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Article

Isodesmic metathesis chemistry - a novel way to recycle P^(V)

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SUMMARY

Owing to the thermodynamic inertness of the P=O bond, the reduction of phosphine oxides to phosphines is notoriously challenging. In this preview, we highlight the recent findings of Jing *et al.* describing a novel synthetic pathway for phosphine oxide reduction employing isodesmic reactions without stoichiometric activators emphasized with a thermodynamic and mechanistic investigation.

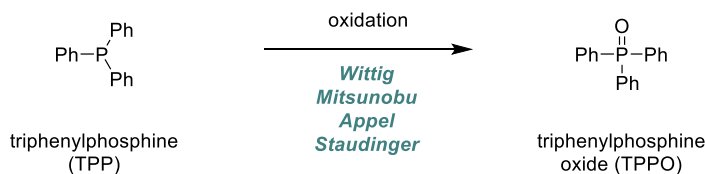
Triphenylphosphine (Ph₃P, TPP) plays a crucial role in various important transformations such as in Wittig, Mitsunobu, Appel, or Staudinger reactions (Scheme 1a).¹ In the traditional course of these reactions, triphenylphosphine oxide (TPPO) is produced as a stable and stoichiometric by-product leading to a significant amount of troublesome waste. Thus, a facile methodology for reducing TPPO to TPP has been in great demand from a standpoint of minimizing waste and recycling the phosphine resources. However, P=O bond dissociation energies exceed 120 kcal mol⁻¹ meaning these bonds are thermodynamically inert which makes their reduction challenging. Indeed, in the established reactions described above, and recently reported transformations, the formation of P=O is a thermodynamic driving force.^{1,2} Thus, the isolation of TPPO and its selective reduction to TPP is a challenging task.^{1,3} Previous approaches rely on the use of harsh reaction conditions to activate P=O bonds with Lewis or Brønsted acids (e.g. Cu(OTf)₂, CeCl₃, B(C₆F₅)₃)^{4,5} or stoichiometric metal hydrides (e.g., LiAlH₄, HSiCl₃, and DIBAL-H)⁴ (Scheme 1b) along with electrochemical reduction techniques *via* Lewis acid activation with borate or aluminium cations.^{6,7} However, in some cases, an undesired C–P bond cleavage also occurs as a side reaction. For Mitsunobu reactions, a modified phosphine oxide catalyst has been reported allowing a redox-neutral conversion.⁸ However, a general process for the reduction of phosphine oxides under mild conditions in the absence of stoichiometric activating reagents is still elusive.

In a recent publication in the *Journal of the American Chemical Society*,⁹ Jing and co-workers reported an innovative catalytic approach to the simple and effective deoxygenation of phosphine oxides *via* a series of isodesmic P=O and P–Br metathesis reactions. Isodesmic reactions are transformations where the type of bond generated in the product is comparable the one broken in the reactant.¹⁰ The strong P=O bond in the phosphine oxide reactant is broken by a thermodynamic driving force that was counteracted by the simultaneous formation of a new P=O bond. Notably, the thermoneutrality and reversibility of an isodesmic reaction are advantageous traits for the development of an efficient catalyst. The P=O bond dissociation energies for alkyl phosphines are considerably larger than for aryl phosphines. Therefore, an oxygen transfer from arylphosphine oxides to alkylphosphines is energetically favourable. Because cyclic alkylphosphine oxides were considered to be easily reduced by silanes, it was hypothesized that this reaction could terminate the deoxygenation of arylphosphine oxides. However, initial attempts were unsuccessful due to the polarity mismatch between the electron-rich O atom of the polarized P=O and the catalyst's electron-rich P atom. Halogenation of the catalyst to an electron-deficient phosphonium cation (P_{cat}⁺–Br[–]) then facilitated the oxygen-transfer *via* an isodesmic P=O and P–Br bond metathesis as shown in Scheme 1d. A quantitative deoxygenation of TPPO occurred upon addition of a substoichiometric amount of diethyl 2-bromomalonate as a brominating reagent (Br-source) to the reaction system containing 5 mol% of catalyst P_{cat} (Scheme 1d) using 1,2-dichloroethane as a solvent at room temperature.

Mechanistic investigations of the deoxygenation process through *in situ* ³¹P NMR spectroscopic studies revealed that P_{cat}⁺–Br[–] is the catalytically active species. Kinetic studies were also performed which suggest that the reaction process initially endured an induction

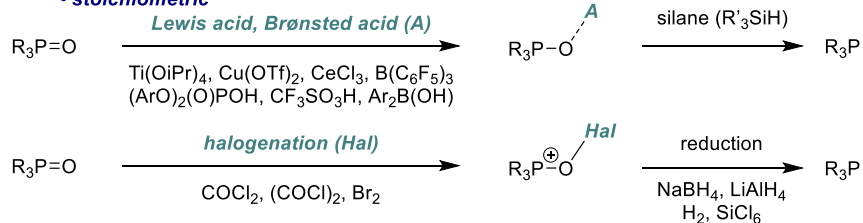
period, where subsequently TPP is generated with the synchronous consumption of TPPO, indicating a first-order dependency on TPPO.

(A) Phosphine oxide generation as by-products in important reactions

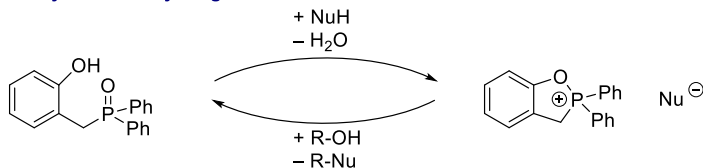


(B) Strategies for phosphine oxide reduction

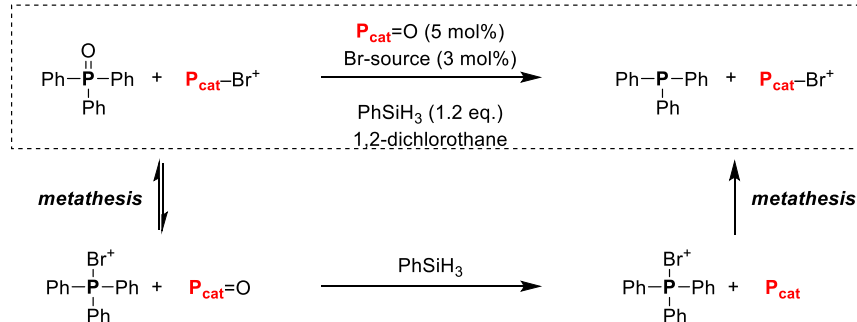
• stoichiometric



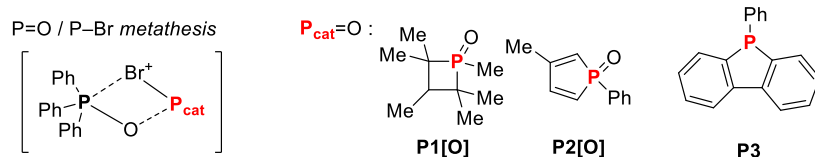
• catalytic redox-cycling



(C) This work: Isodesmic phosphine oxide reduction



(D) Catalysts and intermediates



Scheme 1. Reported pathways for phosphine oxide reduction and design of the reaction for the isodesmic metathesis. A) P^{III} to P^{V} in stoichiometric reactions. B) Strategies for phosphine oxide reduction. C) Jing and co-workers work on isodesmic phosphine reduction. D) Catalysts and intermediates in Jing's study.

An increased PhSiH_3 concentration reduced the induction period of the reaction without affecting the reaction rate, signifying a zero-order dependency of PhSiH_3 . The reaction rate is proportional to the $[\text{P1}-\text{Br}]^+\text{Br}^-$ concentration, revealing a first-order catalyst dependency. Consequently, $\text{Ph}_3\text{P}=\text{O}$ and $\text{P}_{\text{cat}}-\text{Br}^+$ are engaged in the rate-limiting step, while the reduction of $\text{P}_{\text{cat}}=\text{O}$ with PhSiH_3 is rapid. Further to emphasize their hypothesis of a protic acid-governed reduction of $\text{P}_{\text{cat}}=\text{O}$, the authors used triethylammonium dicyano(4-nitrophenyl)methanide ($\text{pK}_a = 11.6$ in MeCN) as an indicator, which regulated the interaction of $\text{Ph}_3\text{P}-\text{Br}^+$ with PhSiH_3 .

as the reaction mixture was sufficiently acidic to protonate. In conclusion, the $\text{P}_{\text{cat}}=\text{O}$ reduction is a slow step in the early stage of the reaction. Once the reaction has commenced, trace protic acid promotes the $\text{P}_{\text{cat}}=\text{O}$ reduction.

Moreover, the loading of diethyl 2-bromomalonate demonstrated an unforeseen inhibitory response as it increased the O=PPh_3 intake, but hindered TPP production revealing that the bromophosphonium cation ($\text{Ph}_3\text{P}-\text{Br}^+$) is generated as an intermediate between O=PPh_3 and PPh_3 through $\text{P}=\text{O}$ and $\text{P}-\text{Br}$ bond metathesis. PhSiH_3 quickly converted the newly formed catalyst oxide ($\text{P}_{\text{cat}}=\text{O}$) to phosphine (P_{cat}). As alkylphosphines are more nucleophilic than arylphosphines, P_{cat} removes a bromonium cation from $\text{Ph}_3\text{P}-\text{Br}^+$ in the second isodesmic reaction to enhance the product yield. In light of this observation, diethyl 2-bromomalonate has the potential of brominating P_{cat} to form $\text{P}_{\text{cat}}-\text{Br}^+$, but an excess of diethyl 2-bromomalonate restricted the PPh_3 synthesis by decreasing the P_{cat} concentration. Additionally, a Hammett analysis revealed that phosphine oxides with electron-donating groups react faster than those with electron-withdrawing groups, and a positive charge developed over the phosphorus atoms aided in $\text{Ph}_3\text{P}-\text{Br}^+$ cation formation. The thermodynamic driving force (ΔG°) of the isodesmic processes revealed that oxygen atom transfer from $\text{Ph}_3\text{P}=\text{O}$ to **[P2]** was thermodynamically favorable with $-3.1 \text{ kcal mol}^{-1}$. In the absence of diethyl 2-bromomalonate, the reduction failed due to the kinetic infeasibility between two electron-rich partners with mismatched polarities. In addition, isodesmic $\text{P}=\text{O}$ and $\text{P}-\text{Br}$ bond metathesis between $\text{Ph}_3\text{P}=\text{O}$ and **[P2]**- Br^+ were endergonic with $+3.2 \text{ kcal mol}^{-1}$.

In conclusion, Jing and co-workers have developed a novel phosphine oxide reduction pathway under very mild reaction conditions employing isodesmic metathesis chemistry. The $\text{P}^{\text{III}}/\text{P}=\text{O}$ redox sequences were governed by cyclic organophosphorus catalyst together with the terminal reductant PhSiH_3 . This catalytic process has a large substrate scope, excellent reactivities, and mild reaction conditions without the need of a stoichiometric activator. Thermodynamic and mechanistic investigations demonstrated a dual synergistic role of the catalyst and it is believed that this catalytic isodesmic strategy will open up novel reaction pathways for mild reduction of pnictogens.

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