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Nickel catalyzed alkylation of N-aromatic heterocycles with Grignard reagents through direct C–H bond functionalization†

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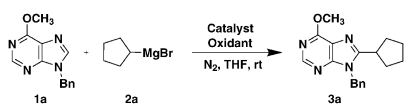
A novel protocol for nickel-catalyzed direct sp^2 C–H bond alkylation of N-aromatic heterocycles has been developed. This new reaction proceeded efficiently at room temperature using a Grignard reagent as the coupling partner. This approach provides new access to a variety of alkylated N-aromatic heterocycles which are potentially of great importance in medicinal chemistry.

The (hetero)aryl moieties are important components in many advanced materials, natural products and pharmaceutical drugs.[1] Consequently, development of an efficient method for the synthesis of diversely substituted (hetero)arenes has become a hot topic in synthetic chemistry.[2] To date, direct C–H bond functionalization has been one of the most important strategies for the synthesis of this kind of compounds. Transition metal-catalyzed direct C–H bond arylation of (hetero)arenes has been used extensively in organic synthesis over the past few years.[3] And the direct C–H bond alkenylation of (hetero)arenes also made significant progress in recent years.[4] But due to the easy β-H elimination of alkyl species, the direct C–H alkylation of (hetero)arenes is still in its incipient stage.[5] Based on the review of related literature reports, we found that most of the successful direct C–H alkylation examples rely on the use of directing groups containing heteroatoms and give *ortho*-alkylated products from alkyl halides,[6] olefins[7] or organometallic reagents[8] under transition metal catalysis. Generally, the second-row transition metal catalysts are particularly needed for these reactions, which participate in cyclometalation with various directing groups to complete the anchoring process.[9] While these protocols can afford various *ortho*-alkylated products, these directing groups are not easily removed from the desired products, thus limiting the generality of the reaction. So development of a directing group free procedure for the alkylation of an aromatic C–H bond is of great significance. Recently, Yu *et al.*[10] and others[11] have successfully developed nondirected C–H bond arylation and alkenylation procedures. However, the direct C–H bond alkylation of (hetero)arenes without a directing group is still a challenge despite a few reports[12] which are usually restricted to the undesired isomerization products and poor yields.

Recently, as inexpensive and readily available catalysts, the first-row transition metals have shown a strong competitiveness in C–H bond functionalization chemistry.[3c,8c,e,f] Herein we report our investigations aiming at the establishment of an alternative strategy based on the use of an alkyl Grignard reagent as a new and efficient coupling partner for directing group free N-aromatic heterocycles alkylation with a nickel catalyst.

We started our studies with the optimization of the catalytic system and reaction conditions for the model reaction of 9-benzyl-6-methoxy-9*H*-purine with cyclopentylmagnesium bromide. Several classic catalysts for transition-metal-catalyzed C–H functionalization reaction were tested in this experiment. As shown in Table 1, the reaction did not work with $Pd(OAc)_2$ and $Fe(acac)_3$ (entries 1 and 2). When $Ni(dppp)Cl_2$ was used as the catalyst, acceptable conversion of **1a** was obtained (entry 3). Therefore, other nickel catalysts were tested, and none showed better activities than $Ni(dppp)Cl_2$ (entries 4 and 5), so $Ni(dppp)Cl_2$ was the suitable catalyst for this reaction. Then, the effect of the catalyst amount was examined, and the results showed that reduction of the amount of the catalyst led to lower conversion of **1a** (entries 6 and 7). When we used 20% mol $Ni(dppp)Cl_2$ and 8 equiv. of cyclopentylmagnesium bromide, a full conversion was obtained and the isolated yield of **3a** reached 81% (entry 8). Disappointedly,

Table 1 Optimization of reaction conditions[a]



1a 2a 3a

Entry	Catalyst (mol%)	Conv. (%)[b]
1	$Pd(OAc)_2$ (30)	Trace
2	$Fe(acac)_3$ (30)	Trace
3	$Ni(dppp)Cl_2$ (30)	91 (74)
4	$NiCl_2$ (30)	83 (58)
5	$Ni(acac)_2$ (30)	79 (51)
6	$Ni(dppp)Cl_2$ (10)	43
7	$Ni(dppp)Cl_2$ (20)	65
8[c]	**$Ni(dppp)Cl_2$ (20)**	**100 (81)**
9[c]	$Ni(dppp)Cl_2$ (10)	86 (67)

[a] Reaction conditions: **1a** (0.125 mmol), **2a** (0.625 mmol), DCE (3 equiv.), THF (1 mL), at room temperature, under a N_2 atmosphere, 24 h. [b] Determined by HPLC, and the yields in parentheses are isolated yields. [c] 8 equiv. of **2a** was used.

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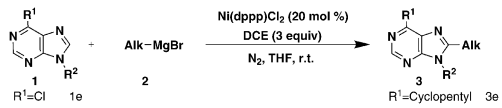
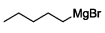
when we reduced the amount of the catalyst to 10% mol, the lower conversion of **1a** was obtained even when increasing the amount of cyclopentylmagnesium bromide to 8 equiv. (entries 9). Further screening of reaction time showed that 24 h was the best choice. Therefore, optimal reaction conditions involved Ni(dppp)Cl_2 (20% mol) as the catalyst, 1,2-dichloroethane (3 equiv.) as the oxidant and 8 equiv. of cyclopentylmagnesium bromide as the coupling partner at room temperature for 24 h under a N_2 atmosphere.

To evaluate the generality of the reaction, this new direct C–H alkylation protocol was extended to a scope of purine derivatives, and the results are shown in Table 2. Firstly, a series of purine derivatives were subjected to the optimized reaction conditions and the corresponding products were obtained in good to high yields (entries 1–6, 75–91%). As expected, different types of substituents at C-6 and N-9 had little impact on the yields of the products. When 6-chloro-9-cyclopentyl-9*H*-purine was used as a substrate, the traditional Kumada cross-coupling reaction and direct C–H alkylation reaction occurred simultaneously to give the multi-cyclopentyl product in good yield (entry 5, 77%). And then, a series of alkyl Grignard reagents were chosen as coupling partners to probe whether the direct sp^2 C–H bond alkylation of purines could be easily accessed. To our delight, the reaction with different primary and secondary alkyl magnesium bromides proceeded efficiently (entries 7–10, 53–94%).

Intrigued by the results described above, various benzimidazole derivatives were chosen as substrates to probe the generality of this direct sp^2 C–H bond alkylation reaction. The results are shown in Table 3. Fortunately, various N-1 substituted benzimidazoles could be cyclopentylated in good to high yields (entries 1–4, 68–82%). And the reactions between 1-benzyl-1*H*-benzoimidazole and various alkyl Grignard reagents also smoothly gave satisfactory yields (entries 5–8, 47–86%).

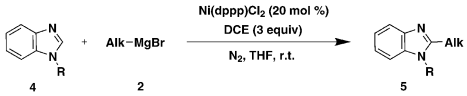
Table 2 Direct C–H alkylation of various purines with Grignard reagents[a]

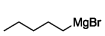
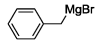
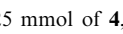


Entry	R^1	R^2	Alk-MgBr	Product	Yield/%[b]
1	OMe	Bn		**3a**	81
2	OMe	Me		**3b**	87
3	OMe	Et		**3c**	91
4	OMe	Cyclo-pentyl		**3d**	75
5	Cl	Cyclo-pentyl		**3e**	77
6	4-Ethyl-phenyl	Bn		**3f**	89
7	OMe	Bn		**3g**	76
8	OMe	Bn		**3h**	72
9	OMe	Bn		**3i**	94
10	4-Ethyl-phenyl	Bn		**3j**	53

[a] Reaction conditions: 0.125 mmol of **1**, 8 equiv. of **2**, 20 mol% of Ni(dppp)Cl_2, 3 equiv. of 1,2-dichloroethane, and 1 mL of THF in a Schlenk tube at rt for 24 h under a N_2 atmosphere. [b] Isolated yields.

Table 3 Direct C–H alkylation of various benzimidazoles with Grignard reagents[a]



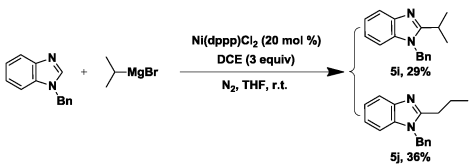
Entry	R	Alk-MgBr	Product	Yield/%[b]
1	Bn		**5a**	79
2	Phenethyl		**5b**	71
3	Me		**5c**	82
4	*n*-Pentyl		**5d**	68
5	Bn		**5e**	57
6	Bn		**5f**	86
7	Bn		**5g**	61
8	Bn		**5h**	47

[a] Reaction conditions: 0.125 mmol of **4**, 8 equiv. of **2**, 20 mol% of Ni(dppp)Cl_2, 3 equiv. of 1,2-dichloroethane, and 1 mL of THF in a Schlenk tube at rt for 24 h under a N_2 atmosphere. [b] Isolated yields.

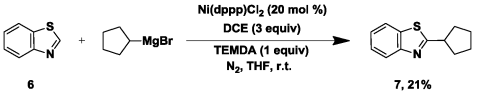
When we used *i*-PrMgBr as a coupling partner to perform this reaction, a mixture of 1-benzyl-2-isopropyl-1*H*-benzoimidazole (**5i**, 29% yield) and 1-benzyl-2-propyl-1*H*-benzoimidazole (**5j**, 36% yield) was obtained (Scheme 1), which might be due to the β-hydride elimination of *i*-PrMgBr.

Other N-aromatic heterocycles such as benzothiazole were also tolerated by this novel coupling reaction and afforded the target product **7** (21%, Scheme 2).

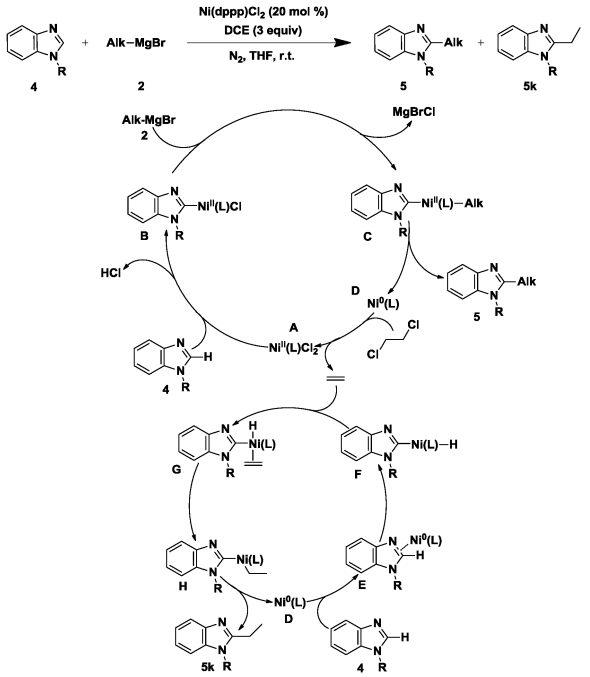
Interestingly, we got a minimal amount of product **5k** (<5%) as well as the desired product **5** when we used benzimidazole derivatives as substrates to evaluate the generality of the reaction. In accord with the established precedent mechanisms in previous studies,[13] a possible mechanism that accounts for C–H bonds alkylation of N-aromatic heterocycles with Grignard reagents is presented in Scheme 3. A combination of **4** and Ni(dppp)Cl_2 provides the metalated intermediate **B**. Subsequently, an (alkyl)-nickel(II) intermediate **C** is generated by transmetalation between alkyl Grignard reagents and the metalated intermediate **B**. Followed by reductive elimination to produce the desired product **5**, the Ni(0) species **D** is generated. We speculate that most of Ni(0) species **D** is reoxidized to Ni(II) species by DCE, but a minimal amount of Ni(0) species **D** conducts oxidative



Scheme 1 Direct C–H alkylation of 1-benzyl-1*H*-benzoimidazole with *i*-PrMgBr.



Scheme 2 Direct C–H alkylation of benzothiazole with cyclopentyl-magnesium bromide.



Scheme 3 Proposed preliminary mechanism.

addition by an sp^2 C–H bond to give nickel hydride **F** through η^2-arenenickel **E**. A combination of ethylene and nickel hydride **F** gives vinylarenes **G**. Then, hydronickelation of vinylarenes **G** provides metalated intermediate **H**, which then produces the product **5k** by reductive elimination.

In conclusion, a novel protocol for the nickel-catalyzed sp^2 C–H bond alkylation of N-aromatic heterocycles with Grignard reagents has been developed. Different types of heterocycles are compatible under these mild reaction conditions. To the best of our knowledge, this reaction is the first example that uses Grignard reagents as coupling partners to perform direct sp^2 C–H bond alkylation of N-aromatic heterocycles without a directing group. And this protocol will dramatically expand the scope of a direct C–H alkylation process. Further investigation of the detailed mechanism and expansion of this novel method to a broad spectrum of substrates are underway in our laboratory.

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