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Unexpected rapid *P*-stereomutation of phosphine oxides catalysed by chlorophosphonium salts†

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***P*-Stereomutation of phosphine oxides is extremely slow. We show that it is catalysed by chlorophosphonium salts (CPS) which can directly be formed in the system *in situ*. The racemization of phosphine oxides at ambient conditions catalysed by 1 mol% of CPS takes 1–2 hours and can be arrested by addition of a primary alcohol. The process probably proceeds via the development of oxodiphosphonium P–O–P species.**

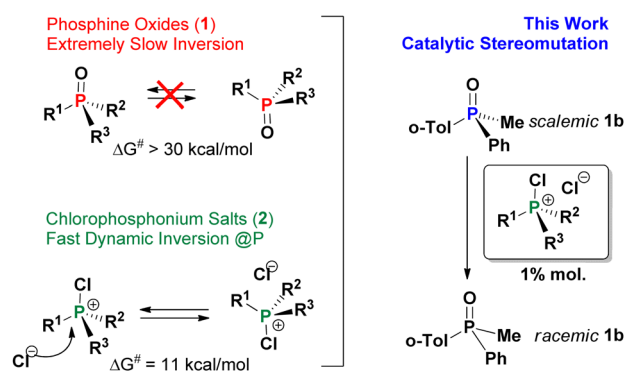
Enantioselectivity is considered as one of the key goals in synthetic chemistry and often requires careful adjustment of conditions. Stereoselective reactions and novel approaches to chiral materials attract immense attention from the organic,¹ inorganic² and supramolecular³ communities. Rapid stereomutation of an intermediate can be critical to many successful stereoselective strategies⁴ but must be avoided for the product as it leads to loss of chiral information. Although understanding of stereomutation helps to maintain high enantiopurity of the product (the “know thy enemy” principle) it is fair to say that stereomutation has rarely been studied systematically.

In most cases, tri- and tetracoordinate *P*-stereogenic compounds such as phosphines, their oxides (PO, **1**) and quaternary phosphonium salts (QPS) are configurationally very stable due to high activation barriers of typically *ca.* 30–40 kcal mol^{−1},⁵ making them valuable scaffolds for the design of stereoselective systems.⁶ Little is known however about potentially detrimental to these methodologies catalytic stereomutation of the *P*-center leading to racemisation. A few very recent reports indicate that such reactions, for example acid-catalysed and SET-facilitated processes, do occur under certain conditions.⁷ Relatively recently, we have shown that halophosphonium salts [R₃P-X]⁺X[−] (XPS, X = Cl, Br) which are the key dynamic

resolution intermediates in *P*-asymmetric Appel reaction⁸, undergo rapid epimerization characterized by low activation barriers *ca.* 10–12 kcal mol^{−1}.⁹ Having proposed a possible^{8b} mechanism for adverse parasitic effect of this epimerization in the asymmetric Appel process, its role remains to be fully understood. With that in mind, we undertook the present study and we show that dynamically racemic XPS species are very efficient catalysts of *P*-stereomutation of **1**.

Compounds **1** are renowned for their configurational stability, and are very different from the dynamically interconverting species **2** as shown in Scheme 1. However, it was not at all obvious that, as shown here, these halogenated species *e.g.* mixed arylalkylchlorophosphonium salts (CPS) are not innocent bystanders and can catalyze stereomutation of the otherwise configurationally stable PO **1** under mild ambient conditions.

In this work, we designed a set of experiments around the historically well documented structures, PAMPO (**1a**), PMTPO (**1b**) and PETPO (**1c**) and their respective CPS **2a–c** as displayed in Scheme 2. The PO **1a–c** can be prepared in high ee of either sense^{8b} and are characterized by excellent configurational stability in the absence of catalytic agents such that no discernable drift of ee can be observed in toluene at elevated temperature.



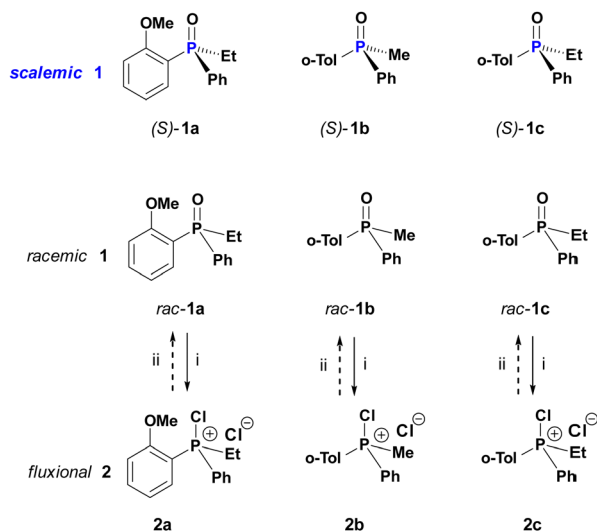
Scheme 1 Discovery of catalytic stereomutation of configurationally stable phosphine oxides (**1**) in the presence of dynamically racemic chlorophosphonium salts CPS (**2**).

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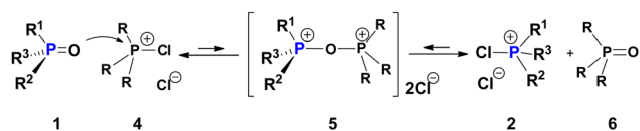


Scheme 2 Relationships between configurationally stable phosphine oxides **1** and dynamically racemic chlorophosphonium salts CPS (**2**). Reagents: (i) oxalyl chloride (**3**); (ii) excess ethanol.

In an initial landmark catalytic racemisation experiment, a sample of scalemic (*S*)-**1b** (93% ee) was treated with CPS **2a** generated from **1a** in DCM. Just after 1 h at room temperature, complete racemisation of the entire amount of PO **1b** was observed.

A possible interaction of a *P*-chiral **1** with a generic CPS **4** (Scheme 3) can result in oxodiphosphonium (POP) species **5** structurally analogous to the well-documented $[\text{Ph}_3\text{P}-\text{O}-\text{PPh}_3]^{2+}$ dication.¹⁰ Internal nucleophilic collapse of **5** can generate the dynamically racemic species **2** in the system. If CPS **2** itself is used in place of **4** (self-racemisation), this POP-equilibrium is energy-degenerate ($K_{\text{eq}} = 1$). Assuming that the POP-equilibrium is established quickly, addition of just 1 mol% of CPS **2**, for example, to enantiomerically pure (*S*)-**1** will result in 0.5 mol% of (*S*)-**1** being converted into the fluxional **2** which, in dynamic equilibrium with PO **1**, drives its complete catalytic racemisation.

However, since our hypothesis raised a number of questions, a dedicated study of CPS-catalysed racemisation was undertaken. We focused on stereomutation of PO **1b** in the presence of CPS **2b** (self-racemization) or a CPS **4** derived from another structure (cross-racemization) in which case the POP-equilibrium in Scheme 3 is not anymore degenerate. The impact of the loading, temperature, solvent and CPS structure, on the racemisation of PO **1b** was studied. Mechanistically, the



Scheme 3 Plausible "POP-equilibrium": chiral PO **1** (three different R-groups attached) and generic CPS **4** generate the dynamically racemic CPS **2** via a minor P–O–P species **5**. This explains racemisation of *P*-chiral PO **1**.

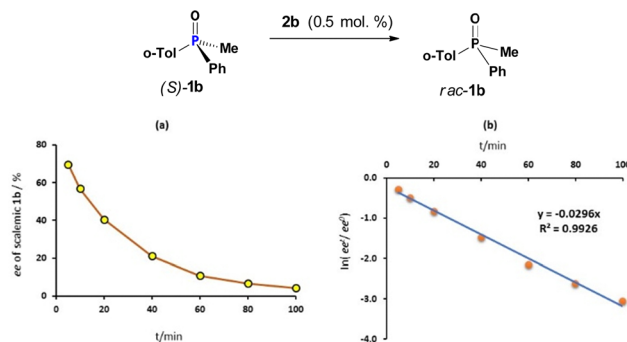


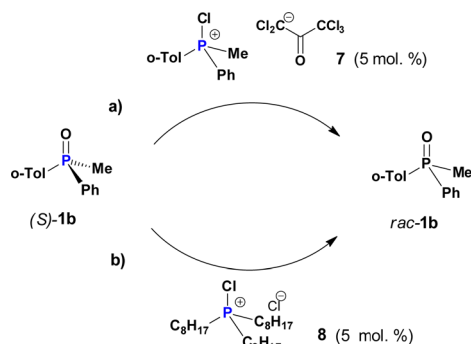
Fig. 1 Catalytic racemisation of (*S*)-**1b**: (a) kinetic plot (0.5 mol% of **2b**); (b) the corresponding log plot.

interconversion of the dynamically racemising CPS and the corresponding phosphine oxide was established *via* dynamic 2D EXSY NMR experiments. The results are discussed based on the proposed mechanism involving the formation of the POP species **5**.

In a first set of experiments, the amount of dynamically racemising CPS **2b** was controlled by the amount of oxalyl chloride **3** added to the solution of scalemic (*S*)-**1b** (93% ee) in dry DCM under nitrogen atmosphere. The reaction mixture was stirred at ambient temperature and, at time intervals, aliquots were taken. The racemisation was arrested by adding ethanol which instantly converts catalytically active species **2b** into *rac*-**1b** and analyzed by HPLC. Fig. 1(a) and (b) correspondingly show the ee values of PO **1b** and the log plot for this first-order racemisation in the presence of 0.5 mol % of CPS **2b** generated *in situ*. It can be seen that the half-life time for this pseudo-first order process is ~23 min which corresponds to a rate constant $k = 4.9 \times 10^{-4} \text{ s}^{-1}$. A two-fold increase of rate, $k = 1.0 \times 10^{-3} \text{ s}^{-1}$ in the presence of double amount of **2b**, 1 mol%, indicates a first-order process in the catalyst (Tables S1–S3, ESI†). The rate constant changes rapidly with the temperature, it is *ca.* 7 times lower at -19.3°C (Table S6, ESI†). The rate of racemisation of PO **1b** is drastically lower about 150 times in the less polar toluene compared to DCM (Table S7, ESI†). Although it is recognized that CPS structures occur in their pentacoordinate neutral form in toluene,¹¹ the presence of excess **1b** acts possibly as a highly polar additive such that dichloride **2b** may exist partially in its tetrahedral ionic form, amenable to the POP equilibrium with species **5** (Scheme 3).

Importantly, not only CPS **2** but also other related species can catalyse the racemisation of PO **1b**. For example, we have earlier shown¹² that *P*-asymmetric Appel reaction can conveniently be applied to the corresponding phosphines by using a chlorinating agent, and thus racemisation of PO **1b** under similar conditions was studied. First, chlorinated **7** (section 2.6, ESI†) carrying a pentachloroacetate enol-type anion was generated from the parent phosphine. Racemisation of PO **1b** in the presence of 5 mol% of **7** (Scheme 4a) was *ca.* 8 times slower as compared to CPS **2b** (Table S8, ESI†). The reason is that the polychlorinated counterion has a lower nucleophilicity than the chloride ion and a larger size that slows down the dynamics of POP-equilibrium.





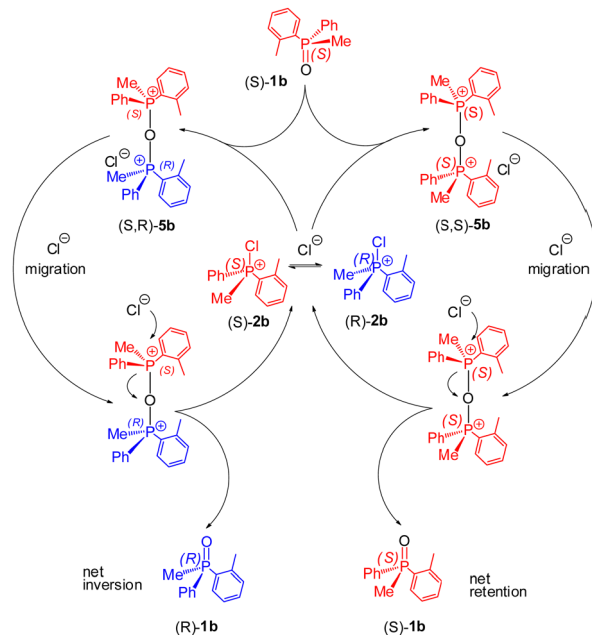
Scheme 4 Slow racemisation of *P*-chiral **1b** induced by: (a) mixed-group species **7**; (b) tri-*n*-alkyl CPS **8**.

Having demonstrated that self-racemisation of PO **1b** is efficiently catalyzed by its own CPS **2b** we questioned the possibility of a cross-racemisation by using another CPS (e.g. **2a**, *vide supra*). As an example, we chose CPS **8** (Scheme 4b) comprising only *n*-octyl substituents. When **8** (5 mol%) was introduced, it was found that catalytic racemisation of PO **1b** occurs very slowly $k = 1.2 \times 10^{-6} \text{ s}^{-1}$ which is about 3×10^3 times lower than for self-racemisation using CPS **2b** under equivalent conditions.

A possible explanation of this effect is linked to the relative P–O and P–Cl bond strength in different types of phosphine oxides and CPS and the position of the POP-equilibrium. Recently, our efforts to study the relative strength of P–Cl bonds in CPS demonstrated that the strength of this bond increases by 3–4 kcal mol^{−1} per addition of an alkyl group attached to phosphorus atom.¹³ This effect, very significantly reduces the amount of mixed aryl-alkyl CPS species **2** available *via* the POP-equilibrium with a generic CPS **4** shown in Scheme 3. We estimate that in the case of CPS **8** used as catalyst the concentration of fluxional chiral CPS **2b** present is reduced by a factor of 10⁴ which can explain much slower cross-racemisation in this system.

Our further experiments were designed to detect the development of POP species under racemisation conditions in a system containing higher concentrations of *rac*-**1b** and the fluxional **2b** (~0.1 M each). The ³¹P NMR spectrum showed a signal, 0.4% intensity, at 80.7 ppm indicating possibly the new POP species **5b**. This evidence was quite significant as it is consistent with the proposed catalytic cycle for rapid stereomutation of **1b** in the presence of dynamically racemising CPS **2b** *via* POP-species **5b** as depicted in Scheme 5. We postulate that either enantiomer of the dynamically racemising **2b** can be attacked by (*S*)-**1b** with close to equal probability. The resulting diastereomeric POP species **5b** undergo rapid ion migration followed by reversal of the nucleophilic attack. The outcome is formation of near-equal amounts of (*S*)-**1b** and (*R*)-**1b** and hence racemisation of scalemic (*S*)-**1b**.

To observe the dynamics of proposed POP species **5b** a ¹H-¹H 2D EXSY NMR experiment¹⁴ was carried out at 25 °C at 600 MHz with a mixing time of 0.100 s but no cross peak of **5b** could be identified due to its relatively low concentration in the system.



Scheme 5 Catalytic stereomutation pathways: nucleophilic attack of *P*-chiral (*S*)-**1b** leads to diastereomeric POP species (*S,S*)-**5b** and (*S,R*)-**5b** which upon anion migration give both enantiomers of PO **1b**.

Significantly, the ¹H-¹H 2D EXSY experiment in the system containing equimolar amounts (50 mol% each) of *rac*-**1b** and dynamically racemic **2b** clearly showed exchange cross-peaks which are an unequivocal evidence of interconversion **2b** ↔ **1b** (Fig. 2). An analysis of the cross peak corresponding to the methyl group (CH₃-P) gave a rate constant $k_{\text{ex}} = 8.0 \times 10^{-2} \text{ s}^{-1}$ at 25 °C. This result is in very good agreement with the earlier observed racemisation rate constant $k_r = 1.0 \times 10^{-3} \text{ s}^{-1}$ (20.5 °C, quoted above) in the system containing only of 1 mol% of **2b**. Clearly, the same set of dynamic stereomutation processes, described in Scheme 5, is responsible for slow, on the NMR-timescale, interconversion between **2b** and **1b**. This explains the phenomenon of racemisation of **1b** in the presence of catalytic amounts of CPS in this study (**2a**, **2b**, **7** and **8**).

In short, racemization of chiral PO **1** is a very slow process characterized by high activation barriers. Rapid stereomutation was directly observed for the first time due to an equilibrium involving dynamic fluxional CPS species **2**. The racemisation can be conveniently stopped at any moment by adding primary alcohols. The key factors affecting racemisation rate are the structure and the loading of catalyst **2**, reaction temperature, the counter ion and the solvent. It was found that achiral trialkyl-CPS can also catalyse racemisation of **1** but at a lower rate. A mechanism evoked here implies a catalytic cycle *via* development of the oxodiphosphonium POP species **5**. This mechanistic proposal involves a Cl-anion migration followed by nucleophilic inversion of the *P*-centre. The interconversion of a CPS and a phosphine oxide has been directly detected by using the 2D EXSY NMR technique. These findings are consistent with the potential negative effect of CPS in our asymmetric Apple process and its involvement is critical for the asymmetric



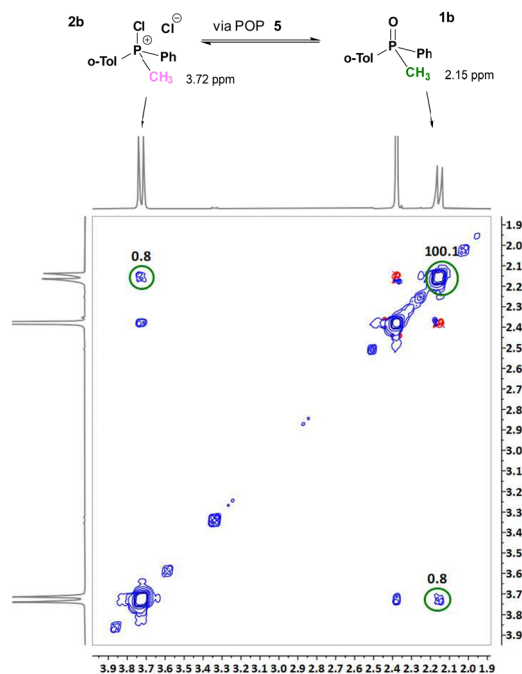


Fig. 2 ^1H - ^1H 2D EXSY observation of dynamic interconversion between **1b** and **2b**: cross peak of the CH_3 group is observed at δ 2.15/3.72 ppm ($T_m = 0.1$ s).

reverse Appel reaction^{8b} too: a slow reaction of CPS with chiral auxiliary alcohol provides a window of opportunity for scalemic phosphine oxide to interact with the CPS which unavoidably leads to decreased ee of the resulting *P*-chiral product. From a broader perspective, this study has shown that the presence of minor by-products or intermediates can adversely affect the outcome of a stereoselective process.

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Conflicts of interest

There are no conflicts to declare.

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