Organocatalytic asymmetric hydrophosphination of nitroalkenes†

Giuseppe Bartoli, Marcella Bosco, Armando Carlone, Manuela Locatelli, Andrea Mazzanti, Letizia Sambri and Paolo Melchiorre*

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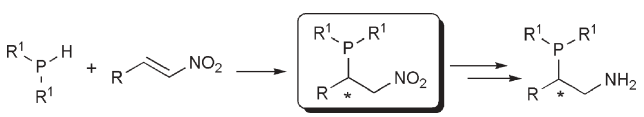
The use of a bifunctional *Cinchona* alkaloid catalyst has provided a new organocatalytic strategy for the enantioselective addition of diphenylphosphine to a range of nitroalkenes, affording optically active β-nitrophosphines (up to 99% ee after crystallization); this organocatalytic approach, providing a direct route to a new class of potentially useful enantiopure P,N-ligands, constitutes a bridge between the two complementary areas of asymmetric catalysis: organo- and metal-catalyzed transformations.

Chiral phosphines, valuable ligands for metal-catalyzed enantioselective transformations,[1] are generally prepared by resolution or by using stoichiometric amounts of chiral auxiliaries.[2] Thus, the development of more efficient catalytic methods for the enantioselective synthesis of optically active phosphines is of pressing current importance.[3] Asymmetric hydrophosphination (AHP),[4] the stereocontrolled addition of trivalent phosphine compounds, containing a P–H bond, to electron-deficient olefins, provides direct, atom-efficient access to potentially useful chiral phosphine ligands containing different chemical functionalities. These heterofunctional systems, which enable electronic and steric tuning along with unique dynamic features such as hemilability,[5] facilitate the optimization of the parameters that engender high stereocontrol in metal-catalyzed reactions. However, to our knowledge, just one effective catalytic AHP reaction has been reported recently by the group of Togni.[6]

In this context, the direct conjugate additions of secondary phosphines to nitroalkenes (Scheme 1) would constitute a particularly attractive strategy for the synthesis of optically active nitrophosphines, which, due to the synthetic versatility of the nitro group, can be considered as direct precursors for a wide range of diverse organic functionalities;[7] simple reduction of the nitro moiety, for example, affords non-proteinogenic amino acid-derived β-aminophosphines, potentially useful P,N-ligands.[8]



Scheme 1 Conjugate addition of secondary phosphines to nitroalkenes.

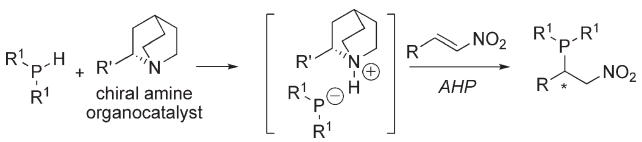
Dipartimento di Chimica Organica "A. Mangini", Alma Mater Studiorum – Università di Bologna, V.le Risorgimento 4 - 40136 Bologna, Italy. E-mail: pm@ms.fci.unibo.it; Fax: +39 051 2093654; Tel: +39 051 2093624

† Electronic supplementary information (ESI) available: Catalysts and conditions screening studies, results for the uncatalyzed hydrophosphination, experimental procedures and full characterization. See DOI: 10.1039/b613477g

Surprisingly, to date, no effective methods for the conjugate addition of phosphines to unsaturated nitro compounds are available.[9,10]

Herein, we describe a simple, general and efficient protocol for the hydrophosphination reaction of nitroalkenes to produce β-nitrophosphines. Additionally, an asymmetric organocatalytic version of this process, based on the use of a chiral bifunctional organocatalyst, affording optically active compounds (up to 99% ee after a single crystallization), has been disclosed.

Recently, it was reported that hydrophosphination reactions of activated olefins can be carried out under mild basic conditions.[11] On this basis, and considering our interest in the development of new organocatalytic transformations promoted by chiral tertiary amines,[12] we questioned recently whether the stereocontrolled conjugate addition of secondary phosphines to nitroalkenes might be accomplished using a chiral organic base-catalyst (Scheme 2). Specifically, we proposed that exposure of phosphines[13] to a chiral base would result in the formation of an intermediate ionic species that would undergo an asymmetric addition to nitroalkenes. This organocatalytic tactic,[14] as compared with a metal-catalyzed process, would prevent product inhibition arising from the coordination ability of the phosphorus atom.

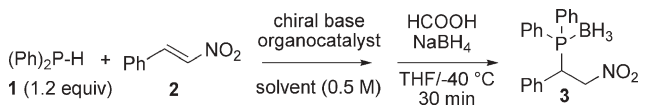


Scheme 2 Organocatalytic asymmetric hydrophosphination strategy.

To assess the feasibility of such an organocatalytic hydrophosphination strategy, we examined the addition of diphenylphosphine **1** to β-nitrostyrene **2** in toluene as the model reaction (Table 1). The sequential one-pot formation of the air-stable phosphine–borane complex derivative **3**, generated *in situ* by employing a trivial procedure,[15] facilitates the purification process, rendering the adduct bench stable for a long time.

Importantly, in the initial studies we noted that, even performing the model reaction at room temperature (RT) in the absence of a base-catalyst, complete conversion was achieved after 3 h. This type of uncatalyzed hydrophosphination strategy proved to be effective for a variety of aromatic and aliphatic nitroalkenes by using both diphenylphosphine **1** and di-*tert*-butylphosphine; detailed results are provided as supporting information† (yields ranging from 65% to 94%). Although the intrinsic reactivity of the process accounts for a direct and operationally simple synthesis of β-nitrophosphines, this feature constitutes an important hurdle to overcome in order to accomplish an asymmetric organocatalytic

Table 1 Organocatalytic AHP of **2**[a]



Entry	Catalyst	Solvent	Conversion (%)[b]	ee (%) of **3**[c]
1	—	Toluene	24	—
2	Quinine	Toluene	85	0
3	$(DHQ)_2PHAL$	Toluene	76	18
4	**A**	Toluene	92	15
5	**B**	Toluene	80	27
6	**C**	Toluene	89	36
7	**D**	Toluene	93	49
8	**D**	CH_2Cl_2	>95	34
9	**D**	THF	55	24
10	**D**	Et_2O	88	60
11	**D**	*i*-PrOH	>95	13
12	**D**	Et_2O–*i*-PrOH 9 : 1	80	65
13[d]	**D**	Et_2O–*i*-PrOH 9 : 1	>95	67
14[d,e]	**D**	Et_2O–*i*-PrOH 9 : 1	92 (86)[f]	66

[a] Reactions were carried out at −40 °C under N_2 using 20 mol% of the catalyst on a 0.2 mmol scale (16 h). [b] Determined by ^1H NMR spectroscopy of the crude mixture. [c] ee of **3** was determined by HPLC analysis. [d] $[\mathbf{2}]_0$ = 1 M. [e] 10 mol% of the catalyst, 24 h. [f] Number in parentheses indicates yield of the isolated **3**.

version as the chiral base-catalyzed reaction of **1** with **2** must proceed at a higher rate than the relatively fast uncatalyzed background reaction.

With this in mind, we undertook an extensive screen† of *Cinchona* alkaloids derivatives as potential catalysts (20 mol%) for the model reaction in toluene (0.5 M, 16 h) at −40 °C; under these conditions, a minimal rate of background reaction was observed (entry 1, Table 1).

The asymmetric induction observed when using $(DHQ)_2PHAL$ as the catalyst (entry 3), albeit not satisfactory, was interpreted as an encouraging clue for a successful development of our asymmetric organocatalytic approach. We speculated that the use of thiourea-based bifunctional catalysts capable of a simultaneous activation of both the electrophilic and nucleophilic components, might lead to higher catalytic activity and, more importantly, to better stereocontrol. A survey of chiral thiourea frameworks (Fig. 1), of established ability to act as efficient bifunctional organocatalysts in many asymmetric transformations,[16] led to identification of compound **D**[17] as a promising catalyst (49% ee, entry 7).

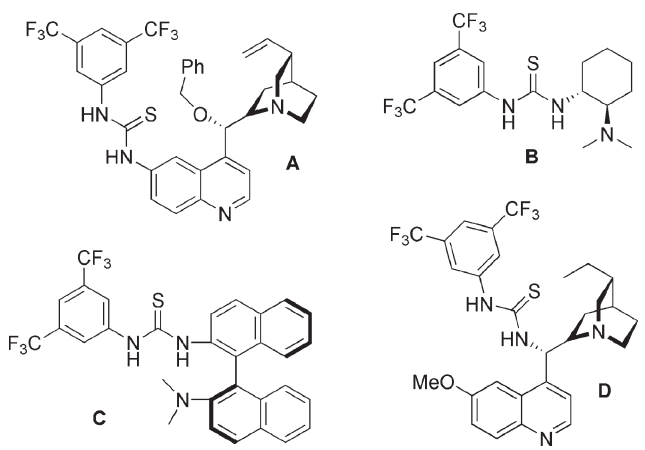
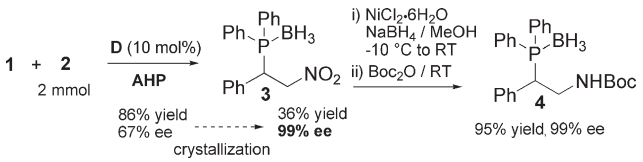


Fig. 1 Thiourea bifunctional organocatalysts.

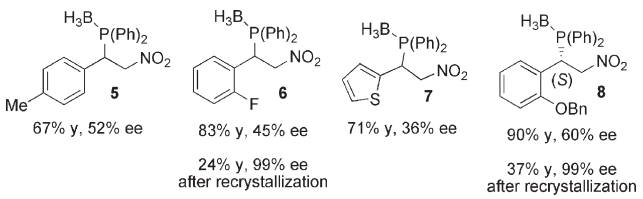
Among the standard reaction parameters, solvent choice and reagent concentration proved particularly important. Examination of the reaction media with catalyst **D** revealed that Et_2O gave better selectivity (entry 10). While the use of *i*-PrOH as the reaction solvent was less than fruitful, the addition of 10% of *i*-PrOH as a cosolvent resulted in improved stereocontrol,† albeit at the expense of reactivity (entries 11–12). However, at higher concentration ($[\mathbf{2}]_0$ = 1 M) complete conversion was achieved after 16 h (entry 13). Importantly, under these conditions, lowering the catalyst loading to 10 mol% did not affect the efficiency of the system (entry 14).[18]

The synthetic potential of this method was evaluated using a 2 mmol scale reaction (Scheme 3); it is noteworthy that the possibility to obtain **3** in enantiomerically pure form after a single crystallization and the reductive manipulation of the nitro group with concomitant *in situ tert*-butyloxycarbonyl (Boc) protection, affording the enantiopure aminophosphine **4**, provides a direct route to a new, potentially useful class of chiral P,N-ligand.[8] In a broader sense, the organocatalytic AHP constitutes a bridge between the two complementary areas of asymmetric catalysis: organo- and metal-catalyzed transformations.



Scheme 3 Preparation of enantiopure N-protected aminophosphine **4**.

Investigation into the reaction scope was carried out under the optimal reaction conditions (Scheme 4).[19] Although the β-nitrophosphines **5–8** were obtained in moderate enantioselectivity, the optical purity can be easily increased (>99% ee) by simple crystallization, as demonstrated for compounds **6** and **8**. The absolute configuration of compound **8** was established to be (*S*)[20] by X-ray crystallographic analysis.‡



Scheme 4 Reaction scope for the AHP.

In summary, we have developed a direct and very simple methodology for the hydrophosphination of nitroalkenes that provides access to useful and synthetically challenging β-nitrophosphines. Additionally, newly formed stereocenters can be controlled using a chiral thiourea organocatalyst. This organocatalytic approach, highlighting the potential of a chiral base organocatalyst to efficiently activate secondary phosphines toward asymmetric nucleophilic addition, could pave the way for the development of new, synthetically useful asymmetric hydrophosphination transformations. Current efforts are directed toward application of this

promising organocatalytic AHP strategy to other alkene acceptors and fully defining its utility as a new synthetic tool for asymmetric catalysis.

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Notes and references

‡ Crystal data for **8**. $C_{27}H_{27}BNO_3P$, M = 455.29, monoclinic, a = 9.7738(12), b = 13.1358(16), c = 9.8656(12) Å, β = 109.146(2)°, U = 1196.5(3) Å^3, T = 100(2) K, space group $P2_1$ (no. 4), Z = 2, μ(Mo-Kα) = 0.144 mm^{-1}, 13 673 reflections measured, of which 5605 independent (R_{int} = 0.0277) and 5533 observed ($I > 2\sigma$). The final $R1$ ($I > 2\sigma$) was 0.0271 and w$R2$ was 0.0779 (all data). The Flack parameter was −0.03(4). CCDC 615184. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b613477g

1 (*a*) *Asymmetric Catalysis on Industrial Scale. Challenges, Approaches, and Solutions*, ed. H.-U. Blaser and E. Schmidt, Wiley-VCH, Weinheim, Germany, 2004; (*b*) K. V. L. Crépy and T. Imamoto, *Top. Curr. Chem.*, 2003, **229**, 1.
2 (*a*) K. M. Pietrusiewicz and M. Zablocka, *Chem. Rev.*, 1994, **94**, 1375; (*b*) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029.
3 For recent examples, see: (*a*) V. S. Chan, I. C. Stewart, R. G. Bergman and F. D. Toste, *J. Am. Chem. Soc.*, 2006, **128**, 2786; (*b*) C. Scriban and D. S. Glueck, *J. Am. Chem. Soc.*, 2006, **128**, 2788; (*c*) B. Join, D. Mimeau, O. Delacroix and A.-C. Gaumont, *Chem. Commun.*, 2006, 3249.
4 M. Tanaka, *Top. Curr. Chem.*, 2004, **232**, 25.
5 P. Braunstein and F. Naud, *Angew. Chem., Int. Ed.*, 2001, **40**, 680.
6 (*a*) A. D. Sadow and A. Togni, *J. Am. Chem. Soc.*, 2005, **127**, 17012; (*b*) A. D. Sadow, I. Haller, L. Fadini and A. Togni, *J. Am. Chem. Soc.*, 2004, **126**, 14704; (*c*) for a low-selectivity AHP, see: I. Kovacik, D. K. Wicht, N. S. Grewal, D. S. Glueck, C. D. Incarvito, I. A. Guzei and A. L. Rheingold, *Organometallics*, 2000, **19**, 950.
7 (*a*) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, 2001; (*b*) C. Czekelius and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2005, **44**, 612.
8 For a review on the utility of bidentate P,N-ligands, see: P. J. Guiry and C. P. Saunders, *Adv. Synth. Catal.*, 2004, **346**, 497.
9 For the addition of alkali-phosphorus compounds to nitrostyrene, see: K. Issleib and P. Von Malotki, *J. Prakt. Chem. (Leipzig)*, 1973, **315**, 463.
10 For the asymmetric addition of chiral phosphites to nitroalkenes, see: D. Enders, L. Tedeschi and J. W. Bats, *Angew. Chem., Int. Ed.*, 2000, **39**, 4605.
11 T. Bunlaksananusorn and P. Knochel, *J. Org. Chem.*, 2004, **69**, 4595 and references cited therein.
12 (*a*) G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, P. Melchiorre and L. Sambri, *Angew. Chem., Int. Ed.*, 2005, **44**, 6219; (*b*) G. Bartoli, M. Bosco, A. Carlone, A. Cavalli, M. Locatelli, A. Mazzanti, L. Sambri and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2006, **45**, 4966.
13 For studies on the acidity of phosphines, see: (*a*) A. Streitwieser, A. E. McKeown, F. Hasanayn and N. R. Davis, *Org. Lett.*, 2005, **7**, 1259; (*b*) W. A. Henderson, Jr. and C. A. Streuli, *J. Am. Chem. Soc.*, 1960, **82**, 5791.
14 For recent studies on organocatalytic addition of pentavalent phosphorus compounds to unsaturated substrates, see: (*a*) D. Pettersen, M. Marcolini, L. Bernardi, F. Fini, R. P. Herrera, V. Sgarzani and A. Ricci, *J. Org. Chem.*, 2006, **71**, 6269; (*b*) T. Akiyama, H. Morita, J. Itoh and K. Fuchibe, *Org. Lett.*, 2005, **7**, 2583.
15 (*a*) J. McNulty and Y. Zhou, *Tetrahedron Lett.*, 2004, **45**, 407. Phosphine–borane deprotection can be easily accomplished under mild conditions, see: (*b*) H. Brisset, Y. Gourdel, P. Pellon and M. Le Corre, *Tetrahedron Lett.*, 1993, **34**, 4523.
16 For recent reviews, see: (*a*) M. S. Taylor and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1520; (*b*) S. J. Connon, *Chem.–Eur. J.*, 2006, **12**, 5418.
17 (*a*) B. Vakulya, S. Varga, A. Csámpai and T. Soós, *Org. Lett.*, 2005, **7**, 1967; (*b*) S. H. McCooey and S. J. Connon, *Angew. Chem., Int. Ed.*, 2005, **44**, 6367; (*c*) A. L. Tillman, J. Ye and D. J. Dixon, *Chem. Commun.*, 2006, 1191.
18 Other nucleophilic phosphorus reagents examined included di-*tert*-butylphosphine (0% ee), **1**–borane complex (0% ee) and diphenylphosphine oxide (20% ee, 30% conversion, 24 h).
19 The organocatalytic AHP of aliphatic nitroalkenes afforded racemic products (aliphatic substituent: isopropyl: 0% ee; *n*-pentyl: 0% ee). Other aromatic nitroalkenes tested gave poor enantioselectivity (aromatic substituent: *p*-MeO–C_6H_4: 25% ee; *p*-Br–C_6H_4: 22% ee; 2-furanyl: 11% ee; *p*-NO_2–C_6H_4: 0% ee; 2,6-Cl–C_6H_3: 0% ee).
20 The sense of stereochemical induction is in agreement with a previously reported selectivity model, in which the selective binding of the nitroolefin with the thiourea framework of the bifunctional catalyst **D** through a double-hydrogen bonding mechanism directs the nucleophilic attack at the *Si*-face of the electrophile. See ref. 17*b*.

