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Chiral ferrocenyl phosphine-phosphoramidite ligands for Cu-catalyzed asymmetric conjugate reduction of α,β-unsaturated esters

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ABSTRACT

Unsymmetrical hybrid chiral ferrocenyl phosphine-phosphoramidite ligands have been applied for the first time in the Cu-catalyzed asymmetric 1,4-reduction of β-aryl substituted α,β-unsaturated esters. The results show that the ligand bearing (S_c)-central, (R_p)-planar, and (R_a)-axial chiralities gave the best performance. The present catalytic system proved to be highly substrate-dependent, catalyzing the conjugate reduction of α,β-unsaturated esters in moderate to excellent enantioselectivities.

1. Introduction

The catalytic asymmetric 1,4-reduction of α,β-unsaturated compounds is an important method for the construction of tertiary stereogenic centers in organic synthesis. In the past decades, significant progress has been made in the development of efficient and economic protocols for achieving this transformation with substantial emphasis on the use of transition metal catalysts, of which copper hydride complexes ligated by non-racemic ligands have arguably demonstrated the greatest synthetic utility.[1] In 1999, Buchwald et al. reported for the first time that a catalyst formed from *p*-tol-BINAP, CuCl, and NaO*t*-Bu could affect the asymmetric conjugate reduction of α,β-unsaturated esters in the presence of 4 equiv of polymethylhydrosiloxane (PMHS) relative to the substrate.[2] Since then, a series of α,β-unsaturated compounds (i.e., enones,[3] α,β-unsaturated esters,[2,4] α,β-unsaturated phosphonates,[5] α,β-unsaturated lactones and lactams,[6] α,β-unsaturated sulfones,[7] α,β-unsaturated nitrile,[8] nitroalkenes,[9] and 2-alkenylheteroarenes[10]) has been subjected to the 1,4-reduction with the Cu/diphosphine catalytic system, giving the reduction products with excellent enantioselectivities. Despite these achievements, chiral ligands employed in the Cu-catalyzed asymmetric 1,4-reduction remain very limited, and only a few diphosphine ligand types, such as BINAP, BIPHEP, SEGPHOS, JosiPhos, and Taniaphos, have been found to be efficient for this important transformation. The search for new chiral ligands for the Cu-catalyzed asymmetric 1,4-reduction is, therefore, of great interest.

Recently, we and some other groups developed a series of unsymmetrical hybrid chiral phosphine-phosphoramidite ligands.[11] These ligands have the advantages of easy accessibility, modularity, and stability toward air and moisture, which make them highly practical for both academic and industrial applications. Indeed, these ligands have been found to display wide utility in asymmetric catalysis, and give excellent results in Rh-catalyzed asymmetric hydrogenations,[12] Rh-catalyzed asymmetric hydroformylations,[13] Pd-catalyzed asymmetric allylic alkylations,[14] Cu-catalyzed asymmetric conjugate additions of diethylzinc to enones[15] and Ag-catalyzed [3+2] cycloadditions of azomethine ylides with dimethyl maleate.[16] To the best of our knowledge, however, there is no reported example of an asymmetric conjugate reduction with a phosphine-phosphoramidite ligand. Herein, we report our investigation on the use of a Cu/ferrocenyl phosphine-phosphoramidite catalytic system in the asymmetric 1,4-reduction of α,β-unsaturated esters, in which up to 99% ee was obtained although this reduction was found to be highly substrate-dependent.

2. Results and discussion

As we have reported, these chiral ferrocene-based phosphine-phosphoramidite ligands (PPFAPhos) can be easily prepared from Ugi's amine through a modular procedure.[12c] With these ligands in hand (Fig. 1), we then examined their efficiency in the Cu-catalyzed asymmetric conjugate reduction of α,β-unsaturated esters. Ethyl (*E*)-3-phenylbut-2-enoate **2a** was selected as a model substrate for the screening process, and the results are summarized in Table 1. Initially, we examined a range of chiral ferrocenyl phosphine-phosphoramidite ligands for effecting the conjugate reduction of (*E*)-3-phenylbut-2-enoate **2a** with polymethylhydrosiloxane (PMHS) under catalytic conditions: $Cu(OAc)_2{\cdot}H_2O$ (5 mol %), ligand (6 mol %), and *t*-BuOH (4 equiv) in THF for 24 h. At first was tested (S_c,R_p,S_a)-PPFAPhos, which was found to possess the matched chiralities and display the best performance in the

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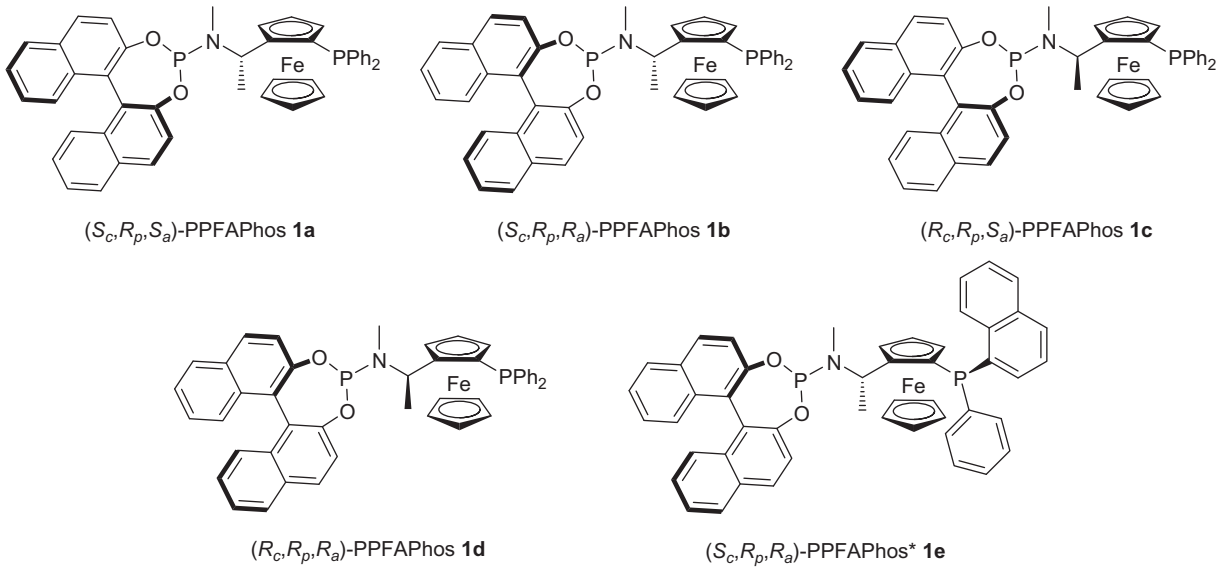
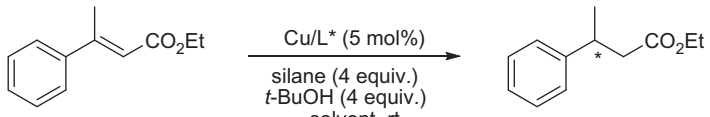


(S_c,R_p,S_a)-PPFAPhos **1a** (S_c,R_p,R_a)-PPFAPhos **1b** (R_c,R_p,S_a)-PPFAPhos **1c**

(R_c,R_p,R_a)-PPFAPhos **1d** (S_c,R_p,R_a)-PPFAPhos* **1e**

Figure 1. Ferrocene-based phosphine-phosphoramidite ligands, PPFAPhos **1a**–**e** for Cu-catalyzed asymmetric conjugate reduction.

Table 1
Cu-catalyzed asymmetric conjugate reduction of ethyl (*E*)-3-phenylbut-2-enoate **2a**[a]



2a **3a**

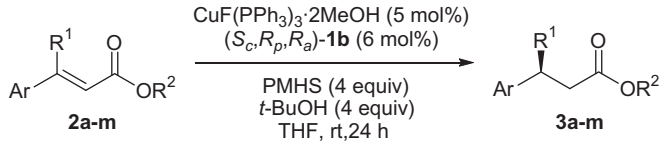
Entry	Ligand	Cu source	Silane	Solvent	Conversion[b] (%)	Ee[c] (%)
1	(S_c,R_p,S_a)-**1a**	$Cu(OAc)_2·H_2O$	PMHS	THF	100	25
2	(S_c,R_p,R_a)-**1b**	$Cu(OAc)_2·H_2O$	PMHS	THF	100	79
3	(R_c,R_p,S_a)-**1c**	$Cu(OAc)_2·H_2O$	PMHS	THF	56	46
4	(R_c,R_p,R_a)-**1d**	$Cu(OAc)_2·H_2O$	PMHS	THF	32	6
5	(S_c,R_p,R_a)-**1e**	$Cu(OAc)_2·H_2O$	PMHS	THF	31	32
6	(S_c,R_p,R_a)-**1b**	CuCl/*t*-BuONa	PMHS	THF	95	81
7	(S_c,R_p,R_a)-**1b**	$CuF(PPh_3)_3·2MeOH$	PMHS	THF	100	82
8	(S_c,R_p,R_a)-**1b**	$CuF(PPh_3)_3·2MeOH$	$PhSiH_3$	THF	70	74
9	(S_c,R_p,R_a)-**1b**	$CuF(PPh_3)_3·2MeOH$	Ph_2SiH_2	THF	96	62
10	(S_c,R_p,R_a)-**1b**	$CuF(PPh_3)_3·2MeOH$	TMDS	THF	44	56
11	(S_c,R_p,R_a)-**1b**	$CuF(PPh_3)_3·2MeOH$	Et_3SiH	THF	<5	—[d]
12	(S_c,R_p,R_a)-**1b**	$CuF(PPh_3)_3·2MeOH$	PMHS	Et_2O	99	79
13	(S_c,R_p,R_a)-**1b**	$CuF(PPh_3)_3·2MeOH$	PMHS	Toluene	100	78
14	(S_c,R_p,R_a)-**1b**	$CuF(PPh_3)_3·2MeOH$	PMHS	CH_2Cl_2	11	57

[a] All reactions were performed at 5 mol % of catalyst loadings prepared in situ from Cu-precursor and 1.2 equiv of chiral diphosphine ligand with 0.25 mmol of substrate **2a**, 4 equiv. of *t*-BuOH and 4 equiv of silanes at room temperature in 2 mL of solvent for 24 h.
[b] Degrees of conversion were determined by GC.
[c] Enantiomeric excesses were determined by chiral HPLC.
[d] Not determined due to low conversion.

Rh-catalyzed asymmetric hydrogenation of various functionalized olefins.[12c] However, only low enantioselectivity was achieved although full conversions were observed (entry 1). Since the absolute configuration of a chiral ligand normally affects the catalytic activity and enantioselectivity, we then investigated the efficiency of the diastereomeric ligands **1b**–**d** of (S_c,R_p,S_a)-**1a** in this transformation. In most cases, the reduction proceeded very slowly, giving only low enantioselectivity (entries 3 and 4). However, ligand **1b**, which holds (S_c)-central, (R_p)-planar, and (R_a)-axial chiralities, gave an ee-value of 79% and full conversion (entry 2). The introduction of a stereogenic P-donor atom into (S_c,R_p,R_a)-**1b** resulted in significantly decreased conversion and enantioselectivity (entry 5). An optimization study with (S_c,R_p,R_a)-**1b** revealed that copper salts, such as CuCl and $CuF(PPh_3)_3·2MeOH$, gave similar results (entries 6 and 7), but $CuF(PPh_3)_3·2MeOH$ was slightly superior to CuCl with respect to the selectivity (entry 7). Silanes significantly affected the reactivity and enantioselectivity, and the best results were achieved with PMHS (entries 7–11). It is noteworthy that $PhSiH_2$ showed greater reactivity than $PhSiH_3$, which is different with most other hydrosilylation reactions reported so far.[5,17] For further reaction optimization, the solvent effect was also investigated (entries 12–14). The best result was obtained with a THF as solvent (entry 7).

With the optimal catalyst combination and reaction conditions in hand, the scope of the reduction of a series of β-aryl substituted α,β-unsaturated esters was then investigated, and the results are summarized in Table 2. The results disclosed that the ester functional group had an important influence on the reactivity and enantioselectivity. Thus, a modest change from an ethyl ester **2a** to a methyl ester **2b** led to greatly decreased enantioselectivities

Table 2
Cu-catalyzed asymmetric 1,4-reduction of β-aryl substituted α,β-unsaturated esters **2** with (S_c,R_p,R_a)-PPFAPhos **1b**[a]



Entry	Substrate (Ar, R^1, R^2)	Conversion[b] (%)	ee[d] (%)
1	**2a** (Ph, Me, Et)	100 (95)[c]	82 (*S*)
2	**2b** (Ph, Me, Me)	100	44 (*S*)
3	**2c** (Ph, Me, *i*-Pr)	55	50 (*S*)
4	**2d** (Ph, Me, *t*-Bu)	61	38 (*S*)
5	**2e** (Ph, Et, Et)	100	86 (*S*)
6	**2f** (Ph, *i*-Pr, Et)	93	81 (+)
7	**2g** (4-$CH_3C_6H_4$, Me, Et)	75	77 (*S*)
8	**2h** (4-$CH_3OC_6H_4$, Me, Et)	87	76 (+)
9	**2i** (4-ClC_6H_4, Me, Et)	100	>99 (+)
10	**2j** (4-BrC_6H_4, Me, Et)	100	97 (+)
11	**2k** (4-$NO_2C_6H_4$, Me, Et)	100	80 (+)
12	**2l** (3-$NO_2C_6H_4$, Me, Et)	49	89 (+)
13	**2m** (2-thienyl, Me, Et)	88	83 (+)

[a] Reaction conditions: substrate **2** (0.25 mmol), $CuF(PPh_3)_3$·2MeOH (5 mol %), (S_c,R_p,R_a)-**1b** (6 mol %), PMHS (4 equiv), *t*-BuOH (4 equiv) in THF at room temperature for 24 h.
[b] Degrees of conversion were determined by ^{1}H NMR.
[c] Isolated yield in parentheses.
[d] The ee values were determined by HPLC on a chiral column (Chiralcel OD-H, chiralpak AD-H or Chiralcel OJ-H). The absolute configuration was determined by comparison of the sign of the specific rotation with the reported data.

(entries 1 and 2). The introduction of a bulkier *i*-Pr ester or *t*-Bu ester functional group also resulted in reduced conversion (entries 3 and 4). An alkyl group at the β-position had little effect on this reaction, and all substrates **2a**, **2e,** and **2f** were reduced with similar enantioselectivities (entries 1, 5, and 6). It is noteworthy that the substituent on the phenyl ring of the substrate had a major influence on the conversion and enantioselectivity (entries 7–12), and the substrates with an electron-donating group at the *para*-position of the phenyl ring (entries 7 and 8) tended to be reduced in lower conversion and enantioselectivity than those with an electron-withdrawing group (entries 9–11). However, substrate **2l** bearing a *meta*-nitro group on the phenyl ring was reduced in low conversion (entry 12). Goods results were also obtained in the reduction of β-heteroaromatic-substituted substrate **2m** (entry 13). These results indicate that the present catalytic system is efficient for the asymmetric conjugate reduction of α,β-unsaturated esters. However, in comparison with those traditional Cu/diphosphine catalytic systems,[2,4] this catalyst displayed less generality in terms of enantioselectivity and showed slightly lower enantioselectivities for some substrates such as **2a**.

3. Conclusion

In conclusion, we have demonstrated that chiral ferrocene-based phosphine-phosphoramidite ligands are efficient for the Cu-catalyzed asymmetric 1,4-reduction of β-aryl substituted α,β-unsaturated esters, giving ee-values of up to >99%. The research revealed that ligand **1b** bearing (S_c)-central, (R_p)-planar, and (R_a)-axial chiralities showed the best performance. The present catalytic system proved to be highly substrate-dependent. With the $CuF(PPh_3)_3$·2MeOH/(S_c,R_p,R_a)-**1b** catalytic system, a wide range of β-aryl substituted α,β-unsaturated esters were reduced in moderate to excellent enantioselectivities in the presence of PMHS and *t*-BuOH. The reduction was sensitive to the electronic properties of the substituent on the phenyl ring of the substrate. Generally, the substrates with an electron-withdrawing group at the *para*-position of the phenyl ring were reduced in higher yields than those with an electron-donating group. Further applications of chiral ferrocene-based phosphine-phosphoramidite ligands are currently in progress.

4. Experimental

4.1. General

All reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques. All solvents were dried and degassed by standard methods and stored under nitrogen. Ligands **1a**–**e** were prepared according to the literature.[12c] α,β-Unsaturated esters **2a**–**m** were synthesized according to the literature method.[2] All other chemicals were obtained commercially. ^{1}H NMR was recorded on a Bruker DPX400 NMR spectrometer. Chemical shifts are expressed in δ value (ppm) using tetramethylsilane (TMS) as an internal standard. HPLC analysis was performed on an Agilent 1100 series instrument with a chiral column (chiralcel OD-H, chiralcel OJ-H or chiralpak AD-H).

4.2. General procedure for Cu-catalyzed asymmetric conjugate reduction of α,β-unsaturated esters

Copper salt (0.0125 mmol) and ligand (0.015 mmol) were added into an oven-dried Schlenk tube. Then, dry THF (2.0 mL) was added under nitrogen. The mixture was stirred at room temperature for 30 min to give a solution. Next, PMHS (60 μL, 1.0 mmol) was added to the reaction mixture and stirred for 30 min. The substrate (0.25 mmol) was then added, followed by *t*-BuOH (95 μL, 1.0 mmol). The reaction was sealed, and stirred for 24 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The product was purified by chromatography on silica gel.

4.2.1. Ethyl (*S*)-3-phenylbutanoate 3a[2]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, J = 7.1 Hz, 3H), 1.30 (d, J = 7.0 Hz, 3H), 2.52–2.64 (m, 2H), 3.25–3.29 (m, 1H), 4.07 (q, J = 7.1 Hz, 2H), 7.19–7.23 (m, 3H), 7.28–7.31 (m, 2H). $[\alpha]_D^{20} = +9.3$ (c 1.43, $CHCl_3$). HPLC analysis: chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: *n*-hexane/*i*-PrOH (99.5:0.5); detection at 210 nm; t_1 = 11.93 min, t_2 = 22.87 min; ee = 82%.

4.2.2. Methyl (*S*)-3-phenylbutanoate 3b[18,19]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (d, J = 7.0 Hz, 3H), 2.52–2.66 (m, 2H), 3.25–3.31 (m, 1H), 3.67 (s, 3H), 7.18–7.23 (m, 3H), 7.28–7.32 (m, 2H). $[\alpha]_D^{20} = +7.3$ (c 1.36, $CHCl_3$). HPLC analysis: chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: *n*-hexane/*i*-PrOH (99.5:0.5); detection at 215 nm; t_1 = 11.97 min, t_2 = 23.15 min; ee = 44%.

4.2.3. *iso*-Propyl (*S*)-3-phenylbutanoate 3c[18,20]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, J = 6.2 Hz, 3H), 1.17 (d, J = 6.2 Hz, 3H), 1.30 (d, J = 6.9 Hz, 3H), 2.50–2.61 (m, 2H), 3.24–3.27 (m, 1H), 4.93–4.96 (m, 1H), 7.17–7.21 (m, 3H), 7.26–7.31 (m, 2H). $[\alpha]_D^{20} = +5.2$ (c 1.28, $CHCl_3$). HPLC analysis: chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: *n*-hexane/*i*-PrOH (99.5:0.5); detection at 215 nm; t_1 = 9.20 min, t_2 = 10.29 min; ee = 50%.

4.2.4. *tert*-Butyl (*S*)-3-phenylbutanoate 3d[18]

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (d, J = 7.0 Hz, 3H), 1.35 (s, 9H), 2.45 (dd, J = 7.3, 14.7 Hz, 1H), 2.52 (dd, J = 8.1, 14.7 Hz, 1H),

3.18–3.26 (m, 1H), 7.17–7.22 (m, 3H), 7.25–7.30 (m, 2H). $[\alpha]_D^{20} = +8.3$ (*c* 1.53, $CHCl_3$). HPLC analysis: chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: *n*-hexane/*i*-PrOH (99.5:0.5); detection at 215 nm; t_1 = 8.94 min, t_2 = 9.77 min; ee = 38%.

4.2.5. Ethyl (*S*)-3-phenylpentanoate 3e[20]

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (t, J = 7.4 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H), 1.60–1.71 (m, 2H), 2.54–2.66 (m, 2H), 3.00 (m, 1H), 4.00–4.05 (m, 2H), 7.17–7.21 (m, 3H), 7.27–7.30 (m, 2H). $[\alpha]_D^{20} = +7.8$ (*c* 1.18, $CHCl_3$). HPLC analysis: chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: *n*-hexane/*i*-PrOH (99.5:0.5); detection at 215 nm; t_1 = 10.54 min, t_2 = 17.63 min; ee = 86%.

4.2.6. Ethyl (+)-4-methyl-3-phenylpentanoate 3f[20]

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 (d, J = 5.7 Hz, 3H), 0.97 (d, J = 5.7 Hz, 3H), 1.06 (t, J = 6.9 Hz, 3H), 1.85–1.88 (m, 1H), 2.55–2.61 (m, 1H), 2.75–2.80 (m, 1H), 2.87–2.88 (m, 1H), 3.96 (q, J = 6.8 Hz, 2H), 7.14–7.20 (m, 3H), 7.25–7.28 (m, 2H). $[\alpha]_D^{20} = +13.4$ (*c* 1.08, $CHCl_3$). HPLC analysis: chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: *n*-hexane/*i*-PrOH (99.5:0.5); detection at 215 nm; t_1 = 10.64 min, t_2 = 20.36 min; ee = 81%.

4.2.7. Ethyl (*S*)-3-(4-methylphenyl)butanoate 3g[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (t, J = 7.1 Hz, 3H), 1.24–1.29 (m, 3H), 2.31 (s, 3H), 2.48–2.62 (m, 2H), 3.22–3.27 (m, 1H), 4.08 (q, J = 7.1 Hz, 2H), 7.11–7.26 (m, 5H). $[\alpha]_D^{20} = +8.8$ (*c* 1.48, $CHCl_3$). HPLC analysis: chiralcel OJ-H column; flow rate: 0.5 mL/min; eluent: *n*-hexane/*i*-PrOH (99.5:0.5); detection at 215 nm; t_1 = 19.76 min, t_2 = 20.79 min; ee = 77%.

4.2.8. Ethyl (+)-3-(4-methoxyphenyl)butanoate 3h[21]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, J = 6.8 Hz, 3H), 1.27 (d, J = 6.8 Hz, 3H), 2.51–2.57 (m, 2H), 3.21–3.26 (m, 1H), 3.78 (s, 3H), 4.07 (q, J = 6.8 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H). $[\alpha]_D^{20} = +11.6$ (*c* 1.43, $CHCl_3$). HPLC analysis: chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: *n*-hexane/*i*-PrOH (99.5:0.5); detection at 215 nm; t_1 = 15.82 min, t_2 = 18.47 min; ee = 76%.

4.2.9. Ethyl (+)-3-(4-chlorophenyl)butanoate 3i[21]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16–1.18 (m, 3H), 1.26–1.29 (m, 3H), 2.53–2.56 (m, 2H), 3.25–3.27 (m, 1H), 4.07 (q, J = 7.0 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H). $[\alpha]_D^{20} = +16.5$ (*c* 1.27, $CHCl_3$). HPLC analysis: chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: *n*-hexane/*i*-PrOH (99.5:0.5); detection at 215 nm; t_1 = 11.34 min, t_2 = 18.09 min; ee >99%.

4.2.10. Ethyl (+)-3-(4-bromophenyl)butanoate 3j[22]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, J = 7.2 Hz, 3H), 1.30 (d, J = 6.8 Hz, 3H), 2.49–2.60 (m, 2H), 3.22–3.27 (m, 1H), 4.07 (q, J = 7.1 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H). $[\alpha]_D^{20} = +9.9$ (*c* 1.81, $CHCl_3$). HPLC analysis: chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: *n*-hexane/*i*-PrOH (99.5:0.5); detection at 215 nm; t_1 = 11.43 min, t_2 = 17.28 min; ee = 97%.

4.2.11. Ethyl (+)-3-(4-nitrophenyl)butanoate 3k[23]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16–1.21 (m, 3H), 1.33–1.35 (m, 3H), 2.61–2.63 (m, 2H), 3.38–3.44 (m, 1H), 4.05–4.09 (m, 2H), 7.41 (d, J = 8.3 Hz, 2H), 8.17 (d, J = 8.6 Hz, 2H). $[\alpha]_D^{20} = +11.9$ (*c* 1.63, $CHCl_3$). HPLC analysis: chiralpak AD-H column; flow rate: 0.5 mL/min; eluent: *n*-hexane/*i*-PrOH (99.5:0.5); detection at 215 nm; t_1 = 32.58 min, t_2 = 35.43 min; ee = 80%.

4.2.12. Ethyl (+)-3-(3-nitrophenyl)butanoate 3l

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16–1.20 (m, 3H), 1.30–1.36 (m, 3H), 2.58–2.68 (m, 2H), 3.39–3.46 (m, 1H), 4.09 (q, J = 6.3 Hz, 2H), 7.45–7.49 (m, 1H), 7.57–7.59 (m, 1H), 8.07–8.11 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 21.5, 36.1, 42.3, 60.4, 121.5, 121.6, 129.3, 133.2, 147.7, 148.4, 171.5. $[\alpha]_D^{20} = +3.6$ (*c* 1.36, $CHCl_3$). HPLC analysis: chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: *n*-hexane/*i*-PrOH (99.5:0.5); detection at 215 nm; t_1 = 23.87 min, t_2 = 25.38 min; ee = 89%.

4.2.13. Ethyl (+)-3-(thiophen-2-yl)butanoate 3m[24]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21–1.28 (m, 3H), 1.38–1.41 (m, 3H), 2.52–2.58 (m, 1H), 2.65–2.71 (m, 1H),3.57–3.62 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 6.83 (d, J = 3.2 Hz, 1H), 6.91 (t, J = 4.3 Hz, 1H), 7.13 (d, J = 5.1 Hz, 1H). $[\alpha]_D^{20} = +10.4$ (*c* 1.51, $CHCl_3$). HPLC analysis: chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: *n*-hexane/*i*-PrOH (99.5:0.5); detection at 215 nm; t_1 = 14.49 min, t_2 = 20.14 min; ee = 83%.

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