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Chiral additive induced self-disproportionation of enantiomers under MPLC conditions: preparation of enantiomerically pure samples of 1-(aryl)ethylamines from racemates

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ABSTRACT

Mixtures of enantiomerically pure (*S*)-*N*-formyl-1-phenylethyamine and various racemic *N*-formyl-1-arylethylamine derivatives, when submitted to achiral medium pressure liquid chromatography, afforded elution profiles in which the enantiomers of *N*-formyl-1-arylethylamines standout as separate peaks and can be isolated. In all of the investigated *N*-formyl-1-arylethylamine substrates, the virtually enantiomerically pure (*S*)-enantiomer eluted as a less polar fraction and subsequently, the (*R*)-enriched enantiomer mixtures were eluted in the more polar fractions.

1. Introduction

In the achiral chromatography of enantiomerically enriched compounds, it has been occasionally reported that the enantiomeric excess (ee) of a compound in various fractions usually differs from the original enantiomeric excess, i.e., the enantiomeric excess of a compound in some fractions is higher than the original enantiomeric excess, while that in other fractions it is lower. Such a phenomenon is known as the self-disproportionation of enantiomers. The self-disproportionation of enantiomers has also recently received much attention as a new method for enantiomeric purification.[1,2] Recently we discovered the efficient self-disproportionation of enantiomers of enantiomerically enriched *N*-acyl-1-phenylethylamine derivatives under the conditions of medium pressure liquid chromatography (MPLC).[3] The magnitude of the self-disproportionation of enantiomers strongly depended on the substituent on the amino group. Although phenethylamines bearing sterically small *N*-acyl substituents, such as acetyl and formyl groups, showed significant self-disproportionation of enantiomers (Fig. 1), in substrates bearing sterically bulky or strongly electron-withdrawing *N*-*tert*-butoxycarbonyl, benzoyl, tosyl and trifluoroacetyl groups, the self-disproportionation of enantiomers magnitude was noticeably reduced.

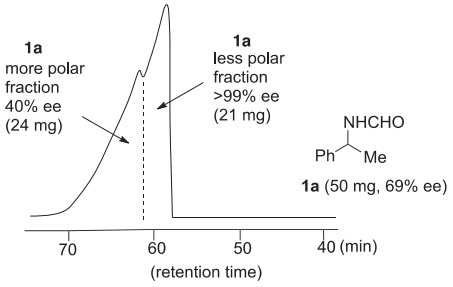

Figure 1. Self-disproportionation of enantiomers of *N*-formyl-1-phenylethylamine (69% ee) through MPLC using achiral SiO_2 column.

Self-disproportionation of enantiomers via achiral chromatography is well known to be caused by the preferential formation of heterochiral higher order associations with a higher retention time as compared with homochiral lower order associations formed by excess enantiomer (Eq. 1).[4–6] Hence, the self-disproportionation of enantiomers cannot be observed in the chromatography of racemates. We theorized that if an enantiomerically pure additive, such as compound **1**, strongly associates with one or both enantiomers of racemate **2**, then either mixed homochiral or heterochiral associations may be kinetically induced in the solution. These in situ formed higher-order species are expected to have different chromatographic behavior (Eq. 2) and may lead to the

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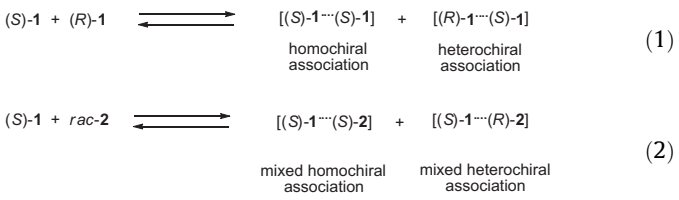
separation of the enantiomers of starting racemate **2**. Such a process, if realized, would constitute a new methodology for resolution.[7]



Recently, we reported preliminary results on a successful self-disproportionation of enantiomers of three racemic *N*-formyl-1-arylethylamine substrates via the addition of enantiomerically pure (*S*)-*N*-formyl-1-phenylethylamine followed by achiral MPLC of the resultant mixture.[8] In all three racemic substrates, the (*S*)-enantiomers were separated with high enantiomeric purity by this new chiral additive induced self-disproportionation of enantiomers. Herein we report a full account of this study emphasising the generality of the chiral additive induced self-disproportionation of enantiomers method as a new approach for the resolution of various racemic substrates.

2. Results and discussion

On the basis of our preliminary results, which showed a quite impressive magnitude of the self-disproportionation of enantiomers in non-racemic chiral *N*-acyl-1-phenylethyl amine derivatives,[3] we decided to use similar compounds as model substrates for the chiral additive induced self-disproportionation of enantiomers. In addition to their known self-disproportionation of enantiomers profile, 1-phenylethylamine derivatives are structurally very simple, commercially available, represent classical targets in asymmetric synthesis and are widely used in the pharmaceutical industry.[9]

Since the substituent on the amino function has been found to have a significant influence on the magnitude of the self-disproportionation of enantiomers, we initially performed a detailed screening of various *N*-acyl derivatives of chiral additive **1** and racemate **2** by mixing them in a ratio of 1:1 and performing achiral MPLC experiments (Fig. 2). Among the several possible combinations in the (*S*)-1-phenylethylamine derivatives (*S*)-**1a**–**d** and racemic 1-(3-methoxyphenyl)ethylamine derivatives *rac*-**2a**,**b**, chiral additive induced self-disproportionation of enantiomers was observed only in the pairs of *N*-formyl derivative (*S*)-**1a** (50 mg) and *rac*-**2a** (60 mg) and *N*-acetyl derivative (*S*)-**1b** (49 mg) and *rac*-**2b** (50 mg).[8] MPLC of these pairs brought about the elution of optically active **2a** (1.2 mg, 99% ee) and **2b** (1.0 mg, 90% ee), respectively.

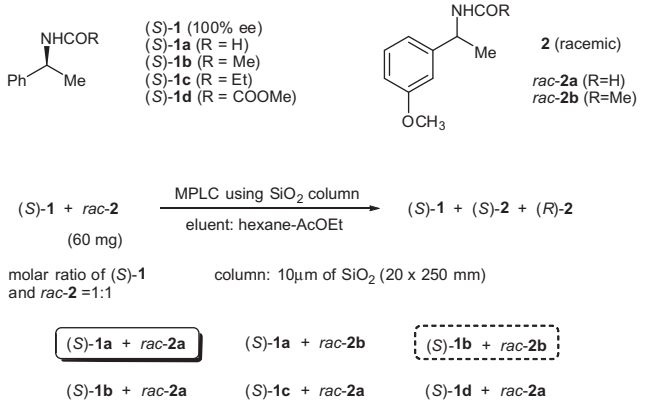


Figure 2. MPLC experiment of mixture of (*S*)-**1** and *rac*-**2**.

We further envisioned that the efficiency of these results could be improved upon by increasing the amount of chiral additive (*S*)-**1a** and so increase the number of quality interactions between (*S*)-**1a** and enantiomers of *rac*-**2a**. After a survey of the molar ratio between (*S*)-**1a** and *rac*-**2a**, it was found that a ratio of 5.5:1 gave the best result.[10]

This (*S*)-**1a** and *rac*-**2a** were mixed in a molar ratio of 5.5:1 (276 mg:60 mg), 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 shown in Figure 3. It should be noted that, as it was designed, the chiral additive was completely separated, as the first eluted fraction, from the components of compound **2a**. The latter peak due to **2a** has several noticeable boundaries (shoulders). Analysis of the enantiomeric composition of these fractions, using chiral HPLC showed that the less polar fraction contained enantiomerically pure **2a** (>99% ee, 7.9 mg, recovery yield: 26%), while the more polar fraction was of 16% ee (48.9 mg), accounting for the complete mass and 50:50 initial enantiomeric composition of the racemate **2a**.

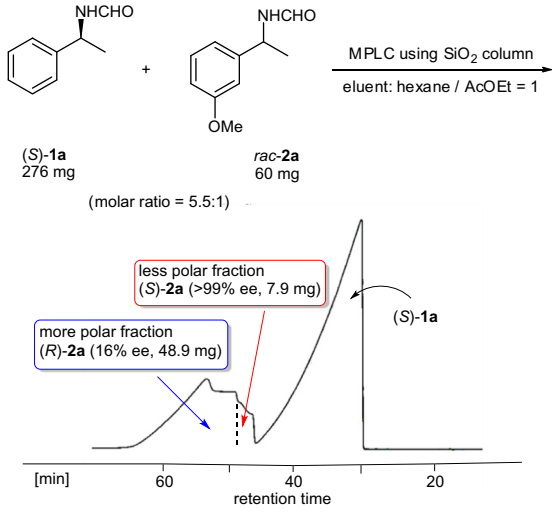


Figure 3. MPLC chart of mixture in a molar ratio of (*S*)-**1a** and *rac*-**2a** = 5.5:1.

The composition in the area of **2a** with several shoulders was investigated 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*)-**2a**, while the rest of the fractions (from the second to the sixth) contained an excess of (*R*)-**2a** with gradually decreasing enantiomeric purity from 23% to 10% ee.

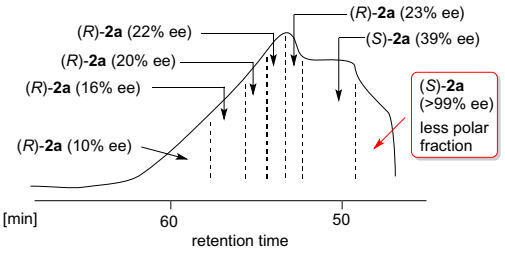
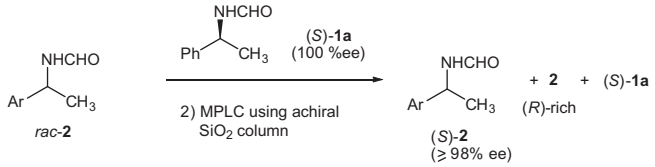


Figure 4. Detailed ee change of **2a** in chart of Figure 3.

Subsequently, the application of the present chiral additive induced self-disproportionation of enantiomers to various *N*-formyl-1-arylethylamine derivatives was examined under the same conditions (Table 1). Thus, in addition to 3-methoxyphenyl

derivative **2a**, the procedure performed using 4-methoxy and 2-methoxy derivatives *rac*-**2c** and *rac*-**2d** and led to the elution of **2c** (99% ee) and **2d** (98% ee) with high enantiomeric purity in recovery yields of 14% and 21%, respectively (entries 2 and 3). This method could be applied to *N*-formyl-1-phenyl-ethylamines *rac*-**2e**–**2i** bearing various substituents such as bromo, chloro, fluoro and methyl groups on the benzene ring (entries 4–8). For these substrates, optically active **2e**–**2i** were obtained with recovery yields of 14–28% with 98–99% ee. It should be noted that the chiral additive induced self-disproportionation of enantiomers was observed not only in *N*-formyl-1-phenyl-ethylamine derivatives *rac*-**2a**–**2i** but also in *N*-formyl-1-naphthylethylamine derivatives *rac*-**2j** and *rac*-**2k**, and almost enantiomerically pure **2j** (98% ee) and **2k** (99% ee) were obtained with recovery yields of 16% and 27%, respectively (entries 9 and 10).

Table 1
Application of chiral additive induced self-disproportionation of enantiomers to various racemic *N*-formyl-1-arylethylamines rac-**2**



Entry	Ar *rac*-**2**	*rac*-**2** (mg)	(*S*)-**2**: recovery weight[a] (mg)	and ee[b] (%)
1	3-MeOC_6H_4 **2a**	60	7.9	99
2	4-MeOC_6H_4 **2c**	60	4.3	99
3	2-MeOC_6H_4 **2d**	57	6.1[c]	98
4	3-BrC_6H_4 **2e**	60	7.6[c]	99
5	4-BrC_6H_4 **2f**	60	5.3	99
6	4-ClC_6H_4 **2g**	60	6.7	98
7	4-FC_6H_4 **2h**	60	7.1	99
8	4-MeC_6H_4 **2i**[d]	60	8.5	99
9	Naphth-1-yl **2j**	60	5.0	98
10	Naphth-2-yl **2k**	54	7.2[c]	99

[a] Isolated recovery weight.
[b] The ee was determined by HPLC analysis using a chiral column.
[c] Since **2d**, **2e**, **2k** contained chiral additive (*S*)-**1a**, their recovery weights were evaluated by ^{1}H NMR and HPLC.
[d] Chiral additive induced self-disproportionation of enantiomers was conducted in a molar ratio of (*S*)-**1a** and *rac*-**2i** = 3:1, while in MPLC using 5.5 equiv of (*S*)-**1a**, the clear peak due to (*S*)-**2i** was not detected because of the complete overlap with the peak of (*S*)-**1a**.

In entries 2 and 5–7, the chiral additive (*S*)-**1a** was completely separated from the components of substrates **2c**, **2f**–**2h** such as MPLC shown in Figure 3. Meanwhile in the cases of entries 3, 4 and 10, (*S*)-**1a** could not be completely separated from the substrates **2d**, **2e**, **2k** because of a similar retention time between the substrates and (*S*)-**1a**, and the obtained almost enantiomerically pure (*S*)-**2d**, **2e**, **2k** contained chiral additive (*S*)-**1a** [the recovery weight of (*S*)-**2d**, **2e**, **2k** was evaluated by ^{1}H NMR or HPLC analysis]. In entries 8 and 9, although (*S*)-**1a** was not completely separated from the components of substrates **2i** and **2j**, the fraction involving the almost enantiomerically pure (*S*)-**2i** and **2j** did not contain (*S*)-**1a** (see Fig. 7).

Typical MPLC charts on the chiral additive induced self-disproportionation of enantiomers are shown in Figures 5–7. Figure 5 shows the chiral additive induced self-disproportionation of enantiomers of *p*-fluorophenyl derivative *rac*-**2h**. Similar to the chiral additive induced self-disproportionation of enantiomers of *rac*-**2a** (Fig. 3), chiral additive (*S*)-**1a** initially eluted and was completely separated from substrate **2h**. Subsequently almost enantiomerically pure **2h** (99% ee) and slightly enantioenriched **2h** (11–23% ee) were eluted. Similar chromatographic profiles were also observed in the chiral additive induced self-disproportionation of enantiomers of **2c**, **2f**, **2g** (Table 1, entries 2 and 5–6).

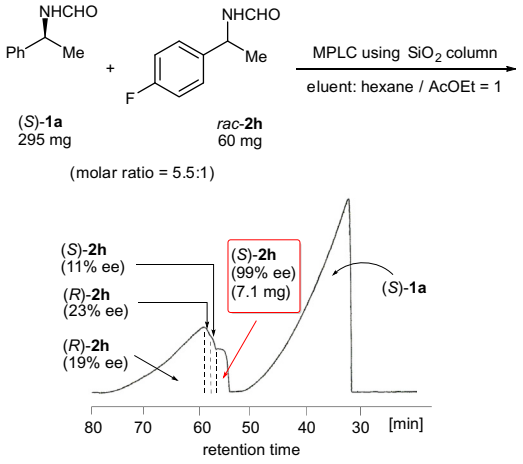


Figure 5. Chiral additive induced self-disproportionation of enantiomers of *rac*-**2h** with (*S*)-**1a**.

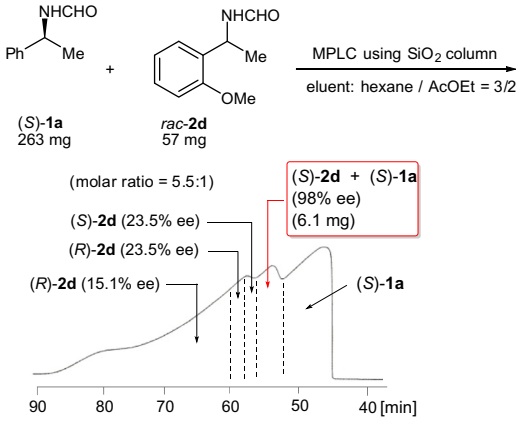


Figure 6. Chiral additive induced self-disproportionation of enantiomers of *rac*-**2d** with (*S*)-**1a**.

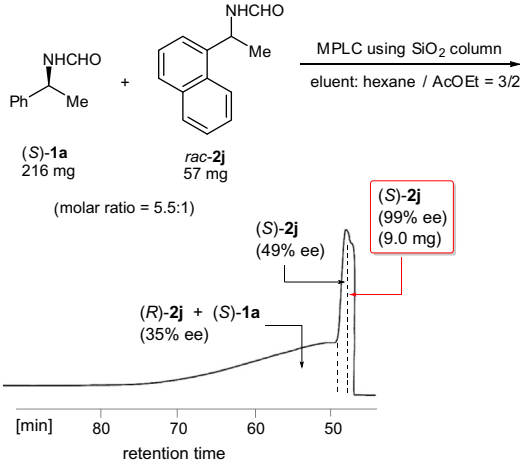


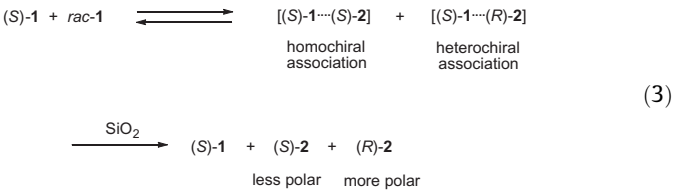
Figure 7. Chiral additive induced self-disproportionation of enantiomers of *rac*-**2j** with (*S*)-**1a**.

Figure 6 shows the MPLC chart of the mixtures of *rac*-**2d** and (*S*)-**1a**. In this case, (*S*)-**1a** could not be completely separated from **2d**; instead **2d** was obtained with high enantiomeric purity as a mixture with (*S*)-**1a**. Similar chromatographic profiles were also observed in 3-bromophenyl and naphth-2-yl derivatives **2e** and **2k** (Table 1, entries 4 and 10).

The MPLC chart in Figure 7 shows the chiral additive induced self-disproportionation of enantiomers of *rac*-**2j**. In this case, almost enantiomerically pure (*S*)-**2j** was eluted first and subsequently a mixture of (*S*)-**1a** and slightly (*R*)-rich **2j** was eluted. The elution of this type was also observed in the case of 4-methylphenyl derivative **2i** (Table 1, entry 8).

In all of the chiral additive induced self-disproportionation of enantiomers shown in Table 1, **2a**–**2k** with high enantiomeric purity was always eluted as the less polar fractions and subsequently the slightly (*R*)-enriched enantiomer mixture was eluted in the end. Furthermore, the absolute stereochemistry of **2a**–**2k** in the less polar fractions was found to be (*S*).[11] Thus, when (*S*)-**1** was used as the chiral additive, (*S*)-**2** was obtained with high enantiomeric purity as the less polar fractions without exception.

These results may be rationalized as follows (Eq. 3). We have previously suggested[3] that compounds of this class prefer to form syndiotactic mixed heterochiral associations consisting of different enantiomers more than isotactic mixed homo-chiral associations consisting of the same enantiomers.[5] Thus, it may be assumed that the (*S*)-chiral additive reagent (*S*)-**1a** selectively forms high-order species with the (*R*)-enantiomer of *rac*-**2**, which have longer retention times compared to monomeric species of the (*S*)-enantiomer which elute first.



(3)

We also investigated the chiral additive induced self-disproportionation of enantiomers of *N*-formyl-1-phenylpropylamine **3** and *N*-formy-2-phenylpropylamine **4** (Fig. 8). However, under the same conditions, the efficient chiral additive induced self-disproportionation of enantiomers such as *N*-formyl 1-arylethylamine derivatives **2** was not observed. In MPLC with **3**, slightly enantioenriched (*S*)-**3** (13% ee) was obtained as a less polar fraction, and with **4**, no elution of enantioenriched **4** was found. Thus, 1-arylethylamine skeleton may be required for the present chiral additive induced self-disproportionation of enantiomers using (*S*)-**1**.

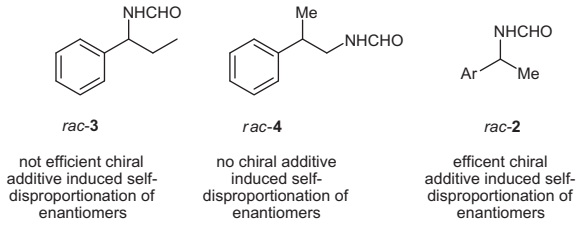


Figure 8. Application of chiral additive induced self-disproportionation of enantiomers to other substrates **3** and **4** except for **2**.

3. Conclusion

We have found that self-disproportionation of the enantiomers of various racemic *N*-formyl-1-arylethylamines *rac*-**2** occurs via the addition of (*S*)-*N*-formyl-1-phenylethylamine (*S*)-**1** followed by MPLC of the mixtures to bring about the elution of almost enantiomerically pure (*S*)-**2**. Direct resolution methods of racemates via chromatography using chiral mobile[12] or stationary phases[13] are known.[14] However, a chiral mobile phase method requires the use of a very large excess (>100 equiv) of a chiral selector added to an eluent, inevitably resulting in mixtures of resolved enantiomers with the chiral selector at all times. Although separation of the enantiomers using the chiral stationary phase method is the most popular on an analytical scale, the only disadvantage of this approach is that the preparative chiral stationary phase columns are still very expensive. Our approach based on the chiral additive induced self-disproportionation of enantiomers provides an inexpensive and facile research laboratory technique for the generation of enantiomerically pure compounds starting from racemates, although structural similarities between the racemic substrates and a chiral additive are required to achieve the chiral additive induced self-disproportionation of enantiomers. The application of the present chiral additive induced self-disproportionation of enantiomers method to other compounds except for 1-arylethylamines is currently in progress.

4. Experimental

4.1. General

Medium-pressure liquid chromatography (MPLC) was performed on a 25 × 4 cm i.d. prepacked column (silica gel, 10 μm) with a UV detector. High-performance liquid chromatography (HPLC) was performed on a 25 × 0.46 cm i.d. chiral column with a UV detector.

4.2. Chiral additive 1a and racemic substrates 2a–2k

Chiral additive **1a** and racemic substrates **2a**–**2k**, **3**, **4** are commercially available.

4.3. General method for the chiral additive induced self-disproportionation of enantiomers

At first, *rac*-**2a** (61 mg) and (*S*)-**1a** (276 mg) were mixed in a molar ratio of 1:5.5, and then the mixtures were separated to the less polar fraction [(*S*)-**2a**, 7.9 mg, >99% ee] and the more polar fraction (48.9 mg, 16% ee) by MPLC (hexane/AcOEt = 1). The ee of **2b** was determined by HPLC analysis using a CHIRALCEL OD-3 column [25 cm × 0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 1.5 mL/min; (*S*)-**2b**; t_R = 17.0 min, (*R*)-**2b**; t_R = 11.3 min]. The absolute configuration was determined based on the comparison with authentic sample of (*S*)-**2a**, which was prepared from (*S*)-1-(3-methoxyphenyl)ethylamine.

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