Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 1337–1340
Tetrahedron Letters

Remote asymmetric trifluoromethylation induced by chiral sulfinyl group: synthesis of enantiomerically pure 1-(2-naphthyl)-2,2,2-trifluoroethanol

Hideki Sugimoto, Shuichi Nakamura, Yoshihiro Shibata, Norio Shibata and Takeshi Toru*

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

Received 14 October 2005; revised 5 December 2005; accepted 9 December 2005
Available online 9 January 2006

Abstract—The reaction of 1-[(2,4,6-triisopropylphenyl)sulfinyl]-2-naphthaldehyde with (trifluoromethyl)trimethylsilane using tetramethylammonium fluoride gave trifluoromethylated compounds in high yield with high diastereoselectivity. Desilylation and subsequent recrystallization yielded the enantiomerically and diastereomerically pure trifluoroethanol, which afforded chiral 1-(2-naphthyl)-2,2,2-trifluoroethanol after removal of the sulfinyl group.

1. Introduction

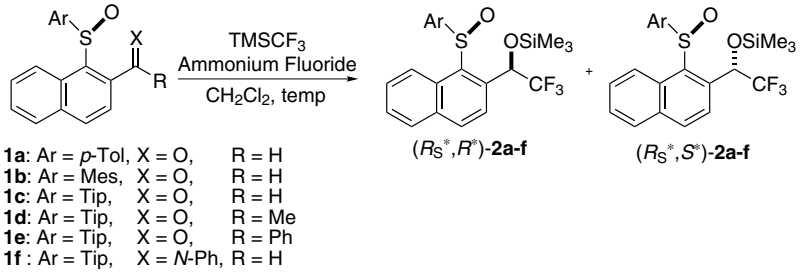
The synthesis of trifluoromethylated compounds entails a problem to be solved, which involves an interesting aspect of the reaction mechanism and pharmaceutical chemistry.[1] However, there are only a few reports for the preparation of chiral 1-substituted 2,2,2-trifluoroethanols, which include, for example, enzymatic resolution,[2] asymmetric hydrogenation,[3] and reduction.[4] The nucleophilic addition of a trifluoromethyl group using (trifluoromethyl)trimethylsilane ($TMSCF_3$) is another efficient method for the trifluoromethylation.[5] Enantioselective trifluoromethylation with $TMSCF_3$ has so far been reported to be unsuccessful probably because of a reactive trifluoromethylating intermediate formed during the reaction; for example, the moderately enantioselective trifluoromethylation[6,7] of aldehydes and ketones with $TMSCF_3$ on treatment with chiral quaternary ammonium fluoride derived from cinchonine and highly enantioselective trifluoromethylation of a specific acetophenone derivative.[8] On the other hand, no nucleophilic trifluoromethylation through the 1,4-asymmetric induction has been reported[9] among the diastereoselective addition reactions of $TMSCF_3$ to aldehydes[1b] and imines.[10] Recently, we have reported diastereoselective reactions of 1-[(2,4,6-triisopropylphenyl)sulfinyl]-2-naphthaldehyde with several nucleophiles by the use of the rotational barrier around the C–S bond axis.[11] We report herein the first remote asymmetric induction in the trifluoromethylation with $TMSCF_3$ caused by a rotational barrier around the C–S bond axis of 1-sulfinyl-2-naphthaldehydes.

2. Results and discussion

First of all, the reaction of 1-(arylsulfinyl)-2-naphthaldehydes **1a–c** with $TMSCF_3$ was examined using a catalytic amount (0.2 equiv) of tetramethylammonium fluoride (Me_4NF). The reaction of 1-(*p*-tolylsulfinyl)-2-naphthaldehyde **1a** with $TMSCF_3$ in CH_2Cl_2 afforded the trimethylsilylated alcohols **2a** with low diastereoselectivity (Scheme 1 and Table 1, entry 1). On the other hand, the reaction of 1-[(2,4,6-trimethylphenyl)sulfinyl]- and 1-[(2,4,6-triisopropylphenyl)sulfinyl]-2-naphthaldehydes **1b** and **1c** showed high diastereoselectivity (entries 2 and 3). When the reaction of **1c** was performed in toluene, THF, or acetonitrile, the trifluoromethylated product was not formed. The reaction using a catalytic amount of tetrabutylammonium fluoride (Bu_4NF) afforded the product **2a** with high diastereoselectivity

Keywords: Trifluoromethylation; 1,4-Asymmetric induction; Chiral alcohol; Sulfinyl group.
* Corresponding author. Tel./fax: +81 52 735 5217; e-mail: toru@nitech.ac.jp

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.12.061



1a: Ar = *p*-Tol, X = O, R = H
1b: Ar = Mes, X = O, R = H
1c: Ar = Tip, X = O, R = H
1d: Ar = Tip, X = O, R = Me
1e: Ar = Tip, X = O, R = Ph
1f : Ar = Tip, X = *N*-Ph, R = H

Scheme 1.

Table 1. Nucleophilic trifluoromethylation of 1-(arylsulfinyl)-2-naphthaldehydes **1a–c**

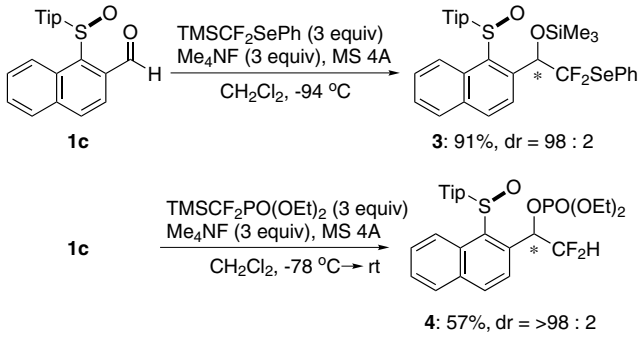
Entry	Substrate	X	R	Ammonium fluoride (equiv)	$TMSCF_3$ (equiv)	Temp (°C)	Product	Yield (%)	Diastereomer ratio[a] $(R_S^*,R^*):(R_S^*,S^*)$
1	**1a**	O	H	Me_4NF (0.2)	1.5	−78	**2a**	85	55:45
2	**1b**	O	H	Me_4NF (0.2)	1.5	−78	**2b**	79	79:21
3	**1c**	O	H	Me_4NF (0.2)	1.5	−78	**2c**	92	85:15
4	**1c**	O	H	Bu_4NF (0.2)	1.5	−78	**2c**	31[b]	92:8
5	**1c**	O	H	Me_4NF (0.2)	1.5	−94	**2c**	17	92:8
6	**1c**	O	H	Me_4NF (1.5)	1.5	−78	**2c**	89	88:12
7	**1c**	O	H	Me_4NF (3)	3	−78	**2c**	97	88:12
8	**1c**	O	H	Me_4NF (3)	3	−94	**2c**	97	90:10
9[c]	**1c**	O	H	Me_4NF (3)	3	−94	**2c**	96	91:9
10[c]	**1d**	O	Me	Me_4NF (3)	3	−78→rt	**2d**	—	—
11[c]	**1e**	O	Ph	Me_4NF (3)	3	−78→rt	**2e**	—	—
12[c]	**1f**	*N*-Ph	H	Me_4NF (3)	3	−78→rt	**2f**	—	—

[a] Determined by ^{19}F NMR.
[b] The desilylated alcohol was also obtained in 32% yield in a diastereomer ratio of 79:21.
[c] Molecular sieves 4 Å was added.

together with the desilylated alcohol with moderate diastereoselectivity (entry 4). The reaction of **1c** using $TMSCF_3$ and a catalytic amount of Me_4NF at −94 °C gave the product **2c** with higher diastereoselectivity than the reaction performed at −78 °C, but the yield was lowered (entry 5). When the reaction was carried out using an excess amount of $TMSCF_3$ at −78 °C, **2c** was obtained in high yield with high diastereoselectivity (entries 6 and 7). The yield and stereoselectivity were even better in the reaction at −94 °C (entry 8). All these reactions afforded the (R_S^*,R^*)-isomer predominantly. On the other hand, ketones **1d**, **1e** and the imine **1f** did not afford the trifluoromethylated products on treatment with $TMSCF_3$ in the presence of Me_4NF even at room temperature (entries 10–12).

Difluoromethylation of **1c** with $TMSCF_2SePh$[12] at −94 °C also succeeded in forming product **3** in high yield with high diastereoselectivity. Completion of the reaction of **1c** with $TMSCF_2PO(OEt)_2$[13] needed higher temperature, giving the product **4** that resulted from intramolecular rearrangement (Scheme 2).[14]

The relative stereochemistry of the major diastereomer of **2c** was determined to be (R_S^*,R^*) by the X-ray crystallographic analysis (Fig. 1). In order to prepare an optically active chiral trifluoroethanol derivative, the enantiomerically pure sulfoxide (*R*)-**1c** was prepared as previously reported.[11a] The reaction of (*R*)-**1c** with $TMSCF_3$ and Me_4NF afforded **2c** in high diastereoselec-



Scheme 2.

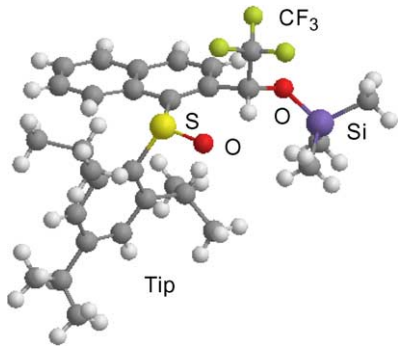
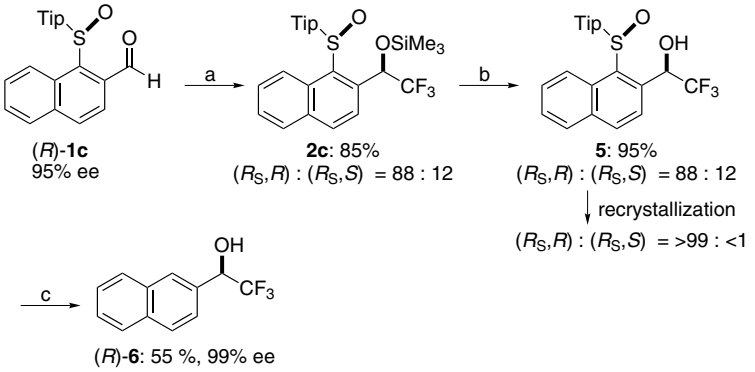


Figure 1. The Chem 3D structure derived from X-ray crystallography of (R_S^*,R^*)-**2c**.



Scheme 3. Reagents and conditions: (a) $TMSCF_3$, Me_4NF, MS 4 Å, CH_2Cl_2, −94 °C; (b) Bu_4NF, CH_2Cl_2, 0 °C; (c) *n*-BuLi, HMPA, THF, −78→−30 °C.

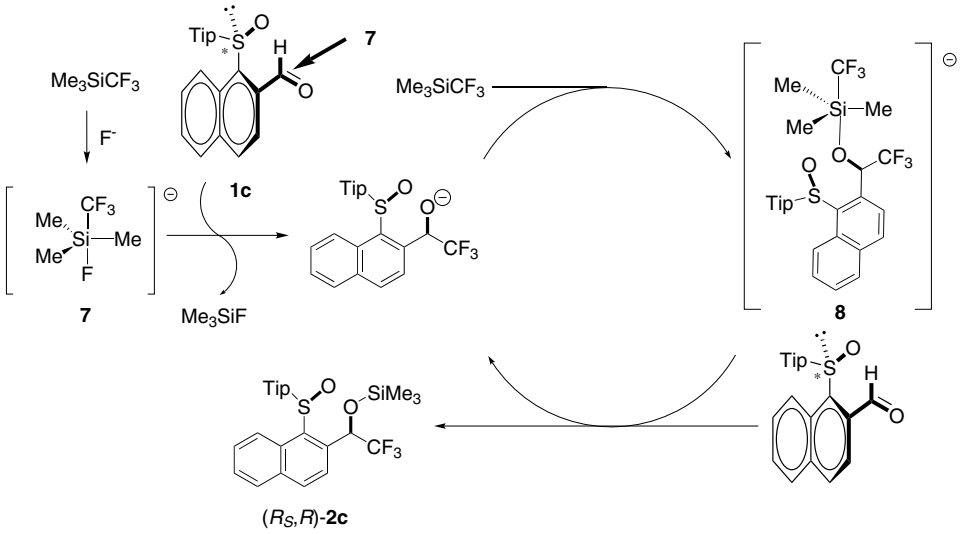
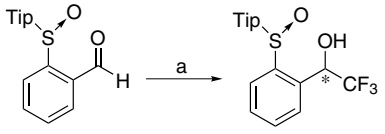


Figure 2. Preferred conformation of **1c** and the assumed reaction mechanism.

tivity (Scheme 3).[15] After the removal of the trimethylsilyl group from **2c** with Bu_4NF, recrystallization of **5** from hexane/CH_2Cl_2 afforded the enantiomerically as well as diastereomerically pure trifluoroethanol (R_S,*R*)-**5**. Subsequent cleavage of the sulfinyl group with *n*-BuLi gave 2-naphthyltrifluoroethanol (*R*)-**6** with 99% ee.[16]

We previously reported a highly stereoselective reaction of 1-[(2,4,6-triisopropylphenyl)sulfinyl]-2-naphthaldehyde **1c** with Grignard reagents controlled by restriction of the rotation around the C–S bond axis.[11] The X-ray crystallographic analysis, ^1H and ^{13}C NMR, and MO calculation of **1c** clearly showed that the sulfinyl oxygen is arranged away from the *peri*-H[8] proton in the naphthalene ring and the carbonyl oxygen away from the sulfinyl group (Fig. 2). In this structure, one of the faces of the aldehyde is highly shielded by the bulky 2,4,6-triisopropylphenyl group. Thus, the hypervalent silicate intermediates **7** and **8** assumed as trifluoromethylating agents[5,17] approach the less hindered face of the naphthaldehyde to form the (R_S,*R*)-isomer. In fact, the nucleophilic trifluoromethylation of 2-[(2,4,6-triisopropylphenyl)sulfinyl]benzaldehyde **9**[18] afforded the product **10** in high yield but with low diastereoselectivity because of the low rotational barrier about the C_{ph}–S bond (Scheme 4). These results suggest that the stereochemical outcome in the reaction of **1c** is strongly related to the rotational barrier about the C_{naph}–S bond.



Scheme 4. Reagents and conditions: (a) (1) $TMSCF_3$ (3 equiv), Me_4NF (3 equiv), MS 4 Å, CH_2Cl_2, −94 °C, (2) 6 N HCl.

3. Conclusion

In summary, we have disclosed the first remote asymmetric induction in the nucleophilic trifluoromethylation by the sulfinyl group as a chiral auxiliary.

Acknowledgments

We thank Dr. Shinya Kusuda, Ono Pharmaceutical Co., Ltd., for the X-ray crystallographic analyses and TOSOH F-TECH INC. for a gift of Me_3SiCF_3. This work was partly supported by a Grant-in Aid for Scientific Research (No. 11650890) from the Ministry of Education, Science, Sports and Culture of Japan.

References and notes

1. For reviews, see: (a) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1–16; (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119–6146.
2. (a) Bravo, P.; Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661–692, and references cited therein; (b) Kato, K.; Gong, Y.-F.; Tanaka, S.; Katayama, M.; Kimoto, H. *J. Mol. Catal. B: Enzym.* **2001**, *11*, 287–294.
3. (a) Koenig, K. E.; Bachman, G. L.; Vineyard, B. D. *J. Org. Chem.* **1980**, *45*, 2362–2365; (b) Sayo, N.; Akutagawa, S.; Saito, T.; Noyori, R.; Kumobayashi, H.; Takaya, H. EP 295109 A1, 1988; (c) Sayo, N.; Akutagawa, S.; Saito, T.; Noyori, R.; Takaya, H. EP 297752 A2, 1989.
4. (a) Hanzawa, Y.; Kawagoe, K.; Kobayashi, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2609–2612; (b) Corey, E. J.; Link, J. O.; Bakshi, R. K. *Tetrahedron Lett.* **1992**, *33*, 7107–7110, and references cited therein.
5. Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393–395.
6. Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 3137–3138.
7. For other enantioselective trifluoromethylation, see: (a) Kuroki, Y.; Iseki, K. *Tetrahedron Lett.* **1999**, *40*, 8231–8234; (b) Roussel, S.; Billard, T.; Langlois, B. R.; Saint-James, L. *Chem. Eur. J.* **2005**, *11*, 939–944.
8. Caron, S.; Do, N. M.; Arpin, P.; Larivee, A. *Synthesis* **2003**, *11*, 1693–1698.
9. For electrophilic 1,4-asymmetric trifluoromethylations, see: (a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 2169–2170; (b) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186–5192.
10. The preparation of optically active amines by the diastereoselective addition of $TMSCF_3$ to *N*-*tert*-butylsulfinylimines has been reported. (a) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589–590; (b) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847–2850.
11. (a) Nakamura, S.; Yasuda, H.; Watanabe, Y.; Toru, T. *J. Org. Chem.* **2000**, *65*, 8640–8650; (b) Nakamura, S.; Yasuda, H.; Watanabe, Y.; Toru, T. *Tetrahedron Lett.* **2000**, *41*, 4157–4160; (c) Nakamura, S.; Yasuda, H.; Toru, T. *Tetrahedron: Asymmetry* **2002**, *13*, 1509–1518.
12. Qin, Y. Y.; Qin, X. L.; Yang, Y. Y.; Meng, W. D.; Qing, F. L. *J. Org. Chem.* **2005**, *70*, 9040–9043.
13. Obayashi, M.; Kondo, K. *Tetrahedron Lett.* **1982**, *23*, 2327–2328.
14. (a) Obayashi, M.; Ito, E.; Matsui, K.; Kondo, K. *Tetrahedron Lett.* **1982**, *23*, 2323–2326; (b) Waschbüsch, R.; Samadi, M.; Savignac, P. *J. Organomet. Chem.* **1997**, *529*, 267–278.
15. Typical procedure: $TMSCF_3$ (0.07 mL, 0.50 mmol) and Me_4NF (46.6 mg, 0.14 mmol) were successively added to a −94 °C solution of (*R*)-**1c** (67.8 mg, 0.167 mmol) in CH_2Cl_2, and the mixture was stirred for 30 min at the same temperature. The reaction was quenched with water and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave a residue, which was purified by column chromatography (silica gel 10 g, hexane/ethyl acetate = 95/5) to give **2c** (77.5 mg, 85%).
16. To a solution of (R_S,*R*)-**3** (25.0 mg, 0.053 mmol) and HMPA (0.037 mL, 0.21 mmol) in THF (2 mL) was added *n*-BuLi (0.194 mL, 1.35 mol L^{-1} in hexane, 0.262 mmol) at −78 °C. The mixture was then allowed to warm to −30 °C and stirred for 2 h. After water was added, the mixture was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave a residue, which was purified by column chromatography (silica gel 10 g, benzene) to give (*R*)-**4** (6.5 mg, 55%). The enantiomer excess was determined to be 99% ee by the HPLC analysis: Daicel Chiralcel OJ-H, hexane/^{i}PrOH = 80/20, flow rate 1.5 mL/min; t_R, 12.1 (*R*), 17.2 (*S*) min.
17. Maggiarosa, N.; Tyrra, W.; Naumann, D.; Kirij, N. V.; Yagupolskii, Y. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2252–2253.
18. Nakamura, S.; Oda, M.; Yasuda, H.; Toru, T. *Tetrahedron* **2001**, *57*, 8469–8480.