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Enantioselective addition of diethylzinc to *N*-diphenylphosphinoylimines employing cinchonidine and cinchonine as chiral ligands

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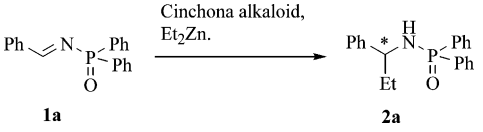
Abstract—The use of the 'pseudoenantiomeric pair' of cinchonine and cinchonidine as ligands for the addition of diethylzinc to *N*-diphenylphosphinoylimines has been investigated. With 1 equiv of cinchonidine as ligand, a series of chiral amines was prepared in good yield and enantiomeric excesses of up to 94%. The use of 2.0 equiv of methanol as an achiral additive was found significantly to improve the selectivity of the addition when using 0.2 equiv of ligand, yielding ee's close to those obtained with a stoichiometric amount of ligand.

Optically active amines have an important role as intermediates in the synthesis of biologically active natural and nonnatural products.[1] In addition, optically active amines are used extensively as chiral auxiliaries and as resolving agents.[2] An attractive and direct approach to the synthesis of chiral amines is the enantioselective addition of organometallic reagents to imines.[3] We have recently reported the highly enantioselective addition of diethylzinc to *P*,*P*-diphenyl-*N*-(phenylmethylene)phosphinic amide **1a** employing the inexpensive and readily available cinchona alkaloids as chiral ligands (Scheme 1).[4] Optimum selectivity in this reaction was realised with the 'pseudoenantiomeric pair' of cinchonine and cinchonidine (Fig. 1). We now wish to report our most recent progress in the extension of this methodology as a tool to synthesise chiral building blocks.



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

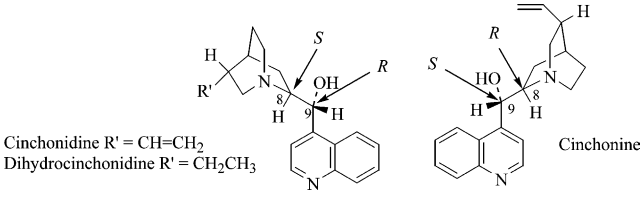


Figure 1. Structure, numbering and absolute configuration of cinchonine, cinchonidine and dihydrocinchonidine.

With 1.0 equiv of cinchonidine and 12 equiv of diethylzinc in toluene at room temperature the *R* enantiomer of **2a** was obtained in 76% yield and 93% ee (Table 1, entry 1). Under the same reaction conditions using cinchonine (entry 8), (*S*)-**2a** was afforded in 77% yield and 91% ee. Reducing the quantity of cinchonidine to 0.5 equiv gave an ee of 87% with similar yield (entry 2). With 0.2 and 0.05 equiv of cinchonidine (entries 3 and 4) further reductions in enantiomeric excess were observed together with a reduction in both yield and reaction rate. With 1 equiv of cinchonidine the reaction was found to be complete after 3 h. With 0.2 and 0.05 equiv of ligand, starting material was found to persist despite the reaction being stirred overnight. This reduction in rate is indicative of a ligand acceleration effect.[5] Room temperature appears to be optimum for the reaction in

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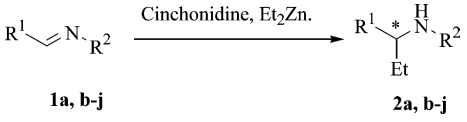
Table 1. Addition of diethylzinc to **1a** promoted by cinchona alkaloids

Entry[a]	Ligand	Ligand (equiv)	Temperature	Yield (%)[b]	Ee (%)[c]	Config.[d]
1	Cinchonidine	1.0	Rt	76	93	*R*
2	Cinchonidine	0.5	Rt	77	87	*R*
3	Cinchonidine	0.2	Rt	52	80	*R*
4	Cinchonidine	0.05	Rt	50	69	*R*
5	Cinchonidine	1.0	−18 °C	33	67	*R*
6	Cinchonidine	0.2	4 °C	37	75	*R*
7	Cinchonidine	0.2	60 °C	50	41	*R*
8	Cinchonine	1.0	Rt	77	91	*S*
9	Cinchonidine Li salt[e]	1.0	Rt	55	21	*R*
10	Dihydrocinchonidine	1.0	Rt	70	96	*R*

[a] Reaction carried out in toluene using 12 equiv of diethylzinc.
[b] Isolated yield after flash chromatography.
[c] Determined by HPLC analysis on a chiral column (Chiralcel OD).
[d] Assigned by comparison of the retention times with the literature.[6,7]
[e] Prepared in situ by reaction of cinchonidine with 1 equiv of *n*-BuLi.

terms of selectivity and yield. With 1.0 equiv of cinchonidine under the same reaction conditions, reducing the temperature to −18 °C reduced both the enantiomeric excess and yield (entry 5). At 4 °C with 0.2 equiv of cinchonidine (entry 6) the ee decreased from 80% at room temperature to 75%, and the yield from 52% to 37%. Increasing the reaction temperature to 60 °C with 0.2 equiv of cinchonidine (entry 7) also had a detrimental effect on ee, although the yield remained unchanged. The lithium salts of amino alcohols have, in certain cases, been shown to give better selectivity than the corresponding amino alcohol in the catalytic addition of diethylzinc to aldehydes.[8] Using 1 equiv of the lithium salt of cinchonidine as ligand was found to reduce significantly both the enantiomeric excess and yield (entry 9), indicating the importance of the hydroxyl group in cinchonidine for high selectivity. Changing the ligand to dihydrocinchonidine (Fig. 1), prepared by the reduction of cinchonidine with hydrogen and 10% Pd/C (90% yield), was found to give slightly better selectivity than cinchonidine, 1 equiv affording (*R*)-**2a** in 70% yield and 96% ee (entry 10).

The scope of the reaction in terms of substrate structure was examined by preparing a series of *N*-diphenylphosphinoylimines,[9] and reacting these with diethylzinc using 1.0 equiv of cinchonidine under the reaction conditions used previously for the phenyl derivative (Scheme 2). The imines derived from *p*-anisaldehyde, *p*-chlorobenzaldehyde, *p*-tolualdehyde, 1-naphthaldehyde, 2-naphthaldehyde, 2-furanal and piperonal were all found to give the corresponding amines in good yields and enantioselectivities as shown in Table 2 (entries 2–8). In each case the *R* enantiomer was the major product. The effect of the group on the imine nitrogen was also examined. As anticipated,[7] the imine prepared from benzaldehyde and *p*-anisidine **1i** was found to undergo no reaction at room temperature, or when heated to 60 °C (entry 9). A similar result was obtained with the corresponding *o*-anisidine derived imine. The *N*-(*p*-toluenesulfonyl)imine **1j** was found to give the corresponding chiral amine **2j** in 43% yield but with only 3% ee (entry 10). This decrease in selectivity between *N*-(diphenylphosphinoyl) and *N*-tosyl imines has also been observed when using aziridino alcohols as promoters for the addition of diethylzinc.[7]



1a, b-j **2a, b-j**

Scheme 2. Addition of diethylzinc to imines promoted by cinchonidine.

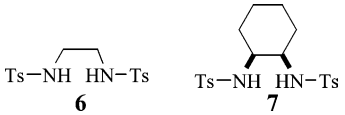
Table 2. Addition of diethylzinc promoted by cinchonidine

Entry[a]	**1**	R^1	R^2	Yield (%)[b]	Ee (%)[c]
1	**a**	Ph	$P(O)Ph_2$	77	93
2	**b**	4-$MeOC_6H_4$	$P(O)Ph_2$	70	92
3	**c**	4-ClC_6H_4	$P(O)Ph_2$	69	90
4	**d**	4-MeC_6H_4	$P(O)Ph_2$	61	94
5	**e**	1-Naphthyl	$P(O)Ph_2$	65	78
6	**f**	2-Naphthyl	$P(O)Ph_2$	61	84
7	**g**	2-Furyl	$P(O)Ph_2$	62	86
8	**h**	3,4-$OCH_2OC_6H_3$	$P(O)Ph_2$	64	90
9	**i**	Ph	4-$MeOC_6H_4$	0	—
10[d]	**j**	Ph	Ts	43	3

[a] Reaction carried out in toluene using 1 equiv of cinchonidine and 12 equiv of diethylzinc at room temperature.
[b] Isolated yield after flash chromatography.
[c] Determined by HPLC analysis on a chiral column (Chiralcel OD). All *R* configuration.
[d] Reaction carried out in toluene using 1 equiv of ligand and 3 equiv of diethylzinc at room temperature.

The use of achiral additives and co-catalysts has been found to have a significant effect on the enantioselectivity of a number of catalytic asymmetric reactions.[10] In a recent publication[11] the achiral bis(sulfonamide) **6** was found to improve significantly the rate, yield and enantioselectivity in the addition of diethylzinc to benzaldehyde catalysed by chiral amino alcohols. The effect of achiral additives on the addition of diethylzinc to **1a** using 0.2 equiv of cinchonidine are presented in Table 3.[12] With 0.2 equiv of **6** under the previously used reaction conditions a decrease in selectivity from 80% (entry 1) to 70% ee (entry 2) occurred. A similar result was obtained with 0.2 equiv of the achiral bis(sulfonamide) **7**[13] (entry 3). With 1 equiv of methanol an improvement in ee to 83% (entry 4) was observed. A similar result was obtained using 1 equiv of isopropanol under the same reaction conditions (entry 8). The more sterically demanding *tert*-butanol was found to give **2a** in 66% ee (entry 7). A significant improvement in both yield and ee was realised by increasing the amount of methanol added to 2.0 equiv. Using 0.2 equiv of cinchonidine and 2.0 equiv of methanol, under the same reaction conditions, (*R*)-**2a** was obtained in 70% yield and 93% ee (entry 5). This value for enantiomeric excess is the same as that achieved using a stoichiometric amount of cinchonidine. A further increase in methanol to 3.0 equiv resulted in a slight decrease in both yield and ee (entry 6). With 0.2 equiv of cinchonine and 2.0 equiv of methanol under the same reaction conditions the *S* enantiomer of **2a** was obtained in 71% yield and 89% ee. As 2 equiv of alcohol appeared to be necessary for the highest selectivity, the use of diols as additives were investigated (entries 9–11). Ethylene glycol (1 equiv) and cinchonidine (0.2 equiv) was found to give **2a** in 60% ee. Propylene glycol and butylene glycol were both found to give better selectivity, but no significant improvement on the result obtained without an additive. Triethylamine, diisopropylamine and pyridine (entries 12–16) were each found to give slightly better selectivity than the reaction with no additive. Unlike methanol however, increasing the amount of triethylamine and diisopropylamine from 1.0 to 2.0 equiv did not produce an increase in selectivity. With 1 equiv of triphenylphosphine oxide (entry 17) **2a** was obtained in 65% yield and 85% ee. Problems were encountered during chromatography in this reaction due to the co-running of triphenylphosphine oxide and **2a**.

Table 3. Effects of additives on the addition of diethylzinc to **1a** promoted by 0.2 equiv of cinchonidine



6 **7**

Entry[a]	Additive	Additive (equiv)	Yield (%)[b]	Ee (%)[c]
1	None	—	52	80
2	**6**	0.2	64	70
3	**7**	0.2	48	74
4	MeOH	1.0	52	83
5	MeOH	2.0	70	93
6	MeOH	3.0	64	89
7	*t*-BuOH	1.0	64	66
8	*i*-PrOH	1.0	51	82
9	$HOCH_2CH_2OH$	1.0	48	60
10	$HOCH_2CH_2CH_2OH$	1.0	75	81
11	$HOCH_2CH_2CH_2CH_2OH$	1.0	52	78
12	Et_3N	1.0	67	83
13	Et_3N	2.0	47	81
14	*i*-Pr_2NH	1.0	49	82
15	*i*-Pr_2NH	2.0	51	81
16	Py	1.0	41	83
17	Ph_3PO	1.0	65	85

[a] Reaction carried out in toluene using 0.2 equiv of cinchonidine and 12 equiv of diethylzinc at room temperature.
[b] Isolated yield after flash chromatography.
[c] Determined by HPLC analysis on a chiral column (Chiralcel OD). All *R* configuration.

In summary, it has been demonstrated that the 'pseudo-enantiomeric pair' of cinchonine and cinchonidine are an attractive, inexpensive and readily available alternative to synthetic chiral amino alcohols in promoting the addition of diethylzinc to a range of *N*-diphenylphosphinoylimines. With 1 equiv of cinchonidine as ligand a series of chiral amines were perpared in good yield and enantiomeric excesses of up to 94%. Dihydrocinchonidine was shown to afford slightly better selectivity than cinchonidine in the addition of diethylzinc to **1a**, giving the corresponding chiral amine in 96% ee. The use of 2.0 equiv of methanol as an achiral additive was found to improve significantly the selectivity of the addition when using 0.2 equiv of ligand, yielding enantiomeric excesses close to those obtained with a stoichiometric amount of ligand. This latter result illustrates the potential that achiral additives have for enhancing the enantioselectivity and yields obtained with asymmetric catalytic systems.

Acknowledgements

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12. Experimental procedure: The achiral additive was added to a cooled (ice bath) stirred solution of cinchonidine (19 mg, 0.066 mmol) and diethylzinc (3.6 mL of a 1.1 M solution in toluene, 3.960 mmol). The resulting solution was warmed to room temperature and stirred for 1 h. A solution of **1a** (100 mg, 0.328 mmol) in toluene (1.0 mL) was added and the resulting solution 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 **2a** as a white solid. Analytical data were in accordance with literature.
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