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Samarium diiodide-mediated reductive couplings of chiral nitrones with aldehydes/ketones and acyl chlorides

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ABSTRACT

The SmI_2-mediated and H_2O-promoted reductive cross-coupling reactions of the L-tartaric acid derived nitrone (3*S*,4*S*)-**8** with aldehydes/ketones, and the L-malic acid derived nitrone (*S*)-**6** with aliphatic acyl chlorides have been investigated, respectively. (2*R*,3*S*,4*S*)-1,3,4-Trihydroxyprolinol derivatives **9a**–**f** were obtained with high C-2/C-3 *trans*-selectivities, and 72:28–85:15 diastereoselectivities at the carbinol center from aromatic ketones/aldehydes, while low diastereoselectivities for aliphatic aldehydes. Conditions have been established for the syntheses of (2*R*,3*S*,4*S*)-3,4-dihydroxyprolinol derivatives such as **18**, by *N*–*O* bond cleavage of the corresponding *N*-hydroxyprolinol derivatives **9b**–**f**, or more conveniently by a one-pot reductive coupling of nitrone **8** and in situ *N*–*O* bond cleavage of the resultant coupling product. The 2-acyl-3-benzyloxy-1-hydroxypyrrolidines **10a**–**f** were formed in 48–82% yields, and in 74:26–78:22 diastereoselectivities. It was revealed that the amount of water required for the reaction is substrate-depending.

1. Introduction

Nitrones (**A**, Fig. 1) are well recognized as an important class of versatile synthetic intermediates, which have gained widespread application in organic synthesis.[1–3] However, as versatile 1,3-dipoles and electrophiles, they were largely limited to the application in 1,3-dipolar cycloadditions[1] and nucleophilic additions.[2] Until 2002, by an ingenious combination of nitrones with samarium diiodide, a versatile one-electron reducing agent originally developed by Kagan and co-workers,[4] Py–Vallée have reported a samarium diiodide-induced reductive cross-coupling of nitrones with aldehydes and ketones.[5] This seminal work opened a new page in the nitrone chemistry, namely, umpoled nitrones.[6] Indeed, in the almost meantime, the SmI_2-induced nitrones coupling with activated olefins have independently been reported by Skrydstrup[7] and Py–Vallée;[8a] both the application of this method to the total synthesis of natural products or bioactive compounds,[8] and the extension of this concept to the SmI_2-mediated coupling of alicyclic nitrones with chiral *N*-*tert*-butanesulfinyl imines[9] have been reported. However, to the best of our knowledge, investigation of these reactions with enantiomerically pure nitrones[10] has not been reported.

In view of the presence of β-hydroxyprolinol as the key structural feature in many aza-sugars[11] (e.g., **1**–**3**, Fig. 1), and the widespread use of prolinol-based organocatalysts[12] (e.g., **4a**,**b**) and chiral ligands (e.g., **5**),[13] very recently, we reported a versatile

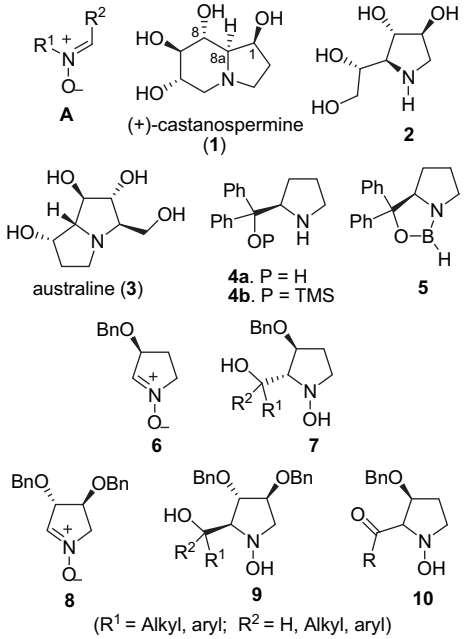

Figure 1.

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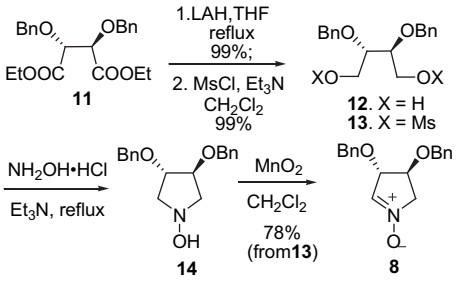
approach to β-hydroxyprolinol derivatives **7** via SmI_2-mediated couplings of aldehydes/ketones with nitrone **6**.[14] As a continuation of this work, we set to investigate the reductive cross-coupling reactions not only of the (3*S*,4*S*)-tartaric acid derived chiral nitrone **8** with aldehydes/ketones but also of chiral nitrone **6** with aliphatic acyl chlorides, and the results are reported herein.

2. Results and discussion

In order to investigate the reductive coupling of the tartaric acid derived chiral nitrone **8** with carbonyl compounds, the requisite nitrone (3*S*,4*S*)-**8**[15] was prepared from L-tartaric acid by the route shown in Scheme 1. Diethyl *O*,*O*-bisbenzyltartarate **11** was converted to the bis-mesylate **13** by successive lithium aluminum hydride reduction (LAH, THF, reflux) and bis-mesylation (MsCl, NEt_3, CH_2Cl_2, rt). The reaction of the resultant bis-mesylate **13** with hydroxylamine hydrochloride salt gave 3,4-bis(benzyloxy)pyrrolidin-1-ol **14**. Although the oxidation of 1-hydroxypyrrolidine **14** to nitrone (3*S*,4*S*)-**8** by highly toxic HgO has been repoted,[15] the use of a less toxic oxidant is highly desirable. Thus treatment of **14** with freshly prepared manganese dioxide[16] in dichloromethane gave the desired nitrone (3*S*,4*S*)-**8** in 78% overall yield from **13**. The nitrone (3*S*,4*S*)-**8** exhibited reasonable stability, which can be stored for several weeks at −20 °C under an inert atmosphere.

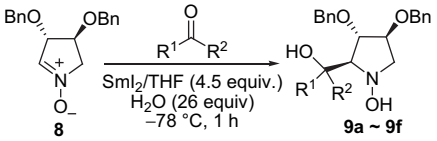


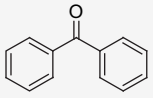
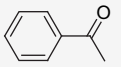
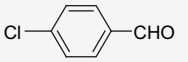
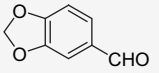
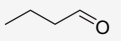
Scheme 1. Synthesis of the chiral nitrone **8**.

With the desired nitrone (3*S*,4*S*)-**8** in hand, we turned our attention to investigate its reductive coupling with carbonyl compounds. We first attempted the conditions established for nitrone **6**,[14a] namely, in the presence of 78 mol equiv of water, treatment of 3.0 mol equiv of benzophenone and nitrone **8** with 6.5 mol equiv of SmI_2 produced the desired product **9a** in only 41% yield. After extensive investigations, it was found that the yields of the reductive coupling of nitrone (3*S*,4*S*)-**8** with benzophenone can be significantly improved by justicious selection of the ratio of SmI_2–H_2O–carbonyl compounds–nitrone. In the presence of 26 mol equiv of water, treatment of 3.0 mol equiv of benzophenone and **8** with 4.5 mol equiv of SmI_2 produced the *N*-hydroxyprolinol derivative **9a** in 90% yield (Table 1). Under these optimized conditions, the coupling reaction of nitrone (3*S*,4*S*)-**8** with other carbonyl compounds were investigated, and the results are summarized in Table 1.

As can be seen from Table 1, the reductive hydroxyalkylation of (3*S*,4*S*)-**8** with symmetric ketone (benzophenone) gave only one diastereomer **9a** (Table 1, entry 1); and when unsymmetrical ketones or aromatic aldehydes were used, only two diastereomers were produced in each case (Table 1, entries 2–5); the coupling with *n*-butyraldehyde produced a total of four diastereomers (Table 1, entry 6) with low diastereoselectivities at the two newly formed steric centers. These results indicate that the reductive cross-coupling reactions of nitrone **8** with ketones and aromatic aldehydes were 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. The *cis*/*trans*

Table 1
The reductive cross-coupling of nitrone **8** with carbonyl compounds



Entry	Carbonyl compounds	Product (% yield)[a]	dr
1		**9a** (90)	—
2		**9b** (50)	84:16[b]
3		**9c** (75)	85:15[b]
4		**9d** (42)	72:28[b]
5		**9e** (92)	83:17[b]
6		**9f** (90)	43:27:17:13[c]

[a] Isolated yields based on nitrone **8**.
[b] Ratio determined by ^1H NMR.
[c] Ratio determined by HPLC.

stereochemistry of the products was determined as 2,3-*trans* on the basis of 2D NOESY experiments undertaken on the major diastereomer of **9e** (Fig. 2). The observed vicinal coupling constant of this compound ($J_{2,3}$=4.5 Hz) is also consistent with the pyrrolidine derivatives that possess a 2,3-*trans* stereochemical relationship (e.g., **15**–**17** in Fig. 3).[17] As can be seen from Figure 2, the vicinal coupling constants ($J_{2,3}$) of the 2,3-*trans* pyrrolidine derivatives **15**–**17** range from 3.6 Hz to 4.6 Hz. The 2,3-relative stereochemistries of the major diastereomers of **9b**–**d** were thus deduced as *trans* according to their $J_{2,3}$ (Table 2). The stereochemistry of the exocyclic chiral center was no determined. The same diastereoselectivity was assumed to be retained for benzophenone. For aliphatic aldehydes (cf. entry 6, Table 1) both the two new stereocenters were formed with low stereoselectivities.

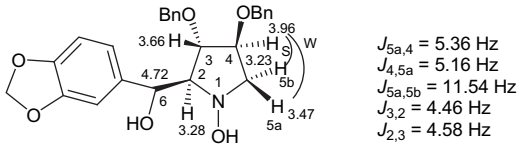


Figure 2. NOE correlations on the major diastereomer of **9e**.

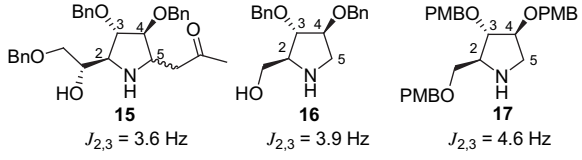
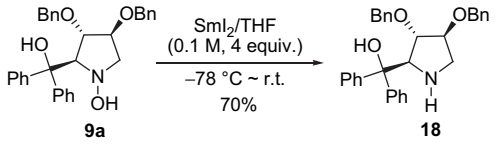


Figure 3. The vicinal coupling constants ($J_{2,3}$) of some known 2,3-*trans*-substituted pyrrolidines.

Table 2
The ^{1}H NMR spectroscopic data (in part) of the major diastereomers of *N*-hydroxypyrolinol derivatives **9a–e**

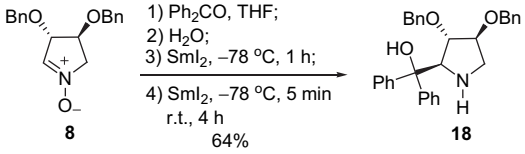
Compound	$\delta_{H\text{-}2}$, multiplicity	$\delta_{H\text{-}3}$, multiplicity	$\delta_{H\text{-}6}$, multiplicity	$J_{2,3}$	$J_{2,6}$
9a	4.25, d	3.93–3.89, m	—	2.7	—
9b	3.42, d	4.18, d	—	3.7	—
9c	3.29, dd	3.70, d	4.77, d	4.6	7.3
9d	3.32, dd	3.66, d	4.75, d	4.5	8.3
9e	3.28, dd	3.66, d	4.72, d	4.5	8.3

To demonstrate the possibility for the use of *N*-hydroxypyrrolidines **9a–f** as ready precursors of the corresponding proline derivatives, a SmI_2-mediated cleavage of the *N–O* bond[8c,14a,18] of **9a** was undertaken (Scheme 2). In the event, the *N*-hydroxypyrrolidine **9a** was treated with 4.0 equiv of SmI_2 in THF at −78 °C for 1 h. After warming up and stirring at rt overnight, the desired pyrrolidine derivative **18** was obtained in 70% yield.



Scheme 2. Cleavage of the *N–O* bond of **9a**.

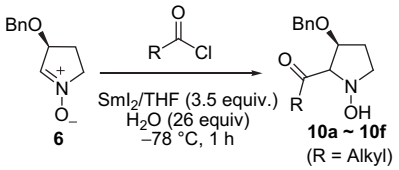
A one-pot reductive coupling-in situ *N–O* bond cleavage[8c] was also investigated. Treatment of a water-containing THF solution of 1.0 equiv of nitrone **8** and 3.0 equiv of benzophenone with 4.5 equiv of SmI_2 at −78 °C for 1 h, followed by addition of another 6.0 equiv of SmI_2 and reacted at rt for 4 h, produced directly pyrrolidine derivative **18** in 64% yield (Scheme 3).

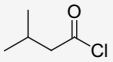
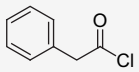
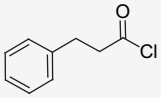


Scheme 3. One-pot reductive coupling-in situ *N–O* bond cleavage of nitrone **8**.

We next investigated the reductive cross-coupling reaction of the chiral nitrone **6** with aliphatic acyl chlorides. To perform the reductive coupling of the enantiopure nitrone **6** with acyl chlorides (Table 3), the *O*-acylation of nitrone **6** with acyl chlorides should be avoided. Keeping this in mind, a protocol was established, which consisted in successive addition of 3.0 equiv of acyl chlorides and a 0.1 M THF solution of SmI_2 (3.5 equiv) to a pre-cooled H_2O (26.0 equiv)—containing THF solution (−78 °C) of nitrone **6** (1.0 equiv). Under these conditions, the reductive coupling of nitrone **6** with acetyl chloride gave **10a** (mono-spot on TLC) in 80% yield, which was a mixture of two isomers as shown by ^{1}H NMR analysis. To determine the nature of the two isomers (diastereomeric or tautomeric), the isolated product **10a** was subjected to variant temperature ^{1}H NMR analysis. The fact that the ^{1}H NMR spectra recorded, respectively, at 25 °C and at 85 °C showed no notable difference allowed concluding that the product contained two diastereomers. Namely, the reductive coupling of nitrone **6** with acetyl chloride gave two diastereomers of **10a** in a ratio of 78:22. The reductive coupling reactions of nitrone **6** with other acyl chlorides were studied, and the results are summarized in Table 3. As can be seen from Table 3, while all acyl chlorides gave

Table 3
The reductive coupling of nitrone **6** with aliphatic acyl chlorides

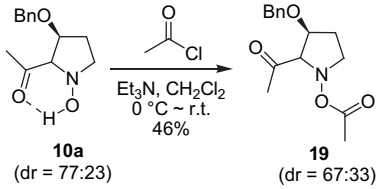


Entry	Acyl chlorides	Product (% yield)[a]	d.r.[b]
1		**10a** (80)	78:22
2		**10b** (73)	77:23
3		**10c** (79)	75:25
4		**10d** (56)	74:26
5		**10e** (50)	75:25
6		**10f** (82)	78:22
7		**10a** (48)	77:23

[a] Isolated yields, based on nitrone **6**.
[b] Ratio determined by ^{1}H NMR.

similar diastereoselectivities, lower yields were obtained with more hindered acyl chlorides such as pivalyl chloride and phenylacetyl chloride. Noteworthy is that the coupling with chloroacetyl chloride yielded the concomitantly dechlorinated product **10a** (Table 3, entry 7).

To further confirm the structure of the products, **10a** was acetylated to give the *O*-acetyl product **19** in 46% yield as a mixture of two diastereomers in 67:33 ratio (Scheme 4). This result confirmed that the coupling products are indeed the desired *C*-acyl products **10** instead of *O*-acyl products. The IR spectra of compounds **10a** and **19** showed carbonyl absorptions at ν 1629 cm^{-1} and 1671 cm^{-1}, respectively, which indicated that an intramolecular hydrogen bond exists in **10a** (Scheme 4). It is to be noted that a partial epimerization occurred during the *O*-acetylation as indicated by the change of diastereomeric ratio from 77:23 to 67:33.



Scheme 4.

3. Conclusions

The SmI_2-mediated reductive coupling of enantiopure pyrrolidine nitrone (3*S*,4*S*)-**8** with aldehydes/ketones gave (2*R*,3*S*,4*S*)-

1,3,4-trihydroxyprolinol derivatives **9a–f** in 42–92% yields with excellent 2,3-*trans*-diastereoselectivity for ketones and aromatic aldehydes. Through the syntheses of prolinol derivative **18**, we demonstrated that (2*R*,3*S*,4*S*)-3,4-dihydroxyprolinol derivatives could be obtained by *N–O* bond cleavage of the corresponding *N*-hydroxyprolinol derivatives **9a–f**, or more conveniently by a one-pot reductive coupling of nitrone **8**-in situ *N–O* bond cleavage of the resultant coupling product. The SmI_2-mediated chemoselective reductive cross-coupling reactions of chiral nitrone **6** with aliphatic acyl chlorides gave 2-acyl-3-benzyloxy-1-hydroxypyrrolidines **10a–f** in 48–82% yields with diastereoselectivities ranged from 74:26 to 78:22. To the best of our knowledge, this is the first reductive coupling of nitrones with acyl chlorides. Conditions have been defined to achieve the required chemoselectivity. The coupling products provide the possibility to construct aza-quaternary chiral center, which is found in many natural products. The methods may also found applications in the synthesis of organocatalysts and aza-sugars.

4. Experimental

4.1. 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 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. THF was 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).

4.2. General procedure for the preparation of chiral cyclic nitrones

*4.2.1. (2S,3S)-2,3-Bis(benzyloxy)butane-1,4-diol (**12**).* A THF solution (5 mL) of the known diester[15] **11** (1.86 g, 4.81 mmol) was added dropwise to a suspension of $LiAlH_4$ (403 mg, 10.6 mmol) in THF (10 mL) under a N_2 atmosphere. The white suspension was vigorously stirred and refluxed for 4.5 h. The mixture was cooled to 0 °C, and quenched by successive dropwise addition of H_2O (0.4 mL), 10%NaOH solution (0.8 mL), and H_2O (1.2 mL). After diluting with ethanol (60 mL), the mixture was refluxed for 3 h. The suspension was filtered through Celite and washed with ethanol for several times. The solvent was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent:EtOAc–PE, 1:1) to give diol **12** (1.438 g, 99%) as a white solid. R_f 0.24 (EtOAc–PE=1:1); mp 51–52 °C (EtOAc–PE) {lit.[19a] mp 50–52 °C}; $[\alpha]_D^{20}$ +13.1 (*c* 4.89, ethanol) {lit.[19b] $[\alpha]_D^{20}$ +13.2 (*c* 4.91, ethanol)}; IR (film): 3440, 2917, 1584, 1462, 1408, 1084 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 10H, Ph-H), 4.66 (d, 2H, *J*=11.9 Hz, PhCH_2), 4.64 (d, 2H, *J*=11.9 Hz, PhCH_2), 3.83 (br d, 2H, *J*=9.9 Hz, –CH_2OH), 3.72 (br d, 2H, *J*=9.9 Hz, –CH_2OH), 3.70–3.67 (m, overlapped, 2H, –CHOBn), 2.38–2.27 (br, 2H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9 (2C), 128.6 (4C), 128.0 (2C), 127.9 (4C), 78.9 (2C), 72.6 (2C), 60.9 (2C); MS (ESI, *m*/*z*): 325 (M+Na$^+$, 100), 341 (M+K$^+$, 26). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.54; H, 7.25.

*4.2.2. (2S,3S)-2,3-Bis(benzyloxy)butane-1,4-bis(methanesulfonyloxy)butane (**13**).* To a cooled (0 °C) CH_2Cl_2 (6 mL) solution of compound **12** (1.27 g, 4.2 mmol) and TEA (3.5 mL, 25.1 mmol) was added dropwise methanesulfonyl chloride (1.4 mL, 18.0 mmol) under a N_2 atmosphere. The mixture was stirred at rt for 2 h, then cooled to 0 °C and treated with a saturated aqueous NH_4Cl solution (10 mL). The two phases were separated and the aqueous phase extracted with CH_2Cl_2 (80 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent:EtOAc–PE, 1:2) to give compound **13** (1.90 g, 99%) as a colorless oil. R_f 0.40 (EtOAc–PE=1:1); $[\alpha]_D^{20}$ +16.6 (*c* 0.53, $CHCl_3$) {lit.[20] $[\alpha]_D^{20}$ +17.9 (*c* 0.5, $CHCl_3$)}; IR (film): 3444, 2934, 2870, 1584, 1454, 1408, 1353, 1173, 1084 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 10H, Ph-H), 4.69 (d, 2H, *J*=11.7 Hz, PhCH_2), 4.58 (d, 2H, *J*=11.7 Hz, PhCH_2), 4.41 (dd, 2H, *J*=4.6, 11.0 Hz, –CH_2OMs), 4.29 (dd, 2H, *J*=4.6, 11.0 Hz, –CH_2OMs), 3.88–3.81 (m, 2H, *J*=4.6, –CHOBn), 2.94 (s, 6H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1 (2C), 128.6 (4C), 128.2 (4C), 128.2 (2C), 75.8 (2C), 73.4 (2C), 68.0 (2C), 37.5 (2C); MS (ESI, *m*/*z*): 481 (M+Na$^+$, 100), 497 (M+K$^+$, 49). Anal. Calcd for $C_{20}H_{26}O_8S_2$: C, 52.39; H, 5.72. Found: C, 52.51; H, 5.83.

*4.2.3. (3S,4S)-3,4-Bis(benzyloxy)-1-pyrroline-N-oxide (**8**).* A suspension of compound **13** (1.79 g, 3.9 mmol) and hydroxylamine hydrochloride salt (1.20 g, 17.2 mmol) in Et_3N (19.5 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 **14**, which was used in the next step without purification.

To a CH_2Cl_2 (12.6 mL) solution of the crude *N*-hydroxypyrrolidine **14** was added portionwise active manganese dioxide (407 mg, 4.7 mmol) at 0 °C and under a N_2 atmosphere. The suspension was stirred at room temperature overnight. The resultant mixture was washed with EtOAc, and the filtrate concentrated under reduced pressure. Chromatography of the residue on silica gel (eluent:EtOAc–PE, 1:1) gave compound **8** (904 mg, 78%) as a colorless oil. R_f 0.12 (EtOAc–PE=1:2); $[\alpha]_D^{20}$ +78.8 (*c* 1.39, $CHCl_3$) {lit.[15] $[\alpha]_D^{20}$ +76.7 (*c* 0.88, $CHCl_3$)}; IR (film): 3062, 3030, 2866, 1579, 1454, 1435, 1356, 1285, 1090, 1068, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (m, 10H, Ph-H), 6.89–6.86 (m, 1H, H-2), 4.68–4.65 (m, 1H, H-3), 4.58 (d, 1H, *J*=11.7 Hz, PhCH_2), 4.55 (d, 1H, *J*=11.7 Hz, PhCH_2), 4.54 (s, 2H, PhCH_2), 4.28 (dt, 1H, *J*=1.6, 6.5 Hz, H-4), 4.26–4.22 (m, 1H, H-5), 3.90–3.81 (m, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 136.7, 132.2, 128.7 (2C), 128.6 (2C), 128.3, 128.3, 128.0 (2C), 127.9 (2C), 83.7, 78.4, 72.0, 71.9, 66.9; MS (ESI, *m*/*z*): 320 (M+Na$^+$, 100), 298 (M+H$^+$, 68). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.32; H, 6.16; N, 4.93.

4.3. General procedure for the SmI_2-mediated α-hydroxyalkylations of nitrone 8

To a slurry of Sm powder (flame dried under Ar atmosphere, 826 mg, 5.49 mol) in THF (50 mL) was added I_2 (1.270 g, 5.00 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.

To a stirring and carefully deoxygenated solution of nitrone **8** (143 mg, 0.48 mmol) and a carbonyl compound (1.44 mmol) in THF (10 mL) was added H_2O (225 μL, 12.5 mmol) under an Ar atmosphere. The mixture was cooled to −78 °C, and to which a freshly prepared THF solution of SmI_2 (0.1 mol L^{-1}, 22 mL, 2.2 mmol) was

added. After the reaction was judged to be completed by TLC monitoring, saturated aqueous solutions of $Na_2S_2O_3$ (4 mL) and $NaHCO_3$ (15 mL) were added successively. The yellow mixture was extracted with EtOAc (3×30 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent:EtOAc–PE) to give the coupling product **9**.

*4.3.1. (2R,3S,4S)-3,4-Bis(benzyloxy)-2-(hydroxydiphenylmethyl)-N-hydroxypyrrolidine (**9a**).* Following the general procedure, the SmI_2-mediated α-hydroxyalkylations of **8** (134 mg, 0.451 mmol) with benzophenone (246 mg, 1.35 mmol) gave compound **9a** as a single diastereomer (eluent:EtOAc–PE=1:10; 196 mg) in 90% yield. **9a**: colorless wax. R_f 0.60 (EtOAc–PE=1:4); $[\alpha]_D^{20}$ −30.3 (*c* 0.98, $CHCl_3$); IR (film): 3437, 2922, 2853, 1585, 1402, 1122, 1084 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74–7.68 (m, 2H, Ph-H), 7.67–7.61 (m, 2H, Ph-H), 7.36–7.13 (m, 16H, Ph-H), 4.53 (d, 1H, *J*=11.8 Hz, PhC*H*$_2$), 4.38 (d, 1H, *J*=11.8 Hz, PhC*H*$_2$), 4.25 (br d, 1H, *J*=2.7 Hz, H-2), 4.16 (br s, 1H, OH, D_2O exchangeable), 4.11 (d, 1H, *J*=11.0 Hz, PhC*H*$_2$), 4.00 (d, 1H, *J*=11.0 Hz, PhC*H*$_2$), 3.96 (br s, 1H, OH, D_2O exchangeable), 3.93–3.89 (m, 1H, H-3), 3.81 (d, 1H, *J*=4.2 Hz, H-4), 3.45 (d, 1H, *J*=10.6 Hz, H-5), 3.26 (dd, 1H, *J*=4.2, 10.6 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 145.0, 137.6, 137.4, 128.5 (2C), 128.4 (2C), 128.1 (2C), 128.0 (2C), 127.9 (2C), 127.9, 127.9 (2C), 127.8, 126.8, 126.6, 126.2 (2C), 126.1 (2C), 83.4, 81.0, 77.9, 72.1, 70.8, 60.9; MS (ESI, *m*/*z*): 482 ($M+H^+$, 100), 504 ($M+Na^+$, 81). Anal. Calcd for $C_{31}H_{31}NO_4$: C, 77.31; H, 6.49; N, 2.91. Found: C, 77.12; H, 6.47; N, 2.89.

*4.3.2. (2R,3S,4S)-3,4-Bis(benzyloxy)-2-(1-hydroxy-1-phenylethyl)-N-hydroxypyrrolidine (**9b**).* Following the general procedure, the SmI_2-mediated α-hydroxyalkylations of **8** (100 mg, 0.336 mmol) with acetophenone (0.12 mL, 1.01 mmol) gave compound **9b** as a mixture of two diastereomers in 84:16 ratio (determined by ^1H NMR, δ_H 3.32, 3.13) (eluent:EtOAc–PE=1:4; 68 mg, combined yield: 50%). A part of the major diastereomer was isolated in pure form from column chromatographic separation. Major diastereomer: R_f 0.39 (EtOAc–PE=1:3); colorless wax; $[\alpha]_D^{20}$ +2.7 (*c* 0.48, $CHCl_3$); IR (film): 3342, 3030, 2922, 2851, 1600, 1495, 1453, 1207, 1096, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.48 (m, 2H, Ph-H), 7.39–7.28 (m, 12H, Ph-H), 7.24–7.20 (m, 1H, Ph-H), 4.58 (d, 1H, *J*=11.8 Hz, PhC*H*$_2$), 4.52 (2d, overlapped, 2H, *J*=11.8 Hz, *J*=11.4 Hz, PhC*H*$_2$), 4.48 (d, 1H, *J*=11.4 Hz, PhC*H*$_2$), 4.18 (d, 1H, *J*=3.7 Hz, H-3), 3.90 (d, 1H, *J*=4.7 Hz, H-4), 3.42 (d, 1H, *J*=3.7 Hz, H-2), 3.41 (d, 1H, *J*=10.8 Hz, H-5), 3.13 (dd, 1H, *J*=4.7, 10.8 Hz, H-5), 1.54 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 137.6, 137.5, 128.5 (2C), 128.5 (2C), 128.2 (2C), 128.0 (2C), 127.9 (2C), 127.9 (2C), 127.8, 126.7, 125.4, 82.9, 82.1, 78.2, 73.7, 71.7, 71.0, 60.8, 26.8; MS (ESI, *m*/*z*): 420 ($M+H^+$, 100), 442 ($M+Na^+$, 77). Anal. Calcd for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.51; H, 7.30; N, 3.01.

*4.3.3. (2S,3S,4S)-3,4-Bis(benzyloxy)-2-[(4-chlorophenyl)hydroxymethyl]-N-hydroxypyrrolidine (**9c**).* Following the general procedure, the SmI_2-mediated α-hydroxyalkylations of **8** (100 mg, 0.34 mmol) with 4-chlorobenzaldehyde (142 mg, 1.01 mmol) gave compound **9c** as a mixture of two diastereomers in 85:15 ratio (determined by ^1H NMR, δ_H 3.29, 3.16) (eluent:EtOAc–PE=1:4; 111 mg, combined yield: 75%). A part of the major diastereomer was isolated in pure form from column chromatographic separation. Major diastereomer: R_f 0.31 (EtOAc–PE=1:2); colorless wax; $[\alpha]_D^{20}$ +4.2 (*c* 1.19, $CHCl_3$); IR (film): 3432, 3033, 2898, 1596, 1490, 1454, 1410, 1145, 1088, 1028, 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.22 (m, 12H, Ph-H), 6.97–6.90 (m, 2H, Ph-H), 4.77 (d, 1H, *J*=7.3 Hz, ArC*H*), 4.52 (d, 1H, *J*=11.9 Hz, PhC*H*$_2$), 4.44 (d, 1H, *J*=11.9 Hz, PhC*H*$_2$), 4.18 (d, 1H, *J*=11.5 Hz, PhC*H*$_2$), 4.09 (d, 1H, *J*=11.5 Hz, PhC*H*$_2$), 3.98 (d, 1H, *J*=5.4 Hz, H-4), 3.70 (d, 1H, *J*=4.6 Hz, H-3), 3.46 (d, 1H, *J*=11.4 Hz, H-5), 3.29 (dd, 1H, *J*=4.6, 7.3 Hz, H-2), 3.23 (dd, 1H, *J*=5.4, 11.4 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 137.4, 137.2, 133.6, 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.3 (2C) 128.0, 127.9 (2C), 127.8, 127.7 (2C), 83.7, 80.3, 78.7, 74.5, 71.6, 71.5, 61.5; MS (ESI, *m*/*z*): 462 ($M+Na^+$, 100), 440 ($M+H^+$, 51). Anal. Calcd for $C_{25}H_{26}ClNO_4$: C, 64.77; H, 6.04; N, 4.20. Found: C, 64.91; H, 6.42; N, 4.45.

*4.3.4. (2S,3S,4S)-3,4-Bis(benzyloxy)-2-[hydroxy(4-methoxyphenyl)methyl]-N-hydroxypyrrolidine (**9d**).* Following the general procedure, the SmI_2-mediated α-hydroxyalkylations of **8** (160 mg, 0.54 mmol) with 4-methoxybenzaldehyde (0.2 mL, 1.61 mmol) gave compound **9d** as a mixture of two diastereomers in 72:28 ratio (determined by ^1H NMR, δ_H 3.27, 3.14) (eluent:EtOAc–PE=1:3; 98 mg, combined yield: 42%). A part of the major diastereomer was isolated in pure form from column chromatographic separation. Major diastereomer: R_f 0.10 (EtOAc–PE=1:3); colorless wax; $[\alpha]_D^{20}$ +12.6 (*c* 2.29, $CHCl_3$); IR (film): 3404, 3030, 2921, 1612, 1513, 1454, 1394, 1247, 1173, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.18 (m, 10H, Ph-H), 6.91–6.84 (m, 4H, Ph-H), 4.75 (d, *J*=8.3 Hz, 1H, ArC*H*), 4.50 (d, 1H, *J*=12.0 Hz, PhC*H*$_2$), 4.42 (d, 1H, *J*=12.0 Hz, PhC*H*$_2$), 4.05 (d, 1H, *J*=11.6 Hz, PhC*H*$_2$), 4.00 (d, 1H, *J*=11.6 Hz, PhC*H*$_2$), 3.98–3.95 (m, 1H, *J*=5.4 Hz, H-4), 3.79 (s, 3H, OCH_3), 3.66 (d, 1H, *J*=4.5 Hz, H-3), 3.46 (d, 1H, *J*=11.5 Hz, H-5), 3.32 (dd, 1H, *J*=4.5, 8.3 Hz, H-2), 3.24 (dd, 1H, *J*=5.4, 11.5 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 137.6, 137.4, 133.3, 128.5 (2C), 128.3 (2C), 128.2 (2C), 127.8 (2C), 127.6 (2C), 127.6, 113.8 (2C), 113.6, 80.7, 79.0, 77.7, 75.2, 71.5, 71.3, 61.2, 55.2; MS (ESI, *m*/*z*): 436 ($M+H^+$, 100), 458 ($M+Na^+$, 18); HRMS (ESI) calcd for $[C_{26}H_{29}NO_5+H]^+$: 436.2124; found: 436.2127.

*4.3.5. (2S,3S,4S)-2-{(Benzo[d][1,3]dioxol-5-yl)hydroxymethyl}-3,4-bis(benzyloxy)-N-hydroxypyrrolidine (**9e**).* Following the general procedure, the SmI_2-mediated α-hydroxyalkylations of **8** (100 mg, 0.34 mmol) with piperonal (151 mg, 1.01 mmol) gave compound **9e** as a mixture of two diastereomers in 83:17 ratio (determined by ^1H NMR, δ_H 3.26, 3.15) (eluent:EtOAc–PE=1:3; 139 mg, combined yield: 92%). A part of the major diastereomer was isolated in pure form from column chromatographic separation. Major diastereomer: R_f 0.15 (EtOAc–PE=1:3); colorless wax; $[\alpha]_D^{20}$ +7.5 (*c* 0.47, $CHCl_3$); IR (film): 3373, 3030, 2922, 1605, 1503, 1488, 1443, 1246, 1095, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.22 (m, 8H, Ph-H), 6.99–6.93 (m, 2H, Ph-H), 6.92–6.88 (m, 1H, Ph-H), 6.83–6.78 (m, 1H, Ph-H), 6.74–6.70 (m, 1H, Ph-H), 5.92–5.87 (m, 2H, OC*H*$_2$O), 4.72 (d, 1H, *J*=8.3 Hz, ArC*H*), 4.51 (d, 1H, *J*=12.0 Hz, PhC*H*$_2$), 4.42 (d, 1H, *J*=12.0 Hz, PhC*H*$_2$), 4.11 (d, 1H, *J*=11.6 Hz, PhC*H*$_2$), 4.02 (d, 1H, *J*=11.6 Hz, PhC*H*$_2$), 3.96 (d, 1H, *J*=5.2 Hz, H-4), 3.66 (d, 1H, *J*=4.5 Hz, H-3), 3.47 (d, 1H, *J*=11.5 Hz, H-5), 3.28 (dd, 1H, *J*=4.5, 8.3 Hz, H-2), 3.23 (dd, 1H, *J*=5.2, 11.5 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 147.2, 137.5, 137.4, 135.2, 128.7, 128.5 (2C), 128.2 (2C), 127.8 (2C), 127.6, 127.5 (2C), 120.5, 108.0, 107.6, 100.9, 84.0, 80.6, 78.8, 75.5, 71.5, 71.3, 61.3; MS (ESI, *m*/*z*): 472 ($M+Na^+$, 100), 450 ($M+H^+$, 34). Anal. Calcd for $C_{26}H_{27}NO_6$: C, 69.47; H, 6.05; N, 3.12. Found: C, 69.80; H, 6.03; N, 2.94.

*4.3.6. (3S,4S)-3,4-Bis(benzyloxy)-2-(1-hydroxybutyl)-N-hydroxypyrrolidine (**9f**).* Following the general procedure, the SmI_2-mediated α-hydroxyalkylations of **8** (100 mg, 0.336 mmol) with butyraldehyde (0.127 mL, 1.44 mmol) gave compound **9f** as a mixture of four inseparable diastereomers in 43:27:17:13 ratio (determined by HPLC) (eluent:EtOAc–PE=1:3; 112 mg, combined yield: 90%). R_f 0.20 (EtOAc–PE=1:3); colorless wax; IR (film): 3341, 3030, 2957, 2925, 2870, 1587, 1496, 1454, 1360, 1094, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.22 (m, 10H, Ph-H), 4.64–4.39 (m, 4H, PhC*H*$_2$), 4.05–4.00, 4.00–3.96 (2 m, 1H, CH_2CHOH), 3.95–3.90,

3.74–3.67 (2 m, 1H, H-3), 3.88, 3.84 (2d, 1H, J=5.1, 5.0 Hz, H-4), 3.46 (br t, 1H, J=10.5 Hz, H-5), 3.23, 3.11 (2dd, 1H, J=5.0, 10.5 Hz; J=5.1, 10.5 Hz, H-5), 2.99, 2.83 (br t, d, 1H, J=5.3, 5.5 Hz, H-2), 1.61–1.33 (br m, 4H, $CH_3CH_2CH_2$), 0.94–0.83 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 137.9, 128.6 (2C), 128.4 (2C), 128.4, 128.1, 127.8 (2C), 127.8, 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; MS (ESI, m/z): 372 ($M+H^+$, 100), 394 ($M+Na^+$, 59). Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.11; H, 7.65; N, 3.45.

4.4. (2*R*,3*S*,4*S*)-3,4-Bis(benzyloxy)-2-(diphenylhydroxymethyl) pyrrolidine (18)

A stirring and carefully deoxygenated solution of the coupling product **9a** (131 mg, 0.27 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}, 10.9 mL, 1.09 mmol) was then added. After stirring at −78 °C for 1 h, the temperature was allowed to warm-up and the mixture was stirred overnight. The reaction was quenched by introduction of air, which was followed by successive addition of saturated aqueous solutions of $Na_2S_2O_3$ (4 mL) and $NaHCO_3$ (20 mL). The yellow mixture was extracted with EtOAc (3×20 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent:EtOAc–PE, 1:3) to yield pyrrolidine **18** (44 mg, yield: 70%) as a colorless wax. R_f 0.13 (EtOAc–PE: 1:5); $[\alpha]_D^{20}$ +42.5 (c 1.9, $CHCl_3$); IR (film): 3361, 3061, 3029, 2918, 2850, 1597, 1494, 1385, 1363, 1092, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.63 (m, 2H, Ph-H), 7.62–7.56 (m, 2H, Ph-H), 7.37–7.34 (m, 4H, Ph-H), 7.31–7.13 (m, 10H, Ph-H), 7.05–6.98 (m, 2H, Ph-H), 4.52 (d, 1H, J=11.8 Hz, PhCH_2), 4.46 (d, 1H, J=11.8 Hz, PhCH_2), 4.29 (d, 1H, J=3.2 Hz, H-2), 4.04 (d, 1H, J=10.9 Hz, PhCH_2), 3.92–3.90 (m, 1H, H-3), 3.89 (d, 1H, J=10.9 Hz, PhCH_2, overlapped with H-3), 3.88 (d, 1H, J=0.5, 3.7 Hz, H-4), 3.21 (dd, 1H, J=0.5, 10.8 Hz, H-5), 3.15 (dd, 1H, J=3.7, 10.8 Hz, H-5); ^{13}C NMR (100 M Hz, $CDCl_3$) δ 147.0, 145.2, 137.8, 137.7, 128.5 (2C), 128.3 (2C), 128.3 (2C), 128.1 (2C), 127.9 (2C), 127.8, 127.7, 127.7, 126.6, 126.5, 126.0, 126.0 (2C), 83.9, 81.7, 77.3, 72.0, 71.6, 70.6, 50.5; MS (ESI, m/z): 466 ($M+H^+$, 100), 488 ($M+Na^+$, 48); HRMS (ESI) calcd for $[C_{31}H_{31}NO_3+H]^+$: 466.2382; found: 466.2393.

4.5. Procedure for the SmI_2-mediated one-pot reductive coupling-in situ *N–O* bond cleavage of nitrone 8

To a THF solution (10 mL) of nitrone **8** (124 mg, 0.42 mmol) and benzophenone (228 mg, 1.25 mmol) was added H_2O (194 μL, 10.9 mmol) under an Ar atmosphere. The mixture was cooled to −78 °C, and to which a freshly prepared THF solution of SmI_2 (0.1 mol·L^{-1}, 19 mL, 1.9 mmol) was added. After stirring at −78 °C for 1 h, another 0.1 M THF solution of SmI_2 (25 mL, 2.5 mmol) was added; 5 min later the reaction was allowed to warm-up, and stirred at rt for 4 h. The reaction was quenched by introduction of air, which was followed by successive addition of saturated aqueous solutions of $Na_2S_2O_3$ (4 mL) and $NaHCO_3$ (20 mL). The yellow mixture was extracted with EtOAc (3×20 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent:EtOAc–PE, 1:3) to yield pyrrolidine **18** (124 mg, yield: 64%) as a colorless wax.

4.6. General procedure for the SmI_2-mediated C-acylation of nitrone 6

To a stirring and carefully deoxygenated solution of nitrone **6** (95 mg, 0.50 mmol) in THF (10 mL) was added H_2O (0.23 mL, 13 mmol) under an Ar atmosphere. The mixture was cooled to −78 °C, and to which an acyl chloride (1.50 mmol) and a freshly prepared THF solution of SmI_2 (0.1 mol L^{-1}, 17.5 mL, 1.75 mmol) were added successively. After the reaction was judged to be completed by TLC monitoring, 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 anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to yield the coupling product **10**.

*4.6.1. 1-((3S)-3-(Benzyloxy)-1-hydroxypyrrolidin-2-yl)ethanone (**10a**).* Following the general procedure, the SmI_2-mediated C-acylation of **6** (103 mg, 0.54 mmol) with acetyl chloride (0.12 mL, 1.62 mmol) gave compound **10a** as a mixture of two inseparable diastereomers in 78:22 ratio (determined by ^{1}H NMR, δ_H 5.62, 5.26) (eluent:EtOAc–PE=1:1; 101 mg, combined yield: 80%). Colorless wax. R_f 0.20 (EtOAc–PE=2:1); IR (film): 3342, 2961, 1629, 1453, 1354, 1261, 1084, 1066 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, two isomers) δ 7.39–7.27 (m, 5H, Ph-H), 5.66–5.58 (m, 1H, H-2), 5.29–5.23 (m, 1H, H-2, for minor isomer), 4.63 (d, 1H, J=11.9 Hz, PhCH_2), 4.62 (d, 1H, J=11.9 Hz, PhCH_2, for minor isomer), 4.55 (d, 1H, J=11.9 Hz, PhCH_2, for minor isomer), 4.54 (d, 1H, J=11.9 Hz, PhCH_2), 4.18–4.15 (m, 1H, OH), 4.00 (m, 1H, H-3, for minor isomer), 3.98 (m, 1H, H-3), 3.67–3.54 (m, 2H, H-5), 2.33–2.22 (m, 1H, H-4), 2.17 (s, 3H, CH_3, for minor isomer), 2.07 (s, 3H, CH_3), 2.11–2.02 (m, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 137.6, 128.6, 128.5, 128.4 (2C), 127.8, 127.7 (2C), 127.5, 84.0, 81.7, 71.3, 71.1, 45.5, 43.7, 29.1, 26.6, 22.3; MS (ESI, m/z): 258 ($M+Na^+$, 100), 274 ($M+H^+$, 26); HRMS (ESI) calcd for $[C_{13}H_{17}NO_3+Na]^+$: 258.1106; found: 258.1107.

*4.6.2. 1-((3S)-3-(Benzyloxy)-1-hydroxypyrrolidin-2-yl)propan-1-one (**10b**).* Following the general procedure, the SmI_2-mediated C-acylation of **6** (156 mg, 0.82 mmol) with propionyl chloride (0.21 mL, 2.45 mmol) gave compound **10b** as a mixture of two inseparable diastereomers in 77:23 ratio (determined by ^{1}H NMR, δ_H 5.64, 5.30) (eluent:EtOAc–PE=1:2; 148 mg, combined yield: 73%). Colorless wax. R_f 0.42 (EtOAc–PE=1:1); IR (film): 3345, 3331, 2940, 1628, 1496, 1437, 1337, 1308, 1205, 1068, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, two isomers) δ 7.41–7.27 (m, 5H, Ph-H), 5.68–5.59 (m, 1H, H-2), 5.32–5.27 (m, 1H, H-2, for minor isomer), 4.63 (d, 1H, J=11.8 Hz, PhCH_2), 4.54 (d, 1H, J=11.8 Hz, PhCH_2), 4.34 (m, 1H, OH), 4.10 (m, 1H, OH, for minor isomer), 4.00 (m, 1H, H-3, for minor isomer), 3.97 (m, 1H, H-3), 3.66–3.52 (m, 2H, H-5), 2.35–2.21 (m, 2H, H-4), 2.18–1.98 (m, 2H, CH_2CH_3), 1.19–1.10 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 137.7, 128.4 (2C), 127.8 (2C), 127.7 (2C), 127.5, 84.4, 81.6, 71.3, 44.7, 29.2, 27.6, 26.5; MS (ESI, m/z): 272 ($M+Na^+$, 100), 288 ($M+K^+$, 12); HRMS (ESI) calcd for $[C_{14}H_{19}NO_3+Na]^+$: 272.1263; found: 272.1271.

*4.6.3. 1-((3S)-3-(Benzyloxy)-1-hydroxypyrrolidin-2-yl)-3-methylbutan-1-one (**10c**).* Following the general procedure, the SmI_2-mediated C-acylation of **6** (176 mg, 0.92 mmol) with 3-methylbutanoyl chloride (0.34 mL, 2.76 mmol) gave compound **10c** as a mixture of two inseparable diastereomers in 75:25 ratio (determined by ^{1}H NMR, δ_H 5.65, 5.31) (eluent:EtOAc–PE=1:3; 202 mg, combined yield: 79%). Colorless wax. R_f 0.22 (EtOAc–PE=1:3); IR (film): 3346, 2956, 2869, 1624, 1496, 1453, 1342, 1206, 1169, 1106, 1069 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, two isomers) δ 7.41–7.28 (m, 5H, Ph-H), 5.70–5.60 (m, 1H, H-2), 5.35–5.26 (m, 1H, H-2, for minor isomer), 4.64 (d, 1H, J=11.8 Hz, PhCH_2), 4.55 (d, 1H, J=11.8 Hz, PhCH_2), 4.00 (m, 1H, H-3, for minor isomer), 3.98 (m, 1H, H-3), 3.62 (m, 2H, H-5), 3.36 (m, 2H, H-5, for minor isomer), 2.44–2.18 (m, 2H, H-4), 2.17 (m, 1H, –CH(CH_3)$_2$), 2.16–1.96 (m, 2H, –CH_2CO–), 0.97 (m, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 137.7, 128.7, 128.4 (2C), 127.9, 127.8 (2C), 127.7 (2C), 84.5, 81.6, 71.3, 45.0, 43.3, 42.9, 41.9,

29.7, 29.2, 25.2, 22.6, 22.6; MS (ESI, *m*/*z*): 300 (M+Na^+, 100), 316 (M+K^+, 23); HRMS (ESI) calcd for $[C_{16}H_{23}NO_3+Na]^+$: 300.1576; found 300.1577.

*4.6.4. 1-((3S)-3-(Benzyloxy)-1-hydroxypyrrolidin-2-yl)-2,2-dimethylpropan-1-one (**10d**).* Following the general procedure, the SmI_2-mediated C-acylation of **6** (93 mg, 0.49 mmol) with pivaloyl chloride (0.18 mL, 1.46 mmol) gave compound **10d** as a mixture of two inseparable diastereomers in 74:26 ratio (determined by ^1H NMR, δ_H 5.99, 5.61) (eluent:EtOAc–PE=1:4; 75 mg, combined yield: 56%). Colorless wax. R_f 0.28 (EtOAc–PE=1:3); IR (film): 3354, 3031, 2960, 2870, 1732, 1640, 1529, 1479, 1454, 1365, 1207, 1102, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, two isomers) δ 7.41–7.21 (m, 5H, Ph-H), 6.10–5.90 (m, 1H, H-2), 5.63–5.60 (m, 1H, H-2, for minor isomer), 4.75 (d, 1H, *J*=11.5 Hz, PhCH_2), 4.64 (d, 1H, *J*=11.5 Hz, PhCH_2, for minor isomer), 4.55 (d, 1H, *J*=11.5 Hz, PhCH_2, for minor isomer), 4.52 (d, 1H, *J*=11.5 Hz, PhCH_2), 3.94 (m, 1H, H-3, for minor isomer), 3.89 (m, 1H, H-3), 3.84–3.74 (m, 2H, H-5, for minor isomer), 3.48–3.28 (m, 2H, H-5), 2.33–2.17 (m, 2H, H-4, for minor isomer), 2.13–1.80 (m, 2H, H-4), 1.27 (m, 9H, CH_3, for minor isomer), 1.07 (m, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 136.9, 128.6 (2C), 128.4 (2C), 128.3 (2C), 128.3 (2C), 127.7, 127.6, 82.1, 72.7, 45.9, 38.4, 36.0, 29.3, 27.3; MS (ESI, *m*/*z*): 300 (M+Na^+, 100), 278 (M+H^+, 54); HRMS (ESI) calcd for $[C_{16}H_{23}NO_3+H]^+$: 278.1756; found: 278.1764.

*4.6.5. 1-((3S)-3-(Benzyloxy)-1-hydroxypyrrolidin-2-yl)-2-phenylethanone (**10e**).* Following the general procedure, the SmI_2-mediated C-acylation of **6** (90 mg, 0.47 mmol) with 2-phenylacetyl chloride (0.19 mL, 1.41 mmol) gave compound **10e** as a mixture of two inseparable diastereomers in 75:25 ratio (determined by ^1H NMR, δ_H 5.65, 5.30) (eluent:EtOAc–PE=1:2; 73 mg, combined yield: 50%). Colorless wax. R_f 0.16 (EtOAc–PE=1:3); IR (film): 3354, 3062, 3029, 2951, 1631, 1496, 1454, 1410, 1400, 1300, 1177, 1106, 1070, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, two isomers) δ 7.38–7.28 (m, 7H, Ph-H), 7.26–7.19 (m, 3H, Ph-H), 5.68–5.62 (m, 1H, H-2), 5.33–5.27 (m, 1H, H-2, for minor isomer), 4.62 (d, 1H, *J*=11.8 Hz, PhCH_2), 4.47 (d, 1H, *J*=11.8 Hz, PhCH_2, for minor isomer), 4.53 (d, 1H, *J*=11.8 Hz, PhCH_2), 4.36 (d, 1H, *J*=11.8 Hz, PhCH_2, for minor isomer), 3.99–3.93 (m, 1H, H-3), 3.91–3.88 (m, 1H, H-3, for minor isomer), 3.84–3.73 (m, 2H, PhCH_2CO–, for minor isomer), 3.67–3.65 (m, 2H, PhCH_2CO–), 3.65–3.57 (m, 2H, H-5), 2.28–2.18 (m, 1H, H-4), 2.09–1.98 (m, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 137.6, 133.9, 129.1, 129.0 (2C), 128.9, 128.7, 128.6 (2C), 128.5, 128.4 (2C), 127.9, 127.8, 127.6 (2C), 127.4, 84.7, 81.5, 72.2, 71.3, 45.0, 42.3, 41.7, 41.1, 29.3; MS (ESI, *m*/*z*) 334 (M+Na^+, 100), 350 (M+K^+, 5); HRMS (ESI) calcd for $[C_{19}H_{21}NO_3+Na]^+$: 334.1419; found: 334.1424.

*4.6.6. 1-((3S)-3-(Benzyloxy)-1-hydroxypyrrolidin-2-yl)-3-phenylpropan-1-one (**10f**).* Following the general procedure, the SmI_2-mediated C-acylation of **6** (156 mg, 0.82 mmol) with 3-phenylpropanoyl chloride (0.36 mL, 2.45 mmol) gave compound **10f** as a mixture of two inseparable diastereomers in 78:22 ratio (determined by ^1H NMR, δ_H 5.64, 5.23) (eluent:EtOAc–PE=1:3; 218 mg, combined yield: 82%). Colorless wax. R_f 0.17 (EtOAc–PE=1:3); IR (film): 3381, 3062, 3028, 2928, 1724, 1626, 1496, 1453, 1343, 1104, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, two isomers) δ 7.43–7.11 (m, 10H, Ph-H), 5.72–5.56 (m, 1H, H-2), 5.29–5.07 (m, 1H, H-2, for minor isomer), 4.61 (d, 1H, *J*=11.8 Hz, PhCH_2), 4.52 (d, 1H, *J*=11.8 Hz, PhCH_2), 3.98–3.92 (m, 1H, H-3), 3.89–3.79 (m, 1H, H-3), 3.65–3.55 (m, 2H, H-5, for minor isomer), 3.55–3.43 (m, 2H, H-5), 3.04–2.92 (m, 2H, PhCH_2CH_2CO–), 2.90–2.61 (m, 2H, Ph CH_2CH_2CO–), 2.61–2.54 (m, 2H, Ph CH_2CH_2CO–, for minor isomer), 2.28–2.14, 2.14–1.89 (2 m, 2H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 140.9, 137.6, 128.6, 128.5 (2C), 128.4 (2C), 128.4, 128.3 (2C), 128.2, 127.8, 127.8, 127.7 (2C), 127.4, 126.2, 84.2, 81.6, 78.0, 71.3, 71.0, 44.8, 36.3, 36.1, 30.6, 29.1; MS (ESI, *m*/*z*): 348 (M+Na^+, 100), 364 (M+K^+, 24); HRMS (ESI) calcd for $[C_{20}H_{23}NO_3+Na]^+$: 348.1576; found: 348.1587.

*4.6.7. 1-((3S)-3-(Benzyloxy)-1-hydroxypyrrolidin-2-yl)ethanone (**10a**) (prepared by the cross-coupling of nitrone **8** with chloracetyl chloride).* Following the general procedure, the SmI_2-mediated C-acylation of **8** (102 mg, 0.53 mmol) with chloroacetyl chloride (0.119 mL, 1.50 mmol) gave compound **10a** as a mixture of two inseparable diastereomers in 77:23 ratio (determined by ^1H NMR, δ_H 5.62, 5.25) (eluent:EtOAc–PE=1:1; 56 mg, combined yield: 48%).

4.7. Acetic acid 2-acetyl-(*S*)-3-benzyloxypyrrolidin-1-yl ester (19)

To a cooled (0 °C) CH_2Cl_2 (6 mL) solution of compound **10a** (90 mg, 0.383 mmol) and TEA (0.11 mL, 0.765 mmol) was added dropwise acetyl chloride (0.042 mL, 0.573 mmol) under a N_2 atmosphere. The mixture was stirred at rt for 4.5 h, then cooled to 0 °C and treated with a saturated aqueous NH_4Cl solution (3 mL). The two phases were separated and the aqueous phase extracted with CH_2Cl_2 (75 mL). The combined organic phases were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent:EtOAc–PE=2:1) to give compound **19** (50 mg, 46%) as a colorless oil. R_f 0.5 (EtOAc–PE=1:1); IR (film): 2927, 1735, 1673, 1482, 1406, 1349, 1248, 1214, 1110, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, two isomers) δ 7.45–7.27 (m, 5H, Ph-H), 6.68–6.56 (m, 1H, H-2, for minor isomer), 6.34–6.23 (m, 1H, H-2), 4.75 (d, 1H, *J*=12.0 Hz, PhCH_2, for minor isomer), 4.66 (d, 1H, *J*=12.0 Hz, PhCH_2), 4.64 (d, 1H, *J*=12.0 Hz, PhCH_2), 4.60 (d, 1H, *J*=12.0 Hz, PhCH_2, for minor isomer), 4.05–3.98 (m, 1H, H-3), 3.98–3.90 (m, 1H, H-3, for minor isomer), 3.76–3.58 (m, 2H, H-5), 2.39–2.17 (m, 1H, H-4), 2.12 (s, 3H, CH_3, for minor isomer), 2.07 (s, 3H, CH_3), 2.11–2.05 (m, 1H, H-4), 2.04 (s, 3H, CH_3, for minor isomer), 2.03 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.0, 129.7, 128.5 (2C), 128.4, 127.9 (2C), 127.5 (2C), 85.7, 83.7, 82.1, 79.9, 71.4, 44.6, 29.7, 29.5, 27.5, 21.9, 21.0; MS (ESI, *m*/*z*): 300 (M+Na^+, 100), 315 (M+K^+, 39); HRMS (ESI) calcd for $[C_{15}H_{19}NO_4+Na]^+$: 300.1212; found: 300.1218.

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