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Asymmetric conjugate addition reactions of polymer-supported highly enantioenriched β-(trimethylsilyl)ethyl sulfoxides

Shuichi Nakamura, Youhei Uchiyama, Satoshi Ishikawa, Ryuta Fukinbara, Yoshihiko Watanabe[†]
and Takeshi Toru*

Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan

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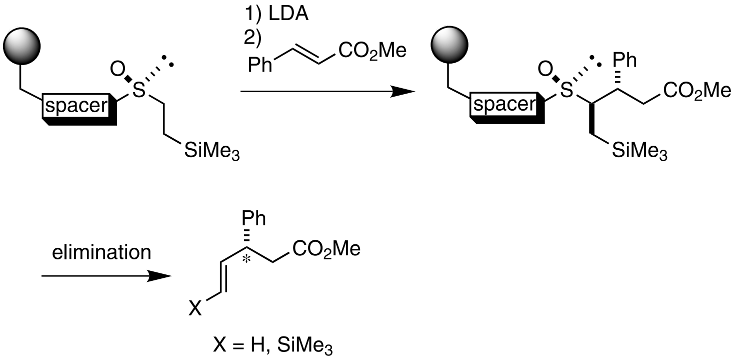
Abstract—Optically active β-(trimethylsilyl)ethyl sulfoxides supported on Merrifield resin were treated with LDA and subsequently with methyl cinnamate at −78°C. Thermal treatment or reaction with TBAF liberated the optically active methyl 3-phenyl-5-trimethylsilylpent-4-enoate or methyl 3-phenylpent-4-enoate, respectively, in good yields with high enantioselectivity. © 2002 Elsevier Science Ltd. All rights reserved.

Solid-phase organic reactions have been extensively studied as a tool for the synthesis of chemical libraries.[1] Among them, solid-phase asymmetric reactions are of great importance in the pharmaceutical industry. Recently, we reported highly efficient asymmetric conjugate addition reaction of the α-sulfinyl carbanion, derived from *p*-tolyl β-(trimethylsilyl)ethyl sulfoxide, to α,β-unsaturated carbonyl compounds.[2] We have examined its application to the solid-phase reaction. More recently, Solladié and co-workers have reported the stereoselective reduction of β-ketosulfoxides on Wang resin[3] and the electrophilic reaction of their enolates.[4] These reports prompted us to communicate our reactions of polymer-supported sulfoxides. We now report a convenient synthesis of optically active pentenoates by conjugate addition of resin-bound chiral β-(trimethylsilyl)ethyl sulfoxides including a new method for cleavage of the products from the resin. Our strategy is shown in Scheme 1.

We focused on the spacer as a crucial key fragment in the solid-phase synthesis. Scheme 2 summarizes the synthetic routes for the preparation of chiral 4-hydroxyphenyl 2-(trimethylsilylethyl) sulfoxide **4a** and 4′-hydroxybiphenyl 2-(trimethylsilyl)ethyl sulfoxide **4b**. The optically active sulfoxides **2a**,**b** were prepared from (*S*)-diacetone-D-glucosyl methanesulfinate **1**[5] with 4-(*tert*-butyldimethylsiloxy)phenyl- and 4′-(*tert*-butyldimethylsiloxy)biphenylmagnesium bromide in good yields. The reaction of the DAG methanesulfinate



Scheme 1.

Keywords: solid-phase synthesis; sulfoxides; Michael reactions; asymmetric reactions; desulfurization.

* Corresponding author. Tel.: 81-52-735-5217; fax: 81-52-735-5217; e-mail: toru@ach.nitech.ac.jp

[†] Deceased, June 23, 2001.

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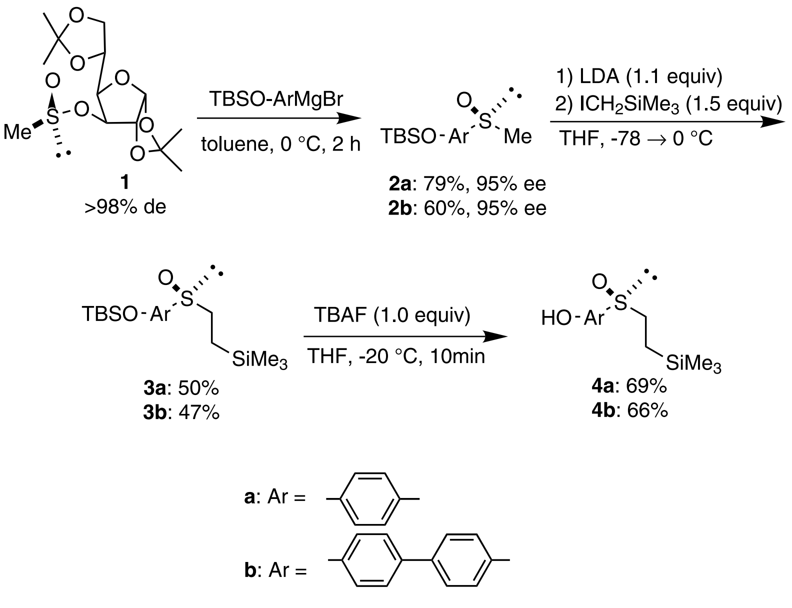
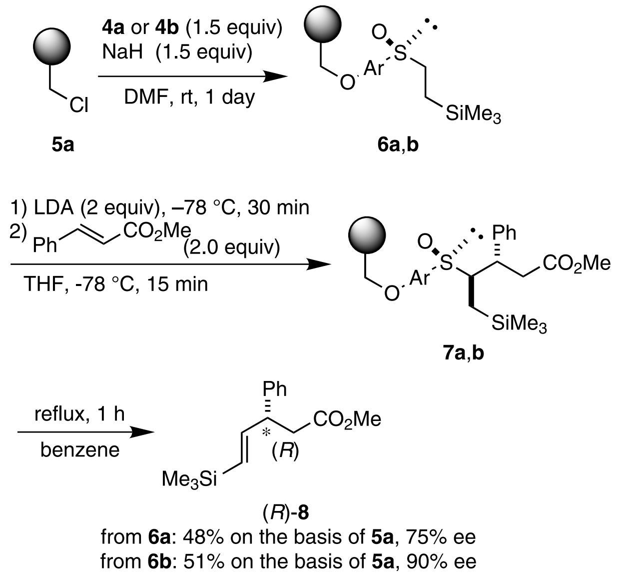


Scheme 2.

1 with Grignard reagents in THF gave the sulfoxides with low optical purity. The racemization was minimized when the reaction was performed in toluene, and both sulfoxides **2a**,**b** were obtained with 95% ee. Treatment of **2a**,**b** with LDA and (iodomethyl)-trimethylsilane gave the siloxyaryl β-silylethyl sulfoxides **3a**,**b**,[6] which were then selectively deprotected with tetrabutylammonium fluoride (TBAF) to afford chiral 4-hydroxyphenyl- and 4′-hydroxybiphenyl β-silylethyl sulfoxides **4a**,**b** (Scheme 2).

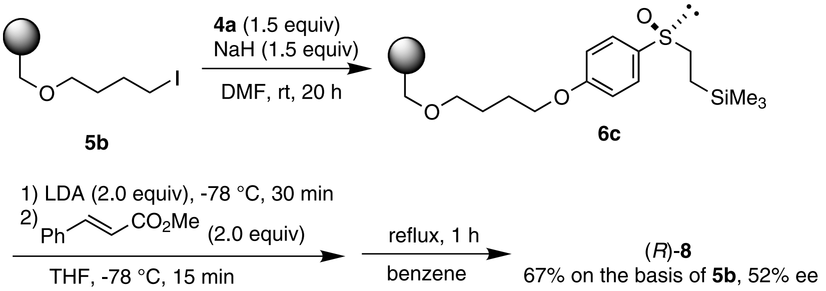
The polymer-supported β-silylethyl sulfoxide **6a** was prepared by treatment of Merrifield resin **5a** (0.9 mmol/g) with hydroxyphenyl β-silylethyl sulfoxide **4a** in the presence of NaH in DMF at room temperature (Scheme 3). Incorporation of the β-silylethyl sulfoxide in the resin **6a** was confirmed by the absorption at 1045 $\mathrm{cm}^{-1}(\nu_{\mathrm{S-O}})$ and the disappearance of the absorption at 1267 cm^{-1} $(\nu_{\mathrm{C-Cl}})$ in the FT-IR spectrum. The resin **6a** was treated with 2 equiv. of LDA in THF at −78°C. After 30 min, 2 equiv. of methyl cinnamate was added. After stirring for 15 min, the reaction was quenched with aqueous NH_4Cl solution. The resin **7a** was filtered, washed with cold ether and subsequently with ethyl acetate. The conjugate reaction was confirmed to occur by the absorption at 1737 cm^{-1} $(\nu_{\mathrm{C=O}})$.[7] Then the resin **7a** was heated in benzene for 1 h to undergo successful cleavage of methyl 3-phenyl-5-trimethylsilylpent-4-enoate (*R*)-**8** in 48% yield on the basis of **5a**. The thermal *syn* elimination of the sulfoxides often encounters non-regioselectivity.[8] It should be noted that the β-silyl group not only accelerated the PhSOH elimination but also controlled the regioselective formation of the double bond even in the polymer-supported reaction as in the solution reaction reported before.[2,9] By the ^{1}H NMR spectral and HPLC (Chiralcel OD-H) analyses, the stereochemistry of the major enantiomer of **8** was determined to be the (*R*,*E*)-isomer. The optical purity of (*R*)-**8** was 75% ee in contrast to the exclusive formation of a single diastereomer of the product in the solution reaction. We found that the stereoselectivity of the conjugate addition depended on the spacer. The 4′-hydroxybiphenyl β-silylethyl sulfoxide **4b** with 95% ee, prepared as shown in Scheme 2, was reacted with the resin **5a** to give **6b**. The conjugate addition to methyl cinnamate and subsequent heating in benzene gave the ester (*R*)-**8** in 51% yield with 90% ee.[10]

On the other hand, the β-silylethyl sulfoxide bound to the modified Merrifield resin **5b**,[11] was subjected to the conjugate addition, and subsequent elimination afforded (*R*)-**8** in 67% yield with 52% ee (Scheme 4). These results show that stereoselectivity depends on the linker, and the linear spacer may give high stereoselectivity as obtained in the reaction of the biphenylsulfinyl carbanion.

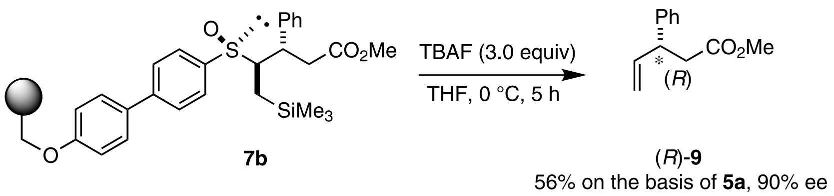


from **6a**: 48% on the basis of **5a**, 75% ee
from **6b**: 51% on the basis of **5a**, 90% ee

Scheme 3.



Scheme 4.



Scheme 5.

Cleavage of the vinyl analogue was also achieved by the desilylsulfinylation. Thus, treatment of **7b** with tetrabutylammonium fluoride in THF at 0°C gave (*R*)-**9** in 56% yield with 90% ee (Scheme 5).

In summary, we have shown a highly efficient asymmetric conjugate addition of the polymer-supported β-silylethyl sulfoxides as an extremely useful linker for the solid synthesis. The products were efficiently obtained with high stereoselectivity by cleavage of the products from the resin together with the formation of a double bond.

References

1. For reviews, see: (a) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lasky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288–2337; (b) Dörwald, F. Z. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, 2000; (c) Seneci, P. *Solid-Phase Synthesis and Combinatorial Technologies*; John Wiley: New York, 2000.
2. (a) Toru, T.; Nakamura, S.; Takemoto, H.; Ueno, Y. *Synlett* **1997**, *5*, 449–450; (b) Nakamura, S.; Watanabe, Y.; Toru, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3403–3404; (c) Nakamura, S.; Watanabe, Y.; Toru, T. *J. Org. Chem.* **2000**, 1758–1766.
3. Rolland, C.; Hanquet, G.; Ducep, J.; Solladié, G. *Tetrahedron Lett.* **2001**, *42*, 7563–7566.
4. Rolland, C.; Hanquet, G.; Ducep, J.; Solladié, G. *Tetrahedron Lett.* **2001**, *42*, 9077–9080.
5. (a) Fernandez, I.; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789–6979; (b) Khiar, N.; Fernandez, I.; Alcudia, F. *Tetrahedron Lett.* **1994**, *35*, 5719–5722. We reported an efficient method for the preparation of sulfinates, see: Watanabe, Y.; Mase, N.; Tateyama, M.; Toru, T. *Tetrahedron: Asymmetry* **1999**, *10*, 737–745.
6. (a) Kusuda, S.; Ueno, Y.; Toru, T. *Tetrahedron* **1994**, *50*, 1045–1062; (b) Nakamura, S.; Takemoto, H.; Ueno, Y.; Toru, T.; Kakumoto, T.; Hagiwara, T. *J. Org. Chem.* **2000**, *65*, 469–474, see also Ref. 2.
7. Solladié and co-workers have observed the unsuccessful methylation of the α-sulfinyl carbanion derived from the methyl sulfoxide on Wang resin, see Ref. 4.
8. (a) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Selenoxides and Selenones. Pergamon: Oxford, 1986; Chapter V, pp. 125–161; (b) Emerson, D. W.; Craig, A. P.; Potts, I. W., Jr. *J. Org. Chem.* **1967**, *32*, 102–105.
9. Cleavage by the selenoxide elimination from resin has been reported, see: (a) Michels, R.; Kato, M.; Heitz, W. *Makromol. Chem.* **1976**, *177*, 2311–2320; (b) Nicolaou, K. C.; Pastor, J.; Barluenga, S.; Winssinger, N. *Chem. Commun.* **1998**, *18*, 1947–1948; (c) Nicolaou, K. C.; Cho, S. Y.; Hughes, R.; Winssinger, N.; Smethurst, C.; Labischinski, H.; Endermann, R. *Chem. Eur. J.* **2001**, *7*, 3798–3823; (d) Horikawa, E.; Kodaka, M.; Nakahara, Y.; Okuno, H.; Nakamura, K. *Tetrahedron Lett.* **2001**, *42*, 8337–8339.
10. We have demonstrated an important role of the β-silyl group in high stereoselectivity in the electrophilic reaction of the α-sulfinyl carbanion, see Refs. 2 and 6.
11. Nicolaou, K. C.; Winssinger, N.; Vourloumis, D.; Oshima, T.; Kim, S.; Pfefferkorn, J.; Xu, J.-Y.; Li, T. *J. Am. Chem. Soc.* **1998**, *120*, 10814–10826.