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Highly enantioselective copper-catalyzed conjugate addition of diethylzinc to cyclic enones with spirocyclic phosphoramidite ligands

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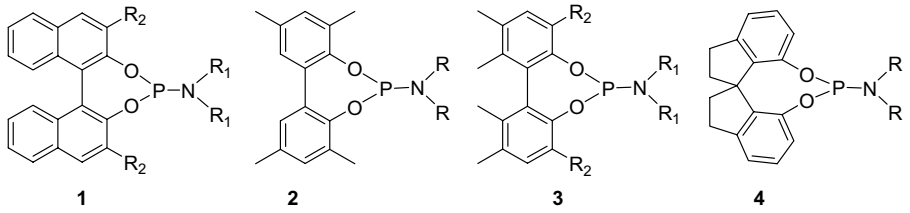
Abstract—A series of spirocyclic phosphoramidite ligands **6**–**9** with different substituents on the amine moiety were synthesized from the chiral spirocyclic diol (*R*)-**5**. These monodentate ligands have been applied in copper-catalyzed conjugate addition of diethylzinc to cyclic enones. Excellent enantioselectivities (up to 99% ee) can be achieved by the use of ligand (*R*,*S*,*S*)-**9** bearing stereochemically matched structure derived from the C_2-symmetric (*S*,*S*)-bis(α-methylbenzyl)amine.

Enantioselective conjugate addition of organometallic reagents to α,β-unsaturated compounds is an important synthetic method for the construction of carbon–carbon bonds bearing a new stereogenic center.[1] Parallel to the development of chiral auxiliaries and stoichiometric reagents,[2] the more challenging catalytic strategy for this transformation has recently become an actively studied area. Among the many catalytic systems reported so far, chiral monodentate phosphoramidite ligands combined with copper salts have shown excellent enantioselectivities in the conjugate addition of organozinc reagents to enones,[3] dienones,[4] nitroolefins,[5] lactams,[6] malonates,[7] and meldrum's acid derived acceptors.[8] A common structural feature of these trivalent phosphorous ligands is the existence of a C_2-symmetric diol-based framework as well as a sterically demanding chiral secondary amine moiety. Representative ligands include the BINOL-based phosphoramidites **1**,[3a–f] biphenol-based **2**,[3g,5c] **3**,[3h,5d] and SPINOL-based **4**[3i] (Scheme 1).

Recently, we have designed and synthesized a new spirocyclic diol—9,9′-spirobixanthene-1,1′-diol **5**, which has more rigid coordinating conformation than BINOL. The monodentate phosphoramidite ligand (*R*)-**6** derived from (*R*)-**5** has shown excellent enantioselectivities in Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives and itaconic acid.[9] In an effort to extend the utility of this type of monodentate ligands for other asymmetric catalytic reactions, we reported herein the preparation of a series of new spirocyclic phosphoramidites based on (*R*)-**5** and their application in copper-catalyzed conjugate addition of diethylzinc to cyclic enones.

Several methods have been reported for the synthesis of phosphoramidites.[10] While (*R*)-**6** and (*R*)-**7** were prepared routinely by refluxing (*R*)-**5** with hexamethylphosphorous triamide (HMPT) or hexaethylphosphorous triamide (HEPT) in toluene, a different procedure[11] was



Scheme 1. Representative chiral monodentate phosphoramidite ligands for copper-catalyzed enantioselective conjugate addition.

Keywords: Asymmetric catalysis; Conjugate addition; Enones; Spirocyclic compound.
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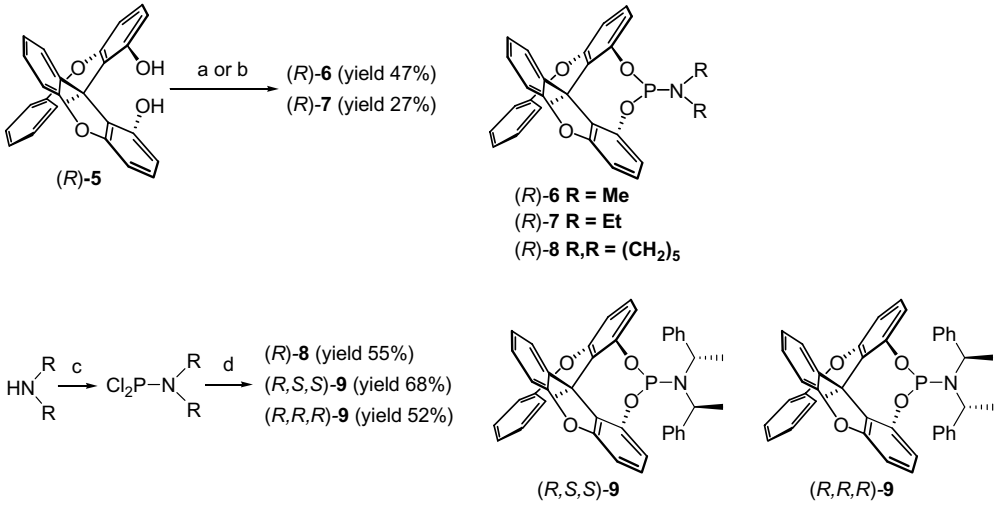
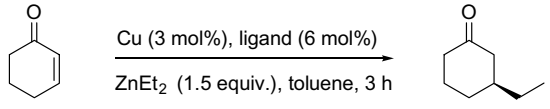
optimized for the synthesis of (*R*)-**8**, (*R*,*S*,*S*)-**9**, and (*R*,*R*,*R*)-**9** with sterically hindered structure (Scheme 2). Thus reacting the starting amine sequentially with equivalent amount of *n*-butyllithium, trichlorophosphine and then (*R*)-**5** afforded the product in a moderate yield.

These ligands were then tested in copper-catalyzed conjugate addition of diethylzinc to cyclohex-2-enone **10**, a benchmark substrate for the quick determination of ligand efficiency. As shown in Table 1, the combination of $Cu(OTf)_2$ (3 mol%) and ligand (*R*)-**6**, (*R*)-**7**, or (*R*)-**8** (6 mol%) led to only low enantioselectivities at 0 °C



Scheme 2. Synthesis of spirocyclic phosphoramidite ligands. Reagents and conditions: (a) HMPT, toluene, reflux, 72 h; (b) HEPT, toluene, reflux, 72 h; (c) (1) *n*-BuLi (1 equiv), −78 °C; (2) PCl_3 (1 equiv), −78 °C; (d) (*R*)-**5** (1 equiv), NEt_3, 0 °C to rt overnight, then 60 °C 24 h.

Table 1. Copper-catalyzed enantioselective conjugate addition of diethylzinc to cyclohex-2-enone **10** with spirocyclic phosphoramidite ligands **6**–**9**[13,a]

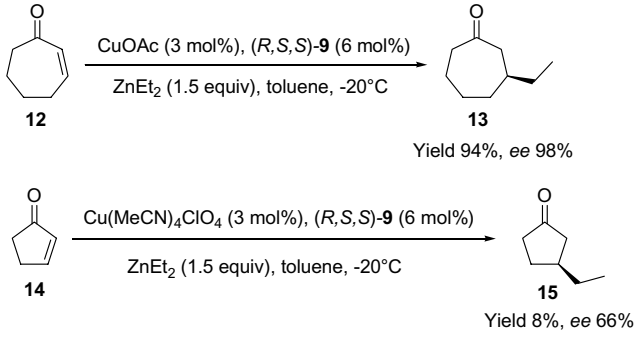


10 **11**

Entry	Ligand	Cu catalyst	Solvent	*T* (°C)	Yield[b] (%)	ee[c,d] (%)
1	(*R*)-**6**	$Cu(OTf)_2$	Toluene	0	92	57 (*S*)
2	(*R*)-**7**	$Cu(OTf)_2$	Toluene	0	93	53 (*S*)
3	(*R*)-**8**	$Cu(OTf)_2$	Toluene	0	89	41 (*S*)
4	(*R*,*S*,*S*)-**9**	$Cu(OTf)_2$	Toluene	0	90	93 (*S*)
5	(*R*,*R*,*R*)-**9**	$Cu(OTf)_2$	Toluene	0	86	10 (*S*)
6	(*R*,*S*,*S*)-**9**	$Cu(OTf)_2$	Toluene	25	91	75 (*S*)
7	(*R*,*S*,*S*)-**9**	$Cu(OTf)_2$	Toluene	−20	92	94 (*S*)
8	(*R*,*S*,*S*)-**9**	$Cu(OTf)_2$	Toluene	−30	91	96 (*S*)
9	(*R*,*S*,*S*)-**9**	$(CuOTf)_2$·toluene	Toluene	−20	87	49 (*S*)
10	(*R*,*S*,*S*)-**9**	CuOAc	Toluene	−20	92	99 (*S*)
11	(*R*,*S*,*S*)-**9**	$Cu(OAc)_2·H_2O$	Toluene	−20	90	98 (*S*)
12	(*R*,*S*,*S*)-**9**	$Cu(MeCN)_4ClO_4$	Toluene	−20	89	97 (*S*)
13	(*R*,*S*,*S*)-**9**	$Cu(MeCN)_4PF_6$	Toluene	−20	90	52 (*S*)
14[e]	(*R*,*S*,*S*)-**9**	CuOAc	Toluene	−20	94	98 (*S*)
15[f]	(*R*,*S*,*S*)-**9**	CuOAc	Toluene	−20	93	96 (*S*)
16[e]	(*R*,*S*,*S*)-**9**	CuOAc	CH_2Cl_2	−20	77	90 (*S*)
17[e]	(*R*,*S*,*S*)-**9**	CuOAc	Et_2O	−20	92	96 (*S*)
18[e]	(*R*,*S*,*S*)-**9**	CuOAc	THF	−20	75	96 (*S*)
19[e]	(*R*,*S*,*S*)-**9**	CuOAc	EtOAc	−20	73	90 (*S*)

[a] Reaction conditions: cyclohex-2-enone (0.33 mmol), $ZnEt_2$ (0.5 mmol), copper catalyst (0.01 mmol), ligand (0.02 mmol) in 6 mL solvent for 3 h.
[b] Isolated yield.
[c] Enantiomeric excesses (ee) were determined by chiral GC (Supelco γ-dex 225 column, 70 °C, 120 min, $t_1 = 67.8$ min, $t_2 = 71.2$ min).
[d] Absolute configuration was determined by comparing with the literature values.
[e] CuOAc:(*R*,*S*,*S*)-**9**:**10** = 1:2:100.
[f] CuOAc:(*R*,*S*,*S*)-**9**:**10** = 1:2:1000.

(entries 1–3). Under the same reaction condition, however, good enantioselectivity (Table 1, entry 4, 93% ee) was achieved by the use of ligand (*R*,*S*,*S*)-**9** bearing a bulky chiral amine. In contrast, the use of its diastereomer (*R*,*R*,*R*)-**9** resulted in only 10% ee. These results indicate that a stereochemically matched ligand structure is fundamental to induce high enantioselectivities. Our investigation is in agreement with what were reported in other copper/phosphoramidite catalytic systems.[1b,3b,i] Having identified (*R*,*S*,*S*)-**9** as the best ligand, further enhancement of enantioselectivity can be achieved by lowering the reaction temperature. When the reaction was carried out at room temperature (25 °C), the ee dropped dramatically to 75%. On the other hand, at −20 °C and −30 °C, the enantioselectivity can be improved to 94% ee and 96% ee, respectively (Table 1, entries 7 and 8). Another tunable factor is the copper salt, which also plays an essential role accounting for high catalytic activity and enantioselectivity.[1b] Recent mechanistic studies via EPR experiments,[12] provided unequivocal evidence in favor of the earlier assumption[3d,g] that the real catalytic species is the in situ reduced Cu^{I} complex. Therefore, both Cu^{I} and Cu^{II} salts can be successful in this reaction. Although $(CuOTf)_2$·toluene led to much lower ee than its divalent counterpart (compare Table 1, entries 7 and 9, 49% ee vs 94% ee), copper carboxylate, both CuOAc and $Cu(OAc)_2·H_2O$, gave excellent enantioselectivities (Table 1, entries 10 and 11). High ee was also achieved when $Cu(MeCN)_4ClO_4$ was used (Table 1, entry 12). However, the use of $Cu(MeCN)_4PF_6$ is detrimental, leading to only 52% ee (Table 1, entry 13). This dramatic influence of copper salt on enantioselectivity demonstrated that although $Cu(OTf)_2$ is the most commonly used precursor, some other copper salts, especially Cu carboxylates, can be more effective.[1b,3g] It is noted that with reduced catalyst loading, no remarkable decrease in ee was observed. For example, when 1% and 0.1% CuOAc were used, the ee is 98% and 96%, respectively (Table 1, entries 14 and 15). In addition to toluene, some other solvents have been tested in this catalytic reaction. Although ethereal solvents such as ether and THF lead to slightly higher ee's than CH_2Cl_2 and EtOAc, toluene is still the best solvent (Table 1, entries 16–19).



Scheme 3. Copper-catalyzed enantioselective conjugate addition of diethylzinc to cyclohept-2-enone **12** and cyclopent-2-enone **14** with spirocyclic ligand (*R*,*S*,*S*)-**9**.

The other two cyclic enones **12** and **14** were also tested in this catalytic system using ligand (*R*,*S*,*S*)-**9**. When **12** was used, 98% ee was achieved. However, side reactions[1a] dominate in the case of **14**, resulting in low yield and enantioselectivity (Scheme 3).

In conclusion, new monodentate spirocyclic phosphoramidite ligands were prepared from chiral spirocyclic diol (*R*)-**5**. Among them ligand (*R*,*S*,*S*)-**9** with a C_2-symmetric chiral secondary amine moiety can lead to up to 99% ee in copper-catalyzed conjugate addition of diethylzinc to cyclic enones. Further application of these rigid ligands for other asymmetric catalytic reactions will be studied.

Acknowledgment

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11. Typical synthetic procedure ((*R*,*S*,*S*)-**9**): in a flame-dried Schlenk flask, *n*-BuLi (2 mmol, 2.5 M in hexane) was added into (*S*,*S*)-bis(α-methylbenzyl)amine (2 mmol) in 20 mL THF at −78 °C within 15 min. After stirring for 10 min, it was warmed to room temperature for 20 min. Then the solution was transferred into PCl_3 (2 mmol) in 10 mL THF at −78 °C. After stirring for 30 min, it was warmed slowly to room temperature over 1 h. Then it was cooled to 0 °C, (*R*)-**5** (2 mmol) and NEt_3 (6 mmol) in 10 mL THF were added, and stirred overnight. The reaction mixture was stirred at 60 °C for 24 h. After the solvent was evaporated, flash chromatography on silica gel (EtOAc–hexane = 1:15) afforded the product as white powder (856 mg, yield 68%). ^{1}H NMR (360 MHz, CD_2Cl_2) δ 1.65 (s, 6H), 4.33 (s, 2H), 6.25 (d, $J = 8.0$ Hz, 1H), 6.44 (d, $J = 7.9$ Hz, 1H), 6.79 (d, $J = 7.8$ Hz, 1H), 6.86–7.30 (m, 19H), 7.40 (t, $J = 8.0$ Hz, 1H), 7.57 (t, $J = 8.0$ Hz, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 19.2, 25.0, 30.1, 43.7, 113.5, 113.8, 113.8, 116.9, 117.1, 118.9, 120.3, 120.4, 120.9, 121.0, 121.8, 124.0, 126.2, 127.1, 128.1, 128.5, 128.7, 129.6, 129.7, 149.2, 149.3, 150.2, 150.5, 152.0, 152.1, 155.3, 155.5; ^{31}P NMR (146 MHz, CD_2Cl_2) δ 130.0 (s). HRMS ($M+Na^+$) calculated: 656.1961. Found: 656.1948.
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13. Typical procedure for conjugate addition: a solution of copper salt and ligand in toluene was stirred at room temperature for 1 h under N_2. After it was cooled to −20 °C, cyclohex-2-enone and $ZnEt_2$ were added sequentially. The reaction was running for 3 h at this temperature, and then quenched with saturated aqueous NH_4Cl solution. The mixture was extracted twice with ether. The combined organic phase was dried with anhydrous Na_2SO_4 and concentrated. Chromatography on silica gel (ether–pentane = 1:6) gave the desired product as colorless oil.