

A new approach to 3-hydroxyprolinol derivatives by samarium diiodide-mediated reductive coupling of chiral nitronone 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 (nitronone)(*S*)-**10** with carbonyl compounds. The reductive hydroxyalkylation of nitronone **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, Miglitol² and Zavesca³ (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 A⁹ (Scheme 1), a disconnection at the C₁–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 realiza-

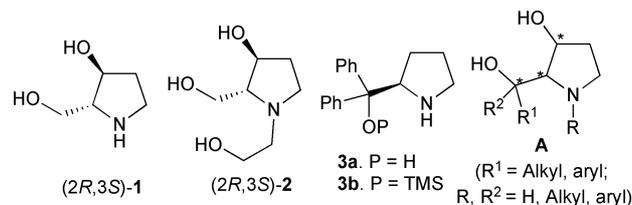
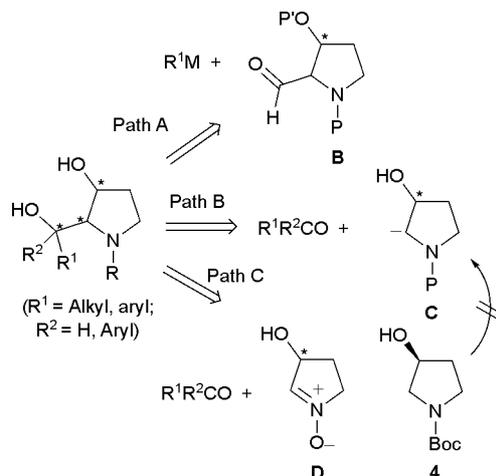


Fig. 1 Structure of prolinol-containing azasugars and organocatalysts.



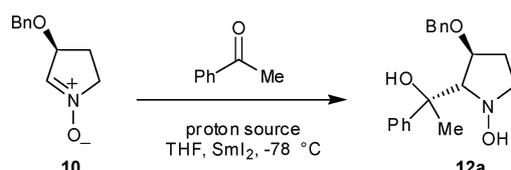
Scheme 1 Three possible approaches for the synthesis of β -hydroxyprolinol derivatives.

tion 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 direct¹² and indirect¹³ as well as synthetic equivalent-based¹⁴ approaches to realize synthon **C**. Among these approaches, the SmI₂-mediated method¹² is straightforward, because it allows direct access to differently substituted pyrrolidines in one step.

The widespread application of nitronones^{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 nitronones¹⁵ have served as versatile building

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Table 1 Optimization of the reductive coupling reaction

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	<i>t</i> -BuOH (2)	3	-78	4	50	62:38
3	1.5	H ₂ O (8)	3	-78	4	64	71:29
4	1.1	H ₂ O (8)	3	-50	3	59	72:28
5	1.1	H ₂ O (8)	3	-20	4	36	60:40
6	3	H ₂ O (78)	6.5	-78	1.5	84	79:21

^a Isolated yields. ^b Ratio determined by ¹H 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 SmI₂-induced nitrones coupling with activated olefins.^{18g–j} In 2002, Py, Vallée and co-workers reported the first SmI₂-mediated¹⁹ coupling of achiral alicyclic nitrones with aldehydes.²⁰ While our work was in progress, Py and co-workers reported the SmI₂-mediated coupling of carbonyl compounds with achiral pyrrolidine nitrone.²¹ We now report the first asymmetric coupling²² 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, Ag₂O, EtOAc, r.t.), lithium aluminium hydride reduction (LAH, THF, refl.), and bis-mesylation (MsCl, NEt₃, CH₂Cl₂, 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

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 MnO₂,^{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 ¹H-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 protocol²⁰ 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 SmI₂-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 SmI₂ 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,

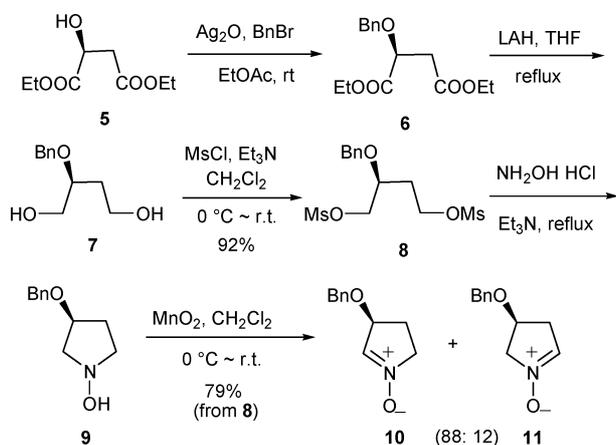
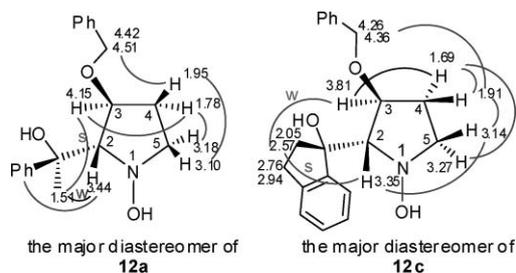
**Scheme 2** Synthesis of the chiral nitrone **10**.

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

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

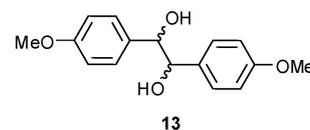
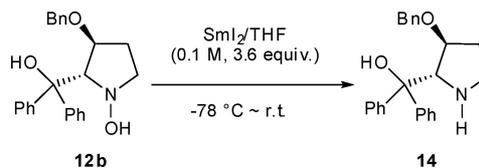
^a Isolated yields, based on nitron **10**. ^b Ratio determined by ¹H NMR. ^c 31% of **13** was obtained based on the starting 4-methoxybenzaldehyde.

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.

**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 SmI₂^{18i,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).

**Fig. 3** Structure of the pinacol coupling product **13**.**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 nitron **10** with aldehydes/ketones underwent a smooth reaction to give the corresponding coupling products **12a–12l** in good to excellent yields. This proves that nitron **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. ¹H NMR spectra were recorded in CDCl₃ on a Bruker 400 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. ¹³C NMR spectra were determined at

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 N₂. Dichloromethane was distilled over calcium hydride under N₂. 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; [α]_D²⁰ –59.9 (*c* 6.8 in CHCl₃); ν_{max}/cm⁻¹: 1738, 1454, 1373, 1274, 1176, 1124 and 1028; δ_H 7.38–7.27 (5H, m, Ph-H), 4.77 (1H, d, *J* = 11.4 Hz, PhCH₂), 4.54 (1H, d, *J* = 11.4 Hz, PhCH₂), 4.39 (1H, dd, *J* = 5.1, 7.8 Hz, -CHOBN), 4.27–4.19 (2H, m, CH₃CH₂O-), 4.19–4.11 (2H, m, CH₃CH₂O-), 2.85–2.72 (2H, m, -OCHCH₂CO-), 1.30, 1.24 (6H, 2t, *J* = 7.15, 7.15 Hz, CH₃CH₂O-); 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 C₁₅H₂₀O₅: 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 LiAlH₄ (1.98 g, 52 mmol) in THF (20 mL) under a N₂ 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 H₂O (2 mL), 10% NaOH solution (4 mL) and H₂O (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 Na₂SO₄, 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); [α]_D²⁰ –15.6 (*c* 2.0 in CHCl₃) {lit.^{33a} +15.0 (*c* 1.0 in CHCl₃) for (*R*)-enantiomer}; [α]_D²⁰ –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, PhCH₂), 4.55 (1H, d, *J* = 11.6 Hz, PhCH₂), 3.77–3.62 (4H, m, -CH₂OH), 3.58–3.48 (1H, m, -CHOBN), 3.07–2.96 (2H, br, OH), 1.89–1.68 (2H, m, -OCHCH₂CH₂-); 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 C₁₁H₁₆O₃: C, 67.32; H, 8.22%.

(S)-2-(Benzyloxy)-1,4-bis(methanesulfonyloxy)butane (8). To a cooled (0 °C) CH₂Cl₂ (12 mL) solution of compound **7** (1.70 g, 8.7 mmol) and Et₃N (7.5 mL, 52.0 mmol) was added dropwise methanesulfonyl chloride (2.9 mL, 37.0 mmol) under a N₂ atmosphere. The mixture was stirred at rt for 7 h, then cooled

to 0 °C and treated with saturated aqueous NH₄Cl (14 mL). The two phases were separated and the aqueous phase extracted with CH₂Cl₂ (100 mL). The combined organic phases were washed with brine (5 mL), dried over Na₂SO₄, 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); [α]_D²⁰ –42.4 (*c* 3.0 in CHCl₃); 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, PhCH₂), 4.49 (1H, d, *J* = 11.3 Hz, PhCH₂), 4.35–4.21, 4.17–4.10 (4H, 2 m, -CH₂OMs), 3.84–3.77 (1H, m, -CHOBN), 2.94 (3H, s, -CH₃), 2.88 (3H, s, -CH₃), 2.01–1.87 (2H, m, -OCHCH₂CH₂-); 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 C₁₃H₂₀O₇S₂: 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 Et₃N (17 mL) was heated at reflux for 6 h under N₂ 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 CH₂Cl₂ (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 N₂ 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; [α]_D²⁰ –97.6 (*c* 2.7 in CHCl₃); 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, -CHOBN), 4.51 (1H, d, *J* = 11.6 Hz, PhCH₂), 4.46 (1H, d, *J* = 11.6 Hz, PhCH₂), 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 C₁₁H₁₃NO₂: 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, PhCH₂), 4.45–4.37 (m, 1H, -CHOBN), 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 SmI₂ 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 I₂ (1.270 g, 5.0 mmol) at rt, and the mixture was stirred for 2 h at 45 °C to give a SmI₂ (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 H₂O (0.70 mL, 39 mmol) under an Ar

atmosphere. The mixture was cooled to $-78\text{ }^{\circ}\text{C}$, 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 $\text{Na}_2\text{S}_2\text{O}_3$ (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**.

(2S,3S)-3-Benzoyloxy-2-(1-hydroxy-1-phenylethyl)-N-hydroxy-pyrrolidine (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 ¹H 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; $[\alpha]_{\text{D}}^{20}$ 5.44 (*c* 0.84 in CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$: 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, PhCH_2), 3.71 (1H, d, $J = 11.5$ Hz, PhCH_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, CH_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 $\text{C}_{19}\text{H}_{23}\text{NO}_3$: 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; $[\alpha]_{\text{D}}^{20}$ 46.3 (*c* 1.82 in CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$: 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, PhCH_2), 4.35 (1H, d, $J = 11.5$ Hz, PhCH_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, CH_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).

(2S,3S)-3-Benzoyloxy-2-(diphenylhydroxymethyl)-N-hydroxy-pyrrolidine (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); $[\alpha]_{\text{D}}^{20}$ 76.1 (*c* 0.93 in CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$: 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, PhCH_2), 3.90 (1H, d, $J = 11.1$ Hz, PhCH_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 $\text{C}_{24}\text{H}_{25}\text{NO}_3$: C, 76.77; H, 6.71; N, 3.73%.

(2S,3S)-3-Benzoyloxy-2-(1-hydroxy-2,3-dihydro-1H-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 ¹H 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; $[\alpha]_{\text{D}}^{20}$ 53.0 (*c* 1.93 in CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$: 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, PhCH_2), 4.20 (1H, d, $J = 11.7$ Hz, PhCH_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, PhCH_2CH_2), 2.75–2.65 (1H, m, PhCH_2CH_2), 2.51 (1H, ddd, $J = 13.1, 8.6, 3.9$ Hz, PhCH_2CH_2), 2.04–1.94 (1H, m, PhCH_2CH_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 $\text{C}_{20}\text{H}_{24}\text{NO}_3$ [M + H⁺]: 326.1756; found: 326.1745.

Minor isomer: 41 mg, yield: 25%; R_f 0.16 (EtOAc: PE = 1: 4); colorless wax; $[\alpha]_{\text{D}}^{20}$ 1.35 (*c* 4.9 in CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$: 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, PhCH_2), 4.04 (1H, d, $J = 11.6$ Hz, PhCH_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, PhCH_2CH_2), 2.79–2.68 (1H, m, PhCH_2CH_2), 2.32–2.23 (1H, m, PhCH_2CH_2), 2.13–2.03 (1H, m, PhCH_2CH_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).

(2R,3S)-3-Benzoyloxy-2-(hydroxy-phenyl-methyl)-N-hydroxy-pyrrolidine (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 ¹H NMR, PhCH , 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; $[\alpha]_{\text{D}}^{20}$ 24.0 (*c* 1.38 in CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$: 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, PhCH), 3.89 (1H, dd, $J = 5.1, 4.1$ Hz, H-3), 3.84 (1H, d, $J = 11.4$ Hz, PhCH_2), 3.73 (1H, d, $J = 11.4$ Hz, PhCH_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 $\text{C}_{18}\text{H}_{21}\text{NO}_3$: 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; $[\alpha]_{\text{D}}^{20}$ 53.9 (*c* 0.93 in CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$: 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, PhCH), 4.03 (1H, d, $J = 11.5$ Hz, PhCH_2), 3.93 (1H, d, $J = 11.5$ Hz, PhCH_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

(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).

(2R,3S)-3-Benzoyloxy-2-[hydroxy-(4-methoxyphenyl)methyl]-N-hydroxypyrrolidine (12e). Following the general procedure, the SmI₂ 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; $[\alpha]_{\text{D}}^{20}$ 30.9 (*c* 0.99 in CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$: 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, PhCH), 3.93 (1H, d, $J = 11.5$ Hz, PhCH₂), 3.88 (1H, dd, $J = 6.7, 3.9$ Hz, H-3), 3.82 (1H, d, $J = 11.5$ Hz, PhCH₂), 3.73 (3H, s, CH₃), 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; $[\alpha]_{\text{D}}^{20}$ 58.3 (*c* 1.16 in CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$: 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, PhCH), 4.06 (1H, d, $J = 11.5$ Hz, PhCH₂), 3.95 (1H, d, $J = 11.5$ Hz, PhCH₂), 3.74 (3H, s, CH₃), 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 C₁₉H₂₃NO₄: C, 69.28; H, 7.04; N, 4.25%.

(2R,3S)-2-[(Benzo[d][1,3]dioxol-5-yl)hydroxymethyl]-3-benzoyloxy-N-hydroxypyrrolidine (12f). Following the general procedure, the SmI₂ 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; $[\alpha]_{\text{D}}^{20}$ 37.6 (*c* 1.69 in CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$: 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, OCH₂O), 4.98 (1H, d, $J = 2.6$ Hz, PhCH), 4.00 (1H, d, $J = 11.5$ Hz, PhCH₂), 3.87 (1H, d, $J = 11.5$ Hz, PhCH₂), 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 C₁₉H₂₁NO₅: 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; $[\alpha]_{\text{D}}^{20}$ 53.8 (*c* 1.10 in CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$: 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, OCH₂O), 4.51 (1H, d, $J = 5.4$ Hz, PhCH), 4.09 (1H, d, $J = 11.6$ Hz, PhCH₂), 3.94 (1H, d, $J = 11.6$ Hz, PhCH₂), 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).

(2R,3S)-3-Benzoyloxy-2-[(2-chlorophenyl)hydroxymethyl]-N-hydroxypyrrolidine (12g). Following the general procedure, the SmI₂ 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; $[\alpha]_{\text{D}}^{20}$ 10.6 (*c* 2.36 in CHCl₃); $[\alpha]_{\text{D}}^{20}$ 4.33 (*c* 1.10, CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$: 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, PhCH), 3.96–3.89 (1H, m, H-3), 3.80 (1H, d, $J = 11.4$ Hz, PhCH₂), 3.72 (1H, d, $J = 11.4$ Hz, PhCH₂), 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 C₁₈H₂₀ClNO₃: 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; $[\alpha]_{\text{D}}^{20}$ 35.0 (*c* 0.80 in CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$: 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, PhCH), 4.22 (1H, d, $J = 11.8$ Hz, PhCH₂), 4.18 (1H, d, $J = 11.8$ Hz, PhCH₂), 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).

(2R,3S)-3-Benzoyloxy-2-[(4-chlorophenyl)hydroxymethyl]-N-hydroxypyrrolidine (12h). Following the general procedure, the SmI₂ 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; $[\alpha]_{\text{D}}^{20}$ 56.1 (*c* 0.59 in CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$: 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, PhCH), 4.11 (1H, d, $J = 11.5$ Hz, PhCH₂), 3.91 (1H, d, $J = 11.5$ Hz, PhCH₂), 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 C₁₈H₂₁ClNO₃ [M + H⁺]: 334.1210; found: 334.1212.

Minor isomer: 58 mg, yield: 35%; R_f 0.38 (EtOAc: PE = 1: 2); colorless wax; $[\alpha]_{\text{D}}^{20}$ 38.1 (*c* 1.30 in CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$: 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, PhCH), 4.05 (1H, d, $J = 11.4$ Hz, PhCH₂), 4.00–3.89 (1H, m, H-3), 3.86 (1H, d, $J = 11.4$ Hz, PhCH₂), 3.32–3.24 (1H, pseudo t, $J = 7.5$ Hz, H-2), 3.23–3.18

(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).

(2R,3S)-3-Benzoyloxy-2-[(2,4-dichlorophenyl)hydroxymethyl]-N-hydroxypyrrolidine (12i). Following the general procedure, the SmI₂ mediated α -hydroxyalkylations of **10** with 2,4-dichlorobenzaldehyde gave **12i** as a mixture of two inseparable diastereomers in 61:39 ratio (determined by ¹H 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, PhCH), 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, PhCH₂, PhCH₂, PhCH₂, PhCH₂ 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 C₁₈H₂₀ClNO₃: C, 58.71; H, 5.20; N, 3.80%.

(3S)-3-Benzoyloxy-2-(1-hydroxybutyl)-N-hydroxypyrrolidine (12j). Following the general procedure, the SmI₂ mediated α -hydroxyalkylations of **10** with butyraldehyde gave **12j** as a mixture of four inseparable diastereomers in 43:36:11:10 ratio (determined by ¹H 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, PhCH₂), 4.41 (1H, overlapped, 2d, $J = 11.5$ Hz, PhCH₂), 3.99 (1H, m, CHOH), 3.75–3.67 (1H, m, H-3), 3.26–3.21 (1H, m, CHNCH₂), 3.20–3.02 (1H, m, CHNCH₂), 2.99–2.86 (1H, m, CHNCH₂), 2.07–1.70 (2H, m, H-4), 1.61–1.32 (4H, m, CH₂CH₂CH₂), 0.91 (3H, overlapped, 2t, $J = 7.1$ Hz, CH₃); 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 C₁₅H₂₃NO₃: C, 67.90; H, 8.74; N, 5.28%.

(3S)-3-Benzoyloxy-2-(1-hydroxy-2-methylpropyl)-N-hydroxypyrrolidine (12k). Following the general procedure, the SmI₂ mediated α -hydroxyalkylations of **10** with isobutyraldehyde gave **12k** as a mixture of three inseparable diastereomers in 45:36:19 ratio (determined by ¹H 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, PhCH₂), 4.42, 4.38 (1H, 2d, $J = 11.5$ Hz, PhCH₂), 4.06, 3.85 (1H, 2 m, CHOH), 3.60–3.30 (1H, m, H-3), 3.31–3.05 (3H, m, CHNCH₂), 2.18–1.97 (2H, m, H-4), 1.97–1.77 (2H, m, H-5), 1.71–1.55 (1H, m, CHMe₂), 1.07–1.03, 1.01–0.96 (6H, 2m, 2CH₃); 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 C₁₅H₂₃NO₃: C, 67.90; H, 8.74; N, 5.28%.

(3S)-3-Benzoyloxy-2-(1-hydroxyhexyl)-N-hydroxypyrrolidine (12l). Following the general procedure, the SmI₂ mediated α -hydroxyalkylations of **10** with hexanal gave **12l** as a mixture of four inseparable diastereomers in 40:35:10:15 (ratio determined by ¹H 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, PhCH₂), 4.34 (1H, overlapped, 2d, $J = 11.5$ Hz, PhCH₂), 3.99, 3.85 (1H, 2 m, CHOH), 3.60–3.30 (1H, m, H-3), 3.20–2.95 (2H, m, CHNCH₂), 2.91–2.81 (1H, m, CHNCH₂), 1.95–1.65 (2H, m, H-4), 1.51–1.35 (3H, m, CH₂CH₂CH₂CH₂Me), 1.32–1.15 (5H, m, CH₂CH₂CH₂CH₂Me), 0.82 (3H, t, CH₃); 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 C₁₇H₂₇NO₃: 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 nitron **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, PhCH), 3.77 (6H, s, OCH₃), 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, PhCH), 3.80 (6H, s, OCH₃), 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).

(2S,3S)-3-Benzoyloxy-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 SmI₂ (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 Na₂S₂O₃ (4 mL) and NaHCO₃ (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 Na₂SO₄ 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); $[\alpha]_D^{20}$ –24.2 (*c* 1.16, CHCl₃); 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, PhCH₂), 3.94 (1H, d, $J = 5.7$ Hz, H-2), 3.91 (1H, d, $J = 11.3$ Hz, PhCH₂), 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),

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 C₁₅H₂₀O₅: C, 80.19; H, 7.01; N, 3.90%.

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