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Synthesis of Alcohols from *m*-Fluorophenylsulfones and Dialkylboranes: Application to the C14−C35 Building Block of E7389

Lei Liu, James A. Henderson, Akihiko Yamamoto, Paul Brémond, and Yoshito Kishi*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138, United States

kishi@chemistry.harvard.edu

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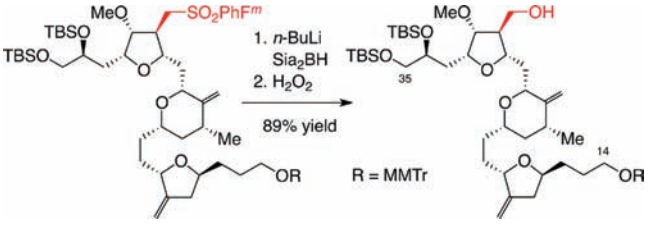
ABSTRACT



The reaction of *m*-fluorophenylsulfone anions with dialkylboranes, followed by alkaline hydroperoxide oxidation, yields alcohols in high yields. Optimization of the process, scope and limitation, and application to the synthesis of one of the C14−C35 building blocks of E7389, a right half analogue of halichondrin B, are reported.

The use of arylsulfones for the formation of carbon−carbon bonds is a well-recognized strategy in organic synthesis.[1] Transformations using this versatile auxiliary include (1) alkylation, acylation, and aldol-type reactions of α-arylsulfonyl carbanions, (2) Michael-type addition of a nucleophile to α,β-unsaturated sulfones, and (3) Diels−Alder reactions with electron-deficient dienophiles such as phenyl vinyl sulfones and others. Once the task is completed, the arylsulfone group is readily removed from the intermediate by reduction, oxidation, or alkylative desulfonylation, as well as β-elimination to form olefins and vinyl sulfones or pyrolytic extrusion of sulfur dioxide.

Related to our ongoing program in the halichondrin area,[2] we were interested in the transformation of RCH_2SO_2Ph to RCH_2OH. A literature search revealed only one example known. In 1981, Uguen reported the conversion of *n*-heptylphenylsulfone to *n*-heptanol by reaction of the α-lithiated phenylsulfone with 9-borabicyclo-[3.3.0]nonane (9-BBN), followed by treatment with alkaline hydroperoxide (Scheme 1).[3] Despite its modest efficiency, this example served as a lead to our current study. In this letter, we report optimization of Uguen's transformation to a synthetically useful level and its application to the synthesis of one of the C14−C35 building blocks of E7389 (Eribulin).[4]

Considering the application of this process to the β-branched phenylsulfone present in the C14−C35 building block of E7389 (cf., **13** in Scheme 3), we first tested Uguen's transformation on cyclohexylmethyl phenylsulfone, i.e., the substrate in entry 2, Table 1. Employing the conditions described by Uguen, we were able to detect only a trace amount of the desired cyclohexylmethyl alcohol,

(1) For reviews, see: (a) Nielsen, M.; Jacobsen, C. B.; Holub, N.; Paixão, M. W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 2668. (b) El-Awa, A.; Noshi, M. N.; Jourdin, X. M.; Fuchs, P. L. *Chem. Rev.* **2009**, *109*, 2315. (c) Simpkins, N. S. *Sulphones in Organic Synthesis*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, 1993.

(2) Shan, M.; Kishi, Y. *Org. Lett.* **2012**, *14*, 660 and references therein.

(3) Uguen, D. *Bull. Soc. Chim. Fr. II* **1981**, 99.

(4) (a) Zheng, W.; Seletsky, B. M.; Palme, M. H.; Lydon, P. J.; Singer, L. A.; Chase, C. E.; Lemelin, C. A.; Shen, Y.; Davis, H.; Tremblay, L.; Towle, M. J.; Salvato, K. A.; Wels, B. F.; Aalfs, K. K.; Kishi, Y.; Littlefield, B. A.; Yu, M. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5551. (b) Littlefield, B. A.; Palme, M. H.; Seletsky, B. M.; Towle, M. J.; Yu, M. J.; Zheng, W. U.S. Patents 6214865, 1999 and 6365759, 2000 and International Patent WO99/65894. (c) Yu, M. J.; Kishi, Y.; Littlefield, B. A. In *Anticancer Agents from Natural Products*; Cragg, G. M., Kingston, D. G. I., Newman, D. J., Eds.; CRC Press: Boca Raton, FL, 2005; p 41.

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Scheme 1. Conversion of a Phenylsulfone to a Primary Alcohol as Reported by Uguen

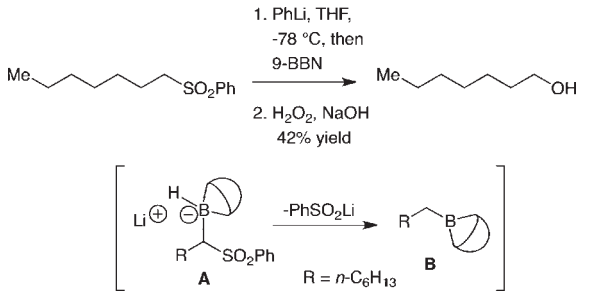
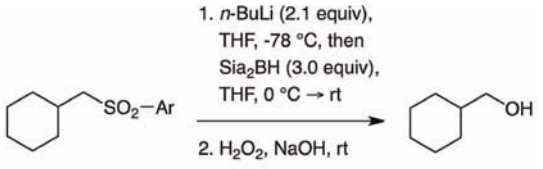


Table 1. Substitution Effect of Phenylsulfones



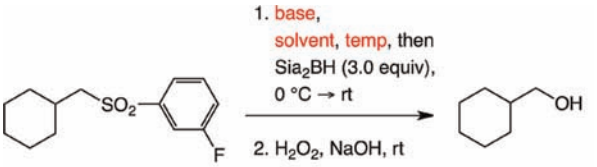
entry	Ar	conversion[a] (%)	yield[b] (%)
1	-C_6H_4-Me(p)	83	58
2	-C_6H_4-H	89	64
3	-C_6H_4-CN(p)	95	72
4	-C_6H_4-CF_3(p)	95	80
5	-C_6H_4-Cl(p)	97	92
6	-C_6H_4-F(p)	99	93
7	-C_6H_4-F(m)	100	94
8	-C_6H_3-Cl_2(m,p)	100	50
9	-C_6H_3-$(CF_3)_2$(m,m)	decomposition	NA
10	-C_6H_4-NO_2(p)	decomposition	NA

[a] Conversions: estimated from ^{1}H NMR spectra of the crude products. [b] Yields: chromatographically isolated product.

with the mass balance being recovered starting material. Interestingly, we found that, with use of an excess of *n*-butyllithium (2.1 equiv), this transformation vastly improved (approximately 90% conversion; 77% isolated yield). Yet, we desired to improve one aspect of the transformation: the reaction never completed, even with use of a large excess of *n*-butyllithium.

Uguen suggested that this transformation proceeds through the intermediates **A** and **B** (Scheme 1). On the basis of the fact that the starting material was recovered even with an excess of *n*-BuLi, we assumed the formation of **A** from the α-lithiated phenylsulfone and 9-BBN to be a reversible step. Thus, we first studied the substitution effect on the phenylsulfone, with the hope of facilitating the elimination of $PhSO_2Li$ from **A** (Table 1). In this screening, we used disiamylborane (Sia_2BH), instead of 9-BBN, because Sia_2BH appeared to be slightly better for this substrate than 9-BBN.

Table 2. Studies on Base, Solvent, Concentration, and Reaction Temperature



entry	base (equiv)	solvent	concentration (M)	t (°C)	conversion[a] (%)
1	n-BuLi (1.2)	THF	0.11	-78	20
2	n-BuLi (1.7)	THF	0.11	-78	100
3	n-BuLi (2.1)	THF	0.11	-78	100
4	n-BuLi (2.7)	THF	0.11	-78	70
5	n-BuLi (2.1)	THF	0.11	-45	33
6	n-BuLi (2.1)	THF	0.06	-78	100
7	n-BuLi (2.1)	THF	0.17	-78	98
8	n-BuLi (2.1)	Et_2O	0.11	-78	91
9	n-BuLi (2.1)	DME	0.11	-78	75
10	n-BuLi (2.1)	toluene	0.11	-78	89
11	n-BuLi (2.1)	hexanes	0.11	-78	80
12	s-BuLi (2.1)	THF	0.11	-78	83
13	t-BuLi (2.1)	THF	0.11	-78	72
14	MeLi (2.1)	THF	0.11	-78	98
15	PhLi (2.1)	THF	0.11	-78	98
16	LHMDS (2.1)	THF	0.11	-78	85
17	KHMDS (2.1)	THF	0.11	-78	60
18	t-BuOK (2.1)	THF	0.11	-78	33

[a] Conversions: estimated from ^{1}H NMR spectra of the crude products.

As anticipated from the proposed step of **A** → **B** (Scheme 1), we observed a better conversion for phenylsulfones bearing an electron-withdrawing group(s); indeed, a complete conversion was observed for *m*-fluorophenylsulfone and *m*,*p*-dichlorophenylsulfone (entries 7 and 8, Table 1). However, the former was found far superior to the latter in terms of the isolated yield.

With *m*-fluorophenylsulfone fixed, we then studied the effect of base, solvent, concentration, and reaction temperature (Table 2). This study revealed the conditions employed for entries 2 and 3 to be optimum for this transformation.

Under the optimized conditions, we then tested the scope and limitation of this transformation (Figure 1). In this study, we tested both Sia_2BH and 9-BBN. For nonconjugated primary and secondary substrates **1**–**5**, the efficiency of this transformation was good to excellent. In addition, Sia_2BH was superior to 9-BBN for primary substrates **1**–**3**, whereas 9-BBN was superior for secondary substrates **4** and **5**.

For the substrates bearing a carbanion-stabilizing group(s), except **8**, this reaction gave a substantial amount of the starting materials back. This result is not totally surprising, when one assumes the reversibility of

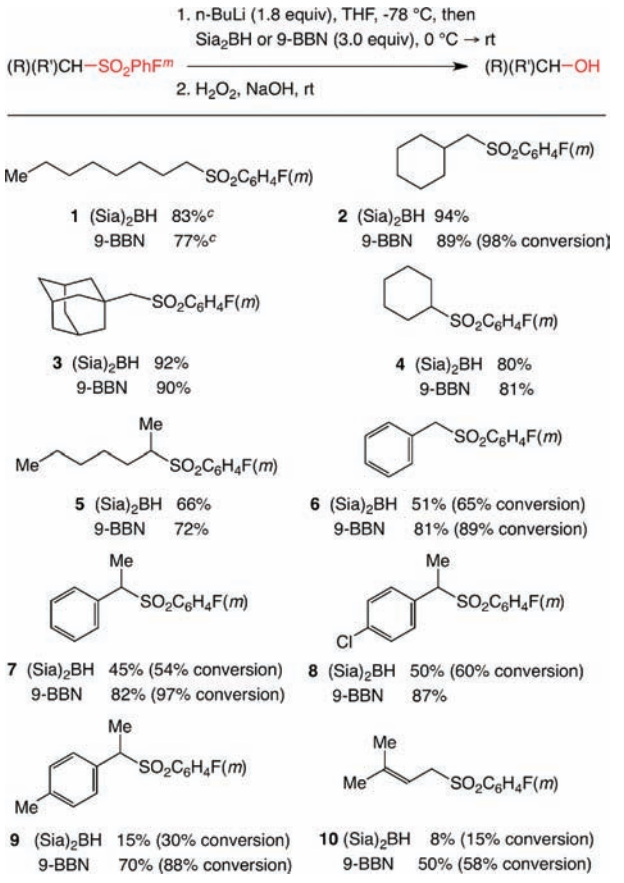


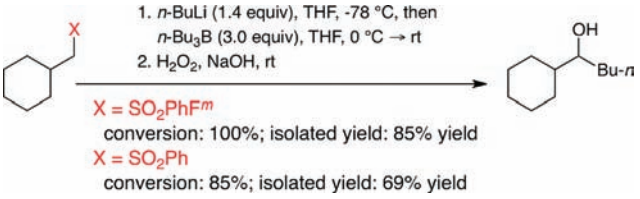
Figure 1. Scope and limitation. Sia_2BH and 9-BBN were tested for all the substrates. Yields represent chromatographically isolated products. Conversions are estimated from ^1H NMR spectra of the crude products. For compound **1**, 1.4 equiv, instead of 1.8, of *n*-BuLi was used.

(**A** to α-lithiated phenylsulfone + R_2BH). In addition, the relative reactivity observed for **7**–**9** is consistent with this explanation. It is noteworthy that 9-BBN was superior to Sia_2BH for all of **6**–**10**.

Although the starting materials were not completely consumed, this reaction still gave the expected alcohol in good yields for the benzyl phenylsulfones **6**–**9**. However, it was not yet satisfactory for some substrates such as (3,3-dimethylallyl)phenylsulfone **10**.

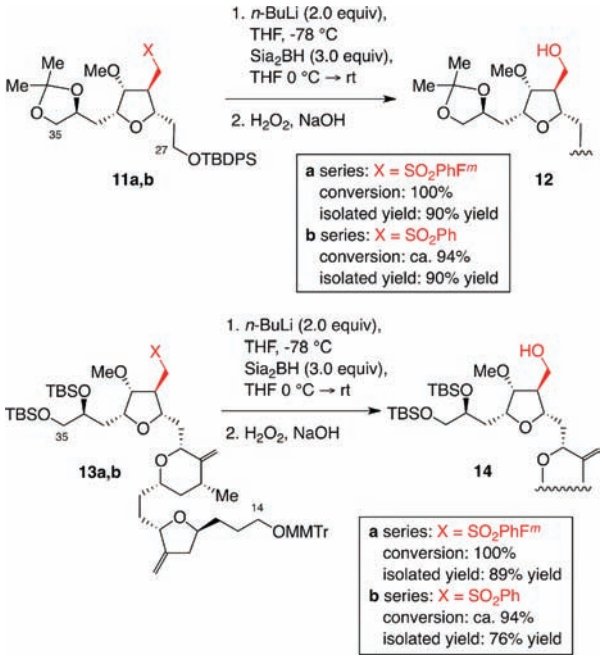
As reported by Uguen, phenylsulfones yield secondary alcohols on treatment with R_3B, instead of Sia_2BH or 9-BBN. To test the relative performance of *m*-fluorophenylsulfones and phenylsulfones, we used cyclohexylmethyl

Scheme 2. Example for the Transformation of a *m*-Fluorophenylsulfone to a Secondary Alcohol[a]



[a] Conversions: estimated from ^1H NMR spectra of the crude products. Yields: chromatographically isolated product.

Scheme 3. Application to the C27–C35 and C14–C35 Building Blocks of E7389[a]



[a] Yields: chromatographically isolated product. Conversions: chromatographically isolated starting material for **13b** and estimated from ^1H NMR spectrum of the crude product for **11b**.

substrates, thereby demonstrating once again the beneficial effect from the *m*-fluorophenylsulfone group (Scheme 2).

Finally, the transformation of phenylsulfones to primary alcohols was applied for the C27–C35 and C14–C35 building blocks of E7389 (Scheme 3).[5] For this

(5) Experimental procedure from **13a** to **14**. To a stirred solution of **13a** (230 mg, 0.2 mmol) in THF (1.1 mL) at −78 °C was added *n*-BuLi (206 μL, 1.9 M in hexane) dropwise. The resulting solution was stirred at −78 °C for 5 min and subsequently warmed to 0 °C for 10 min. Sia_2BH (728 μL, 0.825 M in THF) was added dropwise, and the reaction was allowed to warm to rt and was stirred overnight. The reaction was then quenched by the sequential addition of H_2O (0.3 mL), 3 N NaOH (0.3 mL), and 30 wt % H_2O_2 (0.3 mL). After 30 min of stirring, the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue was passed through a short silica gel column to give **14** (177 mg, 89%).

(6) During the review process, one of the reviewers suggested an involvement of dianion, first α-sulfonylanion formation followed by directed *ortho*-metalation. At the early stage of study, we had also suspected an involvement of dianion and conducted deuterium exchange experiments. Thus, ((cyclohexylmethyl)sulfonyl)benzene, the substrate shown under entry 2 in Table 1, was treated with 2.2 equiv of *n*-BuLi in THF at −78 °C and quenched with AcOH-d_4, MeOH-d_4, or D_2O. The product was then subjected to MS and ^1H NMR analyses, thereby demonstrating (1) a monodeuterium incorporation, (2) a deuterium exchange at -CH_2SO_2Ph, and (3) no noticeable change in the aromatic region in the ^1H NMR. On the basis of these observations, we felt the involvement of dianion to be unlikely. Obviously, further studies are required to unveil the mechanistic reason for the requirement of an excess base.

demonstration, we compared *m*-fluorophenylsulfones over phenylsulfones in each series, thereby revealing (1) its remarkable effectiveness even for polyfunctional substrates and (2) a beneficial effect from the *m*-fluorophenylsulfone group, as seen in the C14−C35 series.

In summary, we report a method to convert *m*-fluorophenylsulfones to the corresponding alcohols in high yields. Optimization study of the process revealed the beneficial effect from the *m*-fluorophenyl group. We then applied this transformation to the synthesis of one of the C14−C35 building blocks of E7389, thereby demonstrating its remarkable effectiveness even for a polyfunctional substrate such as **13a**.[6]

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Supporting Information Available. Experimental details and ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.