ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 11140–11142

www.rsc.org/chemcomm

COMMUNICATION

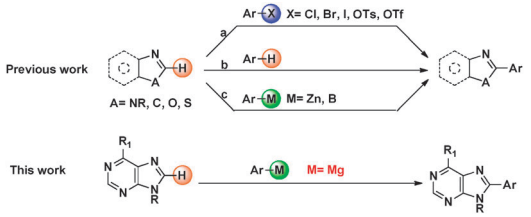
Nickel-catalyzed sp^2 C–H bonds arylation of N-aromatic heterocycles with Grignard reagents at room temperature†

Gui-Rong Qu,*[a] Peng-Yang Xin,[a] Hong-Ying Niu,[b] Dong-Chao Wang,[a] Rui-Fang Ding[a] and Hai-Ming Guo*[a]

Received 26th July 2011, Accepted 26th August 2011
DOI: 10.1039/c1cc14558d

A novel protocol for nickel-catalyzed direct sp^2 C–H bond arylation of purines has been developed. This new reaction proceeded efficiently at room temperature using Grignard reagent as the coupling partner within 5 hours in good to high yields. This approach provides a new access to a variety of C8-arylpurines which are potentially of great importance in medicinal chemistry.

The bis(hetero)aryl moiety is a key structure motif in many advanced materials, natural products and other biologically active compounds.[1] Over the past few decades, transition metal-catalyzed cross-coupling reactions that rely on the use of (hetero)aryl halides and organometallic reagents as pre-activated substrates have become the standard method for the synthesis of this kind of compounds (*i.e.*, Suzuki–Miyaura, Stille, Hiyama, Kumada, and Negishi reactions).[2] This protocol can afford various bis(hetero)aryl products, but the preparation of preactivated substrates will add one or more additional steps to the synthetic sequence and cause the formation of byproducts. Therefore, transition-metal-catalyzed C–H bond activation as a potentially green and efficient process has received great attention over the past few years.[3] Generally, the direct C–H arylation of (hetero)arene is performed by a coupling reaction of an unactivated (hetero)arene with a coupling partner. As we know, (hetero)aryl halides as coupling partners are widely used in the direct C–H arylation of (hetero)arene (Scheme 1, route a).[4] While these transformations have been well developed, they suffer from strict reaction conditions (such as long reaction time and high temperature) and poor selectivities. (Hetero)arylation can also be performed by coupling two unactivated (hetero)arenes, affording bis(hetero)aryl products with high efficiency (Scheme 1, route b),[5] but the reported methods are still restricted to a narrow substrate scope and it is difficult to prevent the undesired homodimer formations. In addition, organometallic reagents



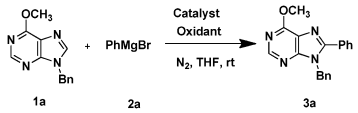
Scheme 1 Synthesis of bis(hetero)aryls *via* C–H activation.

(such as arylzinc reagents,[6] arylboron reagents[7]) as another kind of coupling partners have received considerable attention (Scheme 1, route c). Among them, Nakamura's group[6a,b] and Chatani's group[6c] reported the direct arylation of heteroaromatic compounds with arylzinc reagents as the coupling partners, respectively. It is well known that either arylboron reagents or arylzinc reagents are often prepared from the corresponding magnesium or lithium species. Based on the review of the related literatures, we found that there are only two reports on the use of the arylmagnesium reagent as the coupling partner to perform direct arylation of the sp^2 C–H bond *via* C–H bond activation. Professor Shi and co-workers[8] reported a cobalt-catalyzed direct cross-coupling reaction of Grignard reagent with a nitrogen-containing arene possessing a directing group through C–H transformation. In addition, Professor Nakamura[9] reported an iron-catalyzed reaction of aryl Grignard reagent with an olefin possessing a directing group *via* olefinic C–H bond activation. So there remains much room to improve the direct C–H arylation though a significant progress has been made in recent years. For example, finding a new and broad adaptable coupling partner without a directing group is still a major challenge and will dramatically expand the scope of the direct C–H arylation process. According to our study on synthesis of purine analogues,[10] herein, we report our investigations aiming at the establishment of an alternative strategy based on the use of aryl Grignard reagent as a new and efficient coupling partner for nickel-catalyzed purine arylation at room temperature.

Initially, we tried to optimize the catalytic system and reaction conditions on the model reaction of 9-benzyl-6-methoxy-9*H*-purine with phenylmagnesium bromide. Several classic catalysts for transition-metal-catalyzed C–H functionalization reactions were used in this experiment. As shown in Table 1, the reaction

[a] *College of Chemistry and Environmental Science, Key Laboratory of Green Chemical Media and Reactions of Ministry of Education, Henan Normal University, Xinxiang 453007, Henan, China. E-mail: guohm518@hotmail.com, guguir@sina.com; Fax: +86 373 3329276; Tel: +86 373 3329255*
[b] *School of Chemistry and Chemical Engineering, Henan Institute of Science and Technology, Xinxiang 453003, China*
† Electronic supplementary information (ESI) available: Experimental procedures, compound characterizations, and the copies of ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/c1cc14558d

Table 1 Optimization of reaction conditions[a]



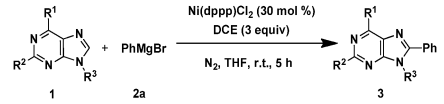
Entry	Catalyst (mol %)	Oxidant (equiv.)	Conv.[b] (%)
1[c]	$Pd(OAc)_2$ (30)	O_2	Trace
2[c]	$Pd(dppf)Cl_2$ (30)	O_2	Trace
3[c]	$Fe(acac)_3$ (30)	O_2	15
4[c]	$Ni(dppp)Cl_2$ (30)	O_2	88(67)
5[c]	$NiCl_2$ (30)	O_2	21
6[c]	$Ni(acac)_2$ (30)	O_2	38
7	$Ni(dppp)Cl_2$ (30)	Oxone (3)	58
8	$Ni(dppp)Cl_2$ (30)	$K_2S_2O_8$ (3)	52
9	$Ni(dppp)Cl_2$ (30)	$K_2Cr_2O_7$ (3)	46
10	**$Ni(dppp)Cl_2$ (30)**	**DCE (3)**	**100(89)**
11	$Ni(dppp)Cl_2$ (10)	DCE (3)	63(43)
12	$Ni(dppp)Cl_2$ (20)	DCE (3)	81(61)
13	$Ni(dppp)Cl_2$ (20)	DCE (5)	86(66)
14[d]	$Ni(dppp)Cl_2$ (30)	DCE (3)	100(87)

[a] Reaction conditions: **1a** (0.125 mmol), **2a** (0.625 mmol), 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] Under a O_2 atmosphere. [d] For 5 h.

did not work with $Pd(OAc)_2$ and $Pd(dppf)Cl_2$ (entries 1–2). When $Fe(acac)_3$ was used as the catalyst, a minimal conversion of **1a** was observed (entry 3). The reaction gave a moderate conversion of **1a** in the presence of $Ni(dppp)Cl_2$ (entry 4). Therefore, we considered that nickel catalysts might be an appropriate choice for this reaction. Then, other nickel catalysts were tested, and none showed better activities than $Ni(dppp)Cl_2$ (entries 5–6), so we chose $Ni(dppp)Cl_2$ as the suitable catalyst. Next, we investigated the effect of oxidants. Disappointedly, oxone, $K_2S_2O_8$ and $K_2Cr_2O_7$ did not give acceptable conversions of **1a** (entries 7–9). When we used 1,2-dichloroethane (DCE) as the oxidant, a full conversion was obtained and the isolated yield of **3a** reached 89% (entry 10). Reducing the amount of the catalyst led to lower conversion of **1a** even increasing the amount of the oxidant (entries 11–13). Further screening of reaction time showed that 5 h was the best choice (entry 14). Therefore, the optimal reaction conditions involve in $Ni(dppp)Cl_2$ as the catalyst, 1,2-dichloroethane as the oxidant at room temperature for 5 h under a N_2 atmosphere.

To evaluate the generality of the reaction, this new direct C–H arylation protocol was extended to a scope of purines, and the results are shown in Table 2. A series of 6-methoxy-9-substituted purines were subjected to the optimized reaction conditions and the corresponding products were obtained in high yields (entries 1–7, 76–87%). And then, we investigated whether different types of substituents at C-6 have impact on the yields. The results demonstrated that different substituents at C-6, including chloro, benzyl, benzylthio and phenyl, had little impact on the yields of the products (entries 8–13, 83–91%). Interestingly, when 9-benzyl-6-chloro-9*H*-purine, 9-benzyl-2,6-dichloro-9*H*-purine and 6-(benzylthio)-9-methyl-9*H*-purine were used as substrates, the reactions proceeded to give the multi-arylation products in good to high yields (entries 9–10, 13). In these reactions, both the traditional Kumada cross-coupling reaction and the direct C–H

Table 2 Direct C–H arylation of various purines with PhMgBr[a]



Entry	R1	R2	R3	Product	Yield[b]/%
1	OMe	H	Bn	**3a**	87
2	OMe	H	Phenethyl	**3b**	82
3	OMe	Cl	Bn	**3c**	78
4	OMe	H	Me	**3d**	86
5	OMe	H	Et	**3e**	81
6	OMe	H	*n*-Pr	**3f**	82
7	OMe	H	Cyclopentyl	**3g**	76
8	Ph	H	Me	**3h**	89
9[c]	Cl	H	Bn	**3i**	91
10[d]	Cl	Cl	Bn	**3j**	83
11	Bn	H	Bn	**3k**	84
12	Bn	H	*n*-Bu	**3l**	87
13[c]	Benzylthio	H	Me	**3h**	88

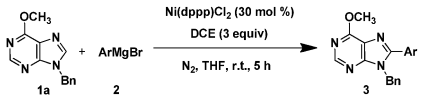
[a] Reaction conditions: 0.125 mmol of **1**, 5 equiv. of **2a**, 30 mol% of $Ni(dppp)Cl_2$, 3 equiv. of 1,2-dichloroethane, and 1 mL of THF in a Schlenk tube at rt for 5 h under a N_2 atmosphere. [b] Isolated yields. [c] 6 equiv. of **2a** was used. [d] 8 equiv. of **2a** was used.

arylation reaction occurred. This might be a good protocol to provide multi-arylation products. Disappointedly, these reactions with other N-aromatic heterocycles (such as benzimidazoles, oxazoles, indoles, benzothiazoles *etc.*) did not work under present optimal reaction conditions.

Intrigued by the results described above, a series of aryl Grignard reagents were chosen as aryl agents to probe whether the direct sp^2 C–H bond arylation of purines could be easily accessed. The results are shown in Table 3. As expected, the reaction with various electron-donating substituted Grignard reagents (*i.e.*, *p*-Me, *m*-Me, *p*-Et, *p*-MeO and 3,5-dimethyl) proceeded efficiently (entries 1–5, 74–89%) except that the yield of the desired product **3r** was somewhat low (entry 6, 42%), which might be due to the steric hindrance of *o*-Me. The electron-withdrawing substituted Grignard reagent (*i.e.*, *p*-Ph) was also tolerated under this novel coupling reaction and afforded the targeted products in moderate yield (entry 7, 61%).

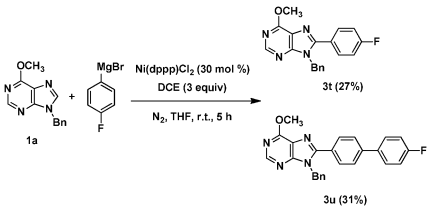
Interestingly, when (4-fluorophenyl)-magnesium bromide was used as a coupling partner, the reaction proceeded to give

Table 3 Direct C–H arylation of 9-benzyl-6-methoxy-9*H*-purine with various aryl Grignard reagents[a]

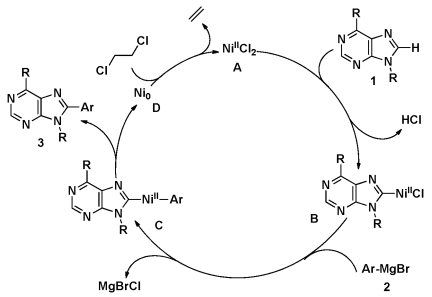


Entry	Ar	Product	Yield[b]/%
1	4-Me-Ph	**3m**	85
2	3-Me-Ph	**3n**	82
3	4-Et-Ph	**3o**	89
4	4-OMe-Ph	**3p**	74
5	3,5-diMe-Ph	**3q**	87
6	2-Me-Ph	**3r**	42
7	4-Ph-Ph	**3s**	61

[a] Reaction conditions: 0.125 mmol of **1a**, 5 equiv. of **2**, 30 mol% of $Ni(dppp)Cl_2$, 3 equiv. of 1,2-dichloroethane, and 1 mL of THF in a Schlenk tube at rt for 5 h under a N_2 atmosphere. [b] Isolated yields.



Scheme 2 Direct C–H arylation of 9-benzyl-6-methoxy-9*H*-purine with (4-fluorophenyl)-magnesium bromide.



Scheme 3 Proposed preliminary mechanism.

two products, **3t** and **3u** (Scheme 2). From this we can speculate that the direct sp^2 C–H bond arylation might be the first step, and then a Kumada cross-coupling reaction occurred as a second step.

A possible mechanism that accounts for C–H bonds arylation of purine with Grignard reagents is presented in Scheme 3. Combination of **1** and Ni(dppp)Cl_2 provides the metalated intermediate **B**. Subsequently, an (aryl)-nickel(II) intermediate **C** is generated by transmetalation between aryl Grignard reagent and the metalated intermediate **B**. Followed by reductive elimination to produce the desired product **3**, the Ni(0) species **D** is generated, which is reoxidized to Ni(II) species by DCE to complete the catalytic cycle.

In conclusion, a novel protocol for the nickel-catalyzed sp^2 C–H bond arylation of purines with Grignard reagents has been developed. To the best of our knowledge, this reaction is the first example that uses Grignard reagent as the coupling partner to perform direct sp^2 C–H bond arylation of N-aromatic heterocycles without a directing group. Further investigation on the detailed mechanism and expanding this novel method to broad spectrum substrates are underway in our laboratory.

We are grateful for financial support from the National Nature Science Foundation of China (Grant No. 20802016, 21072047, and 21172059), the Program for New Century Excellent Talents in University of Ministry of Education (No. NCET-09-0122), Excellent Youth Foundation of Henan Scientific Committee (No. 114100510012), the Program for Changjiang Scholars and Innovative Research Team in University (IRT1061), and the Excellent Youth Program of Henan Normal University.

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