DOI: 10.1002/ejoc.201200285

A U-Turn in the Asymmetric Appel Reaction: Stereospecific Reduction of Diastereomerically Enriched Alkoxyphosphonium Salts Allows the Asymmetric Synthesis of *P*-Stereogenic Phosphanes and Phosphane Boranes

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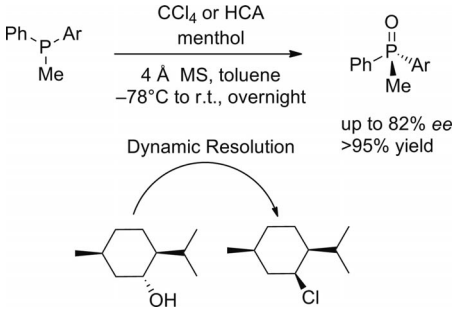
Keywords: Phosphanes / Boranes / Chirality / Asymmetric synthesis / Reduction

An efficient one-pot synthesis has been developed of enantioenriched *P*-stereogenic phosphanes and phosphane boranes from the corresponding racemic phosphanes in excellent yield under asymmetric Appel conditions. The chiral auxiliary (menthol) can also be recovered unchanged. The simple and efficient protocol significantly expands the scope of our asymmetric Appel process. The crucial step in the preparation involves stereospecific reduction of intermediate diastereomeric alkoxyphosphonium salts, which are obtained in the reaction of phosphane, hexachloroacetone, and menthol. Thereby, reaction with $LiAlH_4$ or $NaBH_4$ gives the corresponding phosphanes or phosphane boranes, respectively.

Introduction

Asymmetric catalysis has become an essential strategy for carrying out various asymmetric transformations,[1] and enantioenriched phosphane ligands are common catalyst components.[1a–1c] Thus, significant effort has been expended in the design, synthesis, and testing of new enantiomerically pure phosphanes for various synthetic purposes.[2] An important part of that effort has seen the development of a large number of methodologies for the synthesis of *P*-stereogenic phosphanes,[3] and a large number of such enantiomerically pure phosphane ligands have been reported.[1c,4,5] Some of these methods are very effective, but each of them has its own limitations, and it is true that a general procedure for the synthesis of *P*-stereogenic phosphanes has not been developed thus far. In seeking a general solution to this problem, we developed[6] a dynamic kinetic resolution (DKR) in the oxidation of phosphanes under Appel[7] reaction conditions (Scheme 1). The purpose of this communication is to disclose a significant improvement to this methodology that allows the expansion of the range of compounds synthesized to include enantioenriched tertiary *P*-stereogenic phosphanes or their protected phosphane boranes.



Scheme 1. DKR in oxidation under Appel conditions.

Results and Discussion

Our asymmetric Appel methodology (Scheme 1) utilizes hexachloroacetone (HCA) as a chlorine source and a chiral alcohol such as menthol to make enantioenriched phosphane oxides from racemic phosphanes. Although this is an efficient way to make *P*-stereogenic phosphorus compounds, it suffers from some drawbacks, one of which is that a subsequent (and potentially problematic) stereospecific reduction of the product phosphane oxide[4d,8] is required to obtain the target phosphane. Another drawback is that the menthol auxiliary is converted into the derived chloride making its reuse difficult.

As part of our studies of this process with various alcohol/phosphane combinations, we observed, in the ^{31}PNMR spectrum, an unequal pair of signals in the region δ = 65–67 ppm. These were identified[6] as diastereomeric alkoxyphosphonium salts (DAPS), which undergo Arbuzov collapse to form the phosphane oxide (Scheme 2). Denton

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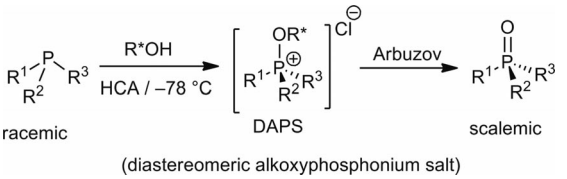
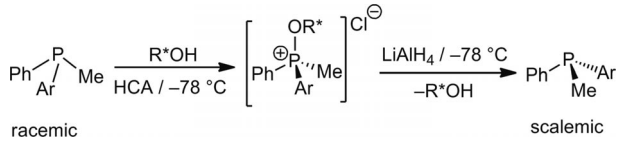
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200285.

and co-workers have recently isolated and characterized similar alkoxyphosphonium salt intermediates in their catalytic Appel reactions.[9]



Scheme 2. DAPS intermediates in the asymmetric Appel process.

To isolate a stable form of these intermediates we used (*R*)-BINOL as the alcohol in an Appel-type reaction with methyl(phenyl)-*o*-tolylphosphane at –78 °C in dry toluene. On addition of HCA, a mixture of diastereomeric aryloxyphosphonium salts precipitated [Scheme 3; R*OH = (*R*)-BINOL]. Because they are unable to undergo Arbuzov collapse, these could be isolated and characterized (as the mixture) by ^{31}P NMR spectroscopy, HRMS, and elemental analysis (see the Supporting Information for details). The salts were found to have been formed in 46%*de* (as measured by integration[10] of their ^{31}P signals at δ = 74.7 and 76.6 ppm). The salts were then subjected to reduction by using $LiAlH_4$, resulting in full conversion to enantioenriched methyl(phenyl)-*o*-tolylphosphane (Scheme 3). The enantiomeric excess of the phosphane was determined to be 46% (by CSP-HPLC analysis of the corresponding phosphane borane formed by treatment with BH_3·THF). This indicated that there had been no loss of stereochemical information during the reduction step. (*R*)-BINOL was also recovered.



Scheme 3. One-pot generation and stereospecific reduction of **DAPS** using $LiAlH_4$.

We realized that this transformation might also be applied to the transient DAPS formed with menthol under Appel conditions, by application of the reducing agent before Arbuzov collapse to the phosphane oxide takes place. In such a way, the Appel reaction might effectively undergo a "U-turn", re-forming the phosphane but in enantiomerically enriched form, without the need for additional stereospecific reduction. Literature precedent suggests competing alcohol reduction is inhibited in the case of menthol.[11,12]

In initial studies, methyl(phenyl)-*o*-tolylphosphane underwent reaction with HCA and (–)-menthol in toluene at –78 °C to form DAPS (confirmed by ^{31}P NMR spectroscopy showing two peaks at δ = 65.7 and δ = 67.4 ppm with 80%*de*). Ten minutes after the start of the reaction,[13] DAPS was reduced in the same pot by adding $LiAlH_4$ in THF to give the corresponding phosphane quantitatively. However, extensive optimization of the reaction protocol was required to find conditions that did not result in erosion of isomeric excess (see the Supporting Information for details). Finally we were able to obtain methyl(phenyl)-*o*-tolylphosphane in 79%*ee* from DAPS of 80%*de*. We applied this methodology to a variety of phosphane/alcohol (Figure 1) combinations with the results detailed in Table 1, again measuring the *ee* following subsequent conversion to the borane with BH_3·THF.

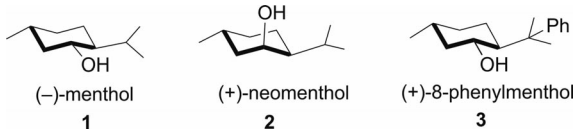


Figure 1. Chiral non-racemic alcohols used in Tables 1 and 2.

Table 1. Enantiomeric excess of phosphanes (ArPhMeP) prepared by treatment of diastereomerically enriched alkoxyphosphonium salts with $LiAlH_4$ according to Scheme 3.[a]

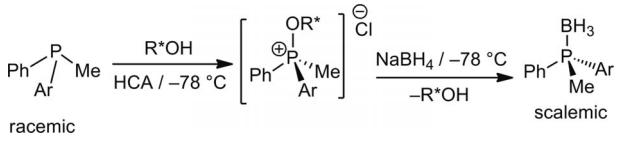
Entry	Ar	R*OH[b]	% *ee*[c] of phosphane (config.)	% *ee* of analogous oxide[d]
1	*o*-tolyl[e]	**1**	79(*R*)	80
2	*o*-tolyl	*ent*-**1**	–76(*S*)	78
3	*o*-tolyl	**2**	–71(*S*)	71
4	*o*-anisyl[e]	**1**	50(*R*)	50
5	*o*-anisyl	*ent*-**1**	–48(*S*)	49
6	*o*-anisyl	**3**	64(*R*)	77
7	*o*-biphenyl[e]	**1**	65[f]	64
8	*o*-*tert*-butylphenyl[e]	**1**	60[f]	57
9	*o*-trifluoromethylphenyl[e]	**1**	70[f]	71
10	*o*-isopropylphenyl[e]	**1**	58(*R*)	80
11	*o*-methyl-*p*-fluorophenyl	**1**	57[f]	76
12	*o*,*p*-dimethylphenyl[e]	**1**	60[f]	76

[a] Reaction conditions: Phosphane (1.1 mmol), alcohol (1.32 mmol), HCA (1.1 mmol), $LiAlH_4$ (1.1 mmol), all at –78 °C, crude yields >95% (as determined by ^{31}P NMR spectroscopy). [b] See Figure 1. [c] Measured following conversion to the borane with BH_3·THF, determined by CSP HPLC; a negative *ee* value denotes that the major enantiomer was eluted second; absolute configurations determined as described in the Supporting Information. [d] The *ee* value of the analogous phosphane oxide formed when DAPS was allowed to undergo Arbuzov collapse, from ref.[6] [e] Isolated yields >85%. [f] Configuration not assigned.

Table 1 also gives, for comparison, the analogous enantioselectivities of the phosphane oxide products obtained in the regular asymmetric Appel reaction of the same phosphanes, reported in our previous work.[6] It can be seen that, mostly, these are the same, the exceptions being where there are notable changes in the alcohol (Table 1, Entry 6) or phosphane used (Table 1, Entries 10–12). We attribute these variations to the need for optimization of the conditions in these cases.

At the same time that this work was in progress, we had been investigating the use of $NaBH_4$ as a reductant for other phosphonium salts including enantioenriched alkoxy cases.[14] We had found that the phosphane borane could be produced directly in such reactions.[11] As much attention has been directed towards phosphane boranes in recent

years,[3e,3j,3n,15] we also studied this variant (Scheme 4), with various phosphane/alcohol combinations with the results shown in Table 2. In most cases the *ee* values obtained are the same as those obtained in the $LiAlH_4$ reduction.



Scheme 4. One-pot generation and stereospecific conversion of DAPS into phosphane borane by using $NaBH_4$.

Table 2. Enantiomeric excess of phosphane boranes ($ArPhMePBH_3$) prepared by treatment of diastereomerically enriched alkoxyphosphonium salts with $NaBH_4$ according to Scheme 4.[a]

Entry	Ar	R*OH[b]	% *ee*[c] of *P*-borane (config.)	% *ee* of analogous oxide[d]
1	*o*-tolyl[e]	**1**	75(*R*)	80
2	*o*-tolyl	*ent*-**1**	–74(*S*)	78
3	*o*-anisyl[e]	**1**	50 (*R*)	50
4	*o*-anisyl	*ent*-**1**	–51 (*S*)	49
5	*o*-anisyl	**3**	63(*R*)	77
6	*o*-biphenyl[e]	**1**	66[f]	64
7	*o*-trifluoromethylphenyl[e]	**1**	71[f]	71
8	*o*-isopropylphenyl[e]	**1**	40(*R*)	80

[a] Reaction conditions: Phosphane (1.1 mmol), alcohol (1.32 mmol), HCA (1.1 mmol), $NaBH_4$ (5.5 mmol), yields >95% (as determined by ^{31}P NMR spectroscopy). [b] See Figure 1. [c] Determined by CSP HPLC; a negative *ee* value denotes that the major enantiomer was eluted second; absolute configurations determined as described in the Supporting Information. [d] The *ee* value of the analogous phosphane oxide formed when the DAPS was allowed to undergo Arbuzov collapse, from ref.[6] [e] Isolated yields >85%. [f] Configuration not assigned.

The significance of the results in Tables 1 and 2 does not lie in the absolute degree of selectivity obtained. We have focused mostly on the use of inexpensive menthol as the chiral auxiliary to show proof of principle that the asymmetric Appel process can be manipulated to produce scalemic phosphanes or phosphane boranes in one pot from a racemic phosphane. Also, the selectivities are, in most cases, the same as those previously seen in the regular asymmetric Appel process.[6] Thus, we have significantly expanded the utility of our asymmetric Appel process. With this methodology in hand, we have embarked on an intensive study aimed at raising the degree of stereoselectivity in our process. In that context, an important point is that the chiral auxiliary can now be recovered intact in the present process, which gives us a greater scope in our choice of chiral alcohols for our selectivity studies, knowing that they can be recovered at the end of the reaction.

Conclusions

In conclusion, we have achieved an unprecedented one-pot enantioenrichment of racemic phosphanes, and we have demonstrated the one-pot conversion of racemic phosphanes into enantioenriched phosphane boranes. Both methods rely on the interception of diastereomeric alkoxyphosphonium salts formed by dynamic resolution of racemic phosphanes under asymmetric Appel reaction conditions. Further investigations into the scope of this reaction are underway.

Experimental Section

(a) Preparation and Predrying of Stock Solutions: Moisture was rigorously excluded in these experiments. Dry solvent used to make stock solutions was obtained after processing through an Innovative Technology Inc. Pure Solv-400–3-MD solvent purification system (Grubbs still). The water contents of the solvent and stock solutions were determined by Karl Fischer titration to be less than 5 ppm. The alcohols, phosphanes, and hexachloroacetone (HCA) used were dried thoroughly before preparing the stock solutions as follows. The individual alcohols (1.32 mmol.) were weighed into flame-dried and N_2-purged round-bottomed flasks and sufficient dry toluene (approx. 10 mL) was added to dissolve the alcohol. The toluene was removed by using a rotary evaporator to remove water as an azeotrope. This process was repeated three times and then sufficient dry toluene was added to the alcohols under N_2 to make solutions of the required concentration (0.132 M). Molecular sieves (4 Å), which were flame-dried until red hot, were added after cooling to flame-dried Young's flasks. The flasks were heated under vacuum with a heat gun focusing on the molecular sieves for 2 min each and then flushed with N_2. This was repeated twice. The Young's flask screw crown was removed under a good flow of N_2 and replaced with a rubber septum. While both vessels were under nitrogen the stock solutions were removed by syringe from the round-bottomed flasks and placed over the sieves in the Young's flasks and left overnight. For the HCA solution, molecular sieves (4 Å), which were flame-dried until red hot, were added to flame-dried Young's flasks. The flasks were heated under vacuum with a heat gun focusing on the molecular sieves for 2 min each and then flushed with N_2. This was repeated twice. The screw cap of the Young's flask was removed under a good flow of N_2 and replaced with rubber septa. Distilled HCA (1.1 mmol) was weighed into the Young's flask and dry toluene was added to make a solution of the required concentration (0.11 M), which was then left overnight. A similar procedure was followed to make up 0.11 M stock solutions of distilled phosphanes in dry toluene.

(b) Optimized Procedure for $LiAlH_4$ Reduction with Methyl(phenyl)-*o*-tolylphosphane as Example: A solution of methyl(phenyl)-*o*-tolylphosphane (0.11 M, 10.0 mL, 1.1 mmol) in anhydrous toluene was placed in a dry flask under N_2. In a separate flask, dry toluene solutions of HCA (0.11 M, 10.0 mL, 1.1 mmol) and (–)-menthol (0.132 M, 10.0 mL, 1.32 mmol) were placed, also under N_2. Both flasks were cooled to –78 °C and allowed to stir at this temperature for 10 min. After this time the phosphane solution was added steadily by cannula over 2 min. The temperature was maintained for 10 min, at which point the formation of the diastereomeric salts was confirmed by ^{31}P NMR spectroscopy (sampled as described in the Supporting Information) showing two peaks at δ = 65.7 ppm and δ = 67.4 ppm. To the mixture was added a solution of $LiAlH_4$ (0.11 M in toluene, 10.0 mL, 1.1 mmol) dropwise at –78 °C. After the addition was complete, the vessel was removed from the cooling bath and warmed to room temperature. The reaction was stirred for a further 60 min, at which point the diastereomeric salts were shown to have been consumed and the phosphane formed (^{31}P NMR signal at δ = –36.2 ppm). BH_3·THF complex (0.75 mL of a

2.0 M solution in THF, 1.5 mmol) was added. ^{31}P NMR spectroscopy analysis of the clear solution revealed one peak for the phosphane borane at δ = 10.1 ppm. A portion of the reaction mixture was removed, concentrated under reduced pressure, diluted in HPLC mobile phase, filtered though a 0.2-μM Millipore Acrodisc and directly injected (10 μL) onto the HPLC system (see the Supporting Information) for *ee* analysis. The remaining reaction mixture was diluted with EtOAc (15 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was passed through a column of basic alumina by using degassed Et_2O. The solvent was removed under vacuum and column chromatography was carried out on silica gel (EtOAc, R_f = 0.11) to yield the enantioenriched phosphane borane as a white solid [0.20 g, 96%, 79% *ee* (*R*)].

(c) Optimized Procedure for $NaBH_4$ Reduction with Methyl(phenyl)-*o*-tolylphosphane as Example: Experimental procedure as per section (b) up to the analysis of diastereomeric salts by ^{31}P NMR spectroscopy. To the mixture was added a solution of $NaBH_4$ (11 mL of a 0.5 M solution in diglyme, 5.5 mmol) dropwise at –78 °C. After the addition was complete, the vessel was removed from the cooling bath and warmed to room temperature. The reaction was stirred for another 60 min, at which point the diastereomeric salts were shown to have been consumed and the phosphane borane formed (^{31}P NMR signal at δ = 10.1 ppm). Workup and analysis as per section (b) gave the enantioenriched phosphane borane as a white solid [0.19 g, 94%, 75% *ee* (*R*)].

Supporting Information (see footnote on the first page of this article): General experimental, synthesis and reduction of BINOLDAPS, development of reaction conditions, phosphane boranes, NMR spectra and HPLC chromatograms.

Acknowledgments

We sincerely thank Science Foundation Ireland (SFI) for funding this research under grants 08/RFP/CHE1251 and 09/IN.1/B2627. We are also grateful to the Centre for Synthesis and Chemical Biology and the UCD School of Chemistry and Chemical Biology for access to their extensive analysis facilities.

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Received: March 7, 2012
Published Online: April 5, 2012

