Tetrahedron Letters 54 (2013) 5220–5223

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Chiral initiator-induces self-disproportionation of enantiomers via achiral chromatography: application to enantiomer separation of racemate

Kaori Tateishi [a], Shiori Tsukagoshi [a], Tsuyoshi Nakamura [a], Shotaro Watanabe [b], Vadim A. Soloshonok [c,d], Osamu Kitagawa [a,*]

[a] Department of Applied Chemistry, Shibaura Institute of Technology, 3-7-5 Toyosu, Kohto-ku, Tokyo 135-8548, Japan
[b] TAIHO Pharmaceutical Co., Ltd., 200-22, Motohara, Kamikawa-machi, Kodama-gun, Saitama 367-0241, Japan
[c] Department of Organic Chemistry I, University of the Basque Country UPV/EHU, 20018 San Sebastián, Spain
[d] IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain

ARTICLE INFO

Article history:
Received 17 June 2013
Revised 9 July 2013
Accepted 11 July 2013
Available online 17 July 2013

Keywords:
Enantiomers
Disproportionation
Optical resolution
Chromatography
Association

ABSTRACT

We report here the theoretical design and proof of principle of the first example of a conceptually new approach for the preparation of enantiomerically pure compounds from the racemates by chiral initiator-induced Self-Disproportionation of Enantiomers (SDE) via achiral chromatography.

One of the promising recent developments in the area of non-conventional enantiomeric purification methods is the SDE (Self-Disproportionation of Enantiomers) resulting in the separation of the racemate from the excess enantiomer under totally achiral conditions of physicochemical phase transitions or achiral chromatography.[1,2]

Recently, we reported an efficient method for the preparation of a series of enantiomerically pure *N*-Ac derivatives of α-(phenyl)ethylamine type compounds via SDE of the corresponding enantiomerically enriched samples under the conditions of achiral MPLC.[3] In particular, as shown in Figure 1, MPLC of non-racemic *N*-acetyl-1-phenylethylamine **1a** (71% ee) gave the elution profile with a clear boundary between two fractions. The less polar fraction contained enantiomerically pure **1a** (>99% ee), while the more polar fraction was considerably enantiomerically depleted (28% ee). The magnitude of the SDE was found to strongly depend on a substituent on the amino group.

Thus, while similar to **1a** level of the SDE was observed also in the case of *N*-formyl derivative, the magnitude of the SDE of *N*-benzoyl, *N*-trifluoroacetyl, *N*-tosyl, and *N*-methoxycarbony derivatives was noticeably reduced. Mechanistic rationale for these results was based on the assumption of a preferential formation of heterochiral high-order species having a higher retention time as compared with monomers of the excess enantiomer.[4–6]

While this approach holds quite tremendous practical potential, the SDE makes use of the internal chirality of enantiomerically enriched compounds and cannot be applied for resolution of racemates.

We hypothesized that if an optically pure compound **1** strongly interacts with one or both enantiomers of a racemic compound **2**, then mixed homo-/heterochiral high-order species might be formed in a solution, having different chromatographic behavior (Scheme 1). Consequently, the original racemate will be

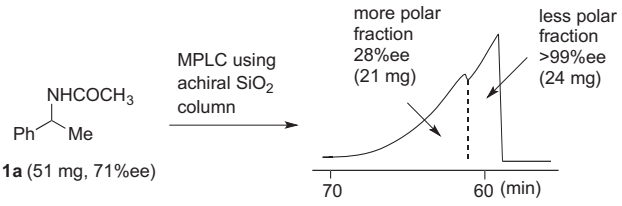
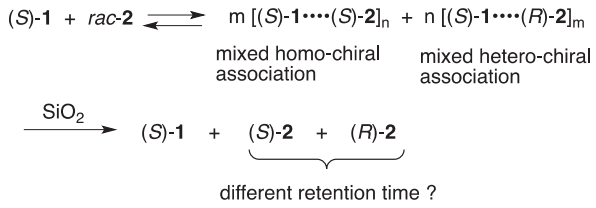


Figure 1. SDE via achiral chromatography of non-racemic *N*-acethyl-1-phenylethylamine.

* Corresponding author. Tel.: +81 3 5859 8161; fax: +81 3 5859 8101.
E-mail address: kitagawa@shibaura-it.ac.jp (O. Kitagawa).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.07.061



Scheme 1. A working hypothesis for chromatographicenantiomeric separation based on the formation of mixed homo-/heterochiral high-order species.

transformed into the (*S*)- and (*R*)-enantiomerically enriched portions which will further undergo SDE resulting, in turn, in enantiomerically pure fractions.

In this Letter we present a conceptually new approach for the preparation of enantiomerically pure compounds from the racemates by chiral initiator-induced Self-Disproportionation of Enantiomers (SDE) via achiral chromatography. The present resolution is based, presumably, on a preferential formation of heterochiral high-order associations between (*R*)-enantiomer of a racemic substrate and (*S*)-enantiomer of an optically pure inducing reagent, leading to the formation of species with a different chromatographic mobility, which in turn results in a transformation of the initial racemate into enantiomerically enriched fractions and subsequent SDE.

Building on our previous results of quite impressive SDE in a series of chiral (phenyl)ethyl amine derivatives,[3] we decided to use a similar type of compounds as model substrates. Besides their known SDE profile, these compounds are structurally very simple, represent classical targets in asymmetric synthesis, and widely used in pharmaceutical industry.

Knowing that the nature of a substituent on the amino function has a significant effect on the magnitude of SDE, we started our study with a detailed screening of various *N*-acyl derivatives of chiral inducing reagent **1** and racemic compound **2** by mixing them in a ratio of 1:1 and performing achiral MPLC experiments (Fig. 2). Among several possible combinations in the (*S*)-1-phenylethylamine derivatives (*S*)-**1a–d** and 1-(3-methoxyphenyl)ethylamine derivatives *rac*-**2a**,**b**, the pair of *N*-formyl derivatives (*S*)-**1b** and *rac*-**2b** gave the best result.

In a typical experiment (*S*)-**1b** and *rac*-**2b** were mixed, and subsequently subjected to MPLC on an achiral column (packed 10 μm of silica gel, 20 × 250 mm) using an achiral eluent (hexane–AcOEt = 1). The obtained chromatographic profile is presented in Figure 3. The graph (A) in Figure 3 shows MPLC chart of mixtures of (*S*)-**1b** (50 mg) and *rac*-**2b** (60 mg) with a mole ratio of 1:1.

First of all, it should be noted that, as it was designed, the chiral inducing reagent was completely separated, as the first eluted

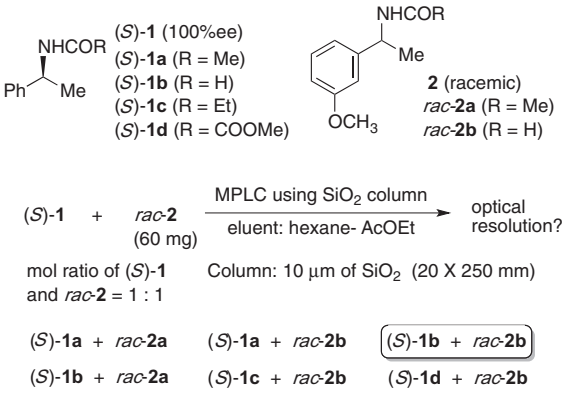


Figure 2. MPLC experiment of mixtures of (*S*)-**1** and *rac*-**2**.

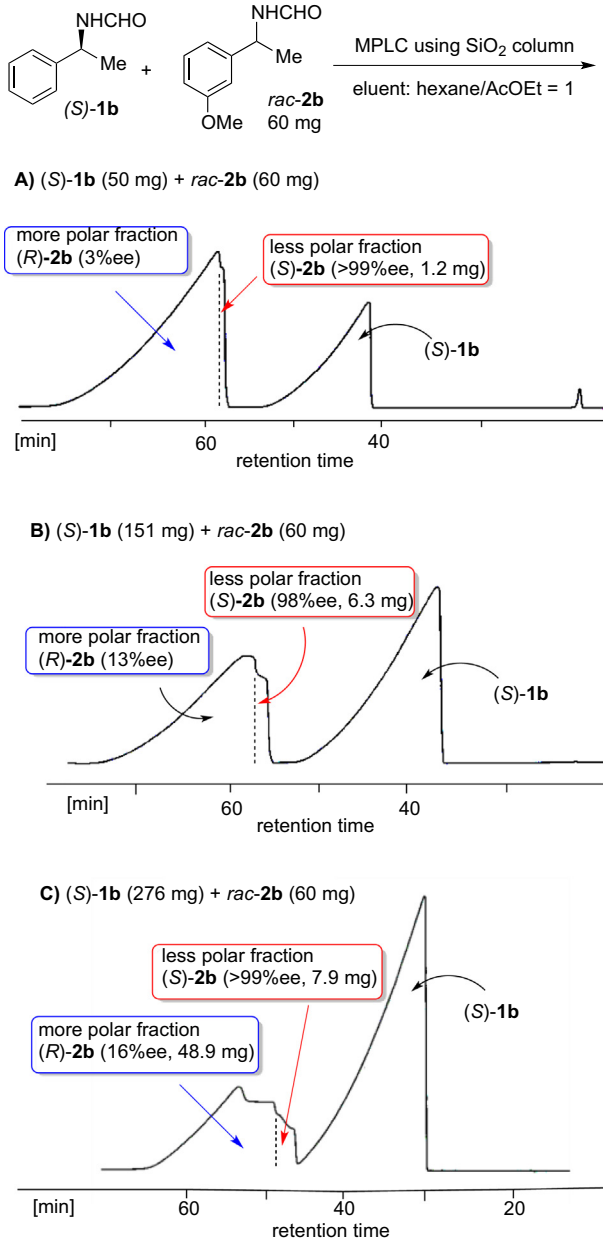


Figure 3. MPLC chart of mixtures of (*S*)-**1b** and *rac*-**2b**.

fraction, from the components of compound **2b**. The latter appeared as two overlapped fractions with a noticeable boundary between them. Analysis of enantiomeric composition of these fractions, using chiral HPLC, showed that, quite remarkably, the less polar fraction contained enantiomerically pure **2b** (1.2 mg, >99% ee), while the more polar fraction was of 3% ee, accounting for the complete mass and a 50:50 initial enantiomeric composition of the racemate **2b**. We further envisioned, that efficiency of these results might be improved with increasing the amount of chiral inducing reagent (*S*)-**1b** by the virtue of increasing the number of quality interactions between (*S*)-**1b** and enantiomers of *rac*-**2b**. Figure 3, charts B and C present the results of MPLC experiments using mixtures of (*S*)-**1b** and *rac*-**2b** (60 mg) taken in mole ratios of 3:1 and 5.5:1, respectively. As one can see, in the case of 3:1 ratio, a more clear boundary between the two fractions was observed, and almost optically pure **2b** [6.3 mg (98% ee)] was isolated as the less polar fraction. This result was further improved using the 5.5:1 ratio allowing to isolate 7.9 mg of enantiomerically pure

2b (>99% ee) in the less polar fraction. In terms of practicality and isolated yield, these data constitute a meaningful 21% and 26%, respectively, of the enantiomerically pure product, obtained from the starting racemic mixture. Determination of the absolute configuration of the enantiomerically pure product **2b**, by comparison with the authentic sample, has revealed its (*S*)-configuration.[7]

As one can see from chart C, the area of **2b** has several shoulders prompting us to investigate their composition in more detail. To this end we isolated six fractions, as shown in Figure 4, and studied their enantiomeric composition as well as the absolute configuration of the excess enantiomer. The first fraction was found to be noticeably enriched (39% ee) in (*S*)-**2b** enantiomer, while rest of the fractions (from the second to the sixth) contained excess of (*R*)-**2b** with gradually decreasing enantiomeric purity from 23 to 10% ee. One may assume that a similar enantiomeric composition might be also observed in the experiments conducted with 1 and 3 equiv of reagent (*S*)-**1b**, charts (A) and (B), respectively. However, in these cases the separation of the enantiomeric species is less efficient and the corresponding shoulders are not pronounced. Considering these preliminary results we may conclude that our design was quite successful as the inducing reagent (*S*)-**1b** led to a separation of (*S*)-**2b** enantiomer transforming the initial racemate **2b** into an enantiomerically enriched state which further underwent the SDE previously described for this type of compounds.

Finally, we decided to briefly assess the generality of this method for resolution of other racemic *N*-formyl (phenyl)ethylamine derivatives. For example, racemate **3b** [*N*-formyl 1-(4-methoxyphenyl)ethylamine] (60 mg) was mixed with (*S*)-**1b** (275 mg), in a mole ratio of 1:5.5 and subjected to MPLC under the standard conditions (Fig. 5). Similar to the results obtained for resolution of **2b**, the chiral reagent **1b** was eluted first followed by the area of compound **3b**, clearly showing several shoulders. The first, less polar fraction, contained enantiomerically pure (99% ee) (*S*)-**3b**,[7] which was obtained in 14% recovery yield (4.3 mg). The next fraction was enantiomerically enriched (31% ee) in the same (*S*)-enantiomer, followed by the fractions containing (*R*)-enantiomer in excess of various enantiomeric purity.

In another experiment, using racemate **4b** [*N*-formyl 1-(4-methylphenyl)ethylamine] (60 mg), mixed with the inducing reagent (*S*)-**1b** (164.5 mg) in a mole ratio of 1:3, we obtained a bit different results as compared with the derivatives **2b** and **3b**. In this case (Fig. 6) the first collected fraction contained enantiomerically pure (*S*)-**4b** (>99% ee, 8.5 mg, recovery yield 28%) followed by another (*S*)-enantiomerically enriched fraction (15% ee, 15.6 mg). The last, third collected fraction, contained the inducing reagent (*S*)-**1b** and (*R*)-enantiomerically enriched **4b**. Thus, the elution order of enantiomers of **4b** and the reagent (*S*)-**1b** were different form the **2b** and **3b** cases, but the stereochemical outcome, resulting in the separation of the (*S*)-enantiomer **4b**,[7] was virtually the same. Accordingly, one may agree that this new method might have some degree of generality, at least in a series of structurally

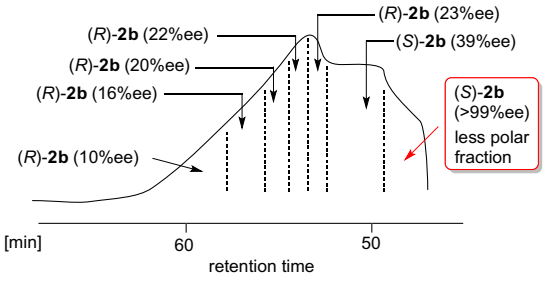


Figure 4. Detailed ee change of **2b** in chart C (Fig. 3).

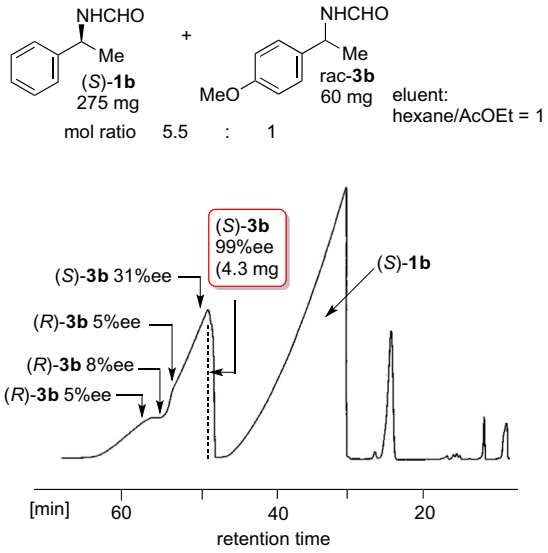


Figure 5. MPLC chart of the mixtures of (*S*)-**1b** and *rac*-**3b** with a mole ratio of 5.5:1.

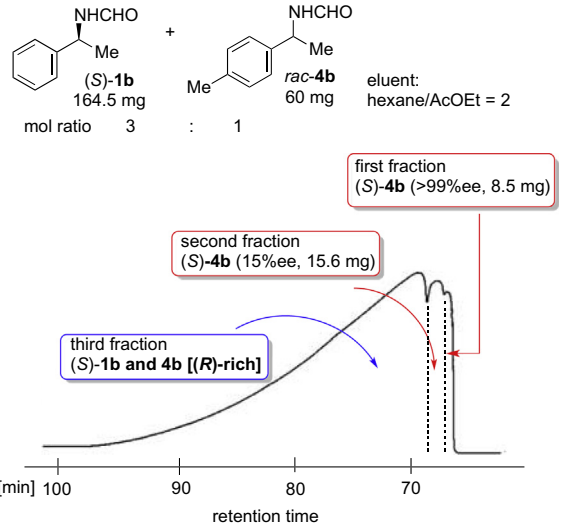


Figure 6. MPLC chart of the mixtures of (*S*)-**1b** and *rac*-**4b** with a mole ratio of 3:1.

similar compounds, using the same chiral inducing reagent (*S*)-**1b**. Obviously, different classes of compounds may require another inducing reagent or modified conditions, but clearly, the concept discovered in this study constitutes a new, non-conventional approach for racemate resolution.

One may agree, that elucidation of the detailed mechanism of the observed in this study chromatographic profiles will require a separate investigation. However, what seems to be obvious is that the chiral inducing reagent interacts selectively with one of the enantiomers of the starting racemate producing high-order species having different retention times. As we have suggested in the previous work,[3] compounds of this class, tend to form syndiotactic hetero-chiral, hydrogen bonded associations which are preferred in a solution over isotactic homo-chiral associations.[5] Thus, we may assume that (*S*)-chiral inducing reagent, selectively forms high-order species with (*R*)-enantiomer of the racemate (Scheme 1, m > n), which have longer retention times as compared to monomeric species of the (*S*)-enantiomer, being eluted first.

In conclusion, we have designed a new approach for racemate resolution based on chiral initiator-induced self-disproportionation of enantiomers via achiral chromatography. Direct resolution methods of racemates via chromatography using chiral mobile[8] or stationary phases[9] are known.[10] However, chiral mobile phase method requires the use of very large excess (>100 equiv) of a chiral selector added to an eluent, resulting in mixtures of resolved enantiomers with the chiral selector. Although separation of enantiomers using chiral stationary phase method is the most popular on analytical scale, the only disadvantage of this approach is that preparative chiral stationary phase columns are still very expensive. Our approach opens up a new area of research with a remarkable practical potential for inexpensive, available in any research laboratory technique for generation of enantiomerically pure compounds starting from racemates. The following features of this work should be particularly emphasized: (1) This Letter presents the proof of principle of a new approach for racemate resolutions via achiral chromatography; (2) Methodologically, this new approach offers an unexpected and practically advantageous benefit of combining chiral mobile method with the SDE. Taking separately, the chiral mobile method has a significant shortcoming requiring to use large quantities of enantiomerically pure reagent, and the SDE is limited to the application to already enantiomerically enriched mixtures. (3) Taking into account that the chiral mobile method and the SDE are of very general nature, this new approach is also expected to be of general application for the preparation of enantiomerically pure samples from racemic mixtures.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.061.

References and notes

1. Typical examples of SDE through achiral chromatography: (a) Cundy, K. C.; Crooks, P. A. *J. Chromatogr.* **1983**, *281*, 17; (b) Charles, R.; Gil-Av, E. *J. Chromatogr.* **1984**, *298*, 516; (c) Dobashi, A.; Motoyama, Y.; Kinoshita, K.; Hara, S.; Fukasaku, N. *Anal. Chem.* **1987**, *59*, 2209; (d) Matusch, R.; Coors, C. *Angew. Chem., Int. Ed. Engl.* **1989**, *101*, 624; (e) Carman, R. M.; Klika, K. D. *Aust. J. Chem.* **1991**, *44*, 895; (f) Diter, P.; Taudien, S.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1994**, *59*, 370; (g) Takahata, H. *Yuki Gosei Kagaku Kyokaishi* **1996**, *54*, 708; (h) Kosugi, H.; Abe, M.; Hatsuda, R.; Uda, H.; Kato, M. *Chem. Commun.* **1997**, 1857; (i) Tanaka, K.; Osuga, H.; Suzuki, H.; Shogase, Y.; Kitahara, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 935; (j) Stephani, R.; Cesare, V. J. *J. Chromatogr. A* **1998**, *813*, 79; (k) Ernholt, B. V.; Thomsen, I. B.; Lohse, A.; Plesner, I. W.; Jensen, K. B.; Hazell, R. G.; Liang, X.; Jacobsen, A.; Bols, M. *Chem. Eur. J.* **2000**, *6*, 278; (l) Suchy, M.; Kutschy, P.; Monde, K.; Goto, H.; Harada, N.; Takasugi, M.; Dzurilla, M.; Balentova, E. *J. Org. Chem.* **2001**, *66*, 3940; (m) Soloshonok, V. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 766; (n) Soloshonok, V. A.; Berbasov, D. O. *J. Fluor. Chem.* **2006**, *127*, 597; (o) Takahashi, M.; Tanabe, H.; Nakamura, T.; Kuribara, H.; Yamazaki, T.; Kitagawa, O. *Tetrahedron* **2010**, *66*, 288; (p) Ogawa, S.; Nishimine, T.; Tokunaga, E.; Nakamura, S.; Shibata, N. *J. Fluorine Chem.* **2010**, *131*, 521; (q) Aceña, J. L.; Sorochinsky, A. E.; Katagiri, T.; Soloshonok, V. A. *Chem. Commun.* **2013**, 373; (r) Sorochinsky, A. E.; Katagiri, T.; Ono, T.; Wzorek, A.; Aceña, J. L.; Soloshonok, V. A. *Chirality* **2013**, *25*, 365.
2. For reviews on SDE via achiral chromatography: (a) Soloshonok, V. A.; Berbasov, D. O. *Chim. Oggi/Chem. Today* **2006**, *24*, 44; (b) Soloshonok, V. A.; Roussel, C.; Kitagawa, O.; Sorochinsky, A. E. *Chem. Soc. Rev.* **2012**, *41*, 4180; (c) Sorochinsky, A. E.; Aceña, J. L.; Soloshonok, V. A. *Synthesis* **2013**, *45*, 141.
3. Nakamura, T.; Tateishi, K.; Tsukagoshi, S.; Hashimoto, S.; Watanabe, S.; Soloshonok, V. A.; Aceña, J. A.; Kitagawa, O. *Tetrahedron* **2012**, *68*, 4013.
4. (a) Williams, T.; Pitcher, R. G.; Bommer, P.; Gutzwiller, J.; Uskokovic, M. *J. Am. Chem. Soc.* **1969**, *91*, 1871; (b) Dobashi, A.; Saito, N.; Motoyama, Y.; Hara, S. *J. Am. Chem. Soc.* **1986**, *108*, 307; (c) Baciocchi, R.; Juza, M.; Classen, J.; Mazzotti, M.; Morbidelli, M. *Helv. Chim. Acta* **2004**, *87*, 1917; (d) Klika, K. D.; Budovská, M.; Kutschy, P. *J. Fluorine Chem.* **2010**, *131*, 46; (e) Klika, K. D.; Budovská, M.; Kutschy, P. *Tetrahedron: Asymmetry* **2010**, *21*, 647; (f) Blackmond, D. G. *Tetrahedron: Asymmetry* **2010**, *21*, 1630.
5. Druot, S.; Petit, M. N.; Petit, S.; Coquerel, G.; Chanh, N. B. *Mol. Cryst. Liq. Cryst.* **1996**, *275*, 271.
6. (a) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353; (b) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877; (c) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028; (d) Katagiri, T.; Yoda, C.; Furuhashi, K.; Ueki, K.; Kubota, T. *Chem. Lett.* **1996**, 115; (e) Roussel, C.; Bonnet, B.; De Riggi, I.; Suteu, C. *Biomed. Chromatogr.* **2001**, *15*, 173; (f) Roussel, C.; Rafii, E.; Del Rio, A.; Vanthuyne, N. *Biomed. Chromatogr.* **2005**, *19*, 434; (g) Soloshonok, V. A.; Ueki, H.; Yasumoto, M.; Mekala, S.; Hirschi, J. S.; Singleton, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 12112; (h) Ueki, H.; Yasumoto, M.; Soloshonok, V. A. *Tetrahedron: Asymmetry* **2010**, *21*, 1396.
7. The absolute stereochemistry of the separated enantiomers (*S*)-**2b**-**4b** were determined by comparison with the authentic samples that were prepared by *N*-formylation of optically pure 1-(3-methoxyphenyl)ethyamine, 1-(4-methoxyphenyl)ethyamine, and 1-(4-methylphenyl)ethyamine (commercially available).
8. Representative literatures on chiral mobile phase methods: (a) Lam, S.; Chow, F.; Karmen, A. *J. Chromatogr.* **1980**, *199*, 295; (b) Nimura, N.; Toyama, A.; Kinoshita, T. *J. Chromatogr.* **1982**, *234*, 482; (c) Dobashi, Y.; Hara, S. *J. Am. Chem. Soc.* **1985**, *107*, 3406; (d) Keith, J.; Duff, K. J.; Gray, H. L.; Gracy, R. J.; Bahler, C. C. *Chirality* **1993**, *5*, 201; (e) Sun, Q.; Olesik, S. V. *J. Chromatogr. B* **2000**, *745*, 159.
9. Representative literatures on chiral stationary phase methods: (a) Hara, S.; Dobashi, A. *J. Liq. Chromatogr.* **1979**, *2*, 883; (b) Okamoto, Y.; Suzuki, K.; Ohta, K.; Hatada, K.; Yuki, H. *J. Am. Chem. Soc.* **1979**, *101*, 4673; (c) Yuasa, S.; Shimada, A.; Kameyama, K.; Yasui, M.; Azuma, K. *J. Chromatogr. Sci.* **1980**, *18*, 311; (d) Pirkle, W. H.; Fin, J. M. *J. Org. Chem.* **1981**, *46*, 2935; (e) Allenmark, S.; Bomgrem, B. *J. Chromatogr.* **1983**, *264*, 63; (f) Armstrong, D. W.; DeMand, W. J. Chromatogr. Sci. Analyst **1984**, *22*, 411; (g)*Drug Stereochemistry, Analytical Methods and Pharmacology 2ndÄi0*; Wainer, I. W., Ed.; Marcel Dekker: New York, 1993; (h) Okamoto, Y.; Yashima, E. *Angew. Chem., Int. Ed.* **1998**, *37*, 1020; (i) Gübitz, G.; Schmid, M. G. *Biopharm. Drug Dispos.* **2001**, *22*, 291; (j) Ward, T. J.; Ward, K. D. *Anal. Chem.* **2012**, *84*, 626; (k) Piras, P.; Roussel, C. *J. Pharm. Bio. Anal.* **2008**, *46*, 839.
10. (a) Pirkle, J. M.; Fin, J. M. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, p 87; (b) Allenmark, S. G. In *Chromatogtaphic Enantioseparation*; Chalmers, R. A., Mason, M., Eds., 2nd ed.; Horwood Ltd: Chichester, 1991; (c) Ahuja, S. *Chiral Separations by Chromatography*; New York: Oxford, 2000.