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Reduction of Activated Carbonyl Groups Using Alkylphosphanes as Reducing Agents: A Mechanistic Study

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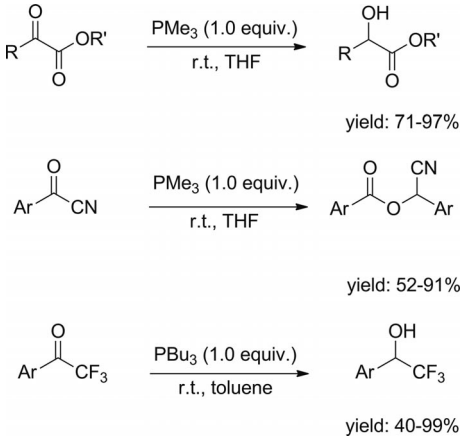
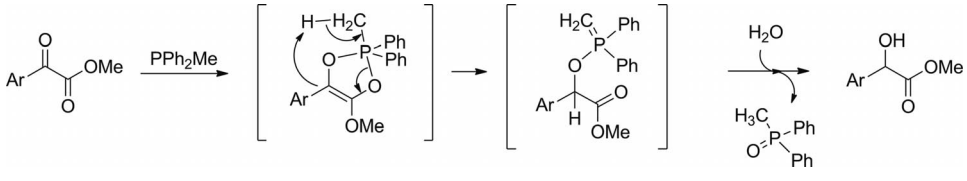
A comprehensive mechanistic investigation on the reduction of activated carbonyl groups using alkylphosphanes as reducing agents has been conducted through a combination of experimental as well as computational studies. Both approaches show that this kind of reduction proceeds either through proton transfer from alkylphosphanes and cleavage by water during work-up or through another reaction pathway involving the participation of water at the initial stage and a two-fold proton transfer to afford the product.

Introduction

Organophosphorus compounds have proven to be particularly versatile as catalysts or reagents in many types of reactions, and are extensively applied in organic synthesis. The common applications of organophosphorus compounds include the use of phosphonium ylides in the Wittig reaction,[1] the use of phosphanes in the Staudinger and Mitsunobu reactions,[2] and the use of phosphanes as ligands in transition-metal-mediated processes.[3] In the recent decade, phosphanes have been intensively used as nucleophilic catalysts in Morita–Baylis–Hillman/aza-Morita–Baylis–Hillman reactions, and Michael addition reactions and their related reactions.[4] However, the use of phosphanes as reductants accompanied by a proton transfer has rarely been seen. In 2006, we first reported an interesting reduction of activated carbonyl groups using alkylphosphanes as reducing agents that provides a convenient method to afford α-hydroxyl esters, ketones, and phosphonates (Scheme 1).[5] Subsequently, the scope of this reduction process was extended to other compounds including activated carbonyl groups such as 2,2,2-trifluoro-1-arylethanones, and reductive coupling of acyl cyanides was also achieved (Scheme 1).[6] Recently, our group also demonstrated that the C=C double bond in isatin-derived electron-deficient alkenes could be exclusively reduced in the presence of alkylphosphanes and water.[7] Based on the preliminary results of deuterium and ^{18}O labeling experiments, the mechanism



Scheme 1. Reduction of activated carbonyl groups by alkylphosphanes.



Scheme 2. Proposed mechanism for reduction of α-keto esters by phosphanes.

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for reduction of α-keto esters by alkylphosphanes was proposed to proceed as shown in Scheme 2, which involves proton transfer from alkylphosphanes and cleavage by water during work-up.[5]

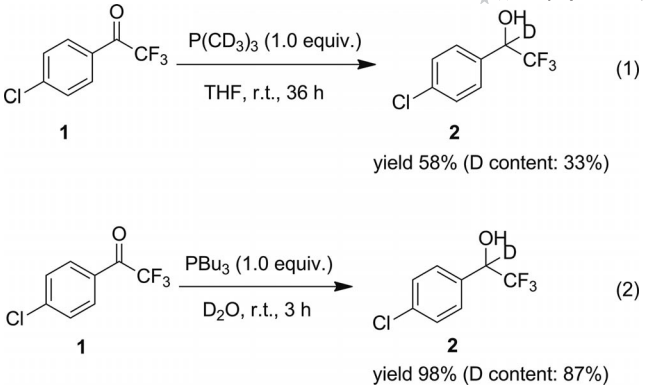
To the best of our knowledge, a comprehensive mechanistic investigation into this reduction process has not been reported, and several intricacies involved in the reaction mechanism are unclear. Herein, we wish to elucidate the mechanistic details of this interesting reduction through combined experimental as well as computational studies.

Results and Discussion

Experimental Studies on Mechanism

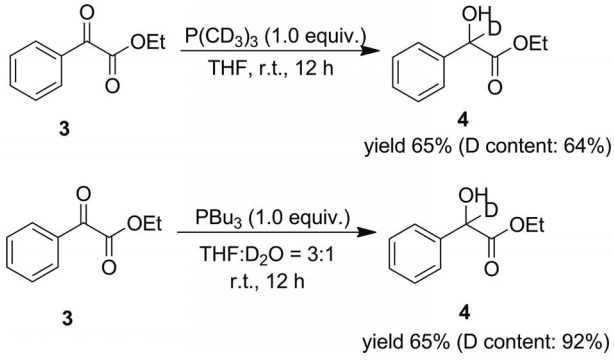
Our investigation began with a series of deuterium labeling experiments to examine which proton sources were transferred to the products in this reduction reaction in the presence of alkylphosphanes. The reduction of 1-(4-chlorophenyl)-2,2,2-trifluoroethanone (**1**) was initially carried out in the absence of water using $P(CD_3)_3$ as a reducing agent, affording the product **2** in 58% yield with relatively low deuterium content (33%) at the C-1 position [Scheme 3, Equation (1)]. This observation agreed with our previous findings that the proton was directly transferred from the alkylphosphane to the product **2**, however, the low deuterium content implied that the proton comes not only from phosphane, but also from other sources. Presumably, water may be another proton source that could directly participate in the reaction. Subsequently, we examined the same reduction reaction using PBu_3 with water at the initial stage. The reduction of **1** took place smoothly within three hours at room temperature in the presence of PBu_3 and D_2O, leading to the corresponding product **2** in 99% yield with high deuterium content (87%) at the C-1 position [Scheme 3, Equation (2)]. This result indicated that the proton in water was indeed transferred into the product, namely, water is another proton source in the reduction reaction using alkylphosphane as a reducing agent. It should be mentioned here that this reduction does not occur when only **1** and H_2O are mixed in the absence of alkylphosphane. Presumably, there are two reaction pathways for the reduction reaction of activated carbonyl compounds in the presence of alkylphosphanes, which includes our previously suggested reaction pathway through the proton transfer from alkylphosphanes and cleavage by H_2O during work-up, and another reaction pathway involving water participation in the reaction at the initial stage.

We then conducted similar reduction reactions of α-keto ester **3** without water using $P(CD_3)_3$ as reducing agent and with D_2O in the presence of PBu_3, respectively. The results are shown in Scheme 4. The product **4** was obtained in 65% yield with 64% deuterium content at the C-1 position when the reaction was conducted without water in the presence of $P(CD_3)_3$. The same product was also acquired in 65% yield with high deuterium content (92%) when the reaction was conducted in the presence of D_2O and PBu_3. These results are consistent with the above observations for the



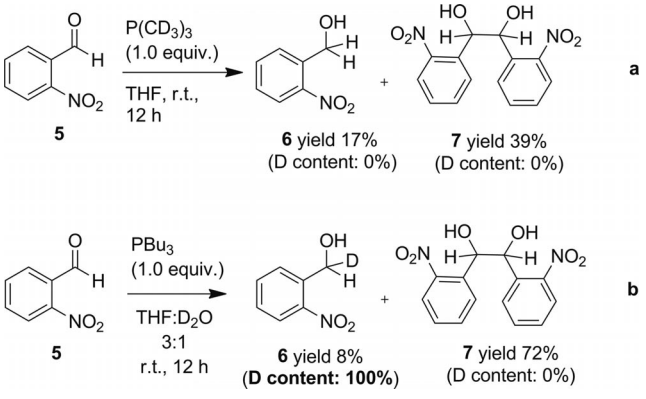
Scheme 3. Reduction of **1** using alkylphosphanes as reducing agents.

reduction of **1**, suggesting that there are also two reaction pathways for the reduction reaction of α-keto ester **3** and the proton transferred in the reduction process is either from alkylphosphanes or from water.



Scheme 4. Reduction of **3** using alkylphosphanes as reducing agents.

To examine the scope of this reduction reaction promoted by alkylphosphanes, we further investigated the reduction of *o*-nitrobenzaldehyde (**5**) under similar reaction conditions; the results are presented in Scheme 5. The reaction still occurred in the presence of $P(CD_3)_3$, however, dimer **7** was formed as the main product in moderate yield (39%) along with the reduced product **6** in very low yield



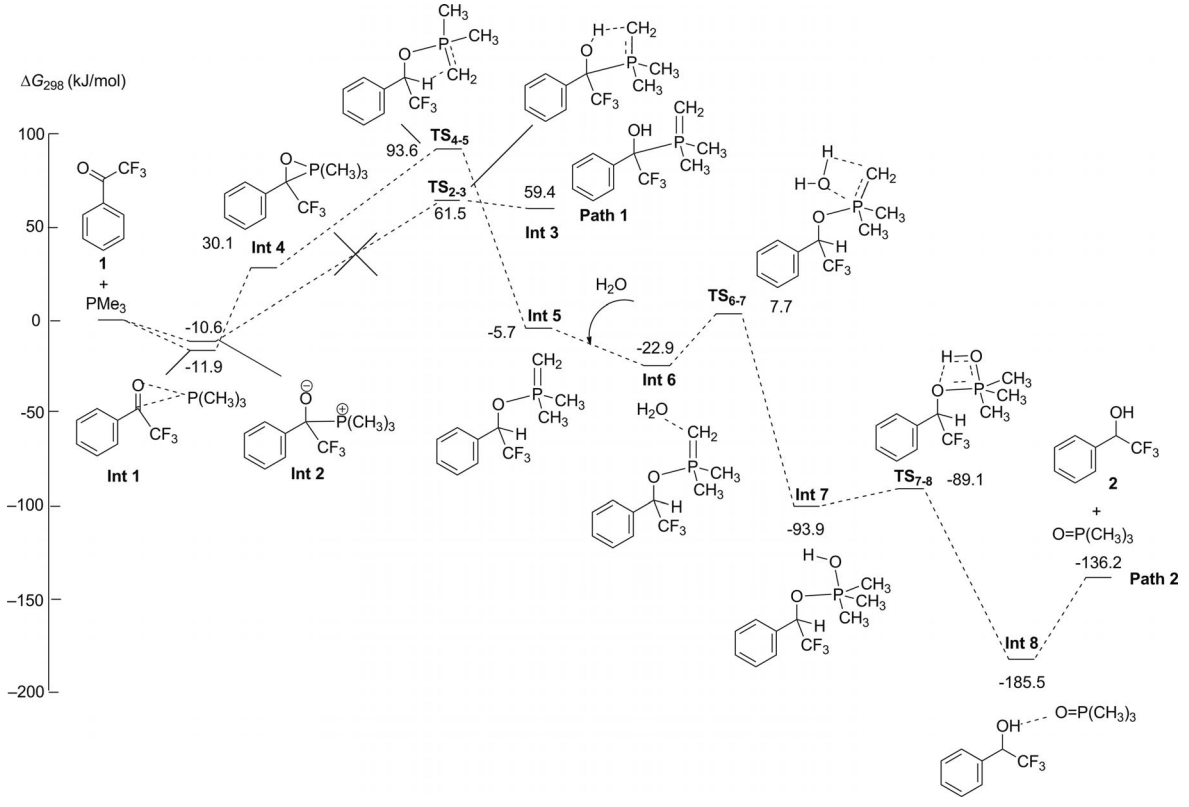
Scheme 5. Reduction of **5** using alkylphosphanes as reducing agents.

(17%), which indicated that some other reactions proceeded when aldehydes were employed as substrates [Scheme 5, Equation (a)]. Surprisingly, no deuterium was detected in the products, indicating that the transferred proton during the reaction does not stem from the alkylphosphane. These results implied that the reaction pathway through proton transfer from alkylphosphane and cleavage by H_2O during work-up does not proceed when aldehydes are used as substrates. The reaction was also carried out in the presence of D_2O and PBu_3, affording the dimeric product **7** in 72% yield without deuterium content, and the reduced product **6** in 8% yield with 100% deuterium content. These results show that water must be required to start the reduction reaction; however, it is not the main reaction in this system.

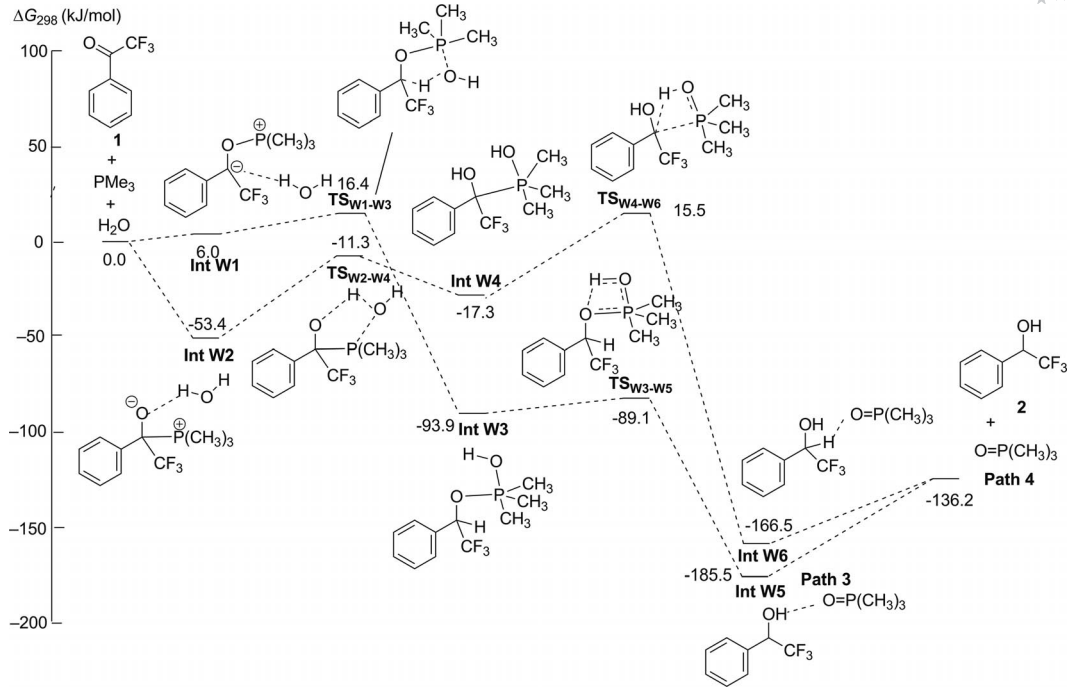
Theoretical Investigations on the Reaction Pathways

We first computationally explored possible reaction pathways using the reduction reaction of **1** with PMe_3 as a model system. As aforementioned, this kind of reduction reaction may proceed through two pathways, thus, we investigated several possible reaction pathways at the B2PLYP-M2/6-31+G(2d)//mPW1K/6-31+G(d) level of theory.[8] We first examined the possible reaction pathways using **1** and PMe_3 without H_2O at the initial stage. The attack of PMe_3 on the carbonyl group of **1** initiates the reaction, which results in a relaxed complex **Int 1** of **1** and PMe_3 or zwitterionic intermediate **Int 2**. After crossing a barrier through transition state $\mathbf{TS_{2-3}}$ of 61.5 kJ/mol, intermediate **Int 3** is formed (Path 1 shown in Scheme 6). However, intermediate **Int 3** is thermodynamically much less stable (58.7 kJ/mol), indicating that this reaction pathway (Path 1) is less likely to occur than Path 2 shown in Scheme 6. Because the experiments were conducted at room temperature, we excluded this thermodynamically unfavorable reaction pathway (Path 1) and focused our attention on another reaction pathway (Path 2). We found that the phosphane can approach the carbonyl group to give intermediate **Int 4** without an energy barrier. One hydrogen atom from PMe_3 is transferred to afford intermediate **Int 5**, which is thermodynamically more stable, by passing through transition state $\mathbf{TS_{4-5}}$ (90.6 kJ/mol). Then, one water molecule is induced at this stage, giving the relaxed complex **Int 6**. The O–H bond in water is then cleaved over transition state $\mathbf{TS_{6-7}}$, leading to the more stable intermediate **Int 7**, which undergoes a second hydrogen transfer to afford product complex **Int 8** via transition state $\mathbf{TS_{7-8}}$. Cleavage of this complex to yield the separate components **2** and $O{=}PMe_3$ is therefore endothermic by approximately 136 kJ/mol. The results of these calculations show that the hydrogen atom from PMe_3 could be transferred to give thermodynamically stable intermediates that undergo hydrolysis to afford a more stable product, which are in line with the aforementioned experimental findings.

Subsequently, we also investigated the possible reaction pathways at the B2PLYP-M2/6-31+G(2d)//mPW1K/6-31+G(d) level using **1** and PMe_3 with H_2O present at the initial stage. Thus, the attack of PMe_3 on the carbonyl group of **1** initiates the reaction and is associated with one water molecule, leading to two kinds of intermediates



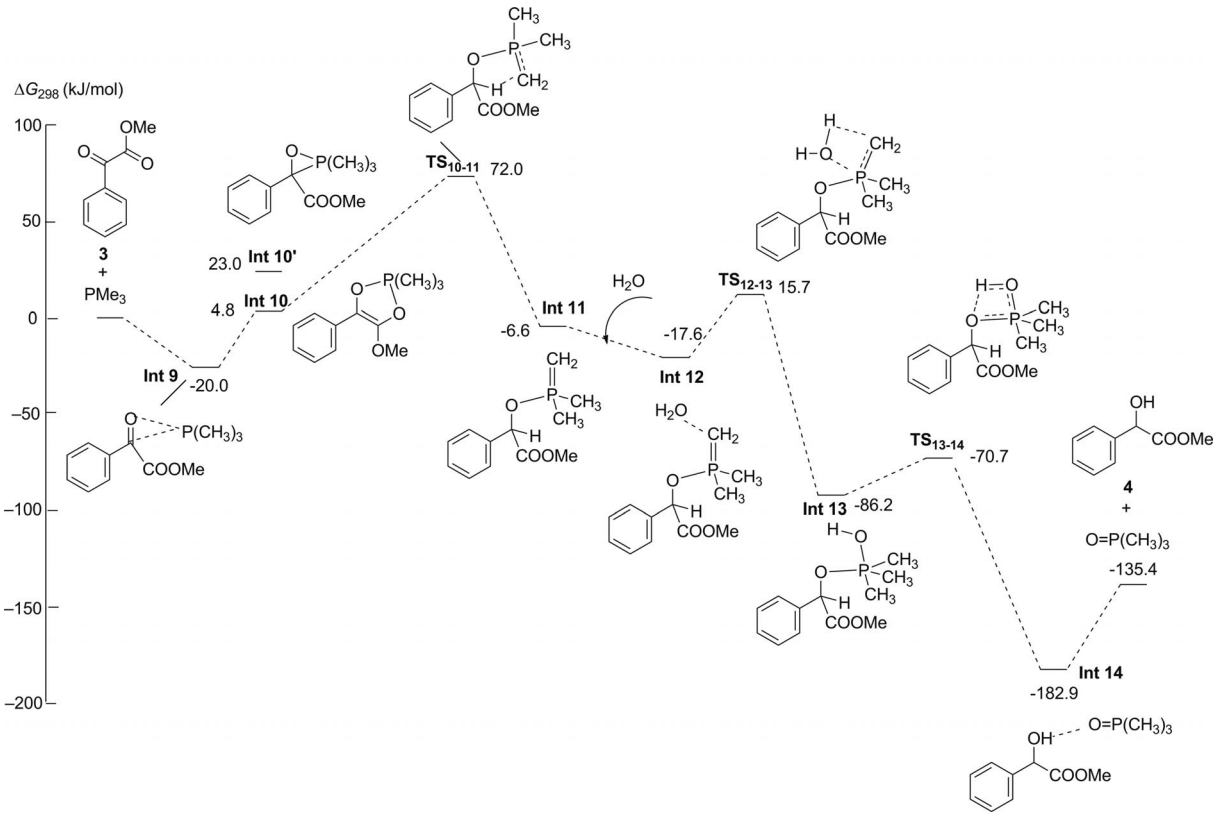
Scheme 6. Energy profiles for the reduction of **1** using PMe_3 without water at the initial stage.



Scheme 7. Energy profiles for the reduction of **1** using PMe_3 with water at the initial stage.

Int W1 and **Int W2**. The formation of intermediate **Int W1** is slightly endothermic by 6.0 kJ/mol with respect to the separated reactants. In contrast, the formation of intermediate **Int W2** is more exothermic by 53.4 kJ/mol with respect to the separated reactants, indicating that intermediate **Int W2** is much more stable. We then investigated two possible reaction pathways (see Scheme 7) starting from intermediates **Int W1** and **Int W2**, respectively. Starting from intermediate **Int W1**, the O–H bond of water is cleaved and the hydrogen is first transferred to the carbon center, leading to the formation of intermediate **Int W3** through a five-membered cyclic transition structure $\mathbf{TS_{W1–W3}}$ with an energy barrier of 10.4 kJ/mol. Subsequently, intermediate **Int W3** undergoes another proton transfer via a second four-membered ring transition structure $\mathbf{TS_{W3–W5}}$, leading to the product complex **Int W5**, which then affords the separated products. Another possible reaction pathway starts from intermediate **Int W2**; in this case the O–H bond of water is cleaved and the hydrogen is transferred to the oxygen center, leading to the formation of intermediate **Int W4** through a five-membered cyclic transition structure $\mathbf{TS_{W2–W4}}$ with an energy barrier of 42.1 kJ/mol. Subsequently, the second proton is also transferred via another four-membered cyclic transition structure $\mathbf{TS_{W4–W6}}$, leading to the product complex **Int W6**, which then affords the separated products. Because the formation of the intermediate **Int W2** is exothermic, the initial steps of the reaction take place easier at room temperature. Thus, we propose that the reaction takes place following the Path 4.

We further investigated the reduction reaction of **3** theoretically using PMe_3 as reducing agent with and without water at the initial stage. First, we investigated the reaction pathway for the reduction of **3** in the presence of PMe_3 without H_2O at the initial stage. Thus, attack of PMe_3 to the carbonyl group of **3** initiates the reaction, which results in a relaxed complex **Int 9** of compound **3** and PMe_3 or zwitterionic intermediate **Int 9′** (Scheme 8). Because the reaction starting from **Int 9′** leads to the more thermodynamically unfavorable intermediate (for details, see the Supporting Information), we focused our investigations on the reaction pathway starting from the relaxed complex **Int 9**. When PMe_3 further approaches the carbonyl group, either intermediate **Int 10**, which was proposed previously,[5] or intermediate **Int 10′**, which is similar to **Int 4**, could be formed without an energy barrier. Intermediate **Int 10** is more stable than intermediate **Int 10′** by approximately 20 kJ/mol. Thus, we examined the next step from intermediate **Int 10**, which is thermodynamically more stable. One hydrogen atom from PMe_3 is transferred to give intermediate **Int 11** by passing through transition state $\mathbf{TS_{10–11}}$ (72.0 kJ/mol). At this stage, one water molecule is induced into the reaction, giving the relaxed complex **Int 12**. The O–H bond in water is then cleaved over transition state $\mathbf{TS_{12–13}}$, leading to the more stable intermediate **Int 13**, which undergoes a second hydrogen transfer process to afford product complex **Int 14** via transition state $\mathbf{TS_{13–14}}$. Cleavage of this complex to yield the separate components **4** and $O{=}PMe_3$ is therefore endothermic by approximately 47.5 kJ/mol. The results of these calculations show that the hydrogen atom from PMe_3 could also be transferred to α-keto ester, giving thermodynamically stable intermediates that subsequently undergo hydrolysis to afford the more stable reduction product, which are in line with the aforementioned experimental findings.

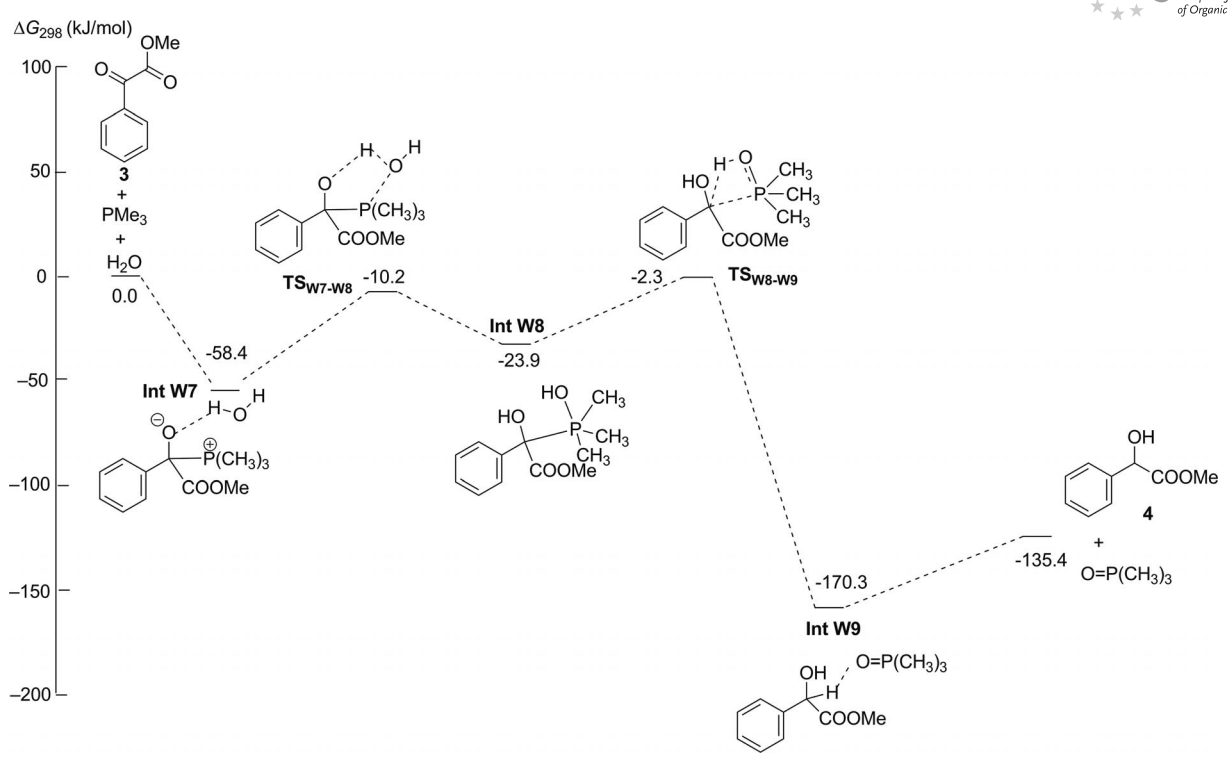


Scheme 8. Energy profile for the reduction of **3** using PMe_3 without water at the initial stage.

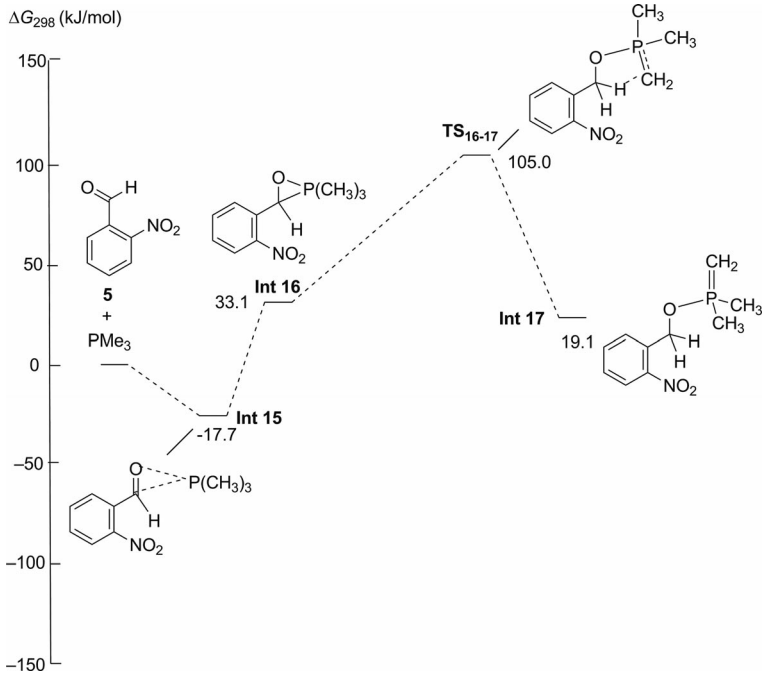
We subsequently investigated the reaction pathway at the B2PLYP-M2/6-31+G(2d)//mPW1K/6-31+G(d) level using **3** and PMe_3 with H_2O at the initial stage. The reaction is initiated by attack of PMe_3 on the carbonyl group of **3** and association with one water molecule, leading to two kinds of intermediates **Int W7** and **Int W7′**. Because intermediate **Int W7′** is less stable than intermediate **Int W7** by approximately 43.0 kJ/mol (for details, see the Supporting Information), we focused on the reaction pathway starting from intermediate **Int W7**, which is more stable by 20.0 kJ/mol with respect to the separated reactants. We then investigated the possible reaction pathway from intermediate **Int W7** (see Scheme 9). Starting from intermediate **Int W7**, the O–H bond of water is cleaved and the hydrogen is first transferred to the carbon center, leading to the formation of intermediate **Int W8** through a five-membered cyclic transition structure $\mathbf{TS_{W7–W8}}$ with an energy barrier of 10.4 kJ/mol. Subsequently, intermediate **Int W8** undergoes a second proton transfer via a second five-membered ring transition structure $\mathbf{TS_{W8–W9}}$, leading to the product complex **Int W9**, which then affords the separated products.

We also investigated the reduction of *o*-nitrobenzaldehyde **5** using PMe_3 as a reducing agent with and without water at the initial stage. First, we investigated the reaction pathway at the B2PLYP-M2/6-31+G(2d)//mPW1K/6-31+G(d) level using **5** and PMe_3 without H_2O at the initial stage (Scheme 10). The attack of PMe_3 on the carbonyl group of **5** initiates the reaction, leading to a relaxed complex **Int 15** of **5** and PMe_3. It should be mentioned here that the stable zwitterionic intermediate similar to **Int 2** could not be generated in this case. We found that another intermediate, **Int 16**, could be formed from a relaxed complex **Int 15** without an energy barrier. One hydrogen atom from PMe_3 is transferred to afford intermediate **Int 17**, which is thermodynamically more stable than intermediate **Int 16**, by passing through transition state $\mathbf{TS_{16–17}}$ (105.0 kJ/mol). However, intermediate **Int 17** is thermodynamically less stable with respect to the separated reactants, indicating that this process is thermodynamically unfavorable. Moreover, the reaction energy barrier of 123.7 kJ/mol is certainly too high for a room temperature reaction. Thus, the reduction reaction of compound **5** without water at the initial stage cannot occur under the standard experimental conditions shown above. This result is in line with experimental findings that no H/D exchange takes place during the course of the reaction using **5** and $P(CD_3)_3$ without water at the initial stage.

Subsequently, we investigated the reaction pathway at the B2PLYP-M2/6-31+G(2d)//mPW1K/6-31+G(d) level using **5** and PMe_3 with H_2O at the initial stage. Thus, attack of PMe_3 on the carbonyl group of compound **3** initiates the reaction and is associated with one water molecule, leading to two kinds of intermediates, **Int W10** and **Int W10′**. Because the formation of intermediate **Int W10′** is slightly exothermic by 15.6 kJ/mol with respect to the separated reactants (for details, see the Supporting Information), we focused on the reaction pathway starting from intermediate **Int W10**, which is more stable by 52.2 kJ/mol with respect

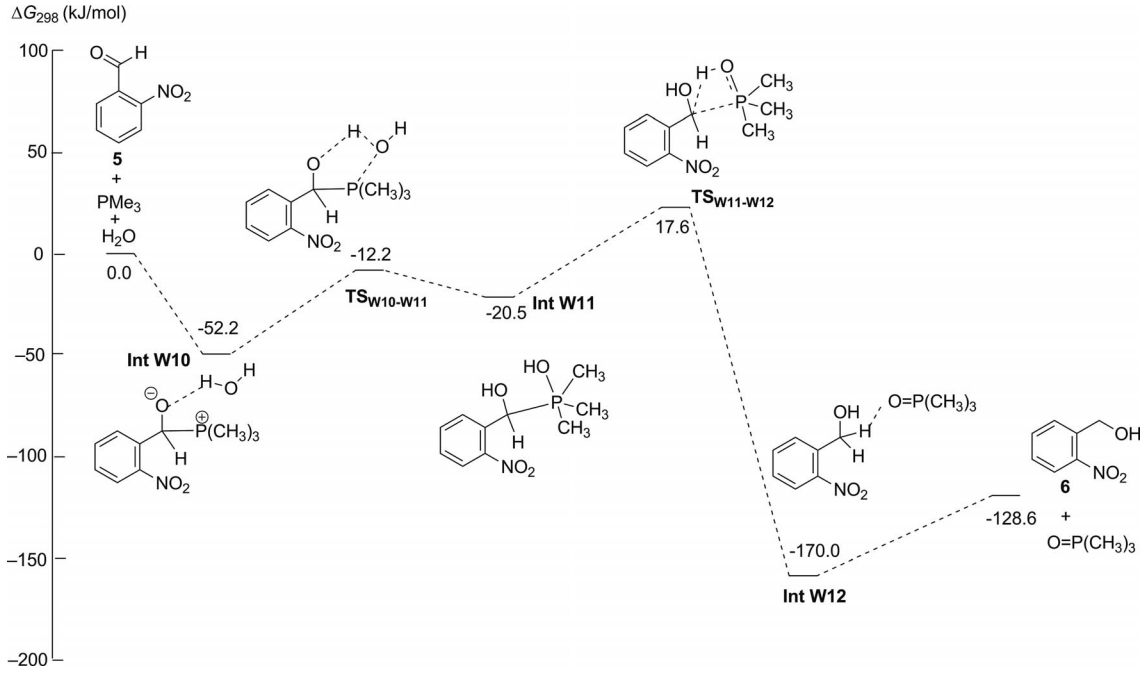


Scheme 9. Energy profile for the reduction of **3** using PMe_3 with water at the initial stage.



Scheme 10. Energy profile for the reduction of **5** using PMe_3 without water at the initial stage.

to the separated reactants. We then investigated the possible reaction pathway (see Scheme 11) starting from intermediate **Int W10**. Starting from this intermediate, the O–H bond of water is cleaved and the hydrogen is first transferred to the carbon center, leading to the formation of intermediate **Int W11** through a five-membered cyclic transition structure $\mathbf{TS_{W10–W11}}$ with an energy barrier of 38.1 kJ/mol. Subsequently, intermediate **Int W11** undergoes a second proton transfer via the second five-membered cyclic transition structure $\mathbf{TS_{W11–W12}}$, leading to the product complex **Int W12**, and then to the separated products. These computational results suggest that there is only one reaction path-



Scheme 11. Energy profile for generation of **6** in the reduction reaction of **5** using PMe_3 with water at the initial stage.

way for the reduction reaction of *o*-nitrobenzaldehyde **5** and that the proton transferred during the course of reaction is only from water. According to the aforementioned experimental results, the main product obtained for this reaction was the dimeric diol product **7**, which was probably formed by initial benzoin condensation, followed by reduction of the hydroxy ketone.

Conclusions

We have performed a detailed investigation into the mechanism for reduction of activated carbonyl groups using alkylphosphanes as reducing agents through computational analysis and deuterium labeling experiments. Both theoretical and experimental studies show that this kind of reduction reaction proceeds either through proton transfer from alkylphosphanes and cleavage by water during work-up, or through another reaction pathway involving water participation from the initial stage and through double proton transfer to afford the product. These two reaction pathways may exist simultaneously during the course of the reaction.

Experimental Section

General Remarks: Melting points were obtained with a Yanagimoto micro melting point apparatus. ^1H and ^{13}C NMR spectra were recorded for a solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard; *J* values are given in Hertz. Mass spectra were recorded with a HP-5989 instrument and HRMS were measured with a Finnigan MA+ mass spectrometer. Solid compounds reported in this paper gave satisfactory CHN microanalyses with a Carlo–Erba 1106 analyzer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF254 silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure. Reactions were performed under argon. $P(CD_3)_3$ was prepared by the reaction of tri-*o*-tolyl phosphite with CD_3MgI, which was prepared from CD_3I (D content >90%) with magnesium, under standard conditions.[8]

Typical Reaction Procedure for the Preparation of 2: A mixture of 1-(4-chlorophenyl)-2,2,2-trifluoroethanone (0.5 mmol) and PBu_3 (0.5 mmol) in solvent was stirred under an argon atmosphere at room temperature for the required time. After the reaction, the solution was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/petroleum ether, 1:20) to afford pure **2**.

Computational Details: The geometries of all systems were optimized at the mPW1K/6-31+G(d) level of theory. Subsequent frequency calculations on the stationary points were carried out at the same level of theory to ascertain the nature of the stationary points as minima or first-order saddle points on the respective potential energy surfaces. All transition states were characterized by one and only one imaginary frequency pertaining to the desired reaction coordinate. The intrinsic reaction coordinate (IRC) calculations were carried out at the same level of theory to further authenticate the transition states. The conformational space of flexible systems was first searched using the MM3 force field and the systematic search routine in the TINKER program. All stationary points located at force field level were then reoptimized at the mPW1K/6-31+G(d) level as described before.[9] Thermochemical corrections to 298.15 K were calculated for all minima from unscaled vibrational frequencies obtained at the same level. The thermochemical corrections were combined with single-point energies calculated at the B2-PLYP-M2/6-31+G(2d)//mPW1K/6-31+G(d) level to yield free energy G_{298} at 298.15 K. In conformationally flexible systems, enthalpies were calculated as Boltzmann-averaged values over all available conformers. All quantum mechanical calculations were performed with the Gaussian 03[10] software.

Supporting Information (see footnote on the first page of this article): Spectroscopic data and computational details are available.

Acknowledgments

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