Pergamon

Tetrahedron 55 (1999) 6453–6464

TETRAHEDRON

Design, Synthesis, and Optical Resolution of a Novel Non-natural Chiral Auxiliary, 1-(2,5-Dimethoxyphenyl)ethylamine. Application to Diastereoselective Alkylation of Aldimines

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Received 10 February 1999; accepted 5 April 1999

Abstract: A chiral amine, 1-(2,5-dimethoxyphenyl)ethylamine, was found to be an effective chiral auxiliary for the diastereoselective alkylation of its aldimines with alkylmetals. The 1-(2,5-dimethoxyphenyl)ethyl group of the chiral auxiliary could be removed by the acetylation and then oxidation of the resultant alkylated product, accompanying an amino-transfer from the chiral auxiliary to the final product. Racemic 1-(2,5-dimethoxyphenyl)ethylamine could be easily synthesized from 1,4-dimethoxybenzene and resolved by the diastereomeric salt formation with mandelic acid to give both enantiomers in pure forms.

Keywords Alkylation; Chelation; Diastereoselection; Imines

1. Introduction

In recent two decades, many kinds of chiral auxiliaries have been developed in order to achieve efficient asymmetric syntheses.[1,2] For the construction of most of the chiral auxiliaries, natural chiral compounds have been properly selected and derivatized into appropriate structures. However, so long as natural chiral compounds and their derivatives are used as chiral auxiliaries, there are some serious limitations: 1) The possible or available structural modification of the natural chiral compounds is sometimes limited. 2) The availability of both enantiomers is not always guaranteed, meaning that a target compound with desired absolute configuration is not necessarily produced. In order to solve these problems, a lot of efforts[1,2] have been made in recent years on the development of non-natural chiral auxiliaries on the basis of the considerations that a non-natural chiral auxiliary is flexible in design and that its both enantiomers can be equally obtained if a method for its efficient optical resolution is developed.[3,4]

Among non-natural chiral auxiliaries developed so far, 1-phenylethylamine is a typical and simple chiral auxiliary.[5] Although the amine is widely used in asymmetric reactions, including those with an amino-

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0040-4020/99/$ - see front matter
PII: S0040-4020(99)00307-5

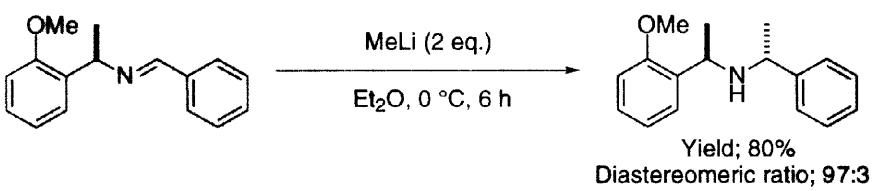
transfer,[6-8] satisfactory stereoselectivity is not necessarily observed, depending on the reaction. However, upon introducing substituent(s) on the aromatic ring of 1-phenylethylamine, the stereoselectivity is influenced by the steric and/or electronic effect of the substituent(s), as we have shown in the asymmetric Staudinger reaction of aldimines derived from 1-(2,6-dichlorophenyl)ethylamine.[9] The result indicates that the stereoselectivity of asymmetric reactions can be highly improved even upon a slight modification of a simple chiral auxiliary.

The asymmetric nucleophilic alkylation of the carbon-nitrogen double bond of aldimines has been intensively studied in order to prepare optically active amines.[10-13] In the course of our continuing studies on the development of new non-natural chiral auxiliaries,[9,14-19] we have found that the alkylation of aldimines, derived from 1-(2-methoxyphenyl)ethylamine, with alkyllithiums proceeded smoothly to give the corresponding alkylated products with excellent diastereoselectivity by means of the chelations not only between the aldimine nitrogen and the lithium but also between the methoxy oxygen and the lithium.[19] However, the removal of the 1-(2-methoxyphenyl)ethyl group with an amino-transfer from the auxiliary to the final products could not be realized.

In this paper, we report the design, synthesis, and optical resolution of a non-natural chiral auxiliary, and its application to the diastereoselective alkylation of aldimines with alkylmetals.

2. Results and Discussion

The methylation of benzaldimine of 1-(2-methoxyphenyl)ethylamine with methyllithium proceeded with excellent diastereoselectivity,[19] compared with the results reported for the alkylation of aldimines of 1-phenylethylamine[6-8] (eq. 1).

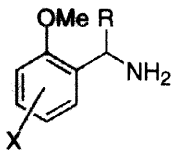


Yield; 80%
Diastereomeric ratio; 97:3

(eq. 1)

However, when reductive methods, widely used for the removal of a benzyl group in amines, were applied to the product, [1-(2-methoxyphenyl)ethyl][1-phenylethyl]amine, the scission of the undesired C-N bond exclusively occurred to give 1-(2-methoxyphenyl)ethylamine and ethylbenzene. Moreover, oxidative methods by using oxidants such as ceric ammonium nitrate (CAN) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) resulted in no reaction or the formation of complex mixtures.

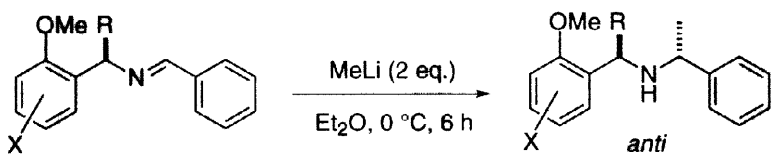
From these results, we considered that the 2-methoxy group would be essential in order to achieve excellent diastereoselectivity and that the introduction of another hetero substituent would make the arylethyl group susceptible to oxidative removal. On the basis of these considerations, we designed several chiral auxiliaries **1a-f**, which have two methoxy groups on the phenyl group of 1-phenylethylamine. The racemic amines *rac*-**1a-f** were easily prepared by the reductive amination of the corresponding ketone, the reduction of the corresponding azide, and so on.



1a ; R=Me, X=3-OMe
1b ; R=Me, X=4-OMe
1c ; R=Me, X=5-OMe
1d ; R=Me, X=6-OMe
1e ; R=*i*-Pr, X=5-OMe
1f ; R=Ph, X=5-OMe

We at first carried out the methylation of benzaldimines **2-7**, derived from benzaldehyde and the racemic amines *rac*-**1a-f**, with methyllithium (2 eq.) in Et_2O at 0 °C (the optimal conditions for the methylation of benzaldimine derived from 1-(2-methoxyphenyl)ethylamine[19]). The results are summarized in Table 1. The reactions proceeded very smoothly to afford the corresponding methylated products **8-13** in good to high yields with high to excellent diastereoselectivity. Noteworthy is that the position of the second substituent slightly influences both the yield and the diastereoselectivity; 1-(2,3-dimethoxyphenyl)ethylamine (**1a**) and 1-(2,5-dimethoxyphenyl)ethylamine (**1c**) were a little superior to 1-(2-methoxyphenyl)ethylamine (compare entries 1, 2, and 4). In contrast, the bulkiness of the α-alkyl or aryl group had no influence on the diastereoselectivity, although the yield decreased with increasing the bulkiness (compare entries 4, 6, and 7). Among the amines we examined, 1-(2,3-dimethoxyphenyl)ethylamine (**1a**) and 1-(2,5-dimethoxyphenyl)ethylamine (**1c**) were found to be the most effective chiral auxiliaries from the viewpoints of yield and diastereoselectivity.

Table 1. Effect of the Second Substituent in the Aromatic Ring and the α-Alkyl or Aryl Group of Aldimines **2-7** on the Diastereoselectivity.



rac-**2-7** *rac*-**8-13**

Entry	Imine	R	X	Product	Yield/%	Diastereomeric Ratio[1] *Anti:Syn*
1		Me	H		80	97:3 [2]
2	**2**		3-OMe	**8**	88	99:1
3	**3**		4-OMe	**9**	60	90:10
4	**4**		5-OMe	**10**	89	99:1
5	**5**		6-OMe	**11**	67	83:17
6	**6**	*i*-Pr	5-OMe	**12**	78	98:2
7	**7**	Ph	5-OMe	**13**	68	98:2

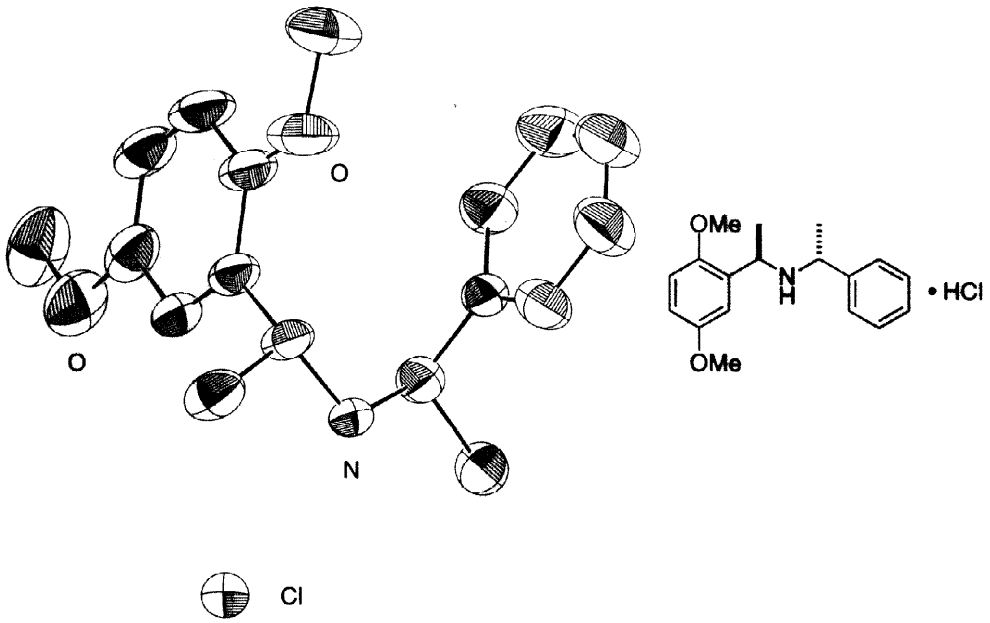
1) The diastereomeric ratio was determined by gas chromatography.
2) Ref 19.

The racemic amines, *rac*-**1a** and *rac*-**1c**, were prepared from 1-(2,3-dimethoxyphenyl)ethyl mesylate by azidation followed by reduction and from 2,5-dimethoxyacetophenone by reductive amination, respectively. From the viewpoints of availability of the starting material and easiness of the derivatization, we finally decided to use **1c** as a new non-natural chiral auxiliary in the following study.

In order to clarify the relative configuration of the major products, we carried out the X-ray crystallographic analysis of *rac*-**10**•HCl (Fig. 1). As can be seen from Figure 1, the relative configuration between the methyl groups, originated from the chiral auxiliary and newly introduced by the reaction, is *anti*. The relative

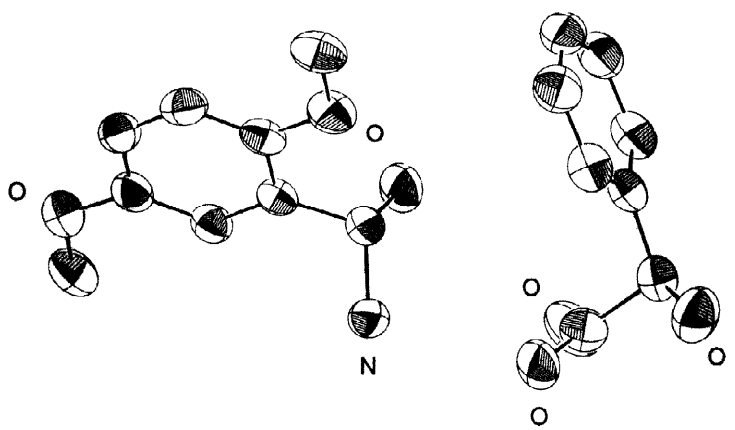
configuration of the other products were deduced to be also *anti* upon comparing the GC retention order, and the ^{1}H-NMR chemical shifts and coupling constants of the products with those of *rac*-**10**.

Figure 1. ORTEP Drawing of [(*RS*)-1-(2,5-Dimethoxyphenyl)ethyl][(*RS*)-1-phenylethyl]amine Hydrochloride (*rac*-**10**•HCl).



Next, we tried the optical resolution of the racemic amine *rac*-**1c** by the diastereomeric salt formation, referring the result on the partial resolution with mandelic acid reported in our previous paper.[20] Upon optimizing the solvent system and repeating recrystallization, both less-soluble diastereomeric salts of **1c** with both enantiopure mandelic acids were obtained in pure forms: Equimolar amounts of *rac*-**1c** and (*R*)-mandelic acid was mixed in MeOH/H_2O and crystallized, and then the precipitate appeared was recrystallized three times from MeOH/H_2O to give one of the less-soluble diastereomeric salts ((*R*)·(*R*)-salt) in pure form. Moreover, crystallization followed by recrystallizations for four times of a mixture of equimolar amounts of the free

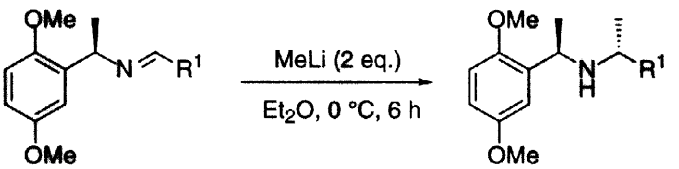
Figure 2. ORTEP Drawing of the More-soluble Diastereomeric Salt of 1-(2,5-Dimethoxyphenyl)ethylamine with (*R*)-Mandelic Acid.



amine, recovered from the combined filtrates, and (*S*)-mandelic acid from MeOH/H_2O gave the other less-soluble diastereomeric salt ((*S*)·(*S*)-salt) in pure form. Upon treating the pure salts thus obtained with an alkaline solution, both enantiomers of **1c** were obtained in almost enantiopure forms. The absolute configuration of the enantiopure amine **1c** was determined by X-ray crystallographic analysis of the more-soluble diastereomer with (*R*)-mandelic acid (Fig. 2); $(-)_{589}$-**1c** has an absolute configuration of *S*.

In the next stage, we carried out the methylation of enantiopure aldimines (*R*)-**4a-e**, prepared from (*R*)-**1c** and various aldehydes, with methyllithium (Table 2). The reactions proceeded smoothly to give the methylated products in good yields with excellent diastereoselectivity, except for the reaction of aldimine (*R*)-**4e** prepared from *trans*-cinnamaldehyde. The enantiopure aldimine (*S*)-**4a**, prepared from (*S*)-**1c**, reacted with methyllithium with excellent diastereoselectivity as same as did (*R*)-**4a** (entry 1, in parentheses).

Table 2. Nucleophilic Addition of Methyllithium to Various Aldimines (*R*)-**4**.



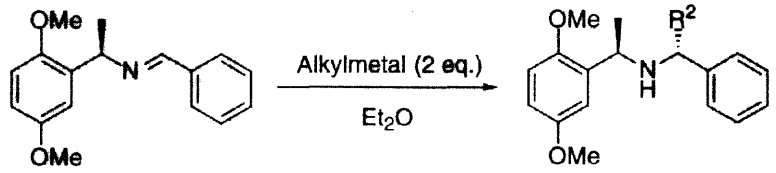
(*R*)-**4a-e** (*R,R*)-**10a-e**

Entry	R^1	Product	Yield/%	Diastereomeric Ratio[1] *Anti:Syn*
1[2]	C_6H_5	**10a**	89 (80)	99:1 (99:1)
2	*p*-MeC_6H_4	**10b**	84	98:2
3	*p*-ClC_6H_4	**10c**	89	97:3
4	1-Naphthyl	**10d**	83	>99:1
5	*trans*-Styryl	**10e**	77	86:14

1) The diastereomeric ratio was determined by gas chromatography, or ^{1}H-NMR.
2) The values in parentheses are those when (*S*)-amine was used.

The butylation and allylation of enantiopure aldimine (*R*)-**4a** also proceeded smoothly upon properly selecting organometallic reagents (Table 3). The aldimine (*R*)-**4a** did not react with methylmagnesium bromide (entry 1), while it reacted with methyllithium (entry 2). In contrast, the reaction of (*R*)-**4a** with allyllithium resulted in low diastereoselectivity (entry 4), whereas the reaction with allylmagnesium bromide proceeded with excellent diastereoselectivity (entry 5). These results indicate that the yield and the diastereoselectivity of the present aldimine-alkylation strongly depend on the reactivity of organometals.[21-28]

Table 3. Nucleophilic Addition of Alkylmetals to Aldimine (*R*)-**4a**.



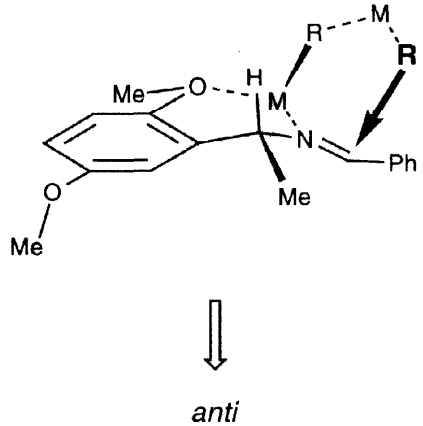
(*R*)-**4a** (*R*, *R*)-**10a, f, g**

Entry	Alkylmetal	Conditions	Product	Yield/%	Diastereomeric Ratio[1] *Anti:Syn*
1	MeMgBr	0 °C, 6 h	–	n.r.	–
2	MeLi		**10a**	89	99:1
3	*n*-BuLi		**10f**	78	98:2
4	AllylLi		**10g**	58	68:32
5	AllylMgBr	−78 °C–0 °C, 18 h	**10g**	99	98:2

1) The diastereomeric ratio was determined by gas chromatography.

The *anti* selectivity of the present reaction would be explained as follows: The lithium of an alkyllithium molecule coordinates to the nitrogen of the aldimine and to the oxygen of the methoxy group at the 2-position to form a six-membered chelate; here, the fact that the bulkiness of the α-substituent did not influence the selectivity indicates that the α-substituent would occupy the position of pseudo equatorial. Moreover, both of the methyl of the methoxy group at the 2-position and the alkyl of the alkyllithium would be also located at the positions of pseudo equatorial in order to avoid the steric repulsion between them as shown in Figure 3. Then, the alkyl group of another alkyllithium molecule attacks the carbon of the aldimine with the assistance of the coordination with the alkyl group of the alkyllithium in the chelate. The methoxy group at the 5-position would work as an electron-donating group to make the electron density of the methoxy group at 2-position is higher than that in the aldimine of 1-(2-methoxyphenyl)ethylamine. As a result, the six-membered chelate becomes more rigid to give more excellent selectivity.

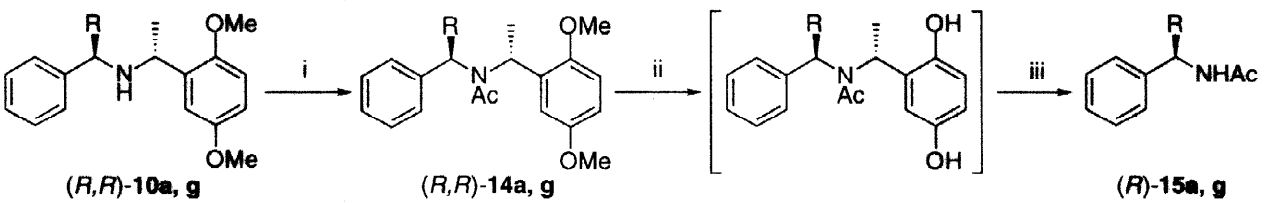
Figure 3. Transition State of Alkylation of Imine **4**.



anti

Finally, the removal of 1-(2,5-dimethoxyphenyl)ethyl group with an amino-transfer from the alkylated products to the final amino products was examined. Since the scission of the undesired C-N bond exclusively occurred by reductive methods as was reported by Bringmann *et al.*,[29] an oxidative method was applied to remove the 1-(2,5-dimethoxyphenyl)ethyl group in **10**. However, treatment of **10** with BBr_3 for demethylation to afford a hydroquinone derivative, followed by the MnO_2-oxidation, gave complex mixtures. In contrast, N-acetylated secondary amines **14** gave the amines **15** in acceptable yields upon treatment with BBr_3, followed by the MnO_2-oxidation, as shown in Scheme 1.

Scheme 1. Removal of the Chiral Auxiliary Part in (*R*, *R*)-**10a, g** with an Amino-transfer to the Final Product.



Reagents and conditions; i: **10a** (R=Me); Ac_2O, Et_3N, CH_2Cl_2, r.t., 12 h, 81%
10g (R=Allyl); Ac_2O, Pyridine, reflux, 5 h, 84%
ii: BBr_3, Benzene, reflux, 6 h
iii: MnO_2, $MgSO_4$, AcOEt, r.t., 12 h. **10a**, 71%; **10g**, 46% (2 steps).

3. Conclusion

We applied 1-arylethylamine derivatives to the asymmetric alkylation of aldimines as simple chiral auxiliaries. Among the amines we examined, 1-(2,5-dimethoxyphenyl)ethylamine was found to be the most effective for this reaction. The amine could be easily resolved with mandelic acid into both enantiomers in pure forms. The aldimines, prepared from the amine and various aldehydes, reacted smoothly with organometallic reagents to give the corresponding alkylated products in good yields with excellent diastereoselectivity. The removal of 1-(2,5-dimethoxyphenyl)ethyl group in the alkylated products with an amino-transfer was accomplished by a three-step procedure; acetylation, demethylation, and then oxidation. In conclusion, we developed an efficient method for the preparation of enantiopure amines by the nucleophilic alkylation of aldimines of enantiopure 1-(2,5-dimethoxyphenyl)ethylamine, which could be easily synthesized, resolved, and removed with an amino-transfer.

4. Experimental Section

General: All starting materials were obtained from commercial suppliers and used with purification. Diethyl ether was immediately distilled from sodium benzophenone ketyl, prior to use. Dichloromethane was distilled over calcium hydride and preserved with molecular sieves (MS) 4A. Preparative thin layer chromatography was performed on a glass plate using Wako gel W-B5F. ^{1}H-NMR spectra were recorded on a Varian Mercury 300 at 300 MHz using tetramethylsilane (TMS) as an internal standard. Chemical shifts were reported as ppm in a δ scale down field from TMS. ^{13}C-NMR spectra were recorded at 75.3 MHz upon referring residual $CHCl_3$ (δ

77.00 ppm) in $CDCl_3$. Infrared spectra were recorded on a JASCO IR 810 for a neat film on a NaCl plate or a tablet of KBr. Melting points were determined on a Mitamura Riken Kogyo MEL-TEMP. Optical rotations were recorded on a JASCO DIP-360. Analytical GC were performed using a 25 m methyl silicone column (CBP1-M25-025). Analytical HPLC were performed using a DAICEL CROWNPAK CR-(+) column with a detector wavelength of 210 nm, or a DAICEL CHIRALCEL OB column with a detector wavelength of 254 nm.

Preparation of Racemic Amines 1a-f.

Racemic 1-(2,3-dimethoxyphenyl)ethylamine (**1b**) was prepared from the corresponding azide,[30] and racemic α-(2,5-dimethoxyphenyl)benzylamine (**1f**) was prepared by the reaction of *N*-trimethylsilyl-benzaldimine with 2,5-dimethoxyphenyllithium.[31] The other racemic amines were prepared by reductive amination from the corresponding ketones.[32]

Optical Resolution of 1-(2,5-Dimethoxyphenyl)ethylamine (1c).

To a hot solution of *rac*-**1c** (17.1 g, 95.1 mmol) in $MeOH/H_2O$ (12 ml/45 ml) was added a hot solution of (*R*)-mandelic acid (14.5 g, 95.3 mmol) in $MeOH/H_2O$ (12 ml/45 ml), and the mixture was heated for 1 h. Then the clear solution was cooled at room temperature, and the precipitate appeared was collected by filtration. The precipitate was recrystallized from $MeOH/H_2O$ (1/4, 175 ml); the clear hot solution was allowed to stand at room temperature for 1 day and then at 0 °C for 2 h, and the precipitate was collected by filtration and washed with cold $MeOH/H_2O$ (1/4, 20 ml). Recrystallization of the precipitate from $MeOH/H_2O$ (1/4) for additional two times (100 ml then 50 ml) under similar conditions gave the diastereomerically pure (*R*)·(*R*)-salt (10.2 g, 30.7 mmol, 33% based on *rac*-**1c** used); colorless crystals; mp 170-173 °C; $[\alpha]_D^{26}$ –41.9 (*c* 1.00, MeOH); IR (KBr) 1560, 1500, 1225, 1035, 730 cm^{-1}.

To the powder of the diastereomerically pure (*R*)·(*R*)-salt was added aqueous NaOH (1M, 100 ml). The mixture was stirred for 1 h at room temperature and then extracted with Et_2O (3 × 50 ml). The combined extracts were dried with $MgSO_4$ and concentrated under reduced pressure. The oily product was purified by Kugelrohr distillation (122 °C, 2.5 mmHg) to give (*R*)-**1c** (4.27 g, 23.7 mmol, 30%); colorless oil; $[\alpha]_D^{22}$ +22.7 (*c* 1.01, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.37 (d, 3H, *J* = 6.8 Hz), 3.78 (s, 3H), 3.80 (s, 3H), 4.30 (q, 1H, *J* = 6.6 Hz), 6.71 (dd, 1H, *J* = 8.9, 3.0 Hz), 6.79 (d, 1H, *J* = 8.9 Hz), 6.94 (d, 1H, *J* = 3.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 23.2, 46.0, 55.7, 55.7, 111.2, 111.3, 112.3, 137.0, 150.9, 153.6; IR (NaCl) 1640, 1495, 1450, 1270, 1210, 1050 cm^{-1}; HPLC 148.8 min [DAICEL CROWNPAK CR-(+), Flow rate 0.8 ml/min, aqueous $HClO_4$ (pH=2)].

The combined filtrates of the crystallization and recrystallizations, performed above, were concentrated under reduced pressure to give the solid mass. The solid mass was treated with aqueous NaOH (1M, 200 ml), and the mixture was extracted with Et_2O (3 × 100 ml). The combined extracts were dried with $MgSO_4$ and concentrated under reduced pressure to give (*S*)-enriched amine (8.9 g, 49 mmol). The (*S*)-enriched amine was similarly treated with (*S*)-mandelic acid (7.5 g, 49 mmol), and the salt thus obtained was recrystallized from $MeOH/H_2O$ (1/4) for four times (75 ml, 25 ml, 25 ml, then 25 ml) to give diastereomerically pure (*S*)·(*S*)-salt (8.64 g, 26.0 mmol, 28%); colorless crystals; mp 171-173 °C; $[\alpha]_D^{24}$ +40.0 (*c* 1.00, MeOH); IR (KBr) 1560, 1500, 1225, 1035, 730 cm^{-1}. Similar treatment of this salt with an alkaline gave (*S*)-**1c** (3.89 g, 21.6 mmol, 27%); colorless

oil; $[\alpha]_D^{23}$ –22.1 (*c* 1.01, $CHCl_3$); HPLC 112.7 min [DAICEL CROWNPAK CR-(+), Flow rate 0.8 ml/min, aqueous $HClO_4$ (pH=2)].

Preparation of Aldimines.

To a solution of the aldehyde (1 mmol) in CH_2Cl_2 (5 ml) was added the neat amine (1 mmol) and MS 4A (2 g) at room temperature. After 12 h, the MS was filtered off through a celite pad and the filtrate was concentrated under reduced pressure. The aldimine thus obtained was used without further purification.

General Procedure for the Alkylation of Aldimines.

To a solution of the aldimine (1 mmol) in dry Et_2O (3 ml) was added dropwise the alkylmetal solution (2 mmol) at 0 °C under argon, and then the mixture was stirred at the same temperature for 6 h. After the reaction was quenched with saturated aqueous NH_4Cl (5 ml), the organic layer was separated and the aqueous layer was extracted with AcOEt (3 × 10 ml). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by preparative thin layer chromatography to give the alkylated product.

[(*RS*)-1-(2,3-Dimethoxyphenyl)ethyl][(*RS*)-1-phenylethyl]amine (8). Light yellow oil; ^{1}H-NMR ($CDCl_3$) δ 1.27 (d, 6H, *J* = 6.6 Hz), 3.57 (q, 1H, *J* = 6.9 Hz), 3.60 (s, 3H), 3.85 (q, 1H, *J* = 6.9 Hz), 3.85 (s, 3H), 6.81 (dd, 1H, *J* = 8.0, 1.4 Hz), 6.87 (dd, 1H, *J* = 8.0, 1.4 Hz), 7.05 (t, 1H, *J* = 8.0 Hz), 7.16-7.34 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 24.0, 25.2, 50.1, 55.2, 55.5, 60.4, 110.3, 118.9, 123.9, 126.6, 126.7, 128.2, 139.0, 145.8, 146.9, 152.6; IR (NaCl) 1475, 1450, 1265, 1065, 700 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.53; H, 8.11; N, 4.85. GC 10.9 min (99 %), 11.6 min (1 %) (Column temp. 200 °C).

[(*RS*)-1-(2,4-Dimethoxyphenyl)ethyl][(*RS*)-1-phenylethyl]amine (9). Light yellow oil; ^{1}H-NMR ($CDCl_3$) δ 1.26 (d, 3H, *J* = 6.6 Hz), 1.28 (d, 3H, *J* = 6.6 Hz), 3.50 (q, 1H, *J* = 6.6 Hz), 3.67 (q, 1H, *J* = 6.6 Hz), 3.77 (s, 3H), 3.81 (s, 3H), 6.43-6.46 (m, 2H), 7.02 (d, 1H, *J* = 8.8 Hz), 7.21-7.32 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 22.9, 25.1, 51.2, 55.1, 55.2, 98.8, 103.8, 125.5, 126.6, 126.8, 128.1, 128.5, 145.9, 158.4, 159.4; IR (NaCl) 1505, 1210, 1040, 700 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.50; H, 8.21; N, 4.86. GC 15.3 min (90 %), 16.3 min (10 %) (Column temp. 200 °C).

[(*RS*)-1-(2,6-Dimethoxyphenyl)ethyl][(*RS*)-1-phenylethyl]amine (11).[29] Light yellow oil; ^{1}H-NMR ($CDCl_3$) δ 1.24 (d, 3H, *J* = 6.6 Hz), 1.34 (d, 3H, *J* = 6.9 Hz), 3.45 (q, 1H, *J* = 6.6 Hz), 3.70 (s, 3H), 3.75 (s, 3H), 4.14 (q, 1H, *J* = 6.9 Hz), 6.54 (d, 2H, *J* = 8.3 Hz), 7.11-7.31 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ 20.9, 25.3, 46.2, 55.3, 55.5, 104.0, 120.5, 126.4, 126.7, 127.1, 127.4, 127.8, 128.0, 146.1, 158.6; IR (NaCl) 1595, 1475, 1245, 1110 cm^{-1}. GC 10.7 min (83 %), 11.3 min (17 %) (Column temp. 200 °C).

[(*RS*)-1-(2,5-Dimethoxyphenyl)-2-methylpropyl][(*RS*)-1-phenylethyl]amine (12). Light yellow oil; ^{1}H-NMR ($CDCl_3$) δ 0.62 (d, 3H, *J* = 6.9 Hz), 0.99 (d, 3H, *J* = 6.6 Hz), 1.21 (d, 3H, *J* = 6.6 Hz), 1.92 (m, 1H), 3.45 (q, 1H, *J* = 6.6 Hz), 3.67 (s, 3H), 3.70 (d, 1H, *J* = 7.3 Hz), 3.75 (s, 3H), 6.64-6.80 (m, 3H), 7.21-7.32 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 20.0, 20.3, 25.6, 33.0, 55.3, 55.6, 55.7, 111.2, 111.6, 115.7, 126.5, 127.1, 128.0, 133.2, 146.3, 152.2, 153.3; IR (NaCl) 1495, 1220, 1050, 700 cm^{-1}. Anal. Calcd for

$C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.60; H, 8.53; N, 4.47. GC 21.5 min (98 %), 22.3 min (2%) (Column temp. 190 °C).

[(*RS*)-α-(2,5-Dimethoxyphenyl)benzyl][(*RS*)-1-phenylethyl]amine (13). Light yellow oil; ^{1}H-NMR ($CDCl_3$) δ 1.35 (d, 3H, *J* = 6.6 Hz), 3.57 (s, 3H), 3.68 (q, 1H, *J* = 6.6 Hz), 3.78 (s, 3H), 4.88 (s, 1H), 6.76-6.80 (m, 2H), 7.02 (d, 1H, *J* = 2.3 Hz), 7.14-7.31 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ 24.6, 55.4, 55.6, 56.0, 58.6, 111.8, 112.3, 114.9, 126.4, 126.7, 126.8, 127.3, 127.9, 128.3, 132.9, 144.1, 145.8, 151.8, 153.7; IR (NaCl) 1495, 1460, 1450, 1275, 1240, 1215, 1175, 1045, 1025, 760, 740, 700 cm^{-1}. Anal. Calcd for $C_{25}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.40; H, 7.16; N, 4.03. GC 31.1 min (98%), 32.1 min (2%) (Column temp. 220 °C).

[(*R*)-1-(2,5-Dimethoxyphenyl)ethyl][(*R*)-1-phenylethyl]amine ((*R*,*R*)-10a). Light yellow oil; $[\alpha]_D^{27}$ +126.4 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.27 (d, 3H, *J* = 6.6 Hz), 1.28 (d, 3H, *J* = 6.9 Hz), 3.54 (q, 1H, *J* = 6.6 Hz), 3.71 (q, 1H, *J* = 6.9 Hz), 3.71 (s, 3H), 3.77 (s, 3H), 6.70-6.84 (m, 3H), 7.20-7.34 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 22.8, 25.1, 51.6, 55.3, 55.6, 55.8, 111.4, 111.8, 114.1, 126.6, 126.8, 128.2, 134.7, 145.9, 151.7, 153.6; IR (NaCl) 1495, 1220, 1050, 700 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.65; H, 8.14; N, 4.98. GC 9.5 min (99%), 10.3 min (1%) (Column temp. 210 °C).

[(*S*)-1-(2,5-Dimethoxyphenyl)ethyl][(*S*)-1-phenylethyl]amine ((*S*,*S*)-10a). Light yellow oil; $[\alpha]_D^{27}$ −127.7 (*c* 1.00, $CHCl_3$). The IR, ^{1}H-NMR, and ^{13}C-NMR were the same as those of (*R*, *R*)-**10a**. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.52; H, 8.14; N, 4.88.

[(*R*)-1-(2,5-Dimethoxyphenyl)ethyl][(*R*)-1-(*p*-tolyl)ethyl]amine ((*R*,*R*)-10b). Light yellow oil; $[\alpha]_D^{26}$ +140.1 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.26 (d, 3H, *J* = 6.6 Hz), 1.27 (d, 3H, *J* = 6.6 Hz), 2.33 (s, 3H), 3.50 (q, 1H, *J* = 6.6 Hz), 3.71 (q, 1H, *J* = 6.6 Hz), 3.72 (s, 3H), 3.76 (s, 3H), 6.70-6.81 (m, 3H), 7.12 (s, 4H); ^{13}C-NMR ($CDCl_3$) δ 21.1, 22.8, 25.1, 51.6, 55.0, 55.6, 55.7, 111.4, 111.7, 114.1, 126.7, 128.9, 134.8, 136.1, 142.9, 151.7, 153.6; IR (NaCl) 1495, 1465, 1275, 1220, 1050 cm^{-1}. Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.43; H, 8.36; N, 4.76. GC 17.1 min (98%), 17.8 min (2%) (Column temp. 200 °C).

[(*R*)-1-(4-Chlorophenyl)ethyl][(*R*)-1-(2,5-dimethoxyphenyl)ethyl]amine ((*R*,*R*)-10c). Light yellow oil; $[\alpha]_D^{26}$ +225.3 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.23 (d, 3H, *J* = 6.6 Hz), 1.27 (d, 3H, *J* = 6.6 Hz), 3.51 (q, 1H, *J* = 6.6 Hz), 3.65 (q, 1H, *J* = 6.6 Hz), 3.72 (s, 3H), 3.76 (s, 3H), 6.71-6.81 (m, 3H), 7.18 (d, 2H, *J* = 8.9 Hz), 7.27 (d, 2H, *J* = 8.9 Hz); ^{13}C-NMR ($CDCl_3$) δ 22.7, 25.1, 51.6, 54.7, 55.6, 55.7, 111.3, 111.5, 111.7, 114.1, 128.2, 128.3, 132.0, 134.4, 144.5, 151.6, 153.6; IR (NaCl) 1495, 1465, 1275, 1220, 1050, 1015, 835 cm^{-1}. Anal. Calcd for $C_{19}H_{22}ClNO_2$: C, 67.60; H, 6.93; N, 4.38. Found: C, 67.80; H, 6.98; N, 4.44. GC 17.4 min (97%), 18.0 min (3%) (Column temp. 210 °C).

[(*R*)-1-(2,5-Dimethoxyphenyl)ethyl][(*R*)-1-naphthylethyl]amine ((*R*,*R*)-10d). Light yellow oil; $[\alpha]_D^{26}$ +29.6 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.33 (d, 3H, *J* = 6.6 Hz), 1.39 (d, 3H, *J* = 6.6 Hz), 3.49 (s, 3H), 3.70 (s, 3H), 3.82 (q, 1H, *J* = 6.6 Hz), 4.42 (q, 1H, *J* = 6.6 Hz), 6.73 (s, 3H), 7.34-7.53 (m, 3H), 7.72-7.89 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 22.7, 24.6, 50.8, 51.2, 55.4, 55.5, 111.6, 111.6, 113.7, 122.9, 123.1, 125.0, 125.2, 125.7, 126.8, 128.6, 131.5, 133.8, 134.8, 141.7, 151.6, 153.6; IR (NaCl) 1500, 1465, 1275, 1220, 1180, 1050, 1030, 800, 780 cm^{-1}. Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.77; H, 7.65; N, 4.12. GC 20.5 min (>99%), 22.7 min (<1%) (Column temp. 230 °C).

[(*R*)-1-(2,5-Dimethoxyphenyl)ethyl][(*E*, *R*)-α-methylcinnamyl]amine ((*R*,*R*)-10e). Light yellow oil; $[\alpha]_D^{23}$ +176.9 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.18 (d, 3H, *J* = 6.6 Hz), 1.34 (d, 3H, *J* = 6.6 Hz), 3.12 (dq, 1H, *J* = 7.9, 6.6 Hz), 3.75 (s, 3H), 3.77 (s, 3H), 4.06 (q, 1H, *J* = 6.6 Hz), 6.05 (dd, 1H, *J* = 15.8, 7.9 Hz), 6.25 (d, 1H, *J* = 15.8 Hz), 6.72-6.89 (m, 3H), 7.20-7.37 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 22.7, 22.8, 51.5, 53.4, 55.6, 55.8, 111.5, 111.6, 111.7, 114.0, 126.2, 127.1, 128.4, 130.0, 134.3, 134.6, 137.3, 151.7, 153.7; IR (NaCl) 1500, 1470, 1455, 1275, 1220, 1050, 700 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.85; H, 8.15; N, 4.35. The d.e. was determined by ^{1}H-NMR [3.12 ppm (86%), 3.31 ppm (14%)].

[(*R*)-1-(2,5-Dimethoxyphenyl)ethyl][(*R*)-1-phenylpentyl]amine ((*R*,*R*)-10f). Light yellow oil; $[\alpha]_D^{26}$ +91.1 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 0.80 (t, 3H, *J* = 6.6 Hz), 1.00-1.29 (m, 4H), 1.27 (d, 3H, *J* = 6.6 Hz), 1.57 (m, 2H), 3.30 (t, 1H, *J* = 6.9 Hz), 3.64 (q, 1H, *J* = 6.9 Hz), 3.71 (s, 3H), 3.76 (s, 3H), 6.71-6.81 (m, 3H), 7.19-7.32 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 14.0, 22.6, 22.8, 28.7, 38.7, 51.9, 55.6, 55.6, 60.4, 111.6, 111.6, 114.3, 126.6, 127.4, 128.1, 134.5, 145.0, 151.7, 153.6; IR (NaCl) 1500, 1470, 1455, 1220, 1050, 705 cm^{-1}. Anal. Calcd for $C_{21}H_{29}NO_2$: C, 77.03; H, 8.93; N, 4.28. Found: C, 76.87; H, 8.80; N, 4.39. GC 22.9 min (98%), 24.8 min (2%) (Column temp. 200 °C).

[(*R*)-1-(2,5-Dimethoxyphenyl)ethyl][(*R*)-1-phenyl-3-butenyl]amine ((*R*,*R*)-10g). Light yellow oil; $[\alpha]_D^{27}$ +78.1 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.29 (d, 3H, *J* = 6.6 Hz), 2.32 (dd, 2H, *J* = 8.0, 7.1 Hz), 3.39 (dd, 1H, *J* = 7.7, 6.3 Hz), 3.65 (q, 1H, *J* = 6.9 Hz), 3.69 (s, 3H), 3.75 (s, 3H), 5.06 (ddd, 2H, *J* = 14.5, 8.9, 1.0 Hz), 5.64 (m, 1H), 6.64 (d, 1H, *J* = 3.0 Hz), 6.72 (dd, 1H, *J* = 8.9, 3.0 Hz), 6.78 (d, 1H, *J* = 8.9 Hz), 7.20-7.36 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 22.5, 43.5, 52.0, 55.5, 59.4, 111.5, 111.6, 114.3, 117.2, 126.8, 127.3, 128.1, 134.2, 135.8, 144.3, 151.7, 153.5; IR (NaCl) 1500, 1465, 1455, 1275, 1220, 1180, 1050, 1030, 705 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.29; H, 8.23; N, 4.56. GC 12.9 min (99%), 13.6 min (1%) (Column temp 210 °C).

Removal of Chiral Auxiliary from (*R*,*R*)-10a.

To a solution of (*R*, *R*)-**10a** (98%de, 205.3 mg, 0.72 mmol) in CH_2Cl_2 (5 ml) were added Et_3N (0.1 ml, 0.72 mmol) and Ac_2O (0.1 ml, 0.90 mmol) at room temperature. After 12 h, the solution was successively washed with aqueous HCl (1M, 3 × 5 ml), aqueous NaOH (1M, 3 × 5 ml), water (3 × 5 ml), and brine (3 × 5 ml), and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by preparative thin layer chromatography to give *N*-[(*R*)-1-(2,5-dimethoxyphenyl)ethyl]-*N*-[(*R*)-1-phenylethyl]acetamide (*R*, *R*)-**14a** (190.2 mg, 0.58 mmol, 81%); yellow oil; $[\alpha]_D^{18}$ +80.8 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.61 (d, 3H, *J* = 7.1 Hz), 1.76 (d, 3H, *J* = 6.9 Hz), 2.33 (s, 3H), 3.62 (s, 3H), 3.76 (s, 3H), 4.26 (q, 1H, *J* = 6.9 Hz), 5.35 (q, 1H, *J* = 7.1 Hz) 6.62-7.20 (m, 8H); ^{13}C-NMR ($CDCl_3$) δ 17.7, 19.5, 23.6, 51.8, 53.1, 55.3, 55.7, 110.8, 112.3, 115.1, 125.7, 127.0, 127.1, 128.7, 142.2, 152.2, 153.3, 170.4; IR (NaCl) 1645, 1495, 1425, 1220 cm^{-1}. HR-MS Calcd for $C_{20}H_{25}NO_3$: 327.1834. Found: 327.1863.

To a solution of (*R*,*R*)-**14a** (160.0 mg, 0.49 mmol) in benzene (10 ml) was added dropwise a solution of BBr_3 (0.3 g, 1.2 mmol) in benzene (2 ml) at room temperature. After the solution was refluxed for 6 h, the reaction was quenched with MeOH (10 ml). The solvents were evaporated under reduced pressure to give the crude product, which was used to the next reaction without further purification.

To a solution of the crude product in AcOEt (10 ml) was added MnO_2 (127.0 mg, 1.47 mmol) and $MgSO_4$ (3 g) at room temperature. After 12 h, the insoluble mass was filtered off and the filtrate was concentrated under

reduced pressure. The crude product was purified by preparative thin layer chromatography to give *N*-[(*R*)-1-phenylethyl]acetamide (*R*)-**15a** (56.9 mg, 0.35 mmol, 71%, >99%ee); white crystals; mp 102-104 °C [lit.[33] 101-103 °C]; $[\alpha]_D^{19}$ +129.5 (*c* 1.00, $CHCl_3$); HPLC 23.5 min [DAICEL CHIRALCEL OB, Flow rate 1.0 ml/min, 2-PrOH/Hexane=1/9].

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