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Enantioselective conjugate addition of diethylzinc to cyclohexenone catalyzed by a chiral aminophosphine–copper(II) triflate

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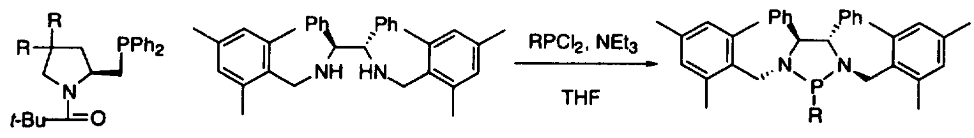
Abstract

Enantioselective conjugate addition of diethylzinc to cyclohexenone and 4,4-dimethylcyclohexenone was catalyzed by the combination of 0.1 equiv. of a chiral monodentate aminophosphine **3** and 0.05 equiv. of copper(II) triflate to give the corresponding adducts **4** in up to 70% ee.

We have been involved in the development of external chiral phosphine ligands for the catalytic asymmetric conjugate addition reaction of organocopper reagents with α,β-unsaturated carbonyl compounds.[1,2] Bidentate amidophosphines **1** have been developed based on the concept of metal differentiating coordination and have successfully proven their utility in copper-catalyzed conjugate addition of Grignard reagents.[3] The drawback of the catalytic reaction system is, however, the use of 32 mol% of chiral phosphines **1** to achieve high enantiofacial differentiation. The formation of an organocopper species freed from the chiral phosphine is probably a reason for the poor efficiency. A solution to this problem is the use of a poor alkylating reagent as well as a chiral phosphine ligand of stronger coordinating ability to copper.



1 **2** **3a** R = Ph **3b** R = Me

Combined with our experiences on chiral external ligands[4] for organolithium,[5] lithium ester enolate,[6] lithium phosphonate,[7] and lithium arylthiolate,[8] we designed new monodentate aminophosphines for the conjugate addition of organocoppers. The chiral five-membered aminophosphine **3** has a characteristic feature that the four substituents, two phenyl groups on the ethylene bridge and two substituents on the nitrogen atoms, take an all-*trans* arrangement due to steric factors and hence the nitrogen substituents

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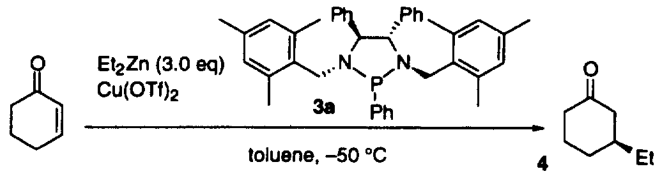
Table 1
Enantioselectivity dependency on the amount of Cu–**3a**



entry	$Cu(OTf)_2$/eq	**3a**/eq	time/h	yield/%	ee/%
1	0.025	0.05	5	70	41
2	0.05	0.10	3	74	44
3	0.10	0.20	1	72	40

provide a chiral environment around the phosphorus atom. The most important factor is the C_2-symmetric chiral environment of the complex of **3** coordinated by copper.[9] Tuning of the coordinating ability of phosphorus is possible by the selection of the R group on the phosphorus atom. We describe herein that enantioselective conjugate addition of diethylzinc to cyclohexenone and 4,4-dimethylcyclohexenone is catalyzed by **3**–copper triflate to afford the corresponding adducts **4** in up to 70% ee.[10,11]

The chiral aminophosphines **3a**,**b** were prepared from the known C_2-symmetric chiral diamine **2**.[12] Treatment of **2** with dichlorophosphine (R=Ph, Me) in the presence of triethylamine in THF afforded **3a** (R=Ph, purified through alumina column chromatography (AcOEt/hexane), mp 94.5–96°C (recrystallization from AcOEt), $[\alpha]_D^{25}$ +18.1 (c 1.09, $CHCl_3$)) and **3b** (R= Me, purified through alumina column chromatography (Et_2O/hexane), mp 59–65°C (dec.), $[\alpha]_D^{25}$ −4.7 (c 1.00, EtOH)) as solids in 77 and 65% yields, respectively.

At first, we examined the reaction of cyclohexenone under the previously established asymmetric reaction conditions for **1**[3] with 2.4 equiv. of butylmagnesium chloride, 1.2 equiv. of copper iodide and 1.5 equiv. of **3a** in diethyl ether at −78°C for 25 min to give 3-butylcyclohexanone[13] in 83% yield, but in 1% ee. The poor efficiency of **3a** in the reaction of organocopper derived from Grignard reagent is attributable to the monodentate character, instead of the bidentate feature of **1**.[3]

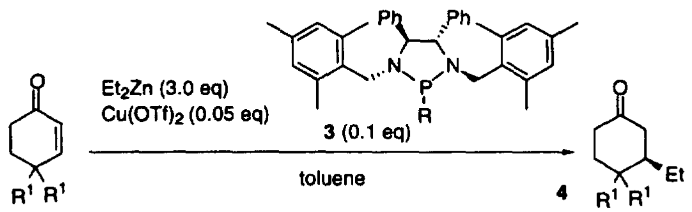
Then, we turned our attention to the reaction of diethylzinc with cyclohexenone in the presence of 0.1 equiv. of **3a** and 0.05 equiv. of Cu(II) triflate. The reaction proceeded smoothly in toluene at −40°C for 2 h to afford (*S*)-3-ethylcyclohexanone **4**[14] in 41% ee and 73% yield. Of the solvents examined, toluene was the one of choice with respect to ee, yield and reaction time. The reactions in diethyl ether, THF, and methylene chloride gave (*S*)-**4** in 11, 8, and 1% ees, respectively. The temperature effect was not beneficial, the reaction at −50°C for 3 h and −60°C for 24 h gave (*S*)-**4** in 44 and 39% ees, respectively.

The equivalence of **3a** to copper had little influence on the efficiency. Three variations, 1.2, 2, and 3 equiv. of **3a** for copper(II) triflate gave rise to a similar level of enantioselectivity, 42–39% ee. In the absence of a copper source, however, **3a** did not mediate the addition reaction to give **4** in only 2% yield.

The most promising result is the amount of catalyst, for example 0.025 equiv. of copper(II) triflate and 0.05 equiv. of **3a** or 0.1 equiv. of copper(II) triflate and 0.2 equiv. of **3a** gave the same level of efficiency as shown in Table 1.

The substituent on phosphorus exerts a marked effect on reactivity and enantioselectivity. The reaction catalyzed by copper triflate and the ligand **3b** bearing a methyl substituent on phosphorus was completed within 15 min at −50°C to afford (*S*)-**4** in 51% ee as shown in Table 2, entry 2. The reaction at −78°C for 1 h gave (*S*)-**4** in 55% ee (entry 3).[15] These results clearly indicate that the methyl substituent on phosphorus is much more effective than the phenyl group in activation of the reactivity of copper species.

Table 2
Enantioselectivity and reactivity dependency on Cu–3 catalyst



entry	R^1	3/R	temp/°C	time/h	yield/%	ee/%
1	H	**3a**/Ph	−50	3	74	44
2	H	**3b**/Me	−50	0.25	75	51
3	H	**3b**/Me	−78	1	70	55
4	Me	**3b**/Me	−78 to rt	5.5	80	70

Under the catalysis of copper triflate–**3b**, 4,4-dimethylcyclohexenone was converted to (*R*)-3-ethyl-4,4-dimethylcyclohexenone[16] in 70% ee and 80% yield as shown in Table 2, entry 4.

Encouraged by the promising behavior of the new chiral monodentate phosphine ligands **3**, further studies directed toward the development of efficient ligand are in progress in our laboratories.

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