Redox Catalysis

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Reduction of Activated Alkenes by P^{III}/P^{V} Redox Cycling Catalysis

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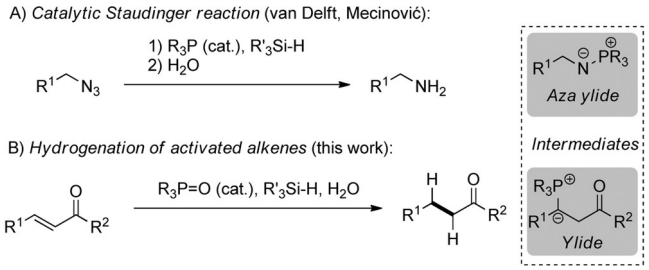
Abstract: *The carbon–carbon double bond of unsaturated carbonyl compounds was readily reduced by using a phosphetane oxide catalyst in the presence of a simple organosilane as the terminal reductant and water as the hydrogen source. Quantitative hydrogenation was observed when 1.0 mol% of a methyl-substituted phosphetane oxide was employed as the catalyst. The procedure is highly selective towards activated double bonds, tolerating a variety of functional groups that are usually prone to reduction. In total, 25 alkenes and two alkynes were hydrogenated to the corresponding alkanes in excellent yields of up to 99%. Notably, less active poly(methylhydrosiloxane) could also be utilized as the terminal reductant. Mechanistic investigations revealed the phosphane as the catalyst resting state and a protonation/deprotonation sequence as the crucial step in the catalytic cycle.*

The selective hydrogenation of unsaturated carbonyl compounds is a reaction of major importance. In nature, enoate reductases are capable of selectively reducing the activated carbon–carbon double bond of an α,β-unsaturated substrate, which plays a crucial role in multiple important processes such as the biosynthesis of fatty acids.[1] In organic synthesis, reduction reactions are dominated by transition-metal catalysis or the use of stoichiometric amounts of metal hydride reagents.[2] A metal-free organocatalytic approach can overcome some problems regarding purification encountered by these systems and also lead to new useful reaction pathways. In recent years, multiple organocatalytic systems have been developed for the reduction with hydrogen[3] or other reactive reducing agents such as the Hantzsch ester[4] to achieve metal-free double bond hydrogenation. An alternative strategy for the reduction of unsaturated carbonyl compounds involves Lewis base addition to the double bond and subsequent hydrolysis.[5] In this respect, alkyl phosphanes and N-heterocyclic carbenes show good chemoselectivities and allow for efficient reduction at room temperature. However, stoichiometric amounts of these expensive and sensitive reagents are still required. We envisioned phosphorus redox cycling as a solution to the challenge of metal-free reductions. In phosphorus redox cycling catalysis, the active phosphane reagent is regenerated in situ by a terminal reducing agent, most commonly an organosilane. This can avoid stoichiometric phosphane oxide waste in reactions such as the Wittig,[6] Appel,[7] or Mitsunobu[8] reactions.[9] Recently, phosphorus redox cycling catalysis has also been employed for the deoxygenation of α-keto esters, nitroarenes, and sulfonyl chlorides by the Radosevich group.[10] Another example is the catalytic Staudinger reduction, where an azide is converted into an amine (Scheme 1 A).[11] In this case, an aza ylide is formed, which is reduced to a silylamine and subsequently hydrolyzed to liberate the amine. Based on our investigations on the catalytic base-free Wittig reaction,[12] we envisioned that alkenes could be reduced via the in situ formation of an ylide and subsequent reaction with water under phosphorus redox cycling conditions (Scheme 1 B).



Scheme 1. Phosphorus redox cycling in the reduction of azides (catalytic Staudinger reaction)[11] and the reduction of activated alkenes using water as the hydrogen source (this work).

We started our investigations using diethyl fumarate (**1a**) as the model substrate and phosphetane oxide **3a** as the oxidized form of the catalyst. Using a slight excess of silane (1.5 equiv) and an excess of water (3.0 equiv) in BuOAc, the alkane was obtained in an excellent yield of 95% (Table 1, entry 1).[13] Under the reaction conditions at 80 °C, silane hydrolysis was very slow, and the reduction of the phosphane oxide **3a** proceeded smoothly. We lowered the catalyst loading to 0.5 mol% and observed a significant decrease in yield (entry 2). In commonly used solvents for phosphorus redox cycling catalysis such as 1,4-dioxane or toluene the yield increased to 35 and 38%, respectively (entries 3 and 4). A catalyst screen was carried out using toluene as the solvent. The introduction of a sterically more demanding group or an aryl substituent on the phosphetane scaffold led to lower yields (entries 5 and 6). Furthermore, other catalysts based on phosphorus heterocycles, **3d** and **3e**, performed poorly as well (entries 7 and 8). A common strategy in phosphorus redox cycling is the addition of a Brønsted acid to facilitate the phosphane oxide reduction. However, with 5.0 mol% of benzoic acid as an additive, a lower yield of only 16% was

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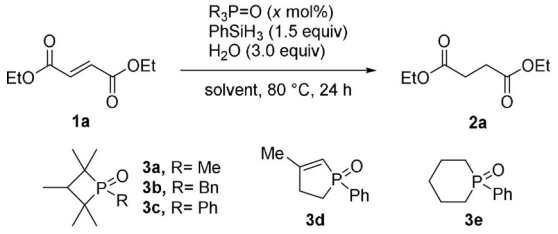
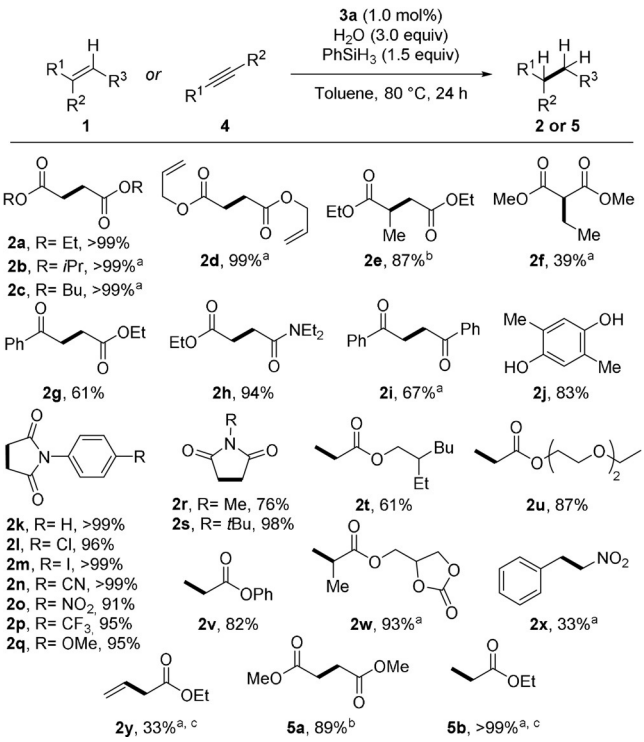
Table 1: Optimization of the reaction conditions and catalyst screen for the organocatalytic reduction of activated alkenes.



Entry	Catalyst (mol%)	Solvent	Yield **2a** [%][a]
1	**3a** (1.0)	BuOAc	95
2	**3a** (0.5)	BuOAc	18
3	**3a** (0.5)	1,4-dioxane	35
4	**3a** (0.5)	toluene	38
5	**3b** (0.5)	toluene	4
6	**3c** (0.5)	toluene	8
7	**3d** (0.5)	toluene	11
8	**3e** (0.5)	toluene	4
9[b]	**3a** (0.5)	toluene	16
10	**3a** (1.0)	toluene	>99

Reaction conditions: **1a** (0.50 mmol, 1.0 equiv), $PhSiH_3$ (1.5 equiv), H_2O (3.0 equiv), phosphane oxide (**3**, 0.5 or 1.0 mol%), solvent (0.33 M), 80°C, 24 h. [a] Yields determined by ^1H NMR spectroscopy using mesitylene as an internal standard. [b] $PhCO_2H$ (5.0 mol%) was used as an additive.

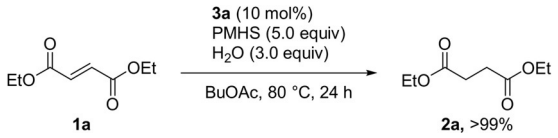


Scheme 2. Substrate scope of activated alkenes and alkynes. Reaction conditions: **1** or **4** (1.0 mmol, 1.0 equiv), $PhSiH_3$ (1.5 equiv), H_2O (3.0 equiv), **3a** (1.0 mol%), toluene (0.33 M), 80°C, 24 h. [a] 5.0 mol% **3a**. [b] 20 mol% **3a**, 100°C, $PhSiH_3$ (3.0 equiv), H_2O (6.0 equiv). [c] Yield determined by ^1H NMR spectroscopy using mesitylene as an internal standard.

observed (entry 9). We increased the catalyst loading to 1.0 mol%, and alkane **2a** was formed in a yield of ≥99% (entry 10). With these optimized conditions in hand, the substrate scope of the reaction was evaluated, although in some cases, the catalyst loading was adjusted to 5.0 mol% or 20 mol% for more challenging substrates (Scheme 2).

Other fumaric or maleic acid diesters **1b–d** were reduced to the respective succinic acid derivates in yields of ≥99%. Notably, the terminal unsubstituted double bonds in substrate **1d** stayed untouched during the reaction, demonstrating the selectivity of the procedure towards electron-deficient alkenes. The trisubstituted alkene **1e** was also a suitable substrate, although harsher reaction conditions were required to obtain a yield of 87%. The malonic acid derived substrate **2f** was isolated in a yield of only 39% likely because of partial hydration of the double bond as described by Toste and co-workers.[14] Other disubstituted alkanes **2g–i** bearing different electron-withdrawing groups were obtained in moderate to excellent yields. When 2,5-dimethyl-1,4-benzoquinone (**1j**) was employed as the substrate, aromatization occurred after the reduction of one double bond, and dihydroquinone **2j** was isolated in a good yield of 83%. Next, several differently functionalized aryl-substituted maleimides were employed as the substrates to evaluate the functional group tolerance of our method. In total, seven succinimides **2k–q** were obtained in yields greater than 90%. Functional groups that might be problematic when using traditional reduction methods, such as an aryl chloride (**2l**), aryl iodide (**2m**), benzonitrile (**2n**) or nitroarene (**2o**), were well tolerated. The methyl- and *tert*-butyl-substituted succinimides **2r** and **2s** were isolated from the corresponding maleimides in 76 and 98%, respectively. Monosubstituted alkenes, such as the cinnamate methyl ester or α,β-unsaturated esters bearing a β-alkyl chain, were unsuitable substrates, and only poor conversion was observed even at elevated temperatures.[13] Interestingly, acrylates also proved to be compatible substrates, and moderate to good yields were observed for substrates **2t–v**. The glycerol-derived acrylate **1w** was readily reduced, and the product **2w** was obtained in an excellent yield of 93%. Furthermore, β-nitrostyrene (**1x**) was converted, but only an unsatisfying yield of **2x** was obtained. The scope was extended to other unsaturated substrates, such as the acceptor-substituted allene **1y**, which resulted in the formation of the partially hydrogenated product **2y** in a yield of 33%. It was also possible to reduce alkyne **4a** to the corresponding alkane **5a** in a yield of 89%. The monosubstituted substrate **5b** was obtained in a yield of ≥99% after reduction of alkyne **4b**.

An essential idea of phosphorus redox cycling catalysis is the shift from a stoichiometric phosphorus reagent to a stoichiometric amount of organosilane, which is beneficial in terms of reaction efficiency and product purification. A further improvement is the use of siloxanes produced as waste in the silicone industry, for example, poly(methylhydrosiloxane) (PMHS).[15] Even though PMHS is preferred over other common organosilanes, the low activity of the polymer limits its application.[16] To showcase the compatibility of catalyst **3a** with low-activity siloxanes as terminal reductants, the reaction conditions were optimized utilizing five equivalents of PMHS.[13] Product **2a** was isolated in a yield of ≥99%

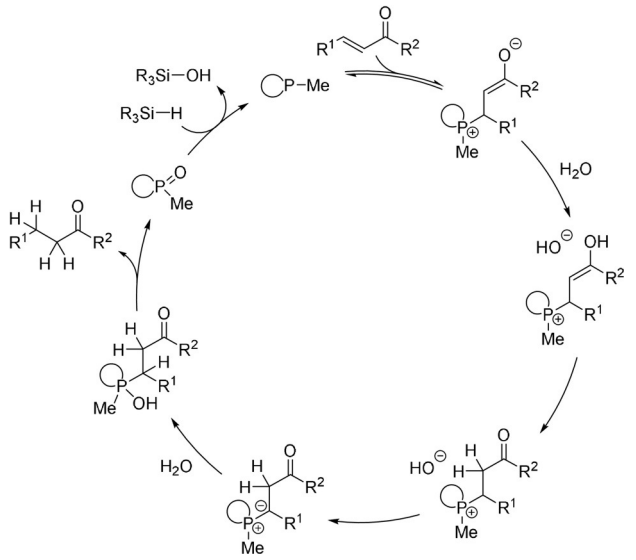


Scheme 3. Reduction of diethyl fumarate (**1a**) using PMHS as the terminal reductant and water as the hydrogen source.

employing 10 mol% of catalyst using BuOAc as a renewable solvent (Scheme 3).[17]

We set out to investigate the mechanism of the reaction, which can be divided into four steps: phosphane oxide reduction, Michael addition, ylide formation, and hydrolysis. First, in situ ^{31}P NMR spectroscopy was used to investigate the resting state of the catalyst, which was found to be the phosphane as the reduced form of the catalyst.[13] No other species such as the ylide were observed even in control experiments using stoichiometric amounts of phosphane and alkene in the absence of water.[13] Even though the product of the Michael addition cannot be observed by NMR spectroscopy, the quick isomerization of diethyl maleate ((*Z*)-**1a**) into diethyl fumarate ((*E*)-**1a**) in the presence of the phosphetane indicates a reversible addition to the alkene. In our previous report on the base-free intramolecular Wittig reaction, deuterium labeling experiments led to the assumption that the ylide is formed by a intermolecular protonation/deprotonation sequence and not by an intramolecular 1,2-hydrogen shift.[12b,18] We investigated the reactivity of the deuterated fumarate [D_2]-**1a**, and a mixture of deuterated products was obtained with an overall H/D ratio of 71:29. The loss of one deuterium from the substrate supports the protonation/deprotonation steps as the ylide-forming mechanism. Furthermore, when deuterated water (D_2O) was used, incorporation of deuterium in the alkane was observed (H/D = 55:45). When $PhSiD_3$ was employed as the deuterium source instead, only traces of deuterium could be found in the product (H/D = 97:3), likely because of H/D exchange with the water. This result confirms that all additional hydrogen atoms in the alkane originate from the water. Furthermore, no major difference was observed in the reaction rate when either H_2O or D_2O was used in the reaction.[13] On the basis of the results of our investigations and recent literature reports, we propose the following mechanism (Scheme 4).[5a,c,12b,19] First, the oxidized form of the catalyst is reduced by the silane to form the corresponding phosphane. The phosphane reacts with the alkene in a reversible Michael addition. Subsequently, the ylide intermediate is formed by a protonation/deprotonation sequence. Hydrolysis of the ylide liberates the product, and the phosphane oxide is regenerated.[20]

In conclusion, a procedure for the organocatalytic reduction of alkenes has been developed using water as the hydrogen source. A phosphetane oxide catalyst enables phosphorus redox cycling in the presence of water and allows for the selective reduction of activated alkenes to alkanes. The substrate scope was evaluated, and several disubstituted and monosubstituted alkenes were converted into the corresponding alkanes in yields of up to ≥99% with high functional group tolerance. It was possible to use



Scheme 4. Proposed mechanism for the organocatalytic reduction of activated alkenes by phosphorus redox cycling.

inexpensive and less active poly(methylhydrosiloxane) as the terminal reductant, and a yield of ≥99% was obtained in the renewable solvent BuOAc. The mechanism of the reaction was investigated, and it was revealed that the phosphane oxide is first reduced to the respective phosphane, which subsequently reacts with the substrate in a Michael reaction. A protonation/deprotonation sequence finally leads to the formation of an ylide, which is then hydrolyzed under the reaction conditions.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkenes · organocatalysis · phosphorus · redox catalysis · reduction

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