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Independent Generation of Intermediates in the Asymmetric Appel Process leads to a One Pot Stereoselective Synthesis of P-Stereogenic Phosphines and Phosphine Boranes from Racemic Phosphine Oxides

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Sequential treatment of racemic phosphine oxide with oxalyl chloride and chiral non-racemic alcohol generates, via chlorophosphonium salt, two alkoxyphosphonium salts having the same diastereoselectivity as in the asymmetric Appel process, strongly supporting its proposed mechanism of stereoselection. Subsequent reduction allows a novel synthesis of enantiomerically pure P-stereogenic phosphines/phosphine boranes.

The use of enantiomerically pure phosphine ligands in asymmetric catalysis is a popular strategy for asymmetric synthesis and much effort has been directed towards the design, synthesis and testing of new enantiomerically pure phosphines. Several methodologies have been developed for the synthesis of enantiomerically pure P-stereogenic phosphines and a large number of such ligands have been reported in the literature. Some of these methods may be very effective, but each of them has its own demerits and, to date, there is no straightforward general way to synthesise P-stereogenic phosphines. Herein we describe a new, simple and effective method for obtaining enantiomerically pure P-stereogenic phosphines or phosphine boranes from racemic P-stereogenic phosphine oxides.

We previously developed a successful method for the dynamic kinetic resolution of racemic arylmethylphenyl phosphines. This was achieved in their oxidation using an asymmetric version of the Appel reaction conditions by treatment (at -78 °C) with hexachloroacetone (HCA) in the presence of a chiral non-racemic alcohol (Scheme 1). Although this reaction is an effective way to make P-stereogenic phosphine oxides, it too has its demerits. Subsequent stereospecific reduction is required to reach the target phosphines and, even with much care and process development, this can lead to a loss of stereochemical control. Additionally, the starting phosphines may be difficult to prepare and may require storage and manipulation under inert atmosphere. Finally, the need for HCA is not ideal, its by-product pentachloroacetone (PCA) sometimes makes purification tedious and the chiral alcohol adjuntant is lost as its chloride. We also were initially unsure of the course of the reaction and the mechanism of stereoselection and we have performed extensive investigations into it. We now report the independent generation of the proposed intermediates and a novel P-stereogenic methodology based on it.

Scheme 1. Hypothesis for the course of the asymmetric Appel process.

Our working hypothesis for the course of the asymmetric Appel process is also shown in Scheme 1. It involves the transient generation of an intermediate chlorophosphonium salt (CPS) that reacts rapidly with the chiral non-racemic alcohol (R*OH) present, producing unequal amounts of diastereomeric alkoxyphosphonium salts (DAPS-A), which subsequently undergo slow Arbuzov collapse to form scalemic phosphine oxide. It had become clear from our previous work that the diastereomeric excess (de) in these salts was the better measure of the stereoselective step of the reaction because the enantiomeric excess (ee) in the product oxides was subject to a selectivity eroding process. Therefore to study the selectivity, we devised a consistent procedure (see ESI) to measure the de of DAPS by 31P-NMR spectroscopy and Table 1 (column A) shows how it varies with a range of phosphine/alcohol combinations.

We also became interested in the proposed chlorophosphonium salts and how they might be independently generated as a probe of the reaction. We were intrigued to discover that it had been known for a long time that they can be easily obtained from the phosphine oxide by reaction with oxalyl chloride. Recently we utilised this reaction in a novel direct (achiral) conversion of phosphine oxides to the corresponding boranes, and Denton and co-workers have also used it in their catalytic Appel reaction. When treated with chiral alcohol (at -78 °C), these independently generated CPS indeed yielded the same diastereomeric alkoxyphosphonium salts as in the asymmetric Appel reaction (DAPS-B, Scheme 2). The side-by-side comparison of the diastereomeric excesses (de) in the salts produced by the two different routes for the same set of phosphine/alcohol combinations is shown in Table 1 (columns A/B). It can be seen that the selectivities of both routes are very
similar, providing very strong support for our mechanistic hypothesis and that the selectivity of the asymmetric Appel process is set in the conversion of CPS to DAPS. The de is very slightly higher for the oxalyl chloride route in nearly all cases and we ascribe this to the difference in counterion (CT vs. PCA).

Concurrent with these studies, separate work from our laboratory\textsuperscript{13} had shown that DAPS (obtained from the asymmetric Appel reaction) could be stereospecifically reduced with LiAlH\textsubscript{4} to give phosphine or with NaBH\textsubscript{4} to give phosphine borane directly. In this reaction the de in DAPS corresponded to the ee of the reduced products, with only small losses of chiral information. Combining the three ideas of chlorination, dynamic resolution and reduction then suggested a one-pot stereoselective synthesis of phosphines and phosphine boranes from racemic phosphine oxides (Scheme 3).

In the early experiments, the produced boranes showed significant loss of erosion of the stereoselectivity: for example, the borane derived from methylphenyl(o-tolyl)phosphine oxide (entry 1, Table 1) initially revealed an ee of only 40%.

Monitoring the reaction closely by \textsuperscript{31}P NMR, we discovered that DAPS (obtained from the asymmetric Appel reaction of DAPS) was being eroded over time (Scheme 4). This resulted from reaction of the excess oxalyl chloride, used to ensure complete conversion to CPS, with non-racemic phosphine oxide formed from Arbuzov collapse of DAPS. This reforms CPS, which reacts with NaBH\textsubscript{4} to give racemic phosphine borane.\textsuperscript{15} The reaction protocol was therefore altered; limiting the amount of oxalyl chloride strictly to one equivalent and employing excess alcohol. An advantage of the process is that all the alcohol used can be recovered, as it is regenerated in the reduction.\textsuperscript{18}

\begin{table}
\centering
\begin{tabular}{l c c c c c c}
\hline
\# & o-sub. in Ar group & \% de (A) & \% de (B) & \% ee (C) & \% ee\textsuperscript{0} (D) & (config) & (config) \\
\hline
1 & Me & ent-1 & 82 & 84 & 76 (R) & 78 (R) \\
2 & Me & 1 & 81 & 83 & 74 (S) & 76 (S) \\
3 & Me & 2 & 62 & 64 & 65 (S) & 63 (S) \\
4 & Me & 3 & 63 & 65 & 63 (S) & 63 (S) \\
5 & Me & 5 & 46 & 46 & 46 (R) & 46 (R) \\
6 & OMe & ent-1 & 50 & 49 & 40 (R) & 48 (R) \\
7 & OMe & 1 & 48 & 46 & 44 (S) & 48 (S) \\
8 & OMe & 4 & 70 & 74 & 65 (R) & 67 (R) \\
9 & OMe & 2 & 60 & 64 & 37 (S) & 37 (S) \\
10 & OMe & 3 & 68 & 71 & 63 (S) & 54 (S) \\
11 & CF\textsubscript{3}\textsuperscript{[i]} & ent-1 & 70 & 71 & 71 & 78 \\
12 & CF\textsubscript{3}\textsuperscript{[i]} & 1 & 68 & 73 & 76 & 76 \\
13 & CF\textsubscript{3}\textsuperscript{[i]} & 2 & \cdots & \cdots & \cdots & \cdots \\
14 & CF\textsubscript{3}\textsuperscript{[i]} & 3 & \cdots & \cdots & \cdots & \cdots \\
15 & Ph & ent-1 & 81 & 82 & 41 (R) & 68 (R) \\
16 & Ph & 1 & 80 & 82 & 64 (S) & 66 (S) \\
17 & Ph & 2 & 67 & 70 & 51 & 78 \\
18 & Ph & 1 & 65 & 68 & 52 & 52 \\
19 & Me, p-F & ent-1 & 76 & 78 & 58 & 58 \\
\hline
\end{tabular}
\caption{Enantiomeric excesses\textsuperscript{20} of phosphine boranes ArMePhP-BH\textsubscript{4} (C) and phosphines (ArMePhP) (D) prepared by treating DAPS-B with NaBH\textsubscript{4} and LiAlH\textsubscript{4}, respectively\textsuperscript{20} (Scheme 3).
\label{table1}
}
\end{table}

\begin{table}
\centering
\begin{tabular}{l c c c c c c}
\hline
\# & o-sub. in Ar group & \% de (A) & \% de (B) & \% ee (C) & \% ee\textsuperscript{0} (D) & (config) & (config) \\
\hline
1 & Me & ent-1 & 82 & 84 & 76 (R) & 78 (R) \\
2 & Me & 1 & 81 & 83 & 74 (S) & 76 (S) \\
3 & Me & 2 & 62 & 64 & 65 (S) & 63 (S) \\
4 & Me & 3 & 63 & 65 & 63 (S) & 63 (S) \\
5 & Me & 5 & 46 & 46 & 46 (R) & 46 (R) \\
6 & OMe & ent-1 & 50 & 49 & 40 (R) & 48 (R) \\
7 & OMe & 1 & 48 & 46 & 44 (S) & 48 (S) \\
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12 & CF\textsubscript{3}\textsuperscript{[i]} & 1 & 68 & 73 & 76 & 76 \\
13 & CF\textsubscript{3}\textsuperscript{[i]} & 2 & \cdots & \cdots & \cdots & \cdots \\
14 & CF\textsubscript{3}\textsuperscript{[i]} & 3 & \cdots & \cdots & \cdots & \cdots \\
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\hline
\end{tabular}
\caption{Stereoselective formation of phosphine boranes showing pathway for ee erosion (in red) and alternative reductions (in blue). Colour removed
\label{table2}
}
\end{table}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart1}
\caption{Chiral alcohols used in Schemes 1-3 and Table 1.
\label{chart1}
}
\end{figure}

Using the altered reaction protocol (see ESI) we screened a variety of racemic phosphine oxides, focussing, for proof-of-
principle, on inexpensive menthol as chiral auxiliary to produce scalemic phosphines or borane oxides in one pot. The results are shown in Table 1. The selectivity and the configuration of phosphines and boranes obtained followed the same general trends as observed in the asymmetric Appel reaction. The best result obtained was 84% ee, which is the highest reported to date for the dynamic resolution of a phosphine. It is noticeable that some substrate/alcohol combinations are more prone to erosion of selectivity in the reduction (e.g. Table 1, entries 1,6,11,17 vs. entry 15). We believe that this is due to diastereoselection in the alternative reduction to give oxide and menthane (Scheme 4) and we are presently working to minimize it.

In summary, we have adduced convincing evidence for our proposed course for the asymmetric Appel process. This will enable us to work to improve its selectivity. Also during the study, we discovered an unprecedented alternative method for the creation of P-stereogenicity. The one-pot method starts from the more convenient oxides, has more easily removed by-products (CO, CO₂, HCl) and yields the protected phosphine directly. To be sure, much development work is needed, both to raise the selectivity and minimise its erosion. However, in that regard, we now have greater scope in our choice of chiral alcohol auxiliary because it can be recovered at the end of the reaction.

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Notes and references

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8 A fuller description of our working hypothesis is given in the ESI.

9 Diastereomeric excess (de) is used rather than diastereomeric ratio (dr) to facilitate comparison with the enantiomeric excess (ee) of the ultimate products of the reactions (oxides or boranes).

10 E.g.: the reaction mixture derived from oxalyl chloride treatment of methyl(phenyl)(toly)phosphate oxide directly after addition of (-)-menthol shows two narrow signals for DAPS of unequal heights (92:8) at δ 67.8 and 67.3 ppm, replacing the CPS signal at δ 71.0. An acquisition period of 3 s was set for all 1H spectra to allow full relaxation, extensive precautions taken to ensure that the measured de truly reflected that produced in the reactions: see ESI for details.


