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Highly enantioselective tandem double Michael reactions catalyzed by Ni(acac)$_2$/(+)-MINBOL complex

Yu-Ming Hung, Chih-Hao Tseng, Biing-Jiun Uang *

Department of Chemistry, National Tsing Hua University, Hsinchu 300, Taiwan

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ABSTRACT

An in situ prepared complex of chiral ligand (+)-MINBOL **1** and Ni(acac)$_2$ (12.5 mol % and 0.5 mol % respectively) can efficiently catalyze enantioselective tandem double Michael reactions. In this reaction, aryl or alkyl nitroalkenes were employed as electrophiles. The corresponding tandem adducts were obtained in good yields and with high enantioselectivities (up to 97% ee).

1. Introduction

Asymmetric tandem transformations are considered as useful tools for the preparation of chiral compounds with multiple stereogenic centres. The noteworthy feature of tandem reactions is the access to complex molecules without any purification of possible intermediates. As such, considerable efforts have been focused on the development of asymmetric tandem reactions.[1] The Michael addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds is one of the most powerful carbon–carbon bond forming reactions. Over the past few decades, enantioselective metal-catalyzed conjugate additions of dialkyl zinc reagents to Michael acceptors have been studied extensively.[2] The crucial characteristic of these reactions is the generation of optically active zinc enolates. These enolates can further react with various electrophilic reagents and generate a wide range of products with complex functionalities.[3,4]

Nitro compounds have been extensively utilized in organic synthesis due to their synthetic versatility.[5] Moreover, nitroolefins are good Michael accepters because they are easily accessible and the resulting products can be further elaborated upon to give important synthetic intermediates or natural products.[6] Previously, we reported that enantioselective conjugate addition of dialkylzincs to acylic α,β-unsaturated enones could be successfully catalyzed by the chiral ligand (+)-MINBOL **1** and Ni(acac)$_2$.[7,8] Nitroalkenes were therefore selected as electrophiles to extend the scope of this methodology. Herein, we report highly diastereoselective and enantioselective tandem double Michael reactions catalyzed by (+)-MINBOL **1** and Ni(acac)$_2$.

2. Result and discussion

At first, we investigated the temperature effect on the electrophilic trapping reaction of the chiral zinc enolate that was formed in the Ni(acac)$_2$/(+)-MINBOL **1** complex catalyzed asymmetric conjugate addition of Et$_2$Zn to chalcone **2a** at −50 °C. When chalcone **2a** was completely transformed into the corresponding chiral zinc enolate, as judged by TLC analysis, one equivalent of *trans*-β-nitrostyrene **3a** was added to the reaction mixture for the second Michael addition. After the addition of *trans*-β-nitrostyrene **3a**, the reaction temperature was set at −30 °C. γ-Nitro ketone **4a** was obtained after 48 h in 65% yield and with 92% ee (Table 1, entry 1). Moreover, only one of four possible diastereomers was detected (>20:1 dr, determined by crude ^{1}H NMR). With this encouraging result, we decided to further screen for the optimal conditions. When the reaction temperature was increased from −30 °C to 0 °C, the electrophilic trapping reaction time shortened from 48 h to 3 h with a gradual improvement of yield (65–82%) (Table 1, entries 1–4) and enantioselectivities (92–95%) (Table 1, entries 1–4). However, it showed no significant improvement in yield when the reaction temperature was increased to 10 °C (Table 1, entry 5). The control experiment was also investigated as illustrated in Figure 1.[3o] The β-ethylated Michael adduct **5** was converted into the corresponding enolate by using LDA. After the addition of nitroalkene **3a**, the enolate was captured without Ni(acac)$_2$ and (+)-MINBOL **1**. The double Michael product **4a** was obtained in relatively poor yield with the same enantioselectivity as the starting material **5** but moderate diastereoselectivity (dr 6:1). On the other hand, the lithium enolate was reacted with nitroalkene **3a** in the presence of a chiral complex to provide the γ-nitro ketone **4a** in 50% yield with the similar stereoselectivity as the previous one. These results were then compared with those obtained from the catalytic system. It was suggested that

* Corresponding author.
E-mail address: bjuang@mx.nthu.edu.tw (B.-J. Uang).

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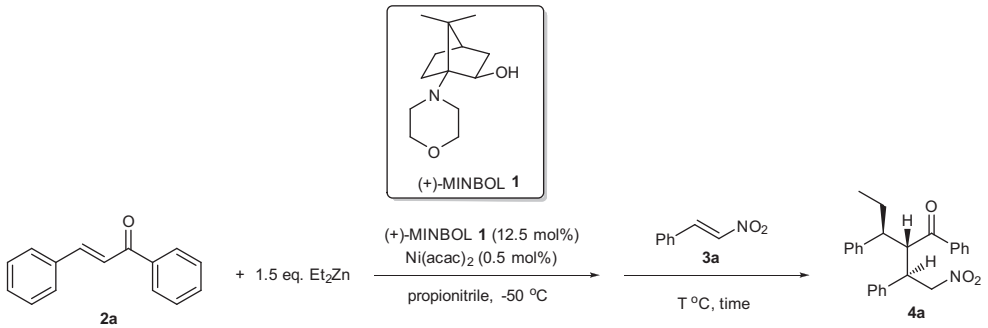
Table 1
Temperature effects on the electrophilic trapping reaction



Entry	*T* (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1	−30	48	65	92
2	−20	24	70	95
3	−10	10	79	95
4	0	3	82	95
5	10	2	82	88

[a] Isolated yield.
[b] Determined by chiral HPLC using Chiralcel AD-H column.

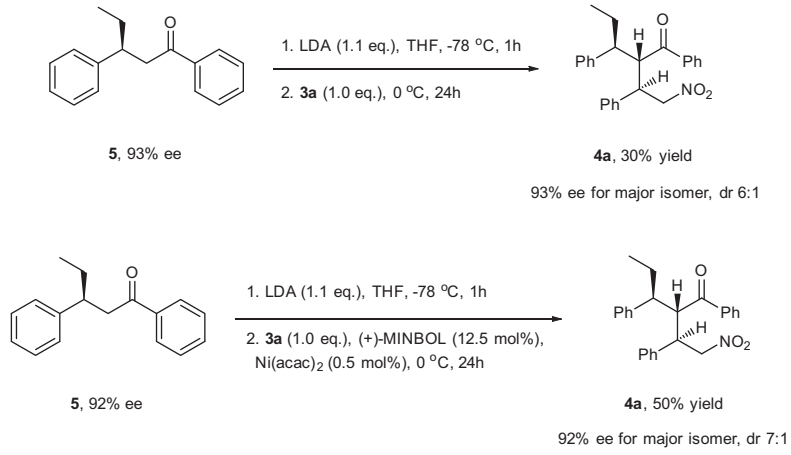
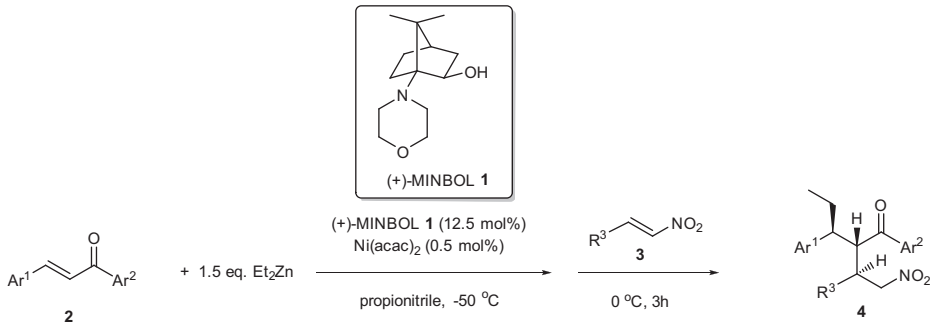


Figure 1. The control experiment of tandem double Michael reaction.

the zinc enolate was critical for chelating with the in situ prepared chiral complex from $Ni(acac)_2$ and (+)-MINBOL **1** and that the complex promotes the second Michael addition.

The optimized condition (Table 1, entry 4) was adopted for studying the substrate scope. At first, *trans*-β-nitrostyrenes **3** with electron-donating or electron-withdrawing groups at the *para*- or *meta*-position of the β-phenyl group of the aromatic nitroolefins were subjected to the catalytic system. The results are summarized in Table 2. The substituents at the *para*- or *meta*-position of the β-phenyl group of the nitroolefin did not significantly affect the reactivity, diastereoselectivity or enantioselectivity. The corresponding adducts were all obtained in good yields and with excellent enantioselectivities (Table 2, entries 1–9). Notably, the branched aliphatic nitroalkene **3j** and unbranched aliphatic nitroalkene **3k** were examined and both provided the corresponding product in satisfactory yields with high enantioselectivities (Table 2, entries 10 and 11). To further explore the scope of the catalytic system, we also applied the reaction to several substituted chalcones **2**. Moderate yields and high enantioselectivities were observed regardless of the various chalcones **2** (Table 2, entries 12–17). However, the reaction time of the electrophilic trapping step required 6 h to consume the *trans*-β-nitrostyrenes **3** completely, probably due to the electronic effect of the substituted chalcones. It is worthwhile noting that all of the corresponding adducts were determined as nearly a single diastereomer from crude ^{1}H NMR studies. In order to determine the absolute configuration of the adduct, we prepared the bromo-containing adduct **4q** (Table 2, entry 17). We were able to obtain single crystals of compound **4q**. The absolute configuration of tandem adduct **4q** was confirmed unambiguously to be (2*S*,3*S*,2′*R*) by X-ray crystallography (Fig. 2)[9] given the known configuration of (*S*)-**5**.[8] The relative configuration within the other adducts was assigned by the correlation of their ^{1}H NMR splitting patterns with those in **4q** and the absolute configuration assigned by analogy.

Table 2
The scope of the selected substrates



Entry	Ar^1	Ar^2	Ar^3	Yield[a] (%)	ee[b] (%)
1	Ph	Ph	Ph	**4a**, 82	95
2	Ph	Ph	4-MePh	**4b**, 78	95
3	Ph	Ph	4-BrPh	**4c**, 79	96
4	Ph	Ph	4-MeOPh	**4d**, 76	97
5	Ph	Ph	4-ClPh	**4e**, 84	97
6	Ph	Ph	3-CF_3Ph	**4f**, 76	96
7	Ph	Ph	3-ClPh	**4g**, 83	94
8	Ph	Ph	3-BrPh	**4h**, 74	96
9	Ph	Ph	3-MeOPh	**4i**, 68	97
10	Ph	Ph	^{i}Pr	**4j**, 70	97
11	Ph	Ph	^{n}Pr	**4k**, 75	97
12[c]	4-MeOPh	Ph	Ph	**4l**, 73	96
13[c]	4-MePh	Ph	Ph	**4m**, 73	96
14[c]	4-ClPh	Ph	Ph	**4n**, 70	93
15[c]	3-ClPh	Ph	Ph	**4o**, 67	93
16[c]	Ph	4-ClPh	Ph	**4p**, 66	95
17[c]	4-MeOPh	Ph	4-BrPh	**4q**, 84	91

[a] Isolated yield.
[b] Determined by chiral HPLC using Chiralcel AD-H column.
[c] The electrophilic trapping reaction required 6 h to complete the reaction.

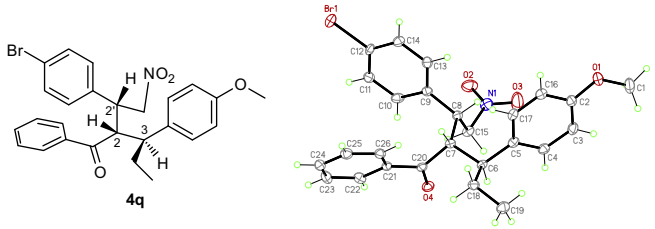


Figure 2. X-ray crystallography of **4q**.

In order to further demonstrate the synthetic utility of this methodology, we successfully conducted the gram-scaled reaction by using 1 g of *trans*-chalcone **2a** as the starting material. The tandem adduct **4a** was readily obtained after 3 h in 66% yield and with 97% ee (Fig. 3).

3. Conclusion

We have demonstrated that the in situ prepared catalytic system from the $Ni(acac)_2$/(+)-MINBOL **1** complex could catalyze the asymmetric tandem double Michael reactions effectively. This reaction leads to the synthesis of γ-nitro ketones with three contiguous stereogenic centres. The tandem adducts were obtained in good yields and with 91–97% ee, which could be further elaborated to enantioenriched pyrrolidines through reported methods.[3p,q] These results encourage us to further investigate their application in the synthesis of chiral intermediates for biologically active molecules or natural products.

4. Experimental

4.1. General

All reactions were performed in flame-dried apparatus under an argon atmosphere. All chemicals were purchased from commercial

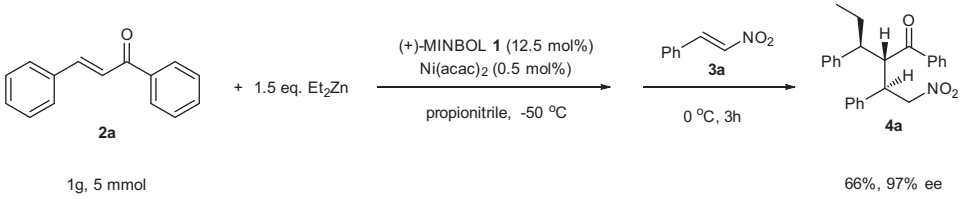


Figure 3. Gram-scale reaction.

suppliers and used as received. Propionitrile was distilled under an argon atmosphere from CaH_2 before use. Column chromatography was performed on silica gel with the indicated eluent. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz with Bruker-400 MHz spectrometer. Abbreviations for ^1H NMR: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass analyses were recorded on Bruker Impact HD. Optical rotations were determined by using a JASCO DIP-100 polarimeter.

4.1.1. General procedure for the enantioselective tandem double Michael reactions

To a flask were added chiral ligand (+)-MINBOL **1** (0.028 g, 0.125 mmol), $Ni(acac)_2$ (0.0013 g, 0.005 mmol) and propionitrile (1.0 mL). The mixture was refluxed for 1 h, then cooled to room temperature followed by the addition of *trans*-chalcone **2a** (0.209 g, 1 mmol) in propionitrile (1.0 mL). The resulting mixture was stirred for 15 min. at room temperature then cooled to −50 °C. A diethylzinc solution (1.0 M in hexane, 1.5 mmol) was added dropwise to the above mixture. After complete conversion of the enone to the zinc enolate, which was confirmed by TLC, *trans*-β-nitrostyrene **3a** (0.150 g, 1 mmol) in 2.0 mL of propionitrile was added and the corresponding mixture was further stirred at 0 °C for an additional 3 h. The reaction was quenched by 1 M $HCl_{(aq)}$. The mixture was extracted with ether (10 mL for three times), and the combined organic layer was dried over anhydrous Na_2SO_4, and concentrated to give the crude product. The desired product was obtained after column chromatography on silica gel (ethyl acetate/hexane = 1:20). The dr ratio was determined by ^1H NMR. The ee values were determined by HPLC on a chiralcel AD-H column.

4.1.1.1. (2*S*,3*S*)-2-((*R*)-2-Nitro-1-phenylethyl)-1,3-diphenylpentan-1-one 4a[3o,p]. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.56 (t, J = 7.2 Hz, 3H), 1.38–1.53 (m, 2H), 2.90 (td, J = 3.2 Hz, 10.4 Hz, 10.4 Hz, 1H), 3.60 (m, 1H), 4.1 (dd, J = 4.8 Hz, J = 10.0 Hz, 1H), 4.90 (dd, J = 3.6 Hz, J = 13.6, 1H), 5.02 (t, J = 11.6 Hz, 1H), 6.95 (m, 2H), 7.07–7.13 (m, 3H), 7.22–7.31 (m, 5H), 7.36–7.46 ppm (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 27.0, 44.0, 49.4, 56.0, 75.2, 127.3, 127.6, 128.0, 128.3, 128.8, 129.1, 133.2, 138.1, 138.6, 140.9, 204.0 ppm. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 1.0 mL/min, UV 254 nm; t(minor) = 10.9 min, t(major) = 17.4 min; 95% ee. $[\alpha]_D^{22.4}$ = −26.9 (c 1.0, CH_2Cl_2).

4.1.1.2. (2*S*,3*S*)-2-((*R*)-2-Nitro-1-*p*-tolylethyl)-1,3-diphenylpentan-1-one 4b[3o]. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.56 (t, J = 7.2 Hz, 3H), 1.41–1.53 (m, 2H), 2.17 (s, 3H), 2.89 (td, J = 3.2 Hz, 10.4 Hz, 10.4 Hz, 1H), 3.57 (m, 1H), 4.10 (dd, J = 4.8 Hz, J = 10.6, 1H), 4.86 (dd, J = 3.6 Hz, J = 13.6 Hz, 1H), 4.96 (t, J = 12.4 Hz, 1H), 6.84 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 8.0, 2H), 7.20–7.29 (m, 5H), 7.34–7.47 ppm (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 20.9, 26.7, 43.8, 49.4, 56.0, 75.6, 127.2, 127.3, 128.0, 128.3, 129.0, 129.5, 133.1, 135.0, 137.3, 138.7, 141.0, 204.1 ppm. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 1.0 mL/min, UV 254 nm; t(minor) = 10.8 min, t(major) = 13.3 min; 95% ee. $[\alpha]_D^{22.6}$ = −27.0 (c 1.0, CH_2Cl_2).

4.1.1.3. (2*S*,3*S*)-2-((*R*)-1-(4-Bromophenyl)-2-nitroethyl)-1,3-diphenyl-pentan-1-one 4c[3o,p]. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.56 (t, J = 7.2 Hz, 3H), 1.41–1.52 (m, 2H), 2.90 (td, J = 3.6 Hz, 10.4 Hz, 10.4 Hz, 1H), 3.51–3.56 (m, 1H), 4.07 (dd, J = 4.8 Hz, J = 10.0 Hz, 1H), 4.89 (dd, J = 4.4 Hz, J = 14 Hz, 1H), 4.92–4.99 (m, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.21–7.31 (m, 7H), 7.36–7.40 (m, 2H), 7.45–7.51 ppm (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 27.0, 43.7, 49.5, 55.6, 75.2, 122.5, 127.5, 127.9, 128.1, 128.5, 129.1, 129.2, 131.9, 133.5, 137.2, 138.4, 140.1, 203.6 ppm. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 1.0 mL/min, UV 254 nm; t(major) = 11.6 min, t(minor) = 13.7 min; 96% ee. $[\alpha]_D^{22.8}$ = −30.2 (c 1.0, CH_2Cl_2).

4.1.1.4. (2*S*,3*S*)-2-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)-1,3-diphenyl-pentan-1-one 4d[3o,p]. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.56 (t, J = 7.2 Hz, 3H), 1.37–1.55 (m, 2H), 2.90 (td, J = 3.2 Hz, 10.4 Hz, 10.4 Hz, 1H), 3.55–3.60 (m, 1H), 3.65 (s, 3H), 4.10 (dd, J = 4.8 Hz, J = 9.6 Hz, 1H), 4.87 (dd, J = 3.6 Hz, J = 13.2 Hz, 1H), 4.92–4.98 (m, 1H), 6.64 (d, J = 8.4, 2H), 6.87 (d, J = 8.4 Hz, 2H), 7.21–7.30 (m, 5H), 7.36 (t, J = 7.2 Hz, 2H), 7.43 (t, J = 7.2 Hz, 1H), 7.49 ppm (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 26.7, 43.4, 49.3, 55.1, 56.0, 75.7, 114.1, 127.2, 127.9, 128.1, 128.4, 128.9, 129.9, 133.2, 138.6, 140.9, 158.8, 204.1 ppm. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 1.0 mL/min, UV 254 nm; t(minor) = 13.0 min, t(major) = 15.5 min; 97% ee. $[\alpha]_D^{22.8}$ = −23.7 (c 1.0, CH_2Cl_2).

4.1.1.5. (2*S*,3*S*)-2-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)-1,3-diphenyl-pentan-1-one 4e[3o,p]. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.56 (t, J = 7.2 Hz, 3H), 1.41–1.52 (m, 2H), 2.90 (td, J = 3.6 Hz, 10.4 Hz, 10.4 Hz, 1H), 3.53–3.58 (m, 1H), 4.08 (dd, J = 4.4 Hz, J = 10.0 Hz), 4.89 (dd, J = 4.0 Hz, J = 13.6 Hz, 1H), 4.93–4.99 (m, 1H), 6.87 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.22–7.31 (m, 5H), 7.36–7.40 (m, 2H), 7.45–7.51 ppm (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 27.0, 43.6, 49.4, 55.7, 75.2, 127.4, 127.9, 128.1, 128.5, 128.7, 128.9, 129.1, 133.4, 133.48, 136.7, 138.4, 140.7, 203.6 ppm. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 1.0 mL/min, UV 254 nm; t(major) = 10.3 min, t(major) = 11.8 min; 97% ee. $[\alpha]_D^{22.8}$ = −29.9 (c 1.0, CH_2Cl_2).

4.1.1.6. (2*S*,3*S*)-2-((*R*)-2-Nitro-1-(3-(trifluoromethyl)phenyl) ethyl)-1,3-diphenylpentan-1-one 4f. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.58 (t, J = 7.2 Hz, 3H), 1.39–1.52 (m, 2H), 2.94 (td, J = 4.0 Hz, 10.4 Hz, 10.4 Hz, 1H), 3.60–3.65 (m, 1H), 4.11 (dd, J = 4.8 Hz, J = 10.4 Hz, 1H), 4.93 (dd, J = 4.0 Hz, J = 14.0 Hz, 1H), 4.99–5.05 (m, 1H), 7.09–7.14 (m, 2H), 7.20 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 6.8 Hz, 2H), 7.32 (t, J = 7.2 Hz, 2H), 7.39–7.46 (m, 3H), 7.50 ppm (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 27.5, 43.9, 49.4, 55.5, 74.7, 124.2, 124.5, 127.5, 127.9, 128.0, 128.3, 128.5, 129.2, 129.3, 130.7, 130.9, 133.6, 138.2, 139.2, 140.5, 203.3 ppm. HRMS (ESI) calcd for $C_{26}H_{24}F_3NNaO_3$ [M+Na]: 478.1600, found 478.1611. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 1.0 mL/min, UV 254 nm; t(minor) = 6.7 min, t(major) = 11.4 min; 96% ee. $[\alpha]_D^{22.9}$ = −17.9 (c 1.0, CH_2Cl_2).

4.1.1.7. (2*S*,3*S*)-2-((*R*)-1-(3-Chlorophenyl)-2-nitroethyl)-1,3-diphenyl-pentan-1-one 4g[3o]. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.57 (t, J = 7.2 Hz, 3H), 1.40–1.52 (m, 2H), 2.92 (td, J = 3.6 Hz, 10.4 Hz, 10.4 Hz, 1H), 3.51–3.55 (m, 1H), 4.08 (dd, J = 4.8 Hz, J = 10.4 Hz, 1H), 4.90 (dd, J = 3.6 Hz, J = 13.6 Hz, 1H), 4.95–5.00 (m, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.92 (s, 1H), 6.97–7.05 (m, 2H), 7.26–7.33 (m, 3H), 7.39 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 7.2 Hz, 1H), 7.52 ppm (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 27.2, 43.7, 49.4, 55.5, 74.8, 125.2, 127.4, 127.7, 127.8, 127.9, 128.0, 128.5, 129.2, 129.9, 133.4, 134.6, 138.4, 140.2, 140.6, 203.5 ppm. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 1.0 mL/min, UV 254 nm; t(minor) = 9.1 min, t(major) = 20.7 min; 94% ee. $[\alpha]_D^{22.9}$ = −24.3 (c 1.0, CH_2Cl_2).

4.1.1.8. (2*S*,3*S*)-2-((*R*)-1-(3-Bromophenyl)-2-nitroethyl)-1,3-diphenyl-pentan-1-one 4h. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.57 (t, J = 7.2 Hz, 3H), 1.40–1.52 (m, 2H), 2.92 (td, J = 3.6 Hz, 10.4 Hz, 10.4 Hz, 1H), 3.49–3.54 (m, 1H), 4.08 (dd, J = 4.8 Hz, J = 10.4 Hz, 1H), 4.89 (dd, J = 3.6 Hz, J = 13.6 Hz, 1H), 4.93–4.99 (m, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 7.06 (s, 1H), 7.19 (d, 8.0 Hz, 1H), 7.25–7.33 (m, 5H), 7.39 (d, J = 7.6 Hz,

2H), 7.46 (t, J = 7.6 Hz, 1H), 7.52 ppm (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 27.3, 43.7, 49.4, 55.6, 74.8, 122.8, 125.7, 127.5, 127.9, 128.1, 129.2, 130.3, 130.7, 130.8, 133.5, 138.4, 140.5, 140.6, 203.5 ppm. HRMS (ESI) calcd for $C_{25}H_{24}BrNNaO_3$ [M+Na]: 488.0832, found 488.0835. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 1.0 mL/min, UV 254 nm; t(minor) = 9.3 min, t(major) = 22.0 min; 96% ee. $[\alpha]_D^{22.9}$ = −21.4 (c 1.0, CH_2Cl_2).

4.1.1.9. (2*S*,3*S*)-2-((*R*)-1-(3-Methoxyphenyl)-2-nitroethyl)-1,3-diphenyl-pentan-1-one 4i[3p]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.57 (t, J = 7.6 Hz, 3H), 1.41–1.55 (m, 2H), 2.93 (td, J = 3.2 Hz, 10.4 Hz, 10.4 Hz, 1H), 3.57 (s, 3H), 4.10 (dd, J_1 = 4.8 Hz, J_2 = 10 Hz, 1H), 4.89 (dd, J_1 = 4.0 Hz, J_2 = 13.6 Hz, 1H), 4.95–5.01 (m, 1H), 6.45 (s, 1H), 6.53 (d, J = 7.6 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 7.01 (t, J = 8.0 Hz, 1H), 7.23–7.30 (m, 5H), 7.36–7.45 (m, 3H), 7.50 ppm (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 26.6, 43.9, 49.1, 54.6, 55.4, 75.1, 112.7, 112.9, 119.3, 127.0, 127.8, 128.1, 129.6, 132.9, 138.3, 139.5, 140.7, 159.5, 203.6 ppm. HRMS (ESI) calcd for $C_{26}H_{27}NNaO_4$ [M+Na]: 440.1832, found 440.1839. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 1.0 mL/min, UV 254 nm; t(minor) = 12.1 min, t(major) = 23.3 min; 97% ee. $[\alpha]_D^{22.8}$ = −38.8 (c 1.0, CH_2Cl_2).

4.1.1.10. (2*S*,3*S*)-4-Methyl-3-(nitromethyl)-1-phenyl-2-((*S*)-1-phenylpropyl)pentan-1-one 4j. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.56 (t, J = 7.6 Hz, 3H), 0.63 (d, J = 6.8 Hz, 3H), 0.70 (d, J = 7.2 Hz, 3H), 1.43–1.54 (m, 2H), 2.18–2.24 (m, 1H), 2.85 (td, J = 4.0 Hz, 10.8 Hz, 10.8 Hz), 4.13 (dd, J = 2.4 Hz, J = 10.4 Hz), 4.48 (dd, J = 10.4 Hz, J = 14.4 Hz), 4.99 (dd, J = 2.4 Hz, J = 14.0 Hz), 7.22–7.30 (m, 2H), 7.35–7.39 (m, 2H), 7.51–7.50 (m, 2H), 7.60–7.64 (m, 1H), 8.04 ppm (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4, 19.3, 19.9, 27.9, 29.7, 44.0, 48.6, 50.4, 75.6, 127.2, 128.2, 128.3, 128.8, 128.9, 133.6, 138.7, 141.3, 204.4 ppm. HRMS (ESI) calcd for $C_{22}H_{27}NNaO_3$ [M+Na]: 376.1883, found 376.1883. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 0.5 mL/min, UV 254 nm; t(minor) = 14.1 min, t(major) = 17.0 min; 97% ee. $[\alpha]_D^{25.8}$ = −138.7 (c 1.0, CH_2Cl_2).

4.1.1.11. (2*S*,3*S*)-3-(Nitromethyl)-1-phenyl-2-((*S*)-1-phenylpropyl)hexan-1-one 4k. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.56–0.62 (m, 6H), 1.05–1.30 (m, 4H), 1.47–1.52 (m, 2H), 2.14–2.19 (m, 1H), 2.90–2.96 (m, 1H), 4.09 (dd, J = 3.2 Hz, J = 10.8 Hz, 1H), 4.20 (dd, J = 10.0 Hz, J = 12.8 Hz, 1H), 4.77 (dd, J = 3.2 Hz, J = 13.2 Hz, 1H), 7.22–7.29 (m, 3H), 7.34–7.40 (m, 2H), 7.49–7.54(m, 2H), 7.59–7.64 (m, 1H), 8.01 ppm (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2, 13.4, 19.8, 28.3, 33.1, 37.6, 48.9, 50.9, 127.2, 128.1, 128.5, 128.9, 133.7, 138.9, 141.1, 204.3 ppm. HRMS (ESI) calcd for $C_{22}H_{27}NNaO_3$ [M+Na]: 376.1883, found 376.1886. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 0.5 mL/min, UV 254 nm; t(minor) = 31.1 min, t(major) = 42.8 min; 97% ee. $[\alpha]_D^{26.1}$ = −85.4 (c 1.0, CH_2Cl_2).

4.1.1.12. (2*S*,3*S*)-3-(4-Methoxyphenyl)-2-((*R*)-2-nitro-1-phenylethyl)-1-phenyl pentan-1-one 4l[3o,p]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.56 (t, J = 7.6 Hz, 3H), 1.34–1.40 (m, 1H), 1.44–1.48 (m, 1H), 2.87 (td, J = 3.2 Hz, 10.8 Hz, 10.8 Hz, 1H), 3.57–3.62 (m, 1H), 3.82 (s, 3H), 4.04 (dd, J = 4.8 Hz, J = 10.4 Hz, 1H), 4.90 (dd, J = 3.6 Hz, J = 13.6 Hz, 1H), 4.99–5.05 (m, 1H), 6.91–6.95 (m, 4H), 7.10, (m, 3H), 7.16 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 15.6, 2H), 7.40–7.46 ppm (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 27.2, 44.0, 48.7, 55.2, 56.3, 75.2, 114.4, 127.3, 127.6, 128.1, 128.3, 128.8, 128.9, 132.7, 133.2, 158.6, 204.2 ppm. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 1.0 mL/min, UV 254 nm; t(minor) = 14.5 min, t(major) = 29.6 min; 96% ee. $[\alpha]_D^{22.9}$ = −57.0 (c 1.0, CH_2Cl_2).

4.1.1.13. (2*S*,3*S*)-2-((*R*)-2-Nitro-1-phenylethyl)-1-phenyl-3-*p*-tolylpentan-1-one 4m[3o]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.56 (t, J = 7.2 Hz, 3H), 1.37–1.49 (m, 2H), 2.36 (s, 3H), 2.88 (td, J = 3.6 Hz, 10.8 Hz, 10.8 Hz, 1H), 3.55–3.60 (m, 1H), 4.07 (dd, J = 4.4 Hz, J = 10.4 Hz, 1H), 4.90 (dd, J = 3.6 Hz, J = 13.6 Hz, 1H), 5.01–5.07 (m, 1H), 6.94 (d, 7.6 Hz, 2H), 7.06–7.18 (m, 3H), 7.20–7.23 (m, 3H), 7.24–7.40 (m, 3H), 7.40–7.45 ppm (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 21.1, 27.3, 43.9, 49.1, 56.2, 75.1, 127.3, 127.6, 127.8, 128.1, 128.3, 128.8, 129.8, 133.1, 136.9, 137.7, 138.2, 138.7, 204.2 ppm. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 1.0 mL/min, UV 254 nm; t(minor) = 9.00 min, t(major) = 14.6 min; 96% ee. $[\alpha]_D^{22.9}$ = −46.8 (c 1.0, CH_2Cl_2).

4.1.1.14. (2*S*,3*S*)-3-(4-Chlorophenyl)-2-((*R*)-2-nitro-1-phenylethyl)-1-phenylpentan-1-one 4n[3o,p]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.56 (t, J = 7.2 Hz, 3H), 1.36–1.43 (m, 1H), 1.47–1.54 (m, 1H), 2.90 (td, J = 3.2 Hz, 11.6 Hz, 11.6 Hz, 1H), 3.56–3.61 (m, 1H), 4.06 (dd, J = 5.2 Hz, J = 9.6 Hz, 1H), 4.85 (dd, J = 3.6 Hz, J = 13.6 Hz, 1H), 4.93–4.99 (m, 1H), 6.94–6.96 (m, 2H), 7.11–7.16 (m, 5H), 7.23–7.27 (m, 3H), 7.34 (d, J = 8.4 Hz, 2H), 7.45 ppm (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0, 26.6, 44.1, 48.7, 55.7, 75.4, 127.3, 127.7, 128.1, 128.4, 128.9, 129.2, 129.3, 132.9, 133.3, 137.8, 138.4, 139.5, 203.5 ppm. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 1.0 mL/min, UV 254 nm; t(minor) = 12.7 min, t(major) = 27.0 min; 93% ee. $[\alpha]_D^{23.0}$ = −49.2 (c 1.0, CH_2Cl_2).

4.1.1.15. (2*S*,3*S*)-3-(3-Chlorophenyl)-2-((*R*)-2-nitro-1-phenylethyl)-1-phenylpentan-1-one 4o[3o]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.56 (t, J = 7.2 Hz, 3H), 1.38–1.52 (m, 2H), 2.88 (td, J = 3.2 Hz, 11.2 Hz, 11.2 Hz, 1H), 3.59–3.64 (m, 1H), 4.07 (dd, J = 5.2 Hz, J = 9.6 Hz, 1H), 4.83 (dd, J = 3.6 Hz, J = 13.2 Hz, 1H), 4.92–4.98 (m, 1H), 6.95–6.98 (m, 2H), 7.07–7.16 (m, 4H), 7.18 (s, 1H), 7.25–7.30 (m, 4H), 7.42–7.47 ppm (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 26.4, 44.2, 49.0, 55.7, 75.6, 126.6, 127.4, 127.7, 127.8, 128.1, 128.9, 130.3, 133.4, 134.9, 137.8, 138.4, 143.2, 203.3 ppm. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 1.0 mL/min, UV 254 nm; t(minor) = 10.6 min, t(major) = 26.2 min; 93% ee. $[\alpha]_D^{22.8}$ = −28.6 (c 1.0, CH_2Cl_2).

4.1.1.16. (2*S*,3*S*)-1-(4-Chlorophenyl)-2-((*R*)-2-nitro-1-phenylethyl)-3-phenylpentan-1-one 4p[3o,p]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.56 (t, J = 7.2 Hz, 3H), 1.36–1.50 (m, 2H), 2.89 (td, J = 3.6 Hz, 10.4 Hz, 10.4 Hz, 1H), 3.56–3.61 (m, 1H), 4.03 (dd, J = 4.8 Hz, J = 10.0 Hz, 1H), 4.86 (dd, J = 4.0 Hz, J = 13.6 Hz, 1H), 4.95–5.02 (m, 1H), 6.94 (d, J = 8.0 Hz, 2H), 7.10–7.15 (m, 3H), 7.19–7.23 (m, 4H), 7.28–7.32 (m, 1H), 7.35–7.40 ppm (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 26.9, 43.9, 49.3, 56.2, 75.0, 127.2, 127.4, 127.9, 128.7, 129.1, 129.5, 136.9, 137.9, 139.8, 140.7, 202.8 ppm. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 1.0 mL/min, UV 254 nm; t(minor) = 12.4 min, t(major) = 16.9 min; 95% ee. $[\alpha]_D^{22.8}$ = −29.8 (c 1.0, CH_2Cl_2).

4.1.1.17. (2*S*,3*S*)-2-((*R*)-1-(4-Bromophenyl)-2-nitroethyl)-3-(4-methoxyphenyl)-1-phenylpentan-1-one 4q[3o]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.55 (t, J = 7.2 Hz, 3H), 1.35–1.49 (m, 2H), 2.85 (td, J = 3.2 Hz, 10.4 Hz, 10.4 Hz, 1H), 3.53–3.57 (m, 1H), 3.82 (s, 3H), 4.03 (dd, J = 5.6 Hz, J = 10.4 Hz, 1H), 4.89 (dd, J = 4.0 Hz, J = 13.6 Hz, 1H), 4.93–4.99 (m, 1H), 6.81 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H),

7.27–7.30 (m, 2H), 7.45–7.51 ppm (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 27.3, 43.7, 48.7, 55.2, 55.9, 75.1, 114.5, 121.5, 128.1, 128.5, 128.8, 129.1, 131.9, 132.5, 133.5, 137.4, 138.4, 158.7, 203.8 ppm. HPLC analysis: Chiralcel AD-H, 2-propanol/hexane (5:95), 1.0 mL/min, UV 254 nm; t(major) = 15.5 min, t(minor) = 16.9 min; 91% ee. $[\alpha]_D^{22.9} = -57.8$ (c 1.0, CH_2Cl_2).

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9. CCDC 993020 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data_request/cif.