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Systematic survey of positive chlorine sources in the asymmetric Appel reaction: oxalyl chloride as a new phosphine activator

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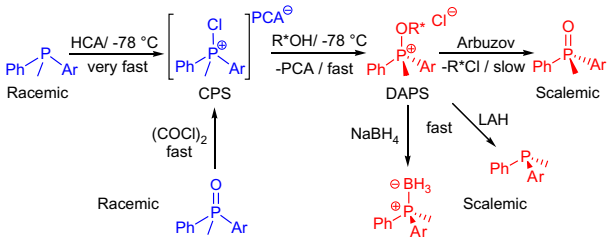
ABSTRACT

A wide selection of phosphine activators has been screened to improve the selection process in the asymmetric Appel reaction. Of the activators screened, hexachloroacetone (HCA) gave the highest selectivity with excellent yield, but at least one of its by-products, pentachloroacetone (PCA), can become involved in the selection process. In addressing this, a new reaction of phosphines with oxalyl chloride was discovered that can also generate the key intermediate chlorophosphonium salt (CPS), gives better enantioselectivity and possesses significant advantages over other phosphine activators.

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] Many 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]

Our own methodology for *P*-stereogenic phosphorus is based on an asymmetric version of the Appel reaction system. This is an oxidation/reduction/dehydration system in which a tertiary phosphine interacts initially with a source of positively charged chlorine, sometimes referred to as the phosphine activator.[5] The original Appel conditions utilized carbon tetrachloride for this purpose but, later, the less toxic and more reactive hexachloroacetone (HCA) was introduced.[6] We found that this system could be used for the asymmetric oxidation of racemic phosphines by interaction with a chiral non-racemic alcohol giving a dynamic resolution of racemic *P*-stereogenic phosphines in high yield with up to 82% ee.[7,8] We have established the reaction sequence shown in Scheme 1.[9,10] Thus, the initially formed chlorophosphonium salt (CPS) is captured stereoselectively by the chiral auxiliary (e.g., menthol) to form a pair of diastereomeric alkoxyphosphonium salts (DAPS), which in turn undergo Arbuzov collapse to enantioenriched phosphine oxides.



Scheme 1. Asymmetric Appel reaction: HCA = hexachloroacetone; PCA = pentachloroacetone; CPS = chlorophosphonium salt; DAPS = diastereomeric alkoxyphosphonium salt; blue: racemic; red: stereoenriched.

Complementarily to this, we also showed[9] that the key intermediate CPS could be generated from racemic phosphine oxide with oxalyl chloride, allowing the oxide to be used as starting material in lieu of phosphine. We also reported[11] that the DAPS can be intercepted by hydride reduction to give enantioenriched phosphine or phosphine borane (Scheme 1).

Although the reaction manifold shown in Scheme 1 provides a potentially powerful suite of methodologies for *P*-stereogenic phosphorus, it is clearly limited by the moderate selectivities. As part of our studies to raise selectivity and expand substrate scope, we turned our attention to the influence of the phosphine activator. This can play a major role in determining the selectivity: for example, we had noticed up to a 40% increase in selectivity on switching from carbon tetrachloride to HCA.[7a]

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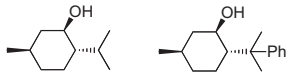
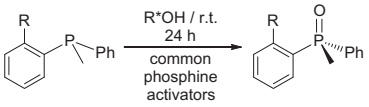
For our studies, we used model phosphines, the well-known phenyl(*o*-anisyl)methylphosphine (**PAMP**) and, to a lesser extent, phenyl(*o*-tolyl)methylphosphine (**PTMP**). We had previously found[7] that the latter gave the best selectivity with the cheap chiral auxillary menthol (**1**), whereas the former was best with 8-phenylmenthol (**2**). Using these systems, we screened initially a variety of other known phosphine activators for comparison to HCA, with the results shown in Table 1.

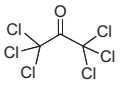
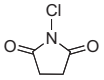
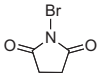
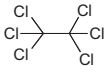
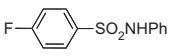
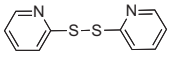


(-)-menthol **1** (-)-8-phenylmenthol **2**

It is plain that, although all these activators give moderate or very good yields in the reaction, only HCA gives moderate stereoselectivity, approached only by N-chlorosuccinimide (entry 2). We were surprised by the case of hexachloroethane (HCE, entry 4) because it is known to react with phosphines to form cleanly dichlorophosphoranes, which are putative intermediates in our process.[7] To check that this was the case, **PAMP** was treated with HCE in $CDCl_3$ at room temperature overnight, and indeed furnished a single resonance at δ_P +70.5, consistent with literature precedent.[12] However, treatment of the resulting solution with (−)-8-phenylmenthol still resulted in no selectivity in the resulting **PAMPO**.

Table 1
Results of asymmetric Appel reactions[a] using common phosphine activators with **PAMP** and **PTMP**



Entry	Phosphine activator	*R* = Me *R**OH = **1** ee[b] (%)	*R* = OMe *R**OH = **2** ee[b] (%)	Yield [c] (%)
1		50	64	76/95
2		35[d]	53[d]	46/70
3		—	5[d]	50
4		29	0[e]	84/95
5	CCl_4	6[f]	24[d,g,h]	60
6	CBr_4 or Br_2 or I_2	<5	<5	60–80
7	Selectfluor®	—	<5	75
8		—	<2	34
9		<1	—	40

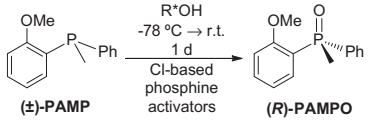
[a] Phosphine (0.11 mmol), alcohol (1.2 equiv), phosphine activator (1 equiv) at room temperature in toluene (0.11 M with respect to phosphine) unless noted otherwise, procedure as noted in the ESI.
[b] Determined by CSP-HPLC, (*R*)-enantiomer in excess in all cases, see ESI for details.
[c] As determined by ^{31}P NMR, see ESI.
[d] In benzene.
[e] Repeated with a 1 day delay between initial addition of HCE and subsequent addition of the alcohol.
[f] In carbon tetrachloride.
[g] At reflux.
[h] From Ref. 7a.

The lack of selectivity with bromine-based activators is also noteworthy.

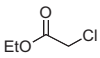
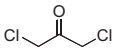
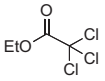
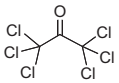
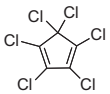
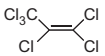
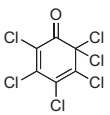
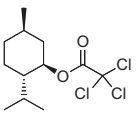
We then carried out a more systematic study of chlorine-based activators with **PAMP** at low temperature and the results are shown in Table 2.

Table 2 (entries 1–7) shows that at least three chlorines are required in the activator to induce both reactivity and stereoselectivity. That this is related to the stability of the anion produced on chlorine abstraction seems to be confirmed by the reasonable re-

Table 2
Results of asymmetric Appel reactions[a] using chlorine-based activators for **PAMP** with (−)-menthol (**1**)[b] and (−)-8-phenylmenthol (**2**)[c]



(±)-PAMP (*R*)-PAMPO

Entry	Phosphine activator	*R**OH = **1** ee[d] (%)	*R**OH = **2** ee[d] (%)	Yield range[e] (%)
1		0	0	12–19
2		0	0	10–13
3		0	0	12–17
4		1	1	40–59
5		30	42	61–70
6		25	—	73–77
7		50[f,g]	77[f]	90–100
8		48[g]	74	63–72
9		28	50	47–59
10		—	66[h]	88
11		25[h,i]	—	35–39

[a] Phosphine (0.11 mmol), alcohol (1.2 equiv), phosphine activator (1 equiv) at −78 °C in toluene (0.11 M with respect to phosphine) unless noted otherwise, rigorous drying of all materials; procedure as noted in the ESI.
[b] All (−)-menthol cases repeated with (+)-menthol with the same results—see ESI Table 1.
[c] Results also obtained for isomenthol, neomenthol and *tert*-butylcyclohexanol with similar conclusions—see ESI, Table 1.
[d] Determined by CSP-HPLC, (*R*)-enantiomer in excess in all cases see ESI for details.
[e] As determined by ^{31}P NMR, see ESI.
[f] From Ref. 7a.
[g] DAPS de = 50%.
[h] At room temperature.
[i] 25% ee also with (+)-menthol and 2% ee with isopropanol.

sults obtained with other systems that would result in stabilized carbanions (entries 8–10), with hexachlorocyclopentadiene (entry 8) being competitive with HCA.

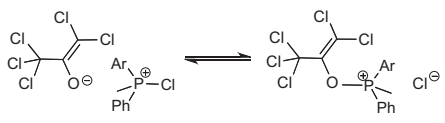
In the study with **PAMP**, we also briefly examined a chiral non-racemic activator, menthyl trichloroacetate[13] (Table 2, entry 11), hoping to detect any intervention of exchange of anions in the CPS, Scheme 2. On use of the chiral activator, no selectivity difference was detected between the enantiomers of menthol and almost no selectivity was obtained with an achiral alcohol (isopropanol) suggesting little influence of the enolate salt (Scheme 2). However, this is not conclusive because the actual selectivity obtained (25% ee) is the same as that obtained with the analogous achiral activator (entry 6), suggesting that the chirality is too far from the phosphorus centre to be influential.

Returning to the use of hexachloroacetone (HCA), now that we had established that multiple chlorinated ketones could act as activators, we were quite concerned that the pentachloroacetone (PCA) produced in the reaction (Scheme 1) might itself react with unreacted phosphine with different selectivity. With a synthesis of PCA in hand,[14] we were able to confirm that this was indeed the case because when it was used to activate **PTMP** at low temperature, it gave substantially lower selectivity (Table 3, entries 1 and 2), clearly signalling involvement of the CPS counter ion somehow in the selection process.

By now it had become clear that that we required an activator that did not give as by-product an alternative activator, and we wished to examine both hexachlorocyclopentadiene (HCCP) and hexachlorocyclohexadienone (HCCH). However, before doing so, we had to consider another aspect of the measurement of the selectivity, shown in Table 3. In our previous work,[7b,9] we found that the diastereomeric excess (de)[15] in the DAPS was the better measure of the stereoselective step of the reaction because the enantiomeric excess (ee) in the product oxides is subject to a selectivity eroding process that may occur during the Arbuzov collapse. Therefore, to study the selectivity, we devised a consistent procedure[16] to measure the de of DAPS and these figures are also included in Table 3. It can be seen that in the case of HCA and PCA, these figures are the same. However this is not true for either HCCP or HCCH (entries 3 and 4). The former gives the same de as HCA, but ultimately lower ee of the oxide, while the latter gives lower selectivity in general.

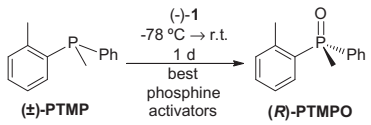
In seeking a solution to this problem, we turned to oxalyl chloride, which had proven useful for the generation of the CPS from phosphine oxide.[9] The latter reaction of oxalyl chloride was well known,[17] but its reaction with a phosphine has, remarkably, apparently never been studied. We therefore thought it was worth a test reaction and we found that, most conveniently and gratifyingly, oxalyl chloride reacted with the tertiary phosphine to produce the identical CPC.[18] On its employment in the asymmetric Appel process for **PTMP** (Table 3, entry 5), it gave a notably improved 88% de, compared to HCA. Although there was still some erosion of the selectivity, the isolation of the scalemic **PTMPO** was significantly easier in the absence of by-product.[19] One other advantage is that the phosphine starting material now does not have to be rigorously oxide-free because both will now be converted into CPC. Previously, contaminating racemic oxide resulted in a lowered ee of the product scalemic oxide.

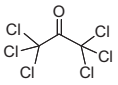
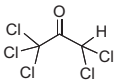
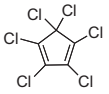
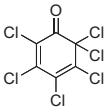
Together with our other work, this confirmation of the importance of the CPS counterion leads us towards the conclusion that



Scheme 2. Possible exchange of counterions in the CPS intermediate.

Table 3
Results of asymmetric Appel reactions[a] using the best phosphine activators for **PTMP** with (−)-menthol[b] with measurement of the diastereoselectivity of DAPS formation



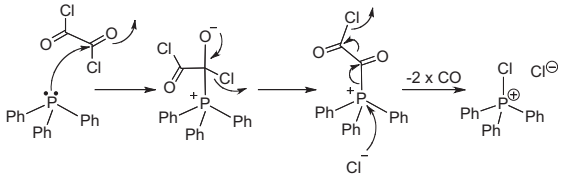
Entry	Phosphine activator	de[c] (%)	ee[d] (%)	Yield[e] (%)
1[f]		82[g]	82[g]	94
2		70	69	95
3[f]		82	75	79
4		76[h]	63[i]	94
5[j]		88	82	88

[a] Phosphine (0.11 mmol), alcohol (1.2 equiv), phosphine activator (1 equiv) at −78 °C in toluene (0.11 M with respect to phosphine), rigorous drying of all materials, procedure as noted in the ESI.
[b] All cases repeated with (+)-menthol with the same results, see ESI.Table 2.
[c] Determined as described in the ESI.
[d] Determined by CSP-HPLC, (*R*)-enantiomer in excess in all cases see ESI for details.
[e] As determined by ^{31}P NMR, see ESI.
[f] Other chiral alcohols gave comparable results, see ESI.Table 2.
[g] From Ref. 9.
[h] 20% Phosphine oxide also produced.
[i] 65% ee with (−)-8-phenylmenthol.
[j] See footnote 19 for reaction conditions.

the speed of counterion exchange, such as in Scheme 2, is significant for the selectivity, with chloride perhaps allowing faster exchange. We will report kinetic investigations of that possibility at a later date.

Finally, a mechanism for the newly discovered generation of chlorophosphonium chloride from oxalyl chloride and phosphine is proposed in Scheme 3. This is shown for the case of triphenylphosphine, the progress of which reaction we monitored by ^{31}P NMR spectroscopy (spectra in ESI).

This mechanism is only one of several possibilities.[20] Evidence supporting it includes: (i) the 1:1 stoichiometry; (ii) the appearance of transients in the ^{31}P NMR spectra arguing against direct formation via ethylene dione; (iii) the absence of phosphine oxide in the ^{31}P NMR spectra, and (iv) the presence of ketene traps has no effect on the reaction. We note that it is ironic that we started out seeking an alternative source of positive chlorine for our method



Scheme 3. Proposed mechanism for the generation of CPS from phosphine.

and have now settled on a phosphine activator that we propose does not work as an electrophilic chlorine source.

In conclusion, a systematic study of phosphine activators in the asymmetric Appel reaction has been carried out. Although HCA gave high selectivity, along with excellent yield, it has the disadvantage that its by-product can become involved in the process leading to erosion of selectivity. In searching for a replacement we discovered an interesting new reaction of oxalyl chloride with tertiary phosphine that allows us to run our process with higher selectivity, without complicating by-products and without the need for extensive purification of the starting material. We are now positioned to study the asymmetric Appel reaction to improve its scope and selectivity by screening various chiral non-racemic alcohols and phosphines, which will be the subject of future reports.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.044.

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19. Oxalyl chloride (0.17 mL, 2.0 mmol 2 equiv) was added dropwise at room temperature to a solution of **PTMP** (10.0 mL, 0.11 M, 1.0 mmol in dry toluene, 1 equiv), which was taken in a flame-dried degassed Young's tube. The reaction was allowed to stir for 30 min. ^{31}P NMR was taken to identify the intermediate which shows full conversion of phosphine oxide into chlorophosphonium salt (CPS) 70.5 ppm. Excess oxalyl chloride was completely removed through a dedicated cold trap connected to a Schlenk manifold for 60 min. Dry CH_2Cl_2 (10 mL) was added to dissolve CPS again and the mixture was cooled to −82 °C using an EtOAc/N_2 mixture and (−)-menthol (15 mL, 0.132 M, in dry toluene, 2.0 equiv) was added dropwise to the mixture over 30 min. The reaction was allowed to reach room temperature and was allowed to stir overnight at 0 °C. ^{31}P NMR was taken to identify the intermediate which shows full conversion of (CPS) into diastereomeric alkoxyphosphonium salts (DAPS) at 66.6 and 66.8 ppm. IPA (10 mL) was added dropwise to the mixture, which was then refluxed for 2 h. ^{31}P NMR shows full conversion from DAPS into phosphine oxide. The solvent was removed and column chromatography was carried out on silica gel (EtOAc:cyclohexane 50:50) to separate excess menthol, neomenthyl chloride and menthol oxalate followed by (MeOH—CH_2Cl_2) yielding (*R*)-**PTMPO** as a white solid; ^{31}P NMR 32.2 ppm (lit. 32.5 ppm) (0.22 g 88%). A portion of the sample (~3 mg) was dissolved in 2 mL of HPLC solvent (HPLC grade solvents purchased from Aldrich were used as supplied) and filtered through a PTFE syringe filter into a HPLC vial. High-performance liquid chromatography was performed on an Agilent Technologies 1200 series connected to a 6-column switcher. HPLC (CHIRALPAK® IA column, 80:20 heptane/EtOH, 1 mL/min): 81.4% ee R_t = 6.8 (*S*), 7.6 (*R*) min.
20. For example: via transient formation of ethylene dione or phosphine oxide/ketene. Some of these mechanisms are shown in the ESI along with the spectra resulting from ^{31}P NMR spectroscopic monitoring of the reaction mixture.