

Computational Exploration of a Redox-Neutral Organocatalytic Mitsunobu Reaction

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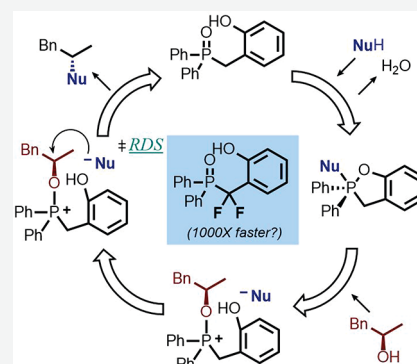
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ABSTRACT: The mechanism of the redox-neutral organocatalytic Mitsunobu reaction, catalyzed by (2-hydroxybenzyl)diphenylphosphine oxide, reported by Denton et al., has been studied computationally with ω B97X-D density functional theory. We discovered that the nucleophilic substitution reaction between carboxylate and alkoxyphosphonium ions, to reform the phosphine oxide catalyst, is the rate-determining step of the overall process and is significantly accelerated compared with a general-acid-catalyzed S_N2 reaction. The (2-hydroxybenzyl)diphenylphosphine oxide is regenerated and activated in every catalytic cycle via intramolecular dehydration/cyclization. We also designed several phosphine oxide catalysts that we predict to be more effective catalysts.



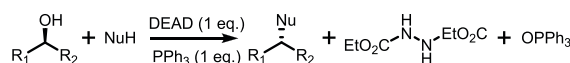
INTRODUCTION

The Mitsunobu reaction converts an alcohol into a variety of derivatives with inversion of configuration at the carbinol carbon.¹ Alcohols are converted into esters, ethers, amines, amides, and related derivatives.² Due to this advantage, Mitsunobu reactions have been widely applied not only in the field of small molecule synthesis^{2,3} but also in the field of bioorganic chemistry, such as structural modifications of saccharides,⁴ peptides,⁵ and nucleic acids,⁶ and also in polymer synthesis.⁷ However, a major drawback of conventional Mitsunobu reactions is that stoichiometric amounts of the azodicarboxylate and phosphine reagents must be used, and the hydrazine and phosphine oxide side products are not easily separated from the crude product mixtures (Figure 1A), although various methods have been developed to address this issue.⁸ In last few decades, the Mitsunobu reaction has been made catalytic, first based on the redox cycling of the azodicarboxylate reagent⁹ and then catalytic in the phosphine¹⁰ (Figure 1B). In spite of the advantages of these catalytic protocols, a stoichiometric amount of oxidant or reductant must still be used.

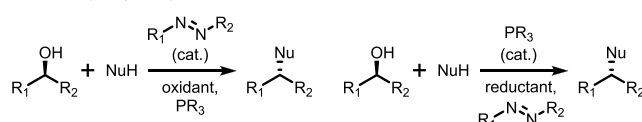
In 2019, Denton et al. reported a fully catalytic and redox-neutral Mitsunobu reaction protocol using only a catalytic amount of an organophosphine oxide catalyst (Figure 1C).¹¹ The phosphine oxide, usually the byproduct of the Mitsunobu reactions, is now the catalyst. This protocol generates water as the only side product while still retaining merits of the classical Mitsunobu reaction, such as outstanding stereochemical control and excellent substrate tolerance.

Mitsunobu and co-workers studied various intermediates experimentally and proposed a reaction pathway^{1,3} for the

A. Classical Mitsunobu reactions



B. Redox-cycling catalytic Mitsunobu reactions



C. Redox-free catalytic Mitsunobu reactions

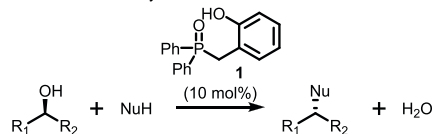
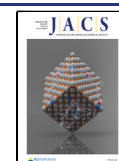


Figure 1. Mitsunobu reactions.

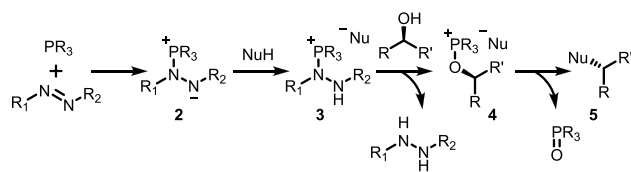
original Mitsunobu reaction which involves four stages (Figure 2A): (i) generation of quaternary phosphonium–azoate zwitterionic intermediate 2 from the phosphine and azodicarboxylate reactants; (ii) protonation of 2 leading to hydrazyl phosphonium 3 and nucleophilic Nu^- ; (iii) alcohol attack on the phosphorus center of 3 leading to alkoxy–

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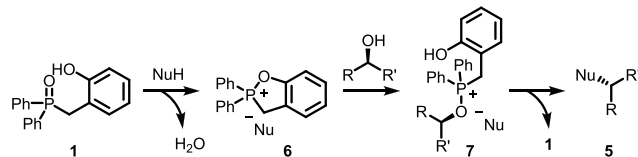
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A. Mechanism of a classical Mitsunobu reaction



B. Mechanism of a redox-free catalytic Mitsunobu reaction

**Figure 2.** Mechanism of a classical and a redox-neutral catalytic Mitsunobu reaction.

phosphonium salt **4**; (iv) an essentially intramolecular S_N2 displacement by the nucleophile anion in an ion pair to generate product **5**. The acidity of the nucleophile (NuH), often a carboxylic acid, significantly influences the reaction pathway and outcome.¹² This mechanism was further elaborated¹³ by multiple research groups via investigations of unusual reaction outcomes,¹⁴ factors that affect reaction rate,^{10c,15} reactive intermediates,¹⁶ and stereochemical outcomes.¹⁷ Nevertheless, the structures of various hypervalent phosphorus intermediates involved in the Mitsunobu reaction are largely unknown. QM calculations allow systematic investigations of reaction pathways and reveal the structural features of various intermediates. To date, the only reported computational studies of the Mitsunobu reaction were by Anders et al. in 2005 using PH_3 as a model reagent and methanol as the alcohol.¹⁸ Comprehensive DFT studies were carried out to describe the interconversions of different phosphonium intermediates and ligand exchange processes on the phosphorus center, which established a detailed reaction pathway. Interestingly, both retention and inversion pathways are predicted to occur with different phosphines and substrates, but the inversion path is favored with the usual substrates and conditions.¹⁸

COMPUTATIONAL METHODS

Density functional theory (DFT) calculations were performed with Gaussian 09.¹⁹ The geometry of each species was optimized using the $\omega\text{B97X-D}$ functional²⁰ and the 6-311G(d,p) basis set with the CPCM²¹ solvation model for toluene. For the reaction pathway involving triflic anhydride (Figure S1), the calculations were performed with the CPCM solvation model for chloroform. Frequency calculations were performed at the same theoretical level as for geometry optimizations to verify the stationary points as either minima or first-order saddle points on the potential energy surface as well as to obtain thermal Gibbs free energy corrections at 298 K. All DFT calculations were with an ultrafine integration grid. Optimized structures are presented using CYLview.²² Conformational searches were performed with the Merck molecular force field (MMFF) implemented in the Spartan 16 program package²³ to locate the low-energy conformations.

RESULTS AND DISCUSSION

Denton et al. proposed a mechanism and catalytic cycle (Figure 2B) for the catalytic reaction that involves (i) dehydrative generation of cyclo-phosphonium salt **6** from phosphine oxide catalyst **1**, (ii) generation of alkoxy-phosphonium salt **7** via ring opening of **6** and proton transfer

from the alcohol, and finally (iii) a S_N2 attack from the nucleophile to generate the product with the inverted stereochemistry and regeneration of the phosphine oxide catalyst. Experiments were performed to support this mechanism that include structure–activity relationship studies of the catalyst, isotope labeling, and capture of the reactive species. The first cyclo–dehydration step was proposed to be the turnover-limiting step.

Extensive experimental studies showed that phosphonium **6** is the active species prior to the S_N2 reaction. A key phosphonium species **6** was captured with trifluoromethanesulfonate counterion and characterized by NMR experiments. Dehydrative generation of **6** was suggested to be the rate-limiting step. Intermediate **6** was assumed to be water sensitive, and Dean–Stark azeotropic distillation was required during the reaction. However, it is not clear that the dehydration step is rate determining since no kinetic studies are available. In contrast to the mild conditions of conventional Mitsunobu reactions, this catalytic Mitsunobu reaction is water sensitive and requires high temperature (reflux in toluene or xylenes) and extended reaction time (16–120 h) to achieve a synthetically satisfying yield. With these considerations in mind, we launched a computational study on this redox-neutral catalytic Mitsunobu reaction, in particular focusing on the initial dehydration step and the final substitution step, applying DFT calculations using the $\omega\text{B97X-D}$ functional with the 6-311G(d,p) basis set.²⁴

We explored the reaction of (*R*)-1-phenylpropan-2-ol, involving the experimental results where a (>99% ee) sample reacts with 2,4-dinitrobenzoic acid to produce (*S*)-ester **10** in 92% yield and 96% ee (Figure 3).¹⁰ Initially, phosphine oxide **1** forms a hydrogen-bonded complex (**11**) with acid **9**. This process is exergonic by 1.8 kcal/mol. Complex **11** is assigned as a minimum on the energy landscape. Addition of the phenolic OH to the $\text{P}=\text{O}$ double bond can proceed via transition state **12**, in which the $\text{P}-\text{O}$ single bond forming distance is 2.4 Å, with an energy barrier of 23.3 kcal/mol. There may be a variety of mechanisms for this to occur by adventitious acid or base catalysis, and we consider this an upper limit to the barrier for formation of **13** from **9**. Notably in this process, the tetrahedral geometry of **1** changes to the trigonal bipyramidal **13**. Transition state **12** also possesses a trigonal bipyramidal geometry with the hydroxy group occupying an equatorial position. Due to the apicophilicity of a hydroxy group on an oxo-phosphorane,²⁵ **13** isomerizes into **14** with the $-\text{OH}$ in the axial position with a 5.7 kcal/mol decrease in free energy. This isomerization process can be achieved via either a Berry pseudorotation or a turnstile rotation mechanism with only a few kcal/mol barrier²⁶ or by conformational change via rotation of the $\text{C3}-\text{C4}$ bond with a ca. 4 kcal/mol barrier acquired from dihedral scanning (Figure S4, Supporting Information). Note that the bond length of a $\text{P}-\text{O}$ single bond is typically 1.43–1.67 Å.²⁷ However, the X-ray structures of similar cyclic phosphorane species have been reported with some $\text{P}-\text{O}$ bond distances being more than 1.8 Å.²⁸ In cyclic oxo-phosphoranes **13** and **14**, the $\text{P}-\text{O}$ lengths are more than 1.8 Å.

We studied **15** and **16** and found that the natural bond orbital (NBO) bond orders between P and O1 are 0.41 and 0.47 for **15** and **16**, respectively. Hirshfeld charge analyses (Figure S2, Supporting Information) show a large charge separation between P and O1 (ca. +0.3 and −0.3 respectively); there is a partial covalent and ionic character between $\text{P}-\text{O1}$ of

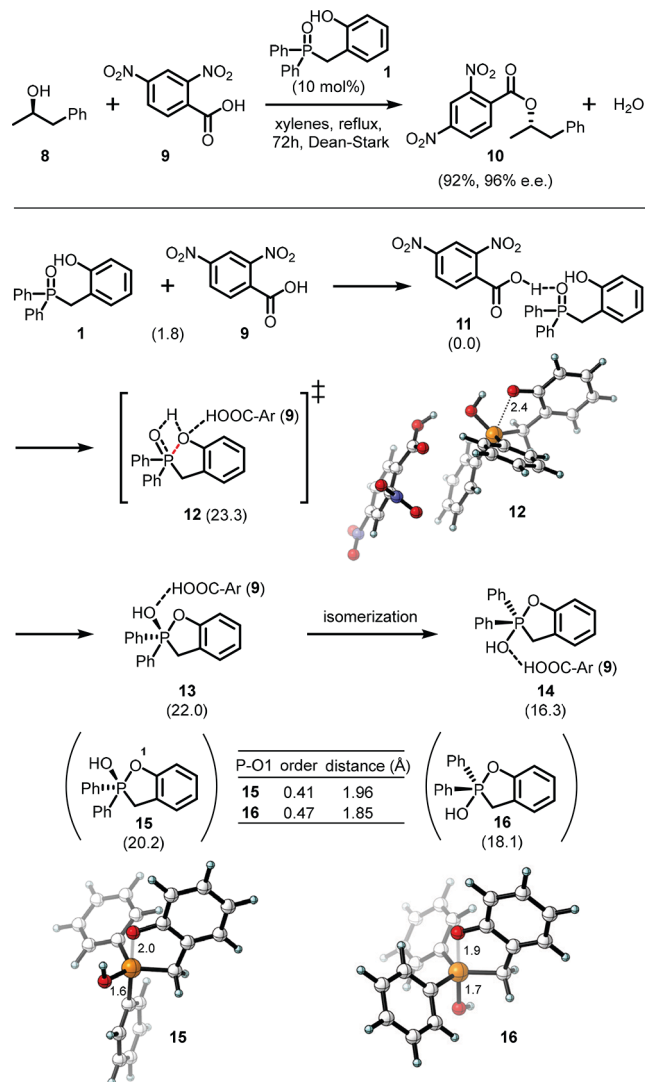


Figure 3. DFT investigation of the initial step with ω B97X-D/6-311G(d,p)/CPCM(toluene).

15 and 16. The bonding parameters of various related phosphorane species (vide infra) were also investigated. In general, when the two axial ligands are both oxygen groups, the more basic group forms a P–O single bond whereas the less basic group forms a partial (approximately one-half) P–O bond. These results are summarized in Figure S3 of the Supporting Information.

Having established the nature of the phosphorane intermediate, we studied the dehydration step which leads to the active phosphorane species. Dehydration of the phosphorane –OH group is mediated by the carboxylic acid. Denton et al. speculated that this dehydration was likely to be the rate-determining step. Dehydration of the cis intermediate (13, Figure 4) proceeds via transition state 17 with a free energy barrier of 31.6 kcal/mol and leads to 19 with a high-energy intermediate (28.6 kcal/mol). These are indeed very high barriers. However, dehydration from the trans intermediate (14) takes place with a free energy barrier of only 22.0 kcal/mol via transition state 18 which leads to 20, which has a free energy of 14.4 kcal/mol. The preference for the dehydration of 14 is due to the trans effect of the phosphoranes on which water is more prone to dissociate when being trans to the

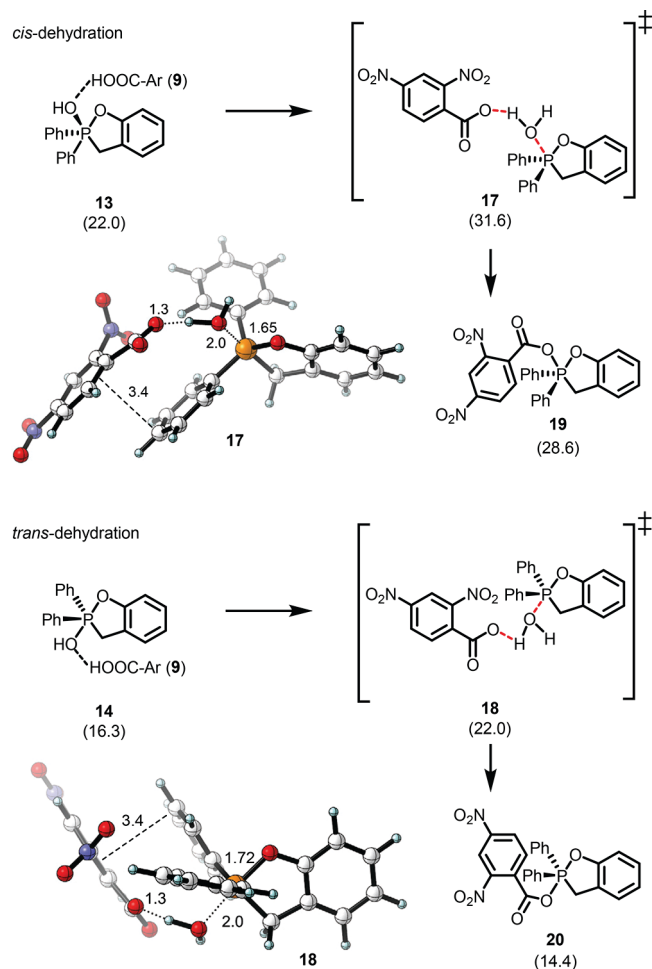


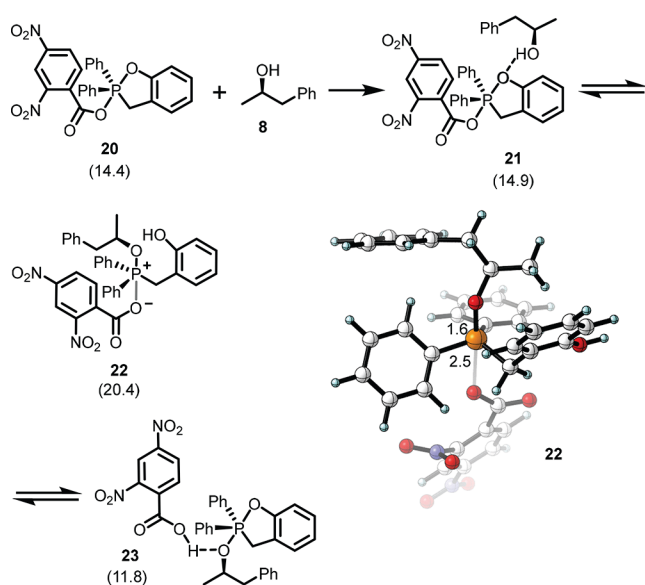
Figure 4. Dehydration and coordination of carboxylate to phosphorus.

phenoxy oxygen.²⁹ The dehydration step generates a trigonal bipyramid 20 with the carboxylate and phenoxide apical.³⁰ The relative energy of 20 is 14.4 kcal/mol, which explains why it was not observed in NMR experiments.¹⁰ In contrast, the change of the apical anion from carboxylate to triflate resulted in S1 (see Supporting Information) with a –23.3 kcal/mol relative free energy, explaining why this species could be observed and characterized experimentally.

From 20, the reaction of alcohol 8 to form 23 occurs. This process can be initiated by formation of the hydrogen-bonded complex 21 (Pathway A, Figure 5). Phosphorane ring opening of 21 followed by association of the alkoxide upon proton transfer leads to 22. Reassociation of the phenoxy oxygen and dissociation of the carboxylate with proton transfer then leads to 23. Alternatively, as depicted in Pathway B, hydrogen bonding of 8 with 20 leads to complex 24 (Figure 5, Pathway B) with a 2.4 kcal/mol decrease in free energy. Proton transfer from alcohol to carboxylate of 24 takes place almost barrierlessly via transition state 25 (13.5 kcal/mol). We computed the energetics for various steps but generally did not attempt to compute proton transfers that might involve solvent assistance and tunneling.³¹ Phosphorane 23 (11.8 kcal/mol) can equilibrate with 24 (12.0 kcal/mol).

Complex 26 (Figure 6) is generated from 23 via proton transfer from carboxylic acid to the phenoxide and ring opening of the phosphorane.³² This complex, 26, has the

Pathway A: ligand exchange by ring-opening



Pathway B: ligand exchange by protonation/dissociation

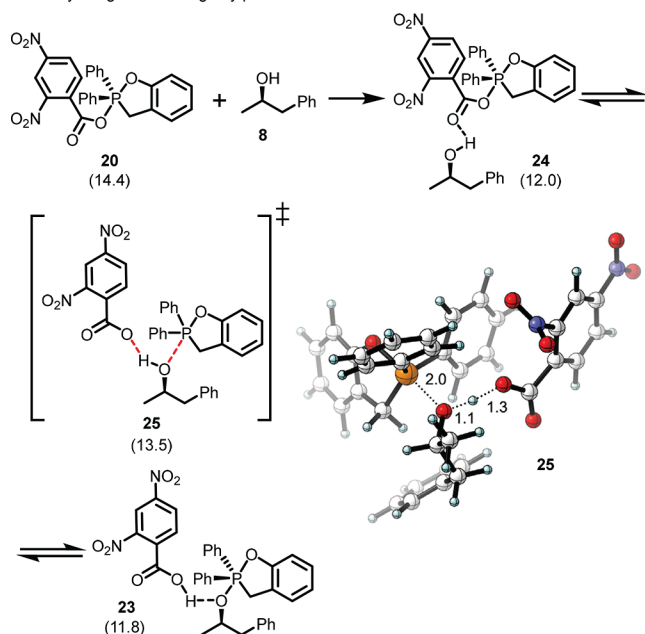


Figure 5. Ligand exchange on the phosphorus center.

carboxylate set up for the S_N2 transition state **27** that is relatively high in energy (32.6 kcal/mol). While this rate-determining step is rather slow, **27** is low compared with the uncatalyzed (or general-acid-catalyzed) reaction barrier (from **28** to **29**, which we compute to be 43.3 kcal/mol). The reasonably harsh reaction conditions [xylenes (bp ca. 140 °C), reflux, 72 h] are necessary to overcome the 32.6 kcal/mol S_N2 barrier. Product **10** is generated with inverted stereochemistry and regeneration of phosphine oxide **1**.

Redesign of Phosphine Oxide Catalyst. Computational design is an essential component of rational design of catalysts and has achieved considerable success.³³ We attempted to redesign the phosphine oxide catalyst to decrease the activation energy of the rate-determining 2 step and increase the activity of the catalyst. Electron-withdrawing groups on the aromatic substituents of the phosphorus should make the

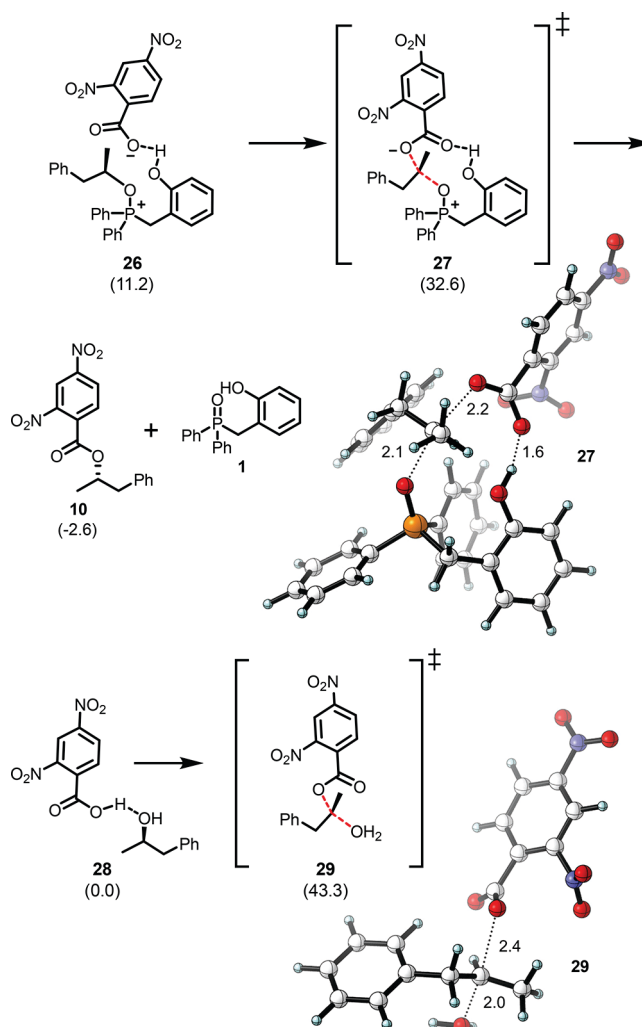


Figure 6. Nucleophilic substitution steps.

corresponding phosphine oxide a better leaving group and thereby afford a faster S_N2 reaction. We first replaced the bis-phenyl substituents with bis-perfluorophenyl (**32**); this substitution causes an increase in the energy of the cyclization (**33**) and dehydration (**34**) transition states but a 2.8 kcal/mol decrease in the rate-determining S_N2 activation barrier (**35**) (Figure 7). We also replaced the benzylic methylene hydrogens with fluorine atoms (**36**). This resulted in a significant decrease in both the cyclization (**37**) and the S_N2 activation barrier (**39**). All three transition states (**37**, **38**, and **39**) are stabilized the most in low-polar solvent such as toluene.³⁴ Both the perfluorophenyl catalyst of **32** and the difluoromethylene catalyst of **36** are predicted to be more active than the original catalyst with **36** being the best. Catalyst **36** likely can be synthesized from commercially available phosphine oxide **30** and known compound **31**.³⁵

CONCLUSIONS

To summarize, the mechanism of a redox-neutral organo-catalytic Mitsunobu reaction has been investigated. The steps proposed by Denton et al. are verified, and the bonding details in the phosphorane intermediates were determined. This protocol provides a novel way to generate the active phosphonium species from dehydration of the phosphine oxide. The dehydration process, originally speculated to be rate

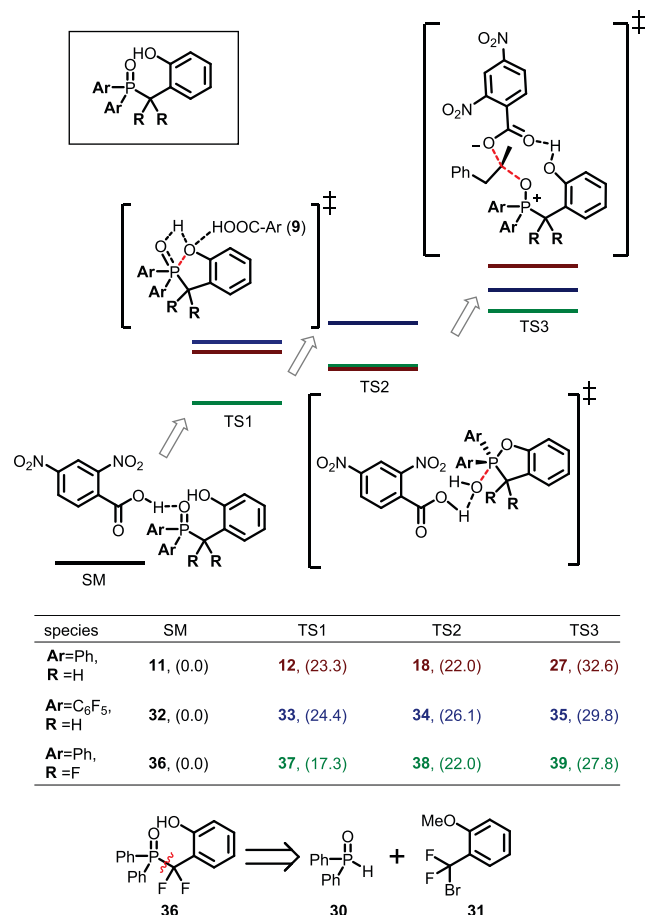


Figure 7. Redesign of the catalyst for a higher activity.

determining, occurs with a relatively low energy barrier. The final S_N2 step from an ion-pair intermediate is the rate-determining step. We studied other derivatives of the catalyst and predict improved catalysts with faster rates involving fluorine substituents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.0c07487>.

Energies and coordinates of computed structures (PDF)

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Notes

The authors declare no competing financial interest.

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