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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

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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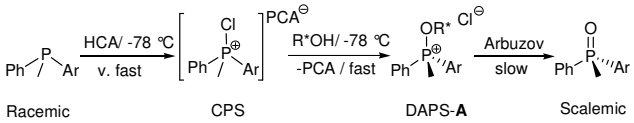
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

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 enantioenriched *P*-stereogenic phosphines/phosphine boranes.

The use of enantiomerically pure phosphine ligands in asymmetric catalysis is a popular strategy for asymmetric synthesis[1] and much effort has been directed towards the design, synthesis and testing of new enantiomerically pure phosphines.[2] Several methodologies have been developed for the synthesis of enantiomerically pure *P*-stereogenic phosphines[3] and a large number of such ligands have been reported in the literature.[3,4,5] Some of these methods can 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 enantioenriched *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.[6] This was achieved in their oxidation using an asymmetric version of the Appel reaction conditions[7] 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,[8] 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.[3b,e,9] 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 adjuvant 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.

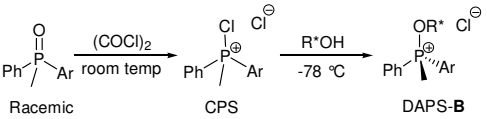


Scheme 1. Hypothesis for the course of the asymmetric Appel process.

Our working hypothesis for the course of the asymmetric Appel process[6,7,10] 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[6b] that the diastereomeric excess (de)[11] 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 ^{31}P-NMR spectroscopy[12] and Table 1 (column A) shows how it varies with a range of phosphine/alcohol combinations.

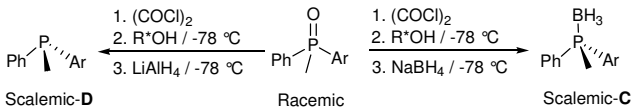
We also became interested in the proposed chlorophosphonium salts[13] and how they might be independently generated as a probe of the reaction. We were intrigued to discover that it had been known for a long time that they can be easily obtained *from the phosphine oxide* by reaction with oxalyl chloride.[14] Recently we utilised this reaction in a novel direct (achiral) conversion of phosphine oxides to the corresponding boranes,[15,16] and Denton and co-workers have also used it in their catalytic Appel reaction.[17] 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 (Cl^- vs. PCA^-).



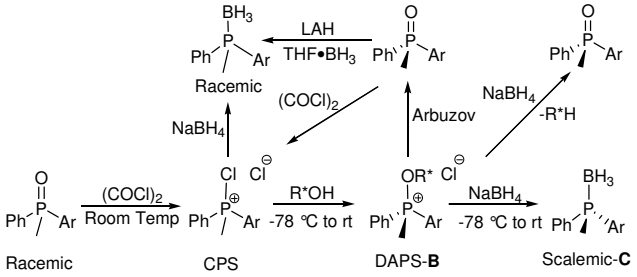
Scheme 2. Production of DAPS by independent generation of CPS from phosphine oxide and subsequent reaction with chiral alcohol.

Concurrent with these studies, separate work from our laboratory[18] had shown that DAPS (obtained from the asymmetric Appel reaction) could be stereospecifically reduced with $LiAlH_4$ to give phosphine or with $NaBH_4$ 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).



Scheme 3. Synthesis of *P*-stereogenic phosphines and phosphine boranes.

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 ^{31}P NMR, we discovered that the de of DAPS-B 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 $NaBH_4$ to give racemic phosphine borane.[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.[18]



Scheme 4. Stereoselective formation of phosphine boranes showing pathway for ee erosion (in red) and alternative reductions (in blue). **Colour removed**

Table 1 Stereoselectivities measured in this work. **A/B**: Comparison of diasteromeric excesses[a] of DAPS prepared from phosphines ArMePhP (Scheme 1; **A**)[b] and their oxides ArMePhP=O (Scheme 2; **B**)[c]. **C/D**: Enantiomeric excesses[d] of phosphine boranes ArMePhP-BH_3 (**C**) and phosphines (ArMePhP) (**D**) prepared by treating DAPS-**B** with $NaBH_4$ and $LiAlH_4$ respectively[e] (Scheme 3).

#	*o*-sub. in Ar group	R*OH[f]	% de (**A**)	% de (**B**)	% ee (**C**) (config)	% ee[g] (**D**) (config)
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*)	-----
4	Me	**3**	63	65	-63 (*S*)	-----
5	Me	**5**	46	46	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	64 (*R*)	67 (*R*)
9	OMe	**2**	60	64	-37 (*S*)	-30 (*S*)
10	OMe	**3**	68	71	-63 (*S*)	-54 (*S*)
11	CF_3[h]	**ent-1**	70	71	71	68
12	CF_3[h]	**1**	68	73	-76	-66
13	CF_3[h]	**2**	--[i]	--[i]	-84[j]	-----
14	CF_3[h]	**3**	--[i]	--[i]	-76[j]	-----
15	^{i}Pr	**ent-1**	81	82	41 (*R*)	68 (*R*)
16	^{i}Pr	**1**	80	82	-64 (*S*)	-66 (*S*)
17	Ph	**ent-1**	67	70	51	68
18	Ph	**1**	65	68	-52	-----
19	Me, *p*-F	**ent-1**	76	78	58	-----

[a] Determined by ^{31}P-NMR (see ESI); de is given rather than dr to facilitate comparison with the ees in the derived **C/D**; [b] Reaction conditions: Phosphine (1.1 mmol), alcohol (1.32 mmol.), HCA (1.1 mmol.) at –78 °C, all yields >95 % (as judged by ^{31}P NMR); [c] Reaction conditions: Phosphine oxide (1.1 mmol.), oxalyl chloride (1.1 mmol) followed by alcohol (1.32 mmol) at –78 °C, all yields are >95 % (as judged by ^{31}P NMR); [d] Determined by CSP HPLC (see ESI), negative ee denotes that the major enantiomer was eluted second; yields >90% except where noted (as judged by ^{31}P NMR; isolated yields for all (-)-menthol cases), configurations, where given, determined as described in ESI; [e] $LiAlH_4$ (1.1 mmol in PhMe) or $NaBH_4$ (5.5 mmol in diglyme) added to DAPS-**B** at –78 °C; [f] see Chart 1; [g] measured by CSP HPLC (see ESI), after subsequent conversion to the borane with BH_3.THF; [h] for route **B**: oxalyl chloride reaction warmed to 50 °C to ensure full conversion to chlorophosphonium salt; [i] Unable to measure de due to faster Arbuzov collapse of the DAPS; [j] Yielded 60-65% of phosphine borane and 35-40% of phosphine oxide which was also enantioenriched.

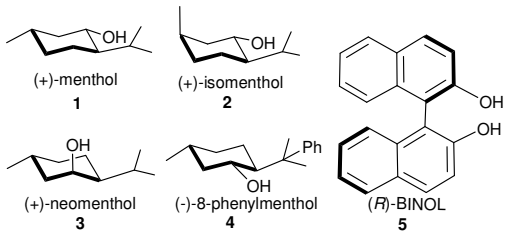


Chart 1. Chiral alcohols used in Schemes 1-3 and Table 1.

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 phosphine boranes 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.[6] 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[19] 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, CO_2, 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.

We thank sincerely Science Foundation Ireland (SFI) for funding this chemistry under Grant RFP/08/CHE1251. We are also grateful to UCD Centre for Synthesis and Chemical Biology (CSCB) and the UCD School of Chemistry and Chemical Biology for access to their extensive analysis facilities. DGG thanks sincerely University College Dublin for a President's Research Fellowship during which the conception of this work took place. The Fellowship was held partly in Stanford University in the laboratory of Professor James Collman, to whom DGG is warmly appreciative for both his hospitality and stimulating intellectual discussions.

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† Electronic Supplementary Information (ESI) available: Full experimental procedure, and full characterization data for phosphine oxides and boranes; HPLC traces of all scalemic phosphine boranes. See DOI: 10.1039/b000000x/

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

11 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).

12 E.g.: the reaction mixture derived from oxalyl chloride treatment of methylphenyl(*o*-tolyl)phosphine oxide directly after addition of (-)-menthol shows two narrow signals for DAPS of unequal heights (92:8) at δ 67.8 and δ 67.3 ppm, replacing the CPS signal at δ 71.0. An acquisition period of 3 s was set for all ^{31}P 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

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