DOI: 10.1002/chem.201001631

Palladium- and Nickel-Catalyzed Direct Alkylation of Azoles with Unactivated Alkyl Bromides and Chlorides

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Metal-mediated direct C–C bond-forming reactions involving C–H bond cleavage are commonly of great interest in modern organic chemistry, because of their potential for providing an alternative to the conventional cross-coupling strategy with a stoichiometric amount of organometallic reagents and transformation of ubiquitous C–H bonds into diverse functions in a single synthetic operation.[1] In particular, various catalytic systems for the direct arylation,[2] alkenylation,[3] and alkynylation[4] of arenes and heteroarenes with the corresponding organic halides and pseudohalides have been widely explored. On the other hand, the direct alkylation reaction with alkyl halides has received less attention, probably due to its substantial difficulty in controlling undesired β-H elimination. Although recent efforts have enabled the use of activated alkylating reagents, such as benzylic electrophiles,[5] the reaction with unactivated alkyl halides, especially those possessing the β-hydrogen atoms,[6] thus, remains largely elusive.[7] Hoarau,[5c] Yu,[8] Wang,[9] and Daugulis[10] independently reported palladium-catalyzed alkylation processes, whereas Ackermann[11] also succeeded in a similar alkylation by using a ruthenium catalyst. However, most of them are restricted in substrate scope to arenes containing directing groups, and the alkyl donors are still limited to relatively reactive alkyl iodides and bromides. Here, we report effective palladium- and nickel-based catalysts for the direct alkylation of azole compounds. The present catalytic systems are composed of common catalyst precursors, and especially, the palladium-based system allows unactivated alkyl chlorides as well as bromides to serve as the promising alkyl sources.[12]

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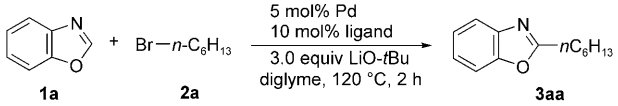
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201001631.

Based on the literature for the successful cross-coupling reaction with alkyl electrophiles,[13] we began our study with a Pd/bulky phosphine catalyst system. Indeed, treatment of benzoxazole (**1a**, 0.50 mmol) with 1-bromohexane (**2a**, 0.60 mmol) in the presence of $Pd(OAc)_2$ (5 mol%), PCy_3 (Cy = cyclohexyl; 10 mol%), and LiO-*t*Bu (1.5 mmol) in diglyme (3.0 mL) at 120 °C for 2 h provided the desired 2-hexylbenzoxazole (**3aa**) albeit in 34% yield (GC; Table 1, entry 1). With this interesting preliminary result in hand, we screened various monodentate bulky ligands involving

Table 1. Optimization studies for palladium-catalyzed direct C–H alkylation of benzoxazole (**1a**) with 1-bromohexane (**2a**).[a]



1a 2a 3aa

Entry	Pd	Ligand	Yield of **3aa** [%][b]
1	$Pd(OAc)_2$	PCy_3	34
2	$Pd(OAc)_2$	$PPhCy_2$	18
3	$Pd(OAc)_2$	PPh_2Cy	43
4	$Pd(OAc)_2$	$P(t\text{Bu})_3$	0
5	$Pd(OAc)_2$	PPh_3	18
6	$Pd(OAc)_2$	SPhos[c]	trace
7	$Pd(OAc)_2$	RuPhos[d]	0
8	$Pd(OAc)_2$	IMes·HCl[e]	14
9	$PdCl_2$	PPh_2Cy	30
10	$[Pd_2(dba)_3]$[i]	PPh_2Cy	43
11	$[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$	PPh_2Cy	48
12[f]	$[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$	PPh_2Cy	55 (44)
13[f]	$[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$	$PCyp_3$[g]	34
14[f]	$[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$	$P(i\text{Bu})_3$	20
15[f]	$[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$	$P(n\text{Bu})_3$	66
16[f]	$[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$	PMe_3	16
17[f,h]	$[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$	$P(n\text{Bu})_3$	77 (64)

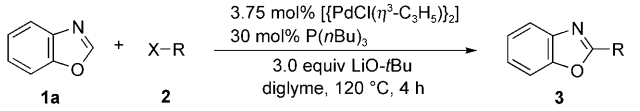
[a] A mixture of Pd (0.025 mmol), ligand (0.050 mmol), LiO-*t*Bu (1.5 mmol), **1a** (0.50 mmol), and **2a** (0.60 mmol) in diglyme (3.0 mL) was heated at 120 °C for 2 h under N_2. [b] Yield determined by GC methods. Yield of isolated product is in parentheses. [c] 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl. [d] 2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl. [e] 1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride. [f] Used 1.0 mmol of **2a**. [g] Cyp = cyclopentyl. [h] 20 mol% of $P(n\text{Bu})_3$. [i] dba = dibenzylideneacetone.

Buchwald's biaryl phosphines and NHC (entries 2–8) and found the good activity of PPh_2Cy (entry 3). Among other palladium salts tested (entries 9–11), a combination of $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ and PPh_2Cy gave better result (entry 11). While an increase in the amount of **2a** to two equivalents slightly improved the reaction efficiency (entry 12), any changes of other reaction parameters such as base, solvent, and temperature gave no positive effect on yield. Thus, the additional ligand investigation was carried out (entries 13–16). To our surprise, a smaller $P(n\text{Bu})_3$ proved to be optimal, which runs counter to the reported trends[13] (entry 15). With 20 mol% of $P(n\text{Bu})_3$ as the ligand, **3aa** was obtained in 64% isolated yield (entry 17).

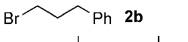
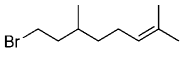
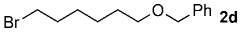
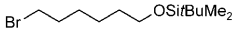
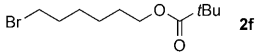
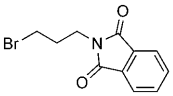
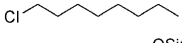
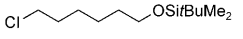
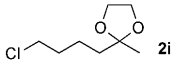
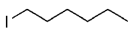
With the $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]/P(n\text{Bu})_3$ catalyst, we performed the direct alkylation of **1a** with an array of alkyl bromides **2** (Table 2). In general, 7.5 mol% (based on Pd) catalyst loading gave the good reproducibility. Phenylpropyl (**2b**) and citronellyl bromide (**2c**) as well as simple **2a** participated in the reaction (entries 1 and 2). Benzyl ether, silyl ether, and pivaloyl ester functionalities were tolerant, and the corresponding alkylated benzoxazoles **3ad–f** were formed in moderate to good yields (entries 3–5), whereas the imide moiety caused in the drop of the yield (entry 6). It is worth noting that not only alkyl bromides, but also unactivated alkyl chlorides worked well as the alkylating reagents. With the prolonged reaction periods (12 h), under the otherwise identical conditions, the direct C–H alkylation proceeded smoothly (entries 7–9). Notably, an acetal protection was compatible toward the reaction (entry 9). However, 1-iodohexane (**2a′**) and the secondary alkyl halide, bromocyclohexane (**2j**) reacted with **1a** sluggishly, probably due to the rapid decomposition under the basic conditions and the steric factors in the oxidative addition step (vide infra), respectively (entries 10 and 11).

Subsequently, we investigated the scope of azoles in the palladium-catalyzed direct coupling (Scheme 1). 5-Substituted benzoxazoles coupled with alkyl bromides and chlorides without any difficulties (**3bi**, **3cb**, and **3db**). It should be noted that the sp^3C–halide bond activation in preference to that of sp^2C–halide bond was observed, which may enjoy further manipulation (**3db**). In addition to benzoxazoles, 5-

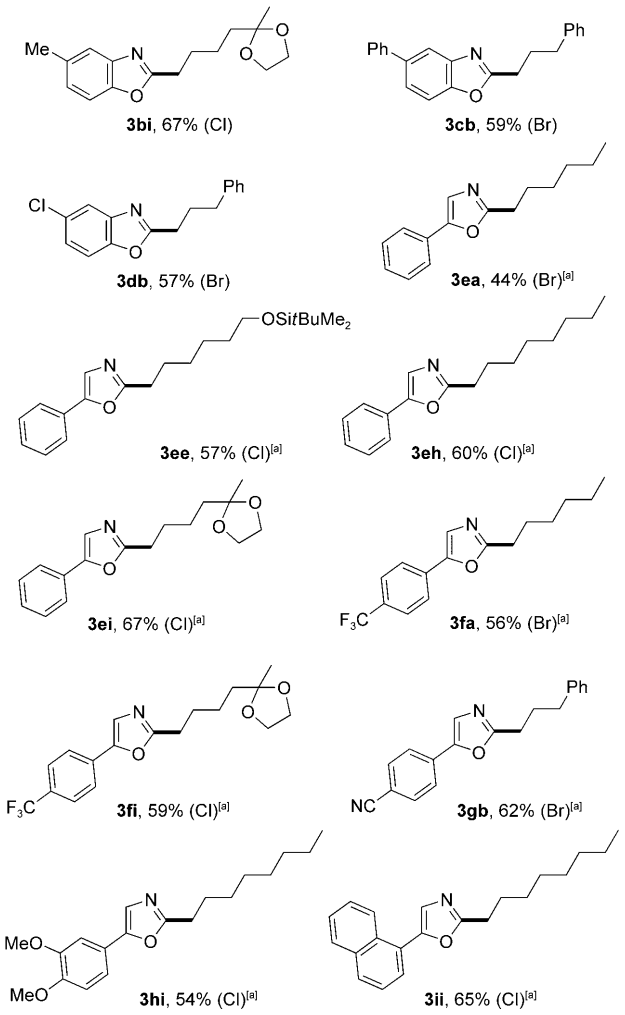
Table 2. Palladium-catalyzed direct C–H alkylation of benzoxazole (**1a**) with various alkyl halides **2**.[a]



1a 2 3

Entry	2	Yield of 3 [%][b]
1	 2b	**3ab**, 71
2	 2c	**3ac**, 48
3	 2d	**3ad**, 65
4	 2e	**3ae**, 59
5	 2f	**3af**, 51
6	 2g	**3ag**, 33
7[c]	 2h	**3ah**, 63
8[c]	 2e′	**3ae**, 65
9[c]	 2i	**3ai**, 75
10[d]	 2a′	**3aa**, 20[e]
11[d]	 2j	**3aj**, trace

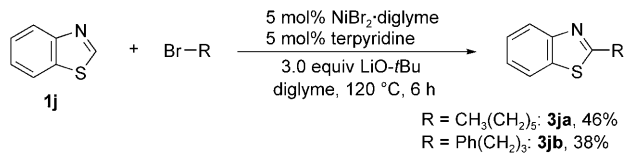
[a] A mixture of $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ (0.019 mmol, 7.5 mol% Pd), $P(n\text{Bu})_3$ (0.15 mmol), LiO-*t*Bu (1.5 mmol), **1a** (0.50 mmol), and **2** (1.0 mmol) in diglyme (3.0 mL) was heated at 120 °C for 4 h under N_2. [b] Yield of isolated product. [c] The reaction time was 12 h. [d] Under the conditions of entry 17 in Table 1. [e] Yield determined by GC methods.



Scheme 1. Products of the palladium-catalyzed direct coupling of azoles **1** with alkyl halides **2**. The forming C–C bond is illustrated with a bold line. The leaving group (Br or Cl) on alkyl halides is in parenthesis. Reaction conditions: A mixture of $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ (0.019 mmol, 7.5 mol% Pd), $P(n\text{Bu})_3$ (0.15 mmol), LiO-*t*Bu (1.5 mmol), **1a** (0.50 mmol), and **2** (1.0 mmol) in diglyme (3.0 mL) was heated at 120 °C for 4 h (Br) or 12 h (Cl) under N_2. [a] Used 1.5 mmol of **2** and 2.0 mmol of LiO-*t*Bu.

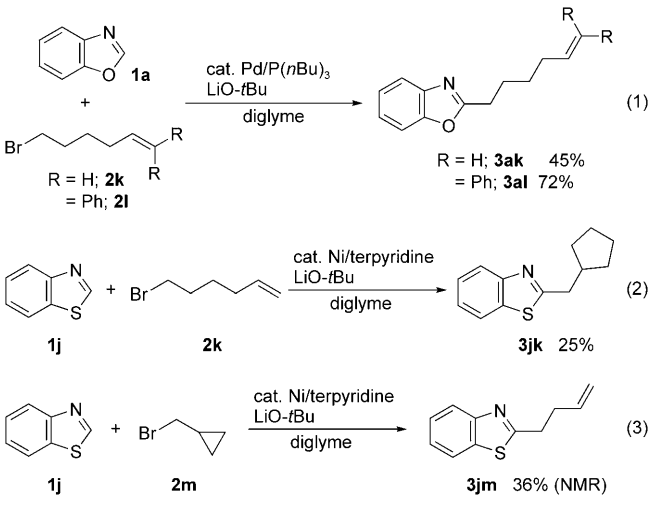
aryloxazoles bearing the electronically and sterically diverse functions such as trifluoromethyl, cyano, methoxy, and naphthyl groups underwent the alkylation. Moreover, the functional group tolerance on alkyl halide was also generally good.

In sharp contrast to the above success with oxazoles, no product was detected when benzothiazole (**1j**) was employed under the standard reaction conditions using palladium. Thus, we turned our attention to a nickel catalyst.[14,15] It was found that a $NiBr_2$·diglyme/terpyridine[16] catalyst catalyzed the alkylation of **1j** with alkyl bromides **2** (Scheme 2). While the yields were moderate, our preliminary studies showed the intrinsic potential of nickel in the direct C–H alkylation.[12,17]

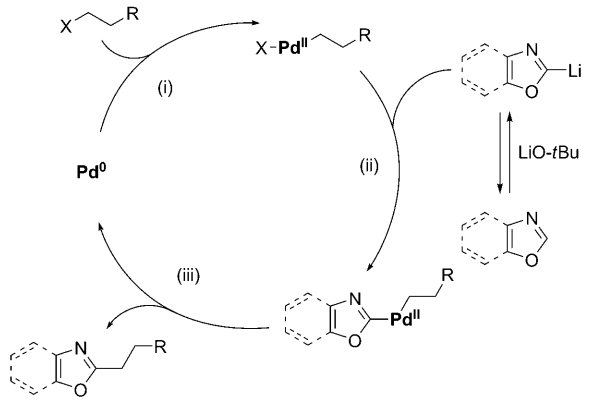


Scheme 2. Nickel-catalyzed direct alkylation of benzothiazole (**1j**) with alkyl bromides **2a**,**b**.

To obtain an insight into the mechanism, we implemented the following reactions [Eqs. (1)–(3)]. The palladium-catalyzed coupling of benzoxazole (**1a**) with alkyl bromide **2k** bearing the pendant olefin moiety exclusively afforded the usual alkylated product **3ak** [Eq. (1)].

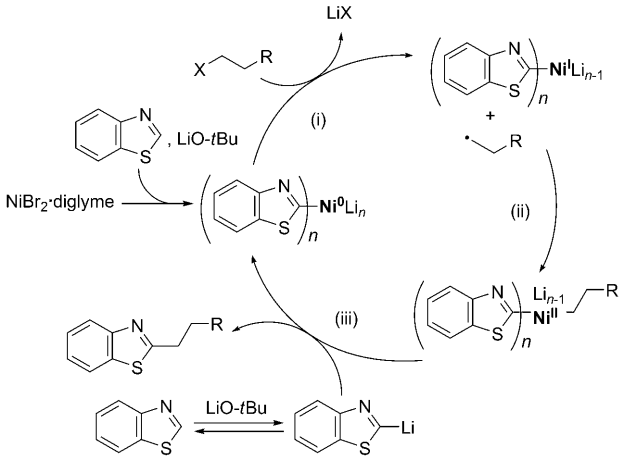


Even with **2l**,[18] the corresponding **3al** was produced with the C=C double bond left intact. In contrast, the nickel catalyst led to the formation of 5-*exo*-cyclized **3jk**, and no linear coupling product was observed [Eq. (2)]. In addition, the radical clock **2m** was transformed to the ring-opened **3jm** as the sole detectable product [Eq. (3)]. The results were highly suggestive of the existence of a radical intermediate arising from the alkyl halide under nickel catalysis. On the basis of these outcomes, we propose the following reaction mechanisms: the palladium catalysis would involve i) S_N2-type oxidative addition of alkyl halide to Pd^0,[19] ii) subsequent transmetalation between the resultant [Pd^{II}(alkyl)X] (X = halide) and heteroaryllithium generated in situ from azole and LiO-*t*Bu,[20] and iii) productive reductive elimination from the [Pd^{II}(alkyl)(heteroaryl)] complex (Scheme 3).



Scheme 3. Plausible mechanism for the palladium catalysis.

On the other hand we propose that the nickel-catalyzed reaction proceeds through i) formation of an alkyl radical triggered by a single-electron transfer from an electron-rich heteroarylnickelate complex to the alkyl halide,[15,16,21] ii) recombination of the formed radical with the heteroarylnickel, and iii) reductive elimination (Scheme 4). Further elucidation of the detailed mechanism including the reason for the suppression of the conceivable β-H elimination from the alkylmetal intermediate[22] is ongoing.



Scheme 4. Plausible mechanism for the nickel catalysis.

In summary, we have demonstrated the effective palladium and nickel catalyst systems for the direct C–H alkylation of electron-deficient arenes, azoles with unactivated alkyl bromides and chlorides, and the striking mechanistic de-

pendence on the metals. The catalytic procedures complement the known direct C–H alkylation methodologies[8–12] as well as the conventional Friedel–Crafts alkylation,[23] which is limited to electron-rich arenes, and provide a straightforward strategy for the introduction of a longer and functional alkyl side chain to heteroarenes, which is known to generally enhance their lipophilicity and solubility and to tune the aromatic π-stacking and -conjugation of their oligomers and polymers.

Experimental Section

Palladium-catalyzed direct C–H alkylation of benzoxazole (1a) with 1-bromohexane (2a) (Table 1, entry 17): [{PdCl(η^3-C_3H_5)}$_2$] (4.6 mg, 0.013 mmol) and LiO-*t*Bu (120 mg, 1.5 mmol) were placed in a 20 mL two-necked reaction flask, which was filled with nitrogen by using the standard Schlenk technique. Diglyme (2.0 mL) and P(*n*Bu)$_3$ (0.5 M in toluene solution, 0.20 mL, 0.10 mmol) were then added to the flask, and the solution was stirred for 10 min at room temperature. Finally, a solution of benzoxazole (**1a**, 60 mg, 0.50 mmol), 1-bromohexane (**2a**, 165 mg, 1.0 mmol), and 1-methylnaphthalene (ca. 50 mg, internal standard) in diglyme (2.0 mL) were added dropwise. The resulting solution was stirred at 120 °C for 2 h. The consumption of **1a** was confirmed by GC analysis, and the resulting mixture was then quenched with water. The mixture was extracted with *n*-hexane/ethyl acetate (10:1, v/v), and the combined organic layer was dried over sodium sulfate. Concentration in vacuo and subsequent chromatography on silica gel with *n*-hexane/ethyl acetate (20:1, v/v) gave 2-hexylbenzoxazole (**3aa**, 65 mg, 0.32 mmol) in 64% yield.

Acknowledgements

This work was partly supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Keywords: alkylation · azoles · C–H activation · nickel · palladium

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Received: June 10, 2010
Published online: September 17, 2010

