Stereospecific $S_N2@P$ reactions: novel access to bulky P-stereogenic ligands

Silvia Orgué, a Arlei Flores-Gaspar,§ a Maria Biosca, b Oscar Pàmies, b Montserrat Diéguez, b Antoni Riera* ac and Xavier Verdaguer* ac

The stereospecific hydrolysis of bulky aminophosphine boranes is reported for the first time. The resulting phosphinous acid boranes, upon activation, undergo stereospecific nucleophilic substitution reaction at the phosphorous center with amine nucleophiles. The combination of these two processes provides a novel access to bulky P*-ligands.

Chiral phosphines are the cornerstone of asymmetric metal catalysis. Among this class of ligands, bulky P-stereogenic phosphines have proved to be highly efficient in asymmetric hydrogenation and other relevant processes. However, their synthesis in the optically pure form is often not straightforward. The stereoselective synthesis of $S_N2@P$ reactions at the “bulky” P-center ($S_N2@P$) are generally avoided since it is overly unreactive. Furthermore, when forced to react, it usually provides non-stereospecific substitution processes.

A relevant exception to this behavior is the reaction of halophosphines which have been used by us in the preparation of MaxPHOS and SIP type ligands. We recently reported the stereospecific synthesis of amino-phosphines 1a and 1b which have been used by us in the preparation of MaxPHOS and SIP type ligands. We considered that these compounds were ideally suited to evaluate whether the acidolysis of bulky aminophosphines could be performed in a stereospecific manner, and whether the resulting products could be further transformed into valuable ligand structures (Scheme 1). Herein we report on the stereospecific hydrolysis of bulky aminophosphine boranes and how the resulting phosphinous acids can be transformed into P*-ligands through $S_N2@P$ reactions.

The initial acidolysis studies on 1a and 1b were conducted in $H_2SO_4/MeOH$ (Table 1). Methanolysis of 1a at $50 \degree C$ for 16 h did not afford the expected methyl phosphinite borane 2a but the corresponding phosphinous acid borane 3a and the secondary phosphine oxide 4a that results from borane deprotection and $P(III)/P(V)$ tautomerization of 3a (Table 1, entry 1). We attributed the formation of 3a to the residual content of water in the solvent used. To confirm this hypothesis, we next ran the acidolysis reaction of 1a in a MeOH/$H_2O$ (20:1) mixture. This solvent mixture and heating to $40 \degree C$ for 16 h afforded exclusively phosphine oxide 4a in low enantiomeric excess (Table 1, entry 2). By simply reducing the reaction time to 2 h, we were able to isolate the corresponding phosphinous acid 3a with an excellent yield and optical purity (> 99% ee, Table 2, entry 3).

![Scheme 1](image-url)
The hydrolysis of 1b was also carried out stereospecifically to yield the corresponding phosphonic acid 3b in >99% ee and 63% yield (Table 1, entry 4). Hydrolysis of 1a and 1b took place with inversion of the configuration at the P-center as confirmed by X-ray crystallography of the corresponding benzoyl derivative (see ESI).

The opposite enantiomer of 3a and 3b were obtained when starting from (R)<sub>P</sub>-1a and (S)<sub>P</sub>-1b thus confirming that the process is completely stereospecific. These results indicate that the acidolysis of bulky aminophosphines is extremely sensitive to the nature of the incoming nucleophile. We believe that the minimal steric differences between methanol and water allow the latter to act as an efficient nucleophile, while making the former unreactive.

To further explore the scope of this transformation we submitted diastereomerically pure aminophosphines 5a and 5b (the synthetic precursors of aminophosphines 1a and 1b) to acidic hydrolysis in MeOH/H<sub>2</sub>O mixtures (Scheme 2). The reaction was slower than that achieved using the parent compounds 1a and 1b;<sup>13</sup> however, again, an increase in the reaction temperature and a longer reaction time produced the enantioselectively pure phosphonic acids 3a and 3b in 84% and 66% yields respectively. The hydrolysis of 5a and 5b is a practical approach to prepare the corresponding phosphonic acids; furthermore, it allows the recovery of the chiral auxiliary.

The hydrolysis of 1b in 99% yield and 96% ee with the inverted configuration at the P-center (Table 2, entry 1). Importantly, primary amines also acted as efficient nucleophiles in this process, producing the corresponding aminophosphines in satisfactory yield and excellent enantiomeric excess (Table 2, entries 2–5). Chiral primary α-branched amines like (S) and (R)-1-phenylethylamine and phenylglycinamide also yielded the substitution products (R)<sub>P</sub>-10, (R)<sub>P</sub>-11 and (R)<sub>P</sub>-12 in 95–98% diastereomeric excess (Table 2, entries 6–8). A cyclic secondary amine like pyrrolidine and an aromatic amine like p-anisidine also efficiently produced the substitution products in 98 and 91% ee (Table 2, entries 9 and 10). In contrast, dibenzylamine was not good enough as a nucleophile and did not afford the expected aminophosphine (Table 2, entry 11). Also, oxygen nucleophiles failed to provide substitution products (Table 2, entry 12). In contrast, benzthiazol and thiophenol did provide the corresponding sulfides 17 and 18, albeit in low yield (22 and 36% respectively) (Table 2, entries 13 and 14). We attributed these low yields of isolation to the instability of these molecules. Finally, we tested the tert-butylphenylphosphonic acid borane 3b as the electrophile. Reaction with ammonia and (R)-phenylethylamine provided the corresponding aminophosphines 1b and 19 with excellent optical and diastereomeric purity (Table 2, entries 15 and 16).

The hydrolysis of aminophosphine boranes combined with the substitution on the resulting phosphonic acid represents a novel means of obtaining P*-ligands. To highlight the beneficial impact that this methodology could have in asymmetric catalysis, we followed the procedure shown in Table 2 to prepare a novel P-stereogenic N-phosphinooxazoline ligand and its corresponding cationic iridium complex (Scheme 3). Activation of (S)<sub>P</sub>-3a with mesyl anhydride and triethylamine and reaction with aminoazoline 20 provided the borane-protected ligand 21 in 43% yield and in >98% dr, as determined by <sup>1</sup>H NMR. Borane was removed in neat pyrrolidine at 90 °C. We found that the approach of using neat pyrrolidine was superior to that of existing borane-deprotection methods like DABCO or neat diethylamine. Thus, from 21 and using a one pot-three reaction sequence, the cationic iridium complex 22 was obtained as an orange solid in 89% yield.
Table 2 Substitution reactions with several nucleophiles

<table>
<thead>
<tr>
<th>Entry</th>
<th>SM</th>
<th>Nucleophile</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee/de (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>NH₃</td>
<td>(R₁)–1a</td>
<td>99</td>
<td>96 ee</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>Ph₂NH₂</td>
<td>(R₁)–6</td>
<td>60</td>
<td>98 ee</td>
</tr>
<tr>
<td>3</td>
<td>3a</td>
<td>Ph₂NH₂</td>
<td>(R₁)–7</td>
<td>64</td>
<td>&gt;95 ee</td>
</tr>
<tr>
<td>4</td>
<td>3a</td>
<td>Ph₂NH₂</td>
<td>(R₁)–8</td>
<td>87</td>
<td>99 ee</td>
</tr>
<tr>
<td>5</td>
<td>3a</td>
<td>Ph₂NH₂</td>
<td>(R₁)–9</td>
<td>73</td>
<td>96 ee</td>
</tr>
<tr>
<td>6</td>
<td>3a</td>
<td>Ph₂NH₂</td>
<td>(R₁)–10</td>
<td>76</td>
<td>98 de</td>
</tr>
<tr>
<td>7</td>
<td>3a</td>
<td>Ph₂NH₂</td>
<td>(R₁)–11</td>
<td>71</td>
<td>95 de</td>
</tr>
<tr>
<td>8</td>
<td>3a</td>
<td>H₂NCONHN₂</td>
<td>(R₁)–12</td>
<td>63</td>
<td>97 de</td>
</tr>
<tr>
<td>9</td>
<td>3a</td>
<td>Ph₂NH₂</td>
<td>(R₁)–13</td>
<td>65</td>
<td>98 ee</td>
</tr>
<tr>
<td>10</td>
<td>3a</td>
<td>MeO–Ph₂NH₂</td>
<td>(R₁)–14</td>
<td>42</td>
<td>91 ee</td>
</tr>
<tr>
<td>11</td>
<td>3a</td>
<td>HNBn₂</td>
<td>(R₁)–15</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>3a</td>
<td>Ph₂OH</td>
<td>(R₁)–16</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>3a</td>
<td>Ph₂SH</td>
<td>(R₁)–17</td>
<td>22</td>
<td>nd</td>
</tr>
<tr>
<td>14</td>
<td>3b</td>
<td>Ph₂SH</td>
<td>(R₁)–18</td>
<td>36</td>
<td>nd</td>
</tr>
<tr>
<td>15</td>
<td>3b</td>
<td>NH₃</td>
<td>(S₂)–1b</td>
<td>99</td>
<td>99 ee</td>
</tr>
<tr>
<td>16</td>
<td>3b</td>
<td>NH₃</td>
<td>(S₂)–19</td>
<td>72</td>
<td>96 de</td>
</tr>
</tbody>
</table>

*Isolated yield after flash chromatography. †Enantiomeric excess determined by either chiral GC or HPLC analysis, diasteromeric excess determined by ¹H NMR of the crude reaction. ‡Optical purity of 7 was assigned tentatively by analogy with similar primary amines tested. ‡‡Determination of optical purity by chromatographic methods failed. [α]D = −23.5° (c 1.00, CHCl₃). §Determination of optical purity by chromatographic methods failed. [α]D = −21° (c 1.49, CHCl₃). nd = not determined.

Scheme 2 Acidolysis of N-secondary aminophosphines and recovery of the chiral auxiliary.

With the iridium complex 22 in hand, we tested its performance in the asymmetric hydrogenation of α,β-unsaturated esters (Table 3). Reduction of ethyl trans-β-methylcinnamate under standard non-optimized conditions (50 bar of hydrogen in dichloromethane with 1 mol% of 22 as the catalyst) produced the (R) hydrogenated product in 95% ee (Table 3, entry 1). Under the same reaction conditions, hydrogenation of the isopropyl and cyclohexyl β-substituted cinnamates afforded the reduced products in 97% ee (Table 3, entries 2 and 3). Finally, para-methyl-substituted methylcinnamate afforded the reduced compound with complete selectivity (>99% ee, Table 3, entry 4).

In summary, we have shown that the acid hydrolysis of bulky primary and secondary aminophosphine boranes occurs in a completely stereospecific manner with inversion of the configuration at the P-center to yield the corresponding optically pure phosphinous acid boranes. Also, we have demonstrated that, upon activation, phosphinous acid boranes undergo stereospecific nucleophilic substitution reactions at the P-center with amine nucleophiles. The potential of this process has been demonstrated with the synthesis of a P-stereogenic phosphino-oxazoline ligand which has been applied to the asymmetric Ir-catalyzed hydrogenation of trans-β-alkylcinnamates, achieving selectivities of up to 99% ee.

We thank financial support from the Spanish Ministerio de Economia y Competividad (CTQ2014-56361-P and CTQ2013-40568P), the IRB Barcelona, the Generalitat de Catalunya (2014SGR670), the ICREA Foundation (M. Diéguez and O. Pàmies ICREA Academia awards). S.O. thanks the Generalitat de Catalunya for a FI fellowship. A. F.-G. thanks the CONACYT for a postdoctoral fellowship.
Notes and references


7 Buono and co-workers reported the stereodivergent and stereoselective hydrolysis of an unprotected aminophosphine to yield the corresponding secondary phosphine oxide with up to 91% ee, see: A. Leyris, D. Nuel, L. Giordano, M. Achard and G. Buono, Tetrahedron Lett., 2005, 46, 8677.


12 CCDC 1412790.


15 From this point forward the opposite enantiomer of the phosphinous acid borane ([S]P=S)=a was used.

