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Diastereo- and enantioselective conjugate addition of α -keto esters to nitroalkenes: Complete switch in the enantioselectivity by tuning the metal center or rigidity of the ligand

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ABSTRACT

A series of efficient catalytic systems has been developed to control the dual enantioselectivity of the conjugate addition of α -keto esters to nitroalkenes. The use of the chiral diamine (1*S*,1'*S*)-1,1'-biisindoline as a chiral ligand with either $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ or $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ as the catalyst provide facile access to the respective enantiomers resulting from the conjugate addition reaction with high levels of enantioselectivity (94% ee vs 93% ee). Furthermore, the use of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as the metal center allowed the enantioselectivity of the conjugate addition reaction to be switched through the tuning of the rigidity of the chiral diamine ligand (94% ee vs 94% ee).

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1. Introduction

Asymmetric catalysis represents one of the most powerful and efficient methods for the preparation of enantiopure compounds, and this technique has been applied extensively in the fields of pharmaceutical and biological chemistry, where it has been used to prepare important therapeutic agents and biologically active compounds. In general, both enantiomers of new compounds bearing a stereogenic center are synthesized for applications in biosynthesis and medical chemistry, so that the enantiomer responsible for any observed activity against a specific target can be clearly identified [1–6]. In theory, it should be possible to develop a straightforward approach to both enantiomers using two enantiopure antipodal chiral catalysts and a single prochiral starting material. However, enantiopure chiral ligands with the opposite absolute configurations

are not always readily available or easy to prepare, and can be particularly problematic for ligands derived from naturally available chiral sources such as amino acids, carbohydrates and alkaloids. For this reason, several alternative methods have also been developed to induce a reversal in the enantioselectivity of a reaction by either tuning the reaction conditions (e.g., solvent, temperature and additive) [7–14], using a chiral ligand derived from a single chiral source with a modified subunit [15–20] or changing the metal center of the catalyst [21–29]. One of the most widely used methods for turning the enantioselectivity of a reaction involves effectively tuning the metal center of the catalyst. This approach is particularly useful because of the diverse reactivity profiles of different transition metals.

The catalytic enantioselective conjugate addition of carbon nucleophiles to nitroalkenes has received considerable atten-

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tion from synthetic organic chemists because of the versatility of the nitro group in the resulting products [30,31]. Among the many different types of carbon nucleophiles employed in asymmetric conjugate addition reactions, α -keto esters have attracted the greatest synthetic interest because they can undergo a broad range of synthetic transformations and have the potential to allow for a rapid increase in molecular complexity [32–46]. In their pioneering work with α -keto esters, Sodeoka et al. [42] described an efficient catalytic system for the asymmetric conjugate addition of α -keto esters to nitroalkenes, and this strategy was subsequently used in the successful synthesis of biologically interesting kainic acid analogs, following a series of simple functional group transformations involving the enantiomerically pure products. Unfortunately, however, these protocols cannot be used to access both enantiomers with the same chiral ligand, even though both enantiomers are generally required in medicinal chemistry and biochemical applications. With this in mind, the development of an efficient catalytic system for the asymmetric conjugate addition of α -keto esters to nitroalkenes to give both enantiomers in high optical purity using a single chiral ligand is highly desired.

The development of efficient and highly stereoselective catalysts is of principle importance to the field of asymmetric catalysis, and it is possible to generate efficient new catalytic systems from novel chiral scaffolds or the modification of existing catalysts. In this context, we recently designed and synthesized two new types of chiral diamine ligand from a single chiral source (Scheme 1) and proceeded to investigate the complexation behaviors of these ligands with a variety of different metals, including Cu(II), Ni(II) and Ru(II), which have shown powerful catalytic properties in a wide range of synthetic transformations [47–51]. As part of our ongoing research efforts towards the development of novel chiral diamine ligands and the exploration of their reactivity, we report herein the first example of the Cu/Ni controlled reversal of enantioselectivity in the asymmetric conjugate addition of α -keto esters to nitroalkenes using the same chiral ligand. Furthermore, the enantioselectivity could be reversed by tuning the rigidity of the chiral ligand when $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ was used as the precursor for the catalytic system.

2. Experimental

2.1. General experiment

All of the non-aqueous reactions and manipulations were performed under an atmosphere of N_2 using standard Schlenk techniques. All of the solvents used in the current study were

dried and degassed using standard methods and stored under N_2 prior to being used. All of the reactions were monitored by TLC using silica gel-coated plates.

^1H NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer. Chemical shifts have been reported in parts per million (ppm) relative to TMS, which was used as an internal standard. Coupling constants (J) have been reported in Hz and refer to the apparent peak multiplications. High resolution mass spectra (HRMS) were recorded on Bruker Micro TOF-QII (ESI) mass spectrometer. Enantiomeric excess (ee) values were determined by HPLC analysis on an Agilent HP-1200 HPLC system. Optical rotations were measured on a PerkinElmer Model 341LC polarimeter. The chiral ligands were prepared according to the reported methods [47,49]. All of the nitroalkenes used in the current study were prepared according to reported procedures [52]. All of the α -keto esters used here were prepared according to a previously published literature procedure [42].

2.2. General procedure for the conjugate addition reaction

2.2.1. Preparation of the racemic products

$\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (9.92 mg, 0.04 mmol, 20 mol%), Et_3N (5.6 μL , 4.04 mg, 0.04 mmol, 20 mol%) and *i*-propanol (2.0 mL) were added to a flame-dried young-type tube under an atmosphere of Ar, and the resulting mixture was stirred at room temperature for 30 min. *tert*-Butyl-2-oxo-4-phenylbutanoate (**4a**) (70.2 mg, 0.30 mmol, 1.5 equiv) and (*E*)-(2-nitrovinyl)benzene (**5a**) (29.8 mg, 0.20 mmol, 1.0 equiv) were added sequentially to the reaction, and the resulting mixture was stirred at room temperature for 24 h. The reaction was concentrated under vacuum to give a residue, which was purified by flash column chromatography over silica gel eluting with a mixture of EtOAc and hexanes (1/40 to 1/20, v/v) to afford the desired product.

2.2.2. Preparation of the catalyst and general procedure for the asymmetric conjugate addition reaction

Method **a**. A mixture of chiral diamine **2b** (3.0 mg, 0.011 mmol, 5.5 mol%) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 mg, 0.010 mmol, 5 mol%) in dry CH_2Cl_2 (2.0 mL) was added to a flame-dried young-type tube under an atmosphere of argon, and the resulting mixture was stirred at 40 $^\circ\text{C}$ for 30 min. The solvent was then removed under vacuum to give the catalyst as a deep blue powder. *tert*-Butyl-2-oxo-4-phenylbutanoate (**4a**) (51.9 mg, 0.22 mmol, 1.1 equiv), (*E*)-(2-nitrovinyl)benzene (**5a**) (29.8 mg, 0.20 mmol, 1.0 equiv), 2-PrOH (2.0 mL), and triethylamine (1.5 μL , 0.01 mmol, 5 mol%) were added sequentially to the dried catalyst under an atmosphere of argon atmosphere, and the

Scheme 1. Ligands **2** and **3** derived from a single chiral source.

resulting mixture was stirred at room temperature for 10 h. The solvent was removed under reduced pressure to give the crude product as a residue, which was purified by flash column chromatography over silica gel eluting with a mixture of EtOAc and hexanes (1/40 to 1/20, v/v) to afford the desired product. The dr was obtained by checking the ^1H NMR of the crude product.

Method b. A mixture of chiral diamine **2d** (4.4 mg, 0.011 mmol, 5.5 mol%) and $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (2.6 mg, 0.010 mmol, 5 mol%) in dry CH_3CN (2.0 mL) was added to a flame-dried young-type tube under an atmosphere of argon atmosphere, and the resulting mixture was stirred at 40 °C for 2 h. The solvent was then removed under vacuum to give the catalyst as a blue grey powder. *tert*-Butyl-2-oxo-4-phenylbutanoate (**4a**) (51.9 mg, 0.22 mmol, 1.1 equiv), (*E*)-(2-nitrovinyl)benzene (**5a**) (29.8 mg, 0.20 mmol, 1.0 equiv), triethylamine (1.5 μL , 0.01 mmol, 5 mol%), and CPME (2.0 mL) were then added sequentially to the dried catalyst under an atmosphere of argon, and the resulting mixture was stirred at room temperature for 16 h. The solvent was then removed under reduced pressure to give the crude product, which was purified by flash column chromatography over silica gel eluting with a mixture of EtOAc and hexanes (1/40 to 1/20, v/v) to afford the desired product. The dr was obtained by checking the ^1H NMR of the crude product.

Method c. A mixture of chiral diamine **3** (0.5 mg, 0.0022 mmol, 1.1 mol%) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.4 mg, 0.0020 mmol, 1 mol%) in dry CH_2Cl_2 (2.0 mL) was added to a flame-dried young-type tube under an atmosphere of argon, and the resulting mixture was stirred at 40 °C for 30 min. The solvent was then removed under vacuum to give the catalyst as a blue powder. *tert*-Butyl-2-oxo-4-phenylbutanoate (**4a**) (51.9 mg, 0.22 mmol, 1.1 equiv), (*E*)-(2-nitrovinyl)benzene (**5a**) (29.8 mg, 0.20 mmol, 1.0 equiv), triethylamine (1.5 μL , 0.01 mmol, 5 mol%), and *i*-PrOH (2.0 mL) were then added sequentially to the dried catalyst under an atmosphere of argon, and the resulting mixture was stirred at room temperature for 10 h. The solvent was then removed under reduced pressure to give the crude product as a residue, which was purified by flash column chromatography over silica gel eluting with a mixture of EtOAc and hexanes (1/40 to 1/20, v/v) to afford the desired product. The dr was obtained by checking the ^1H NMR of the crude product.

2.3. Experimental characterization data for diamine ligands

(1*S*,1'*S*)-1,1'-Biisindoline (**2a**): white solid, $[\alpha]_{\text{D}}^{20} = +95.0$ (c 0.5, CH_3OH); ^1H NMR (400 MHz, CDCl_3): δ 7.34–7.35 (m, 2H), 7.24–7.30 (m, 6H), 4.95 (s, 2H), 4.19 (dd, $J_1 = 13.6$ Hz, $J_2 = 29.2$ Hz, 4H), 2.21 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 142.5, 141.7, 127.3, 126.9, 122.6, 122.2, 66.3, 52.1. HRMS (ESI) Calcd. for $\text{C}_{16}\text{H}_{17}\text{N}_2$ $[\text{M}+1]^+$: 237.1392; Found: 237.1395.

(1*S*,1'*S*)-6,6'-Difluoro-1,1'-biisindoline (**2b**): white solid, $[\alpha]_{\text{D}}^{20} = +96.1$ (c 0.155, CH_3OH); ^1H NMR (400 MHz, CDCl_3): δ 7.16–7.19 (m, 2H), 7.01–7.03 (m, 2H), 6.93–6.97 (m, 2H), 4.88 (s, 2H), 4.17 (dd, $J_1 = 13.6$ Hz, $J_2 = 29.2$ Hz, 4H), 2.16 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.3 ($J = 243.0$ Hz), 143.7 ($J = 8.0$ Hz), 137.8 ($J = 2.0$ Hz), 123.6 ($J = 9.0$ Hz), 114.4 ($J = 23.0$ Hz),

109.3 ($J = 23.0$ Hz), 66.3 ($J = 2.0$ Hz), 51.6; ^{19}F NMR (376 MHz, CDCl_3) δ –116.3 (s). HRMS (ESI) Calcd. for $\text{C}_{16}\text{H}_{15}\text{F}_2\text{N}_2$ $[\text{M}+1]^+$: 273.1198; Found: 273.1201.

(1*S*,1'*S*)-6,6'-Dichloro-1,1'-biisindoline (**2c**): white solid, $[\alpha]_{\text{D}}^{20} = +143.3$ (c 0.159, CH_3OH); ^1H NMR (400 MHz, CDCl_3): δ 7.30 (s, 2H), 7.22 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.0$ Hz, 2H), 7.15 (d, $J = 8.0$ Hz, 2H), 4.88 (s, 2H), 4.13 (dd, $J_1 = 13.6$ Hz, $J_2 = 30.0$ Hz, 4H), 2.08 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 143.7, 141.0, 132.8, 127.6, 123.7, 122.5, 66.2, 51.8. HRMS (ESI) Calcd. for $\text{C}_{16}\text{H}_{15}\text{Cl}_2\text{N}_2$ $[\text{M}+1]^+$: 305.0607; Found: 305.0609.

(1*S*,1'*S*)-6,6'-Dibromo-1,1'-biisindoline (**2d**): white solid, $[\alpha]_{\text{D}}^{20} = +130.2$ (c 0.152, CH_3OH); ^1H NMR (400 MHz, CDCl_3): δ 7.45 (s, 2H), 7.37 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.0$ Hz, 2H), 7.10 (d, $J = 8.0$ Hz, 2H), 4.87 (s, 2H), 4.14 (dd, $J_1 = 14.0$ Hz, $J_2 = 31.2$ Hz, 4H), 2.07 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 144.1, 141.6, 130.5, 125.5, 124.1, 120.8, 66.2, 51.9. HRMS (ESI) Calcd. for $\text{C}_{16}\text{H}_{15}\text{Br}_2\text{N}_2$ $[\text{M}+1]^+$: 392.9597; Found: 392.9611.

(4*bS*,10*bS*)-4*b*,5,6,10*b*,11,12-Hexahydrodibenzo[*c,h*][1,5]naphthyridine (**3**): white solid, $[\alpha]_{\text{D}}^{20} = -115.1$ (c 0.392, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.39–7.41 (m, 2H), 7.22–7.28 (m, 4H), 7.08–7.10 (m, 2H), 4.08 (dd, $J_1 = 16.0$ Hz, $J_2 = 75.6$ Hz, 4H), 3.81 (s, 2H), 2.04 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 136.7, 136.4, 130.5, 127.4, 126.7, 125.8, 54.0, 49.2. HRMS (ESI) Calcd. for $\text{C}_{16}\text{H}_{17}\text{N}_2$ $[\text{M}+1]^+$: 237.1392; Found: 237.1399.

2.4. Experimental characterization data for products

(3*R*,4*R*)-*tert*-Butyl-3-benzyl-5-nitro-2-oxo-4-phenylpentanoate (**6aa**). The title compound was prepared according to the general procedures described above and purified by column chromatography to give a white solid. The ee values of the product were determined by HPLC using a Chiralcel OD-H column (70:30 hexane:isopropanol, 1 mL/min, 254 nm, 25 °C; $t_1 = 13.4$ min, $t_2 = 30.3$ min) and the dr values were determined by ^1H NMR to be >20:1 in all cases. ^1H NMR (400 MHz, CDCl_3): δ 7.17–7.25 (m, 4H), 7.10–7.17 (m, 4H), 7.04–7.06 (m, 2H), 4.66–4.77 (m, 2H), 4.12–4.18 (m, 1H), 3.83–3.89 (m, 1H), 2.90–2.92 (m, 2H), 1.20 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ 196.4, 159.2, 137.1, 136.8, 129.1, 129.0, 128.8, 128.2, 128.2, 127.0, 84.2, 77.7, 50.8, 45.6, 35.9, 27.5. HRMS (ESI) Calcd. for $\text{C}_{22}\text{H}_{25}\text{NO}_5$ $[\text{M}+\text{Na}]^+$: 406.1625; Found: 406.1621. **Method a:** 63 mg, 82% yield, 91% ee, $[\alpha]_{\text{D}}^{20} = -28.1$ (c 0.40, CHCl_3); **Method b:** 68 mg, 89% yield, –89% ee, $[\alpha]_{\text{D}}^{20} = +24.2$ (c 0.52, CHCl_3); **Method c:** 71 mg, 93% yield, –92% ee, $[\alpha]_{\text{D}}^{20} = +30.1$ (c 0.67, CHCl_3).

(3*R*,4*R*)-*tert*-Butyl-3-(4-methylbenzyl)-5-nitro-2-oxo-4-phenylpentanoate (**6ba**). The title compound was prepared according to the general procedures described above and purified by column chromatography to give a white solid. The ee values of the product were determined by HPLC using a Chiralcel OD-H column (90:10 hexane:isopropanol, 1 mL/min, 254 nm, 25 °C; $t_1 = 26.2$ min, $t_2 = 40.3$ min) and the dr value were determined by ^1H NMR to be > 20:1 in all cases. ^1H NMR (400 MHz, CDCl_3): δ 7.20–7.31 (m, 5H), 6.99–7.07 (m, 4H), 4.70–4.82 (m, 2H), 4.16–4.22 (m, 1H), 3.89–3.95 (m, 1H), 2.94–2.96 (m, 2H), 2.28 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ 196.5, 159.3, 136.9, 136.6, 133.9, 129.5, 129.0, 128.8, 128.2,

84.1, 77.8, 50.9, 45.6, 35.5, 27.4, 21.0. HRMS (ESI) Calcd. for $C_{23}H_{27}NO_5$ $[M+Na]^+$: 420.1781; Found: 420.1786. Method **a**: 50 mg, 63% yield, 89% ee, $[\alpha]_D^{20} = -30.0$ (c 0.30, $CHCl_3$); Method **b**: 51 mg, 64% yield, -80% ee, $[\alpha]_D^{20} = +31.0$ (c 0.26, $CHCl_3$); Method **c**: 65 mg, 82% yield, -91% ee, $[\alpha]_D^{20} = +32.3$ (c 0.34, $CHCl_3$).

(3*R*,4*R*)-*tert*-Butyl-3-(3,4-dichlorobenzyl)-5-nitro-2-oxo-4-phenylpentanoate (**6ca**). The title compound was prepared according to the general procedures described above and purified by column chromatography to give a white solid. The ee values of the product were determined by HPLC using a Chiralcel OD-H column (80:20 hexane:isopropanol, 1 mL/min, 254 nm, 25 °C; $t_1 = 15.9$ min, $t_2 = 18.7$ min) and the dr values were determined by 1H NMR to be >20:1 in all cases. 1H NMR (400 MHz, $CDCl_3$): δ 7.26–7.34 (m, 4H), 7.20–7.22 (m, 3H), 6.92–6.95 (m, 1H), 4.79–4.80 (m, 2H), 4.14–4.20 (m, 1H), 3.90–3.95 (m, 1H), 2.94 (d, $J = 8.0$ Hz, 2H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 159.3, 137.4, 136.3, 132.7, 131.1, 130.9, 130.7, 129.2, 128.5, 128.4, 128.1, 84.6, 77.4, 50.7, 45.5, 34.5, 27.4. HRMS (ESI) Calcd. for $C_{22}H_{23}Cl_2NO_5$ $[M+Na]^+$: 474.0845; Found: 474.0848. Method **a**: 55 mg, 61% yield, 66% ee, $[\alpha]_D^{20} = -10.4$ (c 0.26, $CHCl_3$); Method **b**: 61 mg, 68% yield, -86% ee, $[\alpha]_D^{20} = +13.8$ (c 0.61, $CHCl_3$); Method **c**: 73 mg, 81% yield, -92% ee, $[\alpha]_D^{20} = +12.0$ (c 0.45, $CHCl_3$).

(*R*)-*tert*-Butyl-3-((*R*)-2-nitro-1-phenylethyl)-2-oxo-6-phenylhexanoate (**6da**). The title compound was prepared according to the general procedures described above and purified by column chromatography to give a white solid. The ee values of the products were determined by HPLC using a Chiralcel OD-H column (95:5 hexane:isopropanol, 1 mL/min, 254 nm, 25 °C; $t_1 = 23.5$ min, $t_2 = 26.9$ min) and the dr values were determined by 1H NMR to be >20:1 in all cases. 1H NMR (400 MHz, $CDCl_3$): δ 7.24–7.31 (m, 5H), 7.15–7.20 (m, 3H), 7.10–7.12 (m, 2H), 4.63–4.65 (m, 2H), 3.73–3.84 (m, 2H), 2.53–2.65 (m, 2H), 1.77–1.87 (m, 1H), 1.51–1.66 (m, 3H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 160.3, 141.2, 136.9, 129.1, 128.5, 128.4, 128.1, 126.1, 84.4, 77.6, 49.6, 45.2, 35.5, 28.5, 28.4, 27.6. HRMS (ESI) Calcd. for $C_{24}H_{29}NO_5$ $[M+Na]^+$: 434.1938; Found: 434.1947. Method **a**: 35 mg, 43% yield, 88% ee, $[\alpha]_D^{20} = -15.1$ (c 0.25, $CHCl_3$); Method **b**: 68 mg, 83% yield, -84% ee, $[\alpha]_D^{20} = +13.2$ (c 0.59, $CHCl_3$); Method **c**: 58 mg, 71% yield, -91% ee, $[\alpha]_D^{20} = +15.5$ (c 0.41, $CHCl_3$).

(3*R*,4*R*)-*tert*-Butyl-3-benzyl-5-nitro-2-oxo-4-*p*-tolylpentanoate (**6ab**). The title compound was prepared according to the general procedures described above and purified by column chromatography to give a white solid. The ee values of the products were determined by HPLC using a Chiralcel OD-H column (70:30 hexane:isopropanol, 1 mL/min, 254 nm, 25 °C; $t_1 = 11.3$ min, $t_2 = 24.5$ min) and the dr values were determined by 1H NMR to be >20:1 in all cases. 1H NMR (400 MHz, $CDCl_3$): δ 7.17–7.27 (m, 3H), 7.09–7.13 (m, 6H), 4.70–4.81 (m, 2H), 4.16–4.22 (m, 1H), 3.85–3.91 (m, 1H), 2.99 (d, $J = 7.6$ Hz, 2H), 2.28 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 159.3, 137.9, 137.2, 133.6, 129.8, 129.0, 128.8, 128.0, 126.9, 84.1, 77.9, 50.9, 45.4, 35.9, 27.4, 21.1. HRMS (ESI) Calcd. for $C_{23}H_{27}NO_5$ $[M+Na]^+$: 420.1781; Found: 420.1771. Method **a**: 36 mg, 44% yield, 91% ee, $[\alpha]_D^{20} = -18.8$ (c 0.17, $CHCl_3$); Method **b**:

49 mg, 62% yield, -86% ee, $[\alpha]_D^{20} = +19.6$ (c 0.28, $CHCl_3$); Method **c**: 72 mg, 91% yield, -92% ee, $[\alpha]_D^{20} = +22.1$ (c 0.38, $CHCl_3$).

(3*R*,4*R*)-*tert*-Butyl-3-benzyl-4-(4-methoxyphenyl)-5-nitro-2-oxopentanoate (**6ac**). The title compound was prepared according to the general procedures described above and purified by column chromatography to give a white solid. The ee values of the product were determined by HPLC using a Chiralcel OD-H column (70:30 hexane:isopropanol, 1 mL/min, 254 nm, 25 °C; $t_1 = 14.4$ min, $t_2 = 32.2$ min) and the dr values were determined by 1H NMR to be >20:1 in all cases. 1H NMR (400 MHz, $CDCl_3$): δ 7.17–7.27 (m, 3H), 7.11–7.14 (m, 4H), 6.82 (d, $J = 8.4$ Hz, 2H), 4.67–4.80 (m, 2H), 4.15–4.21 (m, 1H), 3.83–3.89 (m, 1H), 3.75 (s, 3H), 2.98 (d, $J = 8.0$ Hz, 2H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 159.3, 159.2, 137.2, 129.3, 129.0, 128.8, 128.5, 126.9, 114.4, 84.1, 78.1, 55.2, 50.9, 45.1, 36.0, 27.5. HRMS (ESI) Calcd. for $C_{23}H_{27}NO_6$ $[M+Na]^+$: 436.1731; Found: 436.1721. Method **a**: 53 mg, 64% yield, 86% ee, $[\alpha]_D^{20} = -26.9$ (c 0.30, $CHCl_3$); Method **b**: 52 mg, 63% yield, -80% ee, $[\alpha]_D^{20} = +26.3$ (c 0.41, $CHCl_3$); Method **c**: 71 mg, 86% yield, -92% ee, $[\alpha]_D^{20} = +28.7$ (c 0.55, $CHCl_3$).

(3*R*,4*R*)-*tert*-Butyl-3-benzyl-4-(4-fluorophenyl)-5-nitro-2-oxopentanoate (**6ad**). The title compound was prepared according to the general procedures described above and purified by column chromatography to give a white solid. The ee values were determined by HPLC using a Chiralcel OD-H column (70:30 hexane:isopropanol, 1 mL/min, 254 nm, 25 °C; $t_1 = 11.7$ min, $t_2 = 32.8$ min) and the dr values were determined by 1H NMR to be >20:1 in all cases. 1H NMR (400 MHz, $CDCl_3$): δ 7.18–7.29 (m, 5H), 7.11–7.13 (m, 2H), 6.97–7.01 (m, 2H), 4.78–4.83 (m, 1H), 4.68–4.74 (m, 1H), 4.17–4.24 (m, 1H), 3.88–3.94 (m, 1H), 2.96–2.99 (m, 2H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 163.6, 161.2, 159.3, 136.8, 132.5, 132.4, 130.0, 129.9, 129.0, 128.9, 127.1, 116.1, 115.9, 84.3, 77.9, 50.6, 45.0, 36.1, 27.5; ^{19}F NMR (376 MHz, $CDCl_3$): -113.5. HRMS (ESI) Calcd. for $C_{22}H_{24}FNO_5$ $[M+Na]^+$: 424.1531; Found: 424.1520. Method **a**: 28 mg, 35% yield, 87% ee, $[\alpha]_D^{20} = -35.4$ (c 0.44, $CHCl_3$); Method **b**: 59 mg, 74% yield, -90% ee, $[\alpha]_D^{20} = +35.6$ (c 0.44, $CHCl_3$); Method **c**: 64 mg, 80% yield, -91% ee, $[\alpha]_D^{20} = +34.3$ (c 0.26, $CHCl_3$).

(3*R*,4*R*)-*tert*-Butyl-3-benzyl-4-(4-chlorophenyl)-5-nitro-2-oxopentanoate (**6ae**). The title compound was prepared according to the general procedures described above and purified by column chromatography to give a white solid. The ee values of the product were determined by HPLC using a Chiralcel OD-H column (70:30 hexane:isopropanol, 1 mL/min, 254 nm, 25 °C; $t_1 = 13.4$ min, $t_2 = 33.9$ min) and the dr values were determined by 1H NMR to be >20:1 in all cases. 1H NMR (400 MHz, $CDCl_3$): δ 7.25–7.29 (m, 4H), 7.15–7.23 (m, 3H), 7.11–7.13 (m, 2H), 4.78–4.82 (m, 1H), 4.68–4.74 (m, 1H), 4.17–4.23 (m, 1H), 3.87–3.93 (m, 1H), 2.96–2.98 (m, 2H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 159.3, 136.7, 135.3, 134.2, 129.6, 129.3, 129.0, 128.9, 127.1, 84.4, 77.7, 50.5, 45.1, 36.0, 27.5. HRMS (ESI) Calcd. for $C_{22}H_{24}ClNO_5$ $[M+Na]^+$: 440.1235; Found: 440.1234. Method **a**: 32 mg, 38% yield, 92% ee, $[\alpha]_D^{20} = -26.2$ (c 0.21, $CHCl_3$); Method **b**: 40 mg, 48% yield, -91% ee, $[\alpha]_D^{20} = +25.9$ (c 0.28, $CHCl_3$); Method **c**: 65 mg, 78% yield,

–92% ee, $[\alpha]_{\text{D}}^{20} = +27.9$ (c 0.47, CHCl_3).

(3*R*,4*R*)-*tert*-Butyl-3-benzyl-4-(4-bromophenyl)-5-nitro-2-oxopentanoate (**6af**). The title compound was prepared according to the general procedures described above and purified by column chromatography to give a white solid. The ee values of the product were determined by HPLC using a Chiralcel OD-H column (70:30 hexane:isopropanol, 1 mL/min, 254 nm, 25 °C; $t_1 = 14.8$ min, $t_2 = 36.6$ min) and the dr values were determined by ^1H NMR to be >20:1 in all cases. ^1H NMR (400 MHz, CDCl_3): δ 7.41–7.44 (m, 2H), 7.19–7.29 (m, 3H), 7.09–7.13 (m, 4H), 4.68–4.82 (m, 2H), 4.17–4.23 (m, 1H), 4.17–4.23 (m, 1H), 3.86–3.91 (m, 1H), 2.96–2.98 (m, 2H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ 196.2, 159.3, 136.7, 135.8, 132.2, 129.9, 129.0, 128.9, 127.1, 122.4, 84.4, 77.6, 50.4, 45.1, 36.0, 27.4. HRMS (ESI) Calcd. for $\text{C}_{22}\text{H}_{24}\text{BrNO}_5$ $[\text{M}+\text{Na}]^+$: 484.0730; Found: 484.0729. Method **a**: 56 mg, 61% yield, 94% ee, $[\alpha]_{\text{D}}^{20} = -20.9$ (c 0.28, CHCl_3); Method **b**: 78 mg, 84% yield, –94% ee, $[\alpha]_{\text{D}}^{20} = +21.6$ (c 0.25, CHCl_3); Method **c**: 76 mg, 82% yield, –93% ee, $[\alpha]_{\text{D}}^{20} = +20.3$ (c 0.48, CHCl_3).

(3*R*,4*R*)-*tert*-Butyl-3-benzyl-4-(3-chlorophenyl)-5-nitro-2-oxopentanoate (**6ag**). The title compound was prepared according to the general procedures described above and purified by column chromatography to give a white solid. The ee values of the product were determined by HPLC using a Chiralcel OD-H column (70:30 hexane:isopropanol, 1 mL/min, 254 nm, 25 °C; $t_1 = 13.6$ min, $t_2 = 34.1$ min) and the dr values were determined by ^1H NMR to be >20:1 in all cases. ^1H NMR (400 MHz, CDCl_3): δ 7.25–7.29 (m, 4H), 7.15–7.23 (m, 3H), 7.11–7.13 (m, 2H), 4.68–4.82 (m, 2H), 4.17–4.23 (m, 1H), 3.87–3.93 (m, 1H), 2.96–2.98 (m, 2H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ 196.3, 159.3, 136.7, 135.3, 134.2, 129.6, 129.3, 129.0, 128.9, 127.1, 84.4, 77.7, 50.5, 45.1, 36.0, 27.5. HRMS (ESI) Calcd. for $\text{C}_{22}\text{H}_{24}\text{ClNO}_5$ $[\text{M}+\text{Na}]^+$: 440.1235; Found: 440.1235. Method **a**: 46 mg, 55% yield, 91% ee, $[\alpha]_{\text{D}}^{20} = -24.4$ (c 0.27, CHCl_3); Method **b**: 72 mg, 86% yield, –84% ee, $[\alpha]_{\text{D}}^{20} = +26.0$ (CHCl_3 , c 0.36); Method **c**: 75 mg, 90% yield, –93% ee, $[\alpha]_{\text{D}}^{20} = +26.5$ (c 0.37, CHCl_3).

(3*R*,4*R*)-*tert*-Butyl-3-benzyl-4-(2-bromophenyl)-5-nitro-2-oxopentanoate (**6ah**). The title compound was prepared according to the general procedures described above and purified by column chromatography to give a white solid. The ee values of the product were determined by HPLC using a Chiralcel OD-H column (70:30 hexane:isopropanol, 1 mL/min, 254 nm, 25 °C; $t_1 = 10.0$ min, $t_2 = 21.0$ min) and the dr values were determined by ^1H NMR. ^1H NMR (400 MHz, CDCl_3): δ 7.61–7.63 (m, 0.09H), 7.56–7.58 (m, 0.91H), 7.02–7.31 (m, 8H), 4.88–4.93 (m, 1H), 4.81–4.85 (m, 1H), 4.40–4.52 (m, 2H), 3.12–3.17 (m, 1H), 2.90–2.96 (m, 1H), 1.31 (s, 0.83H), 1.25 (s, 8.4H). ^{13}C NMR (100 MHz, CDCl_3): δ 196.9, 159.3, 136.7, 136.1, 134.0, 129.7, 129.1, 129.0, 128.8, 128.7, 128.2, 127.9, 127.0, 124.9, 84.6, 84.2, 77.4, 48.8, 44.0, 36.2, 27.5, 27.5. HRMS (ESI) Calcd. for $\text{C}_{22}\text{H}_{24}\text{BrNO}_5$ $[\text{M}+\text{Na}]^+$: 484.0730; Found: 484.0725. Method **a**: 65 mg, 70% yield, 63% ee, dr = 6:4, $[\alpha]_{\text{D}}^{20} = -30.4$ (c 0.35, CHCl_3); Method **b**: 76 mg, 82% yield, –90% ee, dr = 10:1, $[\alpha]_{\text{D}}^{20} = +66.7$ (c 0.60, CHCl_3); Method **c**: 78 mg, 84% yield, –83% ee, dr = 10:1, $[\alpha]_{\text{D}}^{20} = +56.6$ (c 0.76, CHCl_3).

(3*R*,4*R*)-*tert*-Butyl-3-benzyl-4-(naphthalen-1-yl)-5-nitro-2-

oxopentanoate (**6ai**). The title compound was prepared according to the general procedures described above and purified by column chromatography to give a white solid. The ee values of the product were determined by HPLC using a Chiralcel OD-H column (70:30 hexane:isopropanol, 1 mL/min, 254 nm, 25 °C; $t_1 = 16.3$ min, $t_2 = 29.8$ min) and the dr values were determined by ^1H NMR to be >20:1 in all three cases. ^1H NMR (400 MHz, CDCl_3): δ 8.16 (d, $J = 8.0$ Hz, 1H), 7.78 (d, $J = 8.4$ Hz, 1H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.51–7.55 (m, 1H), 7.41–7.45 (m, 1H), 7.36–7.38 (m, 1H), 7.29–7.32 (m, 1H), 7.06–7.16 (m, 3H), 6.96–6.98 (m, 2H), 4.81–4.87 (m, 3H), 4.37 (br, s, 1H), 2.92–3.03 (m, 2H), 1.14 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ 196.6, 159.4, 137.2, 134.3, 133.2, 131.1, 129.2, 129.0, 128.7, 127.1, 126.9, 126.2, 125.0, 124.6, 122.7, 84.2, 76.2, 50.7, 35.7, 27.4. HRMS (ESI) Calcd. for $\text{C}_{26}\text{H}_{27}\text{NO}_5$ $[\text{M}+\text{Na}]^+$: 456.1781; Found: 456.1775. Method **a**: 70 mg, 81% yield, 66% ee, $[\alpha]_{\text{D}}^{20} = -50.0$ (c 0.28, CHCl_3); Method **b**: 69 mg, 80% yield, –84% ee, $[\alpha]_{\text{D}}^{20} = +78.7$ (c 0.32, CHCl_3); Method **c**: 82 mg, 95% yield, –90% ee, $[\alpha]_{\text{D}}^{20} = +89.9$ (c 0.69, CHCl_3).

(3*R*,4*S*)-*tert*-Butyl-3-benzyl-4-(furan-2-yl)-5-nitro-2-oxopentanoate (**6aj**). The title compound was prepared according to the general procedures described above and purified by column chromatography to give a white solid. The ee values of the product were determined by HPLC using a Chiralcel OD-H column (90:10 hexane: isopropanol, 1 mL/min, 254 nm, 25 °C; $t_1 = 16.8$ min, $t_2 = 33.6$ min) and the dr values were determined by ^1H NMR. ^1H NMR (400 MHz, CDCl_3): δ 7.37–7.38 (m, 0.16H), 7.34–7.35 (m, 0.84H), 7.18–7.29 (m, 3H), 7.12–7.14 (m, 1.75H), 7.07–7.09 (m, 0.33H), 6.31–6.32 (m, 0.16H), 6.28–6.30 (m, 0.84H), 6.24 (d, $J = 3.2$ Hz, 0.15H), 6.21 (d, $J = 3.2$ Hz, 0.84H), 4.75–4.78 (m, 2H), 4.03–4.18 (m, 2H), 2.71–3.00 (m, 2H), 1.39 (s, 7.46H), 1.37 (s, 1.59H). ^{13}C NMR (100 MHz, CDCl_3): δ 197.2, 195.8, 160.0, 159.4, 150.0, 149.9, 142.8, 142.7, 137.2, 136.8, 129.1, 129.0, 128.8, 128.8, 127.0, 126.9, 110.6, 110.5, 109.2, 108.7, 84.6, 84.5, 75.9, 75.4, 49.4, 49.3, 39.0, 38.9, 36.6, 35.0, 27.6. HRMS (ESI) Calcd. for $\text{C}_{20}\text{H}_{23}\text{NO}_6$ $[\text{M}+\text{Na}]^+$: 396.1418; Found: 396.1402. Method **a**: 45 mg, 60% yield, 92% ee, dr = 7:3, $[\alpha]_{\text{D}}^{20} = -1.8$ (c 0.17, CHCl_3); Method **b**: 53 mg, 71% yield, –85% ee, dr = 7:1, $[\alpha]_{\text{D}}^{20} = +4.7$ (c 0.42, CHCl_3); Method **c**: 60 mg, 80% yield, –93% ee, dr = 5.25:1 (the dr value can be calculated from the ^1H NMR using the ratio of the integral belonging to the signal at $\delta = 7.34$ –7.35 (m, 0.84H) and those at $\delta = 7.37$ –7.38 (m, 0.16H), $\delta = 6.31$ –6.32 (m, 0.16H) and $\delta = 6.28$ –6.30 (m, 0.84H), or the ratio of the integral belonging to the signal at $\delta = 6.24$ (d, $J = 3.2$ Hz, 0.15H) to that at $\delta = 6.21$ (d, $J = 3.2$ Hz, 0.84H)), $[\alpha]_{\text{D}}^{20} = +2.2$ (c 0.45, CHCl_3).

3. Results and discussion

The reaction of α -keto ester **4a** with nitrostyrene **5a** was initially evaluated under a variety of previously published conditions for the asymmetric formal [2+2] cyclization reaction [50]. The use of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ /**2a** as a catalytic system at room temperature afforded the desired product **6aa** in 80% yield with 88% ee. Several different ligands bearing a variety of different halo substituents were evaluated to determine the impact of different structural and electronic features on the out-

come of the reaction. Among the fluoro-(**2b**), chloro-(**2c**) and bromo-(**2d**) substituted diamines, the fluoro-substituted diamine ligand **2b** exhibited the highest efficiency and gave the desired product in 82% yield with 91% ee, as well as a distereoselectivity of 20:1 (Table 1, entry 2). Notably, the replacement of the metal precursor with Ni(OAc)₂·4H₂O gave the desired product but with a reversal in the enantioselectivity (74% ee, Table 1, entry 5) under otherwise identical conditions. Furthermore, this reversal in the enantioselectivity was improved to 89% ee using Ni(OAc)₂·4H₂O/**2d** as the catalyst with CPME as the solvent (Table 1, entry 14). The enantioselectivity was also reversed when ligand **2** was replaced by the more rigid ligand **3**, even though Cu(OAc)₂·H₂O was used as the metal source in both cases. Pleasingly, the loading of the Cu(OAc)₂·H₂O/**3** catalyst could be reduced to 1 mol% without an appreciable drop-off in the reactivity of the substrates or the enantioselectivity of the product, which was formed in 93% yield and 92% ee with the antipodal configuration (Table 1, entry 16). However, no switch was observed in the enantioselectivity when Ni(OAc)₂·4H₂O was used in conjunction with the rigid ligand **3** (Table 1, entry 17). These results therefore demonstrate that both enantiomers of the desired product

could be obtained with excellent levels of enantioselectivity by tuning the metal center or the rigidity of the ligand.

Having established the optimal conditions for the catalytic conjugate addition reaction, in terms of the metal and ligand combination systems, we proceeded to investigate the substrate scope of this transformation. A variety of synthetically useful α -keto esters and nitroalkenes bearing different functionalities were well tolerated under the optimized conditions, with excellent levels of stereoselectivity being observed in the majority of cases (Table 2). The initial part of this study focused on the reactions catalyzed by Cu(OAc)₂·H₂O/**2b**. As shown in Table 2, α -keto esters containing an electron-rich phenyl ring and a long chain alkyl group demonstrated good reactivity to give the corresponding adducts with high enantioselectivities (Table 2, **6ba** and **6da**, 89% and 88% ee, respectively). In contrast, α -keto ester **4c** bearing an electron-deficient phenyl ring gave a much lower enantioselectivity of 66% ee under the same conditions. The conjugate reaction was also tolerant of aromatic nitroalkenes bearing a range of different substituents. Several substituted aromatic nitroalkenes (**5a–g**) bearing an electron-donating or electron-withdrawing group at the *para* or *meta* position of their phenyl ring also reacted smoothly under the optimized conditions to give the corresponding addition products **6ab–ag** in moderate to high yields with excellent enantioselectivities and complete diastereoselectivity. Nitroalkenes **5h** and **5i** bearing substituents at the *ortho* position of their phenyl ring reacted smoothly to give the desired products in good yields, although the enantioselectivities observed in these reactions were low (i.e., 63% and 66% ee) because of steric hindrance from the *ortho*-substituents. 2-Furyl-nitroalkene was also well tolerated under the optimized reaction conditions and gave the desired product in 60% yield with 92% ee, although the diastereoselectivity was low in this case (dr = 7:3).

The catalytic ability of Ni(OAc)₂·4H₂O/**2d** was also investigated, with the corresponding antipodal enantiomers being obtained with high enantioselectivities and excellent levels of diastereoselectivity (up to 94% ee and >20:1 dr). In contrast to Cu(OAc)₂·H₂O/**2b**, the enantioselectivity of the reaction catalyzed by Ni(OAc)₂·4H₂O/**2d** appeared to be insensitive to the steric or electronic properties of the substituents on the phenyl ring (**6aa–ai**, 80%–94% ee, 10:1–20:1 dr). This apparent lack of sensitivity to these factors could be attributed to differences in the coordinate modes of the two metals. The 2-furyl-nitroalkene **5j** also reacted with α -keto ester **4a** in the presence of the Ni(OAc)₂·4H₂O/**2d** catalyst to give the corresponding addition product in 71% yield with 85% ee and a diastereoselectivity of 7:1.

The conjugate addition of α -keto esters to nitroalkenes was also investigated in the presence of 1 mol% of the Cu(OAc)₂·H₂O/**3** catalyst under the optimized reaction conditions. Compared to the ligand **2** (BIDN) derived catalytic system, the rigid six-membered ring of the diamine **3** ligated Cu-catalyst showed stronger chiral induction ability and higher reactivity. All of the reactions conducted in the presence of the Cu(OAc)₂·H₂O/**3** catalyst proceeded smoothly to give the desired products in high isolated yields (**6aa–ai**, 78%–93%). A reversal was achieved in the absolute configuration of the

Table 1
Screening of the reaction conditions.^a

Entry	Catalyst	Solvent	6aa	
			Yield ^b (%)	ee (%)
1	Cu(OAc) ₂ ·H ₂ O/ 2a	<i>i</i> -PrOH	80	88 (<i>S,S</i>)
2	Cu(OAc) ₂ ·H ₂ O/ 2b	<i>i</i> -PrOH	82	91 (<i>S,S</i>)
3	Cu(OAc) ₂ ·H ₂ O/ 2c	<i>i</i> -PrOH	51	82 (<i>S,S</i>)
4	Cu(OAc) ₂ ·H ₂ O/ 2d	<i>i</i> -PrOH	59	85 (<i>S,S</i>)
5	Ni(OAc) ₂ ·4H ₂ O/ 2b	<i>i</i> -PrOH	91	74 (<i>R,R</i>)
6 ^c	Ni(OAc) ₂ ·4H ₂ O/ 2a	<i>i</i> -PrOH	90	68 (<i>R,R</i>)
7 ^c	Ni(OAc) ₂ ·4H ₂ O/ 2a	CPME	65	82 (<i>R,R</i>)
8 ^c	Ni(OAc) ₂ ·4H ₂ O/ 2a	Et ₂ O	66	82 (<i>R,R</i>)
9 ^c	Ni(OAc) ₂ ·4H ₂ O/ 2a	THF	91	79 (<i>R,R</i>)
10 ^c	Ni(OAc) ₂ ·4H ₂ O/ 2a	PhCH ₃	84	77 (<i>R,R</i>)
11 ^c	Ni(OAc) ₂ ·4H ₂ O/ 2b	CPME	65	87 (<i>R,R</i>)
12 ^c	Ni(OAc) ₂ ·4H ₂ O/ 2c	CPME	80	85 (<i>R,R</i>)
13 ^c	Ni(OAc) ₂ ·4H ₂ O/ 2d	CPME	64	88 (<i>R,R</i>)
14 ^{c,d}	Ni(OAc) ₂ ·4H ₂ O/ 2d	CPME	89	89 (<i>R,R</i>)
15	Cu(OAc) ₂ ·H ₂ O/ 3	<i>i</i> -PrOH	89	93 (<i>R,R</i>)
16 ^e	Cu(OAc) ₂ ·H ₂ O/ 3	<i>i</i> -PrOH	93	92 (<i>R,R</i>)
17	Ni(OAc) ₂ ·4H ₂ O/ 3	<i>i</i> -PrOH	95	78 (<i>R,R</i>)

^a Reaction conditions: **4a** (0.22 mmol), **5a** (0.20 mmol), [MXn] 5 mol%, ligand 5.5 mol%, and Et₃N 5 mol% stirred in solvent (2.0 mL) at room temperature for 10 h, unless otherwise noted; the ee values were determined by HPLC analysis using a chiral stationary phase.

^b Isolated yield, the dr values were determined to be > 20:1 in all cases.

^c The reaction was stirred for 16 h.

^d **4a** (0.30 mmol) and **5a** (0.20 mmol) were used in the reaction.

^e [MXn] 1 mol% and **3** 1.1 mol% were used in the reaction.

Table 2

Catalytic asymmetric conjugate addition of various α -keto esters to nitroalkenes.

Entry	R	Ar	Yield ^b (%)	ee (%)	dr
1 ^a	PhCH ₂	Ph	6aa (82)	91	>20:1
2 ^{b,d}	PhCH ₂	Ph	6aa (89)	–89	>20:1
3 ^c	PhCH ₂	Ph	6aa (93)	–92	>20:1
4 ^a	<i>p</i> -CH ₃ C ₆ H ₄ CH ₂	Ph	6ba (63)	89	>20:1
5 ^b	<i>p</i> -CH ₃ C ₆ H ₄ CH ₂	Ph	6ba (64)	–80	>20:1
6 ^c	<i>p</i> -CH ₃ C ₆ H ₄ CH ₂	Ph	6ba (82)	–91	>20:1
7 ^a	3,4-bis(Cl)C ₆ H ₃ CH ₂	Ph	6ca (61)	66	>20:1
8 ^b	3,4-bis(Cl)C ₆ H ₃ CH ₂	Ph	6ca (68)	–86	>20:1
9 ^c	3,4-bis(Cl)C ₆ H ₃ CH ₂	Ph	6ca (81)	–92	>20:1
10 ^a	Ph(CH ₂) ₃	Ph	6da (43)	88	>20:1
11 ^b	Ph(CH ₂) ₃	Ph	6da (83)	–84	>20:1
12 ^c	Ph(CH ₂) ₃	Ph	6da (71)	–91	>20:1
13 ^a	PhCH ₂	<i>p</i> -CH ₃ C ₆ H ₄	6ab (44)	91	>20:1
14 ^b	PhCH ₂	<i>p</i> -CH ₃ C ₆ H ₄	6ab (62)	–86	>20:1
15 ^c	PhCH ₂	<i>p</i> -CH ₃ C ₆ H ₄	6ab (91)	–92	>20:1
16 ^a	PhCH ₂	<i>p</i> -CH ₃ OC ₆ H ₄	6ac (64)	86	>20:1
17 ^b	PhCH ₂	<i>p</i> -CH ₃ OC ₆ H ₄	6ac (63)	–80	>20:1
18 ^c	PhCH ₂	<i>p</i> -CH ₃ OC ₆ H ₄	6ac (86)	–92	>20:1
19 ^a	PhCH ₂	<i>p</i> -FC ₆ H ₄	6ad (35)	87	>20:1
20 ^{b,d}	PhCH ₂	<i>p</i> -FC ₆ H ₄	6ad (74)	–90	>20:1
21 ^c	PhCH ₂	<i>p</i> -FC ₆ H ₄	6ad (80)	–91	>20:1
22 ^a	PhCH ₂	<i>p</i> -ClC ₆ H ₄	6ae (38)	92	>20:1
23 ^{b,d}	PhCH ₂	<i>p</i> -ClC ₆ H ₄	6ae (48)	–91	>20:1
24 ^c	PhCH ₂	<i>p</i> -ClC ₆ H ₄	6ae (78)	–92	>20:1
25 ^a	PhCH ₂	<i>p</i> -BrC ₆ H ₄	6af (61)	94	>20:1
26 ^b	PhCH ₂	<i>p</i> -BrC ₆ H ₄	6af (84)	–94	>20:1
27 ^c	PhCH ₂	<i>p</i> -BrC ₆ H ₄	6af (82)	–93	>20:1
28 ^a	PhCH ₂	3-ClC ₆ H ₄	6ag (55)	91	>20:1
29 ^{b,d}	PhCH ₂	3-ClC ₆ H ₄	6ag (86)	–84	>20:1
30 ^c	PhCH ₂	3-ClC ₆ H ₄	6ag (90)	–93	>20:1
31 ^a	PhCH ₂	<i>o</i> -BrC ₆ H ₄	6ah (70)	63	6:4
32 ^b	PhCH ₂	<i>o</i> -BrC ₆ H ₄	6ah (82)	–90	10:1
33 ^c	PhCH ₂	<i>o</i> -BrC ₆ H ₄	6ah (84)	–83	10:1
34 ^a	PhCH ₂	2-naphthyl	6ai (81)	66	>20:1
35 ^b	PhCH ₂	2-naphthyl	6ai (80)	–84	>20:1
36 ^c	PhCH ₂	2-naphthyl	6ai (95)	–90	>20:1
37 ^a	PhCH ₂	2-furanyl	6aj (60)	92	7:3
38 ^b	PhCH ₂	2-furanyl	6aj (71)	–85	7:1
39 ^c	PhCH ₂	2-furanyl	6aj (80)	–93	5.25:1

^a Method **a**: ketoester (0.22 mmol), nitrosytrene (0.20 mmol), Cu(OAc)₂·H₂O/(*S,S*)-**2b** (0.01 mmol, 5 mol%) and Et₃N (1.5 μ L, 5 mol%) stirred in 2-PrOH (2.0 mL) at room temperature for 10 h.

^b Method **b**: ketoester (0.22 mmol), nitrosytrene (0.20 mmol), Ni(OAc)₂·4H₂O/(*S,S*)-**2d** (0.01 mmol, 5 mol%) and Et₃N (1.5 μ L, 5 mol%) stirred in CPME (2.0 mL) at room temperature for 16 h.

^c Method **c**: ketoester (0.22 mmol), nitrosytrene (0.20 mmol), Cu(OAc)₂·H₂O/(*S,S*)-**3** (0.002 mmol, 1 mol%) and Et₃N (1.5 μ L, 5 mol%) in *i*-PrOH (2.0 mL) at room temperature for 10 h.

^d 1.5 equiv of the α -ketoester was added.

products resulting from the reactions of various α -keto esters and nitroalkenes regardless of the steric hindrance and electronic properties of the phenyl ring on the nitroalkene substrates (**6aa–ai**, 83%–93% ee, 10:1–20:1 dr). The heteroaromatic nitroalkene **5j** was also examined under the same conditions, and gave the corresponding product in **6aj** in 80% yield,

93% ee and a diastereoselectivity of 5.25:1 with a reversal in the absolute configuration.

A detailed mechanistic explanation for the switch observed in the enantioselectivity during the asymmetric conjugate addition of α -keto esters to nitroalkenes remains unclear at the present stage. One possible explanation for the observed metal-directed switching in the enantioselectivity of these reactions could be based on differences in the ionic radii, in that the Lewis acidity or coordination pattern between the Cu²⁺ and Ni²⁺ ions may have led to the formation of the corresponding enolate, which would have adopted a different geometry to that of the coordinated α -keto esters [42,50]. Differences in the geometry of the active enolate could lead to the nitroalkene being attacked from the opposite direction during the conjugate addition reaction. This reaction would therefore give rise to the desired product but with the reverse enantioselectivity.

4. Conclusions

We have developed an efficient catalytic system for the highly enantioselective and diastereoselective conjugate addition of α -keto esters to nitroalkenes using chiral diamines as ligands. Dual enantioselective control was achieved with this method through the tuning of the metal center of the catalyst or the rigidity of the chiral diamine ligand. Both enantiomers of various addition products were prepared in this way with high enantioselectivity. The unique rigid structures of the chiral diamine ligands appeared to play a key role in the realization of this dual enantioselective control process.

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Graphical Abstract

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Diastereo- and enantioselective conjugate addition of α -keto esters to nitroalkenes: Complete switch in the enantioselectivity by tuning the metal center or rigidity of the ligand

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The dual enantioselectivity for the conjugate addition of α -keto esters to nitroalkenes has been controlled through the development of an efficient series of catalytic systems. Both enantiomers of the addition products were obtained in good yields with high enantioselectivities by tuning the rigidity of the chiral ligand or metal center.

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中心金属或配体刚性调控的 α -酮酸酯对硝基烯的不对称共轭加成

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摘要: 通过手性二胺配体与Cu或Ni络合合成了手性金属催化剂, 并将其应用于 α -酮酸酯对硝基烯的不对称共轭加成反应中, 发展了通过改变中心金属或调节配体刚性实现反应对映选择性反转的策略. 使用同一手性二胺配体(1*S*,1'*S*)-1,1'-联异喹啉啉, 与不同的金属前体(Cu(OAc)₂·H₂O与Ni(OAc)₂·4H₂O)络合, 可以高选择性地得到绝对构型相反的共轭加成产物(ee值高达94%与93%). 同样, 使用同一金属前体Cu(OAc)₂·H₂O, 与同一手性源出发合成的两种刚性不同的二胺配体络合, 也可以在这个反应中实现产物绝对构型的反转(ee值高达94%与94%).

关键词: 手性二胺; 共轭加成; 对映选择性; 中心金属; 配体刚性

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1. 前言

不对称催化是合成光学纯手性化合物最有效的方法之一, 在有机合成及药物化学中占有重要的地位. 在生物和医药化学研究中, 常常需要同时获得两个构型相反的对映异构体来研究其生理活性方面的差异^[1–6]. 一般而言, 在催化不对称合成中, 获得互为对映异构体的光学纯产物的直接方法是使用两个互为对映异构体的手性催化剂来实现. 然而绝对构型相反的手性配体, 尤其是由氨基酸、糖类和金鸡纳碱等天然产物衍生的手性配体, 通常难以得到. 这种情况下, 通过互为对映体的催化剂来得到相应构型的产物就变得异常困难. 为解决这一问题, 人们通过调节反应条件(如溶剂、温度、添加剂等)^[7–14], 修饰同一手性源衍生的手性配体^[15–20]和改变金属中心^[21–29]来实现产物对映选择性的转变. 其中, 过渡金属具有种类多、配位性能差异大的特点, 因而近年来, 改变手性催化剂中心金属来实现对映选择性转变的方法逐渐引起有机化学家的关注.

不对称共轭加成反应是有机合成中形成C–C键的有效方法, 在天然产物及各种药物分子的合成中得以广泛应用^[30,31]. 在不对称共轭加成反应中, α -酮酸酯与硝基烯是两类非常重要的底物, 其加成产物通过简单的转化, 可以合成胺、酮酸以及酰胺等重要的有机中间体^[32–46]. 2010年, Sodeoka课题组^[42]利用手性(*S,S*)-*N*-苄基-1,2-环己二胺作为手性配体, 实现了Ni催化的硝基烯对 α -酮酸酯的不对称Michael加成反应. 虽然该方法可以高非对映选择性和对映选择性地得到(*R,R*)构型的产物, 但是该策略并不能实现其光学异构体的合成. 因此, 发展适用于 α -酮酸酯对硝基烯共轭加成反应的催化体系,

高效高选择性地合成互为对映异构体的产物仍然是摆在研究工作者面前的重大课题.

在不对称催化中, 合成高效的催化剂有两种典型方法: 一是合成新的手性骨架, 另一种是对已知催化剂结构进行修饰. 本课题组从同一手性源(*S,S*)-**1**出发, 设计合成了五员环二胺配体(*S,S*)-**2**和六员环二胺配体(*S,S*)-**3** (图式1), 在许多不对称催化反应中表现出了极好的催化活性和手性诱导能力^[47–51]. 另外, 二者结构的差异可能会导致两种配体在与金属中心配位时创造不同的手性环境, 从而在不对称催化反应中表现出不同的催化效果和对映选择性. 本文以 α -酮酸酯对硝基烯的不对称共轭加成作为模型反应, 对配体或者中心金属导致的对映选择性反转的不对称催化反应进行研究.

2. 实验部分

2.1. 试剂与仪器

无水反应和操作均使用标准的Schlenk技术在惰性气体氛围下进行. 溶剂在使用之前均采用标准方法进行干燥和脱气处理, 并存储于惰性气体氛围中. 反应均采用薄层色谱硅胶板进行监测. 手性配体^[47,49]、硝基烯^[52]和 α -酮酸酯^[42]根据已有文献方法合成. 实验中使用的仪器有超导核磁共振谱仪(Bruker Avance (III) 400 MHz)、傅立叶变换高分辨质谱(Bruker MicroTOF-QII(ESI))、高效液相色谱仪(Agilent HP-1200)和旋光仪(PerkinElmer, Model 341LC polarimeter).

2.2. 共轭加成反应

2.2.1. 消旋体制备

Ar保护下, 将Ni(OAc)₂·4H₂O (9.92 mg, 0.04 mmol, 20 mol%)、三乙胺(5.6 μ L, 4.04 mmol, 20 mol%)

和异丙醇(2 mL)加入到干燥的杨氏管中, 室温搅拌30 min后, 再依次加入 α -酮酸酯**4a** (70.2 mg, 0.30 mmol, 1.5 equiv)和硝基烯**5a** (29.8 mg, 0.20 mmol, 1.0 equiv), 继续室温搅拌24 h后, 真空减压除去溶剂, 所得残渣经快速柱层析(乙酸乙酯/正己烷(v/v) = 1/40–1/20)纯化得到目标产物。

2.2.2. 催化剂原位制备及不对称共轭加成反应

条件**a**. Ar保护下, 将手性二胺**2b** (3.0 mg, 0.011 mmol, 5.5 mol%), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 mg, 0.010 mmol, 5 mol%)和无水二氯甲烷(2.0 mL)加入到干燥的杨氏管中, 40 °C搅拌30 min, 除去溶剂后得到深蓝色的固体催化剂。在氩气氛围下依次加入 α -酮酸酯**4a** (51.9 mg, 0.22 mmol, 1.1 equiv), 硝基烯**5a** (29.8 mg, 0.20 mmol, 1.0 equiv), 三乙胺(1.5 μL , 0.01 mmol, 5 mol%)和异丙醇(2.0 mL), 室温搅拌10 h后, 减压除去溶剂后得到粗产品。快速柱层析(乙酸乙酯/正己烷(v/v) = 1/40–1/20)纯化得到目标产物。dr值为 ^1H NMR中非对映异构体特征峰的积分面积比。

条件**b**. Ar保护下, 将手性二胺**2d** (4.4 mg, 0.011 mmol, 5.5 mol%), $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (2.6 mg, 0.010 mmol, 5 mol%)和无水乙腈(2.0 mL)加入到干燥的杨氏管中, 40 °C搅拌2 h后, 除去溶剂得到蓝灰色的固体催化剂。在氩气氛围下加入 α -酮酸酯**4a** (51.9 mg, 0.22 mmol, 1.1 equiv), 硝基烯**5a** (29.8 mg, 0.20 mmol, 1.0 equiv), 三乙胺(1.5 μL , 0.01 mmol, 5 mol%)和甲基环戊基醚(2.0 mL), 室温搅拌16 h后, 减压除去溶剂后得到粗产品。快速柱层析(乙酸乙酯/正己烷(v/v) = 1/40–1/20)纯化得到目标产物。dr值为 ^1H NMR中非对映异构体特征峰的积分面积比。

条件**c**. Ar保护下, 将手性二胺**3** (0.5 mg, 0.0022 mmol, 1.1 mol%), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.4 mg, 0.0020 mmol, 1.0 mol%)和无水二氯甲烷(2.0 mL)加入到干燥的杨氏管中, 40 °C搅拌30 min后, 除去溶剂后得到蓝色的催化剂固体。在氩气氛围下依次加入 α -酮酸酯**4a** (51.9 mg, 0.22 mmol, 1.1 equiv), 硝基烯**5a** (29.8 mg, 0.20 mmol, 1.0 equiv), 三乙胺(1.5 μL , 0.01 mmol, 5 mol%)和*i*-PrOH (2.0 mL), 室温搅拌10 h后, 减压除去溶剂后得到粗产品。快速柱层析(乙酸乙酯/正己烷(v/v) = 1/40–1/20)纯化得到目标产物。dr值为 ^1H NMR中非对映异构体特征峰的积分面积比。

2.3. 二胺配体的表征数据

(略, 见英文部分)

2.4. 加成产物的表征数据

(略, 见英文部分)

3. 结果与讨论

本课题组近期报道了 α -酮酸酯和硝基烯的不对称Michael-Michael-Henry串联反应^[50], 其中手性二胺**2**和**3**表现出了良好的催化活性及手性诱导能力。在该工作的基础上, 我们对 α -酮酸酯**4a**和硝基烯**5a**的不对称共轭加成反应进行了研究。当使用 $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}/\text{2a}$ 作催化剂时, 我们以80%的产率和88%的ee值得到了(*S,S*)构型的目标产物**6aa**。通过考察配体结构对反应的影响, 我们发现, 在氟、氯、溴取代的二胺配体**2b**, **2c**, **2d**中, **2b**表现出了最高的催化效率, 以82%的产率、91%的ee值得到目标产物**6aa**, 并且dr值大于20:1 (表1, 实验2)。值得注意的是, 当 $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ 作为金属前体时, 我们得到了构型反转的目标产物(74% ee, 表1, 实验2和实验5)。进一步的条件优化发现, 使用 $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}/\text{2d}$ 作催化剂, CPME作溶剂时, 目标产物的对映选择性能够提高到89% (表1, 实验14)。另外, 当以刚性更强的手性二胺**3**作为配体, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ 作催化剂前体时, 我们也可以高收率、高对映选择性地得到构型反转的产物。更令人高兴的是, 催化剂 $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}/\text{3}$ 用量减少到1 mol%时, 反应活性和对映选择性并没有降低, 而是以更高的产率(93%)和对映选择性(92% ee)得到了构型反转的目标产物(表1, 实验16)。最后, 我们发现, $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}/\text{3}$ 作催化剂时, 同样可以得到(*R,R*)构型的目标产物(表1, 实验17)。

确定了三种最优的反应条件后, 我们对各种 α -酮酸酯和硝基烯的底物进行了拓展, 结果如表2所示。首先, 当以 $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}/\text{2b}$ 为催化剂时, 无论是苯环上带有给电子基团的还是带有长链烷基的 α -酮酸酯, 都可以以较高的对映选择性获得相应的加成产物(**6ba**和**6da**, 分别为89% ee和88% ee)。苯环上含有缺电子基的 α -酮酸酯**4c**的对映选择性明显降低, ee值仅为66%。另外, 硝基烯芳环上的电子效应对反应的影响并不明显, 芳环对位或间位上含有供电子基或吸电子基的硝基烯**5a–g**在优化的条件下均能顺利地参与反应, 以较高的产率和对映选择性得到加成产物**6ab–ag**。由1-萘甲醛和邻位取代的苯甲醛衍生的硝基烯(**5h**和**5i**)虽然能以较高的产率得到加成产物, 但是对映选择性明显降低(**6ah–6ai**, 63% ee和66% ee), 这说明硝基烯底物的位阻效应对反应结果具有非常显著的影响。使用杂环硝基烯2-呋喃硝基烯, 也能

以60%的收率, 92%的ee值得到目标产物, 但是非对映选择性只有7:3.

接着, 我们以 $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}/\mathbf{2d}$ 为催化剂, 考察了**b**条件下反应的底物适用性. 发现, 该条件下得到产物的对映选择性可高达94% ee, 非对映选择性能够大于20:1, 绝对构型与条件**a**中得到的相反. 与 $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}/\mathbf{2b}$ 催化体系不同的是, $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}/\mathbf{2d}$ 催化体系中苯环上的位阻和电子效应对反应的对映选择性影响不大 (**6aa–ai**, 80%–94% ee, 10:1–20:1 dr), 这可能是由于底物与两种金属的配位模式不同. 另外, 2-呋喃硝基烯**5j**与 α -酮酸酯**4a**也能发生反应, 以71%的收率和85%的ee值转化为相应的目标产物, dr值为7:1.

最后, 我们对 $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}/\mathbf{3}$ (1 mol%)催化的 α -酮酸酯与硝基烯的共轭加成反应进行了研究. 与配体**2** (BIDN)衍生的催化体系类似, 刚性较强的六员环手性二胺**3**配位的Cu催化剂表现出较强的手性诱导能力和更高的催化活性, α -酮酸酯与芳环上含有不同位阻和电子性质的硝基烯反应均能得到与 $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}/\mathbf{2b}$ 催化体系中绝对构型相反的产物 (**6aa–ai**, 83%–93% ee, 10:1–20:1

dr). 2-呋喃硝基烯**5j**在 $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}/\mathbf{3}$ 催化下同样实现了产物绝对构型的反转, 以80%的产率、93%的ee值和5.25/1的dr值得到加成产物**6aj**.

目前, 调节金属中心实现 α -酮酸酯对硝基烯的不对称共轭加成反应对映选择性反转的详细机理仍不清楚. 但是根据对该反应基本历程的理解, 我们认为中心金属调控反应对映选择性的一种可能解释是: $\text{Cu}(\text{II})$ 和 $\text{Ni}(\text{II})$ 的离子半径、路易斯酸性或配位模式的差异导致其与 α -酮酸酯配位时形成烯醇式的构型不同^[42,50], 而构型不同的烯醇式再对硝基烯进行进攻, 形成了绝对构型相反的目标产物.

4. 结论

以手性二胺作为配体, 发展了一例Cu/Ni催化的 α -酮酸酯对硝基烯的高效不对称Michael加成反应. 另外, 首次成功地将改变催化剂中心金属或配体刚性实现产物绝对构型翻转的策略应用到该反应中, 通过改变反应条件, 高效、高选择性地得到了互为对映体的共轭加成产物.