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Highly Enantioselective Copper-Catalyzed Conjugate Addition of Diethylzinc to Enones Using Chiral Spiro Phosphoramidites as Ligands

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Abstract: Novel monodentate chiral spiro phosphoramidite ligands have been readily synthesized in good yields from enantiomerically pure 1,1′-spirobiindane-7,7′-diol. The new ligands were highly efficient in the copper-catalyzed conjugate addition of Et_2Zn to enones with up to 98% enantiomeric excess.

The conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is one of the most useful processes for C−C bond formation in organic synthesis.[1] A number of chiral auxiliaries and stoichiometric reagents have been reported during the past decade that have provided high enantioselectivity in the 1,4-addition,[2] while the chiral catalyst has been developed with less success. Recently, the copper complexes with chiral phosphorus ligands have been found to be highly efficient catalysts in the conjugate addition of Et_2Zn to enones.[3] Among those chiral ligands, BINOL-based phosphoramidites developed by Feringa et al.[4] and TADDOL-derived phosphites reported by Alexakis et al.[5] showed a remarkable enantioselectivity in the reaction of Et_2Zn with cyclohexenones. Other efficient chiral ligands include diphosphite[6] and P,N ligands.[7] However, the ligands that have been demonstrated to induce high enantioselectivities are only limited to those with BINOL or TADDOL as a chiral backbone.

We have previously reported the phosphoramidites of general structure **1** (Siphos), which contain a chiral spirobiindane structure to be efficient ligands in the asymmetric Rh-catalyzed hydrogenation of prochiral olefins.[8] It is of interest to study the behavior of these novel monodentate ligands in other types of transition metal-catalyzed transformations. Herein we describe the copper-catalyzed conjugate addition of Et_2Zn to enones using spiro phosphoramidite ligands **1** and **2** with high enantioselectivity. Chiral spiro phosphoramidite ligands **1** and **2** were conveniently synthesized in good yields from enantiomerically pure 1,1′-spirobiindane-7,7′-diol (**3**), which could be easily prepared from 3-methoxybenzaldehyde[9] (Scheme 1). Heating the mixture of diol **3** and $P(NMe_2)_3$ or $P(NEt_2)_3$ in toluene for 2 h afforded ligands **1a** or **1b** in 86−92% yield, while ligands **1c**, **1d**, and **2**, which bear a bulk amino group, were produced with a different procedure. Condensation of diol **3** with PCl_3, followed by treatment with the corresponding lithium dialkylamide provided ligands **1c**, **1d**, and **2** in 50−66% yield.

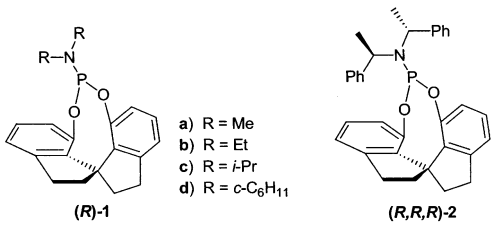
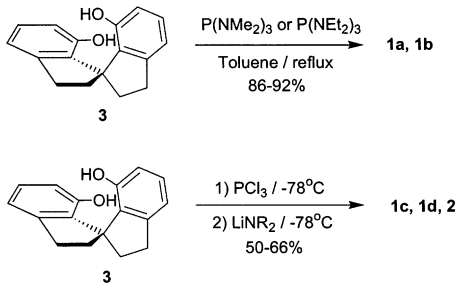


FIGURE 1. Siphos ligands used in Cu-catalyzed conjugate addition of Et_2Zn to enones.

SCHEME 1



2-Cyclohexen-1-one was chosen as a typical substrate to test chiral ligands. The conjugate addition of Et_2Zn to cyclohexenone was carried out in the presence of $Cu(OTf)_2$ (1 mol %) and chiral ligands (2 mol %) in toluene at 0 °C for 2 h producing 3-ethylcyclohexanone in high yields. The results summarized in Table 1 showed that the structure of the ligand has a strong influence on the enantioselectivity of the reaction. Ligands **1a** and **1b**, in which R groups are methyl and ethyl, respectively, gave (*S*)-product **5** in low ee. Introduction of a larger R group in ligands **1**, such as isopropyl in **1c** and cyclohexyl in **1d**, led to higher enantioselectivities. A significant improvement in the enantioselectivity (97% ee) was achieved by using ligand (*R*,*R*,*R*)-**2**, which contains a C_2-symmetric

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TABLE 1. Asymmetric Conjugate Addition of Et_2Zn to Cyclohexenone Catalyzed by $Cu(OTf)_2$−L Complexes[a]

entry	ligand	yield (%)[b]	ee (%)[c]	configuration[d]
1	**1a**	94	34	*S*
2	**1b**	88	35	*S*
3	**1c**	87	57	*S*
4	**1d**	90	70	*S*
5	(*R*,*R*,*R*)-**2**	95	97	*S*
6	(*S*,*R*,*R*)-**2**	93	74	*R*

[a] Reaction conditions: 2-cyclohexen-1-one (1 mmol), Et_2Zn (1.5 mmol), $Cu(OTf)_2$ (0.01 mmol), ligands **1** or **2** (0.02 mmol) in toluene (3 mL). [b] Isolated yields. [c] Ee values were determined by chiral GC on a Supelco γ-DEX-225 column. [d] Absolute configuration was determined by comparison with literature values.[10]

TABLE 2. Asymmetric Conjugate Addition of Et_2Zn to Cyclohexenone with Ligand (*R*,*R*,*R*)-2[a]

entry	Cu salt	solvent	temp (°C)	yield (%)[b]	ee (%)
1	$Cu(OTf)_2$	toluene	0	95	97
2	$Cu(OTf)_2$	Et_2O	0	93	95
3	$Cu(OTf)_2$	CH_2Cl_2	0	95	86
4	$Cu(OTf)_2$	THF	0	85	75
5	$Cu(OTf)_2$	EtOAc	0	91	93
6	$Cu(OTf)_2$	toluene	−20	96	95
7	$Cu(OTf)_2$	toluene	−40	92	91
8	$Cu(OTf)_2$	toluene	25	99	96
9	$Cu(OAc)_2 \cdot 2H_2O$	toluene	0	88	98
10	$CuCl_2 \cdot 2H_2O$	toluene	0	91	96
11	CuCl	toluene	0	92	95
12	CuBr	toluene	0	74	90

[a] All reactions were completed in 2 h. [b] Isolated yields; no 1,2-addition products were observed.

(*R*,*R*)-di(1-phenylethyl)amine moiety, while with ligand (*S*,*R*,*R*)-**2** prepared from (*S*)-**3** and (*R*,*R*)-di(1-phenylethyl)amine, a mismatched case, (*R*)-product **5**, was produced with only 74% ee. By comparing the absolute configuration of products from ligands (*R*,*R*,*R*)-**2** and (*S*,*R*,*R*)-**2** (entries 5 and 6), we can see that the configuration of the product was determined by the chirality of the spiro backbone of the ligand.

Having realized the efficient stereocontrol of ligand (*R*,*R*,*R*)-**2** in the Cu-catalyzed conjugate addition of Et_2Zn to cyclohexenone, we investigated the effects of solvent, temperature, and the catalyst precursor to optimize the reaction conditions (Table 2). Of the solvents screened, nonpolar solvents such as toluene and Et_2O were superior to coordinating solvents such as THF (entries 1−5). By lowering the reaction temperature from 0 to −40 °C, the ee of product **5** decreased from 97 to 91% (entries 6 and 7 vs 1). It is noteworthy that the conjugate addition reaction can be carried out at room temperature with high enantioselectivity (entry 8), which offers an advantage of ligand (*R*,*R*,*R*)-**2** over other monodentate phosphorus ligands that normally need a low temperature.[4,11] In addition to $Cu(OTf)_2$, other copper salts like $Cu(OAc)_2 \cdot 2H_2O$, $CuCl_2 \cdot 2H_2O$, and CuCl were also found to be effective catalyst precursors in the conjugate addition of Et_2Zn to cyclohexenone (entries 9−12).[11]

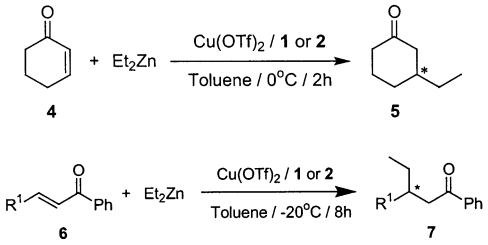
The conjugate additions of Et_2Zn to cycloheptenone and cyclopentenone were also examined. By using ligand (*R*,*R*,*R*)-**2**, the reaction of cycloheptenone produced 1,4-addition product 3-ethylcycloheptanone with 94% ee. However, the reaction of cyclopentenone provided 3-ethylcyclopentanone with only 44% ee.

TABLE 3. Asymmetric Conjugate Addition of Et_2Zn to Acyclic Enones 6[a]

entry	R^1	ligand	yield (%)[b]	ee (%)[c]
1	Ph	**1a**	68	37 (*R*)
2	Ph	**1b**	87	52 (*R*)
3	Ph	**1c**	89	71 (*R*)
4	Ph	**1d**	87	64 (*R*)
5	Ph	(*R*,*R*,*R*)-**2**	65	70 (*R*)
6	Ph	(*S*,*R*,*R*)-**2**	70	30 (*S*)
7	4-CH_3OPh	**1c**	80	44 (nd)
8	4-CH_3OPh	**1d**	74	40 (nd)
9	4-ClPh	**1c**	87	76 (nd)
10	4-ClPh	**1d**	77	72 (nd)

[a] Reaction conditions: enone (1 mmol), Et_2Zn (1.5 mmol), $Cu(OTf)_2$ (0.03 mmol), ligand (0.06 mmol). [b] Isolated yields. [c] Determined by HPLC (Chiracel OJ column, 99:1 *n*-hexane/2-propanol, 1 mL/min). Absolute configurations were determined by comparison with literature values.[12]

To extend the range of substrates for these catalysts, the conjugate addition of Et_2Zn to acyclic enones has been studied (Table 3). In the case of chalcone, the ligands with larger R groups afforded conjugate addition product **7** with higher ee (entries 1−4). Ligand (*R*,*R*,*R*)-**2**, with a matched combination of chiralities of spiro skeleton and amino moiety, however, did not show its superiority in the enantioselectivity over ligand **1c** like that in the reaction of cyclohexenone (entry 5 vs 3). The substitution of the electron-withdrawing chlorine atom on the phenyl ring of chalcone did not have much influence on the enantioselectivity of the reaction, while the introduction of an electron-donating methoxy group led to lower ee values.



In summary, we have demonstrated that monodentate chiral phosphoramidites with a spiro structure are highly efficient ligands in the copper-catalyzed 1,4-addition of Et_2Zn to cyclic enones. The reaction can be carried out under mild conditions. Further studies of other transition metal-catalyzed reactions using our novel ligands are in progress.

Experimental Section

General. All reactions and manipulations were performed in an argon atmosphere using standard Schlenk techniques. Toluene, ether, and THF were distilled from sodium-benzophenone ketyl under argon. Methylene chloride and ethyl acetate were distilled from CaH_2. 1,1′-Spirobiindane-7,7′-diol was prepared and resolved by previously reported methods.[9]

Syntheses of Ligands: Synthesis of *N*-Dimethyl-[(*R*)-1,1′-spirobiindane-7,7′-diyl]phosphoramidite (1a). Typical Pro-

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cedure. A mixture of (*R*)-1,1′-spirobiindane-7,7′-diol (200 mg, 0.8 mmol), HMPT (0.2 mL, 1 mmol), and 2 mL of dry toluene was heated at reflux under argon for 2 h. After cooling to room temperature, the mixture was concentrated and purified by chromatography on a silica gel column with 16:1 petroleum ether/EtOAc to give **1a** as a white solid (237 mg, 92% yield). Mp: 84−85 °C; $[\alpha]_D^{25}$ +519 (*c* 0.092, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22−6.63 (m, 6H), 3.13−3.01 (m, 2H), 2.86−2.78 (m, 2H), 2.34 (s, 3H), 2.31 (s, 3H), 2.29−2.19 (m, 2H), 2.07−1.89 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.3, 146.2, 146.0, 145.7, 145.2, 142.1, 140.8, 128.3, 128.2, 121.5, 121.1, 120.0, 58.7, 38.2, 38.1, 35.4, 35.0, 30.8, 30.5. ^{31}P NMR (121 MHz, $CDCl_3$): δ 124.9. MS: *m*/*z* 325 (M^+, 100). Anal. Calcd for $C_{19}H_{20}NO_2P$: C, 70.13; H, 6.21; N, 4.30. Found: C, 69.95; H, 6.06; N, 4.40.

***N*-Diethyl-[(*R*)-1,1′-spirobiindane-7,7′-diyl]phosphoramidite (1b).** Ligand **1b** was synthesized in 86% yield by the same procedure as that for **1a** using hexaethylphosphorus triamide. Compound **1b** is a colorless oil and solidifies slowly by standing. $[\alpha]_D^{25}$ +393 (*c* 0.098, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26−6.62 (m, 6H), 3.14−2.98 (m, 2H), 2.86−2.52 (m, 6H), 2.52−2.18 (m, 2H), 2.06−1.88 (m, 2H), 1.01 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9, 146.5, 146.1, 145.6, 145.3, 141.6, 141.0, 128.5, 128.1, 121.8, 120.9, 120.4, 59.0, 39.2, 38.4, 31.0, 15.3. ^{31}P NMR (121 MHz, $CDCl_3$): δ 129.1. MS: *m*/*z* 353 (M^+), 338 (100). Anal. Calcd for $C_{21}H_{24}NO_2P$: C, 71.35; H, 6.86; N, 3.96. Found: C, 71.06; H, 6.65; N, 3.82.

Synthesis of *N*-Diisopropyl-[(*R*)-1,1′-spirobiindane-7,7′-diyl]phosphoramidite (1c). Typical Procedure. A solution of (*R*)-1,1′-spirobiindane-7,7′-diol (200 mg, 0.8 mmol) in 10 mL toluene was added over a period of 5 min to a cooled solution (−78 °C) of PCl_3 (69.4 μL, 0.8 mmol), Et_3N (223 μL, 1.6 mmol), and toluene (5 mL). The reaction mixture was stirred for 2 h, warmed to room temperature, and filtered. The filtrate was cooled to −78 °C and treated with a 0.16 M solution of LDA (5 mL, 0.8 mmol, newly prepared) for 3 h. The reaction mixture was warmed to room temperature, stirred overnight, filtered, concentrated, and purified by chromatography on a silica gel column with 30:1 petroleum ether/EtOAc to give **1c** as a white solid (168 mg, 55% yield). Mp: 90−92 °C; $[\alpha]_D^{25}$ +376 (*c* 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22−6.84 (m, 6H), 3.12−3.00 (m, 4H), 2.87−2.75 (m, 2H), 2.28−2.16 (m, 2H), 2.06−1.85 (m, 2H), 1.17 (d, J = 6.3 Hz, 6H), 1.10 (d, J = 6.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.9, 147.2, 146.5, 145.7, 144.1, 141.5, 139.74, 128.0, 127.0, 121.8, 121.3, 120.6, 119.5, 57.6, 37.0, 29.6, 23.3. ^{31}P NMR (121 MHz, $CDCl_3$): δ 135.5. MS: *m*/*z* 381 (M^+), 281 (100). Anal. Calcd for $C_{23}H_{28}NO_2P$: C, 72.49; H, 7.42; N, 3.67. Found: C, 72.24; H, 7.18; N, 3.53.

***N*-Dicyclohexyl-[(*R*)-1,1′-spirobiindane-7,7′-diyl]phosphoramidite (1d).** Ligand **1d** was synthesized in 56% yield by the same procedure as that for **1c** using dicyclohexylamine. White solid, mp 190−192 °C, $[\alpha]_D^{25}$ +272 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27−6.70 (m, 6H), 3.14−2.98 (m, 2H), 2.89−2.74 (m, 2H), 2.62−2.38 (m, 2H), 2.29−2.13 (m, 2H), 2.09−1.83 (m, 2H), 1.82−1.20 (m, 14H), 1.18−0.72 (m, 6H). ^{13}C NMR (75 MHz, CDCl3): δ 149.6, 146.8, 145.6, 144.6, 141.7, 140.1, 128.3, 127.9, 121.9, 121.3, 120.7, 120.1, 58.8, 54.6, 54.4, 38.2, 38.0, 35.6, 35.4, 30.8, 30.4, 26.7, 25.6. ^{31}P NMR (121 MHz, $CDCl_3$): δ 135.0. Anal. Calcd for $C_{29}H_{36}NO_2P$: C, 75.46; H, 7.86; N, 3.03. Found: C, 75.11; H, 7.84; N, 3.03.

***N*-Di[(*R*)-1-phenylethyl]-[(*R*)-1,1′-spirobiindane-7,7′-diyl]phosphoramidite (*R*,*R*,*R*)-2.** Ligand (*R*,*R*,*R*)-**2** was synthesized in 50% yield by the same procedure as that for **1c** using di[(*R*)-1-phenylethyl]amine. White solid, mp 82−84 °C, $[\alpha]_D^{25}$ +1050 (*c* 0.096, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-6.63 (m, 15H), 6.69 (d, J = 7.8 Hz, 1H), 4.50−4.21 (m, 2H), 3.20−2.95 (m, 2H), 2.92−2.70 (m, 2H), 2.40−1.81 (m, 4H), 1.78−1.35 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.6, 146.9, 145.7, 145.0, 143.6, 140.1, 128.4, 127.8, 127.6, 126.4, 122.0, 121.2, 121.0, 120.6, 58.9, 52.3, 52.1, 38.4, 38.1, 30.7, 30.4, 21.9. ^{31}P NMR (121 MHz, $CDCl_3$): δ 130.2. HR-MS (FAB) calcd for $C_{33}H_{32}NO_2P$ + H 506.2243; found 506.2234.

***N*-Di[(*R*)-1-phenylethyl]-[(*S*)-1,1′-spirobiindane-7,7′-diyl]phosphoramidite (*S*,*R*,*R*)-2.** Ligand (*S*,*R*,*R*)-**2** was synthesized in 66% yield from (*S*)-**3** and di[(*R*)-1-phenylethyl]amine by using the same procedure as that for **1c**. White solid, mp 50−52 °C; $[\alpha]_D^{25}$ −31 (*c* 0.92, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26−6.75 (m, 15H), 5.97 (d, J = 7.8 Hz, 1H), 4.40−4.28 (m, 2H), 3.14−2.92 (m, 2H), 2.85−2.72 (m, 2H), 2.30−2.10 (m, 2H), 2.05−1.81 (m, 2H), 1.60 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.1, 145.0, 144.7, 143.6, 142.5, 140.6, 139.0, 127.9, 127.5, 127.0, 126.9, 126.6, 125.6, 120.8, 120.1, 119.3, 59.1, 57.8, 54.2, 37.2, 36.9, 29.6, 29.2, 21.8, 21.6. ^{31}P NMR (121 MHz, $CDCl_3$): δ 137.2. HR-MS (FAB) calcd for $C_{33}H_{32}NO_2P$ + H 506.2243; found 506.2238.

General Procedure for Asymmetric Catalytic Conjugate Addition. A solution of copper salt (0.01 mmol) and ligand (0.02 mmol) in an appropriate solvent (3 mL) was stirred under argon at room temperature for 30 min. The solution was cooled to 0 °C, and Et_2Zn solution in hexane (1.5 mmol) and the enone (1 mmol) were added. After 2 h at 0 °C, the reaction was quenched by aqueous NH_4Cl and the mixture was extracted with Et_2O (2 × 20 mL). The organic phases were combined, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by chromatography on a silica gel column. The ee values of cyclic ketones were determined by chiral GC, and the ee values of acyclic ketone were determined by chiral HPLC. The analytic conditions are as follows.

3-Ethyl-cyclohexanone: Supelco γ-DEX-225 column (30 m × 0.25 mm i.d.) at 95 °C constant, T_R = 27.91 and 28.54 min.

3-Ethyl-cyclopentanone: Supelco γ-DEX-225 column (30 m × 0.25 mm i.d.) at 90 °C constant, T_R = 19.23 and 19.65 min.

3-Ethyl-cycloheptanone: Supelco β-DEX-120 column (30 m × 0.25 mm i.d.), at 95 °C for 5 min, then programmed to increase at 1 °C/min to 150 °C, T_R = 31.88 and 32.27 min.

1,3-Diphenyl-pentan-1-one: Chiracel OJ column (25 cm × 0.46 cm i.d.), 99:1 *n*-hexane/2-propanol, 1 mL/min, T_R = 28.91 and 33.54 min.

1-Phenyl-3-(4-methxoyphenyl)pentan-1-one: Chiracel OJ column (25 cm × 0.46 cm i.d.), 99:1 *n*-hexane/2-propanol, 1 mL/min, T_R = 30.43 and 37.87 min.

1-Phenyl-3-(4-chlorophenyl)pentan-1-one: Chiracel OJ column (25 cm × 0.46 cm ID), *n*-hexane, 1 mL/min, T_R = 41.67 and 50.99 min.

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