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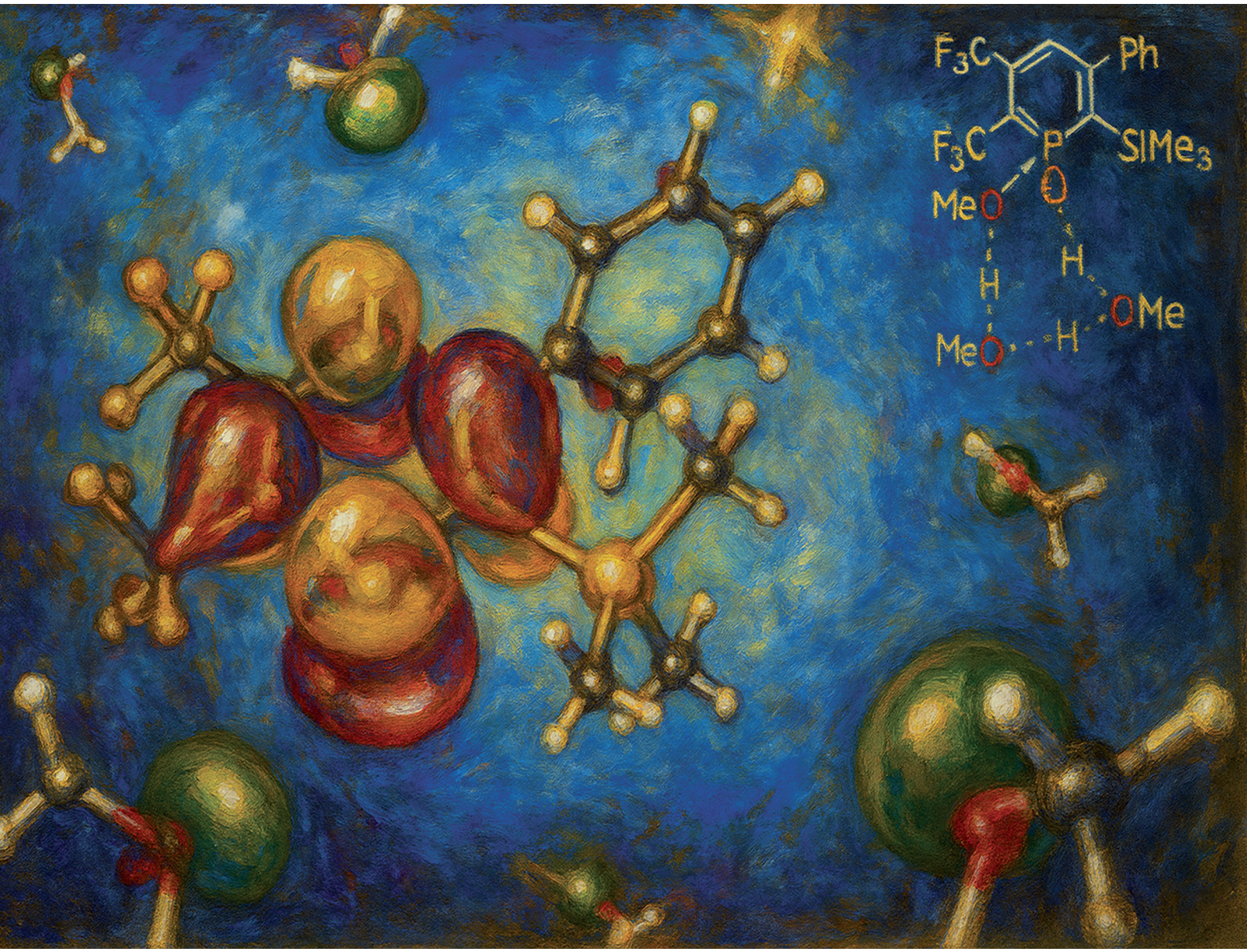

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Dynamic activation of alcohols by an electrophilic phosphinine

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A bis(trifluoromethyl)-substituted phosphinine undergoes reversible oxidative addition of primary and secondary alcohols at the low-coordinate phosphorus(III) atom. This unprecedented reactivity contrasts the general inertness of uncoordinated phosphinines toward protic substrates and provides a rare example of reversible alcohol activation mediated by a main-group element compound. DFT calculations suggest that a hydrogen-bonded methanol network enables the transformation, offering a new concept for dynamic E–H bond activation by electrophilic, aromatic phosphorus heterocycles.

Phosphinines have emerged as versatile phosphorus heterocycles, offering broad opportunities in coordination chemistry, catalysis, small-molecule activation, and photoluminescent materials.[1] The targeted functionalization of the aromatic core enables the fine-tuning of steric and electronic environments, leading to distinctive coordination motifs, tailored optical properties, and notable reactivity toward selected substrates.[2] In numerous cases, transition-metal complexes bearing phosphinine ligands exhibit a pronounced reactivity at the inherently reactive P=C double bond, a consequence of significant disruption of aromaticity upon coordination of the heterocycle to the metal fragment.[2,3] In contrast, uncoordinated phosphinines are generally inert, particularly toward protic reagents.

In 2003, Le Floch and co-workers demonstrated, however, that donor-functionalized SPS-type λ^3-phosphinines (**A**, Fig. 1a) undergo reaction with alcohols and secondary amines *via* formal oxidative addition of the E–H bond (**B**, E = O, N) to the P(III) atom.[4] In the presence of water, this process leads, after tautomerization, to the formation of the corresponding 1,2-dihydrophosphinine oxides. More recently, we have shown that tetrapyridyl-substituted phosphinines (**C**, Fig. 1b) can engage in a selective and, importantly, fully reversible conversion with water to 1,2-dihydrophosphinine oxides (**D**).[5] Mechanistic investigations suggest that, in both cases, the E–H addition proceeds through P/S or P/N cooperativity, facilitated by the additional donor functionality. Re-aromatization of the phosphorus heterocycle and subsequent water elimination drive the backward reaction. In fact, the activation of water is of current interest, as it represents a crucial step in the splitting of water by transition metal complexes. Besides the two examples mentioned above, only a few main-group-element-based compounds such as carbenes, silylenes as well as P(III) compounds are known to cleave heterolytically the strong O–H bond in water and alcohols, in few cases even reversibly.[6–10]

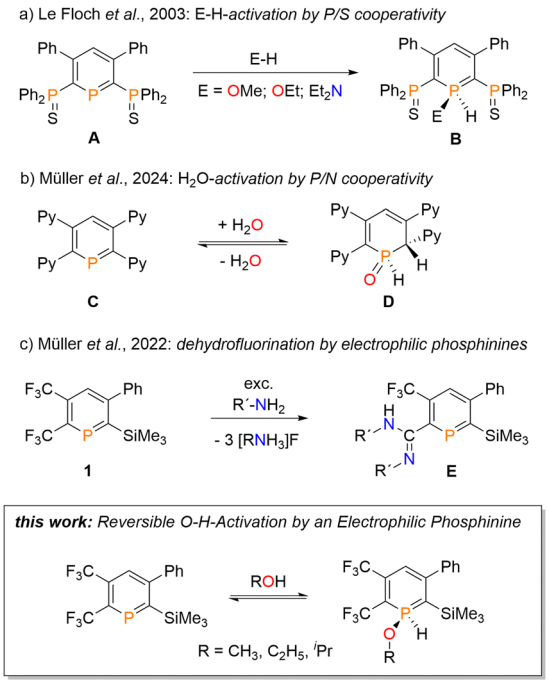

Fig. 1 Reaction of donor-functionalized phosphinines with alcohols, amines and water (a) and (b), triple dehydrofluorination of electrophilic phosphinine **1** with primary amines (c) and brief summary of this work.

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However, it should be emphasized that these compounds differ in their electronic structure substantially from phosphinines and generally display a higher intrinsic reactivity.

In a conceptually distinct approach, we recently developed the CF_3-substituted phosphinine **1** (Fig. 1c).[11] DFT calculations revealed that the LUMO of **1** is stabilized by approximately 0.8 eV relative to the unsubstituted parent phosphinine (C_5H_5P), rendering the phosphorus atom significantly more electrophilic (Fig. 2). We anticipated that such electron-deficient and donor-free phosphinines would be capable of reacting also with less nucleophilic substrates at the phosphorus atom, extending beyond the well-documented reactivity with strong nucleophiles such as organolithium compounds.[12,13] Indeed, phosphinine **1** undergoes a cascade of dehydrofluorination reactions in the presence of primary amines, affording novel amidine-functionalized phosphinines (**E**, Fig. 1).

DFT studies indicated that this transformation is driven by sequential nucleophilic additions of the amine to the electrophilic phosphorus atom, enabling concerted HF elimination reactions. Encouraged by this unprecedented reactivity in phosphinine chemistry, we have now turned our attention to exploring the reactions of **1** with other protic reagents, such as water and alcohols.

The bis(trifluoromethyl)-substituted phosphinine **1** shows a resonance in the ^{31}P NMR spectrum at δ (ppm) = 250.6 (q, $^3J_{P-F}$ = 52.5 Hz). Much to our surprise, **1** is fully inert towards a reaction with H_2O, even if a solution of **1** in THF is heated for 16 h at T = 140 °C in the presence of H_2O (Scheme 1).

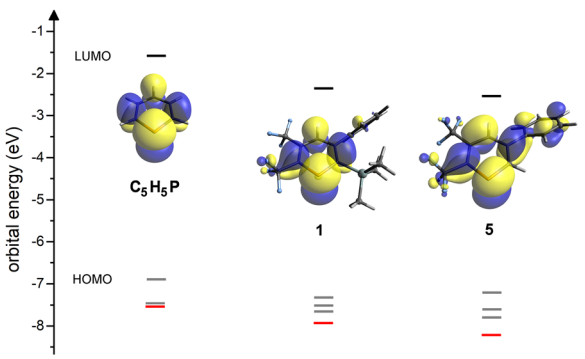
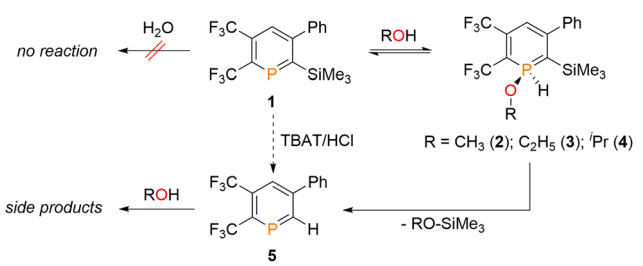


Fig. 2 Frontier Kohn–Sham orbital energies (eV) of the parent phosphinine C_5H_5P, **1** and **5**, the protodesilylated version of **1**. P-Lone pair in red. Calculated at the B3LYP-D3(BJ)/def2-TZVP level of theory.



Scheme 1 Reversible reaction of **1** with methanol to **2** and subsequent reaction to **3**. TBAT: tetrabutylammonium difluorotriphenylsilicate.

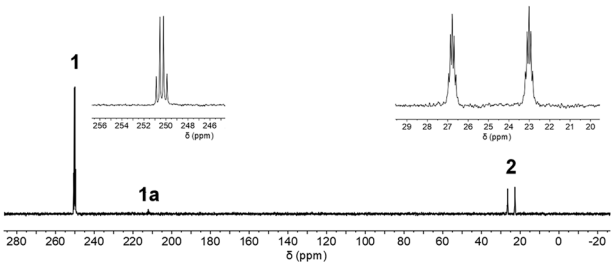


Fig. 3 ^{31}P NMR spectrum of the reaction of **1** with methanol, recorded after 10 minutes and including an enlargement of the respective signals. For trace amount of phosphinine-isomer **1a**: see ref. 14 and Fig. S9.

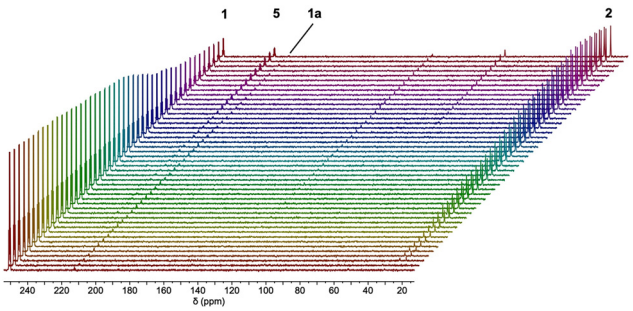


Fig. 4 ^{31}P NMR spectroscopic monitoring of the reaction of **1** in C_6D_6 with 20 equiv. of MeOH over a period of 95 h. The maximal conversion was reached after 45 h. The first 20 measurements were recorded at intervals of 30 minutes, the next 7 at intervals of one hour, 9 at intervals of two hours, and a further 12 at intervals of five hours. Phosphinine-isomer **1a** does not show any reactivity.

In contrast, the slightly more nucleophilic methanol (20 equiv.) slowly reacts with **1**, dissolved in C_6D_6, owing to the distinct chemical shifts in the corresponding ^{31}P NMR spectrum. After 1.5 h of reaction time, a new multiplet at δ (ppm) = 24.9 occurs, from which a large coupling constant of $^1J_{P-H}$ = 609 Hz is observed. Further smaller coupling of the multiplet can be attributed to additional P–F and P–H coupling (Fig. 3). The reaction of **1** with MeOH (20 equiv.) was further monitored by means of ^{31}P NMR spectroscopy (Fig. 4). After 2 days, the maximum conversion of 60% to **2** is reached. Longer reaction times only lead to the formation of side products at δ (ppm) = 220.3, 127.6 and 85.1 (*vide infra*).

The fastest and highest conversion of **1** to **2** (90% after 90 min), along with a minimum formation of by-products, was achieved when the reaction was performed in pure methanol at room temperature. Using CD_3OD instead of CH_3OH, the signal at δ (ppm) = 23.3 splits into a triplet of quartets with $^1J_{P-D}$ = 93.0 Hz and $^3J_{P-F}$ = 14.2 Hz in the ^{31}P NMR spectrum, respectively into a triplet with $^1J_{P-D}$ = 92.9 Hz in the $^{31}P\{^{19}F\}$ NMR spectrum. These results are in line with the formation of the λ^5-phosphinine **2**, respectively the deuterated version **2-D** (Scheme 1).

Much to our delight, single crystals of the reaction product (**2**), suitable for X-ray diffraction, were obtained from this concentrated solution in methanol at T = 4 °C and the molecular structure of the *R*-enantiomer of **2** in the crystal is shown in Fig. 5. The crystallographic characterization of **2** confirms

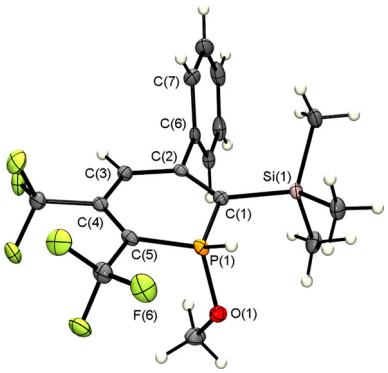


Fig. 5 Molecular structure of the *R*-enantiomer of **2** in the crystal. Displacement ellipsoids are shown at the 50% probability level. Selected bond lengths (Å) and angles (°): P(1)–C(1): 1.732(2); P(1)–C(5): 1.728(2); P(1)–O(1): 1.603(2); O(1)–C(17): 1.448(2); C(1)–C(2): 1.388(3); C(2)–C(3): 1.413(3); C(3)–C(4): 1.376(3); C(4)–C(5): 1.413(3); C(1)–Si(1): 1.900(2). C(1)–P(1)–C(5): 108.24(9).

the formation of the P-chiral λ^5-phosphinine by formal oxidative addition of the strong O–H bond in methanol to the P(III) atom and verifies the observed ^{31}P NMR spectroscopic data. Due to the presence of the CH_3-group at the oxygen atom, no tautomerization to a secondary phosphine oxide can occur, as observed earlier for the reaction of **A** and **C** with H_2O (*vide supra*). It should be mentioned here, that we could achieve for the first time a direct activation of a strong O–H bond to the P(III) atom in a phosphinine that cannot participate in cooperative effects by additional donor-functionalities. We further observed that both the conversion and the selectivity of the O–H bond activation strongly depend on the concentration of the phosphinine and methanol.

As mentioned above, fast and high conversion to **2** along with little formation of by-products is generally observed when high concentrations of phosphinine and methanol are present. In contrast, a much slower conversion and larger amounts of by-products are observed with low concentrations of phosphinine and methanol.

However, in all cases we could not achieve a quantitative formation of the λ^5-posphinine **2**, even in pure methanol. This observation indicates that the O–H activation reaction might be reversible and that an equilibrium between **1** and **2** is present at room temperature. Thus, all volatiles were removed from a concentrated solution of **2** in methanol and the residue was subsequently dissolved in C_6D_6. This process was repeated two times. Remarkably, phosphinine **1** could be recovered almost quantitatively, along with the by-product, that occurs at δ (ppm) = 220.3 in the ^{31}P NMR spectrum. This dynamic reactivity of phosphinine **1** towards methanol strongly resembles our earlier observations, where the tetrapyridyl-functionalized phosphinine **C** reacts reversibly with H_2O.[5] Remarkably, the insertion of the P(III)-atom into the O–H bond of methanol is not restricted to this substrate. We could verify that also ethanol as well as secondary alcohols, such as isopropanol, react with phosphinine **1** reversibly and with a maximum conversion of 80% to the activation products **3** and **4**, respectively (Scheme 1, **3**: R = C_2H_5, $^{31}P\{^{19}F\}$ NMR: δ (ppm) = 22.4, dt, $^1J_{P-H}$ = 606.8 Hz, $^3J_{P-CH_2}$ = 10.1 Hz; **4**: R = ^{i}Pr, $^{31}P\{^{19}F\}$ NMR: δ (ppm) = 18.6, dt, $^1J_{P-H}$ = 607.2 Hz, $^3J_{P-CH}$ = 12.0 Hz, see SI). The sterically more demanding tertiary alcohol ^{t}Bu–OH and the significantly less nucleophilic phenol do, however, not react with phosphinine **1**. Compound **3** (R = C_2H_5) was also characterized crystallographically (see SI).

Subsequently, we turned our attention to the formed side products, observed in the reaction of **1** with CH_3OH. A closer inspection of the NMR spectroscopic data (Fig. 4) revealed that the signal of the species at δ (ppm) = 220.3 can be attributed to the protodesilylated phosphinine **5**, as this compound shows a characteristic quartet of two doublets in the proton-coupled ^{31}P NMR spectrum with $^2J_{P-H}$ = 42.8 Hz (*ortho*-H, Fig. S45). Additionally, we observed that **5** is formed when the maximum conversion to **2** is reached, while the other two minor species are formed simultaneously. This suggests that methanol is not directly responsible for the desilylation of phosphinine **1**, but that product **2** undergoes slow elimination of $Me_3Si–OCH_3$ instead. In fact, the generated siloxane could clearly be identified by means of multinuclear NMR spectroscopy. Moreover, it has been shown for arenes, that MeO-groups in *ortho*-position to a $Si(CH_3)_3$-substituent have a strong influence on the rate of protodesilylation reactions.[15] An alternative, intermolecular process for the elimination of $Me_3Si–OCH_3$ can, however, not be excluded. The two minor side products, which show resonances at δ (ppm) = 127.6 and δ (ppm) = 85.1 could so far not be identified.

From the frontier molecular orbitals (Fig. 2) it is obvious, that phosphinine **5** should be even more electrophilic than **1**, as its LUMO is further stabilized by 0.2 eV. Consequently, **5** should be even more prone to nucleophilic attack at the P(III) atom than **1**. For this purpose, we attempted the targeted synthesis of **5** *via* protodesilylation of **1**. While 2-TMS-substituted phosphinines usually undergo facile protodesilylation in the presence of HCl/Et_2O, this procedure surprisingly failed in this case.[16,17] Nevertheless, **5** could finally be obtained by reaction of **1** with tetrabutylammonium difluorotriphenylsilicate (TBAT)/HCl (Scheme 1, SI).

Phosphinine **5** indeed reacts rapidly with methanol (see Scheme 1). In the $^{31}P\{^{19}F\}$ NMR spectrum, a new species can be detected at δ (ppm) = 19.7, that again shows a doublet with $^1J_{P-H}$ = 623 Hz and an additional $^3J_{P-H}$ coupling of 14.1 Hz. These NMR spectroscopic data are similar to the ones observed for the O–H-activation product **2**. Monitoring the reaction by means of $^{31}P\{^{19}F\}$ NMR spectroscopy (see SI) reveals, that this compound is only a transient species. In fact, several by-products are formed during the course of the reaction, that show resonances at δ (ppm) = 78.0 and between δ (ppm) = 10–35.

In order to propose a reasonable reaction mechanism for the conversion of **1** to **2** (labelled **A** and **B** in the computational study, respectively), we investigated the O–H bond activation reaction computationally. The DFT calculations were performed with Gaussian 16 (Revision C.01) at the TPSS/def2-TZVPP level. First, we considered a direct oxidative addition of the O-H bond to the low-coordinate phosphorus atom *via* **TS(A–B)**. From a thermodynamic point of view, this process is not feasible, as the transition state is very high in energy (+ 9.9 kcal mol^{-1}), as depicted in Fig. 6.

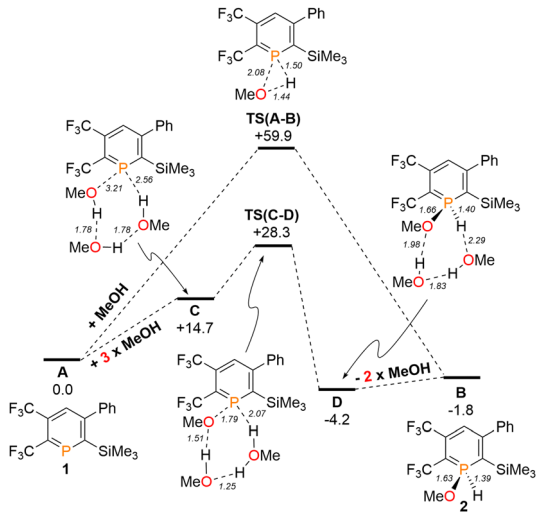


Fig. 6 Free energy profile (calculated with DFT at the TPSS/def2-TZVPP level of theory, energies in kcal mol^{-1}) of CH_3OH addition at **1**. The upper path represents a direct oxidative addition of the O–H bond to the phosphorus atom *via* a three-coordinate transition state. The lower path proceeds *via* a tri-methanol hydrogen bonded network and cascade proton transfer.

However, the involvement of two additional methanol molecules decreases the energy of the corresponding transition state (**TS(C–D)**) considerably to +28.3 kcal mol^{-1}. In **TS(C–D)**, an interaction of the oxygen atom of one methanol molecule with the phosphorus atom (LUMO) occurs. This results in a more basic character of the phosphorus lone-pair, while a network of hydrogen bonding facilitates a cascade proton-transfer to the phosphorus atom under formation of **B**. The involvement of a network of substrate molecules, aggregated by hydrogen bonding, has been postulated for other E–H bond activation reactions, particularly by carbenes.[7] Interestingly, the energy profile for the conversion **1** → **2** further illustrates that product **2** is energetically stabilized against the starting phosphinine **1** by only 1.8 kcal mol^{-1}, and intermediate **D** is stabilized against **1** by 4.2 kcal mol^{-1}.

This is perfectly in line with our experimental observation, that the reaction of **1** with methanol is reversible. Moreover, our here proposed mechanism for the O–H bond activation contrasts the commonly accepted mechanisms for E–H activation reactions by strongly nucleophilic carbenes *via* proton abstraction.[6,7]

In conclusion, we have demonstrated that a bis(trifluoromethyl)-substituted phosphinine undergoes a reversible oxidative addition of primary and secondary alcohols to the low-coordinate phosphorus atom. With methanol and ethanol as a substrate, the resulting λ^5-phosphinines were characterized crystallographically. This transformation represents the first direct O–H bond activation at a non-donor-functionalized phosphinine and establishes a rare case of reversible alcohol activation by a main-group compound. Mechanistic investigations show that a hydrogen-bonded methanol network significantly lowers the activation barrier, in sharp contrast to established pathways for E–H bond activation by strongly nucleophilic main-group compounds. These findings expand the reactivity landscape of electrophilic phosphinines beyond strong nucleophiles and suggest new opportunities for exploiting such electron-deficient heterocycles in dynamic small molecule activation.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the Supplementary information (SI). Supplementary information is available. See DOI: **https://doi.org/10.1039/d5cc05302a**.

CCDC 2487210 (**2**) and 2487209 (**3**) contain the supplementary crystallographic data for this paper.[18a,b]

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