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Highly enantioselective conjugate addition of diethylzinc to substituted chalcones catalyzed by Cu(II) complexes of a tridentate P,N,O ligand

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Abstract—A new series of tridentate P,N,O ligands having hard and soft donor atoms derived from chiral amino alcohols were developed and employed in the Cu(II)-catalyzed conjugate addition of diethylzinc to substituted chalcones. The asymmetric additions to a variety of substituted chalcones afforded products in excellent yields and good to excellent enantioselectivities up to 97% ee.

1. Introduction

The asymmetric conjugate addition of organometallic reagents to unsaturated carbonyl compounds is one of the most useful techniques for C–C bond formation in organic synthesis. Stoichiometric reactions accompanied with chiral auxiliaries were successfully developed in earlier studies. Recently, catalytic conjugate additions have attracted much attention.[1] The first breakthrough in using substoichiometric nickel complexes of ephedrine was demonstrated by Soai et al.[2] In recent studies of metal-catalyzed 1,4-additions using Grignard or dialkylzinc reagents, chiral copper and nickel complexes are the most widely investigated catalytic systems for inducing high enantioselectivities. For chiral ligands, phosphorus amidites,[3] TADDOL-derived phosphates,[4] and biphenol-based phosphoramidites[5] had been established to have remarkable stereocontrol in the $ZnEt_2$ addition to cyclic enones. In addition, diphosphine,[6] diphosphite,[7] P,N ligands,[8] spiro-phosphoramidites,[9] and aminophosphine[10] are also efficient for this transformation. The catalytic systems for $ZnEt_2$ additions to acyclic enones are less common compared with additions to cyclic enones.[11] Recently, Hoveyda et al.[12] developed catalytic systems of peptidic phosphines to induce high enantioselectivities for various acyclic enones. Furthermore, some tridentate phosphorus-containing amines or imines were demonstrated recently for conjugate additions.[13] However, tridentate P,N,O ligands containing both a hard oxygen and a soft phosphorus donor are rare and only a few examples of these ligands have been reported for palladium-catalyzed allylation reactions[14] or ruthenium-catalyzed hydrogenation reactions.[15]

In continuation of our efforts to develop chiral ligands derived from amino alcohols for asymmetric catalysis,[16] we herein report the preparations of a series of chiral P,N,O Schiff base ligands **2a**–**d** and their application in copper-catalyzed asymmetric additions of $ZnEt_2$ to substituted chalcones. The addition reactions afforded the desired products in good to excellent enantioselectivities up to 97% ee.

2. Results and discussion

Amino alcohols **1a**–**d** having one or two stereogenic centers were prepared from L-amino acids according to standard procedures. Treatment of amino alcohols with 2-diphenylphosphinobenzaldehyde in refluxing ethanol for 3–5 h afforded chiral tridentate P,N,O ligands **2a**–**d** in quantitative yields (Scheme1). These ligands were characterized by ^{1}H, ^{13}C, ^{31}P NMR, and elemental analysis, and ^{1}H NMR spectra reveal a doublet at δ 8–9 ppm for the imine proton due to coupling to the phosphorus atom. In addition, ^{13}C NMR spectra show a doublet at δ 160–162 ppm for the imine carbon, and ^{31}P resonances appear at δ −8 to −12 ppm.

The reaction conditions of the asymmetric 1,4-additions to chalcones were optimized with the use of 5 mol % $Cu(acac)_2$ and 5 mol % ligands **2a**–**d** as the catalyst; the results

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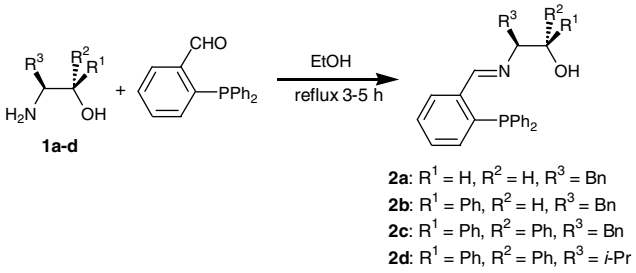
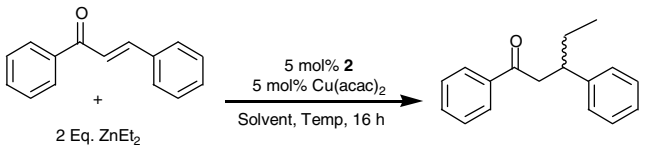


Scheme 1. Preparation of ligands.

are summarized in Table 1. In ligand **2a**, having R^1 and R^2 as both H atoms, the asymmetric 1,4-addition of $ZnEt_2$ to the chalcone in toluene gave the product in 100% yield but with a low enantioselectivity of 14% ee (entry 1). In **2b**, with R^1 as a Ph substituent and R^2 as an H atom, the addition reaction afforded the product with an enantioselectivity of 21% ee (entry 2). In **2c**, where both R^1 and R^2 were Ph groups, the product was obtained in 48% ee (entry 3). In **2d**, tuning the R^3 of the ligand to the *i*-Pr substituent instead of the Bn group afforded the product in a low enantioselectivity of 5% ee (entry 4). This study clearly demonstrates that the steric bulkiness of R^1 and R^2 plays a key role in stereoselectivities, and the best catalytic system is derived from ligand **2c** where both R^1 and R^2 are Ph groups. Stereoselectivities are also sensitive to the R^3 group. In ligand **2c**, where R^3 is a Bn substituent, a higher enantioselectivity was induced compared with the *i*-Pr substituent. We also screened different copper salts such as $Cu(OTf)_2$, $Cu(OTf)_2$·Tol, $CuCl_2$, and $Cu(OAc)_2$. All copper salts gave the product in 100% conversion except for $CuCl_2$, which gave 90% conversion. However, lower enantioselectivities of 26%, 23%, 21%, and 36% were observed. Studies of solvent effects in CH_2Cl_2, THF, hexane, or Et_2O were subsequently examined (entries 5–8) and it was found that the reaction carried out in Et_2O afforded the product in 70% ee (entry 8) at best. For reactions conducted in Et_2O at lower temperatures of −20 and −40 °C, enantioselectivities increase to 72% ee and 79% ee (entries 9 and 10). When the reaction was carried out in a mixed solvent of hexane and Et_2O at −40 °C, the enantioselectivity further improved to 83% ee (entry 11).

We then explored the scope of asymmetric conjugate 1,4-additions of diethylzinc to substituted chalcones using the best performing catalytic system and the results are listed in Table 2. Substituents of the R′ group at the *ortho*-, *meta*-, or *para*-position on the phenyl group attached to the carbonyl carbon were investigated first. For example, for R′ of the methoxy substituent, 1,4-additions afforded products in similar enantioselectivities of 81%, 85%, and 80% ee (entries 1–3). In comparison with 83% ee for the simple chalcone, effects of the substituted positions of the R′ group are minimal. In contrast, substantial effects of substituted positions of the R″ substituent are observed. For R″ of 2-methoxy, the addition product was obtained in an excellent 96% ee (entry 4) compared with products in 78% and 84% ee (entries 5 and 6) for R″ of 3-methoxy or 4-methoxy, respectively. A similar effect of the *ortho*-substituted group, which enhances the stereoselectivities of the products, was also observed by Wang et al.[8e] To further verify the effect, substituted chalcones having the *ortho*-substituted R″ group were then investigated. For

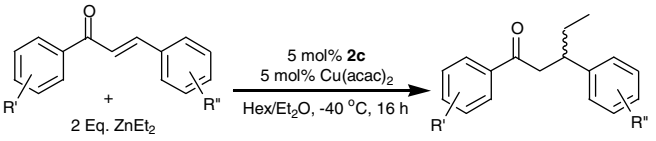
Table 1. Asymmetric $ZnEt_2$ addition to chalcone catalyzed by in situ formed copper complexes of P,N,O ligands[a]



Entry	Ligand	Solvent	Temp. (°C)	Yield[b] (%)	ee[c] (%)
1	**2a**	Toluene	0	100	14 (*S*)
2	**2b**	Toluene	0	95	21 (*S*)
3	**2c**	Toluene	0	100	48 (*S*)
4	**2d**	Toluene	0	91	5 (*S*)
5	**2c**	CH_2Cl_2	0	100	50 (*S*)
6	**2c**	THF	0	90	36 (*S*)
7	**2c**	Hex	0	100	68 (*S*)
8	**2c**	Et_2O	0	100	70 (*S*)
9	**2c**	Et_2O	−20	100	72 (*S*)
10	**2c**	Et_2O	−40	100	79 (*S*)
11	**2c**	Hex/Et_2O[d]	−40	100	83 (*S*)

[a] Chalcone/diethylzinc/$Cu(acac)_2$/ligand = 0.25:0.50:0.0125:0.0125 mmol; solvent, 4 mL.
[b] Yields were calculated from the ^1H NMR multiplet at 8.07 ppm of chalcone and the multiplet at ~7.91 ppm of the product.
[c] Ee values were determined by HPLC analysis with a Chiralcel OJ column from Daicel.
[d] Hex/Et_2O = 2/2 mL.

Table 2. Asymmetric 1,4-addition of $ZnEt_2$ to substituted chalcones catalyzed by the catalytic system of 5 mol % **2c**/$Cu(acac)_2$[a]



Entry	R′	R″	Yield[b] (%)	ee[c] (%)
1	2-OMe	H	94	81
2	3-OMe	H	94	85
3	4-OMe	H	93	80
4	H	2-OMe	98	96
5	H	3-OMe	92	78
6	H	4-OMe	89	84
7	3-OMe	2-OMe	98	97
8	4-OMe	2-OMe	96	93
9	H	2-Br	97	96
10	H	2-Cl	98	96
11	3-OMe	2-Br	96	95
12	4-OMe	2-Br	95	94
13	3-OMe	2-Cl	98	97
14	4-OMe	2-Cl	95	94

[a] Chalcone/diethylzinc/$Cu(acac)_2$/ligand = 0.25:0.50:0.0125:0.0125 mmol; Hex/Et_2O = 2/2 mL.
[b] Isolated yields.
[c] ee values were determined by HPLC analysis with a Chiralcel-OD or OJ columns from Daicel.

substituted chalcones having R″ of 2-methoxy but R′ of either 3-methoxy or 4-methoxy, the addition products were obtained in excellent 97% and 93% ee (entries 7 and 8). For substituted chalcones with R′ of H but with R″ of 2-Br or 2-Cl, both products were obtained in excellent 96% ee (entries 9 and 10). For substituted chalcones having R″ of 2-Br but R′ of either 3-methoxy or 4-methoxy, the addition products were obtained in excellent 95% and 94% ee (entries 11 and 12). Similarly, the additions to substituted chalcones with R″ of 2-Cl afforded products in 97% and 94% ee (entries 13 and 14).

3. Conclusion

In conclusion, a new series of P,N,O Schiff base ligands containing both hard and soft donors have been prepared and the best performing catalytic system of 5 mol % **2c**/$Cu(acac)_2$ was successfully applied to asymmetric 1,4-conjugate additions of diethylzinc to substituted chalcones to afford products in high yields with enantioselectivities up to 97% ee. This study has shown that the *ortho*-substituted R″ bearing lone-paired electrons such as Cl, Br, or methoxy enhances stereoselectivities of the 1,4-addition products. To the best of our knowledge, the above-mentioned catalytic system gives the highest enantioselectivities with excellent yields for substituted chalcone substrates derived from *ortho*-substituted benzaldehyde and *meta*- or *para*-substituted acetophenones.

4. Experimental

4.1. General

^1H NMR and ^{13}C spectra were obtained with a Varian Mercury-400 (^1H, 400 MHz; ^{13}C, 100 MHz) spectrometer, and chemical shifts were measured relative to tetramethylsilane as the internal reference. ^{31}P NMR spectra were recorded with the Varian Mercury-400 (162 MHz) spectrometer, and chemical shifts were relative to H_3PO_4, 85% (^{31}P, 0.0 ppm) as an external standard. Elemental analysis were performed using a Heraeus CHN-OS-RAPID instrument and Mass spectroscopy were performed by using MAT 95 XL ThermoQuest Finnigan and JMS-SX/SX 102A Tendam Mass Spectrometer.

4.2. Reagents and solvents

Amino alcohols with one or two stereogenic centers were synthesized based on the modified procedures reported by Reetz et al.[17] Diphenylphosphinobenzaldehyde was synthesized based on procedures reported by Hoots et al.[18] Diethylzinc was purchased from Aldrich. Absolute ethanol was dried over CaH_2 and freshly distilled prior to use. Other solvents were dried by refluxing for at least 24 h over P_2O_5 (dichloromethane) or sodium-benzophenone and were freshly distilled prior to use. All syntheses and manipulations were carried out under a dry nitrogen atmosphere.

4.3. General procedures for the synthesis of ligands 2a–2d

A solution of 2-diphenylphosphinobenzaldehyde (1.00 mmol, 0.289 g) in 5 mL dry EtOH was added to a solution of amino alcohol (1.05 mmol) and Na_2SO_4 (2.50 mmol, 0.355 g) in 5 mL dry EtOH. The mixture was heated at reflux for 3–5 h under nitrogen. The mixture was filtered and reduced under reduced pressures to produce a yellow liquid. Diethyl ether (3 mL) was then added and the solvent was removed to give the product in quantitative yield.

4.3.1. (*S*)-2-(2-(Diphenylphosphino)benzylideneamino)-3-phenylpropan-1-ol 2a. A yellow semisolid compound was obtained in quantitative yield. $[\alpha]_D^{25} = -117.0$ (*c* 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, $J =$ 3.6 Hz, 1H, C*H*=N), 7.60–6.87 (m, 19H, Ar*H*), 3.58–3.55 (m, 2H, CH_2OH), 3.43–3.40 (m, 1H, C*H*N), 2.71 (dd, $J = 5.2$, 13.6 Hz, 1H, PhC$H_A$$H_B$), 2.48 (dd, $J = 8.4$, 13.6 Hz, 1H, PhC$H_A$$H_B$), 1.87 (br, 1H, OH) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.47 (d, $J = 9.2$ Hz, *C*=N), 139.21, 139.05, 138.51, 137.88, 137.77, 137.70, 137.64, 137.31, 137.11, 134.12, 134.00, 133.92, 133.69, 133.50, 129.77, 129.43, 129.25, 128.61, 128.48, 128.41, 128.33, 128.04, 125.97, 73.76, 65.77, 38.71 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ −8.74 (s) ppm. Anal. Calcd for $C_{28}H_{26}NOP$: C, 79.41; H, 6.19; N, 3.31. Found: C, 79.03; H, 6.24; N, 2.87.

4.3.2. (1*R*,2*S*)-2-[2-(Diphenylphosphino)-benzylideneamino]-1,3-diphenylpropan-1-ol 2b. A yellow solid was obtained in quantitative yield. $[\alpha]_D^{25} = -87.5$ (*c* 1, CH_2Cl_2) ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, $J = 3.6$ Hz, 1H, CH=N), 7.58–6.89 (m, 22H, Ar*H*), 6.55–6.53 (m, 2H, Ar*H*), 4.72 (d, $J = 3.2$ Hz, 1H, C*H*OH), 3.58 (br, 1H, OH), 3.51–3.47 (m, 1H, C*H*N), 2.64–2.54 (m, 2H, PhCH_2) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.20 (d, $J = 9.1$ Hz, C=N), 140.54, 139.33, 139.10, 138.94, 137.79, 137.73, 137.66, 137.39, 137.18, 134.33, 134.19, 133.99, 133.83, 133.63, 130.32, 130.27, 129.89, 129.50, 129.21, 128.69, 128.65, 128.60, 128.53, 128.47, 128.34, 128.16, 128.03, 127.80, 127.17, 126.33, 125.64, 78.70, 76.53, 34.69 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ −9.37 (s) ppm. Anal. Calcd for $C_{34}H_{30}NOP$: C, 81.74; H, 6.05; N, 2.80. Found: C, 80.72; H, 6.08; N, 2.63.

4.3.3. (*S*)-2-(2-(Diphenylphosphino)benzylideneamino)-1,1,3-triphenylpropan-1-ol 2c. A yellow solid was obtained in quantitative yield. $[\alpha]_D^{25} = -83.5$ (*c* 1, CH_2Cl_2) ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, $J = 3.2$ Hz, 1H, C*H*=N), 7.67–6.65 (m, 29H, Ar*H*), 4.34 (s, 1H, C*H*N), 4.31 (s, 1H, OH), 2.79–2.65 (m, 2H, PhCH_2), ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.10 (d, $J = 9.2$ Hz, *C*=N), 146.94, 144.49, 139.73, 138.98, 138.81, 138.16, 138.03, 137.93, 137.24, 137.02, 134.63, 133.91, 133.85, 133.71, 133.65, 133.56, 130.60, 130.56, 129.78, 129.63, 129.23, 128.86, 128.61, 128.58, 128.55, 128.50, 128.48, 128.45, 128.37, 128.27, 127.89, 127.79, 127.22, 126.90, 126.85, 126.48, 126.02, 125.76, 79.50, 79.30, 36.88 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ −10.16 (s) ppm. Anal. Calcd for $C_{40}H_{34}NOP$: C, 83.45; H, 5.95; N, 2.43. Found: C, 83.46; H, 6.03; N, 2.23.

4.3.4. (*S*)-2-(2-(Diphenylphosphino)benzylideneamino)-3-methyl-1,1-diphenylbutan-1-ol 2d. A yellow solid was obtained in quantitative yield. $[\alpha]_D^{25} = -16.05$ (*c* 1, CH_2Cl_2) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, $J = 4.8$ Hz, 1H, C*H*=N), 7.68–6.80 (m, 24H, Ar*H*), 4.12 (br, 1H, OH), 4.01 (d, $J = 2.4$ Hz, 1H, C*H*N), 1.86 (dsept, $J = 2.4$, 6.8, 6.8 Hz, 1H, CH_3CHCH_3), 0.71 (d, $J = 6.8$ Hz, 3H, CH_3), 0.51 (d, $J = 6.8$ Hz, 3H, CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.11 (d, $J = 16.9$ Hz, *C*=N), 147.85, 146.11, 144.80, 143.65, 139.36, 137.28, 137.17, 137.07, 136.88, 136.78, 134.63, 133.99, 133.97, 133.94, 133.81, 133.77, 133.75, 133.55, 130.21, 129.12, 129.08, 129.03, 128.77, 128.66, 128.59, 128.52, 128.33, 128.30, 128.27, 128.23, 128.06, 127.95, 127.78, 127.67, 127.38, 126.96, 126.72, 126.18, 126.07, 125.89, 125.66, 125.59, 88.08, 87.95, 87.88, 80.64, 79.89, 73.74, 29.18, 22.25, 21.97, 17.89, 17.48 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ −12.08 (s) ppm. Anal. Calcd for $C_{36}H_{34}NOP$: C, 81.95; H, 6.50; N, 2.65. Found: C, 82.13; H, 6.29; N, 2.62.

4.4. General procedures for the asymmetric conjugate additions of diethylzinc to substituted chalcones

A suspension of $Cu(acac)_2$ (33.0 mg, 0.0125 mmol) and the ligand (0.0125 mmol) in 2 mL hexane was stirred for 1.5 h at room temperature under a dry nitrogen atmosphere. The mixture was cooled to −40 °C and stirred for 10 min. To the solution, diethylzinc (0.50 mmol, 0.50 mL of 1.0 M solution in hexane) was added slowly and the mixture was stirred for another 15 min followed by the addition of a solution of chalcone (0.25 mmol) in 2 mL diethyl ether. The solution was stirred at −40 °C for 16 h, quenched with saturated aqueous NH_4Cl solution (4 mL), and extracted with diethyl ether (2 × 15 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give a crude product, which was purified by column chromatography using hexane/EtOAc as eluant to afford the ethylated product for HPLC analysis.

4.4.1. 1-(2-Methoxyphenyl)-3-phenylpentan-1-one (entry 1 in Table 2). This compound was obtained in 94% yield. $[\alpha]_D^{25} = -16.05$ (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–6.92 (m, 9H), 3.86 (s, 3H), 3.29 (d, $J = 2.0$ Hz, 1H), 3.27 (d, $J = 0.4$ Hz, 1H), 3.19–3.12 (m, 1H), 1.79–1.68 (m, 1H), 1.65–1.54 (m, 1H), 0.78 (t, $J = 7.2$ Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 202.07, 158.09, 145.00, 132.99, 130.10, 129.09, 128.19, 127.71, 126.00, 120.63, 111.37, 55.45, 50.58, 43.20, 29.33, 12.03 ppm. Enantiomeric excess: 81%, Chiralcel OJ, hexane/*i*-PrOH = 99:1, 1.0 mL/min, $t_{minor} = 15.9$ min, $t_{major} = 25.9$ min.

4.4.2. 1-(3-Methoxyphenyl)-3-phenylpentan-1-one (entry 2 in Table 2). This compound was obtained in 94% yield. $[\alpha]_D^{25} = -16$ (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.06 (m, 9H), 3.83 (s, 3H), 3.31–3.21 (m, 3H), 1.83–1.73 (m, 1H), 1.70–1.59 (m, 1H), 0.81 (t, $J = 7.2$ Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 199.04, 159.82, 144.67, 138.71, 129.47, 128.40, 127.63, 126.26, 120.69, 119.41, 112.33, 55.41, 45.72, 43.11, 29.22, 12.05 ppm. Enantiomeric excess: 85%, Chiralcel OD, hexane/*i*-PrOH = 99:1, 0.5 mL/min, $t_{major} = 17.3$ min, $t_{minor} = 19.8$ min.

4.4.3. 1-(4-Methoxyphenyl)-3-phenylpentan-1-one (entry 3 in Table 2). This compound was obtained in 93% yield. $[\alpha]_D^{25} = -21.65$ (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91–7.87 (m, 2H), 7.30–7.16 (m, 5H), 6.92–6.88 (m, 2H), 3.86 (s, 3H), 3.25–3.17 (m, 3H), 1.81–1.73 (m, 1H), 1.67–1.56 (m, 1H), 0.80 (t, $J = 7.2$ Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 197.75, 163.32, 144.81, 130.41, 130.31, 128.34, 127.62, 126.18, 113.63, 55.39, 45.24, 43.21, 29.15, 12.03 ppm. Enantiomeric excess: 80%, Chiralcel OD, hexane/*i*-PrOH = 99:1, 1.0 mL/min, $t_{major} = 13.2$ min, $t_{minor} = 15.4$ min.

4.4.4. 3-(2-Methoxyphenyl)-1-phenylpentan-1-one (entry 4 in Table 2). This compound was obtained in 98% yield. $[\alpha]_D^{25} = -11.7$ (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95–7.91 (m, 2H), 7.55–7.51 (m, 1H), 7.45–7.41 (m, 2H), 7.19–7.15 (m, 2H), 6.92–6.89 (m, 1H), 6.84 (d, $J = 8.4$ Hz, 1H), 3.78 (s, 3H), 3.68–3.61 (m, 1H), 3.30 (dd, $J = 6.4$, 16.0 Hz, 1H), 3.20 (dd, $J = 7.6$, 15.6 Hz, 1H), 1.79–1.69 (m, 2H), 0.80 (t, $J = 7.2$ Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 199.80, 157.49, 137.40, 132.67, 132.51, 128.39, 128.14, 128.08, 127.10, 120.53, 110.72, 55.27, 44.55, 37.09, 27.25, 12.08 ppm. Enantiomeric excess: 96%, Chiralcel OD, hexane/*i*-PrOH = 99:1, 1.0 mL/min, $t_{major} = 7.6$ min, $t_{minor} = 10.6$ min.

4.4.5. 3-(3-Methoxyphenyl)-1-phenylpentan-1-one (entry 5 in Table 2). This compound was obtained in 92% yield. $[\alpha]_D^{25} = -5.3$ (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92–7.89 (m, 2H), 7.56–7.51 (m, 1H), 7.45–7.41 (m, 2H), 7.23–7.19 (m, 1H), 6.84–6.71 (m, 3H), 3.79 (s, 3H), 3.31–3.18 (m, 3H), 1.82–1.72 (m, 1H), 1.68–1.57 (m, 1H), 0.81 (t, $J = 7.2$ Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 199.17, 159.65, 146.44, 137.33, 132.86, 129.33, 128.51, 128.05, 120.06, 113.69, 111.28, 55.12, 45.56, 43.07, 29.12, 12.05 ppm. Enantiomeric excess: 78%, Chiralcel OD, hexane/*i*-PrOH = 99:1, 1.0 mL/min, $t_{major} = 10.1$ min, $t_{minor} = 11.3$ min.

4.4.6. 3-(4-Methoxyphenyl)-1-phenylpentan-1-one (entry 6 in Table 2). This compound was obtained in 89% yield. $[\alpha]_D^{25} = -14.3$ (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91–7.88 (m, 2H), 7.55–7.51 (m, 1H), 7.45–7.41 (m, 2H), 7.16–7.12 (m, 2H), 6.84–6.81 (m, 2H), 3.77 (s, 3H), 3.26–3.15 (m, 3H), 1.81–1.71 (m, 1H), 1.66–1.55 (m, 1H), 0.80 (t, $J = 7.6$ Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 199.38, 158.01, 137.37, 136.71, 132.83, 128.49, 128.06, 113.81, 55.20, 45.84, 42.30, 29.35, 12.05 ppm. Enantiomeric excess: 84%, Chiralcel OD, hexane/*i*-PrOH = 99.5:0.5, 0.4 mL/min, $t_{minor} = 33.5$ min, $t_{major} = 36.3$ min.

4.4.7. 3-(2-Methoxyphenyl)-1-(3-methoxyphenyl) pentan-1-one (entry 7 in Table 2). This compound was obtained in 98% yield. $[\alpha]_D^{25} = -9.05$ (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54–7.52 (m, 1H), 7.46–6.89 (m, 6H), 6.85–6.83 (m, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.67–3.60 (m, 1H), 3.30 (dd, $J = 6.0$, 16.0 Hz, 1H), 3.17 (dd, $J = 8.0$, 16.0 Hz, 1H), 1.78–1.70 (m, 2H), 0.80 (t,

$J = 7.2$ Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 199.58, 159.73, 157.47, 138.76, 132.48, 129.35, 128.05, 127.08, 120.78, 120.52, 119.14, 112.47, 110.71, 55.36, 55.26, 44.63, 37.15, 27.21, 12.06 ppm. HRMS: [M^+] calcd for $C_{19}H_{22}O_3$, 298.1569; found, 298.1578. Enantiomeric excess: 97%, Chiralcel OD, hexane/*i*-PrOH = 99:1, 1.0 mL/min, $t_{major} = 9.9$ min, $t_{minor} = 14.7$ min.

4.4.8. 3-(2-Methoxyphenyl)-1-(4-methoxyphenyl)pentan-1-one (entry 8 in Table 2). This compound was obtained in 96% yield. $[\alpha]_D^{25} = -10.1$ (*c* 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.95–7.91 (m, 2H), 7.19–7.15 (m, 2H), 6.93–6.88 (m, 3H), 6.84 (d, $J = 8.4$ Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.66–3.59 (m, 1H), 3.25 (dd, $J = 6.0$, 15.6 Hz, 1H), 3.13 (dd, $J = 8.0$, 15.6 Hz, 1H), 1.78–1.68 (m, 2H), 0.79 (t, $J = 7.2$ Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.40, 163.23, 157.53, 132.74, 130.60, 130.42, 128.09, 127.05, 120.56, 113.56, 110.78, 55.41, 55.33, 44.29, 37.28, 27.24, 12.07 ppm. HRMS: [M^+] calcd for $C_{19}H_{22}O_3$, 298.1569; found, 298.1574. Enantiomeric excess: 93%, Chiralcel OD, hexane/*i*-PrOH = 99:1, 1.0 mL/min, $t_{major} = 14.4$ min, $t_{minor} = 39.6$ min.

4.4.9. 3-(2-Bromophenyl)-1-phenylpentan-1-one (entry 9 in Table 2). This compound was obtained in 97% yield. $[\alpha]_D^{25} = -35.7$ (*c* 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.96–7.93 (m, 2H), 7.57–7.53 (m, 2H), 7.46–7.42 (m, 2H), 7.29–7.23 (m, 2H), 7.07–7.03 (m, 1H), 3.89–3.82 (m, 1H), 3.31 (dd, $J = 6.0$, 16.4 Hz, 1H), 3.22 (dd, $J = 7.6$, 16.4 Hz, 1H), 1.86–1.75 (m, 1H), 1.73–1.64 (m, 1H), 0.84 (t, $J = 7.2$ Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.65, 143.53, 137.06, 133.10, 132.95, 128.54, 128.13, 127.85, 127.63, 127.55, 125.36, 44.63, 41.21, 28.21, 11.66 ppm. HRMS: {[M^+]+1} calcd for $C_{17}H_{17}BrO$, 317.0463; found, 317.0539. Enantiomeric excess: 96%, Chiralcel OJ, hexane, 1.0 mL/min, $t_{major} = 22.1$ min, $t_{minor} = 30.1$ min.

4.4.10. 3-(2-Chlorophenyl)-1-phenylpentan-1-one (entry 10 in Table 2). This compound was obtained in 98% yield. $[\alpha]_D^{25} = -32.5$ (*c* 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.95–7.92 (m, 2H), 7.55–7.51 (m, 1H), 7.45–7.41 (m, 2H), 7.36–7.34 (m, 1H), 7.27–7.19 (m, 2H), 7.13–7.09 (m, 1H), 3.90–3.83 (m, 1H), 3.32 (dd, $J = 6.4$, 16.8 Hz, 1H), 3.24 (dd, $J = 7.6$, 16.4 Hz, 1H), 1.87–1.76 (m, 1H), 1.74–1.64 (m, 1H), 0.82 (t, $J = 7.6$ Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.65, 141.77, 137.01, 134.31, 132.89, 129.70, 128.48, 128.03, 127.88, 127.23, 126.85, 44.33, 38.67, 27.97, 11.66 ppm. Enantiomeric excess: 96%, Chiralcel OJ, hexane, 1.0 mL/min, $t_{major} = 20.1$ min, $t_{minor} = 26.8$ min.

4.4.11. 3-(2-Bromophenyl)-1-(3-methoxyphenyl)pentan-1-one (entry 11 in Table 2). This compound was obtained in 96% yield. $[\alpha]_D^{25} = -33.8$ (*c* 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.56–7.52 (m, 2H), 7.46–7.45 (m, 1H), 7.36–7.32 (m, 1H), 7.28–7.22 (m, 2H), 7.10–7.02 (m, 2H), 3.89–3.85 (m, 1H), 3.83 (s, 3H), 3.30 (dd, $J = 6.4$, 16.4 Hz, 1H), 3.20 (dd, $J = 7.6$, 16.4 Hz, 1H), 1.85–1.63 (m, 2H), 0.83 (t, $J = 7.2$ Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.40, 159.81, 143.50, 138.41, 133.06, 129.46, 127.79, 127.60, 127.53, 125.34, 120.74, 119.54, 112.30, 55.38, 44.65, 41.19, 28.22, 11.62 ppm. HRMS: [M^+] calcd for $C_{18}H_{19}BrO_2$, 346.0568; found, 346.0572. Enantiomeric excess: 95%, Chiralcel OD, hexane/*i*-PrOH = 99:1, 1.0 mL/min, $t_{major} = 9.7$ min, $t_{minor} = 15.0$ min.

4.4.12. 3-(2-Bromophenyl)-1-(4-methoxyphenyl)pentan-1-one (entry 12 in Table 2). This compound was obtained in 95% yield. $[\alpha]_D^{25} = -39.3$ (*c* 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.95–7.92 (m, 2H), 7.56–7.54 (d, 1H), 7.29–7.23 (m, 2H), 7.06–7.02 (m, 1H), 6.93–6.90 (m, 2H), 3.87–3.80 (m, 1H), 3.86 (s, 3H), 3.25 (dd, $J = 6.4$, 16.4 Hz, 1H), 3.15 (dd, $J = 7.6$, 16.0 Hz, 1H), 1.85–1.61 (m, 2H), 0.82 (t, $J = 7.2$ Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.17, 163.40, 143.66, 133.05, 130.41, 130.17, 127.86, 127.56, 127.52, 125.33, 113.66, 55.41, 44.32, 41.41, 28.16, 11.64 ppm. HRMS: {[M^+]+1} calcd for $C_{18}H_{19}BrO_2$, 347.0568; found, 347.0645. Enantiomeric excess: 94%, Chiralcel OD, hexane/*i*-PrOH = 99:1, 1.0 mL/min, $t_{major} = 13.1$ min, $t_{minor} = 25.4$ min.

4.4.13. 3-(2-Chlorophenyl)-1-(3-methoxyphenyl)pentan-1-one (entry 13 in Table 2). This compound was obtained in 98% yield. $[\alpha]_D^{25} = -33.0$ (*c* 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.53–7.52 (m, 1H), 7.46–7.45 (m, 1H), 7.37–7.32 (m, 2H), 7.27–7.19 (m, 2H), 7.14–7.07 (m, 2H), 3.90–3.80 (m, 1H), 3.83 (s, 3H), 3.32 (dd, $J = 6.4$, 16.4 Hz, 1H), 3.22 (dd, $J = 7.6$, 16.4 Hz, 1H), 1.86–1.64 (m, 2H), 0.83 (t, $J = 7.2$ Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.46, 159.80, 141.81, 138.42, 134.34, 129.72, 129.46, 127.88, 127.24, 126.87, 120.70, 119.51, 112.27, 55.36, 44.44, 38.76, 28.01, 11.67 ppm. HRMS: [M^+] calcd for $C_{18}H_{19}ClO_2$, 302.1074; found, 302.1079. Enantiomeric excess: 97%, Chiralcel OD, hexane/*i*-PrOH = 99:1, 1.0 mL/min, $t_{major} = 8.7$ min, $t_{minor} = 11.8$ min.

4.4.14. 3-(2-Chlorophenyl)-1-(4-methoxyphenyl)pentan-1-one (entry 14 in Table 2). This compound was obtained in 95% yield. $[\alpha]_D^{25} = -38.6$ (*c* 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.94–7.90 (m, 2H), 7.36–7.34 (m, 1H), 7.27–7.19 (m, 2H), 7.13–7.09 (m, 1H), 6.92–6.89 (m, 2H), 3.88–3.81 (m, 1H), 3.85 (s, 3H), 3.26 (dd, $J = 6.0$, 16.0 Hz, 1H), 3.17 (dd, $J = 7.6$, 16.0 Hz, 1H), 1.86–1.64 (m, 2H), 0.81 (t, $J = 7.6$ Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.22, 163.36, 141.94, 134.31, 130.34, 130.16, 129.68, 127.92, 127.19, 126.84, 113.64, 55.37, 44.05, 38.92, 27.95, 11.67 ppm. Enantiomeric excess: 94%, Chiralcel OD, hexane/*i*-PrOH = 99:1, 1.0 mL/min, $t_{major} = 12.0$ min, $t_{minor} = 19.4$ min.

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