ORGANIC LETTERS

2007
Vol. 9, No. 1
85−87

Application of the Chiral Bis(phosphine) Monoxide Ligand to Catalytic Enantioselective Addition of Dialkylzinc Reagents to β-Nitroalkenes

Alexandre Côté, Vincent N. G. Lindsay, and André B. Charette*

Département de Chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal, Québec, Canada H3C 3J7

andre.charette@umontreal.ca

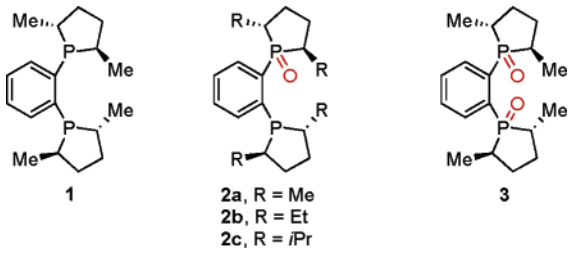
Received November 16, 2006

ABSTRACT

Me-DuPHOS monoxide is shown to be a very effective ligand in the enantioselective copper-catalyzed addition of dialkylzinc reagents to β-nitroalkenes providing access to chiral nitroalkanes. The major advantages of this process are high yields, broad and complementary substrate scope, and high enantioselectivities. The effect of achiral dummy ligands as an additive has also been documented.

The use of bis(phosphine) monoxides as hemilabile ligands has found widespread applications in the field of catalysis.[1] Yet, their potential in asymmetric synthesis has long been overlooked because so few cogent examples have been reported. In addition to the previous work of Faller,[2] we have recently reported that the Me-DuPHOS monoxide (**2a**) could be used to promote the catalytic addition of diorganozinc reagents to imines.[3]

To determine the general scope of reactivity for this family of ligands, we sought to further explore their synthetic utility. To do so, we focused our efforts on the enantioselective catalytic addition of diorganozinc reagents to β-nitroalkenes[4,5]



and, more particularly, on the Cu·**2a** complex, which, based on our previous studies, has proven to be an excellent catalyst

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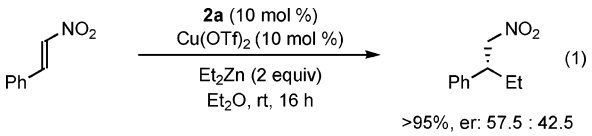
10.1021/ol062792t CCC: $37.00
Published on Web 12/15/2006

for this type of reaction. Considerable interest from the scientific community has been drawn to the use of chiral nitroalkanes as intermediates in synthetic reactions due to the very versatile functionality of the nitro group.[6] In this communication, we report a valuable route to prepare chiral β-nitroalkanes in high isolated yields by using bis(phosphine) monoxide ligands.

We began our study by examining the behavior of ligand **2a** using the same reaction conditions described in our previous work on the addition of diorganozinc compounds to imines (eq 1).[3b]

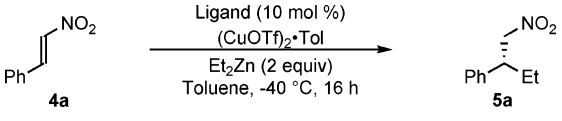


Despite disappointing preliminary results, a variety of conditions were screened and the copper−ligand ratio was identified as a critical factor for controlling the level of enantioinduction (Table 1, entries 1−3). Similarly, when the reaction was carried out with Me-DuPHOS (**1**) or its bis-oxidized form (**3**), very low enantioselectivities were obtained (entries 4−6 and 7), indicating that the hemilabile nature of the ligand is also a key element. We assumed that the active catalyst was a chiral organocopper complex because poor enantioselectivity was observed in the absence of copper salt in the medium. Simple variations of the ligand were also investigated, and a slightly lower selectivity was observed with the bulky ligand **2c** compared to those with ligand **2a** or **2b**. Although Me- and Et-DuPHOS-derived ligands produced comparable selectivities, the higher reactivity of the copper complex derived from **2a** at −70 °C convinced us to focus our attention on this particular ligand. We observed that the use of (**2a**)$_2$·CuOTf, an air-stable complex,[7] has in no way affected the effectiveness of the addition and is preferable because no precomplexation step is required.

The nature of the solvent was also an important factor. In this case, toluene and Et_2O were found to be the solvents of choice, whereas THF and CH_2Cl_2 afforded lower yields and selectivities. Because Et_2O has proven to give more reproducible results than toluene under optimal temperature conditions, i.e., −70 °C, it was used for the remainder of our investigation.

As the data in Table 2 indicate, enantioselective catalytic addition using ligand **2a** is effective for a wide variety of β-nitrostyrenes. The high isolated yields obtained strongly suggest that use of this ligand could significantly reduce the extent of polymerization of nitroalkenes, a common problem found in these reactions.[8] An analysis of substituents on nitroalkenes indicates that their electronic properties also influence enantioselectivities. It appears that the presence of electron-donating groups, which are positioned to enrich the double bond, lowers selectivities. Most notably, our method tends to be complementary to the use of the phosphoramidite ligand optimized by Ojima[4f] and to the peptide phosphine ligand developed by Hoveyda.[4g] For example, the *p*-CF_3-Ph derivative (Table 2, entry 4), which

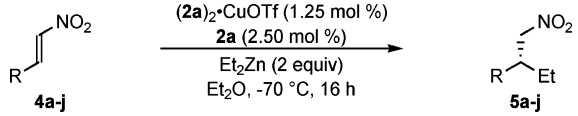
Table 1. Optimization of the Bis(phosphine) Monoxide Ligand and the Copper−Ligand Ratio



entry	ligand	CuOTf (mol %)	yield (%)[a]	er[b]
1	**2a**	10	51	58.5:41.5
2	**2a**	5	83	77:23
3	**2a**	2.5	90	93.5:6.5
4	**1**	2.5	19	51:49
5[c]	**1**	2.5	28	54.5:45.5
6[d]	**1**	2.5	62	53.5:46.5
7	**3**	2.5	71	51:49
8	**2b**	2.5	90	93.5:6.5
9	**2c**	2.5	86	91:9
10	**2a**	0	16	51.5:48.5
11[e]	**2a**	5	79	75:25

[a] NMR yields using an internal standard. [b]Enantiomeric ratios were determined by GC on chiral stationary phases. [c]5 mol % of the ligand was used. [d] 2.5 mol % of the ligand was used. [e]The (**2a**)$_2$·CuOTf complex was used.

Table 2. Scope in the Optimized Conditions for the Conjugate Addition



entry	R	yield (%)[a]	er[b]
1	Ph	92 (**5a**)	97.5:2.5
2	*p*-Cl-Ph	93 (**5b**)	99:1
3	*p*-F-Ph	99 (**5c**)	98:2
4	*p*-CF_3-Ph	92 (**5d**)	97:3
5	*m*-MeO-Ph	98 (**5e**)	97.5:2.5
6	*p*-MeO-Ph	95 (**5f**)	94.5:5.5
7	*p*-Me-Ph	89 (**5g**)	97.5:2.5
8	2-furyl	90 (**5h**)	91.5:8.5
9[c]	*c*-hexyl	70 (**5i**)	99:1
10	*n*-heptyl	91 (**5j**)	97.5:2.5

[a] Isolated yield. [b]Enantiomeric ratios were determined by GC on chiral stationary phases. [c]Slow addition of the β-nitroalkene over 12 h.

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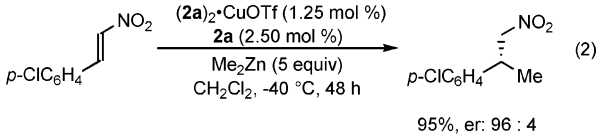
is known to be a problematic substrate, can be obtained in 92% yield and in 97:3 er using **2a** as the chiral ligand.

This method also allows for the addition to aliphatic nitroalkenes. This is synthetically valuable because the resulting chiral nitroalkanes could not be synthesized easily using reduction[9] or arylation[10] methods (Table 2, entries 9 and 10). However, in the case of the *c*-hexyl derivative, the substrate had to be added slowly to circumvent the formation of a substantial quantity of the polymerization product.[11]

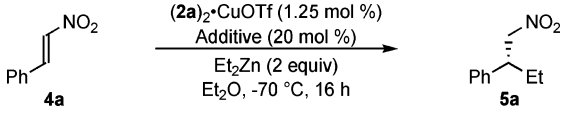
Because of the lower reactivity of Me_2Zn,[12] its stoichiometry, the temperature of the reaction, and the reaction time had to be increased (eq 2). The use of CH_2Cl_2 as solvent



also contributed to increased selectivity. High yields and enantioselectivities were obtained using the conditions shown in eq 2.

It was felt that the need for excess ligand (1:4 copper−ligand ratio) in this reaction was necessary to favor a monomeric or a slightly aggregated ethylcopper species.[13,14] In light of this, the excess chiral ligand was substituted with several achiral ligands that could potentially play the same role (Table 3).[15] Although the addition of strongly α-donor ligands, such as phosphines or amines (entries 2−5), led to a high degree of polymerization, the use of amides was effective. Indeed, the addition of Et_2Zn to both aliphatic and aromatic unsaturated *β*-nitroalkenes was effective with a high level of enantiocontrol in the presence of pivalamide (Table 3, entries 11−13).

Table 3. Effect of Additives in the Conjugate Addition



entry	R	additive	yield (%)[a]	er[b]
1	Ph	none	79	90:10
2		PBu_3	28	92.5:7.5
3		PPh_3	<5	n/a
4		pyridine	76	90:10
5		DABCO	31	93.5:6.5
6		CH_3CONH_2	98	95.5:4.5
7		CF_3CONH_2	94	92.5:7.5
8		$PhCONH_2$	96	97.5:2.5
9		$CH_3CONHCH_3$	95	90:10
10		$TolSO_2NH_2$	88	89:11
11		*t*-$BuCONH_2$	97 (90)[c]	96.5:3.5
12	*p*-Cl−Ph	*t*-$BuCONH_2$	96 (91)[c]	98:2
13	*n*-heptyl	*t*-$BuCONH_2$	76 (69)[c]	97:3

[a] NMR yield using an internal standard. [b]Enantiomeric ratios were determined by GC on chiral stationary phases. [c]Isolated yield in parentheses.

In conclusion, a new application of bis(phosphine) monoxides was disclosed demonstrating the tremendous potential of this class of ligands in asymmetric catalysis. The $(\mathbf{2a})_2$•CuOTf-catalyzed addition of diorganozinc to *β*-nitroalkenes offers a complementary variation to previously reported methods.

Acknowledgment. This work was supported by NSERC (Canada), Merck Frosst Canada, Boehringer Ingelheim (Canada), Ltd., and the Université de Montréal. A.C. is grateful to NSERC (ES D) and TD Bank Financial Group for a postgraduate fellowship. V.N.G.L. is grateful to NSERC (USRA) for an undergraduate fellowship.

Supporting Information Available: Experimental procedures for the preparation of compounds and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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