Catalytic Enantioselective Diethylzinc Addition to *N*-Phosphinoylimine Using Thiophosphoramide of Homologated Binaphthyl *N,O*-Ligand

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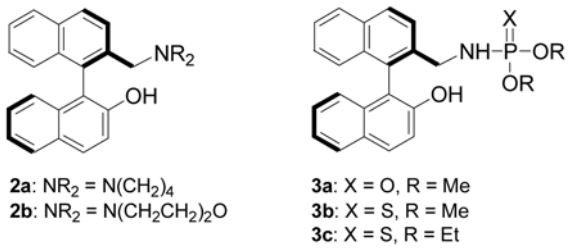
Catalytic enantioselective reactions that convert imines to α-chiral amines hold an important place in asymmetric synthesis, because these chiral amines are among the most common chiral subunits of biologically active molecules.[1] The success of forming an α-chiral amine from an imine depends heavily on the electrophilicity of the imine and the nucleophilicity of the organometals, as well as on the amounts of chiral ligands. Several effective catalytic enantioselective addition reactions of organozinc reagents to activated aryl-,[2] acyl-,[3] or sulfonylimines[4] have been reported, but the addition products require harsh oxidizing, reducing or acidic conditions for the free amino group. Due to the relatively mild revealing conditions that are required in the case where *N*-(diphenylphosphinoyl)imines (**1**) are used as activated substrates, this method is receiving increasing attention.[5] However, as a result of the lower electrophilicity of these imines, significant amounts of chiral ligands (up to one equiv) and an excess of organozincs (up to 10 equiv) are required to ensure high conversion and enantioselectivity. Recently, two practical catalytic asymmetric organozinc additions to *N*-(diphenylphosphinoyl)-imines were reported with the use of chiral diphosphine or thiophosphoramide ligands together with $Cu(OTf)_2$ as the catalytic precursor.[6,7] It is generally believed that organocopper intermediates are involved in these nucleophilic organozinc addition reactions. In our previous reports, highly enantioselective additions of organozincs to aldehydes were accomplished using homologated binaphthyl *N,O*-ligands (**2**)[8] which showed much improved enantioselectivity compared with the corresponding binaphthyl *N,O*-ligand (NOBIN).[9] Thus, we were interested in investigating the application of these homo-NOBINs and their phosphoramide derivatives to the enantioselective additions of organozincs to *N*-phosphinoylimines.



2a: $NR_2 = N(CH_2)_4$
2b: $NR_2 = N(CH_2CH_2)_2O$

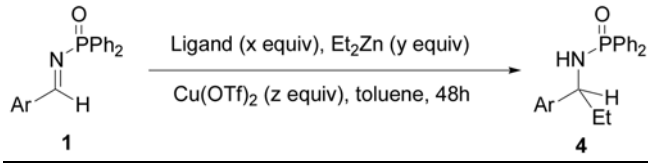
3a: X = O, R = Me
3b: X = S, R = Me
3c: X = S, R = Et

In an initial study with catalytic amounts of homo-NOBIN **2a**, which was prepared in four steps from binaphthol,[8a] for the ethylation of the *N*-(diphenylphosphinoyl)imine of benzaldehyde, we found that the reaction proceeded slowly at room temperature in toluene with the use of five equivalents of diethylzinc to give a low conversion yield and enantioselectivity (entry 1, Table 1). With the use of one equivalent of ligand **2a**, the stereoselectivity of the ethylation was increased to 92% ee with a modest yield of 65% (entry 3). The addition of TIPSCl[5c] to promote the addition reaction (Entry 4) or the use of ligand **2b**[8a] (entry 5), which is a more stereoselective ligand than **2a** in the addition of diphenylzinc to aldehydes, was not effective in improving the reactivity and stereoselectivity of the ethylation.

For the development of more reactive catalysts, we studied the addition of diethylzinc to the imine catalyzed by Cu(II)-phosphoramide. The phosphoramide ligands **3a-c** were easily prepared from the corresponding phosphorylation of (*R*)-2-aminomethyl-2'-hydroxy-1,1'-binaphthyl.[8b] The phosphoramide **3a** was not an effective catalyst in the addition reaction, showing almost no asymmetric induction (entry 6), but the thiophosphoramide **3b** gave a high conversion yield and enantioselectivity at 0 °C (entry 7). The inversion of the absolute configuration of **4** was obtained with the use of ligand **3b**, as compared with the case using ligand **2**. Increasing the reaction temperature and the amounts of the catalysts did not significantly affect the addition reaction (entries 8 and 9). It has been previously reported that the actual copper species involved in Cu-catalyzed organozinc addition reactions are Cu(I) salts, and the use of Cu(OTf) in our study provided similar results to those obtained using $Cu(OTf)_2$ (entry 10). The use of $Cu(OTf)_2$ is preferred due to its stability and consequently greater convenience in handling. Sharp decreases in the reactivity and stereoselectivity were observed by changing the methyl group of **3b** to the ethyl of **3c** (entry 11). These reaction conditions were tested on *N*-phosphinoylimines derived from 4-chlorobenzaldehyde and 1-naphthylaldehyde (entries 12 and 13), and were shown to be applicable to various nonenolizable *N*-phosphinoylimines.

The *R* configuration of **4** obtained with the use of **2a** can be explained based on transition state **I**. The six-membered transition state used to explain the stereochemical result for the addition of diethylzinc to *N*-(diphenylphosphinoyl)imine was proposed by Andersson, on the basis of his calculation for structurally restricted aminoalcohols,[10] and was consistent with the experimental results obtained for confor-

Table 1. Enantioselective Catalytic Diethylzinc Additions to *N*-(diphenylphosphinoyl)imine with Chiral Homologated Binaphthyl *N,O*-ligands and *N*-thiophosphoramide Ligands

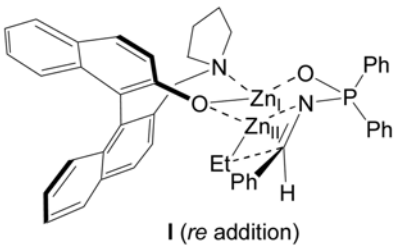


1 4

entry	ligand	Ar	x	y	z	temp	yield (%)[a]	% ee (config.)[b]
1	**2a**	Ph	0.1	5	–	rt	8	66 (*R*)
2	**2a**	Ph	0.5	5	–	rt	55	82 (*R*)
3	**2a**	Ph	1.0	5	–	rt	64	92 (*R*)
4[c]	**2a**	Ph	1.0	5	–	rt	66	92 (*R*)
5	**2b**	Ph	1.0	5	–	rt	57	86 (*R*)
6	**3a**	Ph	0.055	3	0.05	0 °C	35	2
7	**3b**	Ph	0.055	3	0.05	0 °C	83	85 (*S*)
8	**3b**	Ph	0.11	3	0.10	0 °C	80	83 (*S*)
9	**3b**	Ph	0.055	3	0.05	rt	80	85 (*S*)
10[d]	**3b**	Ph	0.055	3	0.05	0 °C	80	83 (*S*)
11	**3c**	Ph	0.055	3	0.05	0 °C	75	54 (*S*)
12	**3b**	4-ClPh	0.055	3	0.05	0 °C	92	81 (*S*)
13[e]	**3b**	1-Naphthyl	0.055	3	0.05	0 °C	82	82 (*S*)

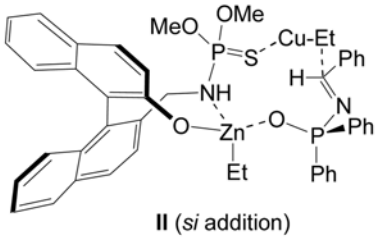
[a]Isolated yields. [b]Determined by chiral HPLC (Chiralcel OD column). [c]TIPSCl (1 equiv) added. [d]$CuOTf\cdot(C_6H_6)_{1/2}$ used instead of $Cu(OTf)_2$. [e]Determined by chiral HPLC (Chiralcel AD-H column).

mationally restricted oxazoline-alcohol ligands. Although the real active species for copper-catalyzed organozinc additions is still not clearly understood, the stereochemical result in the addition reaction catalyzed by Cu(II)-thiophosphoramide **3b** can be rationalized with a simplified and tentative monomeric transition state **II**. The Cu(I)-C bond which is polarized through the coordination of the sulfur to Cu facilitates the delivery of the ethyl group to the *si*-face of the imine bound to the Lewis-acidic zinc center.[11]



I (*re* addition)

(two ethyl groups, each on Zn_I and Zn_{II}, are omitted for clarity)



II (*si* addition)

In summary, we demonstrated the successful application a homologated binaphthyl *N*-thiophosphoramide ligand to the catalytic enantioselective addition of diethylzinc to *N*-(diphenylphosphinoyl)imine. This Cu(II)-binaphthyl-based *N,O*-ligand catalyst provides good yields and enantioselectivities in the reactions of diethylzinc with nonenolizable imines. These binaphthyl-based ligands may constitute a new set of chiral catalysts owing to the convenient ligand preparations, simple reaction conditions and high asymmetric induction that they afford.

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12. Spectral data of **3b**: $[\alpha]_D^{25}$ +12.1 (c 1.18, $CHCl_3$); IR (KBr, cm^{-1}) 3371 (br), 3056, 2945, 2840, 1619, 1595, 1508; ^1H NMR ($CDCl_3$, 300 MHz) δ8.02 (d, J = 8 Hz, 1H), 7.94-7.91 (m, 2H), 7.87 (d, J = 8 Hz, 1H), 7.79 (d, J = 8 Hz, 1H), 7.49 (ddd, J = 8, 7, 2 Hz, 1H), 7.36-7.19 (m, 6H), 6.91 (d, J = 8 Hz, 1H), 4.91 (br s, 1H), 3.92-3.86 (m, 2H), 3.53 (s, 3H), 3.48 (s, 3H), 3.28-3.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.86, 137.39, 137.31, 133.53, 133.33, 132.83, 130.18, 129.55, 129.46, 129.00, 128.16, 128.12, 127.00, 126.98, 126.37, 125.75, 124.19, 123.66, 117.59, 116.42, 53.30 (d, J = 4.9 Hz), 53.27 (d, J = 4.9 Hz), 53.76; HRMS (EI+): Calcd for $C_{23}H_{22}NO_3PS$: 423.1058 $[M]^+$. Found: 423.1048.