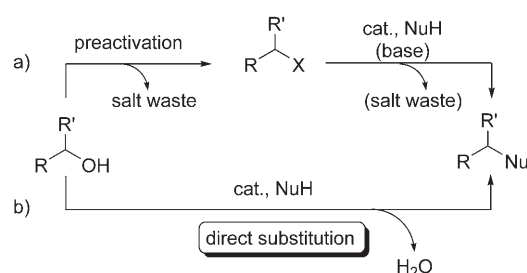


Bismuth-Catalyzed Direct Substitution of the Hydroxy Group in Alcohols with Sulfonamides, Carbamates, and Carboxamides**

Hongbo Qin, Noriyuki Yamagiwa, Shigeki Matsunaga,* and Masakatsu Shibasaki*

The importance of amine derivatives for the synthesis of pharmaceuticals and fine chemicals has aroused considerable interest in allylic and propargylic amination reactions.^[1] Readily available allylic and propargylic alcohols are desirable substrates for the synthesis of allylic and propargylic amines. Substitution of the hydroxy group in alcohols by amine nucleophiles generally requires preactivation of the alcohols because of the poor leaving ability of the hydroxy group. Alcohols are generally transformed into the corresponding halides, carboxylates, carbonates, phosphonates, or related compounds with good leaving groups. The process inevitably produces a stoichiometric amount of salt waste. The substitution of the halides and related compounds also produces salt waste and requires a stoichiometric amount of a base (Scheme 1, path a). In this context, well-established



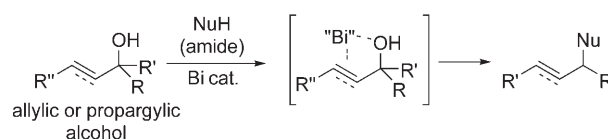
Scheme 1. Substitution of the hydroxy group of an alcohol by: a) preactivation and b) direct catalytic substitution.

transition-metal-catalyzed allylic aminations of allylic acetates and their derivatives have intrinsic drawbacks in terms of atom economy.^[2] Therefore, the direct catalytic substitution of alcohols with amines is desirable. As no stoichiometric hydroxy-group activator is utilized, the products are produced with water as the only waste (Scheme 1, path b).

A number of direct allylic aminations catalyzed by late transition metals have been reported.^[3,4] However, in most

cases either a high reaction temperature is required or a promoter is added to enhance the leaving ability of the hydroxy group. Notable progress was made by using cationic Pd complexes with diphosphinidenecyclobutene ligands (with anilines)^[4a] and a Pd complex in aqueous media (with aryl and alkyl amines).^[4b] The reactions proceeded smoothly at room temperature without any additives,^[4] however, the use of amides, which are less nucleophilic, is still quite rare, and a high reaction temperature is essential.^[5] Nishibayashi, Hidai, Uemura, and co-workers and Toste and co-workers carried out pioneering studies on propargylic substitutions with amides in the presence of a catalytic amount of dinuclear Ru^[6] and oxo-Re complexes^[7] in a catalytic Nicholas reaction.^[8] Good yields were observed with these systems, and a broad range of amine nucleophiles can be used; however, there remains room for improvement, as: a) 3–5 equivalents of the amine nucleophiles were required, b) the reactions were performed at a relatively high temperature (60–65 °C), and c) only secondary propargylic alcohols were used. Herein, we report that bismuth catalysis is suitable for the direct substitution of allylic, propargylic, and benzylic alcohols with sulfonamides, carbamates, and carboxamides under mild reaction conditions. A combination of commercially available Bi(OTf)₃ and KPF₆ (1–5 mol%) promoted the amination reactions at room temperature to give the products in up to 99% yield.

We reported recently the utility of bismuth catalysis^[9] in the hydroamination of 1,3-dienes with amides.^[10] In the hydroamination, a Bi(OTf)₃/MPF₆ (M = K or Cu) system not only acts as a π acid to activate 1,3-dienes, but also acts as a Lewis acid to control the position of attack of the amide nucleophile. We hypothesized that bismuth catalysis would also be suitable for the activation of allylic and propargylic alcohols, as shown in Scheme 2.^[11] To test this hypothesis, the reaction of **1a** with amide **2a** was examined. Bi(OTf)₃/KPF₆ promoted the reaction smoothly, and **3aa** was obtained in 94% yield after 0.2 h (Table 1, entry 1). To study the efficiency of the catalyst, several control experiments were performed (Table 1, entries 2–4). Bi(OTf)₃ alone promoted the reaction, albeit at a lower reaction rate (Table 1, entry 2; 2 h, 76% yield). The reaction was much slower with BiCl₃



Scheme 2. Working hypothesis for the activation of allylic and propargylic alcohols by a Bi catalyst.

[*] H. Qin, Dr. N. Yamagiwa, Dr. S. Matsunaga, Prof. Dr. M. Shibasaki
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-5206
E-mail: smatsuna@mol.f.u-tokyo.ac.jp
mshibasa@mol.f.u-tokyo.ac.jp
Homepage: http://www.f.u-tokyo.ac.jp/~kanai/e_index.html

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Table 1: Optimization of the reaction conditions.

$\text{Ph}-\text{CH}=\text{CH}-\text{CH}(\text{OH})-\text{Ph} + \text{TsNH}_2 \xrightarrow[1,4\text{-dioxane, RT}]{\text{catalyst additives}} \text{Ph}-\text{CH}=\text{CH}-\text{CH}(\text{NH-Ts})-\text{Ph}$						
Entry	Catalyst (mol %)	2a [equiv]	Additive 1 (mol %)	Additive 2	<i>t</i> [h]	Yield [%] ^[a]
1	Bi(OTf) ₃ (10)	2	KPF ₆ (10)	–	0.2	94
2	Bi(OTf) ₃ (10)	2	–	–	2	76
3	BiCl ₃ (10)	2	–	–	12	70
4	–	–	KPF ₆ (10)	–	12	0
5	Bi(OTf) ₃ (2)	1.5	KPF ₆ (2)	–	0.2	94
6	Bi(OTf) ₃ (2)	1.5	KPF ₆ (2)	drierite ^[b]	0.2	96
7	Bi(OTf) ₃ (1)	1.5	KPF ₆ (1)	drierite ^[b]	0.2	95

[a] Yield of the isolated product after column chromatography. [b] A quantity of 45 mg of drierite was used per 0.3 mmol of **1a**. Tf = trifluoromethanesulfonyl, Ts = *para*-toluenesulfonyl.

(Table 1, entry 3; 12 h, 70 % yield).^[12] KPF₆ alone did not afford any of the product **3aa** (Table 1, entry 4). Both Bi(OTf)₃ and KPF₆ were required for high reactivity at room temperature.^[13] With the Bi(OTf)₃/KPF₆ system, the catalyst loading was successfully decreased to 2 mol % (Table 1, entry 5; 94 % yield after 0.2 h). Compound **3aa** was obtained in 96 % yield after 0.2 h in the presence of the desiccant drierite (CaSO₄; Table 1, entry 6).^[14] Under the optimized conditions with drierite, the catalyst loading was decreased to 1 mol % without any problems (Table 1, entry 7; 0.2 h, 95 % yield).

The scope of the reaction with respect to the amide substrate was examined with catalyst concentrations of 2–5 mol % (Table 2). When sulfonamides with electron-donating or electron-withdrawing substituents were used,^[15] the reaction was complete within 0.2–1.5 h, and the corresponding allyl amides were obtained in high yield (Table 2, entries 1–5; 85–99 %). Carbamates **2f–2i** were also suitable substrates and gave the desired products in 97–99 % yield (Table 2, entries 6–9). With carboxamides **2j–2l**, the reaction rate decreased; therefore, the catalyst loading was increased for these substrates. In the presence of 5 mol % of the catalyst, carboxamide **2j** reacted smoothly, and the product was obtained in 86 % yield (Table 2, entry 10; 0.6 h). Carboxamides **2k** and **2l** were much less reactive; the products **3ak** and **3al** were obtained in 88 and 95 % yield, respectively, after 15 or 16 h at room temperature (Table 2, entries 11–12). The reactions of selected substrates in Table 2 were also performed in the absence of drierite. The results of these reactions, which proceeded without any difficulty, are shown in parenthesis (Table 2, entries 1, 2, 7, and 10).^[14]

The scope of the reaction with respect to the alcohol substrate is summarized in Table 3. The present catalyst is also suitable for the reaction of non-benzylic allylic alcohols, such as the cyclic alcohols **1b–1e** (Table 3, entries 1–4; 66–96 % yield) and acyclic alcohols **1f–1i** (Table 3, entries 5–8). The reaction of **1f** afforded **3fa** regioselectively (Table 3, entry 5; 87 %). The desired products were also formed regioselectively from substrates **1g** and **1h**, with substituted aromatic rings, and the *N*-Ts indole **1i** (Table 3, entries 6–8). The reaction of **1i** proceeded smoothly with an equimolar amount of carba-

Table 2: Direct catalytic allylic substitution of **1a** with amides **2a–2l**.^[a]

$\text{Ph}-\text{CH}=\text{CH}-\text{CH}(\text{OH})-\text{Ph} + \text{NuH} \xrightarrow[1,4\text{-dioxane, RT, drierite (CaSO}_4\text{)}]{\text{Bi(OTf)}_3 \text{ (x mol \%), KPF}_6 \text{ (x mol \%)}} \text{Ph}-\text{CH}=\text{CH}-\text{CH}(\text{Nu})-\text{Ph}$						
Entry	NuH 2	Prod.	Cat. [mol %]	<i>t</i> [h]	Yield [%] ^[b]	
1	TsNH ₂	2a 3aa	2	0.2	96 (94) ^[c]	
2	<i>o</i> -NsNH ₂	2b 3ab	2	0.2	93 (82) ^[c]	
3	PhSO ₂ NH ₂	2c 3ac	2	0.2	99	
4	<i>p</i> -CF ₃ C ₆ H ₄ SO ₂ NH ₂	2d 3ad	2	0.2	97	
5	TsNMeH	2e 3ae	2	1.5	85	
6	CbzNH ₂	2f 3af	2	0.2	97	
7		2g 3ag	2	0.2	99 (91) ^[c]	
8		2h 3ah	2	0.2	99	
9		2i 3ai	2	0.2	99	
10		2j 3aj	5	0.6	86 (89) ^[c]	
11		2k 3ak	5	15	88	
12		2l 3al	5	16	95	

[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.45 mmol, 1.5 equiv), Bi(OTf)₃ (0.015 mmol, 5 mol %), KPF₆ (0.015 mmol, 5 mol %), drierite (45 mg), 1,4-dioxane (1.0 mL), room temperature. [b] Yield of the isolated, analytically pure compound after column chromatography. [c] The number in parenthesis is the yield of the isolated product when the reaction was performed in the absence of drierite. Cbz = carbobenzyloxy, *o*-Ns = *ortho*-nitrobenzenesulfonyl.

mate **2g** (Table 3, entry 8; 84 %). With **1j** and **2e** the reaction proceeded regioselectively to afford **3je** (Table 3, entry 9), which was also obtained starting from **1k** (entry 10). Alcohol **1l** also reacted at the less hindered terminal carbon atom to give **3le** (Table 3, entry 11; 60 %). The reaction of alcohol **1m** afforded **3me** as a mixture of regioisomers in a ratio of 6.7:1 (Table 3, entry 12). Diene **3ne** was obtained selectively from alcohol **1n** (Table 3, entry 13) and treatment of the tertiary alcohol **1o** with **2g** afforded the regioisomer **3og** selectively (Table 3, entry 14; *E* isomer). The results in entries 5–14 of Table 3 suggest that the amides attack selectively the sterically less hindered carbon atom of the allylic alcohol functionality. On the other hand, the propargylic alcohols **1p–1s** reacted regioselectively at the propargylic position (Table 3, entries 15–18).^[6,7,16] Allenic products of amide attack at the triple bond were not observed for **1p–1s**. It is noteworthy that the desired products were obtained when the tertiary propargylic alcohols **1r** and **1s** were used. Previously reported propargylic-amination catalysts^[6,7] were not applied to tertiary propargylic alcohols, possibly because of a competitive dehydration reaction to afford enynes. The addition of drierite was essential for the formation of products **3ra** and **3sf** in greater than 60 % yield (Table 3, entries 17–18).^[14] This Bi catalysis was also applicable to the benzylic

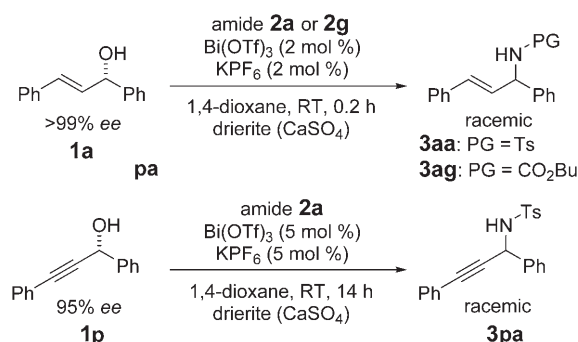
Table 3: Direct catalytic substitution of allylic, propargylic, and benzylic alcohols **1b–1t** with amides **2**.^[a]

$\text{alcohol} + \text{NuH} \xrightarrow[\text{drierite (CaSO}_4\text{)}]{\text{Bi(OTf)}_3 \text{ (5 mol \%)} \atop \text{KPF}_6 \text{ (5 mol \%)} \atop \text{dioxane, RT}} \text{R}^1\text{---C}(\text{Nu})\text{---R}^2\text{---R}^3$							
Entry	Alcohol 1	1b–1t	2 (1–3 equiv)	NuH (equiv)	Product	<i>t</i> [h]	Yield [%] ^[b]
1		1b	2a (2)		3ba	2	96
2		1c	2e (3)		3ce	2	80
3		1d	2e (3)		3de	2	66
4		1e	2e (3)		3ee	17	74
5		1f	2a (1.5)		3fa	17	87
6		1g	2e (3)		3ge	0.2	99
7		1h	2e (3)		3he	0.2	61
8		1i	2g (1)		3ig	0.2	84
9		1j	2e (3)		3je	7	63
10		1k	2e (3)		3je	12	62
11		1l	2e (3)		3le	2	60
12 ^[c]		1m	2e (3)		3me ^[d]	1	55
13		1n	2e (2)		3ne	1	69
14		1o	2g (1.5)		3og	0.1	60
15		1p	2a (1.5)		3pa	18	82
16		1q	2a (1.5)		3qa	8	78
17		1r	2a (2)		3ra	4	63
18		1s	2f (2)		3sf	5	65
19		1t	2e (2)		3te	7	60

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.3–0.9 mmol, 1–3 equiv), Bi(OTf)₃ (0.015 mmol, 5 mol %), KPF₆ (0.015 mmol, 5 mol %), drierite (45 mg), 1,4-dioxane (1.0 mL), room temperature (unless otherwise noted). [b] Yield of the isolated, analytically pure compound after column chromatography. [c] The reaction was performed at 40 °C. [d] Major/minor = 6.7:1.

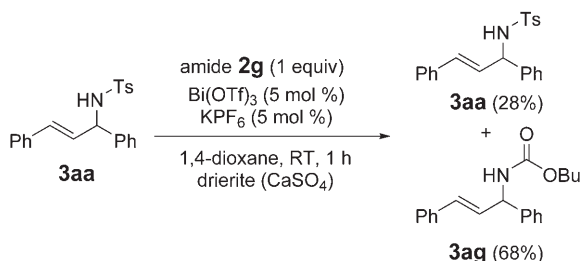
alcohol **1t**, the reaction of which with **2e** gave **3te** in 60% yield after 7 h at room temperature (Table 3, entry 19).

When the optically active alcohols **1a** and **1p** and amides **2a** and **2g** were used, only the racemic products **3aa**, **3ag**, and **3pa** were obtained (Scheme 3). This result suggests a reaction



Scheme 3. Allylic and propargylic amination of the optically active alcohols **1a** and **1i**.

mechanism in which a carbenium intermediate is formed. The observed racemization could also be ascribed to the reversibility of the reaction. The result shown in Scheme 4 indicates that the reaction is reversible under the reaction conditions. When **3aa** was treated with $\text{Bi}(\text{OTf})_3/\text{KPF}_6$ (5 mol %) and carbamate **2g** (1 equiv), a mixture of **3aa** (28%) and **3ag** (68%) was recovered after 1 h. It appears that $\text{Bi}(\text{OTf})_3/\text{KPF}_6$ cleaved the C–N bond in **3aa**, and that **3ag** is thermodynamically more stable than **3aa**.^[17,18]



Scheme 4. Reversibility of the allylic amination.

In summary, we have developed a bismuth-catalyzed direct substitution of allylic, propargylic, and benzylic alcohols with sulfonamides, carbamates, and carboxamides. A combination of commercially available $\text{Bi}(\text{OTf})_3$ and KPF_6 (1–5 mol %) catalyzed the reactions effectively, mostly at room temperature, to give the products in 55–99% yield. Further applications of the $\text{Bi}(\text{OTf})_3/\text{KPF}_6$ system as well as mechanistic studies of the present reaction are under investigation.

Experimental Section

1,4-Dioxane (1.0 mL) was added to a mixture of $\text{Bi}(\text{OTf})_3$ (3.92 mg, 0.006 mmol), KPF_6 (1.11 mg, 0.006 mmol), and drierite (45 mg) in a test tube. The resulting mixture was stirred for 10 min at room

temperature, then TsNH_2 (**2a**; 77.0 mg, 0.45 mmol) was added, followed by **1a** (63.1 mg, 0.3 mmol). The reaction mixture was stirred at 23–26°C for 10 min. It was then diluted with diethyl ether (5 mL), and silica gel (ca. 3 g) was added. After filtration and washing with diethyl ether, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate 8:1–6:1) to give **3aa** (96%) as a colorless solid.

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- [1] For reviews, see: a) J. Tsuji, *Transition Metal Reagents and Catalysis*, Wiley-VCH, Weinheim, **2000**; b) B. M. Trost, C. Lee in *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, Weinheim, **2000**; c) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921.
- [2] B. M. Trost, *Science* **1991**, *254*, 1471.
- [3] For a recent review of palladium-catalyzed C–N bond formation from alcohols, see: a) J. Muzart, *Tetrahedron* **2005**, *61*, 4179; for a review of the palladium-catalyzed activation of allylic alcohols, see: b) Y. Tamaru, *Eur. J. Org. Chem.* **2005**, 2647.
- [4] For examples of allylic aminations with anilines at room temperature without an additive, see: a) F. Ozawa, H. Okamoto, S. Kawagishi, S. Yamamoto, T. Minami, M. Yoshifuji, *J. Am. Chem. Soc.* **2002**, *124*, 10968; for examples of allylic aminations with aryl and alkyl amines at room temperature without an additive, see: b) H. Kinoshita, H. Shinokubo, K. Oshima, *Org. Lett.* **2004**, *6*, 4085; for allylic aminations with Et_3B (30 mol %) as an additive at room temperature, see: c) M. Kimura, M. Futamata, K. Shibata, Y. Tamaru, *Chem. Commun.* **2003**, 234; for allylic aminations without an additive at 80°C, see: d) Y. Kayaki, T. Koda, T. Ikariya, *J. Org. Chem.* **2004**, *69*, 2595; for other examples of Pd-catalyzed aminations at high reaction temperatures and/or in the presence of a stoichiometric or catalytic amount of an additive, such as an inorganic acid, CO_2 , an organic acid, or a Lewis acid, see ref. [3a] and references therein.
- [5] Only one example of the Pd-catalyzed allylation of carboxamides, sulfonamides, and imides has been reported (in articles in Japanese). However, a high reaction temperature (120–140°C) was essential for the allylation: a) J. Qü, Y. Ishimura, N. Nagato, *Nippon Kagaku Kaishi* **1996**, 256; b) J. Qü, Y. Ishimura, N. Nagato, *Nippon Kagaku Kaishi* **1996**, 525.
- [6] 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, and references therein; for other applications of the dinuclear Ru complex in direct propargylic substitutions with other nucleophiles, see: c) Y. Inada, Y. Nishibayashi, S. Uemura, *Angew. Chem.* **2005**, *117*, 7893; *Angew. Chem. Int. Ed.* **2005**, *44*, 7715; d) Y. Nishibayashi, A. Shinoda, Y. Miyake, H. Matsuzawa, M. Sato, *Angew. Chem.* **2006**, *118*, 4953; *Angew. Chem. Int. Ed.* **2006**, *45*, 4835, and references therein.
- [7] a) R. V. Ohri, A. T. Radosevich, K. J. Hrovat, C. Musich, D. Huang, T. R. Holman, F. D. Toste, *Org. Lett.* **2005**, *7*, 2501; for other applications of the oxo-Re complexes in direct propargylic substitutions with other nucleophiles, see: b) B. D. Sherry, A. T. Radosevich, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 6076; c) M. R. Luzung, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 15760, and references therein.
- [8] For other recent examples of direct substitutions of allylic, propargylic, and/or benzylic alcohols with various nucleophiles

- without the use of Pd complexes, see (allylic substitutions): a) M. Yasuda, T. Somyo, A. Baba, *Angew. Chem.* **2006**, *118*, 807; *Angew. Chem. Int. Ed.* **2006**, *45*, 793, and references therein; b) K. Motokura, N. Fujita, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem.* **2006**, *118*, 2667; *Angew. Chem. Int. Ed.* **2006**, *45*, 2605; (propargylic substitutions): c) M. Gregory, V. Boucard, J.-M. Campagne, *J. Am. Chem. Soc.* **2005**, *127*, 14180; d) R. Sanz, A. Martínez, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Eur. J. Org. Chem.* **2006**, 1383; (benzylic substitutions): e) Z. Zhu, J. H. Espenson, *J. Org. Chem.* **1996**, *61*, 324; f) M. Noji, T. Ohno, K. Fuji, N. Futaba, H. Tajima, K. Ishii, *J. Org. Chem.* **2003**, *68*, 9340, and references therein. For other examples in which Pd complexes are used, see ref. [3].
- [9] For a review of the use of Bi(OTf)₃ in organic synthesis, see: a) H. Gaspard-Illoughmane, C. Le Roux, *Eur. J. Org. Chem.* **2004**, 2517; for a chiral Bi(OTf)₃ complex, see the following review: b) S. Kobayashi, C. Ogawa, *Chem. Eur. J.* **2006**, *12*, 5954, and references therein.
- [10] H. Qin, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 1611.
- [11] For the concept of σ–π chelation, see: a) N. Asao, T. Asano, T. Ohishi, Y. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 4817; b) N. Asao, T. Ohishi, K. Sato, Y. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 6931; see also ref. [8c].
- [12] During the preparation of this manuscript, a BiCl₃-catalyzed direct propargylic substitution of secondary propargyl alcohols with TsNH₂ (**2a**) and benzamide (**2j**) was reported; however, a relatively high reaction temperature was required (60–35 °C, 46–80% yield): Z. Zhan, W. Yang, R. Yang, J. Yu, J. Li, H. Liu, *Chem. Commun.* **2006**, 3352.
- [13] A combination of Bi(OTf)₃ and Cu(CH₃CN)₄PF₆ was as effective as Bi(OTf)₃ with KPF₆. KPF₆ was selected for the present study because KPF₆ is less expensive than Cu(CH₃CN)₄PF₆. On the basis of mechanistic studies on the Bi(OTf)₃/MPF₆ system in ref. [10], we speculate that KPF₆ is required to generate a more reactive cationic Bi(OTf)₂PF₆ species by anion exchange.
- [14] Although the addition of a desiccant (drierite: CaSO₄) is not essential for reactive substrate combinations, such as **1a** with **2a**, the use of drierite is recommended for good reproducibility with less reactive substrates in Table 3.
- [15] For the utility of the *o*-Ns group in organic synthesis, see the following review: T. Kan, T. Fukuyama, *Chem. Commun.* **2004**, 353.
- [16] For recent catalytic regioselective propargylic substitutions with sulfonamides, see also: P. A. Evans, M. J. Lawler, *Angew. Chem.* **2006**, *118*, 5092; *Angew. Chem. Int. Ed.* **2006**, *45*, 4970, and references therein.
- [17] We assume that the desiccant (drierite) has a positive effect on the reaction of substrates in Table 3 because of the reversibility of the reaction.
- [18] The possibility that TfOH, generated from Bi(OTf)₃ and H₂O, promotes the present reaction (Tables 1–3) can not be excluded completely, even in the presence of desiccant. However, the result of the reaction in Scheme 4, in which no H₂O is generated, supports the hypothesis that Bi(OTf)₃/KPF₆ functions as a catalyst.