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Enantioselective addition of diethylzinc to a *N*-diphenylphosphinoylimine employing cinchona alkaloids as chiral ligands

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Abstract—The use of cinchona alkaloids to promote the addition of diethylzinc to *P*,*P*-diphenyl-*N*-(phenylmethylene)phosphinic amide has been examined. Using cinchonine and cinchonidine as ligands, the *S* and *R* enantiomers of *N*-(1-phenylpropyl)-*P*,*P*-diphenylphosphinic amide were prepared in good yield with up to 93% ee. The reaction was shown to proceed with catalytic amounts of ligand.

Optically active amines are employed extensively as chiral resolving agents[1] and as chiral auxiliaries.[2] They also have an important role as reagents in the synthesis of natural products and biologically active substances.[3] An attractive and direct approach to the synthesis of optically active amines is the addition of nucleophiles to imines.[4] Several reports have recently been published in which the addition of diethylzinc to *N*-diphenylphosphinoylimines has been promoted by the use of a chiral amino alcohol.[5–8] In order to avoid the need to prepare these chiral reagents, it was decided to investigate the use of the readily available and inexpensive cinchona alkaloids to promote this reaction. Cinchona alkaloids, which are in themselves amino alcohols, have been shown to promote the corresponding addition of diethylzinc to aldehydes with moderate to good enantioselectivity.[9] Although cinchona alkaloids are only available in one enantiomeric form they do exist as 'pseudoenantiomeric pairs.' Thus, quinine (or cinchonidine), although being diastereomeric with quinidine (or cinchonine), is enantiomeric at the key amino alcohol portion of the molecule (Fig. 1). With all known cinchona alkaloid catalysed reactions the configurations at carbons C-8 and C-9 have been shown to determine the configuration of the product formed in excess.[9]

The initial results of the addition of diethylzinc to *P*,*P*-diphenyl-*N*-(phenylmethylene)phosphinic amide **1**[11] in the presence of 1 equiv. of a cinchona alkaloid (Scheme 1) are presented in Table 1. With quinine and cinchonidine as ligands and toluene as solvent the *R* enantiomer of *N*-(1-phenylpropyl)-*P*,*P*-diphenylphosphinic amide **2**[12] was obtained in 59 and 72% ee, respectively (entries 1 and 3). Using quinidine and cinchonine the *S* enantiomer of **2** was obtained in 57 and 68% ee (entries 2 and 4). Thus, as anticipated, both enantiomers of **2** are accessible. It is interesting that

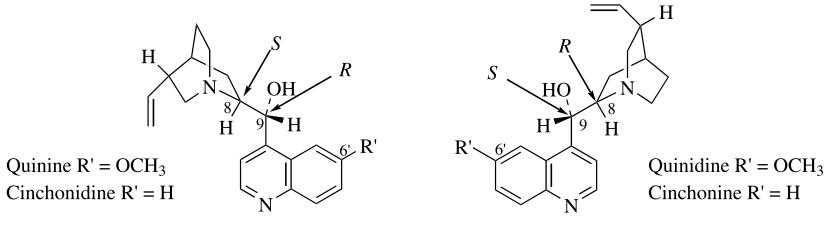

Figure 1. Structure, numbering and absolute configuration of some cinchona alkaloids.

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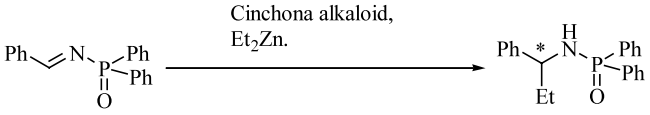

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Scheme 1. Addition of diethylzinc to *P*,*P*-diphenyl-*N*-(phenylmethylene)phosphinic amide.

Table 1. Addition of diethylzinc to *P*,*P*-diphenyl-*N*-(phenylmethylene)phosphinic amide promoted by cinchona alkaloids[a]

Entry	Ligand	Yield (%)[b]	Ee (%)[c]	Config.[d]
1	Quinine	67	59	*R*
2	Quinidine	66	57	*S*
3	Cinchonidine	56	72	*R*
4	Cinchonine	79	68	*S*

[a] Reactions carried out in toluene at room temp. using 1 equiv. of ligand and 3 equiv. of diethylzinc.
[b] Isolated yield after flash chromatography.
[c] Determined by HPLC analysis on a chiral column (Chiralcel OD).
[d] Determined by comparison of the retention time with the literature.[10]

both 'pseudoenantiomeric pairs' of cinchona alkaloids produce the *R* and *S* enantiomers with similar ees. This indicates that the position of the vinyl group in the molecule must have little influence on the enantioselectivity of the reaction. This is in marked contrast to the corresponding addition to aldehydes in which the position of the vinyl group was found to have a significant effect.[9] The lower ee values obtained with quinine and quinidine suggest that the methoxy group at C-6′ in the quinoline ring of these compounds is disfavouring enantioselectivity.

As the solvent used in a reaction can significantly influence the enantioselectivity of a chiral ligand, or catalyst,[7] a solvent study was undertaken with the aim of optimising the enantiomeric excess of the addition (Table 2).Changing the solvent from toluene (entry 1) to chlorobenzene (entry 2) resulted in a decrease in ee from 72 to 60%. This was surprising as in a previous investigation using a synthetic chiral amino alcohol as a ligand,[6] chlorobenzene was found to be the optimum solvent for the reaction. Other aromatic solvents such as benzene (entry 3, 54% ee), anisole (entry 4, 58% ee) and *o*-xylene (entry 5, 67% ee) also showed reductions in ee compared with toluene. With mesitylene (1,3,5-trimethylbenzene) (entry 6, 20% ee), tetrahydrofuran (entry 7, 24% ee) and hexane (entry 10, 18% ee) low enantiomeric excesses were obtained. Dichloromethane (entry 8), however, was found to be almost as effective a solvent as toluene giving an ee of 71%. This again was a surprising result as dichloromethane has previously been shown to be a poor solvent for the addition of diethylzinc to imines promoted by amino alcohols.[6] With chloroform (entry 9) no reaction was observed.

The effect of ligand concentration and diethylzinc excess on yield and enantioselectivity are shown in Table 3. With 1 equiv. of cinchonidine in toluene at room temperature, doubling the quantity of diethylzinc added from 3 to 6 equiv. (entry 1) improved both the yield (56–70%) and enantiomeric excess (72–85%). Although this reaction was stirred overnight at room temperature, thin-layer chromatography indicated that it was complete after approximately 4 h. In an attempt to increase enantiomeric excess further the reaction was

Table 2. Effect of solvent on yield and enantiomeric excess

Entry	Solvent[a]	Yield (%)[b]	Ee (%)[c]
1	Toluene	56	72
2	Chlorobenzene	67	60
3	Benzene	55	54
4	Anisole	60	58
5	*o*-Xylene	78	67
6	Mesitylene	50	20
7	THF	24	24
8	Dichloromethane	58	71
9	Chloroform	–	–
10	Hexane	55	18

[a] Reactions carried out using 1 equiv. of cinchonidine and 3 equiv. of diethylzinc.
[b] Isolated yield after flash chromatography.
[c] Determined by HPLC analysis on a chiral column (Chiralcel OD). *R* enantiomer in each case.

Table 3. Effect of ligand concentration and diethylzinc excess on yield and enantioselectivity[13]

Entry[a]	Ligand	Equiv. of ligand	Equiv. of diethylzinc	Temp.	Yield(%)[b]	Ee (%)[c]	Config.[d]
1	Cinchonidine	1.0	6	rt	70	85	*R*
2	Cinchonidine	1.0	6	−18°C	33	67	*R*
3	Cinchonidine	1.0	12	rt	76	93	*R*
4	Cinchonine	1.0	12	rt	77	91	*S*
5	Cinchonidine	0.5	12	rt	77	87	*R*
6	Cinchonidine	0.2	12	rt	52	80	*R*

[a] Reactions carried out in toluene.
[b] Isolated yield after flash chromatography.
[c] Determined by HPLC analysis on a chiral column (Chiralcel OD).
[d] Determined by comparison of the retention time with the literature.[10]

repeated at −18°C (entry 2, freezer overnight). This, however, had the effect of decreasing the ee to 67% and reducing the yield to 33%. Doubling the concentration of diethylzinc yet again to 12 equiv. (entry 3) improved both yield and enantiomeric excess to 76 and 93%, respectively. With cinchonine as ligand under the same reaction conditions (entry 4) the *S* enantiomer of **2** was obtained in similar yield and ee. In order to determine if the addition could be carried out using a catalytic amount of a cinchona alkaloid, the reaction with cinchonidine was repeated using both 0.5 and 0.2 equiv. of ligand (entries 5 and 6). With 0.5 equiv. of cinchonidine a decrease in ee from 93 to 87% was observed although the yield remained the same. With 0.2 equiv. of cinchonidine (*R*)-**2** was obtained in 52% yield and 80% ee.

In summary, cinchona alkaloids have been demonstrated to be an attractive and readily available alternative to synthetic chiral amino alcohols in promoting the addition of diethylzinc to *N*-diphenylphosphinoylimines. Of the cinchona alkaloids examined, cinchonine and cinchonidine were found to be the 'pseudoenantiomeric pair' which gave **2** in highest enantiomeric excess. Optimisation of the reaction conditions enabled the preparation of either enantiomer of **2** in good yield and high enantiomeric excess. A major influence on the enantioselectivity of the reaction was found to be the excess of diethylzinc added. The reaction was found to proceed with catalytic amounts of ligand with only a small reduction in enantiomeric excess.

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References

1. Jacques, J. K.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolution*; John Wiley and Sons: New York, 1981.
2. Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581–1590.
3. Moser, H.; Rihs, G.; Sauter, H. *Z. Naturforsch.* **1982**, *37*, 451–462.
4. For examples, see: Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094 and references cited therein.
5. Jimeno, C.; Vidal-Ferran, A.; Moyano, A.; Pericás, M. A.; Riera, A. *Tetrahedron Lett.* **1999**, *40*, 777–780.
6. Pinto, P.; Anderson, P. G. *Tetrahedron* **2001**, *57*, 1615–1618.
7. Sato, I.; Kodaka, R.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2912–2914.
8. Zhang, X.; Cong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett.* **2001**, *42*, 6369–6372.
9. Smaardijk, A. A.; Wynberg, H. *J. Am. Chem. Soc.* **1987**, *52*, 135–137.
10. For HPLC conditions and retention times, see: Anderson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem.* **1997**, *62*, 7364–7375.
11. For preparation of **1**, see: Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561–5568.
12. The free amine can be obtained from **1** by acidic hydrolysis, see: Ramage, R.; Hopton, D.; Parrot, M. J.; Kenner, G. W.; More, G. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1357.
13. Experimental procedure: A solution of **1** (100 mg, 0.328 mmol) in toluene (1.0 ml) was added to a cooled (ice bath) stirred solution of the cinchona alkaloid and diethylzinc (1.1 M in toluene). The resulting solution was warmed to room temperature and stirred overnight. The reaction was quenched with satd NH_4Cl solution and extracted with dichloromethane (3×20 ml). The organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. Flash chromatography on silica gel eluting with acetone: hexane (3:7 then 1:1) gave **2** as a white solid. Analytical data were in accordance with literature.