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Enantioselective copper-catalyzed 1,4-addition of dialkylzincs to enones using a novel *N,N,P*–Cu(II) complex

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ABSTRACT

Enantioselective copper-catalyzed 1,4-additions of dialkylzincs to enones were carried out in the presence of 1 mol % of $Cu(OTf)_2$ and 2.5 mol % of an *N,N,P*-ligand possessing a *tert*-butyl group at the adjacent position of the nitrogen of pyridine to afford the corresponding 1,4-adducts in up to 98% ee.

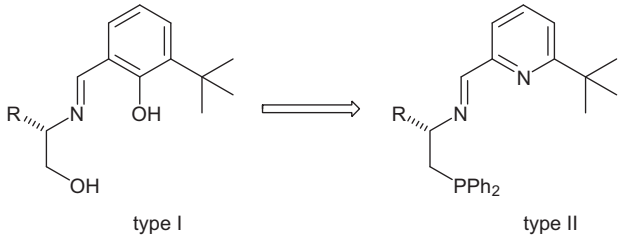
1. Introduction

The conjugate addition (1,4-addition) of organometallic species to electrophilically activated olefins, such as enones, is one of the most important asymmetric carbon–carbon bond forming reactions in organic synthesis.[1] Since the first report of the copper-catalyzed 1,4-addition of diethylzinc to enones by Alexakis et al.,[2,3] many other studies have been carried out, using chiral phosphate ligands,[4] chiral phosphoramidites,[5] chiral aminophosphine ligands,[6] chiral phosphines with amino acid moieties,[7] N-heterocyclic carbene ligands,[8] peptide-based ligands,[9] chiral bis(oxazoline) ligands,[10] and other types of ligand.[11,12] On the other hand, we have developed *O,N,O*-tridentate ligands with a Schiff base framework (type I) for use in various asymmetric carbon–carbon bond-forming reactions, including asymmetric silylcyanations of aldehydes,[13] enantioselective additions of diketenes to aldehydes,[14] enantioselective addition of dialkylzincs to aldehydes,[15] and asymmetric Reformatsky reactions.[16] In order to increase the affinity of the ligands to transition metals such as copper, we recently reported chiral *N,N,P* tridentate ligands containing a quinoline moiety.[17] Herein we report the preparation of newly designed *N,N,P*-tridentate ligands with a *tert*-butyl group at the adjacent position of the nitrogen of pyridine and their application to copper-catalyzed enantioselective 1,4-additions of dialkylzincs to enones.

2. Results and discussion

2.1. Synthesis of type II ligands

We first designed type II ligands as simple analogues of type I Schiff base ligands (Scheme 1).



Scheme 1.

The type II ligand was synthesized as shown in Scheme 2 (R = *tert*-Bu in Scheme 1). The reaction of 2-methylpyridine with *tert*-BuLi gave the 2-methyl-4,6-di-*tert*-butylpyridine (69%), which when treated with *m*CPBA afforded the corresponding *N*-oxide (54%).[18] This *N*-oxide was converted into the primary alcohol using trifluoroacetic anhydride (82%). Finally, oxidation using SeO_2 gave the desired aldehyde (80%).[19] Condensation of the 2-pyridyl aldehyde with amino phosphine afforded *N,N,P*-ligands with a *tert*-butyl group at the adjacent position of the nitrogen of pyridine (71%).

2.2. Enantioselective 1,4-addition using *N,N,P*-ligand–$Cu(OTf)_2$ complex

Next, we examined the 1,4-addition of dialkylzincs to cyclic enones using 1.0 mol % of $Cu(OTf)_2$ and 2.5 mol % of ligand **1** (Table 1).

Table 1 lists the optimized reaction conditions for the reactions of 2-cyclopenten-1-one, 2-cyclohexen-1-one, and 2-cyclohepten-1-one with dialkylzincs. High enantioselectivity was observed for the catalyst loading of 1 mol % $Cu(OTf)_2$ and 2.5 mol % ligand, and the reaction proceeded to afford (*S*)-3-ethylcyclohexanone (98% ee) at −40 °C. It should be mentioned that when the *N,N,P*-ligand was used without *tert*-butyl groups on the pyridine ring, the product was obtained in 95% yield with only 55% ee (*n* = 1, R = Et).

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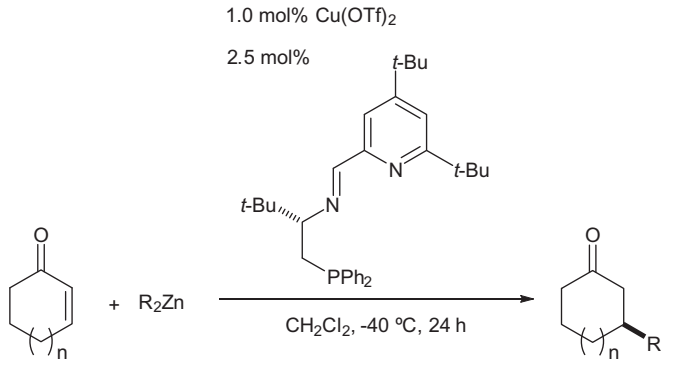
Table 1
Enantioselective 1,4-addition of dialkylzincs to cyclic enones[a]



Entry	*n*	R	Yield[b] (%)	ee[c,d] (%)
1	0	Et	64	98 (*S*)
2	1	Me	70	98 (*S*)
3	1	Et	70	97 (*S*)
4	2	Me	55	92 (*S*)
5	2	Et	79	80 (*S*)

[a] All reactions were carried out at −40 °C.
[b] Isolated yield.
[c] Determined by GC analysis.
[d] The absolute configuration was determined by comparison of the specific rotation value compared with that reported in the literature.[20]

We next examined the reaction of acyclic enones, such as chalcone and substituted chalcone using the same catalyst system (Table 2). Compared with our previously reported 2-quinolyl ligand (63% ee), the present catalyst system exhibited higher enantioselectivity (up to 83% ee).

2.3. Proposed catalytic cycle mechanism and the origin of enantioselection

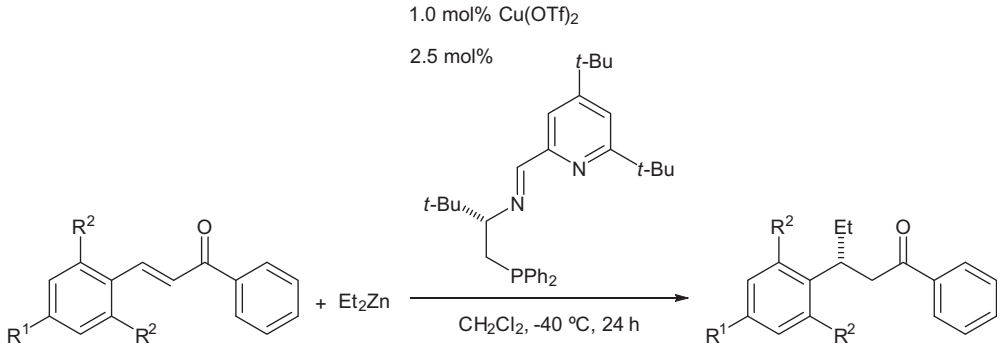
According to Reiser's proposed mechanism,[10a] we suggested mechanisms for the catalytic cycle and enantioselection as shown in Scheme 3. In the catalytic cycle, the reaction of the chiral copper complex and dialkylzinc gives an alkyl-copper species that acts as an alkyl donor. The enone is then activated by the copper and zinc species, coordinated to an alkene moiety and a carbonyl oxygen, respectively.

In order to explain the enantioselectivity, we proposed the mechanism as shown in Schemes 4–6. Assuming the molecule is in the plane of the paper, we suggest that the enone attacks from front side because of the bulkiness of the *tert*-butyl group at the stereogenic center. In addition, the plane of the enone itself is also fixed by the presence of the *tert*-butyl group at the adjacent position of the nitrogen of the pyridine and the PPh_2 group to avoid steric hindrance (Scheme 4). According to Scheme 3, the zinc species would be coordinated with a carbonyl oxygen as the Lewis acid so that the carbonyl group became bulky. As a result, the enone approaches the catalyst plane upward (Scheme 5). Since the copper center of catalyst would activate the olefin moiety, the sp^3 carbons in 2-cyclohexen-1-one should parry the PPh_2 group (Scheme 6). Thus, we surmised that the enantioselectivity was triply-controlled by the stereogenic center, the quinoline moiety, and the PPh_2 group.

3. Conclusion

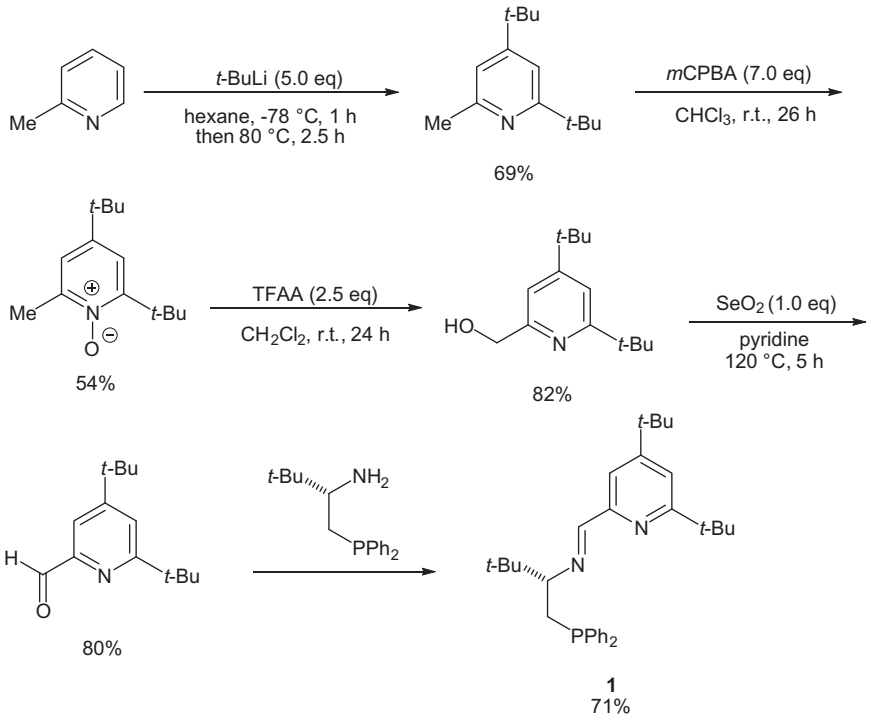
Our new chiral *N,N,P*-tridentate ligand possesses a *tert*-butyl group at the adjacent position of the nitrogen of pyridine and promotes highly enantioselective 1,4-additions of dialkylzinc to enones (up to 98% ee) in combination with $Cu(OTf)_2$.

Table 2
Enantioselective 1,4-addition of diethylzinc to acyclic enones[a]

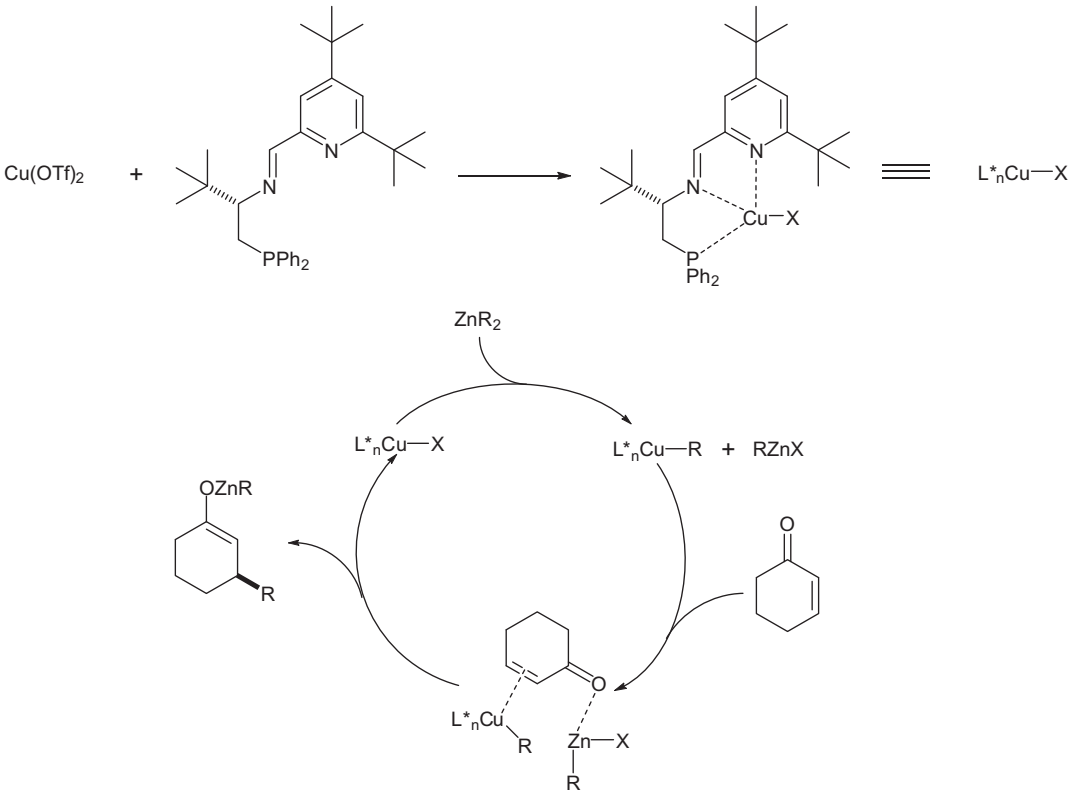


Entry	R^1	R^2	Yield[b] (%)	ee[c] (%)
1	H	H	89	83 (*R*)[d]
2	MeO	H	93	75 (*R*)[e]
3	NO_2	H	56	85 (*R*)[f]
4	F	H	93	85 (*R*)[f]
5	H	Me	75	79 (*R*)[f]

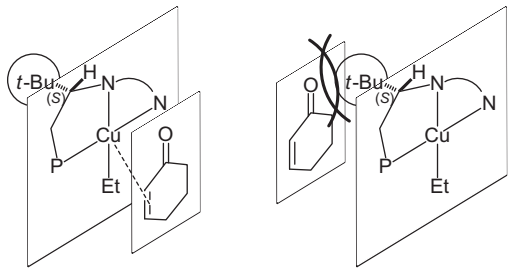
[a] All reactions were carried out at −40 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] Absolute configuration was determined by the specific rotation value as compared with that of the reported one.[20]
[e] Absolute configuration was determined by the comparison of the specific rotation value compared with that of the literature.[21]
[f] Absolute configuration was estimated by the order of retention time during HPLC analysis.



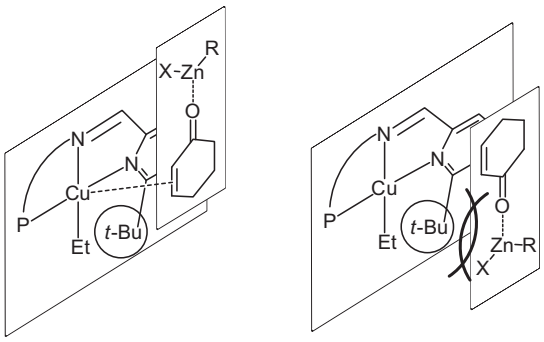
Scheme 2.



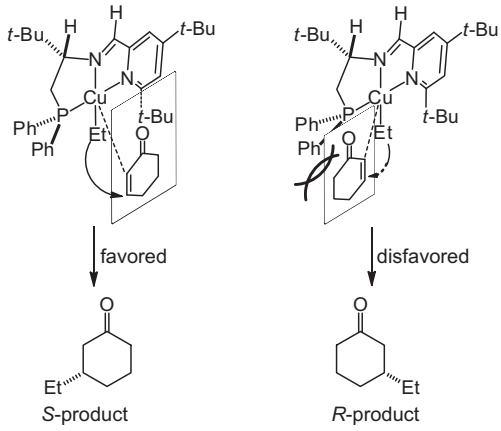
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

4. Experimental

4.1. General

All reactions were carried out in oven-dried glassware with magnetic stirring. All starting materials were obtained from commercial sources and used without further purification unless otherwise stated. ^{1}H and ^{13}C NMR spectra (400 and 100.6 MHz, respectively) were recorded using Me_4Si as an internal standard (0 ppm). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Gas chromatographic (GC) analysis was carried out using an instrument equipped with an FID detector and a capillary column, γ-DEX-225, β-DEX-225. Chiral HPLC was performed using an instrument equipped with a diode array detector and a chiral column CHIRALPAK AD-H (250 mm × 4.6 mm × 5 μm). High resolution mass spectra (HRMS) were measured by JEOL JMS-T100LP AccuTOF LC-Plus (ESI) with JEOL JMS-700 MStation (FAB).

4.2. Preparation of *N,N,P*-ligand 1

4.2.1. 2,4-Di-*tert*-Butyl-6-methylpyridine[18]

tert-Butyllithium (62 mL, 100 mmol, 1.6 M solution in pentane) was added to a solution of 2-methylpyridine (1.86 g, 20.0 mmol) in dry hexane (40 mL) at −78 °C. The mixture was stirred at this temperature for 1 h, then at reflux for 2.5 h at 80 °C. After cooling to room temperature the resulting solution was hydrolyzed with 2-propanol (20 mL) followed by water (20 mL). The aqueous layer was then extracted with hexane (30 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was subjected to column chromatography on silica gel using hexane/ethyl acetate (10:1) as an eluent to afford a yellow oil. Yield: 2.81 g (69%). R_f 0.63 (10:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.13 (s, 9H), 1.20, (s, 9H), 2.48 (s, 3H), 6.88 (s, 1H), 6.96 (s, 1H).

4.2.2. 2,4-Di-*tert*-butyl-6-methylpyridine-*N*-oxide[18]

m-Chloroperbenzoic acid (70%, 21.4 g, 84.5 mmol) was added to a solution of 2,4-di-*tert*-butyl-6-methylpyridine (2.66 g, 13.0 mmol) in $CHCl_3$ (300 mL). The mixture was then stirred at room temperature. After 2 h, more *m*-chloroperbenzoic acid (1.64 g, 6.5 mmol) was added, and stirring was continued for 24 h. A saturated aqueous solution of $NaHCO_3$ was then added to the resulting solution, after which aqueous layer was extracted with $CHCl_3$ (30 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was subjected to column chromatography on silica gel using hexane/ethyl acetate (5:1) as an eluent to afford the yellow solid. Yield: 1.55 g (54%). R_f 0.33 (5:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (s, 9H), 1.54 (s, 9H), 2.51 (s, 3H), 7.12 (d, J = 2.8 Hz, 1H), 7.20 (d, J = 2.8 Hz, 1H).

4.2.3. (4,6-Di-*tert*-Butylpyridin-2-yl)methanol[19]

At first, TFAA (0.17 mL, 1.25 mmol) was added to a solution of 2,4-di-*tert*-butyl-6-methylpyridine-*N*-oxide (111 mg, 0.5 mmol) in dry CH_2Cl_2 (3 mL) at room temperature. After 1 h the reaction was hydrolyzed with an Na_2CO_3 solution and the mixture was stirred overnight. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was subjected to column chromatography on silica gel using hexane/ethyl acetate (5:1) as an eluent to afford a yellow oil. Yield: 90 mg (82%). R_f 0.29 (5:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (s, 9H), 1.37 (s, 9H), 4.6 (br s, 1H), 4.71 (s, 2H), 6.94 (s, 1H), 7.22 (s, 1H).

4.2.4. 4,6-Di-*tert*-butyl-2-pyridylaldehyde[19]

At first, SeO_2 (400 mg, 3.6 mmol) was added to a solution of (4,6-di-*tert*-butylpyridin-2-yl)methanol (797 mg, 3.6 mmol) in dry pyridine (30 mL). The mixture was refluxed for 4 h at 120 °C. The suspension was filtered and evaporated. The residue was subjected to column chromatography on silica gel using hexane/ethyl acetate (10:1) as an eluent to afford a white solid. Yield: 634 mg (80%). R_f 0.51 (10:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (s, 9H), 1.42 (s, 9H), 7.54 (d, J = 2.0 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 10.06 (s, 1H).

4.2.5. (*S,E*)-*N*-((4,6-Di-*tert*-butylpyridin-2-yl)methylene)-1-(diphenylphosphino)-3,3-dimethylbutan-2-amine 1

A mixture of benzene (5 mL), (*S*)-2-amino-1-diphenylphoshino-3,3-dimethylbutane[22] (171 mg, 0.6 mmol), 4,6-di-*tert*-butylpicolinaldehyde (109 mg, 0.5 mmol), and anhydrous Na_2SO_4 (1 g) was stirred at 85 °C for 12 h. The mixture was filtered and the filtrate was evaporated. The residue was subjected to column chromatography on silica gel (pre-neutralized with triethylamine) using hexane/ethyl acetate (5:1) as an eluent to afford a yellow oil. Yield:

173 mg (71%). R_f 0.67 (5:1 hexane/ethyl acetate; TLC plate was pre-neutralized with triethylamine). IR (KBr) cm^{-1}: 2955, 2866, 1646, 1598, 1551, 1478, 1433, 1409, 1392, 1362, 1259, 1214, 1166, 1069, 1026, 999, 959, 898, 880, 805, 738, 694, 635, 524, 516, 509, 505, 501; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.92 (s, 9H), 1.31 (s, 9H), 1.38 (s, 9H), 2.46 (m, 2H), 3.00 (m, 1H), 7.11–7.19 (m, 3H), 7.29 (d, J = 1.2 Hz, 1H), 7.34–7.37 (m, 5H), 7.45–7.49 (m, 2H), 7.71 (d, J = 1.2 Hz, 1H), 8.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.2, 162.9, 159.7, 153.4, 139.6, 138.7, 133.7, 132.5, 128.7, 128.4, 127.9, 127.7, 116.6, 114.5, 77.5, 77.0, 37.4, 35.2, 34.9, 30.7, 30.3, 26.7; $[\alpha]_D$ = +81.3 (c 1.0, $CHCl_3$); HRMS (ESI+) Calcd for $C32H44N_2P$ [M+H]+: 487.3237; found: m/z 487.3237.

4.3. General procedure for the asymmetric 1,4-addition

A solution of $Cu(OTf)_2$ (0.01 mmol) and ligand (0.025 mmol) in dichloromethane (1.5 mL) was stirred under an argon atmosphere at room temperature for 0.5 h. after which enone (1 mmol) was added to this catalyst solution. The solution was then cooled to −40 °C, then it was stirred at −40 °C for 15 min, after which Et_2Zn (1.5 mmol, 0.153 ml) was added slowly. The resulting mixture was stirred at −40 °C for 24 h and then quenched with a 1 M HCl solution (2 mL). After warming the reaction mixture to room temperature, the reaction mixture was extracted with diethyl ether (10 mL × 3). The data of the ee values were determined by chiral-phase GC analysis with a γ-DEX-225 (Supelco®) column (30 m x 0.25 mm) or β-DEX-225 (Supelco®) column (30 m × 0.25 mm).

4.3.1. (*S*)-(−)-3-Ethylcyclopentan-1-one[17] (Table 1, entry 1)

98% ee [t_R of (*S*)-isomer, 29.65 min; t_R of (*R*)-isomer, 30.16 min; GC conditions: γ-DEX-225, initial temp 70 °C, initial time 25 min, progress time 5 °C min^{-1}, final temp 120 °C]. $[\alpha]_D$ = −50.1 (c 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.95 (t, J = 7.2 Hz, 3H), 1.43–1.56 (m, 3H), 1.77–1.84 (m, 1H), 2.08–2.16 (m, 2H), 2.27–2.42 (m, 3H).

4.3.2. (*S*)-(−)-3-Methylcyclohexan-1-one[17] (Table 1, entry 2)

98% ee [t_R of (*S*)-isomer, 34.90 min; t_R of (*R*)-isomer, 36.16 min; GC conditions: γ-DEX-225, initial temp 70 °C, initial time 30 min, progress time 5 °C min^{-1}, final temp 120 °C]. $[\alpha]_D$ = −6.6 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.99 (d, J = 6.4 Hz, 3H), 1.61–1.69 (m, 2H), 1.81–2.04 (m, 4H), 2.16–2.24 (m, 1H), 2.29–2.38 (m, 2H).

4.3.3. (*S*)-(−)-3-Ethylcyclohexan-1-one[17] (Table 1, entry 3)

97% ee [t_R of (*S*)-isomer, 36.54 min; t_R of (*R*)-isomer, 37.18 min; GC conditions: γ-DEX-225, initial temp 80 °C, initial time 40 min, progress time 10 °C min^{-1}, final temp 150 °C]. $[\alpha]_D$ = −10.0 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, J = 7.2 Hz, 3H), 1.32–1.39 (m, 3H), 1.61–1.70 (m, 2H), 1.87–2.07 (m, 3H), 2.25–2.45 (m, 3H).

4.3.4. (*S*)-(−)-3-Methylcycloheptan-1-one[17] (Table 1, entry 4)

92% ee [t_R of (*S*)-isomer, 34.48 min; t_R of (*R*)-isomer, 36.47 min; GC conditions: β-DEX-225, initial temp 80 °C, initial time 30 min, progress time 5 °C min^{-1}, final temp 120 °C]. $[\alpha]_D$ = −62.0 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.00 (d, J = 6.8 Hz, 3H), 1.26–1.46 (m, 2H), 1.81–1.92 (m, 5H), 2.42–2.49 (m, 4H).

4.3.5. (*S*)-(−)-3-Ethylcycloheptan-1-one[17] (Table 1, entry 5)

80% ee [t_R of (*S*)-isomer, 40.05 min; t_R of (*R*)-isomer 41.87 min; GC conditions: β-DEX-225, initial temp 90 °C, initial time 40 min, progress time 5 °C min^{-1}, final temp 120 °C]. $[\alpha]_D$ = −50.4 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, J = 7.2 Hz, 3H), 1.25–1.42 (m, 4H), 1.58–1.65 (m, 2H), 1.85–1.93 (m, 3H), 2.35–2.50 (m, 4H).

4.3.6. (*R*)-(−)-1,3-Diphenylpentan-1-one[17] (Table 1, entry 1)

83% ee [t_R of (*S*)-isomer, 8.23 min; t_R of (*R*)-isomer, 10.69 min; HPLC conditions: column, CHIRALCEL AD-H (DAICEL); eluent, hexane/2-propanol (99:1); 1.0 mL min^{-1}]. $[\alpha]_D$ = −2.0 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.81 (t, J = 7.6 Hz, 3H), 1.61–1.70 (m, 2H), 1.76–1.82 (m, 1H), 3.23–3.31 (m, 3H), 7.16–7.31 (m, 4H), 7.41–7.45 (m, 2H), 7.51–7.56 (m, 1H), 7.89–7.92 (m, 2H).

4.3.7. (*R*)-(−)-3-(4-Methoxyphenyl)-1-phenyl-pentan-1-one[22] (Table 2, entry 2)

75% ee [t_R of (*S*)-isomer, 14.47 min; t_R of (*R*)-isomer, 20.84 min; HPLC conditions: column, CHIRALCEL AD-H (DAICEL); eluent, hexane/2-propanol (95:5); 0.5 mL min^{-1}]. $[\alpha]_D$ = −5.0 (c 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.80 (t, J = 7.2 Hz, 3H), 1.58–1.66 (m, 1H), 1.73–1.79 (m, 1H), 3.17–3.26 (m, 3H), 3.78 (s, 3H), 6.82 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 7.41–7.45 (m, 2H), 7.51–7.55 (m, 1H), 7.89 (d, J = 8.4 Hz, 2H).

4.3.8. (*R*)-(−)-3-(4-Nitrophenyl)-1-phenyl-pentan-1-one (Table 2, entry 3)

85% ee [t_R of (*S*)-isomer, 28.40 min; t_R of (*R*)-isomer, 41.82 min; HPLC conditions: column, CHIRALCEL AD (DAICEL); eluent, hexane/2-propanol (99:1); 1.0 mL min^{-1}]. $[\alpha]_D$ = +22.2 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.83 (t, J = 7.2 Hz, 3H), 1.63–1.74 (m, 1H), 1.79–1.88 (m, 1H), 3.32–3.42 (m, 3H), 7.39–7.46 (m, 4H), 7.56 (t, J = 7.2 Hz, 1H), 7.89 (d, J = 7.2 Hz, 2H), 8.15 (d J = 8.8 Hz, 2H).

4.3.9. (*R*)-(−)-3-(4-Fluorophenyl)-1-phenyl-pentan-1-one (Table 2, entry 4)

85% ee [t_R of (*S*)-isomer, 11.68 min; t_R of (*R*)-isomer, 14.82 min; HPLC conditions: column, CHIRALCEL AD-H (DAICEL); eluent, hexane/2-propanol (99:1); 0.5 mL min^{-1}]. $[\alpha]_D$ = −2.5 (c 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.80 (t, J = 7.6 Hz, 3H), 1.57–1.65 (m, 1H), 1.76–1.81 (m, 1H), 3.20–3.27 (m, 3H), 6.94–6.96 (m, 2H), 7.16–7.19 (m, 2H), 7.41–7.45 (m, 2H), 7.52–7.56 (m, 1H), 7.87–7.90 (m, 2H).

4.3.10. (*R*)-(−)-3-(2,6-Dimethylphenyl)-1-phenyl-pentan-1-one (Table 2, entry 5)

79% ee [t_R of (*S*)-isomer, 5.58 min; t_R of (*R*)-isomer, 6.01 min; HPLC conditions: column, CHIRALCEL AD-H (DAICEL); eluent, hexane/2-propanol (99:1); 1.0 mL min^{-1}]. $[\alpha]_D$ = −23.0 (c 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.83 (t, J = 7.6 Hz, 3H), 1.77–1.93 (m, 2H), 2.36 (s, 3H), 2.48 (s, 3H), 3.33–3.46 (m, 2H), 3.87–3.94 (m, 1H), 6.95–6.98 (m, 3H), 7.44 (t, J = 7.6 Hz, 2H), 7.54 (t, J = 7.6 Hz, 1H), 7.90 (d, J = 7.6 Hz, 2H).

Acknowledgments

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