ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 10040–10042

www.rsc.org/chemcomm

COMMUNICATION

Identification of a key intermediate in the asymmetric Appel process: one pot stereoselective synthesis of *P*-stereogenic phosphines and phosphine boranes from racemic phosphine oxides†

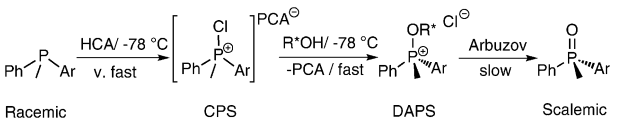
Kamalraj V. Rajendran and Declan G. Gilheany*

Received 8th June 2012, Accepted 15th August 2012
DOI: 10.1039/c2cc34136k

Sequential treatment of racemic phosphine oxides with oxalyl chloride and chiral non-racemic alcohol generates the same ratios of diastereomeric alkoxyphosphonium salts obtained in the corresponding asymmetric Appel process, strongly implicating the intermediate chlorophosphonium salt in the stereoselecting step. Subsequent reduction allows a novel synthesis of enantio-enriched *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.[3–5] 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.

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 demerits. Subsequent stereospecific reduction is required to reach the target phosphines, which can lead to loss of enantiomeric excess;[9] the starting phosphines may be difficult to prepare requiring storage/manipulation under inert atmosphere; the use of HCA is not ideal and its by-product pentachloroacetone (PCA) can make purification tedious; and, finally, the chiral alcohol adjuvant is lost as the chloride. Furthermore we were initially unsure of the course of the reaction and the mechanism of stereoselection. We now report the identification, *via* independent generation, of the key intermediate in the process, which, in turn, led to a new, simpler *P*-stereogenic methodology.



Scheme 1 Hypothesis for the course of the asymmetric Appel process showing the proposed chlorophosphonium salt (CPS) intermediate and its reaction with alcohol to give diastereomeric alkoxyphosphonium salts (DAPS route A).

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)[11] that reacts rapidly with added chiral non-racemic alcohol (R*OH), giving unequal amounts of diastereomeric alkoxyphosphonium salts (DAPS route A), which then undergo slow Arbuzov collapse to form scalemic phosphine oxide.

A complication revealed in our previous work[6b] is that the diastereomeric excess (de)[12] in the DAPS is the better measure of the stereoselective step of the reaction because the enantiomeric excess (ee) observed in the product oxides may be lower due to non-selective processes than can occur during the Arbusov step. Therefore to better study the selectivity, we devised a consistent procedure (see ESI†) to measure the de of DAPS by ^{31}P-NMR spectroscopy[13] and Table 1 (col A) shows how this more reliable selectivity varies for a range of phosphine–alcohol combinations.

A more significant difficulty in our studies was that it proved impossible to definitively detect the presence of CPS during the reaction. This is due to its rapid reaction with the added alcohol, which must be present from the start to prevent certain side reactions within the manifold of the Appel conditions.[7] Therefore we were most interested in how CPS 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, this reaction has been used by us[15] and others[16,17] for other useful transformations. Accordingly, we took a series of racemic phosphine oxides and treated them with oxalyl chloride, which cleanly generated the corresponding CPSs (as judged by ^{31}P NMR – see ESI†). When treated with chiral alcohol at −78 °C, these did indeed yield the same diastereomeric alkoxyphosphonium

Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland. E-mail: declan.gilheany@ucd.ie; Fax: +353-1-7162127; Tel: +353-1-7162308

† 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/c2cc34136k

Table 1 Stereoselectivities measured in this work. A/B: Comparison of diasteromeric excesses[a] of DAPS prepared from phosphines ArMePhP (route A: Scheme 1)[b] and oxides ArMePhP=O (route B: Scheme 2).[c] C/D: Enantiomeric excesses[d] of phosphine boranes ArMePhP-BH_3 (C) and phosphines (ArMePhP) (D) prepared by treating DAPS from' route 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	6868[i]
18	Ph	**1**	65	68	−52	—
19	Me, *p*-F	**ent-1**	76	78	58	—

[a] Determined by ^{31}P-NMR (see ESI). [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 from route 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, also enantioenriched.

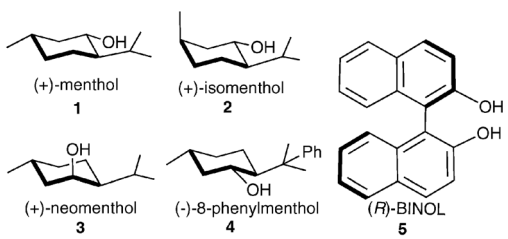
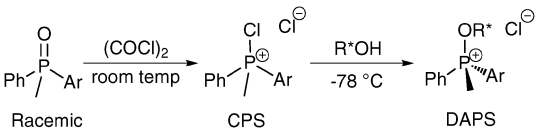


Chart 1 Chiral alcohols used in Scheme 1–3 and Table 1.

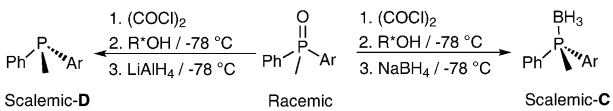
salts as in the asymmetric Appel reaction (DAPS route B, Scheme 2). A side-by-side comparison of the diastereomeric excesses (de) in the salts produced by the two different routes for the same set of phosphine–alcohol combinations is shown in Table 1 (columns A/B). It can be seen that the selectivities of both routes are very similar, providing very strong support for our mechanistic hypothesis and strongly suggesting that the selectivity of both processes 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^-).



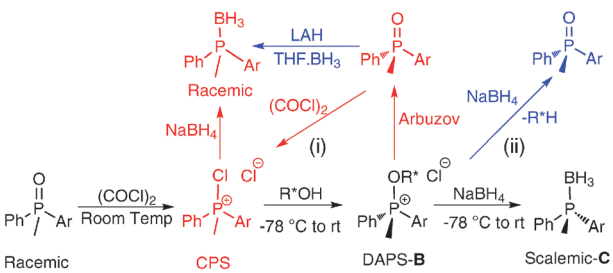
Scheme 2 DAPS route B by independent generation of CPS from phosphine oxide and subsequent reaction with chiral alcohol.

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 these reactions 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 stereoselectivity: for example, the borane derived from methylphenyl(*o*-tolyl)phosphine oxide (entry 1, Table 1) initially revealed an ee of only 40%. By monitoring the reaction closely by ^{31}P NMR, we discovered that this resulted from reaction of excess oxalyl chloride (used to ensure complete conversion to CPS) with non-racemic phosphine oxide formed from some Arbuzov collapse of DAPS. The reformed CPS reacts with $NaBH_4$ to give racemic phosphine borane (Scheme 4(i)).[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] A variety of racemic phosphine oxides was screened, focussing, for proof-of-principle, on inexpensive menthol as chiral auxiliary with results shown in Table 1 (columns C/D). The selectivity and the configuration of the scalemic phosphines and boranes obtained followed the same general trends observed in the asymmetric Appel reaction.[6] The best result obtained was 84% ee, the highest reported to date for the dynamic resolution of a phosphine. It is noticeable that some substrate/alcohol combinations are



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



Scheme 4 Stereoselective formation of phosphine boranes from racemic oxides showing pathway for ee erosion (i) and competing alcohol reduction (ii).

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 small amount of alternative reduction[19] to give oxide and menthane (Scheme 4(ii)).

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 Grants RFP/08/CHE1251 and 09/IN.1/B2627. 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.

Notes and references

1 *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley-VCH, New York, 3rd edn, 2010; *Tetrahedron: Asymmetry*, ed. X. Zhang, 2004, vol. 15, pp. 2099–2311, special issue; K. V. L. Crepy and T. Imamoto, *Top. Curr. Chem.*, 2003, **229**, 1; S. J. Connon, *Angew. Chem., Int. Ed.*, 2006, **45**, 3909; J. L. Methot and W. R. Roush, *Adv. Synth. Catal.*, 2004, **346**, 1035.

2 *Phosphorus Ligands in Asymmetric Catalysis*, ed. A. Börner, Wiley-VCH, Weinheim, 2008, vol. I–III; S. Lühr, J. Holz and A. Börner, *ChemCatChem*, 2011, **3**, 1708.

3 Leading references to the major methods: Methyl phosphinate route: O. Korpium and K. Mislow, *J. Am. Chem. Soc.*, 1967, **89**, 4784; B. D. Gatineau, L. Laurent Giordano and G. Buono, *J. Am. Chem. Soc.*, 2011, **133**, 10728; Q. Xu, C.-Q. Zhao and L.-B. Han, *J. Am. Chem. Soc.*, 2008, **130**, 12648. Cyclic phosphoramidate route: S. Jugé and J. P. Genet, *Tetrahedron Lett.*, 1989, **30**, 2783; C. Darcel, J. Uziel and S. Jugé, in ref. 2, vol. 3, pp. 1211–1233; T. Leon, A. Riera and X. Verdaguer, *J. Am. Chem. Soc.*, 2011, **133**, 5740; Desymmetrisation: A. R. Muci, K. R. Campos and D. A. Evans, *J. Am. Chem. Soc.*, 1995, **117**, 9075; A. Ohashi, S. I. Kikuchi, M. Yasutake and T. Imamoto, *Eur. J. Org. Chem.*, 2002, 2535; J. J. Gammon, V. H. Gessner, G. R. Barker, J. Granander, A. C. Whitwood, C. Strohmann, P. O'Brien and B. Kelly, *J. Am. Chem. Soc.*, 2010, **132**, 13922; J. Granander, F. Secci, S. J. Canipa, P. O'Brien and B. Kelly, *J. Org. Chem.*, 2011, **76**, 4794; Enzymatic resolution: P. Kielbasinski, J. Omelanczuk and M. Mikolajczyk, *Tetrahedron: Asymmetry*, 1998, **9**, 3283; Dynamic resolution: H. Heath, B. Wolfe, T. Livinghouse and S. K. Bae, *Synthesis*, 2001, 2341; C. E. Headley and S. P. Marsden, *J. Org. Chem.*, 2007, **72**, 7185; Catalytic asymmetric synthesis: C. Scriban and D. S. Glueck, *J. Am. Chem. Soc.*, 2006, **128**, 2788; V. S. Chan, R. G. Bergman and F. D. Toste, *J. Am. Chem. Soc.*, 2007, **129**, 15122; G. Cedric, S. J. Canipa, P. O'Brien and S. Taylor, *J. Am. Chem. Soc.*, 2006, **128**, 9336.

4 For reviews of *P*-stereogenic compounds, see:(*a*) A. Grabulosa, J. Granell and G. Muller, *Coord. Chem. Rev.*, 2007, **251**, 25; (*b*) D. S. Glueck, *Synlett*, 2007, 2627; (*c*) M. J. Johansson and N. C. Kann, *Mini-Rev. Org. Chem.*, 2004, **1**, 233; (*e*) K. M. Pietrusiewicz and M. Zablocka, *Chem. Rev.*, 1994, **94**, 1375.

5 P-Stereogenic Ligands in Enantioselective Catalysis, ed. A. Grabulosa, Royal Society of Chemistry, Cambridge, UK, 2011.

6 (*a*) E. Bergin, C. T. O'Connor, S. B. Robinson, E. M. McGarrigle, C. P. O'Mahony and D. G. Gilheany, *J. Am. Chem. Soc.*, 2007, **129**, 9566; (*b*) K. V. Rajendran, L. Kennedy and D. G. Gilheany, *Eur. J. Org. Chem.*, 2010, 5642.

7 R. Appel and M. Halstenberg, *Tertiary Phosphane Halogenoalkane Reagents*, in *Organophosphorus Regents in Organic Synthesis*, ed. J. I. G. Cadogan, Academic Press, London, 1979, ch. 9, p. 387; I. M. Downie, J. B. Holmes and J. B. Lee, *Chem. Ind. (London, U. K.)*, 1966, 900.

8 D. G. Gilheany, S. B. Robinson, C. P. O'Mahony, C. T. O'Connor, E. Bergin, D. M. Walsh, E. F. Clarke, B. G. Kelly and E. M. McGarrigle, *Int. Patent, WO* 118603, 2005. This method has been successfully run on a multikilo scale in an industrial process.

9 K. Naumann, G. Zon and K. Mislow, *J. Am. Chem. Soc.*, 1969, **91**, 7012; K. Naumann, G. Zon and K. Mislow, *J. Am. Chem. Soc.*, 1969, **91**, 2788; G. Zon, K. E. DeBruin, K. Naumann and K. Mislow, *J. Am. Chem. Soc.*, 1969, **91**, 7023; D. Valentine, Jr., J. F. Blount and K. Toth, *J. Org. Chem.*, 1980, **45**, 3691; L. D. Quin, K. C. Caster, J. C. Kislaus and K. A. Masch, *J. Am. Chem. Soc.*, 1984, **106**, 7021.

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

11 For studies of such salts see: S. M. Godfrey, C. A. McAuliffe, R. G. Pritchard and J. M. Sheffield, *Chem. Commun.*, 1998, 921; N. C. Gonnella, C. Busacca, S. Campbell, M. Eriksson, N. Grinberg, T. Bartholomeyzik, S. Ma and D. L. Norwood, *Magn. Reson. Chem.*, 2009, **47**, 461.

12 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).

13 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.

14 M. Masaki and K. Fukui, *Chem. Lett.*, 1977, 151; K. Fukui and N. Kakeya, *U. S. Patent*, 4,301,301 Nov. 17, 1981.

15 Direct (achiral) conversion of phosphine oxides to boranes: K. V. Rajendran and D. G. Gilheany, *Chem. Commun.*, 2011, **48**, 817.

16 Electroreduction of phosphine oxides: M. Kuroboshi, T. Yano, S. Kamenoue, H. Kawakubo and H. Tanaka, *Tetrahedron*, 2011, **67**, 5825.

17 Catalytic Appel reaction: R. M. Denton, J. An and B. Adeniran, *Chem. Commun.*, 2010, **46**, 3025; R. M. Denton, J. An, B. Adeniran, A. J. Blake, W. Lewis and A. M. Poulton, *J. Org. Chem.*, 2011, **76**, 6749.

18 K. V. Rajendran, J. S. Kudavalli, K. S. Dunne and D. G. Gilheany, *Eur. J. Org. Chem.*, 2012, 2720–2723.

19 K. E. Elson, I. D. Jenkins and W. A. Loughlin, *Org. Biomol. Chem.*, 2003, **1**, 2958; J. B. Hendrickson, M. Singer and Md. S. Hussoin, *J. Org. Chem.*, 1993, **58**, 6913. Also in $LiAlH_4$ reductions any produced oxide will be reduced racemically: see ref. 18.

