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Highly Enantioselective Copper-Catalyzed Conjugate Addition of Diethylzinc to Nitroalkenes

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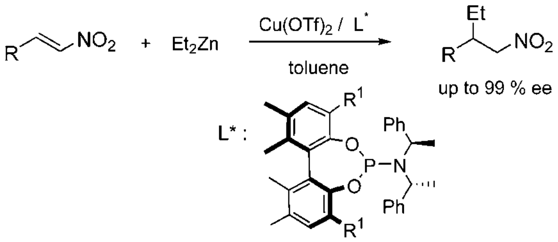
ABSTRACT



Copper-catalyzed asymmetric conjugate addition of diethylzinc to nitroalkenes using new chiral monodentate phosphoramidite ligands proceeds with high enantioselectivity up to 99% ee.

Enantioselective conjugate additions of organometallic reagents to nitroalkenes provides a useful carbon−carbon bond forming process. Among such processes, the copper-catalyzed dialkylzinc addition to nitroalkenes has recently been extensively studied by Alexakis,[1] Feringa,[2] Seebach,[3] Sewald,[4] and their co-workers. This reaction is useful for the synthesis of a variety of enantiomerically enriched synthetic building blocks bearing nitrogen-functional groups, e.g., amines, amino alcohols, amino ethers, β-amino acids, etc. However, the scope of this reaction is still very limited in terms of substrate structures and dialkylzinc species. The enantioselectivity of this reaction has been modest to fairly good except for only a few particular types of substrates with which excellent selectivity was achieved.[1c,2b,c]

We describe here the copper-catalyzed asymmetric conjugate addition of diethylzinc to nitroalkenes using our new chiral monophosphoramidite ligands.

Enantioselective conjugate addition of dialkylzinc to nitroalkenes has been studied by using Ti-TADDOLates,[3] TADDOL,[1c] phosphoramidite,[1,2,4] sulfonamide,[5] and binaphthol-based thioether ligands.[6] Most notably, Feringa and Alexakis have developed and used chiral monodentate phosphoramidite ligands for this reaction in the past several years. The best ligand developed by Feringa is **L1**,[2b,c] and the one by Alexakis is **L2**[1e] (Figure 1).

Enantioselective Cu-catalyzed conjugate addition of dialkylzinc to various cycloalkenones using **L1** and **L2** afforded high enantioselectivity up to 99% ee,[1e,2a] but the enantioselectivity achieved for nitroalkenes using the same ligands ranges from moderate to high % ee values depending on the nature of substrate.[1c,e] In particular, the reaction of

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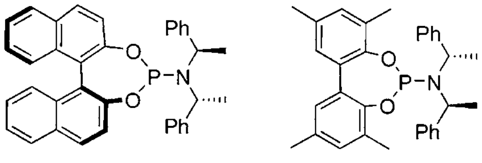
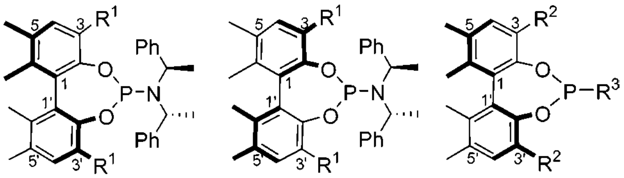


(*S*,*R*,*R*)-**L1** (*S*,*S*)-**L2**

Figure 1. Representative phosphoramidite ligands used for the Cu-catalyzed conjugate addition of dialkylzinc to nitroalkenes.

dialkylzinc with aromatic nitroalkenes is still challenging, achieving up to 69% ee with **L1**[1c,2b] and 82% ee with **L2**.[1e]

New class of readily accessible biphenol-based chiral monodentate phosphoramidite (**L3**−**L7**) and phosphite (**L8**) ligands has recently been developed in these laboratories (Figure 2).[7,8] One of the salient features of these ligands is the fine-tuning capability, which makes it possible to apply these ligands to a variety of catalytic asymmetric reactions. These ligands have been successfully applied to asymmetric hydrogenation of dimethyl itaconate (up to 99.6% ee with **L8** wherein R^2 is *t*-Bu and R^3 is (1*S*,2*R*)-2-phenylcyclohexyloxy),[7] the Cu-catalyzed conjugate addition of dialkylzinc to cycloalkenones (up to 99% ee with **L4**),[8] and Rh-catalyzed asymmetric hydroformylation of allyl cyanide (branch/linear = 96:4, 80% ee with **L8** wherein R^1 is *t*-Bu and R^3 is dimethylamino).[8]



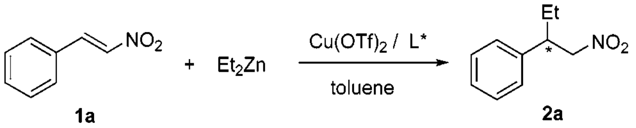
(*S*,*R*,*R*) (*R*,*R*,*R*) (*S*)-**L8**

L3: R^1 = H, **L4**: R^1 = Me
L5: R^1 = Br, **L6**: R^1 = Ph
L7: R^1 = Me

Figure 2. General structure of monodentate phosphoramidite and phosphite ligands.

First, the reactions were carried out at −45 °C for 6 h, using Cu(OTf)$_2$ with ligands **L3**−**L6** as the catalyst and *trans*-β-nitrostyrene (**1a**) as the substrate, to examine if there is any promising ligand for this reaction and to determine possible structure−efficiency relationships. *trans*-β-Nitrostyrene (**1a**) was reported to be one of the most challenging substrates for the Cu-catalyzed diethylzinc addition reactions, i.e., the enantioselectivity reported ranges from 2% ee[1c] to 59% ee[2b] with the **L1**−Cu(OTf)$_2$ catalyst at −30 to −45 °C in toluene and 66% ee with the **L2**-Cu(OTf)$_2$ catalyst at −30 °C in toluene. It was reported that −45 and −30 °C were the optimal reaction temperature for the **L1**-Cu(OTf)$_2$ and **L2**-Cu(OTf)$_2$ catalysts, respectively, i.e., the enantioselectivity did not increase and the reaction rate dropped significantly at lower temperatures.[1,2]

Table 1. Conjugate Addition of Diethylzinc to **1a**[a]



entry	temp (°C)	ligand	conv (%)	% ee[b]
1	−45	**L3**	50	0
2	−45	**L4**	100	47 (*R*)
3	−45	**L5**	100	15 (*R*)
4	−45	**L6**	100	31 (*R*)
5	−55	**L4**	100	67 (*R*)
6	−65	**L4**	100	94 (*R*)
7	−65	**L7**	61	70 (*R*)

[a] The reactions were performed with 0.5 mmol of **1a**, 1 mol % of Cu(OTf)$_2$, and 2 mol % of ligand in 5 mL of toluene. All reactions were run for 6 h unless otherwise noted. All reactions completed in 6 h except for entries 1 and 7. [b] Determined by chiral GC.

As Table 1 shows, the reaction of **1a** with **L4**-Cu(OTf)$_2$ wherein R^1 is a methyl group exhibited the best enantioselectivity (47% ee, entry 2) with complete conversion at −45 °C. The use of ligands with groups bulkier than methyl as R^1 (**L5**, **L6**) resulted in lower enantioselectivity, proportional to the increase in the bulkiness (entries 3 and 4), although the reaction rate was not affected. When R^1 is hydrogen (**L3**, entry 1), the enatioselectivity dropped to 0% ee with only 50% conversion in 6 h. Accordingly, **L4** was selected for optimization.

Next, the effect of reaction temperature was examined. Then, a significant improvement in enantioselectivity was observed at lower reaction temperatures without affecting reaction rate. As Table 1 shows, the reaction with **L4**-Cu(OTf)$_2$ gave (*R*)-**2a** with 67% ee at −55 °C (entry 5) and 94% ee at −65 °C (entry 6) with complete conversion in 6 h. However, the reaction at −75 °C slowed without further improvement in enantioselectivity. Thus, −65 °C appears to be the optimal temperature. From these results, it is clear that **L4**-Cu(OTf)$_2$ possesses catalytic activity higher than that of **L1**-Cu(OTf)$_2$ and **L2**-Cu(OTf)$_2$, so that the reaction can be carried out at a lower temperature to increase the enantioselectivity to 94% ee. Although Feringa and Alexakis reported that (*R*)-**2a** could be obtained with 59% ee using **L1**[2b] and 82% ee using **L2**-Cu(OAc)$_2$−H$_2$O catalyst,[1d] respectively, 94% ee achieved by **L4**-Cu(OTf)$_2$ is by far the best result for this reaction to date. It should be worth mentioning that there is a clear matching/mismatching of the axial chirality and the center chirality in these ligands for this reaction. For example, **L4** (*S*,*R*,*R*) gives much better enantioselectivity than its (*R*,*R*,*R*)-diastereomer, **L7** (entries 6 and 7).

Reactions of various aromatic and heteroaromatic nitroalkenes with diethylzinc catalyzed by **L4**-Cu(OTf)$_2$ were

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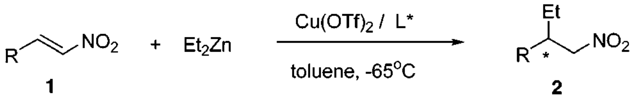
Table 2. Conjugate Addition of Diethylzinc to Nitroalkenes[a]



entry	**1**	ligand	conv (%)	**2**	% ee[c]
1	**1b** (R = *p*-Me-C_6H_4)	**L4**	100	**2b**	98
2	**1c** (R = *p*-MeO-C_6H_4)	**L4**	100	**2c**	99
3	**1d** (R = *m*-MeO-C_6H_4)	**L4**	100	**2d**	84
4	**1e** (R = *o*-MeO-C_6H_4)	**L4**	100	**2e**	67
5	**1f** (R = *p*-F-C_6H_4)	**L4**	100	**2f**	91
6	**1g** (R = *m*-F-C_6H_4)	**L4**	100	**2g**	88
7	**1h** (R = *o*-F-C_6H_4)	**L4**	100	**2h**	74
8	**1i** (R = *p*-CF_3-C_6H_4)	**L4**	100	**2i**	77
9	**1j** (R = *o*-CF_3-C_6H_4)	**L4**	100	**2j**	88
10	**1k** (R = furyl)	**L4**	100	**2k**	92
11	**1l** (R = thienyl)	**L4**	100	**2l**	96
12	**1m**[b] (R = $(MeO)_2CH$)	**L4**	100	**2m**	96
13	**1m**[b] (R = $(MeO)_2CH$)	**L3**	100	**2m**	97

[a] The reactions were performed with 0.5 mmol of nitroalkene, 1 mol % of $Cu(OTf)_2$, and 2 mol % of ligand in 5 mL of toluene. All reactions completed in 6 h. [b] In 15 mL of toluene. [c] Determined by chiral GC or HPLC. Absolute configuration of **2b**, **2d**, and **2l** is known to be *R*, but others are unknown. Nevertheless, it is reasonable to assign *R* configuation to all products.

carried out at −65 °C for 6 h. Results are summarized in Table 2. It should be noted that the reported enantioselectivity for those reactions using a variety of chiral ligands, prior to our investigation, was only 1−75% ee.[1c,2b] As Table 2 shows, the use of **L4**-$Cu(OTf)_2$ in these reactions has achieved much better enantioselectivity, up to 99% ee. There is a clear electronic effect on the enantioselectivity of this reaction. Thus, an electron-donating group such as methyl (98% ee, entry 1) and methoxy (99% ee, entry 2) at the *para* position of the phenyl moiety of *trans*-β-nitrostyrene increases the enantioselectivity as compared to the parent *trans*-β-nitrostyrene (94% ee, Table 1, entry 6), whereas an electron-withdrawing group such as fluoro (91% ee, entry 5) and trifluoromethyl (77% ee, entry 8) decreases the selectivity. Also there is a clear steric effect on the enantioselectivity. An *ortho* substituent has a detrimental effect regardless of the electronic nature, i.e., MeO or F, pushing down the selectivity to lower than 75% ee (entries 4 and 7). Unexpectedly, a *meta* substituent has an unfavorable effect regardless of the electronic nature as well, lowering the selectivity to less than 90% ee (entries 3 and 6). Also, one exception for the *ortho* substitution effect is *trans*-β-nitro-*o*-CF_3-styrene (**1j**). The reaction of **1j** with diethylzinc catalyzed by **L4**-$Cu(OTf)_2$ gave **2j** with 88% ee (entry 9), i.e., the enantioselectivity is much better than that of **1i** bearing a *p*-CF_3 group mentioned above (entry 8). A possible explanation for this result is the noncoplanar structure of this substrate **1j** due to the bulky CF_3 group at the *ortho* position, which cancels the electron-withdrawing effect of the CF_3 group. The observed clear electronic and steric effects on the enantioselectivity provide significant information for the mechanism of this process.

Reactions of heteroaromatic nitroalkenes **1k** and **1l** proceeded smoothly to give **2k** (92% ee, entry 10) and **2l** (96% ee, entry 11), respectively. We also employed 1-nitroprop-1-ene dimethylacetal (**1m**) as substrate for comparison purpose. The reaction afforded **2m** with 96% ee (entry 12). It was reported that **L1**-$Cu(OTf)_2$ achieved the same enantioselectivity for this reaction.[2c] It is worth mentioning that, unlike the reaction of **1a**, **L3**-$Cu(OTf)_2$ also achieved very high enantioselectivity to give **2m** with 97% ee (entry 13). Compound **2m** can be converted to the corresponding *N*-*t*-Boc-β^2-amino acid,[2c] which has been used in the total synthesis of cryptophycins.

In conclusion, new chiral 5,5′,6,6′-tetramethylbiphenol-based monodentate phosphoramidite ligands, especially **L4**, are found to be highly effective for the enantioselective conjugate addition of diethylzinc to nitroalkenes (up to 99% ee). Further studies on the scope and the mechanism of the reaction are actively underway.

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Supporting Information Available: Experimental procedures, identification data for **2a**−**f** and **2i**−**m** and the characterization data of **2g** and **2h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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