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Copper-catalyzed conjugate addition on macrocyclic, cyclic, and acyclic enones with a chiral phosphoramidite ligand having a C_2-symmetric amine moiety

Yong Hyun Choi, Jun Young Choi, Hye Yon Yang and Yong Hae Kim*

Department of Chemistry, Center for Molecular Design and Synthesis, Korea Advanced Institute of Science and Technology, Taejon 305-701, South Korea

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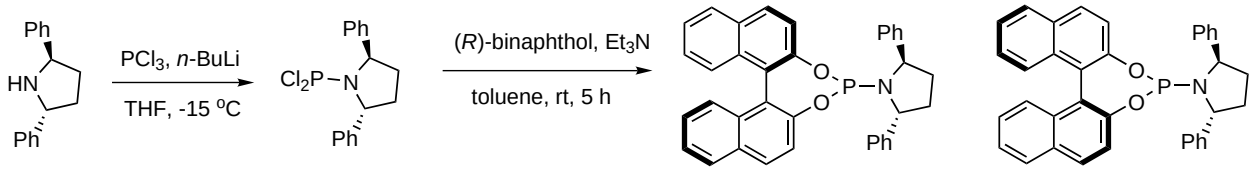
Abstract—A binaphthol-based phosphoramidite ligand (4.2 mol%) having a C_2-symmetric chiral amine moiety was examined for enantioselective 1,4-additions of dialkylzinc reagents to various macrocyclic, cyclic, and acyclic enones catalyzed by copper triflate·toluene complex (2 mol%) to afford high enantiomeric excess (up to >95% ee).

The asymmetric conjugate addition of organometallic reagents to enones is an attractive synthetic method for carbon–carbon bond formation.[1] A number of chiral auxiliaries and stoichiometric reagents have been developed which allow asymmetric 1,4-addition reactions to proceed in an enantioselective manner.[1d] Great efforts have also been made to develop catalysts for asymmetric conjugate additions of organozinc reagents to enones using phosphorus–amidites,[2] phosphite–oxazolines,[3] amido–phosphine,[4] diphosphite,[5] sulfonamide,[6] and Schiff base[7] ligands. Among them, copper and binaphthol–phosphorus type ligand complexes[2,3,5] have been developed for effective enantioselective 1,4-addition reactions. Recently, highly enantioselective alkylation to enones was reported by Feringa and co-workers using chiral phosphorus–amidite ligands with a chiral secondary amine catalyst.[2a,b] While high enantiomeric excesses were achieved for cyclohexenone, the enantioselective 1,4-addition reaction to macrocyclic enones resulted in unsatisfactory enantioselectivity. During the study on asymmetric alkylations of macrocyclic enones, we have established that a new binaphthol phosphoramidite ligand containing a chiral C_2-symmetric pyrrolidine moiety is an excellent ligand for chiral copper complexes which furnish high enantioselectivities in the conjugate addition of dialkylzinc reagent to macrocyclic enones. The chiral ligand (*R*,*R*,*R*)-**1** has been applied to the synthesis of (*R*)-(−)-muscone, a biologically intriguing natural product which has been synthesized by various methods.[8]

Enantiomerically pure ligand **1** was easily prepared by the reaction of (*R*)-binaphthol and (*R*,*R*)-chloroamidite **2** in the presence of triethylamine. (*R*,*R*)-Chloroamidite **2** was synthesized by the reaction of (*R*,*R*)-diphenylpyrrolidine **3** with *n*-BuLi in tetrahydrofuran at −15°C and then following addition of an excess of neat PCl_3 to THF solution of lithium amide (Scheme 1).[10]



(*R*,*R*)-**3** (*R*,*R*)-**2** (*R*,*R*,*R*)-**1** (*S*,*R*,*R*)-**1**

Scheme 1.

* Corresponding author. Tel.: +82-42-869-2818; fax: +82-42-869-5818; e-mail: yhkim@kaist.ac.kr

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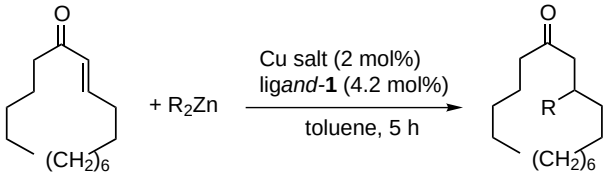
Table 1. The effect of reaction temperature and ligand configuration on the conjugate addition of diethylzinc to 2-cyclopentadecen-1-one **7b**



4a n=3
4b n=6

5a n=3, R=Et
5b n=6, R=Et
5c n=6, R=Me

Entry	Ligand	Cu salt	Substrate	R	Product	*T* (°C)	Yield (%)[a]	Ee (%)[b,d]
1[c]	(*R*,*R*,*R*)-**1**	$Cu(OTf)_2$	**4b**	Me	**5c**	−20	90	86 (*R*)
2[c]	(*S*,*R*,*R*)-**1**	$Cu(OTf)_2$	**4b**	Me	**5c**	−20	75	55 (*S*)
3	(*R*,*R*,*R*)-**1**	$Cu(OTf)_2$	**4b**	Me	**5c**	−40	85	93 (*R*)
4	(*R*,*R*,*R*)-**1**	$Cu(OTf)_2$	**4b**	Me	**5c**	−78	–	–
5	(*R*,*R*,*R*)-**1**	$(CuOTf)_2$·toluene	**4b**	Me	**5c**	−40	87	95 (*R*)
6	(*R*,*R*,*R*)-**1**	$(CuOTf)_2$·toluene	**4a**	Et	**5a**	−40	90	71 (*R*)
7	(*R*,*R*,*R*)-**1**	$(CuOTf)_2$·toluene	**4b**	Et	**5b**	−40	95	74 (*R*)

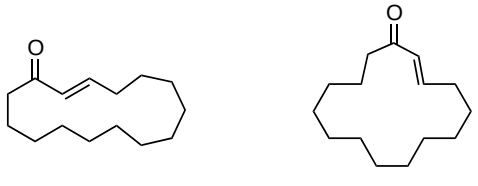
[a] Isolated yield.
[b] The ee was determined by chiral HPLC on a chiraldex AS column.
[c] The reaction time was 3 h.
[d] The absolute configuration was determined from the specific rotation (Ref. 13).

The chiral amine (*R*,*R*)-**3** was prepared by the known method.[9]

In order to establish optimal conditions for the addition reaction, 2-cyclopentadecen-1-one **4b** was chosen as a typical substrate and tested with chiral ligand **1**. The results obtained are summarized in Table 1. In most cases, complete conversions occurred and the 1,2-adduct was not detected by gas chromatographic analysis. The highest enantioselectivity was obtained at –40°C in toluene (95% ee, entry 5). The 1,4-adduct could not be obtained at –78°C: starting material **4a** was recovered (entry 4). The enantioselectivity decreased considerably as the reaction temperature was elevated to –15 or 0°C. Use of $(CuOTf)_2$·toluene complex gave somewhat higher enantioselectivity than the $Cu(OTf)_2$ system (entries 3 and 5). Ligand configuration appears to be important because the mismatched ligand (*S*,*R*,*R*)-**1** diminished both the rate, conversion (75%) and enantioselectivity (55% ee) of the reaction (entry 2).

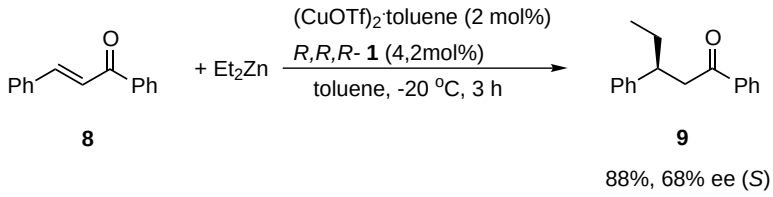
The conformation of the macrocyclic enones could be *s-trans* or *s-cis* (Fig. 1). Since the reactions of **4b** mediated by the (*R*,*R*,*R*)-**1** complex to give products **5** resulted in the same diastereofacial outcome, it was thought that the 1,4-addition reaction might occur from the **4b**-*s-cis* form as in acyclic enone **8** (Scheme 2). Thus, 12- and 15-membered enones were tested using (*R*,*R*,*R*)-**1** and $(CuOTf)_2$·toluene complex. In the 1,4-addition of diethylzinc to **4a**, the ligand (*R*,*R*,*R*)-**1** complex gave **5a** (90%) with high enantioselectivity (71% ee, entry 6, Table 1). Enone **4b** was reacted with diethylzinc with (*R*,*R*,*R*)-**1** at –40°C for 3 h to give **5b** (95%, 74% ee) (entry 7 in Table 1). The Alexakis group reported the synthesis of (*R*)-(–)-muscone using a catalytic amount of copper (2 mol%) and chiral phosphite ligand (4 mol%) with somewhat low yield (53%) and moderate enantioselection (79% ee).[12] However, we were able to obtain (*R*)-(–)-muscone in high yield through the highly enantioselective 1,4-addition of dimethylzinc to **4a** (95% ee) by utilizing (*R*,*R*,*R*)-**1** as a catalytic ligand.[11]

As illustrated in Table 2, small (five-, six-, and seven-membered) rings were examined with 4.2 mol% of (*R*,*R*,*R*)-**1** and 2 mol% of $(CuOTf)_2$·toluene complex. The conversions were determined by GC analysis. In all cases, reactions were completed within 3 h and the regioselectivity for the 1,4-adducts over the 1,2-adducts was higher than 99% (yield: 98%, entry 1 in Table 2). The five-, six- and seven-membered enones gave the corresponding 1,4-products with ee of 52–93%. In the case of 2-cyclopenten-1-one **6b**, the conversion was almost quantitative to the corresponding 1,4-adduct **7b** by GC analysis, but the isolated yield was somewhat lower probably due to the volatility of **7b** (entry 2 in Table 2).



4a-*s-cis* **4a**-*s-trans*

Figure 1.

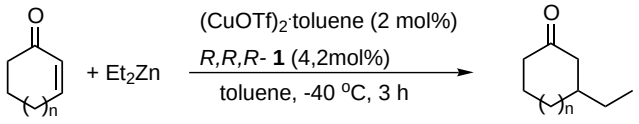


8 **9**

88%, 68% ee (*S*)

Scheme 2.

Table 2. Copper-catalyzed conjugate addition to cyclic enones **6a–c**



6a n=1
6b n=0
6c n=2

7a n=1
7b n=0
7c n=2

Entry	Substrate	Product	Yield (%)[a]	Ee (%)[b,d]
1	**6a**	**7a**	98	93 (*R*)[c]
2	**6b**	**7b**	78	52 (*R*)[c]
3	**6c**	**7c**	97	76 (*R*)[c]

[a] Isolated yield.
[b] The ee was determined by chiral GC on a Chiraldex G-DM (30×0.25 mm) capillary column.
[c] The absolute configuration was determined by chiral GC on a chiraldex G-DM column compared with the known reference (Ref. 3).
[d] The absolute configuration was not determined.

The acyclic α,β-unsaturated ketone, *trans*-chalcone **8** reacted with diethylzinc in the presence of (*R*,*R*,*R*)-**1** (4.2 mol%) and $(CuOTf)_2$·toluene complex (2 mol%) at –20°C in toluene to afford **9** in high yield and moderate enantioselectivity (Scheme 2). When the reaction temperature was decreased to –40°C, the reaction did not proceed at all. The absolute configuration of the product is known.[3]

In conclusion, the binaphthol-based phosphorusamidite ligand bearing a C_2-symmetric pyrrolidine could be successfully utilized as a chiral ligand in the copper-catalyzed enantioselective conjugate addition. In particular, the enantioselective 1,4-addition reaction using catalytic amount of chiral ligand (*R*,*R*,*R*)-**1** was applied to synthesis of chiral macrocyclic ketones such as (*R*)-(–)-muscone with high eanantioselectivity. Until now there is only one reported example of asymmetric 1,4-additions to macrocyclic enones using a catalytic chiral ligand.[10]

Acknowledgements

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10. **Synthesis of *O,O′*-(*R*)-(1,1′-dinaphthyl-2,2′-diyl)-4-((*R,R*)-2,5-diphenylpyrrolidine)-(*R*)-dinaphthodioxaphosphephine (*R,R,R*)-1**

    A solution of (*R,R*)-*trans*-2,5-diphenylpyrrolidine **3** in THF at −78°C under argon was treated dropwise with *n*-butyllithium (2.5 M hexane). The reaction mixture was then stirred for 1 h. Excess PCl_3 (10 equiv.) was then rapidly added to the lithium reagent. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was concentrated and extracted with toluene. Evaporation of the solvent from the combined extracts afforded the product as a pale-yellow oil (*R,R*)-**2** which was used without further purification.

    A solution of (*R*)-binaphthol and triethylamine (5 equiv.) in toluene was added dropwise to a solution of (*R,R*)-**2** in toluene at 0°C. After stirring for 12 h, the precipitated $Et_3N{\cdot}HCl$ was removed by filtration, and concentrated to give the crude product which was purified by silica gel column chromatography (EtOAc/hexane, 1/9) to give pure chiral ligand (*R,R,R*)-**1** as a white solid in 55% yield (99.8% ee); $[\alpha]_D^{24}$ −556.2 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm) 7.12–7.94 (m, 22 H), 5.11–5.04 (m, 2 H), 2.41–2.34 (m, 2 H), 1.76–1.68 (m, 2 H); ^{13}C NMR ($CDCl_3$), δ (ppm) 144.55, 144.49, 132.88, 131.14, 130.59, 129.87, 128.11, 127.08, 126.82, 126.01, 125.81, 124.51, 121.90, 121.40, 63.37, 63.21, 34.19; HRMS observed mass = 537.1906 (calculated mass = 537.1858).
11. **General procedure for the catalytic conjugate addition of dialkylzinc to enones**

    A solution of $(CuOTf)_2{\cdot}$toluene complex (3.6 mg, 0.01 mmol) and chiral ligand (*R,R,R*)-**1** (0.021 mmol) in toluene (3 mL) was stirred for 1 h. The colorless solution was cooled to −40°C and enone (0.5 mmol) was added followed by addition of a solution of dialkylzinc in toluene (1.5 equiv.). After stirring for 3–5 h, the reaction mixture was quenched with 1N aqueous HCl and extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc/hexane, 1/9) to give the 1,4-addition products.
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