View Article Online / Journal Homepage / Table of Contents for this issue

Catalytic coupling of *N*-benzylic sulfonamides with silylated nucleophiles at room temperature†

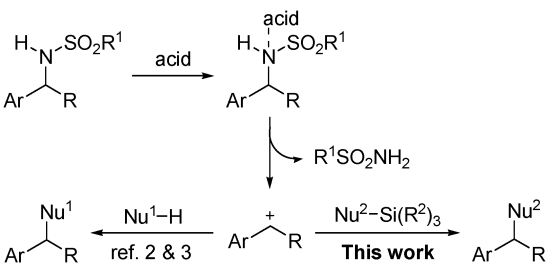
Bai-Ling Yang and Shi-Kai Tian*

Received 5th April 2010, Accepted 30th June 2010
DOI: 10.1039/c0cc00765j

In the presence of 2–10 mol% of Tf_2NH, a range of *N*-benzylic sulfonamides smoothly react with allylic, propargylic, benzylic, or hydrido silanes at room temperature *via* sp^3 carbon–nitrogen bond cleavage to afford structurally diverse products in moderate to excellent yields and with high chemo- and regioselectivity.

Benzylic halides are traditionally employed for the benzylic alkylation of nucleophiles under acidic conditions to construct carbon–carbon and carbon–heteroatom bonds through the cleavage of sp^3 carbon–halogen bonds to generate benzyl cation intermediates (*e.g.* the Friedel–Crafts reaction).[1] Nevertheless, strongly acidic hydrogen halides are inevitably generated as byproducts in the reaction and are able to promote undesired side reactions such as elimination and overalkylation. In this regard, *N*-benzylic sulfonamides have recently emerged as useful benzylic alkylating agents to avoid such problems by yielding primary sulfonamides as byproducts, and consequently, to enhance reaction selectivity and efficiency. Certain Brønsted[2] and Lewis acids[3] have been demonstrated to be able to catalyze the coupling of *N*-benzylic sulfonamides with protic nucleophiles, such as aromatics, active methylene compounds, thiols, thiocarboxylic acids, and sulfinic acids, which involves the catalytic cleavage of the sp^3 carbon–nitrogen bonds to generate benzyl cation intermediates (Scheme 1). Herein, we wish to report an unprecedented coupling reaction of *N*-benzylic sulfonamides with silylated nucleophiles through acid-catalyzed sp^3 carbon–nitrogen bond cleavage at room temperature.

We discovered recently a highly efficient alkylation reaction of protic carbon and sulfur nucleophiles with *N*-benzylic sulfonamides in the presence of a catalytic amount of



Scheme 1 Reactions of *N*-benzylic sulfonamides with various nucleophiles.

Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China. E-mail: tiansk@ustc.edu.cn; Fax: (+86) 551-360-1592; Tel: (+86) 551-360-0871

† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for products. See DOI: 10.1039/c0cc00765j

$ZnCl_2$/TMSCl.[3d] However, such a combination of double Lewis acids proved to be ineffective in catalyzing the coupling of *N*-benzylic sulfonamides with silylated nucleophiles. To find an effective catalyst, we evaluated a number of Brønsted and Lewis acids in the model reaction of *N*-toluenesulfonyl benzhydrylamine (**1a**) with allyltrimethylsilane (**2a**) in dichloromethane at room temperature (Table 1, entries 1–7). While the coupling reaction proceeded very sluggishly with many other acidic catalysts, the use of bis(trifluoromethanesulfonyl)imide (Tf_2NH) resulted in the formation of product **3a** in 57% yield (Table 1, entry 3). It is noteworthy that Tf_2NH has been reported to react with allylic silane **2a** to generate Tf_2N(TMS) that serves as the actual acidic catalyst.[4,5] The efforts to enhance yield proved fruitless by replacing dichloromethane with chloroform, 1,2-dichloroethane, ethyl acetate, acetonitrile, or tetrahydrofuran (Table 1, entries 8–12) and by replacing the toluenesulfonyl group of sulfonamide **1a** with another sulfonyl group, an acyl group, or an alkoxycarbonyl group (Table 1, entries 13–18). Finally, the yield was increased to 79% by employing 2.0 equiv. of allylic silane **2a** in the reaction to suppress the unwanted alkylation of product **3a** with sulfonamide **1a** (Table 1, entry 19).[6]

A range of *N*-bisbenzylic and *N*-monobenzylic sulfonamides coupled with allylic silane **2a** in the presence of 2–10 mol% of Tf_2NH at room temperature to give the corresponding alkene products in moderate to excellent yields (Table 2, entries 1–8). Substituted allyltrimethylsilanes **2b** and **2c** also served as suitable substrates to couple with *N*-benzylic sulfonamides under similar reaction conditions (Table 2, entries 9–11). It is noteworthy that electron-rich aromatic rings and carbon–carbon triple bonds were well tolerated, and no rearrangement was observed for the carbon–carbon double bonds in the alkene products under the acidic reaction conditions.[7] Moreover, excellent chemoselectivity was observed for the cleavage of the sp^3 carbon–nitrogen bonds in *N*-benzylic *N*-alkyl sulfonamides. For example, secondary amine derivative **1i′** exclusively donated its 4-methoxybenzyl group in the coupling reaction with allylic silane **2c** in the presence of 10 mol% of Tf_2NH at room temperature (Table 2, entry 12).

The reaction of optically active *N*-benzylic sulfonamide **1f** (95% ee) with allylic silane **2a** under similar conditions afforded alkene **3f** in nearly racemic form (Table 2, entry 6). This result suggests that a benzyl cation is generated from the corresponding *N*-benzylic sulfonamide through catalytic sp^3 carbon–nitrogen bond cleavage and consequently, the coupling reaction is confirmed to proceed *via* an S_N1 mechanism as shown in Scheme 1.[2,3]

Next, a few other types of silylated carbon nucleophiles were examined with regard to their reactivity toward *N*-benzylic

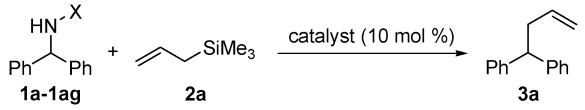
Published on 28 July 2010. Downloaded by UNIVERSITY OF ALABAMA AT BIRMINGHAM on 22/10/2014 12:43:15.

 This journal is © The Royal Society of Chemistry 2010

View Article Online

Published on 28 July 2010. Downloaded by UNIVERSITY OF ALABAMA AT BIRMINGHAM on 22/10/2014 12:43:15.

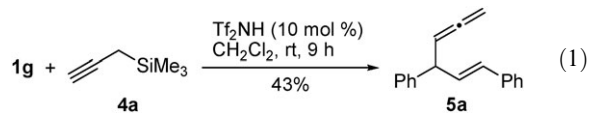
Table 1 Optimization of reaction conditions[a]



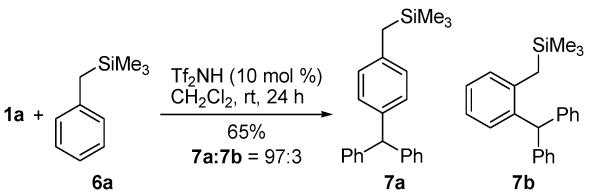
Entry	1a–1ag	X	Catalyst	Solvent	Yield (%)[b]
1	**1a**	Ts	H_2SO_4	CH_2Cl_2	0
2	**1a**	Ts	TfOH	CH_2Cl_2	Trace
3	**1a**	Ts	Tf_2NH	CH_2Cl_2	57
4	**1a**	Ts	TMSOTf	CH_2Cl_2	Trace
5	**1a**	Ts	$FeCl_3$	CH_2Cl_2	Trace
6	**1a**	Ts	$InCl_3{\cdot}4H_2O$	CH_2Cl_2	0
7	**1a**	Ts	$SnCl_4{\cdot}5H_2O$	CH_2Cl_2	14
8	**1a**	Ts	Tf_2NH	$CHCl_3$	19
9	**1a**	Ts	Tf_2NH	$(ClCH_2)_2$	45
10	**1a**	Ts	Tf_2NH	EtOAc	10
11	**1a**	Ts	Tf_2NH	MeCN	14
12	**1a**	Ts	Tf_2NH	THF	0
13	**1ab**	4-$O_2NC_6H_4SO_2$	Tf_2NH	CH_2Cl_2	22
14	**1ac**	2,4,6-$Me_3C_6H_2SO_2$	Tf_2NH	CH_2Cl_2	26
15	**1ad**	2-thienylsulfonyl	Tf_2NH	CH_2Cl_2	19
16	**1ae**	*n*-$C_8H_{17}SO_2$	Tf_2NH	CH_2Cl_2	Trace
17	**1af**	PhCO	Tf_2NH	CH_2Cl_2	0
18	**1ag**	$PhCH_2OCO$	Tf_2NH	CH_2Cl_2	0
19[c]	**1a**	Ts	Tf_2NH	CH_2Cl_2	79

[a] Reaction conditions: amine derivative **1a–1ag** (0.20 mmol), allylic silane **2a** (0.24 mmol), catalyst (10 mol%), solvent (0.30 mL), rt, 24 h. [b] Isolated yield. [c] 0.40 mmol of allylic silane **2a** was used.

sulfonamides under acidic conditions. The desilylative coupling of propargylic silane **4a** with sulfonamide **1g** proceeded smoothly in the presence of 10 mol% Tf_2NH at room temperature to give allene **5a** in a moderate yield (eqn (1)). Notably, a highly regioselective Friedel–Crafts reaction rather than a desilylative coupling reaction took place between benzylic silane **6a** and sulfonamide **1a** under similar reaction conditions (eqn (2)), and significantly, the trimethylsilyl group preserved in the resulting Friedel–Crafts product can serve as a handle for further synthetic elaboration.[8,9]



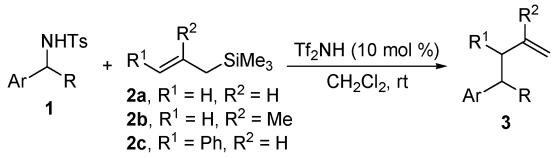
(1)

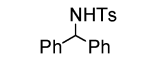
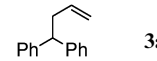
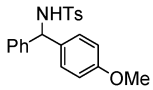
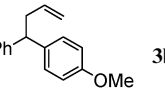
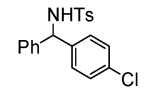
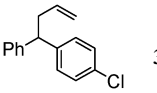
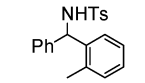
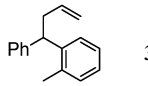
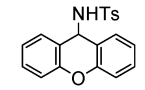
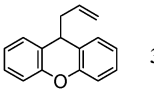
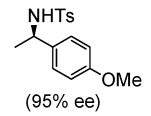
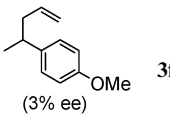
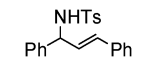
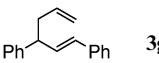
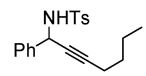
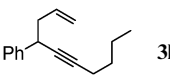
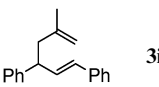
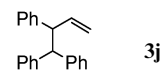
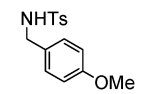
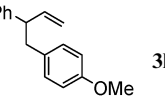
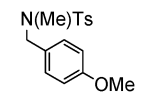


(2)

Finally, a range of *N*-bisbenzylic and *N*-monobenzylic sulfonamides were reduced smoothly with triethylsilane (1.2 equiv.) in the presence of 2–10 mol% of Tf_2NH at room temperature to give the corresponding products in good to excellent yields (Table 3). It is noteworthy that the sulfonamido groups were removed cleanly without reduction of the carbon–carbon multiple bonds present in *N*-benzylic sulfonamides **1g** and **1h** (Table 3, entries 4 and 5).

Table 2 Catalytic coupling of *N*-benzylic sulfonamides with allylic silanes[a]



Entry	Sulfonamide	2	Product	Time/h	Yield (%)[b]
1		**1a** **2a**	 **3a**	24	79
2		**1b** **2a**	 **3b**	22	88
3		**1c** **2a**	 **3c**	30	52
4		**1d** **2a**	 **3d**	24	70
5		**1e** **2a**	 **3e**	3	91
6	 (95% ee)	**1f** **2a**	 (3% ee) **3f**	4	81
7		**1g** **2a**	 **3g**	1	97
8[c]		**1h** **2a**	 **3h**	24	45
9[c]		**1g** **2b**	 **3i**	4	95
10		**1a** **2c**	 **3j**	12	83
11		**1i** **2c**	 **3k**	12	75
12		**1i′** **2c**	**3k**	5	71

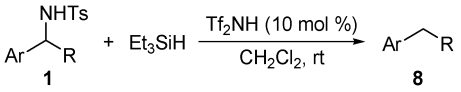
[a] Reaction conditions: sulfonamide **1** (0.20 mmol), allylic silane **2** (0.40 mmol), Tf_2NH (10 mol%), dichloromethane (0.30 mL), rt. [b] Isolated yield. [c] 2 mol% of Tf_2NH was used.

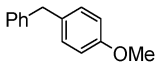
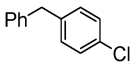
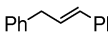
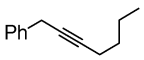
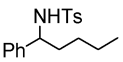
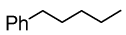
In summary, we have developed an unprecedented coupling reaction of *N*-benzylic sulfonamides with silylated nucleophiles through catalytic sp^3 carbon–nitrogen bond cleavage under acidic conditions. In the presence of 2–10 mol% of

View Article Online

Published on 28 July 2010. Downloaded by UNIVERSITY OF ALABAMA AT BIRMINGHAM on 22/10/2014 12:43:15.

Table 3 Catalytic reduction of *N*-benzylic sulfonamides with triethylsilane[a]



Entry	Sulfonamide	Product		Time/h	Yield (%)[b]
1	**1a**		**8a**	5	93
2	**1b**		**8b**	2	98
3[c]	**1c**		**8c**	2	99
4	**1g**		**8d**	1	98
5	**1h**		**8e**	8	73
6	 **1j**		**8f**	48	71

[a] Reaction conditions: sulfonamide **1** (0.20 mmol), Et_3SiH (0.24 mmol), Tf_2NH (10 mol%), dichloromethane (0.30 mL), rt. [b] Isolated yield. [c] 2 mol% of Tf_2NH was used.

Tf_2NH, a range of *N*-bisbenzylic and *N*-monobenzylic sulfonamides smoothly react with allylic, propargylic, benzylic, or hydrido silanes at room temperature to afford structurally diverse products in moderate to excellent yields and with high chemo- and regioselectivity. This study adds a useful entry to the synthetic applications of sp^3 carbon–nitrogen bond cleavage.

We are grateful for the financial support from the National Natural Science Foundation of China (20972147 and 20732006), the National Basic Research Program of China (973 Program 2010CB833300), and the Chinese Academy of Sciences.

Notes and references

1 For a review, see: G. A. Olah, R. Krishnamurti and G. K. Surya, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 3, p. 293.

2 (*a*) M. R. Seong, H. J. Lee and J. N. Kim, *Tetrahedron Lett.*, 1998, **39**, 6219; (*b*) H.-H. Li, D.-J. Dong and S.-K. Tian, *Eur. J. Org. Chem.*, 2008, 3623; (*c*) D. Enders, A. A. Narine, F. Toulgoat and T. Bisschops, *Angew. Chem., Int. Ed.*, 2008, **47**, 5661; (*d*) C.-R. Liu, M.-B. Li, D.-J. Cheng, C.-F. Yang and S.-K. Tian, *Org. Lett.*, 2009, **11**, 2543; (*e*) Q.-L. He, F.-L. Sun, X.-J. Zheng and S.-L. You, *Synlett*, 2009, 1111; (*f*) F.-L. Sun, X.-J. Zheng, Q. Gu, Q.-L. He and S.-L. You, *Eur. J. Org. Chem.*, 2010, 47.

3 (*a*) J. Esquivias, R. Gómez-Arrayás and J. C. Carretero, *Angew. Chem., Int. Ed.*, 2006, **45**, 629; (*b*) I. Alonso, J. Esquivias, R. Gómez-Arrayás and J. C. Carretero, *J. Org. Chem.*, 2008, **73**, 6401; (*c*) C.-R. Liu, M.-B. Li, C.-F. Yang and S.-K. Tian, *Chem. Commun.*, 2008, 1249; (*d*) C.-R. Liu, M.-B. Li, C.-F. Yang and S.-K. Tian, *Chem.–Eur. J.*, 2009, **15**, 793.

4 For examples, see: (*a*) B. Mathieu and L. Ghosez, *Tetrahedron Lett.*, 1997, **38**, 5497; (*b*) N. Kuhnert, J. Peverley and J. Robertson, *Tetrahedron Lett.*, 1998, **39**, 3215; (*c*) K. Ishihara, Y. Hiraiwa and H. Yamamoto, *Synlett*, 2001, 1851; (*d*) B. Mathieu and L. Ghosez, *Tetrahedron*, 2002, **58**, 8219; (*e*) M.-J. Tranchant, C. Moine, R. B. Othman, T. Bousquet, M. Othman and V. Dalla, *Tetrahedron Lett.*, 2006, **47**, 4477; (*f*) K. Takasu, N. Hosokawa, K. Inanaga and M. Ihara, *Tetrahedron Lett.*, 2006, **47**, 6053.

5 In sharp contrast, only a trace amount of product **3a** was observed by thin layer chromatography (TLC) analysis for the reaction in the presence of 10 mol% of TfOH (Table 1, entry 2), a stronger Brønsted acid relative to Tf_2NH (pK_a values in acetic acid: 4.2 and 7.8, respectively). Both Brønsted acids have been reported to serve as precatalysts that react with allylic silane **2a** to generate the corresponding actual catalysts, TfO(TMS) and Tf_2N(TMS). Significantly, Tf_2N(TMS) has been demonstrated to exhibit stronger Lewis acidity relative to TfO(TMS) according to ^{29}Si NMR analysis. See ref. 4*a* and *d*.

6 The reaction of allylic silane **2a** with benzhydryl bromide, a conventional benzylic alkylating agent, afforded product **3a** in 53% yield in the presence of 10 mol% of Tf_2NH at room temperature. Byproduct TMSBr was generated in this reaction and could promote undesired side reactions that consumed product **3a**. For examples of the reaction of allylic silanes with benzylic halides under acidic conditions, see: (*a*) Y. Morizawa, S. Kanemoto, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, 1982, **23**, 2953; (*b*) H. Mayr and R. Pock, *Tetrahedron*, 1986, **42**, 4211; (*c*) G. Hagen and H. Mayr, *J. Am. Chem. Soc.*, 1991, **113**, 4954; (*d*) J.-P. Dau-Schmidt and H. Mayr, *Chem. Ber.*, 1994, **127**, 205; (*e*) H. Mayr, G. Gorath and B. Bauer, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 788.

7 However, a highercatalyst loading and prolonged reaction time resulted in the rearrangement of 1,1-disubstituted carbon–carbon double bonds. For example, the reaction of sulfonamide **1g** with allylic silane **2b** proceeded in the presence of 10 mol% of Tf_2NH at room temperature for 6 h to afford a 9 : 91 mixture of product **3i** and (1*E*)-1,3-diphenyl-5-methyl-1,4-hexadiene (**3i′**).

8 For reviews, see: (*a*) I. Fleming, A. Barbero and D. Walter, *Chem. Rev.*, 1997, **97**, 2063; (*b*) G. L. Larson, *J. Organomet. Chem.*, 1992, **422**, 1.

9 The reaction of vinyltriphenylsilane with sulfonamide **1a** was very sluggish in the presence of 10 mol% of Tf_2NH at room temperature. By contrast, a complex mixture was obtained from the reaction of trimethyl(phenylethynyl)silane with sulfonamide **1a** under similar conditions.

 This journal is © The Royal Society of Chemistry 2010