Synthesis of a New Chiral Pyrrolidine †

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† This paper is dedicated to Prof. Pelayo Camps on occasion of his 65th birthday.

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Abstract: The synthesis of a new chiral pyrrolidine has been performed using 2,3-0-iso-propylidene-D-erythronolactol as a suitable starting material.

Keywords: organocatalysis; pyrrolidines; sulfones; nitrones

1. Introduction

In the last years there has been a growing interest in organocatalysis [1–6], a new field which has quickly attracted researchers’ attention due to its potential for saving costs, time and energy compared to classic catalysis. Among the many known organocatalysts L-proline is perhaps the one which has been most studied. This fact has led to the appearance of many analogues [7–14]. In the seminal paper of List, Lerner and Barbas III [15], it is described how in the aldol reaction the catalytic activity of L-proline increases using trans-4-hydroxy-L-proline and also how the enantiomeric excess reverses using cis-4-hydroxy-D-proline, (Figure 1).
In our research group we have achieved the synthesis of several chiral pyrrolidines from sulfonylbutadiene 1 or 2,3-\(O\)-iso-propylidene-D-erythronolactol (2) (Scheme 1).

Scheme 1. Synthesis of several pyrrolidines from a sulfonylbutadiene or 2,3-\(O\)-propylidene-D-erythronolactol.

Starting from sulfonylbutadiene 1, pyrrolidines 5 and 6 were obtained through vinyl sulfones 3 and 4, respectively [16–17]. In order to increase the yields, a new route for the synthesis of compound 6 was devised starting from 2,3-\(O\)-iso-propylidene-D-erythronolactol (2) through vinylsulfone 4 [18]. This pyrrolidine 6 has been proved to be an organocatalyst for the intramolecular \(\text{oxa-Michael}\) reaction [19–20]. Moreover, compound 7, which has been reported to catalyze Michael reactions [21], has been synthesized from intermediate vinylsulfone 4 (Scheme 1).

2. Results and Discussion

In this paper we describe our studies on the synthesis of the epimer at C-2 of pyrrolidine 6, as we are interested in comparing the properties of both diastereoisomers in organocatalytic reactions. In previous studies with PPY-derivatives, we had observed the epimerization of that stereogenic center when it was treated with bases [22]. Taking this into account, we first tried the epimerization at C-2 in compound 8, obtained directly from 4 by treatment with benzylamine. However, although several
bases were used, none of them gave the epimerization. Therefore, we devised the following synthesis for the required compound 12 (Scheme 2).

**Scheme 2. Epimerization of C-2 in compound 8.**

![Scheme 2](image)

a. PhCOCl, Py., 0 °C-r.t., 97%; b. n-BuLi, THF, -78 °C-r.t., 50%; c. NH₂-NH₂, EtOH, reflux, 0%; d. HCl 6M, reflux, 0%; e. LiAlH₄, THF, 0 °C-r.t., 30%; f. BH₃·THF, THF, 0 °C-40 °C, 15%; g. H₂, Pd/C, MeOH, r.t., 80%.

Benzoylation of pyrrolidine 6 gave derivative 10 as outlined in Scheme 2. When this compound was submitted to treatment with n-BuLi, the C-2 epimer 11 was obtained in moderate yield. Once the required stereochemistry at C-2 in 11 was achieved, we proceeded to deprotect the nitrogen to obtain the desired pyrrolidine 12. This step was not as simple as it was thought initially, since the desired direct debenzoylation did not take place under several conditions. Finally, it was necessary to reduce the benzyooyl to benzyl group and then deprotect under the usual conditions. Although, the final deprotection took place in good yield, the previous transformation from benzoyl to benzylderivative was only achieved in low yield, making useless this procedure to synthesise 12.

**Scheme 3. Synthesis of 12 from 2,3-O-iso-propyldene-D-erythronolactol.**

![Scheme 3](image)

a. 1. NH₂OSiMe₂t-Bu, Py., r.t., 15h.; 2. MsCl, 0 °C, 2h, 50%; b. MeSO₂Ph, n-BuLi, THF, -78 °C, 48%; c. H₂, Pd(OH)₂/C, HCl / MeOH, 4atm, 27%; d. H₂, Pd/C, MeOH, 39%; e. In, NH₄Cl/EtOH, reflux, 24h, 92%; f. Zn, NH₄Cl/MeOH, reflux, 2h, 50%; g. In(cat), Zn, NH₄Cl/MeOH reflux or r.t., see Table 1.
Therefore, we devised a new synthesis of compound 12 starting from 2,3-O-iso-propylidene-D-erythronolactol (2). Goti [23–25] and Wightman and Closa [26–28] have obtained nitrone 13 from compound 2. Besides, Merino and Goti have applied this versatile nitrone to the synthesis of iminocyclitols, pyrrolizidines and indolizidines [29–30], observing that the addition of organometallics to 13 took place to give the trans compounds. With this procedure in mind, we were able to achieve the desired compound 12 in a simple manner, as depicted in Scheme 3.

When compound 13 was treated with lithio(phenylsulfonyl)methane, only hydroxylamine 14 was obtained stereoselectively in moderate yield. The stereochemistry of 14 was established studying its NMR spectra (whose assignment is given in the Experimental section) and by the observation of the nOes that this molecule displays (Scheme 3). The nOes of the enantiomer of compound 6 has already been reported by our research group [16]. Once this compound 14 was synthesized, different reduction conditions to obtain the pyrrolidine ring were tested.

Hydrogenation under different conditions either Pd(OH)₂ or Pd on carbon only leads to the pyrrolidine 6. When 14 was submitted to reduction with stoichiometric indium or with zinc, hydroxylamine 15 with inversion at C-2 was obtained. Thus, it was necessary to choose the adequate conditions to reduce the hydroxylamine to the required pyrrolidine 12 without epimerization at C-2. This was achieved using catalytic indium and stoichiometric Zn [29–31] (Table 1, entry 8).

| Entry | Zn Equiv. | Tª | t(h) | η (%) | Ratio 6/12 |
|-------|-----------|----|------|-------|------------|
| 1     | 6         | Reflux | 1    | 15    | 40/60      |
| 2     | 4         | Reflux | 2    | 10    | 36/64      |
| 3     | 4         | Reflux | 1    | 15    | 30/70      |
| 4     | 4         | Reflux | 0.5  | NDa   | NDa        |
| 5     | 2         | Reflux | 1    | NDa   | NDa        |
| 6     | 2         | Reflux | 1.5  | 10    | 40/60      |
| 7     | 2         | Reflux | 2    | 20    | 15/85      |
| 8     | 4         | r.t.  | 5.5  | 40    | 5/95       |
| 9     | 3         | r.t.  | 4    | 8     | 45/55      |
| 10    | 2         | r.t.  | 4    | NDa   | NDa        |

a Not determined.

Having obtained our desired compounds 6 and 12, they were tested as organocatalysts in Michael addition reactions of cyclohexanone to nitrostyrene, as shown in Table 2.
Table 2. Solvent effects on the asymmetric Michael addition of cyclohexanone to \textit{trans}-\(\beta\)-nitrostyrene with catalysts 6 and 12.

![Chemical structure](image)

| Entry\[^{[a]}\] | Solv. | Catalyst | Yield [\%]\[^{[b]}\] | d.r. [\%]\[^{[c]}\] | ee [\%]\[^{[d]}\] | Conf. |
|-----------------|-------|----------|------------------|----------------|----------------|-------|
| 1               | CHCl\(_3\) | 6        | -                | -              | -              | -     |
| 2               | CHCl\(_3\) | 12       | 35               | >95            | 38             | 2R, \(1'S\) |
| 3               | DMSO   | 6        | 20               | >95            | 69             | 2S, \(1'R\) |
| 4               | DMSO   | 12       | -                | -              | -              | -     |

\[^{[a]}\] For experimental conditions see the Experimental section. \[^{[b]}\] Yield of the isolated product. \[^{[c]}\] Determined by \(^1\)H-NMR spectroscopic analysis. \[^{[d]}\] Determined by chiral high-performance liquid chromatography (HPLC) analysis (Daicel Chiralpak AD, 25 cm/4.6 mm/5 \(\mu\)).

As can be observed, both compounds 6 and 12 are organocatalysts. However, their behaviour is rather different depending on the solvent chosen to carry out the reaction. It is worthy mentioning that compound 12 lead to the opposite enantiomer of 6 in the Michael addition, as a result of the stereochemistry change in C-2 position. The absolute configuration of the addition product was established by comparison of the HPLC data with the ones reported by us [21] and others [32–33].

3. Conclusions

The synthesis of a new chiral pyrrolidine 12, has been achieved from the same starting material, 2,3-\(O\)-iso-propylidene-D-erythronolactol through two different methodologies. In addition, the reduction of the chiral hydroxylamine into pyrrolidine has been studied under different conditions.

4. Experimental

4.1. General

\(^1\)H-NMR and \(^{13}\)C-NMR spectra were recorded in CDCl\(_3\) at 200 and 400 MHz (\(^1\)H) or 50 and 100 MHz (\(^{13}\)C) on Varian 200 VX and BRUKER DRX 400 instruments, respectively. Multiplicities were determined by DEPT experiments. IR spectra were registered using a BOMEM 100 FTIR spectrophotometer. Optical rotations were determined using a Perkin-Elmer 241 polarimeter in a 1 dm cell and are given in units of 10-1 deg cm\(^2\) g\(^{-1}\). Concentrations are quoted in g per 100mL. The electron impact (EI) mass spectra were run on a VG-TS 250 spectrometer using a 70 eV ionizing voltage. HRMS were recorded using a VG Platform (Fisons) spectrometer using Chemical Ionization (ammonia as gas) or Fast Atom Bombardment (FAB) techniques. Thin layer chromatography (tlc) was performed on aluminum sheets coated with 60 F254 silica. Sheets were visualized using iodine, UV light or 1% aqueous KMnO\(_4\) solution. Column chromatography (CC) was performed with Merck silica
gel 60 (70–230 mesh). Solvents and reagents were generally distilled prior to use: dichloromethane (DCM) from KOH.

4.2. Preparation of (2S,3S,4R)-N-Benzoyl-2-phenylsulfonylmethyl-3,4-isopropylidenedioxypyrrolidine (10)

To a solution of pyrrolidine 6 (40 mg, 0.13 mmol) in pyridine (0.5 mL) at 0 ºC was added PhCOCl (20 µL) and the mixture was stirred for 3 h. The reaction was quenched by the addition of water (0.2 mL) at 0 ºC and then the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with aqueous solutions of CuSO₄ (20%), NaHCO₃ (5%) and brine. After drying (Na₂SO₄), filtering, and concentrating, the crude residue was purified by flash chromatography (silica gel, n-hexane/EtOAc 8:2) to give benzoyl derivative 10 (52 mg, 97%). IR (film) v (cm⁻¹) 3066, 2987, 2939, 1643, 1584, 1447, 1383, 1307, 1249, 1215, 1153, 1085; ¹H-NMR (400 MHz) δ = 8.03–7.34 (m, 10H), 4.83 (t, J = 5.8 Hz, 1H), 4.66–4.61 (m, 2H), 3.98 (dd, J = 14.0 and 3.7 Hz, 1H), 3.84 (dd, J = 14.0 and 9.0 Hz, 1H), 3.59 (m, 2H), 1.54 (s, 3H), 1.32 (s, 3H); ¹³C-NMR (100 MHz) δ = 171.3, 139.7, 135.3, 133.6, 130.8, 129.1, 128.3, 128.1, 127.7, 113.1, 78.7, 77.5, 54.8, 54.5, 53.2, 27.1, 25.2; HRMS (ESI) C₂₁H₂₄NO₅S requires (M+H⁺) 402.1369; found 402.1364. [α]D²₀ = - 67.1 (c 1.4, CHCl₃).

4.3. Preparation of (2R,3S,4R)-N-Benzoyl-2-phenylsulfonylmethyl-3,4-isopropylidenedioxypyrrolidine (11)

A solution of pyrrolidine 10 (40 mg, 0.10 mmol) in THF (1 mL) under argon at -78 ºC, was added n-BuLi (75 µL, 1.6 M in hexanes). The resulting mixture was stirred for 3 h, allowing to warm to rt, whereupon the reaction was quenched with saturated aqueous solution of NH₄Cl (0.2 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, n-hexane/EtOAc 7:3) to obtain 11 (20 mg, 50%). IR (film) v (cm⁻¹) 3064, 2978, 2938, 1634, 1577, 1413, 1319, 1217, 1152, 1074, 1046, 858; ¹H-NMR (400 MHz) δ = 7.98–7.38 (m, 10H), 5.25–5.23 (m, 1H), 4.85 (m, 1H), 4.79 (m, 1H), 3.89 (dd, J = 14.0 and 3.6 Hz, 1H), 3.78–3.71 (m, 2H), 3.44 (d, J = 14.0 Hz, 1H), 1.44 (s, 3H), 1.33 (s, 3H); ¹³C-NMR (100 MHz) δ = 170.0, 139.6, 135.5, 134.0, 130.2, 129.4, 128.3, 127.8, 127.2, 112.2, 82.5, 79.6, 60.2, 54.8, 54.7, 26.9, 24.9; HRMS (ESI) C₂₁H₂₄NO₅S requires (M+Na) 424.1195; found 424.1189. [α]D²₀ = + 33.9 (c 1.1, CHCl₃).

4.4. Preparation of (2R,3S,4R)-N-Benzyl-2-phenylsulfonylmethyl-3,4-isopropylidenedioxypyrrolidine (9)

Scheme 2, step e: LiAlH₄ (7 mg, 0.19 mmol) was added to a solution of 11 (38 mg, 0.1 mmol) in dry THF (1 mL) at 0 ºC. The resulting mixture was stirred for 1h, allowing to warm to rt, whereupon the reaction was quenched with wet ether, dried (Na₂SO₄), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, n-hexane/EtOAc 8:2) to yield benzyl derivative 9 (10 mg, 30%). IR (film) v (cm⁻¹) 2983, 2942, 1454, 1377, 1307, 1209, 1148, 1086, 1054; ¹H-NMR (400 MHz) δ = 7.90–7.15 (m, 10H), 4.70 (m, 1H), 4.64 (m, 1H), 3.81 (d, J = 13.3 Hz, 1H), 3.55 (d, J = 13.3 Hz, 1H), 3.32–3.27 (m, 2H), 3.13 (dd, J = 13.5 and 9.0 Hz, 1H), 2.87 (dd,
$J = 10.7$ and $5.3$ Hz, 1H), 2.68 (d, $J = 10.7$ Hz, 1H), 1.50 (s, 3H), 1.28 (s, 3H); $^{13}$C-NMR (100 MHz) $\delta = 139.4, 137.0, 133.7, 129.2, 128.3, 128.1, 127.1, 112.4, 84.3, 78.7, 63.4, 57.3, 56.6, 55.1, 27.0, 25.0; HRMS (ESI) C$_{21}$H$_{25}$NO$_4$S requires (M+Na) 410.1402; found 410.1397; $\left[\alpha\right]_D^{20} = +20.2$ (c 1.0, CHCl$_3$).

**Scheme 2, step f:** To a solution of 11 (38 mg, 0.1 mmol) in dry THF (1 mL) under argon at rt, was added BH$_3$·THF (0.12 mL, 1M in THF). After stirring for 2 h at 40 ºC, the reaction was quenched by the addition of water (0.3 mL) and extracted with Et$_2$O (3 $\times$ 10 mL). The combined organic layers were washed with H$_2$O and brine, dried (Na$_2$SO$_4$), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, n-hexane/EtOAc 8:2) to obtain benzyl derivative 9 (5 mg, 15%).

**4.5. Preparation of (2R,3S,4R)-2-Phenylsulfonylmethyl-3,4-isopropylidenedioxypyrrolidine (12)**

**Scheme 2, step g:** To a solution of pyrrolidine 9 (10 mg, 0.03 mmol) in MeOH (0.5 mL) was hydrogenated in the presence of a catalytic amount of Pd/C with a H$_2$ balloon at room temperature for 24 h. The catalyst was filtered through a pad of Celite® and washed with MeOH. After concentrating, compound 12 (6 mg, 80%) was obtained. IR (film) $\nu$ (cm$^{-1}$) 3317, 2985, 2936, 1448, 1375, 1306, 1209, 1144, 1083, 1046, 865; $^1$H-NMR (400 MHz) $\delta = 7.93$ (m, 2H), 7.65–7.54 (m, 3H), 4.67 (dd, $J = 4.4$ and 5.3 Hz, 1H), 4.57 (d, $J = 5.3$ Hz, 1H), 3.57 (t, $J = 6.4$ Hz, 1H), 3.13 (d, $J = 13.2$ Hz, 1H), 3.05 (d, $J = 13.6$ Hz, 1H), 2.69 (dd, $J = 4.4$ and 13.2 Hz, 1H), 1.44 (s, 3H), 1.27 (s, 3H); $^{13}$C-NMR (100 MHz) $\delta = 139.4, 133.8, 129.3, 128.1, 111.6, 85.0, 84.9, 60.3, 57.2, 51.8, 26.2, 24.1; HRMS (ESI) C$_{14}$H$_{20}$NO$_4$S requires (M+H$^+$) 298.1113; found 298.1115; $\left[\alpha\right]_D^{20} = -13.1$ (c 1.7, CHCl$_3$).

**4.6. Preparation of (3S,4R)-3,4-Isopropylidenedioxypyrroline-1-oxide (13)**

To a solution of lactol 2 (1.34 g, 8.54 mmol) in dry pyridine (8.6 mL) containing 3 Å activated molecular sieves (pellets, 10 g) was added a solution of NH$_2$OSiMe$_2$-t-Bu (1.51 g, 10.25 mmol) in pyridine (8.6 mL) and the mixture was stirred at rt for 16 h. The reaction mixture was cooled to 0 ºC, and methanesulfonyl chloride (0.8 mL, 10.25 mmol) was added slowly during 40 min. The reaction was stirred for 2 h at 0 ºC, warmed to rt and stirred for 4 h. The mixture was then diluted with CH$_2$Cl$_2$ (9 mL), filtered through Celite®, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, CH$_2$Cl$_2$/EtOAc/MeOH 15/7/1) to give pure nitrone 13 (635 mg, 50%). IR (film) $\nu$ (cm$^{-1}$) 3084, 2993, 2980, 1579; $^1$H-NMR (400 MHz) $\delta = 6.82$ (q, $J = 1.5$ Hz, 1H), 5.24 (d, $J = 6.2$, 1H), 4.86 (ddd, $J = 6.2$, 5.1 and 1.5 Hz, 1H), 4.07–3.99 (m, 2H), 1.40 (s, 3H), 1.31 (s, 3H); HRMS (ESI) C$_{7}$H$_{12}$NO$_3$ requires (M+H$^+$) 158.1785; found 158.0822; $\left[\alpha\right]_D^{20} = -26.9$ (c 1.1, CH$_2$Cl$_2$).

**4.7. Preparation of (2R,3S,4R)-2-Phenylsulfonylmethyl-1-hydroxy-3,4-isopropylidenedioxypyrrolidine (14)**

To a stirred solution of MeSO$_2$Ph (520 mg, 2.58 mmol) in THF (4.7 mL) was added slowly n-BuLi (1.9 mL, 2.58 mmol) and the mixture was reacted at 0 ºC for 10 min. Afterwards, the reaction mixture was cooled to -78 ºC and stirred for 10 min at this temperature. Then, it was added into a solution of nitrone 13 (320 mg, 2.03 mmol) in THF (6.7 mL) and the mixture was stirred at -78 ºC for 30 min and then for 2 h allowing to warm to rt. The reaction was quenched with saturated aqueous solution of...
NH₄Cl and the product was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, n-hexane/EtOAc 1:1) to obtain hydroxylamine 14 (300 mg, 48%).

IR (film) ν (cm⁻¹) 3428, 3207, 2987, 2925, 2856, 1581, 1442, 1385, 1295, 1131, 1074, 845; ¹H-NMR (400 MHz) δ = 7.96 (m, 2H), 7.67–7.53 (m, 3H), 6.25 (s, 1H), 4.75 (m, 1H), 4.62 (dd, J = 4.2 and 6.0 Hz, 1H), 3.69 (dd, J = 6.4 and 14.0 Hz, 1H), 3.44 (m, 1H), 3.37 (m, 1H), 3.25 (dd, J = 6.8 and 14.0 Hz, 1H), 3.12 (dd, J = 4.4 and 12.4 Hz, 1H), 1.43 (s, 3H), 1.27 (s, 3H); ¹³C-NMR (100 MHz) δ = 139.4, 133.9, 129.3, 128.1, 113.7, 82.2, 77.2, 67.3, 62.3, 54.1, 26.7, 24.7; HRMS (ESI) C₁₄H₁₉NO₅S requires (M + Na) 336.0882; found 336.0877; [α]D²⁰ = -20.8 (c 2.2, CHCl₃).

4.8. Preparation of (2S,3S,4R)-2-Phenylsulfonylmethyl-3,4-isopropylidenedioxypyrrolidine (6)

Scheme 3, step c: A stirred solution of hydroxylamine 14 (50 mg, 0.16 mmol) in a 12:1 solution of HCl/MeOH (1 mL) was hydrogenated in the presence of a catalytic amount of Pd (OH)₂/C, at a hydrogen pressure of 4 atm for 48 h. The catalyst was filtered through a pad of Celite®, washed with MeOH and concentrated. The product was purified by flash chromatography (silica gel, n-hexane/EtOAc 1:1) to provide pyrrolidine 6 (13 mg, 27%). IR (film) ν (cm⁻¹) 3000, 2936, 1447, 1381, 1308, 1148, 1086, 650 cm⁻¹; ¹H-NMR (400 MHz) δ = 7.93 (m, 2H), 7.69–7.50 (m, 3H), 4.67 (dd, J = 4.0 and 5.3 Hz, 1H), 4.54 (dd, J = 4.0 and 5.3 Hz, 1H), 3.57 (dd, J = 5.0 and 14.0 Hz, 1H), 3.36 (dd, J = 7.0 and 14.0 Hz, 1H), 3.22 (m, 1H), 3.13 (d, J = 12.7 Hz, 1H), 2.69 (dd, J = 4.0 and 12.7 Hz, 1H), 2.20 (s, 1H), 1.41 (s, 3H) and 1.25 (s, 3H); ¹³C-NMR (100 MHz) δ = 139.7, 133.7, 129.2, 127.2, 111.1, 81.0, 80.8, 57.1, 55.9, 52.6, 25.7, 24.0; HRMS (ESI) C₁₄H₂₀NO₄S requires (M+H⁺) 298.1113; found 298.1128; [α]D²⁰ = -37.3 (c 0.5, CHCl₃).

(Scheme 3, step d): A stirred solution of hydroxylamine 14 (66 mg, 0.21 mmol) in 1 mL of MeOH was hydrogenated in the presence of a catalytic amount of Pd/C with a H₂ balloon at room temperature for 24 h. The catalyst was filtered through a pad of Celite®, washed with MeOH and concentrated. The product was purified by flash chromatography (silica gel, n-hexane/EtOAc 1:1) to provide pyrrolidine 6 (24 mg, 39%).

4.9. Preparation of (2R,3S,4R)-2-Phenylsulfonylmethyl-1-hydroxy-3,4-isopropylidenedioxypyrrolidine (15)

(Scheme 3, step e): To a stirred solution of hydroxylamine 14 (32.1 mg, 0.10 mmol) in a 2:1 solution of EtOH /saturated aqueous NH₄Cl (18.5 mL), powdered indium (14 g, 0.12 mmol) was added and the mixture was heated under reflux. After 24 h the reaction mixture was cooled, filtered through Celite®, and concentrated under reduced pressure. A saturated aqueous Na₂CO₃ solution (5 mL) was then added, and the product was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 1:1) to obtain hydroxylamine 15 (28.8 mg, 92%). IR (film) ν (cm⁻¹) 3448, 2985, 2933, 2854, 1448, 1383, 1306, 1085, 856; ¹H-NMR (400 MHz) δ = 7.97 (m, 2H), 7.67–7.52 (m, 3H), 6.27 (s, 1H), 4.60 (m, 2H), 3.70 (dd, J = 8.4 and 14.0 Hz, 1H), 3.50–3.38 (m, 2H), 3.05 (m, 1H), 2.70 (dd, J = 4.4 and 11.0 Hz, 1H), 1.37 (s, 3H), 1.22 (s, 3H); ¹³C-NMR
Scheme 3, step f: To a stirred solution of hydroxylamine 14 (69 mg, 0.22 mmol) in a solution of MeOH/NH₄Cl sat (3.4/5 mL), powdered Zn (29 mg, 0.44 mmol) was added at 20 ºC and the mixture was stirred for 6h. The solvent was evaporated under vacuum and a saturated aqueous solution of Na₂CO₃ (1.5 mL) was added. The mixture was extracted with EtOAc (3 × 15 mL) and the combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, n-hexane/EtOAc 1:1) to obtain hydroxylamine 15 (34 mg, 50%).

4.10. Preparation of (2R,3S,4R)-2-Phenylsulfonylmethyl-3,4-isopropylidenedioxypyrrolidine (12)

Scheme 3, step g, Table 1, entry 8, as example: To a stirred solution of hydroxylamine 14 (852 mg, 2.58 mmol), in methanol (37 mL), a saturated solution of NH₄Cl (56 mL), powdered Zn (712 mg, 10.9 mmol) and a catalytic amount of indium dust (20 mg) were added at 20 ºC. The mixture was stirred for 6h. The solvent was evaporated under vacuum and a saturated aqueous solution of Na₂CO₃ (5 mL) was added. The mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, n-hexane/EtOAc 1:1) to obtain pyrrolidines 12 (248 mg, 35%) and 6 (13 mg, 2%).

4.11. (2S,1°R)-2-[1°-Phenyl-2°-nitroethyl]-cyclohexanone

To a suspension of catalyst 6 (10 mg, 15%) and 0.438 mL (4.40 mmol) of cyclohexanone in 3.5 mL of DMSO was added 33 mg (0.22 mmol) of trans-β nitrostyrene. The resulting mixture was allowed to stir at room temperature for 16 h, whereupon the reaction was quenched with saturated aqueous ammonium chloride (2 mL) and the aqueous layers were extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered and evaporated in vacuo and the resulting residue was purified by flash column chromatography using (hexane/EtOAc, 9/1) to give the title compound, as a white solid (11 mg, 20%). ¹H-NMR (400 MHz) δ 7.34–7.16 (m, 5H, Ph), 4.93 (dd, J = 12.5 and 4.5 Hz, 1H, CH₂), 4.60 (dd, J = 12.5 and 9.9 Hz, 1H, CH₂), 3.76 (m, 1H, CH), 2.69 (m, 1H, CH), 2.50–1.52 (m, 8H, 4CH₂). The absolute configuration was established by comparison with reported HPLC data [21]. HPLC: Daicel Chiralpak AD; n-hexane/iPrOH: 0.45 mL min⁻¹; λ_max 230 nm: tᵣ (minor)-10.8 min; tᵣ (major)-13.1 min.

4.12. (2R,1°S)-2-[1°-Phenyl-2°-nitroethyl]-cyclohexanone

To a suspension of catalyst 12 (10 mg, 15%) and 0.438 mL (4.40 mmol) of cyclohexanone in 3.5 mL of CHCl₃ was added 33 mg (0.22 mmol) of trans-β nitrostyrene. The resulting mixture was allowed to stir at room temperature for 16 h, whereupon the reaction was quenched with saturated aqueous ammonium chloride (2 mL) and the aqueous layers were extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered and evaporated in vacuo and the resulting residue was purified by flash column chromatography using (n-hexane/EtOAc, 9/1) to give the title
compound, as a white solid (22mg, 35%). The absolute configuration was established by comparison with reported HPLC data [21]. HPLC: Daicel Chiralpak AD; n-hexane/iPrOH: 0.45 mL min⁻¹; λmax230 nm: tR (major)-10.5 min; tR (minor)-12.9 min.

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