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Nonlinear effects in the enantioselective 1,4-conjugate addition of diethylzinc to chalcone

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Abstract—A clear positive nonlinear effect of the enantiopurity of ligand **1** on the product ee was observed in the enantioselective 1,4-conjugate addition of Et_2Zn to chalcone. The experimental data of nonlinear effect meet Kagan's ML_2 model.
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1. Introduction

The 1,4-addition of organometallic reagents to conjugate enones is one of the most important methods for carbon–carbon bond formation.¹ Although some chiral auxiliaries and stoichiometric reagents have been reported to impart high stereoselectivities in 1,4-conjugate additions, the development of catalytic stereoselective 1,4-additions has recently gained much attention. Chiral phosphorus ligands have undergone remarkable progress² in the Cu-catalyzed 1,4-conjugate addition of an organozinc reagent to an enone since it was originally introduced by Alexakis.³ A number of chiral phosphorus ligands such as phosphoramidites,⁴ phosphites,⁵ aryl diphosphites,⁶ MiniPHOS⁷ and other chiral P,N ligands,⁸ have been successfully applied in Cu-catalyzed enantioselective 1,4-conjugate additions of Et_2Zn to enones. The chiral ligands may be monodentate or bidentate. The effect of the ratio of chiral ligand to copper precursor on the enantioselectivities of the addition products has been carefully investigated. The ratio of 2 or more equiv. of ligand per Cu has been the most widely used for monodentate ligands so far,^{2,4,5} whereas the optimum reaction conditions for these bidentate ligands was complicated. In some cases the catalysts prepared from a ratio of ligand to copper more than 2:1 gave the best results^{6,8b–e,g–i} but in other cases less than 2 equiv. of ligand per Cu was enough.^{7,8f,j,k} We recently reported a new type of bidentate phosphite–pyridine (P,N) ligand and obtained high enantioselectivities in Cu(I)-catalyzed 1,4-conjugate addition of Et_2Zn to

chalcones by using 1 mol% $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{BF}_4$ and 2.5 mol% ligand **1a**.⁹ Herein, we report the study of the relationship between ligand enantiopurity, tuned by mixing **1a** and **1b** and the product ee to obtain more information on the active catalytic species (Fig. 1).

Since Kagan first reported the nonlinear effect of the enantiopurity of the ligand or chiral auxiliary on the product ee in 1986,¹⁰ it has become one of the most active fields in catalytic asymmetric reactions.¹¹ Many examples of nonlinear effects have been reported in recent years,^{12,13} and the study of relationship between the enantiopurity of the catalyst and the product ee has become a powerful tool to investigate reaction mechanisms.¹⁴ The nonlinear effects in the enantioselective 1,4-conjugate addition of organometallic reagents to enones have been previously reported.^{4a,8f,15} Bolm reported a strong positive nonlinear effect in the enantioselective Ni(II)-catalyzed 1,4-conjugate addition of Et_2Zn to chalcone using chiral amino alcohols.^{15e} Feringa observed a similar result with other chiral amino alcohol ligands.^{15a} Recently, Feringa^{4a} and Fu^{8f}

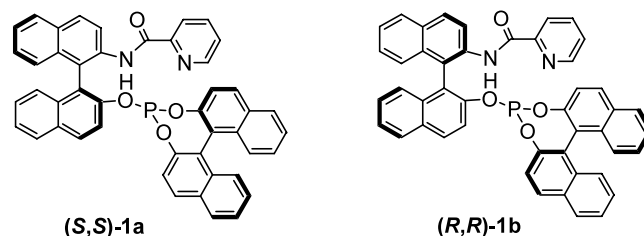


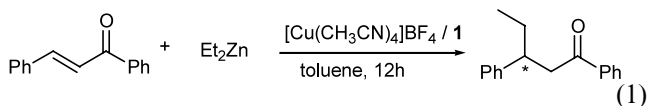
Figure 1.

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also obtained a clear but negative nonlinear effect in Cu-catalyzed 1,4-conjugate addition of Et_2Zn to enones with chiral phosphorus ligands. On the basis of our previous study on the enantioselective addition of Et_2Zn to acyclic enones, we are interested in investigating the relationship between the enantiopurity of ligand **1** and the product ee to obtain some helpful information on the reaction.

2. Results and discussion

Chalcone was chosen as the substrate to evaluate the nonlinear effect. The 1,4-conjugate addition (Eq. (1)) was carried out in toluene at -10°C using 1 mol% of $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{BF}_4$ and 2.5 mol% scalemic¹⁶ **1** with the desired ee that was prepared via mixing (*S,S*)-**1a** with its enantiomer (*R,R*)-**1b** and 1.5 equiv. of Et_2Zn . The results were summarized in Figure 2, when the ee of the adduct product was plotted against the ee of the ligand **1**, a clear positive deviation from the linear relationship was observed.



The positive nonlinear effect suggested the presence of heterochiral bis-(or higher) coordinated complexes in the reaction mixture. The suggestion was verified through adjusting the ratio of ligand to copper for the 1,4-conjugate addition. The experimental results showed that a 2:1 ratio of ligand to copper was essential for obtaining high enantioselectivity and activity for the 1,4-conjugate addition. The catalyst with one mole equivalent of ligand **1a** coordinated to copper gave only trace of addition product (3%) with very low ee (15% ee), while the copper catalyst with 2.5 mol equiv. of

ligand **1a** provided very high activity (92% yield) and enantioselectivity (91% ee) under the same reaction conditions.⁹ These results demonstrated that the efficient catalytic species was an ML_2 -type complex: one metal coordinated with two chiral ligands. Thus, the positive nonlinear effect could be explained by Kagan's ML_2 model system.¹⁰ When scalemic **1** was employed, two homochiral complexes $\{\text{Cu}[(\text{S,S})\text{-1a}]_2\}$ and $\text{Cu}[(\text{R,R})\text{-1b}]_2\}$ and one heterochiral complex $\{\text{Cu}[(\text{S,S})\text{-1a}][(\text{R,R})\text{-1b}]\}$ could be formed. The homochiral complexes provided enantiomeric products with reverse configuration whereas the heterochiral one generated racemic products. The nonlinear effect results from the different activities of homochiral and heterochiral complexes. A lower activity of the heterochiral catalyst provided a positive nonlinear effect. When excess (*S,S*)-**1a** was mixed with (*R,R*)-**1b** and coordinated to copper, the ratio of $\text{Cu}[(\text{S,S})\text{-1a}]_2$ to $\text{Cu}[(\text{R,R})\text{-1b}]_2$ was enlarged because of partial formation of $\text{Cu}[(\text{S,S})\text{-1a}][(\text{R,R})\text{-1b}]$, thus the product ee was higher than the initial ee value of ligand **1**.

In fact, this positive nonlinear effect was in accordance with Kagan's mathematical model (Eqs. (2) and (3)).^{10a} When g was taken as 0.2 and K was taken as 4, we obtained a simulated curve (Fig. 2), which was consistent with the experimental data. The results mean that the heterochiral complex $\text{Cu}[(\text{S,S})\text{-1a}][(\text{R,R})\text{-1b}]$ was much less active ($g = k_{\text{hetero}}/k_{\text{homo}} = 1/5$) than the corresponding homochiral complexes $\text{Cu}[(\text{S,S})\text{-1a}]_2$ and $\text{Cu}[(\text{R,R})\text{-1b}]_2$.

$$EE_{\text{prod}} = EE_0 ee_{\text{aux}} \frac{1+\beta}{1+g\beta} \quad (2)$$

$$\beta = \frac{-Kee_{\text{aux}}^2 + \sqrt{-4Kee_{\text{aux}}^2 + K(4+Kee_{\text{aux}}^2)4+Kee_{\text{aux}}^2}}{4+Kee_{\text{aux}}^2} \quad (3)$$

3. Conclusion

In summary, a clear positive nonlinear effect of the enantiopurity of ligand **1** on the product ee was observed in the enantioselective 1,4-conjugate addition of Et_2Zn to chalcone using chiral phosphite–pyridine ligand **1** with a wide range of ee (from 0 to 100% ee). The observed relationship showed good agreement with Kagan's ML_2 -type mathematical model, which demonstrated that the efficient catalyst should be a 1:2 complex of copper and the ligand. The positive nonlinear effect derived from the different activities of homochiral and heterochiral complexes

4. Experimental

4.1. General methods

Melting points were measured on a Yazawa micro melting point apparatus (uncorrected). Optical rotations were measured on a JASCO 1200 polarimeter. ¹H NMR spectrum was recorded on a BRUKER DRX 400 system with TMS as an internal standard. ³¹P

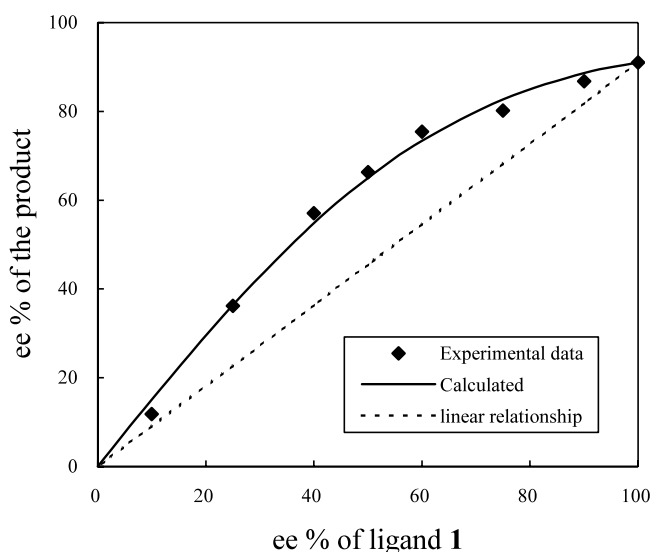


Figure 2. Experimental and calculated (according to Kagan's ML_2 system, with $K=4$ and $g=0.2$) correction between the ee of ligand **1** and the ee of product.

NMR spectrum was recorded with 85% phosphoric acid as the external standard. High resolution mass spectra (HRMS) were recorded on Mat 95 (EI: 70 eV) for (*R,R*)-(-)-**1b**. The ee values were determined by HPLC with a Daicel ChiralPak-AD column. All experiments were carried out under an argon atmosphere using standard Schlenk techniques. All solvents were dried before use according to standard procedures and stored under argon. (*R*)-BINOL was purchased from Nanjing University, NOBIN was prepared according to literature procedure.⁸ⁱ (*R*)-MonoPhos was synthesized and isolated according to literature procedure.¹⁷ The detailed synthesis procedure of ligand (*S,S*)-**1a** has been described in previous report.⁹

4.2. The synthesis of ligand (*R,R*)-(-)-**1b**⁹

With the same method for the synthesis of ligand (*S,S*)-**1a**, ligand (*R,R*)-**1b** (0.660 g, 94%) was prepared from 0.404 g of (*R*)-2-(2-pyridinylcarboxamido)-2'-hydroxy-1,1'-binaphthyl (1.0 mmol) and 0.471 g of (*R*)-MonoPhos (1.3 mmol) as a white solid: mp 291–294°C; [α]_D²⁶ –173.7 (c 0.5, THF); ¹H NMR (DMSO-*d*₆) δ 6.71 (d, *J*=8.8 Hz, 1H), 6.99–7.09 (m, 4H), 7.23–7.51 (m, 10H), 7.78 (d, *J*=8.8 Hz, 1H), 7.84–7.88 (m, 2H), 7.95–8.16 (m, 7H), 8.28–8.35 (m, 2H), 8.89 (d, *J*=8.8 Hz, 1H), 9.86 (s, 1H); ³¹P NMR δ +147.00; HRMS (*m/z*): calcd for C₄₆H₂₉N₂O₄P 704.1865; found, 704.1865.

4.3. Typical procedure for nonlinear Cu(I)-catalyzed 1,4-conjugate addition

4.3.1. Preparation of catalyst. A 60% ee scalemic ligand [17.6 mg, mixed with 14.1 mg of (*S,S*)-**1a** and 3.5 mg of (*R,R*)-**1b**] and 3 ml toluene were added to a 25 ml flame-dried Schlenk tube under an argon atmosphere. After stirring 5 min, 3.1 mg of [Cu(CH₃CN)₄]BF₄ (0.01 mmol) was added to the mixture. After 30 min of stirring at rt, the solvent was stripped off in vacuo, 1 ml of CH₂Cl₂ was added to the flask.

4.3.2. Asymmetric 1,4-conjugate addition. Chalcone (208 mg, 1.0 mmol) was added to above prepared catalyst solution under an argon atmosphere. After stripping off the solvent, 3.0 ml of toluene was added. The slurry was stirred at rt for 10 min. and then cooled to –10°C. After the slurry was stirred for 15 min, 1.4 ml of Et₂Zn (1.1 M in toluene, 1.5 mol equiv.) was added slowly. The resulting mixture was stirred at –10°C for 12 h. Then 4 ml of 5% HCl was added to quench the reaction. The mixture was allowed to warm to rt, and then 15 ml of diethyl ether was added. The organic layer was washed with 5 ml of saturated NaHCO₃ and 5 ml of brine and then dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel and eluted with EtOAc/hexanes (1/20) to afford the addition product. The ee values of the addition products were determined by chiral HPLC as described in the Supporting Information of Ref. 9.

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