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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'-biisoindoline as a chiral ligand with either $Cu(OAc)_2·H_2O$ or $Ni(OAc)_2·4H_2O$ 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 $Cu(OAc)_2·H_2O$ 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 $Cu(OAc)_2{\cdot}H_2O$ 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].

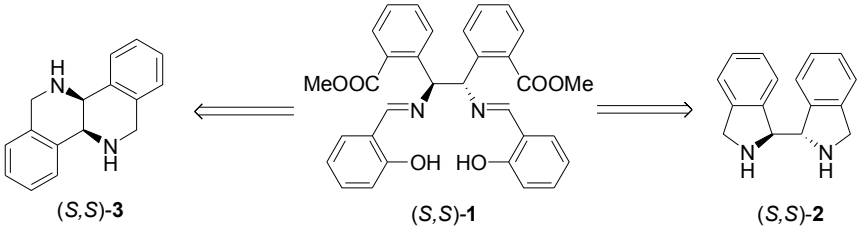
2.2. General procedure for the conjugate addition reaction

2.2.1. Preparation of the racemic products

$Ni(OAc)_2{\cdot}4H_2O$ (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 $Cu(OAc)_2{\cdot}H_2O$ (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 °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 ^{1}H NMR of the crude product.

Method **b**. A mixture of chiral diamine **2d** (4.4 mg, 0.011 mmol, 5.5 mol%) and $Ni(OAc)_2{\cdot}4H_2O$ (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 ^{1}H NMR of the crude product.

Method **c**. A mixture of chiral diamine **3** (0.5 mg, 0.0022 mmol, 1.1 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (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 ^{1}H NMR of the crude product.

2.3. Experimental characterization data for diamine ligands

(1*S*,1'*S*)-1,1'-Biisoindoline (**2a**): white solid, $[\alpha]_D^{20}$ = +95.0 (*c* 0.5, CH_3OH); ^{1}H 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 $C_{16}H_{17}N_2$ $[M+1]^+$: 237.1392; Found: 237.1395.

(1*S*,1'*S*)-6,6'-Difluoro-1,1'-biisoindoline (**2b**): white solid, $[\alpha]_D^{20}$ = +96.1 (*c* 0.155, CH_3OH); ^{1}H 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 $C_{16}H_{15}F_2N_2$ $[M+1]^+$: 273.1198; Found: 273.1201.

(1*S*,1'*S*)-6,6'-Dichloro-1,1'-biisoindoline (**2c**): white solid, $[\alpha]_D^{20}$ = +143.3 (*c* 0.159, CH_3OH); ^{1}H 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 $C_{16}H_{15}Cl_2N_2$ $[M+1]^+$: 305.0607; Found: 305.0609.

(1*S*,1'*S*)-6,6'-Dibromo-1,1'-biisoindoline (**2d**): white solid, $[\alpha]_D^{20}$ = +130.2 (*c* 0.152, CH_3OH); ^{1}H 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 $C_{16}H_{15}Br_2N_2$ $[M+1]^+$: 392.9597; Found: 392.9611.

(4b*S*,10b*S*)-4b,5,6,10b,11,12-Hexahydrodibenzo[c,h][1,5]naphthyridine (**3**): white solid, $[\alpha]_D^{20}$ = –115.1 (*c* 0.392, $CHCl_3$); ^{1}H 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 $C_{16}H_{17}N_2$ $[M+1]^+$: 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 ^{1}H NMR to be >20:1 in all cases. ^{1}H 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 $C_{22}H_{25}NO_5$ $[M+Na]^+$: 406.1625; Found: 406.1621. Method **a**: 63 mg, 82% yield, 91% ee, $[\alpha]_D^{20}$ = –28.1 (*c* 0.40, $CHCl_3$); Method **b**: 68 mg, 89% yield, –89% ee, $[\alpha]_D^{20}$ = +24.2 (*c* 0.52, $CHCl_3$); Method **c**: 71 mg, 93% yield, –92% ee, $[\alpha]_D^{20}$ = +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 ^{1}H NMR to be > 20:1 in all cases. ^{1}H 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 ^{1}H NMR to be >20:1 in all cases. ^{1}H 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 ^{1}H NMR to be >20:1 in all cases. ^{1}H 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 ^{1}H NMR to be >20:1 in all cases. ^{1}H 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 ^{1}H NMR to be >20:1 in all cases. ^{1}H 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 ^{1}H NMR to be >20:1 in all cases. ^{1}H 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 ^{1}H NMR to be >20:1 in all cases. ^{1}H 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, $[\alpha]_D^{20}$ = +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 ^{1}H NMR to be >20:1 in all cases. ^{1}H 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 $C_{22}H_{24}BrNO_5$ $[M+Na]^+$: 484.0730; Found: 484.0729. Method **a**: 56 mg, 61% yield, 94% ee, $[\alpha]_D^{20}$ = –20.9 (*c* 0.28, $CHCl_3$); Method **b**: 78 mg, 84% yield, –94% ee, $[\alpha]_D^{20}$ = +21.6 (*c* 0.25, $CHCl_3$); Method **c**: 76 mg, 82% yield, –93% ee, $[\alpha]_D^{20}$ = +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 ^{1}H NMR to be >20:1 in all cases. ^{1}H 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 $C_{22}H_{24}ClNO_5$ $[M+Na]^+$: 440.1235; Found: 440.1235. Method **a**: 46 mg, 55% yield, 91% ee, $[\alpha]_D^{20}$ = –24.4 (*c* 0.27, $CHCl_3$); Method **b**: 72 mg, 86% yield, –84% ee, $[\alpha]_D^{20}$ = +26.0 ($CHCl_3$, *c* 0.36); Method **c**: 75 mg, 90% yield, –93% ee, $[\alpha]_D^{20}$ = +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 ^{1}H NMR. ^{1}H 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 $C_{22}H_{24}BrNO_5$ $[M+Na]^+$: 484.0730; Found: 484.0725. Method **a**: 65 mg, 70% yield, 63% ee, dr = 6:4, $[\alpha]_D^{20}$ = –30.4 (*c* 0.35, $CHCl_3$); Method **b**: 76 mg, 82% yield, –90% ee, dr = 10:1, $[\alpha]_D^{20}$ = +66.7 (*c* 0.60, $CHCl_3$); Method **c**: 78 mg, 84% yield, –83% ee, dr = 10:1, $[\alpha]_D^{20}$ = +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 ^{1}H NMR to be >20:1 in all three cases. ^{1}H 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), 437 (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 $C_{26}H_{27}NO_5$ $[M+Na]^+$: 456.1781; Found: 456.1775. Method **a**: 70 mg, 81% yield, 66% ee, $[\alpha]_D^{20}$ = –50.0 (*c* 0.28, $CHCl_3$); Method **b**: 69 mg, 80% yield, –84% ee, $[\alpha]_D^{20}$ = +78.7 (*c* 0.32, $CHCl_3$); Method **c**: 82 mg, 95% yield, –90% ee, $[\alpha]_D^{20}$ = +89.9 (*c* 0.69, $CHCl_3$).

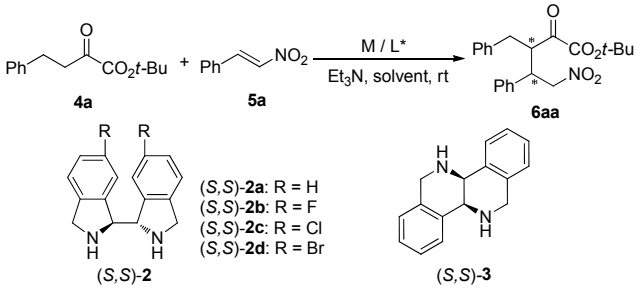
(3*R*,4*S*)-*tert*-Butyl-3-benzyl-4-(furan-2-yl)-5-nitro-2-oxopentanoate (**6aj**). The title compound was prepared according to the general procedures described above and purified by column chromatography to give a white solid. The ee values of the product were determined by HPLC using a Chiralcel OD-H 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 ^{1}H NMR. ^{1}H 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 $C_{20}H_{23}NO_6$ $[M+Na]^+$: 396.1418; Found: 396.1402. Method **a**: 45 mg, 60% yield, 92% ee, dr = 7:3, $[\alpha]_D^{20}$ = –1.8 (*c* 0.17, $CHCl_3$); Method **b**: 53 mg, 71% yield, –85% ee, dr = 7:1, $[\alpha]_D^{20}$ = +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 ^{1}H NMR using the ratio of the integral belonging to the signal at δ = 7.34–7.35 (m, 0.84H) and those at δ = 7.37–7.38 (m, 0.16H), δ = 6.31–6.32 (m, 0.16H) and δ = 6.28–6.30 (m, 0.84H), or the ratio of the integral belonging to the signal at δ = 6.24 (d, *J* = 3.2 Hz, 0.15H) to that at δ = 6.21 (d, *J* = 3.2 Hz, 0.84H)), $[\alpha]_D^{20}$ = +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+2] cyclization reaction [50]. The use of $Cu(OAc)_2{\cdot}H_2O$/**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 $Ni(OAc)_2{\cdot}4H_2O$ 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 $Ni(OAc)_2{\cdot}4H_2O$/**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 $Cu(OAc)_2{\cdot}H_2O$ was used as the metal source in both cases. Pleasingly, the loading of the $Cu(OAc)_2{\cdot}H_2O$/**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 $Ni(OAc)_2{\cdot}4H_2O$ 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.

Table 1
Screening of the reaction conditions.[a]



Entry	Catalyst	Solvent	6aa	
			Yield[b] (%)	ee (%)
1	$Cu(OAc)_2{\cdot}H_2O$/**2a**	*i*-PrOH	80	88 (*S,S*)
2	$Cu(OAc)_2{\cdot}H_2O$/**2b**	*i*-PrOH	82	91 (*S,S*)
3	$Cu(OAc)_2{\cdot}H_2O$/**2c**	*i*-PrOH	51	82 (*S,S*)
4	$Cu(OAc)_2{\cdot}H_2O$/**2d**	*i*-PrOH	59	85 (*S,S*)
5	$Ni(OAc)_2{\cdot}4H_2O$/**2b**	*i*-PrOH	91	74 (*R,R*)
6[c]	$Ni(OAc)_2{\cdot}4H_2O$/**2a**	*i*-PrOH	90	68 (*R,R*)
7[c]	$Ni(OAc)_2{\cdot}4H_2O$/**2a**	CPME	65	82 (*R,R*)
8[c]	$Ni(OAc)_2{\cdot}4H_2O$/**2a**	Et_2O	66	82 (*R,R*)
9[c]	$Ni(OAc)_2{\cdot}4H_2O$/**2a**	THF	91	79 (*R,R*)
10[c]	$Ni(OAc)_2{\cdot}4H_2O$/**2a**	$PhCH_3$	84	77 (*R,R*)
11[c]	$Ni(OAc)_2{\cdot}4H_2O$/**2b**	CPME	65	87 (*R,R*)
12[c]	$Ni(OAc)_2{\cdot}4H_2O$/**2c**	CPME	80	85 (*R,R*)
13[c]	$Ni(OAc)_2{\cdot}4H_2O$/**2d**	CPME	64	88 (*R,R*)
14[c,d]	$Ni(OAc)_2{\cdot}4H_2O$/**2d**	CPME	89	89 (*R,R*)
15	$Cu(OAc)_2{\cdot}H_2O$/**3**	*i*-PrOH	89	93 (*R,R*)
16[e]	$Cu(OAc)_2{\cdot}H_2O$/**3**	*i*-PrOH	93	92 (*R,R*)
17	$Ni(OAc)_2{\cdot}4H_2O$/**3**	*i*-PrOH	95	78 (*R,R*)

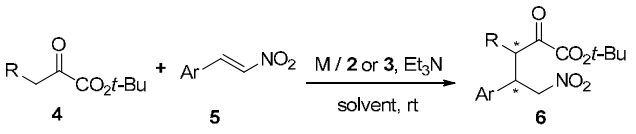
[a] Reaction conditions: **4a** (0.22 mmol), **5a** (0.20 mmol), [MXn] 5 mol%, ligand 5.5 mol%, and Et_3N 5 mol% stirred in solvent (2.0 mL) at room temperature for 10 h, unless otherwise noted; the ee values were determined by HPLC analysis using a chiral stationary phrase.
[b] Isolated yield, the dr 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.

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 $Cu(OAc)_2{\cdot}H_2O$/**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 $Ni(OAc)_2{\cdot}4H_2O$/**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 $Cu(OAc)_2{\cdot}H_2O$/**2b,** the enantioselectivity of the reaction catalyzed by $Ni(OAc)_2{\cdot}4H_2O$/**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 $Ni(OAc)_2{\cdot}4H_2O$/**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 $Cu(OAc)_2{\cdot}H_2O$/**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 $Cu(OAc)_2{\cdot}H_2O$/**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 2
Catalytic asymmetric conjugate addition of various α-keto esters to nitroalkenes.



4 5 6

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]	*p*-$CH_3C_6H_4CH_2$	Ph	**6ba** (63)	89	>20:1
5 [b]	*p*-$CH_3C_6H_4CH_2$	Ph	**6ba** (64)	–80	>20:1
6 [c]	*p*-$CH_3C_6H_4CH_2$	Ph	**6ba** (82)	–91	>20:1
7 [a]	3,4-bis(Cl)$C_6H_3CH_2$	Ph	**6ca** (61)	66	>20:1
8 [b]	3,4-bis(Cl)$C_6H_3CH_2$	Ph	**6ca** (68)	–86	>20:1
9 [c]	3,4-bis(Cl)$C_6H_3CH_2$	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]	$PhCH_2$	*p*-$CH_3C_6H_4$	**6ab** (44)	91	>20:1
14 [b]	$PhCH_2$	*p*-$CH_3C_6H_4$	**6ab** (62)	–86	>20:1
15 [c]	$PhCH_2$	*p*-$CH_3C_6H_4$	**6ab** (91)	–92	>20:1
16 [a]	$PhCH_2$	*p*-$CH_3OC_6H_4$	**6ac** (64)	86	>20:1
17 [b]	$PhCH_2$	*p*-$CH_3OC_6H_4$	**6ac** (63)	–80	>20:1
18 [c]	$PhCH_2$	*p*-$CH_3OC_6H_4$	**6ac** (86)	–92	>20:1
19 [a]	$PhCH_2$	*p*-FC_6H_4	**6ad** (35)	87	>20:1
20 [b,d]	$PhCH_2$	*p*-FC_6H_4	**6ad** (74)	–90	>20:1
21 [c]	$PhCH_2$	*p*-FC_6H_4	**6ad** (80)	–91	>20:1
22 [a]	$PhCH_2$	*p*-ClC_6H_4	**6ae** (38)	92	>20:1
23 [b,d]	$PhCH_2$	*p*-ClC_6H_4	**6ae** (48)	–91	>20:1
24 [c]	$PhCH_2$	*p*-ClC_6H_4	**6ae** (78)	–92	>20:1
25 [a]	$PhCH_2$	*p*-BrC_6H_4	**6af** (61)	94	>20:1
26 [b]	$PhCH_2$	*p*-BrC_6H_4	**6af** (84)	–94	>20:1
27 [c]	$PhCH_2$	*p*-BrC_6H_4	**6af** (82)	–93	>20:1
28 [a]	$PhCH_2$	3-ClC_6H_4	**6ag** (55)	91	>20:1
29 [b,d]	$PhCH_2$	3-ClC_6H_4	**6ag** (86)	–84	>20:1
30 [c]	$PhCH_2$	3-ClC_6H_4	**6ag** (90)	–93	>20:1
31 [a]	$PhCH_2$	*o*-BrC_6H_4	**6ah** (70)	63	6:4
32 [b]	$PhCH_2$	*o*-BrC_6H_4	**6ah** (82)	–90	10:1
33 [c]	$PhCH_2$	*o*-BrC_6H_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-furfuryl	**6aj** (71)	–85	7:1
39 [c]	$PhCH_2$	2-furfuryl	**6aj** (80)	–93	5.25:1

[a] Method **a**: ketoester (0.22 mmol), nitrosytrene (0.20 mmol), $Cu(OAc)_2{\cdot}H_2O$/(*S*,*S*)-**2b** (0.01 mmol, 5 mol%) and Et_3N (1.5 μL, 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), $Ni(OAc)_2{\cdot}4H_2O$/(*S*,*S*)-**2d** (0.01 mmol, 5 mol%) and Et_3N (1.5 μL, 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), $Cu(OAc)_2{\cdot}H_2O$/(*S*,*S*)-**3** (0.002 mmol, 1 mol%) and Et_3N (1.5 μL, 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 Cu^{2+} and Ni^{2+} 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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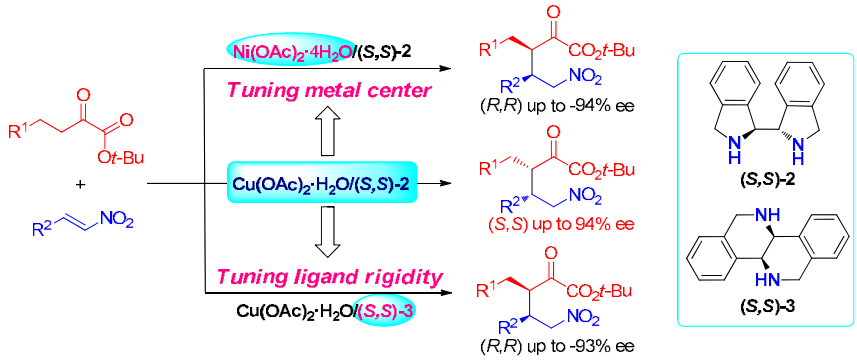

The dual enantioselectivity for the conjugate addition of α-keto esters to nitroalkenes has been controlled through the development of an efficient series of catalytic systems. Both enantiomers of the addition products were obtained in good yields with high enantioselectivities by tuning the rigidity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

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