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Enantioselective conjugate addition of diethylzinc to enones catalyzed by a copper complex of chiral aryl diphosphite

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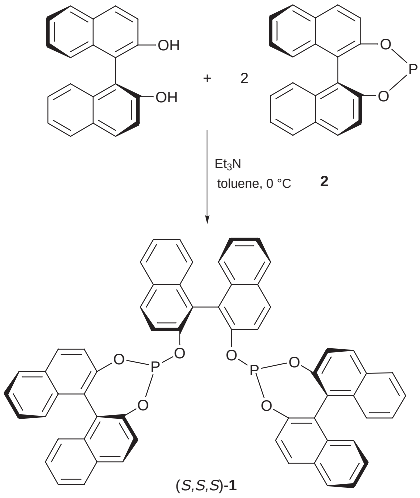
The 1,4-conjugate addition of diethylzinc to cyclohex-2-enone and cyclopent-2-enone catalyzed by a copper complex of a chiral aryl diphosphite gave the desired products with 90.2 and 76.6% ee respectively.

The enantioselective conjugate addition of chiral organometallic reagents to enones is an attractive method for C–C bond formation. A number of successful methods for stereoselective 1,4-addition based on chiral auxiliaries or stoichiometric organometallic reagents have been developed, but a highly enantioselective catalytic version is still rare.[1] Ni^{II} and Co^{II} catalysts containing chiral amino alcohol ligands are of substantial interest, but they show enantioselectivity only for acyclic enones.[2] The copper complexes of chiral phosphites,[3] phosphorus amidites,[4] phosphines,[5] thiols[6] and aminophosphines[7] have been used in the catalytic conjugate addition of Et_2Zn or Grignard reagents to enones with low to moderate enantioselectivity. Recently several chiral phosphorus amidites[8] and phosphite oxazolines[9] have been used in the copper-catalyzed conjugate addition of dialkylzinc to cyclohex-2-enone with excellent enantioselectivity. These ligands shared a common feature of a bridging of binaphthol with a chiral amine through a phosphorus center. The active catalyst in the reaction has been proposed by Feringa *et al*. to be an alkyl–Cu^I species coordinated with two ligand molecules.[8] The C_2-symmetric bidentate ligands in these reactions are of substantial interest.[4a] Here we report the catalytic conjugate addition of Et_2Zn to enones using a C_2-symmetric chiral aryl diphosphite–$Cu(OTf)_2$ complex with good enantioselectivity and high catalytic activity.

Optically pure aryl diphosphite (*S*,*S*,*S*)-**1** was prepared by the reaction of the (*S*)-chlorophosphite **2** and (*S*)-binaphthol in the presence of Et_3N (Scheme 1). The crude product was easily purified by recrystallization in CH_2Cl_2–EtOH. The structure of the compound was supported by elemental analysis and spectral data.[10]

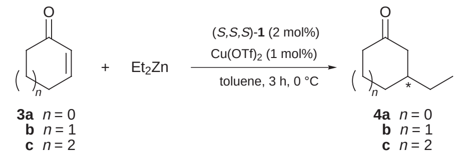


Scheme 1

In 1991 Pringle *et al*. reported the synthesis of (*R*,*R*,*R*)-**1** from trichlorophosphine and (*R*)-binaphthol. A Ni^0 complex of (*R*,*R*,*R*)-**1** was used in the hydrocyanation of norbornene, giving a product with 38% ee.[11] It is noticeable that the structure of **1** is entirely based on chiral binaphthol. (*S*,*S*,*S*)-**1** is fairly stable to oxygen in the solid state but is somewhat air- and moisture-sensitive in solution.

The addition of Et_2Zn to cyclohex-2-enone **3b** was used as a model (Scheme 2). The effects of reaction temperature, solvent and the ratio of (*S*,*S*,*S*)-**1** to $Cu(OTf)_2$ were investigated and the results are summarized in Table 1. In most cases complete conversion and good enantioselectivity were obtained. No 1,2-addition product was detected by GC analysis. The reaction was strongly dependent on the choice of solvents. The best solvent was found to be toluene (90.2% ee, 100% conversion). Coordinative solvents such as THF and MeCN gave substantially lower conversion rates and enantioselectivities (22.4% conversion, 72.2% ee and 6.5% conversion, 0% ee, respectively). The use of 2 equiv. (*S*,*S*,*S*)-**1** increased the enantioselectivity from 83.2 to 90.2% ee (entry 2 *vs*. entry 3). Further increase of the ratio of (*S*,*S*,*S*)-**1** to $Cu(OTf)_2$ decreased the catalytic activity (entry 1). When less than 1 equiv. (*S*,*S*,*S*)-**1** was used, the enantioselectivity decreased but the catalytic activity was still high (entry 4). The optimum reaction temperature was found to be *ca*. 0 °C. When the reaction temperature decreased to -40 °C, the reaction became sluggish and far less enantioselective (entry 8). Although the use of a low catalyst:substrate ratio was rather ineffective, it is of interest to note that increasing the concentration of the catalyst lowered the enantioselectivity (entries 9–11). The preliminary results revealed that a catalyst concentration of 0.0008–0.0012 M was optimum. The copper complexes at different concentrations may form different catalytic species. Similar results had been reported by Feringa *et al*.[4a] When EtMgCl was used in place of Et_2Zn only racemic **4b** was obtained as the major product and small amounts of 1,2-addition product were observed (entry 12).

The ^{31}P NMR spectrum of the catalyst solution (L:Cu = 2:1, toluene-d_8) showed two peaks at δ 231.6 and 149.0. The peak at δ 149.0 corresponded to free (*S*,*S*,*S*)-**1** and the low field peak at δ 231.6 is expected to be (*S*,*S*,*S*)-**1**–$Cu(OTf)_2$. When excess Et_2Zn was added at room temperature, the peak at δ 231.6 disappeared quickly and a new peak at δ 124.0 was observed. This new species may be postulated to be an Et–Cu^I complex containing a molecule of (*S*,*S*,*S*)-**1**. The electron-rich nature of Et–Cu^I caused the significant ^{31}P NMR shift. Coordinative solvents such as THF or MeCN competed with the enone substrates for the coordinating site of the Cu^I catalyst and



Scheme 2

Table 1 Enantioselective 1,4-addition of diethylzinc to cyclohex-2-enone **3b** catalyzed by (*S*,*S*,*S*)-**1**–$Cu(OTf)_2$[a]

Entry	$Cu(OTf)_2$/**3b**	**1**/$Cu(OTf)_2$	*T*/°C	Conversion (%)[b]	Ee (%)[b]	Configuration[c]
1	0.01	4	0	81.7	88.3	*S*
2	0.01	2	0	100 (92.0[d])	90.2	*S*
3	0.01	1	0	100	83.2	*S*
4	0.01	0.5	0	100	79.1	*S*
5	0.01	2	40	100	70.9	*S*
6	0.01	2	20	100	87.7	*S*
7	0.01	2	−20	100	84.6	*S*
8	0.01	2	−40	24.1	39.4	*S*
9	0.001	2	0	54.5	67.5	*S*
10	0.05	2	0	100	57.1	*S*
11	0.2	2	0	100	45.2	*S*
12[e]	0.01	2	−78	100[f]	0	—

[a] 1.5 equiv. of diethylzinc was used and the reactions were carried out in toluene for 3 h. [b] The conversions and ee values were determined by GC with a Chiraldex A-TA column (30 m × 0.25 mm); no 1,2-addition product was observed. [c] The absolute cofiguration was determined by optical rotation (ref. 12). [d] Isolated yield. [e] Ethylmagnesium chloride was used. [f] A small amount of 1,2-addition product was observed.

decreased the rate of reaction as well as the enantioselectivity.

The Cu^{II} complex of (*S*,*S*,*S*)-**1** was also tested in the conjugate addition of diethylzinc to cyclopent-2-enone **3a**, cyclohept-2-enone **3c** and chalcone **5**, and the results are summarized in Table 2. Up to now the catalytic conjugate addition of organometallic reagents to **3a** has been relatively unsuccessful.[4c,8,9] With the (*S*,*S*,*S*)-**1**–$Cu(OTf)_2$ catalyst system, the conjugate addition of Et_2Zn to **3a** gave a good yield of the desired product with 76.6% ee (entry 1). To the best of our knowledge, this enantioselectivity was the best one so far obtained for this reaction. Interestingly the absolute configuration of the product was opposite to that from the conjugate addition to **3b**. The reversal of enantiofacial selectivity for **3a** was also observed previously by Rossiter *et al.*[13] The conjugate addition of Et_2Zn to **3c** gave a lower conversion rate and enantioselectivity than the reaction with **3b** and **3a** (entry 2, Scheme 2).

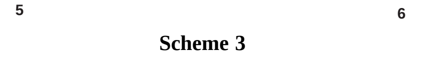
Table 2 The addition of diethylzinc to enones **3a**,**c** and **5** catalyzed by (*S*,*S*,*S*)-**1**–$Cu(OTf)_2$

Entry	Substrate	Solvent	*T*/°C	Conversion (%)[a]	Ee (%)[a]	Configuration
1	**3a**	Toluene	0	100 (71.3[b])	76.6	*R*[c]
2	**3c**	Toluene	0	40.0	56.0	nd[d]
3	**5**	Toluene	0	45	9.3	*R*[e]
4	**5**	THF	0	62	16.5	*R*

[a] The ee value of **4a** and the conversion were determined by GC with a Chiraldex A-TA Column (30 m × 0.25 mm). The ee value of **4c** and the conversion were determined by GC with a Chrompack CP-Chirasil-Dex CB (25 m × 0.25 mm). The ee value of **6** and the conversion were determined by HPLC with a Diacel-OD column. [b] Isolated yield. [c] The absolute configuration was determined by optical rotation (ref. 14). [d] Not determined. [e] Comparison of the retention time of **6** in HPLC with known data (ref. 9).

The conjugate addition of Et_2Zn to chalcone gave **6** with poor enantioselectivity and low conversion (entries 3 and 4, and Scheme 3). The high specificity of the matching of substrate and catalyst had been found in many other catalyst systems.[2c,8,9]

The chiral match of the three binaphthol rings is very important for efficient enantiocontrol. (*S*,*R*,*S*)-**1** was prepared and used for the addition of Et_2Zn to **3b** using the optimum reaction conditions [1 mol% $Cu(OTf)_2$, 2 mol% (*S*,*R*,*S*)-**1**, 0 °C, toluene]. Compound **4b** was obtained with only 30.6% ee (*S*).



Scheme 3

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10 *Selected data* for (*S*,*S*,*S*)-**1** containing 0.5EtOH (solvent of crystallization): Calc. for $C_{60}H_{36}O_6P_2\cdot0.5C_2H_6O$: C, 78.12; H, 4.16%. Found: C, 78.13; H, 4.16%; $\delta_P(CDCl_3)$ 145.7; $\delta_H(CDCl_{3,}$ 400MHz) 7.97 (d, *J* 8.8, 2H), 7.90 (d, *J* 8.0, 2H), 7.82 (dd, J_1 8.0, J_2 8.8, 4H), 7.73 (d, *J* 8.0, 2H), 7.52 (d, *J* 8.8, 2H), 7.37 (m, 8H), 7.16–7.31 (m, 14H), 6.53 (d, *J* 8.8, 2H), 3.72 (q, *J* 6.8, 1H), 2.36 (s, 0.5H), 1.24 (t, *J* 6.8, 1.5H); $\delta_C(CDCl_3)$ 147.2, 147.0, 146.5, 134.2, 132.7, 132.2, 131.4, 131.0, 130.8, 130.2, 130.0, 129.5, 128.3, 128.2, 128.1, 126.9, 126.8, 126.2, 126.0, 125.8, 125.1, 124.9, 124.6, 124.2, 122.4, 121.8, 121.7, 121.1; *m/z* (ESI) 915 (M^+ + 1, 100%); Mp 196–198 °C (decomp.); $[\alpha]_D^{20}$ +346.6 (*c* 1.085, THF) [a rather different $[\alpha]_D^{20}$ value was reported by Pringle *et al.* (ref. 11)].
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