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New pyrrolidine-triazole-based C_2 symmetric organocatalysts and their utility in the asymmetric Michael reaction of β-nitrostyrenes and the synthesis of nitrochromenes

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ABSTRACT

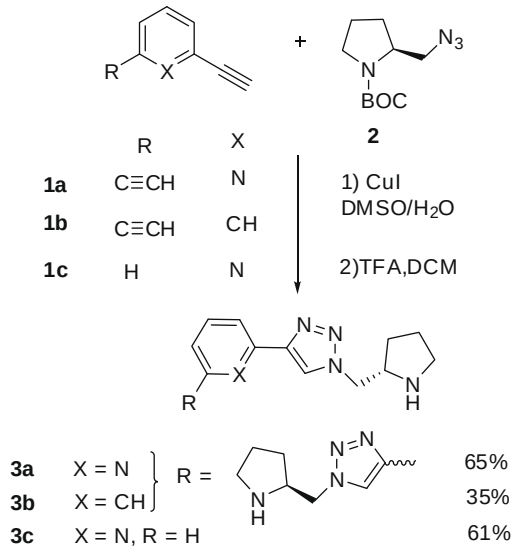
The synthesis of new C_2 symmetric bis(pyrrolidine-triazole)-based organocatalysts and their utility in the asymmetric Michael reaction of β-nitrostyrenes with very high diastereo- and enantioselectivity in water without any additives is reported. The asymmetric synthesis of nitrochromenes is also illustrated.

1. Introduction

Asymmetric synthesis using organocatalysts is at the forefront of organic synthesis; the past decade has witnessed many contributions in this area.[1] The development of new organocatalysts and new synthetic methodologies are two major components of research in this area.[2] Since the discovery of L-proline-catalyzed asymmetric transformations,[3] a number of proline-based organocatalysts have been developed.[4] Among these, pyrrolidine-tetrazole,[5] pyrrolidine-triazole,[6] pyrrolidine-thiourea,[7] and pyrrolidine-imidazolium[8] conjugates, to name a few, have been successfully employed as catalysts for various asymmetric transformations. Asymmetric Michael addition and aldol condensation have been widely used to test the efficacy of new organocatalysts because of the importance of these two C–C bond-forming reactions in organic synthesis.[9] Recent literature reveals the use of excellent pyrrolidine-triazole conjugate-based organocatalysts with a pyrrolidine unit as the catalytically active moiety and a triazole unit as the face-shielding group for the above transformations.[6] Pyrrolidine-triazole-based organocatalysts supported on ionic liquids, polymers or silica gels have also been reported.[10] Herein, the synthesis of three pyrrolidine-triazole conjugate catalysts is reported. It is envisaged that the apparent C_2 symmetry in the bis(pyrrolidine-triazole) catalysts **3a**–**b** might be beneficial for asymmetric transformations. We anticipated that the pyridine ring in **3a** and **3c** might provide additional hydrogen bonding sites and improve the catalytic activity. The catalytic activity and efficiency were tested using the well-known Michael addition of cyclohexanone to β-nitrostyrene. In addition, the asymmetric synthesis of nitrochromenes is reported using these catalysts.

2. Results and discussion

Organocatalysts **3a**–**c** were synthesized by the Huisgen 1,3-dipolar cycloaddition of *N*-Boc-protected proline azide **2** (derived from L-proline)[11] to the corresponding alkynes **1a**–**c** followed by deprotection of the *N*-Boc group using TFA (Scheme 1).



Scheme 1. Synthesis of organocatalysts **3a**–**c**.

Michael addition of cyclohexanone to β-nitrostyrene was used to screen the catalysts (Scheme 2, Table 1). The reactions were performed either in water or without any solvent under neat conditions. In all the cases, the *syn* isomer was obtained as the predominant product which was identified by spectroscopic and specific rotation

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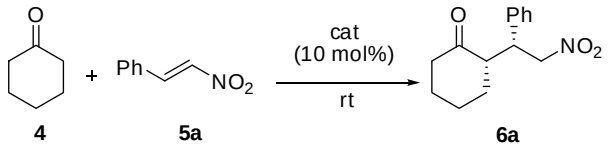


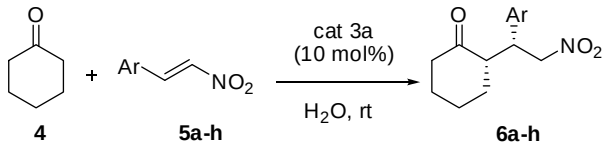
Scheme 2. Michael addition of cyclohexanone to nitrostyrene.

Table 1
Screening of catalysts **3a–c** using the reaction in Scheme 2

Entry	Catalyst	Solvent	Duration	Yield (%)[a]	dr (%)[b]	ee (%)[c]
1	**3a**	H_2O	16 h	70	97:3	99
2	**3a**	Neat	16 h	100	96:4	91
3	**3a**[d]	H_2O	4.5 d	42	96:4	85
4	**3b**	H_2O	16 h	80	92:8	88
5	**3c**	H_2O	65 h	71	95:5	83

[a] Reactions with **5a** (0.67 mmol), **4** (3.3 mmol) in 1.5 mL water, isolated yield after column purification, for entries 2 and 4 **5a** (0.33 mmol), **4** (1.6 mmol).
[b] Determined by peak integration in the ^{1}H NMR spectrum of the crude product.
[c] Determined by chiral HPLC analysis.
[d] With only 1 equiv of **4** and **5a** (1.3 mmol).

data in comparison with the literature.[6b,8a,10,12] Catalyst **3c** with a single active site gave good diastereoselectivities and moderate enantioselectivities. However, compared to **3a**, the rate of the reaction with **3c** was much slower (Table 1, entries 1 and 5). Although the yield was better with **3b** than with **3c** (Table 1, entries 4 and 5), the enantioselectivity was poorer with **3b** than with **3a** (Table 1, entries 1 and 4). Catalyst **3a** gave excellent diastereo- and enantioselectivities in water as well as under neat conditions. Although the reaction was slower with only one equivalent of **4** (Table 1, entry 3), it proceeded to completion without any additives. Therefore catalyst **3a** was chosen for further studies, and reactions were carried out in water. It is noteworthy that this is the highest enantioselectivity obtained so far for this Michael reaction using any pyrrolidine-triazole-based organocatalyst. Furthermore, unlike earlier reports[6,10] on this Michael reaction using pyrrolidine-based catalysts which required additives such as TFA, PEG or CSA, with catalysts **3a–c**, the reactions proceeded smoothly without any additives. The reactions also proceeded with only 5 equiv of **4**, whereas in all the earlier reports, **4** had been used in a large excess (>20 equiv or so as solvent).[6,10] In all these reactions, the diastereoselectivity was determined from the peak integration in the ^{1}H NMR spectrum of the crude product and the enantioselectivity was determined by chiral HPLC analysis. In order to establish substrate scope, Michael reaction was performed with several substituted β-nitrostyrenes in water at rt (Scheme 3, Table 2).



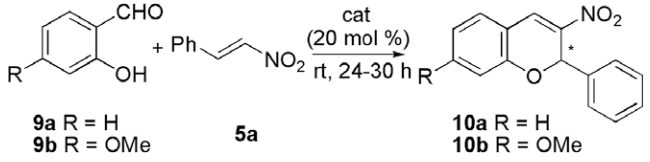
Scheme 3. Michael addition of cyclohexanone to substituted β-nitrostyrenes catalyzed by **3a**.

The Michael addition of cyclohexanone to various substituted β-nitrostyrenes **5a–h** catalyzed by **3a** proceeded smoothly and yielded the corresponding Michael adducts **6a–h** in good to excellent yields. The diastereoselectivity was excellent in all the cases in favor of the *syn* isomer. The enantioselectivity was also excellent, and in case of **6a** recrystallization of the crude product yielded enantiomerically pure Michael adduct. Michael addition of cyclopentanone **7** to **5a** proceeded smoothly in toluene to yield the corresponding Michael adduct, namely 2-(2-nitro-1-phenylethyl)cyclopentanone **8**. However, only moderate diastereoselectivity (75:25) and poor enantioselectivity (50% ee) were observed. Our observations with cyclopentanone are in accordance with previous reports.[6,10]

Table 2
Michael addition to substituted β-nitrostyrenes catalyzed by **3a**

5 Ar	**6** Yield (%)	dr (%)	ee (%)
5a C_6H_5	**6a** 70	97:3	99
5b 4-ClC_6H_4	**6b** 53	95:5	94
5c 2-$MeOC_6H_4$	**6c** 95	94:6	86
5d 2-$NO_2C_6H_4$	**6d** 90	92:8	93
5e 3-$MeOC_6H_4$	**6e** 74	94:6	93
5f 4-MeC_6H_4	**6f** 83	94:6	93
5g 3-$NO_2C_6H_4$	**6g** 60	90:10	90
5h 2-Furanyl	**6h** 66	86:14	80

Having succeeded in the Michael reaction of β-nitrostyrenes, our attention was next focused on the evaluation of the catalysts **3a–c** for the asymmetric synthesis of nitrochromenes. Although the synthesis of nitrochromene by the reaction of salicylaldehyde with β-nitrostyrene is well documented,[13] asymmetric version of the reaction has not been reported so far.[13c] Formation of nitrochromene can be explained by the Michael addition of phenolic hydroxyl to β-nitrostyrene followed by an intramolecular Henry reaction and dehydration. Among the three catalysts **3a–c**, **3a** performed better than the others. Enantioselectivity was better in DMF than in toluene or water as solvent for this reaction. Nevertheless, in all cases, only moderate yield and poor enantioselectivity were observed (Scheme 4, Table 3). The absolute stereochemistries of the major product formed are assigned on the basis of chiral HPLC retention times in comparison with the literature data.[13c]



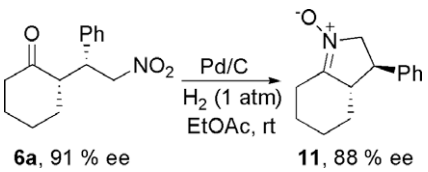
Scheme 4. Asymmetric synthesis of nitrochromenes.

Table 3
Asymmetric synthesis of nitrochromenes

9a/**9b**	Catalyst	Solvent	**10** Yield (%)	ee (%)
9a[a]	**3a**	Toluene	**10a** 40	15
9a	**3a**	DMF	**10a** 30	24
9a	**3a**	H_2O	**10a** 22	19
9a	**3b**	DMF	**10a** 23	12
9a	**3c**	DMF	**10a** 27	11
9b	**3a**	DMF	**10b** 22	7

[a] With 1.0 equiv of triethylamine added.

Reduction of **6a** using Pd/C in ethyl acetate yielded the corresponding nitrone **11** in 38% with retention of enantiomeric purity (Scheme 5).



Scheme 5. Reduction of Michael adduct to nitrone.

3. Conclusion

In conclusion, we have described the synthesis of new bis(pyrrolidine-triazole)-based organocatalysts **3a–c** and their utility in the asymmetric Michael reaction of β-nitrostyrenes. Organocatalyst **3a** can able to mediate the Michael reaction without any additives and only with 5 equiv of cyclohexanone. The asymmetric synthesis of nitrochromenes from salicylaldehyde and β-nitrostyrene is also reported, albeit in poor enantioselectivities.

4. Experimental

4.1. General

All reactions were carried out in oven-dried glasswares. Commercial reagents were used without purification. The reactions were monitored by TLC using silica gel plates (Silica gel 60 F_{254}, Merck) and visualized either with UV light or with phosphomolybdic acid stain followed by heating. Column chromatography was carried out with Acme Silica Gel (100–200 mesh). NMR spectra were recorded in $CDCl_3$ using TMS as internal standard at 400 MHz for ^1H and 100 MHz for ^{13}C using Bruker AV400 spectrometer. IR spectra were recorded on Thermo Nicolet 6700 FT-IR in ATR mode. Mass spectrum was recorded either with Micromass Q-TOF Micro™ spectrometer or with Jeol GC mate spectrometer. Enantiomeric excesses were determined with Waters HPLC connected to a Waters 515 pump and Waters 2487 UV detector. Optical rotations were measured in Autopol® IV polarimeter supplied by Rudolph research analytical. Melting point was determined by melting point apparatus supplied by Cintex industrial corporation, Mumbai. The *N*-BOC-protected proline azide **2** was prepared by literature procedure.[11] 2-Ethynlpyridine **1c** was obtained from Aldrich. 1,6-Diethynylpyridine **1a** and 1,3-diethynyl benzene **1b** were prepared by literature procedures.[14] β-Nitrostyrenes were prepared by literature procedure.[15] All Michael reactions were performed in air in closed vessels. All Michael adducts are known compounds.

4.2. Synthesis of 2,6-bis(1-((*S*)-pyrrolidin-2-ylmethyl)-1*H*-1,2,3-triazol-4-yl)pyridine 3a

Compound **1a** (300 mg, 2.36 mmol) was treated with **2** (1.1 g, 4.7 mmol) in degassed DMSO:H_2O (30 mL, 9:1 v/v) containing CuI (90 mg, 0.47 mmol) at rt. The reaction mixture was stirred for 12 h. The entire reaction mixture was solidified at the end of the reaction. The solid mass was diluted with water (100 mL) and filtered to give the product. The product was dissolved in CH_2Cl_2 (40 mL), washed with brine solution (20 mL), and dried over sodium sulfate. Evaporation of the solvent gave *N*-Boc-protected **3a** (1.1 g, 1.9 mmol) as a pale yellow solid in 78% yield, mp 150–153 °C, $[\alpha]_D^{34} = +32.3$ (*c* 1, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 18 H), 1.71–1.95 (m, 8H), 3.13–3.35 (m, 4H), 4.1–4.58 (m, 6H), 7.7–8.1 (m, 3H), HRMS calcd for $C_{29}H_{42}N_9O_4$ 580.3360, found 580.3366.

To the *N*-Boc-protected **3a** (1.25 g, 2.1 mmol) in CH_2Cl_2 (20 mL) was added TFA (2.4 mL, 31.5 mmol) at 0 °C, and the mixture was allowed to stir at rt for 9 h. The reaction mixture was added to water (75 mL) and the CH_2Cl_2 layer was separated. The aqueous layer was washed sequentially with hexane and ether (20 mL each). The aqueous layer was basified with aq. ammonia and extracted with CH_2Cl_2 (50 mL). The extract was dried over sodium sulfate, and the solvent was evaporated to give **3a** as a pale yellow solid in 83% yield (703 mg, 1.85 mmol), mp 192–195 °C, $[\alpha]_D^{34} = -18.3$ (*c* 1.08, $CHCl_3$), IR (CH_2Cl_2) 3323, 3141, 2957, 2872, 1607, 1574, 1432 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 1.44–1.47 (m, 2 H), 1.66–1.76 (m, 4H), 1.85–1.92 (m, 2H), 2.27 (s, 2H), 2.89 (t, *J* = 6.8 Hz, 4H), 3.55–3.59 (m, 2H), 4.17–4.22 (dd, *J* = 8.0, 13.4 Hz, 2H), 4.37–4.42 (dd, *J* = 4.4, 13.6 Hz, 2H), 7.77 (t, *J* = 8 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 2H), 8.29 (s, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 29.1, 46.5, 55.5, 58.0, 119.0, 123.1, 137.6, 148.1, 150.1, HRMS-ESI calcd for $C_{19}H_{26}N_9$ 380.2311; found 380.2311.

4.3. Synthesis of 1,3-bis(1-((*S*)-pyrrolidin-2-ylmethyl)-1*H*-1,2,3-triazol-4-yl)benzene 3b

Compound **1b** (400 mg, 3.17 mmol) and **2** (1.43 g, 6.3mm) gave *N*-Boc-protected **3b** as a foamy white solid after column chromatography over silica gel using ethyl acetate–hexane mixture (2:3 v/v) in 50% yield (920 mg, 1.6 mmol). mp 97–99 °C, ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 18H), 1.78–2.04 (br, 8H), 3.18–3.42 (br m, 4H), 4.17 (s, 2H), 4.48–4.66 (br m, 4H), 7.49 (t, *J* = 8 Hz, 1H), 7.79–7.86 (br, 4H), 8.27 (s, 1H), HRMS-ESI calcd for $C_{30}H_{42}N_8O_4Na$ ($M+Na^+$) 601.3227; found 601.3221. *N*-Boc-protected **3b** (0.45 g, 0.77 mmol) was treated with TFA to yield **3b** as a pale yellow semi solid (206 mg, 0.544 mmol, 70%), $[\alpha]_D^{34} = +16.6$ (*c* 1.0, $CHCl_3$), IR (neat) 3317, 3127, 2954, 2868, 2359, 1616, 1449, 1223, 1085, 1047 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 1.48–1.55 (m, 2H), 1.72–1.81 (m, 4H), 1.93–2.0 (m, 2H), 2.08 (br s, 2H), 2.94–2.97 (t, *J* = 6.8 Hz, 4H), 3.63–3.66 (m, 2H), 4.21–4.27 (dd, *J* = 8.0, 13.6 Hz, 2H), 4.43–4.48 (dd, *J* = 4.4, 13.6 Hz, 2H), 7.47 (t, *J* = 8Hz, 1H), 7.81–7.82 (d, *J* = 1.6 Hz, 1H), 7.831–7.835 (d, *J* = 1.6 Hz, 1H), 8.04 (s, 2H), 8.27 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 29.1, 46.6, 55.4, 58.03, 121.04, 122.8, 125.2, 129.4, 131.2, 147.1; HRMS-ESI calcd for $C_{20}H_{27}N_8$ 379.2359; found 379.2351.

4.4. (*S*)-2-(1-(Pyrolidine-2-ylmethyl)-1*H*-1,2,3-triazol-4-yl)pyridine 3c

Compound **1c** (500 mg, 4.8 mmol) was treated with **2** (1.097 g, 4.8 mmol) and CuI (92 mg, 0.48 mmol) to afford *N*-Boc-protected **3c** (1.2g, 75%). **3c** (0.55 g, 1.74 mmol) was treated with TFA to yield **3c** as a yellow oil (315 mg, 1.37 mm, 82%). Compound **3c** $[\alpha]_D^{34} = +13.2$ (*c* 1.0, $CHCl_3$), IR (neat) 3330, 2958,2871, 1600, 1467, 1420,1233, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.51–1.54 (m, 1H), 1.72–1.84 (m, 2H), 1.91–2.0 (m, 1H), 2.17 (br s, 1H), 2.9–2.98 (m, 2H), 3.61–3.68 (m, 1H), 4.25–4.31 (dd, *J* = 13.6, 7.6 Hz,1H), 4.42–4.47 (dd, *J* = 13.6, 4.8 Hz, 1H), 7.2–7.23 (m, 1H), 7.74–7.79 (dt, *J* = 7.6, 1.6 Hz, 1H), 8.15–8.17 (d, *J* = 8 Hz, 1H), 8.29 (s, 1H), 8.56–8.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 29.2, 46.6, 55.6, 58.0, 120.3, 122.8, 122.9, 136.9, 148.2, 149.4, 150.5; HRMS-ESI calcd for $C_{12}H_{16}N_5$ 230.1406; found 230.1408.

4.5. Representative procedure for the asymmetric Michael reaction

Compounds **3a** (25 mg, 0.067 mmol) and **5a** (100 mg, 0.67 mmol) were taken in a test tube, and 1.5 mL of water was added. The mixture was stirred, and then **4** (0.36 mL, 3.3 mmol) was added through a syringe at rt. The reaction was monitored by TLC for complete consumption of **5a** (16 h). The crude was extracted with ethyl acetate (15 mL), and the extract was filtered through a small pad of silica to remove **3a**. Removal of the solvent from the filtrate yielded the crude product. The ^1H NMR spectrum of the crude product was recorded and diastereomeric ratio was estimated from the peak integration. The crude product was purified by column chromatography on silica gel using a mixture of hexane and ethyl acetate as eluant to afford **6a** as a colorless solid (116 mg, 0.469 mmol, 70%). The enantiomeric ratio was obtained from chiral HPLC analysis of the purified product on Chiralpak AD-H or AS-H column using a mixture of hexane and 2-propanol as the eluant, as described in the individual cases. The Michael ad-

ducts were thoroughly characterized by NMR, MS, and HRMS data and by comparison with the literature-reported spectroscopic data.[6,9,10]

4.6. (*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclohexanone 6a[12]

Colourless solid, mp 128–130 °C, $[\alpha]_D^{34} = -27.5$ (*c* 1.2, $CHCl_3$); IR 3024, 2955, 2865, 1698, 1549, 1444, 1382 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.22–1.25 (m, 1H), 1.54–1.76 (m, 4H), 2.05 (m, 1H), 2.37–2.45 (m, 2H), 2.68–2.69 (m, 1H), 3.74–3.76 (m, 1H), 4.60–4.66 (dd, *J* = 10.4, 12.4 Hz, 1H), 4.91–4.95 (dd, *J* = 4.4 and 12.4 Hz, 1H), 7.15–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 28.6, 33.3, 42.8, 44.1, 52.7, 79.03, 127.9, 128.3, 129.07, 137.9, 211.9; HRMS-ESI calcd for $C_{14}H_{17}NO_3Na$ ($M+Na^+$) 270.1106; found 270.1101, HPLC: Chiralpak AS-H, hexane/2-propanol = 80/20, 0.5 mL/min, R_t = 16.6 (minor) and 22.3 (major), 99.0% ee. *syn*/*anti* = 97/3.

4.7. (*S*)-2-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone 6b[6b]

Colorless solid, ^1H NMR (400 MHz, $CDCl_3$) δ 1.18–1.27 (m, 1H), 1.5–1.8 (m, 4H), 2.07–2.1 (m, 1H), 2.2–2.48 (m, 2H), 2.61–2.68 (m, 1H), 3.73–3.79 (m, 1H), 4.57–4.63 (m, 1H), 4.9–4.94 (m, 1H), 7.10–7.12 (m, 2H), 7.26–7.3 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 28.5, 33.2, 42.8, 43.5, 52.6, 78.7, 129.3, 129.7, 133.8, 136.5, 211.5; HRMS-ESI calcd for $C_{14}H_{16}NO_3Cl$ Na ($M+Na^+$) 304.0716; found 304.0711, HPLC: Chiralpak AD-H, hexane/2-propanol = 90/10, 0.5 mL/min, R_t = 21.7 (minor) and 36.3 (major), 94.0% ee. *syn*/*anti* = 95/5.

4.8. (*S*)-2-((*R*)-1-(2-Methoxyphenyl)-2-nitroethyl) cyclohexanone 6c[8a]

Colorless oil, IR (neat) 2938, 2859, 1703, 1593, 1546, 1492, 1436, 1376, 1241 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18–1.21 (m, 1H), 1.58–1.75 (m, 4H), 2.03–2.09 (m, 1H), 2.33–2.49 (m, 2H), 2.97 (m, 1H), 3.83 (s, 3H), 3.92–3.98 (m, 1H), 4.78–4.87 (m, 2H), 6.86–6.91 (m, 2H), 7.07–7.09 (m, 1H), 7.18–7.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 28.6, 33.3, 41.3, 42.7, 50.7, 55.4, 77.6, 111.1, 120.9, 125.5, 129.0, 131.06, 157.7, 212.5; HRMS-ESI calcd for $C_{15}H_{19}NO_4$ Na ($M+Na^+$) 300.1212; found 300.1216, HPLC: Chiralpak AS-H, hexane/2-propanol = 90/10, 0.5 mL/min, R_t = 21.5 (minor) and 25.3 (major), 86.0% ee. *syn*/*anti* = 94/6.

4.9. (*S*)-2-((*R*)-2-Nitro-1-(2-nitrophenyl)ethyl) cyclohexanone 6d[8a]

Yellow oil, IR (neat) 2943, 2865, 1705, 1524, 1437, 1352 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 1.44–1.53 (m, 1H), 1.58–1.74 (m, 2H), 1.78–1.85 (m, 2H), 2.1–2.14 (m, 1H), 2.35–2.49 (m, 2H), 2.89–2.96 (m, 1H), 4.36–4.39 (dt, *J* = 8.8, 4.4 Hz, 1H), 4.85–4.96(m, 2H), 7.41–7.48 (m, 2H), 7.56–7.62 (t, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 28.4, 33.3, 38.8, 42.9, 52.3, 77.7, 125.06, 128.7, 129.4, 132.9, 133.2, 150.9, 211.1; HRMS-ESI calcd for $C_{14}H_{16}N_2O_5Na$ ($M+Na^+$) 315.0957; found 315.0958, HPLC: Chiralpak AD-H, hexane/2-propanol = 90/10, 1 mL/min, R_t = 20.86 (minor) and 34.5 (major), 93% ee. *syn*/*anti* = 92/8.

4.10. (*S*)-2-((*R*)-1-(3-Methoxyphenyl)-2-nitroethyl) cyclohexanone 6e[8a]

Colorless solid, mp 133–134 °C, IR 2940, 1699, 1603, 1583, 1549, 1488, 1448, 1433, 1382, 1291 cm^{-1}, ^1H NMR(400 MHz, $CDCl_3$) δ 1.23–1.3(m, 1H), 1.52–1.81(m, 4H), 2.05–2.11(m, 1H), 2.34–2.5 (m, 2H), 2.63–2.67 (m, 1H), 3.70–3.75 (m, 1H), 3.79 (s, 3H), 4.58–4.64 (dd, *J* = 10, 12.4 Hz, 1H), 4.90–4.94 (dd, *J* = 4.4, 12.8 Hz, 1H), 6.71–6.81 (m, 3H), 7.21–7.25 (t, *J* = 7.6 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 28.6, 33.3, 42.8, 44.1, 52.6, 55.3, 78.9, 112.8, 114.6, 120.4, 130.09, 139.5, 160.05, 211.9; HRMS-ESI calcd for $C_{15}H_{19}NO_4Na$ ($M+Na^+$). 300.1212; found 300.1215, HPLC: Chiralpak AS-H, hexane/2-propanol = 90/10, 1 mL/min, R_t = 13.8 (minor) and 31.1 (major), 93% ee. *syn*/*anti* = 94/6.

4.11. (*S*)-2-((*R*)-2-Nitro-1-*p*-tolylethyl)cyclohexanone 6f[8a]

Colorless solid, mp 128–129 °C, IR: 2934, 2862, 1705, 1549, 1437, 1377 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 1.21–1.24 (m, 1H), 1.53–1.8 (m, 4H), 2.02–2.11 (m, 1H), 2.3 (s, 3H), 2.33–2.49 (m, 2H), 2.63–2.69 (m, 1H), 3.68–3.74 (dt, *J* = 10, 4.4 Hz, 1H), 4.57–4.63 (dd, *J* = 9.6 and 12.0 Hz, 1H), 4.89–4.93 (dd, *J* = 4.8, 12.4 Hz, 1H), 7.03 and 7.11 (AA'BB', *J* = 8.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 25.1, 28.6, 33.3, 42.8, 43.7, 52.7, 79.1, 128.1, 129.7, 134.7, 137.5, 212.1; HRMS-ESI calcd for $C_{15}H_{19}NO_3Na$ ($M+Na^+$) 284.1263; found 284.1269; HPLC: Chiralpak AS-H, hexane/2-propanol = 95/5, 1 mL/min, R_t = 11.3 (minor) and 18.5 (major), 93% ee. *syn*/*anti* = 94/6.

4.12. (*S*)-2-((*R*)-2-Nitro-1-(3-nitrophenyl)ethyl) cyclohexanone 6g[12]

Pale yellow oil, IR: 2941, 2864, 2361, 1706, 1538, 1349 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 1.26–1.30 (m, 1H), 1.59–1.85 (m, 4H), 2.04–2.17 (m, 1H), 2.27–2.47 (m, 2H), 2.71–2.79 (m, 1H), 3.91–3.97 (dt, *J* = 9.6 and 4.4 Hz, 1H), 4.68–4.74 (dd, *J* = 10.2, 13 Hz, 1H), 4.98–5.02 (dd, *J* = 12.96, 4.48 Hz, 1H), 7.5–7.58 (m, 2H), 8.08 (t, *J* = 2 Hz, 1H), 8.13–8.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 28.4, 33.3, 42.8, 43.8, 52.4, 78.2, 123.06, 130.09, 134.9, 140.3, 148.7, 210.9; HRMS-ESI calcd for $C_{14}H_{16}N_2O_5Na$ ($M+Na^+$) 315.0957; found 315.0953, HPLC: Chiralpak AD-H, hexane/2-propanol = 90/10, 1 mL/min, R_t = 18.9 (minor) and 23.0 (major), 90% ee. *syn*/*anti* = 90/10.

4.13. (*S*)-2-((*S*)-1-(Furan-2-yl)-2-nitroethyl) cyclohexanone 6h[12]

Pale yellow oil, IR: 2940, 2864, 1706, 1551, 1376 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 1.27–1.3 (m,1H), 1.61–1.83 (m, 4H), 2.08–2.09 (m, 1H), 2.35–2.43 (m, 2H), 2.71–2.82 (m, 1H), 3.94–4.0 (m, 1H), 4.64–4.69 (dd, *J* = 12.2, 9.3 Hz, 1H), 4.76–4.8 (dd, *J* = 12.68, 4.88 Hz, 1H), 6.17 (m, 1H), 6.28 (m, 1H), 7.3 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 28.2, 32.5, 37.6, 42.6, 51.2, 75.2, 109.01, 110.4, 142.3, 151.09, 210.95; HRMS-ESI calcd for $C_{12}H_{15}NO_4Na$ ($M+Na^+$) 260.0899; found 260.0899, HPLC: Chiralpak AD-H, hexane/2-propanol = 95/5, 0.5 mL/min, R_t = 26.8 (major) and 33.6 (minor), 80% ee. *syn* /*anti* = 86/14.

4.14. (*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclo-pentanone 8[12]

Colorless solid, mp 101 °C, IR: 2967, 2360, 1731, 1595, 1550, 1377 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ 1.49–1.55 (m, 1H) 1.6–1.75 (m, 2H), 1.85–1.95 (m, 2H), 2.10–2.19 (m, 1H), 2.33–2.42 (m, 2H), 3.66–3.72 (dt, *J* = 9.2, 5.6 Hz, 1H), 4.68–4.74 (dd, *J* = 12.8, 9.6 Hz, 1H), 5.30–5.34 (dd, *J* = 12.8, 5.6 Hz, 1H), 7.12–7.19(m, 2H), 7.24–7.33 (m, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3, 28.4, 38.7, 44.3, 50.6, 78.4, 128.0, 128.1, 129.02, 137.8, 218.5; HRMS calcd for $C_{13}H_{15}NO_3Na$ (M + Na^+) 256.0950; found 256.0957, HPLC: Chiralpak AS-H, hexane/2-propanol = 80/20, 0.5 mL/min, R_t = 20.1 (minor) and 29.6 (major), 50% ee (syn) *syn*/*anti* = 75/25.

4.15. (3*R*,3a*S*)-3-Phenyl-3,3a,4,5,6,7-hexahydro-2*H*-indole 1-oxide 11[7]

Michael adduct **6a** (83 mg, 0.336 mmol) was dissolved in ethyl acetate (5 mL) in a single-necked flask and Pd/C (20 mg) was added. The flask was evacuated and a balloon filled with hydrogen was connected to the flask, and the contents of the flask was stirred at rt for 24 h. The reaction mixture was filtered through Celite and was concentrated. The crude product was subjected to silica gel chromatography ($MeOH/CH_2Cl_2$ = 1/99 by vol) to isolate the product. The product was dissolved in CH_2Cl_2 and washed with 0.1 M HCl to obtain pure **11** in 38% yield (11 mg, 0.051 mmol) (based on recovered starting material, 50 mg, 0.202 mmol), ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42–1.21 (m, 3H), 1.83 (m, 1H), 2.1–1.97 (m, 3H), 3.25–3.19 (m, 2H), 4.31–4.14 (m, 2H), 7.4–7.23 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 23.9, 24.4, 32.5, 46.1, 50.8, 68.4, 127.4, 127.6, 129.1, 140.0, 148.8, IR: 3060, 2934, 2858, 1630, 1447, 1222, 1177 cm^{-1}. Enantiomeric excess was determined by HPLC using chiralpak AD-H column using 2-propanol/hexane (10/90 v/v), 0.6 mL/min, R_t = 23.8 (major) and 30.6 (minor).

4.16. (*R*)-3-Nitro-2-phenyl-2H-chromene 10a[13c]

General procedure: β-nitrostyrene **5a** (25 mg, 0.16 mmol) and **3a** (12.7 mg, 0.033 mmol) were dissolved in DMF (1 mL) and allowed to stir at rt. Salicyaldehyde (**9a**, 0.025 mL, 0.25 mmol) was then added followed by powdered 4 Å molecular sieves (50 mg). The reaction was allowed to stir at rt for 24 h. The reaction mixture was diluted with 30 mL water and the product was extracted with CH_2Cl_2 (10 mL × 2). The CH_2Cl_2 layer was washed with ice cold 0.1 M NaOH solution, dried over sodium sulfate, filtered, and was evaporated. The crude product was subjected to silica gel column chromatography (0.5 mL ethyl acetate:99.5 mL hexane) to give product **10a** as a yellow solid in 30% yield (13 mg, 0.05 mmol). mp 94 °C, $[\alpha]_D^{34} = 10.4$ (*c* 1, $CHCl_3$), IR (CH_2Cl_2) 3063, 1647, 1604, 1509, 1455, 1322 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.5 (s,1H), 6.8 (d, *J* = 8.4 Hz, 1H), 6.9 (t, *J* = 7.6 Hz, 1H), 7.29–7.38 (m, 7H), 8.04 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 74.4, 117.4, 118.08, 122.6, 127.1, 128.9, 129.3, 129.6, 130.5, 134.4, 136.9, 153.7; Mass (EI): 253, 236, 207, 178. HPLC: Chiralpak AS-H, hexane/2-propanol = 98/2, 0.5 mL/min, R_t = 22.1(major) and 34.6 (minor), 24% ee.

4.17. (*S*)-7-Methoxy-2-methyl-3-nitro-2*H*-chromene 10b[13c]

Yellow solid, mp: 135 °C, IR 2937, 2840, 1608, 1557, 1496, 1325 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.7 (s,1H), 6.39 (d, *J* = 2.4 Hz, 1H), 6.55 (m, 2H) 7.22 (d, *J* = 8.4 Hz, 1H), 7.31–7.38 (m, 5H), 8.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 74.7, 102.4,109.9, 111.3, 127.1, 128.9, 129.5, 129.8, 131.8, 137.2, 155.8, 165.2; mass (ESI): 284 (M+1), 306 ($M+Na^+$), 322 ($M+K^+$), HPLC: Chiralpak AS-H, hexane/2-propanol = 90/10, 0.5 mL/min, R_t = 25.1 (minor) and 36.5 (major), 7% ee.

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