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The first use of chiral oxazoline ligands in the highly enantioselective diethylzinc addition to diphenylphosphinoyl imines

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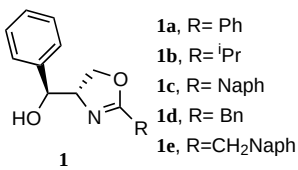
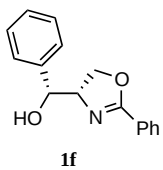
Abstract—A series of chiral oxazolines, which had been conveniently prepared from commercially available (1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol, was applied in the diethylzinc addition to diphenylphosphinoyl imines to give high yields of 68–84% and excellent e.e. values of 90–93%. © 2002 Published by Elsevier Science Ltd.

Optically active amines are very important intermediates for the synthesis of some natural products, physiologically active substances and pharmaceutical compounds.[1] They are also extensively used as resolving reagents and chiral auxiliaries in asymmetric synthesis.[2] For all of these reasons, many methods for the asymmetric synthesis of chiral amines have been developed.[1,3,4] Other than the enantioselective reduction of prochiral imines and enamides,[3,4] the asymmetric addition of nucleophiles to imines is one of the most convenient methodologies for this purpose.[5] Highly enantioselective addition of diethylzinc to imines leading to optically active amines is attracting increasing attention.[6] Although many chiral ligands have been prepared for this transformation, most of them are limited to the derivatives of chiral aminoalcohols.[6a–f] To date, the most efficient ligands for this transformation are the conformationally restricted and structurally rigid aminoalcohols, but they suffer from the inconvenience associated with their multi-step syntheses.[6e] To find more efficient and easily prepared ligands for this addition, families of chiral ligands with backbones other than aminoalcohols still need to be designed.

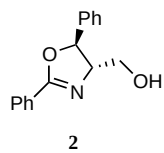


1a, R= Ph
1b, R= ^{i}Pr
1c, R= Naph
1d, R= Bn
1e, R=CH_2Naph

1



1f



2

Chiral oxazolines with a backbone similar to that found in **1** have three structural characteristics that might enable them to be the promising candidates in competition with aminoalcohols in catalyzing the diethylzinc addition of *N*-diphenylphosphinoylimines. (1) They have sp^2 nitrogens restricted by the oxazoline ring, which probably makes the structure of the ligand rigid, so that could minimize the diastereomers formed in the transition state during catalysis. (2) The oxygen in the oxazoline ring is conjugated with C=N, which causes the nitrogen to be more Lewis basic so that would change the Lewis acidity and catalytic activity of their zinc complexes. (3) The chiral environment could be systematically modified for the high enantioselectivity by fine-tuning the size of the R groups in **1**. To the best of our knowledge the use of chiral oxazolines in asymmetric diethylzinc addition to imines has not been presented so far. Herein, we would like to report their *first* application in the titled reaction.

The preparation of **1** and **2**[7a] starting from commercially available compounds (1*S*,2*S*)-2-amino-1-phenyl-

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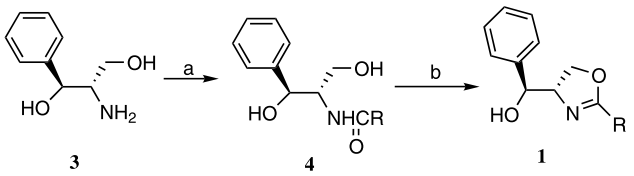
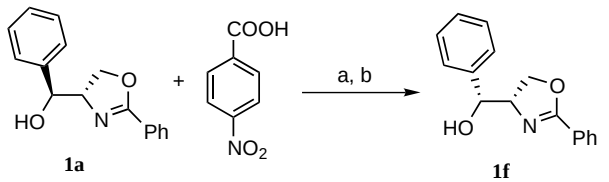
propane-1,3-diol (**3**) according to the known procedure with minor modification is shown in Scheme 1.[7b] The chiral oxazoline **1f** was prepared from **1a** by a Mitsunobu configuration inversion procedure in 20% yield (Scheme 2), in order to investigate the effect of chiral carbon bonded to hydroxyl group on the enantioselectivity.[8]

First, the different chiral oxazolines **1** and **2** were examined for the addition of diethylzinc to *N*-diphenylphosphinoyl benzalimine (**5a**) leading to diphenylphosphinoylamide **6a** to find the optimal ligand. The results of imine **5a** reacting with Et_2Zn in the presence of stoichiometric amounts of **1** and **2** in toluene at room temperature are summarized in Table 1.

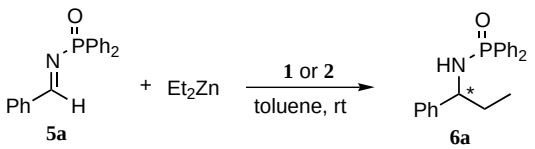


Scheme 1. *Reagents and conditions*: (a) RCOCl or $(PhCO)_2O$ (1 equiv.), Et_3N, THF, rt; (b) TsCl (1 equiv.), Et_3N, CH_2Cl_2, reflux, 51–80%.



Scheme 2. *Reagents and conditions*: (a) Ph_3P, DEAD, THF, reflux; (b) K_2CO_3, CH_3OH, rt, 20% (two steps).

Table 1. Enantioselective diethylzinc addition of *N*-diphenylphosphinoyl benzalimine (**5a**) in the presence of the chiral oxazolines **1** and **2**[a]



Entry	Ligands	Yield (%)[b]	e.e. (%)[c]	Config.[d]
1	**1a**	77	91	*S*
2	**1b**	62	85	*S*
3	**1c**	79	85	*S*
4	**1d**	70	87	*S*
5	**1e**	65	84	*S*
6	**1f**	56	76	*R*
7	**2**	55	23	*S*

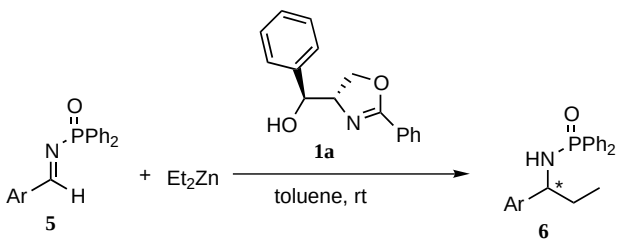
[a] The reaction was carried out at room temperature in the presence of a stoichiometric amount of oxazoline for 48 h.[9]
[b] Isolated yield based on imine.
[c] Determined by HPLC.
[d] Determined by comparison of the retention time with literature values.[6]

As we expected, this set of chiral oxazoline ligands was efficient and highly enantioselective for the titled reaction. Enantioselectivities higher than 84% e.e. were induced by most of the oxazolines **1** (entries 1–5). The chiral carbon bonded to the hydroxyl group in the ligand was very important for achieving high enantioselectivity. Without this chiral center, oxazoline **2** gave a very low enantioselectivity of 23% e.e. (entry 7). The configuration of the product was also controlled by the chiral carbon bonded to the hydroxyl group. When the configuration of this carbon was inverted, but that of the carbon bonded to nitrogen in the oxazoline ring maintained, as exemplified by **1a** and **1f**, the configuration of the product **6a** was inverted from *S* to *R* (entries 1 and 6); however, the enantioselectivity decreased slightly to 76% e.e. Varying the size of the R group resulted in a slight effect on the enantioselectivity (entries 1–5). Chiral oxazoline ligand **1a** in which R was a phenyl group showed the highest level of chiral induction for the diethylzinc addition to imine **5a**, giving an e.e. of 91%.

The utility of the optimal oxazoline **1a** as a promotor in diethylzinc addition to various aromatic imines **5a**–**g** was also investigated. As can be seen in Table 2, all of the reactions worked smoothly to give the corresponding amides in high yields (68–84%) and excellent e.e.'s (90–93%).

In conclusion, a series of chiral oxazolines were conveniently synthesized from commercial material. Their application in catalyzing diethylzinc addition to aromatic *N*-diphenylphosphinoylimines led to high yields and excellent e.e. values of 90–93%. The configuration of the product was controlled by the chirality of the carbon bonded to the hydroxyl group in the oxazoline. This *first* successful example using chiral oxazolines to promote the

Table 2. Asymmetric diethylzinc addition to aromatic *N*-diphenylphosphinoyl imines (**5a**–**g**) promoted by oxazoline **1a**[a]



Ar	Imine	Yield (%)[b]	e.e. (%)[c]
Ph	**5a**	77	91
p-ClC_6H_4-	**5b**	82	92
p-Br-C_6H_4-	**5c**	83	90
p-$CH_3OC_6H_4$-	**5d**	84	90
p-$CH_3C_6H_4$-	**5e**	72	93
m-$CH_3C_6H_4$-	**5f**	68	93
Piperonyl	**5g**	75	90

[a] All reactions were carried out according to the procedure presented in Ref. 9.
[b] Isolated yields based on imines.
[c] Determined by HPLC.

titled reaction implies that a large family of chiral compounds containing an oxazoline ring moiety have the potential, and could be developed for promoting the highly enantioselective dialkylzinc addition to *N*-diphenylphosphinoylimines.

Acknowledgements

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9. Typical experimental procedure for the enantioselective addition of diethylzinc to *N*-diphenylphosphinoyl benzalimine (**5a**) in the presence of **1a**: Imine **5a** (30.5 mg, 0.1 mmol) and oxazoline **1a** (25.3 mg, 0.1 mmol) were dissolved in toluene (1.5 mL) under argon. To the mixture was added Et_2Zn in hexane (1 M, 0.5 mL, 0.5 mmol) at rt. After stirring for 48 h, the reaction was quenched with saturated aqueous ammonium chloride, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified through column chromatography on silica gel to give **6a** (25.8 mg, 0.077 mmol, 77%) as a white solid. The enantiomeric excess of the *S*-isomer 91% (major) was determined by HPLC (Chiracel AD column, hexane/propan-2-ol = 80:20; flow rate 1 mL/min; *R*-isomer, t_R 13.17 min and *S*-isomer, t_R 17.82 min).