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Lewis Acid Catalyzed Benzylic C−H Bond Functionalization of Azaarenes: Addition to Enones

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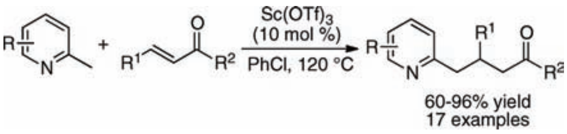
ABSTRACT



A Lewis acid catalyzed benzylic C−H bond functionalization of alkyl-substituted azaarenes is described. $Sc(OTf)_3$ and $Y(OTf)_3$ promoted the direct addition of alkyl-substituted azaarenes and benzoxazole to enones and an α,β-unsaturated *N*-acylpyrrole. Products were obtained in 60−96% yield.

Metal-catalyzed $C(sp^3)$−H bond functionalizations are valuable methods in synthetic organic chemistry.[1,2] Among them, $C(sp^3)$−H bond activation/C−C bond-forming reactions of azaarenes, such as quinolines and pyridines, provide straightforward access to useful building blocks for the design and synthesis of biologically active compounds. To realize the $C(sp^3)$−H functionalization of azaarenes, transition-metal-catalyzed chelation-assisted methods for C−C bond formation have been investigated by many groups.[3] Further studies to expand the reaction scope for the synthesis of diverse sets of functionalized azaarenes by enabling the use of various coupling partners are desirable. To complement transition-metal-catalyzed processes, we herein report a Lewis acid-catalyzed coupling of benzylic $C(sp^3)$−H in alkyl-substituted azaarenes **1** (Figure 1) with electron-deficient alkenes **2**, enones, and an α,β-unsaturated ester surrogate.

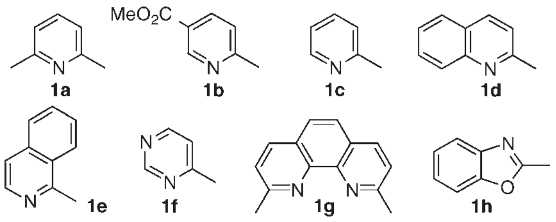


Figure 1. Structures of methyl-substituted azaarenes **1a**−**g** and benzoxazole **1h**.

Based on precedents in Lewis acid catalyzed intramolecular $C(sp^3)$−H functionalization,[4−8] Lewis acid assisted

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(1) Review on $C(sp^3)$−H bond functionalization: Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1683.

(2) Selected recent general reviews on C−H bond functionalization, see: (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (d) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (e) Special Issue on Selective Functionalization of C−H Bonds: *Chem. Rev.* 2010, *110*, 575−1211. (f) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* 2010, *110*, DOI: 10.1021/cr100198w.

(3) For selected leading examples involving C−C bond formation, see: (a) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935. (b) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (c) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657. (d) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (e) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (f) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (g) Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008**, *10*, 1641. (h) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759. (i) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650. (j) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (k) Burton, P. M.; Morris, J. A. *Org. Lett.* **2010**, *12*, 5359. (l) Tsurugi, H.; Yamamoto, K.; Mashima, K. *J. Am. Chem. Soc.* **2011**, *133*, 732.

10.1021/ol200217y

$C(sp^2)$−H functionalization of pyridines and/or quinolines,[9,10] as well as our ongoing projects on acid/base-catalyzed proton transfer processes,[11] we envisioned the use of a Lewis acid for the functionalization of *o*-methyl-substituted azaarenes under proton-transfer conditions.[12]

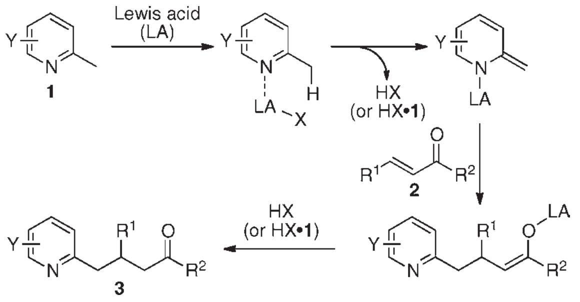
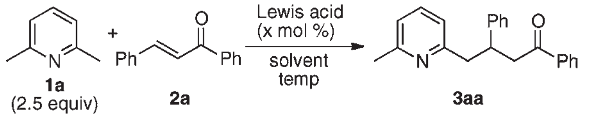


Figure 2. Working hypothesis on Lewis acid catalyzed C−H functionalization of alkyl-substituted azaarenes with enones.

Our working hypothesis is shown in Figure 2. Activation of azaarenes by the coordination to a strong Lewis acid would increase the acidity of benzylic C−H bonds. Cleavage of the C−H bond by either counterions of a Lewis acid or an external base (azaarene **1**) would generate a metal enamide species.[13] The addition of the metal enamide to enones **2** would give an enolate intermediate, which would afford the product **3** after protonation.

To test the feasibility of our hypothesis, we screened Lewis acids using lutidine **1a** and enone **2a** as model substrates. The optimization studies are summarized in Table 1. Initial trials using $Mg(OTf)_2$, $Al(OTf)_3$, $In(OTf)_3$, $Fe(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$, and $Bi(OTf)_3$ did not promote the desired reaction at all (entries 1−7). In contrast, the results using rare earth metal triflates [$RE(OTf)_3$] were promising (entries 8−12). The reactivity changed in correlation with the Lewis acidity of rare earth metal triflates (Sc, Y > Gd > Sm, La),[14] and 20 mol % of $Sc(OTf)_3$ and $Y(OTf)_3$ gave the best reactivity (entries 8 and 9, 71% yield). $ScBr_3$ and $ScCl_3$ were also examined, but the yield was not as satisfactory (entries 13−14). The reaction also proceeded in good yield with 10 mol % of $Sc(OTf)_3$, although a longer reaction time was required at 120 °C (entry 16, 72 h, 90% isolated yield). At 160 °C, the reaction was complete after 48 h using 10 mol % of $Sc(OTf)_3$ (entry 17, 90% isolated yield).

Table 1. Optimization Studies



1a
(2.5 equiv)

2a

3aa

entry	Lewis acid (*x* mol %)	solvent	temp (°C)	time (h)	% yield[a]
1	$Mg(OTf)_2$ (20)	PhCl	120	14	0
2	$Al(OTf)_3$ (20)	PhCl	120	14	0
3	$In(OTf)_3$ (20)	PhCl	120	14	0
4	$Fe(OTf)_3$ (20)	PhCl	120	14	0
5	$Cu(OTf)_2$ (20)	PhCl	120	14	0
6	$Zn(OTf)_2$ (20)	PhCl	120	14	0
7	$Bi(OTf)_3$ (20)	PhCl	120	14	0
8	$Sc(OTf)_3$ (20)	PhCl	120	14	71
9	$Y(OTf)_3$ (20)	PhCl	120	14	71
10	$Gd(OTf)_3$ (20)	PhCl	120	14	33
11	$Sm(OTf)_3$ (20)	PhCl	120	14	0
12	$La(OTf)_3$ (20)	PhCl	120	14	trace
13	$ScBr_3$ (20)	PhCl	120	14	51
14	$ScCl_3$ (20)	PhCl	120	14	30
15	$Sc(OTf)_3$ (10)	PhCl	120	48	73[b]
16	$Sc(OTf)_3$ (10)	PhCl	120	72	90[b]
17	$Sc(OTf)_3$ (10)	$1,2\text{-}Cl_2C_6H_4$	160	48	90[b]

[a] Determined by ^1H NMR analysis with an internal standard (entries 1−14). [b] Isolated yield after purification by silica gel column chromatography (entries 15−17).

The substrate scope and limitations of donors is summarized in Figure 3 and eq 1. Benzylic $C(sp^3)$−H of methyl-substituted pyridines **1a−c**, quinoline **1d**, isoquinoline **1e**, pyrimidine **1f**, phenanthroline **1g**, and

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(4) $BF_3\cdot Et_2O$- and $TiCl_4$-catalyzed intramolecular benzylic C−H functionalization via 1,5-hydride transfer: Wölfling, J.; Frank, É.; Schneider, G.; Tietze, L. F. *Eur. J. Org. Chem.* **2004**, 90.

(5) $Sc(OTf)_3$-, $BF_3\cdot Et_2O$-, and $PtCl_4$-catalyzed intramolecular coupling of $C(sp^3)$−H bonds and electron-deficient alkenes via 1,5-hydride transfer: (a) Pastine, S. J.; MacQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180. (b) MacQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 402. (c) Pastine, S. J.; Sames, D. *Org. Lett.* **2005**, *7*, 5429. (d) MacQuaid, K. M.; Long, J. Z.; Sames, D. *Org. Lett.* **2009**, *11*, 2972. (e) Vadola, P. A.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 402.

(6) $Gd(OTf)_3$-, $Mg(OTf)_2$-, and $Ni(ClO_4)_2$-catalyzed intramolecular (asymmetric) reactions with electron-deficient alkenes via 1,5-hydride transfer: (a) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226. (b) Murarka, S.; Zhang, C.; Konieczynska, M. D.; Seidel, D. *Org. Lett.* **2009**, *11*, 129.

(7) $Rh(O_2CCF_3)$-catalyzed intramolecular reactions with electron-deficient alkynes via 1,5-hydride transfer: Shikanai, D.; Murase, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2009**, *131*, 3166.

(8) Cationic Co Lewis acid-catalyzed intramolecular asymmetric reaction via 1,5-hydride transfer: Cao, W.; Liu, X.; Wang, W.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 600.

(9) $Sc(OTf)_3$-catalyzed alkylation under cross-dehydrogenative-coupling conditions: Deng, G.; Li, C.-J. *Org. Lett.* **2009**, *11*, 1171.

(10) Lewis acid-assisted functionalization under Ni(0) catalysis: (a) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (b) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666. (c) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Ong, T.-G.; Yap, G. P. A. *J. Am. Chem. Soc.* **2010**, *132*, 11887.

(11) For an example using rare earth metal triflate, see: Mihara, H.; Xu, Y.; Shepherd, N. E.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 8384. See also a review: Shibasaki, M.; Matsunaga, S. *J. Synth. Org. Chem., Jpn.* **2010**, *68*, 1142.

(12) During the preparation of this manuscript, Huang et al. reported closely related $Sc(OTf)_3$-catalyzed benzylic C−H functionalization of 2-methyl azaarenes. The reactions with aldimines proceeded in excellent yield under proton transfer conditions. (a) Qian, B.; Guo, S.; Xia, C.; Huang, H. *Adv. Synth. Catal.* **2010**, *352*, 3195. After submission of this manuscript, Rueping's group also reported $Cu(OTf)_2$-catalyzed reactions with aldimines, see: (b) Rueping, M.; Tolstoluzhsky, N. *Org. Lett.* **2011**, *13*, 1095.

(13) Oshima/Yorimitsu et al. and Liu et al. reported the utility of the metal−enamide intermediates generated in situ via C−C bond cleavage. (a) Niwa, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 2643. (b) Shang, R.; Yang, Z.-W.; Wang, Y.; Zhang, S.-L.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 14391.

(14) Evaluation of the relative Lewis acidity of rare earth metals: Tsuruta, H; Yamaguchi, K; Imamoto, T. *Chem. Commun.* **1999**, 1703.

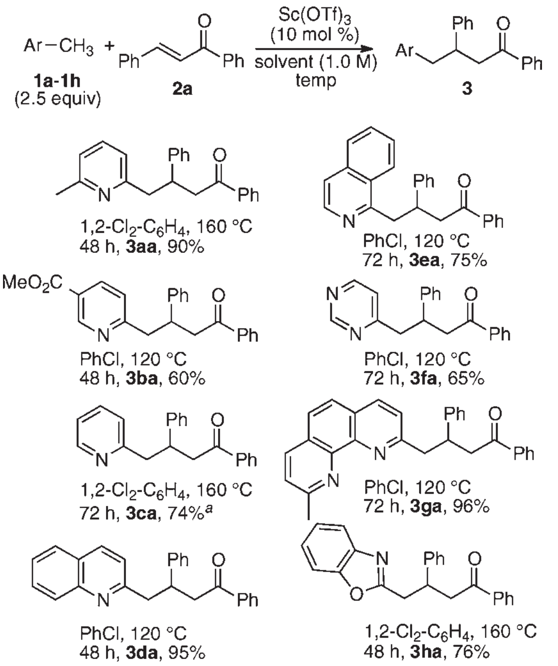
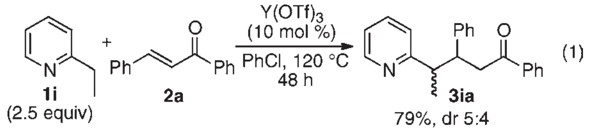


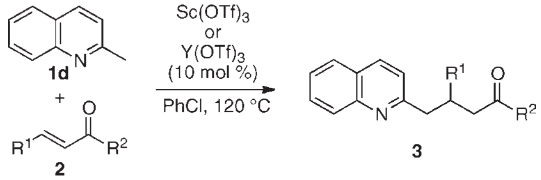
Figure 3. Sc-catalyzed addition of azaarenes **1a**−**h** to enone **2a**: Reagents and conditions: Reaction was run using 2.5 equiv of **1**, enone **2a** (0.25 mmol), and Sc(OTf)$_3$ (10 mol %) in solvent (1.0 M) at 120 or 160 °C unless otherwise noted. Isolated yield after purification by silica gel column chromatography is shown for each run. [a]20 mol % of Sc(OTf)$_3$ was used.

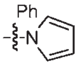
benzoxazole **1h** were investigated. Compound **1b** with an ester functional group was compatible under the reaction conditions, and **3ba** was obtained in 60% yield. 2-Picoline **1c** was less reactive than **1a**, and 20 mol % of Sc(OTf)$_3$ at 160 °C was required to obtain **3ca** in 74% yield. On the other hand, azaarenes **1d**−**g** showed good reactivity with 10 mol % of Sc(OTf)$_3$ at 120 °C, giving products **3da**−**ga** in 65−96% yield. Sc(OTf)$_3$ was also applicable to 2-methylbenzoxazole **1h**, giving product **3ha** in 76% yield. 2-Ethylpyridine **1i** also reacted smoothly selectively at the benzylic position as shown in eq 1. The best conditions for 2-ethylpyridine **1i** were 10 mol % of Y(OTf)$_3$ at 120 °C, and product **3ia** was obtained in 79% yield after 48 h. Diastereoselectivity was, however, poor (5:4 dr). Further studies to improve diastereoselectivity are ongoing.



The substrate scope of acceptors is summarized in Table 2. The reactions of chalcone derivatives **2b**−**e** with either an electron-withdrawing group or an electron-donating group proceeded in good yield (79−91%). Heteroaryl-substituted enones **2f**−**h** were also applicable, giving the products in 72−93% yield. With dienone **2i**, 1,4-addition predominantly proceeded over 1,6-addition, and 1,4-adduct **3di** was obtained in 78% yield. The reaction of α,*β*-unsaturated *N*-acylpyrrole **2j**[15,16] also proceeded to give the product **3dj** in 81% yield. The *N*-acylpyrrole unit can be regarded as an ester surrogate, and its synthetic utility was demonstrated through transformations of **3dj** in Scheme 1. The *N*-acylpyrrole unit was readily converted into an ethyl ester unit by treatment with NaOEt at room temperature for 20 min, giving **4dj** in 92% yield. Substitution with pyrrolidine also proceeded smoothly in the presence of DBU at 60 °C for 12 h (**5dj**, 84% yield). In addition to substitution reactions, the reduction of **3dj** with DIBAL-H gave pyrrole carbinols as diastereomixtures. Under Masamune−Roush conditions,[17] α,*β*-unsaturated ethyl ester **6dj**, which can

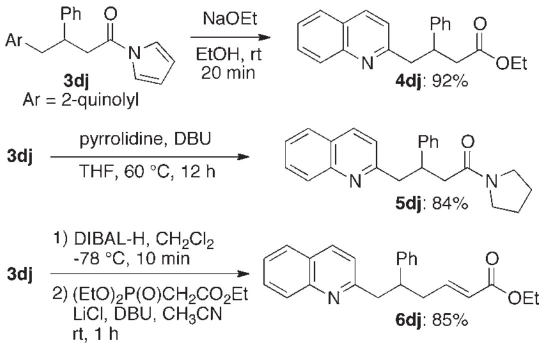
Table 2. Lewis Acid-Catalyzed Addition of Azaarene **1d** to Enones and α,*β*-Unsaturated *N*-Acylpyrrole



entry	R^1	R^2	2	cat.	time (h)	3	% yield[b]
1	Ph	4-F-C$_6$H$_4$	**2b**	Y	36	**3db**	91
2	Ph	4-MeOC$_6$H$_4$	**2c**	Y	48	**3dc**	79
3	4-Cl-C$_6$H$_4$	Ph	**2d**	Sc	72	**3dd**	86
4	4-MeOC$_6$H$_4$	Ph	**2e**	Y	48	**3de**	81
5	Ph	2-thienyl	**2f**	Sc	72	**3df**	72
6	Ph	3-thienyl	**2g**	Sc	72	**3dg**	93
7	2-furyl	Ph	**2h**	Y	36	**3dh**	85
8[c]	(*E*)-PhCH=CH	Ph	**2i**	Y	48	**3di**	78
9	Ph		**2j**	Sc	72	**3dj**	81

[a] Reaction was run using 2.5 equiv of **1d**, enone, or *N*-acylpyrrole **2** (0.25 mmol), and Sc(OTf)$_3$ or Y(OTf)$_3$ (10 mol %) in PhCl (1.0 M) at 120 °C unless otherwise noted. [b] Isolated yield after purification by silica gel column chromatography. [c] 20 mol % of catalyst was used.

Scheme 1. Transformation of *N*-Acylpyrrole Unit in **3dj**



be regarded as 1,6-addition adduct of **1d**, was obtained in 85% yield (two steps) via in situ generation of aldehyde from the crude pyrrole carbinols.

In summary, we succeeded in Lewis acid-catalyzed functionalization of benzylic C(sp^3)−H in alkyl-substituted azaarenes under proton-transfer conditions. Sc(OTf)$_3$ and Y(OTf)$_3$ promoted the reaction of methyl-substituted azaarenes and benzoxazole **1a**−**h** and 2-ethylpyridine **1i** to enones and an α,β-unsaturated *N*-acylpyrrole **2**, giving the products in 60−96% yield. Transformation of the product from α,β-unsaturated *N*-acylpyrrole was also demonstrated. Further studies to expand the reaction scope of Lewis acid promoted benzylic C(sp^3)−H functionalization are ongoing.[18]

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Supporting Information Available. Experimental procedures and spectral data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Utility of α,β-unsaturated *N*-acylpyrroles as highly reactive ester equivalent acceptors in conjugate additions: (a) Matsunaga, S.; Kinoshita, T.; Okada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559. (b) Kinoshita, T.; Okada, S.; Park, S.-R.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4680.

(16) Properties of *N*-acylpyrroles were reported by Evans and coworkers in detail. (a) Evans, D. A.; Borg, G.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3188. Use of enol silane derived from *N*-acylpyrrole:(b) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595. (c) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480.

(17) (a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essefeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183. Applications to pyrrole carbinols:(b) Dixon, D. J.; Scott, M. S.; Luckhurst, C. A. *Synlett* **2003**, 2317. (c) Dixon, D. J.; Scott, M. S.; Luckhurst, C. A. *Synlett* **2005**, 2420. (d) Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4365.

(18) The reaction of 4-methylpyridine with chalcone **1a** gave product but in only less than 10% yield under the optimized conditions for *o*-methyl-substituted azaarenes. Further studies to realize efficient C−H functionalization with 4-methylazaarenes are ongoing.