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Highly Enantioselective Addition of Diethylzinc to Diphenylphosphinoyl Imines under Dual Amino Alcohol/Halosilane Mediation†

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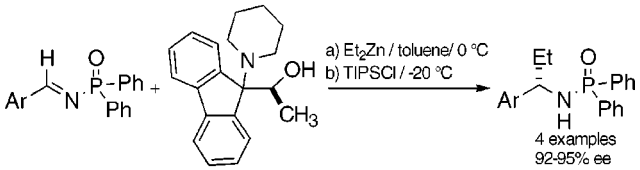
ABSTRACT



Arylethylene-derived, enantiomerically pure amino alcohols have been evaluated as ligands for the dual-catalyzed (amino alcohol/halosilane) enantioselective addition of diethylzinc to diphenylphosphinoyl imines. Among them, the conformationally restricted 9-fluorenone-derived ligand 4c provides the highest enantioselectivities so far reported over a range of substrate imines.

In response to the increasing industrial importance of enantiomerically pure amines,[1] much research directed toward the development of catalytic enantioselective methods for their preparation is currently underway.[2] In addition to the asymmetric reduction of imines,[3] the enantioselective addition of nucleophilic carbon species to derivatives[4] of imines stands as one of the most promising methodologies for this purpose.

In this context, the use of diphenylphosphinoyl imines (**1**) as activated substrates in combination with diethylzinc as the nucleophilic reagent and an amino alcohol promoter is receiving increasing attention.[5] Within this approach, Andersson and co-workers have recently reported the use of theoretical calculations as a design tool for the preparation of an efficient amino alcohol ligand for these additions.[6] However, many aspects of this chemistry still need to be developed. Additions to imine **1a** derived from benzaldehyde have been almost exclusively studied, and as a result of the poor electrophilic character of diphenylphosphinoyl imines, excess dialkylzinc reagent (up to 300%), stoichiometric amounts of amino alcohol ligand, and very prolonged reaction times are normally required to ensure high conversion and enantioselectivity. To solve this problem, we have

† Dedicated to Prof. José Barluenga on the occasion of his 60th birthday.

(1) For some examples, see: (a) Stirling, D. I. In *Chirality in Industry*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; John Wiley and Sons: Chichester, 1992; pp 209−222. (b) Federsel, H.-J. In *Chirality in Industry II*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; John Wiley and Sons: Chichester, 1997; pp 225−244.

(2) For a review on the enantioselective synthesis of amines, see: Johansson, A. *Contemp. Org. Synth.* **1995**, *2*, 393−408.

(3) For a recent comprehensive review, see: Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094. For leading references, see: (a) Verdaguer, X.; Lange, U. E. W.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784−6785. (b) Verdaguer, X.; Lange, U. E. W.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1998**, *37*, 1103−1107.

(4) For reviews, see: (a) Denmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun.* **1996**, 999−1004. (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946.

(5) (a) Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1097−1098. (b) Andersson, P. G.; Guijarro, D.; Tanner, D. *Synlett* **1996**, 727−728. (c) Andersson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem.* **1997**, *62*, 7364−7375. (d) Guijarro, D.; Pinho, P.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2530−2535.

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recently introduced a dual catalytic system consisting of a chiral amino alcohol, to control the enantioselectivity of the addition process, and a bulky silylating agent, to further activate the imine substrate.[7] We now report on the screening for this reaction of three families of modular amino alcohol ligands derived from arylethylenes (**2**−**4**). This survey has led to the identification of the first ligand consistently exhibiting very high enantioselectivities (≥92% ee) in the addition of diethylzinc to a range of imines (**1**) of aromatic aldehydes.

Amino alcohols **2**−**4** (Figure 1) are readily available in enantiomerically pure form through the regiocontrolled ring-

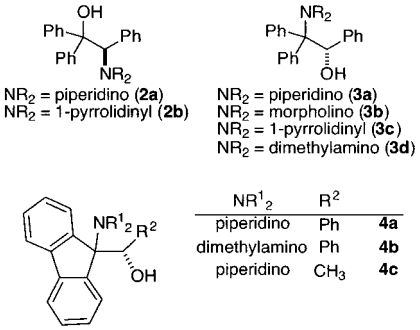
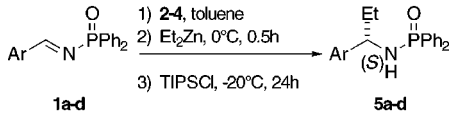


Figure 1. Amino alcohol ligands evaluated in the present study.

opening of enantiomerically pure epoxides obtained, in turn, by Jacobsen epoxidation[8] of arylethylenes. Some of them (**2a**,[9] **3a**−**d**,[10] **4a**, and **4c**[11]) have previously been used with success as ligands for the enantioselective addition of diethylzinc to aldehydes, while the remainder (**2b**, **4b**) have been specifically prepared for the present application by reported methods.[9,11]

In a preliminary stage of this study, the different ligands **2**−**4** were tested in conjunction with triisopropylsilyl chloride[7] for the addition of diethylzinc to imine **1a** leading to amine **5a** (Scheme 1), to determine optimal ligand characteristics.

Scheme 1



Entry	Ar
a	phenyl
b	*p*-tolyl
c	*m*-tolyl
d	2-naphthyl

Yields and enantioselectivities recorded with these ligands have been collected in Table 1. For comparison purposes, the enantioselectivities observed with the same ligands in the addition of Et_2Zn to benzaldehyde leading to (*S*)-1-phenyl-1-propanol (**6a**) are also given.

Table 1. Ligand Optimization in the Addition of Et_2Zn to Diphenylphosphinoyl Imine **1a**

ligand	**5a** yield, %	**5a** ee, %	**6a** ee, %
2a	90	2[a]	98[b]
2b	61	22[a]	81
3a	82	51	95[c]
3b	100	78	97[c]
3c	84	85	97[c]
3d	62	87	94[c]
4a	24	53	33[d]
4b	19	48	
4c	75	92	96[d]

[a] The *R* enantiomer of **5a** is predominantly formed. [b] Reference 9. [c] Reference 10. [d] Reference 11.

While the regioisomeric families of ligands **2** and **3** behave almost equally well in the addition of Et_2Zn to benzaldehyde,[9,10] it is clear that the presence of a chiral center adjacent to the alcohol function in the ligand is necessary for high enantioselectivity in the corresponding addition to the diphenylphosphinoyl imine **1a**. In other words, the chiral information contained in that fragment of the ligand molecule is much more efficiently transmitted to the reacting imine than that contained near the amino group in the ligand.

Among amino alcohols **3**, the morpholino derivative **3b** is particularly active in terms of yield and enantioselectivity. Both this ligand and the 1-pyrrolidinyl derivative **3c** are of practical interest for the studied process as the high crystallinity of the diphenylphosphinoylamines **5** allows for easy enantiomeric enrichment by simple recrystallization from hexane/ether.[5a,7]

The highest enantioselectivity was observed with the fluorenone-derived amino alcohols **4**.[12] These ligands, which can be viewed as conformationally constrained analogues of amino alcohols **3**, exhibit similar behaviors in the additions of Et_2Zn to benzaldehyde and to its diphenylphosphinoyl imine **1a**, with ligand **4c** being optimal for both applications in terms of catalytic activity and enantioselectivity. The results in Table 1 clearly demonstrate the validity of the modular design principle in ligands **3** and **4**, which allows the optimization of catalytic activity and/or enantioselectivity through the variation of readily assembled building blocks.

The dual catalytic system **4c**/TIPSCl is among the most effective so far reported for the addition of Et_2Zn to **1a**.

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(8) (a) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Heidelberg, 1999; pp 649−677. (b) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378−4380.

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(12) Slightly higher enantioselectivities are observed in the addition to this substrate mediated by the 2-azabornyl-3-methanol ligands developed by Andersson (see ref 6).

Accordingly, we expected that good results could also be obtained in the addition to other diphenylphosphinoyl imines **1**. Achievement of high enantioselectivities in these reactions is still a largely unresolved problem.

In fact, when the **4c**/TIPSCl system was used to promote the addition to imines **1b**−**d**, derived from aromatic aldehydes[13] (Table 2), the addition reactions took place with good yields (70−84%) and excellent enantioselectivities (94−95%). In view of these results, the **4c**/TIPSCl system appears as the most promising alternative so far reported for the addition of diethylzinc to aromatic diphenylphosphinoyl imines.[14]

Table 2. Enantioselective Addition of Et_2Zn to Aromatic Diphenylphosphinoyl Imines Mediated by **4c**/TIPSCl

imine	yield, %	ee, %
1a	75	92
1b	73	94
1c	70	95
1d	84	94

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(13) **Typical Experimental Procedure. Enantioselective Addition to *N*-Diphenylphosphinoyl Imine of 2-Naphthaldehyde.** Imine **1d** (100 mg, 0.281 mmol) and ligand **4c** (83 mg, 0.281 mmol) were dissolved in 1 mL of anhydrous toluene under N_2. The mixture was cooled at 0 °C, and 0.9 mL (0.9 mmol) of 1 M Et_2Zn in hexanes was added dropwise. After stirring at 0 °C for 30 min, the reaction mixture was cooled at −20 °C and TIPSCl (60 μL, 0.281 mmol) was added via syringe. Stirring was continued for 24 h at that temperature, the reaction was then quenched with saturated aqueous NH_4Cl, the aqueous phase was extracted with dichloromethane (3 × 15 mL), and the organic extracts were dried over Na_2SO_4. After removal of the solvents, the residue was purified by column chromatography (2.5% v/v triethylamine pretreated SiO_2) eluting with hexanes/ethyl acetate mixtures of increasing polarity (from 90:10 to 50:50) to afford 91 mg (84% yield) of **5d**. The enantiomeric composition of this product was measured by HPLC (Chiralcel OD column, 25 cm, 30 °C.; hexane/propan-2-ol (97:3); flow rate 1 mL/min; *R*-isomer, t_R 27.2 min and *S*-isomer, t_R 35.5 min) and found to be *S* (94% ee).

(14) The addition of diethylzinc to the diphenylphosphinoyl imine of cinnamaldehyde mediated by the **4a**/TIPSCl system takes place in high yield (91%) but with disappointingly low enantioselectivity (5%).