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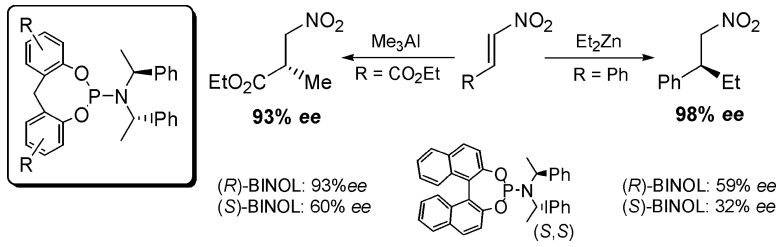
J. Am. Chem. Soc., **2008**, 130 (15), 5012-5013 • DOI: 10.1021/ja710340n • Publication Date (Web): 22 March 2008



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Catalyst Self-Adaptation in Conjugate Addition to Nitroalkenes and Nitroacrylates: Instant Chirality Control in Diphenylmethane-Based Phosphoramidite Ligands

Kazuki Wakabayashi,† Kohsuke Aikawa,† Susumu Kawauchi,‡ and Koichi Mikami*,†

Departments of Applied Chemistry and Organic and Polymeric Materials, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8552, Japan

Received November 15, 2007; E-mail: mikami.k.ab@m.titech.ac.jp

Asymmetric catalysis[1] has long relied on the design of chirally rigid, particularly atropisomeric (*atropos* in Greek),[2] ligands to attain high enantioselectivity. However, even higher enantioselectivity has recently been attained by chirally flexible (*tropos*)[2] achiral benzophenone-derived diphosphine ligands, of which the chirality is *instantaneously* controlled by a chiral activator (A*−A) (Scheme 1a, M = Ru, Rh, Pd, and Pt).[3]

Recently, binaphthol (BINOL)-derived phosphoramidite ligands were developed for asymmetric conjugate additions.[4] The addition to nitroalkenes[5] is one of the most synthetically important methods to provide chiral amino (acid) derivatives[6] but requires the matched combination of BINOL and amine chiralities (Scheme 2, ligand **B**). We report here *tropos* benzophenone-like phosphoramidite ligands (**A**) in which the chirality can be *instantaneously* controlled[7] by a chiral amine built therein (Scheme 1b). Higher enantioselectivity and catalytic activity can be attained in the Cu catalysis, by virtue of instant chirality control in the ligands **A**; the ligands **A** fit well and *instantly* with substrates and reagents (Scheme 2).

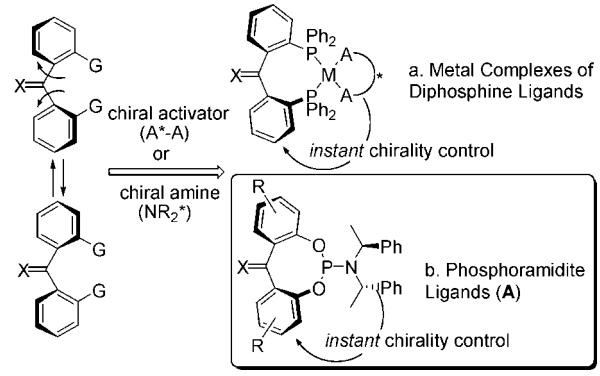
Complexation of phosphoramidite ligands **A** (**A**$^{\mathbf{1}}$: X = H_2, R = 4-Me; **A**$^{\mathbf{2}}$: X = H_2, R = H) and $PdCl_2$(cod) was found to give single $PdCl_2\mathbf{A}_2$ enantiomers within minutes. Single $PdCl_2\mathbf{A}_2$ enantiomers with C_2-symmetry were instantaneously observed in ^{1}H NMR to show two singlets of four 4-Me groups in 2**A** (see Supporting Information).

The advantage of the phosphoramidite ligand **A** can be seen in the conjugate addition of diethylzinc to β-nitrostyrene (Table 1). Even at −78 °C within 3 h, the ligand **A** showed remarkably high catalytic activity and enantioselectivity in the Cu catalysis (>99%, 98% ee, entries 2 and 3).[8]

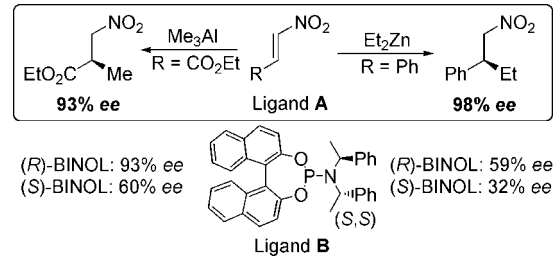
In order to differentiate from the biphenol (BIPOL) counterpart **C**, the conformation of the Cu^{2+} precatalyst with the ligand **A**$^{\mathbf{2}}$ was deduced with DFT calculation. Figure 1 shows the most stable conformation localized in the Cu^{2+} precatalyst with the phosphoramidite ligand **A**$^{\mathbf{2}}$. The side view of the **A**$^{\mathbf{2}}$ complex shows the more effective shielding of phenyl rings to give higher enantioselectivity than the BIPOL or BINOL counterparts (**C**, **B**) as observed in Table 1. The ethane-bridged phosphoramidite **A′** shows a similarly (or more) effective shielding of phenyl rings.[9]

Conjugate additions to other nitroalkene substrates were also examined with the ligand **A**$^{\mathbf{1}}$ to give constantly high enantioselectivities (Table 2). The *p*-, *m*-, and *o*-methoxyphenyl, *p*-methylphenyl, and furyl substrates were also shown to give high enantiomeric excesses (up to 99% ee).[10]

Scheme 1. Instant Chirality Control in Ligands (**A**)



Scheme 2. Conjugate Additions to Nitroalkenes and Nitroacrylates



By contrast, enantioselectivity obtained even by an excellent *atropos* biphenyl phosphoramidite ligand **D** sharply decreased from *p*- to *o*-methoxyphenyl substrates (99 to 68% ee, entries 5, 7, and 9). The high enantioselectivity with ligand **A**$^{\mathbf{1}}$ (97 to 91% ee, entries 4, 6, and 8) exemplifies the advantage of instant chirality control to fit well with the substrate change.

With the success in dialkylzinc reagent, the conjugate addition of trimethylaluminum reagent to nitroacrylate substrate was then

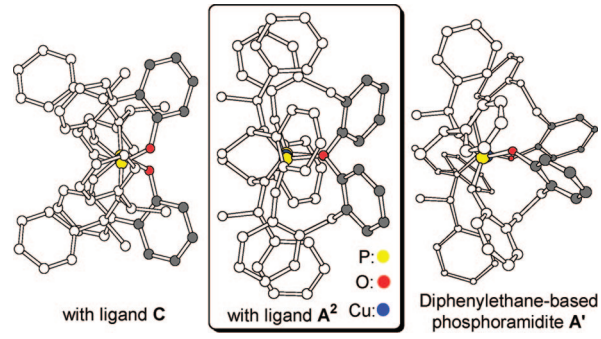
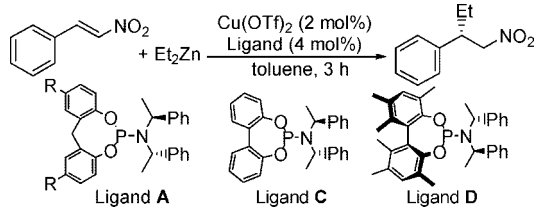


Figure 1. DFT calculations of Cu^{2+} precatalysts.

† Department of Applied Chemistry.
‡ Department of Organic and Polymeric Materials.

10.1021/ja710340n CCC: $40.75

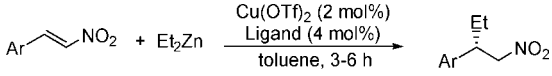
Table 1. Asymmetric Conjugate Additions of Et_2Zn to β-Nitrostyrene



entry	ligand	temp (°C)	conv. (%)	ee (%)
1	**A^1 (R = Me)**	**−45**	**>99**	**94 (*S*)**
2	**A^1 (R = Me)**	**−78**	**>99**	**98 (*S*)**
3	**A^2 (R = H)**	**−78**	**>99**	**98 (*S*)**
4[a]	(*R*)/(*S*,*S*)-**B**	−45	>99	59
5[b]	(*R*)/(*S*,*S*)-**B**	−30	>99	48 (*R*)
6[c]	(*R*)/(*S*,*S*)-**B**	−78	90	48 (*S*)
7[a]	(*S*)/(*S*,*S*)-**B**	−45[d]	>99	32
8[c]	(*S*)/(*S*,*S*)-**B**	−78	80	39 (*S*)
9[a]	**C**	−45	>99	77
10[b]	**C**	−30	>99	8 (*R*)
11[e]	**D**	−65	>99	94 (*R*)

[a] See ref 5d. [b] See ref 5c. [c] See ref 5a. [d] Lower temperature (−78 °C) led to a lower reaction rate. [e] $Cu(OTf)_2$ (1 mol %), ligand (2 mol %), reaction time (6 h) (ref 5g).

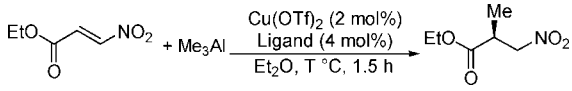
Table 2. Asymmetric Conjugate Additions of Et_2Zn to Nitroalkenes



entry	Ar	ligand	temp (°C)	conv. (%)	ee (%)
1	***p*-MePh**	**A^1**	−78	**>99**	**96**
2[a]	*p*-MePh	(*R*)/(*S*,*S*)-**B**	−30	>99	25
3[b]	*p*-MePh	**D**	−65	>99	98
4	***p*-MeOPh**	**A^1**	−78	**>99**	**97**
5[b]	*p*-MeOPh	**D**	−65	>99	99
6	***m*-MeOPh**	**A^1**	−78	**>99**	**93**
7[b]	*m*-MeOPh	**D**	−65	>99	84
8	***o*-MeOPh**	**A^1**	−78	**99**	**91**
9[b]	*o*-MeOPh	**D**	−65	>99	67
10	***p*-CF_3Ph**	**A^1**	−78	**>99**	**91**
11[b]	*p*-CF_3Ph	**D**	−65	>99	77
12	**furyl**	**A^1**	−78	**>99**	**99**
13[a]	furyl	(*R*)/(*S*,*S*)-**B**	−30	>99	8
14[b]	furyl	**D**	−65	>99	92

[a] See ref 5b. [b] $Cu(OTf)_2$ (1 mol %), ligand (2 mol %), reaction time (6 h) (ref 5g).

Table 3. Conjugate Additions of Me_3Al to Nitroacrylate



entry	ligand	temp (°C)	yield (%)	ee (%)
1	**A^1**	**−78**	**>99**	**93 (*S*)**
2	(*S*)/(*R*,*R*)-**B**	−78	74	93 (*R*)
3	(*R*)/(*R*,*R*)-**B**	−78	72	60 (*R*)
a	(*S*)/(*R*,*R*)-**B**	−50	85	92 (*R*)

[a] See ref 11c.

examined[11] to give synthetically useful β-amino acid derivative, β^2-alanine[12] (Table 3). Phosphoramidite ligand **A^1** afforded high yield and enantioselectivity (>99%, 93% ee). The product can be easily transformed to β^2-alanine ethyl ester by hydrogenation with palladium on charcoal.[11c]

In summary, we have developed the ligands **A** to give higher enantioselectivity and catalytic activity in the Cu-catalyzed conjugate additions to nitroalkenes, by virtue of their instant chirality control. The highly *tropos* phosphoramidite ligands **A** outperform the analogous rigid (*atropos*) BINOL- and even BIPOL-derived phosphoramidite ligands. These results represent emblematic cases of catalyst self-adaptation and tuning.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures for the preparation of ligand **A** and for the conjugative addition to nitroalkenes; DFT calculation data of the Cu(II) precatalyst of ligand **A^2** and **C** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA710340N