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

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Abstract—The highly enantioselective addition of acetone to 2-nitrostyrene, using \textit{N}-diphenylphosphinyl-trans-1,2-diphenylethane-1,2-diamine (PODPEN) as catalyst, is described. © 2010 Elsevier Science. All rights reserved.
The use of enantiomerically pure amines in organocatalysis has enjoyed a period of rapid recent development.\textsuperscript{1-3} Several of these reactions involve the formation of an active species (iminium or enamides) 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.\textsuperscript{2} The asymmetric addition of acetone to 2-nitrostyrene (Figure 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).\textsuperscript{3} Examples include uraeas 1 and 2, which give products 3 in up to 91\%\textsuperscript{4a} and 99\% ee,\textsuperscript{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 (Figure 1).\textsuperscript{14,16} The asymmetric addition of acetone to nitrostyrene (Figure 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).\textsuperscript{3} Examples include uraeas 1 and 2, which give products 3 in up to 91\%\textsuperscript{4a} and 99\% ee,\textsuperscript{4b} respectively (Scheme 1).

Other derivatives of C2-symmetric diamines have been applied to the nitrostyrene addition reaction. These include the mono N-trifluoromethylsulfonyl (Tf) derivative of DACH\textsuperscript{5} and a series of sulfamides, which promoted the addition of aldehydes in up to 99\% ee.\textsuperscript{6} In addition, closely related pyrrolidine derivatives have been employed,\textsuperscript{7}\textsuperscript{bc} including the triflate 4, which catalyses additions of aldehydes and ketones in up to 99\% ee.\textsuperscript{7a} Good results were also obtained using the 3,5-bis(trifluoromethane)phenylsulfonyl derivative.\textsuperscript{8} Closely related 2-amimomethylpyrrolidines have also been studied in the nitrostyrene addition reaction (up to 92\% ee).\textsuperscript{9} Proline supported on hydrotalcite clays has been used as a heterogeneous catalyst.\textsuperscript{10} Diamines derived from cinchona alkaloids have been applied to the addition of 1,3-diketones to nitrostyrenes.\textsuperscript{11}

In a recent report, published during the course of our studies, phosphinamide 5 was described as an excellent organocatalyst for the asymmetric addition of cyclic ketones to nitrostyrenes, furnishing products in >99\% ee and high diastereoselectivity.\textsuperscript{12} Oxide 5, as well as the related compounds 6,\textsuperscript{13} 7,\textsuperscript{14} and 8 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.

Given a long standing interest in phosphinamide catalysts,\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{20} The attempted use of a phosphinamide in an indium catalysed addition to a hydrazine was reported, but this gave a product with low ee.\textsuperscript{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,\textsuperscript{44} 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.\textsuperscript{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\textsuperscript{11c} (100\% conversion after 7 h, 96\% ee). The bis-phosphorylated DPEN derivative 11\textsuperscript{24} was, however, ineffective as a catalyst, thus confirming the expected requirement for a basic amine. Secondary amine derivatives 12-15\textsuperscript{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, i.e. (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, were added. Benzoic acid may be used in
place of acetic acid, but gives lower reaction rates. The
importance of water in such reactions has been investigated
in detail, whilst the acid presumably catalyses the
formation and decomposition of the intermediate enamine
and iminium species. Excess water (>1 eq/ relative to
nitrostyrene) is not beneficial; a series of tests on pure
acetone revealed that the level of water in the technical
grade is close to optimal (see Supporting information). 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
(Figure 2). Of a series of solvents tested, the nonpolar
solvents hexane (94% ee) and toluene (96% ee) gave the
fastest rates, whilst reactions in CH₂Cl₂, 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
ethanol, 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, 7,15 proline derivative 18 represented an
attractive candidate for evaluation. 7 An attempt to
prepare 18 by direct phosphorylation of homochiral
diamine 19 resulted in formation of 20, which was not an
active catalyst (Table 2).

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<th>Catalyst</th>
<th>Pro-</th>
<th>Loading</th>
<th>Added</th>
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<th>Conv</th>
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</table>

* See Scheme 1, all reactions carried out at rt in toluene unless otherwise
  stated. 5 Technical grade acetone used; ca 6.7% H₂O by volume and 2%
  H₂O by mass. 5 Reagent grade acetone used, level of water relative to
  catalyst in parenthesis. 5 At 40 °C. 5 At 60 °C. 5 At 0 °C. 5 No AcOH added.
  5 ee was determined by chiral HPLC, configuration by optical rotation.

Figure 2. Effect of catalyst 10 loading on reaction rate.
The successful synthesis of 18 was achieved starting from a protected proline derivative 21a, following a related method reported in the literature. We favoured the use of 21a because we feared that the acidic conditions required for tBoc 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 tBoc group in the presence of a phosphinamide. The conversion of 21b to 25b followed the previous sequence, and the subsequent conversion into 18 was successful, although the work up required the use of triethylamine to avoid a basic solution from 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.

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.

The use of 18 in other applications is currently being studied.

![Scheme 2. Synthesis of 18.](image)

Table 2. Use of pyrrolidine derivatives in nitrostyrene additions.  

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Product</th>
<th>Loading (%)</th>
<th>Time (h)</th>
<th>Conv (%)</th>
<th>(ee) (%)</th>
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<tr>
<td>(S)-18</td>
<td>3</td>
<td>10</td>
<td>96</td>
<td>100</td>
<td>16 (R)</td>
</tr>
<tr>
<td>(S)-19</td>
<td>3</td>
<td>15</td>
<td>3/23</td>
<td>50/100</td>
<td>17 (R)</td>
</tr>
<tr>
<td>(S)-20</td>
<td>3</td>
<td>15</td>
<td>96</td>
<td>0</td>
<td>-</td>
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</tbody>
</table>

* See Scheme 1, all reactions carried out at rt in toluene unless otherwise stated, with technical grade acetone; ca. 6.7% H2O by volume and 2% H2O by mass. ee was determined by chiral HPLC, configuration by optical rotation.

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 investigating further applications of this system.

Acknowledgements

We thank the EPSRC for funding (postdoctoral grant EP/D031168/1 to DJM) and Rhodia Consumer Specialties Ltd for supporting CVM through a Collaborative Training Account studentship. The EPSRC National MS service (Swansea) is thanked for HRMS analyses as is the EPSRC Chemical Database Service.

References

Supplementary Material

General experimental details, graphs of experimental results, and $^1$H and $^{13}$C NMR of all new compounds.