DOI: 10.1002/ejoc.201301372

Iron-Catalyzed π-Activated C–O Ether Bond Cleavage with C–C and C–H Bond Formation

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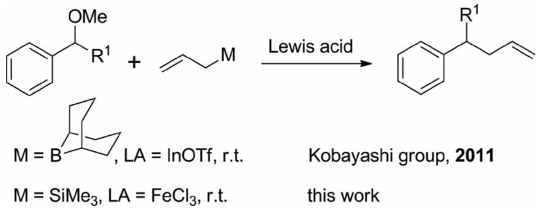
Keywords: Synthetic methods / Allylation / C–O activation / C–C coupling / Hydrogen transfer / Iron

A novel and efficient allylic alkylation reaction between π-activated ethers and allylsilane was realized under mild conditions through iron(III)-catalyzed C_{sp^3}–O ether bond cleavage. The present protocol provides an attractive approach for the construction of sp^3–sp^3 C–C bonds and can be potentially applied for the selective reduction of benzyl and allyl ethers to their corresponding hydrocarbon compounds by using triethylsilane as a hydride-transfer reagent.

Introduction

Carbon–carbon bond formation by using oxygen-based electrophiles as coupling partners is an attractive strategy in terms of both the accessibility of the starting materials and environmental concerns.[1] Ethers are readily available and green compounds that have garnered much attention over the past decade as novel electrophiles in transition-metal-catalyzed cross-coupling reactions, such as using aryl and vinyl ethers instead of halides in Suzuki and Kumada couplings.[2] In contrast to the considerable efforts devoted to exploring C_{sp^2}–O type ethers (e.g., phenol- and enol-derived ethers) as coupling partners to construct C_{sp^3}–C_{sp^2} bonds, very few reaction systems have been developed for the catalytic activation of C_{sp^3}–O ether bonds for the construction of C_{sp^3}–C_{sp^3} bonds,[3] because of the high bond dissociation energy of these bonds and the poor leaving ability of the OR group in alkyl ethers.[1,4] The direct and selective activation of the C_{sp^3}–O bond in unactivated ethers still remains particularly challenging to chemists. Recently, several Ni-complex-catalyzed coupling reactions between benzylic ethers and Grignard reagents to construct C_{sp^3}–C_{sp^3} bonds have been developed by Shi,[5] Jarvo,[6] and others. Nevertheless, the application of soft nucleophiles as coupling partners to such transformations is rare. In 2011, the Kobayashi group uncovered an efficient method for the construction of C_{sp^3}–C_{sp^3} bonds by coupling benzyl and allyl ethers with allyl boron reagents under the catalysis of InOTf (Tf = trifluoromethylsulfonyl).[7] This protocol is of particular interest, as it not only provides efficient access to C_{sp^3}–C_{sp^3} bonds but it also introduces a C=C bond at the same time for further synthetic transformations. Strikingly, only 9-BBN-derived allylborane (BBN = 9-borabicyclo[3.3.1]nonane; Scheme 1) can be used as a nucleophile in this main-group-metal-catalyzed alkyl–allyl cross-coupling reaction; cheaper and conventional allylsilane reagents were shown to be thoroughly incompetent in this transformation.[8–10] Very recently, we reported a novel procedure for the construction of carbon–nitrogen bonds through an iron-catalyzed ether C_{sp^3}–O cleavage protocol.[11] In continuation of our study on the application of ethers as electrophiles in organic synthesis, we are eager to extend this strategy to the assembly of carbon–carbon bonds. A careful literature survey revealed that no precedent for the use of the ecologically benign Lewis acid $FeCl_3$ in combination with readily available ethers and an allylsilane for the construction of C_{sp^3}–C_{sp^3} bonds has been reported; herein, we wish to report our preliminary results on this reaction.



Scheme 1. Methods for the allylation of benzyl ethers.

Results and Discussion

Our work started by testing the allylic alkylation of ether **1a** with allyltrimethylsilane (**2a**, 1.5 equiv.) in 1,2-dichloroethane in the presence of $FeCl_3$ (10 mol-%) in air. The reaction proceeded smoothly at room temperature; the substrate

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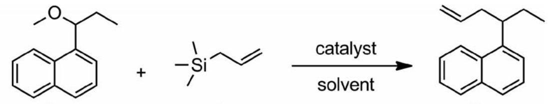
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301372.

was completely consumed within 2.5 h to give desired allylation product **3a** in 69% yield (Table 1, entry 1). Encouraged by this result, a range of solvents were explored (Table 1, entries 1–10). Among the solvents used, the reaction performed in CH_2Cl_2 was significantly better than those performed in other solvents, which led to the isolation of allylated product **3a** in almost quantitative yield (Table 1, entry 10). Unfortunately, lowering the amount of **2a** from 1.5 to 1.3 equiv. (relative to **1a**) or the amount of $FeCl_3$ from 10 to 5 mol-% was clearly unfavorable for the reaction, as the yields of desired product **3a** decreased considerably to 83 and 75%, respectively (Table 1, entries 11 and 12). The reaction showed strong catalyst dependence; no conversion was observed in the absence of $FeCl_3$ (Table 1, entry 13). Ether **1a** could not undergo this transformation under the catalysis of other Lewis acids such as $FeCl_2$, $Fe(acac)_3$, $Fe(acac)_2$, $BF_3{\cdot}OEt_2$, CuI, $Cu(acac)_2$, $Cu(OAc)_2$, and $ZnCl_2$ (Table 1, entries 15–22; acac = acetylacetonate), whereas only 46% yield of the product was formed in the case of $FeCl_3{\cdot}6H_2O$ (Table 1, entry 14). Furthermore, among the examined Brønsted acids (e.g., TfOH and HCl), only triflic acid exhibited catalytic activity in this transformation, and a moderate yield of **3a** was obtained (Table 1, entry 23), which reveals that $FeCl_3$ acts as the true catalyst for the allylation of ether **1a**.

Table 1. Optimization of the reaction conditions.[a]



1a **2a** **3a**

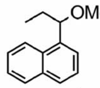
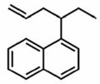
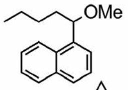
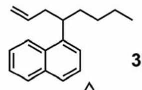
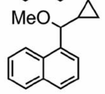
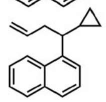
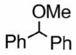
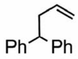
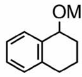
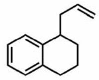
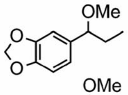
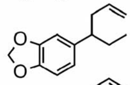
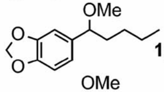
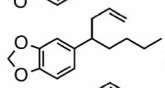
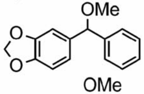
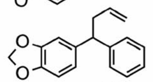
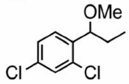
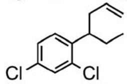
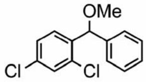
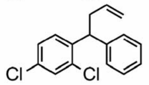
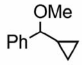
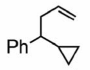
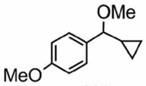
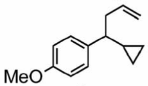
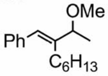
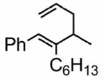
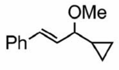
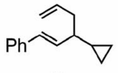
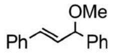
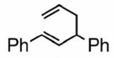
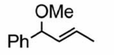
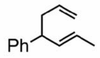
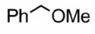
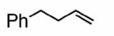
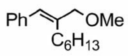
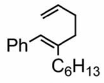
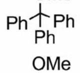
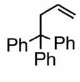
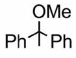
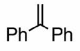
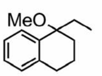
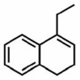
Entry	**2a** (equiv.)	Catalyst (mol-%)	Solvent	Time [h]	Yield [%][b]
1	1.5	$FeCl_3$ (10)	CH_2ClCH_2Cl	2.5	69
2	1.5	$FeCl_3$ (10)	toluene	2.5	62
3	1.5	$FeCl_3$ (10)	$CHCl_3$	2.5	60
4	1.5	$FeCl_3$ (10)	CH_3NO_2	2.5	39
5	1.5	$FeCl_3$ (10)	DMF	2.5	0
6	1.5	$FeCl_3$ (10)	benzene	2.5	56
7	1.5	$FeCl_3$ (10)	THF	2.5	0
8	1.5	$FeCl_3$ (10)	EtOAc	2.5	trace
9	1.5	$FeCl_3$ (10)	CH_3CN	2.5	19
10	1.5	$FeCl_3$ (10)	CH_2Cl_2	0.5	99
11	1.5	$FeCl_3$ (5)	CH_2Cl_2	0.5	75
12	1.3	$FeCl_3$ (10)	CH_2Cl_2	0.5	83
13	1.5	none	CH_2Cl_2	4.0	0
14	1.5	$FeCl_3{\cdot}6H_2O$ (10)	CH_2Cl_2	0.5	46
15	1.5	$FeCl_2$ (10)	CH_2Cl_2	4.0	0
16	1.5	$Fe(acac)_3$ (10)	CH_2Cl_2	4.0	0
17	1.5	$Fe(acac)_3$ (10)	CH_2Cl_2	4.0	0
18	1.5	$BF_3{\cdot}OEt_2$ (10)	CH_2Cl_2	0.5	trace
19	1.5	CuI (10)	CH_2Cl_2	4.0	0
20	1.5	$Cu(acac)_2$ (10)	CH_2Cl_2	4.0	0
21	1.5	$Cu(OAc)_2$ (10)	CH_2Cl_2	4.0	0
22	1.5	$ZnCl_2$(10)	CH_2Cl_2	4.0	0
23[c]	1.5	TfOH (10)	CH_2Cl_2	11	67

[a] Reaction conditions: **1a** (0.35 mmol), solvent (4 mL), r.t., in air. [b] Yield of isolated product. [c] 40 °C.

With the optimized reaction conditions in hand, the scope of this $FeCl_3$-catalyzed allylic alkylation reaction was further expanded to a variety of ethers, and the results are summarized in Table 2. A wide range of secondary benzylic and allylic ethers including those bearing aromatic chloro or methoxy groups, C=C bonds, cyclopropyl, and acetal groups were compatible with the optimal reaction conditions, and all of these substrates furnished the corresponding products in good to excellent yields within a short period of time at room temperature (Table 2, entries 1–16). Primary benzylic ether **1q** was unable to undergo this conversion even under harsh reaction conditions (Table 2, entry 17), presumably because of its higher bond dissociation energy. In contrast, effective transformation was observed in the reaction of primary allylic methyl ether **1r** with **2a** to give corresponding product **3r** in 62% yield (Table 2, entry 18). Upon subjecting tertiary benzylic ethers **1s**, **1t**, and **1u** to this reaction, the results were rather different. Triphenylmethyl methyl ether (**1s**) smoothly underwent this allylation reaction with a prolonged reaction time to provide desired product **3s** in 98% yield (Table 2, entry 19). However, **1t** and **1u** were hampered by a competing elimination reaction, which resulted in the isolation of elimination products **3t** and **3u** exclusively without the observation of the desired allylated products (Table 2, entries 20 and 21). These results reveal that the steric properties of the benzylic ethers have a clear influence on the outcome of the reaction. More sterically hindered tertiary benzylic methyl ethers that have hydrogen atoms in the β position tend to undergo rapid β-hydride elimination to give olefins rather than substituted products. With respect to electronic effects, the reaction was facilitated by electron-rich benzylic methyl ethers bearing an electron-donating group on the phenyl ring. Ethers containing electron-withdrawing groups underwent a slower allylation reaction to give the corresponding products in relatively lower yields (Table 2, entries 6 and 9; 8 and 10). Acid-sensitive groups such as the acetal and cyclopropyl groups tolerated the reaction conditions. Furthermore, the reaction was not sensitive to water and air, which clearly confirms the advantage of this reaction system. In addition, upon submitting (*E*)-1-methoxy-1-phenylbut-2-ene (**1p**) to this allylation reaction, thermodynamically favored C–C double-bond isomeric product **3p′** together with un-rearranged product **3p** were obtained in 70% yield as a 2.4:1 mixture of unseparated regioisomers (Table 2, entry 16; see Supporting Information for details); this suggests that the reaction most likely proceeds through a carbocation pathway. This hypothesis is consistent with our previous mechanistic studies.[11] Notably, non-π-activated ethers, such as 2-phenylethyl methyl ether, were found to be unsuitable substrates for this transformation even under harsh reaction conditions.[12]

Subsequently, triethylsilane (**2b**) was tested as a nucleophile for this transformation under typical reaction conditions for the reduction of the selected ethers to hydrocarbons (Table 3). To our delight, hydride transfer from Et_3SiH to benzylic and allylic C–O ether bonds was successful under the mild conditions, and the reaction even took place in the presence of other groups such as an aromatic methoxy group, a C=C bond, and a cyclopropyl group. Given that methyl ethers could serve as useful protecting

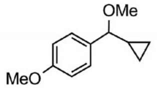
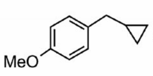
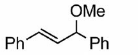
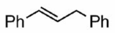
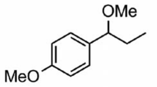
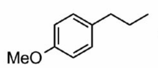
Table 2. Allylation of ethers with allyltrimethylsilane.[a]

Entry	Ether		Product		Time [h]	Yield [%][b]
1		**1a**		**3a**	0.5	99
2		**1b**		**3b**	2.8	99
3		**1c**		**3c**	0.5	92
4		**1d**		**3d**	1.5	99
5		**1e**		**3e**	1.5	82
6		**1f**		**3f**	1.6	99
7		**1g**		**3g**	1.6	99
8		**1h**		**3h**	0.7	99
9		**1i**		**3i**	5.4	89
10		**1j**		**3j**	2.4	77
11		**1k**		**3k**	2	65
12		**1l**		**3l**	0.5	99
13		**1m**		**3m**	1.5	78
14		**1n**		**3n**	1	85
15		**1o**		**3o**	0.5	91
16		**1p**		**3p**[c]	1.5	70
17		**1q**		**3q**	8	n.r.
18		**1r**		**3r**	3.2	62
19		**1s**		**3s**	6.5	98
20		**1t**		**3t**	1	65
21		**1u**		**3u**	2	99

[a] Reaction conditions: benzylic ether (0.35 mmol), **2a** (0.53 mmol), CH_2Cl_2 (4 mL), $FeCl_3$ (10 mol-%), r.t., in air. [b] Yield of isolated product. [c] Mixture of C–C double-bond regioisomers, 2.4:1 (see Supporting Information).

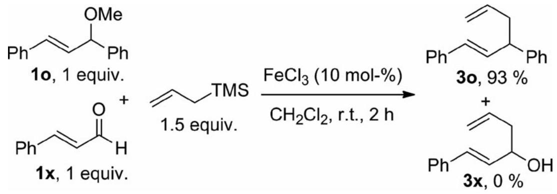
groups for alcohols in organic synthesis,[13] this catalytic system can be potentially used as an efficient method for the reduction of benzylic and allylic alcohols and ethers to their corresponding hydrocarbon compounds.

Table 3. Catalytic reduction of ethers with triethylsilane.[a]

Entry	Ether		Product		Time [h]	Yield [%][b]
1		**1l**		**4a**	1.5	99
2		**1o**		**4b**	2.0	89
3		**1v**		**4c**	1.5	66

[a] Reaction conditions: benzylic ether (0.35 mmol), **2b** (0.53 mmol), CH_2Cl_2 (4 mL), $FeCl_3$ (10 mol-%), r.t., in air. [b] Yield of isolated product.

Finally, with the aim of investigating the reactivity of ethers and aldehydes,[8] the reaction of equimolar amounts of 3-methoxy-1,3-diphenylprop-1-ene (**1o**) and cinnamaldehyde (**1x**) with allyltrimethylsilane (**2a**) was studied (Scheme 2). Under the optimized reaction conditions, only ether **1o** underwent this transformation to afford desired allylation product **3o** in 93 % yield, whereas aldehyde **1x** was completely recovered. This demonstrates that ethers are more suitable electrophiles in this catalytic system.



Scheme 2. Selective allylation of ether against aldehyde.

Conclusions

In summary, we have demonstrated a convenient and economical method for the cross-coupling of benzyl/allyl ethers with allylsilane through iron-catalyzed C_{sp^3}–O ether bond cleavage under mild conditions. The present protocol provides an attractive approach to construct sp^3–sp^3 C–C bonds together with the introduction of a C=C bond in high efficiency, and it can be used for the selective reduction of benzylic and allylic ethers to their corresponding hydrocarbon compounds by employing triethylsilane as a hydride-transfer reagent. Further exploration of ethers as electrophiles in organic synthesis through Lewis acid catalyzed C–O bond activation is in progress in our laboratory.

Experimental Section

General Information: Reactions were monitored by analytical thin-layer chromatography (TLC) by using ultraviolet light, phosphomolybdic acid, or KMnO$_4$ for visualization. Purification of products was accomplished by flash chromatography on silica gel (200–300 mesh) and the purified compounds showed a single spot by analytical TLC. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, by using CDCl$_3$ as the solvent with tetramethylsilane as an internal standard. High-resolution mass spectra (HRMS) were performed with an ICP-MS or ITCI-Orbitrap Elite spectrometer. Melting points were measured with a micromelting apparatus.

Typical Procedure for Iron-Catalyzed Allylation: Allyltrimethylsilane (**2a**) (60.6 mg, 0.53 mmol, 1.5 equiv.), ether **1a**–**u** (0.35 mmol, 1.0 equiv.), and FeCl$_3$ (5.7 mg, 0.035 mmol, 10 mol-%) were added successively under ambient temperature to CH$_2$Cl$_2$ (4 mL) in air. After stirring at room temperature for the appropriate time (monitored by TLC), the reaction was quenched by the addition of H$_2$O (3 mL) and then the mixture was extracted with ethyl acetate (3 × 3 mL). The combined organic layer was washed with brine, dried with Na$_2$SO$_4$, and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether or petroleum ether/ethyl acetate) to afford corresponding product **3a**–**u**.

Supporting Information (see footnote on the first page of this article): Detailed description of the experimental procedures and analytical data for all compounds.

Acknowledgments

The authors thank the National Natural Science Foundation of China (NSFC) (grant number 21162013) and Beijing National Laboratory for Molecular Sciences (BNLMS) for financial support and Prof. Zhi-Xiang Yu and Dr. Yong Liang for helpful discussions.

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[1] a) D.-G. Yu, B.-J. Li, Z.-J. Shi, *Acc. Chem. Res.* **2010**, *43*, 1486–1495, and references cited therein; b) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A. M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346–1416.

[2] a) B.-J. Li, D.-G. Yu, C.-L. Sun, Z.-J. Shi, *Chem. Eur. J.* **2011**, *17*, 1728–1759; b) J. M. Nichols, L. M. Bishop, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2010**, *132*, 12554–12555; c) G. A. Molander, F. Beaumard, *Org. Lett.* **2010**, *12*, 4022–4025; d) T. Shimasaki, Y. Konno, M. Tobisu, N. Chatani, *Org. Lett.* **2009**, *11*, 4890–4892; e) B.-T. Guan, S.-K. Xiang, T. Wu, Z.-P. Sun, B.-Q. Wang, K.-Q. Zhao, Z.-J. Shi, *Chem. Commun.* **2008**, 1437–1439; f) A. Iijima, H. Amii, *Tetrahedron Lett.* **2008**, *49*, 6013–6015; g) S. Ueno, E. Mizushima, N. Chatani, F. Kakiuchi, *J. Am. Chem. Soc.* **2006**, *128*, 16516–16517; h) J. W. Dankwardt, *Angew. Chem.* **2004**, *116*, 2482–2486; *Angew. Chem. Int. Ed.* **2004**, *43*, 2428–2432; i) E. Wenkert, E. L. Michelotti, C. S. Swingdell, M. Tingoli, *J. Org. Chem.* **1984**, *49*, 4894–4899.

[3] a) C. Chen, S. H. Hong, *Org. Lett.* **2012**, *14*, 2992–2995; b) X. Han, Y. Zhang, J. Wu, *J. Am. Chem. Soc.* **2010**, *132*, 4104–4106; c) S. Son, F. D. Toste, *Angew. Chem.* **2010**, *122*, 3879–3882; *Angew. Chem. Int. Ed.* **2010**, *49*, 3791–3794; d) R. E. Mulvey, V. L. Blair, W. Clegg, A. R. Kennedy, J. Klett, L. Russo, *Nat. Chem.* **2010**, *2*, 588–591; e) X. W. Guo, S. G. Pan, J. H. Liu, Z. P. Li, *J. Org. Chem.* **2009**, *74*, 8848–8851; f) B.-Q. Wang, S.-K. Xiang, Z.-P. Sun, B.-T. Guan, P. Hu, K.-Q. Zhao, Z.-J. Shi, *Tetrahedron Lett.* **2008**, *49*, 4310–4312.

[4] Y.-R. Luo (Ed.), *Handbook of Bond Dissociation Energies in Organic Compounds*, CRC Press, Boca Raton, FL, **2005**.

[5] B.-T. Guan, S.-K. Xiang, B.-Q. Wang, Z.-P. Sun, Y. Wang, K.-Q. Zhao, Z.-J. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 3268–3269.

[6] B. L. H. Taylor, E. C. Swift, J. D. Waetzig, E. R. Jarvo, *J. Am. Chem. Soc.* **2011**, *133*, 389–391.

[7] a) H. T. Dao, U. Schneider, S. Kobayashi, *Chem. Asian J.* **2011**, *6*, 2522–2529; b) H. T. Dao, U. Schneider, S. Kobayashi, *Chem. Commun.* **2011**, *47*, 692–694.

[8] Owing to their ready availability and high reactivity, allylsilane reagents are employed as carbon nucleophiles in a number of C–C bond-forming reactions. Traditionally, C_{sp^2}-type electrophiles such as aldehydes and ketones are used as substrates to react with allylsilanes, namely in the Sakurai–Hosomi reaction. For reviews and selected examples, see: a) N. V. Hanhan, Y. C. Tang, N. T. Tran, A. K. Franz, *Org. Lett.* **2012**, *14*, 2218–2221; b) N. Momiyama, H. Nishimoto, M. Terada, *Org. Lett.* **2011**, *13*, 2126–2129; c) U. Schneider, H. T. Dao, S. Kobayashi, *Org. Lett.* **2010**, *12*, 2488–2491; d) J. D. Sellars, P. G. Steel, M. J. Turner, *Chem. Commun.* **2006**, *22*, 2385–2387; e) A. Hosomi, K. Miura, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 835–851; f) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763–2794.

[9] Some methods for allylation of secondary benzylic alcohols with allylsilanes mediated by a catalytic amount of Lewis acid have been reported. However, these methodologies often need relatively costly catalysts and suffered from some undesired competing processes, see: a) G. G. K. S. Narayana Kumar, K. K. Laali, *Org. Biomol. Chem.* **2012**, *10*, 7347–7355; b) L. Y. Chan, S. Kim, W. T. Chung, C. Long, S. Kim, *Synlett* **2011**, *3*, 415–419; c) V. J. Meyer, M. Niggemann, *Eur. J. Org. Chem.* **2011**, 3671–3674; d) J. Han, Z. Cui, J. Wang, Z. Liu, *Synth. Commun.* **2010**, *40*, 2042–2046; e) Y. Kuninobu, E. Ishii, K. Takai, *Angew. Chem.* **2007**, *119*, 3360–3363; *Angew. Chem. Int. Ed.* **2007**, *46*, 3296–3299; f) G. V. M. Sharma, K. L. Reddy, P. S. Lakshmi, R. Ravi, A. C. Kunwar, *J. Org. Chem.* **2006**, *71*, 3967–3969; g) T. Saito, Y. Nishimoto, M. Yasuda, A. Baba, *J. Org. Chem.* **2006**, *71*, 8516–8522; h) S. K. De, R. A. Gibbs, *Tetrahedron Lett.* **2005**, *46*, 8345–8350; i) M. Yasuda, T. Saito, M. Ueba, A. Baba, *Angew. Chem.* **2004**, *116*, 1438–1440; *Angew. Chem. Int. Ed.* **2004**, *43*, 1414–1416.

[10] For the allylation of benzylic acetates and *N*-benzylic sulfonamides with allylsilanes, see: a) G. Onodera, E. Yamamoto, S. Tonegawa, M. Iezumi, R. Takeuchi, *Adv. Synth. Catal.* **2011**, *353*, 2013–2021; b) M. Rubin, V. Gevorgyan, *Org. Lett.* **2001**, *3*, 2705–2707; c) B.-L. Yang, S.-K. Tian, *Chem. Commun.* **2010**, *46*, 6180–6182.

[11] X. Fan, L.-A. Fu, N. Li, H. Lv, X.-M. Cui, Y. Qi, *Org. Biomol. Chem.* **2013**, *11*, 2147–2153.

[12] Besides 2-phenylethyl methyl ether, other unactivated ethers such as 1-methoxydecane and 2-methoxyundecane were also tested in this transformation. However, these substrates remained intact under high temperatures and prolonged reaction times.

[13] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, New York, **1999**, p. 199.

Received: September 10, 2013
Published Online: December 6, 2013