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Transition-metal-catalyzed direct arylations via C–H bond cleavages*

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Abstract: Palladium catalysts allowed for intermolecular direct arylations of heteroarenes with aryl chlorides, tosylates, or mesylates as electrophiles. As an economically attractive alternative, inexpensive copper catalysts could be employed for regioselective C–H bond arylations of 1,2,3-triazoles. On the contrary, intermolecular C–H bond functionalizations of arenes were accomplished with ruthenium complexes derived from air-stable (heteroatom-substituted) secondary phosphine oxide (HASPO) preligands. Particularly, the use of ruthenium(II) carboxylate complexes enabled broadly applicable direct arylations with inter alia aryl tosylates and phenols, and set the stage for unprecedented intermolecular direct alkylations with unactivated alkyl halides bearing β-hydrogens.

Keywords: alkyl halides; aryl halides; catalysis; C–H bond activation; copper; palladium; ruthenium.

INTRODUCTION

Biaryls are indispensable structural motifs of various compounds with valuable activities of relevance to biology or material sciences, among others [1]. Their regioselective syntheses are predominantly achieved through transition-metal-catalyzed cross-coupling reactions between organic (pseudo)halides and stoichiometric amounts of organometallic reagents (Scheme 1, a) [2], which have matured to reliable tools for the formation of $C(sp^2)$–$C(sp^2)$ bonds [3]. However, these organometallic nucleophilic reagents are often not commercially available or expensive. Their syntheses from the corresponding arenes involve a number of synthetic operations, during which undesired by-products are formed, as are during the traditional cross-coupling reactions themselves. Therefore, direct arylation reactions through cleavages of C–H bonds represent environmentally and economically benign alternatives (Scheme 1, b) [4].

Among aryl halides, chlorides are arguably the most useful single class of electrophilic substrates due to their lower costs and a wide diversity of commercially available compounds. While the development of stabilizing ligands enabled *traditional* cross-coupling reactions of these inexpensive substrates [5,6], generally applicable methodologies for the use of aryl chlorides in catalytic direct arylations through C–H bond cleavages are scarce [1,7].

The use of aryl tosylates or mesylates as electrophilic arylating reagents in cross-coupling chemistry is highly desirable, because they can be prepared from readily available phenols or ketones with inexpensive reagents, and because of their moisture-stable and highly crystalline nature. Unfortunately,

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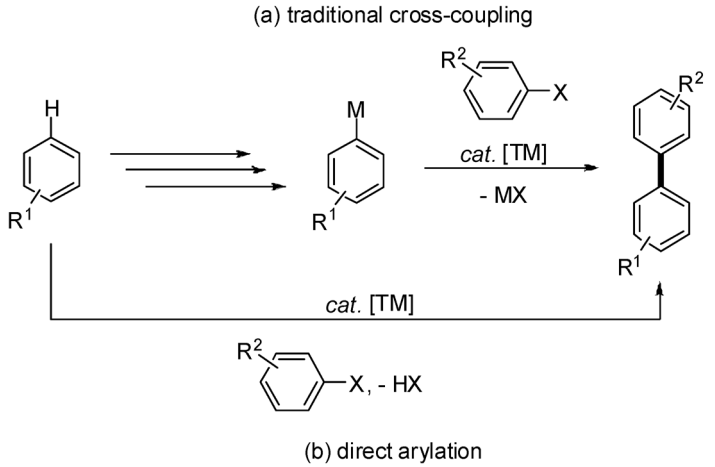


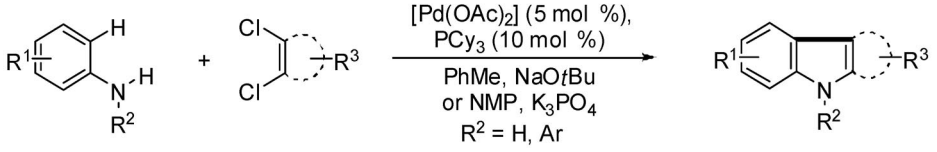
Scheme 1

their improved stabilities translate into significantly reduced reactivities in catalytic coupling chemistry. As a result, methodologies for catalyzed direct [8] arylations through C–H bond cleavages with these convenient sulfonates were previously not reported.

RESULTS AND DISCUSSION

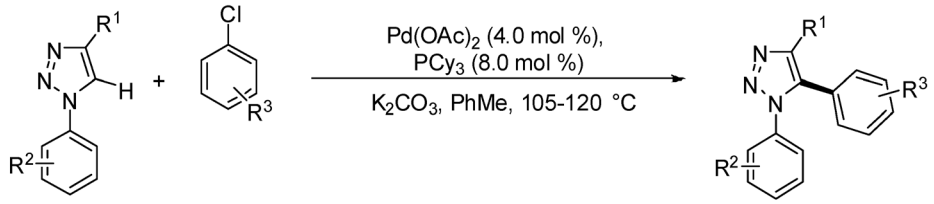
Palladium-catalyzed direct arylations with aryl chlorides, tosylates, or mesylates

We developed a palladium-catalyzed [9] direct arylation-based domino reaction, which enabled efficient syntheses of various *N*-heteroarenes, such as indoles or carbazoles, and proved amenable to substrates bearing solely chlorides as leaving groups [10,11]. This modular one-pot transformation of 1,2-dichlorides proceeded regioselectively to deliver either N-substituted or N–H free carbazoles (Scheme 2).



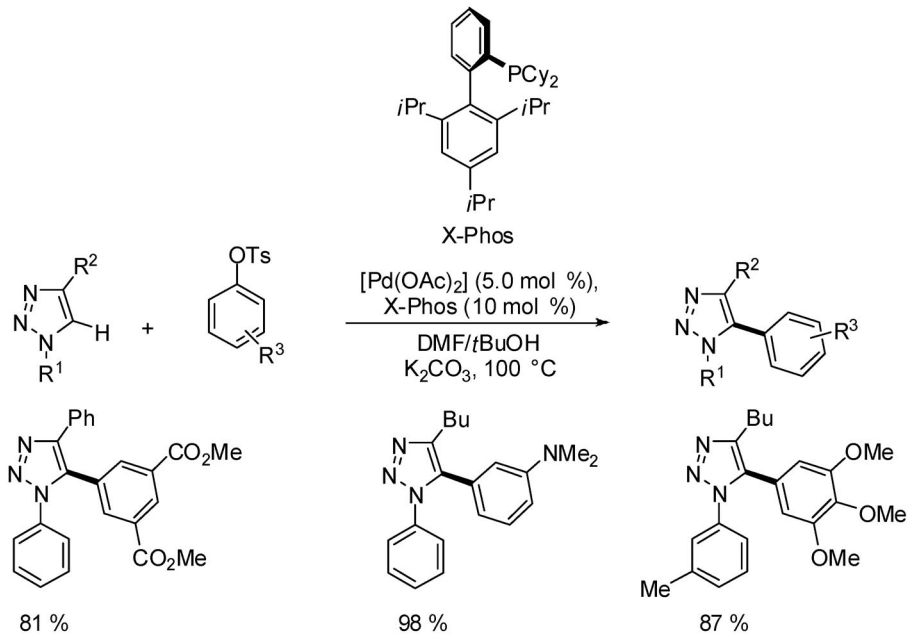
Scheme 2

Subsequently, we devised reaction conditions for intermolecular palladium-catalyzed direct arylations of 1,2,3-triazoles with aryl chlorides as electrophiles, which were accomplished with conventional heating at reaction temperatures as low as 105 °C (Scheme 3) [12,13].



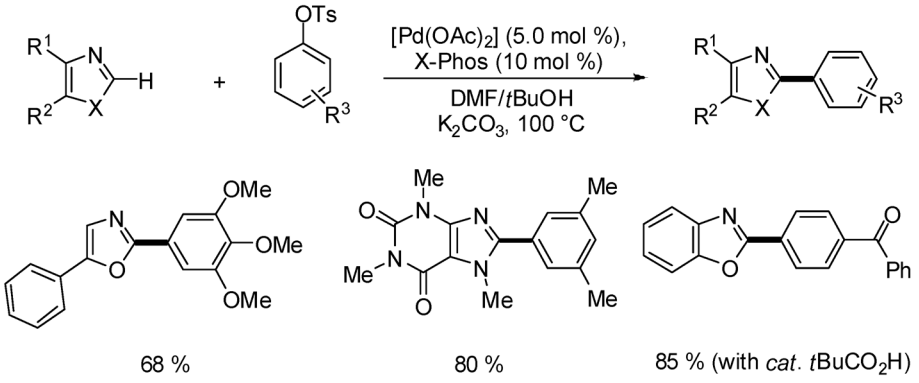
Scheme 3

More recently, we accomplished first palladium-catalyzed direct arylations with tosylates as convenient arylating reagents. Thus, a catalytic system derived from electron-rich monophosphine X-Phos [14] enabled broadly applicable C–H bond functionalizations of 1,2,3-triazoles with electron-deficient, as well as electron-rich aryl tosylates (Scheme 4) [15].



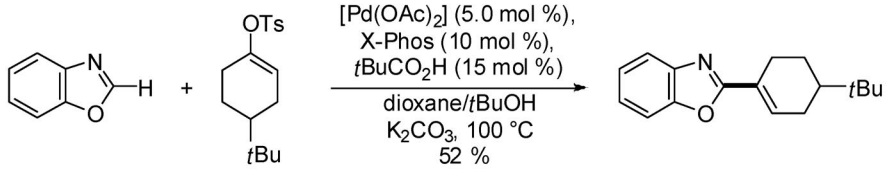
Scheme 4

The optimized palladium catalyst was not restricted to the conversion of 1,2,3-triazoles, but allowed for direct arylations of various electron-rich heteroarenes, such as oxazoles, caffeine, or benzoxazoles (Scheme 5) [15].



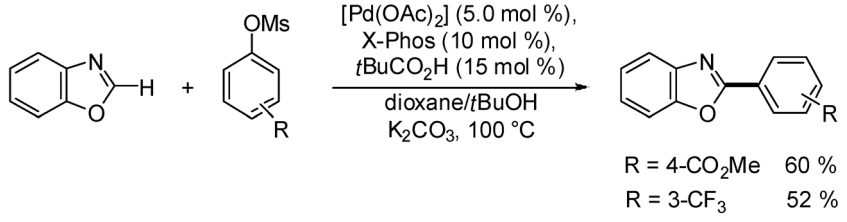
Scheme 5

Importantly, the methodology proved applicable to C–H bond functionalizations with alkenyl tosylates as well (Scheme 6) [15], a valuable asset with respect to diastereoselective syntheses of alkenes.



Scheme 6

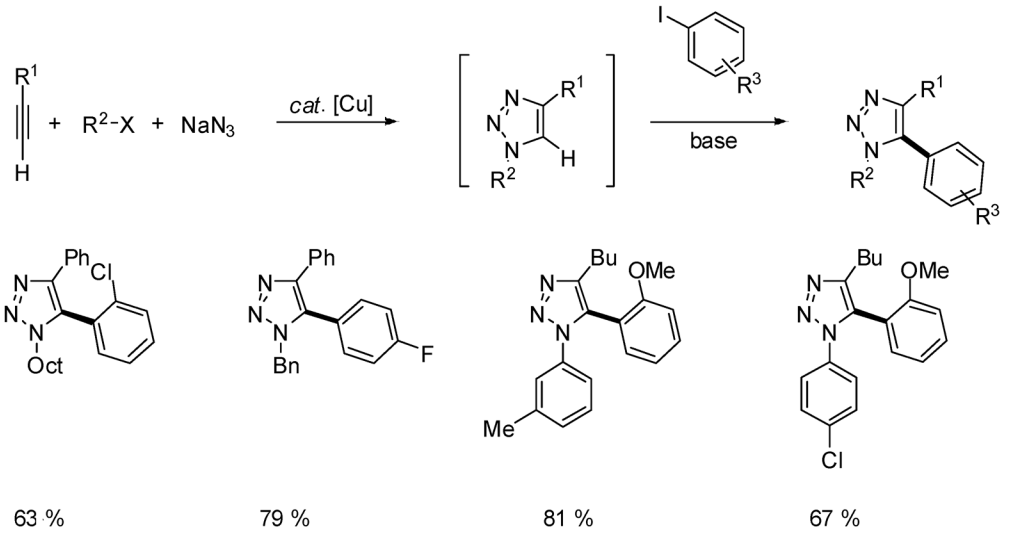
Given the significantly lower molecular weights of aryl mesylates, processes utilizing these electrophiles are more atom-economical than those relying on aryl triflates or tosylates. Therefore, we were delighted to observe that the optimized catalytic system could be employed for first direct arylations with these challenging electrophiles as well (Scheme 7) [15].



Scheme 7

Copper-catalyzed direct arylations of 1,2,3-triazoles

As an economically attractive alternative to the use of palladium complexes in direct arylations of 1,2,3-triazoles, we described copper-catalyzed transformations [16,17], which set the stage for a modular one-pot sequential catalytic approach to diversely substituted 1,2,3-triazoles [14]. The direct arylation-based sequential process relied on a single copper catalyst for two mechanistically distinct transformations, namely, atom-economical 1,3-dipolar cycloadditions ("click" reaction) and C–H bond functionalizations. Thereby, the chemoselective coupling of up to four components through the formation of one C–C and three C–N bonds was achieved (Scheme 8).

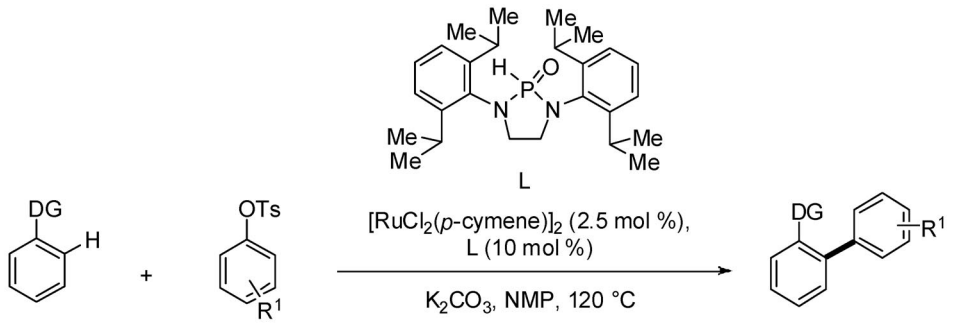


Scheme 8

Ruthenium-catalyzed direct arylations

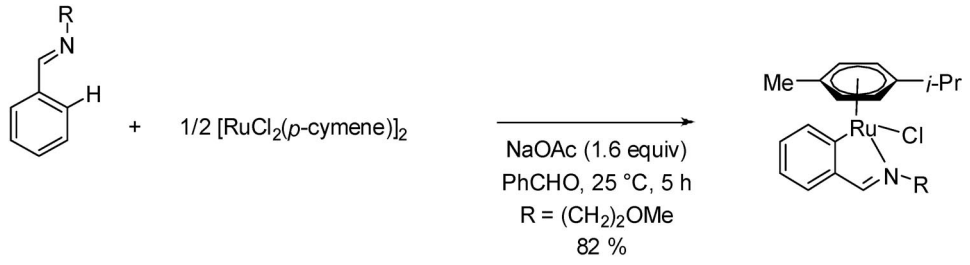
The formation of C_{aryl}–C_{aryl} bonds through transition-metal-catalyzed arylation reactions has been largely dominated by the use of copper, palladium, or nickel complexes [1,3]. In contrast, ruthenium-catalyzed traditional cross-coupling reactions between organometallic reagents and organic halides are scarce [18].

While a ruthenium complex derived from preligand $(1\text{-Ad})_2P(O)H$ enabled broadly applicable intermolecular direct arylations with aryl chlorides [19,20], air-stable heteroatom-substituted secondary phosphine oxide (HASPO) [21] was found to be applicable to first direct arylations of arenes with aryl tosylates (Scheme 9) [18,22].



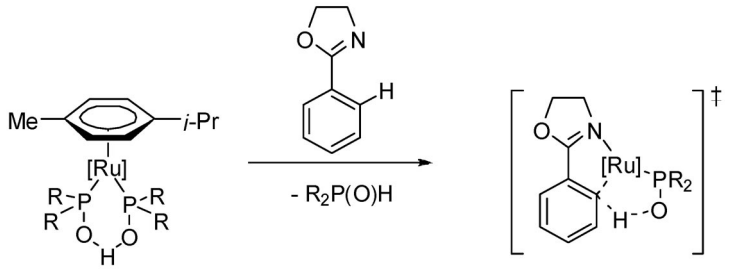
Scheme 9

Experimental mechanistic studies on the working mode of ruthenium-catalyzed direct arylations with organic (pseudo)halides were not available until recently. However, a beneficial effect of NaOAc on stoichiometric syntheses of ruthenacycles at ambient temperature was observed by Davies and co-workers (Scheme 10) [23], which suggested a cooperative metalation/deprotonation mechanism [24,25] for the C–H bond metalation step. Furthermore, recent computational density functional theory (DFT) calculations provided support for such a mechanistic manifold [26].



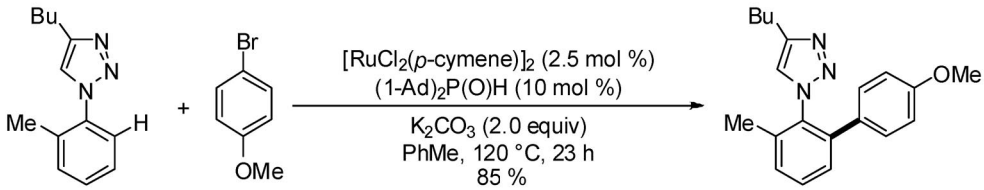
Scheme 10

We proposed a concerted metalation/deprotonation regime to account for the high efficacy observed when using (HA)SPO preligands in ruthenium-catalyzed direct arylation reactions (Scheme 11) [27].



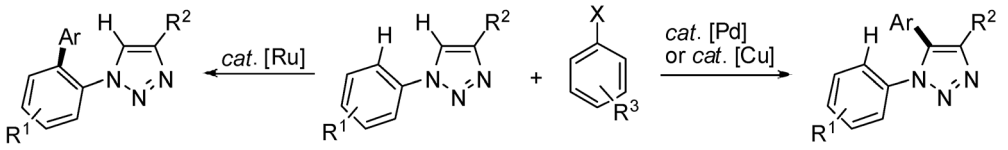
Scheme 11

Hence, ruthenium-catalyzed direct arylations with aryl halides in less-coordinating solvents were probed. Notably, a catalytic system derived from SPO preligand $(1\text{-Ad})_2P(O)H$ enabled regioselective C–H bond functionalizations at the aromatic moieties of *N*-aryl-substituted 1,2,3-triazoles in apolar toluene as solvent (Scheme 12) [27].



Scheme 12

It is noteworthy, that the regioselectivity of this ruthenium-catalyzed direct arylation of *N*-aryl-1,2,3-triazoles proved complementary to the one observed when applying either palladium [12,13] or copper [16] catalysts (Scheme 13).



Scheme 13

Recently, the beneficial effect of carboxylic acids as additives in palladium-catalyzed direct arylations through a concerted deprotonation/metalation mechanism [25,28] was observed [29]. On the contrary, we explored various substituted carboxylic acids as additives in ruthenium-catalyzed direct arylations via the proposed transition-state model depicted in Fig. 1 [27].

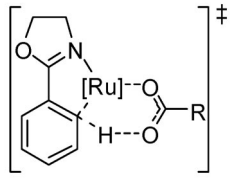
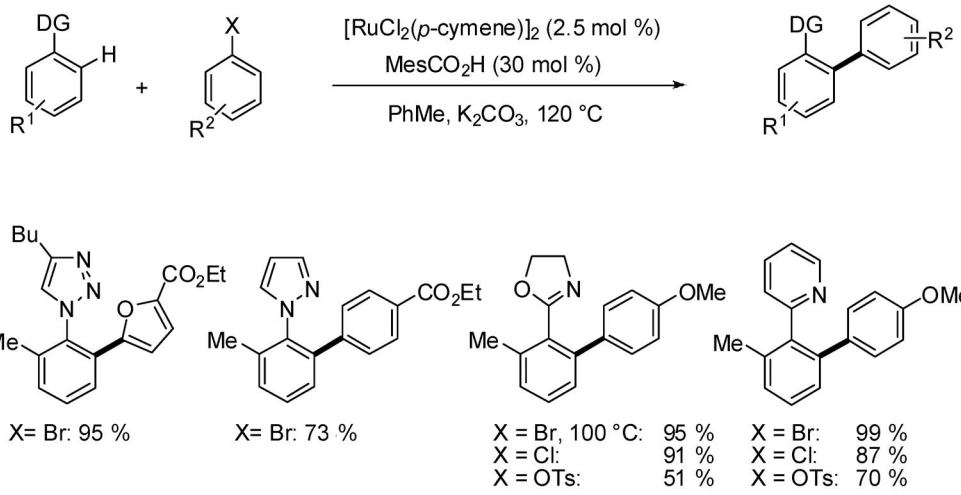


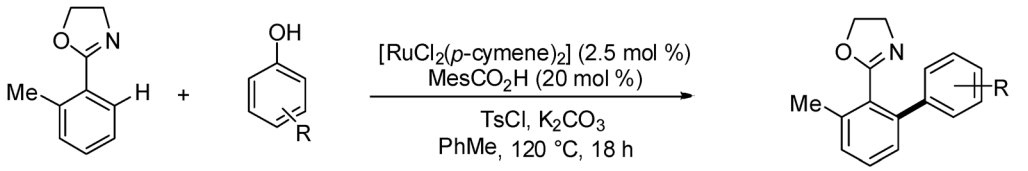
Fig. 1

Hence, a ruthenium complex derived from carboxylic acid $MesCO_2H$ displayed an unparalleled broad scope, which included inter alia efficient direct arylations of 1,2,3-triazoles, pyridines, pyrazoles or oxazolines [27]. Additionally, aryl bromides, chlorides, and tosylates, including *ortho*-substituted derivatives, turned out to be suitable arylating reagents (Scheme 14).



Scheme 14

Thereafter, we devised reaction conditions for first direct arylations between arenes and inexpensive, broadly available phenols as arylating reagents (Scheme 15) [30]. Notably, this operationally simple, formal dehydrative arylation was achieved with a highly chemo- and regioselective ruthenium catalyst, and proceeded through the functionalizations of both C–H as well as C–OH bonds.

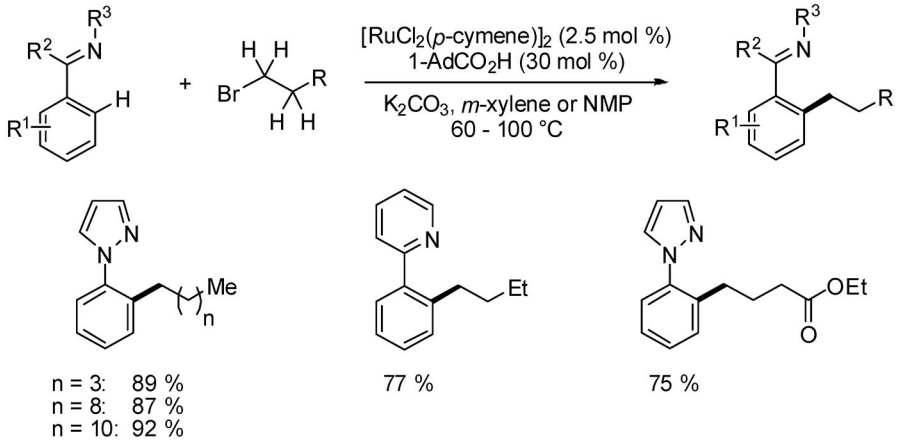


R = 4-CO_2Me: 83 %
R = 4-C(O)Me: 80 %
R = 3-C(O)Me: 76 %

Scheme 15

Ruthenium-catalyzed direct alkylations with alkyl halides bearing β-hydrogens

Having developed ruthenium-catalyzed direct arylations with carboxylic acids as additives [27], we became interested in exploring their use for unprecedented ruthenium-catalyzed [31] intermolecular [32] direct alkylations with unactivated alkyl halides as coupling partners. Hence, we observed that efficient C–H bond functionalizations with alkyl iodides, bromides, or chlorides bearing β-hydrogens were feasible with a ruthenium catalyst generated from carboxylic acid (1-Ad)CO_2H (Scheme 16) [33].



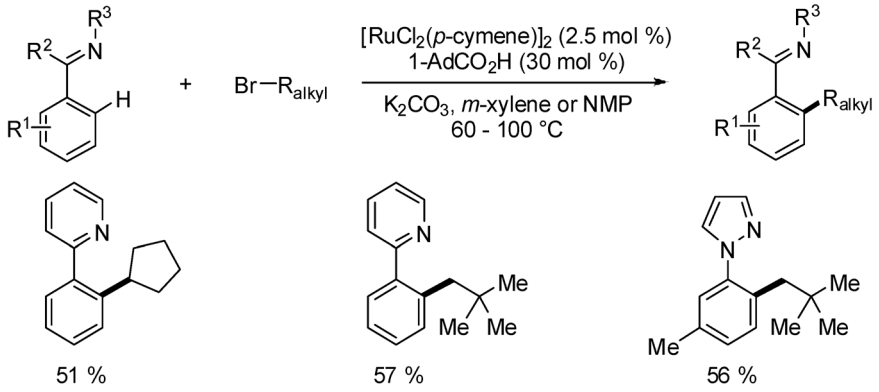
n = 3: 89 %
n = 8: 87 %
n = 10: 92 %

77 %

75 %

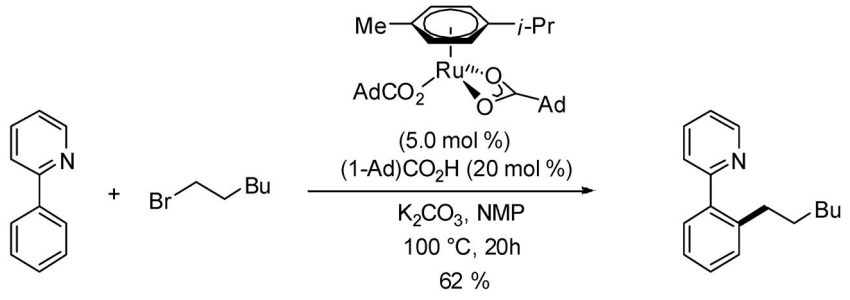
Scheme 16

Notably, this catalytic system allowed also for direct alkylations with sterically more congested secondary alkyl bromides (Scheme 17) [33]. Importantly, neopentyl bromide served also as starting material, which suggested that mechanisms involving either a simple nucleophilic substitution or a Friedel–Crafts-type electrophilic aromatic substitution (S_EAr) were not operative here.



Scheme 17

Finally, we studied the nature of the catalytically active species. Under the reaction conditions of catalytic C–H bond functionalizations, a ruthenium(II) carboxylate complex was quantitatively formed. Importantly, this isolated, well-characterized complex displayed a catalytic activity comparable to the one observed for the in situ generated system (Scheme 18) [33].



Scheme 18

SUMMARY

Our recent efforts to develop protocols for efficient C–H bond functionalizations resulted in broadly applicable palladium catalysts for direct arylations of various heteroarenes with convenient aryl chlorides, tosylates, or mesylates as electrophiles. As an economically sound alternative, inexpensive copper catalysts allowed for direct arylations of 1,2,3-triazoles, which set the stage for direct arylation-based sequential copper catalyses. Regioselective intermolecular C–H bond functionalizations of arenes were achieved with ruthenium complexes through chelation assistance. Thus, complexes derived from air-stable HASPO preligands proved applicable to direct arylations with aryl chlorides or tosylates, as well as phenols as arylating reagents. Further, the use of carboxylic acids as additives provided ruthenium complexes with unparalleled scope in direct arylations, which importantly enabled first direct alkylations with alkyl halides bearing β-hydrogens.

ACKNOWLEDGMENTS

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