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A Biphilic Phosphetane Catalyzes *N-N* Bond Forming Cadogan Heterocyclization via $P^{III}/P^V=O$ Redox Cycling

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Abstract

A small ring phosphacycle (1,2,2,3,4,4-hexamethylphosphetane) is found to catalyze deoxygenative *N-N* bond-forming Cadogan heterocyclization of *o*-nitrobenzaldehydes and related substrates in the presence of hydrosilane terminal reductant. The reaction provides a chemoselective catalytic synthesis of 2*H*-indazoles, 2*H*-benzotriazoles, and related fused heterocyclic systems with good functional group compatibility. On the basis of both stoichiometric and catalytic mechanistic experiments, the reaction is proposed to proceed via catalytic $P^{III}/P^V=O$ cycling, where DFT modelling suggests a turnover limiting (3+1) cheletropic addition between the phosphetane catalyst and nitroarene substrate. Strain/distortion analysis of the (3+1) transition structure highlights the controlling role of frontier orbital effects underpinning the catalytic performance of the phosphetane.

Graphical Abstract

Tricoordinate phosphorus reagents are versatile *O*-atom acceptors,¹ and the conversion $P^{III} \rightarrow P^V=O$ drives numerous valuable synthetic transformations.^{2–4} Despite great utility, the inefficient generation of stoichiometric phosphine oxide waste inherent to these methods is

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Notes

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Supporting Information

Synthetic procedures, ¹H, ¹³C, ¹⁹F and ³¹P NMR spectra, computational details and cartesian coordinates. The Supporting Information is available free of charge on the ACS Publications website.

regarded as a key limitation. In recent years, though, several new catalytic methods involving cycling through phosphine oxide intermediates have emerged,⁵ both in redox-neutral^{6–7} and redox-driven modes.^{8–10} As part of a program aimed at developing designer main group compounds as broadly useful biphilic¹¹ catalysts in organic synthesis,¹² we recently reported the use of phosphetanes as *O*-atom transfer catalysts operating via P^{III}/P^V=O redox cycling.^{12c} In this Communication, we advance this biphilic catalysis concept by describing a catalytic *N-N* bond forming heterocyclization enabled by phosphetane-catalyzed reductive *O*-atom transfer. Beyond broadening the repertoire of phosphine oxide redox-catalyzed organic transformations, this study documents a dominant electronic basis for the superior performance of phosphetane catalysts that provides a framework for future targeted design of geometrically deformed main group compounds as biphilic catalysts.

Cadogan¹³ and Sundberg¹⁴ have shown that phosphine-mediated exhaustive deoxygenation of *o*-functionalized nitrobenzene derivatives drives phenylnitrene-like azacyclizations. Most commonly, these transformations employ superstoichiometric amounts of phosphorus-based reagents at elevated temperatures; the standard Cadogan protocol calls for reaction in neat refluxing triethylphosphite (bp 156 °C), although milder conditions have been reported in some cases.¹⁵ We questioned whether inherently nontrigonal biphilic phosphines, which colocalize donor and acceptor behavior at P, might facilitate *O*-atom transfer from the nitro substrate under milder conditions and in a manner conducive to P^{III}/P^V=O redox cycling (Figure 1).

Starting from our reported conditions for deoxygenative carbonyl functionalization as a point of departure, treatment of **1** with substoichiometric quantities of aminophosphetane *P*-oxide **3**·[O] (15 mol%) and phenylsilane (2 equiv.) in PhMe at 100 °C was indeed found to afford indazole **2**, albeit in modest yield (Table 1, entry 1). Further optimization studies converged on the simple 1,2,2,3,4,4-hexamethylphosphetane *P*-oxide **5**·[O] as the optimal catalyst for this transformation (see SI for details); in the event, phosphetane *P*-oxide **5**·[O] is found to catalyze deoxygenative heterocyclization delivering product **2** in 83% GC yield within 3 h at 100 °C (entry 3). Neither phospholane-based (**6**·[O] and **7**·[O], entries 4, 5) nor acyclic (**8**·[O], entry 6) phosphorus precatalysts exhibit similar catalytic reactivity under otherwise identical conditions. Control experiments (entries 7 and 8) confirm that no reaction is observed in the absence of either **5**·[O] or terminal reductant PhSiH₃; the transformation is demonstrably under catalyst control. Consistent with the notion of P^{III}/P^V=O redox cycling, the use of tricoordinate (σ³-P) precatalyst 1,2,2,3,4,4-hexamethylphosphetane **5** affords indazole **2** with qualitatively similar results as **5**·[O] (entry 9). That said, the ease with which phosphine oxide **5**·[O] –an air stable solid– is both handled on laboratory scale and reduced in situ to **5**¹⁶ recommended its use as precatalyst in subsequent studies.

Results of our studies into the scope of this catalytic transformation are collected in Table 2. With respect to *N*-substitution, aliphatic substituents (Table 2A) are well tolerated including 1° (**9**), 2° (**10**), and 3° (**11**) moieties, and basic nitrogen functionality may be incorporated without incident (compare **12** and **13**). Likewise, aromatic substrates of diverse substitution (Table 2B) are suitable substrates; halogenated (**17**–**19**), electron-rich (**20**, **21**), electron-poor (**23**, **25**), unsaturated (**24**) and sterically demanding (**26**) *N*-aryl substituted substrates all

undergo smooth catalytic indazole formation. Polyheterocyclic products (**30**, **31**) may be similarly prepared. Free hydroxyl moieties do not inhibit deoxygenative heterocyclization (**22**, **32**), although such substrates may undergo in situ silylation by the PhSiH_3 reductant; desilylative workup ensures recovery of the free OH group. Challenging substrates for the current method include, unsurprisingly, those with multiple nitro moieties (Table 2C, 33); evidently the catalyst does not selectively recognize the *o*-imino nitro moiety. However, a range of other reducible functionality including nitriles (**23**), amides (**29**), and esters (**36**) are all carried through the deoxygenative cyclization reaction without incident.

The reaction is similarly amenable to non-benzaldimine substrates, permitting the synthesis of diverse heterocyclic structures through catalytic *N-N* bond formation (Table 2D,E). For instance, deoxygenative heterocyclization of 2-(2-pyridyl)nitrobenzene delivers the fused polyheterocyclic pyrido[1,2-*b*]indazole (**39**) in near quantitative yield under standard catalytic conditions within 4 h. Relatedly, indazolodihydroimidazoles (**40**), -tetrahydropyrimidines (**41**), and -dihydrooxazoles (**42**) are accessible under standard conditions. Stereochemistry adjacent to the reaction centers is retained upon cyclization (**42**). Beyond indazole synthesis, the preparation of *N*-aryl 2*H*-benzotriazoles (**43–45**) is achieved by deoxygenative heterocyclization of the corresponding substituted *o*-nitroazobenzene.

In situ spectral monitoring of catalytic reactions provides information regarding both the mechanistic course of the transformation and speciation of active phosphorus compounds during catalysis. ^1H NMR spectra (400 MHz, toluene- d_8 , 100 °C) of a standard catalytic transformation (1 equiv. of **1**, 15 mol% of **5**·[O], 2 equiv. of PhSiH_3 , 1M in C_7D_8) show the appearance of product indazole **2** over the course of ca. 1.5 h at the expense of starting imine substrate **1**; no long-lived intermediates are observed by ^1H NMR spectroscopy. Under identical conditions, ^{31}P NMR spectra show the rapid conversion of **5**·[O] (δ 53.2 ppm) to an epimeric mixture of the corresponding phosphetane **5** (δ 32.4 ppm (major, *anti*); δ 18.9 ppm (minor, *syn*)), which persists in solution until the reaction is complete (see SI). From these data, we infer that **5** represents the catalytic resting state, with the initial deoxygenation of substrate **1** as the turnover limiting step.¹⁷ Regrettably, direct kinetic observation of reaction steps following initial deoxygenation is therefore precluded; presumably, though, the nitroso derivative formed by deoxygenation of **1** is an obligate intermediate that proceeds on to observed product in a series of fast following steps.¹⁸

Under stoichiometric pseudo-first order conditions with excess phosphine reagent, we find that consumption of substrate **1** is markedly faster with phosphetane **5** than *n* Bu_3P **8** ($k_{\text{rel}} \approx 8$, see SI Figure S2); phosphetane **5** is evidently superior to acyclic **8** for Cadogan cyclization. In an effort to understand the origin of this rate difference, we undertook DFT modelling studies (Figure 2). Direct *O*-atom transfer from nitro-methane to phosphetane **5'** and trimethylphosphine **8'** (via $\text{TS}_1^{5'}$ and $\text{TS}_1^{8'}$, respectively) is found to be high in energy. Instead, a stepwise mechanism proceeding through pentacoordinate azadioxaphosphetanes **I5'** and **I8'** is found at lower energies. The rate-controlling transition structure along this pathway (i.e. $\text{TS}_2^{5'}$ and $\text{TS}_2^{8'}$) involves a (3+1) cheletropic addition^{19,20} of MeNO_2 to **5'** and **8'**, respectively. Subsequent decomposition of **I5'** and **I8'** via retro-(2+2) fragmentation

($\text{TS}_2^{5'}$ and $\text{TS}_2^{8'}$) then follows with low barrier. This (3+1)/retro-(2+2) pathway is mechanistically analogous and orbitally equivalent to known reactivity of phosphines(-ites) with O_3 .²⁰

To understand further the superiority of the phosphetane with respect to deoxygenation, the (3+1) transition structures $\text{TS}_2^{5'}$ and $\text{TS}_2^{8'}$ were analyzed within the distortion/interaction model²¹ (Figure 3). Despite the presence of the small ring in $5'$, the destabilizing distortion energy ($E_d^\ddagger$) within transition structures $\text{TS}_2^{5'}$ and $\text{TS}_2^{8'}$ is nearly identical (39.2 vs. 38.8 kcal/mol, respectively), being driven to an over-whelming extent by pyramidalization of the nitro substrate, not by geometric reorganization about phosphorus. By consequence, the lower overall energy of $\text{TS}_2^{5'}$ arises from a significantly larger stabilizing interaction energy ($E_I^\ddagger$) for phosphetane $5'$ (−17.5 kcal/mol) than $\text{Me}_3\text{P } 8'$ (−9.7 kcal/mol). The inference from this analysis is that the differential performance of the small-ring phosphetane and trimethylphosphine – both of which compositionally are simple trialkylphosphines – is driven primarily by electronic (orbital) as opposed to enthalpic (ring strain) effects.

The difference in interaction energies for the (3+1) addition transition structures can be rationalized by frontier orbital inspection. Figure 4 depicts the Kohn-Sham HOMO and LUMO of each reactant distorted to the transition state structure. Whereas both phosphetane and trimethylphosphine exhibit HOMOs (nonbonding lone pair) of nearly identical energy (−6.95 eV), LUMO($5'$) resides ca. 0.8 eV lower in energy than LUMO($8'$). In effect, the geometric constraint enforced by the 4-membered ring of the phosphetane $5'$ results in a marked lowering of the LUMO that preferentially permits synergistic interactions of $\text{HOMO}(5') \rightarrow \text{LUMO}(\text{MeNO}_2)$ and $\text{HOMO}(\text{MeNO}_2) \rightarrow \text{LUMO}(5')$ in a $[\pi 4_s + \omega 2_s]$ fashion.²² We note that the low frontier orbital energy gap of phosphetanes has previously been invoked by Chesnut and Quin to rationalize nonmonotonic chemical shift anisotropy trends in phosphacycloalkanes.²³ Relatedly, Hudson²⁴ and Westheimer²⁵ have noted the extent to which ring constraint increases electrophilic character at phosphorus. The importance of orbital effects in reactions of strained ring systems has been noted by Hoz.²⁶

In summary, we have found that a readily accessible²⁷ phosphetane is a suitable catalyst for the Cadogan indazole synthesis. The method provides a simple phosphacatalytic approach to a valuable *N*–*N* bond forming mode that has previously been accomplished via (super)stoichiometric reagent chemistry,^{13,28} transition metal catalysis,²⁹ or alternative high energy azide substrates.³⁰ Whereas previous studies involving $\text{P}^{\text{III}}/\text{P}^{\text{V}}=\text{O}$ redox cycling have focused primarily on ring strain arguments underpinning catalytic turnover of phosphine oxides by silane reductants, the results above suggest a dominant electronic component to the overall biphilic function of the phosphetane catalyst. Work continues in an effort to establish further the biphilic reactivity of phosphetanes as generalized platforms for catalytic reductive *O*-atom transfer.

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Figure 1. Phosphine biphilicity and *N-N* bond forming Cadogan heterocyclization via $\text{P}^{\text{III}}/\text{P}^{\text{V}}=\text{O}$ -catalyzed reductive *O*-atom transfer.

Figure 2.
DFT mechanisms of nitro deoxygenation (M06-2X/6-311++g(d,p)). Relative electronic energies in kcal/mol with unscaled zero-point correction.

Figure 3.

Transition structures and distortion/interaction analyses for (3+1)-transition states (M06-2X/6-311++g(d,p)). (A) Phosphetane $\text{TS}_2^{5'}$ (B) $\text{Me}_3\text{P TS}_2^{8'}$. Phosphine distortion energy ($E_{dp}^\ddagger$) in green, nitro-methane distortion energy ($E_{dN}^\ddagger$) in blue, fragment interaction energy ($E_i^\ddagger$) in red, activation energy ($E^\ddagger$) in black. All energies in kcal/mol without zero-point correction.

Figure 4. Frontier Kohn-Sham orbital plots and orbital energies for reactant fragments deformed to transition state structures (M06-2X/6-31g(d)).

Table 1Phosphacycles as catalysts for deoxygenative heterocyclization of *o*-nitrobenzalimine 1.^a

Entry	$\text{R}_3\text{P}=\text{O}$	Silane	Conversion (%)	Yield (%)
1	3-[O]	PhSiH_3	49	20
2	4-[O]	PhSiH_3	45	31
3	5-[O]	PhSiH_3	99	83
4	6-[O]	PhSiH_3	21	1
5	7-[O]	PhSiH_3	96	24
6	8-[O]	PhSiH_3	21	6
7	none	PhSiH_3	14	0
8	5-[O]	none	12	0
9	5	PhSiH_3	99	93

^aConversion and yield determined via GC vs. internal standard.

Table 2

Examples of catalytic Cadogan synthesis.^a ^aYields reported for isolated products.^bTreatment with TBAF prior to silica gel chromatography.^cSingle stereoisomer by HPLC.