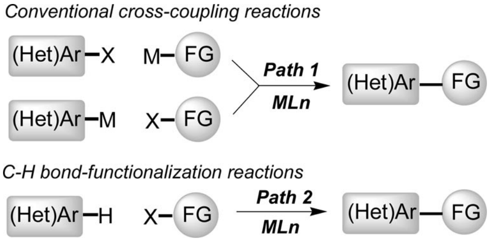
Jean-Daniel Brion, born in 1948 near Paris, obtained a pharmacy degree in 1971 from University of Paris V and received his doctorate in 1977 at the University of Paris VI with Profs. P. Reynaud and P. Maitte. In 1983 he was appointed professor at the Faculty of Pharmacy of Nantes and from 1989 to 1995 he worked at the discovery center of Servier Group in Suresnes as chemical division director. He then returned to the University of Paris XI, where his current positions are Professor of Medicinal Chemistry at the Faculty of Pharmacy, Director of UMR 8076 BioCIS, a research unit associated with the CNRS (1997–2007), and presently Director of Paris-South Institute of Therapeutic Innovation IPSIT. His research interests include medicinal chemistry with syntheses, biological activities, and structure/activity relationships of polyenes and analogues of vitamin A (retinoids), macrolactones, oxygenated heterocycles (chromenes, chromones), or indole derivatives. Antiangiogenesis and neurodegenerative agents are one of his main areas of research.

Mouâd Alami was born in 1959 in Fez (Morocco). He carried out his undergraduate studies at the University Pierre and Marie Curie in Paris and received his PhD in 1987 at the same university (Pr. J.-F. Normant & G. Cahiez). After a two-year postdoctoral position in collaboration with the Elf-Atochem company, in 1989 he joined the CNRS (National Center for Scientific Research) at the Ecole Normale Superieure, ENS-Paris. In 1993 he spent one year of postdoctoral studies at the University of Santa-Barbara in the laboratory of Prof. B. H. Lipshutz and in 1997 he moved as an independent researcher at the CNRS to Cergy-Pontoise University. In 1999 he accepted a position at the Faculty of Pharmacy (University Paris-Sud 11) where he became Director of Research. Dr Alami's field of specialization includes the development of new synthetic methodologies in organometallic chemistry, the selective formation of C–C and C–N bonds in heterocyclic chemistry, multi-components reactions, and the synthesis of natural product analogues with antitumor activities (antimitotic, hsp90-inhibitors, vascular targeting and disrupting agents).

shi), alkynes (Sonogashira), or olefins (Heck) – have enjoyed widespread popularity in synthetic chemistry. In addition, they have emerged as a tremendously powerful synthetic tool, reaching a level of sophistication that allows a wide range of coupling partners to be combined efficiently. Although high yields and selectivities can be obtained, the requisite arene preactivation involves several manipulations prior to the cross coupling, thus generating waste from reagents, solvents, and purifications, which in itself can be a time-consuming and economically inefficient process. Over the past few decades, direct transition-metal-catalyzed functionalization of C–H bonds in heterocycles (path 2, Scheme 1) has received significant attention in modern organic chemistry as an alternative to traditional cross-coupling methods, due to its atom economy, high functional group tolerance, and the potential to transform the unreactive C–H bonds into diverse functions in one operation. In particular, direct arylation of hetero(arenes) has already gained widespread acceptance within the synthetic community, because of its capacity to utilize simpler and cheaper precursors for the construction of complex frameworks.[1] In most cases, the more difficult to prepare organometallic component is replaced, which also reduces the metal waste generated in the overall process (path 2, Scheme 1). All notations and abbreviations can be found in Table 1.

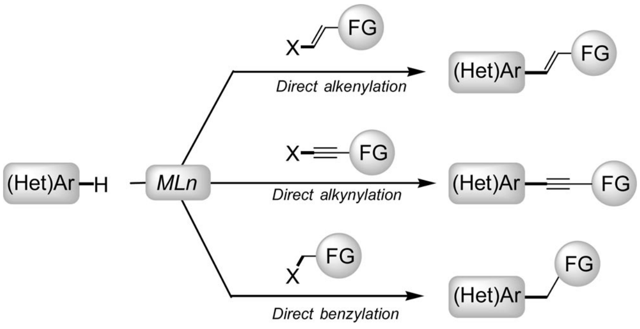
Table 1. Notations and abbreviations.

1-AdCO$_2$H	1-adamantanecarboxylic acid
Ar	aryl
B	base
Bn	benzyl
Bu	butyl
Cp*	η^6-pentamethylcyclopentadienyl
Cy	cyclohexyl
p-cymene	1-methyl-4-(1-methylethyl)benzene
COD	cyclooctadiene
dba	dibenzylideneacetone
DG	directing group
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1′-bis(diphenylphosphanyl)ferrocene
dppm	bis(diphenylphosphanyl)methane
dppp	bis(diphenylphosphanyl)propane
equiv.	equivalents
FG	functional group
Het	heterocycle
(Het) Ar	heteroaryl
HMDS	hexamethyldisilazide
*i*Pr	isopropyl
L	ligand
M	metal
MeOH	methanol
NMP	*N*-methylpyrrolidine
NMR	nuclear magnetic resonance
OAc	acetate
OPiv	pivalate
OTf	triflate
o-Tol	*ortho*-tolyl
Ph	phenyl
PhH	benzene
PhMe	toluene
Piv	pivaloyl
PMP	*para*-methoxyphenyl
PMB	*para*-methoxybenzyl
room temp.	room temperature
S$_E$Ar	electrophilic aromatic substitution
Si(*i*Pr)$_3$	*tri*-isopropylsilyl
*t*Bu	*tert*-butyl
THF	tetrahydrofuran
X	halide
MW	microwave irradiation



Scheme 1. How to couple a (hetero)arene with a functional group (FG). In reaction path 1, both (hetero)arene and FG are preactivated [(hetero)arene with a halide (X) and FG with an electropositive metal (M) or vice versa]. In reaction path 2, only the FG is preactivated.

In contrast with the much more developed palladium-catalyzed C–H arylation reaction of various (hetero)arenes,[1] direct alkenylation, alkynylation, and benzylation of (hetero)aromatics have received much less attention. Various transition metals, including palladium, rhodium, ruthenium, gold, and copper, have been reported as efficient catalysts for these transformations. In these instances, very small numbers of (hetero)arenes were studied. In this microreview we outline the development and advances in transition-metal-catalyzed (hetero)arene-alkenyl, -alkynyl, and -benzyl bond formation through C–H activation at relatively acidic C(sp^2) positions in (hetero)arenes (Scheme 2).



Scheme 2. Direct alkenylation, alkynylation, and benzylation of (hetero)arenes.

1. Direct Intermolecular Alkenylation

The direct alkenylation of (hetero)cycles poses a challenging task with respect to the regioselectivity of the reaction. For heterocycles, however, unlike in the case of direct intermolecular alkenylation of arene systems, the inherent electronic bias of the heterocycle itself is often sufficient to control the regioselectivity of the direct alkenylation reaction, obviating the need for directing groups. Consequently, the regioselectivity of intermolecular direct alkenylation depends on the heterocycle type as well as on the electronic nature of the catalyst employed. More recently, other factors such as solvent, additives (i.e., Cu^I salts), and the steric nature of the catalyst/ligand system have been used to alter the regioselectivity of heterocyclic alkenylation. Accordingly, this portion of the microreview highlights all advances in this area of direct alkenylation of (hetero)arenes according to the nature of catalyst used (Pd, Cu, Ru, Rh···). In addition, comments relating to the stereoselectivity of the C–H alkenylation as well as the proposed mechanism are presented where appropriate.

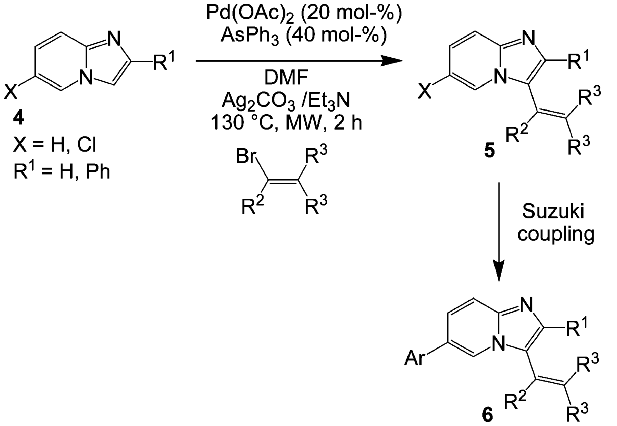
Palladium-Catalyzed Direct Alkenylation (Coupling between sp^2 C–H and sp^2 C–H Bonds)

Intermolecular Processes

Alkenyl(hetero)arenes have attracted significant attention as important structural elements in biologically active compounds.[2] The palladium-catalyzed direct alkenylation of arenes under ligand-free conditions was first reported by Daugulis et al.[3] This pioneering work demonstrated that regioselective $C(sp^2)$–H bond activation could be achieved by heteroatom-assisted coordination. Catalytic coupling of the haloolefin **2** (Scheme 3), in the presence of $PdCl_2$ as the catalyst, with the anilides **1** provided the corresponding coupling products **3** in moderate to good yields. Preliminary mechanistic investigations of this coupling process by the authors suggested the initial formation of the palladated anilide species **I**, which then produced the coupling products through a bromoacrylate ester coordination-insertion mechanism (Scheme 3).

This method proceeding by a C–H activation/C=C insertion mechanism suffers, however, from product inhibition.[4] For anilides possessing electron-withdrawing substituents, the reactions stop at low levels of conversion because the coupling product **3** binds more strongly to palladium than either the anilide or bromoalkene.

In 2008, Guillaumet and co-workers[5] investigated the synthesis of 3-alkenylimidazo[1,2-*a*]pyridines by palladium-catalyzed C–H alkenylation between bromoalkenes and imidazo[1,2-*a*]pyridines (Scheme 4) under microwave activation conditions.

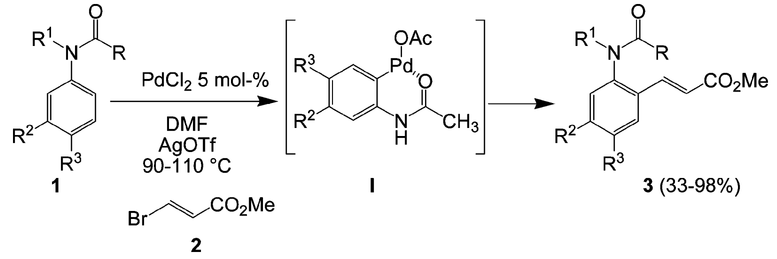


X	R^1	R^2	R^3	Yield of **5** (%)
Cl	H	Me	H	71
Cl	H	H	Me	56
Cl	H	Ph	Ph	54
H	Ph	Me	H	26
H	H	Me	H	69

Scheme 4. Palladium-catalyzed alkenylation of various imidazo[1,2-*a*]pyridines **4** with alkenyl bromides under microwave irradiation conditions.

Representative examples of C3 alkenylation of imidazo[1,2-*a*]pyridines with alkenyl bromides are illustrated in Scheme 4. With $Pd(OAc)_2/AsPh_3$ as the catalytic system and DMF as the solvent at 130 °C in the presence of Ag_2CO_3/Et_3N as bases under microwave irradiation conditions, alkenylation reactions occurred selectively at the C-3 positions in the heteroarenes **4**, producing the products **5** in moderate to high yields.

Interestingly, the authors demonstrated the compatibility of the alkenylation reaction conditions with the presence of

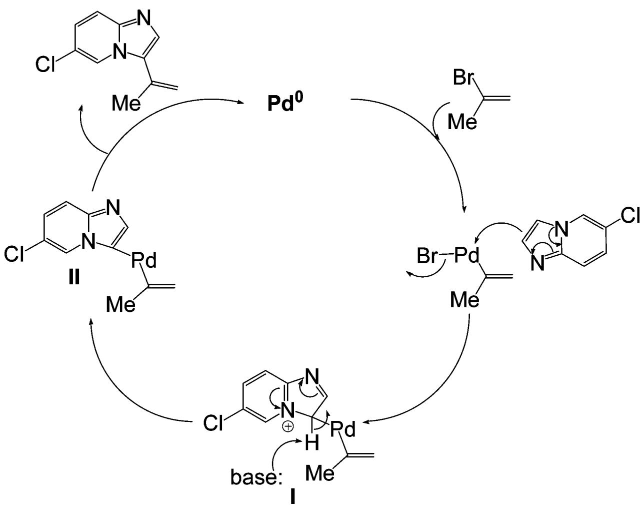


R	R^1	R^2	R^3	Yield (%)
*t*Bu	H	H	H	85
Me	H	H	H	56
*t*Bu	H	Cl	H	33
Me	H	OH	H	65
Me	Me	OMe	H	98
*t*Bu	H	OMe	Br	61

Scheme 3. Palladium-catalyzed coupling between the bromoolefin **2** and the anilides **1**.

a chloro substituent in the 6-position. Further functionalization of the carbon-chlorine bonds in compounds **5** under Suzuki cross-coupling conditions [$Pd(Ph_3)_4$ (0.1 equiv.), NaOH (2 equiv.), $RB(OH)_2$ (1.2 equiv.) in DME/H_2O at 150 °C, MW] provided the 3,6-disubstituted imidazo[1,2-*a*]pyridine derivatives **6** in satisfactory yields (60–68%) (Scheme 4).

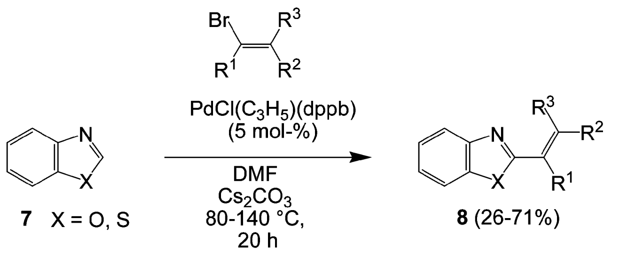
A plausible mechanism was proposed by the authors (Scheme 5); it involves an oxidative addition step followed by nucleophilic attack from the 3-position of the 6-chloroimidazo[1,2-*a*]pyridine onto the isopropenylpalladium halide species to form **I**. This evolves after deprotonation into the isopropenyl-6-chloroimidazo[1,2-*a*]pyridinepalladium intermediate **II**. A subsequent reductive elimination of **II** produces the product **5** and regenerates the palladium(0) catalyst.



Scheme 5.

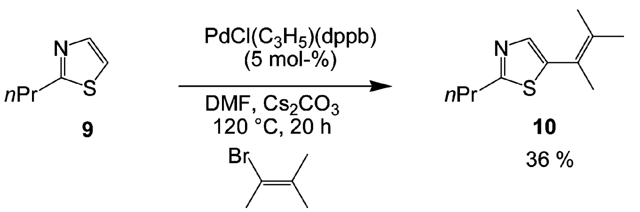
In the same year, Doucet and co-workers[6] had found that the catalyst system [$PdCl(dppb)(\eta^3\text{-}C_3H_5)$] in DMF in the presence of Cs_2CO_3 as the base is able to promote the direct C-2 alkenylation of electron-rich heteroaromatics **7**, such as benzoxazole or benzothiazole (Scheme 6). Optimized conditions were found to require 2 equiv. of heterocyclic coupling partner, due to partial decomposition of these substrates at elevated temperatures (140 °C). Moderate to good yields of the coupling products **8** were obtained with both α- and β-substituted alkenyl bromides or even with trisubstituted alkenyl bromides. The reaction selectivity was also examined when benzoxazole was treated with a mixture of (*Z*)- and (*E*)-2-bromobut-2-ene (1:1). At 140 °C, the reaction selectively furnished the *E* coupling product in 55% yield together with 4% of its *Z* isomer.

Doucet also examined one example of the alkenylation of the heteroaromatic thiazole **9** (Scheme 7) in which the C2-position was substituted. Under optimized conditions, this heteroarene was found to be slightly less reactive than benzothiazole, because its alkenylation reaction with 2-bromo-3-methylbut-2-ene selectively provided the 5-alkenylation product **10** but only in moderate yield.



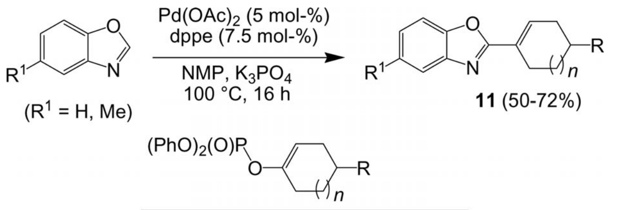
X	R^1	R^2	R^3	Yield (%)
O	H	Ph	H	61
O	H	Me	Me	54
O	Me	Me	Me	51
O	Me	Me	H	55
S	H	Ph	H	69
S	Me	Me	Me	58

Scheme 6. Palladium-catalyzed alkenylation of benzoxazole and benzothiazole (**7**) with alkenyl bromides.



Scheme 7.

More recently, Ackermann and co-workers[7] have investigated the challenging use of moisture-stable alkenyl phosphates[8] as convenient coupling reagents in palladium-catalyzed direct alkenylations of benzoxazole (Scheme 8). The authors discovered that a catalyst system composed of $Pd(OAc)_2$ and dppe promotes reactions between benzoxazoles and alkenyl diphenylphosphates in NMP in the presence of K_3PO_4. Various 2-alkenyl benzoxazole products **11** were obtained in good yields.

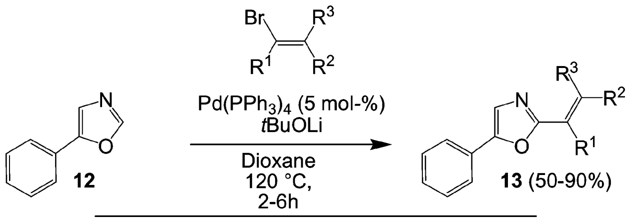


R^1	R	*n*	Yield (%)
H	H	1	72
H	*n*Pent	1	52
Me	*t*Bu	1	50
H	H	2	56

Scheme 8. Palladium-catalyzed alkenylation of benzoxazoles with alkenyl phosphates.

The oxazole ring system, a commonly occurring motif in natural molecules and pharmaceuticals,[9] has been the focus of various works in the field of metal-catalyzed direct arylation[10] or alkenylation.

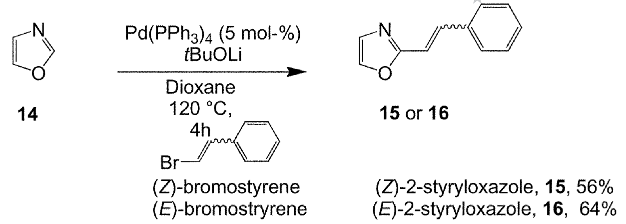
Piguel and co-workers[11] investigated the palladium-catalyzed C–H alkenylation of 5-phenyloxazole (**12**, Scheme 9) with various alkenyl bromides in the presence of $Pd(PPh_3)_4$, *t*BuOLi as the base, and dioxane as the solvent at 120 °C over 2–6 h. These conditions were suitable for the synthesis of various 5-phenyl-2-alkenyloxazoles **13** in good yields. More interestingly, the procedure developed by the authors proved to be selective, with the reactions proceeding equally well with *Z*- or *E*-alkenyl bromides to furnish the *Z*- or *E*-2-alkenyloxazoles **13**, respectively. In this connection, it should be noted that the alkenylation with *Z*-bromoalkenes has to be carefully monitored because isomerization of the *Z* product to the corresponding *E* form (*Z*/*E* ratio from 100:0 to 50:50) can occur when the reaction time is prolonged (overnight). Heating at 120 °C for 2–4 h was found to represent the best compromise between conversion and isomerization.



R^1	R^2	R^3	Yield (%)
H	4-$CF_3C_6H_4$	H	77
H	3-$NO_2C_6H_4$	H	54
H	H	3-FC_6H_4	90
H	H	4-$MeOC_6H_4$	73
H	H	*c*C_6H_{11}	50
Me	Me	Me	66

Scheme 9. Palladium-catalyzed alkenylation of 5-phenyloxazole (**12**) with alkenyl bromides.

The regioselectivity of the C–H alkenylation of unsubstituted oxazole was also investigated (Scheme 10). The authors demonstrated that treatment of oxazole (**14**) with two equivalents of (*Z*)- or (*E*)-β-bromostyrene for 4 h at 120 °C afforded (*Z*)-2-styryloxazole (**15**) and (*E*)-2-styryloxazole (**16**) as single regioisomers in 56% and 64% yields, respectively.

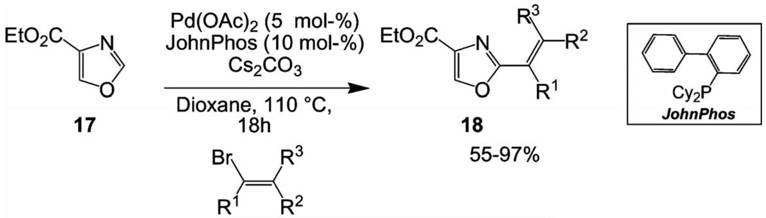


Scheme 10. Palladium-catalyzed alkenylation of unsubstituted oxazole (**14**) with (*Z*)- or (*E*)-β-bromostyrene.

On the other hand, in 2009, Hoarau and co-workers[12] demonstrated that with $Pd(OAc)_2$ as a precatalyst, ethyl oxazole-4-carboxylate (**17**, Scheme 11) would undergo direct regioselective C-2 alkenylation with functionalized alkenyl bromides in dioxane at 110 °C in the presence of Cs_2CO_3 as the base to give the vinylated derivatives **18** in good yields. As illustrated in Scheme 11, Buchwald's JohnPhos ligand [2-(dicyclohexylphosphanyl)biphenyl][13] was the ligand of choice for the C-2 C–H alkenylation.

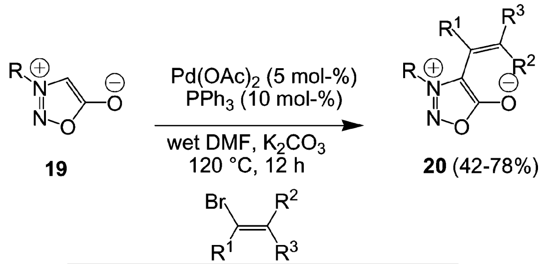
Sydnones are mesoionic heteroaromatic compounds with the 1,2,3-oxadiazole skeleton bearing an oxygen attached to the 5-position.[14] In this case, Moran and co-workers[15] prepared the 4-alkenylated sydnones **20** (Scheme 12) in good yields through the direct C–H alkenylation of the *N*-substituted sydnones **19** with alkenyl halides in DMF at 120 °C, in the presence of K_2CO_3 as the base and a catalyst system composed of $Pd(OAc)_2$ and PPh_3. The reaction was found to be successful with di- and trisubstituted alkenyl halides. In addition, this protocol proceeded successfully with (*Z*)-β-bromostyrene and stereospecifically furnished the (*Z*)-4-styrylsydnones **20**. Surprisingly, aliphatic bromoalkenes such as 1-bromohex-1-ene or (3-bromoallyl)-benzene failed to react under the reaction conditions, returning the starting materials.

The proposed mechanism of the coupling reaction (Scheme 13) involved an oxidative addition of Pd^0 to the alkenyl halide and subsequent electrophilic addition to the sydnone. Ensuing rearomatization and reductive elimination furnished the product and regenerated the Pd^0 catalyst.



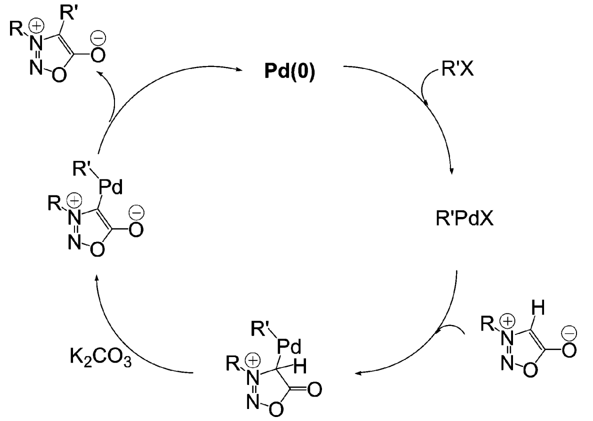
R^1	R^2	R^3	Yield (%)
H	H	Ph	60
H	Me	Me	91
Me	Me	H	97
Me	H	H	55

Scheme 11. Palladium-catalyzed alkenylation of ethyl oxazole-4-carboxylate (**17**) with alkenyl bromides.



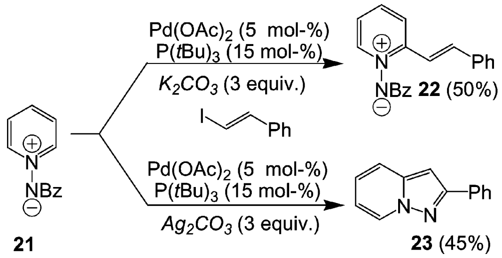
R	R¹	R²	R³	Yield (%)
Ph	Ph	H	H	78
Ph	H	H	Ph	76
Ph	H	H	nC$_4$H$_9$	0
Me	Ph	H	H	51
Ph	H	H	naphthyl	65

Scheme 12. Palladium-catalyzed alkenylation of the sydnones **19** with alkenyl bromides.



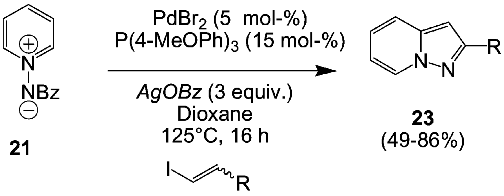
Scheme 13.

2-Substituted pyrazolo[1,5-*a*]pyridines display important biological activities. They are applicable in the treatment of several neurological disorders including schizophrenia, attention-deficit disorder, and Parkinson's disease.[16] In addition, they have been reported to exhibit potent antiherpetic and diuretic activities and may be used in the treatment of cardiac arrhythmias.[17] Very recently, Charette's research group[18] investigated the C–H alkenylation of the *N*-benzoyliminopyridinium ylide **21** with (*E*)-β-iodostyrene in the presence of the Pd(OAc)$_2$/P(tBu)$_3$[19] catalyst system. The authors demonstrated that the outcome of this transformation to furnish either the C-2 alkenyl product **22** or the 2-substituted pyrazolo[1,5-*a*]pyridines **23** depends on the nature of the base used. In the presence of K$_2$CO$_3$, the reaction provides the C-2 alkenylation product **22** in 50% yield (Scheme 14), whereas altering the base from K$_2$CO$_3$ to Ag$_2$CO$_3$ led to the formation of the 2-substituted pyrazolo[1,5-*a*]pyridines **23** in a moderate 45% yield, through a cascade direct alkenylation/cyclization reaction (Scheme 14).



Scheme 14. Palladium-catalyzed alkenylation of *N*-iminopyridinium ylides **21** with alkenyl iodides.

Given the utility of these compounds in medicinal chemistry, this finding prompted the authors to make additional investigations. Screening of catalysts and reaction conditions was performed and excellent results could be achieved with AgOBz as the base in the presence of a catalyst generated from PdBr$_2$ and P(4-MeOPh)$_3$. Representative examples of the alkenylation of **21** with (*E*)- and (*Z*)-β-styryl iodides are illustrated in Scheme 15.



Isomer	R	Yield (%)
E	C$_6$H$_5$	78
Z	C$_6$H$_5$	64
E	4-MeC$_6$H$_4$	79
E	3-MeOC$_6$H$_4$	65
E	4-FC$_6$H$_4$	86
E	2-BrC$_6$H$_4$	70

Scheme 15. Palladium-catalyzed synthesis of the 2-substituted pyrazolo[1,5-*a*]pyridines **23**.

The experimental conditions previously used to synthesize compounds **23** were successfully extended for the tandem alkenylation/cyclization of the *N*-benzoyliminoquinolinium and *N*-benzoyliminoisoquinolinium ylides **24** and **25**, respectively (Figure 1).[18]

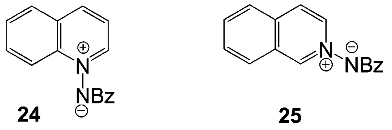
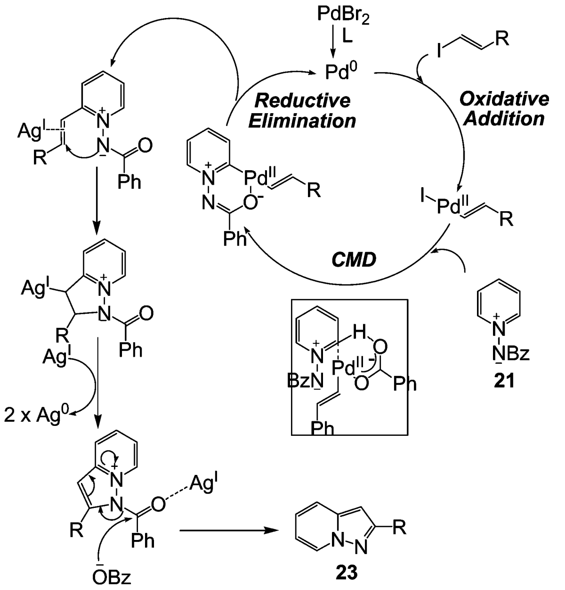


Figure 1. Structures of the *N*-benzoyliminoquinolinium and *N*-benzoyliminoisoquinolinium ylides **24** and **25**.

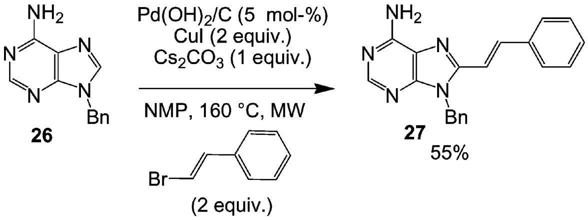
Mechanistic investigation pointed to intimate involvement of the base in the mechanism of this reaction (Scheme 16). The first step involves oxidative addition of the Pd catalyst into the alkenyl iodide and insertion into the pyridinium ylide. Given that acetate/carbonate silver compounds are required, it is thought that these play a role in the carbopalladation involving a concerted metallation/

deprotonation (CMD) sequence.[20] Reductive elimination then gives the alkenylated pyridinium, which undergoes a cyclization. Elimination of silver with disproportionation generates Ag^0. Rearomatization with the expulsion of the benzoyl moiety gives the observed product. This might also be assisted by silver, explaining the requirement for 3 equiv. of AgOBz for the reaction to proceed.



Scheme 16. Proposed mechanism in the palladium-catalyzed synthesis of the 2-substituted pyrazolo[1,5-*a*]pyridines **23**.[18]

In 2008, during our studies on the metal-catalyzed direct arylation reaction of free (NH_2) adenines,[21] our research group disclosed an efficient microwave-promoted C-8 regio- and chemoselective arylation of free (NH_2) 9-substituted adenines with aryl iodides, bromides, and chlorides involving the use of Pearlman's catalyst and a stoichiometric amount of CuI under ligandless conditions. Furthermore, we also reported a preliminary result in which the newly developed catalytic system also enabled, for the first time, efficient Pd/Cu-catalyzed direct vinylation of the free (NH_2) adenine **26** with (*E*)-β-bromostyrene in a satisfactory 55% yield (Scheme 17).

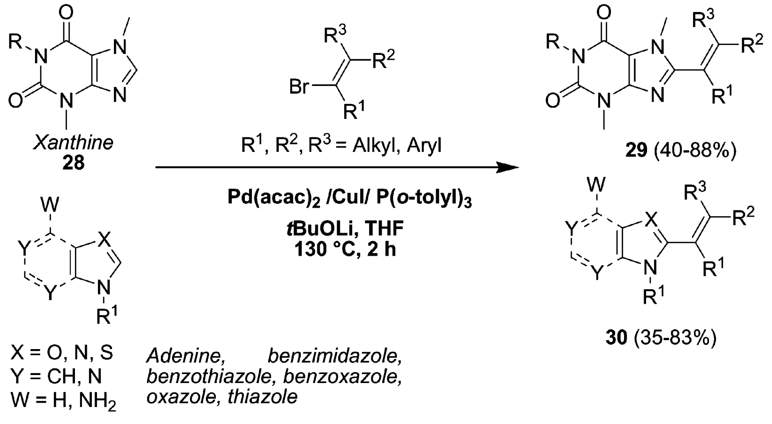


Scheme 17. Palladium-catalyzed alkenylation of the free (NH_2) adenine **26** with (*E*)-β-bromostyrene.

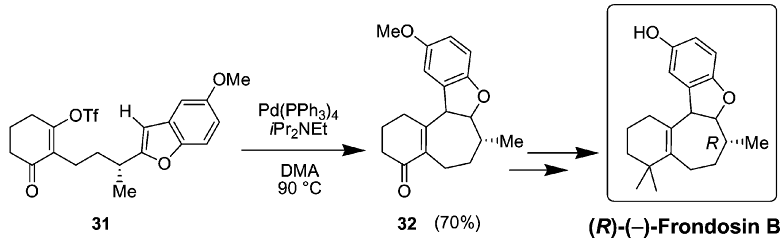
In pursuit of our efforts to extend further the scope of the functionalization of heteroaromatics through C–H bond activation, combined with our interest in discovering new hsp90 inhibitors,[22,23] we have developed highly efficient and versatile Pd/Cu-catalyzed C–H alkenylation reactions of a wide range of azoles. A catalyst system composed of $Pd(acac)_2$/CuI/$P(o\text{-tolyl})_3$ in THF in the presence of *t*BuOLi enables high-yielding reactions with heterocycles, including the xanthines **28**, the adenines **26**, benzimidazoles, benzoxazoles, benzothiazoles, and thiazoles (Scheme 18).[24] The substrate scope of the reaction turned out to be very broad, in terms not only of the azoles but also of a variety of mono-, di-, or trisubstituted alkenyl bromides. This procedure offers an important advance in direct C–H alkenylation to provide various alkenyl heterocycles.

Intramolecular Processes

Intramolecular direct alkenylation reactions have been rarely utilized in organic synthesis as a route to numerous complex polycyclic ring systems. One of the earliest examples was reported by Trauner in 2002.[25] In a study of total synthesis of (*R*)-(–)-frondosin B (Scheme 19), a marine terpenoid isolated from the sponge *Dysidea frondosa*,[26] the authors reported the key bond formation between C10 and C11 to establish the central seven-membered ring of the target by an intramolecular alkenylation process between a vi-



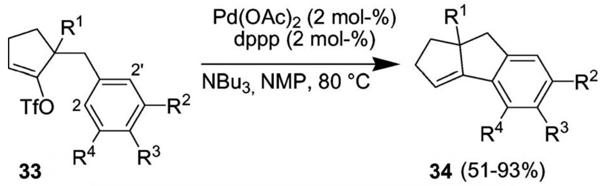
Scheme 18. Palladium/copper-catalyzed alkenylation of the xanthines **28** and various azoles with alkenyl halides.



Scheme 19. Key step in the total synthesis of (*R*)-(–)-frondosin B.

nyl triflate and the C3 position of the benzofuran moiety. Although isolated examples of vinylation reactions involving furans had been reported,[27] none had been used in the total synthesis of a natural product. Moreover, no benzofurans had been employed as substrates. The reaction was achieved by heating the intermediate **31** (Scheme 19) with a catalytic amount of [Pd(PPh$_3$)$_4$] in dimethyl acetamide (DMA) in the presence of Hünig's base. The intermediate **32** was isolated without racemization of the C8 stereocenter in 70 % yield.

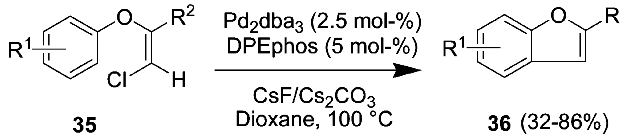
The intramolecular alkenylation of arenes through the use of Pd(OAc)$_2$/dppp as a catalytic system and NBu$_3$ in NMP at 80 °C was reported by Willis[28] (Scheme 20). The process employs the readily available substrates **33**, uses relatively low loadings of a palladium catalyst (2–5 mol-%), tolerates various substituted (hetero)arenes, and delivers the synthetically useful alkene-containing carbocyclic products **34** in good yields (Scheme 20). With substrates containing *meta*-substituted aromatic nuclei, the alkenylation can occur on C2/C2′, providing mixture of regioisomers in ratios ranging from 1.7:1 to 10:1. Although no detailed mechanistic study was performed, the authors ruled out a S$_E$Ar mechanism[29] because the electron-rich substrates displayed consistently slower rates. From an intermolecular kinetic isotopic effect study, alternatives mechanisms involving either σ-bond metathesis[30] or proton-abstraction pathways[31] were suggested.



R^1	R^2	R^3	R^4	Yield (%)
Me	H	Cl	H	80
Me	F	H	F	86
Me	H	OMe	H	86
H	H	H	H	84
Me	OTIPS	H	H	70[a]
Me	H	H	CN	85[b]

Scheme 20. Intramolecular palladium-catalyzed alkenylation of the arenes **33**. [a] A 10:1 mixture of regioisomers; major shown. [b] A 1.7:1 mixture of regioisomers; major shown.

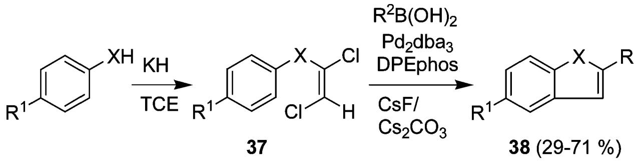
Hultin and co-workers[32] recently reported an efficient modular route to 2-substituted benzofurans through intramolecular C–H alkenylation of the (*Z*)-1-substituted-1′-aryloxy-2-chloroethylenes **35** (Scheme 21). In these Pd/DPEPhos-catalyzed reactions, it was shown that the presence of both CsF and Cs$_2$CO$_3$ as bases afforded more consistent reaction times and higher conversions than were observed in processes employing either of these basic additives alone. Representative examples of this alkenylation to provide a variety of substituted benzofurans are illustrated in Scheme 21.



R^1	R^2	Yield (%)
H	4-F-C$_6$H$_4$	72
H	4-MeO-C$_6$H$_4$	86
H	(*E*)-C$_6$H$_5$-CH=CH-	32
H	–C≡C-C$_6$H$_5$	80
4-MeO	4-MeO-C$_6$H$_4$	82
3-MeO	4-MeO-C$_6$H$_4$	74[a]

Scheme 21. Intramolecular palladium-catalyzed alkenylations of the arenes **35**.

As summarized in Scheme 22, Suzuki coupling and direct alkenylation could be combined in a one-pot procedure starting from compounds **37**, readily obtained by addition of phenols or anilines to trichloroethylene (TCE). The expected benzofurans were produced in good yields after 12–24 h at 65 °C in THF. These one-pot Suzuki coupling/direct intramolecular cyclizations of **37** were extended to form 2-aryl-*N*-tosyl indoles with low to moderate yields.

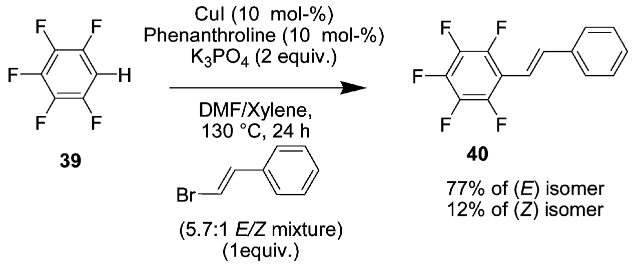


X	R^1	R^2	Yield of **38** (%)
O	H	4-F-C$_6$H$_4$	53
O	H	4-Me-C$_6$H$_4$	51
O	H	(*E*)-C$_6$H$_5$-CH=CH-	71
O	MeO	4-MeO-C$_6$H$_4$	74
NTs	H	4-MeO-C$_6$H$_4$	29
NTs	MeO	4-MeO-C$_6$H$_4$	47

Scheme 22. One-pot Suzuki coupling/direct intramolecular cyclizations of **37**.

Copper-Catalyzed Direct Alkenylation (Coupling between sp^2 C–H and sp^2 C–H Bonds)

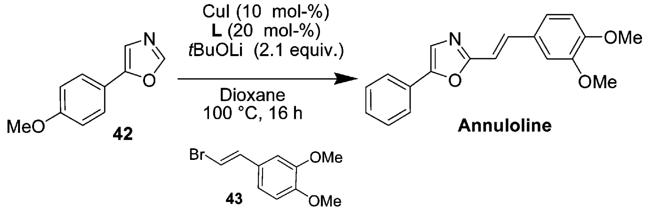
A wide range of metal catalysts including palladium, rhodium, or ruthenium have been exploited in C–H activation processes. However, the use of copper catalysts in this field has seldom been reported. Although palladium catalysts can be replaced by copper in many coupling processes, use of the cheaper and more convenient copper in C–H activation reactions is not common. In 2008, Daugulis et al.[33] developed a method for the Cu-catalyzed arylation of polyfluoroarene C–H bonds with aryl bromides. In addition, the authors described one example of the direct alkenylation of the C–H bond in the pentafluoroarene **39** (Scheme 23) with β-bromostyrene in the presence of K_3PO_4 as the base, CuI as the catalyst, and phenanthroline as the ligand. Notably, this protocol furnished **40** in a good yield as a mixture of *Z* and *E* isomers.



Scheme 23. Copper-catalyzed alkenylation of the C–H bond in the pentafluoroarene **39** with β-bromostyrene.

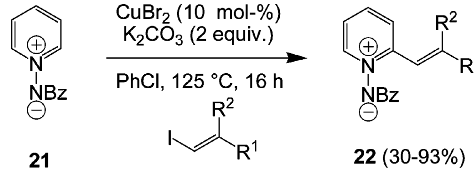
A significant contribution to the development of new and highly efficient general methods in this field was made by Piguel et al.,[34] who reported direct alkenylation of 5-phenyloxazoles such as **12** (Scheme 24) with (*E*)-β-bromostyrenes under copper catalysis conditions in the presence of trans-*N*,*N′*-dimethylcyclohexane-1,2-diamine as the ligand and *t*BuOLi in dioxane at 100 °C. The protocol proved to be both regio- and stereoselective and tolerates a variety of functional groups. Moreover, these new conditions were successfully applied to azole heterocycles such as benzothiazole and benzoxazole. Interestingly, unsubstituted oxazole was also regioselectively vinylated at the C-2 position by this protocol, affording the (*E*)-2-styryloxazole as single regioisomers in 58% yield.

Grierson has also used this approach for the total synthesis of annuloline (Scheme 25), in which the key step of the synthesis involved the direct alkenylation of 5-(4-methoxyphenyl)oxazole (**42**) with the β-bromostyrene **43** under the optimized conditions to afford the desired alkenylated product in 91% yield as an 11.5:1 mixture of *E* and *Z* isomers. Pure annuloline was isolated in 75% yield after crystallization.



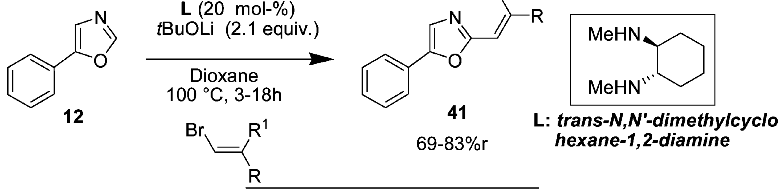
Scheme 25.

In 2009 Charette's group pursued investigations into the C–H alkenylation of *N*-benzoyliminopyridinium ylides such as **21** (Scheme 26) with alkenyl iodides and found that treatment of **21** in the presence of K_2CO_3 and a catalytic



R^1	R^2	Yield (%)
C_6H_5	H	81
2-Me-C_6H_4	H	78
4-CF_3-C_6H_4	H	71
H	C_6H_5	71
2-I-C_6H_4	H	47
4-Br-C_6H_4	H	74

Scheme 26. Copper-catalyzed alkenylations of *N*-benzoyliminopyridinium ylides such as **21** with alkenyl iodides.

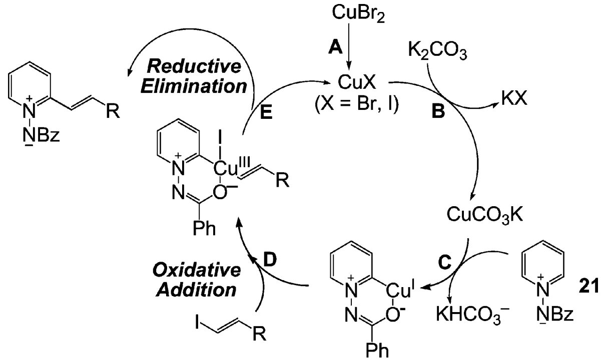


R	R^1	Yield (%)
4-Me-C_6H_4	H	81
3-NO_2-C_6H_4	H	70
4-CF_3-C_6H_4	H	83
3-Br-C_6H_4	H	78
Me	Me	76

Scheme 24. Copper-catalyzed alkenylation of 5-phenyloxazole (**12**) with (*E*)-β-bromostyrenes.

amount of $CuBr_2$ provided the C-2 alkenylated derivatives **22** in moderate to good yields.[35] This protocol constitutes the first ligand-free Cu-catalyzed direct alkenylation of electron-deficient heteroarenes. The scope of the Cu-catalyzed reaction was found to be quite general with various functionalized alkenyl iodides. The reaction is highly chemoselective towards substituted β-iodostyrenes: halogen substituents (Cl, Br, and I) were tolerated on the phenyl ring with the reaction occurring selectively on the alkenyl iodide. Notably, aliphatic alkenyl iodides displayed poorer reactivity.

A mechanistic investigation enabled the authors to establish that these alkenylation reactions could not be interpreted in terms of the concerted metallation/deprotonation (CMD) mechanism (Scheme 27). Cu^{II} is reduced to Cu^I by the pyridinium ylide (A). Next, there is a carbonate/bromide exchange to generate $CuCO_3$, which is likely to be the reactive species in all cases, regardless of the Cu source (B). This species can undergo deprotonation/metallation onto the pyridinium to generate an organocupracycle stabilized by the Lewis basic iminobenzoyl moiety (C). Oxidative addition (D) into the alkenyl iodide and subsequent reductive elimination (E) affords the product.

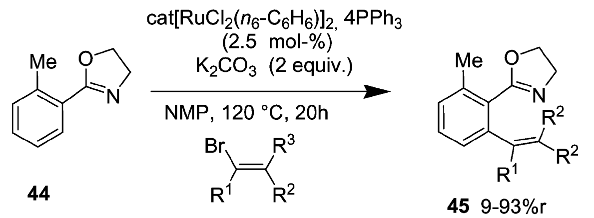


Scheme 27. Proposed mechanism in copper-catalyzed alkenylations of **21** with alkenyl iodides.

Ruthenium(II)- and Rhodium(I)-Catalyzed Direct Alkenylation (Coupling between sp^2 C–H and sp^2 C–H Bonds)

Although the development of alkenylation of sp^2 C–H bonds involving subsequent regioselective formation of new **C**–**C** bonds with assistance by other metals has been less widely reported in the literature, we wish to illustrate two alkenylation processes catalyzed either by ruthenium(II) or rhodium(I) complexes, to highlight the significant advancements in the field (Scheme 28 and Scheme 30, below).

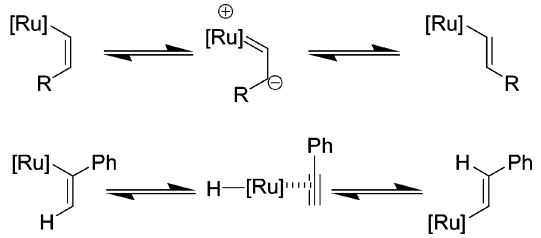
Inoue's[36] group described *ortho*-selective direct alkenylation of 2-aryloxazolines such as **44** with alkenyl halides catalyzed by a ruthenium complex (Scheme 28). (*E*)- or (*Z*)-1-Bromopropene and β-bromostyrene all reacted smoothly with **44**, giving the corresponding products **45** in moderate to excellent yields. It is noteworthy that isomerization of the olefinic moiety occurred in all cases, producing mixtures of *E*/Z alkenylated products **45** in ratios ranging from 91:9 to 97:3. In contrast to β-bromostyrene, the reaction with α-bromostyrene gave only a 9% yield of the expected α-styryl product; the major outcome was the formation of the (*E*)-β-styryl product (43%) in an *E*/Z ratio of 96:4.



R¹	R²	R³	Yield (%)
H	Me	H	53 (*E/Z* = 91:9)
H	H	Me	63 (*E/Z* = 90:10)
H	Ph	H	93 (*E/Z* = 97:3)
Ph	H	H	9

Scheme 28. Ruthenium-catalyzed alkenylations of aryloxazolines such as **44** with alkenyl bromides.

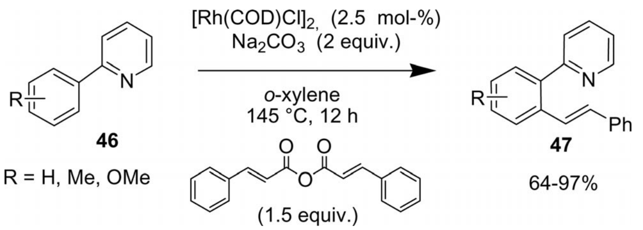
Mechanistically, it is proposed that the isomerization occurs by two pathways: i) between (*E*)- and (*Z*)-alkenylruthenium through the formation of a zwitterionic carbenoid complex as proposed for the transition-metal-catalyzed *trans*-hydrosilylation,[37] or ii) between α- and β-styrylruthenium complexes via an η-alkyne hydrido species as reported by Torres[38] (Scheme 29).



Scheme 29. Ruthenium-catalyzed isomerization mechanism.

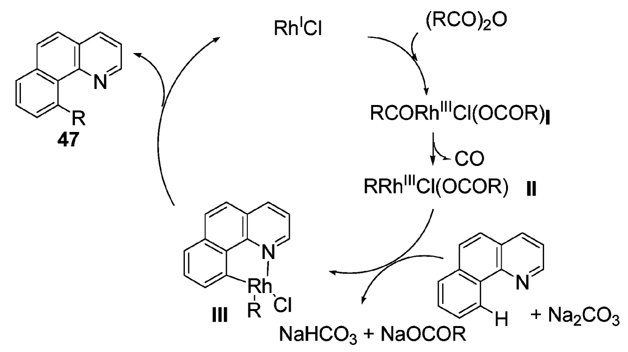
Efficient rhodium(I)-catalyzed regioselective direct alkenylations of aromatic C–H bonds have been reported by Yu and co-workers.[39] The C–H alkenylation reactions involve cinnamic anhydrides as the coupling partners (Scheme 30). The authors discovered that a catalyst system composed of $Rh[(COD)Cl]_2$ under phosphine-free conditions enables chelation-assisted reactions between the arenes **46** and cinnamic anhydride in *o*-xylene in the presence of Na_2CO_3 at 145 °C. The reactions produced the direct alkenylation products **47** in 64–97% yields, suggesting a promising alternative route to compounds **47** instead from Heck reactions of aryl halides and styrene.[40]

A plausible mechanism in which the anhydride is oxidatively added to the Rh^I species to produce an aroylcarboxylate metal complex **I** (Scheme 31) was proposed by the au-



Scheme 30. Rhodium(I)-catalyzed alkenylation of the arenes **46** with cinnamic anhydride.

thors. This undergoes decarbonylation to form the aryl carboxylate–Rh **II**, which reacts with arene to generate the complex **III** by C–H bond activation with intramolecular *ortho*-chelating assistance in the presence of Na_2CO_3 base. Subsequent reductive elimination of **III** produces the desired product **47**.

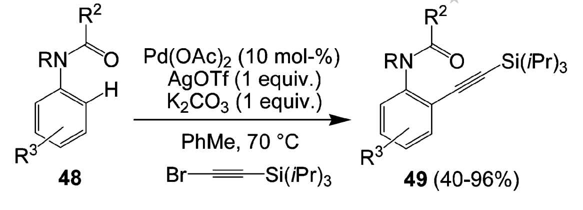


Scheme 31. Proposed mechanism for the rhodium(I)-catalyzed alkenylations of arenes with cinnamic anhydride.

2. Intermolecular Direct Alkynylation (Coupling between sp^2 C–H and sp C–H Bonds)

Metal-catalyzed direct alkynylation[41] of (hetero)arene C–H bonds with alkynyl halides or pseudohalides (formally named the inverse Sonogashira reaction) has recently been receiving much attention as a complementary process to Sonogashira coupling.[42]

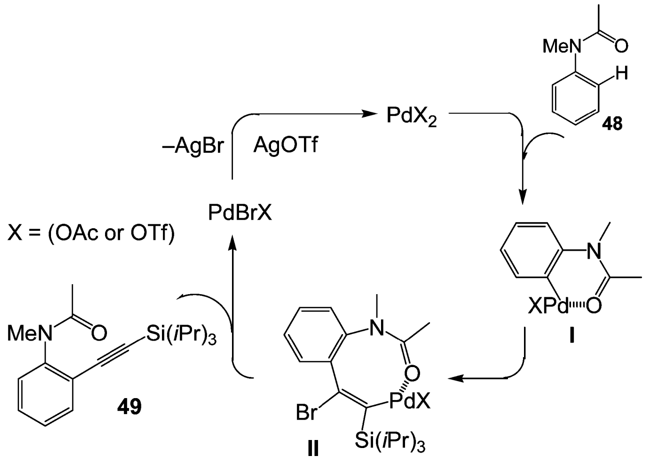
Chatani and co-workers[43] demonstrated the utility of anilides as directing groups for the palladium-catalyzed *ortho*-alkynylation of aromatic C–H bonds in the anilides **48** (Scheme 32) with 1-bromo-2-triisopropylsilylacetylene. To be successful, the reactions require $Pd(OAc)_2$ as the catalyst in the presence of stoichiometric amounts of AgOTf/K_2CO_3 in toluene at 70 °C. Anilide substrates with electron-rich or electron-withdrawing groups furnished the corresponding alkynylarenes **49** in moderate to good yields (Scheme 32). Notably, the scope in terms of the bromoalkyne substrate proved to be limited, with replacement of the triisopropylsilyl group by other substituents, such as Ph, hexyl, or ester, did not afford the corresponding product.



R^1	R	R^3	Yield (%)
Me	Me	3-Br	48
Me	Me	4-CF3	40
Me	Me	4-Cl	54
Me	Me	3,4 (Me)$_2$	82

Scheme 32. Alkynylation of the anilides **48** with alkynyl bromides.

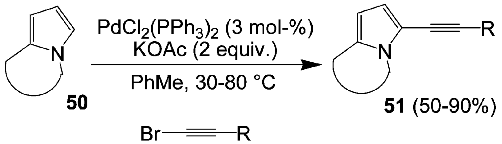
The authors proposed that the alkynylation proceeded through electrophilic *ortho*-metallation of the anilide (e.g., **48**, R = R^3 = H, R^2 = Me) by $Pd(OAc)_2$ to form the palladacycle **I**. Subsequent addition across the bromoalkyne provides the vinylpalladium intermediate **II**, which then undergoes β-bromo elimination to afford the alkynylation product **49** and PdBrX. The presence of AgOTf would allow an exchange of the bromide ligand in PdBrX for a less powerfully coordinating OTf anion (Scheme 33), generating PdX_2, which would be capable of effecting electrophilic metallation of **48**.



Scheme 33. Proposed mechanism for the palladium-catalyzed alkynylation of the anilides **48**.

In 2007, Gevorgyan and co-workers[44] accomplished the first transition-metal-catalyzed direct alkynylation of the electron-rich *N*-fused heterocycles **50** (Scheme 34). The authors showed that in the presence of $PdCl_2(PPh_3)_2$ and KOAc in toluene, indolizine, pyrroloquinoline, pyrroloisoquinoline, and pyrroloxazole cores were efficiently and regioselectively alkynylated with bromoalkynes containing a broad range of substituents.

The mechanism proposed for the direct Pd-catalyzed C–H alkynylation of electron-rich heterocycles operates through an electrophilic substitution pathway (Scheme 35). A subsequent nucleophilic attack from the most electron-rich C-3 position of the heterocycle **50** on the alkynylpalladium species forms the iminium intermediate **I**. Deproton-



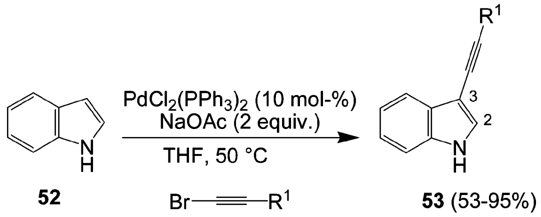
50	R	Yield (%)
Indolozine	Ph	51
Pyrrolo-isoquinoline	*n*Bu	72
pyrroloxazole	Ph	76
Bis(pyrrolo)-pyrimidine	Ph	51

Scheme 34. Palladium-catalyzed alkynylation of the *N*-fused heterocycles **50**.

ation of this furnishes the Pd^{II} intermediate **II**, which upon reductive elimination produces the alkynyl heterocycle **51** (Scheme 35).

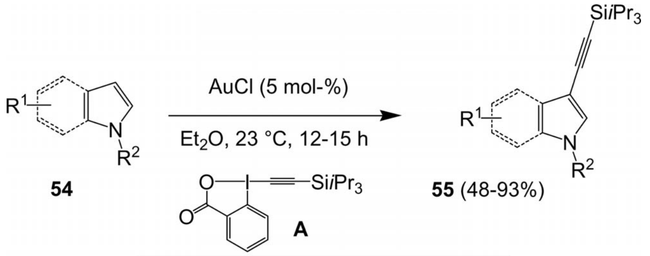
More recently, Wang and co-workers[45] found that free (NH) indole (**52**, Scheme 36) is able to react with various bromoalkynes in THF in the presence of $PdCl_2(PPh_3)_2$ as the catalyst and NaOAc as the base to give the C-3 alkynylated indoles **53** with complete selectivity (>20:1). Importantly, when C-3 was blocked (in 3-methylindole, for example), no C-2 alkynylation product was observed, whereas when C-2 was blocked (in 2-methylindole, for example), C-3 alkynylated indoles were obtained in moderate yields (55%, R^1 = Ph), probably for steric reasons. Mechanistically, it is proposed that the reaction occurs through an electrophilic substitution pathway as above.

Gold is a recent addition, by Waser and co-workers,[46] to the arsenal of transition metal catalysts employed in the C–H alkynylation reaction of the indole heterocycles **54** (Scheme 37). In contrast with previous work, the more reactive benziodoxolone-based hypervalent iodine reagent **A**[47] was used in place of bromoalkynes. This mild procedure (room temperature), which requires the presence of a catalytic amount of AuCl, leads to the C-3 alkynylated indoles **55** in good to excellent yields (Scheme 37). Functional group tolerance in the indole heterocycle was far better than that in the only reported method for the direct alkynylation of indoles,[45] and unprecedented substitution patterns could be obtained (Scheme 37). More interestingly, with 3-methylindole (**56**), a substrate for which no successful alkynylation had ever been reported,[45] this Au-catalyzed reaction provided the C-2 alkynylation product **57** in 76% yield (Scheme 37). Notably, the scope with regard to the hypervalent iodine reagent proved to be limited: only alkynylated indoles with a triisopropylsilyl group attached to the C≡C triple bond were obtained.

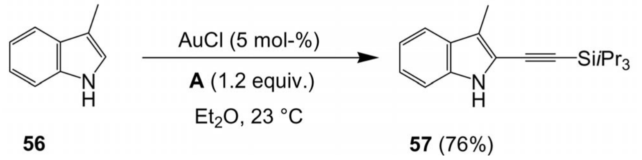


R^1	Yield (%)
Ph	89
2-Cl-C_6H_4	72
1-naphthyl	95
cyclohexenyl	72

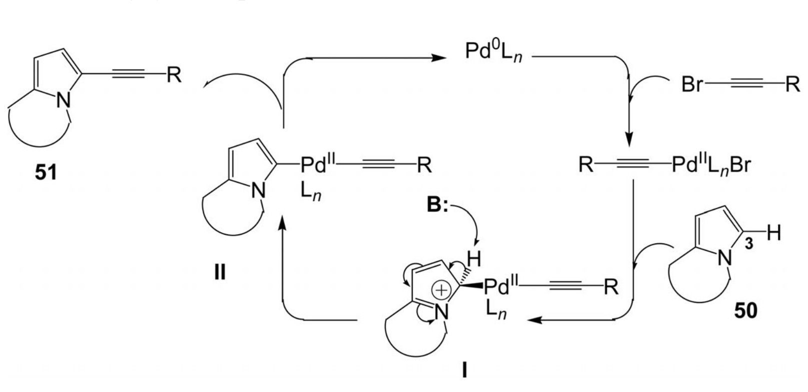
Scheme 36. Palladium-catalyzed alkynylation of indole (**52**).



54	R^1	R^2	Yield (%)
Indole	5-CO_2H	H	67
	5-Br	H	93
	7-Br	H	84
Pyrrole	H	H	62 (at C2)
	H	*i*Pr_3Si	79 (at C3)



Scheme 37. Gold-catalyzed alkynylation of the indole and pyrrole heterocycles **54**.

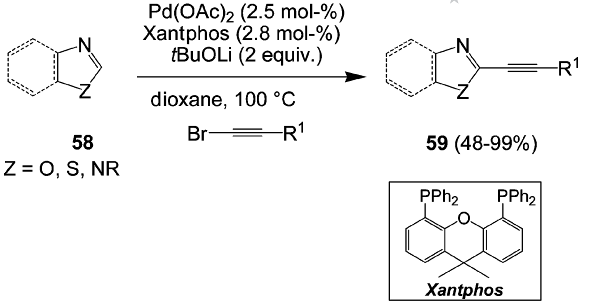


Scheme 35. Proposed mechanism for the palladium-catalyzed alkynylation of the *N*-fused heterocycles **50**.

This protocol was successfully extended to the alkynylation of pyrroles, sensitive heterocycles that usually require protection of the NH group.[48] The authors reported, for the first time, that the Au-catalyzed regioselective alkynylation of pyrroles could be overruled by blocking the C3 (C2) position of the pyrrole nucleus or by introducing a bulky triisopropylsilyl (TIPS) group at the pyrrole N atom (Scheme 37).

Two mechanistic hypotheses were suggested by the authors for this reaction: i) similar to the copper system,[49] with oxidation of gold(I) with **A** to form a gold(III)–acetylene complex **I**, followed by indole metallation and reductive elimination[50] (Scheme 38), or ii) gold-mediated addition of indole to the triple bond of **A** to form a vinyl–gold complex (**III** or **IV**), followed either by β-elimination or by an α-elimination/1,2-shift sequence[51] depending on the regioselectivity of the addition (Scheme 38).

In 2010, a highly efficient and versatile Pd-catalyzed direct alkynylation reaction of the various azoles **58** (Scheme 39) with 1-bromoalkynes was reported by Chang et al.[52] Optimal conditions were found to require Pd$(OAc)_2$ (2.5 mol-%), Xantphos (2.8 mol-%), and *t*BuOLi (2 equiv.) in 1,4-dioxane at 100 °C and afforded the desired 2-alkynyl heterocycles **59** in good to excellent yields. The substrate scope of the reaction turned out to be very broad, encompassing not only azoles, including oxazole, benzoxazole, imidazole, benzimidazole, and benzothiazole, but also partially saturated azolines for the first time. Interestingly, the C-2 position of parent oxazole was selectively alkynylated in high yields. It should be noted that in the reaction between benzothiazole and 1-bromophenylacetylene the product yield was significantly improved by the addition of catalytic amounts of CuI, due to the beneficial effects of the copper additive.

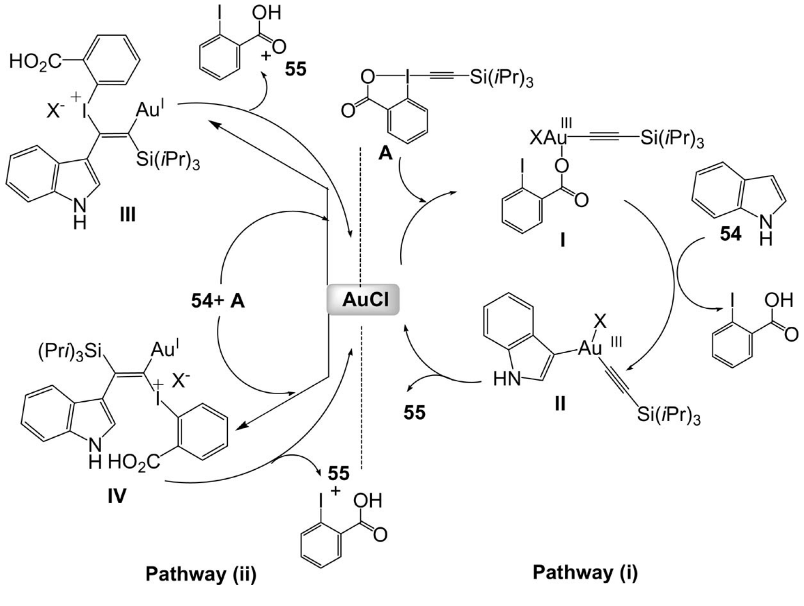


Azole 58	R^1	Yield (%)
5-Methylbenzoxazole	Ph	99
Oxazole	Ph	71
5-Phenyloxazole	$Si(iPr)_3$	78
N-Methylbenzimidazole	$Si(iPr)_3$	53
Benzothiazole	Ph	59
N-Phenylimidazole	$Si(iPr)_3$	63

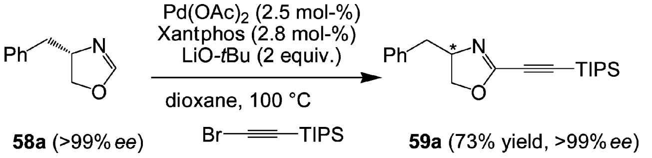
Scheme 39. Palladium-catalyzed alkynylation of the azoles and azolines **58**.

Chiral oxazolines are interesting ligands in asymmetric synthesis, so their direct alkynylation would offer a convenient opportunity for the functionalization of these compounds. The authors demonstrated that alkynylation reactions of optically active 4-benzyloxazoline (**58a**, Scheme 40) proceed with no racemization, thus demonstrating the efficiency of the developed protocol.

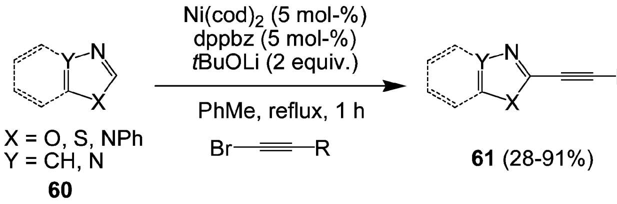
Nickel(0)-catalyzed direct alkynylation of the azoles **60** (Scheme 41) with different alkynyl bromides was also reported by Miura and co-workers.[53] The $Ni(cod)_2$/dppbz catalytic system, in the presence of *t*BuOLi in toluene at reflux, enables various bromoalkynes bearing aryl, alkenyl, alkyl, and silyl substituents to serve as promising alkynyl sources for azoles.



Scheme 38. Two proposed mechanisms for gold(I)-catalyzed alkynylation of the azoles **54**.



Scheme 40. Palladium-catalyzed alkynylation of optically active 4-benzyloxazoline (**58a**).



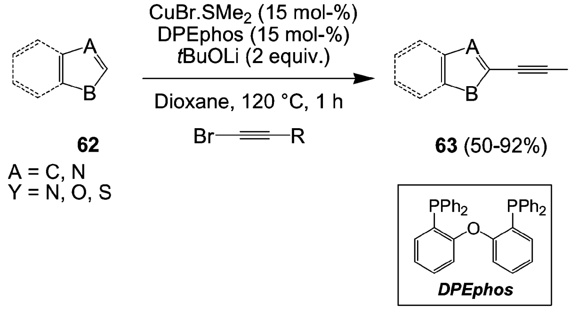
60	R	Yield (%)
Benzoxazole	Ph	84
Benzoxazole	4-CF$_3$-Ph	60
Benzoxazole	*n*C$_6$H$_{13}$	60
5-Phenyloxazole	naphthyl	64
Benzimidazole	Ph	42

Scheme 41. Nickel(0)-catalyzed alkynylation of the azoles **60**.

It should be noted that in cases of the alkynylation of some azoles such as benzothiazole, benzimidazole, and 3,4-diphenyl-4*H*-1,2,4-triazole the addition of catalytic amounts of CuI was found to enhance the reactions dramatically.

The mechanism of this Ni-catalyzed direct alkynylation of azoles starts through an initial oxidative addition of an alkynyl bromide to a zero-valent Ni species to afford the corresponding (alkynyl)nickel intermediate **I** (Scheme 42). A subsequent transmetallation with the heteroaryllithium species **II**, generated in situ from heteroarene and *t*BuOLi, followed by reductive elimination of **III**, furnishes the alkynylated product **61** along with the starting nickel complex to complete the catalytic cycle.

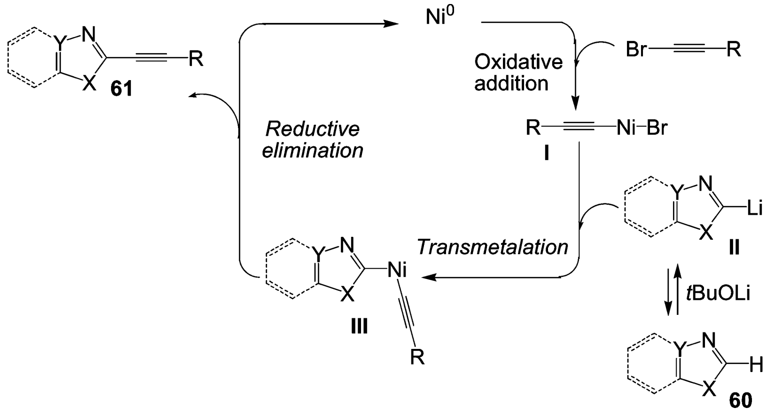
An alternative method to the Pd- or Ni-catalyzed alkynylation of azoles is the Cu-catalyzed procedure reported by Piguel,[54] which exploits the minimal cost and toxicity of copper. The reactions, carried out in the presence of CuBr·SMe$_2$/DPEphos as the catalyst system and *t*BuOLi as the base in dioxane at 120 °C, proved to be successful with various azoles such as oxazole, benzoxazole, benzothiazole, 1,3,4-oxadiazole, 1,2,4-triazole and 6-chloropurine, furnishing the alkynylated azoles **63** (Scheme 43) in good to excellent yields.



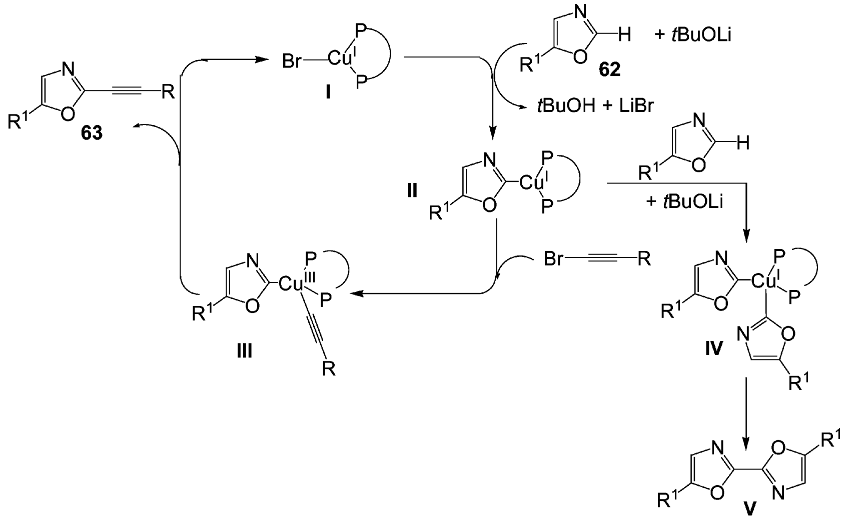
62	R	Yield (%)
5-Phenyloxazole	Ph	89
5-Phenyloxazole	4-CF$_3$-Ph	76
5-Phenyloxazole	*i*Pr$_3$Si	84
Benzoxazole	Ph	75
Benzothiazole	Ph	90
6-Chloropurine	Ph	50

Scheme 43. Copper-catalyzed alkynylations of the azoles **62**.

Although the precise mechanism of this new process is unclear, the authors postulated deprotonation of azoles at the C-2 position by *t*BuOLi (Scheme 44), followed by lithium–copper transmetallation to generate the copper(I) species **II**. Oxidative addition of **II** to the bromoalkyne presumably gives a four-coordinate copper(III) complex (**III**), which then undergoes a reductive elimination to the expected alkynylated compound **63**, with regeneration of the catalytic copper(I) species **I** in the process (Scheme 44). The beneficial effect of the bulky bidentate ligand DPEPhos, rather than the monodentate PPh$_3$, has been interpreted in terms of steric hindrance around the copper center of **II**, which avoids the formation of species **IV**, precursor of the bis(oxazole) dimer **V**.

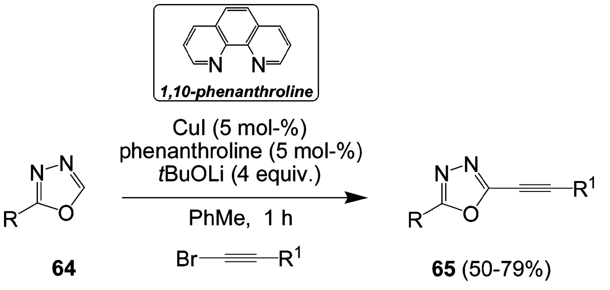


Scheme 42. Proposed mechanism for the nickel(0)-catalyzed alkynylations of the azoles **60**.



Scheme 44. Proposed mechanism for copper(I)-catalyzed alkynylations of the azoles **62**.

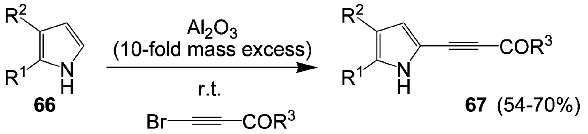
In continuation of their studies on the direct alkynylation of five-membered heteroarenes, Miura and co-workers[55] very recently reported room temperature copper-catalyzed direct alkynylation of the 1,3,4-oxadiazoles **64** (Scheme 45) with bromoalkynes. The reactions take place in the presence of CuI/1,10-phenanthroline as a catalytic system and of *t*BuOLi as the base in toluene.



Oxadiazoles **64**	R	Yield (%)
5-Phenyloxadiazole	4-Me-Ph	70
5-Phenyloxadiazole	naphthyl	66
5-Phenyloxadiazole	Si(*i*Pr)$_3$	50
5-Phenyloxadiazole	1-cyclohexenyl	69
5-(1-Naphthyl)oxadiazole	Ph	66

Scheme 45. Copper-catalyzed alkynylations of the 1,3,4-oxadiazoles **64**.

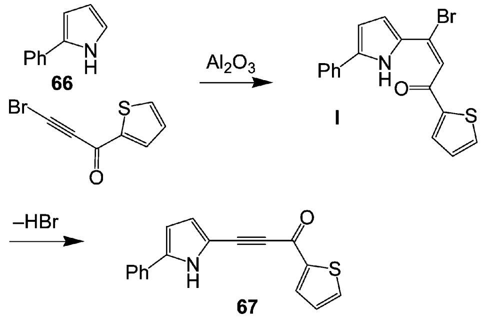
In addition to transition-metal-catalyzed alkynylation reaction of heteroarenes, Trofimov and co-workers[56] reported a transition-metal-free procedure in which a variety of pyrroles **66** (Scheme 46) and indoles were alkynylated with 1-acyl-2-bromoacetylenes in the presence of stoichiometric amounts of Al_2O_3. Notably, this transformation was efficiently promoted by other main-group metal oxide active surfaces besides Al_2O_3, such as BaO and ZnO, and also by K_2CO_3. This solvent-free and room temperature protocol regioselectively afforded the 2-(acylethynyl)pyrroles **67** in good yields.



R^1	R^2	R^3	Yield (%)
H	H	Ph	55
Ph	H	Ph	50
H	H	2-thienyl	70

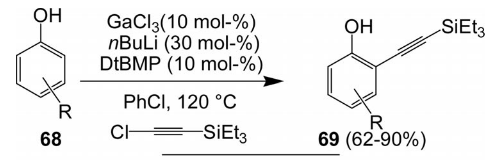
Scheme 46. Alkynylations of the pyrroles **66** with alkynyl bromides.

Mechanistic study of this ethynylation reaction supported an addition–elimination pathway (Scheme 47), the intermediate **I** being identified by ^{1}H NMR in the $CDCl_3$ extract of the reaction mixture.



Scheme 47. Proposed mechanism.

On concluding this section, we should mention that Yamaguchi and co-workers[57] reported the first *ortho*-alkynylations of the phenols **68** (Scheme 48) with 1-triethylsilyl-2-chloroacetylenes in the presence of the main-group-metal salt $GaCl_3$ as the catalyst and of *n*BuLi and 2,6-bis(*tert*-butyl)-4-methylpyridine (DtBMP) in chlorobenzene at 120 °C. A variety of alkynyl phenols **69**, including halo-substituted derivatives, were obtained in this way with exclusive *ortho* selectivity (Scheme 48).

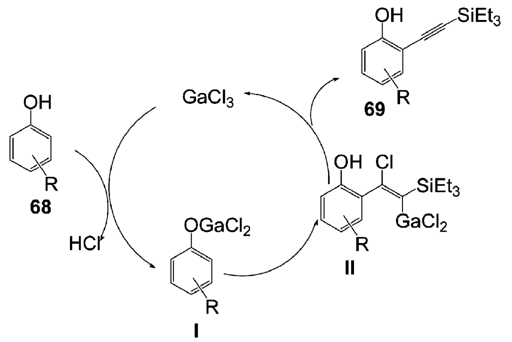


R	Yield (%)
2-*t*Bu	83
3-Cl	62
4-Br	81
4-Cl	87

Scheme 48. Alkynylation of the phenols **68** with chloroalkynes.

Later, the same group adopted this chemistry for direct alkynylations of *N*-benzylanilines.[57b]

Mechanistically, the authors postulated the addition of the gallium phenoxides **I** to the silylated chloroalkynes, providing the vinylgallium intermediates **II** (Scheme 49). Subsequent β-elimination in **II** leads to the *ortho*-ethynylated phenols **69** and regenerates $GaCl_3$, which then reacts with the phenols **68** to form the reactive species **A**.

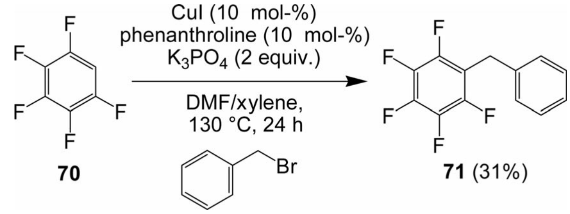


Scheme 49. Proposed mechanism for $GaCl_3$-catalyzed *ortho*-ethylynation of phenols **68**.

3. Intermolecular Direct Benzylation (Coupling between sp^2 C–H and sp^3 C–H Bonds)

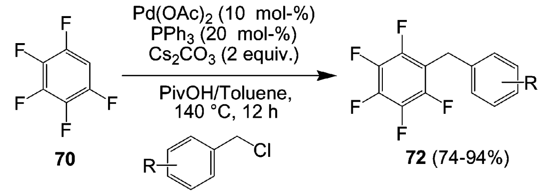
Diarylmethanes (or heteroaryl-arylmethanes) are found ubiquitously in pharmaceuticals and biologically active compounds.[58] A useful and classical approach to these units is Lewis-acid-mediated Friedel–Crafts or S_EAr reactions with arenes and benzylic electrophiles.[59] However, these valuable processes are often associated with significant limitations, including i) their restriction to electron-rich arenes, ii) their low tolerance of acid-labile functional groups, and iii) their low chemo- and regioselectivities. Recently, transition-metal-catalyzed cross-coupling reactions between benzyl halides and organometallics[60] have emerged as alternatives to the use of strong acids or bases. In addition, recent advances in metal-catalyzed direct C–H functionalization provide a potentially more powerful and facile access to these target molecules because the (hetero)-arene preactivation step can be obviated.[61]

The first example of direct benzylation were provided in 2008 by Daugulis,[33] who demonstrated that polyfluoroarenes such as **70** (Scheme 50) can be benzylated by Cu-catalyzed sp^2C–H activation. The authors accomplished the direct benzylation of the pentafluoroarene C–H bond with benzyl bromide in the presence of K_3PO_4 as the base, copper iodide as the catalyst, and phenanthroline as the ligand, in a DMF/xylene mixed solvent at 130 °C. The benzylpentafluorobenzene **71** was obtained in a fair 31% yield (Scheme 50). It should be noted that only one example of a direct benzylation of a pentafluoroarene C–H bond was reported by the authors in this article.



Scheme 50. Copper-catalyzed benzylation of the pentafluoroarene **70**.

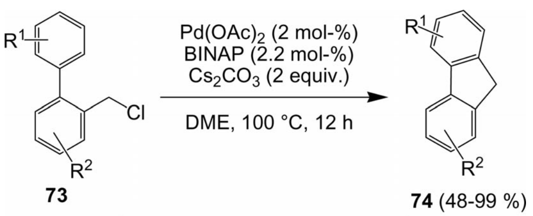
In this regard, it should be mentioned that, very recently, Zhang and co-workers[62] have developed a new palladium-catalyzed benzylation of highly electron-deficient perfluoroarenes such as **70**. This protocol, which involves the use of a catalyst system composed of $Pd(OAc)_2/PPh_3$ and Cs_2CO_3 in toluene at 140 °C, proved to be a practical and efficient method for the preparation of a wide range of perfluorinated unsymmetrical diarylmethanes **72** with good to excellent yields and high selectivities (Scheme 51). The substrate scope with regard to fluoroarenes is not restricted to the pentafluoroarene **70**. Reactions were successfully conducted with functionalized fluoroarenes containing two to four fluorine atoms, affording the expected products in yields ranging from 48 to 98%.



R	Yield (%)
4-MeO	94
4-Cl	88
4-COMe	93
4-CN	82
2-OMe	89

Scheme 51. Palladium-catalyzed benzylation of the pentafluoroarene **70**.

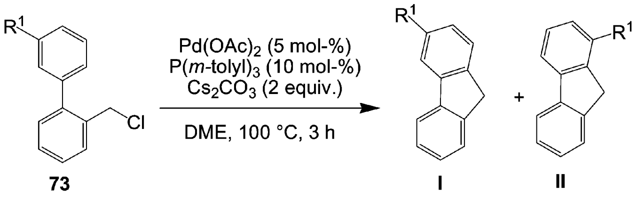
Intramolecular direct benzylation of arenes has been reported by Chang,[63] who demonstrated that the *o*-aryl-substituted benzyl chlorides **73** (Scheme 52) undergo cyclization upon treatment in the presence of a $Pd(OAc)_2/(\pm)$-BINAP catalyst system and Cs_2CO_3 as the base to give the corresponding polyarylfluorene derivatives **74** in good to excellent yields.



R^1	R^2	Yield (%)
H	H	89
4-Cl	H	52
4-OMe	H	99
H	3-F	74
4-COMe	H	48

Scheme 52. Palladium-catalyzed intramolecular direct benzylations of the *N*-(2-halobenzyl)-substituted pyrroles **73**.

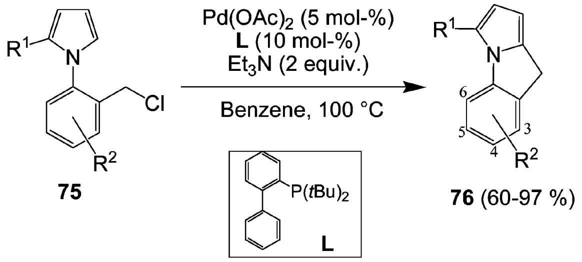
The effects of electronic and/or steric influences of substrates on the regioselectivity were examined and it was found that the steric factors seemed to be more dominant for the regiocontrol than the electronic effects. Representative examples are depicted in Scheme 53. The authors suggested a base-assisted deprotonative metallation mechanism to explain this intramolecular C–H benzylation.



R^1	Yield (%)	Ratio of **I**/**II**
Cl	90	1.2:1
Ac	72	>30:1
CF3	72	>30:1
*i*Pr	91	10:1

Scheme 53. Effects of electronic and/or steric influences of substrates on the regioselectivities of palladium-catalyzed intramolecular direct benzylations of the *N*-(2-halobenzyl)-substituted pyrroles **73**.

In continuation of their studies on the intramolecular benzylation, Chang and co-workers[64] developed highly efficient palladium-catalyzed cyclizations of the *N*-(2-halobenzyl)-substituted pyrroles **75** (Scheme 54) to afford the condensed heterocarbocycles **76**. The protocol proceeded with excellent efficiency irrespective of substrate types, although sterically congested substrates demanded higher temperatures with larger catalyst loadings.

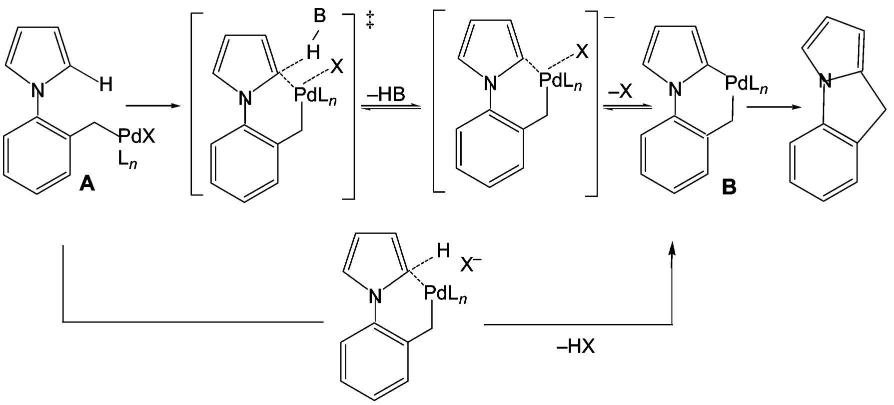


R^1	R^2	Yield (%)
H	H	97
H	4-Cl	95
H	5-Cl	92
CHO	H	68
H	6-Me	60

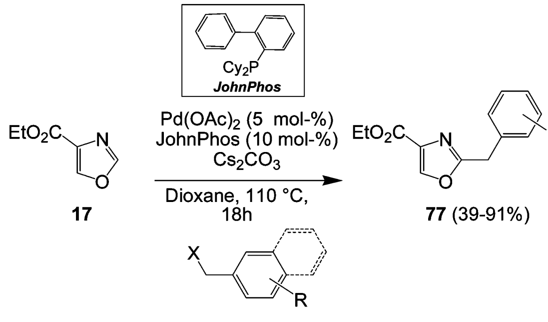
Scheme 54. Palladium-catalyzed intramolecular direct benzylations of the *N*-(2-halobenzyl)-substituted pyrroles **75**.

The proposed mechanism (Scheme 55) begins with an initial oxidative addition of the benzyl halide to Pd^0, leading to the Pd^{II} species **A**. It is proposed that at this stage the most plausible palladacycle **B** for the final reductive elimination forms either through C–H activation or through electrophilic aromatic substitution. The ring closure proceeds by a base-assisted deprotonative metallation pathway with dependence on the acidity of the C–H bond being cleaved.

Heteroarenes containing two or more heteroatoms have been used as substrates in direct Pd-catalyzed intermolecular benzylation reactions. A significant contribution in this field was made by Hoarau et al.,[12] who reported the direct benzylation of ethyl oxazole-4-carboxylate (**17**, Scheme 56) with benzyl chlorides in the presence of Pd(AOc)$_2$/JohnPhos as the catalyst system, together with Cs$_2$CO$_3$ in dioxane at 110 °C. This regioselective protocol furnished the C-2 benzylated products **77** in good yields.



Scheme 55. Proposed mechanistics pathways for palladium-catalyzed intramolecular benzylation of the pyrroles **75**.



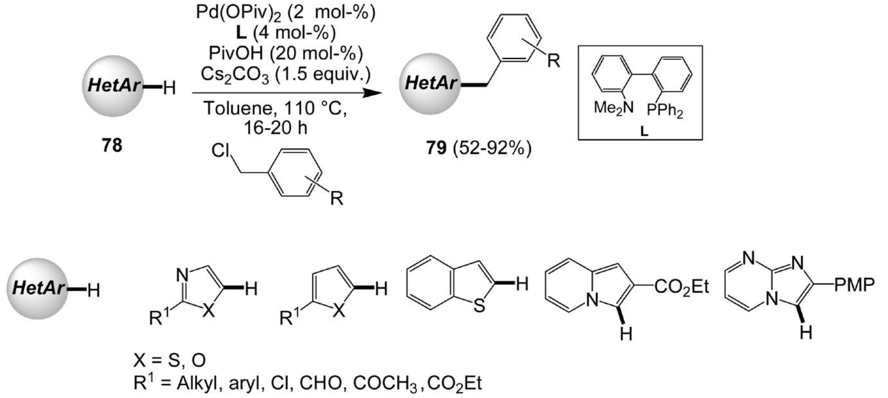
X	R	Yield (%)
Cl	H	60
Br	H	39
Cl	4–OMe	91
Cl	F	82
Cl	naphthyl	80

Scheme 56. Palladium-catalyzed benzylation of ethyloxazole-4-carboxylate (**17**) with benzyl halides.

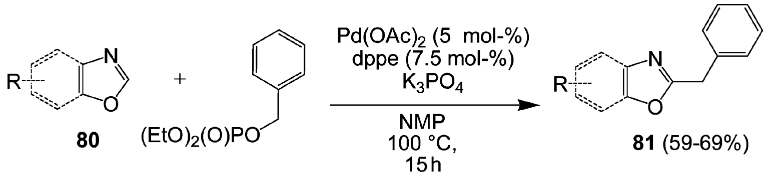
With the goal of developing a new and highly efficient general method, Fagnou and co-workers[65] described the establishment of broadly applicable palladium-catalyzed heteroarene benzylation reactions (Scheme 57). Particular focus was placed on the most challenging heterocycles **78** in traditional benzylation techniques, such as sulfur-containing heterocycles and those bearing functional groups that would be incompatible with Lewis acids and/or strong bases, as shown in Scheme 56, in which the results of representative benzylations of sulfur-containing heterocycles are summarized together with those for other azoles. The method entails the use of 1.5 equiv. of a benzyl chloride, toluene as the solvent, and Cs_2CO_3 as the base in the presence of $Pd(OPiv)_2$/2-Ph_2P-2′-(Me_2N)biphenyl/PivOH as the catalytic system. Notably, the reactions are highly regioselective and form the industrially important (hetero)aryl-arylmethane compounds **79**. Thiazole substrates, which are problematic under S_EAr benzylation conditions or necessitate deprotonation with strong bases followed by electrophilic trapping, are ideal substrates for palladium-catalyzed benzylation.

(Pseudo)benzyl halides are easily accessible from benzyl alcohols and would thus be highly advantageous alternatives to benzyl halides from both ecological and economical standpoints. Most recently, Ackermann[66] demonstrated that the oxazoles and benzoxazoles **80** (Scheme 58) undergo C-2 benzylation upon treatment with the challenging benzyl phosphate in the presence of a $Pd(OAc)_2$/dppe catalyst system and K_3PO_4 as the base to give the corresponding benzyl azoles **81** in good yields.

In 2010, Miura and co-workers[67] used benzyl carbonates[68] as benzyl sources in place of benzyl phosphates in palladium-catalyzed benzylations of the azoles **82**

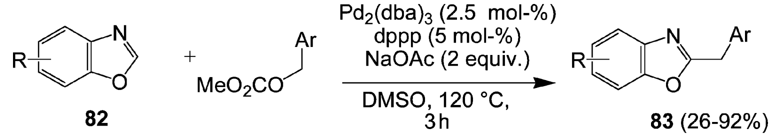


Scheme 57. Palladium-catalyzed benzylations of the heterocyclic aromatic compounds **78** with benzyl halides.



Azoles **80**	Yield (%)
5-EtO_2C-oxazole	69
Benzoxazole	66
6-Me-benzoxazole	59

Scheme 58. Palladium-catalyzed benzylation of the azoles **80** with benzyl phosphates.



82

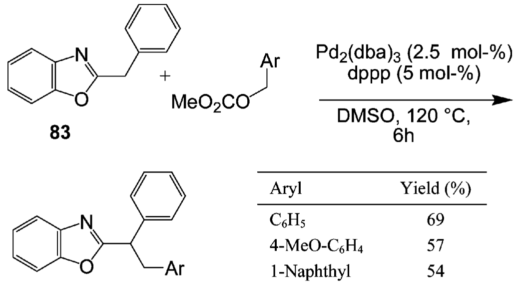
83 (26-92%)

R (**82**)	Ar	Yield (%)
H	C_6H_5	76
H	4-MeO-C_6H_4	64
H	2-MeO-C_6H_4	92
H	3-Thienyl	61
H	3-Furyl	26
6-Cl	C_6H_5	39

Scheme 59. Palladium-catalyzed benzylations of the benzoxazoles **82** with benzyl carbamates.

(Scheme 59). The authors reported that a catalyst system composed of $Pd_2(dba)_3$ and dppp provided high-yielding reactions of benzoxazoles in DMSO in the presence of K_3PO_4 as the base. On the other hand, heteroarenes such as 1,3,4-oxadiazole, 5-aryloxazoles, and benzothiazole reacted sluggishly under the standard or modified conditions.

Interestingly, the authors reported that simple removal of the external base allowed the same palladium complex to catalyze benzylic sp^{3}C–H benzylation. Various benzyl carbamates were applicable to coupling with the benzylazoles **83** to furnish the benzylated diarylmethanes **84** in moderate to good yields (Scheme 60).



83

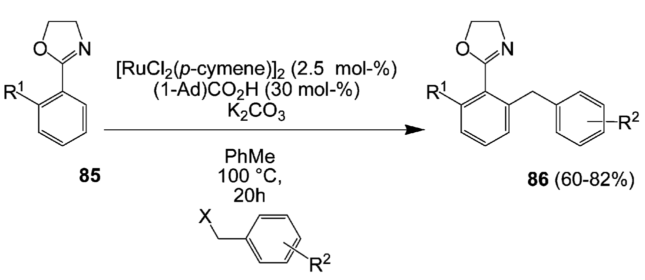
84 (52-71%)

Aryl	Yield (%)
C_6H_5	69
4-MeO-C_6H_4	57
1-Naphthyl	54
3-Thienyl	52

Scheme 60. Palladium-catalyzed direct benzylic sp^3 C–H benzylations of the 2-benzylazoles **83** with benzyl carbamates.

Ackerman and co-workers[69] have recently investigated regioselective ruthenium-catalyzed direct benzylations of the oxazolidine-substituted arenes **85** (Scheme 61) through *ortho*-C–H bond activation. Functional groups such as esters or enolizable ketones on the aromatic nuclei of the benzyl halides were tolerated well. Furthermore, substrates featuring both benzyl and aryl chloride components were coupled chemoselectively at the former functionality.

Interestingly, pyridine-, and pyrazole-substituted arenes were functionalized regioselectively under the above conditions, delivering diarylmethanes with a useful functional group tolerance. Further inter- and intramolecular competition experiments between differently substituted arenes highlighted evidence for a non-S$_E$Ar-type catalytic manifold, and are in good agreement with a concerted cyclometallation/deprotonation mechanism.



85

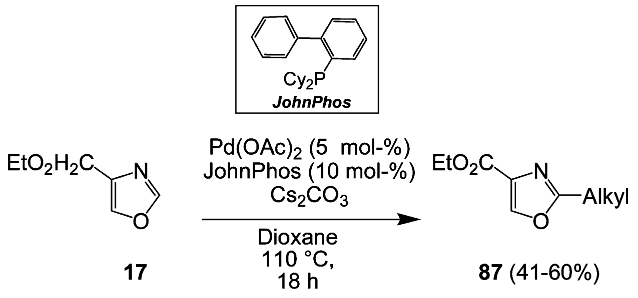
86 (60-82%)

X	R^1	R^2	Yield (%)
Cl	Me	1-Me	68
Br	Me	1-Me	43
Cl	Me	1-Cl	66
Cl	H	4–OMe	61

Scheme 61. Ruthenium-catalyzed direct benzylations of the oxazolidine-substituted arenes **85** with benzyl halides.

4. Intermolecular Direct Alkylation of Heteroarenes (Coupling between sp^2 C–H and sp^3 C–H Bonds)

Direct metal-catalyzed alkylation of heteroarenes is not restricted to the use of benzyl halides as electrophilic coupling partners. Very recently, this coupling technology was



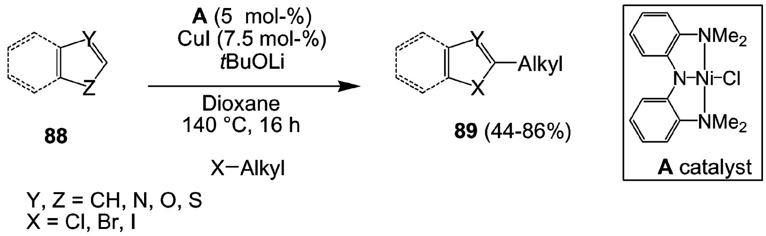
17

87 (41-60%)

X−Alkyl

X	Alkyl	Yield (%)
Br	*n*Bu	60
I	Me	41

Scheme 62. Palladium-catalyzed alkylations of ethyl oxazole-4-carboxylate (**17**) with alkyl halides.



88	Alkyl-X	Yield (%)
Benzoxazole	$cC_6H_{13}CH_2Br$	79
Benzoxazole	$C_6H_5(CH_2)_3Cl$	70
5-PMP-oxazole	$nC_8H_{17}I$	86
Benzothiophene	nC_4H_9I	78
Benzothiazole	nC_4H_9I	78

Scheme 63. Nickel/copper-catalyzed direct alkylations of the azoles **88** with alkyl halides.

shown also to be applicable with non-activated alkyl halides, although metal alkyl intermediates resulting from oxidative addition are prone to β-hydride elimination.

To date, only two examples of successful transition-metal-catalyzed direct alkylations of heteroarenes have been reported. In 2009 Hoarau reported the first palladium-catalyzed reaction between ethyl oxazole-4-carboxylate (**17**, Scheme 62) and *n*-butyl bromide (2 equiv.). The coupling was effective when $Pd(OAc)_2$ was used as a precatalyst together with Buchwald's JohnPhos ligand. Under these conditions, ethyl 2-butyloxazole-4-carboxylate (**87**) was obtained in 60% yield.[12] It should be noted that the butyl chloride proved an ineffective coupling partner even when other ligands were used.

On the other hand, in 2010 Hu and co-workers reported a general and versatile method for the synthesis of the alkylated aromatic heterocycles **89** (Scheme 63).[70] With $[(^{Me}NN_2)NiCl]$/CuI as precatalyst in the presence of *t*BuOLi as the base, the authors demonstrated that the benzoxazoles **88** would undergo direct C-2 alkylation with functionalized alkyl halides, including the inexpensive chlorides. As summarized in Scheme 63, various C2-alkylated benzoxazole derivatives **89** were isolated in good yields.

This nickel/copper catalysis also enables the alkylation of both electron-rich (thiophene) and electron-poor (oxazole and thiazole) heterocycles; this is difficult to achieve with other synthetic procedures. Various nonactivated alkyl halides containing β-hydrogen atoms could be employed. The chemo- and regioselectivities are excellent; only alkyl halide bonds are reactive in the presence of aryl and heteroaryl halide moieties.

The mechanism of the coupling reaction is similar to those of nickel/copper- and copper-catalyzed direct arylations and alkynylations of aromatic heterocycles.[53,54] The authors proposed that the copper facilitates the transmetallation of the anionic azole/thiophene intermediates to nickel. The existence of an anionic benzoxazole was confirmed, with quenching of the reaction mixture at partial conversion with D_2O producing 2-deuterated benzoxazole.

5. Conclusion

In this review, we have detailed a collection of the impressive developments made during the last decade in the area of transition-metal-catalyzed direct alkenylation, alkynylation, benzylation, and alkylation as routes toward the formation of specific C–C bonds. Importantly, $C(sp^2)$–$C(sp^2)$, $C(sp^2)$–$C(sp)$, and $C(sp^2)$–$C(sp^3)$ coupling reactions have all been demonstrated. A number of commercial practical catalysts are available for these transformations. Palladium is still the metal of choice, although other metals such as copper, nickel, ruthenium, and rhodium have been used with some success. Mechanisms by which these procedures can be performed show promise for more frequent use in everyday organic synthesis and should stimulate the development of novel processes with expanded scope and efficacy. Finally, we believe that in the near future, thanks to their excellent functional group tolerances and high chemo- and regioselectivities, the broad scope and simplicity of these valuable protocols will increase their impact on the synthesis of biologically active natural compounds and pharmacologically relevant heteroaromatics substances in both academic and industrial settings.

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After publication in Early View, correct Scheme 10 was included.