Enantioselective nitro-Michael reactions catalyzed by short peptides on water†

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Simple unmodified *N*-proline-based di- and tripeptides in combination with sodium hydroxide additive catalyze the asymmetric Michael reaction of ketones with nitroolefins to furnish the corresponding γ-nitroketones with up to 99% yield, 99:1 dr and 70% ee at room temperature and on water without any organic cosolvent.

Introduction

Catalytic asymmetric reactions that can be performed in or on water are of current interest, because water is cheap, safe, and unique reactivity and selectivity are often observed when water is used as a solvent.[1-3] In recent years, increasing attention has been paid to asymmetric organocatalytic reactions[4] in aqueous media.[3m,n,5-8] Until recently, important contributions were made for some C–C bond formation reactions—aldol,[5] Mannich,[6] Diels–Alder[7] and Michael[8] reactions—using water as a solvent.

Michael reactions, in particular, have in recent years been the subject of numerous advances aimed at the discovery of efficient chiral organocatalysts[9] and prominent examples of water-tolerant organocatalysts have also been noted for this reaction.[8]

While chiral pyrrolidine derivatives have been designed for Michael reactions under aqueous conditions,[8] surprisingly, no report is known on proline-based short peptides, catalyzing such reactions on water and without the addition of any organic cosolvents.[10] However, features such as straightforward accessibility from Nature's toolbox and modularity render unmodified peptidic catalysts with an enzyme-like character attractive alternatives to other organocatalysts.[11]

Herein, we describe a first study of unmodified proline-based di- and tripeptides as enantioselective catalysts for Michael additions of ketones to nitrostyrenes on water, providing access to valuable building blocks—γ-nitroketones.[12]

Results and discussion

Initially, we examined the *nitro*-Michael reaction of cyclohexanone (**6**) with *trans*-β-nitrostyrene (**5**) in the presence of short peptides **1–4** (Fig. 1), easily prepared from readily available α-amino acids using standard procedures of peptide chemistry.[10a,13]

First, we tested the catalytic activity of dipeptide H-Pro-Phe-OH (**1**) under various conditions. Such a reaction failed when carried out on water without any additives (entry 1, Table 1).

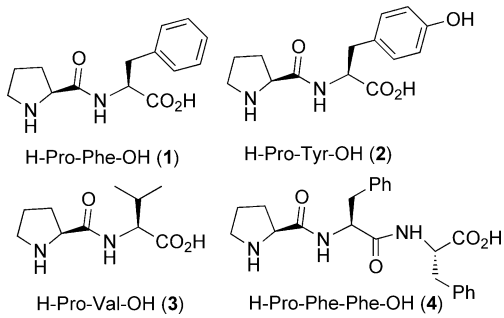

Fig. 1

Since in our previous work on primary amine-thiourea catalyzed nitro-Michael reactions, an improved performance was displayed when $AcOH/H_2O$ was used as an additive,[14] we carried out a further experiment with peptide **1** on water and in the presence of 30 mol% of AcOH. However, while H-Pro-Phe-OH (**1**) has now been dissolved, it still showed no activity under these conditions (entry 2, Table 1). Interestingly, changing the acidic additive to the basic one (NaOH, 30 mol%) led to a full conversion after 17 hours (entry 3, Table 1). We were pleased to see that the peptide has been dissolved very fast in the presence of NaOH and the reaction worked well to afford the product in high yield (99%), diastereoselectivity (95:5) and good enantioselectivity (68% ee). When brine was used instead of water, the reaction was slow (57% yield after 27 h) and the enantioselectivity decreased (12% ee, entry 4).

Phosphate buffer solutions with pH 7 and 10, respectively, were further used as a reaction medium. A buffer solution at pH 10 gave better results, but did not provide an equally good stereoselectivity and yield of the reaction, as was obtained on water with NaOH as an additive (entries 5 and 6 *vs.* entry 3, Table 1).

Next, other short peptides **2–4** were tested on water with NaOH additive. Dipeptide H-Phe-Tyr-OH (**2**) containing a C-terminal tyrosine moiety also mediated the asymmetric nitro-Michael reaction, but surprisingly, with lower yield (36%) and stereoselectivity (88:12 dr and 61% ee) than the corresponding peptide with C-terminal phenylalanine (entry 7 *vs.* entry 3, Table 1). Interestingly, H-Pro-Val-OH (**3**) catalyzed the asymmetric formation of **7** in 71% yield, with 93:7 dr and 66% ee. Thus, while the yield decreased, the stereoselectivity of this reaction remained nearly unchanged when going from C-terminal phenylalanine to valine (cf. entries 3 and 8), showing the beneficial effect of the neutral side chains (L-Phe and L-Val) compared to the functionalized

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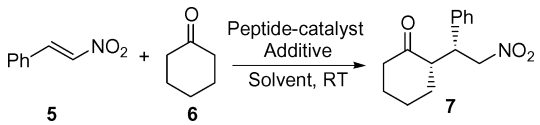
† Electronic supplementary information (ESI) available: NMR spectra of catalysts and catalytic products and HPLC chromatograms of the catalytic products in comparison with authentic racemic compounds. See DOI: 10.1039/b910249c

Table 1 Michael addition of cyclohexanone to *trans*-β-nitrostyrene catalyzed by peptides **1–4** on water and/or aqueous media



5 **6** **7**

Entry	Catalyst (mol%)	Additive (mol%)	Solvent	Time (h)	Yield (%)[a]	*syn*:*anti*[b]	ee (%)[c]
1	**1** (30)	—	H_2O	360	n.r.	—	—
2	**1** (30)	AcOH (30)	H_2O	408	n.r.	—	—
3	**1** (30)	NaOH (30)	H_2O	17	**99**	**95:5**	**68**
4	**1** (30)	NaOH (30)	brine	27	57	92:8	12
5	**1** (30)	—	PB[d] / pH 7	312	40	94:6	54
6	**1** (30)	—	PB[d] / pH 10	96	77	94:6	61
7	**2** (30)	NaOH (30)	H_2O	15	36	88:12	61
8	**3** (30)	NaOH (30)	H_2O	15	71	93:7	66
9	**4** (30)	NaOH (30)	H_2O	15	70	96:4	56
10	**1** (30)	LiOH (30)	H_2O	16	80	94:6	67
11	**1** (30)	KOH (30)	H_2O	18	75	94:6	44
12	**1** (30)	Li_2CO_3 (30)	H_2O	16	71	93:7	54
13	**1** (30)	NMM (30)	H_2O	72	80	94:6	63
14	**1** (10)	NaOH (10)	H_2O	144	72	92:8	59
15	**1** (5)	NaOH (5)	H_2O	264	trace	—	—
16	L-Pro (30)	—	H_2O	17	n.r.	—	—
17	L-Pro (30)	NaOH (30)	H_2O	17	52	86:14	23
18	—	NaOH (30)	H_2O	15	43	n.d.	—
19	AcONa (30)	—	H_2O	15	n.r.	—	—

[a] Yields of isolated products after column chromatography. [b] Determined by chiral-phase HPLC analysis (Daicel Chiralpak IA) of the crude product. [c] Enantioselectivities were determined for *syn*-product by chiral-phase HPLC analysis (Daicel Chiralpak IA) in comparison with authentic racemic material. [d] PB: phosphate buffer. n.r. = no reaction, n.d. = not determined, NMM = *N*-methylmorpholine.

residue (L-Tyr). Furthermore, the tripeptide H-Pro-Phe-Phe-OH (**4**) mediated the asymmetric assembly of product **7** in 70% yield with 96:4 dr and 56% ee (Table 1, entry 9). The size of the small peptide seems to be important for this transformation on water, since the yield and the enantioselectivity of the Michael reaction decreased with an additional C-terminal phenylalanine residue (cf. entry 3 and 9).

Apart from NaOH, we were interested in trying out other additives: LiOH, KOH, Li_2CO_3 and NMM. It can be seen in Table 1 that addition of 0.3 equiv of NaOH gave the best results concerning chemical yield, dr and ee (entry 3 *vs.* entries 10–13). Comparable diastereoselectivities and enantioselectivities, although slightly lower yields, were obtained with LiOH and NMM (entries 10 and 13 *vs.* entry 3). Additionally, NMM required longer time for completion. KOH and Li_2CO_3 gave lower yields and enantioselectivities (entries 11 and 12 *vs.* entry 3). Thus, we found that addition of 0.3 equiv of NaOH furnished the best results.

Next, we investigated the influence of the catalyst and additive loadings on the reaction outcome. A reduction in the amount of catalyst **1** and additive (NaOH) to 10 mol% resulted in a relatively slow reaction and still gave 72% yield, 92:8 dr and 59% ee within 144 h (Table 1, entry 14). No conversion was observed in the presence of 5 mol% of dipeptide **1** and additive (entry 15). Therefore we used 30 mol% of the combination dipeptide **1** and sodium hydroxide in further studies.

Also the potential of L-proline have been tested on water. While no reaction progress was detected after 17 hours in the presence of 30 mol% of L-proline, moderate yield (52%), good dr (86:14) and low enantioselectivity (23% ee) were observed with NaOH additive (entries 16 and 17), demonstrating the importance of the second amino acid moiety (*e.g.* Phe) for high yield and good stereoselectivity.

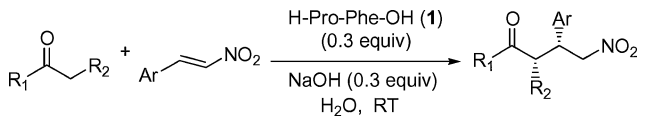
Interestingly, while the use of NaOH alone provided the Michael product with 43% yield, no reaction progress was detected with the salt AcONa (entries 18 and 19, Table 1). This observation implies that the influence of background reaction on the product yield and enantioselectivity in the H-Pro-Phe-OH/NaOH (1:1) catalyzed Michael reaction might be tiny (provided that any excess of NaOH is excluded).

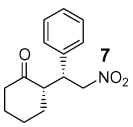
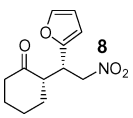
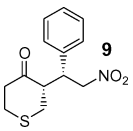
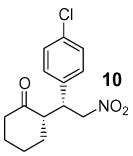
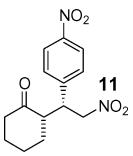
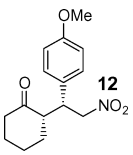
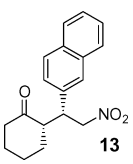
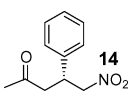
We next probed the scope of the reaction for different aromatic nitroolefins and Michael donors with selected dipeptide catalyst and additive (H-Pro-Phe-OH/NaOH) on water and the results are shown in Table 2. In all cases, reactions afforded *syn*-products. 2-Furyl-1-nitroethene underwent clean reaction with cyclohexanone affording the desired product in high yields and diastereoselectivity, but lower enantioselectivity as compared to *trans*-β-nitrostyrene (entry 1 *vs.* entry 2, Table 2). Interestingly, while only little effect on the stereoselectivity was observed, the yield decreased significantly when tetrahydrothiopyran-4-one was used instead of cyclohexanone in the reaction with β-nitrostyrene (entry 1 *vs.* entry 3, Table 2).

Both electron-rich and electron-deficient nitrostyrenes were shown to be good Michael acceptors for cyclohexanone and the reactions all occurred smoothly on water (Table 2, entries 4–7). The desired Michael products were obtained in good to high yields (75–96%) and showed excellent diastereoselectivities (*syn*:*anti* up to 99:1) and good enantioselectivities (58–70%).

An acyclic ketone donor—acetone—has also been tested under the previously optimized conditions but with less success. The reaction of acetone with *trans*-β-nitrostyrene (**5**) resulted in product with 23% yield and 20% ee.

Table 2 Examples of H-Pro-Phe-OH catalyzed nitro-Michael additions of different ketones to nitroolefins on water



Entry	Time (h)	Product	Yield (%)[a]	*syn*:*anti*[b]	ee (%)[c]
1	17	 **7**	99	95:5	68
2	26	 **8**	92	97:3	41
3	17	 **9**	65	94:6	59
4	28	 **10**	89	92:8	66
5	17	 **11**	78	92:8	70
6	48	 **12**	75	95:5	58
7	16	 **13**	96	99:1	64
8	17	 **14**	23	—	20

[a] Yield of isolated product after column chromatography on SiO_2. [b] Determined by chiral HPLC analysis (Daicel Chiralpak IA, see ESI†). [c] Enantioselectivities were determined by chiral HPLC analysis in comparison with authentic racemic material (Daicel Chiralpak IA, see ESI).

The stereoselectivities observed and the possible role of water we rationalized by means of the assumed transition state depicted in Fig. 2. The hydrogen bond between a water molecule and the amide oxygen atom of the peptide could increase the acidity of the amide NH and strengthen the related hydrogen bond with the nitro group of the *trans*-β-nitrostyrene. The additional positive effect of water could be ascribed to the hydrogen bonds formed between the nitro-group and a water molecule, which at the same time forms the hydrogen bond with the COO^- group of the catalyst, thus, stabilizing the transition state.

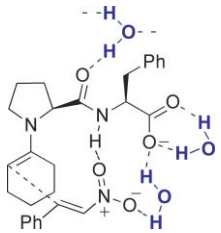


Fig. 2 Proposed transition state for the nitro-Michael reaction catalyzed by the salt H-Pro-Phe-O$^-$Na$^+$ on water.

Conclusion

In summary, we have demonstrated for the first time that short unmodified peptides in combination with basic additives (*e.g.* H-Pro-Phe-OH/NaOH) can catalyze asymmetric nitro-Michael addition reactions of ketones to nitroolefins on water without addition of organic cosolvents, giving good reactivity and stereoselectivity (up to 99% yield, 99:1 dr and 70% ee).

Further studies of short peptide-catalyzed C–C bond-forming reactions on water and DFT calculations on the mechanism of this peptide–aqueous media system are currently underway and will be reported in due course.

Experimental

General information

All commercially available reagents were used without purification and solvents were distilled prior to column chromatography. Optical rotations were measured with *PerkinElmer 341*. NMR spectra were recorded with *Bruker Avance 300*. Because of a better solubility, all peptides were measured as hydrochlorides. J values are given in Hz. FAB mass spectra were measured with a *Micromass: ZabSpec*, MALDI mass spectra were recorded with a *Shimadzu Biotech AXIMA Confidence* spectrometer. The enantiomeric and diastereomeric excess of products was determined by chiral HPLC analysis (using column *Chiralpak IA*) in comparison with authentic racemic material. Relative (*syn*) and absolute configuration of the known products **7–14** was determined by comparison with literature data. HPLC measurements were performed using *Agilent 1200 Series* enginery: *Vacuum Degasser G1322-90010*, *Quaternary Pump G1311-90010*, *Thermostated Column Compartment G1316-90010*, *Diode Array and Multiple Wavelength Detector SL G1315-90012*, *Standard and Preparative Autosampler G1329-90020* and *Agilent Chemstation for LC* software.

(*S*)-Prolyl-(*S*)-phenylalanine (H-Pro-Phe-OH) (1)[15a,b]. $[\alpha]_D^{25}$ –36.1 (c = 1, 1 N aq. HCl); NMR of H-Pro-Phe-OH·HCl: δ_H(300 MHz; DMSO[d6]) 1.69–1.95 (3 H, m, CH_2 Pro), 2.17–2.39 (1 H, m, CH_2 Pro), 2.93 (1 H, dd, *J* 9.4 and 13.9, CH_2 Phe),

3.12 (1 H, dd, *J* 4.6 and 13.9, CH_2 Phe), 3.01–3.31 (2 H, m, CH_2 Pro), 4.07–4.26 (1 H, m, α-C*H* Pro), 4.46 (1 H, ddd, *J* 4.6, 7.8 and 9.4, α-C*H* Phe), 7.16–7.34 (5 H, m, C_6H_5 Phe), 8.47 (1 H, br s, N*H*), 9.05 (1 H, d, *J* 7.8, NH), 10.27 (1 H, br s, N*H*) and 12.86 (1 H, br s, CO_2H); δ_C(300 MHz; DMSO[d6]) 23.76, 30.09, 36.55, 45.86, 54.45, 58.72, 126.90, 128.62, 129.47, 137.78, 168.67 and 172.60; *m*/*z* (FAB) 263 (MH^+, 100%), 154 (17%) and 136 (13%).

(*S*)-Prolyl-(*S*)-tyrosine (H-Pro-Tyr-OH) (2)[15a]. $[\alpha]_D^{25}$ −27.5 (c = 2, 3 N aq. HCl); NMR of H-Pro-Tyr-OH·HCl: δ_H(300 MHz; D_2O) 1.78–2.09 (3 H, m, CH_2 Pro), 2.23–2.42 (1 H, m, CH_2 Pro), 2.90 (1 H, dd, *J* 9.1 and 14.0, CH_2 Tyr), 3.09 (1 H, dd, *J* 5.8 and 14.0, CH_2 Tyr), 3.19–3.42 (3 H, m, CH_2 Pro, C_6H_4OH Tyr), 4.17–4.33 (1 H, m, α-C*H* Pro), 4.55 (1 H, dd, *J* 5.8 and 9.1, α–C*H* Tyr), 6.77 (2 H, d, *J* 8.3, 4-HO-C_6H_4 Tyr) and 7.08 (2 H, d, *J* 8.6, 4-HO-C_6H_4 Tyr); δ_C(300 MHz; D_2O) 23.12, 29.13, 34.90, 45.99, 52.42, 54.09, 58.91, 114.87, 127.68, 129.95, 153.90, 168.75, 172.57 and 173.83; *m*/*z* (MALDI) 279 (MH^+, 100%) and 301 (MNa^+, 25%).

(*S*)-Prolyl-(*S*)-valine (H-Pro-Val-OH) (3)[15c,d]. $[\alpha]_D^{25}$ −58.5 (c = 1, MeOH/concentrated aq. HCl 10:1); NMR of H-Pro-Val-OH·HCl: δ_H(300 MHz; DMSO[d6]) 0.91 (6 H, d, *J* 6.7, CH(CH_3)$_2$ Val), 1.74–1.83 (3 H, m, CH_2 Pro), 2.02–2.18 (1 H, *J* 5.5 and 6.7, CHC*H*(CH_3)$_2$ Val), 2.22–2.41 (1 H, m, CH_2 Pro), 3.07–3.28 (2 H, m, CH_2 Pro), 4.16 (1 H, dd, *J* 5.5 and 8.1, α-C*H* Val), 4.24–4.37 (1 H, m, α-C*H* Pro), 8.54 (1 H, br s, N*H*), 8.74 (1 H, d, *J* 8.1, N*H*), 10.33 (1 H, br s, N*H*) and 12.76 (1 H, br s, CO_2H); δ_C(300 MHz; DMSO[d6]) 17.82, 19.08, 23.41, 29.48, 29.81, 45.51, 57.70, 58.29, 168.55 and 172.22; *m*/*z* (FAB) 215 (MH^+, 100%).

(*S*)-Prolyl-(*S*)-phenylalanyl-(*S*)-phenylalanine (H-Pro-Phe-Phe-OH) (4)[15e]. $[\alpha]_D^{25}$ −27.6 (c = 1, MeOH/concentrated aq. HCl 10:1); NMR of H-Pro-Phe-Phe-OH·HCl: δ_H(300 MHz; DMSO[d6]) 1.40–1.90 (3 H, m, CH_2 Pro), 1.93–2.37 (1 H, m, CH_2 Pro), 2.62–3.24 (6 H, m, 2 × CH_2 Phe and Pro), 4.08 (1 H, m, α-C*H* Pro), 4.34–4.72 (2 H, m, α-C*H* Phe), 7.05–7.73 (10 H, m, 2 × C_6H_5 Phe), 8.39 (1 H, br s, N*H*), 8.53–9.12 (2 H, m, 2 × N*H*) and 10.32 (1 H, br s, CO_2H); δ_C(300 MHz; DMSO[d6]) = 23.38, 29.78, 36.46, 37.30, 45.47, 53.72, 54.54, 58.34, 126.34, 126.48, 128.05, 128.11, 128.18, 129.15, 129.20, 129.25, 137.15, 137.46, 137.53, 137.56, 167.88, 170.65, 170.79, 171.66 and 172.62; *m*/*z* (MALDI) = 410 (MH^+, 81%) and 432 (MNa^+, 100%).

General and representative procedure for Michael additions of cyclohexanone to *trans*-β-nitrostyrenes

The peptide catalyst (199.8 μmol, 0.3 eq) and sodium hydroxide (199.8 μmol, 0.3 eq) were stirred in water (2.127 ml) for 15 min at ambient temperature. Cyclohexanone (7.259 mmol, 10.9 eq) was added and the reaction system was equilibrated for further 15 min. Then the respective *trans*-β-nitrostyrene (667.0 μmol, 1.0 eq) was added. The biphasic system was stirred vigorously, until thin layer chromatography (petrol ether/ethyl acetate 6:1) indicated complete consumption of the *trans*-β-nitrostyrene. By addition of 1 N aqueous hydrochloric acid, the reaction mixture was adjusted to pH 1, the product was extracted with dichloromethane (3 × 20 ml), dried over $MgSO_4$ and evaporated. To purify the product, flash chromatography over silica gel was applied (petrol ether/ethyl acetate mixtures).

2-(2-Nitro-1-phenyl-ethyl)-cyclohexanone (7)[14a,16a,16d]. δ_H(300 MHz; DMSO[d6]) 1.04–1.22 (1 H, m), 1.41–1.79 (4 H, m), 1.88–2.06 (1 H, m), 2.21–2.55 (2 H, m), 2.75–2.93 (1 H, m), 3.72 (1 H, ddd, *J* 3.8, 4.6 and 10.7), 4.81 (1 H, dd, *J* 10.7 and 13.0), 5.00 (1 H, dd, *J* 4.6 and 13.0) and 7.21–7.44 (5 H, m); δ_C(300 MHz; DMSO[d6]) = 24.72, 28.29, 32.69, 42.45, 43.76, 51.75, 79.19, 127.59, 128.75, 128.83, 138.74 and 211.96; Chiral HPLC (Chiralpak IA, 2-PrOH/hexane 3:97, 1.00 ml/min, 210 nm, 25 °C): t_R 15.9 min (minor syn), 20.9 min (major syn), 17.4 min (anti) and 20.0 min (anti).

2-(1-Furan-2-yl-2-nitro-ethyl)-cyclohexanone (8)[16b,16d]. δ_H (300 MHz; $CDCl_3$) 1.12–1.31 (1 H, m), 1.43–1.83 (4 H, m), 1.94–2.10 (1 H, m), 2.22–2.45 (2 H, m), 2.59–2.78 (1 H, m), 3.40 (1 H, ddd, *J* 4.8, 4.8 and 9.3), 4.59 (1 H, dd, *J* 9.3 and 12.5), 4.72 (1 H, dd, *J* 4.8 and 12.5), 6.11 (1 H, dd, *J* 0.6 and 3.2), 6.21 (1 H, dd, *J* 1.9 and 3.2) and 7.27 (1 H, dd, *J* 0.6 and 1.9); δ_C (300 MHz; $CDCl_3$) 25.50, 28.62, 32.89, 37.05, 42.97, 51.46, 77.06, 109.39, 110.72, 142.74, 151.31 and 211.37; Chiral HPLC (Chiralpak IA, 2-PrOH/hexane 10:90, 1.00 ml/min, 210 nm, 25 °C): t_R 9.0 min (anti), 9.5 min (major syn), 10.8 min (anti) and 11.6 min (minor syn).

3-(2-Nitro-1-phenylethyl)-tetrahydro-thiopyran-4-one (9)[14a,16c,16d]. δ_H (300 MHz; $CDCl_3$) 2.38 (1 H, dd, *J* 9.4 and 13.8), 2.53 (1 H, ddd, *J* 1.5, 4.2 and 13.8), 2.64–3.03 (5 H, m), 3.91 (1 H, ddd, *J* 4.6, 4.6 and 9.7), 4.55 (1 H, dd, *J* 9.7 and 12.6), 4.68 (1 H, dd, *J* 4.6 and 12.6) and 7.09–7.33 (5 H, m); δ_C (300 MHz; $CDCl_3$) 31.51, 35.03, 43.39, 44.46, 54.87, 78.53, 128.08, 128.19, 129.21, 136.42 and 209.44; Chiral HPLC (Chiralpak IA, 2-PrOH/hexane 15:85, 0.95 ml/min, 210 nm, 25 °C): t_R 11.3 min (minor syn), 13.4 min (anti), 21.4 min (anti) and 25.6 min (major syn).

2-[1-(4-Chloro-phenyl)-2-nitro-ethyl]-cyclohexanone (10)[16c,16d]. δ_H (300 MHz; $CDCl_3$) 1.06–1.23 (1 H, m), 1.40–1.77 (4 H, m), 1.95–2.07 (1 H, m), 2.22–2.45 (2 H, m), 2.51–2.64 (1 H, m), 3.69 (1 H, ddd, *J* 4.5, 4.5 and 10.1), 4.52 (1 H, dd, *J* 10.1 and 12.6 Hz), 4.87 (1 H, dd, *J* 4.5 and 12.4), 7.05 (2 H, d, *J* 8.5 Hz) and 7.22 (2 H, d, *J* 8.5); δ_C (300 MHz; $CDCl_3$) 25.46, 28.86, 33.58, 43.15, 43.75, 52.75, 79.01, 129.52, 129.97, 133.97, 136.70 and 212.01; Chiral HPLC (Chiralpak IA, 2-PrOH/hexane 15:85, 0.95 ml/min, 210 nm, 25 °C): t_R 10.0 min (minor syn), 10.3 min (anti), 12.9 min (anti) and 13.6 min (major syn).

2-[2-Nitro-1-(4-nitro-phenyl)-ethyl]-cyclohexanone (11)[16e]. δ_H (300 MHz; $CDCl_3$) 1.16–1.37 (1 H, m), 1.49–1.87 (4 H, m), 2.00–2.19 (1 H, m), 2.27–2.55 (2 H, m), 2.65–2.82 (1 H, m), 3.94 (1 H, ddd, *J* 4.3, 4.4 and 10.0), 4.69 (1 H, dd, *J* 10.0 and 13.0), 5.01 (1 H, dd, *J* 4.4 and 13.0 Hz), 7.41 (2 H, d, *J* 8.8) and 8.19 (2 H, d, *J* 8.8); δ_C (300 MHz; $CDCl_3$) 25.50, 28.73, 33.61, 43.14, 44.13, 52.55, 78.40, 124.50, 129.75, 146.03, 147.80 and 211.36; Chiral HPLC (Chiralpak IA, 2-PrOH/hexane 15:85, 0.95 ml/min, 210 nm, 25 °C): t_R 23.0 min (minor syn), 28.1 min (anti), 34.3 min (anti) and 44.3 min (major syn).

2-[1-(4-Methoxy-phenyl)-2-nitro-ethyl]-cyclohexanone (12)[16b,16d]. δ_H (300 MHz; $CDCl_3$) 1.06–1.23 (1 H, m), 1.40–1.77 (4 H, m), 1.94–2.06 (1 H, m), 2.24–2.44 (2 H, m), 2.51–2.63 (1 H, m), 3.64 (1 H, ddd, *J* 4.6, 4.6 and 10.0), 3.70 (3 H, s), 4.50 (1 H, dd, *J* 10.0

and 12.3), 4.84 (1 H, dd, *J* 4.6 and 12.3), 6.77 (2 H, d, *J* 8.7) and 7.01 (2 H, d, *J* 8.7); δ_C (300 MHz; $CDCl_3$) 24.94, 28.47, 33.08, 42.66, 43.14, 52.59, 55.14, 79.04, 114.21, 129.10, 129.46, 158.92 and 212.03; Chiral HPLC (Chiralpak IA, 2-PrOH/hexane 15:85, 0.50 ml/min, 210 nm, 25 °C): t_R 18.8 min (minor syn), 20.1 min (anti), 22.0 min (major syn) and 23.7 min (anti).

2-(1-Naphth-2-yl-2-nitro-ethyl)-cyclohexanon (13)[16b,16d]. δ_H (300 MHz; $CDCl_3$) 1.04–1.24 (1 H, m), 1.27–1.73 (5 H, m), 1.85–2.06 (1 H, m), 2.18–2.46 (2 H, m), 2.58–2.79 (1 H, m), 3.85 (1 H, ddd, *J* 4.4, 4.5 and 10.2), 4.62 (1 H, dd, *J* 10.2 Hz and 12.5), 4.93 (1 H, dd, *J* 4.5 and 12.5), 7.15–7.24 (1 H, m), 7.32–7.44 (2 H, m), 7.56 (1 H, s) and 7.64-7.78 (3 H, m); δ_C (300 MHz; $CDCl_3$) 25.42, 28.93, 33.75, 43.19, 44.51, 52.82, 79.29, 125.67, 126.60, 126.87, 128.10, 128.23, 129.29, 133.22, 133.74, 135.55 and 212.37; Chiral HPLC (Chiralpak IA, 2-PrOH/hexane 15:85, 0.50 ml/min, 210 nm, 25 °C): t_R 24.3 min (minor syn), 27.3 min (major syn) and 29.2 min (both anti).

5-Nitro-4-phenyl-pentan-2-one (14)[14a,16f]. δ_H (300 MHz; DMSO[d6]) 2.03 (3 H, s), 2.92 (2 H, d, *J* 7.1), 3.78–3.90 (1 H, m), 4.77 (1 H, dd, *J* 9.4 and 12.9, 1H), 4.87 (1 H, dd, *J* 6.0 and 12.9) and 7.21–7.36 (5 H, m); δ_C (300 MHz; DMSO[d6]) 29.98, 38.78, 45.59, 79.41, 127.13, 127.57, 128.42, 139.84 and 205.92; Chiral HPLC (Chiralpak IA, 2-PrOH/hexane 3:97, 1.00 ml/min, 210 nm, 25 °C): t_R 16.5 min (*S*) and 17.6 min (*R*).

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