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Highly Enantioselective Diethylzinc Addition to Imines Employing Readily Available *N*-Monosubstituted Amino Alcohols

**Hai-Le Zhang,[†] Xiao-Mei Zhang,[†] Liu-Zhu Gong,*,[†] Ai-Qiao Mi,*,[†] Xin Cui,[†]
Yao-Zhong Jiang,[†] Michael C. K. Choi,[‡] and Albert S. C. Chan[‡]**

*Union Laboratory of Asymmetric Synthesis, Chengdu Institute of Organic Chemistry,
Chinese Academy of Sciences, Chengdu 610041, China, and Open Laboratory of
Chirotechnology of the Institute of Molecular Technology for Drug Discovery and
Synthesis and Department of Applied Biology and Chemical Technology,
The Hong Kong Polytechnic University, Hong Kong, China*

gonglz@cioc.ac.cn

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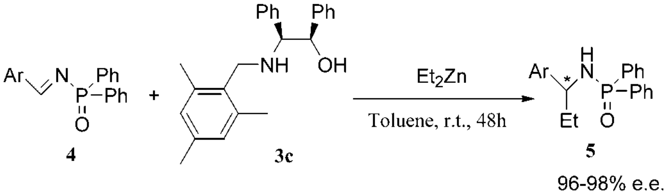
ABSTRACT



An easily accessible chiral ligand 3c, which promoted diethylzinc addition to imines with 96–98% ee, has been found by finely screening *N*,*N*-disubstituted and *N*-monosubstituted amino alcohols. *N*-Monosubstituted amino alcohols, on average, gave slightly higher enantioselectivities than their *N*,*N*-disubstituted analogues. These results imply that the restricted and rigid structure of amino alcohol is not the absolute requirement for the highly enantioselective dialkylzinc addition to diphenylphosphinoylimines.

Optically active amines, serving as chiral intermediates or starting materials, have been comprehensively applied in the synthesis of some natural products and physiologically active substances.[1] They are also employed extensively as resolving reagents and chiral auxiliaries in asymmetric synthesis.[2] The importance of chiral amines has fueled the development of the new synthetic methodologies. Sucessful methods include asymmetric hydrogenation of prochiral imines and enamides.[3] The enantioselective nucleophilic addition of organometallic reagents to imines has been investigated in recent years.[1c,4] Enantioselective addition of dialkylzinc to imines is a convenient route to optically active amines. There have been several reports of the enantioselective addition of dialkylzinc to imines employing chiral amino alcohols,[5] polymeric chiral amino alcohols,[6] and chiral dendrimers[7] as ligands. Recently, Tomioka and co-workers reported their work on the copper-amidophosphine catalyzed asymmetric addition of organozinc

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[†] Chengdu Institute of Organic Chemistry.

[‡] The Hong Kong Polytechnic University.

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to imines with excellent results.[8] Hoveyda, Snapper, and their co-workers have also realized the catalytic asymmetric diethylzinc addition to imines by means of chiral Zr complexes.[9] Many chiral amino alcohol ligands have been developed for the diethylzinc addition to diphenylphosphinoylimines, but most of them are limited to compounds containing a structurally rigid backbone. There is a trend in previous reports that structurally constrained chiral β-amino alcohols generally showed much higher enantioselectivities than structurally flexible ones.[5e−g] However, structurally rigid and restricted amino alcohols have inconveniences along with their multistep synthesis[5e,10] that make the process of diethylzinc addition to imines to prepare the chiral amines too expensive to compete with other families of chiral ligands, especially when stoichiometric amounts were used. Therefore the design and development of easily accessible and economical chiral reagents are still a worthwhile project. If the chiral reagents are cheap enough, the transformation leading to chiral amines, even in the presence of stoichiometric amounts of such kinds of ligands, is also comparable with the asymmetric catalytic process. In our previous work, we have already presented the diethylzinc addition to diphenylphosphinoylimines with up to 94% ee given by a chiral ligand **1** derived from 1,2-diphenyl-2-aminoethanol that has been made in large scale by a very cheap process.[11] Herein, we would like to present our approach to a much more easily available kind of ligand for the highly enantioselective diethylzinc addition to diphenylphosphinoylimines with up to 98% ee, the best result observed so far for this transformation. A finding that *N*-monosubstituted chiral β-amino alcohols **3** generally gave slightly higher enantioselectivities than their *N*,*N*-disubstituted analogue **2** will also be discussed. Chiral ligands were prepared from 1,2-diphenyl-2-aminoethanol according to the literature. Treatment of (1*R*,2*S*)-1,2-diphenyl-2-aminoethanol with aldehydes followed by a reduction with $NaBH_4$ gave the corresponding monosubstituent amino alcohols **3a**−**f**, which were subjected to methylation with HCOOH/HCHO to give compounds **2a**−**g**.[12]

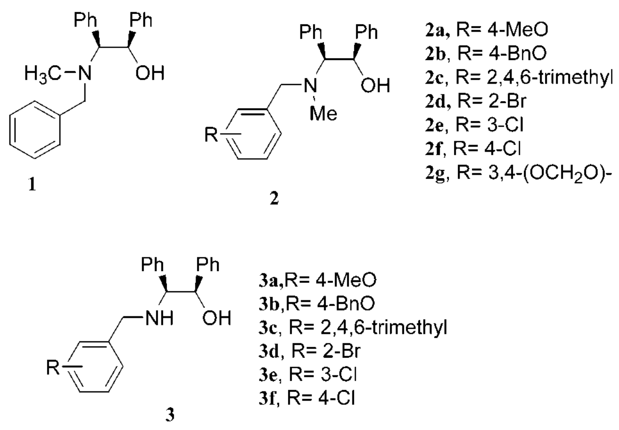
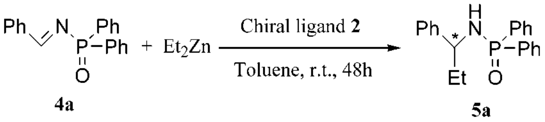


Figure 1. Chiral β-amino alcohols evaluated in this study.

In the presence of stoichiometric amount of *N*,*N*-disubstituted amino alcohols **2**, we systematically examined the effects of substituents bonded to the benzyl ring of the ligands on the enantioselectivities by means of *N*-diphenylphosphinoyl benzalimine as a standard substrate. As can be seen in Table 1, most of chiral *N*,*N*-disubstituted amino alcohols **2** could give good enantioselectivities with up to 95% ee. The nitrogen substituents in the ligands had an obvious effect on the enantioselectivity. It seemed that the ligands bearing a bulkier R group in the benzene ring hindered the enantioselectivity. The ligand **2a**, in which the R was a 4-methoxyl group, promoted the reaction in 94% isolated yield with 95% ee (entry 1), whereas **2b** containing a bulkier R group of

Table 1. Diethylzinc Addition to *N*-Diphenylphosphinoyl Benzalimine **4a** in the Presence of Chiral *N*,*N*-Disubstituted Amino Alcohols **2**[a]



entry	ligand	R	yield (%)[b]	ee (%)[c]
1	**2a**	4-MeO	94	95
2	**2b**	4-BnO	63	92
3	**2c**	2,4,6-trimethyl	93	84
4	**2d**	2-Br	35	91
5	**2e**	3-Cl	87	95
6	**2f**	4-Cl	94	93
7	**2g**	3,4-(OCH_2O)-	80	93

[a] The reaction was carried out at room temperature in the presence of a stoichiometric amount of amino alcohols for 48 h. [b] Isolated yields. [c] Determined on HPLC; the absolute configuration is *R*.

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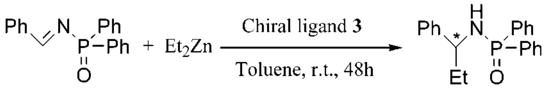
benzoxyl resulted in a slightly less stereochemical outcome of 92% ee (entry 2). Further increase in the bulkiness of the R group by replacement of 4-methoxylbenzyl **2a** with a 2,4,6-trimethylbenzyl group **2c** led to a much lower ee value of 84% (entry 3). Most of ligands bearing a halogen on the benzyl group possessed the excellent stereoselection property. High enantioselectivities of 95% and 93% ee were provided by **2e** (R = 3-Cl) and **2f** (R = 4-Cl), respectively (entries 5 and 6). The ligand **2d** (R = 2-Br) also afforded a good enantioselectivity of 91% ee but only 35% isolated yield (entry 4).

N,*N*-Disubstituted β-amino alcohols have been successfully employed in the diethylzinc addition to carbonyl compounds with extremely high enantioselectivity.[13] Generally, an *N*,*N*-disubstituent of the amino alcohol was the requirement for getting high enantioselectivity. Among the approximately 260 individual chiral amino alcohols recently reviewed by Pu and Yu for diethylzinc addition to aldehydes, only a few of the *N*-monosubstituted amino alcohols have given more than 90% ee in the diethylzinc addition to aldehydes.[14] The use of *N*-monosubstituted β-amino alcohol in promoting the diethylzinc addition to diphenylphosphinoylimines with high enantioselectivity is also rare.[6b] The dramatic dependence of the enantioselectivity on the size of the *N*,*N*-disubstituent of the ligand prompted us to screen the *N*-substituent carefully with a purpose of searching for an excellent chiral ligand. It is encouraging that chiral amino alcohol **3a**, in which a methyl group was removed from the nitrogen as compared with its *N*,*N*-disubstituted analogue **2a**, provided excellent enantioselectivity of 95% ee. This result indicated that *N*-monosubstituted β-amino alcohol could also serve as a good ligand for the diethylzinc addition to imine. Thus we investigated the application of other *N*-monosubstituted β-amino alcohols **3b**−**f** in the above-mentioned reaction. As seen in Table 2, all of the amino alcohols **3b**−**f** afforded higher or comparable enantioselectivties in comparison with corresponding *N*,*N*-disubstituted compounds **2a**−**g**. There was a trend that a ligand bearing a bulkier R group induced higher enantioselectivity. That was quite different from findings in the cases of using *N*,*N*-disubstituted amino alcohols **2** as chiral ligands. For example, ligand **3c** containing a 2,4,6-trimethylbenzyl group generated the highest enantioselectivity of 97% ee (Table 2, entry 3). However, ligand **2c** only resulted in 84% ee (Table 1, entry 3). If the R group is a halogen, as shown in ligands **3d**−**f**, the results also supported the trend that the larger R group was beneficial to the enantioselectivity. For instance, the ligand **3d** processing a Br on the benzyl group gave an enantioselectivity of 95% ee (entry 5), better than those given by **3e**−**f** in which R groups were Cl. However, in the cases of using *N*,*N*-disubstituted amino alcohols **2d**−**f** as promoters, **2e** and **2f** provided a higher stereochemical outcome than **2d** did. In the presence of 50 mol % of the best ligand **3c**, high yield of 81% and 93% ee were afforded (entry 4).

Table 2. Diethylzinc Addition to *N*-Diphenylphosphinoyl Benzalimine (**4a**) in the Presence of Chiral Amino Alcohols **3**[a]



4a

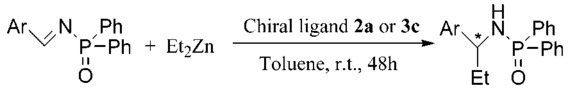
5a

entry	ligands	R	yield (%)[b]	ee (%)[c]
1	**3a**	4-MeO	99	95
2	**3b**	4-BnO	68	95
3	**3c**	2,4,6-trimethyl	92	97
4	**3c**	2,4,6-trimethyl	81	93[d]
5	**3d**	2-Br	99	95
6	**3e**	3-Cl	78	94
7	**3f**	4-Cl	99	94

[a] The reaction was carried out at room temperature in the presence of a stoichiometric amount of amino alcohols for 48 h. [b] Isolated yields. [c] Determined on HPLC; the absolute configuration is *R*. [d] The reaction was promoted by 50 mol % of ligand **3c**.

With the optimal ligands **2a** and **3c** in hand, we extended their application in the diethylzinc addition to other diphenylphosphinoylimines. The corresponding results are recorded in Table 3. In the presence of ligand **2a**, enantioselectivities from 94% to 96% ee values were obtained for all of the imine substrates tested. Basically, the substituents on the substrates had no obvious effect on the enantioselectivity. Ligand **3c**, on average, gave slightly higher enantioselectivities than ligand **2a** did. For all of the substrates examined, from 96% to 98% ee values were given by **3c**;

Table 3. Asymmetric Diethylzinc Addition to Aromatic *N*-Diphenylphosphinoyl Imines **4a**−**e** Promoted by **2a** and **3c**[a]



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5

Ar	imine	ligand	yield (%)[b]	ee (%)[c]
Ph	**4a**	**2a**	94	95
		3c	92	97
		3c	97	98[d]
4-MeOPh	**4b**	**2a**	82	95
		3c	89	97
piperonyl	**4c**	**2a**	90	95
		3c	92	97
4-MePh	**4d**	**2a**	89	96
		3c	95	98
3-MePh	**4e**	**2a**	98	94
		3c	86	96

[a] The reaction was carried out at room temperature in the presence of a stoichiometric amount of amino alcohols for 48 h, unless otherwise specified. [b] Isolated yields based on imines. [c] Determined by HPLC. [d] The reaction was performed in 1 mmol scale.

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not only were these the best results so far reported[15] but also the ligand **3c** that we developed was the most easily accessible. In addition, although a stoichiometric amount of amino alcohol had to be used, the chiral ligand could be recovered by flash chromatography.

In summary, a family of *N*,*N*-disubstituted and *N*-monosubstituted amino alcohols has been screened for the diethylzinc addition to imines. In addition, we found that *N*-monosubstituted amino alcohols gave slightly higher enantioselectivities than *N*,*N*-disubstituted ones. An extremely high enantioselectivity of 98% ee was provided by a very easily accessible ligand **3c**. These results implied that the rigid and restricted structure of amino alcohol was not the absolute requirement for the high enantioselective dialkylzinc addition to diphenylphosphinoylimine.

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Supporting Information Available: Experimental procedure for the asymmetric diethylzinc addition to imines, characterization of new amino alcohols, and HPLC analytical data for chiral amides. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] Very recently, a structurally rigid chiral amino alcohol, which was prepared by a nine-step reaction sequence from commercially available compounds, could give results comparable with those of our ligand **3c** for the titled reaction in chlorobenzene. See: Pinho, P.; Andersson, P. G. *Tetrahedron* **2001**, *57*, 1615.