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User-Friendly [(Diglyme)$NiBr_2$]-Catalyzed Direct Alkylations of Heteroarenes with Unactivated Alkyl Halides through C–H Bond Cleavages

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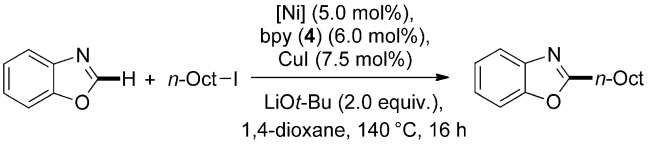
Abstract: A nitrogen and phosphorus ligand-free catalytic system derived from inexpensive [(diglyme)$NiBr_2$] allowed for efficient direct C–H bond alkylations of heteroarenes with unactivated β-hydrogen-containing alkyl halides under basic reaction conditions.

Keywords: alkylation; azoles; C–H activation; heterocycles; mechanism; nickel

Substituted heteroarenes are indispensable substructures of, among others, biologically active compounds and functional materials.[1–3] In particular, strategies relying on direct C–H bond functionalizations arguably constitute the most ecologically benign and economically attractive methods for their preparation.[4] In recent years, various transition metal catalysts were devised for versatile direct arylations, alkenylations or alkynylations of heteroarenes by cleavages of unreactive C–H bonds.[5] In contrast, direct alkylations of (hetero)arenes with unactivated alkyl halides under basic reaction conditions continue to be difficult, predominantly because these challenging electrophiles lead to undesired β-eliminations.[6] Remarkable recent progress was represented by efficient ruthenium[7] and palladium catalyzed[8] direct alkylations of (hetero)arenes.[6] On the contrary, direct alkylations with less expensive nickel catalysts[9] are scarce, and were thus far solely achieved with nickel complexes derived from tridentate nitrogen ligands.[8g,10–12] Thus, Hu and co-workers elegantly devised the nickel complex [($^{Me}NN_2$)NiCl] bearing a tridentate pincer N_2N-ligand for direct functionalizations of heteroarenes with alkyl halides.[10] Unfortunately, the synthesis of this catalyst involves several reaction steps, which can limit its broader applications.[13] Moreover, four direct alkylations of benzothiazole were recently achieved with a nickel complex derived from the tridentate nitrogen ligand terpyridine.[8g] Within our research program directed towards the development of user-friendly and sustainable C–H bond functionalizations,[14] we developed a cost-effective nitrogen- and phosphorus ligand-free[15] free nickel catalyst for direct alkylations of heteroarenes, on which we wish to report herein.

At the outset of our studies, we tested a diverse array of commercially available nickel precursors for the direct C–H bond functionalization of benzoxazole (**1a**) with alkyl iodide **2a** as the electrophile, 2,2′-bipyridine (bpy, **4**) as the ligand, and CuI[10] as cocatalyst (Table 1). Among different nickel sources, [(di-

Table 1. Nickel precursors for the direct C–H bond alkylation.[a]

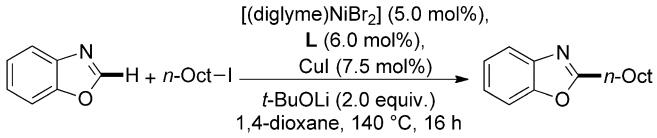


1a **2a** **3aa**

Entry	[Ni]	**3aa**
1	[$(Ph_3P)_2NiCl_2$]	36%
2	$Ni(acac)_2$	35%
3	[$(DME)NiCl_2$]	48%
4	$Ni(COD)_2$	64%
5	[(diglyme)$NiBr_2$]	61%

[a] *Reaction conditions:* **1a** (1.0 mmol), **2a** (1.5 mmol), [Ni] (5.0 mol%), CuI (7.5 mol%), **4** (6.0 mol%), *t*-BuOLi (2.0 mmol), 1,4-dioxane (3.0 mL), 140 °C, 16 h; isolated yields.

Table 2. Ligand effect on the nickel-catalyzed direct alkylation.[a]

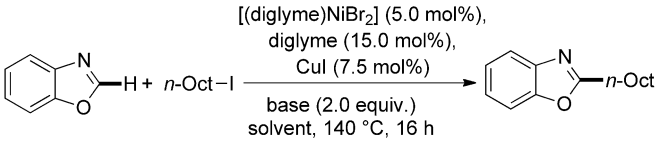


1a 2a 3aa

Entry	L	3aa
1	dppe	37%
2	dppf	31%
3	(*rac*)-BINAP	28%
4	1,10-phenanthroline	55%
5	4,4′-di-*tert*-butylbipyridine	42%
6	bpy (**4**)	62%
7	–	61%
8	diglyme[b]	65%

[a] *Reaction conditions:* **1a** (1.0 mmol), **2a** (1.5 mmol), [(diglyme)$NiBr_2$] (5.0 mol%), CuI (7.5 mol%), **L** (6.0 mol%), *t*-BuOLi (2.0 mmol), 1,4-dioxane (3.0 mL), 140 °C, 16 h; isolated yields.
[b] Diglyme (15 mol%).

Table 3. Optimization of the nickel-catalyzed direct alkylation.[a]



1a 2a 3aa

Entry	Base	Solvent	3aa
1	*t*-BuONa	1,4-dioxane	28%
2	*t*-BuOK	1,4-dioxane	20%
3	K_2CO3	1,4-dioxane	<2%[b]
4	*t*-BuOLi	1,4-dioxane	65%
5	*t*-BuOLi	DME	37%
6	*t*-BuOLi	NMP	23%
7	*t*-BuOLi	toluene	52%
8	*t*-BuOLi	diglyme	22%
9	*t*-BuOLi	1,4-dioxane	43%[c]
10	*t*-BuOLi	1,4-dioxane	<3%[b,d]

[a] *Reaction conditions:* **1a** (1.0 mmol), **2a** (1.5 mmol), [(diglyme)$NiBr_2$] (5.0 mol%), diglyme (15 mol%), CuI (7.5 mol%), base (2.0 mmol), solvent (3.0 mL), 140 °C, 16 h; isolated yields.
[b] GC conversion.
[c] $NiBr_2$ (5.0 mol%).
[d] Without [(diglyme)$NiBr_2$].

glyme)$NiBr_2$][8g] was found to be most suitable, and interestingly showed an activity comparable to the one displayed by air-sensitive $Ni(COD)_2$ (entries 4 and 5).

Thereafter, we explored a set of representative nitrogen as well as phosphorus ligands in the direct alkylation of heteroarene **1a**, and observed that the former ligands delivered the desired product **3aa** in more satisfactory yields, with 2,2′-bipyridine (**4**) furnishing optimal results (Table 2, entries 1–6). Unexpectedly, the simple nickel(II) complex [(diglyme)-$NiBr_2$] provided a comparably high yield in the absence of an additional ligand (Table 2, entry 7). Notably, the catalytic activity could slightly be improved through the addition of co-catalytic amounts of diglyme (entry 8).

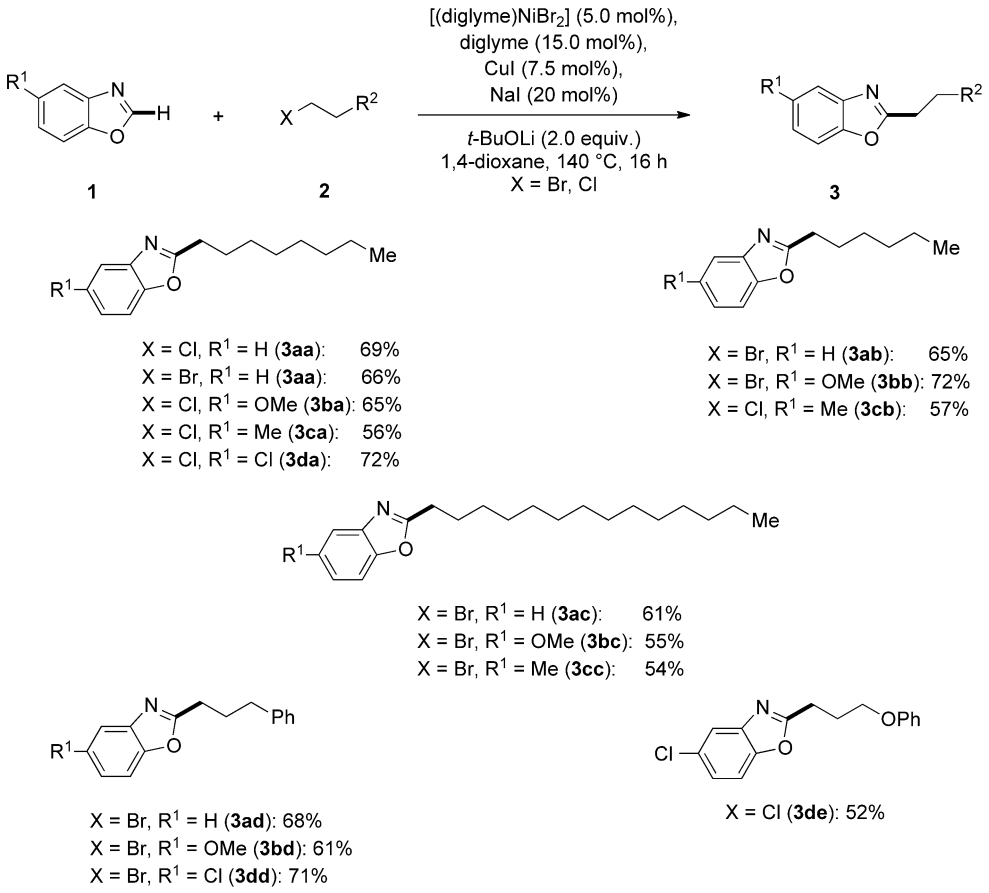
Subsequently, we probed a variety of bases and solvents for the desired direct alkylation of substrate **1a** under nitrogen and phosphine ligand-free reaction conditions (Table 3). As a result, most effective transformations were accomplished with *t*-BuOLi as the base (entries 1–4) in 1,4-dioxane or toluene as the solvent (entries 4–7). On the contrary, C–H bond functionalizations occurred with significantly reduced efficacy when employing diglyme as the solvent (entry 8). It is noteworthy that the direct alkylation proceeded also with simple $NiBr_2$ as the catalyst (entries 9), yet not in the absence of a nickel complex (entry 10).

With an optimized catalytic system in hand, we probed its scope in the C–H bond functionalization of diversely substituted azoles **1** employing unactivated β-hydrogen-containing alkyl halides **2** (Scheme 1). Remarkably, co-catalytic amounts of NaI[10] turned out to be beneficial, when less expensive alkyl bromides or chlorides **2** served as the electrophiles. Thereby, alkyl halides **2** with various chain lengths furnished the desired products **3** in satisfactory yields. Importantly, the inexpensive nickel catalyst displayed a valuable chemoselectivity, and thus tolerated among others methoxy or chloro substituents, the latter of which can be exploited for further metal-catalyzed derivatization reactions. On the contrary, the secondary alkyl bromide 2-bromohexane only led to an unsatisfactory low conversion to the desired product.

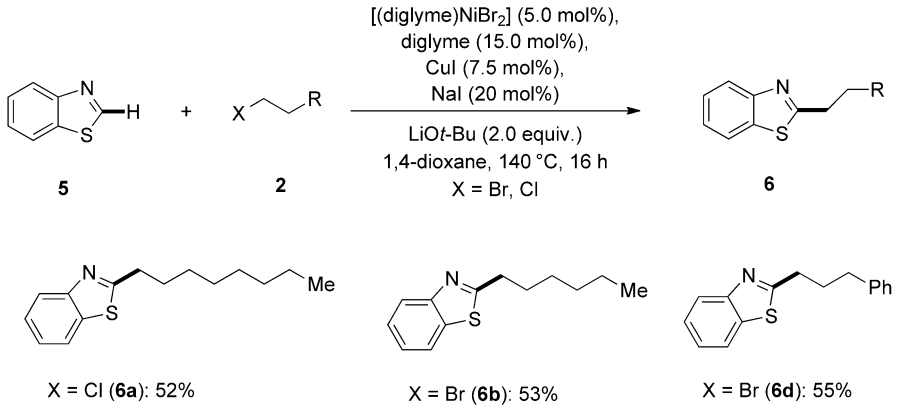
Furthermore, benzothiazole (**5**) turned out to be a viable substrate as well, which set the stage for its site-selective functionalization with unactivated alkyl bromides and chlorides **2** (Scheme 2).

Given the user-friendly nature of our inexpensive catalytic system, we became interested in probing its mode of action.[8g,10] Hence, the direct alkylation of substrate **1a** with 5-bromo-1-pentene (**2f**) delivered the expected *n*-alkylated product **3af** [Scheme 3 (a)]. In contrast, the C–H bond functionalization with electrophile **2g** gave rise to the 5-*exo*-cyclized product **3ag**, hence indicating a radical mechanism [Scheme 3 (b)]. Moreover, the reaction with cyclopropylmethyl bromide (**2h**) provided additional support for the formation of a radical intermediate [Scheme 3 (c)].

Based on these experimental mechanistic studies as well as insights into conventional nickel-catalyzed cross-coupling reactions[12,16] we propose a working



Scheme 1. Scope of the nickel-catalyzed direct alkylation of azoles **1**.



Scheme 2. Nickel-catalyzed alkylation of benzothiazole (**5**).

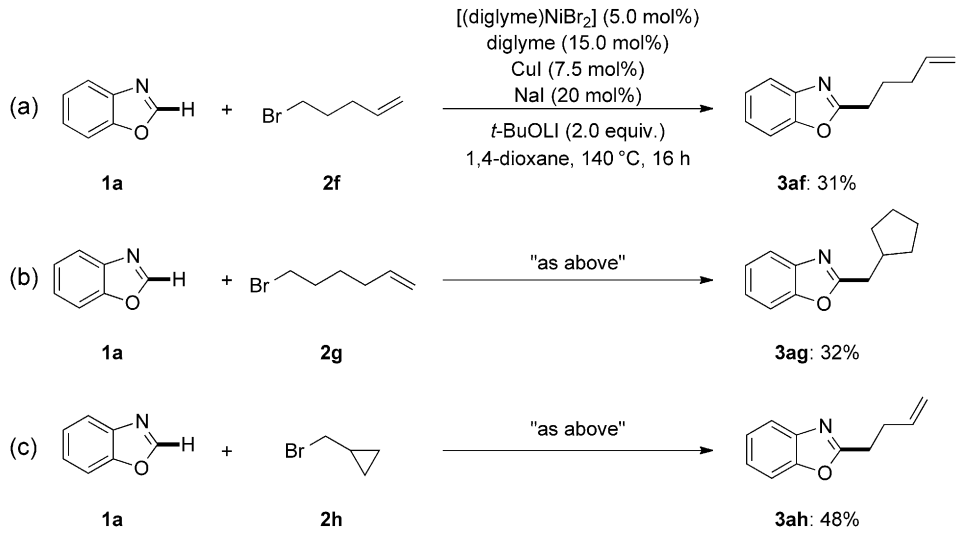
mode for our nickel-catalyzed direct alkylations, which involves odd-electron transfer (Scheme 4).

In summary, we have developed an unprecedented nitrogen and phosphorus ligand-free nickel catalyst for user-friendly direct alkylations of heteroarenes with ample scope. The inexpensive nickel catalyst displayed an excellent chemo- and site-selectivity, which enabled direct C–H bond functionalizations of various azoles with unactivated β-hydrogen-containing alkyl iodides, bromides and chlorides.

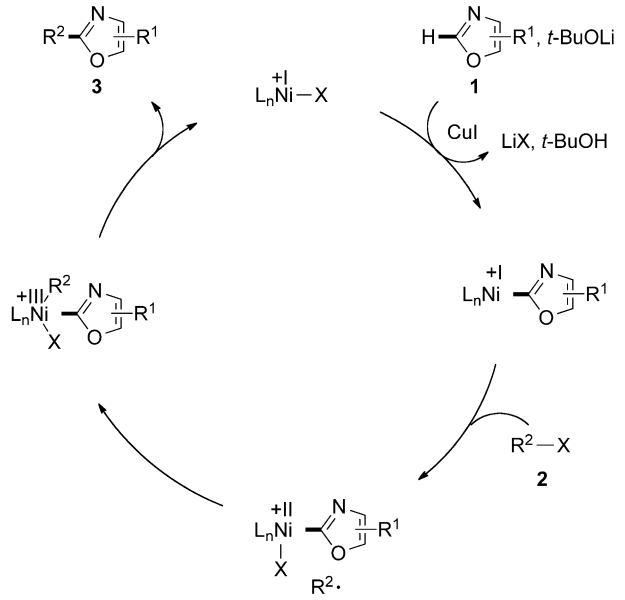
Experimental Section

General Remarks

Catalytic reactions were carried out under a N_2 atmosphere using pre-dried glassware. 1,4-Dioxane was dried over sodium. 5-Substituted benzoxazoles **1** were synthesized according to previously described procedures.[17] Other substrates were obtained from commercial sources, and were used without further purification. Yields refer to isolated compounds, estimated to be >95% pure as determined by



Scheme 3. Mechanistic studies on the nickel-catalyzed direct alkylations.



Scheme 4. Possible pathway for the nickel-catalyzed direct alkylations.

^{1}H NMR and GC. TLC: Macherey–Nagel, TLC plates Alugram® Sil G/UV254, detection under UV light at 254 nm. Chromatographic separations were carried out on Merck Silica 60 (0.063–0.200 mm, 70–230 mesh ASTM). All IR spectra were recorded on a Bruker FT-IR Alpha device. MS: EI-MS: Finnigan MAT 95, 70 eV; ESI-MS: Finnigan LCQ. High resolution mass spectrometry (HR-MS): APEX IV 7T FTICR, Bruker Daltonic. Melting points (mp): Büchi 540 capillary melting point apparatus, values are uncorrected. NMR (^{1}H and ^{13}C) spectra were recorded at 300 (^{1}H) and 75 MHz [^{13}C, APT (attached proton test)], respectively, on Varian Unity-300 and AMX 300 instruments in $CDCl_3$ solutions, if not otherwise specified, chemical shifts (δ) are provided in ppm.

Representative Procedure: Nickel-Catalyzed Direct Alkylation of Benzoxazoles 1 (Table 2, entry 8)

A solution of [(diglyme)$NiBr_2$] (18 mg, 0.05 mmol, 5.0 mol%), diglyme (20 mg, 0.15 mmol, 15 mol%), CuI (14 mg, 0.07 mmol, 7.5 mol%), *t*-BuOLi (160 mg, 2.00 mmol), benzoxazole (**1a**) (119 mg, 1.00 mmol) and *n*-octyl iodide (**2a**) (360 mg, 1.50 mmol) in 1,4-dioxane (3.0 mL) was stirred at 140 °C for 16 h under N_2. At ambient temperature, H_2O (15 mL) and aqueous HCl (0.5 mL, 2 N) were added and the reaction mixture was extracted with MTBE (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under vacuum. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 100/1 → 50/1) to afford **3aa** as a yellow oil; yield: 150 mg (65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.61 (m, 1H), 7.47–7.41 (m, 1H), 7.29–7.23 (m, 2H), 2.90 (t, J = 7.5 Hz, 2H), 1.91–1.81 (m, 2H), 1.42–1.20 (m, 10H), 0.85 (t, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7 (C_q), 151.1 (C_q), 141.7 (C_q), 124.7 (CH), 124.3 (CH), 119.8 (CH), 110.5 (CH), 32.1 (CH_2), 29.5 (2 CH_2), 29.4 (CH_2), 28.9 (CH_2), 27.1 (CH_2), 22.9 (CH_2), 14.4 (CH_3); IR (neat): ν = 2925, 2854, 1615, 1572, 1455, 1241, 1146, 1104, 1002, 925 cm^{-1}; MS (EI): *m/z* (relative intensity) = 231 (8) [M^+], 202 (6), 188 (17), 175 (21), 160 (8), 146 (62), 133 (100), 104 (9), 41 (24). HR-MS (EI): *m/z* = 231.1621, calcd. for $C_{15}H_{21}NO^+$ [M^+]: 231.1623. The analytical data were in accordance with those reported in the literature.[10]

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