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# The *ortho* effect: copper-catalyzed highly enantioselective 1,4-conjugate addition of diethylzinc to chalcones

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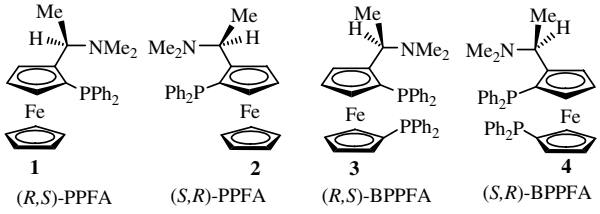
**Abstract**—The copper-catalyzed enantioselective 1,4-conjugate addition of diethylzinc to chalcones was investigated in the presence of a catalytic amount of *N*,*P*-ferrocenyl ligands with central and planar chirality under mild conditions (0 °C→rt). It was found that chalcones with *ortho*-substituents (from *ortho*-substituted benzaldehydes and acetophenone/substituted acetophenones) led to a dramatic improvement in the enantioselectivities. The (*R*)- and (*S*)-antipodes of the addition reaction were obtained with up to 92% ee after this transformation.


## 1. Introduction

The pioneering work of Hayashi and Kumada during the mid-1970s led to the synthesis of the first example of a chiral ferrocenyl phosphine,[1] (*R*)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine (*R*,*S*)-PPFA **1**, by the diastereoselective *ortho*-lithiation of Ugi-amine followed by reaction with an electrophile (e.g., $Ph_2PCl$). Subsequently, a series of chiral ferrocenyl phosphine derivatives were prepared[2] and used as chiral ligands in homogeneous transition metal catalysts.[3] The results showed that (*R*,*S*)-PPFA **1** or (*R*,*S*)-BPPFA **3** were effective ligands for palladium-catalyzed asymmetric cross-coupling reactions,[4] palladium-catalyzed asymmetric allylation reactions[5] and rhodium-catalyzed asymmetric hydrogenations.[6] In order to explore the effectiveness of these chiral ferrocenyl phosphine ligands in other catalytic systems, we reported the application of chiral ligands **1**–**4** in the copper-catalyzed enantioselective addition of diethylzinc to the C=N bond of *N*-diphenylphosphinoylimines with up to 97% ee.[7] The effectiveness of ligands **1**–**4** in the asymmetric ethylation of imines inspired us to further explore their utility in promoting the copper-catalyzed enantioselective 1,4-conjugate addition of diethylzinc to enones.




The conjugate addition reaction, also called the Michael addition, is a major strategy for the construction of carbon–carbon bonds and has been employed in numerous total synthesis.[8] Over the past decade, great efforts have been made to develop efficient chiral catalysts for enantioselective catalytic conjugate additions.[9] In addition, the copper-catalyzed addition of organozinc reagents to enones is a particular focus of interest.[9a] Although early successes in this area were restricted almost entirely to cyclic enones,[10] it has only been until very recently that a few catalysts have been reported, which provide very good enantioselectivity for acyclic enones.[11]

Due to *s-cis* and *s-trans* conformational interconversion, acyclic enones are more demanding substrates. The most widely studied structural type is chalcone and *para*- or *meta*-substituted chalcones. However, to the best of our knowledge, *ortho*-substituted chalcones (from *ortho*-substituted benzaldehydes and acetophenone) acting as substrates for copper-catalyzed asymmetric diethylzinc addition has not been reported yet. Herein, we

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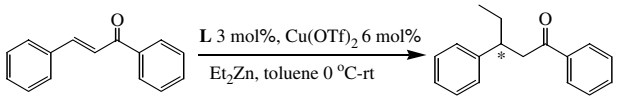
report our results on the copper-catalyzed highly asymmetric addition of diethylzinc to the *ortho*-substituted chalcones in the presence of catalytic amounts of chiral ligands **1**–**2** under mild conditions (0 °C→rt).

## 2. Results and discussion

Chiral ferrocenyl phosphine ligands **1**–**4** were readily synthesized according to the literature.[2] At the outset of our study, we selected chalcone as a typical substrate to examine the effectiveness of chiral ligands **1**–**4** in terms of both yields and enantioselectivities in the presence of 6 mol % of $Cu(OTf)_2$. The results are summarized in Table 1. Contrary to our expectation, in the presence of 3 mol % of chiral ligands **1**–**4**, the addition of diethylzinc to chalcone gave a discouraging result with moderate ees (15–41%) and low yields (30–60%).

**Table 1.** Cu-catalyzed enantioselective 1,4-conjugate addition of $Et_2Zn$ to chalcone[a]




| Entry | Ligand | Yield (%)[b] | Ee (%)[c] | Config.[d] |
|---|---|---|---|---|
| 1 | (*R*,*S*)-PPFA **1** | 60 | 41 | *R* |
| 2 | (*S*,*R*)-PPFA **2** | 60 | 41 | *S* |
| 3 | (*R*,*S*)-BPPFA **3** | 30 | 15 | *R* |
| 4 | (*S*,*R*)-BPPFA **4** | 31 | 15 | *S* |

[a] The reaction was carried out in 4 mL toluene, chalcone/$Et_2Zn$ = 1:1.25.
[b] Isolated yield.
[c] The ee values were determined by HPLC on chiral stationary phase.
[d] Absolute configuration was assigned by comparing retention time on HPLC with the literature values.[11]

It is well known that strong substrate dependence is quite common for transition-metal-catalyzed asymmetric carbon–carbon forming reaction. In fact, in most cases, subtle changes in conformational, steric, and/or electronic properties of the substrates often resulted in a dramatic variation of the enantioselectivity and reactivity. Therefore, we decided to explore the influence of the substituents at different positions on the phenyl ring of chalcone on enantioselectivities and reactivities of this transformation. A variety of substituted chalcones were tested, with the results summarized in Table 2. Firstly, we examined the influence of the substituents at *para*-position on the phenyl ring $Ar^2$ of enones when $Ar^1$ was a phenyl group (Table 2, entries 1–3). As seen from Table 2, neither the electron-donating nor the electron-withdrawing groups at the *para*-position on the benzene ring $Ar^2$ improve the enantioselectivities of this reaction. Next, we investigated the influence of substituents at the *ortho*-, *meta*- and *para*-positions on the phenyl ring $Ar^1$ of enones when $Ar^2$ was a phenyl group (Table 2, entries 4–7). Gratifyingly, an outstanding enantiomeric excess (92% ee) and an excellent yield (95%) were observed when the *ortho*-Cl substituted chalcone **5g**, 3-(2-chlorophenyl)-1-phenyl-2-propene-1-one, was used as a substrate (Table 2, entry 7). This exciting result encouraged us to test the asymmetric addition of diethylzinc to the identical substituted chalcone in the presence of chiral ligand **2**; up to 91% ee and 95% yield were also obtained (Table 2, entry 8). These results suggest that the substituent at the *ortho*-position on the phenyl ring $Ar^1$ play a very important role in the copper-catalyzed highly enantioselective addition of diethylzinc to the substituted chalcones in the presence of bidentate ligands **1** and **2**. To further verify this suggestion, some chalcones **5h**–**i** possessing substituents at the *para*-position on the benzene ring $Ar^2$ were examined under the same condition when $Ar^1$ was a 2-chlorophenyl group. We were delighted to find that the presence of electron-donating or electron-withdrawing substituents at the *para*-position on the benzene ring $Ar^2$ also gave corresponding addition products in excellent yields with high enantioselectivities (Table 2, entries 9–12).

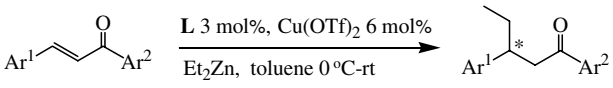
To examine the generality of the *ortho*-effect of the substituents on benzene ring $Ar^1$ for this transformation, a variety of substituted chalcones bearing an electron-donating substituent (–OMe) at the *ortho*-position on the phenyl ring $Ar^1$ were prepared and used as substrates. As can be seen from entries 13–18 in Table 2, under the same conditions, treatment of the various chalcones with the *ortho*-OMe group on the benzene ring $Ar^1$ with diethylzinc afforded the desired conjugate addition product in 79–94% yields and 82–88% ee. Interestingly, by replacing the aromatic group $Ar^2$ with a bulky ferrocenyl group resulted in an increase in enantioselectivities of this reaction (Table 2, entries 19 and 20).

Encouraged by this result obtained for 1-ferrocenyl-3-(2-methoxyphenyl)-2-propene-1-one, we also investigated the *ortho*-Br substituted chalcone **5n**, 3-(2-bromophenyl)-1-ferrocenyl-2-propene-1-one. The performance was similar to that of 1-ferrocenyl-3-(2-methoxyphenyl)-2-propene-1-one. The enantioselectivity achieved was not affected by the electron-withdrawing effect of the substituent Br on the benzene ring $Ar^1$, but the yield of the reaction had a slight decrease (Table 2, entries 21 and 22).

As can also be seen from entries 9–12 and 15–18 in Table 2, for chalcones with a *para*-substituent on the benzene ring $Ar^2$, a major electronic effect was observed. A weak electron-withdrawing group (Cl) at the *para*-position on the benzene ring $Ar^2$ led to a slight decrease in the enantioselectivities of this reaction (Table 2, entries 9, 10, 15, 16 vs 7, 8, 13, 14), whereas a strong electron-withdrawing (–$NO_2$) (Table 2, entries 17, 18 vs 13, 14) or strong electron-donating (–OMe) (Table 2, entries 11, 12 vs 7, 8) resulted in a obvious drop. A similar phenomenon was noted in the copper-catalyzed asymmetric addition of diethylzinc to the substituted chalcones in the presence of catalytic amounts of *N*,*P*-chiral ligands.[11f]

In order to obtain more information on the *ortho*-substituents on benzene ring $Ar^1$, the *ortho*-Me substituted chalcone **5o**, 3-(2-methylphenyl)-1-phenyl-2-propene-1-one, was prepared and tested in the copper-catalyzed

**Table 2.** Cu-catalyzed enantioselective 1,4-conjugate addition of $Et_2Zn$ to substituted chalcones[a]




**5** **6**

| Entry | $Ar^1$ | $Ar^2$ | Substrate | Ligand | Yield (%)[b] | Ee (%)[c] | Config.[d,e] |
|---|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | *p*-$MeOC_6H_4$ | **5a** | **1** | 51 | 27 | *R* |
| 2 | $C_6H_5$ | *p*-$ClC_6H_4$ | **5b** | **1** | 59 | 38 | *R* |
| 3 | $C_6H_5$ | *p*-$MeC_6H_4$ | **5c** | **1** | 40 | 10 | *R* |
| 4 | *p*-$MeOC_6H_4$ | $C_6H_5$ | **5d** | **1** | 51 | 27 | − |
| 5 | *p*-$ClC_6H_4$ | $C_6H_5$ | **5e** | **1** | 59 | 38 | − |
| 6 | *m*-$ClC_6H_4$ | $C_6H_5$ | **5f** | **1** | 60 | 46 | + |
| 7 | *o*-$ClC_6H_4$ | $C_6H_5$ | **5g** | **1** | 95 | 92 | − |
| 8 | *o*-$ClC_6H_4$ | $C_6H_5$ | **5g** | **2** | 95 | 91 | + |
| 9 | *o*-$ClC_6H_4$ | *p*-$ClC_6H_4$ | **5h** | **1** | 96 | 85 | − |
| 10 | *o*-$ClC_6H_4$ | *p*-$ClC_6H_4$ | **5h** | **2** | 95 | 84 | + |
| 11 | *o*-$ClC_6H_4$ | *p*-$MeOC_6H_4$ | **5i** | **1** | 90 | 81 | − |
| 12 | *o*-$ClC_6H_4$ | *p*-$MeOC_6H_4$ | **5i** | **2** | 92 | 81 | + |
| 13 | *o*-$MeOC_6H_4$ | $C_6H_5$ | **5j** | **1** | 94 | 88 | + |
| 14 | *o*-$MeOC_6H_4$ | $C_6H_5$ | **5j** | **2** | 94 | 88 | − |
| 15 | *o*-$MeOC_6H_4$ | *p*-$ClC_6H_4$ | **5k** | **1** | 90 | 86 | + |
| 16 | *o*-$MeOC_6H_4$ | *p*-$ClC_6H_4$ | **5k** | **2** | 90 | 87 | − |
| 17 | *o*-$MeOC_6H_4$ | *p*-$NO_2C_6H_4$ | **5l** | **1** | 79 | 82 | − |
| 18 | *o*-$MeOC_6H_4$ | *p*-$NO_2C_6H_4$ | **5l** | **2** | 80 | 82 | + |
| 19 | *o*-$MeOC_6H_4$ | Fc | **5m** | **1** | 89 | 92 | − |
| 20 | *o*-$MeOC_6H_4$ | Fc | **5m** | **2** | 88 | 92 | + |
| 21 | *o*-$BrC_6H_4$ | Fc | **5n** | **1** | 80 | 91 | − |
| 22 | *o*-$BrC_6H_4$ | Fc | **5n** | **2** | 80 | 91 | + |
| 23 | *o*-$MeC_6H_4$ | Fc | **5o** | **1** | 50 | 20 | − |
| 24 | *o*-$MeC_6H_4$ | Fc | **5o** | **2** | 50 | 20 | + |

[a] The reaction was carried out in 4 mL toluene, chalcone/$Et_2Zn$ = 1:1.25.
[b] Isolated yield.
[c] The ee values were determined by HPLC on chiral stationary phase.
[d] Absolute configuration was assigned by comparing retention time on HPLC with the literature values.[11]
[e] The + or − signs refer to the optical rotation.

asymmetric conjugate addition reaction system under the same conditions. The replacement of Cl or Br or OMe group at the *ortho*-position on the benzene ring $Ar^1$ with an Me group resulted in a dramatic decrease in the enantioselectivity and reactivity of this reaction (Table 2, entries 23 and 24). We cannot explain exactly the above results at the present stage, but we can postulate that the halogen (Cl, Br) or oxygen atoms with the non-bonding electron pairs in the substrates were crucial for achieving the high enantioselectivity in this catalytic asymmetric reaction because the corresponding methyl group has no unshared electron pairs. Based on previous reports on the well-studied chemistry of organocuprates,[12] the catalytically active species for copper-catalyzed conjugate addition reaction is the copper(I) complex, which can be formed at the initial reaction stage through in situ reduction of the copper(II) complex by $Et_2Zn$, followed by 1,4-conjugate addition-type alkylation. We believe that in our catalytic system, besides the π-bond of the carbon–carbon double bond, the halogen (Cl, Br) or oxygen atoms in the substrates also coordinate to Cu(I) to form the catalytically active species—copper(I) complex. Such a coordination might make the structure of the catalytically active species more rigid, which is beneficial to the improvement of the enantioselectivity.

## 3. Conclusion

In conclusion, we have reported the copper-catalyzed highly enantioselective 1,4-conjugate addition of diethylzinc to chalcones in the presence of catalytic amount of chiral *N*,*P*-ligands **1** and **2** under mild conditions (0 °C to rt). It was found that chalcones with *ortho*-substituents (from *ortho*-substituted benzaldehydes and acetophenone/substituted acetophenones) led to a dramatic improvement in the enantioselectivity. To the best of our knowledge, this is the first case for the use of *ortho*-substituted chalcones as substrates in copper-catalyzed asymmetric conjugate diethylzinc addition to achieve good to excellent ee in high to outstanding yields. Further application of chiral *N*,*P*-ligands **1**–**4** for asymmetric synthesis is under investigation in our laboratory.

## 4. Experimental

### 4.1. General

Melting points were determined using YRT-3 melting point apparatus, and were uncorrected. Optical rotations were measured with Perkin–Elmer, model 341 Polarimeter at 20 °C in $CHCl_3$. The ee value was deter-

mined by HPLC using a chiral column with hexane-propan-2-ol (ratio as indicated) as the eluent. The chromatographic system consisted of a JASCO model PU-1580 intelligent HPLC pump and a JASCO model UV-1575 intelligent UV/vis detector (254 nm). The injection loop had a 20 μL capacity. The column used was a Chiralcel OD or a Chiralpak AD (250 × 4.6 mm) from Daicel Chemical Ind., Ltd. (Japan). The column was operated at ambient temperature. NMR Spectra ($^1$H and $^{13}$C) were performed on a Bruker DPX 400 (400 MHz) spectrometer using solutions in $CDCl_3$ (referenced internally to $Me_4Si$); $J$ values are given in Hz. IR spectra were determined on a Therme Nicolet IR 200 spectrophotometer. TLC was performed on dry silica gel plates developed with petroleum (60–90 °C)/ethyl acetate. Mass spectra were obtained using a Waters a-Tof micro™ instrument with an electrospray ionization source (ESIMS). All ESIMS spectra were performed using MeOH as the solvent.

### 4.2. Reagents and solvents

Except for diethylzinc purchased from Aldrich and $Cu(OTf)_2$ from Alfa Aesar, all other reagents were bought in China. Toluene was pre-dried over calcium chloride and then distilled from sodium before use. All other reagents were commercially available and used as received.

### 4.3. General procedure for synthesis of enones 5a–o

To a solution of 2.2 g of NaOH in 20 mL of $H_2O$ and 43 mmol of aromatic ketone in 12 mL ethanol at 0 °C was added gradually 1 equiv of aromatic aldehyde (43 mmol). The mixture was then allowed to warm to room temperature and stirred for 4 h after which a precipitate of the product formed. The product was collected by suction filtration on a Büchner funnel and washed repeatedly with cold water in order to remove all traces of sodium hydroxide. Recrystallization of the product from ethanol afforded enones **5a**–**o**. All spectroscopic data of enones **5a**–**k**, **5m** and **5o** are in good agreement with the literature.[13]

**4.3.1. 3-(2-Methoxyphenyl)-1-(4-nitrophenyl)-2-propene-1-one 5l.** $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.94 (s, 1H), 6.95 (d, $J = 6.4$ Hz, 1H); 7.02 (t, $J = 6.4$ Hz, 1H), 7.43 (t, $J = 6.4$ Hz, 1H), 7.58 (d, $J = 15.8$ Hz, 1H), 7.65 (d, $J = 6.4$ Hz, 1H), 8.14 (d, $J = 8.7$ Hz, 2H), 8.14 (d, $J = 15.8$ Hz, 1H), 8.35 (d, $J = 8.7$ Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 55.59, 111.33, 120.86, 122.20, 123.33, 123.76, 129.41, 129.62, 132.5, 142.48, 143.46, 149.92, 159.05, 198.75. HRMS (ESI): calculation for $C_{16}H_{13}NO_4$ $(M+H)^+$: 284.0923, found: 284.0926; calculation for $(M+Na)^+$ 306.0742, found 306.0746.

**4.3.2. 3-(2-Bromophenyl)-1-ferrocenyl-2-propene-1-one 5n.** $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.23 (s, 5H), 4.61 (s, 2H), 4.92 (s, 2H), 7.04–7.08 (m, 1H), 7.26 (s, 1H), 7.37 (s, 1H), 7.64–7.71 (m, 2H), 8.12 (d, $J = 14.8$ Hz, 1H). HRMS (ESI): calculation for $C_{19}H_{15}BrFeO$-$(M^+)$: 393.9656, found: 393.9657; calculation for $(M+Na)^+$: 416.9553, found: 416.9555.

### 4.4. General procedure for the asymmetric addition of diethylzinc to enones

To a solution of copper triflate (4.3 mg, 0.012 mmol) in dry toluene (4 mL) at room temperature under nitrogen was added 0.5 equiv of ligand (0.006 mmol). The solution was stirred at room temperature for 1 h and then chalcone (0.2 mmol) was added. After stirring for 10 min, the solution was cooled to 0 °C. A solution of $Et_2Zn$ (0.25 mL, 1 M in hexane) was added dropwise at a rate such that the temperature did not rise above 0 °C. The resulting mixture was stirred for 10 h in 0–5 °C and then allowed to warm to room temperature, and kept stirring for another 38 h at the same temperature. The reaction mixture was quenched by the addition of saturated aqueous $NH_4Cl$ (5 mL). The mixture was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. Purification of the residue by the preparative silica gel TLC plate (petroleum/EtOAc = 19:1–5:1) afforded the desired product. Yields are shown in Tables 1 and 2. The ees of the product were determined by HPLC analyses using a chiral column.

**4.4.1. 3-(3-Chlorophenyl)-1-phenyl-1-pentanone 6f (entry 6 in Table 2).** This compound (32.7 mg) was obtained in 60% yield (petroleum/EtOAc = 8:1). $[\alpha]_D^{20} = +39.3$ ($c$ 0.23 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.81 (t, $J = 7.2$ Hz, 3H), 1.60–1.66 (m, 1H), 1.76–1.80 (m, 1H), 3.25–3.22 (m, 3H), 7.10–7.26 (m, 4H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.89–7.91 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 12.04, 29.15, 42.61, 45.29, 126.10, 126.47, 127.63, 128.02, 128.58, 129.65, 133.06, 134.18, 137.06, 146.87, 198.67. HRMS (ESI): calculation for $C_{17}H_{17}ClO$ $(M+Na)^+$: 295.0866, found: 295.0860. Enantiomeric excess: 46%, Chiralpak AD, Hexane/$i$-PrOH = 95:5, 0.2 mL/min, $t_{major} = 20.8$ min, $t_{minor} = 30.8$ min.

**4.4.2. 3-(2-Chlorophenyl)-1-phenyl-1-pentanone 6g (entries 7 and 8 in Table 2).** This compound (51.8 mg) was obtained in 95% yield (petroleum/EtOAc = 7:1). $[\alpha]_D^{20} = -33.8$ ($c$ 0.13 $CHCl_3$) for chiral ligand **1**, $[\alpha]_D^{20} = +32.3$ ($c$ 0.14 $CHCl_3$) for chiral ligand **2**. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.80 (t, $J = 7.6$ Hz, 3H), 1.68–1.72 (m, 1H), 1.75–1.80 (m, 1H), 3.34 (d, $J = 6.8$ Hz, 2H), 3.82–3.86 (m, 1H), 7.11–7.15 (m, 1H), 7.21–7.25 (m, 1H), 7.31–7.37 (m, 2H), 7.43–7.47 (m, 2H), 7.54–7.58 (m, 1H), 7.92–7.94 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 12.03, 32.12, 39.85, 45.20, 128.24, 128.48, 129.13, 129.19, 129.70, 130.54, 134.26, 135.43, 138.38, 143.14, 201.07. HRMS (ESI): calculation for $C_{17}H_{17}ClO$ $(M+Na)^+$: 295.0866, found: 295.0865. Enantiomeric excess: 92%, Chiralpak AD, Hexane/$i$-PrOH = 95:5, 0.5 mL/min, $t_{major} = 14.2$ min, $t_{minor} = 18.5$ min for chiral ligand **1**. Enantiomeric excess: 91%, $t_{minor} = 14.2$ min, $t_{major} = 18.5$ min for chiral ligand **2**.

**4.4.3. 1-(4-Chlorophenyl)-3-(2-chlorophenyl)-1-pentanone 6h (entries 9 and 10 in Table 2).** This compound (59.1 mg and 58.5 mg) was obtained in 96% and 95% yield, respectively, (petroleum/EtOAc = 8:1).

$[\alpha]_D^{20} = -28.6$ ($c$ 0.56 $CHCl_3$) for chiral ligand **1**, $[\alpha]_D^{20} = +27.3$ ($c$ 0.61 $CHCl_3$) for chiral ligand **2**. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.82 (t, $J = 7.6$ Hz, 3H), 1.70–1.74 (m, 1H), 1.77–1.81 (m, 1H), 3.17–3.23 (dd, $J_1 = 16.4$ Hz, $J_2 = 7.6$ Hz, 1H), 3.26–3.31 (dd, $J_1 = 16.4$ Hz, $J_2 = 7.6$ Hz, 1H), 3.82 (m, 1H), 7.10–7.13 (m, 1H), 7.14–7.26 (m, 2H), 7.34–7.36 (m, 1H), 7.39–7.42 (m, 2H), 7.85–7.88 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 11.71, 29.24, 38.72, 44.41, 126.94, 127.37, 127.84, 128.83, 129.51, 129.77, 134.31, 135.25, 139.39, 141.52, 197.51. HRMS (ESI): calculation for $C_{17}H_{16}Cl_2O$ $(M+Na)^+$: 329.0476, found: 329.0479. Enantiomeric excess: 85%, Chiralpak AD, Hexane/*i*-PrOH = 100:3, 0.5 mL/min, $t_{major} = 14.2$ min, $t_{minor} = 18.5$ min for chiral ligand **1**. Enantiomeric excess: 84%, $t_{minor} = 14.2$ min, $t_{major} = 18.5$ min for chiral ligand **2**.

**4.4.4. 3-(2-Chlorophenyl)-1-(4-methoxyphenyl)-1-pentanone 6i (entries 11 and 12 in Table 2).** This compound (54.5 mg and 55.8 mg) was obtained in 90% and 92% yield, respectively, (petroleum/EtOAc = 8:1). $[\alpha]_D^{20} = -21.4$ ($c$ 0.51 $CHCl_3$) for chiral ligand **1**, $[\alpha]_D^{20} = +21.5$ ($c$ 0.53 $CHCl_3$) for chiral ligand **2**. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.82 (t, $J = 7.6$ Hz, 3H), 1.68–1.73 (m, 1H), 1.78–1.83 (m, 1H), 3.14–3.20 (dd, $J_1 = 16.4$ Hz, $J_2 = 8.0$ Hz, 1H), 3.24–3.30 (dd, $J_1 = 16.4$ Hz, $J_2 = 6.4$ Hz, 1H), 3.82–3.85 (m, 1H), 3.86 (s, 3H), 6.90–6.93 (m, 2H), 7.10–7.14 (m, 1H), 7.20–7.28 (m, 2H), 7.34–7.37 (m, 1H), 7.92 (d, $J = 8.8$ Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 11.74, 29.27, 38.90, 44.15, 53.76, 113.66, 126.90, 127.24, 127.93, 129.74, 130.12, 130.41, 134.36, 141.96, 163.38, 197.31. HRMS (ESI): calculation for $C_{18}H_{19}ClO_2$ $(M+Na)^+$: 325.0971, found: 325.0973. Enantiomeric excess: 81%, Chiralpak AD, Hexane/*i*-PrOH = 100:3, 0.5 mL/min, $t_{major} = 25.0$ min, $t_{minor} = 37.7$ min for chiral ligand **1**. Enantiomeric excess: 81%, $t_{minor} = 25.0$ min, $t_{major} = 37.7$ min for chiral ligand **2**.

**4.4.5. 3-(2-Methoxyphenyl)-1-phenyl-1-pentanone 6j (entries 13 and 14 in Table 2).** This compound (50.4 mg) was obtained in 94% yield (petroleum/EtOAc = 19:1). $[\alpha]_D^{20} = +28.5$ ($c$ 0.72 $CHCl_3$) for chiral ligand **1**, $[\alpha]_D^{20} = -28.7$ ($c$ 0.72 $CHCl_3$) for chiral ligand **2**. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.80 (t, $J = 7.2$ Hz, 3H), 1.70–1.79 (m, 2H), 3.16–3.22 (dd, $J_1 = 16.0$ Hz, $J_2 = 8.0$ Hz, 1H), 3.27–3.32 (dd, $J_1 = 16.0$ Hz, $J_2 = 6.0$ Hz, 1H), 3.62–3.66 (m, 1H), 3.77 (s, 3H), 6.83 (d, $J = 8.4$, 1H), 6.88–6.92 (m, 1H), 7.13–7.25 (m, 2H), 7.39–7.43 (m, 2H), 7.49–7.53 (m, 1H), 7.91–7.93 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 12.11, 27.30, 37.16, 44.59, 55.31, 110.78, 120.57, 127.13, 128.14, 128.17, 128.42, 132.57, 132.68, 137.47, 157.53, 199.80. HRMS (ESI): calculation for $C_{18}H_{20}O_2$ $(M+Na)^+$: 291.1356, found: 291.1359. Enantiomeric excess: 88%, Chiralpak AD, Hexane/*i*-PrOH = 95:5, 0.5 mL/min, $t_{major} = 10.7$ min, $t_{minor} = 13.2$ min for chiral ligand **1**. Enantiomeric excess: 88%, $t_{minor} = 10.7$ min, $t_{major} = 13.2$ min for chiral ligand **2**.

**4.4.6. 1-(4-Chlorophenyl)-3-(2-methoxyphenyl)-1-pentanone 6k (entries 15 and 16 in Table 2).** This compound (54.5 mg) was obtained in 90% yield (petroleum/EtOAc = 7:1). $[\alpha]_D^{20} = +18.0$ ($c$ 0.93 $CHCl_3$) for chiral ligand **1**, $[\alpha]_D^{20} = -16.7$ ($c$ 0.98 $CHCl_3$) for chiral ligand **2**. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.80 (t, $J = 7.2$ Hz, 3H); 1.70–1.77 (m, 2H), 3.12–3.18 (dd, $J_1 = 16.0$ Hz, $J_2 = 8.0$ Hz, 1H), 3.25–3.30 (dd, $J_1 = 16.0$ Hz, $J_2 = 6.0$ Hz, 1H), 3.57–3.63 (m, 1H), 3.78 (s, 3H), 6.83 (d, $J = 8.4$ Hz, 1H), 6.89–6.93 (m, 1H), 7.16–7.19 (m, 2H), 7.38–7.41 (m, 2H), 7.85–7.86 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 12.16, 27.14, 37.07, 44.62, 55.26, 110.60, 120.55, 127.24, 127.99, 128.73, 129.63, 132.10, 135.52, 139.12, 157.35, 198.70. HRMS (ESI): calculation for $C_{18}H_{19}ClO_2$ $(M+Na)^+$: 325.0791, found: 325.0794. Enantiomeric excess: 86%, Chiralcel OD, Hexane/*i*-PrOH = 95:5, 0.5 mL/min, $t_{major} = 13.8$ min, $t_{minor} = 22.2$ min for chiral ligand **1**. Enantiomeric excess: 87%, $t_{minor} = 13.8$ min, $t_{major} = 22.2$ min for chiral ligand **2**.

**4.4.7. 3-(2-Methoxyphenyl)-1-(4-nitrophenyl)-1-pentanone 6l (entries 17 and 18 in Table 2).** This compound (49.5 mg and 50.1 mg) was obtained in 79% and 80% yield, respectively, (petroleum/EtOAc = 6:1). $[\alpha]_D^{20} = -11.8$ ($c$ 0.71 $CHCl_3$) for chiral ligand **1**, $[\alpha]_D^{20} = +11.6$ ($c$ 0.75 $CHCl_3$) for chiral ligand **2**. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.82 (t, $J = 7.2$ Hz, 3H), 1.73–1.80 (m, 2H), 3.19–3.24 (dd, $J_1 = 16.0$ Hz, $J_2 = 7.2$ Hz, 1H), 3.33–3.38 (dd, $J_1 = 16.0$ Hz, $J_2 = 6.4$ Hz, 1H), 3.55–3.62 (m, 1H), 3.76 (s, 3H), 6.82 (d, $J = 8.0$ Hz, 1H), 6.88–6.92 (m, 1H), 7.14–7.19 (m, 2H), 8.02–8.04 (m, 2H), 8.24–8.26 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 12.10, 27.21, 37.39, 45.09, 55.21, 110.68, 120.64, 123.62, 127.43, 128.06, 129.08, 131.61, 141.75, 150.05, 157.30, 198.38. HRMS (MALDI): calculation for $C_{18}H_{19}NO_4$ $(M+Na)^+$: 336.1212, found: 336.1210. Enantiomeric excess: 82%, Chiralcel OD, Hexane/*i*-PrOH = 95:5, 0.5 mL/min, $t_{major} = 33.0$ min, $t_{minor} = 48.9$ min for chiral ligand **1**. Enantiomeric excess: 82%, $t_{minor} = 33.0$ min, $t_{major} = 48.9$ min for chiral ligand **2**.

**4.4.8. 1-Ferrocenyl-3-(2-methoxyphenyl)-1-pentanone 6m (entries 19 and 20 in Table 2).** This compound (66.9 mg and 66.2 mg) was obtained in 89% and 88% yield, respectively, (petroleum/EtOAc = 4.5:1). $[\alpha]_D^{20} = -54.4$ ($c$ 0.45 $CHCl_3$) for chiral ligand **1**, $[\alpha]_D^{20} = +54.1$ ($c$ 0.48 $CHCl_3$) for chiral ligand **2**. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.80 (t, $J = 7.2$ Hz, 3H), 1.73–1.80 (m, 2H), 2.84–2.90 (dd, $J_1 = 16.0$ Hz, $J_2 = 7.6$ Hz, 1H), 3.10–3.15 (dd, $J_1 = 16.0$ Hz, $J_2 = 6.4$ Hz, 1H), 3.58–3.65 (m, 1H), 3.85 (s, 3H), 4.09 (s, 5H), 4.46 (s, 2H), 4.76 (d, $J = 4.4$ Hz, 2H, Fc-H), 6.87 (d, $J = 8.0$ Hz, 1H), 6.89–6.96 (m, 1H), 7.17–7.26 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 12.12, 26.92, 36.89, 45.53, 55.28, 69.26, 69.31, 69.66, 71.98, 72.04, 79.38, 110.67, 120.46, 127.06, 128.36, 132.57, 157.46, 203.63. HRMS (ESI): calculation for $C_{22}H_{24}FeO_2$ $(M+Na)^+$: 399.1023, found: 399.1021. Enantiomeric excess: 92%, Chiralpak AD, Hexane/*i*-PrOH = 95/5, 0.5 mL/min, $t_{major} = 9.2$ min, $t_{minor} = 12.9$ min for chiral ligand **1**. Enantiomeric excess: 92%, $t_{minor} = 9.2$ min, $t_{major} = 12.9$ min for chiral ligand **2**.

**4.4.9. 3-(2-Bromophenyl)-1-ferrocenyl-1-pentanone 6n (entries 21 and 22 in Table 2).** This compound (68.0 mg) was obtained in 80% yield (petroleum/

EtOAc = 8:1). $[\alpha]_D^{20} = -84.1$ ($c$ 0.24 $CHCl_3$) for chiral ligand **1**, $[\alpha]_D^{20} = +83.8$ ($c$ 0.31 $CHCl_3$) for chiral ligand **2**. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.84 (t, $J = 7.2$ Hz, 3H), 1.69–1.73 (m, 1H), 1.82–1.87 (m, 1H), 2.87–2.93 (dd, $J_1 = 16.4$ Hz, $J_2 = 7.6$ Hz, 1H), 3.07–3.13 (dd, $J_1 = 16.4$ Hz, $J_2 = 6.2$ Hz, 1H), 3.77–3.84 (m, 1H), 4.11 (s, 5H), 4.47 (s, 2H), 4.75 (s, 1H), 4.80 (s, 1H), 7.04–7.08 (m, 1H), 7.26–7.39 (m, 2H), 7.58 (d, $J = 8.0$ Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 11.78, 27.97, 41.19, 45.78, 69.37, 69.42, 69.81, 72.18, 72.27, 79.18, 125.42, 127.54, 127.68, 128.12, 133.23, 143.73, 202.53. HRMS (ESI): calculation for $C_{21}H_{21}BrFeO$ $(M)^+$: 424.0125, found: 424.0121; calculation for $C_{21}H_{21}BrFeO$ $(M+Na)^+$: 447.0023, found: 447.0030; calculation for $C_{21}H_{21}BrFeO$ $(2M+Na)^+$: 871.0148, found: 871.0129. Enantiomeric excess: 91%, Chiralpak AD, Hexane/*i*-PrOH = 95:5, 0.5 mL/min, $t_{major} = 16.8$ min, $t_{minor} = 24.3$ min for chiral ligand **1**. Enantiomeric excess: 91%, $t_{minor} = 16.8$ min, $t_{major} = 24.3$ min for chiral ligand **2**.

**4.4.10. 1-Ferrocenyl-3-(2-methylphenyl)-1-pentanone 6o (entries 23 and 24 in Table 2).** This compound (36.0 mg) was obtained in 50% yield (petroleum/EtOAc = 8:1). $[\alpha]_D^{20} = -2.7$ ($c$ 0.41 $CHCl_3$) for chiral ligand **1**, $[\alpha]_D^{20} = +2.6$ ($c$ 0.32 $CHCl_3$) for chiral ligand **2**. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.81 (t, $J = 7.2$ Hz, 3H), 1.59–1.68 (m, 1H), 1.75–1.82 (m, 1H), 2.45 (s, 3H), 2.87–2.92 (dd, $J_1 = 16.4$ Hz, $J_2 = 7.6$ Hz, 1H), 3.04–3.10 (dd, $J_1 = 16.4$ Hz, $J_2 = 6.2$ Hz, 1H), 3.45–3.61 (m, 1H), 4.03 (s, 5H), 4.45 (s, 2H), 4.72–4.73 (m, 2H), 7.06–7.26 (m, 4H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 11.92, 20.07, 29.39, 36.84, 46.82, 69.23, 69.30, 69.68, 72.02, 72.13, 79.34, 125.59, 125.81, 126.07, 130.41, 136.73, 143.40, 203.11. HRMS (ESI): calculation for $C_{22}H_{24}FeO$-$(M+H)^+$: 361.1255, found: 361.1259; calculation for $C_{22}H_{24}FeO$ $(M+Na)^+$: 383.1075 found: 383.1061. Enantiomeric excess: 20%, Chiralpak AD, Hexane/*i*-PrOH = 95:5, 0.5 mL/min, $t_{major} = 12.5$ min, $t_{minor} = 15.8$ min for chiral ligand **1**. Enantiomeric excess: 20%, $t_{minor} = 12.5$ min, $t_{major} = 15.8$ min for chiral ligand **2**.

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