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Synthesis of α-diazo-β-hydroxyesters through a one-pot protocol by phase-transfer catalysis: application to enantioselective aldol-type reaction and diastereoselective synthesis of α-amino-β-hydroxyester derivatives

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Abstract—The one-pot synthesis of α-diazo-β-hydroxyesters from sodium azide under phase-transfer-catalyzed conditions has been achieved. This protocol includes three different chemical transformations promoted by a single catalyst in each step to give products in good to excellent yields. The reaction was applied to a catalytic asymmetric aldol-type reaction using α-diazoesters with aldehydes in the presence of a chiral quaternary ammonium salt and gave products with up to 81% ee. The diastereoselective transformation of the products to chiral α-amino-β-hydroxyester derivatives is also described.

1. Introduction

Phase-transfer-catalyzed reactions are some of the most environmentally-friendly processes in synthetic organic chemistry due to their simplicity, mild conditions and high cost performance.[1] Particularly, chiral quaternary ammonium salts have been recognized as powerful asymmetric phase-transfer catalysts (PTCs) since Dolling and O'Donnell independently reported their pioneering studies.[2] In this paper, we report the PTC-promoted one-pot synthesis of α-diazo-β-hydroxyesters from sodium azide, acetoacetate and aldehydes in the presence of a single catalyst without isolation of intermediates. The application to enantioselective carbon–carbon bond-forming reactions and the diastereoselective synthesis of α-amino and α-hydrazino-β-hydroxyesters is also described in detail.[3]

2. Resullts and discussion

2.1. One-pot synthesis of α-diazo-β-hydroxyesters

α-Diazo-β-hydroxyesters are useful as a potential source of amino alcohols or acids and their facile preparation using the aldol-type reaction of α-diazoesters with aldehydes has been investigated.[4,5] Since the starting α-diazoesters and the precursor, tosyl azide are both readily available under PTC conditions,[6] we expected that all three sequences could be promoted by a single phase-transfer catalyst without isolation of any explosive intermediates.

First, we investigated a three-step protocol using tosyl chloride, *t*-butyl acetoacetate **1a** and benzaldehyde **3a** in the presence of tetrahexylammonium bromide (THAB, 10 mol%) as a PTC. The results are summarized in Table 1. The azidation of tosyl chloride (first step) in CH_2Cl_2 proceeded quantitatively (rt, 1 h), however, diazo-transfer (second step) with aqueous 11% NaOH at rt was slow (85 h). Subsequent aldol-type reaction (third step) with **3a** (5 equiv) gave the desired product **4a** in 70% yield (entry 1). Ethylester **1b** was more reactive in diazo-transfer step and the reaction was completed within 9 h, and the aldol-type reaction gave **5a** in 87% (entry 2). The solvent influenced the rate of diazo-transfer, for example, the reaction in diethyl ether enabled rapid conversion in diazo-transfer and **5a** was obtained in 82% yield through three steps (entry 3). Although a longer reaction time was required, benzylester **1c** was also transformed to **2c** in 25 h and subsequent C–C bond formation gave **6** in 51% overall yield (entry 4).

Next, we applied this three-step protocol to various aldehydes under optimized conditions (Table 2). The

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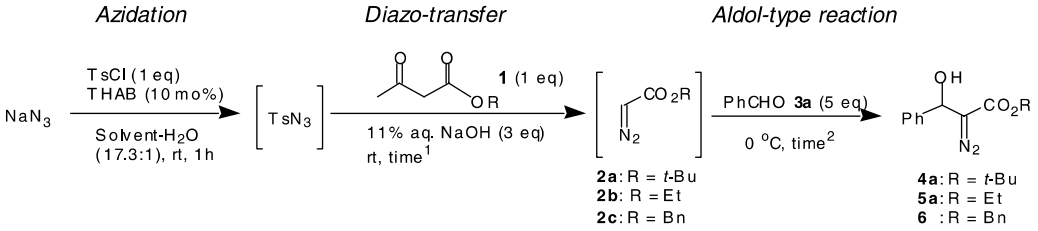
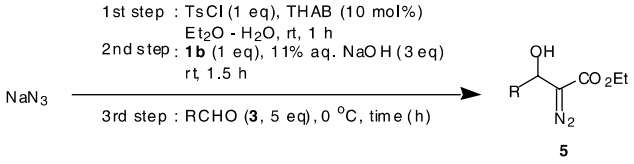
Table 1. One-pot syhthesis of α-diazo-β-hydroxyesters under PTC conditions



Entry	1	Solvent	Time[1] (h)	Time[2] (h)	Yield (%)
1	**1a**: R=*t*-Bu	CH_2Cl_2	85	3	**4a**: 70
2	**1b**: R=Et	CH_2Cl_2	9	3	**5a**: 87
3	**1b**: R=Et	Et_2O	1.5	3	**5a**: 82
4	**1c**: R=Bn	Et_2O	25	7	**6**: 51

Table 2. One-pot reaction using various aldehydes



Entry	**3**: Aldehyde	Time (h)	Yield (%)
1	**3b**: R=4-MeO–C_6H_4	2	**5b**: 73
2	**3c**: R=4-CF_3–C_6H_4	12	**5c**: 76
3	**3d**: R=1-Napthyl	3	**5d**: 80
4	**3e**: R=Ph$(CH_2)_2$	3	**5e**: 86[a]
5	**3f**: R=*i*-Bu	20	**5f**: 82
6	**3g**: R=*i*-Pr	3	**5g**: 75
7	**3h**: R=*c*-Hex	4	**5h**: 75
8	**3i**: R=*t*-Bu	18	**5i**: 73

[a] Three equivalent of **3e** was used.

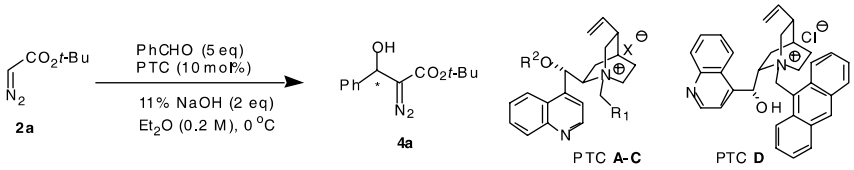
aromatic aldehydes shown in entries 1–3 were smoothly transformed into the corresponding adducts **5b–d** in yields of 73–80%. In the case of aliphatic aldehydes including sterically hindered substrate such as **3i**, the reactions also proceeded without any significant self-condensation with a range of 73–86% yield (entries 4–8).

2.2. Asymmetric aldol-type reaction using a chiral quaternary ammonium salt as a PTC

After succeeding with the one-pot synthesis of α-diazo-β-hydroxyesters, we next investigated catalytic asymmetric synthesis. Only one example of a catalytic asymmetric aldol-type reaction using α-diazoester has been reported.[7] Initially, we surveyed this reaction using cinchoninium salts (**A–C**[9e]) (Table 3). Although the enantioselectivities were poor, an *N*-anthracenyl group gave better results at 0 °C (entry 2). Moreover, a secondary hydroxy group was found to be essential in asymmetric induction, suggesting that hydrogen bonding between the catalyst and substrates is important (entry 2 vs 3). Since the cinchonidinium salt (PTC **D**) gave a slightly better result, the reaction conditions were further optimized using catalyst **D** (Table 4).

With a stronger base such as aqueous KOH, the reaction proceeded to give **4a** at lower temperature (Table 4, entries

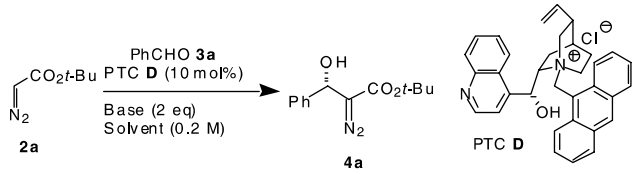
Table 3. Catalytic asymmetric aldol-type reaction of **2a** with **3a** using various PTCs



Entry	PTC	R^1	R^2	X	Time (h)	Yield (%)	ee (%)[a]
1	**A**	Ph	H	Br	2.5	51	6 (*S*)
2	**B**	9-Anthracenyl	H	Cl	2	84	14 (*R*)
3	**C**	9-Anthracenyl	Allyl	Br	3	96	0
4	**D**				3	76	24 (*S*)

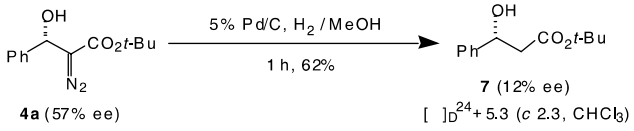
[a] Determined by chiral HPLC analysis using DAICEL CHIRALCEL OD.

Table 4. Catalytic asymmetric aldol-type reaction of **2a** with **3a** using PTC **D**



Entry	Solvent	Base	**3a** (equiv)	Conditions	Yield (%)	ee (%)
1	Et_2O	25% KOH	5	−20°C, 8 h	70	25
2	Et_2O	50% KOH	5	−40°C, 2 h	74	39
3	Et_2O	50% KOH	5	−60°C, 16 h	65	20
4	Et_2O	50% KOH	1.5	−40°C, 14 h	96	48
5	Et_2O	50% RbOH	1.5	−40°C, 10 h	72	51
6	PhMe	50% KOH	1.5	−40°C, 38 h	83	45
7	PhMe	50% RbOH	1.5	−40°C, 10 h	96	56
8	PhMe	50% CsOH	1.5	−40°C, 20 h	76	56

1–3). Under biphase conditions of 50% KOH and Et_2O at −40 °C, 1.5 equiv of **3a** was enough for the reaction to proceed in 96% yield with moderate enantioselectivity (entry 4). The best result (96% yield, 56% ee)[8] was obtained using 50% aqueous RbOH in toluene at −40 °C (entry 7). The absolute stereochemistry of **4a** was determined to be *S* by comparison with the reported optical rotation[10] after diazo decomposition to β-hydroxyester **7** (Scheme 1 and Section 3).

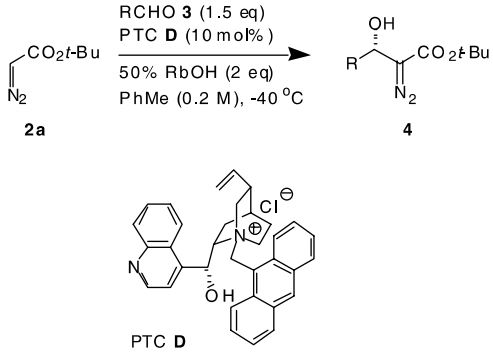


Scheme 1. Determination of the absolute stereochemistry of **4a**.

Next, various aldehydes were used in this reaction under the optimized conditions. The electron density on the aromatic rings was found to strongly influence the enantioselectivity (Table 5). For example, **3b**, which has a 4-MeO group, gave a racemate, while **3c** which has an electron-withdrawing group 4-CF_3, gave **4c** in 81% yield with 73% ee (entries 1 and 2). 4-Alkylated substrates were also converted with lower ee (entries 4 and 5). 1- and 2-Naphthaldehydes were converted to **4d** and **4l** in respective yields of 86% (79% ee) and 94% (56% ee) (entries 3 and 6). In the case of aliphatic substrates, primary and secondary aldehydes such as **3e–h** gave 22–42% ee (entries 7–10), but pivalaldehyde **3i** was transformed to **4i** in 83% yield with 81% ee (entry 11).

The aldol-type reaction of α-diazoesters under basic media has been reported to include an equilibrium process,[4f] so the time course of the chemical yield and ee of **4a** and **4i** during asymmetric reactions were investigated. As shown in Figure 1, in the case of aromatic aldehyde **3a** both the chemical yield and ee of **4a** gradually increased. The chemical yield reached equilibrium after 5 h and the ee remained at about 60% ee after 3 h. In the reaction of aliphatic aldehyde **3i**, the initial ee of **4i** was 70%, and this gradually increased to 80% ee after 5 h. The former result suggests the possibility of a retro-aldol reaction.[11] With regard to this reversible mechanism, enantioselection might occur in the differentiation of the carbonyl plane of

Table 5. Enantioselective synthesis of **4** with various aldehydes using PTC **D**



Entry	Aldehyde **3**	Time (h)	Yield (%)	ee (%)
1	**3b**: R=4-MeO–C_6H_4	120	**4b**: 56	0
2	**3c**: R=4-CF_3–C_6H_4	140	**4c**: 81	73
3	**3d**: R=1-Napthyl	94	**4d**: 86	79
4	**3j**: R=4-Me–C_6H_4	18	**4j**: 66	39
5	**3k**: R=4-Bu–C_6H_4	120	**4k**: 63	32
6	**3l**: R=2-Naphthyl	110	**4l**: 94	56
7	**3e**: R=Ph(Ch_2)$_2$	72	**4e**: 32	33
8	**3f**: R=*i*-Bu	72	**4f**: 85	22
9	**3g**: R=*i*-Pr	20	**4g**: 53	42
10	**3h**: R=*c*-Hex	10	**4h**: 88	33
11	**3i**: R=*t*-Bu	72	**4i**: 84	81

aldehydes in the C–C bond-forming step or the reversal retro-aldol step by kinetic resolution.

To test the latter possibility, (±)-**4a** was subjected to retro-aldol conditions with 50% RbOH in toluene (10 h) in the presence of PTC **D**, and the formation of **2a** and **3a** was observed. However, the ee of the recovered **4a** (72%) was very low (Scheme 2). This result suggests that the asymmetric induction of **4a** occurs mainly not via kinetic resolution in the retro-aldol step but rather through the carbon–carbon bond-forming step. In the case of **4i**, an alcoholic proton might be less acidic than benzyl alcoholic proton in **4a** and the retro-aldol reaction seems to be disfavored. As outlined in Scheme 3, k'_S and k'_R are considered to be equal but the rate of C–C bond formation (k_S) is greater than k_R in the reaction of **3a** with **2a**.

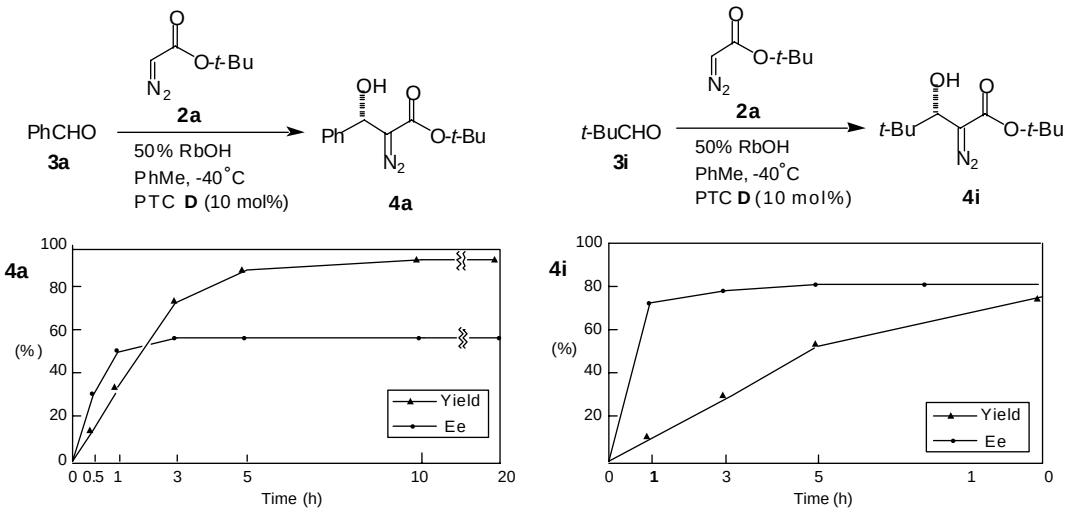
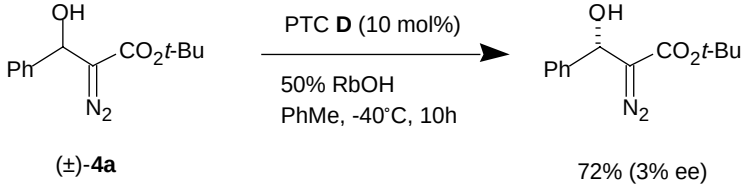
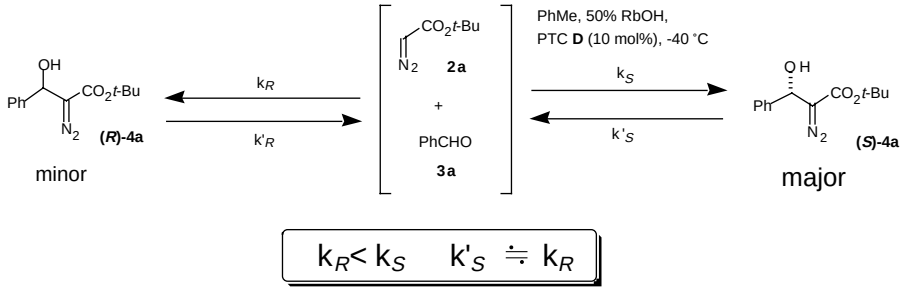


Figure 1. Time course of yield and ee in the reaction of **2a** with **3a** and **3i**.



Scheme 2. Retro aldol-type reaction of (±)-**4a** with PTC **D**.

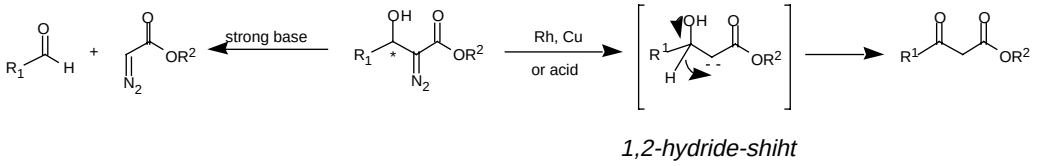


Scheme 3. Postulated reaction pathway for the catalytic asymmetric aldol-type reaction.

The presence of this retro-aldol process for racemic **4a** explains the increase in ee in the initial step of the reaction using **3a**. In the same way, a large excess of **3a** resulted in a lower ee (Table 4, entry 2 vs 4).

2.3. Transformation of optically active α-diazo-β-hydroxyesters to α-amino-β-hydroxyester derivatives

Many organic transformations using a diazo-functionality via diazo-decomposition have been reported[12] due to its high reactivity with late transition metals. However, only limited examples of transformation using α-diazo-β-hydroxyesters have been reported,[13] since they are unstable under basic (retro-aldol reaction) and acidic (diazo decomposition) media. Furthermore, they gave simple 1,3-dicarbonyl compounds via a 1,2-hydride shift by reacting with transition metals (Scheme 4). To establish a new synthetic transformation of α-diazo-β-hydroxyesters without any loss of chiral centers, we attempted the reduction of a diazo group to hydrazone or hydrazine as an amine



Scheme 4. Decomposition of α-diazo-β-hydroxyesters.

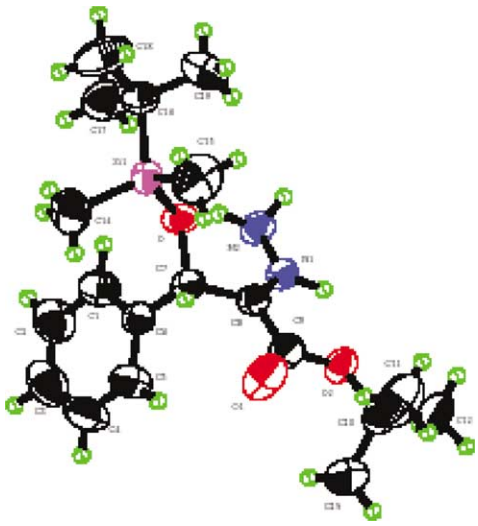


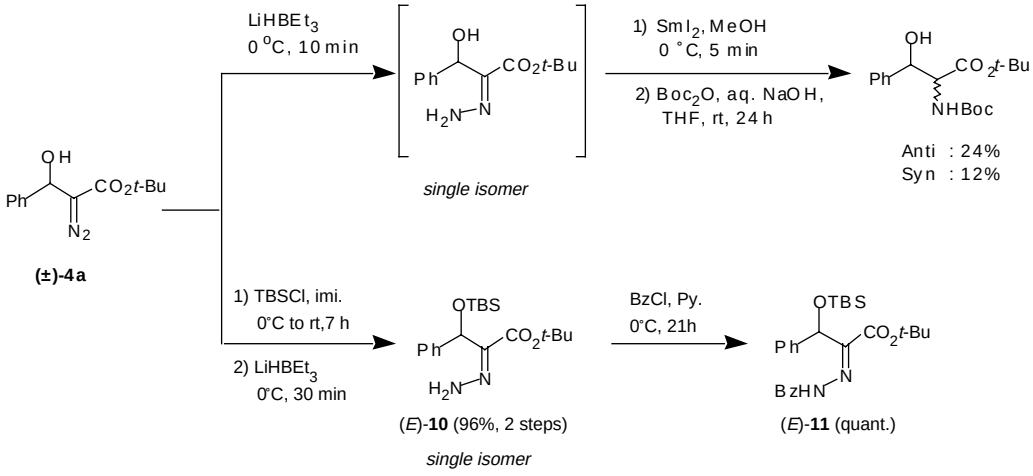
Figure 2. X-ray structure of (*E*)-**10**.

equivalent,[14,15] which are known to be useful building blocks for the synthesis of polypeptides and biologically important molecules.[16,17]

First, we attempted to convert (±)-**4a** to hydrazonoester without protection of its hydroxy group. Reduction with $LiHBEt_3$ proceeded smoothly but the stability of the product was problematic and subsequent reduction with SmI_2 and protection with Boc_2O gave amino alcohols in low yields. Next, the initial protection of (±)-**4a** with TBSCl followed by reduction of the diazo group by $LiHBEt_3$ gave hydrazone **10** as a single isomer in 96% yield. Its configuration was confirmed by X-ray crystallographic analysis to be *E* (Fig. 2). Subsequent *N*-benzoylation (BzCl with pyridine in CH_2Cl_2 at 0 °C) gave (*E*)-**11** without significant isomerization[18] (Scheme 5).

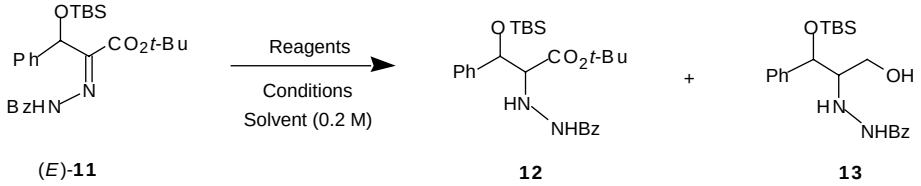
The further diastereoselective reduction of C=N bond was investigated (Table 6). The treatment of (*E*)-**11** with $NaBH_4$ at 0 °C in EtOH gave α-hydrazinoester *anti*-**12** in 92% yield, exclusively (entry 1). In the case of $LiBH_4$, a mixture of **12** and **13** was obtained with respective yields of 55 and 12%. However, no diastereoselectivities were observed in either product (entry 2). The reaction of Red-Al with **11** in toluene gave **13** as a separable diastereomixture in moderate yield, while no selectivity was observed (entry 3).

Further transformations of **12** and **13** are outlined in Scheme 6. N–N bond cleavage of *anti*-**12** with SmI_2 followed by protection with Boc_2O gave **14** (65% yield) as a mixture of *syn*- and *anti*-isomers (1:2.6) due to epimerization at the α-position.[19] In the case of *syn*-**13** and *anti*-**13**, similar transformation gave the corresponding alcohols **15**



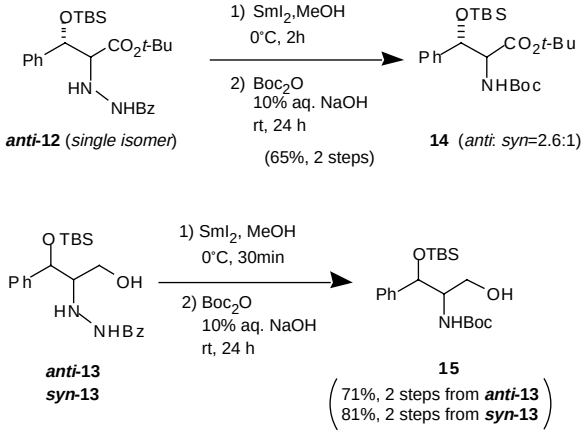
Scheme 5. Preparation of hydrazones.

Table 6. Diastereoselective reduction of (*E*)-**11**

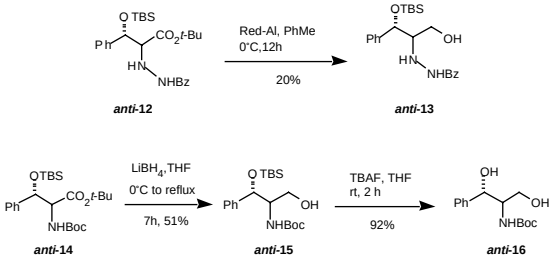


Entry	Reagents (equiv)	Solvent	Conditions	Yield (%)	
				12 (*syn*:*anti*)[a]	**13** (*syn*:*anti*)[a]
1	$NaBH_4$ (5)	EtOH	0°C, 2 h	92 (*anti* only)	0
2	$LiBH_4$ (5)	THF	0°C to rt, 19 h	55 (1:1)	12 (1:1)
3	Red-Al (5)	PhMe	0°C, 2 h	0	60 (1:1)

[a] Determined by ^1H MNR analysis.

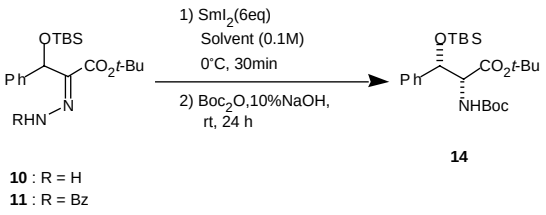


Scheme 6. N–N bond cleavage of **12** and **13** by SmI_2.



Scheme 7. Determination of relative configuration.

Table 7. Diastereoselective reduction of hydrazones



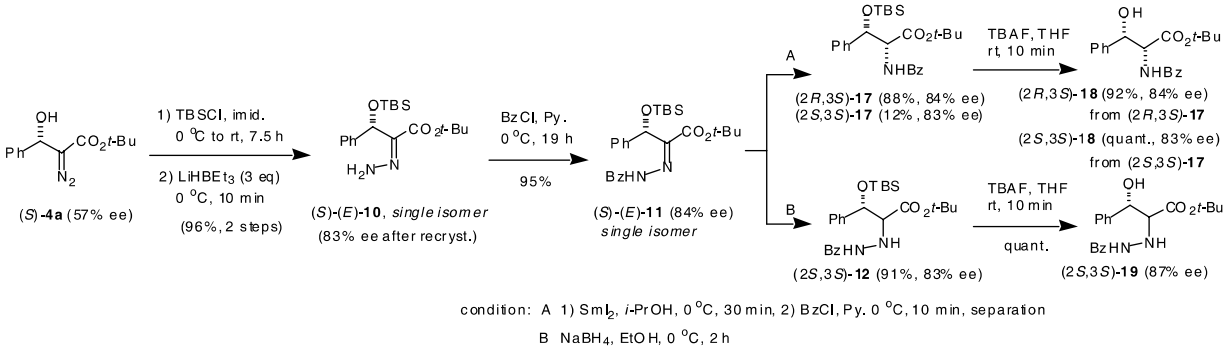
Entry	Substrate	Solvent	Yield (%)	*syn*:*anti*
1	**10**	MeOH	100	2:1
2	**10**	*i*-PrOH	100	3.3:1
3	**11**	MeOH	77	5.4:1
4	**11**	*i*-PrOH	100	6.7:1

in respective yields of 81 and 71%. The stereochemistry of *anti*-**14** was determined by conversion to *anti*-**16** (Scheme 7), the stereochemistry of which was confirmed by comparison to the literature via *anti*-**15**.[20] The relative stereochemistry of *anti*-**12** was also confirmed by conversion to *anti*-**13**.

To enhance the utility of this synthetic protocol, we next investigated the diastereoselective one-pot transformation of hydrazones to amino groups (Table 7). For example, the reaction of (*E*)-**10** with SmI_2[19] in MeOH followed by protection with Boc_2O gave the desired product **14** in quantitative yield (syn/anti=2:1). Higher diastereoselectivity was observed when the reduction was carried out in isopropanol (entries 1 and 2). The reduction of *N*-benzoylhydrazone (*E*)-**11** in isopropanol gave **14** in quantitative yield with better selectivity (syn/anti=6.7:1, entry 4).

After successfully developing an efficient transformation to aminoesters, we next investigated the synthesis of optically active aminoesters from (*S*)-**4a** (57% ee). Initial transformation gave siloxyhydrazone (*E*)-**10**, the ee of which was increased to 83% ee by recrystallization. Subsequent reduction of (*S*)-(*E*)-**11** with SmI_2 followed by BzCl (condition A) gave (2*R*,3*S*)-**17** and (2*S*,3*S*)-**17** in respective yields of 88 and 12% without racemization. The reduction of (*S*)-(*E*)-**11** with $NaBH_4$ (condition B) gave (2*S*,3*S*)-**12** in 91% yield, exclusively, without any loss of optical purity. Treatment of these products with TBAF gave the corresponding hydroxyesters **18** and **19** (Scheme 8).

In summary, we have developed the one-pot synthesis of α-diazo-β-hydroxyesters with a single catalyst without any isolation of explosive intermediates. A PTC-catalyzed asymmetric aldol-type reaction using α-diazoester (up to 81% ee) with unique enantio enrichment and the transformations of α-diazo-β-hydroxyesters to α-amino-β-hydroxyesters in diastereoselective fashion were also established. This synthetic protocol provides a practical synthesis of optically active α-amino-β-hydroxyester derivatives, which have been recognized as useful building blocks for biologically important compounds or pharmaceuticals. Further studies of the application of this method are currently underway.



Scheme 8. Transformation of optically active **4a**.

3. Experimental

3.1. A general procedure for the one-pot synthesis of α-diazo-β-hydroxyester, synthesis of ethyl 2-diazo-3-hydroxy-3-phenylpropionate (5a) (Table 1, entry 3)

To a solution of TsCl (200 mg, 1.05 mmol) and THAB (45.5 mg, 0.1 mmol, 10 mol%) in diethylether (5.2 mL) was added NaN_3 (68.4 mg, 1.05 mmol) and water (0.3 mL) at rt. The mixture was stirred for 1 h and **1b** (0.14 mL, 1.05 mmol) and 3 N NaOH (1.17 g, 3.15 mmol) were added with stirring for an additional 1.5 h. After α-diazoacetoacetate had diappeared, benzaldehyde **3a** (0.53 mL, 5.25 mmol) was added at 0 °C and the mixture was stirred for 3 h at 0 °C. The mixture was extracted with AcOEt (10 mL×3) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Subsequent flash column chromatography (hexane/AcOEt=10:1) gave the desired product **5a** as a yellow oil (189.4 mg, 0.86 mmol, 82%) (reg.# 27262-59-5), ^{1}H NMR δ: ($CDCl_3$, 400 MHz) 1.28 (t, 3H, J=6.8 Hz), 3.03 (br s, 1H), 4.29 (q, 2H, J=6.8 Hz), 5.92 (d, 1H, J=2.8 Hz), 7.31–7.49 (m, 5H).

3.1.1. *tert*-Butyl 2-diazo-3-hydroxy-3-phenylpropionate (4a). Yellow oil; IR (neat) ν: 3442, 2979, 2095, 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.46 (s, 9H), 2.99 (br s, 1H), 5.87 (d, 1H, J=2.8 Hz), 7.30–7.46 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.7, 139.0, 128.5, 128.0, 125.6, 82.0, 68.5, 28.2; LRMS (FAB) *m/z*: 287 (M+K); HRMS (FAB) calcd for $C_{13}H_{16}N_2O_3K$ 287.0798, found: 287.0807.

3.1.2. Benzyl 2-diazo-3-hydroxy-3-phenyl-propionate (6). Yellow oil; IR (neat) ν: 3425, 3032, 2101, 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.90 (br s, 1H), 5.20 (s, 2H), 5.92 (d, 1H, J=3.2 Hz), 7.29–7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.1, 138.7, 135.6, 128.7, 128.5, 128.34, 128.32, 128.1, 125.6, 68.6, 66.6; LRMS (FAB) *m/z*: 321 (M+K); HRMS (FAB) calcd for $C_{16}H_{14}N_2O_3K$ 321.0642, found: 321.0630.

3.1.3. Ethyl 2-diazo-3-hydroxy-3-(4-methoxyphenyl)-propionate (5b) (reg.#39910-24-2). Yellow crystal; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.33 (t, 3H, J=7.2 Hz), 2.95 (br s, 1H), 3.84 (s, 3H), 4.32 (q, 2H, J=7.2 Hz), 5.90 (d, 1H, J=2.0 Hz), 6.94 (d, 2H, J=8.4 Hz), 7.38 (d, 2H, J=8.4 Hz).

3.1.4. Ethyl 2-diazo-3-hydroxy-3-(4-trifluoromethyl-phenyl)propionate (5c). Yellow crystal; mp 55–59 °C (hexane–$CHCl_3$); IR (thin film) ν: 3423, 3019, 2101, 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30 (t, 3H, J=7.2 Hz), 3.14 (br s, 1H), 4.28 (q, 2H, J=7.2 Hz), 5.97 (d, 1H, J=4.0 Hz), 7.57 (d, 2H, J=8.4 Hz), 7.65 (d, 2H, J=8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.2, 142.9, 130.3 (q, J=32.0 Hz), 126.0, 125.6 (q, J=3.3 Hz), 123.9 (q, J=270.7 Hz), 68.0, 61.4, 14.4; LRMS (FAB) *m/z*: 327 (M+K); HRMS (FAB) calcd for $C_{12}H_{11}N_2O_3F_3K$ 327.0359, found: 327.0350. Anal. Calcd for $C_{12}H_{11}F_3N_2O_3$: C, 50.01; H, 3.85; N, 9.72. Found: C, 49.89; H, 3.80; N, 9.83.

3.1.5. Ethyl 2-diazo-3-hydroxy-(1-naphthyl)propionate (5d). Yellow oil; IR (neat) ν: 3430, 3059, 2981, 2091, 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.37 (t, 3H, J=7.2 Hz), 3.09 (br s, 1H), 4.29–4.39 (m, 2H), 6.67 (d, 1H, J=4.0 Hz), 7.55–7.66 (m, 3H), 7.87–8.02 (m, 4H); ^{13}C NMR δ: ($CDCl_3$, 100 MHz) 166.3, 134.0, 133.5, 129.4, 128.86, 128.81, 126.3, 125.8, 125.2, 123.2, 122.4, 66.0, 61.2, 14.3; LRMS (FAB) *m/z*: 309 (M+K); HRMS (FAB) calcd for $C_{15}H_{14}O_3N_2K$ 309.0642, found: 309.0672.

3.1.6. Ethyl 2-diazo-3-hydroxy-5-phenylpentanoate (5e). Yellow oil; IR (neat) ν: 3447, 3026, 2934, 2094, 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30 (t, 3H, J=7.2 Hz), 1.89–2.12 (m, 2H), 2.59 (br s, 1H), 2.70–2.88 (m, 2H), 4.26 (q, 2H, J=7.2 Hz), 4.66–4.70 (m, 1H), 7.19–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.4, 140.8, 128.3, 128.2, 125.9, 65.7, 60.9, 35.6, 31.7, 14.3; LRMS (FAB) *m/z*: 287 (M+K); HRMS (FAB) calcd for $C_{13}H_{16}N_2O_3K$ 287.0798, found: 287.0779.

3.1.7. Ethyl 2-diazo-3-hydroxy-5-methylhexanoate (5f). Yellow oil; IR (neat) ν: 3433, 2959, 2094, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.95 (d, 6H, J=6.8 Hz), 1.28 (t, 3H, J=7.2 Hz), 1.36–1.43 (m, 1H), 1.59–1.68 (m, 1H), 1.72–1.82 (m, 1H), 2.42 (br s, 1H), 4.23 (q, 2H, J=7.2 Hz), 4.75–4.79 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.6, 64.8, 60.9, 42.6, 24.5, 22.8, 22.0, 14.4; LRMS (FAB) *m/z*: 239 (M+K); HRMS (FAB) calcd for $C_9H_{16}N_2O_3K$ 239.0798, found: 239.0780.

3.1.8. Ethyl 2-diazo-3-hydroxy-4-methylpentanoate (5g) (reg.# 38491-54-2). Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.95 (d, 3H, J=6.8 Hz), 1.07 (d, 3H, J=6.8 Hz), 1.29 (t, 3H, J=8.0 Hz), 1.85–1.94 (m, 1H), 2.48 (br s, 1H), 4.22–4.29 (m, 3H).

3.1.9. Ethyl 2-diazo-3-hydroxy-3-cyclohexylpropionate (5h) (reg.# 39910-21-9). Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.97–1.30 (m, 8H), 1.52–1.79 (m, 5H), 2.03 (d, 1H, J=12.4 Hz), 2.38 (br s, 1H), 4.24 (q, 2H, J=7.2 Hz), 4.30 (dd, 1H, J=5.2, 8.4 Hz).

3.1.10. Ethyl 2-diazo-3-hydroxy-4,4-dimethyl-valerate (5i) (reg.# 39910-22-0). Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.98 (s, 9H), 1.28 (t, 3H, J=6.8 Hz), 2.54 (br s, 1H), 4.19–4.27 (m, 3H).

3.2. Typical procedure for asymmetric synthesis of *tert*-butyl 2-diazo-3-hydroxy-3-phenylpropionate (4a) using PTC D (Table 4, entry 7)

To a solution of benzaldehyde **3a** (56 μL, 0.53 mmol), *tert*-butyl diazoacetate (50.0 mg, 0.35 mmol) and PTC **D** (18.2 mg, 0.035 mmol, 10 mol%) in toluene (1.8 mL) was added 50% RbOH (82.0 μL, 0.7 mmol) at −40 °C. The mixture was stirred for 10 h and partitioned between AcOEt and water. The aqueous layer was extracted with AcOEt (5 mL×3) and the organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Subsequent flash column chromatography (hexane/AcOEt=15:1) gave the desired product **4a** as a yellow oil (83.3 mg, 0.33 mmol, 96%). $[\alpha]_D^{23}$ −20.8 (*c* 1.06, $CHCl_3$, 56% ee); HPLC: DAICEL CHIRALCEL OD, 254 nm, flow rate 1.0 mL/min,

hexane/*i*-PrOH=99:1, retention time: 20.7 min (major, *S*) and 23.1 min (minor, *R*).

3.2.1. *tert*-Butyl 2-diazo-3-hydroxy-3-(4-methoxyphenyl)propionate (4b). Yellow oil; IR (neat) ν: 3449, 2978, 2095, 1729, 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.50 (s, 9H), 2.97 (br s, 1H), 3.81 (s, 3H), 5.82 (d, 1H, J=2.0 Hz), 6.89–7.36 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.8, 159.4, 130.9, 127.0, 114.0, 82.0, 68.4, 55.2, 28.3; LRMS (FAB) *m/z*: 317 (M+K); HRMS (FAB) calcd for $C_{14}H_{18}N_2O_4K$ 317.0904, found: 317.0875; HPLC: DAICEL CHIRALCEL OD, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=95:5, retention time: 20.8 and 24.2 min.

3.2.2. *tert*-Butyl 2-diazo-3-hydroxy-3-(4-trifluoromethylphenyl)propionate (4c). Yellow oil; IR (neat) ν: 3448, 2981, 2095, 1734, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.50 (s, 9H), 3.04 (br s, 1H), 5.91 (d, 1H, J=3.4 Hz), 7.55 (d, 2H, J=8.4 Hz), 7.65 (d, 2H, J=8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.5, 143.0, 130.3 (q, J=32.1 Hz), 126.2, 125.7 (q, J=4.1 Hz), 124.0 (q, J=271 Hz), 82.5, 68.3, 28.3; LRMS (FAB) *m/z*: 355 (M+K); HRMS (FAB) calcd for $C_{14}H_{15}F_3N_2O_3K$ 355.0672, found: 355.0657; $[\alpha]_D^{26}$ −21.7 (*c* 1.1, $CHCl_3$, 73% ee); HPLC: DAICEL CHIRALCEL OD, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=97:3, retention time: 14.2 min (major) and 16.1 min (minor).

3.2.3. *tert*-Butyl 2-diazo-3-hydroxy-3-(1-naphthyl)propionate (4d). Yellow solid (racemate); mp: 94 °C (hexane); IR (neat) ν: 3435, 2979, 2094, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.54 (s, 9H), 3.00 (br s, 1H), 6.59 (d, 1H J=2.4 Hz), 7.49–7.56 (m, 3H), 7.82–7.96 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.7, 134.1, 133.5, 129.5, 128.8, 128.7, 126.5, 125.7, 125.2, 123.2, 122.5, 82.1, 66.1, 28.5; LRMS (FAB) *m/z*: 337 (M+K); HRMS (FAB) calcd for $C_{17}H_{18}N_2O_3K$ 337.0955, found: 337.0941. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.30; H, 5.92; N, 9.51; optically active form (yellow oil), $[\alpha]_D^{25}$ −68.0 (*c* 0.7, $CHCl_3$, 79% ee); HPLC: DAICEL CHIRALCEL OD, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=97:3, retention time: 24.3 min (minor) and 37.4 min (major).

3.2.4. *tert*-Butyl 2-diazo-3-hydroxy-5-phenylpentanoate (4e). Yellow oil; IR (neat) ν: 3422, 3026, 2930, 2091, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.48 (s, 9H), 1.84–1.93 (m, 1H), 1.99–2.08 (m, 1H), 2.57 (br s, 1H), 2.67–2.75 (m, 1H), 2.79–2.86 (m, 1H), 4.61–4.65 (m, 1H), 7.19–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.9, 140.9, 128.4, 128.3, 125.9, 81.8, 65.7, 35.6, 31.8, 28.2; LRMS (FAB) *m/z*: 315 (M+K); HRMS (FAB) calcd for $C_{15}H_{20}N_2O_3K$ 315.1111, found: 315.1100; $[\alpha]_D^{23}$ −5.68 (*c* 0.3, $CHCl_3$, 33% ee); HPLC: DAICEL CHIRALCEL OD-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=95:5, retention time: 16.7 min (major) and 19.0 min (minor).

3.2.5. *tert*-Butyl 2-diazo-3-hydroxy-5-methylhexanoate (4f). Yellow oil; IR (neat) ν: 3443, 2958, 2871, 2089, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.95 (d, 6H, J=6.4 Hz), 1.33–1.41 (m, 1H), 1.49 (s, 9H), 1.57–1.67 (m, 1H), 1.73–1.83 (m, 1H), 2.47 (br s, 1H), 4.70–4.75 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.0, 81.7, 64.7, 42.6, 28.3, 24.5, 22.8, 21.9; LRMS (FAB) 267 (M+K); HRMS (FAB) calcd for $C_{11}H_{20}N_2O_3K$ 267.1111, found: 267.1097; $[\alpha]_D^{23}$ −12.0 (*c* 1.0, $CHCl_3$, 22% ee); HPLC: DAICEL CHIRALPAK AD-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=99:1, retention time: 22.3 min (minor) and 23.9 min (major).

3.2.6. *tert*-Butyl 2-diazo-3-hydroxy-4-methylpentanoate (4g). Yellow oil; IR (neat) ν: 3448, 2966, 2090, 1669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.94 (d, 3H, J=6.8 Hz), 1.06 (d, 3H, J=6.8 Hz), 1.49 (s, 9H), 1.82–1.94 (m, 1H), 2.58 (br s, 1H), 4.23 (dd, 1H, J=4.4, 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.1, 81.7, 72.3, 32.8, 28.3, 18.7, 18.6; LRMS (FAB) 253 (M+K); HRMS (FAB) calcd for $C_{10}H_{18}N_2O_3K$ 253.0955, found: 253.0935; $[\alpha]_D^{22}$ −10.3 (*c* 0.6, $CHCl_3$, 42% ee); HPLC: DAICEL CHIRALPAK AD-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=99:1, retention time: 32.2 min (minor) and 38.3 min (major).

3.2.7. *tert*-Butyl 2-diazo-3-hydroxy-3-cyclohexylpropionate (4h). Yellow oil; IR (neat) ν: 3440, 2927, 2088, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.97–1.30 (m, 5H), 1.48 (s, 9H), 1.52–1.79 (m, 5H), 2.02 (d, 1H, J=12.8 Hz), 2.38 (br s, 1H), 4.25 (dd, 1H, J=5.2, 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.1, 81.6, 71.2, 42.0, 29.1, 29.0, 28.3, 26.1, 25.8, 25.6; LRMS (FAB) *m/z*: 293 (M+K); HRMS (FAB) calcd for $C_{13}H_{22}N_2O_3K$ 293.1268, found 293.1284; $[\alpha]_D^{19}$ −3.4 (*c* 0.9, $CHCl_3$, 33% ee) HPLC: DAICEL CHIRALCEL OJ, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=99:1, retention time: 22.1 min (major) and 35.8 min (minor).

3.2.8. *tert*-Butyl 2-diazo-3-hydroxy-4,4-dimethylvalerate (4i). Yellow solid; mp 58–61 °C; IR (KBr) ν: 3469, 2960, 2103, 1647 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.97 (s, 9H), 1.47 (s, 9H), 2.75 (br s, 1H), 4.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.4, 81.6, 73.7, 38.3, 28.3, 25.6; LRMS (FAB) *m/z* 267 (M+K); HRMS (FAB) calcd for $C_{11}H_{20}N_2O_3K$ 267.1111, found: 267.1104. Anal. Calcd for $C_{11}H_{20}N_2O_3$: C, 57.87; H, 8.83; N, 12.27. Found: C, 57.92; H, 8.83; N, 12.51; $[\alpha]_D^{24}$ −20.4 (*c* 1.1, $CHCl_3$, 81% ee); HPLC: DAICEL CHIRALPAK AD-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=99:1, retention time: 25.7 min (minor) and 27.4 min (major).

3.2.9. *tert*-Butyl 2-diazo-3-hydroxy-3-(4-*tert* butylphenyl)propionate (4k). Yellow oil; IR (neat) ν: 3467, 2965, 2093, 1732, 1687 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.31 (s, 9H), 1.50 (s, 9H), 2.86 (br s, 1H), 5.83 (d, 1H, J=3.6 Hz), 7.34 (d, 2H, J=8.0 Hz), 7.40 (d, 2H, J=8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.8, 151.1, 136.0, 125.5, 125.4, 81.9, 68.5, 34.5, 31.2, 28.3; LRMS (FAB) *m/z*: 343 (M+K); HRMS (FAB) calcd for $C_{17}H_{24}N_2O_3K$ 343.1424, found: 343.1432; $[\alpha]_D^{26}$ −6.6 (*c* 0.9, $CHCl_3$, 32% ee); HPLC: DAICEL CHIRALCEL OD, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=97:3, retention time: 13.3 min (major) and 17.3 min (minor).

3.2.10. *tert*-Butyl 2-diazo-3-hydroxy-3-(2-naphthyl)propionate (4l). Yellow oil; IR (neat) ν: 3432, 2978, 2095, 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.51 (s, 9H), 3.21 (br s, 1H), 6.03 (d, 1H, J=2.4 Hz), 7.45–7.54 (m, 3H), 7.82–7.86 (m, 3H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$,

100 MHz) δ: 165.7, 136.2, 133.2, 133.1, 128.6, 128.1, 127.6, 126.3, 126.2, 124.7, 123.6, 82.2, 68.9, 28.3; LRMS (FAB) *m/z*: 337 (M+K); HRMS (FAB) calcd for $C_{17}H_{18}N_2O_3K$ 337.0955, found: 337.0924; $[\alpha]_D^{25}$ −28.2 (*c* 1.0, $CHCl_3$, 56% ee); HPLC: DAICEL CHIRALCEL OD, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=97:3, retention time: 26.7 min (major) and 28.4 min (minor).

3.3. Determination of the absolute configuration of 4a (Scheme 1)

Using a procedure similar to that of Wang et al.,[7] **4a** was converted into the corresponding β-hydroxyester **7** by hydrogenation. To a solution of optically active **4a** (57% ee, 188.5 mg, 0.76 mmol) in MeOH (10.8 mL) was added 5% of palladium charcoal (54.0 mg) and the resulting suspension was stirred for 1 h under a hydrogen atmosphere. After being filtered through a Celite pad, the mixture was concentrated in vacuo. Purification of the crude mixture by flash column chromatography gave **7** as a colorless oil (104.3 mg, 0.47 mmol, 62%, 12% ee); $[\alpha]_D^{24}$ +5.3 (*c* 2.3, $CHCl_3$). Optical purity was determined by a chiral HPLC column using DAICEL CHIRALPAK AS, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=97:3, retention time: 15.9 min (major, *R*) and 17.3 min (minor, *S*).[10]

3.3.1. *tert*-Butyl 2-hydrazono-3-(*tert*-butyldimethylsilyloxy)-3-phenylpropionate (*E*)-10 (Schemes 5 and 8). To a solution of **4a** (1.80 g, 7.25 mmol) in DMF (24 mL) was added imidazole (2.16 g, 31.7 mmol) and TBSCl (1.62 g, 10.8 mmol) at 0 °C and the mixture was stirred for 1 h under the same conditions. After being stirred for 6 h at rt, the reaction mixture was diluted with H_2O (10 mL) and extracted with AcOEt (20 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Subsequent flash column chromatography (hexane/AcOEt=50:1) gave TBS ether as a yellow oil (2.52 g, 6.96 mmol, 96%). IR (neat) ν: 2929, 2857, 2094, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.05 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 1.47 (s, 9H), 5.72 (s, 1H), 7.26–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.8, 141.6, 128.3, 127.5, 125.3, 81.4, 68.7, 28.3, 25.6, 18.1, −5.0, −5.3; LRMS (FAB) *m/z*: 401 (M+K); HRMS (FAB) calcd for $C_{19}H_{30}N_2O_3SiK$ 401.1663, found: 401.1659; $[\alpha]_D^{24}$ −15.1 (*c* 1.1, $CHCl_3$, 56% ee, for *S* isomer).

To a solution of the TBS ether (1.05 g, 2.9 mmol) in dry THF (41 mL) was added $LiHBEt_3$ (1 M solution of THF, 8.7 mL, 8.7 mmol) at 0 °C under an argon atmosphere, and the reaction mixture was stirred for 30 min. The reaction was quenched with cold water (10 mL) and the resulting organic layers were extracted with AcOEt (20 mL×3). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=5:1) gave (*E*)-**10** as a white solid (1.06 g, 2.9 mmol, quant.); mp: 55–56 °C (*n*-hexane, 83% ee); IR (neat) ν: 3411, 3286, 2926, 1689, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.12 (s, 3H), 0.14 (s, 3H), 0.94 (s, 9H), 1.56 (s, 9H), 6.19 (s, 1H), 7.02 (br s, 2H), 7.23–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.0, 139.6, 136.6, 128.2, 127.2, 125.3, 81.2, 70.5, 28.1, 25.7, 18.2, −5.2, −5.3; LRMS (FAB) *m/z*: 365 (M+H); HRMS (FAB) calcd for $C_{19}H_{33}N_2O_3Si$ 365.2260, found: 365.2262. Anal. Calcd for $C_{19}H_{32}N_2O_3Si$: C, 62.60; H, 8.85; N, 7.68. Found: C, 62.63; H, 8.82; N, 7.77; $[\alpha]_D^{23}$ −85.3 (*c* 1.0, $CHCl_3$, 83% ee); HPLC DAICEL CHIRALPAK AD-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=97:3, retention time: 16.3 min (major, *S*) and 18.5 min (minor, *R*).

3.3.2. *tert*-Butyl 2-(*N*-benzoylhydrazono)-3-(*tert*-butyldimethylsilyloxy)-3-phenylpropionate (11) (Scheme 5). To a solution of (*E*)-**10** (298.5 mg, 0.82 mmol) in CH_2Cl_2 (8.2 mL) was added pyridine (0.40 mL, 4.9 mmol) and BzCl (0.19 mL, 1.6 mmol) at 0 °C and the reaction mixture was stirred for 21 h at 0 °C. After being diluted with water (10 mL), the mixture was extracted with CH_2Cl_2 (5 mL×3). The resulting organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/Et_2O=10:1, hexane/AcOEt=5:1) gave (*E*)-**11** as a pale yellow oil (383.7 mg, 0.82 mmol, quant.). IR (neat) ν: 3288, 2930, 1740, 1698, 1680, 1253, 1155, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.14 (s, 3H), 0.18 (s, 3H), 0.95 (s, 9H), 1.58 (s, 9H), 6.31 (s, 1H), 7.23–7.54 (m, 9H), 7.83 (br s, 1H), 11.4 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 162.9, 138.2, 132.1, 128.6, 128.4, 127.9, 127.0, 125.1, 82.7, 72.0, 27.7, 25.4, 17.9, −5.3, −5.4; LRMS (FAB) *m/z*: 469 (M+H); HRMS (FAB) calcd for $C_{26}H_{37}N_2O_4Si$ 469.2523, found 469.2482; HPLC: DAICEL CHIRALCEL OD-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=99:1, retention time: 18.8 min (major) and 23.7 min (minor); $[\alpha]_D^{24}$ +4.60 (*c* 1.0, $CHCl_3$, 84% ee). All carbon signals were observed in DMSO at 120 °C, however, isomerization to (*Z*)-**11** was observed.

Compound (*Z*)-**11** was obtained by acidic treatment of (*E*)-**11** as a colorless oil; IR (neat) ν: 3255, 2954, 2930, 2857, 1704, 1676, 1132 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.10 (s, 3H), 0.12 (s, 3H), 0.97 (s, 9H), 1.29 (s, 9H), 5.75 (s, 1H), 7.21–7.59 (m, 8H), 7.95 (d, 2H, J=7.2 Hz), 13.4 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 163.7, 161.6, 142.5, 141.1, 132.4, 132.3, 128.6, 127.5, 126.7, 125.4, 84.0, 76.0, 27.5, 25.6, 18.0, −4.5, −5.2; LRMS (FAB) *m/z*: 469 (M+H); HRMS (FAB) calcd for $C_{26}H_{37}N_2O_4Si$ 469.2523, found: 469.2494.

3.3.3. Reduction of (*E*)-11, *tert*-butyl 2-(*N*-benzoylhydrazino)-3-*tert*-butyldimethylsilyloxy-3-phenylpropionate (12) (Table 6, entry 1). To a solution of (*E*)-**11** (210.6 mg, 0.45 mmol) in EtOH (2.2 mL) was added $NaBH_4$ (83.6 mg, 2.2 mmol) at 0 °C and the solution was stirred for 2 h under the same conditions. The reaction was quenched with water (10 mL) and the mixture was concentrated in vacuo. The resulting mixture was extracted with AcOEt (5 mL×3) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=5:1) gave *anti*-**12** as a white amorphous solid (193.6 mg, 0.41 mmol, 92%). *syn*-**12** was synthesized under the conditions described in Table 6.

Compound *anti*-**12**. White amorphous solid; IR (KBr) ν: 3262, 2930, 2857, 1700, 1676, 1138 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: −0.14 (s, 3H), 0.07 (s, 3H), 0.91 (s, 9H), 1.39 (s, 9H), 3.98 (t, J=4.4 Hz, 1H), 5.11 (d, J=

4.4 Hz, 1H), 5.36–5.39 (m, 1H), 7.26–7.68 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.4, 166.3, 140.3 132.9, 131.6, 128.5, 127.94, 127.90, 127.3, 126.7, 81.9, 74.9, 70.0, 27.9, 25.7, 18.1, −4.8, −5.1; LRMS (FAB) *m/z*: 471 (M+H); HRMS (FAB) calcd for $C_{26}H_{39}N_2O_4Si$ 471.2679, found: 471.2671; HPLC DAICEL CHIRAPAK AS, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=95:5, retention time: 15.3 (minor: 2*R*,3*R*) and 23.9 (major: 2*S*,3*S*); $[\alpha]_D^{24}$ +10.1 (*c* 1.32, $CHCl_3$, 83% ee, (2*S*,3*S*)).

Compound *syn*-**12**. White amorphous solid; IR (neat) ν: 3306, 2923, 2853, 1717, 1669, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: −0.23 (s, 3H), 0.07 (s, 3H), 0.90 (s, 9H), 1.20 (s, 9H), 3.92 (d, J=7.2 Hz, 1H), 4.88 (d, J=7.2 Hz, 1H), 5.66 (br s, 1H), 7.26–7.81 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.8, 166.5, 140.7, 132.8, 131.7, 128.6, 128.12, 128.10, 127.5, 126.8, 81.6, 75.6, 70.9, 27.7, 25.7, 18.1, −4.5, −5.0; LRMS (FAB) *m/z*: 471 (M+H); HRMS (FAB) calcd for $C_{26}H_{39}N_2O_4Si$ 471.2679, found: 471.2639.

3.3.4. Reduction of (*E*)-11, synthesis of 2-(*N*-benzoylhydrazino)-1-*tert*-butyldimethylsilyloxy-1-phenylpropanol (13) (Table 6, entry 3). To a solution of (*E*)-**11** (56.0 mg, 0.12 mmol) in toluene was added Red-Al (65% solution in toluene, 0.14 mL, 0.48 mmol) at 0 °C under an argon atmosphere and the solution was stirred for an additional 2 h. The reaction mixture was quenched with saturated Rochelle salt solution (2 mL) and MeOH (three portions). The resulting residue was extracted with $CHCl_3$ (5 mL×3) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=3:1) gave a mixture of *syn*-**13** and *anti*-**13** isomers as a white amorphous solid (28.8 mg, 0.07 mmol, 60%). These isomers were separated by additional column chromatography (hexane:AcOEt).

Compound *anti*-**13**. White amorphous solid; IR (KBr) ν: 3256, 2927, 1635, 1251, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: −0.21 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 3.08–3.13 (m, 1H), 3.71 (dd, 1H, J=6.4 Hz, 11.2 Hz), 3.89 (dd, 1H, J=2.8 Hz, 11.2 Hz), 4.66 (d, 1H, J=7.6 Hz), 7.29–7.41 (m, 8H), 7.47–7.52 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.7, 142.5, 132.2, 131.8, 128.5, 128.3, 127.8, 127.0, 126.7, 75.0, 68.6, 59.8, 25.6, 18.0, −4.6, −5.6; LRMS (FAB) *m/z*: 401 (M+H); HRMS (FAB) calcd for $C_{22}H_{33}O_3N_2Si$ 401.2260, found: 401.2227.

Compound *syn*-**13**. White amorphous solid; IR (KBr) ν: 3301, 2929, 1635, 1061, 836, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: −0.18 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 3.07–3.11 (m, 1H), 3.44 (dd, 1H, J=6.8, 11.6 Hz), 3.60 (dd, 1H, J=2.8, 11.6 Hz), 3.83 (br s, 1H), 4.82 (d, 1H, J=6.0 Hz), 5.09 (br s, 1H), 7.27–7.70 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.7, 141.8, 132.5, 131.8, 128.5, 128.3, 127.8, 126.9, 126.7, 75.1, 68.5, 59.7, 25.7, 18.0, −4.5, −5.1; LRMS (FAB) *m/z*: 401 (M+H); HRMS (FAB) calcd for $C_{22}H_{33}N_2O_3Si$ 401.2260, found: 401.2289.

3.3.5. *tert*-Butyl 2-(*tert*-buthoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-3-phenylpropionate (14) (Scheme 6). To a solution of *anti*-**12** (89.3 mg, 0.19 mmol) in MeOH (1.9 mL) was added SmI_2 (0.1 M solution in THF, 4.2 mL, 0.42 mmol) at 0 °C under an argon atmosphere, and the solution was stirred for 2 h at 0 °C. The reaction mixture was quenched with water (1 mL) and concentrated in vacuo. To the crude residue was added THF (1.9 mL), Boc_2O (207 mg, 0.95 mmol) and 10% aqueous NaOH (380 mg, 0.95 mmol) and the resulting solution was stirred for 24 h at rt. The reaction mixture was then diluted with water (3 mL) and extracted with AcOEt (5 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=100:1–20:1) gave *anti*-**14** (less polar) as a colorless oil (40.9 mg, 0.09 mmol 47%) and *syn*-**14** (more polar) as a colorless oil (15.6 mg, 0.03 mmol, 18%), respectively.

Compound *anti*-**14**. Colorless oil; IR (neat) ν: 3444, 2930, 2857, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: −0.08 (s, 3H), 0.08 (s, 3H), 0.93 (s, 9H), 1.25 (s, 8/9H), 1.29 (br s, 1/9H) 1.46 (s, 9H), 4.25 (br s, 1/10H), 4.42 (dd, J=2.8, 7.6 Hz, 0.2/1H), 5.04 (br s, 0.8/1H), 5.15 (s, 8/9H), 5.42 (d, J=7.6 Hz, 1H); 7.20–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.1, 154.9, 141.0, 127.6, 127.0, 126.1, 81.7, 79.5, 75.5, 61.4, 28.3, 27.7, 25.7, 18.2, −4.8, −5.2; LRMS (FAB) *m/z*: 452 (M+H); HRMS (FAB) calcd for $C_{24}H_{42}NO_5Si$ 452.2832, found: 452.2859.

Compound *syn*-**14**. Colorless oil; IR (neat) ν: 3452, 2931, 2857, 1727, 1706 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: −0.20 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 1.21 (br s, 2/9H), 1.35 (s, 7/9H) 1.45 (s, 7/9H), 1.49 (s, 2/9H), 4.07 (d, J=9.6 Hz, 7/9H), 4.25 (dd, J=2.8, 9.6 Hz, 0.8/1H), 5.01 (d, J=9.6 Hz, 0.2/1H), 5.15 (d, J=2.8 Hz, 1H), 5.19 (d, J=2.8 Hz, 0.8/1H), 7.22–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.8, 155.4, 141.0, 127.9, 127.6 126.5, 81.8, 79.3, 74.8, 61.0, 28.2 28.0, 25.7, 18.0, −4.4, −5.2; LRMS (FAB) *m/z*: 452 (M+H); HRMS (FAB) calcd for $C_{24}H_{42}NO_5Si$ 452.2832, found: 452.2815.

3.3.6. 2-*tert*-Buthoxycarbonylamino-1-*tert*-butyldimethylsilyloxy-1-phenylpropanol *anti*-15 (Scheme 6). To a solution of *anti*-**13** (55.0 mg, 0.14 mmol) in MeOH (1.4 mL) was added SmI_2 (0.1 M solution in THF, 3.0 mL, 0.3 mmol) at 0 °C under an argon atmosphere and the reaction mixture was stirred for 30 min. After being quenched with water (1 mL), the resulting mixture was concentrated in vacuo. To the crude residue was added THF (1.4 mL), Boc_2O (90 mg, 0.41 mmol) and aqueous 10% NaOH (165 mg, 0.41 mmol), and the mixture was stirred for 24 h at rt. After the mixture was diluted with water (3.0 mL), it was extracted with AcOEt (5 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=5:1) gave *anti*-**15** as a white solid (36.6 mg, 0.10 mmol, 71%). As described above, *syn*-**15** was synthesized from *syn*-**13** in 81% yield (two steps).

Compound *anti*-**15**. White solid; mp 136 °C (hexane); IR (neat) ν: 3341, 3232, 2926, 1671, 1056 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: −0.09 (s, 3H), 0.08 (s, 3H), 0.93 (s, 9H), 1.47 (s, 9H), 2.97 (d, J=10.8 Hz, 1H), 3.39–3.46 (m, 1H), 3.60 (br s, 1H), 3.84 (d, J=10.8 Hz, 1H), 5.19 (s, 1H), 5.48 (d, 1H, J=8.0 Hz) 7.20–7.40 (m, 5H); ^{13}C NMR

($CDCl_3$, 100 MHz) δ: 155.6, 141.0, 128.2, 127.4, 125.8, 79.5, 77.6, 61.2, 56.5, 28.4, 25.8, 18.0, −4.9, −5.3; LRMS (FAB) *m/z*: 382 (M+H); HRMS (FAB) calcd for $C_{20}H_{36}NO_4Si$ 382.2414, found: 382.2408. Anal. Calcd for $C_{20}H_{35}NO_4Si$: C, 62.95; H, 9.25; N, 3.67. Found: C, 62.74; H, 9.49; N, 3.59.

Compound *syn*-**15**. Colorless oil; IR (neat) *ν*: 3447, 2929 2857, 1697 1496 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: −0.15 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 1.36 (s, 9H), 2.35 (br s, 1H), 3.60–3.77 (m, 3H), 4.90 (br s, 1H), 4.91 (d, 1H, J=3.6 Hz), 7.22–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 156.1, 141.5, 128.1, 127.5, 126.3, 79.5 73.7, 63.0, 58.5, 28.3, 25.8, 18.1, −4.6, −5.2; LRMS (FAB) *m/z*: 382 (M+H); HRMS (FAB) calcd for $C_{20}H_{36}NO_4Si$ 382.2414, found: 382.2448.

3.4. Direct synthesis of 14 via a one-pot procedure (Table 7, entry 4)

To a solution of (*E*)-**11** (75.0 mg, 0.16 mmol) in isopropanol (1.6 mL) was added SmI_2 (0.1 M solution in THF, 9.6 mL, 0.96 mmol) at 0 °C under an argon atmosphere and the mixture was stirred for 30 min. After being quenched with water (1.0 mL), the resulting mixture was concentrated in vacuo. To the crude residue was added THF (1.6 mL), Boc_2O (104 mg, 0.48 mmol) and 10% aqueous NaOH (192 mg, 0.48 mmol), and the mixture was stirred for 24 h at rt. After dilution with water (3.0 mL), the mixture was extracted with AcOEt (5 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=100:1–20:1) gave *anti*-**14** (less polar) as a colorless oil (9.3 mg, 0.02 mmol, 13%) and *syn*-**14** (more polar) as a colorless oil (62.7 mg, 0.14 mmol, 87%), respectively.

3.4.1. Direct synthesis of 17 via a one-pot procedure (Scheme 8, condition A). To a solution of (*S*)-(*E*)-**11** (113.0 mg, 0.24 mmol) in isopropanol (2.4 mL) was added SmI_2 (0.1 M solution in THF, 14.4 mL, 1.44 mmol) at 0 °C under an argon atmosphere and the mixture was stirred for 30 min. After being quenched with water (5.0 mL), the resulting mixture was extracted with AcOEt (10 mL×3). The combined organic layers were washed with brine dry over $MgSO_4$ and concentrated in vacuo. To the crude residue was added CH_2Cl_2 (2.4 mL), BzCl (41 μL, 0.36 mmol) and pyridine (38 μL, 0.48 mmol), and the mixture was stirred for 10 min at 0 °C. After being diluted with water (1.0 mL), the mixture was extracted with AcOEt (5 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=100:1–15:1) gave (2*S*,3*S*)-**17** (less polar) as a colorless oil (13.7 mg, 0.030 mmol, 12%) and (2*R*,3*S*)-**17** (more polar) as a white solid (95.9 mg, 0.21 mmol, 88%), respectively.

3.4.2. *tert*-Butyl 2-benzoylamino-3-(*tert*-butyldimethylsilyloxy)-3-phenylpropionate (17) (Scheme 8). Compound (2*S*,3*S*)-**17**. Colorless oil; IR (neat) *ν*: 3434, 2929, 2857, 1725, 1661 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: −0.10 (s, 3H), −0.01 (s, 3H), 0.93 (s, 9H), 1.30 (s, 9H), 4.88 (dd, 1H, J=2.4, 6.8 Hz), 5.33 (d, 1H, J=2.4 Hz), 7.13 (d, 1H, J=6.8 Hz), 7.24–7.85 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.2, 166.4, 141.1, 133.9, 131.7, 128.6, 127.7, 127.1 126.9, 126.1, 82.2, 75.3, 60.9, 27.8, 25.7, 18.2, −4.7, −5.1; LRMS (FAB) *m/z*: 456 (M+H); HRMS (FAB) calcd for $C_{26}H_{38}NO_4Si$ 456.2570, found: 456.2615; HPLC: DAICEL CHIRALCEL OD-H, 245 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=96:4, retention time: 8.0 min (minor) and 14.8 min (major); $[\alpha]_D^{25}$ +40.6 (*c* 0.9, $CHCl_3$, 84% ee).

Compound (2*R*,3*S*)-**17**. White solid; mp: 68 °C; IR (neat) *ν*: 3448, 2954, 2929, 2856, 1728, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: −0.15 (s, 3H), 0.09 (s, 3H), 0.94 (s, 9H), 1.47 (s, 9H), 4.76 (dd, 1H, J=2.8, 8.8 Hz), 5.31 (d, 1H, J=2.8 Hz) 6.82 (d, 1H, J=8.8 Hz), 7.23–7.74 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.3, 167.0, 140.8, 134.4, 131.4, 128.5, 128.0, 127.8, 126.8, 126.2, 82.2, 74.4, 60.2, 28.0, 25.7, 18.0, −4.4, −5.2; LRMS (FAB) *m/z*: 456 (M+H); HRMS (FAB) calcd for $C_{26}H_{38}NO_4Si$, 456.2570, found: 456.2572. Anal. Calcd for $C_{26}H_{37}NO_4Si$: C, 68.53; H, 8.18; N, 3.07. Found: C, 68.42; H, 8.39; N, 2.99; HPLC: DAICEL CHIRALCEL OD-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=96:4, retention time: 9.9 min (major) and 13.2 min (minor); $[\alpha]_D^{25}$ +52.3 (*c* 1.0, $CHCl_3$, 83% ee).

3.4.3. *tert*-Butyl 2-(*N*-benzoylamino)-3-hydroxy-phenylpropionate (18) (Scheme 8). Compound (2*R*,3*S*)-**18**. To a solution of (2*R*,3*S*)-**17** (71.0 mg, 0.16 mmol) in THF (0.75 mL) was added TBAF (1 M solution of THF, 0.23 mL, 0.23 mmol) at rt under an argon atmosphere and the reaction mixture was stirred for 10 min. After being quenched with water (1.0 mL), the reaction mixture was extracted with AcOEt (5.0 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=2:1) gave (2*R*,3*S*)-**18** (49.2 mg, 0.14 mmol, 92%) as a white solid; mp: 134–138 °C (hexane–AcOEt); IR (neat) *ν*: 3368, 2977, 1731, 1639, 1521, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.42 (s, 9H), 3.13 (br s, 1H), 4.96 (dd, 1H, J=3.6, 7.6 Hz), 5.26 (br s, 1H), 6.85 (d, 1H, J=7.6 Hz), 7.27–7.72 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.3, 167.7, 139.8, 133.8, 131.6, 128.4, 128.3, 128.0, 127.0, 126.1, 82.8, 74.5, 59.0, 27.8; LRMS (FAB) *m/z*: 342 (M+H); HRMS (FAB) calcd for $C_{20}H_{24}NO_4$ 342.1705, found: 342.1689. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.34; H, 6.83; N, 4.10; HPLC: DAICEL CHIRALCEL OJ-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=93:7, retention time: 19.7 min (minor) and 22.6 min (major); $[\alpha]_D^{24}$ +36.1 (*c* 1.04, $CHCl_3$, 98.1% ee).

Compound (2*S*,3*S*)-**18**. According to the procedure described above, (2*S*,3*S*)-**18** was synthesized as a white solid from (2*S*,3*S*)-**17**. White solid; mp: 134–138 °C (hexane–AcOEt); IR (neat) *ν*: 3427, 3322, 2925, 1735, 1636, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.46 (s, 9H), 4.86 (br s, 1H), 5.15 (dd, 1H, J=2.4, 6.0 Hz), 5.39 (s, 1H), 6.95 (d, 1H, J=6.0 Hz), 7.24–7.63 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.7, 168.2, 139.3, 133.1, 132.1, 128.6, 128.1, 127.8, 127.1, 126.0, 83.6, 75.5, 60.2, 27.9; LRMS (FAB) *m/z*: 342 (M+H); HRMS (FAB) calcd for $C_{20}H_{24}NO_4$ 342.1705, found: 341.1676. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.06; H,

6.82; N, 4.04; HPLC: DAICEL CHIRALCEL OJ-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH = 95:5, retention time: 24.4 min (minor) and 28.5 min (major); $[\alpha]_D^{25}$ +69.8 (*c* 0.13, $CHCl_3$, 96.5% ee).

3.4.4. (2*S*,3*S*) *tert*-Butyl 2-(*N*-benzoylhydrazino)-3-hydroxy-phenylpropionate (19), (Scheme 8). According to the procedure described above, (2*S*,3*S*)-**19** was synthesized as a white amorphous material from (2*S*,3*S*)-**12**. White amorphous; IR (neat) *ν*: 3296, 2977, 1721, 1641, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 1.32 (s, 9H), 3.94 (d, 1H, *J* = 4.8 Hz), 5.11 (d, 1H, *J* = 4.8 Hz), 5.25 (br s, 1H), 7.27–7.69 (m, 10H), 7.94 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 169.5, 167.6, 139.6, 132.2, 132.0, 128.6, 128.1, 127.7, 126.9, 126.4, 82.6, 72.6, 69.3, 27.8; LRMS (FAB) *m*/*z*: 395 (M + K); HRMS (FAB) calcd for $C_{20}H_{24}N_2O_4K$ 395.1373, found: 395.1383; HPLC: DAICEL CHIRALPAK AS-H, 254 nm, flow rate 1.0 mL/min, hexane/*i*-PrOH = 80:20, retention time: 15.2 min (minor) and 28.2 min (major); $[\alpha]_D^{23}$ +15.9 (*c* 0.65, $CHCl_3$, 87% ee).

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