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Preparation and application of chiral spiro nitrogen-containing ligands for cobalt-catalyzed asymmetric Michael addition

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Abstract—Two novel chiral spiro nitrogen-containing ligands, 7,7′-bis(2-pyridinecarboxamido)-1,1′-spirobiindane (abbreviated as SIPAD) and 7,7′-bis(2-quinolinecarboxamido)-1,1′-spirobiindane (abbreviated as SIQAD), were conveniently prepared from 1,1′-spirobiindane-7,7′-dicarboxylic acid in high yields (85% and 84%, respectively) in two steps. The cobalt complexes prepared in situ from $Co(OAc)_2$ and the ligands have been proven to be efficient catalysts for the asymmetric Michael addition reaction of malonates to chalcone derivatives. The alkylation products were obtained in high yields with moderate enantiomeric excesses under mild reaction conditions.

1. Introduction

The development of efficient chiral ligands is a central issue in the research of asymmetric catalysis. Nitrogen-containing chiral ligands have distinct advantages, including easy preparation, high stability, recyclability, and more importantly, via the nitrogen atom that can stabilize the central metal at a high valence. For these reasons, nitrogen-containing ligands attract increasing attention and are used more and more in asymmetric catalysis.[1] Among the large amount of nitrogen-containing ligands developed over the last decades, ligands with a C_2-symmetry gave great success. For instance, chiral salen ligands showed a high efficiency in the asymmetric epoxidation of C–C double bonds,[2] and chiral bisoxazoline[3] and bipyridine ligands[4] were widely used in various asymmetric catalytic processes.

The conjugate addition of nucleophiles (usually called Michael addition) is one of the most important bond forming methods; its asymmetric version has also been extensively studied. Among the Michael additions of various nucleophiles, the reactions using neutral carbon nucleophiles have enjoyed limited success. For example, the catalytic asymmetric conjugate addition of malonates to chalcone derivatives remains a challenge. Although different types of chiral catalysts, including chiral heterobimetallic complexes,[5] calcium-BINOL complexes,[6] chiral ionic liquids,[7] and chiral phase-transfer catalysts,[8] have been tested in this reaction the enantioselectivities reported so far are low to moderate. A high enantioselectivity was reached by Maruoka et al.[9] by using a *N*-spiro quaternary ammonium salt as a phase-transfer catalyst. In 1998, Pfaltz et al.[10] reported an asymmetric Michael addition of malonates to chalcone catalyzed by the cobalt complex of tetradentate nitrogen ligand, providing the alkylation products in moderately high enantiomeric excesses (up to 89%), while the yield of the reaction was very low.

Recently, we have developed a series of chiral phosphorus ligands with a spirobiindane backbone and demonstrated that they are highly efficient for asymmetric hydrogenation and other asymmetric reactions.[11] In a previous letter, we reported that the C_2-symmetric bisoxazoline ligands bearing a spirobiindane backbone have moderate to good enantioselectivities in copper-catalyzed asymmetric cyclopropanation and allylic oxidation reactions.[12] During our study on the cobalt-catalyzed asymmetric Michael addition of malonates to chalcone, we found that the spiro bisoxazoline ligands were decomposed in the reaction. In order to increase the stability of chiral spiro nitrogen ligands we replaced the oxazoline moieties of ligand by pyridine and quinoline, which tolerate acids, bases, and even oxidants. Herein, we report the synthesis of C_2-symmetric

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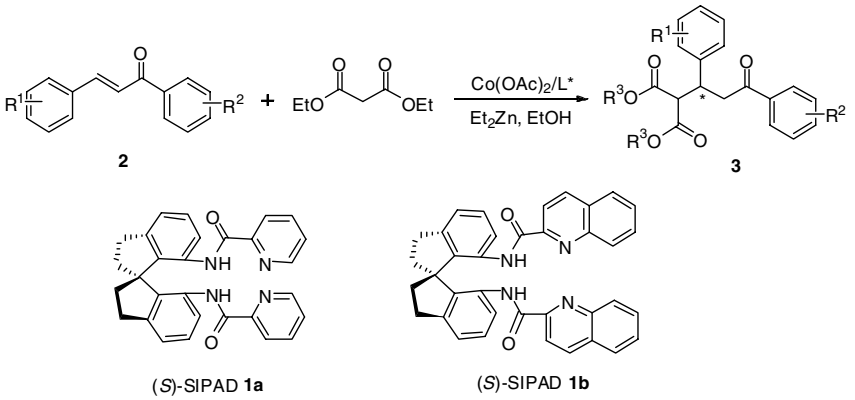


Scheme 1.

spiro nitrogen ligands **1** containing pyridine or quinoline units and their application in cobalt-catalyzed asymmetric Michael addition of malonates to chalcone (Scheme 1).

2. Results and discussion

2.1. Preparation of chiral spiro nitrogen-containing ligands

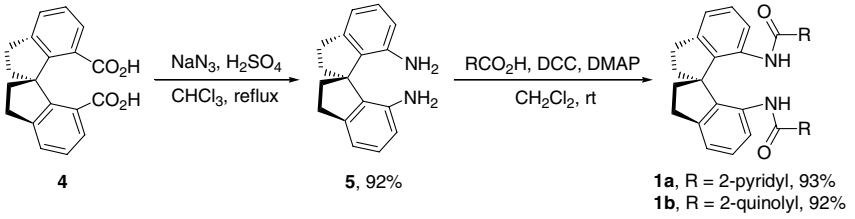
Starting from (*S*)-1,1′-spirobiindane-7,7′-dicarboxylic acid **4**,[13] which was prepared from the enantiomerically pure 1,1′-spirobiindane-7,7′-diol (SPINOL), diamine **5** was produced in a 92% yield through a Curtius rearrangement. Diamine **5** was treated with picolinic acid or quinoline-2-carboxylic acid in the presence of DCC (dicyclohexylcarbodiimide) and DMAP (*N*,*N*-dimethyl-4-diaminopyridine) to give the corresponding ligands **1a** and **1b** in 93% and 92% yields, respectively (Scheme 2).

2.2. Catalytic asymmetric Michael addition of malonate to chalcones

The new nitrogen-containing ligands **1a** and **1b** were tested in the cobalt-catalyzed Michael addition of malonate to chalcone. The conjugate addition of malonate to chalcone was firstly performed with 4 mol % of catalyst generated in situ from cobalt acetate and ligand **1a** in the presence of 1.2 equiv of the base in ethanol at room temperature, and the results are illustrated in Table 1. In the presence of strong bases, such as KOH, $Ba(OH)_2$, Na_2CO_3, the reaction was fast and gave a racemic addition product in a high yield (Table 1, entries 1–3). The use of $NaHCO_3$, $Mg(OEt)_2$, and tertiary amines led to a sluggish reaction, and the addition product was obtained in moderate yields with low enantiomeric excesses (entries 4–8). It was reported that Et_2Zn was able to form a chelating nucleophilic reagent with malonate, which minimized the conformations of the nucleophile and facilitated the enantiocontrol.[14] In fact, when 1.2 equiv Et_2Zn was added as a base in this reaction, the enantioselectivity was increased to 50% ee. Other alkylzinc reagents, including dimethylzinc and dibutylzinc were found to be essentially identical to diethylzinc (entries 8–10).

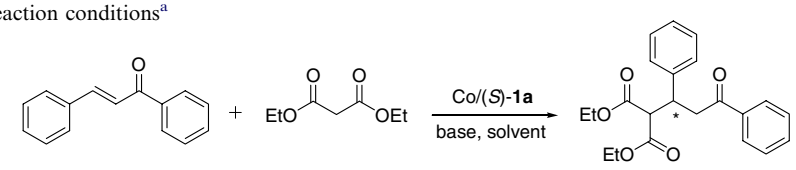
With Et_2Zn as a base, other reaction conditions were optimized sequentially. The solvent was crucial for archiving a good yield and enantioselectivity and the best results were obtained in ethanol. Various additives, such as 4 Å molecular sieves, silica gel, KF, AgOTf, $AgPF_6$, $AgBF_4$, etc. were examined and no positive impact was observed. Changing cobalt source from $Co(OAc)_2$ to $CoCl_2$ or $CoBr_2$ gave lower yields (entries 17 and 18). Compared with ligand **1a**, the quinoline-containing ligand **1b** provided a lower yield, as well as a lower enantiomeric excess (entry 19).

Under the optimized reaction conditions, various substituted chalcones acting as Michael acceptors were reacted with malonate and the results are summarized in Table 2. It was interesting to note that all chalcone derivatives, regardless of the electronic and steric properties of the substituents, gave a similar level of yield ($\geqslant$70%) and moderate enantioselectivity (around 50% ee). The effect of the ester alkyl moiety of malonate on the yield and enantioselectivity was also negligible. However, other α,β-unsaturated carbonyl compounds, such as cinnamyl aldehyde, ethyl cinnamate, (*E*)-4-phenylbut-3-en-2-one, and cyclohex-2-enone have no reaction with malonate under the same conditions.



Scheme 2.

Table 1. Optimization of the reaction conditions[a]

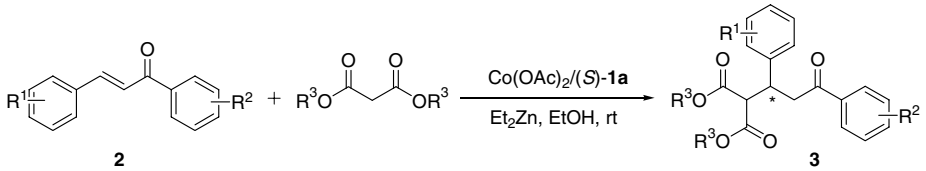


2a **3a**

Entry	[Co]	Solvent	Base	Time (h)	Yield[b] (%)	ee[c] (%)
1	$Co(OAc)_2$	EtOH	KOH	10	80	0
2	$Co(OAc)_2$	EtOH	$Ba(OH)_2$	24	85	0
3	$Co(OAc)_2$	EtOH	Na_2CO_3	48	75	0
4	$Co(OAc)_2$	EtOH	$NaHCO_3$	100	50	7
5	$Co(OAc)_2$	EtOH	$Mg(OEt)_2$	55	70	9
6	$Co(OAc)_2$	EtOH	$^iPr_2NEt$	60	37	23
7	$Co(OAc)_2$	EtOH	HMDSA[d]	70	39	4
8	$Co(OAc)_2$	EtOH	Et_2Zn	60	78	50
9	$Co(OAc)_2$	EtOH	Me_2Zn	50	74	50
10	$Co(OAc)_2$	EtOH	$^nBu_2Zn$	70	63	51
11	$Co(OAc)_2$	CH_2Cl_2	Et_2Zn	100	9	0
12	$Co(OAc)_2$	Et_2O	Et_2Zn	60	66	3
13	$Co(OAc)_2$	THF	Et_2Zn	100	9	0
14	$Co(OAc)_2$	Toluene	Et_2Zn	60	65	4
15	$Co(OAc)_2$	*n*-Hexane	Et_2Zn	100	63	3
16	$Co(OAc)_2$	MeCN	Et_2Zn	100	52	9
17	$CoBr_2$	EtOH	Et_2Zn	80	43	50
18	$CoCl_2$	EtOH	Et_2Zn	100	52	36
19[e]	$Co(OAc)_2$	EtOH	Et_2Zn	70	43	18

[a] Reaction conditions: [Co]/**1a**/chalcone/base/malonate = 0.005/0.0075/0.125/0.15/0.34 mmol, 2 mL ethanol, room temperature.
[b] Isolated yield based on chalcone.
[c] Determined by HPLC using a chiral Chiralcel OJ column.
[d] 1,1,1,3,3,3-Hexamethyldisilazane.
[e] Ligand **1b** was used.

Table 2. Co-catalyzed asymmetric Michael addition of malonate derivatives to chalcones[a]



2 **3**

Entry	R^1	R^2	R^3	Product	Yield[b] (%)	ee[c] (%)	$[\alpha]_D$[d]
1	H	H	Et	**3a**	78	50	+12.4, (*R*)
2	2-Cl	H	Et	**3b**	76	49	+35.3
3	3-Cl	H	Et	**3c**	76	53	+17.0
4	3-MeO	H	Et	**3d**	72	49	+12.0
5	4-Cl	H	Et	**3e**	76	57	+13.6
6	4-NO_2	H	Et	**3f**	76	53	+19.4
7	H	3-Cl	Et	**3g**	78	53	+13.4
8	H	3-Br	Et	**3h**	72	53	+12.4
9	H	4-Cl	Et	**3i**	72	49	+9.3
10	H	4-NO_2	Et	**3j**	76	54	+15.0
11	H	4-MeO	Et	**3k**	72	53	+15.0
12	4-NO_2	4-Me	Et	**3l**	70	51	+19.0
13	H	H	Me	**3m**	71	49	+16.2
14	H	H	Bn	**3n**	74	47	+10.0

[a] Reaction conditions: $Co(OAc)_2$/(*S*)-**1a**/**2**/Et_2Zn (1 M in hexane)/malonate = 0.005/0.0075/0.125/0.15/0.34 mmol, 2 mL ethanol, 60 h.
[b] Isolated yield based on the chalcones.
[c] Determined on HPLC using chiral columns.
[d] Determined at 26 °C in CH_2Cl_2.

It is worth noting that the reactions were carried out at an ambient temperature without any severe protection against the moisture and air, which facilitates the operation of reaction.

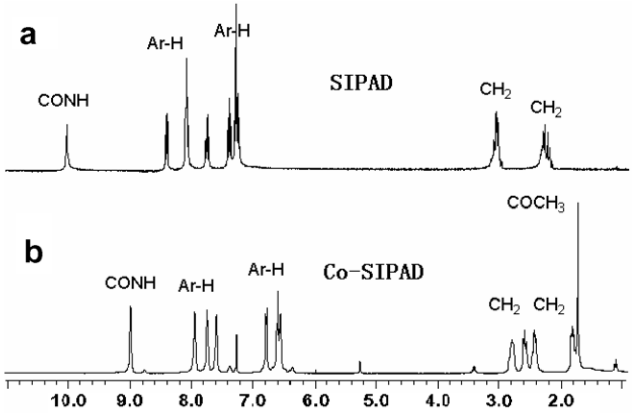


Figure 1. The ^{1}H NMR spectra of free ligand SIPAD (a) and $Co(OAc)_2$/SIPAD complex (b).

2.3. Coordination studies

In order to understand the coordination pattern of ligands **1** with cobalt, the structure of the cobalt complex of ligand **1a** was studied by NMR analysis. A mixture of cobalt acetate with 1 equiv ligand **1a** was stirred for 2 h at room temperature. After the solvent was evaporated under vacuum, the residue was resolved in $CDCl_3$ and analyzed by ^{1}H NMR. As shown in Figure 1 all the proton signals of the ligand were shifted to a higher field after coordinating with cobalt. The amide proton remained in the complex, indicating that ligand **1a** coordinated to cobalt as a bidentate, instead of a tetradentate ligand.

3. Conclusion

Two C_2-symmetric chiral nitrogen-containing ligands **1** with a spirobiindane backbone were conveniently prepared from enantiomerically pure 1,1′-spirobiindane-7,7′-dicarboxylic acid in two steps in high yields. These new nitrogen-containing ligands were evaluated in the cobalt-catalyzed asymmetric Michael addition of malonates to chalcone derivatives. The cobalt complexes prepared from cobalt acetate and **1a** can catalyze the reaction, in the presence of Et_2Zn, providing the Michael adducts in good yields and moderate enantioselectivities.

4. Experimental

4.1. General

$CHCl_3$ was distilled over CaH_2 under an atmosphere of nitrogen. THF was distilled from sodium benzophenone ketyl. Ethanol was distilled over magnesium under an atmosphere of nitrogen. Diethyl malonate was purified by distillation previous use. $Co(OAc)_2$ was dried under vacuum at 160 °C. DCC and DMAP were purchased from Aldrich and used directly. The substrates were prepared according to the literature.[15] NMR spectra were recorded with a Bruker or Varian spectrometer at 400 or 300 (^{1}H NMR), 100 or 75 (^{13}C NMR) MHz spectrometer in $CDCl_3$ solution and chemical shifts were reported in parts per million (δ) relative to the internal standard Me_4Si (0 ppm) and solvent signals (central peak is 77.00 ppm). Elemental analyses were performed on Yanaca CDRDER MT-3 instrument. Mass spectra were recorded on a LCQ Advantage spectrometer with ESI or EI resource. HPLC analyses were performed using a Hewlett Packard Model HP 1100 Series or Waters 2996 chromatography.

4.2. The preparation of ligands 1

4.2.1. (*S*)-1,1′-Spirobiindane-7,7′-diamine (*S*)-5. A solution of (*S*)-1,1′-spirobiindane-7,7′-dicarboxylic acid (*S*)-**4** (4.0 g, 0.013 mol) and 98% H_2SO_4 (9.2 mL) in $CHCl_3$ (280 mL) was stirred until homogeneous and warmed to 40–45 °C. NaN_3 (1.90 g, 0.03 mol) was added carefully in 15 batches within 90 min. After the addition of NaN_3, the reaction mixture was refluxed for 4 h and then cooled to 0 °C with an ice bath. A solution of saturated NaOH (50 mL) was added dropwise into the reaction mixture at 0 °C. The resulting biphasic mixture was diluted with water (150 mL) and extracted with $CHCl_3$ (3×100 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuum to afford the crude product. After purification by silica gel column chromatography (petroleum ether/ethyl acetate = 5:1), a pure product (2.98 g, 93%) was obtained as a pale yellow crystal. Mp 170–171 °C; $[\alpha]_D^{30} = -128$ (*c* 0.2, CH_2Cl_2); ^{1}H NMR δ 7.07–7.02 (t, $J = 7.8$ Hz, 2H), 6.72–6.67 (dd, $J = 0.9$ and 7.5 Hz, 2H), 6.45–6.42 (d, $J = 7.5$ Hz, 2H), 3.23 (m, 4H), 3.06–2.88 (m, 4H), 2.27–2.13 (m, 4H); ^{13}C NMR δ 145.2, 143.5, 130.0, 128.9, 115.4, 113.5, 59.0, 35.6, 31.3; MS (ESI) *m*/*z* 250 (M^+, 100). Anal. Calcd for $C_{17}H_{18}N_2$: C 81.56, H 7.25, N 11.19. Found: C 81.61, H 7.27, N 11.20.

4.2.2. (*S*)-1,1′-Spirobiindane-7,7′-bis(2-pyridinecarboxamide) (*S*)-1a. A suspension of (*S*)-**5** (125 mg, 0.5 mmol), picoline (246 mg, 2.0 mmol), DCC (546 mg, 2.65 mmol), and DMAP (6 mg, 0.05 mmol) in dry CH_2Cl_2 was stirred at room temperature for 8 h. To the resulting mixture was added H_2O (5 mL), and AcOH (0.05 mL). After being stirred at room temperature for 2 h, the mixture was filtrated. The residue was washed by 10 mL of CH_2Cl_2. The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 3:1) to afford pure (*S*)-**1a** (212 mg, 93%) as a white solid; mp 156–158 °C; $[\alpha]_D^{20} = -364$ (*c* 0.5, CH_2Cl_2); ^{1}H NMR δ 9.95 (s, 2H), 8.38–8.35 (d, $J = 7.5$ Hz, 2H), 8.06–8.02 (m, 4H), 7.74–7.69 (m, 2H), 7.39–7.20 (m, 6H), 3.21–3.04 (m, 4H), 2.41–2.23 (m, 4H); ^{13}C NMR δ 162.0, 149.7, 147.5, 145.4, 137.1, 134.9, 134.3, 128.9, 125.8, 121.7, 120.7, 118.7, 59.6, 37.3, 31.1; MS (ESI) *m*/*z* 461 (M+1, 100). Anal. Calcd for $C_{29}H_{24}N_4O_2$: C 75.63; H 5.25; N 12.19. Found: C 75.37, H 5.24, N 12.06.

4.2.3. (*S*)-1,1′-Spirobiindane-7,7′-bis(2-quinolinecarboxamide) (*S*)-1b. With the identical procedure for (*S*)-**1a**, ligand (*S*)-**1b** was prepared from the dicarboxylic acid (*S*)-**4** and quinoline-2-carboxylic acid in a 92% yield as a white solid; mp 155–157 °C; $[\alpha]_D^{20} = -442$ (*c* 0.5, CH_2Cl_2); ^{1}H

NMR δ 9.84 (s, 2H), 8.31–8.29 (d, $J = 6.9$ Hz, 2H), 8.20 (s, 4H), 7.86–7.71 (m, 6H), 7.61–7.56 (m, 2H), 7.29–7.22 (m, 4H), 3.21–3.04 (m, 4H), 2.41–2.23 (m, 4H); ^{13}C NMR δ 162.5, 149.5, 146.2, 145.1, 137.3, 135.4, 134.8, 130.4, 129.5, 129.2, 129.0, 127.9, 127.5, 121.7, 120.0, 118.6, 59.9, 37.4, 31.1; HRMS (MALDI) Calcd for $C_{37}H_{28}N_4O_2$: 561.2289. Found 561.2285.

4.3. Typical procedure for Co(II)-catalyzed asymmetric Michael addition of malonate to chalcone

A mixture of $Co(OAc)_2$ (1.0 mg, 0.005 mmol) and ligand **1a** (3.5 mg, 0.0075 mmol) in EtOH (2 mL) was stirred at room temperature for 2 h. Chalcone (26 mg, 0.125 mmol) and malonate (56 mg, 0.34 mol) were added sequentially and stirred. Et_2Zn (0.15 mL, 1 M in *n*-hexane) was injected into the reaction mixture every 15 h. The reaction was monitored by TLC for a full conversion. The reaction mixture was filtered and concentrated in vacuum and the crude product was purified on a silica gel column with petroleum ether/ethyl acetate (9:1) to afford the addition product. The analyses were illustrated as follows.

4.3.1. Diethyl 2-(3-oxo-1,3-diphenylpropyl)malonate 3a.[10] White solid, yield 78%; mp 69–71 °C; ^{1}H NMR δ 7.91–7.88 (d, $J = 7.2$ Hz, 2H), 7.55–7.51 (t, $J = 7.2$ Hz, 1H), 7.44–7.40 (t, $J = 8.1$ Hz, 2H), 7.26–7.16 (m, 5H), 4.21–4.16 (m, 3H), 4.00–3.92 (q, $J = 7.2$ Hz, 2H), 3.83–3.80 (d, $J = 8.7$ Hz, 1H), 3.58–3.41 (m, 2H), 1.27–1.22 (t, $J = 7.2$ Hz, 3H), 1.03–0.98 (t, $J = 7.2$, 3H); 50% ee [HPLC conditions: Chirapak OJ column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 70:30, flow rate = 1 mL/min, wavelength = 254 nm, $t_R = 26.1$ min (major) for (*R*)-enantiomer, $t_R = 38.5$ min (minor) for (*S*)-enantiomer]; $[\alpha]_D^{26} = +12.4$ (*c* 0.25, CH_2Cl_2).

4.3.2. Diethyl 2-(1-(2-chlorophenyl)-3-oxo-3-phenylpropyl)malonate 3b. Colorless oil, yield 76%; ^{1}H NMR δ 7.92–7.91 (d, $J = 7.2$ Hz, 2H), 7.53–7.49 (t, $J = 7.2$ Hz, 1H), 7.42–7.38 (t, $J = 8.0$ Hz, 2H), 7.30–7.39 (m, 2H), 7.15–7.08 (m, 2H), 4.68–4.62 (m, 1H), 4.21–3.99 (m, 5H), 3.71–3.58 (m, 2H), 1.12–1.16 (t, $J = 7.2$ Hz, 3H), 1.08–1.04 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR δ 197.4, 168.3, 167.8, 137.9, 136.8, 134.2, 133.1, 130.1, 129.5, 128.6, 128.3, 128.1, 126.8, 61.6, 61.5, 55.3, 40.5, 37.5, 14.0, 13.8; MS (EI) *m*/*z* 402 (M^+, 2). Anal. Calcd for $C_{22}H_{23}ClO_5$: C 65.59, H 5.75. Found: C 65.79, H 6.24; 49% ee [HPLC conditions: Chirapak OJ column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, wavelength = 254 nm, $t_R = 14.8$ min (major), $t_R = 22.0$ min (minor)]; $[\alpha]_D^{26} = +35.3$ (*c* 0.15, CH_2Cl_2).

4.3.3. Diethyl 2-(1-(3-chlorophenyl)-3-oxo-3-phenylpropyl)-malonate 3c. White solid, yield 76%; mp 79–81 °C; ^{1}H NMR δ 7.90–7.88 (d, $J = 7.2$ Hz, 2H), 7.55–7.52 (t, $J = 7.2$ Hz, 1H), 7.44–7.41 (t, $J = 7.2$ Hz, 2H), 7.26 (s, 1H), 7.19–7.13 (m, 3H), 4.20–4.13 (m, 3H), 4.01–3.96 (q, $J = 7.2$ Hz, 2H), 3.79–3.77 (d, $J = 9.2$ Hz, 1H), 3.57–3.41 (m, 2H), 1.25–1.22 (t, $J = 7.2$ Hz, 3H), 1.06–1.03 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR δ 197.3, 168.3, 167.7, 142.9, 136.8, 134.3, 133.4, 129.9, 123.8, 128.6, 128.3, 127.6, 62.0, 61.7, 57.5, 42.4, 40.5, 14.2, 14.0; MS (EI) *m*/*z* 402 (M^+, 20). Anal. Calcd for $C_{22}H_{23}ClO_5$: C 65.59, H 5.75. Found: C 65.48, H 6.05; 53% ee [HPLC conditions: Chirapak OJ column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, wavelength = 254 nm, $t_R = 12.3$ min (major), $t_R = 15.65$ min (minor)]; $[\alpha]_D^{26} = +17.0$ (*c* 0.5, CH_2Cl_2).

4.3.4. Diethyl 2-(1-(3-methoxyphenyl)-3-oxo-3-phenylpropyl)malonate 3d. Colorless oil, yield 72%; ^{1}H NMR δ 7.83–7.80 (d, $J = 8.4$ Hz, 2H), 7.47–7.31 (m, 3H), 7.10–7.05 (t, $J = 8.4$ Hz, 1H), 6.78–6.61 (m, 3H), 4.15–4.05 (m, 3H), 3.94–3.87 (q, $J = 6.9$ Hz, 2H), 3.75–3.66 (m, 4H), 3.45–3.32 (m, 2H), 1.18–1.13 (t, $J = 6.9$ Hz, 3H), 0.98–0.93 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR δ 197.5, 168.3, 167.7, 159.5, 142.2, 136.9, 133.0, 129.3, 128.5, 128.1, 120.4, 114.1, 112.5, 61.6, 61.3, 57.5, 55.1, 42.5, 40.8, 13.9, 13.7; MS (EI) *m*/*z* 398 (M^+, 10). Anal. Calcd for $C_{23}H_{26}O_6$: C 69.33, H 6.58. Found: C 69.41, H 6.40; 49% ee [HPLC conditions: Chirapak AS column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 95:5, flow rate = 1 mL/min, wavelength = 254 nm, $t_R = 16.7$ min (minor), $t_R = 19.1$ min (major)]; $[\alpha]_D^{26} = +12.0$ (*c* 0.5, CH_2Cl_2).

4.3.5. Diethyl 2-(1-(4-chlorophenyl)-3-oxo-3-phenylpropyl)malonate 3e.[16] White solid, yield 76%; mp 113–115 °C; ^{1}H NMR δ 7.90–7.88 (d, $J = 7.2$ Hz, 2H), 7.57–7.52 (t, $J = 7.2$ Hz, 1H), 7.46–7.40 (t, $J = 8.1$ Hz, 2H), 7.22 (s, 4H), 4.22–4.13 (m, 3H), 4.02–3.94 (q, $J = 8.1$ Hz, 2H), 3.80–3.76 (d, $J = 9.6$ Hz, 1H), 3.57–3.38 (m, 2H), 1.27–1.22 (t, $J = 7.2$ Hz, 3H), 1.07–1.03 (t, $J = 7.2$ Hz, 3H); 57% ee [HPLC conditions: Chirapak OJ column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, wavelength = 254 nm, $t_R = 14.7$ min (major), $t_R = 17.1$ min (minor)]; $[\alpha]_D^{26} = +13.6$ (*c* 0.5, CH_2Cl_2).

4.3.6. Diethyl 2-(1-(4-nitrophenyl)-3-oxo-3-phenylpropyl)malonate 3f.[16] White solid, yield 76%; mp 111–113 °C; ^{1}H NMR δ 8.12–8.10 (d, $J = 8.8$ Hz, 2H), 7.90–7.87 (d, $J = 8.8$ Hz, 2H), 7.56–7.46 (m, 5H), 4.30–4.18 (m, 3H), 4.02–3.96 (q, $J = 7.2$ Hz, 2H), 3.85–3.83 (d, $J = 9.2$ Hz, 1H), 3.62–3.49 (m, 2H), 1.26–1.22 (t, $J = 7.2$ Hz, 3H), 1.07–1.03 (t, $J = 7.2$, 3H); 53% ee [HPLC conditions: Chirapak OJ column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 70:30, flow rate = 1 mL/min, wavelength = 254 nm, $t_R = 20.1$ min (major), $t_R = 31.5$ min (minor)]; $[\alpha]_D^{26} = +19.4$ (*c* 0.5, CH_2Cl_2).

4.3.7. Diethyl 2-(3-(3-chlorophenyl)-3-oxo-1-phenylpropyl)-malonate 3g. White solid, yield 78%; mp 69–70 °C; ^{1}H NMR δ 7.83 (s, 1H), 7.78–7.76 (d, $J = 7.6$ Hz, 1H), 7.49–7.47 (d, $J = 9.2$ Hz, 1H), 7.37–7.33 (t, $J = 7.6$ Hz, 1H), 7.25–7.16 (m, 5H), 4.25–4.12 (m, 3H), 3.97–3.92 (q, $J = 7.2$ Hz, 2H), 3.81–3.79 (m, 1H), 3.54–3.39 (m, 2H), 1.25–1.22 (t, $J = 7.2$ Hz, 3H), 1.02–0.98 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR δ 196.5, 168.5, 167.9, 140.5, 138.5, 135.0, 133.2, 130.1, 128.7, 128.4, 127.4, 126.6, 61.9, 61.6, 57.6, 42.9, 40.9, 14.2, 14.1; MS (EI) *m*/*z* 402 (M^+, 3). Anal. Calcd for $C_{22}H_{23}ClO_5$: C 65.59, H 5.75. Found: C 65.46, H 6.12; 53% ee [HPLC conditions: Chirapak OJ column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90:10, flow rate =

1 mL/min, wavelength = 220 nm, t_R = 30.5 min (major), t_R = 38.3 min (minor)]; $[\alpha]_D^{26}$ = +13.4 (*c* 0.5, CH_2Cl_2).

4.3.8. Diethyl 2-(3-(3-bromophenyl)-3-oxo-1-phenylpropyl)-malonate 3h. Colorless oil, yield 72%; ^{1}H NMR δ 7.98 (s, 1H), 7.82–7.80 (d, *J* = 7.2 Hz, 1H), 7.63–7.62 (t, *J* = 7.2 Hz, 1H), 7.30–7.15 (m, 6H), 4.23–4.12 (m, 3H), 3.97–3.91 (q, *J* = 7.2 Hz, 2H), 3.81–3.79 (d, *J* = 7.2 Hz, 1H), 3.53–3.39 (m, 2H), 1.25–1.21 (t, *J* = 7.2 Hz, 3H), 1.01–0.97 (t, *J* = 7.2, 3H); ^{13}C NMR δ 196.4, 168.5, 167.9, 140.5, 138.7, 136.1, 131.3, 130.7, 128.7, 128.4, 127.5, 126.9, 123.1, 61.9, 57.6, 42.9, 40.9, 14.3, 14.0; MS (EI) *m*/*z* 446 (M^+, 2). Anal. Calcd for $C_{22}H_{23}BrO_5$: C 59.07, H 5.18. Found: C 59.36, H 4.92; 53% ee [HPLC conditions: Chirapak OJ column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, wavelength = 254 nm, t_R = 20.4 min (major), t_R = 24.7 min (minor)]; $[\alpha]_D^{26}$ = +12.4 (*c* 0.5, CH_2Cl_2).

4.3.9. Diethyl 2-(3-(4-chlorophenyl)-3-oxo-1-phenylpropyl)-malonate 3i.[9] Colorless oil, yield 72%; ^{1}H NMR δ 7.84–7.82 (d, *J* = 8.4 Hz, 2H), 7.40–7.37 (d, *J* = 8.8 Hz, 2H), 7.24–7.15 (m, 5H), 4.23–4.11 (m, 3H), 3.97–3.92 (q, *J* = 7.2 Hz, 2H), 3.81–3.78 (d, *J* = 9.2 Hz, 1H), 3.54–3.36 (m, 2H), 1.25–1.22 (t, *J* = 7.2 Hz, 3H), 1.01–0.98 (t, *J* = 7.2 Hz, 3H); 49% ee [HPLC conditions: Chirapak OJ column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 47.5 min (minor), t_R = 68.7 min (major)]; $[\alpha]_D^{26}$ = +9.3 (*c* 0.15, CH_2Cl_2).

4.3.10. Diethyl 2-(3-(4-nitrophenyl)-3-oxo-1-phenylpropyl)-malonate 3j. Yellow oil, yield 76%; ^{1}H NMR δ 8.28–8.25 (d, *J* = 8.8 Hz, 2H), 8.05–8.03 (d, *J* = 8.8 Hz, 2H), 7.27–7.17 (m, 5H), 4.27–4.10 (m, 3H), 3.98–3.93 (q, *J* = 7.2 Hz, 2H), 3.81–3.79 (d, *J* = 9.6 Hz, 1H), 3.66–3.60 (dd, *J* = 4.8 and 16.4 Hz, 1H), 3.49–3.43 (dd, *J* = 9.6 and 16.4 Hz, 1H), 1.27–1.23 (t, *J* = 7.2 Hz, 3H), 1.02–0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 195.6, 168.5, 167.8, 150.4, 141.4, 140.1, 129.4, 128.7, 128.3, 127.6, 124.0, 62.0, 61.7, 57.5, 43.4, 41.1, 14.2, 13.9; MS (EI) *m*/*z* 413 (M^+, 10). Anal. Calcd for $C_{22}H_{23}NO_7$: C 63.91, H 5.61, N 3.39. Found: C 63.71, H 6.47, N 3.41; 54% ee [HPLC conditions: Chirapak OJ column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 60:40, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 36.6 min (minor), t_R = 57.1 min (major)]; $[\alpha]_D^{26}$ = +15.0 (*c* 0.8, CH_2Cl_2).

4.3.11. Diethyl 2-(3-(4-methoxyphenyl)-3-oxo-1-phenylpropyl)malonate 3k. White solid, yield 72%; mp 67–70 °C; ^{1}H NMR δ 7.90–7.87 (d, *J* = 8.4 Hz, 2H), 7.25–7.14 (m, 5H), 6.90–6.87 (d, *J* = 8.4 Hz, 2H), 4.22–4.12 (m, 3H), 3.98–3.91 (q, *J* = 7.2 Hz, 2H), 3.85–3.80 (m, 4H), 3.52–3.33 (m, 2H), 1.26–1.22 (t, *J* = 7.2 Hz, 3H), 1.02–0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 196.2, 168.6, 168.0, 163.6, 140.8, 130.6, 130.2, 128.5, 128.5, 127.3, 113.9, 61.8, 61.5, 57.8, 55.6, 42.5, 41.3, 14.2, 14.0; MS (EI) *m*/*z* 398 (M^+, 18). Anal. Calcd for $C_{23}H_{26}O_6$: C 69.33, H 6.58. Found: C 69.27, H 7.26; 53% ee [HPLC conditions: Chirapak OJ column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 80:20, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 15.3 min (major), t_R = 23.2 min (minor)]; $[\alpha]_D^{26}$ = +15.0 (*c* 0.5, CH_2Cl_2).

4.3.12. Diethyl 2-(1-(4-nitrophenyl)-3-oxo-3-p-tolylpropyl)-malonate 3l. Yellow oil, yield 70%; ^{1}H NMR δ 8.08–8.06 (d, *J* = 8.4 Hz, 2H), 7.77–7.75 (d, *J* = 8.4 Hz, 2H), 7.48–7.46 (d, *J* = 8.8 Hz, 2H), 7.20–7.18 (d, *J* = 7.6 Hz, 2H), 4.30–4.14 (m, 3H), 3.99–3.93 (q, *J* = 7.6 Hz, 2H), 3.85–3.83 (d, *J* = 7.6 Hz, 1H), 3.57–3.45 (m, 2H), 2.35 (s, 3H), 1.25–1.22 (t, *J* = 7.2 Hz, 3H), 1.01–0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 196.6, 168.0, 167.5, 148.8, 147.1, 144.5, 134.1, 129.6, 129.6, 128.3, 123.7, 129.6, 62.1, 61.9, 57.0, 42.1, 40.6, 21.8, 14.2, 14.0; MS (EI) *m*/*z* 427 (M^+, 2). Anal. Calcd for $C_{23}H_{25}NO_7$: C 64.63, H 5.90, N 3.28. Found: C 64.75, H 6.29 N 3.24; 51% ee [HPLC conditions: Chirapak OJ column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 80:20, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 21.8 min (major), t_R = 41.1 min (minor)]; $[\alpha]_D^{26}$ = +19.0 (*c* 0.2 CH_2Cl_2).

4.3.13. Dimethyl 2-(3-oxo-1,3-diphenylpropyl)malonate 3m.[5a] White solid, yield 71%; ^{1}H NMR δ 7.90–7.88 (d, *J* = 7.6 Hz, 2H), 7.55–7.51 (t, *J* = 7.6 Hz, 1H), 7.44–7.40 (t, *J* = 7.6 Hz,1H), 7.26–7.17 (m, 6H), 4.22–4.16 (m, 1H), 3.86–3.84 (q, *J* = 9.2 Hz, 1H), 3.75–3.69 (m, 1H), 3.57–3.40 (m, 7H); 49% ee [HPLC conditions: Chirapak OJ-H column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 85:150, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 25.9 min (major), t_R = 31.5 min (minor)]; $[\alpha]_D^{26}$ = +16.2 (*c* 0.5, CH_2Cl_2).

4.3.14. Dibenzyl 2-(3-oxo-1,3-diphenylpropyl)malonate 3n.[8a] White solid, yield 74%; ^{1}H NMR δ 7.89–7.87 (m, 2H), 7.53–7.15 (m, 18H), 4.69 (s, 4H), 4.24–4.15 (m, 1H), 3.86–3.82 (m, 1H), 3.55–3.43 (m, 2H); 47% ee [HPLC conditions: Chirapak OJ-H column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 35.1 min (major), t_R = 43.1 min (minor)]; $[\alpha]_D^{26}$ = +10.0 (*c* 0.2, CH_2Cl_2).

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