JOC Notes

P-Chiral *o*-Phosphinophenol as a P/O Hybrid Ligand: Preparation and Use in Cu-Catalyzed Asymmetric Conjugate Addition of Diethylzinc to Acyclic Enones

Yukitoshi Takahashi,[†] Yoshikazu Yamamoto,[†,‡] Kosuke Katagiri,[†,‡] Hiroshi Danjo,[‡] Kentaro Yamaguchi,[‡] and Tsuneo Imamoto*[,†]

Department of Chemistry, Faculty of Science, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan, and Department of Pharmaceutical Technology, Faculty of Pharmaceutical Science at Kagawa Campus, Tokushima Bunri University, 1314-1 Shido, Sanuki, Kagawa 769-2193, Japan

imamoto@faculty.chiba-u.jp

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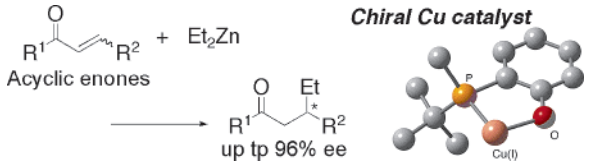

(*S*)-2-(*tert*-Butylmethylphosphino)phenol and its methyl ether were synthesized from *tert*-butyldichlorophosphine via optically active phosphine−boranes as the intermediates. The former compound was used as a P/O hybrid ligand in the Cu-catalyzed asymmetric conjugate addition of diethylzinc to acyclic enones to achieve high enantioselectivity of up to 96%.

Copper- or nickel-catalyzed asymmetric conjugate addition of alkylzinc reagents to α,β-unsaturated carbonyl compounds is one of the most powerful strategies for enantioselective carbon−carbon bond formation, and great attention has been paid to the development of chiral ligands for this reaction.[1] Among a number of ligands known to date, hybrid-type phosphine ligands, including monodentate ones, have been proven to be effective for this organic transformation, owing to their sterically and electronically regulated asymmetric environment.[2] However, whereas most of the ligands provide excellent enantioselectivity in the reactions of cyclic enones, the reactions of acyclic enones result in relatively low enantioselectivity, with only some ligands providing very high enantioselectivity.[3,4]

We have previously prepared new P-chiral P/S and P/N hybrid ligands and demonstrated their high enantioinduction ability in Pd-catalyzed asymmetric allylic alkylations.[5] Of note was that in the reaction that used the P/S hybrid ligands, the P-chirality controlled both the conformation of the cyclic Pd complex and the configuration of the creating S-stereogenic center, eventually providing high enantioselectivity. These facts have inspired us to design and synthesize more electronically different and rigid ligands that are applicable to Cu-catalyzed conjugate additions. As one of the candidates, we selected the *o*-phosphinophenol structure.[6] This ligand is expected to form a highly regulated asymmetric environment based on the rigid *o*-phenylene backbone and the P-stereogenic center possessing the bulky *tert*-butyl group and the smallest alkyl group (methyl group). It is also anticipated that the phenol hydroxy group would coordinate more strongly to a copper atom as an anionic donor site than the phenol ether oxygen atom.[6b] We describe herein the synthesis of (*S*)-2-(*tert*-butylmethylphosphino)phenol and its methyl ether derivative (**3a** and **3b** in Scheme 1) and their enantioinduction abilities in the Cu-catalyzed asymmetric conjugate addition of diethylzinc to acyclic enones.

Synthesis of the desired P/O hybrid ligands was accomplished using phosphine−boranes as the intermediates. The overall reaction sequence is shown in Scheme 1. *tert*-Butyldichlorophosphine was consecutively treated with lithium (1*R*,2*S*,5*R*)-menthoxide, 2-(methoxy)methoxyphenylmagnesium bromide, and borane−THF complex to give phosphine−borane **1a** in 73% yield as a mixture

[†] Chiba University.
[‡] Tokushima Bunri University.

(1) For reviews, see: (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221−3236. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171−196. (c) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346−353. (d) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061. (e) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771−806.

(2) For recent examples, see: (a) de Vries, A. H. M.; Imbos, R.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 1467−1473. (b) Chataigner, I.; Gennari, C.; Piarulli, U.; Ceccarelli, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 916−918. (c) Yin, Y.; Li, X.; Lee, D.-S.; Yang, T.-K. *Tetrahedron: Asymmetry* **2000**, *11*, 3329−3333. (d) Tong, P.-E.; Li, P.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2301−2304. (e) Jensen, J. F.; Søtofte, I.; Sørensen, H. O.; Johannsen, M. *J. Org. Chem.* **2003**, *68*, 1258−1265. (f) Malkov, A. V.; Hand, J. B.; Kocovsky, P. *Chem. Commun.* **2003**, 1948−1949.

(3) For recent examples, see: (a) Hu, X.; Chen, H.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3518−3521. (b) Shadakshari, U.; Nayak, S. K. *Tetrahedron* **2001**, *57*, 8185−8188. (c) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779−781. (d) Wakimoto, I.; Tomioka, Y.; Kawanami, Y. *Tetrahedron* **2002**, *58*, 8095−8097. (e) Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699−3702. (f) Wan, H.; Hu, Y.; Liang, Y.; Gao, S.; Wang, J.; Zheng, Z.; Hu, X. *J. Org. Chem.* **2003**, *68*, 8277−8280. (g) Morimoto, T.; Mochizuki, N.; Suzuki, M. *Tetrahedron Lett.* **2004**, *45*, 5717−5722. (h) Duncan, A. P.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4117−4119.

(4) (a) Bolm, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992**, *125*, 1205−1215. (b) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374−2376. (c) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865−2878. (d) Reetz, M. T.; Gosberg, A.; Moulin, D. *Tetrahedron Lett.* **2002**, *43*, 1189−1191. (e) Alexakis, A.; Benhaim, C.; Rosset, S.; Human, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262−5263. (f) Zhou, H.; Wang, W.-H.; Fu, Y.; Xie, J.-H.; Shi, W.-J.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2003**, *68*, 1582−1584. (g) Alexakis, A.; Polet, D.; Benhaim, C.; Rosset, S. *Tetrahedron: Asymmetry* **2004**, *15*, 2199−2203.

(5) (a) Sugama, H.; Saito, H.; Danjo, H.; Imamoto, T. *Synthesis* **2001**, 2348−2353. (b) Danjo, H.; Higuchi, M.; Yada, M.; Imamoto, T. *Tetrahedron Lett.* **2004**, *45*, 603−606.

(6) For recent examples, see: (a) Serreqi, A. N.; Kazlauskas, R. J. *J. Org. Chem.* **1994**, *59*, 7609−7615. (b) Heinicke, J.; He, M.; Dal, A.; Klein, H.-F.; Hatche, O.; Keim, W.; Flörke, U.; Haupt, H.-J. *Eur. J. Inorg. Chem.* **2000**, 431−440. (c) Suárez, A.; Méndez-Rojas, M. A.; Pizzano, A. *Organometallics* **2002**, *21*, 4611−4621.

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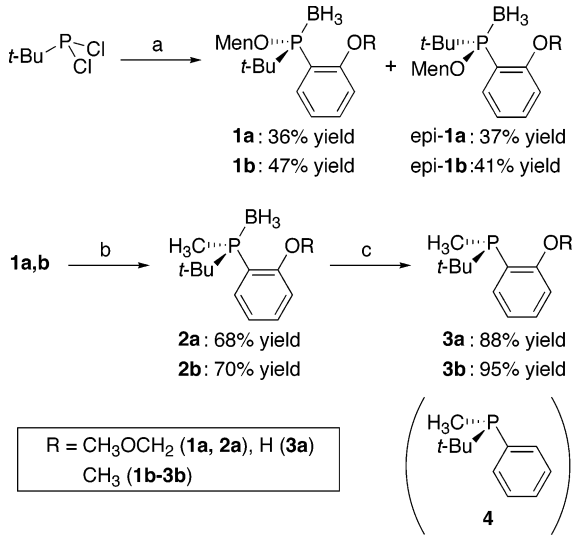
SCHEME 1. Preparation of P-Chiral P/O Hybrid Ligands[a]

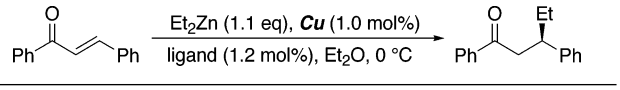


[a] Reagents and conditions: (a) (i) lithium menthoxide, THF, −78 °C to rt, 6 h, (ii) 2-alkoxyphenylmagnesium bromide 0 °C to reflux, 15 h, (iii) BH_3·THF, 0 °C, 2 h; (b) (i) lithium naphthalenide, THF, −40 °C, 2 h, (ii) CH_3I, −40 °C, 1 h; (c) (i) HBF_4·OEt_2, CH_2Cl_2, −20 °C to rt, 15 h, (ii) $NaHCO_3$ aq, 0 °C, 1 h.

of diastereomers. Chromatographic separation of the mixture on a silica gel column afforded each stereoisomer in diastereomerically pure form. Reductive cleavage of the P−O bond with lithium naphthalenide and subsequent addition of methyl iodide produced (2-(methoxy)-methoxyphenyl)(*tert*-butyl)methylphosphine−borane (**2a**) in 68% yield with retention of configuration at the phosphorus atom.[7] Simultaneous removal of the boranato group and the methoxymethyl group was carried out by successive treatments of **2a** with tetrafluoroboric acid and aqueous sodium bicarbonate to give optically active (*S*)-*tert*-butyl(2-hydroxyphenyl)methylphosphine (**3a**) in 88% yield.[8] In a similar manner, (*S*)-*tert*-butylmethyl(2-methoxyphenyl)phosphine (**3b**) was prepared from **1b** via **2b**.[9] The absolute configuration of **2b** was determined to be *S* by X-ray crystallographic analysis.[10] As **2a** could be converted into **2b** by deprotection and subsequent methylation of phenolic oxygen, the absolute configuration of **2a** should be *S* as well.

With these P-chiral P/O hybrid ligands in hand, we tried to perform the highly stereoselective conjugate addition of diethylzinc to α,β-unsaturated enones. Preliminary catalyst screening was performed with various copper salts. The reaction was carried out by mixing chalcone with 1.1 equiv of diethylzinc in the presence of 1.0 mol % of copper salt and 1.2 mol % of chiral ligands in diethyl ether at 0 °C. As shown in Table 1, phosphinophenol **3a** afforded the 1,4-adduct in 54−84% yield and 74−82% enantioselectivity within 1 h in combination with each copper salt. The catalyst performance of the Cu−**3a** system was not affected by the characteristics of the counteranions of copper. This is rationally interpreted by the formation of chelate complex **5** in which the phenoxide moiety is coordinated to Cu(I) as an anionic donor site, which would prevent the intervention of other counteranions in the reaction (Figure 1). In contrast, the reaction with phosphinoanisole **3b** exhibited strong dependence upon the characteristics of the counteranions. The counteranion (X^-) remained on the copper atom to form complex **6**, thereby affecting the reaction.[4e]

TABLE 1. Cu-Catalyzed Asymmetric Conjugate Addition of Diethylzinc to Chalcone with P-Chiral P/O Ligands



entry	ligand	Cu	time (h)	yield[a] (%)	ee[b] (%)
1	**3a**	$Cu(OTf)_2$	0.3	84	77
2	**3b**	$Cu(OTf)_2$	0.3	81	61
3	**3a**	$Cu(OAc)_2$	0.5	64	77
4	**3b**	$Cu(OAc)_2$	0.3	79	40
5	**3a**	$Cu(OCOPh)_2$	0.3	82	81
6	**3b**	$Cu(OCOPh)_2$	0.2	79	40
7	**3a**	$Cu(acac)_2$	0.3	81	81
8	**3b**	$Cu(acac)_2$	0.3	84	19
9	**3a**	$CuCl_2$	0.3	77	81
10	**3b**	$CuCl_2$	0.5	43	22
11	**3a**	$CuCO_3$	0.8	54	74
12	**3b**	$CuCO_3$	24	5	4
13	**3a**	CuOTf	0.3	83	82
14	**3b**	CuOTf	0.3	80	54
15	**3a**	CuI	0.5	73	80
16	**3b**	CuI	3.5	27	7

[a] Isolated yield. [b] Determined by CSP-HPLC analysis.

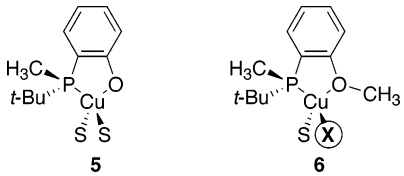


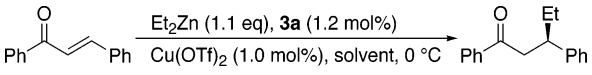
FIGURE 1. Cu complexes of P-chiral P/O ligands.

Solvent dependence was investigated as the second screening step (Table 2). Ligand **3a** gave high yield and stereoselectivity in acyclic ethers (entries 1−3), hydrocarbons (entries 4 and 5), and dichloromethane (entry 6). On the other hand, cyclic ethers gave poor enantioselectivity (entries 7−9). The use of acetonitrile, in particular, resulted in the decrease of both reactivity and selectivity (entry 10). The catalyst performance of the system might be strongly affected by the coordination ability of the solvent used.

The conjugate addition was next performed at various temperatures (Table 3). It is worth noting that lowering the temperature decreased the enantioselectivity, and opposite enantioselectivity was observed at −78 °C when **3a** was used as a ligand (entries 1−5). On the other hand, ligand **3b** afforded higher enantioselectivity at lower temperatures (entries 6 and 7). A similar result was observed when the monodentate phosphine ligand, (*S*)-*tert*-butyl(methyl)phenylphosphine (**4**), was used (entries

(7) Oshiki, T.; Hikosaka, T.; Imamoto, T. *Tetrahedron Lett.* **1991**, *32*, 3371−3374.
(8) McKinstry, M.; Livinghouse, T. *Tetrahedron Lett.* **1994**, *35*, 9319−9322.
(9) Imamoto, T.; Matsuo, M.; Nonomura, T.; Kishikawa, K.; Yanagawa, M. *Heteroatom Chem.* **1993**, *4*, 475−486.
(10) CCDC-280439 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

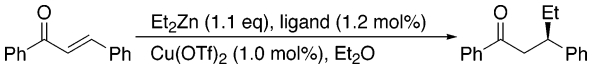
TABLE 2. Cu-Catalyzed Asymmetric Conjugate Addition of Diethylzinc to Chalcone with P-Chiral P/O Ligand 3a



entry	solvent	time (h)	yield[a] (%)	ee[b] (%)
1	Et_2O	0.3	84	77
2	DME	1.2	70	76
3	*t*-$BuOCH_3$	0.3	82	78
4	toluene	0.5	80	75
5	hexane	0.3	62	76
6	CH_2Cl_2	0.3	81	83
7	THF	1	83	−7
8	THP	0.5	82	39
9	dioxane	1	81	26
10	CH_3CN	5	41	7

[a] Isolated yield. [b] Determined by CSP-HPLC analysis.

TABLE 3. Cu-Catalyzed Asymmetric Conjugate Addition of Diethylzinc to Chalcone with P-Chiral Phosphine Ligands



entry	ligand	*T* (°C)	time (h)	yield[a] (%)	ee[b] (%)
1	**3a**	−78	24	22	−13
2	**3a**	−40	20	78	49
3	**3a**	−20	0.7	86	64
4	**3a**	0	0.2	84	77
5	**3a**	25	0.2	75	77
6	**3b**	−78	24	66	80
7	**3b**	0	0.3	81	61
8	**4**	−78	24	44	41
9	**4**	0	0.2	84	26

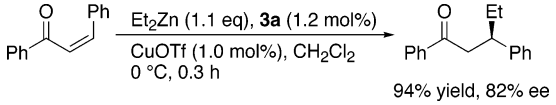
[a] Isolated yield. [b] Determined by CSP−HPLC analysis.

8 and 9). The unusual temperature dependence of the enantioselectivities observed by the use of **3a** cannot be well understood, but we suggest that there might exist more than two active catalyst species with different stereoinduction modes or the reaction might be largely controlled by entropy factor.

Using the conditions established as above, the conjugate additions of diethylzinc to various acyclic α,β-unsaturated ketones were carried out, and the results are summarized in Table 4.[11] In almost all cases, the reactions proceeded smoothly and were completed within 0.3−1.5 h to give the addition products in high to excellent yields. In the conjugate addition to chalcone, the best result was obtained by the use of copper(I) triflate in dichloromethane, for which 1,3-diphenylpentan-1-one was obtained in 88% yield and 85% enantioselectivity (entry 1).[12] The reaction proceeded smoothly with

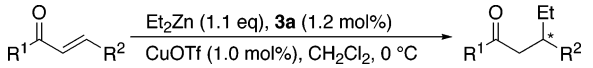
(11) As a representative cyclic enone, 2-cyclohexenone was used in the conjugate addition. However, 3-ethylcyclohexanone of only 5% yield and 8% ee was obtained even after 24 h with the Cu−**3a** system. By contrast, 74% yield of the product was obtained by the use of **3b** within 0.5 h, albeit with low selectivity (18% ee).

(12) The conjugate addition to *cis*-chalcone was examined next. The reaction was completed within 20 min, and 82% ee (*R*) of the product was obtained in 94% yield.



94% yield, 82% ee

TABLE 4. Cu-Catalyzed Asymmetric Conjugate Addition of Diethylzinc to Various Enones with P-Chiral P/O Ligands 3a



entry	R^1	R^2	time (h)	yield[a] (%)	ee[b] (%)
1	Ph	Ph	0.3	88	85 (*R*)
2[c]	Ph	Ph	1.5	77	78 (*R*)
3	Ph	4-$CH_3OC_6H_4$	0.3	93	94 (*R*)
4	Ph	4-$(CH_3)_2NC_6H_4$	1	91	96 (−)
5	Ph	4-ClC_6H_4	1	92	80 (*R*)
6	Ph	4-$CF_3C_6H_4$	0.5	86	61 (+)
7	Ph	1-naphthyl	0.3	98	73 (+)
8	Ph	*n*-pentyl	1	95	64 (−)
9	Ph	^{i}Pr	1	90	65 (+)
10	Ph	*t*-Bu	24	5	74 (−)
11	4-$CH_3OC_6H_4$	Ph	0.5	84	94 (+)
12	4-ClC_6H_4	Ph	1	90	76 (+)
13	^{i}Bu	Ph	0.5	94	92 (−)
14	Cy	Ph	1	90	87 (−)
15	*n*-hexyl	Ph	1	97	90 (−)
16	*n*-hexyl	Me	0.2	77	91 (−)
17	Me	*n*-pentyl	5.0	63	77 (*S*)

[a] Isolated yield. [b] Determined by CSP-HPLC analysis. [c] 0.1 mol % of CuOTf and 0.12 mol % of **3a** were used.

slightly diminished stereoselectivity even with the use of 0.1 mol % catalyst (entry 2). The stereoselectivity was affected by the electronic nature of the substituent on the β-phenyl group. The substitution with a methoxy or a dimethylamino group at the para position led to an increase in enantioselectivity (entries 3 and 4), whereas a chloro or trifluoromethyl substitution decreased the selectivity (entries 5 and 6). Alkyl substituents at the β-position were responsible for the diminished stereoselectivity (entries 8 and 9). We also attempted to use various aryl and alkyl ketones, including fully aliphatic ketones, and high to excellent enantioselectivity was obtained in each case (entries 11−17).

In conclusion, P-chiral phosphinophenol and phosphinoanisole were prepared as new chiral P/O hybrid ligands and used in the Cu-catalyzed asymmetric conjugate addition of diethylzinc to α,β-unsaturated carbonyl compounds. It was revealed that the P-chiral phosphinophenol exhibits high enantioselectivities up to 96% in the reactions of various chalcone derivatives.

Experimental Section

General experimental details can be found in the Supporting Information.

Preparation of (*S*)-*tert*-Butyl((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)(2-(methoxy)methoxyphenyl)phosphine−Borane (1a). Lithium (1*R*,2*S*,5*R*)-menthoxide (105 mmol, 90 mL of 1.16 M THF solution) was added dropwise during 4 h into a solution of *tert*-butyldichlorophosphine (100 mmol, 15.9 g) in dry THF (200 mL) with stirring at −78 °C under argon atmosphere. After addition, the cooling bath was removed, and stirring was continued for 2 h. The mixture was cooled at 0 °C, and 2-(methoxy)methoxyphenylmagnesium bromide (110 mmol, 141 mL of 0.78 M THF solution) was slowly added. The mixture was stirred for 15 h under reflux conditions. The borane−THF complex (120 mmol, 104 mL of 1.15 M THF solution) was added at 0 °C, and stirring was continued for 2 h. The reaction mixture was carefully poured into a mixture of ice−water containing HCl and diluted with diethyl ether. The organic

layer was separated, and the aqueous layer was extracted with diethyl ether. The combined extracts were washed with saturated $NaHCO_3$ and brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography (hexane/ethyl acetate = 20/1) to give the diastereomeric mixture of phosphine−borane, and the diastereomeric mixture was resolved by column chromatography on silica gel (hexane/$CHCl_3$ = 4/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (ddd, J = 11.1, 7.7, 1.8 Hz, 1H), 7.41 (dddd, J = 8.4, 7.3, 1.8, 1.0 Hz, 1H), 7.17 (ddd, J = 8.4, 4.1, 0.9 Hz, 1H), 7.04 (dddd, J = 11.1, 7.3, 1.6, 0.9 Hz, 1H), 5.18 (d, J = 5.2 Hz, 1H), 5.10 (d, J = 5.1 Hz, 1H), 4.29 (dq, J = 4.7, 9.9 Hz, 1H), 3.50 (s, 3H), 2.24−2.18 (m, 1H), 1.79−1.70 (m, 1H), 1.67−1.56 (m, 2H), 1.50−1.39 (m, 1H), 1.34−1.27 (m, 1H), 1.20−1.08 (m, 10H), 1.00−0.78 (m, 5H), 0.72 (d, J = 7.0 Hz, 3H), 0.48 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 135.0 (d, J = 10.0 Hz), 133.0 (d, J = 2.0 Hz), 120.8 (d, J = 10.0 Hz), 119.8 (d, J = 50.0 Hz), 114.4 (d, J = 5.0 Hz), 94.9, 79.9 (d, J = 5.0 Hz), 56.4, 49.0 (d, J = 4.0 Hz), 43.9 (d, J = 2.0 Hz), 34.0, 33.7, 25.2, 25.2 (d, J = 8 Hz), 22.6, 22.2, 21.1, 15.4. ^{31}P NMR (202 MHz, $CDCl_3$): δ 122.9 (d, J = 78.9 Hz). IR (NaCl plates): 2955, 2390, 1590, 1475, 1155, 990 cm^{-1}. $[\alpha]^{22}_D$ = −101.4 (c = 1.06, $CHCl_3$); HRMS calcd for $C_{22}H_{40}BKO_3P$ $[M + K]^+$ 433.2445, found 433.2467.

Preparation of (*S*)-*tert*-Butyl(2-(methoxy)methoxyphenyl)methylphosphine−Borane (2a). Lithium naphthalenide (49 mmol, 49 mL of 1.0 M THF solution) was slowly added to a solution of a phoshine−borane **1a** (9.9 mmol, 3.92 g) in dry THF (20 mL) at −40 °C under argon atmosphere. After the mixture was stirred for 2 h, methyl iodide (49 mmol, 3.0 mL) was added, and stirring was continued for an additional 1 h. The reaction was quenched by the addition of 1 M HCl and diluted with diethyl ether, and the organic layer was separated from the aqueous solution. The aqueous layer was extracted with diethyl ether. The combined extracts were washed with saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (ddd, J = 13.0, 7.6, 1.7 Hz, 1H), 7.44 (dddd, J = 8.3, 7.3, 1.7, 1.1 Hz, 1H), 7.18 (ddd, J = 8.3, 3.2, 0.9 Hz, 1H), 7.08 (dddd, J = 7.6, 7.3, 1.6, 0.9 Hz, 1H), 5.22 (d, J = 6.7 Hz, 1H), 5.19 (d, J = 7.1 Hz, 1H), 3.49 (s, 3H), 1.71 (d, J = 10.4 Hz), 1.15 (d, J = 14.1 Hz, 9H), 0.73 (br q, J = 89.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 137.4 (d, J = 13.1 Hz), 133.1, 121.7 (d, J = 11.0 Hz), 115.6 (d, J = 46.1 Hz), 113.9 (d, J = 4.0 Hz), 94.5, 56.5, 29.9 (d, J = 33.1 Hz), 25.8 (d, J = 3.0 Hz), 7.1 (d, J = 39.1 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 28.0 (dd, J = 52.5, 123.2 Hz). IR (KBr): 2375, 1475, 1155, 1070, 990, 765 cm^{-1}. Mp = 49−50 °C. $[\alpha]^{22}_D$ = +30.0 (c = 1.00, $CHCl_3$). HRMS calcd for $C_{13}H_{24}BKO_2P$ $[M + K]^+$ 293.1244, found 293.1242. Anal. Calcd for $C_{13}H_{24}BO_2P$: C, 61.44; H, 9.52. Found: C, 61.66; H, 9.49.

Preparation of (*S*)-*tert*-Butyl(2-hydroxyphenyl)methylphosphine (3a). An oven-dried 30 mL round-bottomed flask was charged with phosphine−borane **2a** (0.43 mmol, 109 mg) and degassed CH_2Cl_2 (2 mL) under argon. To the solution was added tetrafluoroboric acid in diethyl ether (6.46 mmol, 0.887 mL) at −20 °C. After the solution was stirred at room temperature for 15 h, degassed saturated $NaHCO_3$ was added at 0 °C. After the solution was stirred at ambient temperature for 1 h, the organic layer was separated, and the aqueous layer was extracted with degassed diethyl ether three times. The combined extracts were dried over Na_2SO_4 under argon. The solution was passed through a column of silica gel using degassed diethyl ether. The eluent was evaporated under reduced pressure to give free phosphine as white crystal. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30−7.25 (m, 2H), 6.95−6.90 (m, 2H), 1.30 (d, J = 6.2 Hz, 3H), 1.02 (d, J = 13.4 Hz, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.2 (d, J = 21.0 Hz), 131.6 (d, J = 3.0 Hz), 131.1, 119.9, 114.8, 29.0 (d, J = 4.0 Hz), 26.7 (d, J = 13.0 Hz), 4.2 (d, J = 13.1 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ −43.8 (s). HRMS calcd for $C_{11}H_{17}OP$ $[M]^+$ 196.1017, found 196.1013.

General Procedure for Copper-Catalyzed Asymmetric Conjugate Addition. A mixture of copper(I) triflate (0.03 mmol) and phosphine **3** (0.036 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 1 h under argon. The mixture was added to the enone (3.0 mmol) and cooled to 0 °C. Diethylzinc (3.3 mmol, 3.3 mL of 1.0 M solution in hexane) wad added dropwise and stirred at 0 °C until the starting enone had been completely consumed by monitoring with thin-layer chromatography. The reaction mixture was quenched with 1 M HCl, and the mixture was extracted with diethyl ether. The combined organic layers were washed with $NaHCO_3$ and brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography. The enantiomeric excess of the product was determined by chiral GLC or HPLC.

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Supporting Information Available: Additional experimental procedures, spectroscopic data for *epi*-**1a**, **3b**, (*S*)-*tert*-butyl(2-hydroxyphenyl)methylphosphine−borane (**7**), and 1,4-adducts, copies of NMR spectra for all new phosphine compounds, and X-ray crystallographic data for **2b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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