C–H Activation

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The Nickel/Copper-Catalyzed Direct Alkylation of Heterocyclic C–H Bonds**

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Aromatic heterocycles are an important class of molecules which have been widely used as synthetic building blocks, bioactive molecules, pharmaceuticals, and organic materials.[1–3] There are now many methods available for the preparation of aromatic heterocycles that are substituted with aryl, alkenyl, alkynyl, and even activated alkyl groups, the most recent method involves C–H functionalization.[4–13] However, the synthesis of heterocyclic compounds substituted by non-activated alkyl groups containing β-hydrogen atom remains challenging. Traditional methods such as Friedel–Crafts[14] and radical alkylation reactions[15] pose severe limitations on the electronic properties of the heterocycles, and are often incompatible with sulfur containing heterocycles. Additionally, the Friedel–Crafts alkylation requires strong acids, and suffers from side reactions such as multiple alkylation and isomerization. Likewise, the method of deprotonation by strong bases, for example *n*BuLi, and subsequent electrophilic trapping requires cryogenic conditions, active electrophiles, the protection of acidic and/or electrophilic groups, and special bases.[16–18]

The development of cross-coupling catalysis provides new opportunities in heterocycle synthesis.[19] The alkylated aromatic heterocycles can be produced either by the coupling of a heterocyclic halide with an alkyl organometallic nucleophile (path A, Figure 1),[20] or by the coupling of a heterocyclic organometallic nucleophile with an alkyl halide (path B, Figure 1).[21] Both methods employ organometallic nucleophiles, and are constrained by the stability and availability of these reagents. Furthermore, additional chemical transformations are required for the preparation of the organometallic reagents. Therefore, the direct cross-coupling of aromatic heterocyclic C–H bonds with non-activated alkyl halides (path C, Figure 1) represents an attractive alternative. However, this coupling technology is underdeveloped—consequence of the difficulties involved in the coupling of non-activated alkyl halides.[22–24] Alkyl halides are resistant to oxidative addition; when they do undergo oxidative addition, the resulting metal alkyl intermediates are prone to unproductive β-hydride elimination. To date, the only reported example of a successful coupling was the palladium-catalyzed reaction between ethyl oxazole-4-carboxylate with *n*butyl bromide (2 equiv) that afforded ethyl 2-butyloxazole-4-carboxylate in 60% yield.[25]

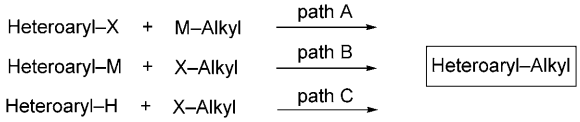
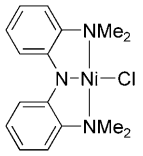


Figure 1. Cross-coupling methods for the synthesis of alkylated aromatic heterocycles; X = halide, M = metal.

In the course of developing catalysts based on inexpensive and readily available first-row transition metals, we identified a nickel complex, [(^{Me}NN$_2$)NiCl] (**1**), as an active precatalyst



[(^{Me}NN$_2$)NiCl]
(precatalyst **1**)

for the coupling of non-activated alkyl halides.[21,26–28,29] Herein, we show that the combination of this complex and a copper salt leads to the efficient coupling of aromatic heterocycles with non-activated alkyl halides containing a β-hydrogen atom. Notably, not only alkyl iodides and bromides, but also alkyl chlorides can be used. The catalysis tolerates a wide range of functional groups in both coupling partners, and has excellent chemo- and regioselectivity.

The cross-coupling of benzoxazole with *n*butyl iodide was used as a model reaction. After investigating various experimental parameters,[30] we found that 2-*n*butyl benzoxazole could be produced in high yields (ca. 80%) using **1** (5 mol%) as the precatalyst and CuI (7.5 mol%) as the co-catalyst [Eq. (1), Scheme 1]. A temperature of 140 °C and a reaction time of 16 hours were required for full conversion. A suitable base was also needed. The most effective bases were *t*BuONa in toluene or *t*BuOLi in dioxane. Other base/solvent combinations gave lower yields. The coupling proceeded even in the absence of the copper co-catalyst, however, with a small amount of CuI, the yields were higher. The yields were nearly constant when the loadings of CuI were varied from 2 to 7.5 mol%. The nickel complex **1** was essential for achieving high efficiency. In the absence of **1**, no coupling occurred. The

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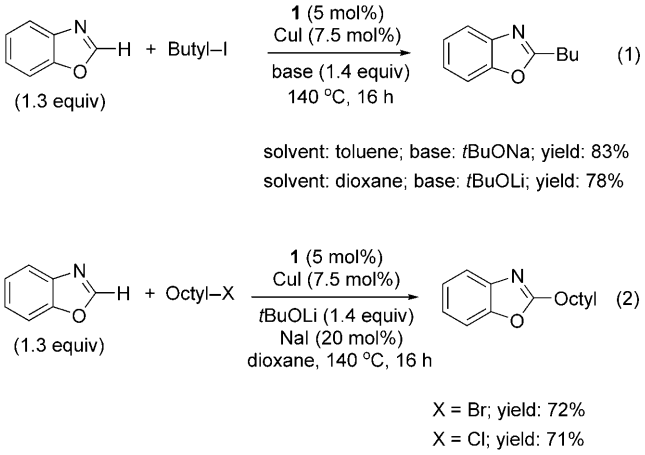
replacement of **1** with another soluble Ni^{II} compound such as $[NiCl_2(dme)]$ and $[NiCl_2(PPh_3)_2]$, led to diminished yields (20–30%; dme = 1,2-dimethoxyethane).

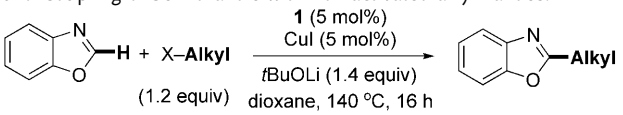
The coupling of benzoxazole with *n*octyl bromide or octyl chloride was also possible by employing similar reaction conditions [Eq. (2), Scheme 1]. The best results were obtained when reactions were carried out in dioxane with *t*BuOLi as the base.[30] The addition of NaI (20 mol%) was beneficial, probably by promoting a halide exchange process.

The optimized reaction conditions are applied to the coupling of benzoxazole with other non-activated alkyl halides (Table 1). Branching at the β position of the halide



Scheme 1. Optimized conditions for the direct alkylation of benzoxazole.

Table 1: Coupling of benzoxazole with non-activated alkyl halides.[a]



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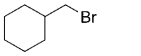
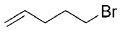
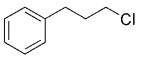
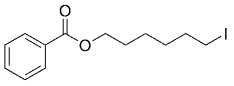
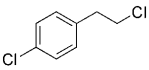
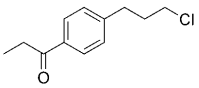
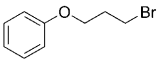
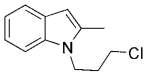
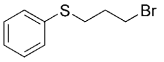
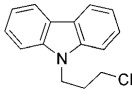
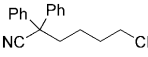
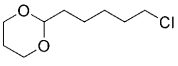
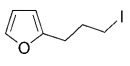
1		79	8		70
2		70	9		71
3		75	10		44
4		84	11		74
5		65	12		75
6		56			
7		86	13		73

[a] Benzoxazole (1.5 mmol) was used. For the coupling of alkyl bromides and chlorides, NaI (0.3 mmol) was added. [b] Yields of isolated product relative to the heteroarenes.

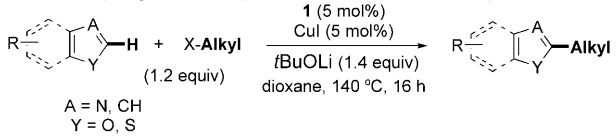
was tolerated (Table 1, entry 1). The coupling of alkyl chloride was selective in the presence of the aryl–Cl bond (Table 1, entry 3). Potentially coordinating groups such as ether, thioether, and nitrile groups did not pose problem (Table 1, entries 4–6). The acetal group was also tolerated (Table 1, entry 7). Olefin and ester groups did not interfere with the coupling (Table 1, entries 8 and 9). Encouragingly, a substrate containing a base sensitive keto group could be employed, albeit in modest yield (Table 1, entry 10). The coupling of substrates containing important heterocyclic groups such as indole, carbazole, and furan were also successful (Table 1, entries 11–13). No coupling occurred with secondary alkyl halides such as cyclohexyl iodide and cycloheptyl bromide. However, base-induced elimination from some alkyl halides, for example 2-bromoethylbenzene, was observed.[30] This side reaction did not pose a problem for all substrates in Table 1.

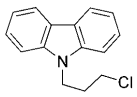
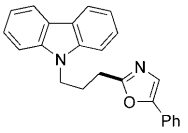
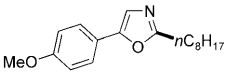
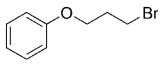
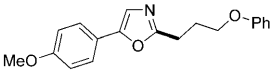
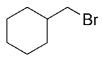
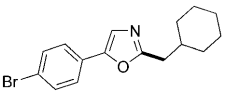
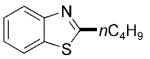
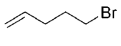
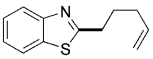
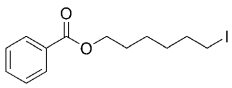
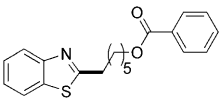
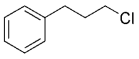
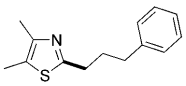
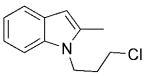
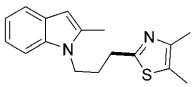
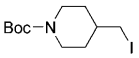
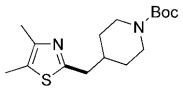
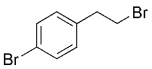
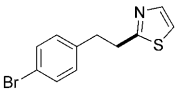
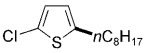
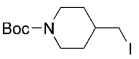
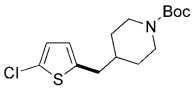
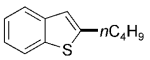
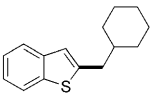
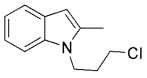
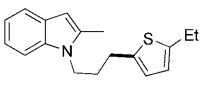
A similar procedure can be used for the coupling of other aromatic heterocycles with non-activated alkyl halides (Table 2). Various 5-aryloxazoles could be readily coupled at the 2-position (Table 2, entries 1–4). The aryl–Br moiety of the oxazole did not interfere with the coupling reaction (Table 2, entry 4). Gratifyingly, the molecules containing important pharmacophores such as thiazole and thiophene were also suitable substrates, which gave rise to 2-alkylated products (Table 2, entries 5–16). In some cases, the more sterically hindered base Et_3COLi was required to achieve higher yields (Table 2, entries 14–16). The catalysis was tolerated by carbazole, ether, olefin, ester, indole, NBoc, aryl and heteroaryl halide groups. For unsubstituted substrates (Table 2, entries 1–4, and 11), no significant amount of double alkylation product was observed.

The mechanism of the coupling reaction might be similar to those of nickel/copper- and copper-catalyzed direct arylation and alkynylation of aromatic heterocycles.[10,13,31] Even though the copper co-catalyst was not necessary for the coupling reaction, it was needed to achieve satisfactory yields. We proposed that the copper facilitates the transmetalation of the anionic azole/thiophene intermediates to nickel. The existence of an anionic benzoxazole was confirmed, as quenching of the reaction mixture at partial conversion with D_2O produced 2-deuterated benzoxazole.[30] Almost no isotopic effect was observed for the coupling of *n*BuI with 2-deuterated benzoxazole, thus suggesting that C–H cleavage might not be the turnover limiting step.[30]

To probe the nature of the nickel catalyst, the catalysis was followed by ^1H NMR spectroscopy (using 20 mol% of nickel precatalyst). $H^{Me}NN_2$ was detected as the only ligand-containing species. Thus, precatalyst **1** appeared to degrade into the active nickel species under the catalytic conditions. To check whether heterogeneous nickel particles were responsible for the coupling, a reaction [Eq. (1), Scheme 1] was conducted in the presence of 100 equivalents of Hg (relative to nickel).[30] The yield of the coupling reaction diminished from about 80% to 19%. In addition, filtering off the insoluble solids from the reaction mixture at partial conversion led to a lower yield.[30] These results suggest that the reactions are most likely catalyzed by nickel metal particles.

Table 2: Coupling of heterocycles with non-activated alkyl halides.[a]



Entry	Alkyl–X	Product	Yield [%][b]
1			74
2	Octyl–I		86
3			81
4			76
5	Butyl–I		78
6			74
7			72
8			76
9			85
10			79
11			60
12	Octyl–Br		81
13			62
14	Butyl–I		78[c]
15			72[c]
16			66[c]

[a] Heteroarenes (1.5 mmol) were used. For the coupling of alkyl bromides and chlorides, NaI (0.3 mmol) was added. [b] Yields of isolated product relative to the heteroarenes. [c] Et_3OLi was used as the base. Boc = *tert*-butoxycarbonyl.

In conclusion, we have developed a general and versatile method for the synthesis of alkylated aromatic heterocycles, which are important organic molecules and materials. The chemistry is based on catalytic C–H functionalization using non-activated alkyl electrophiles—a largely under-explored reaction type.[25,32–34] The nickel/copper catalysis enables the coupling of both electron-rich (thiophene) and electron-poor (oxazole and thiazole) heterocycles which is difficult to achieve using other synthetic procedures. Various non-activated alkyl halides containing a β-hydrogen atom, including the inexpensive chlorides could be employed. This method is applicable in the synthesis and derivatization of a large number of alkylated heterocycles. The coupling protocol is simple and straightforward, the substrates are readily available, and the pure products can be isolated in high yields. Notably, the chemo- and regioselectivities are excellent. Only alkyl halide bonds are reactive in the presence of aryl and heteroaryl halide moieties, thus providing more possibilities for further functionalization. When the alkyl halides possess heterocyclic groups, no intra- or intermolecular self-coupling takes place. The coupling occurred exclusively at the 2-position of the aromatic heterocycles, even when there is more than one reaction site on the heterocycle. No multiple alkylation was observed, which is a desirable feature in comparison to Friedel–Crafts reactions.

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