

Enantioselective Copper-Catalyzed 1,4-Addition of Dialkylzincs to Enones Followed by Trapping with Allyl Iodide Derivatives

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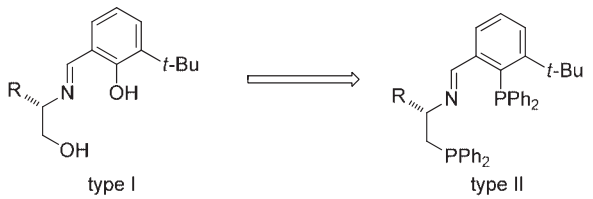
Enantioselective copper-catalyzed 1,4-addition of dialkylzincs to enones proceeded in the presence of 0.1 mol % of $Cu(OTf)_2$ and 0.25 mol % of an *N*,*N*,*P*-ligand containing a quinoline moiety to afford the corresponding conjugated adducts in 99% ee. The intermediate zinc enolates were trapped with substituted allyl iodides to give disubstituted ketones with high diastereoselectivity and enantioselectivity.

Enantioselective 1,4-addition of organometallic species to enones is one of the most important asymmetric carbon–carbon bond-forming reactions in organic synthesis.[1] An example of this type of reaction is the enantioselective 1,4-addition of a dialkylzinc to an enone, which has been the subject of various studies.[2] Following the first report of copper-catalyzed 1,4-addition of diethylzinc to enones by Alexakis et al.,[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 ligands.[4g,4o,6a,7a,11] We 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 silylcyanation of aldehydes,[12] enantioselective addition of diketenes to aldehydes,[13] and enantioselective addition of dialkylzincs to aldehydes.[14] To increase the affinity of the ligands for transition metals, we designed and synthesized new chiral *P*,*N*,*P* (type II) and *N*,*N*,*P* (type III) tridentate ligands. Here, we report the preparation of newly designed *P*,*N*,*P*-tridentate ligands and their application to copper-catalyzed enantioselective addition of dialkylzincs to enones.

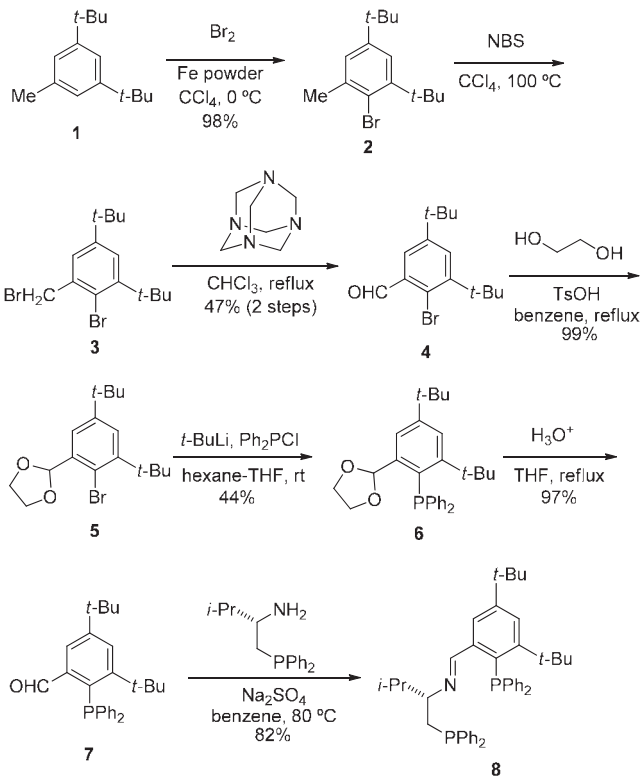


Scheme 1. *O*,*N*,*O*-Ligand (type I) and *P*,*N*,*P*-ligand (type II).

Results and Discussion

Synthesis of Type II Ligand and Its Use in Enantioselective 1,4-Addition. We first designed type II ligands as simple analogs of type I Schiff base ligands (Scheme 1).

The type II ligand was synthesized as shown in Scheme 2 (R = *i*-Pr). Bromination of 3,5-di-*tert*-butyltoluene (**1**) followed by treatment with NBS afforded benzyl bromide compound **3**, which was then oxidatively converted by hexamethylenetetramine into aldehyde **4**. After protecting the aldehyde moiety with ethylene glycol, a diphenylphosphino group was introduced by lithiation of **5** then hydrolysis of **6** gave the phosphinoaldehyde **7**. Condensation of aminophosphine with this aldehyde gave the type II ligand **8** in high yield.



Scheme 2. Preparation of type II ligand.

We then examined the application of the type II ligand **8** in the asymmetric 1,4-addition of diethylzinc to 2-cyclohexen-1-one. However, as shown in Scheme 3, the optical yield was only moderate and the reactivity was so low so that a long reaction time was required even at 0 °C. We concluded that the bulkiness of two PPh_2 groups and the rigidity of the imine moiety inhibited the formation of a copper complex.

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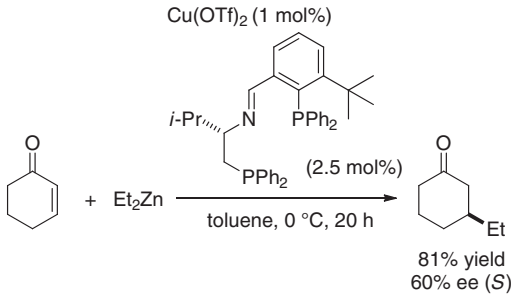
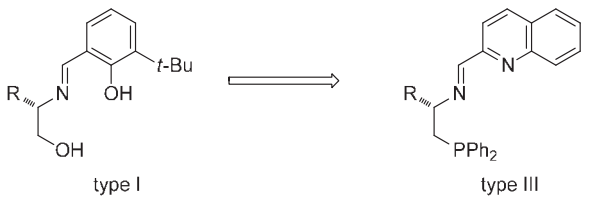
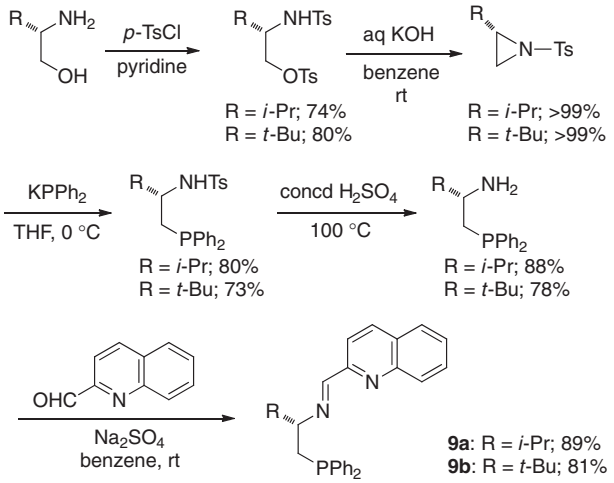


Scheme 3. Enantioselective 1,4-addition of diethylzinc to 2-cyclohexen-1-one.



Scheme 4. *O*,*N*,*O*-Ligand (type I) to *N*,*N*,*P*-ligand (type III).

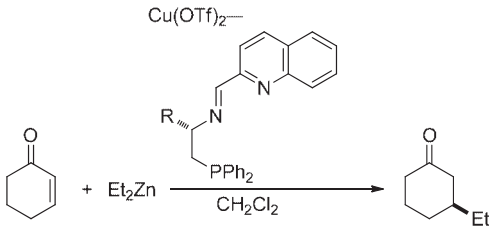


Scheme 5. Preparation of type III ligand.

Preparation of Type III Ligand. Next, we turned our attention to a type III ligand containing a quinoline moiety (Scheme 4),[15] which was prepared as shown in Scheme 5. Ditosylation of β-amino alcohols (starting from L-valinol) followed by treatment with KOH afforded substituted aziridines in high yield, which were then treated with $KPPh_2$ to give the corresponding aminophosphines.[16] Condensation of 2-quinolinecarbaldehyde with these aminophosphines gave the desired type III ligands in high yield.

Enantioselective 1,4-Addition Using *N*,*N*,*P*-Ligand. Table 1 lists the optimized reaction conditions for the reaction of 2-cyclohexen-1-one (**10**) with diethylzinc, including the amount of catalyst ($Cu(OTf)_2$ and ligand), the reaction temperature, and the ligand substituents (**9a**: R = *i*-Pr, **9b**: R = *t*-Bu). High enantioselectivity was observed for both R = *i*-Pr and R = *t*-Bu. Even when the catalyst load was decreased to 0.1 mol % $Cu(OTf)_2$ and 0.25 mol % ligand, the reaction proceeded to afford (*S*)-3-ethylcyclohexanone (98% ee) at

Table 1. Enantioselective 1,4-Addition of Diethylzinc to 2-Cyclohexen-1-one



Entry	R	Cu(OTf) /mol %[a)]	Temp /°C	Time /h	Convn /%[b)]	Ee /%[b)]
1	*i*-Pr	1.0	0	5	>99	97 (*S*)
2	*i*-Pr	0.5	0	5	>99	97 (*S*)
3	*i*-Pr	0.2	0	5	>99	97 (*S*)
4	*i*-Pr	0.2	−20	5	>99	98 (*S*)
5	*i*-Pr	0.2	−40	5	66	99 (*S*)
6	*i*-Pr	0.1	0	5	89	96 (*S*)
7	*i*-Pr	0.1	−40	24	>99	98 (*S*)
8	*t*-Bu	1.0	0	5	>99[c)]	99 (*S*)
9	*t*-Bu	0.2	0	5	>99	95 (*S*)
10	*t*-Bu	0.1	0	5	95	95 (*S*)
11	*t*-Bu	0.1	−40	24	>99	96 (*S*)

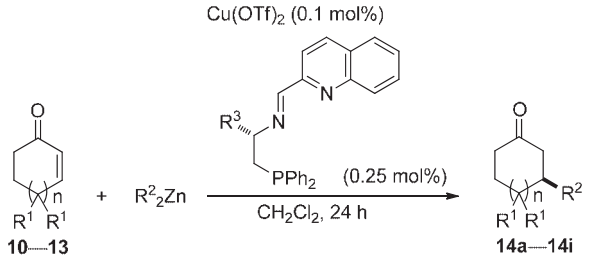
a) $Cu(OTf)_2$:ligand = 1:2.5. b) Conversions and ee values were determined by GC analysis (Supelco® γ-DEX-225). c) Isolated yield was 84%.

−40 °C. In most of the previously reported reactions, 1 mol % catalyst or more was necessary to obtain high ee. Compared with these reported methods,[1,2] our catalyst system exhibited high activity and enantioselectivity.

Pfaltz and co-workers pointed out the utility of the 2-quinolyl moiety in the asymmetric Heck reaction and asymmetric hydrogenation.[17] The ligand containing a 2-quinolyl moiety gave products with higher ee values than that containing a pyridyl moiety: when a pyridyl moiety was used instead of a 2-quinolyl moiety under the same reaction conditions, the product was obtained with only 55% ee, even with the use of 1 mol % $Cu(OTf)_2$ and 2.5 mol % chiral ligand.[11a] This result clearly indicates that the 2-quinolyl moiety is essential for achieving high enantioselectivity. It should also be mentioned that the use of type III ligands resulted in a remarkable enhancement in reaction rate. When the reaction was carried out under the same conditions (Table 1, Entries 7 and 11: 0.1 mol % $Cu(OTf)_2$, −40 °C, 24 h, >99% conversion) but in the absence of ligand, the product was obtained with a conversion of only 31%.

Under optimum conditions—that is, 0.1 mol % $Cu(OTf)_2$ and 0.25 mol % chiral ligand—we examined the reactions of various cyclic enones, including 2-cyclopenten-1-one (**11**), 2-cyclohexen-1-one (**10**), 4,4-dimethyl-2-cyclohexen-1-one (**12**), and 2-cyclohepten-1-one (**13**), with dimethylzinc and diethylzinc (Table 2). Unfortunately, the reaction of *n*-Bu_2Zn with enones **10** and **11** gave *n*-butylated ketones in low ee (12–36% ee) (Table 2, Entries 5, 6, 13, and 14). We concluded that the bulkiness of the ligand or the dialkylzinc substituents affects the structure of transition state at the stage at which enantioselection takes place. For 2-cyclopenten-1-one (**11**), the

Table 2. Enantioselective 1,4-Addition of Dialkylzinc to a Variety of Enones



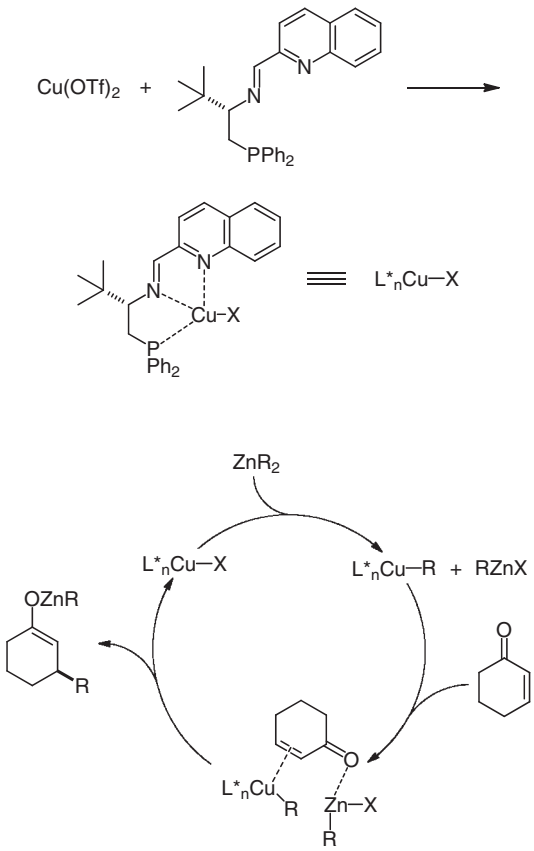
Entry	*n*	R^1	R^2	R^3	Temp /°C	Convn /%[a)]	Ee /%[a)]
1	0	H	Me	*i*-Pr	−20	74	58 (*S*)
2	0	H	Me	*t*-Bu	−20	88	92 (*S*)
3	0	H	Et	*i*-Pr	−40	70	44 (*S*)
4	0	H	Et	*t*-Bu	−40	85	93 (*S*)
5	0	H	*n*-Bu	*i*-Pr	−40	64	36 (*S*)
6	0	H	*n*-Bu	*t*-Bu	−40	67	14 (*S*)
7	1	H	Me	*i*-Pr	−40	59	99 (*S*)
8	1	H	Me	*t*-Bu	−40	35	97 (*S*)
9	1	H	Me	*i*-Pr	−20	88	98 (*S*)
10	1	H	Me	*t*-Bu	−20	77	98 (*S*)
11	1	H	Et	*i*-Pr	−40	99	98 (*S*)
12	1	H	Et	*t*-Bu	−40	99	96 (*S*)
13	1	H	*n*-Bu	*i*-Pr	−40	58	12 (*S*)
14	1	H	*n*-Bu	*t*-Bu	−40	66	18 (*S*)
15	1	Me	Et	*i*-Pr	−20	9	86 (*R*)
16	1	Me	Et	*t*-Bu	−20	6	82 (*R*)
17	2	H	Me	*i*-Pr	−40	44	88 (*S*)
18	2	H	Me	*t*-Bu	−40	32	83 (*S*)
19	2	H	Et	*i*-Pr	−40	61	79 (*S*)
20	2	H	Et	*t*-Bu	−40	47	68 (*S*)

a) Conversions and ee values were determined by GC analysis (Supelco® γ-DEX-225 for Entries 1–16; Supelco® β-DEX-225 for Entries 17–20).

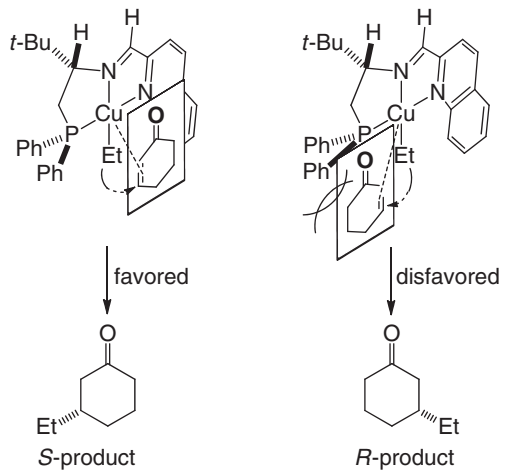
effect of the ligand substituent R^3 was remarkable, with a dramatic increase in enantioselectivity (the ee increased from 58 to 92% in the case of Me_2Zn and from 44 to 93% in the case of Et_2Zn: Table 2, Entries 1–4). In the case of enones **10** and **12**, the nature of R^3 did not markedly influence reactivity or selectivity. For the reaction of 2-cyclohepten-1-one (**13**), the use of a ligand containing an *i*-Pr group gave a higher ee than one containing a *t*-Bu group. This may be compared with the results of the equivalent reaction of 2-cyclopenten-1-one (**11**) (Table 2, Entries 17–20).

Proposed Catalytic Cycle and Enantioselection Mechanism. Considering Reiser's proposed mechanism,[10a] we suggested mechanisms for the catalytic cycle and enantioselection as shown below (Schemes 6 and 7, respectively). 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 (Scheme 6).

To explain the enantioselectivity, we proposed the mechanism shown in Scheme 7. Assuming the molecule is in the

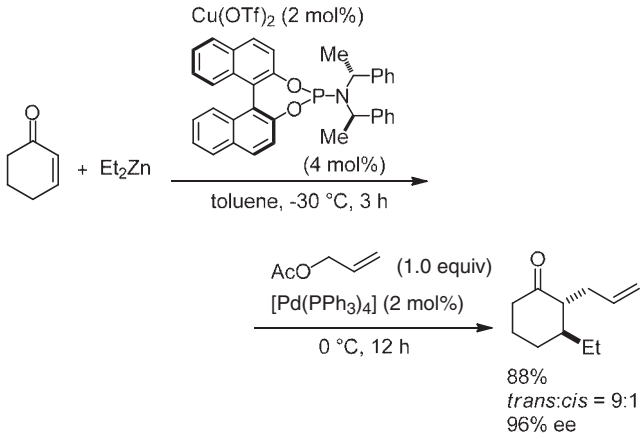


Scheme 6. Proposed catalytic cycle.

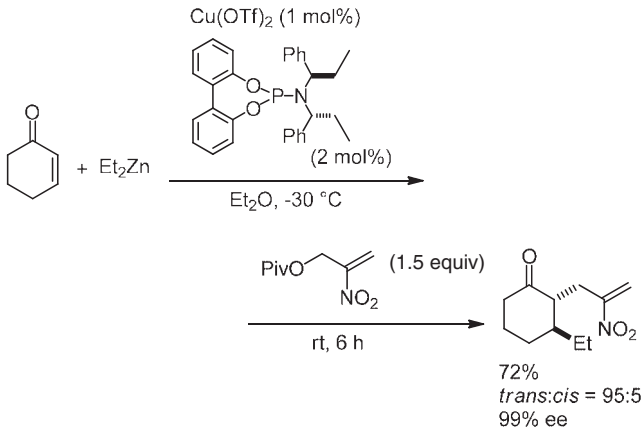


Scheme 7. Enantioselectivity of 1,4-addition.

plane of the paper, we suggest that the enone attacks from front side because of the bulkiness of the *t*-Bu group at the chiral center. In addition, the plane of the enone itself is also fixed by the presence of the quinoline and PPh_2 moieties to avoid steric hindrance: (i) According to Scheme 6, zinc species would be coordinated with carbonyl oxygen as Lewis acid so that the carbonyl group became bulky. As a result, enone approaches the catalyst plane upward. (ii) Since the copper center of the catalyst would activate the olefin moiety, the sp^3



Scheme 8. Asymmetric conjugate addition (Feringa).



Scheme 9. Asymmetric conjugate addition (Alexakis).

carbons in 2-cyclohexenone should parry the PPh_2 group (Scheme 7). Thus, we surmised that the enantioselectivity is triple-controlled by the chiral center, quinoline moiety, and PPh_2 group.

Trapping of Intermediate Zinc Enolates. We next examined the trapping of intermediate zinc enolates by allyl iodide and substituted derivatives.[18] Feringa and his co-workers reported three-component coupling using allyl acetate and a catalytic amount of $[Pd(PPh_3)_4]$,[18a,18b] as shown in Scheme 8.

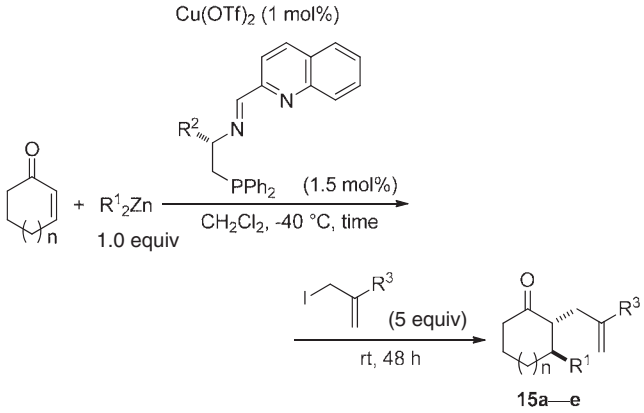
As an example of Pd-free allylation of zinc enolate, Alexakis and his co-workers reported a one-pot procedure by using activated electrophile (Scheme 9).[19]

We investigated direct trapping of intermediate zinc enolates with allyl iodide. The results are summarized in Table 3. The reactions were carried out using 1 mol % $Cu(OTf)_2$ and 2.5 mol % ligand.

The amount of dialkylzinc is the most important factor in this reaction. Because dialkylzinc would behave as a strong base to generate the enolate from monoallylated product, the presence of excess dialkylzinc complicated the reaction so that the diallylated product was obtained. Therefore, it was concluded that strict control of the number of dialkylzinc equivalents was necessary.

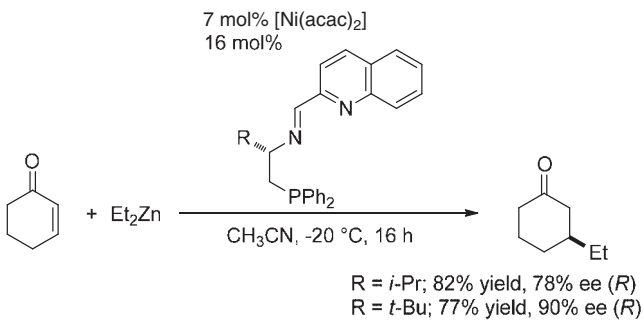
Application of Type III Ligand to a Ni-Catalyzed System. To demonstrate the utility of our new ligand, we examined the

Table 3. Enantioselective 1,4-Addition Followed by Trapping of Zinc Enolate by Allyl Iodides



Entry	n	R^1	R^2	R^3	Time /h	Yield /%[a]	*trans*:*cis*[b]	Ee of *trans* /%[b]
1	1	Et	*i*-Pr	H	5	76	95:5	99[c]
2	1	Me	*i*-Pr	H	24	71	93:7	99[d]
3	1	Et	*i*-Pr	Me	5	85	97:3	99[e]
4	1	Me	*i*-Pr	Me	24	83	96:4	99[f]
5	0	Et	*t*-Bu	H	5	44	95:5	97[d]

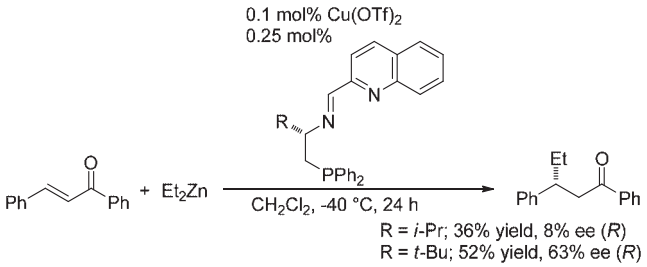
a) Combined yield of *trans*- and *cis*-isomers. b) Determined by GC analysis. The absolute configuration was determined by comparison with literature values of retention time for Entry 1.[18a] c) Supelco® β-DEX-225. d) Supelco® γ-DEX-225. e) CHIRALDEX™ G-TA. f) Supelco® α-DEX-325.



Scheme 10. Ni-Catalyzed asymmetric 1,4-addition.

combination of this ligand and $[Ni(acac)_2]$. Although a large amount of catalyst was required in the Ni system compared with the Cu system, our newly developed ligands **9a** and **9b**—particularly **9b**—gave high enantioselectivity (Scheme 10). The combination of $[Ni(acac)_2]$ with the type III ligands **9a** and **9b** afforded the 1,4-adduct in 78% ee (82% yield) and 90% ee (77% yield), respectively, as shown in Scheme 10. It should be noted that in hitherto reported studies of the utility of Ni catalyst systems in the enantioselective addition of dialkylzincs to enones, most involved addition to acyclic enones; reports of addition to cyclic enones are few.[20] This Ni catalyst system proved to be useful for cyclic enones.

Finally, we examined the reaction of an acyclic enone, chalcone, with Et_2Zn using 0.1 mol % $Cu(OTf)_2$ and the type III ligands **9a** and **9b** to give the 1,4-adduct in 8% ee (36% yield) and 63% ee (52% yield), as shown in Scheme 11.



Scheme 11. Cu-Catalyzed asymmetric 1,4-addition of chalcone.

Conclusion

Our new chiral *N*,*N*,*P*-tridentate ligand promotes highly enantioselective 1,4-addition of dialkylzinc to enones (up to 99% ee) in combination with $Cu(OTf)_2$.[15] The zinc enolate intermediates were trapped with substituted allyl iodides in the absence of a palladium catalyst to give disubstituted ketones with high diastereoselectivity (up to 97:3 *trans*:*cis*) and enantioselectivity (up to 99% ee).

Experimental

General Methods and Materials. 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, α-DEX-325, and G-TA (30 m × 0.25 mm i.d., 0.25 μm film). Chiral HPLC was performed using an instrument equipped with a diode array detector and a chiral column CHIRALPAK AD (250 mm × 4.6 mm × 5 μm).

Synthesis of 2-Bromo-3,5-di-*tert*-butyltoluene (2). To a solution of 3,5-di-*tert*-butyltoluene (5.0 g, 24.4 mmol) in CCl_4 (50 mL) was added Fe powder (0.3 g, 5.1 mmol), and the mixture was cooled to 0 °C. A solution of Br_2 (1.25 mL, 24.4 mmol) in CCl_4 (12 mL) was added with a dropping funnel for 3 h, after which the mixture was stirred at 0 °C for 2 h and then filtered. The filtrate was washed with 10% $NaHCO_3$ (80 mL × 3) and brine (80 mL × 3), dried over Na_2SO_4, and then filtered and evaporated to provide the crude product, which was purified by silica gel column chromatography (hexane) to give the colorless solid **2** (6.83 g, 24.0 mmol, 98%). R_f 0.69 (hexane); mp 27.1–28.1 °C; IR (KBr): ν_{max} (cm^{-1}) 2966, 2869, 1700, 1653, 1476, 1457, 1395, 1363, 1268, 1239, 1210, 1180; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 9H), 1.54 (s, 9H), 2.44 (s, 3H), 7.13 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.6, 30.1, 31.3, 34.5, 37.2, 122.6, 122.9, 125.9, 139.2, 147.3, 149.1; MS m/z: 283 ($M + H^+$); Anal. Calcd for $C_{15}H_{23}Br$: C, 63.61; H, 8.18; N, 0.0%. Found: C, 63.47; H, 8.31; N, 0.27%.

Synthesis of 2-Bromo-3,5-di-*tert*-butyl-1-bromomethylbenzene (3). A mixture of **2** (6.8 g, 24.0 mmol) and NBS (4.7 g, 26.4 mmol) in CCl_4 (9 mL) was stirred at 100 °C for 2 h, and the resulting solution was cooled to room temperature and then evaporated. The crude product was purified by silica gel column chromatography (hexane) to give the colorless solid **3** (8.62 g, 23.8 mmol, 99%). R_f 0.55 (hexane); mp 54.7–55.7 °C; IR (KBr): ν_{max} (cm^{-1}) 2950, 2866, 1700, 1696, 1653, 1589, 1476, 1457, 1437, 1400, 1390, 1363, 1268, 1239; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 9H), 1.54 (s, 9H), 4.72 (s, 2H), 7.33 (d, J = 2.4 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 30.1, 31.1, 34.7, 36.7, 37.5, 122.1, 125.9, 126.4, 138.0, 148.4, 150.0; MS m/z: 361 ($M + H^+$); Anal. Calcd for $C_{15}H_{22}Br_2$: C, 49.75; H, 6.12; N, 0.0%. Found: C, 49.74; H, 6.11; N, 0.22%.

Synthesis of 2-Bromo-3,5-di-*tert*-butylbenzaldehyde (4). A mixture of **3** (17.75 g, 49 mmol) and hexamethylenetetramine (19.2 g, 137 mmol) in chloroform (110 mL) was refluxed for 24 h, and the resulting solution was cooled to room temperature and then evaporated to give a yellow residue. To this residue were added hexamethylenetetramine (19.2 g, 137 mmol) and 50% acetic acid (110 mL), and the solution was refluxed for 24 h. Then, concd HCl (24 mL) was added to the solution and the mixture was stirred at 110 °C for 15 min. The resulting solution was cooled to room temperature and then extracted with Et_2O. The separated organic layer was quickly washed with 2 M HCl (80 mL × 3) and water (80 mL), dried over Na_2SO_4, and then filtered and evaporated to provide the crude material, which was purified by short silica gel column chromatography (80:1 hexane/Et_2O) to give **4** as a colorless oil (6.85 g, 23.0 mmol, 47%). R_f 0.57 (20:1 hexane/ethyl acetate); IR (KBr): ν_{max} (cm^{-1}) 3001, 2963, 2871, 1750, 1689, 1586, 1477, 1427, 1396, 1270, 1230, 1140, 1109; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 9H), 1.58 (s, 9H), 7.73 (d, J = 2.4 Hz, 1H), 7.75 (d, J = 2.4 Hz, 1H), 10.56 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 30.1, 31.0, 34.9, 37.5, 124.6, 124.9, 131.0, 135.3, 148.4, 150.3, 194.1; MS m/z: 297 ($M + H^+$); Anal. Calcd for $C_{15}H_{21}BrO$: C, 60.61; H, 7.12; N, 0.0%. Found: C, 60.24; H, 7.25; N, 0.20%.

Synthesis of 2-Bromo-3,5-di-*tert*-butyl-1-(1,3-dioxolan-2-yl)benzene (5). A mixture of **4** (5.3 g, 17.8 mmol), ethylene glycol (5.52 g, 89 mmol), and *p*-toluenesulfonic acid (0.24 g, 1.4 mmol) in benzene (140 mL) was refluxed for 24 h in a flask equipped with a Dean–Stark apparatus. The resulting solution was separated and the organic layer was washed with water (80 mL × 3) and brine (80 mL), dried over Na_2SO_4, and then filtered and evaporated to provide the crude material, which was purified by silica gel column chromatography (80:1 hexane/Et_2O) to give **5** as a colorless solid (6.1 g, 17.8 mmol, 99%). R_f 0.32 (10:1 hexane/diethyl ether); mp 39–41 °C; IR (KBr): ν_{max} (cm^{-1}) 3455, 2960, 2877, 1636, 1458, 1396, 1362, 1266, 1237, 1207, 1178; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 9H), 1.54 (s, 9H), 4.04–4.12 (m, 2H), 4.13–4.20 (m, 2H), 6.24 (s, 1H), 7.50 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 30.1, 31.2, 34.8, 37.4, 65.3, 103.6, 120.7, 122.4, 126.3, 137.4, 147.6, 149.6; MS m/z: 341 ($M + H^+$); Anal. Calcd for $C_{17}H_{25}BrO_2$: C, 59.83; H, 7.38; N, 0.0%. Found: C, 59.84; H, 7.46; N, 0.26%.

Synthesis of 3,5-Di-*tert*-butyl-2-diphenylphosphino-1-(1,3-dioxolan-2-yl)benzene (6). To a solution of **5** (6.14 g, 18 mmol) in THF (30 mL) and hexane (150 mL), *tert*-butyllithium (24 mL, 1.6 M in pentane, 37.8 mmol) was added dropwise at −45 °C for 20 min. The reaction solution was

stirred at −45 °C for 90 min, and then chlorodiphenylphosphine (4.6 mL, 35.2 mmol) was added. The solution was stirred at −45 °C for 1 h, then allowed to warm to room temperature and stirred for 12 h. The resulting solution was filtered and evaporated and then purified by silica gel column chromatography (50:1 hexane/ethyl acetate) to give the crude product, which was recrystallized from hexane–ethyl acetate under an argon atmosphere to give **6** as colorless crystals (3.5 g, 7.8 mmol, 44%). R_f 0.47 (4:1 hexane/diethyl ether); mp 163–167 °C; IR (KBr): ν_{max} (cm^{-1}) 3047, 2961, 2906, 2880, 1598, 1484, 1392, 1253, 1166; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 9H), 1.66 (s, 9H), 3.28 (dt, $J = 3.8$, 9.4 Hz, 2H), 3.80 (dt, $J = 3.8$, 9.4 Hz, 2H), 5.53 (d, $J_{PC} = 0.8$ Hz, 1H), 7.2–7.3 (m, 10H), 7.50 (d, $J = 2.0$ Hz, 1H), 7.66 (dd, $J_{PC} = 5.2$ Hz, $J_{HH} = 2.0$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 31.1, 33.1, 35.0, 37.9, 64.7, 101.88, 124.1, 125.1, 127.2, 128.2, 129.4, 131.0, 137.9, 143.9, 152.9, 157.1; MS m/z: 447 ($M + H^+$); Anal. Calcd for $C_{29}H_{35}O_2P$: C, 78.00; H, 7.90; N, 0.00%. Found: C, 77.87; H, 8.05; N, 0.10%.

Synthesis of 3,5-Di-*tert*-butyl-2-diphenylphosphinobenzaldehyde (7). To a solution of **6** (0.89 g, 2.0 mmol) in THF (12 mL) and water (1.3 mL) was added *p*-toluenesulfonic acid (9 mg, 0.054 mmol) at room temperature. The mixture was refluxed for 7 h and then cooled to room temperature, diluted with water (24 mL), extracted with Et_2O (30 mL × 3), dried over Na_2SO_4, filtered and evaporated to provide the crude product, which was recrystallized from hexane–ethyl acetate under an argon atmosphere and then purified by silica gel column chromatography (5:1 hexane/ethyl acetate) to give **7** as a yellow solid (0.78 g, 1.94 mmol, 97%). R_f 0.40 (4:1 hexane/diethyl ether); mp 144–146 °C; IR (KBr): ν_{max} (cm^{-1}) 3049, 2965, 2881, 1683, 1589, 1479, 1252; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9H), 1.68 (s, 9H), 7.2–7.3 (m, 10H), 7.81 (d, $J = 2.0$ Hz, 1H), 7.84 (dd, $J_{PC} = 7.4$ Hz, $J_{HH} = 2.0$ Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 31.0, 32.8, 35.2, 38.0, 125.1, 127.8, 128.2, 128.6, 131.0, 133.9, 137.5, 141.3, 153.4, 158.3, 193.4; MS m/z: 403 ($M + H^+$); Anal. Calcd for $C_{27}H_{31}OP$: C, 80.57; H, 7.76; N, 0.0%. Found: C, 80.52; H, 7.96; N, 0.04%.

Synthesis of (*S*)-1-Diphenylphosphino-2-[*N*-(3,5-di-*tert*-butyl-2-diphenylphosphinobenzylidene)amino]-3-methylbutane (8). A mixture of **7** (201 mg, 0.5 mmol), (*S*)-1-diphenylphosphinomethyl-2-methylpropylamine,[15] and Na_2SO_4 in benzene (5 mL) was stirred at 80 °C for 3 days. The resulting mixture was filtered and the filtrate was evaporated to give a yellow residue, which was purified by silica gel column chromatography (10:1 hexane/ethyl acetate) to give the *P*,*N*,*P*-type Schiff base **8** as a yellow solid (268 mg, 0.408 mmol, 82%). R_f 0.65 (5:1 hexane/ethyl acetate); mp 60–62 °C; $[\alpha]_D^{29}$ −42.98 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} (cm^{-1}) 3052, 3013, 2961, 2905, 1949, 1884, 1810, 1628, 1584, 1536, 1479, 1392, 1361, 1340, 1231, 1160; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.49 (d, $J = 6.8$ Hz, 3H), 0.59 (d, $J = 6.8$ Hz, 3H), 1.35 (s, 9H), 1.55 (m, 2H), 1.64 (s, 9H), 2.0–2.1 (m, 1H), 2.2–2.3 (m, 1H), 7.0–7.3 (m, 20H), 7.68 (dd, $J_{PC} = 5.2$ Hz, $J_{HH} = 2.0$ Hz, 1H), 7.98 (d, $J = 2.0$ Hz, 1H), 8.05 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 16.7, 19.5, 31.1, 31.2, 32.1, 33.0, 35.0, 37.9, 71.8, 124.3, 125.6, 127.3, 128.0, 128.1, 128.1, 128.3, 128.5, 129.7, 130.4, 131.3, 132.7, 133.0, 137.3, 138.2, 139.3, 139.4, 142.2, 152.6, 157.6, 162.3; MS m/z: 656 ($M + H^+$); Anal. Calcd for $C_{44}H_{51}NP_2$: C, 80.58; H, 7.84; N, 2.14%. Found: C, 80.49; H, 8.02; N, 2.32%.

General Procedure for Asymmetric 1,4-Addition. A solution of $Cu(OTf)_2$ (0.01 mmol) and ligand (0.025 mmol) in dichloromethane (5 mL) was stirred under an Ar atmosphere at room temperature for 0.5 h. This catalyst solution was used for ten separate experiments (0.1 mol % catalyst load). The enone (1 mmol), the catalyst solution (0.5 mL), and dichloromethane (1 mL) were added to a dried ampoule, and the solution was stirred at room temperature for 10 min and then cooled to −40 °C and stirred for 15 min. Next, Et_2Zn (1.5 mmol, 1.5 mL of 1.0 M solution in hexane) was added slowly, and the resulting mixture was stirred at −40 °C for 24 h and then quenched with a 1 M HCl solution (2 mL). After warming to room temperature, the reaction mixture was extracted with diethyl ether (10 mL × 3).

Conversions and ee values were determined by chiral-phase GC analysis with a γ-DEX-225 (Supelco®) column (30 m × 0.25 mm i.d.) or β-DEX-225 (Supelco®) column (30 m × 0.25 mm i.d.) using undecane as an internal standard.

(*S*)-(−)-3-Methylcyclopentan-1-one (Table 2, Entry 2) (14a): 92% ee (t_R of *S*-isomer, 22.54 min; t_R of *R*-isomer, 22.89 min; GC conditions: γ-DEX-225, initial temp 60 °C, initial time 20 min, progress rate 5 °C min^{-1}, final temp 120 °C); $[\alpha]_D^{29}$ −141.1° (*c* 0.20, $CHCl_3$) (lit.[21a] $[\alpha]_D^{20}$ +152.5° (*c* 1.20, $CHCl_3$, 99% ee (*R*))).

(*S*)-(−)-3-Ethylcyclopentan-1-one (Table 2, Entry 4) (14b): 93% ee (t_R of *S*-isomer, 27.34 min; t_R of *R*-isomer, 28.03 min; GC conditions: γ-DEX-225, initial temp 70 °C, initial time 25 min, progress rate 5 °C min^{-1}, final temp 120 °C); $[\alpha]_D^{29}$ −81.2° (*c* 0.50, $CHCl_3$) (lit.[7a] $[\alpha]_D^{25}$ +94.7° (*c* 1.02, $CHCl_3$, 97% ee (*R*))).

(*S*)-(−)-3-Butylcyclopentan-1-one (Table 2, Entry 5) (14c): 36% ee (t_R of *S*-isomer, 32.59 min; t_R of *R*-isomer, 33.34 min; GC conditions: γ-DEX-225, initial temp 90 °C, initial time 30 min, progress rate 5 °C min^{-1}, final temp 120 °C); $[\alpha]_D^{29}$ −56.0° (*c* 0.75, $CHCl_3$) (lit.[7a] $[\alpha]_D^{25}$ +157.0° (*c* 1.14, $CHCl_3$, 98% ee (*S*))).

(*S*)-(−)-3-Methylcyclohexan-1-one (Table 2, Entry 7) (14d): 99% ee (t_R of *S*-isomer, 33.74 min; t_R of *R*-isomer, 35.10 min; GC conditions: γ-DEX-225, initial temp 70 °C, initial time 30 min, progress rate 5 °C min^{-1}, final temp 120 °C); $[\alpha]_D^{28}$ −13.4° (*c* 0.60, $CHCl_3$) (lit.[7k] $[\alpha]_D^{25}$ −6.7° (*c* 1.14, $CHCl_3$, 45% ee (*S*))).

(*S*)-(−)-3-Ethylcyclohexan-1-one (Table 1, Entry 5) (14e): 99% ee (t_R of *S*-isomer, 42.23 min; t_R of *R*-isomer, 42.76 min; GC conditions: γ-DEX-225, initial temp 80 °C, initial time 40 min, progress rate 10 °C min^{-1}, final temp 150 °C); $[\alpha]_D^{28}$ −15.6° (*c* 1.00, $CHCl_3$) (lit.[4o] $[\alpha]_D^{26}$ −8.8° (*c* 1.60, $CHCl_3$, 82% ee (*S*))).

(*S*)-(−)-3-Butylcyclohexan-1-one (Table 2, Entry 14) (14f): 18% ee (t_R of *S*-isomer, 34.77 min; t_R of *R*-isomer, 35.07 min; GC conditions: γ-DEX-225, initial temp 100 °C, initial time 30 min, progress rate 5 °C min^{-1}, final temp 150 °C); $[\alpha]_D^{27}$ −4.1° (*c* 1.00, $CHCl_3$) (lit.[21b] $[\alpha]_D^{26}$ +19.3° (*c* 1.00, $CHCl_3$, 58% ee (*R*))).

(*S*)-(−)-3-Methylcycloheptan-1-one (Table 2, Entry 17) (14h): 88% ee (t_R of *S*-isomer, 33.92 min; t_R of *R*-isomer, 35.60 min;

GC conditions: β-DEX-225, initial temp 80 °C, initial time 30 min, progress rate 5 °C min^{-1}, final temp 120 °C); $[\alpha]_D^{26}$ −6.2° (*c* 1.00, $CHCl_3$) (lit.[21c] $[\alpha]_D^{26}$ +64.0° (*c* 0.59, CH_3OH, (*R*))).

(*S*)-(−)-3-Ethylcycloheptan-1-one (Table 2, Entry 19) (14i): 79% ee (t_R of *S*-isomer, 48.11 min; t_R of *R*-isomer, 49.47 min; GC conditions: β-DEX-225, initial temp 90 °C, initial time 40 min, progress rate 5 °C min^{-1}, final temp 120 °C); $[\alpha]_D^{30}$ −43.9° (*c* 0.75, $CHCl_3$) (lit.[7k] $[\alpha]_D^{20}$ −52.7° (*c* 1.09, CH_3OH, 86% ee (*S*))).

(*R*)-(−)-1,3-Diphenylpentan-1-one (Scheme 11): 63% ee (t_R of *S*-isomer, 8.11 min; t_R of *R*-isomer, 10.87 min; HPLC conditions: column, CHIRALCEL AD (Daicel); eluent, hexane/2-propanol (99:1); 1.0 mL min^{-1}; $[\alpha]_D^{29}$ −1.7° (*c* 0.50, $CHCl_3$) (lit.[4o] $[\alpha]_D^{26}$ −2.6° (*c* 1.20, $CHCl_3$, 98% ee (*R*))).

General Procedure for Asymmetric 1,4-Addition Followed by Trapping of Zinc Enolate with Allyl Iodide. A solution of $Cu(OTf)_2$ (0.01 mmol) and ligand (0.015 mmol) in dichloromethane (2 mL) was stirred under an Ar atmosphere at room temperature for 0.5 h. Dialkylzinc (1.0 mmol) was added slowly, followed by the enone (1.0 mmol) was added to an ampoule tube and the solution stirred at −40 °C until the reaction was finished. Allyl iodide was added at −40 °C and the reaction solution was stirred at room temperature for 48 h. The reaction was quenched by the addition of saturated NH_4Cl solution (5 mL) in an ice bath. The reaction mixture was extracted with diethyl ether (10 mL × 3), and the organic layer was dried over Na_2SO_4, filtered, and evaporated to give the crude product, which was purified by silica gel column chromatography (10:1 hexane/diethyl ether).

The *trans*:*cis* ratios and ee values were determined by chiral-phase GC analysis using γ-DEX-225 (Supelco®), β-DEX-225 (Supelco®), α-DEX-325 (Supelco®), and G-TA (CHIRALDEX™).

(2*R*,3*S*)-(−)-2-Allyl-3-ethylcyclohexan-1-one (Table 3, Entry 1) (15a): 76% yield, *trans*:*cis* = 95:5, 99% ee for *trans* (t_R of *trans*-isomer: major enantiomer 34.35 min, minor enantiomer 34.77 min; t_R of *cis*-isomer, 36.24 min. GC conditions: β-DEX-225, initial temp 100 °C, initial time 30 min, progress rate 5 °C min^{-1}, final temp 150 °C); $[\alpha]_D^{28}$ −11.1° (*c* 1.02, $CHCl_3$).

(2*R*,3*S*)-(−)-2-Allyl-3-methylcyclohexan-1-one (Table 3, Entry 2) (15b): 71% yield, *trans*:*cis* = 93:7, 99% ee for *trans* (t_R of *trans*-isomer: minor enantiomer 35.42 min, major enantiomer 36.27 min; t_R of *cis*-isomer, 38.65 min. GC conditions: γ-DEX-225, initial temp 90 °C, initial time 30 min, progress rate 5 °C min^{-1}, final temp 150 °C); $[\alpha]_D^{29}$ −14.1° (*c* 1.21, $CHCl_3$).

(2*S*,3*S*)-(−)-3-Ethyl-2-methallylcyclohexan-1-one (Table 3, Entry 3) (15c): 85% yield, *trans*:*cis* = 97:3, 99% ee for *trans* (t_R of *trans*-isomer: major enantiomer 40.71 min, minor enantiomer 41.03 min; t_R of *cis*-isomer, 41.36 min. GC conditions: G-TA, initial temp 100 °C, initial time 30 min, progress rate 5 °C min^{-1}, final temp 150 °C); $[\alpha]_D^{29}$ −4.2° (*c* 1.10, $CHCl_3$); IR (thin film): ν_{max} (cm^{-1}) 3089, 3028, 2884, 1735, 1513, 1401, 1322; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J = 7.4 Hz, 3H), 1.3–1.4 (m, 1H), 1.5 (m, 2H), 1.6–1.8 (m, 5H), 1.9–2.0 (m, 2H), 2.2–2.3 (m, 2H), 2.3–2.5 (m, 3H), 4.67 (s, 1H), 4.75 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.1, 22.4, 24.1, 26.0, 26.8, 36.7, 40.3, 43.6, 53.6, 111.4, 143.7, 213.6; Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18; N, 0.00%. Found: C, 79.84; H, 11.15; N, 0.37%.

(2*S*,3*S*)-(−)-2-Methallyl-3-methylcyclohexan-1-one (Table 3, Entry 4) (15d): 83% yield, *trans*:*cis* = 96:4, 99% ee for *trans* (t_R of *trans*-isomer: minor enantiomer 29.97 min, major enantiomer 30.38 min; t_R of *cis*-isomer, 33.15 min. GC conditions: α-DEX-325, initial temp 100 °C, initial time 30 min, progress rate 5 °C min^{-1}, final temp 150 °C); $[\alpha]_D^{30}$ −9.4° (*c* 1.04, $CHCl_3$).

(2*R*,3*S*)-(−)-2-Allyl-3-ethylcyclopentan-1-one (Table 3, Entry 5) (15e): 44% yield, *trans*:*cis* = 95:5, 97% ee for *trans* (t_R of *trans*-isomer: minor enantiomer 34.88 min, major enantiomer 35.43 min; t_R of *cis*-isomer, 37.18 min. GC conditions: γ-DEX-225, initial temp 90 °C, initial time 30 min, progress rate 5 °C min^{-1}, final temp 150 °C); $[\alpha]_D^{30}$ −4.1° (*c* 0.69, $CHCl_3$); IR (thin film): ν_{max} (cm^{-1}) 3072, 2954, 1741, 1460, 1158; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.9–1.0 (m, 5H), 1.2–1.4 (m, 4H), 1.8–1.9 (m, 1H), 2.0–2.2 (m, 1H), 2.2–2.5 (m, 2H), 5.0–5.1 (m, 2H), 5.7–5.8 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.3, 26.4, 27.0, 32.3, 37.8, 42.5, 54.3, 116.8, 135.5, 220.5; Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59; N, 0.00%. Found: C, 78.65; H, 10.97; N, 0.37%.

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Supporting Information

Details of experimental procedures and characterization data (^{1}H and ^{13}C NMR, IR, mass spectrometry, and elementary analyses) for all new compounds. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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