ORGANIC LETTERS

2011
Vol. 13, No. 5
1095–1097

Copper Catalyzed C−H Functionalization for Direct Mannich Reactions

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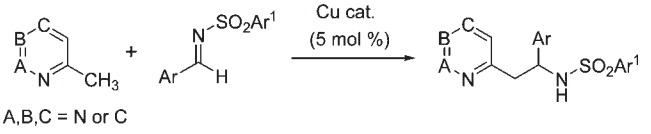
Received December 27, 2010

ABSTRACT



A protocol for a practical and direct addition of α- and γ-alkyl azaarenes to *N*-sulfonyl aldimines has been developed. Copper salts act as efficient Lewis acid catalysts for direct Mannich-type reactions providing a mild and fast access to various functionalized heterocycles.

The concept of atom economy has driven chemists to develop more efficient and sustainable methodologies for new bond forming reactions. In this context, the C−H activation strategy plays a key role. Although the activation of an aromatic C−H bond is well documented,[1] the activation of a methyl group directly attached to an aromatic ring remains much less explored. Significant contributions to this field have been made by Fagnou and Charette who studied the palladium catalyzed C−H activation of alkyl-substituted azine *N*-oxides and *N*-iminopyridinium ylides.[2,3] With regard to the use of substrates that lack a suitably located activating group, Huang and co-workers recently reported the palladium catalyzed benzylic addition of 2-methyl azaarenes to *N*-sulfonylimines.[4,5] In their report, the authors proposed a mechanism involving the activation of the 2-methyl group via a palladium(II) species (Figure 1).

In line with our interest in the development of organocatalytic direct Mannich reactions[6] and with the knowledge that the equilibrium between 2-methylpyridine **A** and its enamine counterpart **B** bearing an exocyclic double bond[7] can be easily shifted, we recently investigated the Brønsted acid catalyzed reaction between 2-methyl azaarenes and *N*-sulfonylimines. Although Brønsted acid catalysis could be achieved the reactions turned out to be sluggish. Therefore, we decided to investigate a different strategy based on the activation of both nucleophilic and electrophilic reagents by use of a Lewis acid. This approach would allow

(1) For recent reviews of heteroarenes direct arylation, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (d) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (e) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013.

(2) (a) Campeau, L.-C.; Schipper, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (b) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155.

(3) Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008**, *10*, 1641.

(4) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650.

(5) For palladium catalyzed acetoxylation of unactivated benzylic C−H bonds: Jiang, H.; Chen, H.; Wang, A.; Liu, X. *Chem. Commun.* **2010**, *46*, 7259.

(6) (a) Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, DOI: 10.1039/C0CC04539J. (b) Rueping, M.; Lin, M.-Y. *Chem.—Eur. J.* **2010**, *16*, 4169. (c) Rueping, M.; Nachtsheim, B. N. *Synlett* **2010**, 119. (d) Rueping, M.; Antonchick, A. P.; Sugiono, E.; Grenader, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 908. (e) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 10090. (f) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 5836. (g) Rueping, M.; Antonchick, A. *Org. Lett.* **2008**, *10*, 1731. (h) Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2007**, 1441. (i) Rueping, M.; Sugiono, E.; Theissmann, T.; Kuenkel, A.; Köckritz, A.; Pews Davtyan, A.; Nemati, N.; Beller, M. *Org. Lett.* **2007**, *9*, 1065. (j) Rueping, M.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7832.

(7) When lutidine is refluxed in D_2O, full incorporation of deuterium on the methyl substitutent is observed.

10.1021/ol103150g
Published on Web 02/02/2011

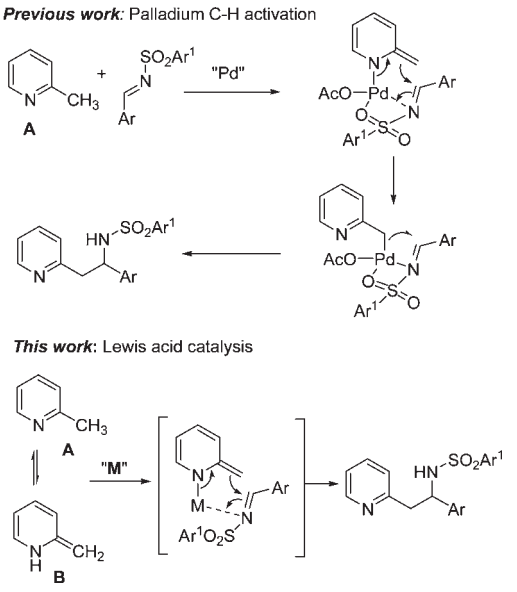


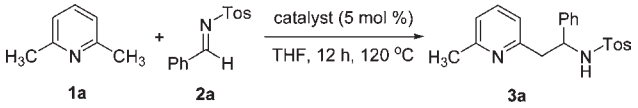
Figure 1. Palladium and Lewis acid catalyzed C−H functionalization.

the application of cheap and readily available metals under mild reaction conditions (Figure 1, bottom).[8] Furthermore, a suitable Lewis acid could shift the equilibrium to the enamine through the formation of a metal enamide species. Herein, we report an efficient and straightforward addition of alkylazaarenes to *N*-sulfonylimines.[9]

In order to validate this concept, 2,6-lutidine **1a** was initially chosen as an alkyl-azaarene model substrate and *N*-benzylidene-tosylamide **2a** as the imine. Regarding the influence of the solvent and temperature, a preliminary study revealed that THF, high temperature (120 °C), and a closed reaction vessel constituted the best conditions for this transformation.

Furthermore, we observed that neither external base nor oxygen is needed for the reaction. Subsequently, an evaluation of various Lewis acids was performed (Table 1). Ytterbium(III) triflate,[10] cobalt(II) acetate, and bismuth(III) triflate[11] gave the amine product **3a** in varying yields (Table 1, entries 1−3). Nevertheless, these results proved that the aforementioned direct amination reaction can be performed applying Lewis acid catalysis. Copper(I) salts exhibited only

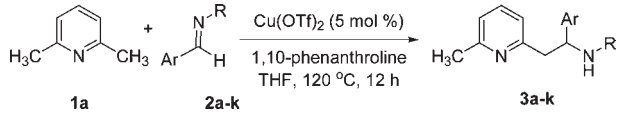
Table 1. Evaluation of Different Lewis Acids[a]



entry	catalyst	ligand	NMR yield (%)[b]
1	$Yb(OTf)_3$	none	10
2	$Co(OAc)_2$	1,10-phenanthroline	22
3	$Bi(OTf)_3$	none	65
4	$CuBr \cdot Me_2S$	none	21
5	CuBr	1,10-phenanthroline	30
6	CuI	1,10-phenanthroline	26
7	CuOAc	none	57
8	$(CuOTf)_2 \cdot C_6H_6$	1,10-phenanthroline	62
9	$CuBr_2$	1,10-phenanthroline	50
10	$CuCl_2$	1,10-phenanthroline	68
11	$Cu(OAc)_2$	1,10-phenanthroline	70 (61)[c]
12	$Cu(OPiv)_2$	1,10-phenanthroline	70 (60)[c]
13	$Cu(OTf)_2$	1,10-phenanthroline	85 (80)[c]
14	$Cu(OTf)_2$	none	77 (70)[c]

[a] Reaction conditions: **1a** (0.76 mmol), **2a** (0.304 mmol), catalyst (5 mol %), ligand (5 mol %), THF (0.2 mL), 120 °C, 12 h. [b] Yield based on ^1H NMR measurement (internal standard 4-MeO-acetophenone). [c] Yield after column chromatography.

Table 2. Substrate Scope of *N*-Sulfonyl Aldimines[a]



entry	Ar	R	product	yield (%)[b]
1	C_6H_5	Ts	**3a**	80
2	C_6H_5	Bs	**3b**	80
3	$4\text{-}MeOC_6H_4$	Bs	**3c**	60
4	$4\text{-}MeOC_6H_4$	Ns	**3d**	61
5	$4\text{-}MeOC_6H_4$	Bos	**3e**	75
6	$4\text{-}CF_3C_6H_4$	Ts	**3f**	80
7	C_6F_5	Ts	**3g**	79
8	$4\text{-}NO_2C_6H_4$	Ts	**3h**	95
9	$2\text{-}BrC_6H_4$	Ts	**3i**	88
10	3-Pyridyl	Ts	**3j**	89
11	$4\text{-}BrC_6H_4$	Ts	**3k**	88

[a] Reaction conditions: **1a** (0.76 mmol), **2** (0.304 mmol), $Cu(OTf)_2$ (5 mol %), 1,10-phenanthroline (5 mol %), THF (0.2 mL), 120 °C, 12 h. [b] Yield after column chromatography.

poor efficiency in this transformation (Table 1, entries 4−8). In contrast, very good results were obtained with the more Lewis acidic copper(II) salts (Table 1, entries 9−14). Among all the tested Cu(II) salts, copper(II) triflate was found to give the best results, affording the desired sulfonamide **3a** in 70% yield (Table 1, entry 14).[12] Furthermore, in combination with 1,10-phenanthroline, copper(II) triflate showed the highest

(8) For Lewis acid activation of pyridines: (a) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. For Lewis acid activation of pyridines and quinolines:(b) Deng, G.; Li, C.-J. *Org. Lett.* **2009**, *11*, 1171.

(9) During the preparation of this manuscript a protocol involving rare earth metal salts has been described: Qian, B.; Guo, S.; Xia, C.; Huang, H. *Adv. Synth. Catal.* **2010**, *352*, 3195.

(10) (a) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W. *Chem. Rev.* **2002**, *102*, 2227. (b) Tolstoluzhsky, N.; Gorobets, N.; Kolos, N.; Desenko, S. *J. Comb. Chem.* **2008**, *10*, 893.

(11) (a) Suzuki, H.; Ikegami, T.; Matano, Y. *Synthesis* **1997**, 249. (b) Rueping, M.; Nachtsheim, B. J.; Scheidt, T. *Org. Lett.* **2006**, *8*, 3717. (c) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W. *Adv. Synth. Catal.* **2006**, *348*, 1033. (d) Rueping, M.; Nachtsheim, B. J.; Kuenkel, A. *Org. Lett.* **2007**, *9*, 825. (e) Rueping, M.; Nachtsheim, B. J.; Kuenkel, A. *Synlett* **2007**, 1391. (f) Rueping, M.; Nachtsheim, B. J.; Sugiono, E. *Synlett* **2010**, 1549.

(12) (a) Li, Y.; Yu, Z.; Wu, S. *J. Org. Chem.* **2008**, *73*, 5647. (b) Remy, P.; Langer, M.; Bolm, C. *Org. Lett.* **2006**, *8*, 1209.

reactivity, providing the product in 80% yield after purification (Table 1, entry 13).

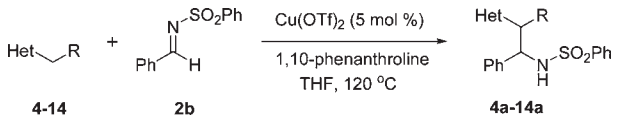
With the optimized conditions in hand, the scope of the reaction with regard to the structure of various *N*-sulfonyl aldimines was investigated (Table 2). Reaction of 2,6-lutidine **1a** with *N*-tosyl and *N*-benzenesulfonyl protected aldimines **2a**−**k**, bearing electron-neutral and electron-withdrawing aryl substituents, proceeded smoothly and provided the desired amino compounds in good to excellent yields (79−95% Table 2, entries 1−2, 6−11). In the case of imines containing electron-donating substituents the reactivity of the imine decreased slightly, resulting in yields ranging from 60% to 75% (Table 2, entries 3−5).

Subsequently the scope of α-alkylazaarenes was examined, and the results are summarized in Table 3. Pyridine derivatives (Table 3, entries 1−5) exhibited varying reactivity and provided the products **4a**−**14a** in moderate to good yields (50−79%).

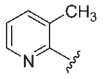
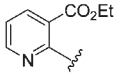
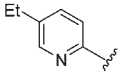
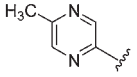
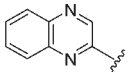
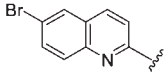
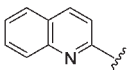
A shorter reaction time was required for the pyrimidine **11** (14 h, Table 3, entry 8) and pyridazine **10** (4 h, Table 3, entry 7). Notably, the 6-bromoquinaldine **13** showed good reactivity and the halogen substituent remained untouched during the process, allowing further transformations (Table 3, entry 10). Surprisingly, due to decomposition of the starting materials, the general procedure was not applicable to simple quinaldine **14** (Table 3, entry 11). In this case, the excess of azaarene was decreased to 1.05 equiv and an additional base $i\mathrm{Pr_2EtN}$ (1.5 equiv) was employed to allow the formation of the targeted compound **14a** in 55% yield.

The reactivity of γ-methylazaarenes and the competition between the two reactive centers of α,γ-dimethylazaarenes were also investigated (Figure 2).

Table 3. Substrate Scope of α-Alkyl Azaarenes[a]



4-14 2b 4a-14a

entry	Het	R	product	time (h)	yield[b] (%)
1		H	**4a**	24	50
2		H	**5a**	12	79
3		H	**6a**	24	62
4		Me	**7a**	24	58
5		H	**8a**	36	54
6		H	**9a**	60	49[c]
7		H	**10a**	4	58
8		H	**11a**	14	50
9		H	**12a**	12	76
10		H	**13a**	12	63
11		H	**14a**	12	55[d]

[a] Reaction conditions: **4**−**14** (2.5 equiv), **2b** (1 equiv), $Cu(OTf)_2$ (5 mol %), 1,10-phenanthroline (5 mol %), THF (0.2−0.4 mL), 120 °C. [b] Isolated yields after column chromatography. [c] Reaction performed at 130 °C. [d] Reaction conditions: **14** (1.05 equiv), **2b** (1 equiv), $i\mathrm{Pr_2EtN}$ (1.5 equiv).

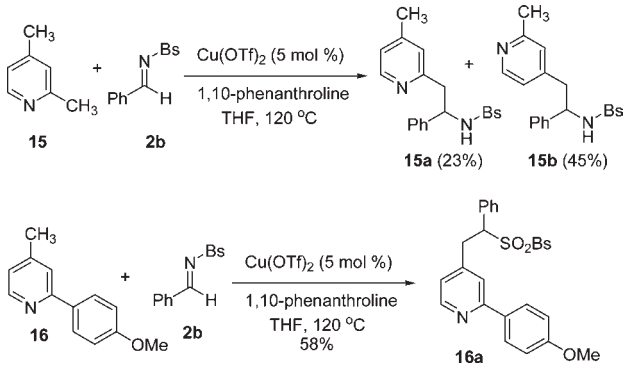


Figure 2. Regioselectivity in the copper catalyzed C−H functionalizatin. 1,3- vs 1,5- C−H functionalization.

The reaction of the 2,4-lutidine **15** with the imine **2b** yielded the α- and γ-addition products **15a** and **15b** in 23 and 45% yield, respectively. Interestingly, 4-picoline was unreactive under the same conditions. However, if an aryl substituent was introduced at the α-position of 4-picoline, the reaction proceeded exclusively in the γ-position and provided, for the first time, the addition product **16a** in a reasonable 58% yield.

In conclusion, we have developed an efficient and atom-economical protocol for the direct α- and γ-addition of 2- and 4-alkyl azaarenes to aldimines. The reaction proceeds through a copper catalyzed direct C−H bond functionalization and provides a set of different heterocycle-containing amines in good yields.

Acknowledgment. The authors acknowledge financial support by RWTH Aachen University.

Supporting Information Available. Experimental procedures and full characterization (^{1}H and ^{13}C NMR data and spectra, MS, and IR analyses) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.