JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo502715f • Publication Date (Web): 25 Mar 2015

Just Accepted

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

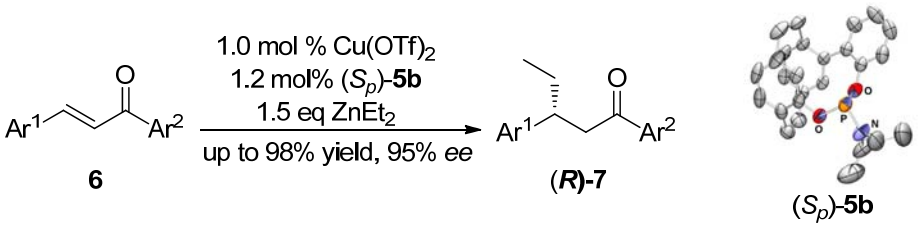
[2.2]Paracyclophane-derived Monodentate Phosphoramidite Ligands for Copper-Catalyzed Asymmetric Conjugate Addition of Diethylzinc to Substituted Chalcones

Lei Han,[†] Yang Lei,[†] Ping Xing,[†] Xiao-Long Zhao[†] and Biao Jiang[*, †, ‡]

E-mail: jiangb@sioc.ac.cn

[†]CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai, 200032, China

[‡]Shanghai Advanced Research Institute, Chinese Academy of Sciences, 99 Haike Road, Shanghai, 201210, China



ABSTRACT: The 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% *ee*) could be realized with low loadings of catalyst and ligand (catalyst loading is 1.0 mol% and ligand loading is 1.2%) .

INTRODUCTION

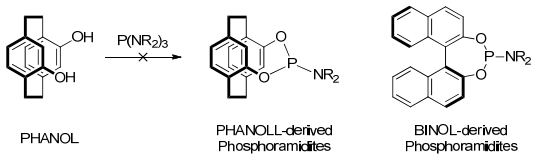
The conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is among the most useful methods for C−C bond formation and has a broad application in the synthesis of numerous biologically active compounds.[1] Many chiral auxiliaries and stoichiometric reagents have been used in this type of reaction with high

stereoselectivity.[1a, 1e 2] Catalytic enantioselective additions have also been developed, among which the use of organozinc reagents as donor and copper complexes with phosphorus ligands as catalysts afforded the most successful results.[3] A lot of these phosphorus ligands are monodentate phosphite and phosphoroamidite type. One of the pioneering examples were phosphoroamidites derived from BINOL, and some others derived from TADDOL, biphenol and SPINOL were also effective for this reaction.

Modifications of this type of ligands on their backbones and exocyclic amines or alcohols were reported, some of the modified ligands demonstrated excellent enantioselectivities in the reactions of organozinc reagents with cyclic or acyclic enones. However, the structures of these phosphoroamidite 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 phosphoroamidite or phosphite ligands. Herein we describe the preparation of 4,12-disubstituted [2.2]paracyclophane derived monodentate phosphoroamidite ligands and their application in the copper-catalyzed asymmetric conjugate addition to acyclic enones.

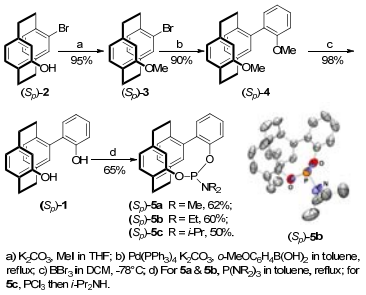
Results & Discussion

Our work started from the chiral PHANOL,[6] for it is the simplest 4,12-disubstituted [2.2]paracyclophane containing two hydroxyl groups. However, PHANOL cannot be modified to its monophosphoroamidite. The failure might be ascribed to PHANOL's high rigidity, and we think that structural rigidity and flexibility of chiral ligands are 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 reacting with BBr_3. Planar chiral phosphoroamidite 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 hours gave (S_p)-**5a** or (S_p)-**5b** in about 60% yield. The structure of (S_p)-**5b** was confirmed by X-ray analysis. (S_p)-**5c** was produced by subsequently condensation of (S_p)-**1** with PCl_3 and *i*-Pr_2NH.

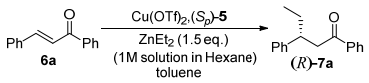


Scheme 2 Preparation of Chiral Phosphoroamidite Ligands.

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% of $Cu(OTf)_2$ at room temperature afforded the product (**7a**) of *R* configuration in 87% yield and 87% *ee* (Table 1, Entry 1). Slightly higher yield and *ee* value could be obtained when the reaction was carried out at lower temperature (Table 1, Entry 2). Reaction at much lower temperature (-30 ºC) did not promote yield and enantioselectivity obviously (Table 1, Entry 3). The yield and *ee* value remained at the same level when reducing the loading of the catalyst (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 0ºC and catalyst loading higher than 1 mol% were found unnecessary for obtaining good result (Table 1, Entries 5-7). Using $ZnEt_2$ 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 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 1mol% of Cu(OTf)$_2$, 1.2 mol% of ligand, 0 ºC (Table 1, Entry 16).

Table 1 Enantioselective Conjugate Addition of $ZnEt_2$ to Chalcone



entry	Cu(OTf)$_2$ (mol %)	ligand (mol %)	T (ºC)	t(h)	yield (%)[a]	*ee* (%)[b]
1	2.0	(S_p)-**5a** (4.0)	r. t.	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.

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 (Column 1-5, Figure 1a). Volume decrease of corresponding anions decreases with loss of enantioselectivity (Column 1 vs 3, 2 vs 4, Figure 1a). For single anions, the smaller the anion is, the lower the *ee* value is afforded (Column 6-8, Figure 1a). However, excellent results could be observed when BF_4^- and PF_6^- salts were used respectively (Column 9-10, Figure 1a). A modest negative non-linear effect implied the existence of a more reactive racemic complex in the catalytic system (Figure 1b).

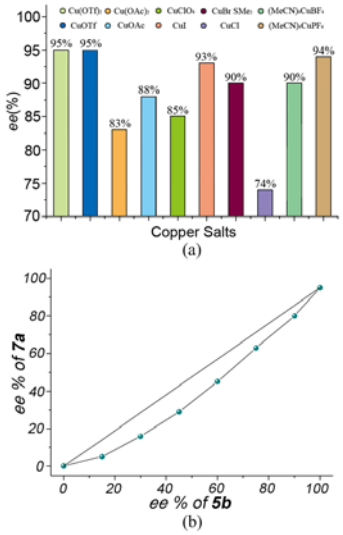


Figure 1. Asymmetric Catalytic Conjugate Addition with (S_p)-5b using Various Copper Salts (a) and Non-Linear Effect of Ligand (S_p)-5b (b).

The scope of 1, 4-addition of $ZnEt_2$ to substituted chalcones catalyzed by $Cu(OTf)_2$/**5b** were then explored using the best performing catalytic system and the results were listed in Table 2. When Ar^1 was *para*- or *meta*- substituted phenyl group, chalcones bearing either electronic 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~~y 7~~). Reaction at lower temperature (-40 ºC) did not help much on 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 (Table 2, Entry 9, 90% yield, 94% *ee*) or bromo substituted (Table 2, entry 11, 98% yield 95% *ee*), as to *para*-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 of these reacted (Table 2, Entries 13-14), double aromatic groups were needed in our methodology perhaps for the existence of intermolecular weak interaction.

带格式的：字体：倾斜

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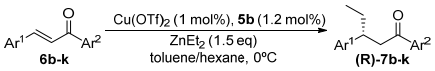
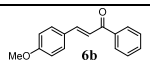
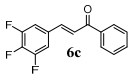
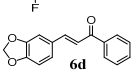
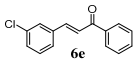
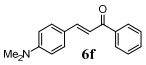
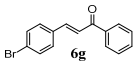
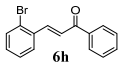
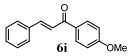
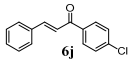
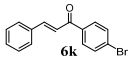
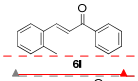
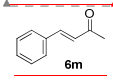
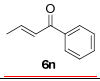
Table 2 Enantioselective Conjugate Addition of $ZnEt_2$ to Substituted Chalcones.



entry	Substrate	yield (%)[a]	*ee* (%)[b]
1		93	95

2		90	95
3		95	95
4		97	93
5		95	93
6		95	95
7		96	55
8		95[c]	58[c]
9		90	94
10		95	87
11		98	95
12		95	71
13		No reaction	-
14		No reaction	-

[a]. Isolated yield; [b]. Determined by chiral HPLC; [c]. The reaction was carried out at -40 ºC.

CONCLUSION

In summary, monodentate phosphoroamidite type ligands (S_p)-**5a/b/c** derived from a flexible 4,12-disubstituted[2.2]paracyclophane were developed. They are highly efficient in the 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 using bidentate P,N-ligands,[9] and until now only several methodologies 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 using silica gel H (10-40 μm). Standard reagents and solvents were purified according to known procedures. Melting points are uncorrected. NMR spectra were recorded using 300 MHz spectrometer. Chemical shifts (δ) are expressed in 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 the 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 the spectroscopy data was in accordance with that reported. m. p. 167-169 ºC. (lit.[7c] 181°C). $[\alpha]_D^{24.6}$ = +10.3 (*c* = 0.50, chloroform).

Procedure for the 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 toluene was heat at 110ºC for 2 h, cooled to room temperature, filtered. After washing the solid 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 colourless 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. 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 the Preparation of (S_p)-4-hydroxyl-12-(2-hydroxylphenyl)[2.2]paracyclophane ((S_p)-1): Cooled a solution of (S_p)-**3** (2.0 g, 5.8 mmol) in 20 mL dichloromethane to -78 ºC followed by added 3.4 mL of BBr_3 (8.73 g, 34.8 mmol). The mixture was warmed to room temperature and stirred overnight. 20 mL of water was slowly added at 0 ºC. 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. m. p. 130-131 ºC. $[\alpha]_D^{20.8}$ = -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, 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), 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. m. p. 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: was obtained as a white solid 150 mg in 65% yield by employing the same procedure as for (S_p)-**5a** using hexaethylphosphorus triamide. m. p. 134-135 ºC. $[\alpha]_D^{21.6}$= -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 dry THF was slowly added a solution of ^{i}Pr$_2$NH in 8 mL THF via syringe pump in 10 min at 0 ºC, after 2 h stirring at 0 ºC (S_p)-**1** was added and the solution was warmed to room temperature. Having been 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 123mg in 50% yield. m. p. 154-155 ºC. $[\alpha]_D^{21.9}$= -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 the 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 indicated temperature. To the solution Et_2Zn (2.25 mL, 2.25 mmol, 1.0 M solution in hexane) and substituted chalcone (1.50 mmol) were added subsequently. The resulting mixture was stirred at the indicated temperature until the reaction was completed according to TLC, quenched with 20 mL 2 M aqueous HCl and extracted with dichloromethane (20 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give a crude product, which was purified by column chromatography using 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: isopropanol = 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*. m. p. 75-76ºC. $[\alpha]_D^{19.8}$ = +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:isopropanol = 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*. m. p. 72-74 ºC. $[\alpha]_D^{18.3}$ = +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: isopropanol =99:1), 1.0mL/min, 214nm. 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, CDCl3): 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: isopropanol = 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), 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:isopropanol = 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*. m. p. 56-58 ºC.$[\alpha]_D^{18.5}$ = -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 : isopropanol = 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 : isopropanol = 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 : isopropanol = 95:5), 0.8 mL/min, 214nm. Retention time: t_{minor} = 8.3 min, t_{major} = 10.5 min. When the reaction was taken at -40 ºC, 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 : isopropanol = 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 : isopropanol = 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*. m. p. 50-52 ºC. $[\alpha]_D^{19.9}$ = +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* = 7.3Hz, 3H). CHIRALPAK® AD-H chromatography (*n*-hexane : isopropanol = 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*. m.p. 53-56 ºC. $[\alpha]_D^{20}$ = -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 : isopropanol = 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 spectra, chiral HPLC spectra, and crystallographic data (CIF file) for (S_p)-**5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: jiangb@sioc.ac.cn

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by the National Basic Research Program of China (973-2010CB833200 and 973-2010CB833300), the National Natural Science Foundation of China (21102167), the Science and Technology Commission of Shanghai Municipality (12DZ1930902), Shanghai Green Chemical Engineering Technology Research Center and the Knowledge Innovation Program of the Chinese Academy of Sciences.

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