Pergamon

TETRAHEDRON

Tetrahedron 57 (2001) 875–887

Asymmetric Mannich-type reactions with a chiral acetate: effect of Lewis acid on activation of aldimine

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Received 26 May 2000; accepted 25 August 2000

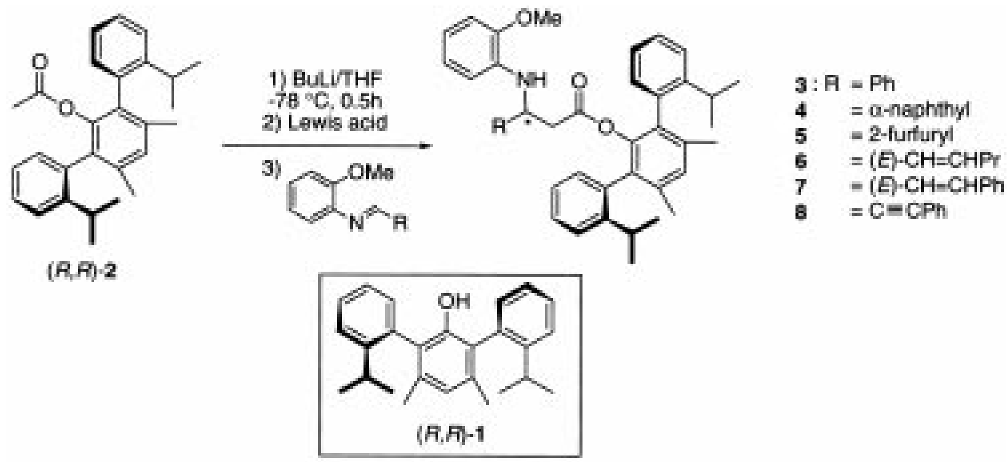
Abstract—We introduce here a strategy that enables effective addition of lithium enolates of acetates to aldimines. The new method depends strongly on the use of *ortho*-alkoxy (or *ortho*-fluoro) aniline-derived aldimines which found to have a potential effect on the enolate addition. This scope was expanded to the asymmetric process using the chiral acetate, which has optically pure 2,6-bis(2-isopropylphenyl)-3,5-dimethylphenol as a chiral auxiliary with axial chirality. A Lewis acid additive is likely to have a complementary role in the pronounced activation of imine functionalities in the Mannich-type addition of the bulky chiral acetate. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Chiral auxiliaries are powerful molecular elements for creating optically active compounds. When covalently attached to the auxiliaries, carboxylic acid derivatives expanded the scope of the asymmetric aldol reaction with aldehydes and have constituted a molecular library of β-hydroxycarbonyl compounds.[1] In contrast, due to the inherent instability of imines (e.g. imine–enamine equilibration) and the poor electrophilicity of stable *N*-substituted imines[2] especially toward *acetate* enolates, there are few reports in the literature[3,4] on the asymmetric Mannich-type reaction using this approach. We address these limitations using 2,6-bis(2-isopropylphenyl)-3,5-dimethylphenol (**1**)[5] as an effective chiral auxiliary in the diastereoselective Mannich-type reaction of acetate **2**[6] with specialized aldimines (Scheme 1).

2. Results and Discussion

Although studies have investigated many aspects of high reactivity of the enolates of propionates and isobutylates,[3a] the lithium enolates of acetates are almost inert to the



Scheme 1.

Keywords: asymmetric reaction; chelation; enolates; imines; Mannich reaction.

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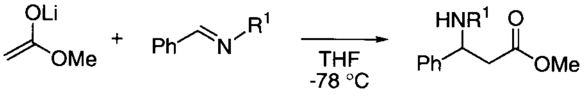
PII: S0040-4020(00)01042-5

Table 1. Reaction of the lithium enolate of methyl acetate with various aldimines (unless otherwise specified, reaction was performed using the acetate (1.0 equiv.), a THF solution of LDA (1.0 equiv.) and aldimine (1.0 equiv.) at −78°C for 3 h)



Entry	Aldimine, R[1]	Yield%[a]	Entry	Aldimine, R[1]	Yield %[a]
1	Ph (**9**)	24[b,c]	9	2,5-$(MeO)_2$–C_6H_3 (**17**)	73
2	Me_3Si (**10**)	14[b,d]	10	2,6-$(MeO)_2$–C_6H_3 (**18**)	NR
3	2-MeO–C_6H_4 (**11**)	71	11	2-MeO-6-Me–C_6H_4 (**19**)	NR
4	3-MeO–C_6H_4(**12**)	NR	12	2,6-F_2–C_6H_4 (**20**)	NR
5	4-MeO–C_6H_4 (**13**)	NR	13	Bn (**21**)	NR
6	2-MOMO–C_6H_4 (**14**)	69	14	MeO (**22**)	NR
7	2-F–C_6H_4 (**15**)	83	15	Ms (**23**)	4
8	2,4-$(MeO)_2$–C_6H_3 (**16**)	56			

[a] Of isolated β-aminoesters. NR=no reaction.
[b] The isolated yield of the corresponding β-lactam.
[c] See Ref. 7a.
[d] See Ref. 7b.

N-phenyl-[7a] and *N*-trimethylsilylaldimines[7b] of benzaldehyde.[7] Thus, our first attempt was to find a potential aldimine partner that reacts smoothly with the acetate enolates. The results are summarized in Table 1, which shows that the aldimines of *o*-anisidine and *ortho*-fluoroaniline (**11** and **15**) facilitate the reaction most efficiently (entries 3 and 7).[8†] The alkoxy and the fluoro groups are essential and must be attached to the *ortho*-position of the aniline nitrogen. For example, *m*- and *p*-anisidine derivatives **12** and **13** did not lead to the desired adducts (entries 4 and 5). These results imply that the rather low Lewis acidic Li^+ requires chelation to enable the effective activation of aldimines. Indeed, aldimine **14** with which the chelation control further operates had a similar effect on the addition efficacy (entry 6); dimethoxy derivatives **16** and **17** showed similar productivity (entries 8 and 9). However, *o*,*o*-disubstituted derivatives **18**–**20** were absolutely inert under the present conditions even at higher temperature (0°C) (entries 10–12).

Unfortunately, the lithium enolate of **2**, generated by treatment with *n*-BuLi in THF at −78°C for 0.5 h, was almost inert to aldimines **11** and **15** under the above optimized conditions (for aldimine **11**, 15% yield, 86% de). We thus focused on the use of a Lewis acid additive, anticipating the pronounced activation of imine functionalities (Scheme 1 and Table 2). The addition of **2** to aldimine **11** occurred effectively in the presence of 0.5 equiv. of R_2Zn (R=Me, Et) at −78°C to give β-aminoester **3** in 70 and 69% yields with diastereomeric excesses (de) of ca. 91% de. Comparable yield and de were obtained whether a Lewis acid was added after or before treatment of aldimine with the enolate. While varying Lewis acids for **11** (entries 1–9) had appreciable effect, absolute *S* configuration at the emerging chiral center was induced throughout. These results also suggest that Li^+, rather than an externally added Lewis acid, plays a more significant role in enhancing diastereoselectivity. In other words, Li^+ is proximal, while the additional Lewis acid is distal, to a requisite transition structure created. Another critical parameter for high asymmetric induction seems the direct attachment of an aromatic ring to the imine nitrogen (entries 14–18); however, imines **9** and **27** proved to be totally ineffective for productivity even in the presence of Et_2Zn. On the contrary, the attachment of *N*-sulfonyl and *N*-phosphoryl groups gave adducts in higher yields (entries 20 and 21), but unfortunately, a significant decline in de was observed. An attempt to form six-membered chelation with Li^+ to activate imine **30** effectively was disappointing (entry 22).

Other *o*-anisidine-derived aldimines were reacted with (*R*,*R*)-**2** in the presence of a Zn-reagent, and the results are listed in Table 3. With the exception of inertness with the 2-hexenal-derived aldimine (entry 5), the table shows that this method proved to be effective in substrate scope, to give high diastereoselectivities up to 98% de. Using 1.0 equiv. of Et_2Zn was generally ineffective in terms of chemical yield due to side reactions, which in some cases generated a considerable amount of ethylated products (entry 10).[9‡] *o*,*o*-Disubstituted aniline-derived aldimines **18** and **19** underwent no addition to give complete recovery of the acetate.

The equilibrium between (*E*)- and (*Z*)-aldimines is known to be involved in the presence of Lewis acid and to affect the stereochemistry of the asymmetric Mannich-type reaction.[§] Thus, there is a possibility that the isomerization to (*Z*)-

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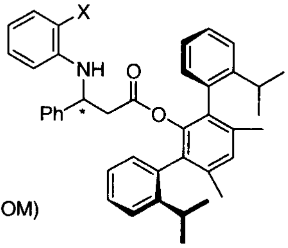
[†] In the meantime, restraining effects of the *ortho*-methoxyphenyl substituent of aldimines on the formation of β-amino esters, not the β-lactams, was reported in the Refomatsky reaction using α-bromoacetate and Zn (Ref. 8). Moreover, Kobayashi, et al. reported marked influence of aldimines **11** and **28** on the enantioselectivity and/or reactivity in the Mannich-type reaction using chiral zirconium reagents (Refs. 3i and 3j). Although both aldimines are employable, the reaction mechanism remains totally unclear.

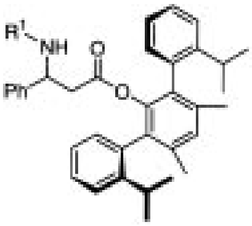
[‡] To explain the difference in the reaction profiles using 0.5 and 1.0 equiv. of Et_2Zn, distinctive zincate species (enolate)R_2ZnLi (Li-enolate: R_2Zn=1:1) and $(enolate)_2R_2ZnLi_2$ (Li-enolate:R_2Zn=2:1) might be invoked. At present, we have no evidence of the formation of these species and further research is needed. Regarding the search on the reactivity difference between R_3ZnLi and R_4ZnLi_2, see Ref. 9.

[§] For example, the reaction of the aldimine derived from 3-trimethylsilyl-2-propynal with a ketene silyl acetal exhibits reversal in the absolute configuration, compared with the aldimine derived from benzaldehyde using a chiral boron reagent. This implies that the (*Z*)-structure is the reactive form of the former aldimine, whereas it is (*E*)-isomer of the latter, see Ref. 3k. In good contrast, the present reaction using the *o*-anisidine-derived aldimines derived from these two types of aldehydes showed an identical *S* configuration.

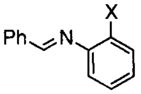
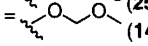
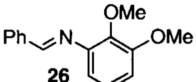
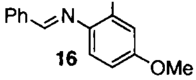
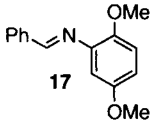
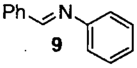
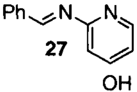
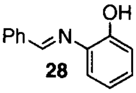
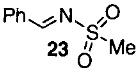
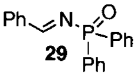
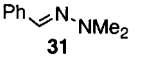
Table 2. Asymmetric Mannich-type reaction of aldimines derived from PhCHO with (*R*,*R*)-**2** (unless otherwise specified, reaction was performed by mixing enolate (1.0 eq), aldimine (1.0 equiv.) and Lewis acid (0.5 equiv.) in this order at −78°C for 8∼48 h)



3b : X = F
3c : X = -O(CH$_2$)OMe (OMOM)
3d : X = -O(CH$_2$)$_2$OMe

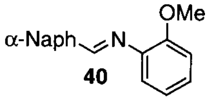
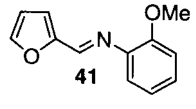
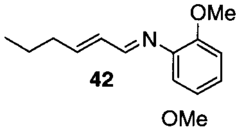
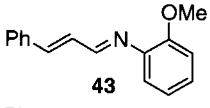
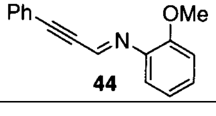


32: R^1 = 2,3-(MeO)$_2$-(C$_6$H$_3$)-
33: = 2,4-(MeO)$_2$-(C$_6$H$_3$)-
34: = 2,5-(MeO)$_2$-(C$_6$H$_3$)-
35: = Ph
36: = 2-Py
37: = 2-(OH)-Ph-
38: = -SO$_2$Me
39: = -POPh$_2$

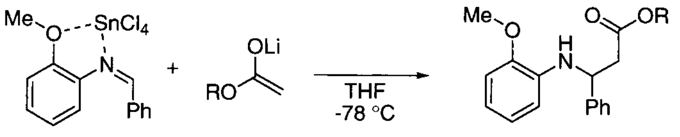
entry	aldimine (RCH=NR^1)	additive	product	yield %[a] (de)[b]	absolu config[c]
1	 X = OMe (**11**)	Et$_2$Zn	**3**	69 (91% de)	*S*
2	X = OMe (**11**)	Et$_2$Zn[d]	**3**	82 (91% de)	*S*
3	X = OMe (**11**)	Et$_2$Zn[e]	**3**	24 (85% de)	*S*
4	X = OMe (**11**)	Me$_2$Zn	**3**	70 (92% de)	*S*
5	X = OMe (**11**)	*i*-Bu$_3$Al[d]	**3**	69 (92% de)	*S*
6	X = OMe (**11**)	*i*-Bu$_3$Al	**3**	60 (89% de)	*S*
7	X = OMe (**11**)	Et$_3$Al[d]	**3**	40 (86% de)	*S*
8	X = OMe (**11**)	BF$_3$•OEt$_2$[d,f]	**3**	34 (65% de)	*S*
9	X = OMe (**11**)	Me$_3$Ga	**3**	67 (94% de)	*S*
10	X = F (**15**)	Et$_2$Zn	**3b**	55 (94% de)	
11	X = Cl (**24**)	Et$_2$Zn	-	-	
12	X =  (**25**)	Et$_2$Zn	**3c**	46 (91% de)	
13	X =  (**14**)	Et$_2$Zn	**3d**	70 (90% de)	
14	 **26**	Et$_2$Zn	**32**	68 (87% de)	
15	 **16**	Et$_2$Zn	**33**	49 (94% de)	*S*
16	 **17**	Et$_2$Zn	*anti*-**34**[g]	63 (85% de)	
17	 **9**	Et$_2$Zn	*anti*-**35**[g]	25 (92% de)	
18	 **27**	Et$_2$Zn	**36**	19 (86% de)	
19	 **28**	Et$_2$Zn[d,f]	**37**	43 (54 %de)	*S*
20	 **23**	Et$_2$Zn[d]	**38**	63 (27% de)	
21	 **29**	Et$_2$Zn	**39**	83 (27% de)	
22	 **30**	Et$_2$Zn	-	-	
23	 **31**	Et$_2$Zn	-	-	

[a] Of isolated purified product.
[b] Determined by HPLC analysis.
[c] Absolute configuration of the chiral centers, which was determined in comparison with authentic samples.
[d] 1.0 equiv. of a Lewis acid was used.
[e] 0.1 equiv. of a Lewis acid was used.
[f] Aldimine and Lewis acid were mixed prior to treatment with enolate.
[g] (*S*,*S*)-**2** was used.

Table 3. Asymmetric Mannich-type reaction of aldimines derived from *o*-anisidine with (*R*,*R*)-**2** (unless otherwise specified, reaction was performed by mixing enolate (1.0 equiv.), aldimine (1.0 equiv.) and R_2Zn (0.5 equiv.) at −78°C for 18 h~48 h)

Entry	Aldimine ($RCH{=}NR^1$)	Additive	Product	Yield %[a] (de)[b]	Absolu config.[c]
1	 **40**	Et_2Zn	**4**	73 (91% de)	
2		Et_2Zn	**4**	50 (84% de)	
3	 **41**	Me_2Zn	**5**	62 (84% de)	
4		Et_2Zn	**5**	75 (84% de)	
5	 **42**	Et_2Zn	**6**	28 (99% de)	
6	 **43**	Me_2Zn	**7**	70 (93% de)	*S*
7		Et_2Zn	**7**	72 (91% de)	*S*
8	 **44**	*t*-Bu_2Zn[e]	**8**	55 (91% de)	*S*
9		Et_2Zn	**8**	63 (85% de)	*S*
10		Et_2Zn[d]	**8**	51 (86% de)[f]	*S*

[a] Of isolated purified product.
[b] Determined by HPLC analysis.
[c] Absolute configuration of the chiral centers, which was determined in comparison with authentic samples.
[d] Et_2Zn (1.0 equiv.) was used.
[e] Salt free reagent. See Ref. 10.
[f] Ethylated product was obtained (10%).



$SnCl_4$–(*Z*)-**11**

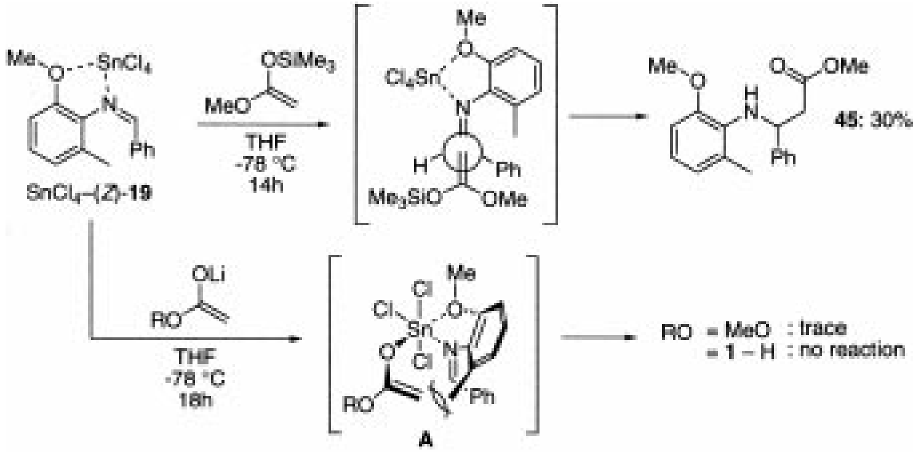
3: RO = **1** – H : 26% (70% de (3*S* major))

Scheme 2.

aldimines could have potential effect on the rate acceleration of the Mannich addition. In fact, when the $SnCl_4$-(*Z*)-**11** complex[11] was exposed to the lithium enolate of (*R*,*R*)-**2**, adduct **3** was obtained in 70% de (3*S*:3*R*=85:15) (Scheme 2), the absolute configuration being consistent with the other examples we tested (entries 1–9, Table 2; entries 6–10, Table 3). As expected, the reaction of $SnCl_4$-(*Z*)-**19** with the lithium enolate of (*R*,*R*)-**2** or methyl acetate did not lead to the desired adducts (Scheme 3). In contrast, the corresponding ketene silyl acetal afforded the Mannich-type addition to give **45**, where an extended transition state was likely to be invoked (Scheme 3). This implies that the lithium enolates first attack the Sn-center to give a tin–enolate intermediate such as **A**, which prefers a cyclic transition state rather than an extended one. However, steric constraints may not allow intramolecular enolate addition to the imine carbon via a cyclic transition structure which is usually sterically more unfavorable. Indeed, Fig. 1 shows that both the *si* and *re* face of $SnCl_4$-(*Z*)-**19** are sterically more shielded synergistically by the methyl, phenyl and the chloro groups compared with $SnCl_4$-(*Z*)-**11**. In addition, $SnCl_4$-(*Z*)-**19** has a higher rotational barrier around the C–N single bond axis, and thus exposure of the imine faces to a favorable enolate addition would be highly restricted. Although we cannot rule out other possible mechanisms at this point, it is thus conceivable that $SnCl_4$-(*Z*)-**11** might also be attacked by lithium enolates via a cyclic transition structure, resulting in 3*S*- configuration. The structure of $SnCl_4$-(*Z*)-**19** was rigorously established by the X-ray single crystal analysis.[12]

The reactions showed general preference for the *si* face attack of aldimines, which is opposite to that for the addition of aldehydes.[6] Steric considerations of the single crystal structure of **2**[6] and high probability in the U-form (Fig. 2)[13¶] of the corresponding enolate give us a putative transition structure for the asymmetric induction (Fig. 3). The twist boat model, which is accommodated by the U-form and by the chelation complex of a putative (*Z*)-aldimine with a Lewis acid, validates the *si* face attack by the chiral enolate. Significant steric repulsion has been confirmed by modeling of the (*E*)-aldimines in possible transition structures.

[¶] It was proposed that the boron enolates of α-unsubstituted ketones favor the more stable U-form by 1–2 kcal/mol than the W-form (Ref. 13). Similarly, it is conceivable that the bulky phenoxy group of the enolate of **2** renders the U-form most likely, and gives a twist-boat transition structure.



Scheme 3.

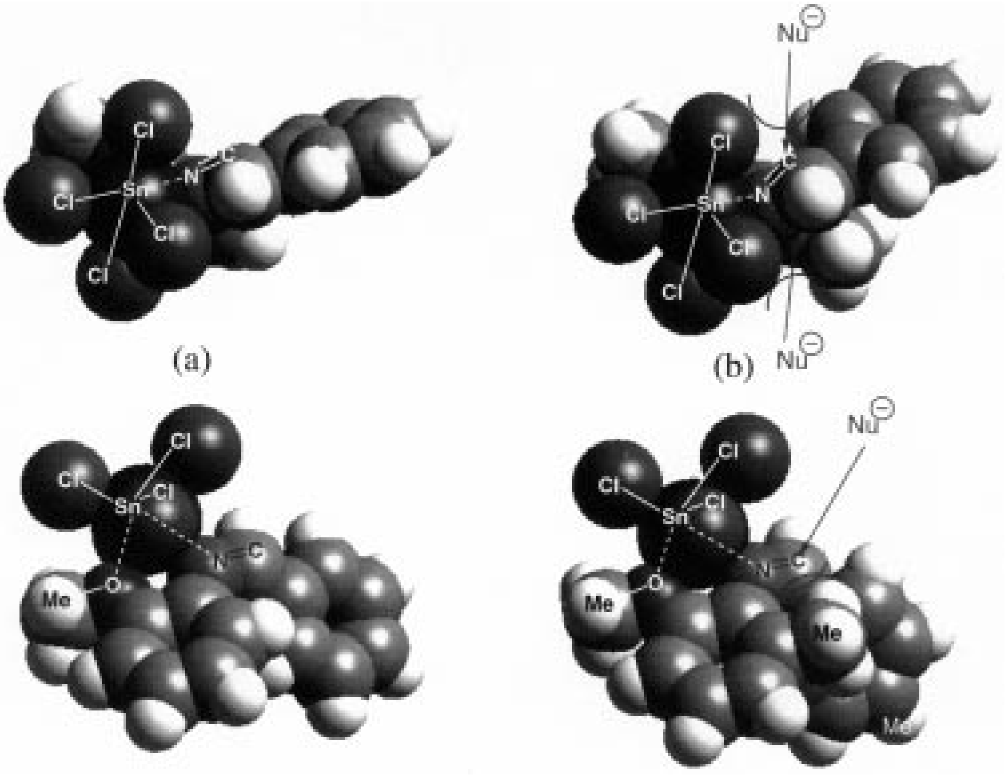


Figure 1. The X-ray crystal structures of (a) $SnCl_4$-(*Z*)-**11** and (b) $SnCl_4$-(*Z*)-**19**. The structure of $SnCl_4$-(*Z*)-**11** was cited from the CD-ROM data deposited at CCDC.

The chiral auxiliary can readily be recovered (>99%) from the Mannich adduct **3** (91% de) by treatment with Bu_4NOH in THF,[14] followed by subsequent methylation of the resulting acid with $TMSCHN_2$. Oxidative cleavage of the methoxyphenyl group was effected by catalytic $AgNO_3$ (0.29 equiv.) in the presence of excess $(NH_4)_2S_2O_8$ (7.0 equiv.)[15] to afford aminoester **49** in 53% yield (90% ee) (Scheme 4). When we used CAN as an alternative oxidant, aminoester **46** underwent considerable dimerization, resulting in negligible formation of **49**.[16,‖] An attempt to remove the *o*-fluorophenyl group from **47** under similar conditions using CAN gave **49** in only 14% yield. This can be circumvented by use of **16** as an aldimine to give

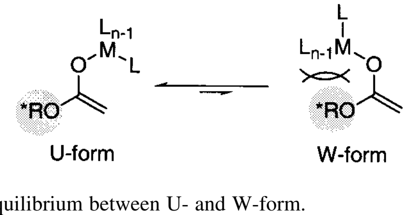


Figure 2. Equilibrium between U- and W-form.

[‖] Although it has been reported that aminoester **46** was readily oxidized by CAN to give **49** (Ref. 8), we were unable to detect the formation of **49** using CAN by varying numerous reaction conditions. No attempt was made here to characterize the exact structure of the dimer. Competitive dimerization is a significant problem in certain cases using CAN.

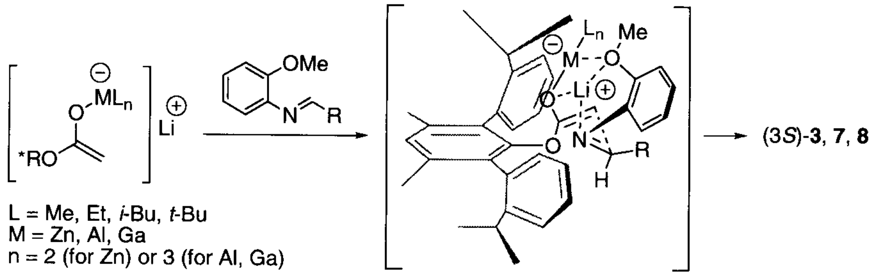
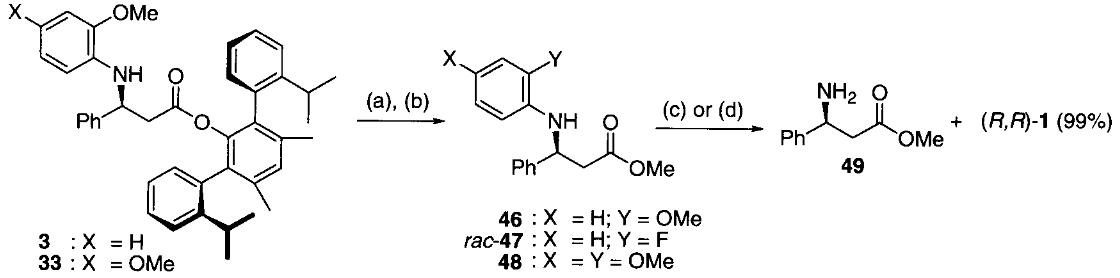


Figure 3. One plausible transition structure.



Scheme 4. (a) Bu_4NOH, THF, 0°C, 99%; (b) $TMSCHN_2$, MeOH, rt, 99% for **3** and **33**: (c) $AgNO_3$, $(NH_4)_2S_2O_8$, THF–H_2O–MeCN, 60°C, 53% for **46**; (d) CAN, H_2O–MeCN, 0°C, 91% for **48**; 14% for *rac*-**47**.

Mannich adduct **33** in 63% yield (92% de, using Me_2Zn). Sequential hydrolysis and methylation was followed by oxidation of **48** with CAN (4 equiv.) to give **49** in 91% yield (92% ee), where no dimerization was observed.

3. Conclusion

This work features a strategy that enabled effective addition of acetate enolates to aldimines and expanded this scope to the asymmetric process using a chiral auxiliary. We propose that the successful asymmetric reaction originated in part from: (1) the control of the two possible aldimine configurations (*E* and *Z*) by chelation effect of Lewis acids using readily isomerizable aldimine;[11] and (2) the control of the two possible enolate conformations W-form and U-form[13] using the bulky auxiliary, which have been proposed to contribute to the chair and twist boat transition structures, respectively. However, an understanding of further mechanistic aspects of the reaction is required to give marked improvement in synthetic efficiency. Efforts toward this end are currently being made in our laboratory.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a Shimazu FTIR-8100 spectrometer. ^1H NMR spectra were measured on a Varian Gemini-300 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (b=broad, s=singlet, d=doublet, t=triplet, and m=multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were recorded on Varian Gemini-300 (75 MHz) spectrometer at ambient temperature. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.07 ppm). Chiral high-performance liquid chromatography (chiral HPLC) analyses were conducted using Shimazu LC-10AD coupled with diode array-detector SPD-MA10A-VP and the chiral column of CHIRALCEL OD–H or AD (Daicel Chemical Industries, Ltd). All experiments were carried out under an atmosphere of dry argon. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254 0.25 mm) were used. The products were purified by preparative column chromatography on normal silica gel (Merck Art. 9385: Cl <0.02%; Fe, <0.02%) or for some instances, on silanized silica gel (Merck Art. 7719) or on extra pure one (Merck Art. 7754: Cl <0.008%; Fe, <0.002%). Microanalyses were accomplished at the Faculty of Agriculture, Nagoya University.

In experiments which required dry solvent toluene and CH_2Cl_2 were freshly distilled from calcium hydride, and tetrahydrofuran (THF) was freshly distilled from sodium metal using benzophenone ketyl as indicator. Organic substrate **21** was commercially available, and was used without any purification. *n*-BuLi (hexane solution) was obtained from Mitsuwa. Compounds **1**,[5] **2**[6] and aldimines **9**,[7a] **10**,[7b] **11**,[17] **12**,[18] **13**,[19] **15**,[20] **16**,[21] **19**,[22] **22**,[23] **23**,[24] **24**,[25] **27**,[26] **28**,[27] **29**,[28] **30**,[29] **31**,[30] **40**,[31] **41**,[32] **43**,[33] **46**[8] and **49**[34] are all known compounds, and were prepared as described in the literature. However, in many cases spectroscopic properties of aldimines have not been recorded and are included here to provide full or partial documentation of structural evidence.

4.2. Preparation of (*R*,*R*)-2

To a solution of (*R*,*R*)-**1** (1.57 g, 4.4 mmol) in anhydrous THF (9 mL) was added a 1.62 M hexane solution of *n*-BuLi

(3.27 mL, 5.3 mmol) dropwise at 0°C under an argon atmosphere. After 15 min of stirring, to the mixture was added acetyl chloride (469 μL, 6.6 mmol) dropwise at this temperature, and stirring was maintained for additional 1.5 h. The reaction mixture was quenched with H_2O, extracted with diethyl ether, dried, and concentrated. The residue was purified by column chromatography on silanized silica gel (hexane only as the eluent. The top of the silica gel-column should be cooled with dry-ice or something in order to avoid decomposition of the desired chiral acetate prior to charging the crude mixture) to give (*R*,*R*)-**2** (1.78 g, yield >99%) as a colorless solid.

4.3. General procedure for asymmetric Mannich-type addition using chiral acetate 2 and aldimine 11

To a solution of (*R*,*R*)-**2** (80.0 mg, 0.2 mmol) in THF (0.80 mL) was added a 1.61 M hexane solution of *n*-BuLi (0.12 mL, 0.20 mL) at −78°C under argon atmosphere, and the mixture was stirred at this temperature for 0.5 h. Sequential treatment with a 1.0 M hexane solution of Et_2Zn (0.10 mL, 0.1 mmol) for 0.5 h and aldimine **9** (42 mg, 0.2 mmol) in THF (0.40 mL) was followed by being stirred at −78°C for 27 h. The reaction mixture was quenched with H_2O, and extracted with diethyl ether, and dried over Na_2SO_4. Evaporation of solvents and purification by column chromatography on silica gel (diethyl ether/hexane=1/20 to 1/5 as the eluent) gave β-aminoester **3** (84 mg, yield, 69%) in 91% de as colorless solids.

4.3.1. (*R*,*R*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-(2-methoxyphenyl) amino-3-phenylpropionate (3). IR (KBr) 3425, 1759, 1514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, 1H, J=7.8 Hz), 7.25 (s, 1H), 7.20–7.13 (m, 5H), 7.12 (s, 1H), 6.98–6.96 (m, 6H), 6.71 (dd, 1H, J=2.4, 7.2 Hz), 6.66–6.60 (m, 2H), 6.03 (dd, 1H, J=2.7, 7.2 Hz), 4.54 (bs, 1H), 3.98 (bdd, 1H, J=6.3, 6.6 Hz), 2.70 (bs, 2H), 2.18 (dd, 1H, J=8.1, 15.3 Hz), 2.04 (s, 6H), 2.00 (dd, 1H, J=5.4, 15.3 Hz), 1.14 (d, 6H, J=6.9 Hz), 1.07 (bd, 6H, J=5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 147.3, 146.9, 146.5, 142.4, 136.7, 136.6, 134.4, 132.1, 130.3, 128.8, 128.6, 127.8, 127.0, 126.1, 125.3, 125.2, 120.8, 116.6, 111.4, 109.0, 55.3, 53.8, 41.9, 30.1, 24.2, 20.1. Anal. Calcd for $C_{42}H_{45}NO_3$: C, 82.45, H, 7.41, N, 2.29; Found: C, 82.24, H, 7.62, N, 2.24. The chiral HPLC analytical data (column OD–H) of **3**: retention times: t_R=5.9 min for (3*S*)-**3** and t_R=10.3 min for (3*R*)-**3** using *i*-PrOH/hexane (1/200) as eluent at a flow rate of 1.0 mL/min.

4.3.2. (*R*,*R*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-(2-fluorophenyl) amino-3-phenylpropionate (3b). IR (KBr) 3422, 1759, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–6.88 (m, 15H), 6.74 (dd, 1H, J=7.5, 7.5 Hz), 6.59–6.50 (m, 1H), 6.10 (dd, 1H, J=7.8, 7.8 Hz), 4.21 (bs, 1H), 4.00 (bs, 1H), 2.80–2.60 (m, 2H), 2.13 (dd, 1H, J=8.7, 15.1 Hz), 2.05 (s, 6H), 2.01 (dd, 1H, J=4.2, 15.1 Hz), 1.14 (d, 6H, J=6.6 Hz), 1.07 (bs, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 151.6 (d, $^1J_{CF}$=237.9 Hz), 147.3, 146.4, 135.2 (d, $^2J_{CF}$=11.4 Hz), 134.3, 132.0, 130.5, 130.2, 128.9, 128.7, 127.9, 127.7, 127.2, 125.8, 125.3, 125.1, 124.0 (d, $^4J_{CF}$=2.9 Hz), 116.8 (d, $^3J_{CF}$=7.1 Hz), 114.0 (d, $^2J_{CF}$=18.5 Hz), 113.7 (d, $^3J_{CF}$=3.2 Hz), 53.8, 41.7, 30.0, 24.2, 20.1. HRFABMS (PEG) m/z Calcd for $C_{41}H_{42}FNO_2$ (M^+): 599.3200; Found: 599.3198. The de% was determined by conversion into the corresponding methyl ester by: (1) removal of (*R*,*R*)-**1**; and (2) methylation. See the Experimental below for this derivation. The chiral HPLC analytical data (column OD–H) of the methyl ester derived from **3b**: retention times: t_R=8.3 min (minor): t_R=15.8 min (major) using *i*-PrOH/hexane (1/9) as eluent at a flow rate of 1.0 mL/min.

4.3.3. (*R*,*R*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-[(2-methoxyethoxy)phenyl] amino-3-phenylpropionate (3c). IR (neat) 3372, 1750, 1521 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, 2H, J=8.1 Hz), 7.19–6.94 (m, 12H), 6.75 (dd, 1H, J=1.5, 7.8 Hz), 6.68 (ddd, 1H, J=1.5, 7.5, 7.8 Hz), 6.57 (ddd, 1H, J=1.5, 7.5, 7.8 Hz), 6.33 (dd, 1H, J=1.5, 7.8 Hz), 4.71 (bs, 1H), 4.08 (t, 2H, J=4.8 Hz), 3.95 (bs, 1H), 3.71 (t, 2H, J=4.8 Hz), 3.63 (s, 3H), 2.70 (bs, 2H), 2.17 (dd, 1H, J=7.2, 15.6 Hz), 2.04 (s, 6H), 2.03 (dd, 1H, J=6.0, 15.6 Hz), 1.14 (bd, 6H, J=6.9 Hz), 1.08 (bs, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 146.5, 146.0, 142.4, 137.3, 136.7, 134.3, 132.1, 130.2, 128.8, 128.5, 127.9, 127.0, 126.1, 125.2, 125.17, 121.7, 116.4, 112.1, 111.7, 71.1, 68.5, 59.1, 53.7, 41.3, 30.0, 24.2, 20.1. Anal. Calcd for $C_{44}H_{49}NO_4$: C, 80.58, H, 7.53, N, 2.14; Found: C, 80.45, H, 7.74, N, 2.15. The chiral HPLC analytical data (column AD) of **3c**: retention times: t_R=12.8 min (major); t_R=16.6 min (minor) using *i*-PrOH/hexane (1/200) as eluent at a flow rate of 0.5 mL/min.

4.3.4. (*R*,*R*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-[(2-methoxymethoxy)phenyl] amino-3-phenylpropionate (3d). IR (neat) 3391, 1748, 1514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–6.95 (m, 15H), 6.70 (dd, 1H, J=7.5, 7.8 Hz), 6.58 (dd, 1H, J=6.9, 7.8 Hz), 6.05 (d, 1H, J=7.5 Hz), 5.15 (s, 2H), 4.63 (bs, 1H), 3.91 (bs, 1H), 3.48 (s, 3H), 2.80–2.60 (m, 2H), 2.17 (dd, 1H, J=8.1, 15.3 Hz), 2.04 (s, 6H), 2.03 (dd, 1H, J=5.4, 15.3 Hz), 1.15 (d, 6H, J=6.9 Hz), 1.09 (bs, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 147.2, 146.4, 144.5, 142.3, 137.3, 136.7, 134.3, 132.0, 130.2, 128.8, 128.5, 127.9, 127.0, 126.0, 125.2, 125.16, 122.2, 116.7, 113.7, 112.1, 95.0, 56.1, 53.8, 41.3, 30.0, 24.3, 24.2, 20.1. Anal. Calcd for $C_{43}H_{47}NO_4$: C, 80.47, H, 7.38, N, 2.18; Found: C, 80.47, H, 7.65, N, 2.18. The chiral HPLC analytical data (column AD) of **3d**: retention times: t_R=9.7 min (major); t_R=11.1 min (minor) using *i*-PrOH/hexane (1/200) as eluent at a flow rate of 0.5 mL/min.

4.3.5. (*R*,*R*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-(2-methoxyphenyl) amino-3-(2-naphthyl)propionate (4). IR (KBr) 3430, 1759, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85–6.90 (m, 16H), 6.74 (d, 1H, J=7.8 Hz), 6.58 (dd, 1H, J=7.5, 7.8 Hz), 6.54 (dd, 1H, J=7.8, 7.8 Hz), 5.86 (d, 1H, J=7.5 Hz), 4.72 (bs, 2H), 3.84 (s, 3H), 2.71 (bs, 2H), 2.29 (dd, 1H, J=3.6, 15.9 Hz), 2.15 (dd, 1H, J=9.6, 15.9 Hz), 2.05 (s, 6H), 1.16 (d, 6H, J=6.9 Hz), 1.06 (d, 6H, J=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 147.0, 146.5, 136.8, 136.5, 134.3, 134.0, 132.1, 130.2, 130.1, 128.9, 128.8, 127.9, 127.6, 126.1, 125.7, 125.3, 125.2, 122.9, 122.6, 122.4, 120.7, 116.6, 111.6, 108.9, 50.1, 40.1, 30.1, 24.2, 20.1. Anal. Calcd for $C_{46}H_{47}NO_3$: C, 83.47, H, 7.16, N, 2.12; Found: C, 83.42, H, 7.23, N, 2.22. The de% was determined by conversion into the corresponding methyl ester by: (1) removal of (*R*,*R*)-**1**; and (2) methylation. See the experimental procedure below for this derivation. The chiral HPLC analytical data (column AD) of the methyl ester derived from **4**: retention times: t_R=15.7 min (minor); t_R=18.9 min (major) using *i*-PrOH/hexane (1/20) as eluent at a flow rate of 0.5 mL/min.

4.3.6. (*R*,*R*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-(2-methoxyphenyl) amino-3-(2-furfuryl)propionate (5). IR (KBr) 3419, 1759, 1513 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.00 (m, 10H), 6.75 (ddd, 1H, *J*=1.8, 7.8, 7.8 Hz), 6.65 (ddd, 1H, *J*=1.5, 7.2, 7.2 Hz), 6.71 (dd, 1H, *J*=2.1, 7.8 Hz), 6.27 (dd, 1H, *J*=1.8, 7.8 Hz), 6.08 (dd, 1H, *J*=1.8, 3.8 Hz), 5.59 (dd, 1H, *J*=0.9, 3.3 Hz), 4.38 (bs, 2H), 3.76 (s, 3H), 2.71 (bs, 2H), 2.25 (dd, 1H, *J*=4.8, 16.2 Hz), 2.17 (dd, 1H, *J*=7.2, 16.2 Hz), 2.06 (s, 6H), 1.15 (d, 6H, *J*=6.9 Hz), 1.08 (bs, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 153.6, 147.3, 146.9, 146.5, 141.5, 136.7, 135.8, 134.4, 132.0, 130.9, 130.3, 128.8, 127.8, 125.3, 125.2, 120.9, 117.0, 110.6, 110.4, 109.3, 106.3, 55.2, 47.3, 37.3, 30.0, 24.2, 20.1. HREIMS *m*/*z* Calcd for $C_{40}H_{43}NO_4$ (M^+): 601.3192; Found: 601.3206. The chiral HPLC analytical data (column: an array of two ADs) of **5**: retention times: t_R=10.8 min (minor); t_R=11.5 min (major) using *i*-PrOH/hexane (1/200) as eluent at a flow rate of 1.0 mL/min.

4.3.6. (*R*,*R*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-(2-methoxyphenyl) amino-4-octenoate (6). IR (neat) 3425, 1756, 1514 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.03 (m, 9H), 6.75 (dd, 1H, *J*=7.2, 7.8 Hz), 6.70 (d, 1H, *J*=7.8 Hz), 6.36 (dd, 1H, *J*=7.2, 7.8 Hz), 6.25 (d, 1H, *J*=7.8 Hz), 5.24 (dt, 1H, *J*=6.9, 15.6 Hz), 4.77 (dd, 1H, *J*=5.4, 15.6 Hz), 4.05 (bs, 1H), 3.80 (s, 3H), 3.62 (bs, 1H), 2.70 (bs, 2H), 2.06 (s, 6H), 2.02 (dd, 1H, *J*=4.2, 15.0 Hz), 1.80 (dt, 2H, *J*=7.2, 7.2 Hz), 1.75 (dd, 1H, *J*=15.0, 8.4 Hz), 1.25 (tq, 2H, 7.2, 7.5 Hz), 1.17 (d, 6H, *J*=6.9 Hz), 1.13 (d, 6H, *J*=6.3 Hz), 0.81 (t, 3H, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 147.3, 146.7, 146.6, 136.7, 136.3, 134.5, 132.1, 131.0, 130.4, 129.4, 128.8, 127.9, 125.3, 125.2, 121.0, 116.3, 110.7, 109.2, 55.2, 50.1, 39.4, 34.1, 30.1, 24.1, 22.3, 20.1, 13.7. Anal. Calcd for $C_{41}H_{49}NO_3$: C, 81.55, H, 8.18, N, 2.32; Found: C, 81.67, H, 8.36, N, 2.39. The chiral HPLC analytical data (column OD–H) of **6**: retention times: t_R=9.0 min (minor); t_R=9.7 min (major) using *i*-PrOH/hexane (1/100) as eluent at a flow rate of 0.5 mL/min.

4.3.7. (*R*,*R*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-(2-methoxyphenyl) amino-5-phenyl-4-pentenoate (7). IR (KBr) 3420, 1755, 1509 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.02 (m, 14H), 6.76 (ddd, 1H, *J*=2.0, 7.5, 7.5 Hz), 6.73 (dd, 1H, *J*=1.7, 8.3 Hz), 6.64 (ddd, 1H, *J*=1.5, 8.0, 8.0 Hz), 6.31 (d, 1H, *J*=1.5, 7.8 Hz), 6.29 (d, 1H, *J*= 15.9), 5.68 (dd, 1H, *J*=5.7, 15.9 Hz), 4.20 (bs, 1H), 3.82 (bs, 1H), 3.80 (s, 3H), 2.80–2.60 (bs, 2H), 2.15 (dd, 1H, *J*= 4.8, 15.6 Hz), 2.06 (s, 6H), 1.89 (dd, 1H, *J*=8.4, 15.5 Hz), 1.16 (bs, 6H), 1.00 (bs, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 147.3, 146.8, 146.5, 136.73, 136.67, 136.1, 134.4, 132.1, 130.3, 129.5, 128.8, 128.2, 127.9, 127.3, 126.6, 125.4, 125.2, 125.15, 121.0, 116.6, 110.8, 109.2, 55.2, 50.5, 39.0, 31.6, 30.0, 24.4, 24.1, 22.6. Anal. Calcd for $C_{44}H_{47}NO_3$: C, 82.85, H, 7.43, N, 2.20; Found: C, 82.71, H, 7.65, N, 2.26. The chiral HPLC analytical data (column OD–H) of **7**: retention times: t_R=8.9 min for (3*R*)-**7** (minor) and t_R=23.0 min for (3*S*)-**7** (major) using *i*-PrOH/hexane (1/200) as eluent at a flow rate of 1.0 mL/min. The absolute configuration was determined by derivation to the authentic aminocarboxylic acid:[35] (1) Pd/C, H_2 (1 atm), EtOAc, rt, 12 h; (2) Bu_4NOH, THF, rt (see below for details); (3) oxidation with Ag(I) (see below for details).

4.3.8. (*R*,*R*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-(2-methoxyphenyl) amino-5-phenyl-4-pentynoate (8). IR (KBr) 3394, 1761, 1510 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.04 (m, 14H), 6.81 (ddd, 1H, *J*=2.1, 7.2, 7.2 Hz), 6.74 (dd, 1H, *J*=2.1, 8.1 Hz), 6.70 (dd, 1H, *J*=8.4, 8.4 Hz), 6.48 (d, 1H, *J*=7.2 Hz), 4.31 (bs, 1H), 4.09 (bs, 1H), 3.79 (s, 3H), 2.80–2.60 (bs, 2H), 2.15 (dd, 1H, *J*= 4.8, 15.6 Hz), 2.06 (s, 6H), 1.89 (dd, 1H, *J*=8.2, 15.5 Hz), 1.15 (d, 6H, *J*=6.6 Hz), 1.05 (bs, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 147.2, 146.5, 136.7, 135.5, 134.3, 132.1, 131.8, 130.2, 128.8, 128.0, 127.89, 127.85, 125.4, 125.2, 122.8, 120.9, 117.5, 111.4, 109.4, 88.3, 82.7, 55.2, 41.8, 39.4, 30.0, 24.3, 24.2, 20.1. Anal. Calcd for $C_{44}H_{45}NO_3$: C, 83.11, H, 7.13, N, 2.20; Found: C, 83.10, H, 7.25, N, 2.14. The chiral HPLC analytical data (column OD–H) of **8**: retention times: t_R=12.9 min for (3*R*)-**8** (minor) and t_R=16.6 min for (3*S*)-**8** (major) using *i*-PrOH/hexane (1/200) as eluent at a flow rate of 0.5 mL/min. The absolute configuration was determined by derivation to the authentic aminocarboxylic acid:[35] (1) Pd/C, H_2 (1 atm), EtOAc, rt, 2 h; (2) Bu_4NOH, THF, rt (see below for details); (3) oxidation with Ag(I) (see below for details).

4.3.9. 3-Methoxy-*N*-(phenylmethylene)benzenamine (12).[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.94–7.88 (m, 2H), 7.50–7.48 (m, 3H), 7.26 (s, 1H), 6.81–6.78 (m, 3H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 160.2, 153.4, 136.0, 131.6, 129.8, 128.7, 112.8, 111.7, 106.6, 55.2.

4.3.10. 2-(Methoxymethoxy)-*N*-(phenylmethylene)benzenamine (14). IR (neat) 1630, 1242, 1078 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.92 (dd, 2H, *J*=2.1, 7.5 Hz), 7.47 (d, 2H, *J*=2.1 Hz), 7.46 (s, 1H), 7.19 (d, 1H, *J*=8.1 Hz), 7.15 (dd, 1H, *J*=8.1, 8.1 Hz), 7.04 (d, 1H, *J*=7.8 Hz), 7.02 (dd, 1H, *J*=7.8, 7.8 Hz), 5.23 (s, 2H), 3.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 149.7, 143.1, 136.3, 131.4, 128.9, 128.7, 126.5, 122.9, 120.5, 117.2, 95.7, 56.3. HRFABMS (NBA) *m*/*z* Calcd for $C_{15}H_{15}NO_2$ (M^+): 241.1103; Found: 241.1114.

4.3.11. Methyl 3-[(2-methoxymethoxy)phenyl]amino-3-phenylpropionate. (Table 1, entry 6). IR (KBr) 3400, 1740, 1516 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, 2H, *J*=7.8 Hz), 7.30 (dd, 2H, *J*=7.2, 7.8 Hz), 7.21 (d, 1H, *J*= 7.2 Hz), 6.98 (d, 1H, *J*=7.8 Hz), 6.75 (dd, 1H, *J*=7.5, 7.8 Hz), 6.58 (dd, 1H, *J*=7.5, 7.8 Hz), 6.44 (d, 1H, *J*= 7.8 Hz), 5.21 (s, 2H), 5.08 (bs, 1H), 4.85 (t, 1H, *J*= 6.6 Hz), 3.62 (s, 3H), 3.50 (s, 3H), 2.83 (d, 2H, *J*= 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 144.4, 142.2, 137.2, 128.7, 127.3, 126.1, 122.4, 116.9, 113.8, 111.7, 95.0, 56.0, 54.7, 51.7, 42.9. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55, H, 6.71, N, 4.44; Found: C, 68.40, H, 6.89, N, 4.44.

4.3.12. 2-Fluoro-*N*-(phenylmethylene)benzenamine (15).[20] ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.51 (s, 1H), 7.94–7.91 (m, 2H), 7.49–7.47 (m, 3H), 7.16–7.14 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 162.7, 155.1 (d, $^{1}J_{\mathrm{CF}}$=247 Hz), 139.9 (d, $^{2}J_{\mathrm{CF}}$=10.3 Hz), 135.8, 131.6, 128.9, 128.6, 126.6 (d, $^{3}J_{\mathrm{CF}}$=7.7 Hz), 124.4 (d, $^{3}J_{\mathrm{CF}}$=3.7 Hz), 121.8 (d, $^{4}J_{\mathrm{CF}}$=1.7 Hz), 116.1 (d, $^{2}J_{\mathrm{CF}}$=19.9 Hz).

4.3.13. 2,4-Dimethoxy-*N*-(phenylmethylene)benzenamine (16).[21] ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.51 (s, 1H), 7.92–7.89 (m, 2H), 7.46–7.44 (m, 3H), 7.02 (d, 1H, *J*=8.4 Hz), 6.55–6.48 (m, 2H), 3.88 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 159.4, 159.0, 153.6, 136.5, 134.9, 130.9, 128.6, 120.3, 104.2, 99.4, 55.8, 55.4.

4.3.14. 2,5-Dimethoxy-*N*-(phenylmethylene)benzenamine (17). IR (KBr) 1628, 1264, 1075 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.47 (s, 1H), 7.94–7.91 (m, 2H), 7.48–7.45 (m, 3H), 6.88 (d, 1H, *J*=9.0 Hz), 6.71 (dd, 1H, *J*=3.0, 9.0 Hz), 6.63 (d, 1H, *J*=3.0 Hz), 3.82 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 161.7, 153.9, 146.4, 142.5, 136.1, 131.4, 128.9, 128.6, 112.7, 110.6, 106.8, 56.5, 55.7. HRFABMS (NBA) *m/z* Calcd for $C_{15}H_{15}NO_2$ (M+H$^+$): 242.1181; Found: 242.1140.

4.3.15. Methyl 3-(2,5-dimethoxyphenyl)amino-3-phenylpropionate. (Table 1, entry 9). IR (KBr) 3407, 1736, 1518 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38–7.22 (m, 5H), 6.65 (d, 1H, *J*=8.4 Hz), 6.11 (dd, 1H, *J*=3.0, 8.4 Hz), 6.04 (d, 1H, *J*=3.0 Hz), 5.06 (bs, 1H), 4.81 (t, 1H, *J*=6.6 Hz), 3.82 (s, 3H), 3.64 (s, 3H), 3.62 (s, 3H), 2.86 (dd, 1H, *J*=7.8, 15.0 Hz), 2.81 (dd, 1H, *J*=6.3, 15.0 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 171.3, 154.4, 142.0, 141.5, 137.6, 128.7, 127.4, 126.1, 109.9, 99.3, 99.2, 56.0, 55.3, 54.6, 51.8, 42.8. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55, H, 6.71, N, 4.44; Found: C, 68.52, H, 6.90, N, 4.49.

4.3.16. 2,6-Dimethoxy-*N*-(phenylmethylene)benzenamine (18). IR (neat) 1640, 1252, 1036 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.50 (s, 1H), 7.95–7.92 (m, 2H), 7.47–7.45 (m, 3H), 7.06 (t, 1H, *J*=8.4 Hz), 6.64 (d, 2H, *J*=8.4 Hz), 3.80 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 165.5, 151.5, 136.4, 131.2, 128.7, 128.5 (two peaks are overlapped), 124.8, 104.8, 56.1. HRFABMS (NBA) *m/z* Calcd for $C_{15}H_{15}NO_2$ (M$^+$): 241.1103; Found: 241.1088.

4.3.17. (*E*)-2-Methoxy-6-methyl-*N*-(phenylmethylene)-benzenamine (19).[22] IR (KBr) 1624, 1283 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.34 (s, 1H), 7.95–7.91 (m, 2H), 7.49–7.47 (m, 3H), 7.00 (dd, 1H, *J*=7.8, 8.1 Hz), 6.86 (d, 1H, *J*=7.8 Hz), 6.82 (d, 1H, *J*=8.1 Hz), 3.75 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 163.9, 149.4, 140.4, 136.4, 131.1, 131.0, 128.54, 128.46, 124.3, 122.5, 109.4, 55.7, 18.0. The *E* structure was determined by NOE measurement.

4.3.18. 2,6-Difluoro-*N*-(phenylmethylene)benzenamine (20). IR (KBr) 1634 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.56 (s, 1H), 7.93 (d, 2H, *J*=8.1 Hz), 7.50 (d, 1H, *J*=7.8 Hz), 7.47 (dd, 2H, *J*=7.8, 8.1 Hz), 7.10–7.00 (m, 1H), 6.95 (dd, 2H, *J*=6.9, 7.8 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.8, 155.1 (dd, $^{1}J_{\mathrm{CF}}$=247.6 Hz; $^{3}J_{\mathrm{CF}}$=5.4 Hz), 135.7, 132.1, 129.0, 128.7, 125.0 (dd, $^{3}J_{\mathrm{CF}}$=8.9, 10.8 Hz), 111.8 (d, $^{2}J_{\mathrm{CF}}$= 23.9 Hz), 111.8 (d, $^{3}J_{\mathrm{CF}}$=8.9 Hz). Anal. HRFABMS (NBA) *m/z* Calcd for $C_{13}H_9F_2N$ (M$^+$): 217.0703; Found: 217.0717.

4.3.19. 2-Chloro-*N*-(phenylmethylene)benzenamine (24).[25] ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.39 (s, 1H), 7.97–7.51 (m, 2H), 7.43–7.15 (m, 3H), 7.28 (dd, 1H, *J*=7.2, 7.5 Hz), 7.14 (dd, 1H, *J*=7.2, 7.5 Hz), 7.02 (dd, 1H, *J*=7.5, 7.5 Hz).

4.3.20. 2-(Methoxyethoxy)-*N*-(phenylmethylene)benzenamine (25). IR (neat) 1630, 1248, 1116 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.49 (s, 1H), 7.91 (dd, 2H, *J*=3.6, 3.6 Hz), 7.47 (d, 3H, *J*=3.6 Hz), 7.15 (dd, 1H, *J*=8.1, 8.4 Hz), 7.05–6.97 (m, 3H), 4.18 (t, 2H, *J*=5.1 Hz), 3.73 (t, 2H, *J*=5.1 Hz), 3.40 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 161.5, 151.1, 142.3, 136.4, 131.1, 128.7, 128.5, 126.3, 121.7, 121.0, 114.4, 71.0, 68.8, 59.2. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27, H, 6.71, N, 5.49; Found: C, 74.57, H, 6.74, N, 5.67.

4.3.21. 2,3-Dimethoxy-*N*-(phenylmethylene)benzenamine (26). IR (KBr) 1634 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.45 (s, 1H), 7.94–7.91 (m, 2H), 7.49–7.45 (m, 3H), 7.04 (dd, 1H, *J*=8.1, 8.1 Hz), 6.79 (d, 1H, *J*=8.1 Hz), 6.66 (d, 1H, *J*= 8.1 Hz), 3.89 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 161.7, 153.2, 146.4, 141.4, 136.2, 131.4, 128.8, 128.7, 123.8, 113.1, 109.5, 60.7, 56.0. Anal. HREIMS (PFK) *m/z* Calcd for $C_{15}H_{15}NO_2$ (M$^+$): 241.1103; Found: 241.1121.

4.3.22. 2-(Phenylmethylene)aminophenol (28).[27] IR (KBr) 3130, 1630 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.68 (s, 1H), 7.92–7.89 (m, 2H), 7.51–7.46 (m, 3H), 7.30 (dd, 1H, *J*=1.5, 7.8 Hz), 7.20 (ddd, 1H, *J*=1.5, 7.2, 8.1 Hz), 7.02 (dd, 1H, *J*=1.5, 8.1 Hz), 6.90 (ddd, 1H, *J*=1.5, 7.2, 7.8 Hz).

4.3.23. (*R,R*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-(2,3-dimethoxyphenyl)amino-3-phenylpropionate (32). IR (CHCl$_3$) 3432, 1752, 1510 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.31–6.23 (m, 14H), 6.70 (dd, 1H, *J*=8.1, 8.4 Hz), 6.26 (dd, 1H, *J*=1.2, 8.4 Hz), 5.76 (dd, 1H, *J*=1.2, 8.1 Hz), 4.66 (bs, 1H), 3.97–3.90 (m, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 2.70 (bs, 2H), 2.15 (dd, 1H, *J*=7.8, 15.6 Hz), 2.04 (s, 6H), 2.00 (dd, 1H, *J*=5.4, 15.6 Hz), 1.15 (d, 6H, *J*=6.6 Hz), 1.06 (bs, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 168.4, 152.2, 147.2, 146.5, 142.4, 140.9, 136.7, 135.5, 134.3, 132.0, 130.3, 128.8, 128.5, 127.9, 127.0, 125.9, 125.3, 125.2, 123.8, 105.9, 101.3, 59.8, 55.6, 53.7, 41.3, 30.0, 24.2, 20.1. Anal. Calcd for $C_{43}H_{47}NO_4$: C, 80.47, H, 7.38, N, 2.18; Found: C, 80.45, H, 7.28, N, 2.15.

4.3.24. (*R,R*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-(2,4-dimethoxyphenyl)amino-3-phenylpropionate (33). IR (KBr) 3400, 1754, 1518 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.28 (d, 1H, *J*=7.5 Hz), 7.26 (s, 1H), 7.20–7.12 (m, 6H), 7.10 (s, 1H), 6.98 (bd, 5H, *J*=6.3 Hz), 6.39 (d, 1H, *J*=3.0 Hz), 6.17 (dd, 1H, *J*=3.0, 8.4 Hz), 5.92 (d, 1H, *J*=8.4 Hz), 4.23 (s, 1H), 3.88 (dd, 1H, *J*=4.8, 8.4 Hz), 2.70 (bs, 2H), 2.15 (dd, 1H, *J*=8.4, 15.3 Hz), 2.04 (s, 6H), 1.99 (dd, 1H, *J*=4.8, 15.3 Hz), 1.14 (d, 6H, *J*=6.6 Hz), 1.09 (bs, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 168.5, 151.4, 147.9, 147.0, 146.4, 142.6, 136.5, 134.2, 131.9, 130.8, 130.1, 128.7, 128.3, 127.7, 126.8, 125.8, 125.1, 111.6, 103.0, 98.5, 55.3, 55.1, 54.3, 41.9, 29.9, 24.1, 20.0. Anal. Calcd for $C_{43}H_{47}NO_4$: C, 80.47, H, 7.38, N, 2.18; Found: C, 80.48, H, 7.68, N, 2.22. The chiral HPLC analytical data (column OD–H) of **19**: retention times: t_R=9.4 min for (3*S*)-**19** and t_R=14.7 min for (3*R*)-**19** using *i*-PrOH/hexane (1/200) as eluent at a flow rate of 1.0 mL/min.

4.3.25. (*S*,*S*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-(2,5-dimethoxyphenyl)amino-3-phenylpropionate. (*anti*-**34**), which was derived from (*S*,*S*)-**2**. IR ($CHCl_3$) 3447, 1750, 1522 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–6.97 (m, 14H), 6.60 (d, 1H, *J*=8.4 Hz), 6.09 (dd, 1H, *J*=2.7, 8.4 Hz), 5.66 (d, 1H, *J*=2.7 Hz), 4.40 (d, 1H, *J*=4.2 Hz), 3.92–3.86 (m, 1H), 3.78 (s, 3H), 3.58 (s, 3H), 2.76–2.60 (m, 2H), 2.15 (dd, 1H, *J*=8.7, 15.6 Hz), 2.04 (s, 6H), 1.98 (dd, 1H, *J*=4.8, 15.6 Hz), 1.14 (d, 6H, *J*=6.9 Hz), 1.08 (bs, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 154.2, 147.3, 146.5, 142.3, 141.6, 137.6, 136.7, 134.3, 132.0, 130.2, 128.8, 128.6, 127.8, 127.0, 125.9, 125.3, 125.2, 109.4, 99.8, 99.1, 55.9, 55.3, 53.8, 41.6, 30.0, 24.2, 20.1. Anal. Calcd for $C_{43}H_{47}NO_4$: C, 80.47, H, 2.18, N, 2.18; Found: C, 80.31, H, 2.14, N, 2.14. The chiral HPLC analytical data (column AD) of *epi*-**34**: retention times: t_R=12.2 min (minor isomer) and t_R=16.8 min (major isomer) using *i*-PrOH/hexane (1/100) as eluent at a flow rate of 0.5 mL/min.

4.3.26. (*S*,*S*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-phenylamino-3-phenylpropionate. (*anti*-**35**), which was derived from (*S*,*S*)-**2**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.49–7.00 (m, 16H), 6.63 (t, 1H, *J*=7.2 Hz), 6.22 (d, 2H, *J*=7.5 Hz), 3.99–3.95 (m, 1H), 3.90–3.50 (bs, 1H), 2.73–2.65 (m, 2H), 2.13–1.95 (m, 2H), 2.05 (s, 6H), 1.16 (d, 6H, *J*=6.9 Hz), 1.12 (d, 6H, *J*=6.9 Hz). Anal. HREIMS *m/z* Calcd for $C_{41}H_{43}ON$ (M^+): 581.3294; Found: 581.3318. The chiral HPLC analytical data (column OD–H) of *epi*-**35**: retention times: t_R=8.6 min (major isomer) and t_R=9.8 min (minor isomer) using *i*-PrOH/hexane (1/100) as eluent at a flow rate of 0.5 mL/min.

4.3.27. (*R*,*R*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-(2-pyridyl)amino-3-phenylpropionate (36). IR (KBr) 3416, 3245, 1759, 1599, 1572 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, 1H, *J*=1.5, 4.8 Hz), 7.29–6.93 (m, 15H); 6.53 (ddd, 1H, *J*=1.5, 4.8, 7.2 Hz), 6.03 (d, 1H, *J*= 8.4 Hz), 4.76 (d, 1H, *J*=6.9 Hz), 4.52 (ddd, 1H, *J*=5.1, 6.9, 7.8 Hz), 2.74–2.60 (m, 2H), 2.22 (dd, 1H, *J*=7.8, 15.9 Hz), 2.04 (s, 6H), 2.01 (dd, 1H, *J*=5.1, 15.9 Hz), 1.13 (d, 6H, *J*=6.9 Hz), 1.12–0.80 (bs, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 157.4, 147.9, 146.5, 141.7, 136.8, 136.7, 134.3, 132.0, 130.3, 128.8, 128.5, 127.8, 126.9, 125.9, 125.4, 125.1, 113.1, 107.7, 51.4, 40.1, 30.0, 24.2, 20.1. Anal. Calcd for $C_{40}H_{42}N_2O_2$: C, 82.44, H, 7.26, N, 4.81; Found: C, 82.42, H, 7.32, N, 4.71. The chiral HPLC analytical data (column OD–H) of **36**: retention times: t_R=25.8 min (major isomer) and t_R=30.4 min (minor isomer) using *i*-PrOH/hexane (1/400) as eluent at a flow rate of 1.0 mL/min.

4.3.28. (*R*,*R*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-(2-hydroxyphenyl)amino-3-phenylpropionate (37). IR ($CHCl_3$) 3410, 1749, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82–6.94 (m, 14H), 6.71 (dd, 1H, *J*=1.8, 7.5 Hz), 6.69 (ddd, 1H, *J*=1.8, 7.2, 7.8 Hz), 6.61 (ddd, 1H, *J*=1.8, 7.2, 7.5 Hz), 6.18 (dd, 1H, *J*=1.8, 7.8 Hz), 5.44 (bs, 1H), 3.96 (dd, 1H, *J*=4.2, 9.6 Hz), 3.80–3.70 (bs, 1H), 2.71 (bs, 2H), 2.19 (dd, 1H, *J*=9.6, 15.6 Hz), 2.05 (s, 6H), 1.96 (dd, 1H, *J*=4.2, 15.6 Hz), 1.15 (d, 6H, *J*=6.9 Hz), 1.07 (bs, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 146.4, 141.9, 136.9, 134.5, 134.3, 131.9, 130.3, 128.9, 128.5, 127.9, 127.2, 126.2, 126.1, 125.3, 125.2, 120.5, 120.0, 117.0, 114.4, 55.2, 41.4, 30.1, 24.2, 20.1. Anal. HREIMS *m/z* Calcd for $C_{41}H_{43}ON$ (M^+): 597.3243; Found: 597.3228. The chiral HPLC analytical data (column OD–H) of **36**: retention times: t_R= 6.2 min [(3*S*)-**37**] and t_R=12.0 min [(3*R*)-**37**] using *i*-PrOH/hexane (1/200) as eluent at a flow rate of 1.0 mL/min. The absolute configuration was determined by derivation to **3** by methyl ether formation (MeI, K_2CO_3 acetone, rt, 2.5 h).[3j]

4.3.29. (*R*,*R*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-methansulfonylamino-3-phenylpropionate (38). IR ($CHCl_3$) 3375, 1755, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major diastereomer: δ 7.38–6.88 (m, 14H), 5.04 (s, 1H, *J*=7.8 Hz), 4.37 (ddd, 1H, *J*=4.5, 7.2, 7.5 Hz), 2.67 (bs, 2H), 2.57 (s, 3H), 2.15 (dd, 1H, *J*=4.5, 17.4 Hz), 2.07 (s, 6H), 2.00 (dd, 1H, *J*=7.5, 17.4 Hz), 1.20–1.00 (m, 12H); minor diastereomer: δ 7.38–6.88 (m, 14H), 4.52 (d, 1H, *J*=6.9 Hz), 4.28 (ddd, 1H, *J*=5.4, 5.7, 7.2 Hz), 2.67 (bs, 2H), 2.50 (s, 3H), 2.29 (dd, 1H, *J*=5.7, 17.4 Hz), 2.05 (s, 6H), 1.98 (dd, 1H, *J*=6.0, 17.4 Hz), 1.20–1.00 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) major diastereomer: δ 168.0, 147.6, 146.3, 139.5, 136.9, 134.3, 131.7, 130.4, 129.1, 128.7, 128.1, 127.8, 126.3, 125.7, 125.3, 53.1, 41.3, 39.7, 30.0, 24.2, 20.10; minor diastereomer: δ 168.4, 147.5, 146.3, 139.2, 136.9, 134.2, 131.7, 130.4, 129.0, 128.6, 128.1, 127.6, 126.2, 125.7, 125.3, 53.0, 41.7, 39.1, 30.0, 24.1, 20.08. Anal. Calcd for $C_{36}H_{41}NO_4S$: C, 74.04, H, 7.08, N, 2.40; Found: C, 74.05, H, 6.99, N, 2.50.

4.3.30. (*R*,*R*)-2,6-Bis(2-isopropylphenyl)-3,5-dimethylphenyl 3-diphenylphosphinylamino-3-phenylpropionate (39). IR (KBr) 3388, 1759, 1439, 1206, 1142 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major diastereomer: δ 7.80–6.78 (m, 24H), 4.19–4.10 (m, 1H), 3.66 (dd, 1H, *J*=8.7, 10.2 Hz), 2.71–2.54 (m, 2H), 2.31 (dd, 1H, *J*=6.0, 17.1 Hz), 2.16 (dd, 1H, *J*=4.5, 17.1 Hz), 2.02 (s, 6H), 1.11 (d, 6H, *J*=6.9 Hz), 1.0–0.50 (m, 6H); minor diastereomer: δ 4.05 (d, 1H, *J*=10.5 Hz), other peaks are identical; ^{13}C NMR (75 MHz, $CDCl_3$) major diastereomer: δ 168.6, 147.3, 146.4, 141.0 (J_{CP}=15.9 Hz), 136.7, 134.2, 133.2 (J_{CP}=41.1 Hz), 133.1 (J_{CP}=40.8 Hz), 132.24 (J_{CP}= 19.5 Hz), 132.18 (J_{CP}= 19.2 Hz), 131.9, 131.8 (J_{CP}= 9.3 Hz), 131.68, 130.3, 128.8, 128.4, 128.27, 128.23, 127.9, 126.8, 126.2, 125.15, 50.5, 40.3 (J_{CP}=18.3 Hz), 29.9, 24.1, 20.1; minor diastereomer: δ 168.9, 147.3, 146.2, 140.8 (J_{CP}=16.5 Hz), 136.7, 134.2, 133.2 (J_{CP}= 41.1 Hz), 133.1 (J_{CP}=40.8 Hz), 132.24 (J_{CP}=19.5 Hz), 132.18 (J_{CP}=19.2 Hz), 132.1 (J_{CP}=9.0 Hz), 132.0, 131.8 (J_{CP}=9.3 Hz), 131.71, 130.2, 128.8, 128.4, 128.34, 128.1, 127.9, 126.6, 126.1, 125.05, 49.8, 39.0 (J_{CP}=19.5 Hz), 29.9, 24.1, 20.1. Anal. Calcd for $C_{47}H_{48}NO_3P$: C, 79.97, H, 6.85, N, 1.98; Found: C, 79.57, H, 7.15, N, 1.99. The chiral HPLC analytical data (column OD–H) of **39**: retention times: t_R=6.5 min (minor) and t_R= 8.5 min (major) using *i*-PrOH/hexane (1/20) as eluent at a flow rate of 1.0 mL/min.

4.3.31. Methyl 3-(methanesulfonyl)amino-3-phenylpropionate (Table 1, entry 15). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.34–7.27 (m, 5H), 5.70 (bs, 1H), 4.93 (dt, 1H, *J*=6.3, 8.4 Hz), 3.66 (s, 3H), 2.89 (d, 2H, *J*=6.3 Hz), 2.69 (s, 3H)).

4.3.32. 2-Methoxy-*N*-(2-naphthylenylmethylene)benzenamine (40).[31] ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.16 (s, 1H), 8.95 (d, 1H, *J*=8.4 Hz), 8.17 (d, 1H, *J*=7.2 Hz), 7.97 (d, 1H, *J*=8.1 Hz), 7.91 (d, 1H, *J*=8.1 Hz), 7.65–7.52 (m, 3H), 7.26–7.19 (m, 1H), 7.11–6.98 (m, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 160.3, 152.1, 142.2, 133.6, 131.5, 131.4, 131.3, 129.2, 128.4, 127.1, 126.4, 125.9, 125.0, 123.9, 120.8, 120.1, 111.4, 55.6.

4.3.33. *N*-(Furfurylidene)-2-methoxybenzenamine (41).[32] ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.33 (s, 1H), 7.60 (d, 1H, *J*= 0.9 Hz), 7.19 (ddd, 1H, *J*=1.8, 7.8, 8.1 Hz), 7.04 (dd, 1H, *J*=1.8, 8.1 Hz), 6.96–6.30 (m, 3H), 6.53 (ss, 1H, *J*=1.8, 3.6 Hz), 3.88 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 152.3, 152.0, 148.3, 145.2, 140.6, 126.7, 120.6, 120.0, 115.7, 111.8, 111.1, 55.4.

4.3.34. 2-Methoxy-*N*-(2-hexenylidene)benzenamine (42). This compound was prepared by treatment of (*E*)-2-hexenal with *o*-anisidine over MS 4A in toluene at rt and used without any purification. The aldimine mixture was transferred by a cannula to a mixture of the lithium enolate of **2** and Et$_2$Zn.

4.3.35. 2-Methoxy-*N*-(3-phenyl-2-propylenylidene)benzenamine (44). IR (KBr) 2203, 1601 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.00 (s, 1H), 7.60–7.40 (m, 2H), 7.41–7.30 (m, 3H), 7.22 (d, 1H, *J*=6.6 Hz), 7.02 (d, 1H, *J*=8.1 Hz), 6.97 (d, 1H, *J*=6.6 Hz), 6.95 (d, 1H, *J*=8.1 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 152.5, 144.3, 140.4, 132.4, 129.7, 128.4, 128.0, 121.5, 120.9, 120.1, 111.5, 94.6, 88.0, 55.7. HRFABMS (NBA) *m/z* Calcd for C$_{16}$H$_{13}$NO (M$^+$): 235.0997; Found: 235.1010.

4.3.36. Methyl 3-(2-methoxyphenyl)amino-3-phenylpropionate (46).[8] IR (neat) 3376, 1730 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35 (d, 2H, *J*=7.8 Hz), 7.29 (dd, 2H, *J*=7.2, 7.8 Hz), 7.22 (d, 1H, *J*=7.2 Hz), 6.74 (d, 1H, *J*=7.8 Hz), 6.71 (dd, 1H, *J*=7.5, 7.8 Hz), 6.61 (dd, 1H, *J*=7.5, 7.8 Hz), 6.42 (d, 1H, *J*=7.8 Hz), 5.03 (bd, 1H, *J*=6.3 Hz), 4.87 (dt, 1H, *J*=6.3, 6.9 Hz), 3.84 (s, 3H), 3.62 (s, 3H), 2.86 (dd, 1H, *J*=7.8, 15.0 Hz), 2.80 (dd, 1H, *J*=6.3, 15.0 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 171.4, 146.8, 142.2, 136.5, 128.6, 127.3, 126.1, 121.0, 116.8, 111.1, 109.3, 55.4, 54.6, 51.7, 42.9. Anal. Calcd for C$_{17}$H$_{19}$NO$_3$: C, 71.56, H, 6.71, N, 4.91; Found: C, 71.73, H, 6.80, N, 5.02.

4.3.37. Methyl 3-(2-fluorophenyl)amino-3-phenylpropionate. (*Rac*-**47**), IR (KBr) 3382, 1717, 1534 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.39–7.22 (m,5H), 6.95 (dd, 1H, *J*= 8.1, 11.7 Hz), 6.84 (dd, 1H, *J*=7.8 Hz), 6.59 (ddd, 1H, *J*= 5.1, 7.8, 8.1 Hz), 6.51 (d, 1H, *J*=8.1 Hz), 4.86 (dt, 1H, *J*= 6.6, 6.9 Hz), 4.75 (bs, 1H), 3.67 (s, 3H), 2.85 (d, 2H, *J*= 6.9 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 171.2, 151.6 (d, $^1J_{CF}$=237 Hz), 141.7, 135.1 (d, $^2J_{CF}$=11.3 Hz), 128.8, 127.6, 126.1, 124.4, (d, $^3J_{CF}$=3.2 Hz), 117.1 (d, $^3J_{CF}$= 7.1 Hz), 114.3 (d, $^2J_{CF}$=18.4 Hz), 54.6, 51.9, 42.7. Anal. Calcd for C$_{16}$H$_{16}$FNO$_2$: C, 70.31, H, 5.90, N, 5.13; Found: C, 70.18, H, 6.07, N, 5.13.

4.3.38. Methyl 3-(2,4-dimethoxyphenyl)amino-3-phenylpropionate (48). IR (neat) 3407, 1736, 1518 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36–7.18 (m, 5H), 6.42 (d, 1H, *J*=2.4 Hz), 6.34 (d, 1H, 8.7 Hz), 4.78 (dd, 1H, *J*=6.3, 7.5 Hz), 4.97 (bs, 1H), 3.82 (s, 3H), 3.66 (s, 3H), 3.62 (s, 3H), 2.85 (dd, 1H, *J*=7.5 15.0 Hz), 2.78 (dd, 1H, *J*=6.3, 15.0 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 171.5, 151.9, 147.9, 142.5, 130.8, 128.6, 127.2, 126.1, 111.6, 103.4, 99.0, 55.5, 55.4, 55.3, 51.7, 42.9. Anal. Calcd for C$_{18}$H$_{21}$NO$_4$: C, 68.55, H, 6.71, N, 4.44; Found: C, 68.55, H, 6.70, N, 4.50.

4.4. Removal and recovery of chiral auxiliary 1

To a solution of **3** (184 mg, 0.3 mmol) in dry THF (1.20 mL) was added dropwise a concentrated *n*-Bu$_4$NOH in THF (1.50 mL), which was prepared from commercially available *n*-Bu$_4$NOH (565 μL: 40 wt% in H$_2$O) by azeotropic removal of H$_2$O by evaporation after treatment with DME (1.50 mL) and toluene (1.50 mL) which was repeated twice. After being stirred at 0°C for 1.5 h, the reaction mixture was quenched with 3N HCl, extracted with EtOAc five times and dried over Na$_2$SO$_4$. Filtration and concentration of solvents afforded a crude mixture, which was dissolved in MeOH (1.0 mL), followed by addition of a 1.0 M hexane solution of Me$_3$SiCHN$_2$ at rt. The mixture was stirred until no gas evolution was observed, and subsequently quenched with HCO$_2$H until no more N$_2$ evolution was observed, and washed with H$_2$O. The organic layer was dried oved Na$_2$SO$_4$. Evaporation of solvents and purification by column chromatography on extra pure silica gel (EtOAc/hexane=1/20 to 1/0 as the eluent) gave β-aminoester **46** (81 mg, >99%) in 91% ee as colorless solids.

4.5. Oxidative removal of methoxyphenyl moiety using AgNO$_3$ and (NH$_4$)$_2$S$_2$O$_8$,[15] and determination of the absolute configuration

To a solution of **46** (145 mg, 0.50 mmol) in a mixture of H$_2$O (2.5 mL)-MeCN (5.0 mL)-THF (0.5 mL) was added catalytic AgNO$_3$ (24 mg, 0.15 mmol), followed by portionwise addition of excess (NH$_4$)$_2$S$_2$O$_8$ (807 mg, 3.54 mmol) over 7.5 min, during which time the temperature was kept at 60°C. After 4 h, the mixture was cooled at rt, neutralized with NaHCO$_3$ and extracted with EtOAc. The organic layer was dried over Na$_2$SO$_4$. Evaporation of solvents and purification by column chromatography on extra pure silica gel (EtOAc/hexane=1/1 to 1/0 as the eluent) gave β-aminoester **49** (49 mg, 53%) in 91% ee as colorless solids. The absolute configuration of **49**, derived from (*R*,*R*)-**2**, was determined to be 3*S* in comparison with the authentic sample.[34]

4.5. Oxidative removal of dimethoxyphenyl moiety using cerium ammonium nitrate (CAN)[16]

Following the above procedure for the reaction of aldimine

11 with the lithium enolate of **2** except that aldimine **16** was used, β-aminoester **33** was obtained in 63% yield (92% de) using 0.5 equiv. of Me_2Zn. Subsequently following the above procedures for the sequential removal of auxiliary **1** from **3** and methylation with Me_3SiCHN_2, β-aminoester **48** was obtained quantitatively. To a solution of CAN (537 mg, 0.98 mmol) in H_2O (3.30 mL) was added **48** (78.0 mg, 0.24 mmol) in MeCN (2.50 mL) at 0°C over 10 min. After being stirred for 40 min, H_2O (5.0 mL) was added to the reaction mixture, which was extracted with diethyl ether. After separation of the two layers, the aqueous layer was treated with Na_2CO_3 until pH of the solution became 7, and filtered through a pad of celite. The obtained aqueous filtrate was extracted with EtOAc, and the organic layer was dried over Na_2SO_4. Filtration and evaporation of solvents, followed by purification by column chromatography on extra pure silica gel (EtOAc/hexane=1/0 as the eluent) gave β-aminoester **49** (90–99% yield) in 91% ee as colorless solids.

4.6. Mannich-type addition of chiral acetate 2 to the $SnCl_4$-(Z)-11 complex

To a solution of (*R*,*R*)-**2** (80 mg, 0.2 mmol) in THF (0.80 mL) was added a 1.59 M hexane solution of *n*-BuLi (0.13 mL, 0.20 mL) at −78°C under argon atmosphere, and the mixture was stirred at this temperature for 0.5 h. The $SnCl_4$-(*Z*)-**11** complex,[12a] which was prepared by treatment of (*E*)-**11** (42 mg, 0.2 mmol) with $SnCl_4$ (200 μL, 0.2 mmol) in CH_2Cl_2 (1.4 mL) at 0°C followed by being stirred at for 5 min, was transferred by a steel cannula to the solution of the lithium enolate of acetate **2** at −78°C. After 20 h, the reaction mixture was quenched by addition of aqueous $NaHCO_3$, filtered through a short path of celite pad, extracted with diethyl ether, and dried over Na_2SO_4. Filtration and evaporation of solvents, followed by purification by column chromatography on silica gel (EtOAc/hexane=1/20 to 1/5 as the eluent) gave β-aminoester **3** (34 mg, 26% yield) in 70% de as colorless solids.

4.7. Preparation and reaction of the $SnCl_4$-(Z)-19 complex

To a solution of (*E*)-**19** (45 mg, 0.2 mmol) in CH_2Cl_2 (0.7 mL) was added a 1.0 M solution of $SnCl_4$ (0.20 mL, 0.2 mmol) at 0°C under argon atmosphere and stirring was continuted for 1 h at rt. After being cooled to −78°C, to this mixture was added the ketene silyl acetal or the lithium enolate of methyl acetate and the mixture was stirred for 14 h or 18 h, respectively. For the X-ray single cystal analysis, hexane (0.9 mL) was added to the $SnCl_4$-(*Z*)-**19** mixture obtained above at rt. The resulting solution was allowed to stand at −28°C for a week with rigorous exclusion of air and moisture.

4.8. X-ray crystallographic determinations of $SnCl_4$-(Z)-19

A single crystal of the $SnCl_4$-(*Z*)-**19** complex suitable for X-ray diffraction analysis was transferred to a glass capillary tube as quickly as possible under air atmosphere, and the glass capillary was mounted with a sticky compound on a goniometer for measurement. Diffraction data were obtained with graphite-monochromated MoKα radiation on a MAC Science DIP2030 diffractometer at 298 K. Standard reflections for each data set showed no significant decrease in intensity throughout acquisition. The structure was solved by direct method and refined by full-matrix least-squares on F^2. All non-hydrogen atoms were refined anisotropically, and hydrogens were found by Fourier synthesis, using isotropic temperature factors. Crystallographic computations were performed on a Silicon Graphics INDY computer using the maXus program for data reduction, determining the structure, refining the structure, and molecular graphics. MAC DENZO software was used for cell refinement. Crystal data: $a=12.2120$ (9), $b=9.9470$ (3), $c=9.9060$ (6) Å, $\alpha=74.263$ (4)°, $\beta=94.465$ (3)°, $\gamma=99.377$ (4)°, triclinic, $P\bar{1}$, $Z=2$, $\mu(\text{Mo})=15.86\ \text{cm}^{-1}$, $R=0.044$, $R_w=0.059$, GOF=1.163, 4242 unique reflections with $I>3.0\sigma(I)$.

Acknowledgements

We are grateful to Mr S. Komai and H. Choshi (Nagoya University) for performing high resolution mass spectrometric analysis.

References

1. (a) Evans, D. In *Asymmetric Synthesis*, Morrison, J. D., Ed.; Academic: San Diego, CA, 1984; Vol. 3 (chapter 1). (b) In *Asymmetric Synthesis*, Procter, G., Ed.; Oxford University: Oxford, 1996 (Chapter 5). (c) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.
2. (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1044. (b) Denmark, S. E.; Nicaise, O. J.-C. *Chem. Commun.* **1996**, 999. (c) Risch, N.; Arend, M. In *Stereoselective Synthesis (Houben-Weyl)*, Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. E21/b, pp 1833.
3. Most examples concerning the asymmetric Mannich-type reaction employ chiral sources appended to the N atom of aldimines. For leading reviews, see: (a) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447 (b) *Enantioselective Synthesis of β-Amino Acids*, Juraisti, E., Ed.; Wiley: New York, 1997. For recent outstanding examples using chiral aldimines and related reactions. (c) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12. (d) Müller, R.; Goesmann, H.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 184. (e) Davis, F. A.; Szewczyk, J. M.; Reddy, R. E. *J. Org. Chem.* **1996**, *61*, 2222. For reactions using chiral metal catalysts, see: (f) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2472. (g) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (h) Ferraris, D.; Young, B.; Cox, C.; Drury, W. J.; Dudding, T.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 6090. (i) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431. (j) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. (k) Ishihara, K.; Miyata, M.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520.
4. For asymmetric Mannich-type reaction using chiral acetate equivalent (chiral Iron acyl complex): (a) Liebeskind, L. S.; Welker, M. E.; Fengel, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 6328. (b) Liebeskind, L. S.; Welker, M. E.; Goedken, V.

J. Am. Chem. Soc. **1984**, *106*, 441. Very recent example, see: (c) Palomo, C.; Oiarbide, M.; Concepción, M.; González-Rego, C.; Sharma, A. K.; García, M.; González, A.; Landa, C.; Linden, A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1063. Our preliminary communication: (d) Saito, S.; Hatanaka, K.; Yamamoto, H. *Org. Lett.* **2000**, *2*, 1891.

5. For preliminary synthesis of **1**, see: (a) Saito, S.; Kano, T.; Hatanaka, K.; Yamamoto, H. *J. Org. Chem.* **1997**, *62*, 5651. (b) For the more efficient synthesis we developed recently for **1**, see: (b) Saito, S.; Kano, T.; Muto, H.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 8943.
6. Saito, S.; Hatanaka, K.; Kano, T.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3378.
7. (a) Gluchowski, C.; Cooper, L.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413. (b) Ha, D.-C.; Hart, D. J.; Yang, T.-K. *J. Am. Chem. Soc.* **1984**, *106*, 4819. The trimethylsilyl ketene acetal of methyl acetate also shows poor reactivity, see: (c) Colvin, E. W.; MacGarry, D. *J. Chem. Soc., Chem. Commun.* **1985**, 539. (d) Colvin, E. W.; MacGarry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157.
8. Adrian, J. C.; Barkin, J. L.; Hassib, L. *Tetrahedron Lett.* **1999**, *40*, 2457.
9. Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934.
10. Bussche-Hünnefeld, J. L.; Seebach, D. *Tetrahedron* **1992**, *48*, 5719.
11. (a) Rasmussen, K. G.; Hazaell, R. G.; Jorgensen, K. A. *Chem. Commun.* **1997**, 1103. (b) Rasmussen, K. G.; Juhl, K.; Hazaell, R. G.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1347.
12. Crystallographic data (excluding structure factors) for the X-ray crystal structure analysis reported in this paper have been deposited with the Cambridge Crystallographic Data Center (CCDC) as supplementary publication no. CCDC-143742. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033, e-mail: deposit@ccdc.cam.ac.uk).
13. (a) Gennari, C.; Todeschini, R.; Beretta, M. G.; Favini, G.; Scolastico, C. *J. Org. Chem.* **1986**, *51*, 612. (b) Hoffmann, R. W.; Ditrich, K.; Froech, S. *Tetrahedron* **1985**, *41*, 5517. (c) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24.
14. Hasegawa, T.; Yamamoto, H. *Synlett* **1998**, 882. See also Ref. 5.
15. Bhattarai, K.; Cainelli, G.; Panunzio, M. *Synlett* **1990**, 229.
16. Jacob, P.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627.
17. Okubo, M.; Ueda, S. *Bull. Chem. Soc., Jpn.* **1979**, *52*, 3346.
18. (a) Kawasaki, A. *J. Chem. Soc. Perkin Trans. 2* **1990**, 223. (b) Ogata, Y.; Kawasaki, A. *J. Chem. Soc. (B)* **1971**, 325.
19. Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron* **1994**, *50*, 4429.
20. Császár, J. *Acta Pys. Chem.* **1986**, *32*, 17.
21. Beland, C.; Roussakis, C.; Letonunrux, Y.; Alomi, N. El. *Synth. Commun.* **1985**, *15*, 1233.
22. Müller, R.; Goesmann, H.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 184.
23. Keck, G. E.; Wager, T. T.; Mchardy, S. F. *Tetrahedron* **1999**, *55*, 11755.
24. Georg, G. I.; Harriman, G. C. B.; Peterson, S. A. *J. Org. Chem.* **1995**, *60*, 7366.
25. Bortolotti, B.; Leardini, R.; Nanni, D.; Zanardi, G. *Tetrahedron* **1993**, *49*, 10157.
26. Nongkunsarn, P.; Ramsden, C. A. *Tetrahedron* **1997**, *53*, 3805.
27. Fulup, F.; Mattinen, J.; Pihlaja, K. *Tetrahedron* **1990**, *46*, 6545.
28. Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561.
29. Grigg, R.; McMeekin, P.; Sridharan, V. *Tetrahedron* **1995**, *48*, 13331.
30. Sharma, S. D.; Pand, S. B. *J. Org. Chem.* **1990**, *55*, 2196.
31. Lugorkin, B. P. *Zh. Obshch. Khim.* **1976**, *46*, 555.
32. Israilva, Sh. A.; Tsukervanik, I. P. *Dokl. Akd. Nauk. Uzb. SSR* **1996**, *23*, 29.
33. Knolker, H.-J.; Baum, G.; Goesmann, H.; Gonser, P.; Jones, P. G.; Rottele, H.; Eur *J. Inorg. Chem.* **1998**, 993.
34. Kuroki, Y.; Ishihara, K.; Hanaki, N.; Ohara, S.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1221.
35. Andrés, C.; González, A.; Pedrosa, R.; Perez-Encabo, A. *Tetrahedron Lett.* **1992**, *33*, 2895.