

# Enantioselective Copper-Catalyzed Conjugate Addition of Dialkyl Zinc to Nitro-Olefins

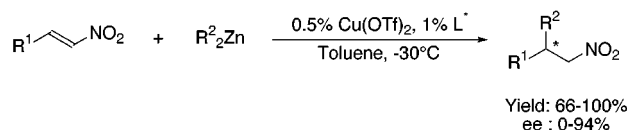
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## ABSTRACT



The copper-catalyzed asymmetric conjugate addition of dialkylzinc onto various nitro-olefins has been carried out with excellent results. An enantiomeric excess of up to 94% was obtained using 0.5% Cu(OTf)<sub>2</sub> and 1% of chiral trivalent phosphorus ligand.

The copper-catalyzed conjugate addition of dialkyl zinc to various enones<sup>1a</sup> was later extended to a range of other Michael acceptors.<sup>1b</sup> As little as 0.5% of copper salt and 1% trivalent phosphorus ligand were needed for high yields. Over the course of the past few years we<sup>1a,2</sup> and others<sup>3</sup> have reported the use of several chiral phosphorus ligands in the enantioselective version of this reaction on enones. As an extension to our previous work, we become interested in the conjugate addition to nitro-olefins, which were excellent substrates in the racemic version of this reaction.<sup>1b</sup>

Being among the best Michael acceptors, nitro-olefins add a range of functionalized nucleophiles.<sup>4</sup> Seebach showed that

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it was possible to carry out the enantioselective conjugate additions of diethyl zinc through the use of stoichiometric amount of titanium TADDOLates<sup>5</sup> as chiral Lewis acids. During the course of our studies, a catalytic version was disclosed by Sewald,<sup>6a</sup> on two examples **1** and **5**, as well as by Feringa,<sup>6b</sup> on benzylidene nitroacetates and nitrocoumarins, both using the same chiral phosphorus ligand **L5**.<sup>3a</sup>

We report herein the results of our investigations on several nitro-olefins **1–6**, using various chiral phosphorus ligands according to Scheme 1.

In the conjugate addition to enones, there is no single ligand of wide efficiency. For example, **L1** and **L5** are excellent for cyclohexenone,<sup>1c,3a</sup> whereas **L6** affords the best results for acyclic enones.<sup>1d</sup> For this reason, several structurally different trivalent phosphorus ligands were tested. In the present study, we shall see that **L3**<sup>7</sup> appears to be the optimal choice for aryl nitro-olefins. The results obtained with diethylzinc and a selection of most representative ligands are shown in Table 1.

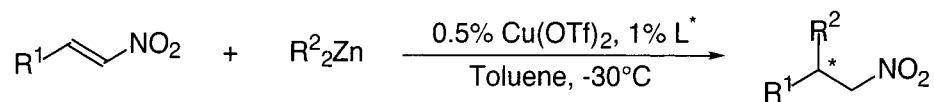
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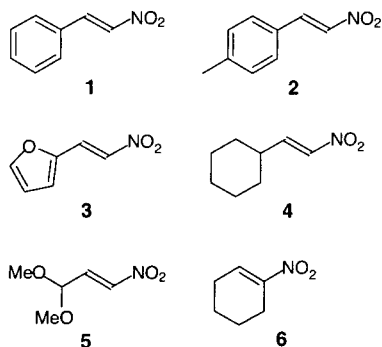
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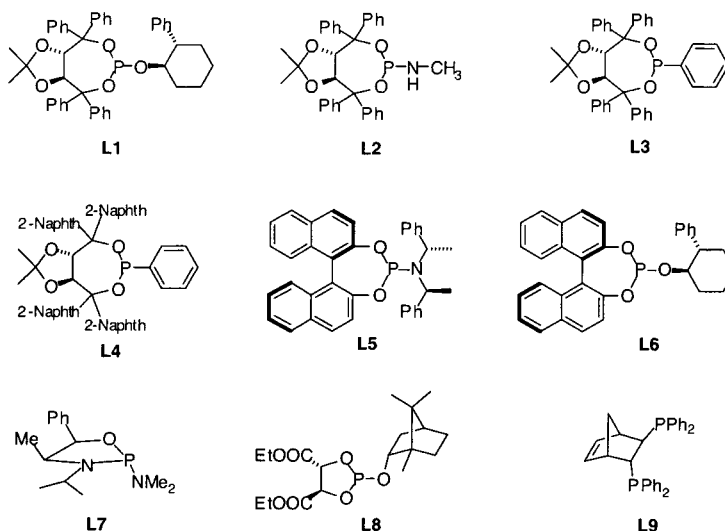
## Scheme 1



## Substrates



## Ligands



We have found that running the reactions in toluene at  $-30^\circ\text{C}$  for 1–3 h, using 0.5 mol % of copper(II) triflate and just 1 mol % of ligand, afforded the highest enantioselectivity along with high chemical yields (83–100%). Other solvents, such as  $\text{CH}_2\text{Cl}_2$ ,  $\text{Et}_2\text{O}$ , or THF, gave lower asymmetric induction, although the chemical yield remains excellent. The optimum reaction temperature was found to be  $-30^\circ\text{C}$ . Higher temperature is detrimental to the ee, whereas lower temperature does not improve it, with prohibitively long reaction time. Increasing the amount of catalyst to 1% or 2% of  $\text{Cu}(\text{OTf})_2$  and 2% or 4% of  $\text{L}^*$  is useless. We have also checked that at  $-30^\circ\text{C}$  the reaction does not proceed in the absence of catalyst.

Ligand **L1**, one of the best in the conjugate addition to cyclohexenone,<sup>2c</sup> gave good to moderate ee's on all of the tested nitro-olefins (entry 1). It is worth noting that aryl-substituted nitro-olefins (**1–3**) afford better results than the alkyl-substituted ones (**4–6**). This trend in the two classes of substrates will be noticed throughout all this study. In the TADDOL series of ligands, **L2** was among the best for acyclic enones.<sup>7</sup> However, only poor results were obtained with nitro-olefins (entry 2).

The main surprise came from ligand **L3**. This ligand was successfully used in the Rh-catalyzed hydrosilylation and hydroformylation reactions.<sup>8</sup> In our hands (entry 3), it appears to be the ligand of choice for aryl-substituted nitro-olefins

**Table 1.** Reaction of Diethyl Zinc with Nitro-Olefins **1–6**, with 0.5%  $\text{Cu}(\text{OTf})_2$  and 1% Chiral Ligands **L1–L9**

entry	ligand	nitro-olefin (yield, ee, conf)					
		<b>1</b> <sup>a</sup>	<b>2</b> <sup>a</sup>	<b>3</b> <sup>b</sup>	<b>4</b> <sup>a</sup>	<b>5</b> <sup>a</sup>	<b>6</b> <sup>d</sup>
1	<b>L1</b>	100%, 64, R	100%, 56, R	100%, 35, (+)	100%, 35, (+)	100%, 10, (+)	85%, 28, (–)
2	<b>L2</b>	88%, 28, S			85%, 13, (–)	95%, 13, (–)	
3	<b>L3</b>	100%, 81, S	100%, 86, S	95%, 78, (–)	92%, 63, (–)	100%, 31, (+)	95%, 60, (+)
4	<b>L4</b>	100%, 50, S			100%, 40, (+)	100%, 0	
5	<b>L5</b>	100%, 2, R	100%, 25, S	96%, 8, (–)	100%, 94, (+)	95%, 60, (–)	85%, 67, (+)
6	<b>L6</b>	100%, 35, S		95%, 20, (–)			95%, 3, (+)
7	<b>L7</b>	100%, 0			95%, 0	100%, 7, (+)	100%, 0
8	<b>L8</b>	100%, 0	66%, 33, S		96%, 5, (–)		
9a	<b>L9</b>		100%, 2, S				
9b			100%, 13, S <sup>c</sup>				

<sup>a</sup> The ee was determined by chiral GC on a LipodexE (25 mm  $\times$  0.25 mm) capillary column. <sup>b</sup> The ee was determined by chiral GC on a CP chiral-Dex (25 mm  $\times$  0.25 mm) capillary column. <sup>c</sup> The reaction was performed in  $\text{CH}_2\text{Cl}_2$ . <sup>d</sup> See comment in the text.

(1–3), with ee's as high as 86% in the case of **2**. It also displays good enantioselectivity with two of the alkyl-substituted substrates, **4** (ee 63%) and **6** (ee 60%). It was reported that the 2-naphthyl-TADDOLs usually afford increased stereoselectivities.<sup>8</sup> However, in our case, ligand **L4** gave only moderate asymmetric induction (entry 4).

In addition to diethyl zinc, we also tested the reaction with dibutyl zinc and dimethyl zinc on nitro-olefin **2** and with ligand **L3**. Both reacted quantitatively, with 71% and 20% ee, respectively. The lower ee with Me<sub>2</sub>Zn could be the result of its lesser reactivity, since the reaction temperature had to be raised to 0 °C.

Two ligands of the binaphthol series were tested. Ligand **L5** is among the best for conjugate addition to cyclic enones.<sup>3a</sup> It was also used by Sewald on nitro-olefins **1** and **5**.<sup>6</sup> Under our above-mentioned conditions (entry 5), this ligand appears to give the best results for alkyl-substituted nitro-olefins (**4–6**). Thus, in the case of **4** it gave a better result than **L3** (94% instead of 63% ee) and was clearly much better for nitro acetal **5** (60% ee). However, Sewald reported a higher ee value in this case (86%). Repetition of this experiment, using exactly Sewald's conditions (12 times more dilute),<sup>9</sup> indeed increased the ee to the reported value. The result on nitrostyrene **1** was also improved to almost the reported one (42% instead of 48%). These results point to the sensitivity of the copper-catalyzed conjugate addition to the reaction conditions. However, the "high dilution effect" could not improve any result with the other ligands. The other binaphthol-based ligand, **L6**, was the most efficient for many acyclic enones<sup>2d</sup> but did not give any good result with nitro-olefins (entry 6).

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The last ligands tested were representative of other classes of ligands. Ligand **L7** has been successfully employed for the conjugate addition with stoichiometric lithium dialkyl cuprate reagents,<sup>1a,10</sup> and ligand **L8**<sup>11</sup> was the best one in the tartrate-phosphite series.<sup>2b</sup> Neither, however, gave good result with nitro-olefins (entries 7 and 8). Finally, a diphosphine ligand was also tested. Norphos **L9** (entry 9) gave 44% ee in the addition of diethyl zinc to cyclohexenone<sup>2a</sup> but only 2% ee (entry 9a) and 13% in CH<sub>2</sub>Cl<sub>2</sub> (entry 9b) with nitro-olefin **2**.

Concerning the reactivity of nitro-olefins **1–6**, we noticed that the nitro acetal **5** was the most reactive, but no improvement of ee could be gained by running the reaction at –80 °C (although the yield was quantitative). On the other hand, the trisubstituted **6** was the least reactive. The reaction temperature had to be raised to 0 °C for complete conversion. The crude adduct 1-nitro-2-ethyl cyclohexane was obtained as a mixture of *cis* and *trans* isomers (80:20 ratio with, respectively, 65% and 68% ee, for entry 5). This could be isomerized into the *trans* (67% ee) isomer by treatment with DBU at room temperature.

In addition to being truly catalytic, these results represent the highest ee's reported to date in the enantioselective conjugate addition of alkyl groups to nitro-olefins. The scope and limitations of this reaction is presently under investigation.

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**Supporting Information Available:** Experimental procedure, <sup>1</sup>H and <sup>13</sup>C spectra, and GC chromatograms. This material is available free of charge via Internet at <http://pubs.acs.org>.

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