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[2.2]Paracyclophane-Derived Monodentate Phosphoramidite Ligands for Copper-Catalyzed Asymmetric Conjugate Addition of Diethylzinc to Substituted Chalcones

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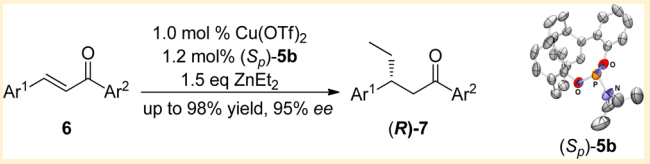
Supporting Information

ABSTRACT: Copper-catalyzed asymmetric conjugate addition of diethylzinc to chalcones could be realized by using [2.2]paracyclophane-derived monodentate phosphoramidite ligands. The excellent yield and enantioselectivity (up to 98% yield and 95% enantiomeric excess) could be realized with low catalyst loading of 1.0 mol % and low ligand loading of 1.2%.



INTRODUCTION

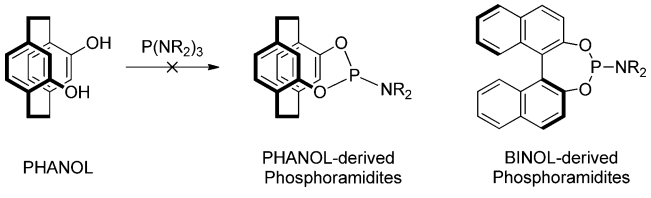
Conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is among the most useful methods for C−C bond formation and has broad application in the synthesis of numerous biologically active compounds.[1] Many chiral auxiliaries and stoichiometric reagents have been used in this type of reaction with high stereoselectivity.[1a,e,2] Catalytic enantioselective additions have also been developed, among which the use of organozinc reagents as donors and copper complexes with phosphorus ligands as catalysts afforded the most successful results.[3] Many of these phosphorus ligands are monodentate phosphites and phosphoramidites. One of the pioneering examples was phosphoramidites derived from 1,1′-bi-2-naphthol (BINOL), and some others derived from tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL), biphenol, and 1,1′-spirobiindane-7,7′-diol (SPINOL) were also effective for this reaction.

Modifications of this type of ligand on their backbones and exocyclic amines or alcohols were reported, and some of the modified ligands demonstrated excellent enantioselectivities in the reactions of organozinc reagents with cyclic or acyclic enones. However, the structures of these phosphoramidite ligands were limited to axially and centrally chiral backbones, and until now planar chiral phosphoramidite and phosphite ligands were rarely studied.[3j−l,4] As to the [2.2]paracyclophane backbone,[5] chiral monodentate phosphite ligand derived from 4-hydroxyl[2.2]paracyclophane[4b] and bidentate phosphite ligands[4a] derived from 4,5-dihydroxyl[2.2]paracyclophane were reported recently. Due to its high rigidity, it is interesting to explore the potential of [2.2]paracyclophane in the research field of chiral monodentate phosphoramidite or phosphite ligands. Herein we describe the preparation of 4,12-disubstituted [2.2]paracyclophane derived monodentate phosphoramidite ligands and their application in the copper-catalyzed asymmetric conjugate addition to acyclic enones.

RESULTS AND DISCUSSION

Our work started from the chiral 4,12-dihydroxy[2.2]-paracyclophanediol (PHANOL),[6] for it is the simplest 4,12-disubstituted [2.2]paracyclophane containing two hydroxyl groups. However, PHANOL cannot be modified to its monophosphoramidite. The failure might be ascribed to PHANOL's high rigidity, and we think that structural rigidity and flexibility of chiral ligands is also an important issue in asymmetric catalysis involving [2.2]paracyclophane-based ligands (Scheme 1).[7]

Scheme 1. Some Skeletons for Phosphoramidite Ligands



Then our attention turned to compound **1**.[8] Methylation of (S_P)-**2** followed by Suzuki coupling with *o*-methoxyphenylboronic acid afforded dimethoxyl compound (S_P)-**4**, which could be used to prepare (S_P)-**1** after removal of the two methyl groups by reaction with BBr_3. Planar chiral phosphoramidite ligands **5a−c** were easily prepared from (S_P)-**1**. Heating the mixture of diol (S_P)-**1** and $P(NMe_2)_3$ or $P(NEt_2)_3$ in toluene for 4 h gave (S_P)-**5a** or (S_P)-**5b** in about 60% yield (Scheme 2).

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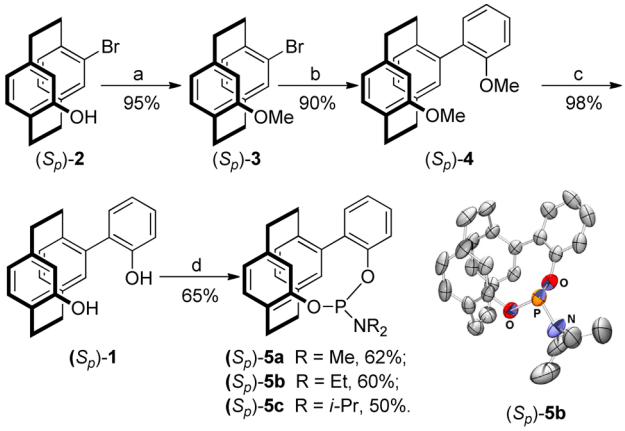
The structure of (S_P)-**5b** was confirmed by X-ray analysis. (S_P)-**5c** was produced by subsequent condensation of (S_P)-**1** with PCl_3 and *i*-Pr_2NH.

Scheme 2. Preparation of Chiral Phosphoroamidite Ligands

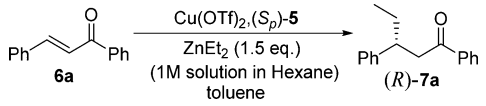


a) K_2CO_3, MeI in THF; b) $Pd(PPh_3)_4$ K_2CO_3, *o*-$MeOC_6H_4B(OH)_2$ in toluene, reflux; c) BBr_3 in DCM, -78°C; d) For **5a** & **5b**, $P(NR_2)_3$ in toluene, reflux; for **5c**, PCl_3 then *i*-Pr_2NH.

Chalcone (**6a**) served as substrate to study the behavior of ligand (S_P)-**5** in the asymmetric conjugate addition. The reactions were carried out in the presence of $Cu(OTf)_2$ and the chiral ligands in toluene. The use of 4 mol % (S_P)-**5a** and 2 mol % $Cu(OTf)_2$ at room temperature afforded the product (**7a**) of *R* configuration in 87% yield and 87% ee (Table 1, entry 1). Slightly higher yield and enantiomeric excess values could be obtained when the reaction was carried out at lower temperature (Table 1, entry 2). Reaction at much lower temperature (−30 °C) did not promote yield and enantioselectivity (Table 1, entry 3). The yield and ee value remained at the same level when loading of the catalyst was reduced (Table 1, entry 4). (S_P)-**5b** and (S_P)-**5c** were subsequently investigated at different temperatures and with different loadings. A great improvement of the enantioselectivity (up to 95% ee) was achieved by employing (S_P)-**5b** as ligand (Table 1, entries 5−8). Temperature lower than 0 °C and catalyst loading higher than 1 mol % were found unnecessary for obtaining good results (Table 1, entries 5−7). Use of $ZnEt_2$ solution in toluene instead of $ZnEt_2$ solution in hexane did not affect the result either (Table 1, entry 8). (S_P)-**5c** seemed less efficient than (S_P)-**5b** since the ee dropped to 87% (Table 1, entries 9−12). It is conspicuous that (S_P)-**5b** is the most appropriate ligand for the reaction. (S_P)-**5b**/$Cu(OTf)_2$ ratio was brought down from 2.0:1 to 1.2:1 and high enantioselectivities were maintained (Table 1, entries 7 and 13−17). When the ratio came down to 1.0:1, the enantioselectivity began to slightly decrease. Therefore, the optimal condition was chosen as 1 mol % $Cu(OTf)_2$, 1.2 mol % ligand, and 0 °C (Table 1, entry 16).

Behaviors of different copper salts used in the reaction were then explored, and the results are listed in Figure 1a. Cu(I) and Cu(II) salts could result in high enantioselectivity (columns 1−5, Figure 1a). Decreasing volume of anions correlates with loss of enantioselectivity (columns 1 vs 3 and 2 vs 4, Figure 1a). For single anions, the smaller the anion, the lower the ee value afforded (columns 6−8, Figure 1a). However, excellent results could be observed when BF_4^- and PF_6^- salts were used (columns 9 and 10, Figure 1a). A modest negative nonlinear

Table 1. Enantioselective Conjugate Addition of $ZnEt_2$ to Chalcone



entry	$Cu(OTf)_2$ (mol %)	ligand (mol %)	T (°C)	t (h)	yield[a] (%)	ee[b] (%)
1	2.0	(S_P)-**5a** (4.0)	rt	12	87	87
2	2.0	(S_P)-**5a** (4.0)	−20	1	93	89
3	2.0	(S_P)-**5a** (4.0)	−30	3	93	87
4	1.0	(S_P)-**5a** (2.0)	−20	3	92	88
5	2.0	(S_P)-**5b** (4.0)	−20	3	93	93
6	2.0	(S_P)-**5b** (4.0)	0	2	96	95
7	1.0	(S_P)-**5b** (2.0)	0	2	95	95
8[c]	1.0	(S_P)-**5b** (2.0)	0	6	95	95
9	1.0	(S_P)-**5c** (2.0)	−20	20	87	80
10	2.0	(S_P)-**5c** (4.0)	−20	20	86	86
11	1.0	(S_P)-**5c** (2.0)	0	12	89	82
12	2.0	(S_P)-**5c** (4.0)	0	12	91	87
13	2.0	(S_P)-**5b** (3.6)	0	2	91	95
14	1.0	(S_P)-**5b** (1.6)	0	2	95	95
15	1.0	(S_P)-**5b** (1.4)	0	2	95	95
16	1.0	(S_P)-**5b** (1.2)	0	2	94	95
17	1.0	(S_P)-**5b** (1.0)	0	2	90	94

[a]Isolated yield. [b]Determined by chiral HPLC. [c]1.0 M $ZnEt_2$ solution in toluene was used.

effect implied the existence of a more reactive racemic complex in the catalytic system (Figure 1b).

The scope of 1,4-addition of $ZnEt_2$ to substituted chalcones catalyzed by $Cu(OTf)_2$/**5b** were then explored in the best-performing catalytic system, and the results are listed in Table 2. When Ar^1 was a para- or meta-substituted phenyl group, chalcones bearing either electron-donating or -withdrawing groups have been successfully converted to the corresponding chiral ketones with high yield and enantioselectivities (Table 2, entries 1−6, 90−97% yield, 93−95% ee). However, changing Ar^1 to *o*-bromophenyl or *o*-tolyl group greatly reduced the selectivities (55% or 71% ee) while the yield remained high (Table 2, entries 7 and 12). Reaction at lower temperature (−40 °C) did not help much in enhancing enantioselctivity (Table 2, entry 8). Three substrates with different para-substituted Ar^2 were then tested, and satisfactory results could be observed when the aryl group was methoxy-substituted (Table 2, entry 9, 90% yield, 94% ee) or bromo-substituted (Table 2, entry 11, 98% yield, 95% ee); with *p*-chlorophenyl group, the yield was still high while the ee was slightly lower than others (Table 2, entry 10, 95% yield, 87% ee). Some alkyl substrates **6m** and **6n** were also tested, but unfortunately none

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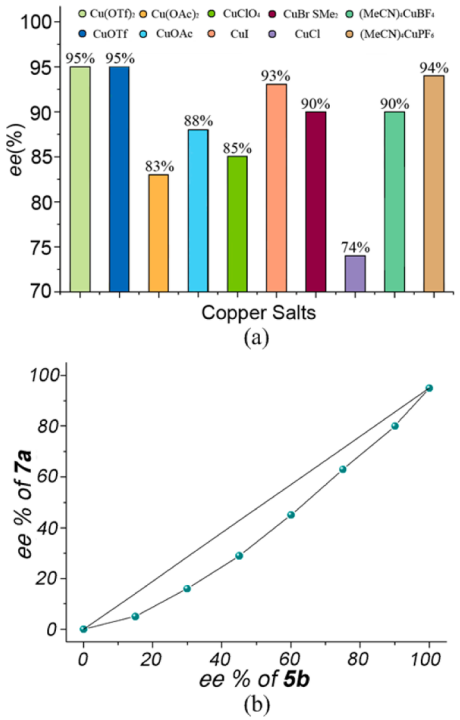


Figure 1. (a) Asymmetric catalytic conjugate addition with (S_P)-**5b** and various copper salts. (b) Nonlinear effect of ligand (S_P)-**5b**.

of these reacted (Table 2, entries 13 and 14). Double aromatic groups were needed in our methodology, perhaps due to the existence of intermolecular weak interactions.

CONCLUSION

In summary, monodentate phosphoramidite-type ligands (S_P)-**5a/b/c** derived from a flexible 4,12-disubstituted[2.2]-paracyclophane were developed. They are highly efficient in copper-catalyzed asymmetric conjugate addition of diethylzinc to substituted chalcones; the results obtained (up to 95% ee) were among the best in this field. To the best of our knowledge, higher than 95% ee have been usually obtained by use of bidentate P,N-ligands,[9] and until now only a fewmethodologies have been reported at low temperatures.[3b,10] Further studies to explore the scope of these ligands in more asymmetric catalytic reactions are currently in progress.

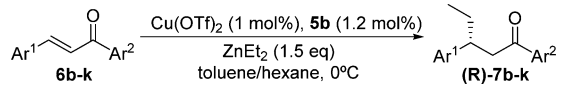
EXPERIMENTAL SECTION

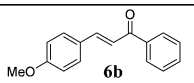
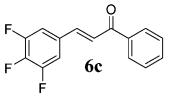
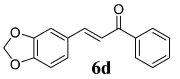
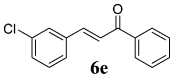
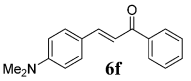
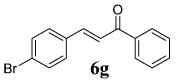
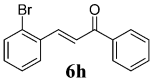
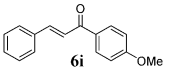
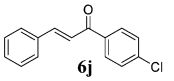
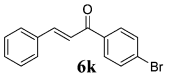
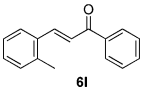
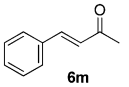
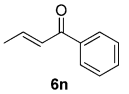
General Remarks. Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. All reactions were carried out under argon atmosphere. Flash chromatography was performed on silica gel H (10−40 μm). Standard reagents and solvents were purified according to known procedures. Melting points are uncorrected. NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm) relative to $CHCl_3$ at δ = 7.26 ppm for ^{1}H NMR and to $CDCl_3$ at δ = 77.00 ppm for ^{13}C NMR. (R_P)-PHANOL,[6a] (S_P)-**2**,[6d] and (S_P)-**3**[7c] and were prepared according to the literature.

Procedure for Preparation of (S_P)-4-Bromo-12-methoxy-[2.2]paracyclophane [(S_P)-3]. (S_P)-**3** was prepared according to the procedure for synthesizing (R_P)-**3**.[7c] All spectroscopic data were in accordance with that reported. mp 167−169 °C (lit.[7c] 181 °C). $[\alpha]_D^{24.6}$ = +10.3 (c = 0.50, chloroform).

Procedure for Preparation of (S_P)-4-Methoxy-12-(2-methoxyphenyl)[2.2]paracyclophane [(S_P)-4]. A mixture of (S_P)-**3** (1.95 g, 6.1 mmol), 2-methoxyphenylboronic acid (1.12 g, 7.4 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (50 mg, 61 μmol), K_3PO_4 (2.61 g, 12.3 mmol), and 10 mL of toluene was heated at 110 °C for 2 h, cooled to room temperature, and filtered. After the solid was washed with dichloromethane, the combined filtrate was concentrated and purified by chromatography on a silica gel column with 40:1 petroleum ether/EtOAc to give (S_P)-**4** as a colorless oil, 2.01 g, 95% yield. $[\alpha]_D^{20.8}$ = −120.0 (c = 0.30, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, J = 7.5, 1.5 Hz, 1H), 7.36 (dt, J = 8.2, 1.7 Hz, 1H), 7.16 (t, J = 7.1 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.83 (d, J = 1.3 Hz, 1H), 6.60−6.56 (m, 2H), 6.44 (dd, J = 7.6, 1.2 Hz, 1H), 6.37 (d, J = 7.6 Hz, 1H), 6.03 (s, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.49−3.40 (m, 1H), 3.15−2.94 (m, 4H), 2.91−2.79 (m, 1H), 2.74−2.58 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 156.0, 142.4, 138.8, 135.3, 134.4, 133.2, 132.5, 130.7, 130.6, 129.4, 128.4, 128.2, 125.8, 120.6, 117.2, 110.8, 57.3, 55.3, 34.3, 33.9, 33.6, 31.0. IR (cm^{-1}) 2928, 1596, 1495, 1409, 1254, 1033, 755.

Table 2. Enantioselective Conjugate Addition of $ZnEt_2$ to Substituted Chalcones[a]



entry	Substrate	yield (%)[a]	ee (%)[b]
1	 6b	93	95
2	 6c	90	95
3	 6d	95	95
4	 6e	97	93
5	 6f	95	93
6	 6g	95	95
7	 6h	96	55
8		95[c]	58[c]
9	 6i	90	94
10	 6j	95	87
11	 6k	98	95
12	 6l	95	71
13	 6m	No reaction	-
14	 6n	No reaction	-

[a]Isolated yield. [b]Determined by chiral HPLC. [c]Reaction was carried out at −40 °C.

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MS (EI) m/z 344 [M^+] (24.2). HRMS (EI-quadrupole) calcd for $C_{24}H_{24}O_2$ 344.1776, found 344.1773.

Procedure for Preparation of (S_P)-4-Hydroxyl-12-(2-hydroxylphenyl)[2.2]paracyclophane [(S_P)-1]. A solution of (S_P)-**3** (2.0 g, 5.8 mmol) in 20 mL of dichloromethane was cooled to −78 °C, followed by addition of 3.4 mL of BBr_3 (8.73 g, 34.8 mmol). The mixture was warmed to room temperature and stirred overnight. Water (20 mL) was slowly added at 0 °C. The mixture was then extracted with dichloromethane (20 mL × 3). The combined organic layer was concentrated and purified by chromatography on a silica gel column with 10:1 petroleum ether/EtOAc to give (S_P)-**1** as a white solid, 1.54 g, 84% yield. mp 130−131 °C. $[\alpha]_D^{20.8}$ = −131.8 (c = 0.30, chloroform). ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 9.15 (s, 1H), 8.72 (s, 1H), 7.61 (dd, J = 7.6, 1.5 Hz, 1H), 7.16 (dt, J = 7.6, 1.6 Hz, 1H), 6.97 (td, J = 7.4, 1.1 Hz, 1H), 6.86 (dd, J = 8.0, 0.9 Hz, 1H), 6.73 (d, J = 1.6 Hz, 1H), 6.51 (d, J = 7.7 Hz, 1H), 6.45−6.40 (m, 1H), 6.34 (dd, J = 7.7, 1.6 Hz, 1H), 6.17 (dd, J = 7.7, 1.5 Hz, 1H), 5.70 (d, J = 1.5 Hz, 1H), 3.39−3.32 (m, 1H), 3.06−2.53 (m, 6H), 2.31 (ddd, J = 12.5, 10.3, 4.8 Hz, 1H). ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ 7.91 (br s, 1H), 7.74 (s, 1H), 7.58 (d, J = 7.3 Hz, 1H), 7.21 (dt, J = 7.8, 1.6 Hz, 1H), 7.02−6.96 (m, 3H), 6.62 (d, J = 7.7 Hz, 1H), 6.52 (d, J = 7.7 Hz, 1H), 6.40 (d, J = 7.6 Hz, 1H), 6.31 (dd, J = 7.7, 1.2 Hz, 1H), 5.80 (s, 1H), 3.48 (ddd, J = 12.7, 8.6, 2.6 Hz, 1H), 3.16−3.04 (m, 3H), 3.02−2.91 (m, 1H), 2.81−2.63 (m, 2H), 2.56−2.47 (m, 1H). ^{13}C NMR [75 MHz, $(CD_3)_2SO$] δ 154.8, 153.7, 141.4, 138.5, 138.3, 136.0, 134.7, 133.2, 131.9, 131.4, 128.7, 128.6, 128.0, 125.2, 123.6, 119.5, 118.1, 115.2, 34.0, 33.7, 32.9, 31.0. IR (cm^{-1}) 3483, 3450, 2930, 2580, 1573, 1415, 1261, 1224, 938, 768. MS (ESI) m/z 315.1 [M − H]$^-$. HRMS (MALDI-TOF) calcd for $C_{22}H_{20}O_2Na^+$ 339.1356, found 339.1365.

(S_P)-5a. A mixture of (S_P)-**1** (174 mg, 0.55 mmol), hexamethylphosphorous triamide (HMPT; 99 mg, 0.60 mmol), and 1.5 mL of dry toluene was heated at reflux under argon for 4 h. After cooling to room temperature, the mixture was concentrated and purified by chromatography on a silica gel column with 10:1 petroleum ether/EtOAc to give (S_P)-**5a** as a white solid, 133 mg, 62% yield. mp 169−171 °C. $[\alpha]_D^{23.3}$ = −158.6 (c = 0.17, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 1.5 Hz, 1H), 7.39−7.30 (m, 2H), 7.23−7.14 (m, 2H), 6.75 (d, J = 7.8 Hz, 1H), 6.63 (d, J = 7.7 Hz, 1H), 6.47−6.44 (m, 2H), 6.23 (d, J = 5.8 Hz, 1H), 3.63 (ddd, J = 13.0, 10.5, 4.9 Hz, 1H), 3.36−3.27 (m, 1H), 3.22−3.17 (m, 2H), 3.09−2.72 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 152.8, 151.7, 151.6, 141.7, 138.7, 138.5, 137.3, 134.3, 133.8, 132.9, 131.3, 130.0, 128.2, 127.6, 127.0, 123.4, 122.7, 122.6, 117.7, 117.3, 35.3, 35.1, 35.0, 34.8, 32.8, 29.1. ^{31}P NMR (161.92 MHz, $CDCl_3$) δ 139.6. IR (cm^{-1}) 2926, 1595, 1566, 1443, 1250, 1213, 977, 876, 764. MS (EI) m/z 353 [M^+] (100.0). HRMS (EI-quadrupole) calcd for $C_{24}H_{24}NO_2P$ 389.1545, found 389.1548.

(S_P)-5b. (S_P)-**5b** was obtained as a white solid, 150 mg, 65% yield, by employing the same procedure as for (S_P)-**5a** with hexaethylphosphorous triamide. mp 134−135 °C. $[\alpha]_D^{21.6}$ = −156.3 (c = 0.20, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 1.5 Hz, 1H), 7.30 (dt, J = 7.7, 1.6 Hz, 1H), 7.25 (dd, J = 7.8, 1.7 Hz, 1H), 7.16−7.10 (m, 2H), 6.71 (d, J = 7.8 Hz, 1H), 6.58 (d, J = 7.7 Hz, 1H), 6.43−6.39 (m, 2H), 6.17 (d, J = 5.5 Hz, 1H), 3.59−3.39 (m, 5H), 3.29−3.11 (m, 3H), 3.03−2.69 (m, 4H), 1.34 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 153.1, 152.1, 152.0, 141.7, 138.8, 138.6, 137.4, 134.3, 133.8, 132.9, 131.4, 130.2, 128.2, 127.5, 126.9, 123.3, 122.4, 122.4, 117.7, 117.3, 77.4, 77.0, 76.5, 39.3, 39.0, 35.2, 34.9, 32.9, 29.2, 15.2. ^{31}P NMR (161.92 MHz, $CDCl_3$) δ 140.0. IR (cm^{-1}): 2972, 2926, 1494, 1469, 1443, 1411, 1245, 1205, 1179, 1026. MS (EI) m/z 417 [M^+] (69.4). HRMS (EI-quadrupole) calcd for $C_{26}H_{28}NO_2P$ 417.1858, found 417.1852.

(S_P)-5c. To a solution of PCl_3 (391 mg, 2.8 mmol)) and NEt_3 (1.44 g, 14.2 mmol) in 8 mL of dry tetrahydrofuran (THF) was slowly added a solution of $^iPr_2NH$ in 8 mL of THF via syringe pump over 10 min at 0 °C. After 2 h of stirring at 0 °C, (S_P)-**1** was added and the solution was warmed to room temperature. After being stirred overnight, the reaction mixture was filtered. The filtrate was concentrated and purified by chromatography on a silica gel column with 10:1 petroleum ether/EtOAc to give (S_P)-**5c** as a white solid, 123 mg, 50% yield. mp 154−155 °C. $[\alpha]_D^{21.9}$ = −156.1 (c = 0.13, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 1.5 Hz, 1H), 7.29 (dd, J = 7.4, 1.5 Hz, 1H), 7.22 (dd, J = 7.9, 1.7 Hz, 1H), 7.13−7.10 (m, 2H), 6.68 (d, J = 7.8 Hz, 1H), 6.55 (d, J = 7.7 Hz, 1H), 6.39−6.37 (m, 2H), 6.14 (d, J = 5.6 Hz, 1H), 4.09−3.98 (m, 2H), 3.53 (ddd, J = 13.1, 10.6, 4.9 Hz, 1H), 3.25−3.06 (m, 3H), 3.01−2.85 (m, 2H), 2.81−2.66 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 153.3, 152.9, 152.7, 141.8, 141.7, 138.9, 138.6, 137.4, 134.3, 134.2, 133.8, 132.9, 131.5, 130.2, 128.2, 127.5, 127.5, 126.6, 123.1, 122.3, 122.2, 117.6, 117.2, 44.9, 44.7, 35.2, 34.9, 32.9, 29.3, 24.5, 24.4, 24.4, 24.3. ^{31}P NMR (161.92 MHz, $CDCl_3$) δ 140.2. IR (cm^{-1}) 2969, 2925, 1595, 1565, 1494, 1445, 1247, 1201, 975, 879. MS (EI) m/z 445 [M^+] (85.7). HRMS (EI-quadrupole) calcd for $C_{28}H_{32}NO_2P$ 445.2171, found 445.2169.

General Procedure for Copper-Catalyzed Conjugate Addition. A solution of $Cu(OTf)_2$ (5.5 mg, 15.0 μmol) and ligand **5** (30.0 μmol) in dry toluene (10 mL) was stirred for 40 min at room temperature under an argon atmosphere. The solution was then cooled to the indicated temperature. To the solution were added Et_2Zn (2.25 mL, 2.25 mmol, 1.0 M solution in hexane) and substituted chalcone (1.50 mmol) subsequently. The resulting mixture was stirred at the indicated temperature until the reaction was completed according to thin-layer chromatography (TLC), quenched with 20 mL of 2 M aqueous HCl and extracted with dichloromethane (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product, which was purified by column chromatography with petroleum ether/EtOAc as eluant to afford the ethylated product for HPLC analysis.

7a. Colorless oil, 296 mg, 95% yield, 95% ee. $[\alpha]_D^{18.7}$ = −8.4 (c = 2.4, ethanol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93−7.90 (m, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.46−7.41 (m, 2H), 7.32−7.17 (m, 5H), 3.36−3.21 (m, 3H), 1.87−1.73 (m, 1H), 1.71−1.58 (m, 1H), 0.82 (t, J = 7.3 Hz, 1H). Chiralpak OJ-H chromatography (n-hexane:2-propanol = 99:1) 1.0 mL/min, 214 nm. Retention time: t_S = 23.6 min, t_R = 31.2 min. The compound was already known.[11a]

7b. White solid, 249 mg, 93% yield, 95% ee. mp 75−76 °C. $[\alpha]_D^{19.8}$ = +7.6 (c = 0.92, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 7.8 Hz, 2H), 7.53 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 3.77 (s, 3H), 3.28−3.14 (m,3H), 1.83−1.69 (m, 1H), 1.67−1.53 (m, 1H), 0.80 (t, J = 7.3 Hz, 3H). Chiralpak OJ-H chromatography (n-hexane:2-propanol = 99:1) 1.0 mL/min, 214 nm. Retention time: t_{minor} = 33.3 min, t_{major} = 46.8 min. The compound was already known.[11b]

7c. Colorless oil, 263 mg, 90% yield, 95% ee. mp 72−74 °C. $[\alpha]_D^{18.3}$ = +10.5 (c = 1.4, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 6.94−6.80 (m, 2H), 3.25−3.16 (m, 3H), 1.83−1.70 (m, 1H), 1.65−1.50 (m, 1H), 0.82 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 147.5, 145.7, 138.4, 137.0, 132.8, 128.4, 127.9, 120.6, 108.0, 107.6, 100.7, 45.7, 42.7, 29.3, 12.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ −135.1, −135.2 (m, 2F), −164.15 (tt, J = 20.6, 6.5 Hz, 1F). MS (EI) m/z 292 [M^+] (6.5). HRMS (EI-quadrupole) calcd for $C_{17}H_{15}OF_3$ 292.1075, found 292.1072. IR (cm^{-1}) 2962, 1682, 1533, 1449, 1028, 854, 750. Chiralpak OJ-H chromatography (n-hexane:2-propanol = 99:1) 1.0 mL/min, 214 nm. Retention time: t_{minor} = 11.5 min, t_{major} = 13.7 min.

7d. Colorless oil, 268 mg, 95% yield, 95% ee. $[\alpha]_D^{19.6}$ = −16.9 (c = 0.60, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94−7.84 (m, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.4 Hz, 2H), 6.72−6.65 (m, 3H), 5.91 (s, 2H), 3.29−3.11 (m, 3H), 1.81−1.68 (m, 1H), 1.64−1.49(m, 1H), 0.80 (t, J = 7.3 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 147.5, 145.7, 138.4, 137.0, 132.8, 128.4, 127.9,120.6, 108.0, 107.6, 100.7, 45.7, 42.7, 29.3, 12.0. MS (EI) m/z 282 [M^+] (53.6). HRMS (EI-quadrupole) calcd for $C_{18}H_{18}O_3$ 282.1256, found 282.1246. IR (cm^{-1}) 1683, 1488, 1247, 1041, 940, 895, 805. Chiralpak OJ-H chromatography (n-hexane:2-propanol = 99:1) 1.0 mL/min, 214 nm. Retention time: t_{minor} = 32.8 min, t_{major} = 54.8 min.

7e. Colorless oil, 265 mg, 97% yield, 93% ee. $[\alpha]_D^{19.4}$ = −1.1 (c = 0.75, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92−7.89 (m, 2H), 7.57−7.52 (m, 1H), 7.46−7.41 (m, 2H), 7.24−7.11 (m, 4H),

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3.30−3.19 (m, 3H), 1.85−1.72 (m, 1H), 1.69−1.55 (m, 1H), 0.81 (t, J = 7.3 Hz, 3H). Chiralpak AD-H chromatography (*n*-hexane:2-propanol = 95:5) 0.4 mL/min, 214 nm. Retention time: t_{minor} = 15.2 min, t_{major} = 16.8 min. The compound was already known.[11c]

7f. Yellow solid, 267 mg, 95% yield, 93% ee. mp 56−58 °C. $[\alpha]_D^{18.5}$ = −18.0 (c = 2.2, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 7.6 Hz, 2H), 7.53 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.4 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 6.69 (d, J = 8.5 Hz, 2H), 3.27−3.09 (m, 3H), 2.91 (s, 6H), 1.82−1.68 (m, 1H), 1.68−1.51 (m, 1H), 0.80 (t, J = 7.3 Hz, 3H). Chiralpak AD-H chromatography (*n*-hexane:2-propanol = 95:5) 0.4 mL/min, 214 nm. Retention time: t_{minor} = 9.9 min, t_{major} = 13.9 min. The compound was already known.[11d]

7g. Colorless oil, 301 mg, 95% yield, 95% ee. $[\alpha]_D^{18.3}$ = +2.8 (c = 2.3, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96−7.93 (m, 2H), 7.57−7.53 (m, 2H), 7.47−7.41 (m, 2H), 7.30−7.23 (m, 2H), 7.05 (ddd, J = 8.0, 6.3, 2.7 Hz, 1H), 3.90−3.81 (m, 1H), 3.26 (dq, J = 16.5, 7.0 Hz, 2H), 1.88−1.64 (m, 2H), 0.83 (t, J = 7.4 Hz, 3H). Chiralpak AD-H chromatography (*n*-hexane:2-propanol = 95:5) 0.8 mL/min, 214 nm. Retention time: t_{minor} = 8.7 min, t_{major} = 12.7 min. The compound was already known.[10]

7h. Colorless oil, 304 mg, 96% yield, 55% ee. $[\alpha]_D^{18.4}$ = +22.1 (c = 1.1, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91−7.88 (m, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.46−7.39 (m, 4H), 7.11 (d, J = 8.4 Hz, 2H), 3.29−3.17 (m, 3H), 1.68−1.53 (m, 1H), 1.69−1.61 (m, 1H), 0.80(t, J = 7.3 Hz, 3H). Chiralpak AD-H chromatography, (*n*-hexane:2-propanol = 95:5) 0.8 mL/min, 214 nm. Retention time: t_{minor} = 8.3 min, t_{major} = 10.5 min. When the reaction was taken at −40 °C, 95% yield, 58% ee. The compound was already known.[11a]

7i. Colorless oil, 241 mg, 90% yield, 94% ee. $[\alpha]_D^{19.9}$ = +3.0 (c = 0.50, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 8.8 Hz, 1H), 7.31−7.15 (m, 5H), 6.90 (d, J = 8.8 Hz, 1H), 3.85 (s, 3H), 3.27−3.16 (m, 3H), 1.85−1.72 (m, 1H), 1.70−1.55 (m, 1H), 0.79 (t, J = 7.3 Hz, 3H). Chiralpak AD-H chromatography (*n*-hexane:2-propanol = 90:10) 0.5 mL/min, 214 nm. Retention time: t_{minor} = 15.3 min, t_{major} = 22.1. The compound was already known.[11b]

7j. Colorless oil, 259 mg, 95% yield, 87% ee. $[\alpha]_D^{19.5}$ = +2.5 (c = 0.75, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H), 7.31−7.26 (m, 2H), 7.22−7.16 (m, 3H), 3.31−3.16 (m, 3H), 1.85−1.71 (m, 1H), 1.69−1.57 (m,1H), 0.80 (t, J = 7.3 Hz, 3H). Chiralpak AD-H chromatography (*n*-hexane:2-propanol = 90:10) 0.5 mL/min, 214 nm. Retention time: t_{minor} = 7.0 min, t_{major} = 8.7 min. The compound was already known.[11b]

7k. White solid, 311 mg, 98% yield, 95% ee. mp 50−52 °C. $[\alpha]_D^{19.9}$ = +1.9 (c = 1.34, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77−7.74 (m, 2H), 7.58−7.55 (m, 2H), 7.31−7.26 (m, 2H), 7.22−7.16 (m, 3H), 3.26−3.17 (m, 3H), 1.84−1.71 (m, 1H), 1.69−1.61 (m, 1H), 0.80 (t, J = 7.3 Hz, 3H). Chiralpak AD-H chromatography (*n*-hexane:2-propanol = 95:5) 0.8 mL/min, 214 nm. Retention time: t_{minor} = 10.4 min, t_{major} = 13.4 min. The compound was already known.[11b]

7l. White solid, 311 mg, 95% yield, 71% ee. mp 53−56 °C. $[\alpha]_D^{20}$ = −9.3 (c = 1.03, ethanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.88 (m, 2H), 7.55−7.50 (m, 1H), 7.45−7.40 (m, 2H), 7.22−7.05 (m, 4H), 3.66−3.55 (m, 1H), 3.30−3.20 (m, 2H), 2.38 (s, 3H), 1.85−1.57 (m, 2H), 0.80 (t, J = 7.4 Hz, 3H). Chiralpak AD-H chromatography (*n*-hexane:2-propanol = 98:2) 1.0 mL/min, 214 nm. Retention time: t_{minor} = 15.4 min, t_{major} = 16.5 min. The compound was already known.[11b]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR and chiral HPLC spectra of compounds in this paper (PDF); crystallographic data for (S_P)-**5b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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