

Crystallization-induced Deracemisation of P-stereogenic Phosphine Oxides

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Phosphine oxides play an important role as precursors for chiral phosphine ligands as well as powerful ligands themselves. Chirality either resides in the backbone of the ligand or at phosphorus (P-chiral or P-stereogenic ligands). Although transition metal-based asymmetric catalysis with phosphine ligands started with P-stereogenic ligands (the monodentate ligand CAMP and its dimer DiPAMP), ligands with backbone chirality are considerably more accessible and turned up subsequently in numerous variations. Nevertheless, the use of P-stereogenic ligands currently faces a remarkable revival as illustrated by the advent of the POP, BIBOP, and BigFoot ligands, among others, which frequently surpass backbone-chiral ligands in enantioselectivity and turnover frequency.¹

As synthetic accessibility of enantiopure P-stereogenic compounds is a fundamental challenge, considerable efforts have been devoted to develop practical strategies. Of the several approaches, the Juge-Stephan method based on the addition of organolithium reagents to ephedrine phosphine-boranes, and the addition of organometallic reagents to diastereomerically pure menthol phosphinates, obtained via resolution, are mostly used.

We have developed an alternative approach that relies on the use of air and moisture stable phosphine oxides. Secondary phosphine oxides can undergo radical-mediated racemization. Combined with a resolution,² this has been shaped into a highly efficient crystallization induced deracemisation.³ A fundamental aspect of this process is that the efficiency of the resolution is less critical, which contributes significantly to the applicability of the method. The so-obtained enantiopure phosphine oxide can be used in a crystallization-induced diastereoselective aldehyde addition, thereby producing the corresponding enantio- and diastereomerically pure hydroxyphosphine oxides in excellent yields.

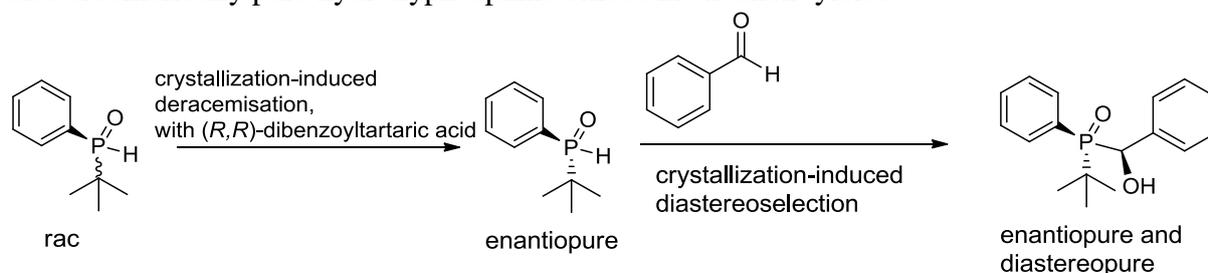


Figure 1. Crystallization-induced deracemisation of a secondary phosphine oxide with a resolving agent is followed by a crystallization-induced diastereoselective addition to an aldehyde.

The developed reactions are robust, scalable, and are currently developed for a general route to enantiopure phosphine ligands.

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