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Asymmetric organocatalysis of the addition of acetone to 2-nitrostyrene using *N*-diphenylphosphinyl-1,2-diphenylethane-1,2-diamine (PODPEN)

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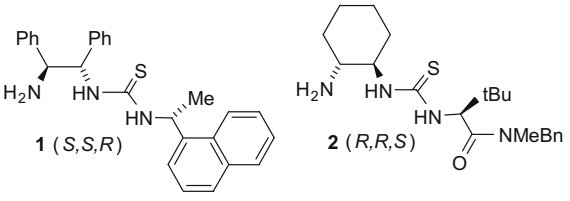
ABSTRACT

The highly enantioselective addition of acetone to 2-nitrostyrene, using *N*-diphenylphosphinyl-*trans*-1,2-diphenylethane-1,2-diamine (PODPEN) as a catalyst, is described.

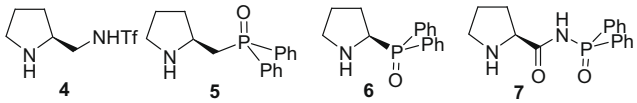
The use of enantiomerically pure amines in organocatalysis has enjoyed a period of rapid recent development.[1–3] Several of these reactions involve the formation of an active species (iminium or enamide) by a reversible condensation reaction between the amine catalyst and the carbonyl group in one of the reagents. In a large proportion of examples of amine-catalysed reactions, a second functional group in the catalyst serves to activate and direct the reaction. In the case of proline, the carboxylic acid may act in this capacity.[2] The asymmetric addition of acetone to 2-nitrostyrene (Fig. 1) may be catalysed by a number of amine derivatives including thiourea derivatives of *S,S*-1,2-diphenyl-1,2-ethylenediamine (DPEN) and *R,R*-1,2-diaminocyclohexane (DACH).[4] Examples include ureas **1** and **2**, which give products **3** in up to 91%[4a] and 99% ee,[4b] respectively (Scheme 1).



The mechanism of the amine-catalysed addition reaction is believed to proceed via the enamine, whilst the urea engages the nitro group in a hydrogen bond (Fig. 1).[1d]

Other derivatives of C_2-symmetric diamines have been applied to the nitrostyrene addition reaction. These include the mono *N*-trifluoromethylsulfonate (Tf) derivative of DACH[5] and a series of sulfamides, which promoted the addition of aldehydes in up to 99% ee.[6]

In addition, closely related pyrrolidine derivatives have been employed,[7–16] including the triflate **4**, which catalyses additions of aldehydes and ketones in up to 99% ee.[7] Good results were also obtained using the 3,5-bis(trifluoromethane)phenylsulfonyl derivative.[8] Closely related 2-aminomethylpyrrolidines have also been studied in the nitrostyrene addition reaction (up to 92% ee).[9] Proline supported on hydrotalcite clays has been used as a heterogeneous catalyst.[10] Diamines derived from cinchona alkaloids have been applied to the addition of 1,3-diketones to nitrostyrenes.[11]



In a recent report, published during the course of our studies, phosphine oxide **5** was described as an excellent organocatalyst for the asymmetric addition of cyclic ketones to nitrostyrenes, furnishing products in >99% ee and high diastereoselectivity.[12] Oxide **5**, as well as the related compounds **6**,[13] and **7**,[14] have been applied to asymmetric aldol reactions. In previous reports on the use of pyrrolidine-based catalysts, cyclic ketones gave the best results. In contrast, the addition of acetone is less enantioselective.

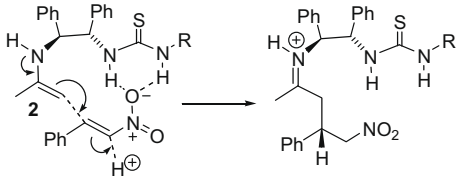


Figure 1. Secondary directing effect of urea.

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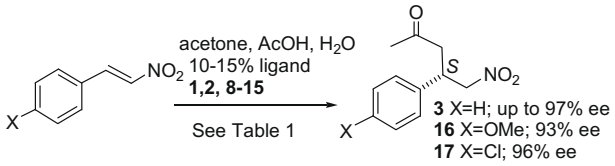
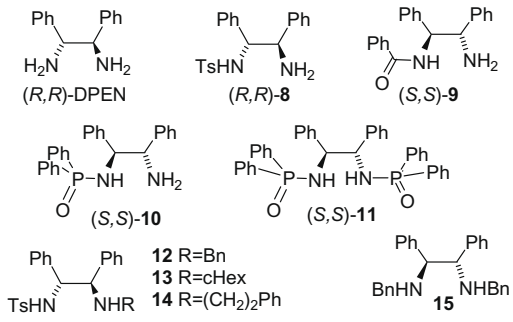


Scheme 1. Asymmetric addition of acetone to nitrostyrene.

Given a long standing interest in phosphinamide catalysts,[17] we wished to establish whether other functional groups, and particularly those based on P═O directing groups, could be applied to catalytic reactions. Phosphinamides have been used as catalysts in other reactions which may be described as organocatalytic (no metals are present in the catalyst).[17,18] These include the catalysis of the asymmetric reduction of ketones using borane, and the addition of trichloroallylsilanes and silyl enol ethers to aldehydes. Phosphinamide **10** has been reported as a chiral directing group in a Rh-catalysed asymmetric Michael addition reaction.[19] Phosphinylated compounds closely related in structure to **10** have been formed in nucleophilic addition reactions to *N*-diphenylphosphinyl ketimines, but were not used as asymmetric catalysts.[20] The attempted use of a phosphinamide in an indium-catalysed addition to a hydrazone was reported, but this gave a product with low ee.[21]

A series of homochiral DPEN derivatives were prepared and screened as organocatalysts in nitrostyrene addition (Scheme 1, Table 1). DPEN alone proved to be capable of high enantioinduction (78% ee), as previously reported,[4a] but did not furnish a product in high yield. Of its derivatives, N-tosylated amine TsDPEN **8** gave a product of high ee but the reaction was slow. TsDPEN **8** has been successfully used in a closely related addition to nitrostyrene.[22] *N*-Benzoyl amide **9** gave a good result in terms of ee (82% conversion after 96 h, 89% ee) however, the best catalyst, of those tested, proved to be the phosphinamide **10**[23] (100% conversion after 7 h, 96% ee). The bis-phosphorylated DPEN derivative **11**[24] was, however, ineffective as a catalyst, thus confirming the expected requirement for a basic amine. Secondary amine derivatives **12**–**15**[18] also proved to be essentially inactive, possibly for reasons of steric hindrance. All the DPEN derivatives tested gave the same product enantiomer relative to the diamine, that is, (*R*,*R*)-DPEN derivatives gave the *S*-configured product. The ee did not change with conversion (samples were taken at regular 1–2 h intervals) in the reaction catalysed by **10** and did not deteriorate when the reaction was allowed to stand after completion (up to 4 days), suggesting that the addition is essentially irreversible. These results indicate that the phosphinamide group plays an activating role in the reaction, and contributes to the enantiocontrol, possibly in an analogous mechanism to that shown in Figure 1.



Further studies revealed that added acetic acid and water are important to the reaction. The conversion dropped to just 15% in 96 h when both AcOH and water were omitted from the reaction, and to 75% in 18 h when only AcOH, but not water, was added. Benzoic acid may be used in the place of acetic acid, but gives lower reaction rates. The importance of water in such reactions has been investigated in detail,[25] whilst the acid presumably catalyses the formation and decomposition of the intermediate enamine and iminium species. Excess water (>1 equiv/relative to nitrostyrene) is

Table 1
Use of DPEN derivatives in nitrostyrene additions[a]

Catalyst	Product	Loading (%)	Added water	Time (h)	Conv (%)	ee[h] (*R*/*S*)
(*R*,*R*)-DPEN	**3**	15	[b]	96	46	78 (*S*)
(*R*,*R*)-**8**	**3**	15	[b]	96	68	91 (*S*)
(*S*,*S*)-**9**	**3**	15	[b]	96	82	89 (*R*)
(*S*,*S*)-**10**	**3**	15	[b]	7	100	96 (*R*)
(*S*,*S*)-**11**	**3**	15	[b]	96	0	—
(*R*,*R*)-**12**	**3**	15	[b]	96	0	—
(*R*,*R*)-**13**	**3**	15	[b]	96	0	—
(*R*,*R*)-**14**	**3**	15	[b]	96	0	—
(*S*,*S*)-**15**	**3**	15	[b]	96	0	—
(*S*,*S*)-**10**	**3**[g]	15	(0)[c]	96	16	—
(*R*,*R*)-**10**	**3**	10	[b]	5	65	95 (*S*)
(*R*,*R*)-**10**[d]	**3**	10	[b]	5	100	93 (*S*)
(*R*,*R*)-**10**[e]	**3**	10	[b]	3	62	88 (*S*)
(*R*,*R*)-**10**[f]	**3**	10	[b]	5	41	94 (*S*)
(*R*,*R*)-**10**	**3**	10	(0.75)[c]	18	96	94 (*S*)
(*R*,*R*)-**10**	**3**	10	(0.50)[c]	18	89	92 (*S*)
(*R*,*R*)-**10**	**3**	10	(0.25)[c]	18	96	94 (*S*)
(*R*,*R*)-**10**	**3**	10	(0.10)[c]	18	84	97 (*S*)
(*R*,*R*)-**10**	**3**	10	(0)[c]	18	75	95 (*S*)
(*R*,*R*)-**10**	**16**	10	[b]	24	100	93 (S)
(*R*,*R*)-**10**	**17**	10	[b]	24	100	96 (S)

[a] See Scheme 1, all reactions were carried out at rt in toluene unless otherwise stated.
[b] Technical grade acetone was used; ca. 6.7% H_2O by volume and 2% H_2O by mass.
[c] Reagent grade acetone was used, level of water relative to the catalyst in parentheses.
[d] At 40 °C.
[e] At 60 °C.
[f] At 0 °C.
[g] No AcOH added.
[h] ee was determined by chiral HPLC, configuration by optical rotation.

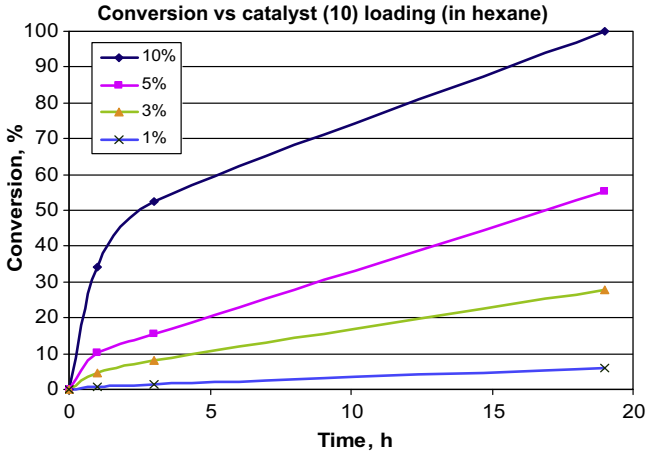


Figure 2. Effect of catalyst **10** loading on reaction rate.

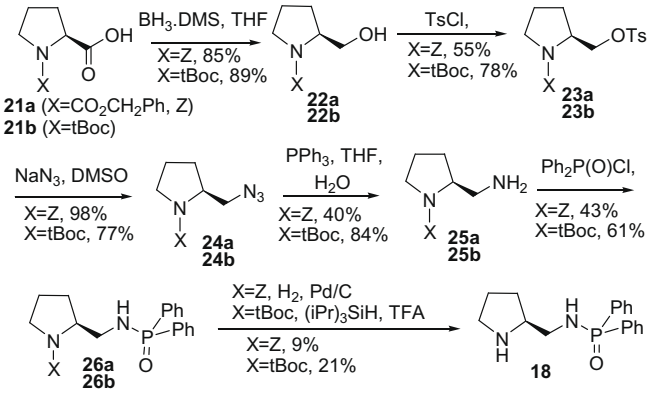
not beneficial; a series of tests on pure acetone revealed that the level of water in the technical grade is close to optimal (see Supplementary data). In hexane, the catalyst loading can be reduced to 10%, which gives full reaction in 24 h at rt or 5 h at 40 °C (with a drop in the ee to 93%) but at <5 mol % catalyst loading the reaction requires unacceptable (>72 h) times for completion (Fig. 2). Of a series of solvents tested, the nonpolar solvents hexane (94% ee) and toluene (96% ee) gave the fastest rates, whilst reactions in CH_2Cl_2, THF, EtOAc and acetone were much slower.

Although catalyst **10** worked well in the specific addition of acetone to nitrostyrenes, poor results were obtained in attempts to use both cyclohexanone and ethanal, with <5% formation of products in each case. In view of the known value of pyrrolidine derivatives in the nitrostyrene addition reaction, but mindful of their only moderate reported enantioselectivities for the acetone addition reaction,[7–16] proline derivative **18** represented an attractive candidate for evaluation.[7–15] An attempt to prepare **18** by direct phosphinylation of homochiral diamine **19** resulted in formation of **20**, which was not an active catalyst (Table 2).

Table 2
Use of pyrrolidine derivatives in nitrostyrene additions[a]

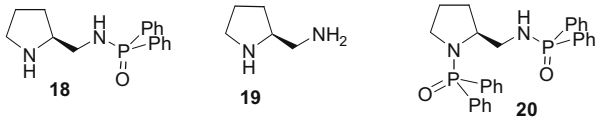
Catalyst	Product	Loading (%)	Time (h)	Conv (%)	ee[b] (*R*/*S*)
(*S*)-**18**	**3**	10	96	100	16 (*R*)
(*S*)-**19**	**3**	15	3/23	50/100	17 (*R*)
(*S*)-**20**	**3**	15	96	0	—

[a] See Scheme 1, all reactions were carried out at rt in toluene unless otherwise stated, with technical grade acetone; ca. 6.7% H_2O by volume and 2% H_2O by mass.
[b] ee was determined by chiral HPLC, configuration by optical rotation.



Scheme 2. Synthesis of **18**.

The successful synthesis of **18** was achieved starting from a protected proline derivative **21a**, following a related method reported in the literature.[26] We favoured the use of **21a** because we feared that the acidic conditions required for *t*Boc removal would also result in loss of the phosphinamide. In the event, **21a** was successfully converted into **18** through the sequence shown in Scheme 2, however, the last step gave a very poor yield of product. A search of the literature yielded an example of a method for the removal of a *t*Boc group in the presence of a phosphinamide.[21] The conversion of **21b** to **25b** followed the previous sequence,[26] and the subsequent conversion into **18** was successful, although the work-up required the use of triethylamine[21] to avoid a highly basic solution being formed. A better yield was obtained using a combination of isopropylsilane and TFA, but this remained low due to concomitant cleavage of the phosphinamide group.[27]



Compound **18** proved to be an efficient, but not highly enantioselective, catalyst for the nitrostyrene addition reaction (Table 2). The 16% ee of the product was similar to that of the unprotected diamine **19**, suggesting that its mechanism of action may be related. This low ee with pyrrolidine derivatives mirrors those obtained in the same reaction using related pyrrolidine-based organocatalysts.[7–16] The use of **18** in other applications is currently being studied.

In conclusion, we have described the promising results of a study directed at establishing the ability of the phosphinamide group to direct asymmetric organocatalytic additions to nitrostyrene. To the best of our knowledge, the phosphinamide group has not been studied in this capacity before and this therefore represents a novel subject for investigation. We are currently examining further applications of this system.

Acknowledgements

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Supplementary data

General experimental details, graphs of experimental results, and ^1H and ^{13}C NMR of all new compounds are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.131.

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