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Benchmarking Methanophosphocines as Versatile PIII/PV Redox Organocatalysts

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Abstract: PIII/PV redox cycling has recently emerged as a valuable strategy to minimize the chemical waste generated by phosphine-mediated reactions, as well as enabling asymmetric transformation. In this article, we detail our contribution to this field by designing a series of diversely functionalized, electron-rich bridgehead phosphine oxides with structural features that make them well-suited as PIII/PV redox organocatalysts. Their catalytic performance has been assessed in various model reactions, including Wittig or Staudinger reactions, along with the reduction of activated alkenes and allenes. For each of these scenarios, we performed a comparative analysis with existing catalysts in order to demonstrate the applicability and limitation of methanophosphocines.

Introduction

Phosphorus-mediated reactions, such as Wittig, Appel, Staudinger or Mitsunobu reactions constitute fundamental tools in the synthetic chemist arsenal.[1] These reactions enable a wide range of functional group transformations, and play pivotal roles in forming key carbon-carbon, carbon-nitrogen and carbon-oxygen bonds, making them widely embraced by synthetic chemists in academia. However, scaling-up these reactions poses a significant challenge due to the stoichiometric production of phosphine oxide by-products. The substantial generation of this highly polar species commonly results in intricate work-up and purification procedures, hampering the overall efficiency of the reactions. Furthermore, addressing the phosphine oxide issue becomes paramount on an industrial scale, as current recycling phosphine oxide methods are often hazardous and expensive, and have notable environmental impacts.[2] Among the solutions developed to alleviate this challenge, PIII/PV redox cycling emerged in 2009 with O'Brien's groundbreaking report on the first phosphorus-based catalytic Wittig reaction.[3] This approach employs substoichiometric amounts of an electron-rich and strained phosphine, coupled with a silane serving as a chemoselective reducing agent (Figure 1, A).[4] Following this initial milestone, PIII/PV redox cycling has been successfully applied to a variety of common phosphine-mediated reactions.[5] Furthermore, it has also demonstrated its efficacy in addressing more complex transformations, including nitrenoid chemistry[6] and heterocycle synthesis.[7] Another advantage of this methodology is its use of chiral phosphines in substoichiometric amounts for enantioselective synthesis.[8]

Concurrently with the development of such methodology, organocatalyst structure evolved from O'Brien's phospholane cat-1 to more active scaffolds, such as dibenzophospholes cat-2 or phosphetanes cat-3 (Figure 1, C). Both experimental and theoretical findings highlighted a correlation between the formal charge on the phosphorus atom of phosphine oxide and the ease of reduction by silanes: a lower formal charge corresponds to a lower energy barrier.[4][9] In addition, the shape of phosphine oxide also has an important role on the reduction process, with optimal geometry recommended to closely resemble the trigonal bipyramid transition state, thereby minimizing distortion energy.[9b] This justifies the prevalence of cyclic phosphine oxide constituted by small 4- or 5-membered rings, restraining the phosphorus atom substituents at a narrow angle close to the optimal 90°, as illustrated by O'Brien bicyclo[4,2,1]nonane cat-4 and Kwon chiral phosphine oxides cat-5. In this series, tributylphosphine cat-6, although electron-rich phosphine, appears as a notable structural exception. While phosphetanes cat-3 represent a significant advance in terms of efficiency, structural modifications of the heterocyclic backbone are limited. Therefore, there is a real challenge in designing

organocatalysts that are equally effective and also bring forth novel functionalities, thereby exploring new chemical space. In a 2020 DFT study, Krenske group highlighted the theoretical low energy barrier of the reduction of 1- phosphabicyclo[3,3,0]-octane oxide by silane,[9b] previously isolated by Mügge.[10] Although the synthesis of the latter goes through an unstable primary alkylphosphine intermediate, the bridgehead phosphine oxide activity as P^{III}/P^V organocatalysts are yet to be explored and holds promises. Based on these calculations and on our ongoing research on methanophosphocine cat-7 a, which features a bridgeheaded phosphorus atom, we herein present their first experimental applications as P^{III}/P^V organocatalysts in well-established benchmark reactions (Figure 1, B).[11]

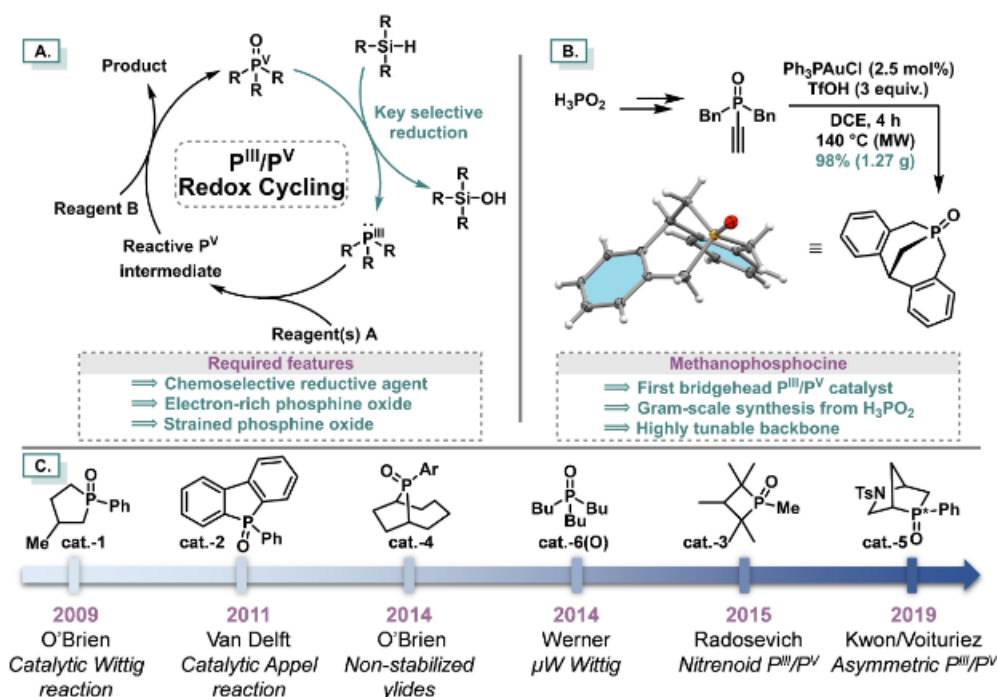


Figure 1. P^{III}/P^V redox cycling. (A) General mechanism. (B) Dibenzomethanophosphocines as new P^{III}/P^V organocatalysts. ORTEP plot (50% thermal ellipsoids) of the solid-state structure of methanophosphocine cat-7 a. Phosphorus atom is shown in orange and oxygen in red. (C) P^{III}/P^V organocatalysts evolution toward more strained and electron-rich phosphine.

Results and Discussion

Design and Synthesis of Methanophosphocines

A set of methanophosphocines cat-7 a–i were prepared using an improved procedure based on a previously reported methodology within our research group.[11] Specifically, we employed an effective gold-catalyzed intramolecular double hydroarylation of bis(arylmethyl)(alkynyl)phosphine oxides as a key step to efficiently synthesize the catalysts (detailed information can be found in the SI).[11a] It is noteworthy that the aforementioned precursor can be prepared from environmentally benign hypophosphorous acid, unlike most other catalysts which are made from phosphorus trichloride. Similarly, bisbiaryl derivatives cat-7 b were produced through a double Suzuki-Miyaura coupling.[11b] In our previous work, we determined that dibenzomethanophosphocine cat-7 a exhibited a percent buried volume (%V_{bur}) similar to that of trimethylphosphine (%V_{bur} = 26.1), emphasizing the easy accessibility of the phosphorus atom even for hindered reagents. Moreover, the electronic properties showed a strong σ donor character in line with the nature of the alkyl substituents. By contrast the π-acceptor character was significantly affected by the ring strain, resulting in methanophosphocine cat-7 a being a poor acceptor. The combination of these properties

makes it suitable for PIII/PV redox organocatalysis. To explore the potential of such compounds, we consecutively added specific structural features. To tune the steric hindrance of the phosphorus centre, hydrogen atoms of methylene groups were replaced by methyl, yielding tetramethyl methanophosphocine cat-7 b. Additionally, to promote π -stacking interactions, we prepared bisbiaryl methanophosphocines cat-7 c–i. Aryl or heteroaryl motifs were introduced to generate a spectrum of electronically rich and poor aromatic compounds. With a large family of potential organocatalysts cat-7 a–i in hands, we decided to benchmark their catalytic activity in standard synthetic strategies where well-established phosphorus-based catalysts work, namely catalytic-Wittig reaction, Staudinger reaction and reduction of activated alkenes and allenes. The organocatalytic potential of methanophosphocines has been evaluated by comparing them with standard phosphines or phosphine oxides, namely triphenylphosphine cat-8, tributylphosphine cat-6, phospholene cat-9, phospholane oxide cat-1, dibenzophosphole cat-2, and pentamethylphosphetane oxide cat-3.

Organocatalytic Activity Assessment of Methanophosphocine Derivatives

Catalytic Wittig Reaction

We initiated our study by evaluating the organocatalytic activities of dibenzomethanophosphocine cat-7 a in a model Wittig reaction (Figure 2).^{[3][5a]} We selected benzaldehyde 1 a and methyl bromoacetate 2 a as substrates, diisopropylethylamine (DIPEA) as a base, diphenylsilane as the reducing agent and bis(4-nitrophenyl)phosphate (BNPA) as an additive to facilitate the reduction of phosphine oxide.^[12] The reactions were carried out on a 1 mmol scale of benzaldehyde 1a, at 100 °C in dry toluene for 24 h under an inert atmosphere. Following optimization process of the reaction parameters using cat-7 a as organocatalyst (see optimization details in SI), diversely functionalized methanophosphocines cat-7 b–i were tested. By reducing the quantities of DIPEA and diphenylsilane to a slight excess (1.1 equiv.) and utilizing a 5 mol% catalyst loading, the simplest dibenzomethanophosphocine cat-7 a successfully yielded the desired olefin 3 a in 93% ¹H NMR yield and an E/Z-ratio of 8:2 (Figure 2). Increasing the amounts of base and diphenylsilane to 1.4 equiv. resulted in a complete conversion into the alkene 3 a (monitored by ¹H NMR) and 90% isolated yield (E/Z-ratio of 9:1). None of the other methanophosphocines cat-7 b–i demonstrated an enhancement in yield. The use of tetramethyl-dibenzomethanophosphocine cat-7 b resulted in a loss of catalytic activity. This significant change is likely attributed to the increased steric hindrance of cat-7 b, which presented a buried volume of 40%. The substituents significantly influence this parameter, and it was calculated to be 27% for phosphetane cat-3. Bisbiaryl catalysts exhibit similar trends with an ¹H NMR yield of 15% for biphenyl derivative cat-7 c and 24% yield for cat-7 d (xylyl). Other biaryl-dibenzomethanophosphocines (phenyl cat-7 e, 4-pyridyl cat-7 f and the 4-trifluoromethylphenyl cat-7 g) displayed comparable catalytic activity, affording the desired cinnamate 3 a in NMR yields ranging from 50% to 60%. The presence of a methyl or methoxy electron donating group localized on the phenyl substituent cat-7 h and cat-7 i, impacted positively the catalyst turnover, leading to the alkene 3 a in 87% ¹H NMR yield and an 8:2 E/Z-ratio.

Based on these encouraging observations, our attention shifted towards exploring the substrate scope of the catalytic Wittig reaction using the most efficient methanophosphocine cat-7 a as organocatalyst (Scheme 1). To gain insights, we conducted a comparative analysis of the effectiveness of our methano-phosphocine cat-7 a with the phospholane catalyst cat-1 reported by O'Brien using 10 mol% loading during 24 h at 100 °C,^[3] and the most recent method published by the Werner group in 2019, relying on 2 mol% of phosphetane cat-3 at room temperature for 48 h.^[13] Using 5 mol% of methanophosphocine cat-7 a, along with 10 mol% of BNPA, 1.4 equiv. of diphenylsilane, 1.4 equiv. of DIPEA and 1.2 equiv. of methyl bromoacetate, various aldehydes (1 mmol scale) were subjected to the reaction. Under these conditions, benzaldehyde provided methyl cinnamate 3 a in high yield and stereoselectivity (90% and E/Z 9:1, respectively). Moreover, the reaction could be readily scaled up to 10 mmol, affording the desired product with an increased yield of 98%, albeit at the cost of

stereoselectivity (8:2). Remarkably, this reaction showed good tolerance towards electron-withdrawing groups, as evidenced by the 78% yield of 2-nitrocinnamate 3 b, and the 85% yield of the 4-chloro-derivative 3 c.

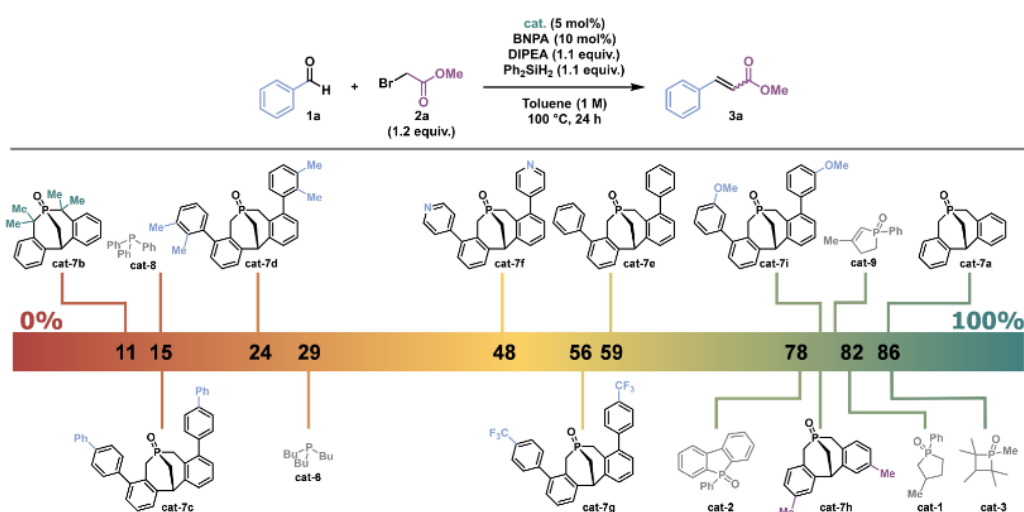
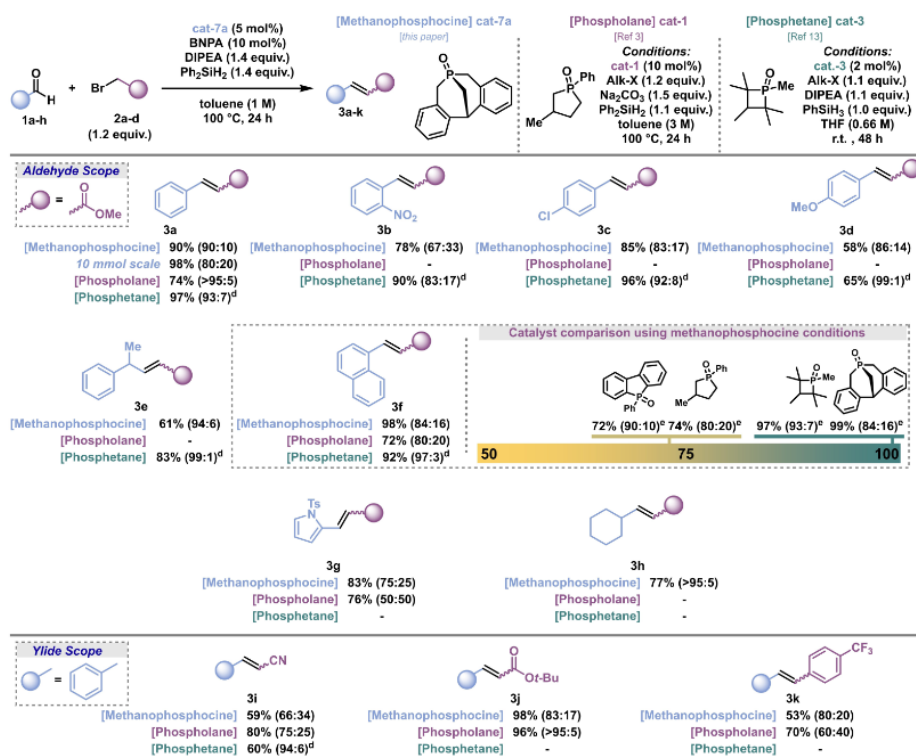


Figure 2. Organocatalyst screening on a model Wittig reaction (see optimization details in the SI). a All reactions were conducted with 1 mmol of aldehyde, 1.2 equiv. of alkyl halide, 5 mol% of catalyst cat-7 a–i, 10 mol% of BNPA, 1.1 equiv. of DIPEA and 1.1 equiv. of diphenylsilane in toluene ($C = 1 \text{ M}$) at 100°C during 24 h. b Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.



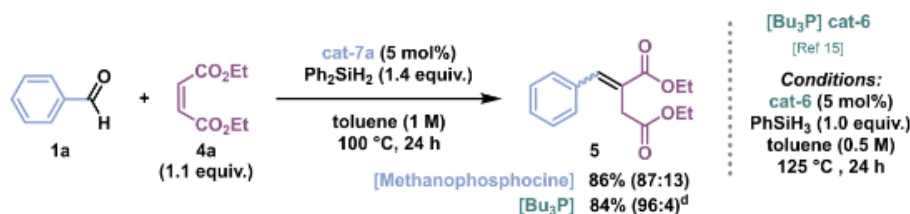
Scheme 1. Scope of the catalytic Wittig reaction using methanophosphocine cat-7a as a PIII/PV organocatalyst. Comparison with literature data using phospholane cat-1 catalyst,[3] or a phosphetane cat-3 catalyst.[13] a Unless otherwise indicated, all reactions were conducted with 1 mmol of aldehyde 1, 1.2 equiv. of alkyl halide 2, 5 mol% of catalyst cat-7 a, 10 mol% of BNPA, 1.4 equiv. of DIPEA and 1.4 equiv. of diphenylsilane in toluene ($C = 1 \text{ M}$) at 100°C during 24 h. b Isolated yield. c E/Z ratio determined by ^1H NMR integration of the ethylenic signals on the crude reaction mixture. d E/Z ratio determined by ^1H NMR on the isolated product. e Catalysts activity compared using methanophosphocine conditions. Yield and E/Z ratio determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Consistent with Werner's findings, 2-nitrobenzaldehyde gave the olefin with a slightly lower yield of 78%. Notably, no by-products resulting from the formation of a reactive nitrenoid intermediate, commonly observed with nitroaryl compounds, were observed.[6] Similarly, in line with Werner,[13] electronrich 4-methoxybenzaldehyde furnished the olefin 3 d in 58% yield and a 9:1 E/Z-isomer ratio. Steric hindrance on the aldehyde did not seem to be a limiting factor, as evidenced by the synthesis of 4-phenyl-2-pentenoate 3 e in a 61% yield, and a nearly quantitative yield observed for the 3-(1-naphthyl)acrylate 3 f. The same reaction was also reported by O'Brien,[3] albeit with a lower yield of 72%. Compared to phospholane cat-1, methanophosphocine cat-7 a achieved improved yields, reaching 98%, while using a catalyst loading reduced by a factor 2. This was validated by trying the other catalysts in the exact same condition as methanophosphocine cat-7 a. Overall, the performance of our methanophosphocine cat-7 a was similar to that of phosphetane cat-3 and compared favorably with phospholane cat-1. Both heteroaromatic and aliphatic aldehydes proved to be reactive in our system, affording the 2-pyrrolylacrylate 3 g in a satisfying 83% yield, and the cyclohexylacrylate 3 h in 77% yield. We expanded our investigation by reacting various alkyl bromides with benzaldehyde. Bromoacetonitrile 2 b gave the cinnamitrile 3 i in a 59% yield, consistent with Werner's report.[13] Surprisingly, the selectivity was poor, with an E/Z-ratio of 6:4. Hindered ester, such as tert-butyl bromoacetate 2 c, was well tolerated and afforded the olefin product 3 j in a nearly quantitative yield. Finally, 4-trifluoromethylbenzyl bromide 2 d was also reactive, giving stilbene derivative 3 k in a 53% yield with an improved E/Z-selectivity (8:2). It is worth noting that this reagent led to a semi-stabilized ylide intermediate, and its utilization typically resulted in modest E/Z-selectivities in classical Wittig olefination.[3][14] In this example as well as for the other substrates, the difference of E/Z- selectivity might be accounted to the ability of the catalyst to promote isomerization of the product. Indeed, in his pioneer report O'Brien observed an enrichment of the thermodynamically favored E olefin driven by the free rotation of the C C single bond after phospholane cat-1 addition.[3] In our catalytic system, olefin Z isomerized as opposed to the other diastereoisomer that does not react (see supporting information for details). The isomerization process is probably governed by the stereo-electronic parameters of the phosphine, which differ from one catalyst to another and might explain the various outcome. Under comparable conditions, a base-free Wittig reaction between diethyl maleate 4 and benzaldehyde 1 a was successfully performed, producing diethyl 2-benzylidenesuccinate 5 in 86% yield and a 9:1 E/Z- ratio (Scheme 2). Werner has previously reported this reaction using tributylphosphine cat-6 (5 mol %) as a catalyst and 1.0 equiv. of phenylsilane in toluene, at 125 °C for 24 h.[15] Notably, in our experiments, diphenylsilane demonstrated effectiveness in contrast to Werner's findings (20% yield using 10 mol% of tributylphosphine cat-6 and 1.0 equiv. of diphenylsilane). Similar yields were obtained using either methanophosphocine cat-7 a or tributylphosphine cat-6.

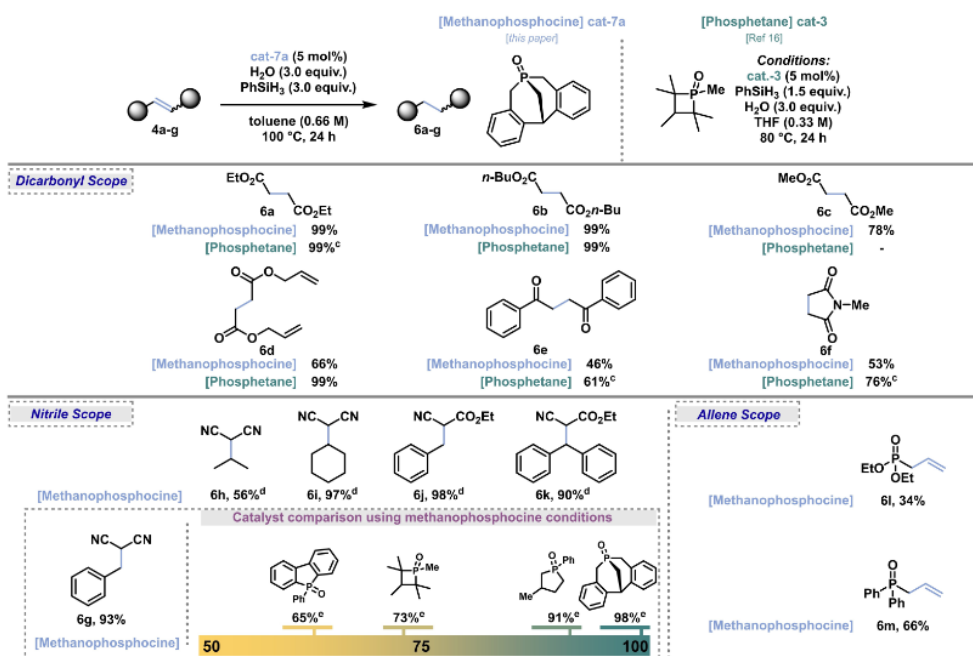
Catalytic Reduction of Activated Alkenes and Allenes

The second benchmark reaction under consideration involved the reduction of activated alkenes, a method published in 2020 by the Werner group.[16] This elegant reaction capitalizes on the oxophilicity of the phosphonium salts, and the selective cleavage of P-C bonds in the presence of hydroxide as nucleophile.[17] In their original report, Werner employed 1 to 5 mol% of phosphetane catalyst cat-3 in combination with phenylsilane and three equivalents of water in THF at 80 °C for 24 h. After optimization (see optimization details in SI), diethyl maleate 4 a was reduced quantitatively into diethyl succinate 6 a, employing 5 mol% of methanophosphocine cat-7 a, at 100 °C in the presence of 3.0 equiv. of phenylsilane and 3.0 equiv. of water (Scheme 3). Using the aforementioned conditions, the scope of the reaction was investigated on a 1 mmol scale. Similarly to Werner, di n-butyl maleate reacted smoothly, giving quantitatively succinate 6 b.[16] Dimethyl succinate 6 c was isolated in 78% yield. The reaction was also selective toward activated alkenes such as diallyl maleate 4 d, which bears terminal double bonds usually prone to reduction, yielding the corresponding diallyl succinate 6 d in a satisfactory 66% yield, albeit lower than the Werner's published yield.

Additionally, 1,4-diphenyl-2-butene-1,4-dione 4 e, as well as N-methyl maleimide 4 f, were also reduced, providing moderate yields of 46% and 53%, respectively. Subsequently, we broadened the spectrum of the reaction to encompass novel substrates. The reduction of benzylidenemalonitrile 4 g provided an excellent 93% yield. On this substrate, phosphetane cat-3 and dibenzophosphole cat.-2 showed inferior activity (~70% NMR yield). Other dinitrile derivatives were evaluated, resulting in formation of the desired products 6 h in 56% yield and 6 i in 97% yield. Arylalkylidene cyanoacetates 4 j and 4 k were also subjected to the reaction conditions, furnishing the desired products in excellent yields of 98% (6 j) and 90% (6 k). Allene compounds also exhibited reactivity in this process. The reduction of phosphorylallenes in the presence of methanophosphocine cat-7 a led to complete and selective conversion, as monitored by ^{31}P NMR. While allylphosphonate 6 l was isolated in a modest 34% yield likely due to purification issues, allyl diphenylphosphine oxide 6 m was obtained in a satisfactory 66% yield. It's worth noting that Werner reported the reduction of ethyl buta-2,3-dienoate in presence of phosphetane cat-3 with only a 33% yield (not isolated).[16] The relatively low electron-withdrawing character of diethyl phosphonate or diphenylphosphine oxide moieties, compared to a carboxylic ester, is sufficient for achieving complete regioselectivity and high conversion.



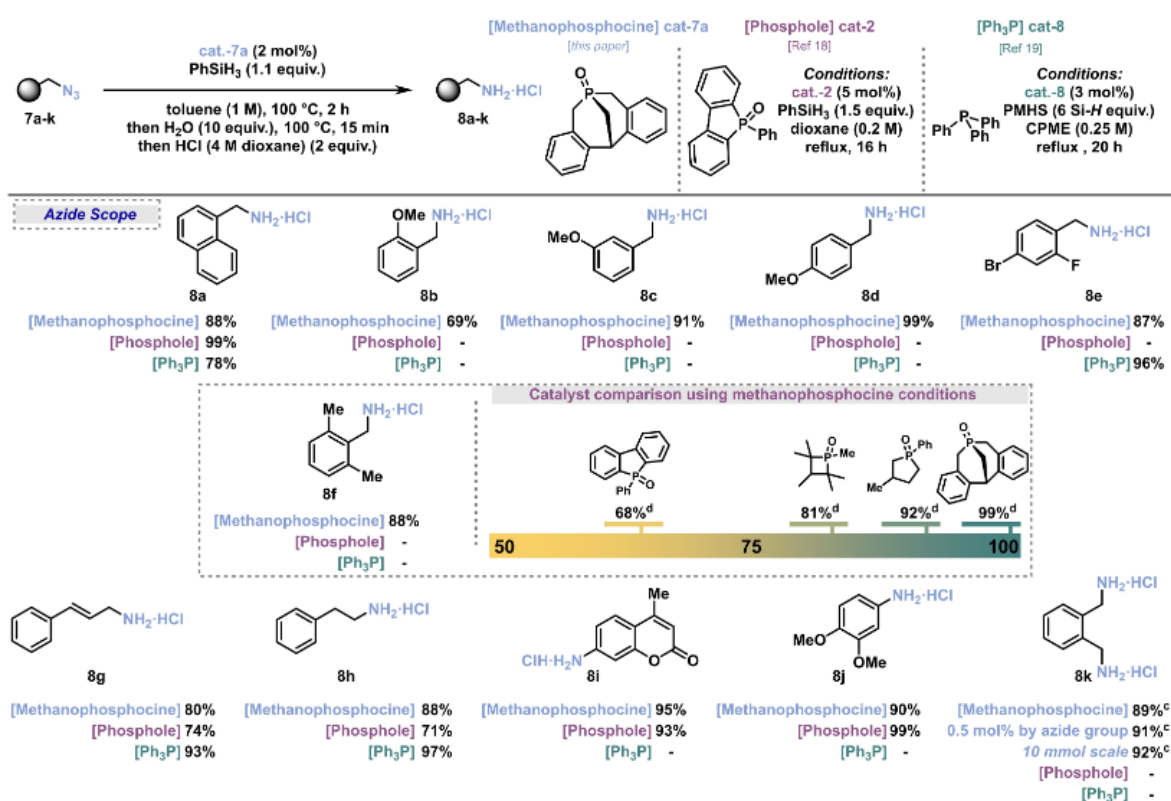
Scheme 2. Base free catalytic Wittig reaction using methanophosphocine cat-7 a as PIII/PV organocatalyst. Comparison with literature data using a substoichiometric amount of tributylphosphine cat-6.[15] a Reaction was conducted with 1 mmol of aldehyde, 1.1 equiv. of diethyl maleate, 5 mol% of catalyst cat-7 a and 1.4 equiv. of diphenylsilane in toluene ($C = 1 \text{ M}$) at 100 °C during 24 h. b Isolated yield. c E/Z ratio determined by ^1H NMR integration of the ethylenic signals on the crude reaction mixture. d E/Z ratio determined by GC/FID on the isolated product.



Scheme 3. Scope of the reduction of activated unsaturated carbon-carbon bond using methanophosphocine cat-7 a as PIII/PV organocatalyst. Comparison with literature data using a phosphetane catalyst.[16] a Unless otherwise indicated, all reactions were conducted with 1 mmol of substrate, 3.0 equiv. of water, 5 mol% of catalyst cat-7 a and 3.0 equiv. of phenylsilane in toluene ($C = 0.66 \text{ M}$) at 100 °C during 24 h. b Isolated yield. c 1 mol% of phosphetane cat-3. d 48 h. e Catalysts activity compared using methanophosphocine conditions. Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Catalytic Staudinger Reduction

Finally, we assessed the efficacy of methanophosphocine cat-7 a in the Staudinger reduction, one of the earliest reactions to have been converted into a catalytic version. In 2012, the van Delft group pioneered this functional transformation using dibenzophosphole cat-2 (5 mol%), phenylsilane (1.5 equiv.) in refluxing dioxane for 16 h.[18] The PIII/PV catalytic system was later improved twice by the Mecinović group, employing either triphenylphosphine cat-8 (3 mol%) and PMHS (6 Si-H equiv.) in refluxing CPME for 20 h,[19] or triphenylphosphine cat-8 (10 mol%) and diphenyldisiloxane (1.5 equiv.) in CPME at room temperature for 24 h.[20] With this background in mind, we optimized the catalytic Staudinger reaction using methanophosphocine cat-7 a in combination with phenylsilane (see optimization details in SI). Remarkably, this system proved highly efficient, with just 2 mol% of the catalyst enabling complete conversion of 1-(azidomethyl)naphthalene 7 a into the corresponding amine in 2 h at 100 °C (Scheme 4). Furthermore, consistent with Mecinović's findings,[19] the amine was easily isolated through a straightforward acidic precipitation-filtration workup, yielding the hydrochloride salt 8 a in 88% yield. Under these established conditions, we further explored the scope of the reaction using various benzylazides 7 a–k. The reaction proceeded smoothly, affording the corresponding amines 8 c–f in excellent yields (> 85%), irrespective of the substitution on the aryl, thereby ruling out steric or electronic factors. An exception was noted with compound 8 b, featuring an ortho-methoxy substituent, which was isolated in 69% yield.




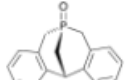

Scheme 4. Scope of the catalytic Staudinger reduction using methanophosphocine cat-7 a as PIII/PV organocatalyst. Comparison with literature data using a dibenzophosphole cat-2 catalyst,[18] or a substoichiometric amount of triphenylphosphine cat-8.[19] a Unless otherwise indicated, all reactions were conducted with 1 mmol of substrate, 2 mol% of catalyst cat-7 a and 1.1 equiv. Of phenylsilane in toluene (C = 1 M) at 100 °C during 2 h. b Isolated yield. c 2.2 equiv. of phenylsilane. d Catalysts activity compared using methanophosphocine conditions. Yield determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Comparing to other phosphine oxide on a model substrate 8 f, methanophosphocine demonstrated again a similar or higher catalytic activity, hence validating its great versatility. The reaction also exhibited tolerance towards allyl and alkyl azides. Cinnamyl amine hydrochloride 8 g was successfully obtained in 80% yield, while 2-phenylethan-1-amine hydrochloride 8 h was isolated in 88% yield. Notably, aryl azides also demonstrated suitability as substrates for this transformation. For instance, both aminocoumarin 8 i and 4-aminoveratrole 8 j were synthesized in excellent 95% and 90% yields, respectively. Remarkably, the bis(azide) 7 k was fully reduced, affording the diamine 8 k in only 2 h in a remarkable 89% yield. Even more interestingly, the reduction of 8 k using the same reaction condition but with 1 mol% of methanophosphocine cat-7 a, which means in fact only 0.5 mol% of catalyst per azide functionality, still provided a high chemical isolated yield of 91%. Furthermore, the robustness of this process was demonstrated by conducting the reduction of 8 k on a 10 mmol scale, giving the desired product, without compromising the chemical isolated yield. To the best of our knowledge, bis(azide) reactivity has never been assessed in PIII/PV redox cycling.

DFT Calculations and Rationalization

Krenke et al. performed DFT calculations in order to decipher the effects governing the hydride transfer from the silicon atom to the P-center.[9b] This step is rate-limiting for the reduction of a phosphine oxide by a silane and corresponds to an early transition state with a trigonal bipyramid geometry. An NBO analysis indicated that the main second order perturbation in the transition state stems from the donation of the oxygen lone pair of the phosphine oxide into a vacant $\sigma^*(\text{Si-H})$ at the silane part. This could account for the counterintuitive fact that, although trialkylphosphine oxides are electron-rich, they are more easily reduced than their triaryl counterparts. In the case of cyclic derivatives, such as model phospholane cat-1, this interaction is sub-optimal because of the constrained environment around the phosphorus atom. However, this forced geometry is ultimately beneficial, because it decreases the energetic cost of the distortion of the reactants from their ground-state geometries into their TS geometries.

Table 1. Compared distortion and interaction energies of methanophosphocine cat-7 a and phosphetane cat-3 with phosphine oxides from literature.

	Ph ₃ PO	Me ₃ PO	 cat-1 ^c	 cat-7 a	 cat-3
ΔG^+	+32.4	+30.6	+28.3	+30.1	+27.3
ΔH^+	+18.2	+17.8	+14.4	+15.8	+13.5
ΔE^+	+17.7	+17.1	+14.2	+15.1	+12.8
<i>Main NBO Second Order Perturbation Energies in the transition state</i>					
O lone pair- $\rightarrow\sigma^*(\text{Si-H}_{\text{tr}})$	59.5	69.0	63.5	58.7	59.2
O lone pair- $\rightarrow\sigma^*(\text{Si-H}_{\text{sp}})$	37.2	39.0	38.0	37.4	38.2
$\sigma(\text{Si-H})\rightarrow\sigma^*(\text{P-C})$	19.5	21.8	20.5	18.7	16.6
$\sigma(\text{Si-H})\rightarrow\sigma^*(\text{P-O})$	15.8	17.0	15.8	14.8	15.2
<i>Distortion and interaction energies in the transition state, according to Houk's analysis</i>					
$E^+_{\text{dist}}(\text{R}_3\text{PO})^{[a]}$	+11.8	+16.7	+11.6	+9.5	+9.0
$E^+_{\text{dist}}(\text{SiH}_3\text{Ph})^{[a]}$	+38.4	+42.0	+40.7	+38.2	+39.1
$E^+_{\text{int}}^{[a]}$	-32.5	-41.7	-38.1	-32.6	-35.3

[a] Distortion and interaction energies in the transition state, according to Houk's analysis.[21] Energies are in kcal.mol⁻¹.

We examined phosphine oxides cat-3 and cat-7 a at the same level of theory and the results are summarized in Table 1 (M06-2X/6-311 + G(d,p) with SMD implicit solvent model for toluene). On one hand, as expected for cyclic derivatives, the Si-O interactions in the transition state (59 kcal.mol⁻¹) were found weaker than in trimethylphosphine (69 kcal.mol⁻¹). On the other hand, this was counterbalanced by a lower energetic cost for

the distortion of the reactants (E_{dist}), as defined by Houk and Bickelhaupt.[21] Overall, Gibbs energies of activation predict cat-3 to be the most efficient. However, differences in calculated energies are small and, as indicated by the experimental results, they may be insufficient to account for all the subtleties of these catalytic systems.

Conclusions

In summary, as highlighted in this paper, methanophosphocines, represented by cat-7 a–i, are electron-rich bridgehead phosphine oxides possessing structural features that make them well-suited for PIII/PV redox organocatalysis. These compounds can be synthesized at a gram-scale from simple and cost-effective hypophosphorous acid. Notably, their substituents can be diversely tuned, which is rather difficult or often not possible with other conventional organocatalysts typically used in PIII/PV catalyzed reactions. Furthermore, we have demonstrated the efficacy of methanophosphocine cat-7 a as a potent organocatalyst in well-established PIII/PV redox cycling reactions. Specifically, its catalytic activity has been evaluated in various model reactions, encompassing Wittig or Staudinger reactions, as well as the reduction of activated alkenes and allenes. In each of these reactions, the catalytic performance of our in-house methanophosphocine cat-7 a compared well with the most highly regarded catalysts. Notably, the literature documents only a limited number of phosphine oxides proving effective in the evolving realm of PIII/PV redox organocatalysis, and none possess a bridgehead structure. Consequently, we firmly believe that our findings would not only contribute to the scientific community but also augment the toolbox of synthetic methods for these valuable transformations, thereby paving the way for the discovery of new catalytic pathways. Based on DFT calculation, ongoing experimental efforts continue with the aim of broadening the scope and enhancing the efficiency of these novel methanophosphocines in other useful PIII/PV redox cycling transformations. Development of a chiral version of our electron-rich bridgehead phosphine oxides is another focal point of interest within our research group, and orthcoming discoveries will be shared in due course.

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