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Mechanism of the Mitsunobu Reaction: An Ongoing Mystery

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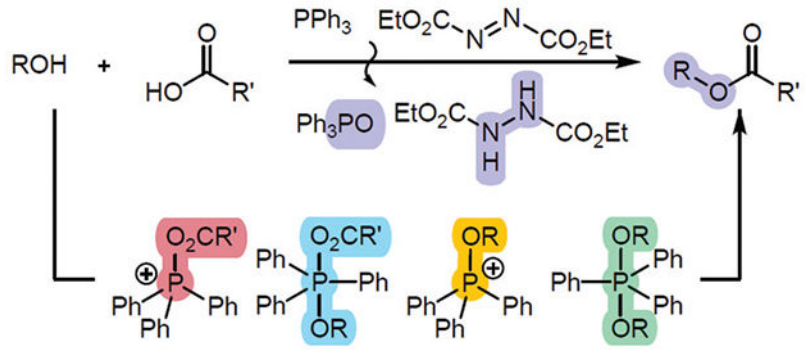
Abstract

The Mitsunobu reaction is one the most widely known reactions in the organic chemistry canon. Despite its fame, some aspects of the mechanism remain poorly understood, 55 years after its initial discovery. This short review collates the findings of several publications focused on the mechanism of the Mitsunobu reaction, highlighting both the current state of knowledge and the remaining missing pieces.

Graphical Abstract



Keywords

Mitsunobu; mechanism; phosphine; alcohol; diazodicarboxylate

1 Introduction

The Mitsunobu reaction is one of the best-known reactions in organic synthesis. Since its first publication by Oyo Mitsunobu and Masaaki Yamada in 1967,[1] the reaction has been used in thousands of total syntheses; as of July 2023, the original article has been cited 772 times and the followup article (from 1981)[2] 5,336 times. The ability to replace a primary or secondary hydroxyl group with almost any pronucleophile having an appropriate pK_a value renders the reaction both versatile and powerful. The Mitsunobu reaction also has the

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Conflict of Interest
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advantage of being generally stereospecific, allowing inversion of stereochemistry relative to a chiral secondary alcohol starting material. Given that hydroxyl groups are present in nearly 60% of all natural products, there is little wonder as to why this reaction is of such use to organic chemists, especially those in the realm of complex natural product synthesis.[3,4]

The classical Mitsunobu reaction does, however, have some drawbacks. It has relatively poor atom-economy and sometimes requires troublesome purification, thereby leading to the development of many variations on the central theme. These novel processes typically aim to make the reaction greener and safer, decrease the number of reagents and their quantities, and ease purification. Such ideas have also led to the development of catalytic Mitsunobu reactions, which aim to use either the phosphine or diazo compound in sub-stoichiometric amounts.[5] Despite many papers referencing the Mitsunobu reaction, a much smaller subset has focused on the reaction mechanism. When perusing those papers, it becomes clear that the mechanism is more nuanced and complicated than it might appear at first glance. This short review aims to summarize previous mechanistic investigations while highlighting the complexities of this popular reaction.

2 Mechanism Overview

While many different mechanisms have been proposed for the Mitsunobu reaction over the years, a consensus has been reached on a general scheme and several of the intermediates. Scheme 1 and the following discussion are a synthesis and summary of the various proposed pathways and intermediates. Most mechanistic investigations have used diethyl azodicarboxylate (DEAD), triphenylphosphine (TPP), an alcohol substrate, and a carboxylic acid pronucleophile as the standard model system. Some studies have used diisopropyl azodicarboxylate (DIAD) as a more stable and less toxic alternative to DEAD. Herein, alternatives to the other reagents are mentioned when relevant. Starting in the upper right-hand corner of Scheme 1, upon initial mixing of TPP and DEAD, the betaine intermediate is formed, as has been confirmed using ^{31}P NMR spectroscopy and electrospray ionization mass spectrometry (ESI-MS).[6–8] At this point, if the carboxylic acid nucleophile is added first, the betaine is protonated to form the phosphonium intermediate **A1**. This species can then react with either the newly deprotonated carboxylate or with the substrate alcohol (once added). With the former, the carboxylate anion will attack the phosphonium center, leading to the formation of the acyloxyphosphonium intermediate **A2-I** (if a chiral phosphine reagent were used in this scenario, there would be an inversion of stereochemistry about the phosphorus center). With the latter, the alcohol can attack in one of two ways: in an S_N2-like manner with traditional back-side attack, leading to the alkoxyphosphonium intermediate **A3-I**, or through a less commonly suggested front-side attack, leading to the intermediate **A3-Re**. The use of a chiral phosphine in this case would result in inversion (back side) or retention (front side), about the phosphorus centers of these intermediates. These two alkoxyphosphonium species can then react with the carboxylate nucleophile to produce the prototypical esterified final products of the Mitsunobu reaction with an inversion of stereochemistry with respect to the R group. In the classical Mitsunobu reaction, triphenylphosphine oxide (TPPO) would be generated as a byproduct from the reactions of both **A3-I** and **A3-Re**. If a chiral phosphine were used, however, the resultant phosphine oxide would have a retention of stereochemistry following from **A3-Re** and an inversion of

stereochemistry following from **A3-I**. In contrast, the intermediate **A2-I** can react with an alkoxide ion to produce the esterified product with retention of stereochemistry with respect to R and inverted stereochemistry with respect to the phosphorus center of the phosphine oxide if a chiral phosphine were used. These three intermediates (**A2-I**, **A3-I**, **A3-Re**) can also react through alternative pathways. Either the alkoxy or carboxylate nucleophile can add to produce the trigonal bipyramidal phosphorane intermediate **B1**. This species can undergo Berry pseudorotation, resulting in the intermediate **B1'**, which can produce the esterified product in one of two ways. First, through intramolecular addition of the alkoxide ligand to the carbonyl group, producing the esterified product with retention of stereochemistry about R. Second, through attack onto the R group by the carboxylate ligand, forming the product with inversion of stereochemistry about R. **B1** is also in equilibrium with **A2-Ra**, allowing for the presence of some free alkoxide, which can then act as a nucleophile. This process results in the esterified product with retention of stereochemistry with respect to R. Both routes passing through the achiral intermediate **B1**/**B1'** would result in a racemic mixture of the phosphine oxide if a chiral phosphine were used. Retracing our steps to the betaine formation, if the alcohol substrate were added first (instead of the carboxylic acid), the dialkoxyphosphorane intermediate **B2** would be formed. If a chiral phosphine species were used, this intermediate would be achiral at phosphorus and, thus, would result in a racemic mixture of the phosphine oxide. The phosphorane intermediate **B2** will then react with the carboxylic acid nucleophile, resulting in the alkoxyphosphonium intermediate **A3-Ra**, the carboxylate, and the re-formed alcohol. The carboxylate nucleophile will attack R in a standard back-side attack, leading to the Mitsunobu product with inversion of stereochemistry with respect to R. The phosphonium intermediate **A3-Ra** can also be attacked by the carboxylate anion at the phosphorus center, leading to the acyloxyalkoxyphosphorane intermediate **B1**, which, as discussed earlier, can follow several different pathways to generate the ester product.

While the Mitsunobu reaction is fairly robust, there are a few degradation pathways that can lead to the formation of undesired products. These products include anhydrides and acylated azodicarboxylates, which often form when a mismatch exists in the basicity and nucleophilicity of the alcohol and carboxylic acid substrates, as discussed in several of the papers covered in this short review.[8–10] The pathway of the Mitsunobu reaction can be influenced to suppress undesired product formation and encourage both high yield and enantiospecificity, if relevant. The formation of anhydrides occurs when an acyloxyphosphonium ion **A2** is attacked by another carboxylate anion at its carbonyl carbon atom, yielding the undesired anhydride and the phosphine oxide byproduct (Scheme 2). This situation occurs most often when using a sterically hindered alcohol and/or a less basic carboxylic acid, because the carboxylate anion may be unable to deprotonate the alcohol and the alcohol may have a difficult time attacking the phosphorus center to form a productive intermediate.[9–11] Anhydride formation can also occur if the carboxylate anion is too nucleophilic and attacks faster than the alcohol substrate. An overly nucleophilic carboxylate can also cause the formation of acylated DEAD through attack of the phosphonium intermediate **A1**, competing with the alcohol substrate. This situation can lead to the formation of the pentavalent phosphorane species **B3**, which can then undergo decomposition to yield the phosphine oxide and the acylated hydrazine (Scheme 2).[9] Given

that the two main degradation products are formed as a result of undesired reactivity of the carboxylic acid, the nature of this substrate plays a critical role in influencing the pathway of the Mitsunobu reaction. Prudent selection of the carboxylic acid species can influence the reaction outcome in terms of both formation of the desired product and mitigation of any undesired product.

3 Mechanistic Investigations

The Mitsunobu reaction was first reported in 1967 when Mitsunobu and Yamada described the reaction of benzoic acid with TPP and DEAD; in the presence of allyl alcohol, this mixture yielded allyl benzoate, triphenylphosphine oxide (TPPO), and diethyl hydrazodicarboxylate (Scheme 3).[1] The originally proposed mechanism involved the familiar steps of betaine formation, betaine protonation, alcohol attack to form the tetravalent alkoxyphosphonium **A3** intermediate, and carboxylate attack to form the esterified product and the phosphine oxide as byproduct. The essence of this mechanism was supported by later findings, but many groups have contributed further details to help elucidate a surprisingly complex mechanism. Mitsunobu and Yamada's original paper was followed by another by Mitsunobu in 1981 that expanded upon the original findings.[2] This second publication provided a number of examples, different applications, and a more detailed description of their proposed mechanism. Mitsunobu confirmed the structures of the originally proposed intermediates and established the S_N2 nature of the carboxylate attack on the alkoxyphosphonium intermediate, resulting in inversion of the stereochemistry of the alcohol in the final product.

The initial two publications were quickly followed by a report from Grochowski, Michejda, and co-workers, providing ^{31}P, ^{13}C, and ^{1}H NMR spectroscopic evidence for the formation of the dialkoxyphosphorane **B2** upon mixing the betaine with two equivalents of the substrate alcohol.[6a] They interpreted the identical NMR spectral signals as an indicator that both of the alkoxy groups in **B2** occupy the apical positions. However, it is important to note that phosphorane species can undergo Berry pseudorotation on a timescale that is faster than that of NMR spectroscopy, so these findings are not necessarily indicative of diapical alkoxy groups.[12] Grochowski also referenced his previous study in which a chiral non-racemic methylphenylpropylphosphine was transformed from enantiopure to racemic over the course of the reaction (Figure 1).[6b] They postulated that this transformation occurred because the reaction proceeded through an unstable **A2-I** acyloxyphosphonium species before forming the achiral intermediate **B1**, leading to racemization of the phosphorus species. Their study validated the existence of the dialkoxyphosphorane species **B2**, which had not previously been associated with the mechanism of the Mitsunobu reaction.

More in-depth mechanistic studies followed and resulted in contradictory and perplexing results, highlighting the complexity of the overall reaction. Walker and co-workers noted that past studies had been conducted in the presence of only the substrate alcohol (i.e., without addition of the carboxylic acid substrate) and so did not properly model the actual conditions of the Mitsunobu reaction.[7] They were among the first to suggest that the order of addition of the reagents plays a crucial role in the pathway and outcome of the reaction. Like Grochowski, Michejda, and co-workers[6a] they found evidence for formation of the betaine

and the dialkoxyphosphorane **B2** upon the mixing of DEAD, TPP, and the alcohol substrate. They also noted that after adding the carboxylic acid they immediately observed the desired esterified product and the phosphine oxide byproduct. If they added their carboxylic acid substrate before the alcohol, the protonated betaine **A1** and the carboxylate formed, thereby slowly forming the alkoxyphosphonium **A3**, which, in turn, reacted with the carboxylate in standard S_N2 manner to furnish the desired product with inverted stereochemistry. Walker and co-workers also noted that both the value of pK_a and the nucleophilicity of the carboxylic acid substrate mattered significantly in terms of the rate and the possibility of degradation pathways.

A study from Hughes, Reamer, and co-workers followed soon thereafter, affirming many of Walkers' findings and filling in missing details in the mechanistic picture.[13] They found that the rate of the reaction to form the alkoxyphosphonium **A3** from the protonated betaine was dependent on the carboxylate counterion present after the protonation, and suggested that the counterion deprotonates the alcohol to form an alkoxide prior to its attack on **A1**, likely leading to the formation of an **A3-I** intermediate. They observed a variation in reaction rate that was dependent on the carboxylate-to-carboxylic acid ratio. They attributed this finding to hydrogen bonding between the two species; combined with the inherent basicity of the carboxylate ion; it would influence the effective basicity of the carboxylate species. Hughes, Reamer, and co-workers also contended that the dialkoxyphosphorane **B2** was formed sparingly, because, upon addition of a salt, the reaction rate increased, pointing to a charged intermediate.

This report from Hughes, Reamer, and co-workers was promptly followed by two studies in 1989 from the Jenkins group, who also found evidence for formation of the dialkoxyphosphorane **B2** in the absence of a carboxylic acid substrate, as revealed by the presence of broad ^{31}P NMR spectral peaks.[8] After addition of the carboxylic acid substrate, they observed a peak corresponding to the alkoxyphosphonium intermediate **A3-Ra** in equilibrium with the dialkoxyphosphorane **B2**. If the carboxylic acid substrate was added to the TPP and DEAD mixture first, formation of the betaine occurred, followed by the appearance of the same two **B2** and **A3-Ra** peaks in equilibrium after addition of the alcohol substrate. Overall, the Jenkins group found that using excess carboxylic acid, a strong acid, and/or polar solvents favored formation of the alkoxyphosphonium **A3** over the dialkoxyphosphorane **B2**. In their second study, the Jenkins group reported ^{31}P NMR spectral evidence for the formation of the acyloxyalkoxyphosphorane intermediate **B1**, which appeared to be in equilibrium with **A3** and **A2-Ra**. Based on those findings, they postulated that the alkoxyphosphonium **A3** is the most common intermediate, while the dialkoxyphosphorane **B2** plays a minor role and the acyloxyalkoxyphosphorane **B1** acts mostly as a spectator. Another study by Pautard-Cooper and Evans found that the intermediate **B2** is formed even if the carboxylic acid is added before the alcohol, supporting Jenkins's theory that there is likely an equilibrium between **B2** and **A3**, with the equilibrium shifted toward **A3** when using a stronger carboxylic acid.[14]

A study in 1993 by Macor and Wehner disagreed with these findings, stating that they witnessed no formation of the dialkoxyphosphorane **B2** when adding the carboxylic acid before the alcohol, but they did observe **B2** when adding the alcohol in the absence of

the carboxylic acid.[15] Notably, Macor and Wehner used an activated methylene as a carbon-based acid, rather than a traditional carboxylic acid, potentially affecting their results. They also made many of their hypotheses about the traditional Mitsunobu mechanism by comparing the results of reactions run using a carbon-based acid with those run using a heteroatom-based acid. Macor and Wehner hypothesized that rather than being deprotonated by the carboxylate prior to attack, the alcohol reacts with the intermediate **A1** through a four-membered-ring transition state structure, leading to formation of the alkoxyphosphonium **A3-Re**. This intermediate is then attacked by the carboxylate, forming the intermediate **B1**, which can readily undergo Berry pseudorotation to **B1'** with one of the non-phenyl ligands moving from an apical to an equatorial position. From there, they suggested that, due to inductive effects, the P–O bond with the alkoxide group was stronger and, thus, the carboxylate P–O bond would be broken, resulting in an intramolecular S_N2-like reaction. This process would give the standard esterified product of the Mitsunobu reaction with inverted stereochemistry relative to the starting material. Macor and Wehner believed that this mechanism was supported by both their findings and those of previous mechanistic studies, citing the fact that changing the identity of the alcohol had little effect on the rate of the reaction, supporting an intramolecular reaction mechanism. These hypotheses would later be contested by the results of other studies.

In 1989, Crich and co-workers found solid evidence for the irreversible formation of the betaine when using *m*-chloroperoxybenzoic acid (MCPBA) in place of the standard carboxylic acid substrate.[16] First, they mixed TPP and DEAD, and then added tributylphosphine (TBP). They observed no liberation of TPP, suggesting that betaine formation was irreversible. This hypothesis was further supported by running the opposite experiment, mixing TBP and DEAD and then adding TPP, and observing no liberation of TBP. Once they moved on to the main objective of their study, they found no formation of the desired peracid product and obtained only the standard esterified product. Crich and co-workers postulated that this result was due to the formation of dialkoxyphosphorane **B2** intermediates from one equivalent of the betaine and two equivalents of the alcohol, leaving one equivalent of unreacted betaine to interact with the peracid. This situation would result in DEAD, the phosphine oxide, and one equivalent of the carboxylic acid, which could then interact with the intermediate **B2**. This mechanism agrees with the findings of Grochowski[6] and Jenkins,[8] who also implicated the dialkoxyphosphorane intermediate **B2**.

Further evidence for other reaction intermediates was provided in 1993 by Wilson and co-workers using ESI-MS. They detected betaine formation after mixing TPP and DEAD, followed by the alkoxyphosphonium intermediate **A3** and TPPO after addition of the alcohol and carboxylic acid substrates.[17]

As more details of the mechanism of the Mitsunobu reaction came to light, researchers realized that they could proceed through a number of different intermediates and that the reaction pathways could be navigated through substrate control. Dodge and co-workers found that more acidic carboxylic acid substrates gave higher yields of the desired inverted product, but noted that solvent played a role as well, with tetrahydrofuran and benzene performing better than acetonitrile and dichloromethane.[18] In agreement with the work of Hughes, Reamer, and co-workers,[13] they found that when using more acidic carboxylate

species, the steps of alcohol activation and S_N2 displacement to form the product had similar rates. In contrast, more basic carboxylates slowed down only the S_N2 reaction to form the product. Nevertheless, Dodge and co-workers had little explanation for the mechanism underpinning their findings.

In 1979, Mulzer and co-workers found that the steric bulk of the groups on the alcohol and carboxylic acid substrates (R and R') could play significant roles affecting the reaction outcome.[19] They studied a system of 3-hydroxycarboxylic acids with different R' and R groups at the α- and β-position, respectively, along with TPP and DEAD, potentially reacting to form β-lactones with differences in stereochemistry depending on the reaction mechanism. In a competition study comparing activation of the hydroxyl and carboxylate groups, they found that hydroxyl groups were the first to react with the protonated betaine intermediate **A1** when the R and R' groups were small, leading to the alkoxyphosphonium **A3** intermediate. When the R and R' groups were bulky, however, the carboxylate group reacted first and formed an acyloxyphosphonium intermediate **A2**, which they postulated was due to unfavorable steric interactions between the R and R' groups in the alternative alkoxyphosphonium **A3** intermediate. In 1993, Kodaka and co-workers studied a similar system containing a hydroxyl and a carbamate group, in which the hydroxyl group would react with TPP faster than the carbamate, through an alkoxyphosphonium **A3** intermediate.[20] Interestingly, when using a different phosphine, such as TBP, they found that the carbamate reacted faster traversing through an acyloxyphosphonium **A2** intermediate. This study was one of the first to show that the identity of the phosphine moiety could influence the mechanistic pathway of the Mitsunobu reaction. Subsequently, in 1996, Hughes and Reamer discovered that the aminophosphonium intermediate **A1** could also play a large role in the reaction outcome. They obtained the best results when the alcohol was able to attack **A1** faster than the carboxylate ion.[9] This meant that the carboxylic acid substrate must strike a delicate balance between basicity and nucleophilicity, because it needs to deprotonate the alcohol without interacting with the intermediate **A1**. They claimed that this interaction led mostly to degradation products through the acyloxyphosphonium intermediate **A2**, explaining why stronger acids performed better than weak ones. In 2002, Ahn and co-workers also claimed that the formation of the intermediate **A2** led to the formation of the anhydride, rather than the desired esterified product.[10] When using ethanol as their alcohol substrate and benzoic acid as their carboxylic acid, they observed only the formation of the anhydride, with no desired esterified product. They surmised that this anhydride formed because benzoate is not sufficiently basic to deprotonate the alcohol, suppressing the main pathway of the Mitsunobu reaction: the inverted product formed through an alkoxyphosphonium **A3** intermediate. They also demonstrated that if this main pathway could not be traversed, the acyloxyphosphonium ion **A2** could act as an acyl transfer reagent, a pathway that had not previously been confirmed.

The report by Ahn and co-workers[10] was followed, in 2003, by a report by McNulty and co-workers, who also looked at the role of the acyloxyphosphonium intermediate **A2**.[21] Using a benzoyl peroxide and a trialkylphosphine, which are prone to form acyloxyphosphonium **A2** intermediates, they found that the presence of a basic species in the reaction mixture had a significant effect on the stereochemical outcome of the resulting esterification. In the

absence of a base, an intermediate like **A2** led directly to product formation with retention of stereochemistry relative to the starting material. However, with a base present, a 'crossover' event could occur, leading to an equilibrium between **A2** and the alkoxyphosphonium **A3**, allowing for the formation of the traditional inversion product. From these findings, McNulty and co-workers concluded that the acyloxyphosphonium intermediates **A2** were the main contributors to the formation of retention products and that basic species could have a large effect on the outcome of the Mitsunobu reaction.

With many of the details of the mechanism of the Mitsunobu reaction having been identified, there was a lull in related mechanistic studies for a while until the Jenkins group reported two papers in 2015, outlining the effect of solvents and providing a deeper dive into the initial formation of the betaine.[22,23] They found that Mitsunobu reactions were faster and gave higher yields when they were performed in nonpolar solvents.[22] They attributed these findings to the fact that competitive pathways (e.g., the formation of acylated DEAD) are faster in polar solvents, whereas product formation is slower. The Jenkins group also obtained ^{1}H NMR spectroscopic evidence for both the alkoxyphosphonium **A3** and dialkoxyphosphorane **B2** intermediates during this investigation. When using sterically hindered alcohols, they found that the reactions were much slower, postulating that they proceeded mostly through the standard alkoxyphosphonium intermediate **A3**. They noted, however, the possibility of forming an acyloxyalkoxyphosphorane **B1** intermediate that can adopt a **B1'** geometry and decompose through intramolecular addition of the alkoxide to the carbonyl, giving the resulting esterified product with retention of stereochemistry.

Next, the Jenkins group examined the initial step of the Mitsunobu reaction: betaine formation.[23] A previous computational study by Anders and co-workers had found that, when using PH_3 as a model phosphine, the formation of a five-membered oxadiazaphosphole ring was favored over traditional betaine formation.[24] The Jenkins group[23] investigated these types of early intermediates by using 9-phenyl-9-phosphafluorene in hopes of observing the aforementioned phosphorane. This species was chosen as an analogue of TPP containing a five-membered ring, which would facilitate formation of another five-membered ring when mixed with DEAD. They found strong ^{31}P NMR spectroscopic evidence for the formation of the said phosphorane, as well as for rapid equilibrium between the phosphorane and betaine forms. Conversely, they found no evidence for oxadiazaphosphole ring formation when using TPP, presumably because the three phenyl ligands stabilized the betaine form. Studies from Swamy and co-workers have also shown that formation of a five-membered oxadiazaphosphole ring was favored over betaine formation when the tertiary phosphine contains alkoxy or amino substituent(s).[25] They isolated and characterized these pentacoordinate intermediates using ^{1}H, ^{13}C, and ^{31}P NMR, as well as showed that these cyclic intermediates could still participate in the Mitsunobu reaction. Together with the work from Kodaka and co-workers,[20] this shows that the choice of the phosphine reagent can have an effect on the overall reaction mechanism, especially on the early intermediates.[20,23,25] Returning to the work of the Jenkins group, they also discovered that the first step of this Mitsunobu mechanism proceeded through Michael-type nucleophilic attack of the phosphine on DEAD, rather than through a concerted or single-electron-transfer mechanism.[23]

While these more fundamental mechanistic studies were underway, several groups were teasing out the stereochemical details of the mechanism by using chiral non-racemic phosphines. One of the earliest examples was provided by Heesing and Steinkamp in 1982, using the chiral phosphine (*S*)-methylphenylpropylphosphine to explore several types of reactions, including the Mitsunobu reaction (Figure 1).[26] Although they did employ the standard diazo reagent DEAD, they applied *p*-toluenesulfonamide instead of an alcohol substrate and did not include any carboxylic acid equivalents. After mixing the three reactants, they suggested that a betaine formed, followed by protonation by the tosylamide, which would then attack the phosphine. They expected the resulting *N*-tosylphosphazene to have inverted stereochemistry about the phosphorus center, but instead observed a racemic mixture. They postulated that the final pentavalent phosphorane intermediate was sufficiently long-lived to undergo pseudorotation, ultimately racemizing the final product.

Watanabe and co-workers followed in the footsteps of Heesing and Steinkamp and, in 2000, used the chiral phosphine (*S*)-cyclohexylmethyl(1-naphthyl)phosphine to probe the mechanism of the Mitsunobu reaction and determine which intermediates were the most relevant (Figure 1).[11] When a carboxylic acid was present at the beginning of the reaction, the resulting phosphine oxide had inverted stereochemistry about the phosphorus center and a high enantiomeric excess (ee). The ee decreased when a 10-fold excess of alcohol was used, presumably due to a larger contribution of the achiral dialkoxyphosphorane **B2** intermediate, which caused racemization about the phosphorus center. When the carboxylic acid was added after all of the other reagents, the yield of the desired esterified product remained the same, but complete racemization of the phosphorus species occurred, again implicating an achiral **B2** intermediate. Inversion of stereochemistry of the esterified products occurred when using a variety of alcohols, but the ee of the phosphine oxide decreased when using less sterically hindered alcohols, possibly implying that sterically bulky alcohols disfavored the formation of achiral **B2** intermediates. Watanabe and co-workers also observed that using a strong acid increased the ee of the resulting chiral phosphine oxide. They postulated that a stronger carboxylic acid would react with the initial betaine faster to give only alkoxyphosphonium **A3-I** intermediates, which would result in inversion of stereochemistry at the phosphorus center. When using a weaker carboxylic acid, the rates of formation of the intermediates **A3-I** and **B2** were more comparable, resulting in a partially racemized phosphine oxide. This mechanism agrees with the findings of the kinetic studies performed by Dodge and co-workers.[18]

The only computational study of the mechanism of the classical Mitsunobu reaction, published in 2005 by Anders and co-workers, attempted to put together all of the pieces that had been previously discovered through synthetic work.[24] Notably, they used PH_3 in their model system, instead of the more traditional TPP or a trialkylphosphine. As mentioned in our discussion of Jenkins's studies on betaine formation,[23] Anders and co-workers found that a five-membered oxadiazaphosphole ring was favored over the formation of the betaine in the initial step of the mechanism. They noted, however, that this behavior was possibly due to the use of PH_3 and that a bulkier phosphine (e.g., TPP) might not have the same inclination. In other calculations, they found that many of the intermediates suggested by previous studies were valid, but that acyloxyalkoxyphosphorane and dialkoxyphosphorane

intermediates, such as **B1** and **B2**, respectively, were the most stable (i.e., energy minima). Anders and co-workers found that these types of intermediates were likely to exist in equilibrium through either acyloxyphosphonium **A2** intermediates or alkoxyphosphonium **A3** intermediates. They postulated that esterified products with retention of stereochemistry would likely arise from two different pathways. First, through those acyloxyphosphonium **A2** intermediates that are unstable but can be stabilized with sterically hindered alcohols. Second, through acyloxyalkoxyphosphorane **B1** species undergoing Berry pseudorotation to give **B1'** intermediates, which can then decompose through intramolecular addition of the alkoxide to the carbonyl to give retention products. Anders and co-workers noted that the use of PH_3 in their computations led to the formation of a large percentage of retention products, whereas using other ligands (e.g., methyl or phenyl groups) led to the formation of almost exclusively inversion products. This finding is in line with the majority of experimental findings in the literature.

4 Conclusion

With prudent selection of the reactants and reaction conditions, one can influence the pathway of the Mitsunobu reaction in significant ways. The mechanistic studies highlighted in this short review have allowed progress toward a full understanding of the mechanistic complexities of the Mitsunobu reaction, but some questions remain unanswered. Are there truly as many pathways as have been proposed? Are acyloxyphosphonium **A2** intermediates ever actually formed? After undergoing Berry pseudorotation, how does the acyloxyalkoxyphosphorane intermediate **B1'** decompose to form the product? What is the stereochemical outcome of the phosphorus species, and what does that tell us about the mechanistic pathway? Along the main pathway, how does the alcohol attack the phosphonium species, for example, is it always deprotonated first? Given that both the alcohol and the carboxylic acid can engage in hydrogen bonding, does that play a role in intermediate formation and reaction mechanism? Are the different pathways in equilibrium or does a single pathway usually dominate? Further mechanistic studies, and perhaps a more advanced computational study, would be useful in seeking to answer some of these lingering questions. While Anders and co-workers provided valuable insights, the drawbacks of using an abbreviated phosphine (PH_3) instead of the classical TPP are large and cast reasonable doubt on some of their findings, many of which they note themselves.[24] With computational chemistry advancing significantly in complexity and computing power since the publication of Anders's paper in 2005, a study using modern computational methods would greatly help fill in the remaining missing pieces. A clear understanding of the mechanism and how each species plays a role would allow chemists to make reagent selections that optimally furnish the desired products in high yield. Especially for catalytic variants of the Mitsunobu reaction, a stronger grasp of the mechanistic nuances would allow for the efficient development of reactions that are widely useful and provide access to a broad chemical space. Regardless of the mechanistic details, it is clear from its widespread use and high level of predictability that the Mitsunobu reaction has earned its place among the best organic reactions and will likely be used for many years of research to come.

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Biography

Ohyun Kwon (right) is a Professor of Chemistry and Biochemistry at UCLA. She received her B.S. and M.S. degrees from Seoul National University in 1991 and 1993, respectively. After obtaining her Ph.D. from Columbia University in 1998, and a postdoctoral stint at Harvard University, Kwon began her independent career at UCLA in 2001. Her research involves the development of defunctionalative C–C activation chemistry and phosphorus organocatalysis processes, and their application in the synthesis of compounds of biological significance. She has played key roles in establishing nucleophilic phosphine catalysis as one of the main areas of organocatalysis and is recognized as one of the leaders in the field. **Elizabeth A. Croll** (left) received her B.A. in chemistry from Macalester College in 2020.

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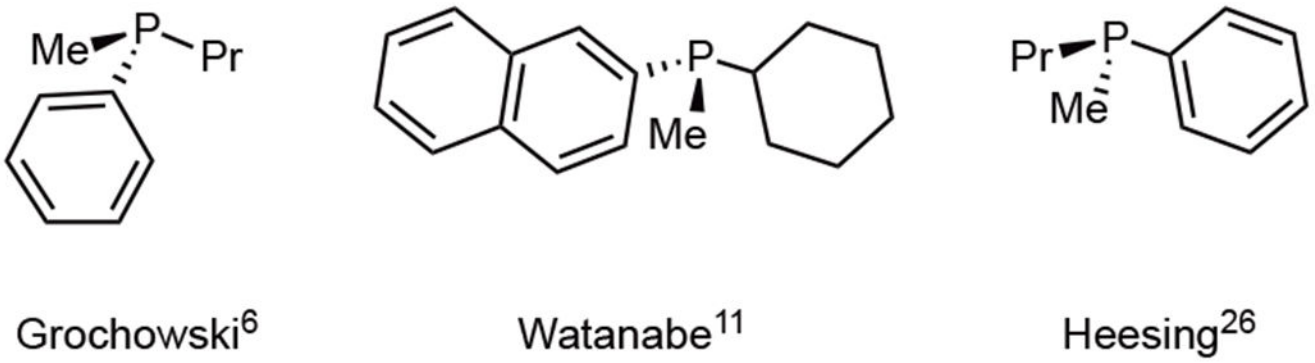
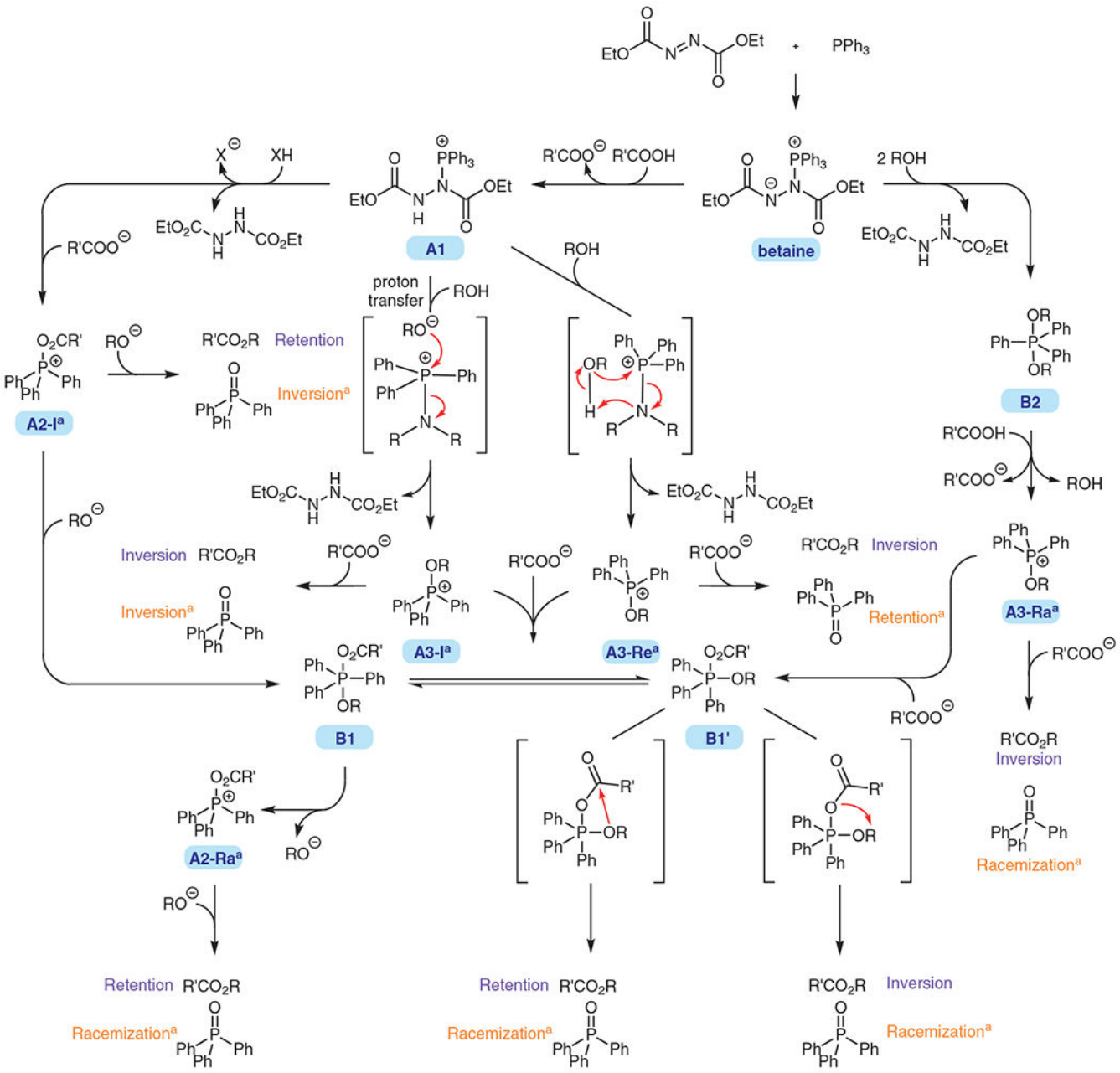


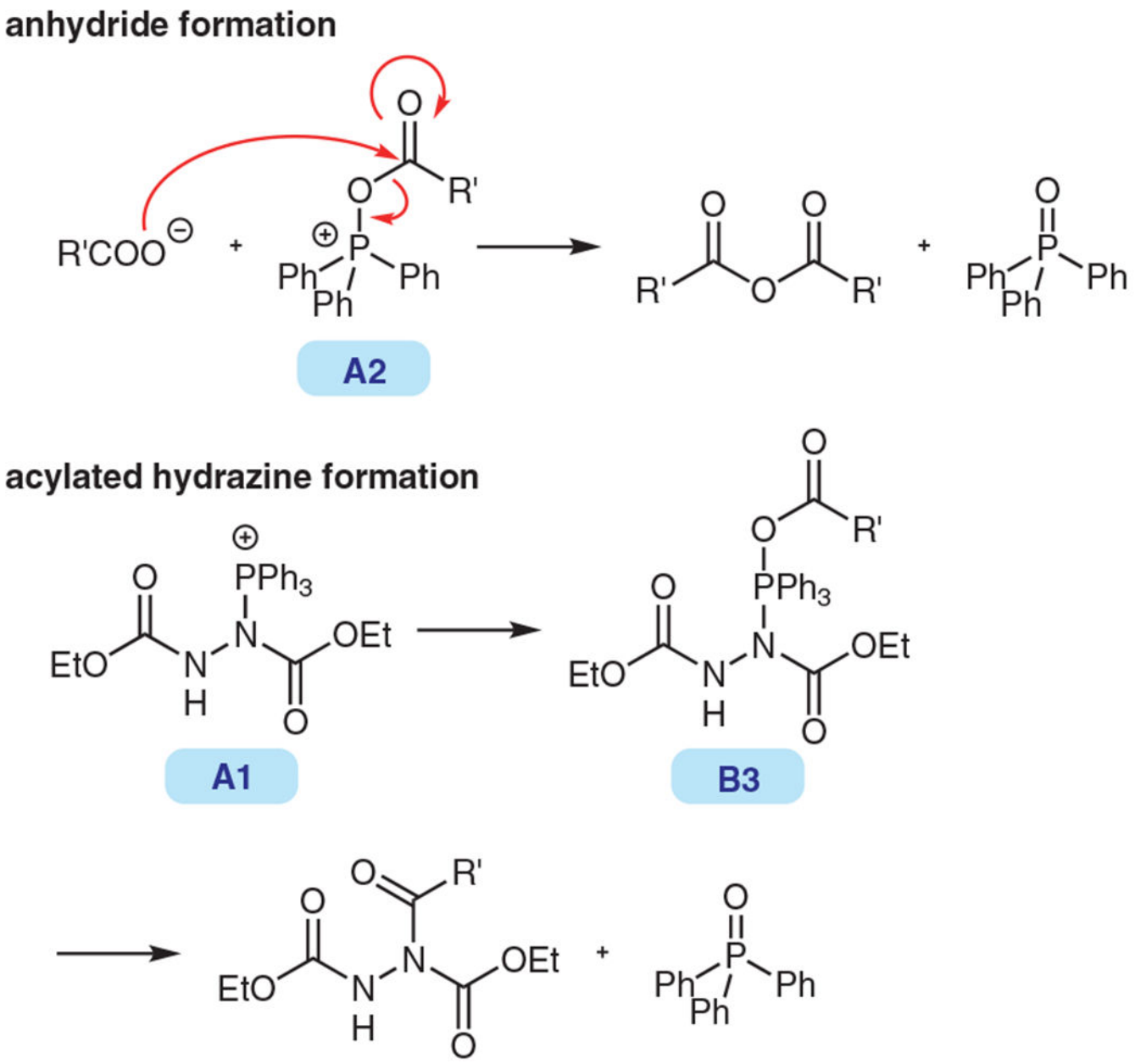
Grochowski[6] Watanabe[11] Heesing[26]

Figure 1.
The various chiral phosphines that have been used in mechanistic studies

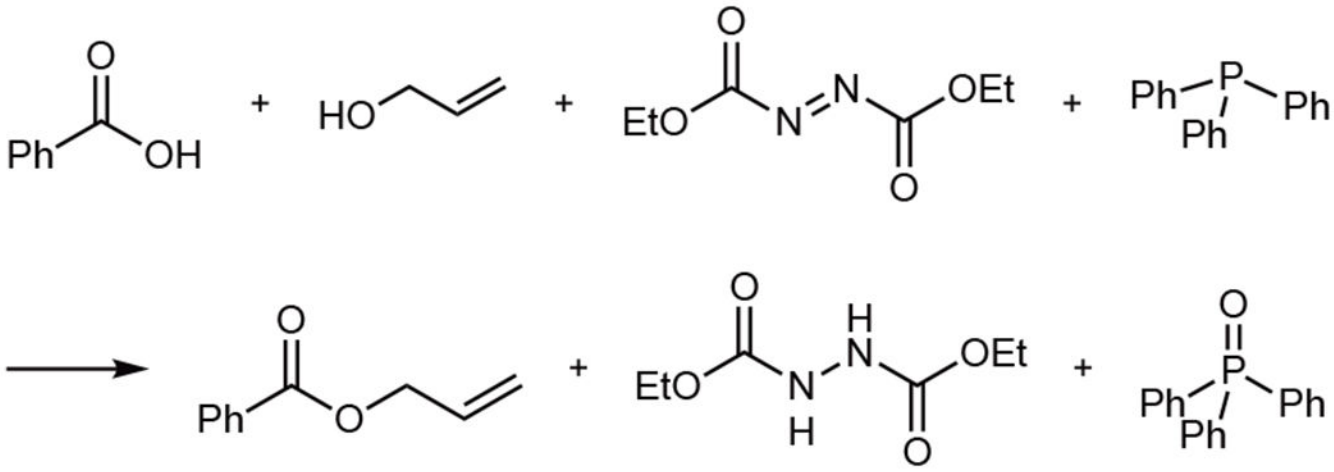


Scheme 1.

This scheme shows all possible pathways of the Mitsunobu reaction in accordance with the current literature and is both a summary and a synthesis of the mechanistic details outlined in the papers reviewed. It includes only productive pathways that result in the desired esterified product and does not show any degradation pathways or undesired products, which are discussed in Scheme 2. X = RO or R'CO_2. **I** indicates inversion, **Re** indicates retention, and **Ra** indicates racemization. [a] What the stereochemistry would be if a chiral phosphine species were used instead of TPP.



Scheme 2.
The two most commonly referenced degradation pathways and undesired products



Scheme 3.
The first Mitsunobu reaction