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A new approach to 3-hydroxyprolinol derivatives by samarium diiodide-mediated reductive coupling of chiral nitrone with carbonyl compounds†

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A flexible diastereoselective approach to *trans*-(3*S*)-hydroxyprolinol derivatives is described, which is based on the samarium diiodide-mediated reductive coupling of the chiral 1-pyrroline *N*-oxide (nitrone)(*S*)-**10** with carbonyl compounds. The reductive hydroxyalkylation of nitrone **10** with ketones and aromatic aldehydes is highly diastereoselective in establishing the C-2 chiral center of the pyrrolidine ring.

Introduction

Prolinol is the key structural feature of many azasugars (e.g. **1** and **2** in Fig. 1) and organocatalysts (e.g. **3a,b** in Fig. 1). Azasugars (also known as iminosugars) are polyhydroxylated alkaloids with either five or six-membered ring structures.[1] Many azasugars exhibit potent inhibitory activity toward carbohydrate-processing enzymes,[1] that make them promising both for the treatment of metabolite disorder-associated diseases, and as invaluable molecular tools for the study of the mechanism of action of carbohydrate-processing enzymes. For example, Miglitol[2] and Zavesca[3] (Miglustat) are in clinical use as drugs for the treatment of Type II diabetes and Gaucher's disease, respectively, and MBI-3253 (celgosivir) a derivative of castanospermine, is in Phase II clinical trials for the treatment of patients with chronic HCV.[4] The synthesis of azasugars, their stereoisomers, and analogues has attracted considerable attention, and a number of methods have been developed.[1,5]

Prolinol derivatives (e.g. **3a** and **3b** in Fig. 1) are structurally related, but less hydroxylated molecules, which are gaining popularity as versatile organocatalysts for a number of asymmetric reactions.[6,7] The rapid development of organocatalysis as a promising field in organic chemistry calls for the development of novel organocatalysts. On the basis of these considerations, we were interested in the synthesis of heterocycles of generic structure **A**. It was considered that such molecules, combining in a molecule both hydrophilic and lipophilic groups, would be beneficial for both inhibitory activity and asymmetric catalytic profile.

For a flexible synthesis of molecules of type **A**, although a number of methods can be envisioned,[8] such as that shown in path A[9] (Scheme 1), a disconnection at the C_1–$C_{1'}$ bond (Path B) is quite attractive for its flexibility in the synthesis of diversely substituted prolinols. However, the execution of such a strategy is challenging, because it involves the realization of synthon **C**, which is either prone to β-elimination (for *O*-protected derivatives),[10] or gives the wrong regioselectivity (in the deprotonation of **4**).[11] Recently, we have developed direct[12] and indirect[13] as well as synthetic equivalent-based[14] approaches to realize synthon **C**. Among these approaches, the SmI_2-mediated method[12] is straightforward, because it allows direct access to differently substituted pyrrolidines in one step.

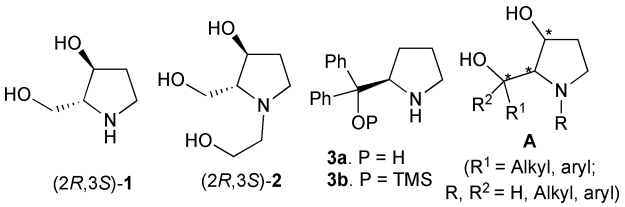
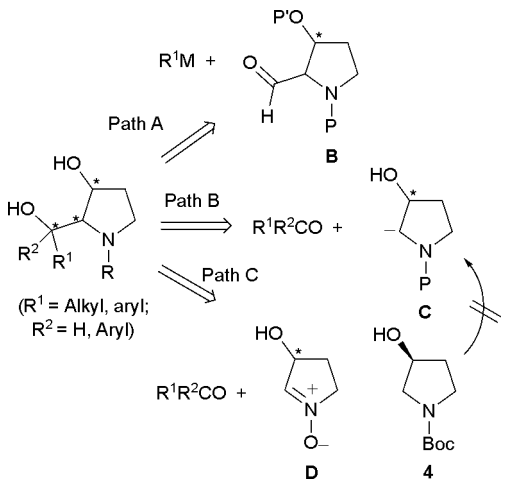


Fig. 1 Structure of prolinol-containing azasugars and organocatalysts.



Scheme 1 Three possible approaches for the synthesis of β-hydroxyprolinol derivatives.

The widespread application of nitrones[15–19] as versatile electrophiles over the last thirty years led us to consider them as suitable components for the synthesis of hydroxylated prolinol derivatives of type **A**. A survey of the literature showed that while chiral non-racemic cyclic nitrones[15] have served as versatile building

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† Electronic supplementary information (ESI) available: NMR spectra of **6**, **7**, **8**, **10**, **11**, **12a–l**, **13**, **14**. See DOI: 10.1039/b906224f

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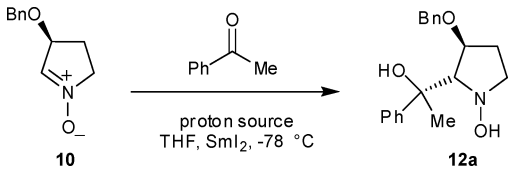
Table 1 Optimization of the reductive coupling reaction



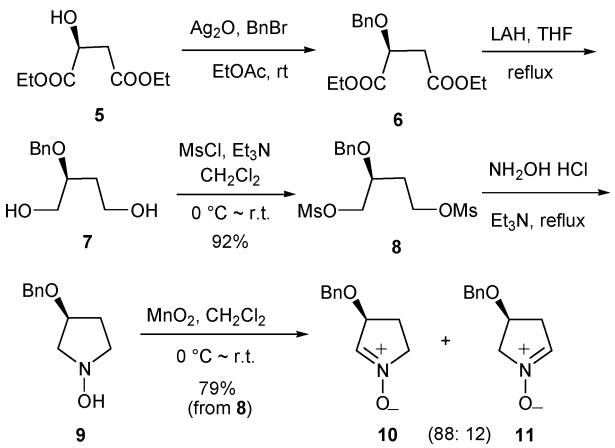
10 **12a**

Entry	Mol. equiv. of acetophenone	Proton source (eq)	Equiv. of SmI_2	T (°C)	Time (h)	Yield (%)[a]	d.r.[b]
1	1.5	—	3	−78	4	48	59:41
2	1.5	*t*-BuOH (2)	3	−78	4	50	62:38
3	1.5	H_2O (8)	3	−78	4	64	71:29
4	1.1	H_2O (8)	3	−50	3	59	72:28
5	1.1	H_2O (8)	3	−20	4	36	60:40
6	3	H_2O (78)	6.5	−78	1.5	84	79:21

[a] Isolated yields. [b] Ratio determined by ^{1}H NMR.

blocks, the methods used for the carbon–carbon bond formation at the *N* α-position were limited to 1,3-dipolar cycloadditions,[16] nucleophilic additions,[17] and SmI_2-induced nitrones coupling with activated olefins.[18g–j] In 2002, Py, Vallée and co-workers reported the first SmI_2-mediated[19] coupling of achiral alicyclic nitrones with aldehydes.[20] While our work was in progress, Py and co-workers reported the SmI_2-mediated coupling of carbonyl compounds with achiral pyrrolidine nitrone.[21] We now report the first asymmetric coupling[22] of chiral non-racemic pyrroline *N*-oxides **D** with aldehydes/ketones, which allows a flexible and high-yielding access to hydroxylated prolinol derivatives of type **A** (Scheme 1).

As the first phase of our investigation, and in combination with our interest in the development of malic acid-based synthetic methodology,[23] nitrone (*S*)-**10** was selected as the starting point for our study, which is available from (*S*)-malic acid. The hitherto unknown nitrone[15,24] (*S*)-**10** was synthesized as shown in Scheme 2. Diethyl L-malate **5** was converted to bis-mesylate **8** by *O*-benzylation (BnBr, Ag_2O, EtOAc, r.t.), lithium aluminium hydride reduction (LAH, THF, refl.), and bis-mesylation (MsCl, NEt_3, CH_2Cl_2, r.t.). In the presence of triethylamine, treatment of bis-mesylate **8** with hydroxylamine hydrochloride at reflux gave the *O*-benzyl-*N*-hydroxy-3-pyrrolidinol **9**, which upon oxidation with freshly prepared manganese dioxide[25a] in dichloromethane gave



Scheme 2 Synthesis of the chiral nitrone **10**.

the desired nitrone (*S*)-**10** and its regioisomer (*S*)-**11** in 88:12 ratio with a combined yield of 79% over two steps. Noteworthy is that acceptable yield and regioselectivity were obtained with MnO_2,[25a–c] which replaced the commonly used highly toxic oxidant HgO.[24] The structural assignment was made on the basis of the coupling pattern of the HC=N[24a,c] proton in the ^{1}H-NMR spectra (δ 6.87, quintet, J = 1.6 Hz for **10**, and δ 6.85, broad multiplet for **11**). The nitrone **10** exhibited reasonable stability and could be stored for several weeks at −20 °C under an inert atmosphere.

With the desired nitrone (*S*)-**10** in hand, we turned our attention to investigate its reductive coupling with carbonyl compounds. Initial attempts to couple nitrone **10** with *n*-butanal by Py and Vallée's protocol[20] gave the desired coupling product in only 32% yield, along with some unreacted starting material. The observation of a higher reactivity of acetophenone in the coupling reaction led us to select it for the optimization of the reaction. Thus treatment of acetophenone with nitrone **10** at −78 °C for 2 h gave the desired product **12a** as a diastereomeric mixture in a 59:41 ratio with a 48% combined yield (Table 1, entry 1). In view of the well documented beneficial effects of proton sources such as alcohols[19–22,26,27] and water[19–22,28] as promoters for the SmI_2-mediated reactions, we then tested their effects on the reaction. The results summarized in Table 1 showed that addition of 2.0 molar equiv. of *t*-butanol (Table 1, entry 2) or 8.0 equiv. of water (Table 1, entry 3) could speed up the coupling reaction, but the yields were not significantly improved. Higher reaction temperatures led to lower yields (Table 1, entries 3–5). After extensive studies, it was found that when 78 molar equiv. of water, 6.5 molar equiv. of SmI_2 and 3.0 molar equiv. of acetophenone were used, the coupling with nitrone (*S*)-**10** produced the desired product **12a** in a significantly improved yield of 84%. Moreover, the diastereoselectivity was also improved to 79:21 (Table 1, entry 6).

Under the optimized conditions, the coupling reaction of the nitrone (*S*)-**10** with other carbonyl compounds was investigated, and the results are summarized in Table 2. As can be seen from Table 2, the reductive hydroxyalkylation of **10** with symmetric ketone (benzophenone) gave only one diastereomer **12b** (Table 2, entry 2); and when unsymmetrical ketones or aromatic aldehydes were used, only two diastereomers were obtained in each case (Table 2, entries 1, 3–9); the coupling with aliphatic aldehydes produced a total of four diastereomers in each case (Table 2,

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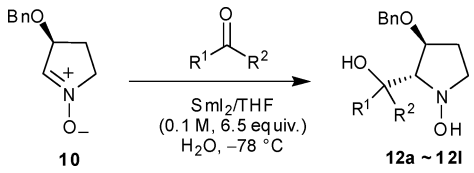
Table 2 The reductive coupling of nitrone **10** with carbonyl compounds

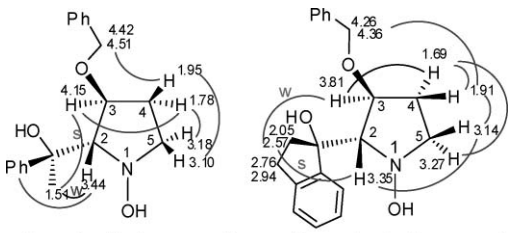


10 **12a ~ 12l**

Entry	Carbonyl compounds	Time (h)	Product (% yield)[a]	d.r.[b]
1	acetophenone	1.5	**12a** (84)	79:21
2	benzophenone	1.2	**12b** (83)	—
3	2,3-dihydroinden-1-one	1.2	**12c** (91)	72:28
4	benzaldehyde	1.2	**12d** (93)	61:39
5[c]	4-methoxybenzaldehyde	1.5	**12e** (95)[c]	62:38
6	piperonal	1	**12f** (74)	61:39
7	2-chlorobenzaldehyde	1.2	**12g** (72)	67:33
8	4-chlorobenzaldehyde	1.3	**12h** (95)	63:37
9	2,4-dichlorobenzaldehyde	1.2	**12i** (93)	61:39
10	butyraldehyde	1.2	**12j** (80)	43:36:11:10
11	isobutyraldehyde	1.5	**12k** (88)	45:36:19
12	hexanal	0.8	**12l** (88)	40:35:10:15

[a] Isolated yields, based on nitrone **10**. [b] Ratio determined by ^{1}H NMR. [c] 31% of **13** was obtained based on the starting 4-methoxybenzaldehyde.

entries 10–12). These results clearly indicate that the reductive α-hydroxyalkylation of **10** with ketones and aromatic aldehydes was highly diastereoselective in establishing the C-2 stereocenter of the pyrrolidine ring, and the diastereo-isomerism arose from the newly formed exocyclic chiral carbinol center; while the reaction with aliphatic aldehydes gave low diastereoselectivities at the two newly formed stereocenters. The stereochemistry of the product was determined as 2,3-*trans* on the basis of 2D NOESY experiments undertaken on the major diastereomers of **12a** and **12c** (Fig. 2). The $J_{2,3}$ of **12a** (2.3 Hz) is also consistent with the pyrrolidines that possess a 2,3-*trans* stereochemical relationship.[29] The stereochemistry of the exocyclic chiral center was not determined. The same diastereoselection was assumed to be retained for benzophenone and aromatic aldehydes. For aliphatic aldehydes (entries 10–12, Table 2), obviously it is different.

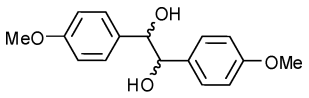


the major diastereomer of **12a** the major diastereomer of **12c**

Fig. 2 NOE correlations on the major diastereomers of **12a** and **12c**.

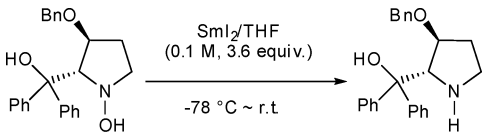
Regarding the mechanism of the reductive coupling, Py and Vallée proposed an aminoxyl radical-based mechanism in which a ketyl radical was excluded as an intermediate.[20] In our case, the observation of pinacol coupling products such as **13** (Fig. 3) suggested that the ketyl radical might be involved in the reaction.

As a demonstration of the suitability of the method for the synthesis of prolinol derivatives, the coupling product **12b** was treated with an excess of SmI_2[18j,21,30,31] at –78 °C for 1 h, then allowed to warm up and was stirred at rt overnight. The pyrrolidine **14** was obtained in 77% yield (Scheme 3).



13

Fig. 3 Structure of the pinacol coupling product **13**.



12b **14**

Scheme 3 Cleavage of the *N–O* bond.

Conclusions

To summarize, we demonstrated that in the presence of a large excess of water, the samarium diiodide-mediated chemoselective reductive coupling of optically active pyrrolidine nitrone **10** with aldehydes/ketones underwent a smooth reaction to give the corresponding coupling products **12a**–**12l** in good to excellent yields. This proves that nitrone **D** is an effective synthetic equivalent of synthon **C**, and thus paves a flexible approach to enantio-enriched hydroxylated prolinol derivatives as exhibited by the synthesis of prolinol derivative **14**.

Experimental

General

Melting points were determined on a Yanaco MP-500 micro melting point apparatus and were uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker 400 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. ^{13}C NMR spectra were determined at

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100 MHz. Mass spectra were recorded on a Bruker Dalton ESquire 3000 plus liquid chromatography-mass spectrum (direct injection). HRMS spectra were recorded on a Shimadzu LCMS-IT-TOF apparatus. Optical rotations were measured with a Perkin-Elmer 341 automatic polarimeter. Silica gel (300–400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with an ethyl acetate/petroleum ether (PE) (60–90 °C) mixture. Ether and THF were distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2. Water used as the additive in the coupling reactions was doubly distilled and deaerated with argon for 24 h prior to use. Sm was purchased from Yuelong New Materials Co. Ltd. (China).

(*S*)-Diethyl 2-benzyloxysuccinate (6). To a suspension of diethyl (*S*)-malate **5** (2.15 g, 11.3 mmol) and silver oxide (7.90 g, 34.1 mmol) in 30 mL of EtOAc was added benzyl bromide (2.70 mL, 22.6 mmol). The mixture was stirred at dark for two days at rt. The resulting mixture was filtered through Celite and concentrated in vacuo. Short column chromatography purification afforded diethyl (*S*)-2-benzyloxysuccinate **6**[32] (2.22 g, 70%). R_f 0.31 (EtOAc: PE = 1: 10); colorless oil; $[\alpha]^{20}_D$ −59.9 (*c* 6.8 in $CHCl_3$); ν_{max}/cm^{-1}: 1738, 1454, 1373, 1274, 1176, 1123 and 1028; δ_H 7.38–7.27 (5H, m, Ph-H), 4.77 (1H, d, *J* = 11.4 Hz, PhCH_2), 4.54 (1H, d, *J* = 11.4 Hz, PhCH_2), 4.39 (1H, dd, *J* = 5.1, 7.8 Hz, -C*H*OBn), 4.27–4.19 (2H, m, CH_3CH_2O-), 4.19–4.11 (2H, m, CH_3CH_2O-), 2.85–2.72 (2H, m, -OCHCH_2CO-), 1.30, 1.24 (6H, 2t, *J* = 7.15, 7.15 Hz, CH_3CH_2O-); δ_C 171.4, 170.1, 137.3, 128.3 (2C), 128.1 (2C), 127.9, 74.6, 73.0, 61.2, 60.9, 38.1, 14.1, 14.1; *m*/*z* (ESI) 303 (M + Na^+, 100%), 281 (M + H^+, 34); Found: C, 64.35; H, 7.38. Calc. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19%.

(*S*)-2-(Benzyloxy)butane-1,4-diol (7). A THF solution (45 mL) of diester **6** (6.18 g, 22.1 mmol) was added dropwise to a suspension of $LiAlH_4$ (1.98 g, 52 mmol) in THF (20 mL) under a N_2 atmosphere. The white suspension was vigorously stirred and refluxed for 5 h. The mixture was cooled to 0 °C, and quenched by successive dropwise addition of H_2O (2 mL), 10% NaOH solution (4 mL) and H_2O (6 mL). After diluting with ethanol (60 mL) the mixture was refluxed for 3 h. The suspension was filtered through Celite and washed with ethanol several times. The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography on silica gel (eluent: EtOAc: PE, 2: 1) to give the known diol **7** (3.620 g, 84%) as a colorless oil. R_f 0.38 (EtOAc: PE = 2: 1); $[\alpha]^{20}_D$ −15.6 (*c* 2.0 in $CHCl_3$) {lit.[33a] +15.0 (*c* 1.0 in $CHCl_3$) for (*R*)-enantiomer}; $[\alpha]^{20}_D$ −41.7 (*c* 1.6 in ethanol) (lit.[33b] −37.9); ν_{max}/cm^{-1}: 3382, 3031, 2933, 2878, 1454, 1400, 1350, 1208, 1055; δ_H 7.38–7.25 (5H, m, Ph-H), 4.59 (1H, d, *J* = 11.6 Hz, PhCH_2), 4.55 (1H, d, *J* = 11.6 Hz, PhCH_2), 3.77–3.62 (4H, m, -CH_2OH), 3.58–3.48 (1H, m, -C*H*OBn), 3.07–2.96 (2H, br, OH), 1.89–1.68 (2H, m, -OCHCH_2CH_2-); δ_C 138.1, 128.4 (2C), 127.8, 127.8 (2C), 77.7, 71.5, 63.7, 59.2, 33.9; *m*/*z* (ESI) 219 (M + Na^+, 100%), 197 (M + H^+, 10); Found: C, 67.18; H, 7.99. Calc. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22%.

(*S*)-2-(Benzyloxy)-1,4-bis(methanesulfonyloxy)butane (8). To a cooled (0 °C) CH_2Cl_2 (12 mL) solution of compound **7** (1.70 g, 8.7 mmol) and Et_3N (7.5 mL, 52.0 mmol) was added dropwise methanesulfonyl chloride (2.9 mL, 37.0 mmol) under a N_2 atmosphere. The mixture was stirred at rt for 7 h, then cooled to 0 °C and treated with saturated aqueous NH_4Cl (14 mL). The two phases were separated and the aqueous phase extracted with CH_2Cl_2 (100 mL). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography on silica gel (eluent: EtOAc: PE = 2: 3) to give compound **8** (2.81 g, 92%) as a colorless oil. R_f 0.42 (EtOAc: PE = 3: 1); $[\alpha]^{20}_D$ −42.4 (*c* 3.0 in $CHCl_3$); ν_{max}/cm^{-1}: 1455, 1352, 1174, 1125, 1059, 1027; δ_H 7.34–7.21 (5H, m, Ph-H), 4.63 (1H, d, *J* = 11.3 Hz, PhCH_2), 4.49 (1H, d, *J* = 11.3 Hz, PhCH_2), 4.35–4.21, 4.17–4.10 (4H, 2 m, -CH_2OMs), 3.84–3.77 (1H, m, -C*H*OBn), 2.94 (3H, s, -CH_3), 2.88 (3H, s, -CH_3), 2.01–1.87 (2H, m, -OCHCH_2CH_2-); δ_C 137.3, 128.5 (2C), 128.1 (3C), 72.7, 72.4, 69.8, 65.9, 37.5, 37.2, 31.3; *m*/*z* (ESI) 375 (M + Na^+, 100%), 391 (M + K^+, 40); Found: C, 44.07; H, 5.32. Calc. for $C_{13}H_{20}O_7S_2$: C, 44.30; H, 5.72%.

(*S*)-3-Benzyloxy-1-pyrroline *N*-oxide (10) and (*S*)-4-benzyloxy-1-pyrroline *N*-oxide (11). A suspension of compound **8** (1.14 g, 3.3 mmol) and hydroxylamine hydrochloride (993 mg, 14.3 mmol) in Et_3N (17 mL) was heated at reflux for 6 h under N_2 atmosphere. The solvent was then evaporated and the resulting yellow solid was washed thoroughly with diethyl ether. Ethereal extracts were concentrated to give the crude *N*-hydroxypyrrolidine **9**, which was used in the next step without further purification.

To a CH_2Cl_2 (11 mL) solution of the crude *N*-hydroxypyrrolidine **9** was added portionwise active manganese dioxide (390 mg, 3.9 mmol) at 0 °C and under a N_2 atmosphere. The suspension was stirred at rt overnight. The resultant mixture was filtered through Celite and concentrated under reduced pressure. Chromatography purification of the residue on silica gel (eluent: ethyl acetate: EtOH, 5: 1) yielded two regioisomeric nitrones **10** and **11** in 88:12 ratio (combined yield: 79%).

(*S*)-10 (major isomer). 431 mg, yield: 70%; R_f 0.23 (EtOAc); colorless oil; $[\alpha]^{20}_D$ −97.6 (*c* 2.7 in $CHCl_3$); ν_{max}/cm^{-1}: 1582, 1455, 1359, 1257, 1089, 1070, 1044, 1028; δ_H 7.33–7.22 (5H, m, Ph-H), 6.87 (1H, quintet, *J* = 1.6 Hz, H-2), 4.72–4.66 (1H, m, -C*H*OBn), 4.51 (1H, d, *J* = 11.6 Hz, PhCH_2), 4.46 (1H, d, *J* = 11.6 Hz, PhCH_2), 4.18–4.03 (1H, m, H-5), 3.85–3.74 (1H, m, H-5), 2.54–2.41 (1H, m, H-4), 2.24–2.12 (1H, m, H-4); δ_C 137.2, 133.5, 128.6 (2C), 128.1, 127.8 (2C), 78.2, 71.5, 61.3, 27.6; *m*/*z* (ESI) 214 (M + Na^+, 100%), 192 (M + H^+, 72); Found: C, 69.29; H, 7.07; N, 7.38. Calc. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32%.

(*S*)-11 (minor isomer). 59 mg, yield: 9%; R_f 0.05 (EtOAc); colorless oil; ν_{max}/cm^{-1}: 1592, 1453, 1357, 1270, 1228, 1206, 1159, 1089, 1028; δ_H 7.40–7.28 (m, 5H, Ph-H), 6.87–6.82 (br m, 1H, H-2), 4.54–4.51 (m, 2H, PhCH_2), 4.45–4.37 (m, 1H, -C*H*OBn), 4.16–4.08 (m, 1H, H-5), 4.02–3.95 (m, 1H, H-5), 3.05–2.95 (m, 1H, H-4), 2.85–2.76 (m, 1H, H-4); δ_C 136.8, 132.8, 128.5 (2C), 128.0, 127.7 (2C), 72.1, 71.1, 67.6, 36.4; *m*/*z* (ESI) 214 (M + Na^+, 100%), 192 (M + H^+, 75).

General procedure for the SmI_2 mediated α-hydroxyalkylation of nitrone 10. To a slurry of Sm powder (flame dried under Ar atmosphere, 826 mg, 5.5 mol) in THF (50 mL) was added I_2 (1.270 g, 5.0 mmol) at rt, and the mixture was stirred for 2 h at 45 °C to give a SmI_2 (0.1 M in THF) reagent as a dark blue solution.[18h]

To a stirring and carefully deoxygenated solution of nitrone **10** (95 mg, 0.50 mmol) and a carbonyl compound (1.50 mmol) in THF (10 mL) was added H_2O (0.70 mL, 39 mmol) under an Ar

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atmosphere. The mixture was cooled to −78 °C, to which was added a freshly prepared THF solution of SmI_2 (0.1 mol·L^{-1}, 32 mL, 3.2 mmol). After the reaction was judged to be completed by TLC, saturated aqueous solutions of $Na_2S_2O_3$ (30 mL) and $NaHCO_3$ (40 mL) were added successively. The yellow mixture was extracted with EtOAc (3 × 40 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. After concentration in vacuum, the residue was purified by flash chromatography on silica gel to yield the coupling product **12**.

(2*S*,3*S*)-3-Benzyloxy-2-(1-hydroxy-1-phenylethyl)-*N*-hydroxypyrrolidine (12a). Following the general procedure, the SmI_2-mediated α-hydroxyalkylations of **10** with acetophenone gave **12a** as a mixture of two separable diastereomers in 79:21 ratio (determined by ^{1}H NMR, δ_H 4.45, 3.81) (eluent: EtOAc: PE = 1: 8; combined yield: 84%). Major isomer: 103 mg, yield: 66%; R_f 0.34 (EtOAc: PE = 1: 4); colorless wax; $[\alpha]^{20}_D$ 5.44 (*c* 0.84 in $CHCl_3$); ν_{max}/cm^{-1}: 3229, 2925, 2853, 1728, 1598, 1462, 1447, 1119; δ_H 7.45–7.42 (2H, m, Ph-H), 7.31–7.26 (2H, m, Ph-H), 7.22–7.13 (4H, m, Ph-H), 6.91–6.88 (2H, m, Ph-H), 3.81 (1H, d, *J* = 11.5 Hz, PhC*H*$_2$), 3.71 (1H, d, *J* = 11.5 Hz, PhC*H*$_2$), 3.54 (1H, dd, *J* = 5.6, 2.3 Hz, H-3), 3.31 (1H, d, *J* = 2.3 Hz, H-2), 3.32–3.25 (1H, m, H-5), 3.23–3.14 (1H, m, H-5), 1.76 (1H, dd, *J* = 13.2, 5.6 Hz, H-4), 1.64–1.53 (1H, m, H-4), 1.59 (3H, s, C*H*$_3$); δ_C 145.2, 138.1, 128.1 (2C), 128.1 (2C), 127.6 (2C), 127.3, 126.7, 125.2 (2C), 82.2, 79.4, 74.5, 70.5, 57.5, 29.6, 28.9; *m*/*z* (ESI) 336 (M + Na$^+$, 100%), 314 (M + H$^+$, 96); Found: C, 72.88; H, 7.74; N, 4.56. Calc. for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47%.

Minor isomer: 27 mg, yield: 18%; R_f 0.37 (EtOAc: PE = 1: 4); colorless wax; $[\alpha]^{20}_D$ 46.3 (*c* 1.82 in $CHCl_3$); ν_{max}/cm^{-1}: 3229, 2925, 2852, 1670, 1601, 1494, 1447, 1093; δ_H 7.42 (2H, d, *J* = 7.4 Hz, Ph-H), 7.30–7.15 (8H, m, Ph-H), 4.45 (1H, d, *J* = 11.5 Hz, PhC*H*$_2$), 4.35 (1H, d, *J* = 11.5 Hz, PhC*H*$_2$), 4.12–4.05 (1H, m, H-3), 3.37 (1H, d, *J* = 2.5 Hz, H-2), 3.23–3.13 (1H, m, H-5), 3.04 (1H, ddd, *J* = 12.6, 9.6, 6.4 Hz, H-5), 1.88 (1H, dd, *J* = 13.5, 6.4 Hz, H-4), 1.76–1.66 (1H, m, H-4), 1.46 (3H, s, C*H*$_3$); δ_C 147.2, 138.1, 128.4 (2C), 128.2 (2C), 127.8 (2C), 127.7, 126.7, 125.1 (2C), 82.3, 78.9, 74.2, 71.0, 56.2, 29.7, 28.1; *m*/*z* (ESI) 336 (M + Na$^+$, 100%), 314 (M + H$^+$, 84).

(2*S*,3*S*)-3-Benzyloxy-2-(diphenylhydroxymethyl)-*N*-hydroxypyrrolidine (12b). Following the general procedure, the SmI_2 mediated α-hydroxyalkylations of **10** with benzophenone gave **12b** as a single diastereomer (eluent: EtOAc: PE = 1: 6; 155 mg, yield: 83%). Colorless wax. R_f 0.24 (EtOAc: PE = 1: 6); $[\alpha]^{20}_D$ 76.1 (*c* 0.93 in $CHCl_3$); ν_{max}/cm^{-1}: 3415, 3060, 2935, 1598, 1493, 1449, 1353, 1060; δ_H 7.55–7.48 (4H, m, Ph-H), 7.27–7.07 (11H, m, Ph-H), 4.19 (1H, br d, *J* = 2.3 Hz, H-3), 4.14 (1H, d, *J* = 11.1 Hz, PhC*H*$_2$), 3.90 (1H, d, *J* = 11.1 Hz, PhC*H*$_2$), 3.77 (1H, br s, H-2), 3.21–3.14 (2H, m, H-5), 1.88–1.81 (1H, m, H-4), 1.68–1.55 (1H, m, H-4); δ_C 146.4, 144.4, 138.1, 128.3 (2C), 128.2 (2C), 128.2 (2C), 127.8 (2C), 127.6, 126.8, 126.7, 125.9 (2C), 125.8 (2C), 81.1, 80.6, 77.9, 71.1, 56.3, 28.0; *m*/*z* (ESI) 398 (M + Na$^+$, 100%), 376 (M + H$^+$, 61); Found: C, 76.55; H, 6.60; N, 3.89. Calc. for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73%.

(2*S*,3*S*)-3-Benzyloxy-2-(1-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-*N*-hydroxypyrrolidine (12c). Following the general procedure, the SmI_2 mediated α-hydroxyalkylations of **10** with 2,3-dihydroinden-1-one gave **12c** as a mixture of two separable diastereomers in 72:28 ratio (determined by ^{1}H NMR, δ_H 3.80-3.50) (eluent: EtOAc: PE = 1: 4; combined yield: 91%). Major isomer: 106 mg, yield: 66%; R_f 0.21 (EtOAc: PE = 1: 4); colorless wax; $[\alpha]^{20}_D$ 53.0 (*c* 1.93 in $CHCl_3$); ν_{max}/cm^{-1}: 3383, 3028, 2939, 2854, 1677, 1605, 1454, 1355, 1206, 1093, 1062, 1028; δ_H 7.43 (1H, d, *J* = 7.4 Hz, Ph-H), 7.26–7.10 (8H, m, Ph-H), 4.30 (1H, d, *J* = 11.7 Hz, PhC*H*$_2$), 4.20 (1H, d, *J* = 11.7 Hz, PhC*H*$_2$), 3.79–3.73 (1H, m, H-3), 3.30 (1H, d, *J* = 3.3 Hz, H-2), 3.26–3.19 (1H, m, H-5), 3.08 (1H, ddd, *J* = 12.5, 9.2, 6.4 Hz, H-5), 2.88 (1H, ddd, *J* = 16.3, 8.6, 3.9 Hz, PhC*H*$_2$CH$_2$), 2.75–2.65 (1H, m, PhC*H*$_2$CH$_2$), 2.51 (1H, ddd, *J* = 13.1, 8.6, 3.9 Hz, PhCH$_2$C*H*$_2$), 2.04–1.94 (1H, m, PhCH$_2$C*H*$_2$), 1.85 (1H, dd, *J* = 13.4, 6.4 Hz, H-4), 1.69–1.57 (1H, m, H-4); δ_C 144.9, 143.9, 138.0, 128.4, 128.3 (2C), 127.7 (2C), 127.6, 126.4, 124.8, 124.6, 84.2, 79.6, 78.8, 70.5, 56.6, 38.2, 29.4, 28.4; *m*/*z* (ESI) 348 (M + Na$^+$, 100%), 326 (M + H$^+$, 45); HRMS (ESI) calcd for $C_{20}H_{24}NO_3$ [M + H$^+$]: 326.1756; found: 326.1745.

Minor isomer: 41 mg, yield: 25%; R_f 0.16 (EtOAc: PE = 1: 4); colorless wax; $[\alpha]^{20}_D$ 1.35 (*c* 4.9 in $CHCl_3$); ν_{max}/cm^{-1}: 3348, 3029, 2929, 2854, 1679, 1604, 1454, 1358, 1204, 1093, 1060, 1028; δ_H 7.41–7.38 (1H, m, Ph-H), 7.22–7.14 (6H, m, Ph-H), 7.06–7.03 (2H, m, Ph-H), 4.17 (1H, d, *J* = 11.6 Hz, PhC*H*$_2$), 4.04 (1H, d, *J* = 11.6 Hz, PhC*H*$_2$), 3.64–3.58 (1H, m, H-3), 3.33 (1H, d, *J* = 3.1 Hz, H-2), 3.24–3.30 (1H, m, H-5), 3.11 (1H, ddd, *J* = 12.1, 6.4, 5.6 Hz, H-5), 2.95 (1H, ddd, *J* = 16.1, 9.2, 7.1 Hz, PhC*H*$_2$CH$_2$), 2.79–2.68 (1H, m, PhCH$_2$C*H*$_2$), 2.32–2.23 (1H, m, PhC*H*$_2$CH$_2$), 2.13–2.03 (1H, m, PhCH$_2$C*H*$_2$), 1.88 (1H, dd, *J* = 13.7, 6.4 Hz, H-4), 1.80–1.69 (1H, m, H-4); δ_C 145.7, 143.2, 137.9, 128.6, 128.3 (2C), 127.6 (2C), 127.5, 126.8, 125.2, 123.7, 84.7, 80.7, 79.1, 70.8, 56.6, 36.7, 29.7, 28.5; *m*/*z* (ESI) 348 (M + Na$^+$, 100%), 326 (M + H$^+$, 35).

(2*R*,3*S*)-3-Benzyloxy-2-(hydroxy-phenyl-methyl)-*N*-hydroxypyrrolidine (12d). Following the general procedure, the SmI_2 mediated α-hydroxyalkylations of **10** with benzaldehyde gave **12d** as a mixture of two separable diastereomers in 61:39 (by ^{1}H NMR, PhC*H*, 5.10, 4.69) ratio (eluent: EtOAc: PE = 1: 3; combined yield: 93%). Major isomer: 84 mg, yield: 57%; R_f 0.46 (EtOAc: PE = 1 : 2); colorless wax; $[\alpha]^{20}_D$ 24.0 (*c* 1.38 in $CHCl_3$); ν_{max}/cm^{-1}: 3395, 3030, 2930, 2862, 1604, 1496, 1452, 1400, 1064; δ_H 7.40–7.35 (2H, d, *J* = 7.5 Hz, Ph-H), 7.32–7.27 (2H, t, *J* = 7.9 Hz, Ph-H), 7.25–7.17 (1H, m, Ph-H), 7.14–7.10 (3H, m, Ph-H), 6.80–6.76 (2H, m, Ph-H), 5.10 (1H, d, *J* = 2.4 Hz, PhC*H*), 3.89 (1H, dd, *J* = 5.1, 4.1 Hz, H-3), 3.84 (1H, d, *J* = 11.4 Hz, PhC*H*$_2$), 3.73 (1H, d, *J* = 11.4 Hz, PhC*H*$_2$), 3.24 (1H, dd, *J* = 8.6, 7.1 Hz, H-5), 3.18 (1H, dd, *J* = 4.1, 2.4 Hz, H-2), 3.10 (1H, ddd, *J* = 12.3, 8.6, 7.1 Hz, H-5), 1.93–1.86 (1H, m, H-4), 1.85–1.74 (1H, m, H-4); δ_C 140.6, 137.9, 128.4 (2C), 128.1 (2C), 127.5 (2C), 127.4, 127.3, 125.8 (2C), 80.4, 75.8, 70.6, 70.5, 56.3, 28.9; *m*/*z* (ESI) 322 (M + Na$^+$, 100%), 300 (M + H$^+$, 78); Found: C, 72.12; H, 6.81; N, 4.60. Calc. for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68%.

Minor isomer: 54 mg, yield: 36%; R_f 0.28 (EtOAc: PE = 1: 2); colorless wax; $[\alpha]^{20}_D$ 53.9 (*c* 0.93 in $CHCl_3$); ν_{max}/cm^{-1}: 3354, 3030, 2925, 2858, 1633, 1495, 1454, 1399, 1060; δ_H 7.44–7.13 (8H, m, Ph-H), 6.92–6.88 (2H, m, Ph-H), 4.69 (1H, d, *J* = 8.6 Hz, PhC*H*), 4.03 (1H, d, *J* = 11.5 Hz, PhC*H*$_2$), 3.93 (1H, d, *J* = 11.5 Hz, PhC*H*$_2$), 3.73–3.66 (1H, m, H-3), 3.39 (1H, dd, *J* = 8.6, 4.0 Hz, H-2), 3.31–3.24 (1H, m, H-5), 3.24–3.15 (1H, m, H-5), 2.02–1.85 (2H, m, H-4); δ_C 141.3, 137.7, 128.5 (2C), 128.2 (2C), 128.0, 127.6

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(2C), 127.5, 127.1 (2C), 80.0, 79.4, 75.2, 71.0, 56.7, 29.1; *m/z* (ESI) 322 (M + Na^+, 100%), 300 (M + H^+, 88).

(2*R*,3*S*)-3-Benzyloxy-2-[hydroxy-(4-methoxyphenyl)methyl]-*N*-hydroxypyrrolidine (12e). Following the general procedure, the SmI_2 mediated α-hydroxyalkylations of **10** with 4-methoxybenzaldehyde gave **12e** as a mixture of two separable diastereomers in 62:38 ratio (determined by ^1H NMR, δ_H 3.93, 4.06) (eluent: EtOAc: PE = 1: 1; combined yield: 95%). Major isomer: 96 mg, yield: 59%; R_f 0.39 (EtOAc: PE = 2: 1); colorless wax; $[\alpha]^{20}_D$ 30.9 (*c* 0.99 in $CHCl_3$); ν_{max}/cm^{-1}: 3345, 2924, 2854, 1611, 1513, 1452, 1363, 1173, 1029; δ_H 7.29–7.27 (2H, m, Ph-H), 7.15–7.12 (3H, m, Ph-H), 6.85–6.81 (4H, m, Ph-H), 5.01 (1H, d, *J* = 2.8 Hz, PhC*H*), 3.93 (1H, d, *J* = 11.5 Hz, PhCH_2), 3.88 (1H, dd, *J* = 6.7, 3.9 Hz, H-3), 3.82 (1H, d, *J* = 11.5 Hz, PhCH_2), 3.73 (3H, s, CH_3), 3.32–3.28 (1H, m, H-5), 3.20 (1H, dd, *J* = 3.9, 3.1 Hz, H-3), 3.06–3.11 (1H, m, H-5), 1.81 (1H, dd, *J* = 13.5, 6.5 Hz, H-4), 1.77–1.67 (2H, m, H-4); δ_C 158.8, 138.0, 132.7, 128.1 (2C), 127.5 (2C), 127.4, 127.0 (2C), 113.7 (2C), 80.2, 76.0, 70.7, 70.4, 56.3, 55.3, 28.8; *m/z* (ESI) 330 (M + H^+, 100%), 352 (M + Na^+, 41).

Minor isomer: 59 mg, yield: 36%; R_f 0.30 (EtOAc: PE = 2 : 1); colorless wax; $[\alpha]^{20}_D$ 58.3 (*c* 1.16 in $CHCl_3$); ν_{max}/cm^{-1}: 3332, 2925, 2855, 1612, 1514, 1455, 1356, 1176, 1029; δ_H 7.25 (2H, d, *J* = 8.7 Hz, Ph-H), 7.16 (3H, dd, *J* = 5.0, 1.8 Hz, Ph-H), 6.92–6.87 (2H, m, Ph-H), 6.84–6.79 (2H, m, Ph-H), 4.53 (1H, d, *J* = 8.1 Hz, PhC*H*), 4.06 (1H, d, *J* = 11.5 Hz, PhCH_2), 3.95 (1H, d, *J* = 11.5 Hz, PhCH_2), 3.74 (3H, s, CH_3), 3.66–3.61 (1H, m, H-3), 3.31 (1H, dd, *J* = 8.2, 3.8 Hz, H-2), 3.27–3.20 (1H, m, H-5), 3.19–3.09 (1H, m, H-5), 1.92–1.84 (2H, m, H-4); δ_C 159.4, 137.8, 133.3, 128.4 (2C), 128.1 (2C), 127.6 (2C), 127.5, 113.9 (2C), 80.0, 79.5, 71.0, 56.6, 55.3, 29.1; *m/z* (ESI) 330 (M + H^+, 100%), 352 (M + Na^+, 99); Found: C, 69.38; H, 6.83; N, 4.10. Calc. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25%.

(2*R*,3*S*)-2-{(Benzo[*d*][1,3]dioxol-5-yl)hydroxymethyl)}-3-benzyloxy-*N*-hydroxypyrrolidine (12f). Following the general procedure, the SmI_2 mediated α-hydroxyalkylations of **10** with piperonal gave **12f** as a mixture of two separable diastereomers in 61:39 ratio (determined by ^1H NMR, δ_H 4.09, 4.00) (eluent: EtOAc: PE = 1 : 2; combined yield: 74%). Major isomer: 77 mg, yield: 45%; R_f 0.35 (EtOAc: PE = 1: 1); colorless wax; $[\alpha]^{20}_D$ 37.6 (*c* 1.69 in $CHCl_3$); ν_{max}/cm^{-1}: 3404, 3030, 2872, 1504, 1490, 1444, 1241, 1095, 1040; δ_H 7.20–7.13 (3H, m, Ph-H), 6.93–6.87 (3H, m, Ph-H), 6.81 (1H, d, *J* = 8.4 Hz, Ph-H), 6.72 (1H, d, *J* = 8.0 Hz, Ph-H), 5.87–5.84 (2H, m, OCH_2O), 4.98 (1H, d, *J* = 2.6 Hz, PhC*H*), 4.00 (1H, d, *J* = 11.5 Hz, PhCH_2), 3.87 (1H, d, *J* = 11.5 Hz, PhCH_2), 3.88–3.84 (1H, m, H-3), 3.27–3.20 (1H, m, H-5), 3.10 (1H, dd, *J* = 2.6, 3.7 Hz, H-3), 3.10–3.04 (1H, m, H-5), 1.81 (1H, dd, *J* = 13.5, 6.6 Hz, H-4), 1.79–1.67 (1H, m, H-4); δ_C 147.6, 146.6, 137.8, 134.6, 128.1 (2C), 127.5 (2C), 127.4, 118.9, 108.1, 106.5, 100.9, 80.3, 75.7, 70.7, 70.3, 56.3, 28.7; *m/z* (ESI) 344 (M + H^+, 100%), 366 (M + Na^+, 51); Found: C, 66.34; H, 6.46; N, 3.95. Calc. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08%.

Minor isomer: 49 mg, yield: 29%; R_f 0.17 (EtOAc: PE = 1: 1); colorless wax; $[\alpha]^{20}_D$ 53.8 (*c* 1.10 in $CHCl_3$); ν_{max}/cm^{-1}: 3332, 3030, 2881, 1503, 1488, 1443, 1245, 1096, 1039, 737; δ_H 7.20-7.14 (3H, m, Ph-H), 6.96–6.89 (2H, m, Ph-H), 6.86–6.65 (5H, m, Ph-H), 5.85 (2H, dd, *J* = 1.4, 5.5 Hz, OCH_2O), 4.51 (1H, d, *J* = 5.4 Hz, PhC*H*), 4.09 (1H, d, *J* = 11.6 Hz, PhCH_2), 3.94 (1H, d, *J* = 11.6 Hz, PhCH_2), 3.64–3.57 (1H, m, H-3), 3.25 (1H, dd, *J* = 5.4, 1.4 Hz, H-2), 3.22–3.08 (2H, m, H-5), 1.97–1.78 (2H, m, H-4); δ_C 147.8, 147.3, 137.7, 135.2, 128.2 (2C), 127.5 (2C), 127.5, 120.6, 108.0, 107.6, 101.0, 79.9, 79.5, 75.1, 71.1, 56.7, 29.0; *m/z* (ESI) 366 (M + Na^+, 100%), 344 (M + H^+, 71).

(2*R*,3*S*)-3-Benzyloxy-2-[(2-chlorophenyl)hydroxymethyl]-*N*-hydroxypyrrolidine (12g). Following the general procedure, the SmI_2 mediated α-hydroxyalkylations of **10** with 2-chlorobenzaldehyde gave **12g** as a mixture of two separable diastereomers in 67:33 ratio (determined by ^1H NMR, δ_H 5.44, 5.16) (eluent: EtOAc: PE = 1: 4; combined yield: 72%). Major isomer: 80 mg, yield: 48%; R_f 0.42 (EtOAc: PE = 1: 2); colorless wax; $[\alpha]^{20}_D$ 10.6 (*c* 2.36 in $CHCl_3$); $[\alpha]^{20}_D$ 4.33 (*c* 1.10, $CHCl_3$); ν_{max}/cm^{-1}: 3405, 3030, 2925, 2860, 1595, 1496, 1454, 1441, 1356, 1093, 1049; δ_H 7.60 (1H, dd, *J* = 7.6, 1.9 Hz, Ph-H), 7.30 (1H, dd, *J* = 7.5, 1.6 Hz, Ph-H), 7.21–7.14 (2H, m, Ph-H), 7.13–7.09 (3H, m, Ph-H), 6.80–6.74 (2H, m, Ph-H), 5.44 (1H, d, *J* = 1.7 Hz, PhC*H*), 3.96–3.89 (1H, m, H-3), 3.80 (1H, d, *J* = 11.4 Hz, PhCH_2), 3.72 (1H, d, *J* = 11.4 Hz, PhCH_2), 3.45–3.41 (1H, m, H-2), 3.28–3.24 (1H, m, H-5), 3.16–3.09 (1H, m, H-5), 1.83–1.77 (2H, m, H-4); δ_C 138.2, 137.8, 131.9, 129.4, 128.6, 128.1 (2C), 127.5, 127.5 (2C), 127.4, 127.0, 77.1, 75.5, 70.5, 67.8, 56.5, 29.1; *m/z* (ESI) 356 (M + Na^+, 100%), 334 (M + H^+, 76); Found: C, 64.65; H, 5.90; N, 3.96. Calc. for $C_{18}H_{20}ClNO_3$: C, 64.77; H, 6.04; N, 4.20%.

Minor isomer: 39 mg, yield: 24%; R_f 0.34 (EtOAc: PE = 1: 2); colorless wax; $[\alpha]^{20}_D$ 35.0 (*c* 0.80 in $CHCl_3$); ν_{max}/cm^{-1}: 3374, 3031, 2924, 2856, 1594, 1496, 1454, 1440, 1356, 1093, 1057; δ_H 7.55–7.52 (1H, m, Ph-H), 7.30–7.11 (6H, m, Ph-H), 7.04–6.99 (2H, m, Ph-H), 5.16 (1H, d, *J* = 6.2 Hz, PhC*H*), 4.22 (1H, d, *J* = 11.8 Hz, PhCH_2), 4.18 (1H, d, *J* = 11.8 Hz, PhCH_2), 3.92–3.86 (1H, m, H-3), 3.45 (1H, dd, *J* = 6.2, 3.7 Hz, H-2), 3.29–3.24 (1H, m, H-5), 3.15 (1H, dd, *J* = 18.5, 9.4 Hz, H-5), 1.94–1.87 (2H, m, H-4); δ_C 139.2, 137.7, 132.3, 129.6, 128.9, 128.4, 128.2 (2C), 127.6 (2C), 127.5, 127.2, 79.2, 79.0, 71.0, 70.7, 56.6, 29.2; *m/z* (ESI) 356 (M + Na^+, 100%), 334 (M + H^+, 79).

(2*R*,3*S*)-3-Benzyloxy-2-[(4-chlorophenyl)hydroxymethyl]-*N*-hydroxypyrrolidine (12h). Following the general procedure, the SmI_2 mediated α-hydroxyalkylations of **10** with 4-chlorobenzaldehyde gave **12h** as a mixture of two separable diastereomers in 63:37 ratio (determined by ^1H NMR, δ_H 4.11, 4.05) (eluent: EtOAc: PE = 1: 3; combined yield: 95%). Major isomer: 99 mg, yield: 60%; R_f 0.23 (EtOAc: PE = 1: 2); colorless wax; $[\alpha]^{20}_D$ 56.1 (*c* 0.59 in $CHCl_3$); ν_{max}/cm^{-1}: 3361, 3030, 2865, 1597, 1492, 1453, 1408, 1355, 1089, 1058, 1027; δ_H 7.30–7.22 (7H, m, Ph-H), 6.93–6.82 (2H, m, Ph-H), 4.73–4.54 (1H, br s, PhC*H*), 4.11 (1H, d, *J* = 11.5 Hz, PhCH_2), 3.91 (1H, d, *J* = 11.5 Hz, PhCH_2), 3.68–3.57 (1H, m, H-3), 3.30 (1H, dd, *J* = 9.0, 4.4 Hz, H-5), 3.27–3.21 (1H, m, H-2), 3.21–3.14 (1H, m, H-5), 1.98–1.83 (2H, m, H-4); δ_C 139.6, 137.3, 133.8, 128.7 (2C), 128.6 (2C), 128.2 (2C), 127.6 (2C), 127.6, 79.7, 79.0, 71.1, 56.7, 28.8; *m/z* (ESI) 356 (M + Na^+, 100%), 334 (M + H^+, 36); HRMS (ESI) calcd for $C_{18}H_{21}ClNO_3$ [M + H^+]: 334.1210; found: 334.1212.

Minor isomer: 58 mg, yield: 35%; R_f 0.38 (EtOAc: PE = 1: 2); colorless wax; $[\alpha]^{20}_D$ 38.1 (*c* 1.30 in $CHCl_3$); ν_{max}/cm^{-1}: 3435, 3030, 2941, 2862, 1596, 1492, 1454, 1401, 1359, 1200, 1090, 1027; δ_H 7.36–7.28 (4H, m, Ph-H), 7.26–7.19 (3H, m, Ph-H), 6.85–6.78 (2H, m, Ph-H), 5.15–5.10 (1H, m, PhC*H*), 4.05 (1H, d, *J* = 11.4 Hz, PhCH_2), 4.00–3.89 (1H, m, H-3), 3.86 (1H, d, *J* = 11.4 Hz, PhCH_2), 3.32–3.24 (1H, pseudo t, *J* = 7.5 Hz, H-2), 3.23–3.18

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(1H, m, H-5), 3.18–3.10 (1H, m, H-5), 1.93–1.71 (2H, m, H-4); δ_C 139.0, 137.4, 132.9, 128.4 (2C), 128.2 (2C), 127.5 (2C), 127.5, 127.1 (2C), 80.2, 75.2, 70.8, 69.6, 56.3, 28.4; *m/z* (ESI) 356 (M + Na^+, 100%), 334 (M + H^+, 56).

(2*R*,3*S*)-3-Benzyloxy-2-[(2,4-dichlorophenyl)hydroxymethyl]-*N*-hydroxypyrrolidine (12i). Following the general procedure, the SmI_2 mediated α-hydroxyalkylations of **10** with 2,4-dichlorobenzaldehyde gave **12i** as a mixture of two inseparable diastereomers in 61:39 ratio (determined by ^{1}H NMR, δ_H 5.40-5.15) (eluent: EtOAc: PE = 1: 4; 170 mg, combined yield: 93%). Colorless wax. R_f 0.52 (EtOAc: PE = 1: 2); ν_{max}/cm^{-1}: 3390, 3031, 2863, 1590, 1562, 1470, 1454, 1383, 1357, 1101, 1057; δ_H 7.57–6.77 (8H, m, Ph-H), 5.43, 5.14 (1H, 2 m, PhC*H*), 4.33, 4.21, 4.03, 3.94–3.84 (3H, d (min., *J* = 11.7 Hz), d (min., *J* = 11.7 Hz), d (maj., *J* = 11.4 Hz), m, PhCH_2, PhCH_2, PhCH_2, PhCH_2 and H-3), 3.42 (1H, dd, *J* = 6.4, 4.0 Hz), 3.34–3.25 (1H, m), 3.24–3.10 (1H, m, H-5), 2.02–1.67 (2H, m, H-4); δ_C 137.4, 137.3, 136.9, 134.1, 133.6, 133.0, 132.3, 129.2, 129.0, 128.3, 128.3, 128.2 (2C), 127.6, 127.6, 127.5, 127.4 (2C), 127.2, 79.0, 78.5, 75.0, 70.5, 67.2, 56.7, 56.3, 28.5; *m/z* (ESI) 391 (M + Na^+, 100%), 369 (M + H^+, 74); Found: C, 58.51; H, 5.22; N, 3.72. Calc. for $C_{18}H_{20}ClNO_3$: C, 58.71; H, 5.20; N, 3.80%.

(3*S*)-3-Benzyloxy-2-(1-hydroxybutyl)-*N*-hydroxypyrrolidine (12j). Following the general procedure, the SmI_2 mediated α-hydroxyalkylations of **10** with butyraldehyde gave **12j** as a mixture of four inseparable diastereomers in 43:36:11:10 ratio (determined by ^{1}H NMR, δ_H 4.54, 4.51, 4.29, 4.27) (eluent: EtOAc: PE = 1: 2; 105 mg, combined yield: 80%). Colorless wax. R_f 0.41 (EtOAc: PE = 1: 1); ν_{max}/cm^{-1}: 3356, 3030, 2957, 2870, 1605, 1497, 1454, 1432, 1357, 1093, 1067; δ_H (two isomers) 7.38–7.25 (5H, m, Ph-H), 4.56, 4.52 (1H, 2d, *J* =11.5 Hz, PhCH_2), 4.41 (1H, overlapped, 2d, *J* = 11.5 Hz, PhCH_2), 3.99 (1H, m, C*H*OH), 3.75–3.67 (1H, m, H-3), 3.26–3.21 (1H, m, C*H*NCH_2), 3.20–3.02 (1H, m, C*H*NCH_2), 2.99–2.86 (1H, m, C*H*NCH_2), 2.07–1.70 (2H, m, H-4), 1.61–1.32 (4H, m, $CH_3CH_2CH_2$), 0.91 (3H, overlapped, 2t, *J* = 7.1 Hz, CH_3); δ_C 138.1, 137.9, 128.6, 128.4 (2C), 128.4 (2C), 128.1, 127.8 (2C), 127.8 (2C), 127.7, 127.7, 79.9, 78.3, 78.3, 71.2, 71.1, 68.1, 56.7, 47.4, 36.9, 35.4, 27.9, 19.4, 18.9, 14.1; *m/z* (ESI) 266 (M + H^+, 100%), 288 (M + Na^+, 51); Found: C, 67.91; H, 8.84; N, 5.17. Calc. for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28%.

(3*S*)-3-Benzyloxy-2-(1-hydroxy-2-methylpropyl)-*N*-hydroxypyrrolidine (12k). Following the general procedure, the SmI_2 mediated α-hydroxyalkylations of **10** with isobutyraldehyde gave **12k** as a mixture of three inseparable diastereomers in 45:36:19 ratio (determined by ^{1}H NMR, δ_H 4.34, 4.32, 4.24) (eluent: EtOAc: PE = 1: 2; 116 mg, combined yield: 88%). Colorless wax. R_f 0.24 (EtOAc: PE = 1: 2); ν_{max}/cm^{-1}: 3358, 3031, 2959, 2870, 1604, 1496, 1454, 1363, 1092, 1065; δ_H (two isomers) 7.38–7.27 (5H, m, Ph-H), 4.54 (1H, overlapped, 2d, *J* = 11.5 Hz, PhCH_2), 4.42, 4.38 (1H, 2d, *J* = 11.5 Hz, PhCH_2), 4.06, 3.85 (1H, 2 m, C*H*OH), 3.60–3.30 (1H, m, H-3), 3.31–3.05 (3H, m, C*H*NCH_2), 2.18–1.97 (2H, m, H-4), 1.97–1.77 (2H, m, H-5), 1.71–1.55 (1H, m, C*H*Me_2), 1.07–1.03, 1.01–0.96 (6H, 2m, 2CH_3); δ_C 138.1, 138.0, 128.5, 128.4 (2C), 128.3, 128.1, 127.9, 127.7 (2C), 127.6, 80.3, 77.2, 76.4, 75.8, 74.1, 71.8, 71.2, 56.8, 55.9, 32.0, 31.0, 30.7, 27.8, 27.6, 20.1, 19.9, 19.5, 19.0, 16.6; *m/z* (ESI) 266 (M + H^+, 100%), 288 (M + Na^+, 44); Found: C, 67.54; H, 8.65; N, 5.19. Calc. for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28%.

(3*S*)-3-Benzyloxy-2-(1-hydroxyhexyl)-*N*-hydroxypyrrolidine (12l). Following the general procedure, the SmI_2 mediated α-hydroxyalkylations of **10** with hexanal gave **12l** as a mixture of four inseparable diastereomers in 40:35:10:15 (ratio determined by ^{1}H NMR, δ_H 4.35, 4.34, 4.24, 4.22) (eluent: EtOAc: PE = 2: 1; 128 mg, combined yield: 88%). Colorless wax. R_f 0.25 (EtOAc: PE = 2: 1); ν_{max}/cm^{-1}: 3317, 3031, 2929, 2858, 1497, 1454, 1352, 1091, 1064; δ_H (three isomers) 7.31–7.20 (5H, m, Ph-H), 4.49, 4.45 (1H, 2d, *J* = 11.5 Hz, PhCH_2), 4.34 (1H, overlapped, 2d, *J* = 11.5 Hz, PhCH_2), 3.99, 3.85 (1H, 2 m, C*H*OH), 3.60–3.30 (1H, m, H-3), 3.20–2.95 (2H, m, C*H*NCH_2), 2.91–2.81 (1H, m, C*H*NCH_2), 1.95–1.65 (2H, m, H-4), 1.51–1.35 (3H, m, $CH_2CH_2CH_2CH_2Me$), 1.32–1.15 (5H, m, $CH_2CH_2CH_2CH_2Me$), 0.82 (3H, t, CH_3); δ_C 138.1, 137.9, 128.6, 128.4 (2C), 128.4 (2C), 127.8 (2C), 127.8 (2C), 127.7, 127.7, 80.0, 78.3, 78.2, 77.2, 75.7, 71.3, 71.1, 68.6, 56.8, 56.1, 34.7, 33.4, 31.9, 31.8, 28.7, 28.0, 25.8, 25.3, 22.6, 22.6, 14.1; *m/z* (ESI) 316 (M + Na^+, 100%), 294 (M + H^+, 90); Found: C, 69.33; H, 9.12; N, 4.76. Calc. for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.77%.

1,2-Bis(4-methoxyphenyl)ethane-1,2-diol (13) (meso and dl). Compound **13**[34,35] was obtained as a side product from the coupling of nitrone **10** with 4-methoxybenzaldehyde. 63 mg, yield: 31%, based on the starting 4-methoxybenzaldehyde. White solid; mp 164–165 °C (EtOAc/PE) (lit.[34] mp 167 °C, meso and dl, determined by thermal analysis); R_f 0.64 (EtOAc: PE = 2: 1); ν_{max}/cm^{-1}: 3354, 2901, 2836, 1611, 1585, 1515, 1460, 1246, 1177, 1032; δ_H (isomer 1): 7.08–7.01 (4H, m, Ph-H), 6.80–6.74 (4H, m, Ph-H), 4.63 (2H, s, PhC*H*), 3.77 (6H, s, OCH_3), 2.82 (2H, br s, OH); δ_H (isomer 2): 7.18–7.24 (4H, m, Ph-H), 6.90–6.84 (4H, m, Ph-H), 4.73 (2H, s, PhC*H*), 3.80 (6H, s, OCH_3), 2.12 (2H, br s, OH); δ_C 159.4, 159.2, 132.1, 132.0, 128.3 (2C), 128.1 (2C), 113.7 (2C), 113.5 (2C), 78.8, 77.8, 55.3, 55.2; *m/z* (ESI) 297 (M + Na^+, 100%), 313 (M + K^+, 10).

(2*S*,3*S*)-3-Benzyloxy-2-(diphenylhydroxymethyl)pyrrolidine (14). A stirred and carefully deoxygenated solution of coupling product **12b** (108 mg, 0.28 mmol) in THF (10 mL) was cooled to −78 °C under an Ar atmosphere. A freshly prepared THF solution of SmI_2 (0.1 mol·L^{-1}, 11.5 mL, 1.15 mmol) was then added. After stirring at −78 °C for 1 h, the temperature was allowed to warm up overnight. The reaction was then quenched by introduction of air, and then a saturated aqueous solution of $Na_2S_2O_3$ (4 mL) and $NaHCO_3$ (15 mL) were added successively. The yellow mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine and dried over Na_2SO_4 and filtered. After concentration in vacuum, the residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE, 2: 1) to yield the pyrrolidine **14** (77.4 mg, yield: 77%) as a colorless wax. R_f 0.25 (EtOAc); $[\alpha]^{20}_D$ −24.2 (*c* 1.16, $CHCl_3$); ν_{max}/cm^{-1}: 3283, 3060, 3030, 2924, 1598, 1449, 1385, 1357, 1097, 1061; δ_H 7.63–7.55 (4H, m, Ph-H), 7.34–7.25 (7H, m, Ph-H), 7.21–7.14 (2H, m, Ph-H), 7.08–7.01 (2H, m, Ph-H), 4.45–4.41 (1H, m, H-3), 4.02 (1H, d, *J* = 11.3 Hz, PhCH_2), 3.94 (1H, d, *J* = 5.7 Hz, H-2), 3.91 (1H, d, *J* = 11.3 Hz, PhCH_2), 3.10 (1H, ddd, *J* = 5.7, 9.5, 12.3 Hz, H-5), 2.87–2.75 (1H, m, H-5), 1.91 (1H, dd, *J* = 5.7, 13.4 Hz, H-4), 1.82–1.74 (1H, m, H-4); δ_C 144.2, 137.9, 128.6 (2C),

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128.3 (2C), 128.2 (2C), 127.8 (2C), 127.6, 126.9, 126.8 (2C), 125.9 (2C), 125.7 (2C), 80.5, 77.6, 71.7, 71.1, 45.5, 31.8; *m/z* (ESI) 360 (M + H^+, 100); Found: C, 80.54; H, 7.33; N, 3.70. Calc. for $C_{15}H_{20}O_5$: C, 80.19; H, 7.01; N, 3.90%.

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