DOI: 10.1002/adsc.201200536

Aluminum Triflate as a Powerful Catalyst for Direct Amination of Alcohols, Including Electron-Withdrawing Group-Substituted Benzhydrols

Takashi Ohshima,[a,*] Junji Ipposhi,[b] Yasuhito Nakahara,[b] Ryozo Shibuya,[a] and Kazushi Mashima[b,*]

[a] Graduate School of Pharmaceutical Sciences, Kyushu University, Maidashi Higashi-ku, Fukuoka 812-8582, Japan
Fax: (+81)-92-642-6650; phone: (+81)-92-642-6650; e-mail: ohshima@phar.kyushu-u.ac.jp
[b] Department of Chemistry, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka 560-8531, Japan
Fax: (+81)-6-6850-6249; phone: (+81)-6-6850-6245; e-mail: mashima@chem.es.osaka-u.ac.jp

Received: June 18, 2012; Published online: ■■ ■■, 0000

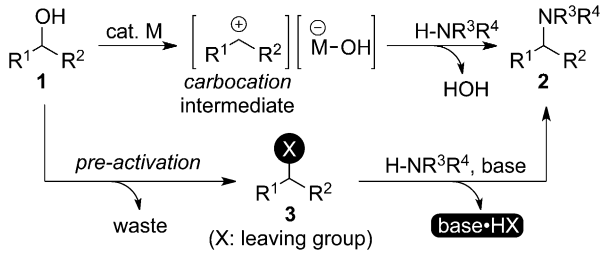
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200536.

Abstract: Direct aminations of allylic alcohols, benzylic alcohols, and benzhydrols with electron-withdrawing (F, Br, I, NO_2, or CN) substituents were efficiently catalyzed by aluminum triflate [$Al(OTf)_3$] to afford the corresponding biarylamines in high yield, and the dibromo-substituted product was further transformed into letrozole.

Keywords: aluminum; amination; benzhydrols; direct substitution; letrozole

Direct catalytic amination of *underivatized* alcohols (**1**→**2**), which generates only water as a coproduct, is a straightforward and desirable process for carbon-heteroatom and carbon-carbon bond formations compared with the common stepwise process through pre-activation of a hydroxy group to a leaving group (**1**→**3**→**2**), which generates more than stoichiometric amounts of unwanted chemical waste (Scheme 1).

Such ideal direct reactions, however, are rarely explored because of the poor leaving ability of the hydroxy group. Various Lewis acids (Re,[1] Ru,[2] rare earth metals,[3] Au,[4] In,[5] Bi,[6] Fe,[7] Ag,[8] Mo,[9] Hg,[10] etc.[11]), I_2,[12] and Brønsted acids[13] were recently reported to efficiently catalyze the substitution reaction.[14,15] Although nucleophiles of the reported acid-catalyzed reaction were limited to rather stable compounds, such as 4-nitroaniline, tosylamide, methyl and benzyl carbamate, simple amides, alcohols, and active methylenes, we recently succeeded in developing direct substitutions of allylic and benzylic alcohols with acid-sensitive *tert*-butoxycarbonyl (Boc), thiophenesulfonyl,[16] *tert*-butylsulfonyl (Bus),[17] and 2-(1,3-dioxan-2-yl)ethylsulfonyl (Dios)[18] protected amine nucleophiles using only 1 mol% of Au(III) salt.[19] These acid-catalyzed reactions, however, still have much room for improvement with respect to the substrate generality of the alcohols. Because the reaction proceeds *via* a carbocation intermediate, the substrate requires a substituent that stabilizes the carbocation intermediate. A variety of allylic, propargylic, and benzylic alcohols has been utilized as substrates, and generally those with electron-donating substituents are reactive, those with electron-withdrawing substituents have been rarely explored (Figure 1). Weak electron-withdrawing groups: X=F (σ_p[20]=0.06) and Cl (σ_p=0.22) were observed in several allylic,[6b,8,12a] propargylic,[4d,e,f,9a,11b,c] and benzylic[5b,7b,c,11a] types of substrates (**4**, **5**, and **6**, respectively), resulting in good to high yields. By contrast, a more electron-withdrawing Br (σ_p=0.23) substituent was examined in rather reactive substrates.[1b,5b,7f,12a] Reactions of the substrates with a more electron-withdrawing group such as an I (σ_p=0.28), NO_2 (σ_p=0.78), or CN (σ_p=1.00) substituent have never succeeded.



Scheme 1. Direct catalytic amination of alcohol (**1**→**2**) and common stepwise process through pre-activation of alcohol (**1**→**3**→**2**).

Biarylamines are found in a number of biologically active and pharmaceutical compounds,[21] such as the non-steroidal aromatase inhibitor letrozole (**8**).[22]

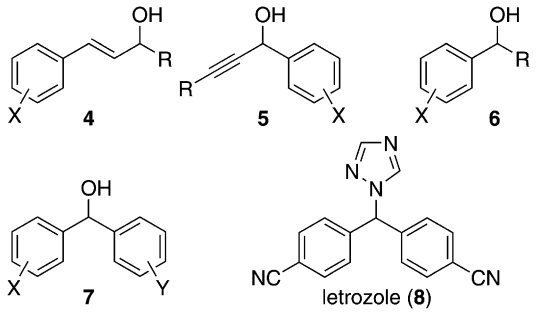
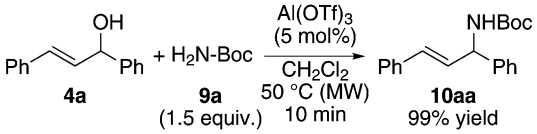


Figure 1. Structures of representative substrates **4**–**7** for acid-catalyzed direct nucleophilic substitution and letrozole (**8**).

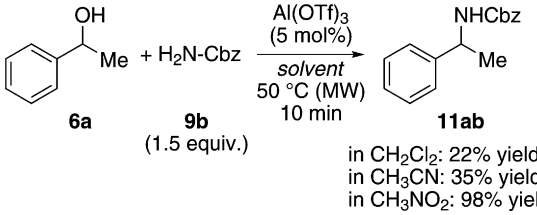
One of the most efficient synthetic methods for those biaryl compounds would be a direct nucleophilic substitution of benzhydrol derivatives **7**. As mentioned above, however, benzhydrols with electron-withdrawing group(s) are unreactive substrates. To date, only reactions of monochloro (2 examples)[13b,c] and difluoro (1 example)[13d] benzhydrols have been reported, whereas reactions of those with more electron-withdrawing Br, I, or NO_2 substituents have not been achieved. Here, we report that direct substitutions of allylic and benzylic alcohols, including benzhydrols, with various nitrogen nucleophiles are efficiently catalyzed by $Al(OTf)_3$.[23] Under the optimized conditions, benzhydrols with an electron-withdrawing F, Br, I, NO_2, or CN substituent were successfully converted to the corresponding biarylamine derivatives in high yield, and the dibromo-substituted product was further transformed into letrozole (**8**). Moreover, although the catalytic activity of $Al(OTf)_3$ is usually described as similar to that of a super-acid,[23] direct substitutions with synthetically useful but acid-sensitive Boc- and Bus-protected amine nucleophiles were efficiently catalyzed by $Al(OTf)_3$ without decomposition of the acid-sensitive functionalities.

As an extension of our previous studies on Au-catalyzed direct substitutions of allylic and benzylic alcohols with acid-sensitive nitrogen nucleophiles,[19] we focused our attention on the development of a more powerful catalyst system to expand the substrate generality of alcohols while still maintaining high functional group tolerance. Thus, using 1,3-diphenylprop-2-en-1-ol (**4a**) and *tert*-butyl carbamate (**9a**) as representative substrates, we re-screened various metal salts and complexes, and $Al(OTf)_3$ was found to be a highly efficient catalyst. The desired product **10aa** was obtained in 99% yield without decomposition of the Boc group under microwave heating conditions (Eq. 1).[24] Commercially available $Al(OTf)_3$ has several advantages, such as its high Lewis acidic, water resistance, and reusable properties, but it has not been well studied compared with other Lewis acid catalysts.[23] High catalyst activity and mildness of the reaction conditions shown in Eq. (1) encouraged us to examine $Al(OTf)_3$ as a catalyst for direct substitutions of various other alcohols.[25]



(1)

Solvent effects on the substitution reaction were first examined using less reactive 1-phenylethanol (**6a**) and Cbz-amide **9b** [Eq. (2)].[24] Although none or

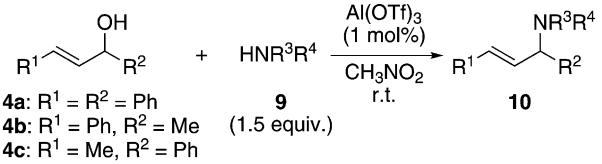


(2)

only trace amounts of product **11ab** were obtained in either non-polar or polar solvents (toluene, EtOAc, THF, DMF, DMSO, etc.), 22% and 35% yields of **11ab** were achieved in CH_2Cl_2 and CH_3CN, respectively, and CH_3NO_2 was the best solvent (98%). Conventional heating was much less effective than microwave heating conditions, indicating the beneficial effects of microwave irradiation.[24]

We then explored the substrate generality of the $Al(OTf)_3$-catalyzed direct substitution using various allylic alcohols **4** and nitrogen nucleophiles (Table 1). Because allylic alcohols **4** are generally more reactive than benzylic alcohols **6**, most of the reactions in CH_3NO_2 were completed at room temperature in the presence of only 1 mol% of $Al(OTf)_3$. Under the optimized conditions, the reaction of **4a** with **9a**, as shown in Eq. (1), smoothly proceeded at a lower temperature (room temperature) to give product **10aa** in 98% yield (entry 1). Other carbamates **9b**–**d** were also good nucleophiles (entries 2–4). Although amides **9e**–**h** were less reactive nucleophiles than carbamates, increasing the reaction temperature to 50 °C (MW), extending the reaction time, and including an additive (KPF_6) effectively accelerated the reactions and the corresponding amides **10ae**–**ah** were obtained in high yield (entries 5–8). It is noteworthy that the 2-picolinamide group, which is a highly efficient directing group for the Pd-catalyzed C–H bond activation reaction,[26] can be directly introduced at the benzylic position (Entry 7). Reactions with sulfonamide **9i** and electron-deficient 4-nitroaniline (**9j**) were efficiently catalyzed by $Al(OTf)_3$ (entries 9 and 10). Alkyl-substituted allylic alcohols **4b** and **4c** were converted to

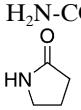
Table 1. Direct catalytic substitution of allylic alcohol **4** with various nitrogen nucleophiles **9**.[a]



4a: $R^1 = R^2 = Ph$
4b: $R^1 = Ph$, $R^2 = Me$
4c: $R^1 = Me$, $R^2 = Ph$

9 (1.5 equiv.)

10

Entry	Alcohol (**4**)	Nucleophile (**9**)		*t* [min]	Yield [%][b]
1	**4a**	H_2N-Boc	(**9a**)	20	98
2	**4a**	H_2N-Cbz	(**9b**)	10	92
3	**4a**	H_2N-CO_2Me	(**9c**)	10	94
4	**4a**		(**9d**)	10	98
5[c]	**4a**	H_2N-Ac	(**9e**)	10	94
6	**4a**	H_2N-Bz	(**9f**)	120	96
7[c,d]	**4a**	H_2N-CO-2-Py	(**9g**)	120	92
8[c]	**4a**		(**9h**)	30	95
9	**4a**	H_2N-Ts	(**9i**)	10	94
10	**4a**	H_2N-C_6H_4-4-NO_2	(**9j**)	5	92
11	**4b**	H_2N-Cbz	(**9b**)	60	83
12	**4c**	H_2N-Cbz	(**9b**)	60	88[e]

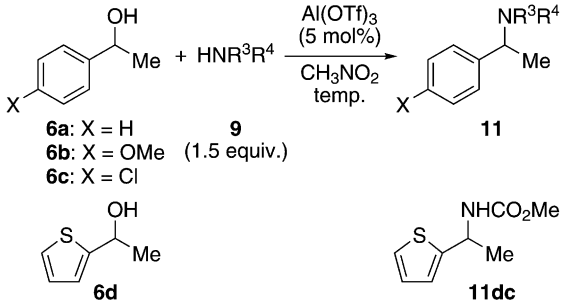
[a] *Reaction conditions:* **4** (1.0 mmol), **9** (1.5 mmol, 1.5 equiv.), $Al(OTf)_3$ (0.01 mmol, 1 mol%), CH_3NO_2 (2 mL), room temperature.
[b] Isolated yield.
[c] Reaction was heated at 50 °C under microwave irradiation.
[d] KPF_6 (1 mol%) was added as an additive.
[e] Cbz-protected α-methyl cinnamylamine (**10bb**) was obtained instead of γ-methyl cinnamylamine (**10cb**).

the same α-methyl cinnamylamine (**10bb**), suggesting an S_N1-type reaction pathway *via* the same allyl cation intermediate (entries 11 and 12).

We further examined the scope and limitations using benzylic-type alcohols **6a–d** (Table 2). Other than benzyl carbamate (**9b**), as shown in Eq. (2), methyl carbamate (**9c**) and sulfonamides **9i** and **9k** also participated in the reaction of 1-phenylethanol (**6a**) to successfully give the corresponding coupling products **10ac** (entry 1, 96%), **10ai** (entry 2, 92%), and **10ak** (entry 3, 94%). Introduction of an electron-donating methoxy group increased the reactivity, and thus the reactions of **6b** proceeded at room temperature (entries 4–6). The reactivity of electron-withdrawing Cl-substituted alcohol **6c** was similar to that of non-substituted alcohol **6a** (Entry 7). The substrate incorporating the electron-rich thiophene **6d** was also reactive (entry 8).

Because of the high utility of biarylamine derivatives, we examined the scope of the reaction using various benzhydrols **7** (Table 3). First, using non-substituted benzhydrol **7a**, a variety of nitrogen nucleophiles, such as carbamate (entry 1), amide (entries 2–4), and sulfonamide (entries 5–8), were examined. In all cases, the reactions completed within 1 h at 50 to 70 °C, affording the corresponding products in high yield. Importantly, no decomposition was observed, even when using a nucleophile with a reactive α-halocarbonyl group **9l** (entry 3). An acid-sensitive Bus group was also compatible with the conditions of the $Al(OTf)_3$ catalysis (entry 8). Triazole (**9o**) was a less reactive nucleophile, but the desired coupling product **12ao** was obtained almost quantitatively after heating for 2 h at 80 °C (entry 9). As expected, bis(4-methoxyphenyl)methanol (**7b**) was a highly reactive substrate (entry 10). We then focused on using benzhydrols with an electron-withdrawing group **7c–g** (entries 11–15), which have never been applied for a direct substitution reaction, except for one example of **7c** in which a supramolecular host-guest complex was used.[13d] At an elevated temperature (90 °C), the reaction of bis(4-fluorophenyl)methanol (**7c**) proceeded smoothly to give amide **12ce** in 92% yield (entry 11). More challenging substrates, bis(4-bromophenyl)methanol (**7d**) and bis(4-iodophenyl)methanol (**7e**), were also successfully converted to the desired coupling products **12do** and **12eo** in 98% and 96% yield, respectively (entries 12 and 13), allowing for further transformation using aryl bromide and aryl iodide units (*vide infra*). Although the introduction of strong electron-withdrawing nitro and cyano groups would generally prohibit the formation of a carbocation intermediate,

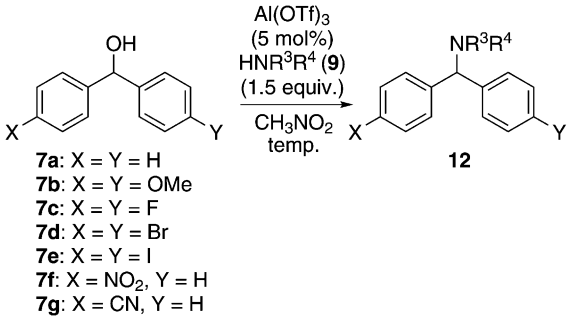
Table 2. Direct catalytic substitution of benzylic-type alcohols **6** with various nitrogen nucleophiles **9**.[a]



Entry	Alcohol (**6**)	Nucleophile (**9**)		T [°C]	t [min]	Yield [%][b]
1	**6a**	H_2N-CO_2Me	(**9c**)	50[c]	10	96
2	**6a**	H_2N-Ts	(**9i**)	50[c]	10	92
3	**6a**	H_2N-SO_2-2-thiophenyl	(**9k**)	50[c]	30	94
4	**6b**	H_2N-Boc	(**9a**)	r.t.	180	90
5	**6b**	H_2N-Cbz	(**9b**)	r.t.	60	97
6	**6b**	H_2N-Bz	(**9f**)	r.t.	180	86
7	**6c**	H_2N-CO_2Me	(**9c**)	50[c]	10	86
8	**6d**	H_2N-CO_2Me	(**9c**)	r.t.	10	93

[a] *Reaction conditions:* **6** (1.0 mmol), **9** (1.5 mmol, 1.5 equiv.), $Al(OTf)_3$ (0.05 mmol, 5 mol%), CH_3NO_2 (2 mL).
[b] Isolated yield.
[c] Reaction was heated under microwave irradiation.

Table 3. Direct catalytic substitution of benzhydrols **7** with various nitrogen nucleophiles **9**.[a]



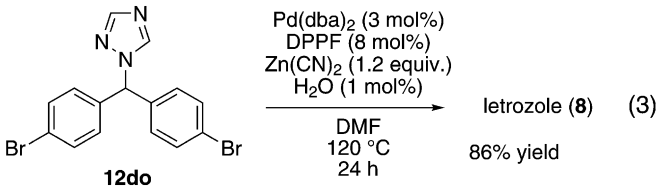
Entry	Alcohol (**7**)	Nucleophile (**9**)		T [°C]	t [min]	Yield [%][b]
1	**7a**	H_2N-Cbz	(**9b**)	50	10	99
2	**7a**	H_2N-Ac	(**9e**)	70	60	96
3	**7a**	H_2N-$COCH_2Cl$	(**9l**)	70	60	95
4	**7a**	H_2N-Bz	(**9f**)	50	30	99
5	**7a**	H_2N-Ts	(**9i**)	50	10	99
6	**7a**	H_2N-SO_2-2-thiophenyl	(**9k**)	50	30	95
7	**7a**	H_2N-Ns	(**9m**)	50	10	90
8	**7a**	H_2N-SO_2-*t*-Bu	(**9n**)	50	30	87
9	**7a**		(**9o**)	80	120	99
10	**7b**	H_2N-Boc	(**9a**)	r.t.	10	97
11	**7c**	H_2N-Ac	(**9e**)	90	60	92
12	**7d**		(**9o**)	90	360	98
13	**7e**		(**9o**)	90	360	96
14	**7f**	H_2N-Ts	(**9i**)	90	60	91
15	**7g**	H_2N-Ts	(**9i**)	90	120	77

[a] *Reaction conditions:* **7** (1.0 mmol), **9** (1.5 mmol, 1.5 equiv.), $Al(OTf)_3$ (0.05 mmol, 5 mol%), CH_3NO_2 (2 mL) under microwave irradiation except entry 10.
[b] Isolated yield.

$Al(OTf)_3$ efficiently catalyzed the direct substitution of **7f** and **7g** with **9i** (entries 14 and 15). To the best of our knowledge, this is the first example of catalytic direct substitution of benzhydrols with an electron-withdrawing Br, I, NO_2, or CN substituent.

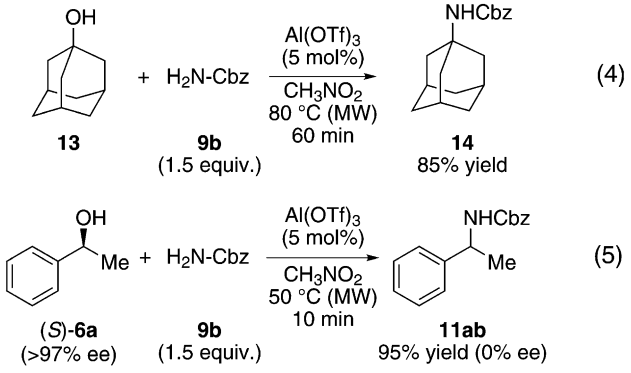
To compare $Al(OTf)_3$ with other efficient catalysts, we performed the direct amination of bis(4-bromophenyl)methanol (**7d**) under exactly the same reaction conditions as shown in entry 12 of Table 3 except using $Sc(OTf)_3$,[3] $Yb(OTf)_3$,[3] $FeCl_3$,[7] or $NaAuCl_4 \cdot 2H_2O$[19] as the catalyst instead of $Al(OTf)_3$. Among them, only $Yb(OTf)_3$ gave the product **12do** in 26% yield, and the reactions using the other catalysts resulted in only recovery of **7d**,[24] clearly showing the superiority of $Al(OTf)_3$ for the reaction of unreactive substrates such as **7d**.

Based on the great success of the direct substitution of functionalized benzhydrols, we performed an efficient synthesis of the non-steroidal aromatase inhibitor letrozole (**8**) through the $Al(OTf)_3$-catalyzed direct substitution reaction. Although direct substitution of bis(4-cyanophenyl)methanol with triazole (**9o**) did not proceed,[24] the coupling product having the aryl bromide unit **12do** was a good precursor of **8**. Pd-catalyzed cyanation of **12do** smoothly proceeded in the presence of a small amount of water (1 mol%)[27] and letrozole (**8**) was obtained in 86% yield [Eq. (3).]



(3)

Finally, experiments using adamantanol (**13**) [Eq. (4)] and optically active (*S*)-**6a** (>97% *ee*) [Eq. (5)] also supported the S_N1-type reaction pathway.



Moreover, the present Al catalysis was also effective for direct substitution with carbon, oxygen, and hydride nucleophiles.[24]

In summary, we have developed $Al(OTf)_3$-catalyzed direct substitutions of allylic, propargylic, and benzylic alcohols with various nitrogen nucleophiles, including acid-sensitive Boc- and Bus-protected amines. This new catalysis was applied to the first general direct substitution of benzhydrols with an electron-withdrawing F, Br, I, NO_2, or CN substituent, affording the corresponding biarylamine derivatives in high yield. One of the coupling products, 1-[bis(4-bromophenyl)methyl]-1*H*-1,2,4-triazole, was successfully converted to the non-steroidal aromatase inhibitor letrozole (**8**) in high yield.

Experimental Section

Typical Procedure

To a 10-mL vessel were added 1-phenylethanol (**6a**) (122.2 mg, 1.0 mmol), benzyl carbamate (**9b**) (226.7 mg, 1.5 mmol, 1.5 equiv.), $Al(OTf)_3$ (23.7 mg, 0.05 mmol, 5 mol%) and $MeNO_2$ (2.0 mL). The reaction vessel was sealed with a rubber cap and then the mixture was subjected to microwave irradiation for 10 min at 50 °C. After 10 min of irradiation, the crude mixture was purified by silica gel column chromatography (hexane:EtOAc = 10:1) to give the product **11ab**; yield: 98%.

Acknowledgements

This work was supported by Grant-in-Aid for Scientific Research (A) and (B) and Scientific Research on Innovative Areas (No. 2105) from MEXT and CREST from JST. Y.N. thanks Global COE Program 'Global Education and Research Center for Bio-Environmental Chemistry' of Osaka University and JSPS Research Fellowship.

References

[1] a) Z. Zhu, J. H. Espenson, *J. Org. Chem.* **1996**, *61*, 324; b) R. V. Ohri, A. T. Radosevich, K. J. Hrovat, C. Musich, D. Huang, T. R. Holman, F. D. Toste, *Org. Lett.* **2005**, *7*, 2501.

[2] a) Y. Nishibayashi, I. Wakiji, M. Hidai, *J. Am. Chem. Soc.* **2000**, *122*, 11019; b) Y. Nishibayashi, M. D. Milton, Y. Inada, M. Yoshikawa, I. Wakiji, M. Hidai, S. Uemura, *Chem. Eur. J.* **2005**, *11*,1433.

[3] a) M. Noji, T. Ohno, K. Fuji, N. Futaba, H. Tajima, K. Ishii, *J. Org. Chem.* **2003**, *68*, 9340; b) W. Huang, Q.-S. Shen, J.-L. Wang, X.-G. Zhou, *Chin. J. Chem.* **2008**, *26*, 729.

[4] a) V. Terrasson, S. Marque, M. Georgy, J.-M. Campagne, D. Prima, *Adv. Synth. Catal.* **2006**, *348*, 2063; b) S. Guo, F. Song, Y. Liu, *Synlett* **2007**, 964; c) Y. Lu, X. Fu, H. Chen, X. Du, X. Jia, Y. Liu, *Adv. Synth. Catal.* **2009**, *351*, 129; d) O. Debleds, C. D. Zott, E. Vrancken, J.-M. Campagne, P. Retailleau, *Adv. Synth. Catal.* **2009**, *351*, 1991; e) M. Georgy, V. Boucard, O.

Debleds, C. Dal Zotto, J.-M. Campagne, *Tetrahedron* **2009**, *65*, 1758; f) P. Mukherjee, R. A. Widenhoefer, *Org. Lett.* **2010**, *12*, 1184; g) X. Giner, P. Trillo, C. Nájera, *J. Organomet. Chem.* **2011**, *696*, 357.

[5] a) P. Vicennati, P. G. Cozzi, *Eur. J. Org. Chem.* **2007**, 2248; b) Y.-L. Liu, L. Liu, D. Wang, Y.-J. Chen, *Tetrahedron* **2009**, *65*, 3473.

[6] a) Z.-P. Zhan, W.-Z. Yang, R.-F. Yang, J.-L. Yu, J.-P. Li, H.-J. Liu, *Chem. Commun.* **2006**, 3352; b) H. Qin, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2007**, *119*, 413; *Angew. Chem. Int. Ed.* **2007**, *46*, 409.

[7] a) Z.-P. Zhan, J.-L. Yu, H.- J. Liu, Y.-Y. Cui, R.-F. Yang, W.-Z. Yang, J.-P. Li, *J. Org. Chem.* **2006**, *71*, 8298; b) U. Jana, S. Maiti, S. Biswas, *Tetrahedron Lett.* **2008**, *49*, 858; c) K. Y. Lee, H. S. Lee, J. N. Kim, *Bull. Korean Chem. Soc.* **2008**, *29*, 1099; d) F. Shi, M. K. Tse, S. L. Zhou, M. M. Pohl, J. Radnik, S. Hubner, K. Jahnisch, A. Bruckner, M. Beller, *J. Am. Chem. Soc.* **2009**, *131*, 1775; e) A. Guérinot, A. Serra-Muns, C. Gnamm, C. Bensoussan, S. Reymond, J. Cossy, *Org. Lett.* **2010**, *12*, 1808; f) J.-J. Yu, L.-M. Wang, F.-L. Guo, J.-Q. Liu, Y. Liu, N. Jiao, *Synth. Commun.* **2011**, *41*, 1609.

[8] B. Sreedhar, P. S. Reddy, M. A. Reddy, B. Neelima, R. Arundhathi, *Tetrahedron Lett.* **2007**, *48*, 8174.

[9] a) C. R. Reddy, P. P. Madhavi, A. S. Reddy, *Tetrahedron Lett.* **2007**, *48*, 7169; b) H. W. Yang, L. Fang, M. Zhang, C. J. Zhu, *Eur. J. Org. Chem.* **2009**, 666; c) M. Zhang, H. Yang, Y. Cheng, Y. Zhu, C. Zhu, *Tetrahedron Lett.* **2010**, *51*, 1176.

[10] a) K. Namba, Y. Nakagawa, H. Yamamoto, H. Imagawa, M. Nishizawa, *Synlett* **2008**, 1719; b) H. Yamamoto, E. Ho, K. Namba, H. Imagawa, M. Nishizawa, *Chem. Eur. J.* **2010**, *16*,11271.

[11] a) S. Podder, J. Choudhury, S. Roy, *J. Org. Chem.* **2007**, *72*, 3129; b) G. Hattori, H. Matsuzawa, Y. Miyake, Y. Nishibayashi, *Angew. Chem.* **2008**, *120*, 3841; *Angew. Chem. Int. Ed.* **2008**, *47*, 3781; c) R. N. Chatterjee, S. Roy, *J. Org. Chem.* **2010**, *75*, 4413.

[12] a) W. Wu, W. Rao, Y. Q. Er, J. K. Loh, C. Y. Poh, P. W. H. Chan, *Tetrahedron Lett.* **2008**, *49*, 2620; b) X. Lin, J. Wang, F. Xu, Y. Wang, *J. Chem. Res.* **2009**, 638.

[13] a) K. Motokura, N. Nakagiri, K. Mori, T. Mizugaki, K. Ebitani, K. Jitsukawa, K. Kaneda, *Org. Lett.* **2006**, *8*, 4617; b) K. Motokura, N. Nakagiri, T. Mizugaki, K. Ebitani, K. Kaneda, *J. Org. Chem.* **2007**, *72*, 6006; c) G.-W. Wang, Y.-B. Shen, X.-L. Wu, *Eur. J. Org. Chem.* **2008**, 4367; d) S. Shirakawa, S. Shimizu, *Synlett* **2008**, 1539.

[14] For representative examples of transition metal-catalyzed direct allylation, see: a) F. Ozawa, H. Okamoto, S. Kawagishi, S. Yamamoto, T. Minami, M. Yoshifuji, *J. Am. Chem. Soc.* **2002**, *124*, 10968; b) Y. Kayaki, T. Koda, T. Ikariya, *J. Org. Chem.* **2004**, *69*, 2595; c) H. Kinoshita, H. Shinokubo, K. Oshima, *Org. Lett.* **2004**, *6*, 4085; d) O. Piechaczyk, M. Doux, L. Ricard, P. le Floch, *Organometallics* **2005**, *24*, 124; e) M. Utsunomiya, Y. Miyamoto, J. Ipposhi, T. Ohshima, K. Mashima, *Org. Lett.* **2007**, *9*, 3371; f) I. Usui, S. Schmidt, M. Keller, B. Breit, *Org. Lett.* **2008**, *10*, 1207; g) T. Ohshima, Y. Miyamoto, J. Ipposhi, Y. Nakahara, M. Utsunomiya, K. Mashima, *J. Am. Chem. Soc.* **2009**, *131*, 14317; h) M. Roggen, E. M. Carreira, *J. Am. Chem. Soc.* **2010**, *132*, 11917.

[15] For recent reviews of direct catalytic amination reaction of alcohols through redox processes, see: a) M. Hamid, P. A. Slatford, J. M. J. Williams, *Adv. Synth. Catal.* **2007**, *349*, 1555; b) T. D. Nixon, M. K. Whittlesey, J. M. J. Williams, *Dalton Trans.* **2009**, 753; c) G. Guillena, D. J. Ramon, M. Yus, *Chem. Rev.* **2010**, *110*, 1611; G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681.

[16] a) A. S. Gonzlez, R. G. Arrays, J. C. Carretero, *Org. Lett.* **2006**, *8*, 2977; b) H. Morimoto, G. Lu, N. Aoyama, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 9588.

[17] a) P. Sun, S. M. Weinreb, M. Shang, *J. Org. Chem.* **1997**, *62*, 8604; b) A. V. Gontcharov, H. Liu, K. B. Sharpless, *Org. Lett.* **1999**, *1*, 783.

[18] I. Sakamoto, N. Izumi, T. Yamada, T. Tsunoda, *Org. Lett.* **2006**, *8*, 71.

[19] T. Ohshima, Y. Nakahara, J. Ipposhi, Y. Miyamoto, K. Mashima, *Chem. Commun.* **2011**, *47*, 8322.

[20] L. P. Hammett, *J. Am. Chem. Soc.* **1937**, *59*, 96.

[21] a) J. L. Anderson, R. W. McNutt, H. Xu, L. E. Smith, E. J. Bilsky, P. Davis, K. C. Rice, *J. Med. Chem.* **1994**, *37*, 2125; b) Y. Bolshan, R. A. Batey, *Org. Lett.* **2005**, *7*, 1481.

[22] a) W. R. Miller, *Cancer Treat. Rev.* **1997**, *23*, 171; b) A. U. Buzdar, S. E. Jones, C. L. Vogel, J. Wolter, P. Plourde, A. Webster, *Cancer* **1997**, *79*, 730; c) J. N. Ingle, P. A. Johnson, V. J. Suman, J. B. Gerstner, J. A. Mailliard, J. K. Camoriano, D. H. Gesme Jr, C. L. Loprinzi, A. K. Hatfield, L. C. Hartmann, *Cancer* **1997**, *80*, 218.

[23] a) D. B. G. Williams, M. Lawton, *Org. Biomol. Chem.* **2005**, *3*, 3269; b) L. Coulombel, M. Rajzmann, M. J.-M. Pons, S. Olivero, E. Duñach, *Chem. Eur. J.* **2006**, *12*, 6356; c) D. B. G. Williams, M. Lawton, *Tetrahedron Lett.* **2006**, *47*, 6557; d) X. Chaminade, S. Chiba, K. Narasaka, E. E. Dunñch, *Tetrahedron Lett.* **2008**, *49*, 2384; e) D. B. G. Williams, M. L. Shaw, M. J. Green, C. W. Holzapfel, *Angew. Chem.* **2008**, *120*, 570; *Angew. Chem. Int. Ed.* **2008**, *47*, 560; f) D. B. G. Williams, S. B. Simelane, M. Lawton, H. H. Kinfe, *Tetrahedron* **2010**, *66*, 4573.

[24] For details, see the Supporting Information.

[25] During the preparation of this manuscript, $Al(OTf)_3$-catalyzed direct substitution of *propargylic alcohols* in CH_3CN was reported, see: M. Gohain, C. Marais, B. C. B. Bezuidenhoudt, *Tetrahedron Lett.* **2012**, *53*, 1048.

[26] a) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154; b) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965; c) G. He, G. Chen, *Angew. Chem.* **2011**, *123*, 5298; *Angew. Chem. Int. Ed.* **2011**, *50*, 5192; d) Y. Zhao, G. Chen, *Org. Lett.* **2011**, *13*, 4850; e) G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3.

[27] P. E. Maligres, M. S. Waters, F. Fleitz, D, Askin, *Tetrahedron Lett.* **1999**, *40*, 8193.