CARBON-CARBON BOND FORMING REACTIONS FACILITATED BY KUKHTIN-RAMIREZ ADDUCTS

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by
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Abstract

The preparation of carbon-carbon bonds is an essential goal of organic synthesis. This thesis describes research efforts directed toward the use of Kukhtin-Ramirez type oxyphosphoranes derived from α-ketoesters as reagents to initiate carbon-carbon bond formation in three transformations. First, a non-metal mediated Barbier-type addition is described with diastereoselection under both substrate and reagent control. Second, diastereoselective epoxidation resulting from reaction of Kukhtin-Ramirez adducts with aldehydes is described and the impact of Lewis acid additives on diastereoselection is explored. Third, the potential of Kukhtin-Ramirez adducts as carbene transfer precursors in transition metal-catalyzed reactions is investigated within the context of cyclopropanation and insertion reactions. Concisely, this thesis explores the ambiphilic properties of Kukhtin-Ramirez adducts by attempting to carry out new carbon-carbon bond forming reactions.
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Chapter 1

Overview of the Kukhtin-Ramirez Reaction and Synthetic Utility of its Adducts

This chapter discusses the formal [4+1]-cycloaddition of 1,2-dicarbonyl compounds and trivalent phosphorus species to form five-coordinate phosphorus adducts through what is known as the Kukhtin-Ramirez reaction. The structure of these adducts and their synthetic utility to date is discussed to illustrate their broad range of reactivity and mechanistic versatility. This introductory overview provides the backdrop for the subsequent chapters of this thesis, which focus on the synthetic studies of new C-C bond forming reactions involving Kukhtin-Ramirez adducts.

1.1 The Kukhtin-Ramirez Reaction

1.1.1 Discovery and Definition

In 1962, Fausto Ramirez discovered that upon addition of diacetyl (1.1) to trimethylphosphite (1.2), a redox condensation reaction to generate a five-coordinate phosphorus species 1.3 was possible, as shown in Scheme 1.1. At roughly the same time, Kukhtin was investigating new forms of the Arbuzov rearrangement and also reported the reaction of diacetyl (1.1) with trimethylphosphite (1.2) to form adduct 1.3. These transformations to give five-
coordinate species 1.3 were the first examples of what is now called the Kukhtin-Ramirez reaction.

Subsequently, this reactivity has been expanded to include other trivalent phosphorus species and 1,2-dicarbonyl substrates. In general terms, the Kukhtin-Ramirez reaction can be defined as the reductive condensation of a trivalent phosphorus species with a 1,2-dicarbonyl compound to produce a cyclic oxyphosphorane or an open-dipolar oxyphosphonium species.

1.1.2 Factors Affecting Structure of the Adducts – Cyclic Oxyphosphoranes or Dipolar Oxyphosphonium Enolates

As shown in Figure 1.1, Kukhtin-Ramirez adducts can exist as either cyclic oxyphosphoranes (closed) or dipolar oxyphosphonium enolates (open). Several factors affect which structure is preferred, including: 1) the identity of the phosphorus reagent, 2) the identity of the dicarbonyl compound, and 3) the solvent in which the adducts are dissolved.

![Figure 1.1. Cyclic oxyphosphorane vs. dipolar oxyphosphonium enolate.](image)

1.1.2.1 Effect of Altering the P(III) Reagent. To study the preferred structure of these adducts, Ramirez synthesized adduct 1.8 from tris(dimethylamino)phosphine and phenanthraquinone. A single-crystal X-ray diffraction study showed that the oxygen atoms of the dioxaphospholene ring occupy apical and equatorial positions of a phosphorus-centered trigonal
bipyramid (Figure 1.2).\textsuperscript{3} Distortion of the N-P-O and P-N-C bond angles is observed due to the crowding around the phosphorus center due to short nonbonding distances. As shown in Figure 1.2, due to the observed crowding and short nonbonding distances that would be observed in the closed form \textbf{1.4}, the adduct made from tris(dimethylamino)phosphine (\textbf{1.7}) will prefer the open dipolar form \textbf{1.8} (Scheme 1.2). Oppositely, an adduct of a cyclic aminophosphine \textbf{1.9} will prefer the closed, oxyphosphorane form \textbf{1.10} due to less crowding around the phosphorus atom.\textsuperscript{5} These
observations show that the phosphinamide used ultimately affects whether a cyclic or acyclic phosphorus(V) species is favored.

With regard to the phosphite-dicarbonyl adducts, a similar study was performed with triisopropyl phosphite and phenanthraquinone forming adduct 1.5 (Figure 1.2). It was observed that the phospholene ring spans the apical and equatorial sites of the trigonal bipyramid. The apical P-O bonds are longer than the equatorial P-O bonds due to a difference in bonding character of the σ-bond. Furthermore, the apical P-O bond of the phospholene ring is longer than the apical P-O bond of the alkoxy group. Similarly, the equatorial P-O bond of the phospholene ring is longer than the equatorial P-O bond of the alkoxy groups. Distortion of the O-P-O and P-O-C bond angles and the crowding in the trigonal bipyramid due to short bond distances induce increased stability in the five-membered cyclic oxyphosphorane when compared to the acyclic, dipolar oxyphosphonium enolate. These results indicate that for adducts desired from phosphite reagents, the closed cyclic oxyphosphorane is the preferred structure.

1.1.2.2 Effect of Altering the 1,2-Dicarbonyl Compound. While the above mentioned examples only utilize dicarbonyl compounds with alkyl and aryl groups attached, Kukhtin-Ramirez adducts can also be observed with α-ketoester and oxomalonate derivatives. As with the structure of adduct 1.3, Burgada depicted the adduct of tris(dimethylamino)phosphine (1.7) and diethyl oxomalonate (1.11) as a cyclic oxyphosphorane structure (1.12). It was experimentally shown later that a zwitterionic, acyclic oxyphosphonium enolate structure 1.13 is also possible. α-Ketoesters have also been observed as zwitterionic, acyclic oxyphosphonium enolate 1.16 (Scheme 1.3).
1.1.2.3 Impact of Solvent. Another major factor affecting whether the Kukhtin-Ramirez adduct is open or closed is the solvent. When monitoring the adduct of tris(dimethylamino)phosphine (1.7) with benzil by $^{31}$P NMR, an equilibrium between the closed form 1.17 and open form 1.18 was observed (Figure 1.3).\(^9\) The closed, oxyporphorane structure 1.17 is preferred in hexanes; however, when the adduct is dissolved in dichloromethane, the position of the equilibrium shifts in favor of the open-dipolar oxyphosphonium enolate 1.18. This observation is intuitive because non-polar solvents would not be able to stabilize a charged species, whereas more polar solvents such as dichloromethane would.
1.2 Mechanism of the Kukhtin-Ramirez Reaction

![Mechanistic pathways of the Kukhtin-Ramirez reaction.](image)

**Scheme 1.4.** Mechanistic pathways of the Kukhtin-Ramirez reaction.

The mechanism of the Kukhtin-Ramirez reaction has been the subject of numerous investigations. Both concerted and stepwise pathways (Scheme 1.4) have been proposed based on the kinetic observation of a second order rate constant as shown in Equation (1).

\[ v = k[\text{trialkyl phosphite}][\text{benzil}] \] (1)

The concerted pathway can be viewed as a formal six-electron [4+1] cycloaddition, or more precisely as a cheletropic addition. Support for this mechanism derives from the analogous McCormack reaction in which the addition of a dihalophosphine to a 1,3-diene is proposed to occur via a pericyclic [4+1] addition.

While there is some precedent for a concerted pathway, most of the kinetic data supports a stepwise pathway. Based on a kinetic study of the reaction with trialkyl phosphites (1.19) and benzil (1.20), initial irreversible nucleophilic attack of 1.19 on the carbonyl carbon of 1.20 to
form the P-C bound zwitterionic species 1.22 has been proposed.\textsuperscript{12} Subsequent rearrangement through a nucleophilic attack of the phosphorus atom by the anionic oxygen species then generates the P-O bound zwitterionic species 1.23. This rearrangement is reminiscent of the phospha-Brook rearrangement in which a 1,2-migration of a phosphorus species from carbon to oxygen occurs.\textsuperscript{13} The pendant anionic oxygen then binds with phosphorus to generate the cyclic oxyphosphorane product 1.21.

Additional support for a stepwise mechanism derives from the enthalpy of activation, which was found to be 8.41 kcal/mol. This value is in the range of typical nucleophilic additions to carbons of carbonyls.\textsuperscript{14} Furthermore, the entropy of activation was determined to be -47.5 eu. This value is much different than a typical Diels-Alder type cycloaddition which is generally not more than -30 eu, dismissing the potential for a concerted [4+1] cycloaddition. All kinetic parameters point to a preferred stepwise mechanism.\textsuperscript{3,4,15}

1.3 Synthetic Utility of Kukhtin-Ramirez Adducts

In 1967, Ramirez predicted that oxyphosphoranes have the potential to exhibit unique synthetic properties and their utility would be worth pursuing in the future.\textsuperscript{5} Over the past 45 years, a variety of reaction methods have been developed that substantiate this perspective. The Kukhtin-Ramirez adduct can undergo three main modes of reactivity: radical, carbenic, and polar (Scheme 1.5). The following sections describe the recent and past synthetic utility of these adducts and their unique reactivity with different species discovered in our lab and others.
1.3.1 Radical Reactivity of Kukhtin-Ramirez Adducts through Addition of Bromotrichloromethane.

One of the first reported synthetic reactions of oxyphosphoranes was the free-radical addition of bromotrichloromethane (1.24) to the trimethylphosphite-diacetyl adduct 1.3. The many examples of radical addition of small molecules to alkenes led Bentrude to consider utilizing the double bond in an oxyphosphorane for radical addition. As shown in Scheme 1.6, the presumed mechanistic pathway proceeds through initial radical addition of Cl\(_3\)C\(^+\) (1.26) to the oxyphosphorane 1.3 to form radical intermediate 1.27. The radical addition product 1.27 next undergoes a ring-opening rearrangement to form the phosphoranyl radical intermediate 1.28. Radical 1.28 then reacts with another molecule of bromotrichloromethane (1.24) to form quasiphosphonium salt 1.29, which undergoes an Arbuzov dealkylation to form product 1.30 in high yield.

Scheme 1.5. Potential mechanistic pathways for transformations of Kukhtin-Ramirez adducts.
1.3.2 Kukhtin-Ramirez Adducts as Carbene Precursors.

There are several cases in which the Kukhtin-Ramirez adduct has exhibited carbenic reactivity, either as a free transient carbene or as a metal carbenoid through loss of phosphine oxide (Scheme 1.7). This reactivity has been exploited in intermolecular cyclopropanation of P(NMe₂)₃/1,2-dicarbonyl adducts with olefins, intramolecular cyclopropanation reactions of oxalimides to generate penems, and transition metal-mediated dimerization processes of dicarbonyl compounds.
1.3.2.1 Cyclopropanation. Cyclopropanation was first observed with α-diketones and their adducts with tris(dimethylamino)phosphine (1.7) in the presence of activated monosubstituted olefins with electron-withdrawing substituents, as can be seen in Scheme 1.8.\(^{17}\)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R} \\
\text{1.32} & \\
\downarrow & \\
\text{(Me}_2\text{N)}_3\text{P}^+ & \\
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R} \\
\text{1.34} & \\
\downarrow & \\
\text{P(NDMe)}_3 & \\
\text{1.7} & \\
\text{R} & \quad \text{R} \\
\text{1.33} & \\
\downarrow & \\
\text{EWG} & \\
\text{1.36} & \\
\end{align*}
\]

**Scheme 1.8.** Cyclopropanation with alkenes with electron-withdrawing groups.

This reaction is proposed to occur through a nucleophilic attack of the open dipolar adduct 1.34 on the electrophilic carbon atom of the alkene 1.33, followed by cyclization to generate cyclopropane 1.36. This reactivity was later utilized in the synthesis of methanofullerenes\(^{18}\) by Romanova, wherein cyclic α-diketones as acenaphthenequinone, aceanthrenequinone, and N-alkylisatins were treated with hexaethyltriaminophosphine and reacted with C\(_{60}\). It is proposed this process occurs through a deoxygenation of the dicarbonyl compound mediated by a trivalent phosphorus species to generate an α-ketocarbene.

1.3.2.1 Oxalimide Cyclization Reaction. Intramolecular cyclopropanation has been observed in the deoxygenation of substituted oxalimides by triethyl phosphite (1.38). As can be seen in Scheme 1.9, the mechanism is proposed to occur through a free transient carbene 1.40 since cyclopropanes 1.41 and 1.42 are the only isolable products. The carbene 1.40 is formed...
from betaine 1.39 upon heating and elimination of triethyl phosphate. Compound 1.40 can then add intramolecularly to the appended allyl group, cyclizing to form 2,3-cyclopropano-γ-lactones 1.41 and 1.42.

1.3.2.3 Transition Metal-Mediated Dimerization of Benzil and X-H Insertion Reactions. Dimerization of benzil (1.20) was observed in the presence of triethyl phosphite (1.38) and copper(II) sulfate to produce both cis-dibenzoylstilbene (1.47) and tetraphenylfuran (1.48) as shown in Scheme 1.10. This process was proposed to occur through a phenyl benzoyl carbenoid intermediate 1.46 formed after reaction of the adduct 1.43 with CuSO₄. This transformation allows 1.46 to dimerize and form cis-dibenzoylstilbene (1.47). Due to the proposed carbene intermediate, O-H and N-H insertions were also attempted. The O-H insertion of the benzil-triethylphosphite adduct 1.43 with ethanol resulted in only 30% of the desired
benzoin ethyl ether. N-H insertion was tested under similar conditions with aniline, resulting in a 63% yield of the aniline deoxybenzoin product.

### 1.3.3 Reactivity of Kukhtin-Ramirez Adducts through a Polar Mechanism.

The most common reactivity observed with Kukhtin-Ramirez adducts proceeds through a polar mechanism. As shown in Scheme 1.11, this pathway typically occurs through initial attack of an electrophilic species on the Kukhtin-Ramirez adduct 1.50 to generate intermediate 1.51. A
nucleophilic species then attacks the α-position of 1.51 to displace phosphine oxide and form product 1.52. The following examples illustrate this general method of sequential electrophilic/nucleophilic attack.

1.3.3.1 Reaction with Isocyanates to Synthesize Hydantoins. Kukhtin-Ramirez adducts have been utilized in the synthesis of hydantoins, one of the common precursors of α-amino acids. As shown in Scheme 1.12, Ramirez et al. found that in the presence of trimethyl phosphite (1.2), an α-dicarbonyl compound 1.1 and an isocyanate 1.53 can condense to form 5-acyl-hydantoins 1.57. Initial formation of the oxyphosphorane 1.3 is observed. Subsequent addition of phenylisocyanate (1.53) generated the dioxaphospholane 1.54. Neither of the possible open dipolar structures was observed by NMR. Compound 1.54 then reacted with another equivalent of phenylisocyanate (1.53) to generate 1,3-diphenyl-5-acetyl-5-methylhydantoin (1.57) and a stoichiometric amount of trimethyl phosphate (1.58). The mechanism of this process is proposed to occur through a nucleophilic addition of the nitrogen of 1.54 to the carbon of 1.53.
to produce the dipolar intermediate 1.56. This intermediate 1.56 can then cyclize to form the hydantoin ring through ejection of trimethyl phosphate (1.58).

1.3.3.2 Reactivity with Carbonyl Compounds. Oxyphosphoranes have additionally shown reactivity towards carbonyl electrophiles. Initial reactivity was observed in the case of the cyclic unsaturated oxyphosphorane 1.3 with acenaphthenequinone (1.59), making possible a selective and mild pinacol reduction of aliphatic dicarbonyl compounds to diketols, as can be seen in Scheme 1.13.\textsuperscript{21} The Kukhtin-Ramirez adduct 1.3 attacks the electrophile 1.59 generating intermediate 1.60, which will then ring close to generate the cyclic species 1.61. Compound 1.61 can then undergo hydrolysis to form diketol 1.62.

This reactivity prompted expansion to other reactive carbonyl compounds such as ketenes. In the case of the reaction of ketene (1.63) with the diacetyl-trimethyl phosphite adduct 1.3, generation of the dioxaphospholane 1.64 is observed in high yield (Scheme 1.14).\textsuperscript{22} Mechanistically, this transformation is proposed to occur through a direct, concerted nucleophilic

![Scheme 1.13. Condensation of oxyphosphorane 1.3 with acenaphthenequinone (1.59).](image-url)
addition of 1.3 to electrophile 1.63 without formation of a dipolar species. Compound 1.64 can then undergo additional transformations. To generate the dimethyl phosphate ester 1.66, compound 1.64 can react with hydrogen chloride to form a tetraalkoxyphosphonium chloride intermediate. This intermediate can then undergo deprotonation to form 1.66. Additionally, 1.64 can be treated with Br₂ to synthesize phosphate ester 1.65 in a similar manner to the reaction with HCl.

1.3.3.3 α-Chloro-β-Ketosulfide Synthesis via S-Cl Insertion. α-Chloro-β-ketosulfides (1.69, Scheme 1.15) have been synthesized from oxyphosphoranes and sulfenyl chlorides in high yields.²³ Thus, the dioxaphospholene 1.67 reacts with phenylsulfenyl chloride (1.68) to generate the corresponding α-chloro-β-ketosulfide 1.69 and a stoichiometric amount of trimethyl phosphate (1.58). Compound 1.69 can be further transformed into a range of useful organic compounds (e.g. α-hydroxy acids, α-keto aldehydes, etc.), including β-keto sulfides 1.70 via reduction with trichlorosilane/tri-n-butylamine.
Mechanistically, the chlorosulfenylation of 1.67 is unlikely to proceed via free radical intermediates. For instance, no change in rate is observed for the condensation in the presence of the radical inhibitor 1,3,5-trinitrobenzene.

The intermediacy of free carbenes can also be excluded. Specifically, while benzoylphenylcarbene 1.71 [obtained by decomposition of benzoylphenyldiazomethane (1.74)] reacts with p-toluenesulfenyl chloride (1.72) to form α-chloro-β-ketosulfide 1.73 in good yield, it also undergoes reaction with styrene (1.75) to give cyclobutanone 1.76. By contrast, the dioxaphospholene 1.67 is unreactive towards styrene (1.75). Therefore, an ionic mechanism is considered to be the primary route for chlorosulfenylation (Scheme 1.16). The electrophilic p-toluenesulfenyl chloride 1.72 is attacked by the oxyphosphorane 1.67 to give intermediate 1.78, which subsequently undergoes displacement of trimethyl phosphate (1.58) by chloride ion to give formal S-Cl insertion product 1.73.

**Scheme 1.15.** Formal insertion of Kukhtin-Ramirez oxyphosphoranes to S-Cl bonds.
1.3.3.4 Synthesis of Nitrones through the Reaction of Nitroso Electrophiles. Recently, Ashfeld et al. utilized oxyphosphoranes in the presence of nitroso compound 1.79 as an umpolung approach to synthesize nitrone 1.82.\(^{25}\) As depicted in Scheme 1.17, methyl

\[ \text{Scheme 1.16. Potential mechanism for formal S-Cl insertion.} \]

\[ \text{Scheme 1.17. Reactivity of Kukhtin-Ramirez adduct 1.80 with nitroso compounds.} \]
benzoylformate (1.14) in the presence of tris(dimethylamino)phosphine (1.7) reacted with nitrosobenzene (1.79) to generate the corresponding nitrone 1.82. It was proposed that after formation of oxyphosphonium enolate 1.80, this species attacks the nitrosobenzene electrophile (1.79) to produce intermediate compound 1.81. The subsequent nitrone is formed via expulsion of HMPA, allowing the synthesis of ketonitrone with α-electron withdrawing groups without the need for nucleophilic amines. This reaction is chemoselective towards the nitroso compound 1.79 and, in a competition experiment, did not react with an aldehyde present in solution. This method was not just specific to the reactions with α-diketo esters, but was also compatible with benzil (1.20) and isatin 1,2-dicarbonyl compounds.

1.3.3.5 Reductive Trimerization. Reductive homocondensation of benzylidene- and alkylidene-pyruvate esters initiated by tris(dimethylamino)phosphine (1.7) has been performed in our lab to synthesize a diverse array of oxygenated heterocycles. The reactivity of the Kukhtin-Ramirez adducts was broadened through utilization of vinyl-substituted ketoesters 1.83 by formation of oxyphosphonium dienolate adducts 1.84 and 1.85. The electron density can then be delocalized over both the α- and γ-positions with respect to the ester functionality; therefore, it was envisioned that nucleophilic reactivity at the γ-position could be possible. Initial studies with methyl (E)-benzylidene-pyruvate and tris(dimethylamino)phosphine (1.7) at low temperatures showed formation of dihydropyran 1.93 upon warming from a trimerization of the unsaturated ketoester substrate. Two equivalents of the phosphorus species were consumed for each molecule of 1.93 synthesized. A variety of (E)-benzylidene-pyruvate esters 1.93 with variations on the ester functionality and the aryl functionality were well tolerated.
Scheme 1.18. Proposed mechanism for P(NMe₂)₃-mediated reductive trimerization of benzylidene pyruvate 1.83.

The proposed mechanism of this process is shown in Scheme 1.18. Initial formation of the oxyphosphonium dienolate intermediate 1.85 with tris(dimethylamino)phosphine (1.7) and the unsaturated keto ester 1.83 ensues, followed by subsequent nucleophilic attack by the γ-position of 1.85 to an additional equivalent of electrophilic substrate 1.83 to form 1.86. Compound 1.86 then undergoes intramolecular oxycyclization to afford dipolar intermediate 1.87. The trans stereochemistry of the new C-C bond formed can be understood by considering nonbonding steric interactions. This intermediate forms another oxyphosphonium enolate 1.87 that can then react with an additional equivalent of substrate 1.83, generating cyclopropane 1.90.
Another Kukhtin-Ramirez addition occurs between the keto ester moiety and an additional equivalent of tris(dimethylamino)phosphine (1.7). Cyclopropane 1.90 then opens and HMPA is expelled resulting in the trimerization product 1.93.

1.3.3.6 Formal Reductive X-H (X= OR, NR2) Insertion. Kukhtin-Ramirez adducts have shown utility as carbene synthon precursors 1.98 in X-H (X= OR, NH2) functionalization.27 Typically, metal-catalyzed decomposition of α-diazo esters 1.94 is used to access such reactive carbenes that can undergo X-H insertion reactions. The drawbacks to this method of carbene generation are the hazards in preparing and storing these compounds due to their high reactivity. An alternative method was sought that could generate a carbene precursor in one-pot from simple substrates such as α-keto esters 1.96. Compound 1.96 reacts with PR3 to give α-keto ester-tris(dimethylamino)phosphine adduct 1.97 which mimics the dipolar structure of an α-diazo ester 1.95, as seen in Scheme 1.19.

![Scheme 1.19. Potential routes for carbene formation.](image-url)
Our lab envisioned that through loss of phosphine oxide from 1.97, a carbene synthon 1.98 could be generated to carry out X-H insertion of alcohols and amines. Initial studies were performed with methyl benzoylformate 1.14 in the presence of p-cresol with tris(dimethylamino)phosphine (1.7) yielding 75% of the desired insertion product.\textsuperscript{23} This method tolerates electronically and sterically diverse α-keto esters, as well as a variety of phenols and carboxylic acids. Some aliphatic alcohols are tolerated, such as propargyl alcohol; however, simple alcohols, such as ethanol, only proceed to form trace amounts of the corresponding insertion product. Reactivity is correlated to the pK\textsubscript{a} of the alcohols used. This observation suggests an O-H bond heterolysis in the coupling reaction. Further reactivity is also seen with low pK\textsubscript{a} amines such as sulfonyl-protected amine derivatives and N-heterocyclic compounds leading to the insertion products.

The X-H functionalization starts with initial Kukhtin-Ramirez addition of tris(dimethylamino)phosphine (1.7) to the α-keto ester 1.96. This reaction, shown in Scheme 1.20, presumably establishes an equilibrating mixture of the resonance-delocalized dipolar intermediate 1.97↔1.100, and the dioxaphospholene 1.101.\textsuperscript{23} From these adducts, the X-H functionalization can occur in two possible ways: 1) initial expulsion of hexamethylphosphoramide could produce free carbene 1.98, which could then be trapped by X-H to form the desired insertion product 1.99 or 2) protonation of the Kukhtin-Ramirez adducts from the pronucleophile generating the alkoxyphosphonium intermediate 1.102. Intermediate 1.102 can then form the desired product 1.99 through nucleophilic displacement, releasing HMPA.

To determine which X-H functionalization pathway is occurring, a stereochemical experiment was conducted utilizing homochiral phosphorus reagent 1.104 (Scheme 1.21).\textsuperscript{23} A
chiral phosphorus reagent would desymmetrize the Kukhtin-Ramirez intermediates, which would allow facially selective protonation and a stereospecific product 1.105 in a stepwise polar process. If the mechanism occurred through a carbene intermediate, no enantioselectivity would be expected due to initial loss of the corresponding homochiral phosphine oxide to generate the achiral free carbene. Reaction with homochiral phosphorus species 1.104 in the presence of...
methyl benzoyl formate (1.14) and carboxylic acid 1.103 resulted in formation of 1.105 with exceptional enantioselectivity (98% ee), supporting a stepwise dipolar mechanism.

### 1.3.3.7 Reductive Condensation to Synthesize 1,4-Dicarbonyl Compounds

A recent synthetic application of the Kukhtin-Ramirez reaction illustrated by our lab was a reductive condensation of α-ketoesters with an enolizable carbonyl pronucleophiles to generate functionalized unsymmetrical 1,4-dicarbonyl compounds. This process, shown in Scheme 1.22, was attempted with methyl benzoylformate (1.14) and dimethyl malonate (1.106) in the presence of tris(dimethylamino)phosphine (1.7) resulting in the 1,4-dicarbonyl compound 1.110 through formation of a C\text{sp}^3-C\text{sp}^3 bond. This reductive condensation method could be extended to alkyl substituted α-keto esters, nitrile substituted pronucleophiles, α-cyano esters and amides, and other carbon pronucleophiles, such as 1,3-diketone and 1,3-keto esters. This mechanism is similar to that proposed for the X-H functionalization of Kukhtin-Ramirez adducts (vide
After formation of the alkoxyphosphonium ion 1.107 to the enolate intermediate, a nucleophilic displacement with 1.108 ensues, forming a new C$_{sp^3}$-C$_{sp^3}$ bond and producing the highly functionalized 1,4-dicarbonyl compound 1.110.

1.3.4 Miscellaneous Transformations.

The following sections discuss the hydrogenation of Kukhtin-Ramirez adducts and the reduction of carbonyls to form benzoin derivatives.

1.3.4.1 Hydrogenation. Catalytic hydrogenation of unsaturated oxyphosphoranes 1.111 has been effected by Stephenson et al.$^{29}$ This method was employed to facilitate ketone transposition and conversion of acyloin condensation products to monoketones. Oxyphosphorane 1.111, in the presence of H$_2$ and PtO$_2$, produced the monoketone 1.112 and trimethyl phosphate (1.58) in quantitative yield (Scheme 1.23). High selectivity toward one hydrogenation product is observed in the case where electronic and steric factors exist, such as in the case of the trimethyl phosphite-1-phenyl-1,2-propanedione adduct.$^{25}$ The only product observed is phenylacetone. In the case where electronic and steric factors are not as pronounced, such as in the case of the
trimethyl phosphite-2,3-pentanedione adduct, an almost equal amount of both 2- and 3-pentanone is observed.

1.3.4.2 Reduction of 1,2-Dicarbonyl compounds. A variety of activated 1,2-dicarbonyl compounds have been shown to undergo reduction to form α-hydroxy esters or ketones. Such reduction was effected with α-keto esters, benzils, 1,2-cyclohexanedione, and α-ketophosphonates. The reduction of the α-ketoester was observed through utilization of Kuhktin-Ramirez adducts with alkyl phosphine 1.113 to generate the corresponding acyloin products, as shown in Scheme 1.24. This transformation is proposed to occur through initial reaction of the alkyl phosphine 1.113 with the dicarbonyl compound 1.14 to afford the dipolar oxyphosphonium ylide 1.114. An intramolecular proton transfer from the methyl group of the alkyl phosphine to the activated carbonyl carbon results in intermediate 1.115. Nucleophilic attack by water then expels phosphine oxide 1.116 to produce reduction product 1.117.

Scheme 1.24. Mechanism for the phosphine-mediated reduction of 1,2-dicarbonyl compounds.
1.4 Summary

The efforts contributed by both our lab and others towards the utilization of Kukhtin-Ramirez adducts as reactive intermediates to carry out different bond-forming reactions has been rather limited. Consequently, there exists opportunity for discovery of new bond forming transformations. The following chapters describe explorations of the reactivity of these adducts and their ability to generate new C-C bonds.
Chapter 2

Synthetic Studies on Non-Transition Metal Mediated C-C Bond Forming Methods via Kukhtin-Ramirez Adducts

The following chapter details the reactivity of Kukhtin-Ramirez adducts with carbon-based electrophiles. First, a C-alkylation of Kukhtin-Ramirez adducts with C\text{sp}3 electrophiles (i.e. benzylic and allylic bromides) is discussed. This process allows for the preparation of tert-alkanols via a formal Barbier-type transformation. Second, the reaction of Kukhtin-Ramirez adducts with C\text{sp}2 electrophiles (i.e. aldehydes) to give epoxides is discussed. Attempts to control the diastereoselectivity of these reactions with Lewis acids are described.

2.1 Reductive Alkylation of Carbonyl Compounds - The Barbier Reaction

This section discusses the utility of the classic Barbier reaction in synthesis. The development of a metal-free, trivalent phosphorus-mediated variant is subsequently detailed.

2.1.1 Synthetic Utility and General Reaction Conditions for the Barbier Reactions

Developed in 1899, the Barbier reaction is the classical reaction of an alkyl halide with a carbonyl compound in the presence of a metallic reductant (Scheme 2.1). This transformation

\[
\text{R}_1\text{C} = \text{O} \xrightarrow{1) \text{R}^3-\text{X} + \text{M}} \xrightarrow{2) \text{aqueous work-up}} \text{R}_1\text{R}_2\text{OH} \rightarrow \text{R}_1\text{R}_2\text{R}^3
\]

Scheme 2.1. General scheme of the Barbier reaction.
inspired the development of Grignard reagents and has historically been one of the key methods used to generate C-C bonds in organic synthesis. The Barbier reaction is advantageous because it is simple to perform and the procedures are relatively safe. The mechanism of the reaction, shown in Scheme 2.2, is presumed to be initiated by a single-electron transfer (SET) from the metal reductant to the alkyl halide; an additional SET reduction of the alkyl radical thus formed generates the equivalent of a Grignard reagent. This intermediate can then add to the carbonyl group through either a stepwise radical or concerted nucleophilic process to afford the metal alkoxide, which delivers the final product upon aqueous workup.

Another mechanistic possibility for the Barbier transformation is through a two electron umpolung of the carbonyl, facilitating the C-C bond forming reaction by inversion of polarity. This process cannot be achieved through use of the typical metal reductants currently utilized because the reduction tends to proceed via open shell intermediates. To initiate an umpolung
Barbier reaction, it is necessary to select an appropriate chemoselective reductant that will facilitate a two-electron umpolung of the carbonyl, as described below.

### 2.1.2 Metal-free P(NMe$_2$)$_3$-Mediated Barbier Reaction Between Methyl Aroylformates and Benzyl/Allyl Bromides

Through the Kukhtin-Ramirez reaction (Scheme 2.3), 1:1 adducts of α-dicarbonyl compounds 2.1 can be formed as either a dioxaphospholene 2.2 or an oxyphosphonium enolate 2.3. In unpublished results from our group, Dr. Rixin Wang has shown that these adducts can be trapped with alkyl halides 2.4 to generate the corresponding alkoxyphosphonium salt 2.5. Salts 2.5 can then further be transformed into tertiary alcohols 2.6 (via hydrolysis) or (Z)-selective trisubstituted alkenes 2.7 (via elimination) depending on choice of reaction conditions.\(^{35}\)

![Scheme 2.3](image)

**Scheme 2.3.** Barbier-type reductive alkylation via Kukhtin-Ramirez adducts.

A specific implementation of the trivalent phosphorus-mediated Barbier reaction is shown in Scheme 2.4. Tris(dimethylamino)phosphate (2.8) is added to a solution of a methyl benzoylformate (2.9) and benzyl bromide (2.10) in toluene at -78 °C. Warming of that mixture to room temperature and stirring for 2 hours results in precipitation of a white solid, which was
collected by filtration and was characterized as alkoxyphosphonium salt 2.11. Subsequent hydrolysis by dissolution of 2.11 in water at 60 °C results in a mixture predominantly comprised of the corresponding alcohol 2.12 (75%), with a small amount of elimination product 2.13 (20%, >95/5 Z/E). This method can be further simplified to a one-pot synthesis; starting from methyl benzoylformate (2.9) and benzyl bromide (2.10), decantation of solvent from alkoxyphosphonium 2.11 followed by introduction of H$_2$O gives tert-alkanol 2.12 in 71% yield (compared to 75% for the two-step process). This modified procedure is especially suitable for alkoxyphosphonium salts 2.5 that are unstable or hygroscopic.

In the absence of water, product 2.13 can be made the primary product of alkoxyphosphonium decomposition via an elimination reaction (Scheme 2.5). Specifically, heating of alkoxyphosphonium salt 2.11 (prepared from 2.9 and 2.10 under the previously described conditions) in acetonitrile solution results in the formation of α,β-disubstituted acrylates 2.13 as the major product. This phosphorus-mediated olefination reaction, which proceeds via an ylide-free pathway, delivers products with high (Z)-selectivity. For instance,
product 2.13 was isolated in 84% yield and 93:7 Z/E selectivity from methyl benzoylformate (2.9) and benzyl bromide (2.10).\textsuperscript{35}

\begin{equation}
\begin{array}{c}
\text{Ph} \quad \text{CO}_2\text{Me} \\
\text{2.9} \\
\end{array}
\begin{array}{c}
\text{Ph} \quad \text{Br} \\
\text{2.10} \\
\end{array}
\xrightarrow{1)} \text{P(NMe}_2\text{)}_3, \text{CH}_3\text{CN}
\xrightarrow{-40^\circ\text{C} \text{to rt}}
\begin{array}{c}
\text{Ph} \quad \text{CO}_2\text{Me} \\
\text{2.13} \\
\end{array}
\xrightarrow{2)} \text{CH}_3\text{CN-H}_2\text{O, 60^\circ\text{C}}
\end{equation}

\textbf{Scheme 2.5.} P(NMe}_2\text{)}_3\text{-promoted olefination reaction of methyl benzoylformate and benzyl bromide.}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme25}
\end{figure}

\textbf{2.1.3 Mechanism of Metal-free P(NMe}_2\text{)}_3\text{-Mediated Barbier Reaction Between Methyl Aroylformates and Benzyl/Allyl Bromides}\textsuperscript{35}

The mechanism of the observed transformations is most likely initiated by condensation of tris(dimethylamino)phosphine (2.8) with the methyl aroylformate 2.9 to generate Kukhtin-Ramirez adduct 2.14. Dimerization followed by epoxidation to form 2.17 is not observed in this case due to the presence of an alkylating agent which facilitates the formation of phosphonium salt 2.11. Alkylation of tris(dimethylamino)phosphine (2.8) by benzyl bromide (2.10) is not observed because that pathway is not kinetically competitive with the Kukhtin-Ramirez condensation, which occurs below –60 °C. Furthermore, the benzylphosphonium salt formed through alkylation of P(NMe}_2\text{)}_3 was shown to be unreactive toward methyl aroylformate, supporting initial generation of the Kukhtin-Ramirez adduct 2.14 (Scheme 2.6).

Once the adduct 2.14 is alkylated by benzyl bromide (2.10), loss of HMPA would give a tertiary benzylic carbocation 2.18. Trapping of carbocation 2.18 by H\textsubscript{2}O (essentially an S\textsubscript{N}1-like solvolysis) would then form the Barbier product 2.12. Alternatively, in the absence of trapping
water, further loss of a proton (an E\textsubscript{1} elimination) would generate alkene \textit{2.13}. Support for formation of the tertiary carbocation \textit{2.18} is evident in the reaction of the alkoxyphosphonium salt (\textit{2.20}, Scheme 2.7) derived from prenyl bromide (\textit{2.19}) and methyl benzoyleformate (\textit{2.9}). Upon hydrolysis, a mixture of cyclopropane products \textit{2.21} and \textit{2.22} is observed through homoallylic participation.

\textbf{2.1.4 Attempts at Friedel-Crafts Cyclization of Aryl oxo(phenyl)acetate}

In view of the putative intermediacy of tertiary carbocations in the mechanism of the hydrolysis step in the P(NMe\textsubscript{2})\textsubscript{3}-mediated Barbier reaction, we considered that it should be possible to trap these fleeting intermediates with other carbon-based nucleophilies. Along these lines, an intramolecular trapping through a Friedel-Crafts-type cyclization was pursued. In an
initial test, phenyl benzoylformate (2.24a) and benzyl bromide (2.10) were reacted with tris(dimethylamino)phosphine (2.8) to generate the corresponding alkoxyphosphonium salt 2.25a, which was isolated as a white solid. The salt 2.25a was then dissolved in nitromethane and stirred for 2 h. Unfortunately, the desired cyclization product 2.26a was not observed; however, formation of the corresponding elimination product 2.27a was seen.

In an effort to promote cyclization in preference to elimination, α-keto ester 2.24b with a nucleophilic meta methoxyphenyl ester moiety was prepared. Under the same conditions previously mentioned, the alkoxyphosphonium salt 2.25b was generated and treated with a variety of polar aprotic solvents as can be seen in Table 2.1, at both room temperature and 40 °C. No cyclization product 2.26b was observed; however, the elimination product 2.27b did form.

Based on these results, it is evident that the elimination pathway is kinetically preferred, perhaps due to the anionic bromide readily deprotonating the β position to facilitate formation of the elimination product. To promote Friedel-Crafts cyclization, it may be beneficial to further
substitute the aromatic ring with more electron donating groups or even to alter the counter anion of the alkoxyphosphonium salt 2.25 to an anion that is more stable and less basic.

**Table 2.1.** Solvent screen for Friedel-Crafts cyclization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Solvent</th>
<th>Observed product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>MeNO₂</td>
<td>2.27a</td>
</tr>
<tr>
<td>2</td>
<td>OMe</td>
<td>MeNO₂</td>
<td>2.27b</td>
</tr>
<tr>
<td>3</td>
<td>OMe</td>
<td>DMSO</td>
<td>2.27b</td>
</tr>
<tr>
<td>4</td>
<td>OMe</td>
<td>DMF</td>
<td>2.27b</td>
</tr>
</tbody>
</table>

**2.1.5 Diastereoselectivity in Metal-free P(NMe₂)₃-Mediated Barbier Reaction**

Since the previously mentioned metal-free P(NMe₂)₃-mediated Barbier reaction generates a new stereogenic center, a method to control the absolute stereochemistry under either substrate or reagent control was explored.
Initial attempts involved the use of chiral auxiliary-substituted α-diketoesters 2.28 to promote substrate-control of diastereoselectivity. The first auxiliary used was Corey’s naphthylsulfonyl-substituted cyclohexanol auxiliary 2.28a (Scheme 2.8).

Scheme 2.8. Diastereoselective P(NMe$_2$)$_3$-mediated Barbier reaction.

Substrate α-diketoester 2.28a was prepared by DCC-mediated esterification of phenylglyoxylic acid with the corresponding chiral alcohol. Reaction of α-diketoester derivative 2.28a with benzyl bromide (2.10) and tris(dimethylamino)phosphine generated the corresponding alkoxynaphthaldehyde salt 2.29a in 74% yield and with a diastereomeric ratio of 16:1 determined by $^{31}$P NMR with peaks corresponding to diastereomeric phosphonium salt 2.29a at δ 30 ppm (major peak) and δ 35 ppm (minor peak). This result indicates that the alkylation event can indeed be subjected to substrate-controlled diastereoselection. Subsequent hydrolysis of the salt 2.29a was then attempted. However, the salt 2.29a was not soluble in water even at 60 °C. Attempts were made to solubilize the salt 2.29a in both 1:1 mixtures of acetone/water and DMSO/water. However, the desired products 2.30a and 2.31a were not formed but instead, a complex mixture was observed. Furthermore, the stoichiometric byproduct, HMPA, was not observed by $^{31}$P NMR, leading to the conclusion that formation of the desired hydrolysis product 2.30a did not occur.
To improve solubility of the generated salt, phenylcyclohexane auxiliary 2.28b, which is smaller and correspondingly less hydrophobic than the Corey auxiliary 2.28a, yet still mimics its general spatial orientation, was used. In the presence of benzyl bromide (2.10) and tris(dimethylamino)phosphine, auxiliary-modified substrate 2.28b generated the alkoxyphosphonium salt 2.29b. This salt 2.29b was rather hygroscopic, so instead of isolating the salt 2.29b through filtration, the solvent was removed under high vacuum and water was then added and the mixture was heated at 60 °C. The hydrolysis product 2.30b was isolated in 12% yield with diastereomeric ratio of 3:1. While this result validates the notion that both the alkylation and subsequent hydrolysis can be conducted in a diastereoselective fashion, neither the chemical yield nor diastereomeric ratio represent satisfactory results.

After observing the challenges with the chiral auxiliary derived α-ketoesters, a reagent controlled method was attempted (Scheme 2.9). It had been shown previously that homochiral phosphorus reagent 2.32 was capable of promoting diastereoselective transformations involving a Kukhtin-Ramirez adduct of methyl benzoylformate (2.9). We foresaw the possibility that 2.30 might be capable of controlling the stereoselectivity of umpolung alkylation of a Kukhtin-Ramirez adduct with benzyl bromide (2.10); however, challenges arose. Under the previously optimized conditions, tentative formation of the five-coordinate adduct of the chiral phosphorus

\[ \text{Scheme 2.9. Attempted reagent-controlled stereoselective Barbier-like benzylation.} \]
compound 2.32 and methyl benzoylformate (2.9) was observed by \(^{31}\)P NMR as a peak at \(\delta -50\) ppm which is in the range of typical oxyphosphorane species.\(^{38}\) In an attempt to drive alkylation, the reaction mixture was heated at 50 °C, but still no phosphonium salt was generated.

At present, a satisfactory diastereoselective variant of the phosphorus-mediated Barbier-type reaction remains elusive. A more suitable chiral auxiliary may be needed that is sufficiently bulky and also soluble in water to promote the hydrolysis. Furthermore, it may be necessary to develop other homochiral phosphorus reagents that are able to both generate the Kukhtin-Ramirez adduct and further undergo alkylation to afford the desired phosphonium salt.

### 2.2 Epoxide Synthesis by Phosphorus-Mediated Reductive Condensation of \(\alpha\)-Ketoesters and Aldehydes – Effect of Lewis Acid Additives

The following sections discuss a reductive synthesis of epoxides initiated by Kukhtin-Ramirez adducts of \(\alpha\)-diketoesters, followed by trapping with aldehydes. Efforts to control the diastereoselectivity of this transformation with Lewis acid additives are detailed.

#### 2.2.1 Reductive Epoxidation Facilitated by Trivalent Phosphorus Species

Epoxides are important structural motifs in organic synthesis.\(^{39}\) Typical methods for generating epoxides involve oxidizing olefins with peroxides. However, these methods can be problematic for preparing epoxides with sensitive functional groups.\(^{40}\) Methods that can effectively and selectively effect epoxidation under milder, non-oxidative methods would be beneficial. One potential solution to overcome functional group sensitivity is through the reductive cross dimerization of carbonyl compounds in the presence of
tris(dimethylamino)phosphine. The literature examples of epoxidation facilitated in this manner to date are discussed below.

Epoxide formation by reductive dimerization of carbonyl compounds with trivalent phosphorus reagents has been known since the 1960s. The first example, shown in Scheme 2.10, involved the reductive dimerization of two molecules of benzaldehyde (2.33) by addition of tris(dimethylamino)phosphine.

![Scheme 2.10. P(NMe_2)_3-mediated deoxygenative epoxidation of benzaldehyde.](image)

As shown in Scheme 2.11, this transformation is proposed to proceed by initial nucleophilic attack of the aldehyde 2.36 by tris(dimethylamino)phosphine to form phosphonium species 2.37. Subsequent attack on another equivalent of aldehyde 2.36 by ylide 2.37 generates intermediate 2.38 which can ring close to form 2.39. Collapse of adduct 2.39 is reminiscent of the Wittig reaction in which a carbon-phosphorus and a carbon-oxygen bond cleavage results in formation of a phosphorus-oxygen bond and carbon-carbon bond formation. Through this

![Scheme 2.11. Mechanism of phosphine-mediated reductive epoxidation of aldehydes.](image)
rearrangement and expulsion of HMPA, the dimerized epoxide 2.40 is observed. The success of the transformation is dependent on the electronic nature of the aldehyde substrate. In the case of aromatic aldehydes with electron withdrawing substituents, the reaction is rapid and exothermic, ultimately forming the corresponding epoxide. If the aromatic substituents are electron donating, the epoxidation is attenuated and only formation of the 1:1 phosphorus-aldehyde adduct 2.37 is observed.

Additional studies involving the intramolecular epoxidation of the dialdehydes 2.41 and tris(dimethylamino)phosphine, shown in Scheme 2.12, and epoxidations with aryl glyoxylic esters 2.9 and tris(dimethylamino)phosphine to generate α,β-dimethoxycarbonylstilbene oxides (2.43) were explored. More recently, a trans-selective epoxidation, shown in Scheme 2.13, was

Scheme 2.12. P(NMe$_2$)$_3$-mediated deoxygenative epoxidation of dialdehydes.

Scheme 2.13. Diastereoselective reductive epoxidation mediated by proazaphosphatrane 2.44.
pursued by Verkade *et al.* using proazaphosphatrane **2.44** as the trivalent phosphorus species.\(^{43}\)

While this diastereoselective method is effective, it is limited to the reductive dimerization of substituted benzaldehydes (**2.33**) and employs a rather expensive phosphorus reagent **2.44**. A diastereoselective method that is not limited to the epoxidation of aldehydes and uses more affordable reagents is needed.

### 2.2.2 Epoxidation with Methyl Benzoylformate and Benzaldehyde

Recent efforts in our lab have shown that the reaction of methyl benzoylformate (**2.9**) and benzaldehyde (**2.33**) in the presence of tris(dimethylamino)phosphine forms epoxide **2.45** in 87\% (51:49 dr), as shown in Scheme 2.14.

![Scheme 2.14. P(NMe\(_2\))\(_3\)-mediated deoxygenative epoxidation of methyl benzoylformate and benzaldehyde.](image)

The reaction is rapid at room temperature and is therefore typically run at -78 °C. We felt that improvements in the reaction, specifically with regard to the diastereoselectivity, would provide a useful synthetic tool that would allow for the formation of epoxides under mild conditions.

Since the epoxidation initiated by tris(dimethylamino)phosphine is rapid, not stereoselective, and probably occurs through an open transition state, we envisioned a process in which altering the phosphine reagent may help to retard the rate of epoxidation slightly, such that epoxide formation would require the presence of a Lewis acid activator (LA, Scheme 2.15). Specifically, upon formation of the Kukhtin-Ramirez adduct, a Lewis acid could bind to the
adduct and template approach of the aldehyde via a closed transition state (Scheme 2.15). This mechanistic pathway could result in a chemoselective method for diastereoselective epoxidation under mild conditions.

Initially, the utilization of phosphite reagents in conjunction with a variety of different Lewis acids was explored due to the decrease in reactivity that has been observed with trialkyl phosphites and α-keto ester substrates in X-H functionalization reactions.\(^{27}\) As shown in Table 2.2, an assortment of phosphite reagents combined with a variety of Lewis acids were used with methyl benzoylformate (2.9) and benzaldehyde (2.33). No reaction was observed with trimethyl phosphite (2.46). Triethyl phosphite (2.47) did promote a reaction that was found, by \(^1\)H NMR, not to be the epoxidation product 2.45. The identity of this compound is currently undetermined. Furthermore, slight reactivity was observed with triisopropyl phosphite (2.48), forming the same unknown product observed in the reaction with triethyl phosphite (2.47). Whereas the phosphorous triamide P(NMe\(_2\))\(_3\) reacts rapidly with 2.9 and 2.31 to give epoxide 2.45, neither diamide 2.49 nor monoamide 2.50 were reactive under the conditions shown in Table 2.3.

**Scheme 2.15.** Proposed impact of Lewis acid catalyst on the phosphine-mediated reductive epoxidation method.
Due to the drastic difference in reactivity observed between different phosphorus reagents, NMR experiments were performed to probe their reactivity. In $^{31}$P NMR experiments, equal molar amounts of methyl benzoylformate (2.9) and a phosphorus reagent were combined at -78 °C and then warmed to room temperature and monitored for 24 hours. Reaction of 2.9 with tris(dimethylamino)phosphine 2.8 (δ 124 ppm) proceeded rather quickly, showing formation of HMPA (δ 25 ppm) via reductive epoxidation of methyl benzoylformate within 10 minutes. Under otherwise identical conditions, reactions of methyl benzoylformate (2.9) with trimethyl
phosphite (2.46) and triethyl phosphite (2.47), respectively, did not proceed cleanly and fully to the corresponding adducts. Instead, after approximately 5 hours, free trimethyl phosphite (2.46, δ 140 ppm, major peak) remained in solution. Additionally, a peak at δ -52 ppm corresponding to the Kukhtin-Ramirez adduct and a small peak at δ 2 ppm corresponding to trimethyl phosphate were observed. Similarly, after approximately 2 hours, triethyl phosphite (2.47, δ 138 ppm) remained in solution, with a peak at δ -55 ppm for the corresponding Kukhtin-Ramirez adduct also present. These reactions were further monitored for 24 hours; no noticeable change in intensity of the peaks was observed.

Ultimately, what can be concluded from this experimental data is that tris(dimethylamino)phosphine is capable of promoting reductive dimerization while phosphite reagents are not. The phosphite reagents are able to form stable pentacoordinate species.

Table 2.3. Epoxidation promoted by various phosphines and Lewis acids.

<table>
<thead>
<tr>
<th>PR₃</th>
<th>LA</th>
<th>Solvent</th>
<th>Temp</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPh(NEt₂)₂</td>
<td>MgI₂</td>
<td>DCM</td>
<td>rt</td>
<td>-</td>
</tr>
<tr>
<td>2.49</td>
<td>MgI₂</td>
<td>PhMe</td>
<td>reflux</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>MgI₂</td>
<td>DMSO</td>
<td>150 °C</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Sc(OTf)₃</td>
<td>DCM</td>
<td>rt</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Sc(OTf)₃</td>
<td>PhMe</td>
<td>reflux</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Sc(OTf)₃</td>
<td>DMSO</td>
<td>150 °C</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>TiF₄</td>
<td>DCM</td>
<td>rt</td>
<td>-</td>
</tr>
</tbody>
</table>
stability prevents them from further reacting to induce epoxidation, while the tris(dimethylamino)phosphine adducts are much less stable and consequently, more reactive.

Further NMR experiments were run with benzaldehyde (2.33) and the above mentioned phosphorus reagents to see if phosphorus binding to the aldehyde was inhibiting the formation of the Kukhtin-Ramirez adduct of methylbenzoylformate and the corresponding phosphorus species; however, no reaction was observed with the phosphite reagents. Alternatively, after 6 hours, the reaction of benzaldehyde (2.33) with tris(dimethylamino)phosphine afforded many phosphorus species with resonances between δ 13 to 30 ppm in the $^{31}$P NMR. The identity of these species is undetermined. Finally, reaction of methyl benzoylformate (2.9), benzaldehyde (2.33), and a trivalent phosphorus reagent was monitored by $^{31}$P NMR, indicating the reaction with tris(dimethylamino)phosphine was mostly complete after 10 minutes as indicated by the formation of (Me$_2$N)$_3$P=O. Similarly, monitoring of the formation of trialkyl phosphate for both trialkyl phosphite reagents was performed. After 7 hours, all of the triethyl phosphate was consumed and mostly triethyl phosphate (at approximately δ -1 ppm) was produced with some Kukhtin-Ramirez adduct still visible (approximately δ -55 ppm). After 7 hours with trimethyl phosphite, a majority of the phosphite still remained with some formation of both the Kukhtin-Ramirez adduct with methyl benzoylformate (2.9) and trimethyl phosphate (peaks around δ -52 ppm and δ 2 ppm, respectively). Ultimately, these experiments illustrate that the trialkyl phosphites are poor trivalent phosphorus species for this transformation.

There is much work that can still be done with regards to diastereoselective epoxidation. Determination of a suitable trivalent phosphorus species is still needed to be able to facilitate this type of reactivity with Lewis acids. It may be beneficial to prepare a phosphorus reagent containing both amino groups and alkoxy groups to temper the reactivity to facilitate
diastereoselective epoxidation. Understanding how to tune the reactivity of these different Kukhtin-Ramirez adducts is imperative to the development of other synthetic methods that rely on their intermediacy.
Chapter 3

Synthetic Studies on Transition Metal-Catalyzed Carbene Transfer from Kukhtin-Ramirez Adducts

This chapter is focused on the study of Kukhtin-Ramirez adducts as carbene transfer reagents in transition metal-catalyzed reactions. The observed reactivity of these adducts and potential challenges for improving reactivity are discussed.

3.1 Background and Reactivity Precedent

Late transition metal carbenoids are involved in many catalytic reactions including cyclopropanation, dipolar additions, insertion reactions, and ylide formation. These highly reactive intermediates are typically generated in situ by metal-mediated decomposition of a dipolar carbene transfer precursor (3.1, Scheme 3.1) in the presence of a suitable substrate for the transfer of the carbene to the metal center.

Scheme 3.1. General synthetic route to metal carbenoids.
desired transformation. Commonly, rhodium(II) and copper(I) salts are exploited for these transformations, and enantioselective variants have been developed. Mechanistically, the carbene transfer precursor 3.1 will bind an electrophilic metal-forming intermediate 3.2 (Scheme 3.1), which will further react to release a reactive metal carbenoid (3.3) and a stoichiometric byproduct 3.4.

As shown in Figure 3.1, the most common carbene transfer precursors used for metal carbenoid formation are diazo compounds and main group ylides. Diazo compounds are the most typical carbene transfer precursors due to their high reactivity and facile ability to generate metal carbenoids. Although diazo compounds are effective carbene transfer precursors, there are challenges with their preparation and storage. Formation of these carbene transfer precursors often involves multiple ex situ synthetic steps. Furthermore, a limited number of diazo compounds are commercially available due to their instability and safety issues.

Alternative carbene transfer precursors with improved characteristics are desired due to the challenges of diazo preparation and handling. One such class of compounds is the main group ylide precursors. In general, these compounds are not as reactive as diazo compounds; however, they tend to be crystalline and are occasionally stable to chromatography, having a

![Figure 3.1](image-url)
drastically improved shelf-life.\textsuperscript{49} Common ylides utilized recently in the literature include sulfonium\textsuperscript{50} and iodonium\textsuperscript{51} ylides. These ylides are typically prepared by multistep sequences,\textsuperscript{52} some of which involve diazo intermediates. The gains in stability and handling associated with carbene transfer from ylide precursors are offset by release of an organic byproduct that must be removed by chromatography.

The development of new carbene transfer precursors that 1) can be prepared \textit{in situ} under mild conditions and 2) generate only easily removable stoichiometric byproduct would advance the utility of existing transition metal carbenoid technologies. We considered that oxyphosphoranes might have potential as new carbene transfer precursors that address the operational deficiencies described for both diazo compounds and ylides. Specifically, oxyphosphoranes can be prepared \textit{in situ} under mild reaction conditions by the Kukhtin-Ramirez redox condensation of 1,2-dicarbonyl compounds with trivalent phosphorus compounds.\textsuperscript{53} As seen in Scheme 3.2, the oxyphosphorane can be present as the closed dioxaphospholene 3.7 or the open dipolar structure 3.8. The open dipolar structure 3.8 bears a similar formal electronic structure to the diazo and ylide precursors in Figure 3.1 indicating the possibility for similar reactivity.

Further evidence from the Mukaiyama group supports the notion that oxyphosphorane 3.7 might serve as a carbene transfer precursor.\textsuperscript{54} Oxyphosphorane 3.7, generated \textit{in situ} from
benzil (3.5) and triethylphosphite (3.6), was found to decompose in the presence of substoichiometric copper(II) sulfate in refluxing toluene to generate the dimerized product cis-dibenzoylstilbene (3.11). The intermediacy of the copper carbenoid 3.10 (Scheme 3.3) was inferred.

**Scheme 3.3.** Reductive dimerization of benzil illustrated by Mukaiyama.

If a copper carbenoid is indeed formed under these conditions, then it should be possible to trap the reactive intermediate with an appropriate substrate for synthetic chemistry. The research that follows describes efforts to exploit this underdeveloped strategy for accessing reactive metal carbenoids in the context of an intermolecular and intramolecular cyclopropanation reaction, as well as an O-H insertion reaction. Given their preparative and operational simplicity, oxyphosphoranes offer new opportunities en route to metal carbenoids that may, in time, address many of the challenges posed by current carbene transfer precursors.
3.2 Initial Study of Intermolecular Cyclopropanation via Generation of a Metal Carbenoid

The first synthetic approach to trap the putative oxyphosphorane-derived metal carbenoid (3.10) was through the cyclopropanation of an alkene. Using the procedure introduced by Ramirez,\textsuperscript{55} the trimethylphosphite-benzil adduct 3.7 was prepared and subjected to substoichiometric copper(II) sulfate and styrene in toluene at reflux for 5 hours (Scheme 3.4). Under this set of conditions, the cyclopropanation product 3.13 was produced in a 33% isolated yield (20:1 $dr$ determined by NMR, relative stereochemistry assigned by analogy to similar reactions with diazoesters\textsuperscript{56}). Two other major products were identified by NMR and GC/MS analysis: cis-dibenzoylstilbene (3.11) from metal carbenoid dimerization (as had been previously shown by Mukaiyama\textsuperscript{54}) and benzil (3.5) from a retro-Ramirez reaction.

**Scheme 3.4.** Reaction of oxyphosphorane and styrene promoted by copper(II) sulfate.

3.3 Optimization of Reaction Conditions

Through the screening of many reaction variables in an effort to optimize the cyclopropanation reaction, it is apparent that there is a slight preference for nonpolar, noncoordinating solvents. The cyclopropanation product 3.13 was observed in refluxing toluene, xylenes, and 1,4-dioxane resulting in 33%, 26%, and 12% yield, respectively as seen in Table
3.1. No cyclopropanation product 3.13 was observed by NMR in lower boiling solvents (dichloromethane, tetrahydrofuran, or acetonitrile, all at reflux), indicative of a larger thermal barrier for carbene transfer with oxyphosphoranes than is seen with diazoalkanes. Even in toluene, this temperature dependence is evident. Cyclopropanation was observed at 80 °C in 9% yield, but at lower temperatures, no product or decomposition of the oxyphosphorane was observed. This observation indicates that carbene transfer from oxyphosphorane compounds requires higher temperatures than from diazo compounds.

**Table 3.1.** Solvent optimization for reaction in Scheme 3.4.

<table>
<thead>
<tr>
<th>Solvent Yield of 3.13</th>
<th>PhMe</th>
<th>Xylenes</th>
<th>1,4-Dioxane</th>
<th>DCM</th>
<th>THF</th>
<th>CH₃CN</th>
</tr>
</thead>
<tbody>
<tr>
<td>33%</td>
<td>26%</td>
<td>12%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

In an attempt to diminish formation of the dimerization product 3.11, the concentration dependence of the cyclopropanation was also explored. The cyclopropanation reaction was carried out at 0.5 M, 0.1 M, 0.05 M, and 0.03 M of the oxyphosphorane adduct 3.7 in toluene at reflux with 3 equivalents of styrene and 60 mol% CuSO₄. These experiments resulted in a steady decrease in the yield of the cyclopropane product 3.13 from 33% to 11% (Table 3.2).

**Table 3.2.** Effect of concentration for reaction in Scheme 3.4.

<table>
<thead>
<tr>
<th>Concentration of 3.7</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 M</td>
<td>33%</td>
</tr>
<tr>
<td>0.1 M</td>
<td>22%</td>
</tr>
<tr>
<td>0.05 M</td>
<td>17%</td>
</tr>
<tr>
<td>0.01 M</td>
<td>11%</td>
</tr>
</tbody>
</table>
Further experimentation showed that cyclopropane 3.13 was itself undergoing further decomposition under the reaction conditions at prolonged reaction times. Specifically, when monitored by GC/MS, the formation of 3.13 was observed to peak at 4-5 hours, after which a new isomeric species grew in at the expense of 3.13. Based on this observation, the optimal reaction time for this transformation was determined to be 4 hours resulting in a 33% yield of the desired product (3.13).

In order to evaluate the effect of catalyst on cyclopropanation efficiency, a panel of known carbene-transfer catalysts were assayed (Table 3.3). Based on the observed results, it seems that the oxidation state of copper is not vital to metal carbenoid generation. CuSO₄ (entry 1), CuI (entry 6), and CuBr (entry 7) are all capable of achieving similar cyclopropanation yields. The halide counterion may be important for catalyst activity; whereas copper(I) bromide and iodide are suitable catalysts, CuCl₂ is incapable of catalyzing the cyclopropanation reaction. Surprisingly, no reactivity was observed with either rhodium or iridium complexes, both of which are effective catalysts for diazo and ylide decomposition. Due to the high affinity of phosphite to bind to copper, [CuCl{P(OCH₃)₃}] (Table 3.3, entry 14), a catalyst previously used to facilitate diazo decomposition, was employed. The phosphite ligand should prevent binding of the promoter and deter the retro-Ramirez reaction, which was anticipated to promote formation of the metal carbenoid. Instead, no cyclopropanation product was observed, which may support the hypothesis that as phosphite binds to the copper catalyst, it inhibits catalytic metal carbenoid formation.

Due to the potential problem of polymerization of styrene at high temperatures, other olefins were analyzed including 4-methylstyrene, indene, and cis-cyclooctene, resulting in the corresponding cyclopropanation products in isolated yields of 15% (dr), 26%, (dr) and 22% (dr),
respectively (Scheme 3.5). The major diastereomers were assigned by analogy to related compounds formed from cyclopropanation with diazoester carbene precursors. In the cases of indene and cis-cyclooctene, yields are observed comparable to that with styrene (3.12). This observation indicates that the use of a highly polymerizable alkene substrate is not the only factor preventing high yield of the corresponding cyclopropane.
With respect to the trivalent phosphorus reagent, substitution at phosphorus was found to significantly influence the reaction. An adduct 3.17 from tris(dimethylamino)phosphine and benzil (3.5) was synthesized and exposed to styrene (3.12) and 60 mol% CuSO₄ in toluene at reflux, but no cyclopropanation was observed (Scheme 3.6). It is unclear whether the failure of this reaction is attributable to inefficient initial formation of the requisite metal carbenoid 3.10,

Scheme 3.5. Cyclopropanation of compatible substrates.

Scheme 3.6. Reactivity of the benzil-tris(dimethylamino)phosphine adduct 3.17 with styrene.
or rather to catalyst inhibition by the liberated phosphine oxide. The latter possibility is supported by a similar inhibition of rhodium catalysts by dimethyl sulfoxide (DMSO) with the use of sulfoxonium ylides. Moreover, when one equivalent of hexamethylphosphoramide (HMPA) was added to an otherwise standard reaction with the trimethyl phosphite adduct 3.7

\[
\text{Table 3.4. Inhibition by P=O-containing byproducts.}
\]

<table>
<thead>
<tr>
<th>Additive</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>O=P(NMe2)3</td>
<td>5%</td>
</tr>
<tr>
<td>O=P(OMe)3</td>
<td>16%</td>
</tr>
</tbody>
</table>

(Table 3.4), the cyclopropane 3.13 was isolated in only 5% yield.

An analogous experiment with one equivalent of trimethyl phosphate (3.9) resulted in a 16% isolated yield of 3.13. The difference in inhibitory behavior between HMPA and trimethyl phosphate may relate to the differential Lewis basicity of the respective P=O moieties. The dimethylamino groups of HMPA are stronger electron donors, making the phosphoryl P=O more basic and able to bind more strongly to the metal center.

Consequently, an attempt to alter the alkyl phosphite so as to generate a very weakly basic phosphate byproduct and thereby minimize the effect of the byproduct inhibition was undertaken. However, formation of the dioxaphosphorane adduct from P(OCH2CF3)3 and benzil (3.5) was not successful. Furthermore, to more closely mimic the conditions used by Mukaiyama, we tried to generate the triethyl phosphite adduct in situ and initiate cyclopropanation with styrene in a one-pot reaction isolating 24% of the cyclopropanation
product 3.13. A one-pot synthesis with trimethyl phosphite and benzil (3.5) under the same conditions was also attempted for comparison, affording 19% of the desired product 3.13. These results show that the slight alteration of the phosphite used does not drastically change the reactivity observed.

In order to evaluate the impact of varied electronic character of the Kukhtin-Ramirez adduct, a variety of dicarbonyl compounds were combined with trimethyl phosphite. The first modification was to use para-substituted benzils. A one-pot synthesis was attempted; the adduct could be generated in situ and further reacted with styrene resulting in 19% (>20:1 dr) and 8% (>20:1 dr) dimethyl-substituted and dimethoxy-substituted cyclopropanation products, respectively (Table 3.5). The major diastereomer was assigned by analogy to related compounds formed from cyclopropanation with diazoester carbene precursors.59

<table>
<thead>
<tr>
<th>X</th>
<th>Yield (dr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>19% (&gt;20:1)</td>
</tr>
<tr>
<td>Me</td>
<td>19% (&gt;20:1)</td>
</tr>
<tr>
<td>OMe</td>
<td>8% (&gt;20:1)</td>
</tr>
</tbody>
</table>

α-Ketoester-derived Kukhtin-Ramirez adducts were also explored. The α-ketoester adducts with tris(dimethylamino)phosphine are known to be more thermally labile than the corresponding benzil-derived adducts.61 For instance, α-ketoesters of the type 3.18 (Scheme 3.7) have been observed to undergo reductive dimerization at temperatures above –40 °C.59 Attempts were therefore made to intercept this intermediate at low temperature with metal salts to generate
metal carbenoids. Trimethyl phosphite and tris(dimethylamino)phosphine complexes of the α-ketoesters 3.20 and 3.23 (Scheme 3.7) were formed *in situ* and subjected to Rh$_2$(OAc)$_4$, CuSO$_4$, and [Ir(COD)Cl]$_2$ at -78 °C. No intramolecular cyclopropanation was observed with α-ketoester 3.20. Instead, upon warming to room temperature, the corresponding epoxidation product was observed with the tris(dimethylamino)phosphine adduct, and no reaction was observed with the trimethyl phosphite adduct. Similarly, no cyclopropanation was observed with α-ketoester 3.23. The corresponding epoxide was observed with the tris(dimethylamino)phosphine adduct, and no reaction occurred with the trimethyl phosphite adduct.

To prevent the oxyphosphorane adduct from undergoing a retro-Ramirez reaction under the cyclopropanation reaction conditions, O-silylated derivatives (3.26, 3.27, Scheme 3.8) were also synthesized by treatment of benzil with the corresponding silyl reagent followed by reaction with tris(dimethylamino)phosphine. tert-Butyldimethylsilyl hexafluorophosphate adduct 3.26
and trimethylsilyl chloride adduct 3.27 were treated with styrene (3.12) and CuSO₄ in refluxing toluene; however, no transformation was observed by NMR. This outcome could be due to the use of tris(dimethylamino)phosphine instead of trimethyl phosphite; however, isolation of the trimethyl phosphite adducts was operationally challenging. It is also possible that the silylated oxyphosphonium salts may be too stable to permit decomposition to the metal carbenoid.

![Scheme 3.8](image)

Scheme 3.8. *O*-Silylated tris(dimethylamino)phosphine adducts of benzil.

3.4 O-H and N-H Insertion Reactions with Kukhtin-Ramirez Adducts as Metal Carbenoid Precursors

Due to the marginal improvement of the cyclopropanation reaction, exploration into carbenoid O-H and N-H insertion reactions was initiated (Scheme 3.9). Under the same conditions that afforded the best yields of cyclopropanation product, O-H insertions of methanol and ethanol were attempted affording 48% and 16% of the insertion products, respectively. Further catalyst optimization of the methanol insertion reaction was attempted (catalyst =

![Scheme 3.9](image)

Rh$_2$(OAc)$_4$ or [Ir(COD)Cl]$_2$, but no insertion product was observed. Cu-catalyzed N-H insertions of 4-chloroaniline and 4-bromoaniline were also attempted, but no reaction was observed. The challenges observed here support the hypothesis that the problematic step in these transformations is metal carbenoid generation from the oxyphosphorane rather than further reaction with an appropriate substrate.

**3.5 Conclusions and Future Outlook**

The research presented here has been focused on discovering a new method to generate metal carbenoids through utilization of Kukhtin-Ramirez adducts. Although the reaction conditions remain to be optimized, new and exciting carbene transfer reactivity has been demonstrated from these adducts. Our results support the capacity of transition metal complexes to react with Kukhtin-Ramirez adducts to give metal carbenoids, which can be further trapped by appropriate substrates to carry out transformations similar to those known from diazo decomposition methods. Future challenges that must be addressed in order to realize the potential of our approach include identifying a phosphorus species that is both oxophilic enough to bind to the 1,2-dicarbonyl compound and be subsequently expelled as phosphine oxide to facilitate generation of the metal carbenoid. Due to the inhibition of the copper catalysts by both the phosphite reagent and phosphate byproduct, it may be necessary to explore transition metals that do not bind the inhibitors effectively. Finally, it may be beneficial to explore other 1,2-dicarbonyl functionalities in combination with different phosphorus reagents. While these reactivity issues persist, it seems that further exploration into the potential synthetic applicability of the Kukhtin-Ramirez adducts is worthwhile. These adducts exhibit truly unique reactivity that, once harnessed appropriately, will be able to carry out many exciting synthetic transformations.
Chapter 4

Experimental Section

General Notes

Toluene, dichloromethane, tetrahydrofuran, dimethylformamide, and acetonitrile were sparged with argon and dried through an activated alumina column. All other solvents were used as received from commercial suppliers. All reaction glassware was dried in a 120 °C oven prior to use. Reagents were used as received from commercial vendors (Sigma-Aldrich, Alfa-Aesar, TCI, and Acros). All NMR spectra were obtained on Bruker 300 and 360 MHz instruments. All signals were referenced to internal residual chloroform of the deuterated solvent for proton and carbon chemical shifts (chloroform: $^1$H δ 7.26 ppm, $^{13}$C δ 77.0 ppm). For phosphorus chemical shifts, an external standard (H$_3$PO$_4$: δ 0.0 ppm) was used. Mass spectrometry was performed at the School of Chemical Sciences Mass Spectrometry Laboratory at the University of Illinois at Urbana-Champaign. All yields reported are isolated yields.

**Preparation of Phenyl Oxo(phenyl)acetate (2.24a).** To a stirred solution of phenylglyoxylic acid (1.10 g, 7.30 mmol, 1.00 equiv) and DMF (0.08 mL, 1.00 mmol, 0.13 equiv) in dichloromethane (15 mL), was added dropwise at 0 °C oxalyl chloride (0.96 mL, 11.20 mmol, 1.54 equiv). The mixture was then stirred for 4 h at room temperature. The solvent was then evaporated at 40 °C. Dichloromethane (25 mL) was added to the residue and DMAP (0.089 g, 0.73 mmol, 0.10 equiv) was added. A solution of phenol (0.70 g, 7.30 mmol, 1.00 equiv) and triethylamine (3.00 mL, 21.00 mmol, 2.87 equiv) in dichloromethane (8 mL) was added dropwise under stirring. The mixture was stirred at room
temperature for 24 h, diluted with dichloromethane (15 mL) and washed with water (2 x 10 mL), 10% NaOH (10 mL), and saturated NaCl solution (15 mL). The organic phase was dried with Na₂SO₄, filtered, and concentrated. The crude material was then purified using column chromatography (5:2 hexane:acetone) affording compound 2.24a as a yellow oil (0.95 g, 58%).

\[ ^1H \text{NMR (CDCl}_3, 360 MHz) \delta 8.16 (d, J = 7.5 Hz, 2H), 7.73 (t, J = 7.3 Hz, 1H), 7.58 (t, J = 7.5 Hz, 2H), 7.49 (t, J = 7.5 Hz, 2H), 7.33 (m, 3H). \] This data matches reported literature data.

**Attempted Preparation of Cyclization Product 2.26a.** Compound 2.24a (0.25 g, 1.10 mmol, 1.10 equiv) and benzyl bromide (0.12 mL, 1.00 mmol, 1.00 equiv) in toluene (10 mL) were cooled to -78 °C and then treated with tris(dimethylamino)phosphate (0.20 mL, 1.10 mmol, 1.10 equiv). After warming the mixture to room temperature and stirring for 2 h, the phosphonium salt precipitated from solution. The solvent was decanted, and the remaining crude solid was dissolved in nitromethane (10 mL) and stirred for 3 h. The mixture was concentrated and the residue was redissolved in ether (10 mL). The solution was washed with water (2 x 10 mL), brine (10 mL), and dried over sodium sulfate. The cyclization product 2.26a was not observed, but rather the elimination product 2.27a was isolated (0.26 g, 85%).

\[ ^1H \text{NMR (CDCl}_3, 360 MHz) \delta 7.64 (d, J = 6.9 Hz, 2H), 7.56 (d, J = 6.7 Hz, 2H), 7.41 (m, 8H), 7.27 (m, 3H), 7.05 (d, J = 7.5 Hz, 2H); ^13C \text{NMR (CDCl}_3, 90 MHz) \delta 168.4, 150.9, 137.1, 136.1, 135.0, 132.9, 129.9, 129.8, 129.3, 129.2, 129.1, 129.0, 128.9, 127.0, 126.5, 121.8; \text{MS (ESI) calcd for C}_{21}H_{17}O_2 (M+H) 301.1229, found 301.1228. \]

**Preparation of 3-methoxyphenyl oxo(phenyl)acetate (2.24b).** To a stirred solution of phenylglyoxylic acid (1.50 g, 10.00 mmol,
1.00 equiv) and DMF (0.10 mL, 1.30 mmol, 0.13 equiv) in dichloromethane (20 mL), was added dropwise at 0 °C oxalyl chloride (1.30 mL, 15.40 mmol, 1.54 equiv). The mixture was stirred for 4 h at room temperature. The solvent was evaporated at 40 °C. Dichloromethane (30 mL) was added to the residue and DMAP (0.12 g, 1.00 mmol, 0.10 equiv) was added. A solution of 3-methoxyphenol (1.24 g, 10.00 mmol, 1.00 equiv) and triethylamine (3.00 mL, 21.00 mmol, 2.87 equiv) in dichloromethane (10 mL) was added dropwise with stirring. The mixture was stirred at room temperature for 24 h, and diluted with dichloromethane (15 mL). The organic phases was washed with water (2 x 10 mL), 10% NaOH (10 mL), and saturated NaCl solution (15 mL), dried with Na₂SO₄ and concentrated. The crude material was then purified using column chromatography (5:2 hexane:acetone) affording compound 2.24b as a yellow oil (0.85 g, 33%).

\[
{^1}H \text{ NMR (CDCl}_3, 300 MHz) \delta 8.13 (d, J = 7.5 Hz, 2H), 7.77 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 7.8 Hz, 2H), 7.36 (t, J = 8.1 Hz, 1H), 6.9 (t, J = 7.2 Hz, 3H); {^{13}}C (CDCl}_3, 90 MHz) \delta 185.7, 162.2, 161.1, 151.2, 135.7, 132.6, 130.6, 129.5, 113.7, 112.9, 107.7, 55.9.
\]

**Attempted Preparation of Cyclization Product 2.26b.** Compound 2.24b (0.15 g, 0.59 mmol, 1.10 equiv) and benzyl bromide (0.06 mL, 0.54 mmol, 1.00 equiv) in toluene (5 mL) were cooled to -78 °C and then treated with tris(dimethylamino)phosphine (0.11 mL, 0.59 mmol, 1.10 equiv). Upon warming and stirring the mixture at room temperature for 2 h, the phosphonium salt was isolated by decanting and then dissolved in nitromethane (5 mL). The mixture was concentrated and dissolved in ether (5 mL). The solution was washed with water (2 x 5 mL), brine (5 mL), and dried over sodium sulfate. The crude material was purified by column chromatography (5:2 hexane:acetone). The Friedel-Crafts cyclization product 2.26b was not observed, but rather the elimination product 2.27b was isolated (0.09 g, 48%).

\[
{^1}H \text{ NMR (CDCl}_3,
\]
300 MHz) 7.72 (d, J = 6.6 Hz, 2H), 7.51-7.41 (m, 4H), 7.30-7.22 (m, 3H), 6.77 (dd, J = 8.4, 1.7 Hz, 1H), 6.68-6.52 (m, 5H), 5.88 (s, 1H), 3.83-3.81 (s, 3H); MS (ESI) calcd for C_{22}H_{19}O_{3} (M+H) 331.1334, found 331.1329.

**Preparation of (1S*, 2S*)-2-(Naphthalene-2-ylsulfanyl)cyclohexanol.**

A stirred solution of 2-naphthalenethiol (1.64 g, 10.25 mmol, 1.25 equiv) in MeOH (25 mL) was heated to 50 °C and treated with a solution of NaOMe in MeOH (4.40 M, 3.02 mmol, 0.68 mL). Cyclohexene oxide (1.01 mL, 10.00 mmol, 1.00 equiv) was then added to the reaction via syringe over a 10 min period. During the addition, the temperature of the oil bath was raised to 80°C. After the addition, the reaction mixture was heated at reflux for 30 min. Upon cooling the mixture to room temperature 1 M aq. HCl (4 mL) was added and MeOH was removed *in vacuo*. The residue was partitioned between water (50 mL) and ether (75 mL). The organic layer separated and the aqueous phase was extracted again with ether (50 mL). The combined organic layers were washed with brine (25 mL) and dried over MgSO_{4}. Evaporation of the solvent followed by silica gel chromatography of the crude material (1:3 ether:pentane) gave a colorless solid (2.07 g, 81%). \(^1\)H NMR (CDCl\(_3\), 360 MHz) \(\delta\) 8.02 (s, 1H), 7.84 (m, 3H), 7.59-7.52 (m, 3H), 3.43 (m, 1H), 3.05-2.88 (m, 2H), 2.19-2.15 (m, 2H), 1.76 (m, 2H), 1.42-1.27 (m, 4H); resolution of enantiomers was achieved by using a Chiralcel OJ column (Daicel Chemical Industries, Ltd.), 2.5% \(i\)-PrOH in hexanes as the eluent at a flow rate of 1 mL/min, detection wavelength of 254 nm with elution times \(t_{\text{fast}} = 25\) min, \(t_{\text{slow}} = 33\) min. This data matches previous literature data.\(^{64}\)
Lipase-Catalyzed Enantioselective Acetylation of (1S*, 2S*)-2-(Naphthalene-2-ylsulanyl)cyclohexanol. A stirred solution of (1S*, 2S*)-2-(naphthalene-2-ylsulanyl)cyclohexanol (2.07 g, 8.00 mmol, 1.00 equiv) in i-PrOH (20 mL) at room temperature was treated with Lipase PS on Celite (0.94 g) and isopropenyl acetate (1.70 mL, 16.00 mmol, 2.00 equiv) for 55 h while being monitored by chiral phase analytical HPLC using a Chiralcel OJ column, until one enantiomer of the starting material was completely consumed. The insoluble enzyme complex was then removed by filtration. The solvent, acetone by-product, and unconsumed isopropenyl acetate were removed in vacuo. The unreacted alcohol and acetate ester were separated by silica gel chromatography (ether-pentane gradient). The unreacted alcohol was isolated as a white solid (0.85 g, 41%).

Preparation of (+)-(1S, 2S)-2-(Naphthalene-2-sulfonyl)cyclohexanol. A stirred solution of (+)-(1S, 2S)-2-(naphthalene-2-ylsulanyl)cyclohexanol (0.85 g, 3.30 mmol) in chloroform (9 mL) at 0 °C was treated dropwise with peroxyacetic acid (35% w/w in acetic acid, 1.40 mL) via an addition funnel over 30 min. The reaction mixture was stirred at 0 °C for 2 h, the cooling bath was removed and the mixture was stirred for 30 min at room temperature. The reaction mixture was cooled to 0 °C and quenched by slow addition of sat. aq. Na$_2$SO$_3$ (15 mL) and sat. aq. NaHCO$_3$ (30 mL). The organic phase was diluted with DCM (20 mL), separated, washed with sat. aq. NaHCO$_3$ (30 mL) and dried over anhydrous MgSO$_4$. Evaporation of the solvent in vacuo gave the desired product (0.94 g, 96%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 8.50 (s, 1H), 8.08-7.89 (m, 4H), 7.77-7.67 (m, 2H), 4.42 (s, 1H), 4.05-3.97 (m, 1H), 3.14-3.06 (m, 1H),
2.20-2.15 (m, 1H), 2.00-1.96 (m, 1H), 1.75-1.72 (m, 2H), 1.42-1.16 (m, 4H). This data matches previous literature data.

**Preparation of Compound 2.28a.** To a solution of phenylglyoxylic acid (0.96 g, 6.4 mmol, 2 equiv) in DCM (75 mL), were added (+)-(1S, 2S)-2-(Naphthalene-2-sulfonyl)cyclohexanol (0.93 g, 3.20 mmol, 1.00 equiv) and DMAP (0.04 g, 0.32 mmol, 0.10 equiv). The solution was cooled to 0 °C for 15 min. DCC (1.32 g, 6.40 mmol, 2.00 equiv) was added to the mixture and stirred for 6 h. The solution was filtered and diluted with 20 mL of saturated NaHCO₃. The aqueous solution was then extracted with DCM and dried with sodium sulfate. Column chromatography (10:1 hexane:ethyl acetate) was used to purify the crude mixture resulting in compound 2.28a as a white solid (0.87 g, 65%). ¹H NMR (CDCl₃, 360 MHz) δ 8.42 (s, 1H), 7.98 (d, J = 7.3 Hz, 2H), 7.85-7.77 (m, 4H), 7.68-7.64 (m, 2H), 7.57-7.49 (m, 3H), 5.53-5.46 (m, 1H), 3.58-3.52 (m, 1H), 2.37-2.33 (m, 2H), 1.96-1.86 (m, 2H), 1.84-1.35 (m, 4H). MS (ESI) calcd for C_{24}H_{23}O_{5}S (M+H) 423.1266, found 423.1264.

**Preparation of Alkoxyphosphonium Salt 2.29a.** To a solution of compound 2.28a (0.42 g, 1.00 mmol, 1.10 equiv), and benzyl bromide (first dried over K₂CO₃, 0.11 mL, 0.91 mmol, 1.00 equiv) in toluene (10 mL), was added dropwise hexamethylphosphorous triamide (0.18 mL, 1.00 mmol, 1.10 equiv) under cooling at -78 °C. Once the addition was complete, the cooling bath was removed and the mixture was warmed to room temperature. The solution was then stirred for 2 h forming a white precipitate, which was filtered and washed with ether. The
compound 2.29a could not be purified further (0.57 g, 83%). $^{31}$P NMR (CDCl$_3$, 145 MHz) δ 35.1, 30.5.

Attempts at Hydrolysis of Alkoxyphosphonium Salt 2.29a. Alkoxyphosphonium salt 2.29a (0.10 g, 0.13 mmol) in a 1:1 mixture of H$_2$O and solvent (2 mL) was stirred and heated to 60 °C for 3 h. The mixture was then extracted with ether (3 x 5 mL), washed with water (2 x 5 mL), brine (5 mL), and dried over sodium sulfate. The solvent was then evaporated in vacuo.

<table>
<thead>
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<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
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<tr>
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</tr>
<tr>
<td>1:1 DMSO:H$_2$O</td>
<td>No reaction</td>
</tr>
<tr>
<td>1:1 Acetone:H$_2$O</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Preparation of (+)-(1R, 2R)-1-Phenylcyclohexane-cis-1,2-diol. In a flask equipped with a mechanical stirrer open to the atmosphere was added water (48 mL). The reagents were added in the following order through a powder funnel: potassium ferricyanide (31.02 g, 94.20 mmol, 3.00 equiv), anhydrous potassium carbonate (13.02 g, 94.02 mmol, 3.00 equiv), methanesulfonamide (3.00 g, 31.40 mmol, 1.00 equiv), potassium osmate dihydrate (0.006 g, 0.016 mmol, 0.0005 equiv), (DHQD)$_2$PHAL (0.12 g, 0.08 mmol, 0.003 equiv), 1-phenylcyclohexene (5.00 mL, 31.40 mmol, 1.00 equiv), and tert-butyl alcohol (63 mL).
The slurry was stirred vigorously for 2 days. During this time, the product began crystallizing out of the top organic phase. The mixture was treated with ethyl acetate (63 mL) with stirring to dissolve the product. The resulting mixture was filtered through a fritted glass funnel and washed with ethyl acetate (3 x 13 mL). The filtrate was washed with 2 M KOH (2 x 13 mL), then dried over magnesium sulfate and concentrated to afford a white solid that was dried overnight (5.24 g, 87%). $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 7.52 (d, $J = 7.3$ Hz, 2H), 7.41 (t, $J = 7.4$ Hz, 2H), 7.30 (t, $J = 5.6$ Hz, 1H), 4.04 (m, 1H), 2.69 (s, 1H), 1.90-1.64 (m, 9H). This data matches previous literature data.$^{65}$

**Preparation of (−)-(1R,2S)-trans-2-Phenyl-1-cyclohexanol.** A three-necked flask equipped with a mechanical stirrer, reflux condenser, thermometer, under nitrogen was placed in an oil bath. The flask was charged with a slurry containing activated W-2 Raney Ni (11.80 g) in wet ethanol (70% v/v, 12 mL) through a powder funnel under a stream of nitrogen. The crude (+)-(1R, 2R)-1-phenylcyclohexane-cis-1,2-diol (2.18 g, 11.34 mmol) was added to the flask, and the mixture was stirred vigorously and refluxed for 2 h. The reaction mixture was cooled to 40-50 °C and filtered through Celite in a fritted funnel making sure the liquid level did not fall below the surface of the filter cake. Ethanol (15 mL) was added in small portions to transfer the slurry completely to the funnel and to wash the filter cake. The filtrate was concentrated in vacuo to remove most of the ethanol. The mixture was diluted with brine (5 mL) and extracted with ethyl acetate (2 x 5 mL). The organic phase was dried over MgSO$_4$, filtered, and evaporated under reduced pressure overnight to give the crude alcohol. The solid was recrystallized from hexanes over 3 h at room temperature and 1 h at 0 °C. The crystalline mass was triturated with cold pentane (2 mL). The slurry was filtered, washed with chilled
pentane (3 x 1.5 mL) and the solid was dried under reduced pressure overnight to form white crystals (1.30 g, 65%). $^1$H NMR (CDCl$_3$, 360 MHz) δ 7.36-7.28 (m, 5H), 3.69 (m, 1H), 2.45 (m, 1H), 2.15 (m, 1H), 1.87-1.80 (m, 3H), 1.87-1.28 (m, 5H). This data matches previous literature data.

**Preparation of Compound 2.28b.** To a solution of phenylglyoxylic acid (3.40 g, 22.60 mmol, 2.00 equiv) in DCM (230 mL), (-)-(1R, 2S)-trans-phenylcyclohexanol (2.00 g, 11.30 mmol, 1.00 equiv) and DMAP (0.14 g, 1.13 mmol, 0.10 equiv) were added. The solution was then cooled to 0 °C for 15 min. DCC (4.7 g, 22.60 mmol, 2.00 equiv) was added to the mixture and warmed to room temperature and stirred for 6 h. The solution was filtered and diluted with saturated NaHCO$_3$. It was extracted with DCM and dried with sodium sulfate. The crude material was purified by column chromatography (10:1 hexanes: ethyl acetate) resulting in a white solid (1.98 g, 57%). $^1$H NMR (CDCl$_3$, 360 MHz) δ 7.54 (t, $J = 7.2$ Hz, 1H), 7.39-7.23 (m, 9H), 5.45 (m, 1H), 2.80 (m, 1H), 2.28 (m, 1H) 2.08-1.97 (m, 2H), 1.88-1.85 (m, 1H), 1.73-1.62 (m, 3H), 1.57-1.30 (m, 1H). This data matches previous literature data.
Attempts at Diastereoselective Barbier Reaction. To a solution of compound 2.28b (0.10 g, 0.32 mmol, 1.00 equiv) and benzyl bromide (first dried over K$_2$CO$_3$, 0.10 g, 0.32 mmol, 1.00 equiv) in pentane (4 mL) cooled to -78 °C, was added dropwise tris(dimethylamino)phosphine (0.06 mL, 0.32 mmol, 1.00 equiv). The cooling bath was then removed and the mixture was stirred and warmed to room temperature for 2 h. A white precipitate formed. The solvent was removed under vacuum. D$_2$O (5 mL) was added and the mixture was heated at 60 °C for 2 h. The mixture was then extracted with ether (3 x 5 mL), washed with brine (5 mL), and dried with sodium sulfate and concentrated. The crude material was purified by column chromatography (20:1 hexanes:ethyl acetate) affording the hydrolysis product 2.30b as a 3:1 mixture of diastereomers (0.14 g, 12%). $^1$H NMR (CDCl$_3$, 360 MHz) δ 7.53 (d, $J$ = 6.6 Hz, 1H), 7.41- 7.04 (m, 16H), 6.53 (d, $J$ = 6.9 Hz, 1H), 5.03-4.94 (m, 1H), 3.54 (s, 1H, major isomer), 3.44 (s, 1H, minor isomer), 3.36- 3.11 (dd, $J$ = 55.5, 13.8 Hz, 2H, major isomer), 3.22- 2.97 (dd, $J$ = 64.2, 13.2 Hz, 2 H, minor isomer), 2.81 (m, 1H), 2.12-1.77 (m, 5H), 1.59-1.30 (m, 7 H).

Preparation of (1R, 2R)-N,N’-bis(4-Methoxybenzyl)-cyclohexane-1,2-diamine. $^{67}$ The racemic cyclohexanediamine was resolved with L-(+)-tartaric acid to synthesize the (R,R)-1,2-diammoniumcyclohexane mono- (+)-tartrate following Jacobsen’s procedure.$^{68}$ The salt (9.00 g, 33.30 mmol, 1.00 equiv) was added to distilled water (156 mL) at room temperature. Potassium carbonate (9.30 g, 66.60 mmol, 2.00 equiv) and ethanol (78 mL) were added to the aqueous suspension. A solution of methanesulfonic acid (0.27 mL, 4.20 mmol, 0.13 equiv) and 4-methoxybenzaldehyde (7.5 mL, 66.6 mmol, 2.00 equiv) in dichloromethane (156 mL) was added to the aqueous suspension and stirred at room temperature for 12 h. The bilayer mixture was refluxed
for 1 h followed by rotary evaporation. The residue was dissolved in methanol (135 mL) and cooled to 0 °C. Sodium borohydride (3.15 g, 74.90 mmol, 2.25 equiv) was added in one portion and the solution was stirred. Once gas evolution ceased, the solution was refluxed for 1 h. The solvent was evaporated and the residue was dissolved in 1 M NaOH (65 mL) and extracted with 1:1 ethyl acetate:hexanes (3x). The crude mixture was purified by column chromatography (20% ethyl acetate:hexanes, then 1:1:0.1 ethyl acetate:hexanes:NEt₃) to give the chiral diamine as a white solid (6.00 g, 55%).¹H NMR (CDCl₃, 360 MHz) δ 7.25 (d, J = 8.3 Hz, 4H), 6.87 (d, J = 8.3 Hz, 4H), 3.89-3.83 (m, 8H), 3.60 (d, J = 12.6 Hz, 2H), 2.28-2.17 (m, 4H), 1.84-1.74 (m, 4H), 1.29-1.23 (m, 2H), 1.06-1.04 (m, 2H). This data matches previous literature data.

Preparation of (3aR, 7aR)-1,3-bis(4-Methoxybenzyl)-N,N-dimethylhexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-amine (2.32). This compound was prepared through a modified procedure reported by Alexakis.⁶⁹ The diamine ligand (6.00 g, 16.93 mmol, 1.00 equiv) was added to a flame dried flask purged with nitrogen. Tris(dimethylamino)phosphine (6.15 mL, 33.86 mmol, 2.00 equiv) was added to the ligand and heated at 150 °C and stirred for 96 h. The excess tris(dimethylamino)phosphine was removed by putting the flask under high vacuum for 24 h. The flask was put into a glovebox and the residue was dissolved in dry pentane. The solution was filtered through a glass frit, and the solvent was evaporated under high vacuum. The product was collected as a light yellow solid (5.03 g, 69%).¹H NMR (CDCl₃, 360 MHz) δ 7.28 (d, J = 7.2 Hz, 4H), 6.86 (d, J = 7.2 Hz, 4H), 4.19-4.08 (t, J = 14.4 Hz, 1H), 3.97 (t, J = 14.4 Hz, 2H), 3.83 (m, 7H), 3.00 (m, 1H), 2.74 (m, 2H), 2.56-2.52 (m, 12H), 1.94 (m, 2H), 1.70 (m, 2H), 1.36-1.21 (m, 4H), 0.95 (m, 2H); ³¹P NMR (CDCl₃, 145 MHz) δ 119.6. This data matches previous literature data.⁶⁶
Attempts of the Barbier Reaction with Homochiral Phosphorus Species 2.32. To a solution of methyl benzoylformate (0.07 mL, 0.50 mmol, 1.10 equiv) and benzyl bromide (0.05 mL, 0.45 mmol, 1.00 equiv) in toluene (6 mL), was added the chiral phosphine (0.21 g, 0.50 mmol, 1.10 equiv) in one portion at room temperature and the mixture was heated at 50 °C and stirred for 2 h. The toluene was removed by high vacuum, and H₂O (6 mL) was added. The reaction mixture was stirred at 60 °C for 2 h. The reaction mixture was extracted with ether (3x), washed with brine, and dried over sodium sulfate. The solvent was removed by rotary evaporation. From NMR analysis of the crude material, it did not appear that the desired product 2.12 had formed.

Epoxidation Attempts with Phosphites. Methyl benzoylformate (0.14 mL, 1.00 mmol, 1.00 equiv), benzaldehyde (0.11 mL, 1.10 mmol, 1.10 equiv), and Lewis acid (1.00 mmol, 1.00 equiv) were dissolved in solvent (10 mL) and cooled to -78 °C and stirred for 10 min. Phosphite reagent (1.05 mmol, 1.05 equiv) was added dropwise and then cooling bath was removed and stirred at the below temperature.
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<td>24 h</td>
<td>-</td>
</tr>
<tr>
<td>MgI$_2$</td>
<td>PhMe</td>
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<td>-</td>
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<tr>
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<td>24 h</td>
<td>-</td>
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</tr>
<tr>
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<td>PhMe</td>
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<td>-</td>
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<td>-</td>
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<td>-</td>
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<td>12 h</td>
<td>-</td>
<td>Conversion &lt;5% to unidentified product</td>
</tr>
</tbody>
</table>

**Epoxidation Attempts with Phosphinamides.** Methyl benzoylformate (0.14 mL, 1.00 mmol, 1.00 equiv), benzaldehyde (0.11 mL, 1.10 mmol, 1.10 equiv), and Lewis acid (1.00 mmol, 1.00 equiv) were dissolved in solvent (10 mL) and cooled to -78 °C and stirred for 10 min. Phosphinamide reagent (1.05 mmol, 1.05 equiv) was added dropwise and then cooling bath was removed and stirred at the below temperature.
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</table>

**Reaction of Methyl Benzoylformate and Phosphorus Reagents.** A mixture of methyl benzoylformate (0.016 mL, 0.10 mmol, 1.00 equiv) and phosphorus reagent (0.10 mmol, 1.00 equiv) in deuterated chloroform (1 g) were monitored by NMR over 24 h.

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<td>P(OEt)$_3$</td>
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</table>

**Reaction of Benzaldehyde and Phosphorus Reagents.** A mixture of benzaldehyde (0.01 mL, 0.10 mmol, 1.00 equiv) and phosphorus reagent (0.1 mmol, 1.00 equiv) in deuterated chloroform (1 g) were monitored by NMR over 24 h.

<table>
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<tr>
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<td>P(OMe)$_3$</td>
<td>140</td>
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<td>P(OEt)$_3$</td>
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</table>
Reaction of methyl benzoylformate, benzaldehyde, and phosphorus reagent. A mixture of methyl benzoylformate (0.016 mL, 0.10 mmol, 1.00 equiv), benzaldehyde (0.10 mL, 0.10 mmol, 1.00 equiv), and phosphorus reagent (0.10 mmol, 1.00 equiv) in deuterated chloroform (1 g) were monitored by NMR over 24 h.

<table>
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<th>³¹P shift (ppm)</th>
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</thead>
<tbody>
<tr>
<td>P(NMe₂)₃</td>
<td>124</td>
</tr>
<tr>
<td>P(OMe)₃</td>
<td>140</td>
</tr>
<tr>
<td>P(OEt)₃</td>
<td>138</td>
</tr>
</tbody>
</table>

Preparation of Oxyphosphorane 3.7.⁷⁰ Trimethylphosphite (2.60 mL, 22.00 mmol, 1.10 equiv) was added to benzil (4.20 g, 20.00 mmol, 1.00 equiv) in a flame dried flask under N₂. The reaction mixture was stirred for 30 min. The reaction flask was then put into an ice bath and pentane (30 mL) was added to the solution to crystallize the product overnight and the solvent was then decanted. The crystals were dried by high vacuum pump in glove box resulting in pale yellow crystals (4.80 g, 72%). ¹H NMR (CDCl₃, 360 MHz) δ 7.56 (d, J = 6.9 Hz, 4H), 7.34-7.29 (m, 6H), 3.77 (d, J = 13.2 Hz, 9H); ³¹P NMR (CDCl₃, 145 MHz) δ -49.4.

Solvent Optimization for Cyclopropanation: Oxyphosphorane 3.7 (0.33 g, 1.00 mmol, 1.00 equiv), styrene (0.23 mL, 2.00 mmol, 2.00 equiv) and CuSO₄ (0.096 g, 0.60 mmol, 0.60
equiv) were stirred at reflux in solvent (2 mL) for 4 h. The reaction mixture was cooled and the solution was filtered through a small pad of Celite. The solution was concentrated and purified using column chromatography (10:1 hexanes:ethyl acetate) if product was observed by TLC.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Mass (% Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>0.098 g (33%)</td>
</tr>
<tr>
<td>Xylenes</td>
<td>0.077 g (26%)</td>
</tr>
<tr>
<td>1,4-Dioxane</td>
<td>0.036 g (12%)</td>
</tr>
<tr>
<td>DCM</td>
<td>-</td>
</tr>
<tr>
<td>THF</td>
<td>-</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>-</td>
</tr>
</tbody>
</table>

**Temperature Optimization for Cyclopropanation.** Oxyphosphorane 3.7 (0.33 g, 1.00 mmol, 1.00 equiv), styrene (0.23 mL, 2.00 mmol, 2.00 equiv) and CuSO₄ (0.096 g, 0.60 mmol, 0.6 equiv) were stirred at one of the below listed temperatures in toluene (2 mL) for 4 h. The reaction mixture was cooled and the solution was filtered through a small pad of Celite. The solution was concentrated and purified using column chromatography (10:1 hexanes:ethyl acetate).

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Mass (% Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflux</td>
<td>0.098 g (33%)</td>
</tr>
<tr>
<td>80 °C</td>
<td>0.027 g (9%)</td>
</tr>
<tr>
<td>50 °C</td>
<td>-</td>
</tr>
<tr>
<td>Rt</td>
<td>-</td>
</tr>
</tbody>
</table>

**Concentration Optimization for Cyclopropanation.** Oxyphosphorane 3.7 (0.33 g, 1.00 mmol, 1.00 equiv), styrene (0.58 mL, 5.00 mmol, 5.00 equiv) and CuSO₄ (0.096 g, 0.60 mmol,
0.60 equiv) were stirred at reflux in toluene at the below listed concentrations for 4 h. The reaction mixture was cooled and the solution was filtered through a small pad of Celite. The solution was concentrated and purified using column chromatography (10:1 hexanes:ethyl acetate).

<table>
<thead>
<tr>
<th>Concentration of Adduct</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 M</td>
<td>0.098 g (33%)</td>
</tr>
<tr>
<td>0.1 M</td>
<td>0.066 g (22%)</td>
</tr>
<tr>
<td>0.05 M</td>
<td>0.051 g (17%)</td>
</tr>
<tr>
<td>0.01 M</td>
<td>0.033 g (11%)</td>
</tr>
</tbody>
</table>

**Time Optimization for Cyclopropanation.** A mixture of oxyphosphorane 3.7 (0.33 g, 1.00 mmol, 1.00 equiv), styrene (0.11 mL, 1.00 mmol, 1.00 equiv), CuSO₄ (0.096 g, 0.60 mmol, 0.60 equiv), and dodecane (0.17 g, 1.00 mmol, 1.00 equiv) as an internal standard in toluene (2 mL) was prepared. The mixture was refluxed for 10 h and monitored by GC. GC (phenyl methylpolysiloxane, 35 °C to 280 °C at 5°C per min) RT 21.07 min.

**Catalyst Selection for Cyclopropanation.** Oxyphosphorane 3.7 (0.33 g, 1.00 mmol, 1.00 equiv), styrene (0.58 mL, 5.00 mmol, 5.00 equiv) and catalyst were stirred at reflux in toluene (2 mL) for 4 h. The reaction mixture was cooled and the solution was filtered through a small pad of Celite. The solution was concentrated and purified using column chromatography (10:1 hexanes:ethyl acetate).
<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Mol %</th>
<th>Solvent</th>
<th>Mass (% Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CuSO₄</td>
<td>60</td>
<td>Toluene</td>
<td>0.098 g (33%)</td>
</tr>
<tr>
<td>CuSO₄</td>
<td>20</td>
<td>Toluene</td>
<td>0.030 g (10%)</td>
</tr>
<tr>
<td>CuSO₄</td>
<td>5</td>
<td>Toluene</td>
<td>0.036 g (12%)</td>
</tr>
<tr>
<td>CuSO₄</td>
<td>300</td>
<td>Toluene</td>
<td>0.036 g (12%)</td>
</tr>
<tr>
<td>[Cu(CH₃CN)₄]PF₆</td>
<td>60</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>CuI</td>
<td>60</td>
<td>Toluene</td>
<td>0.080 g (27%)</td>
</tr>
<tr>
<td>CuBr</td>
<td>60</td>
<td>Toluene</td>
<td>0.083 g (28%)</td>
</tr>
<tr>
<td>Cu(OTf)₂</td>
<td>60</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>CuCl₂</td>
<td>60</td>
<td>Toluene</td>
<td>0.027 g (9%)</td>
</tr>
<tr>
<td>Cu(acac)₂</td>
<td>60</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>(CF₃SO₂Cu)₂·C₆H₆</td>
<td>60</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>Cu</td>
<td>60</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>Cu₂O</td>
<td>60</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>[CuCl{P(OCH₃)₃}]</td>
<td>60</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>AgOTf</td>
<td>10</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>Rh₂(OAc)₄</td>
<td>5</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>Rh₂(OAc)₄</td>
<td>5</td>
<td>DCM</td>
<td>-</td>
</tr>
<tr>
<td>Rh₂(OAc)₄</td>
<td>5</td>
<td>Dioxane</td>
<td>-</td>
</tr>
<tr>
<td>[Ir(COD)Cl]₂</td>
<td>1</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>[Ir(COD)Cl]₂</td>
<td>1</td>
<td>DCM</td>
<td>-</td>
</tr>
<tr>
<td>[Ir(COD)Cl]₂</td>
<td>1</td>
<td>Dioxane</td>
<td>-</td>
</tr>
<tr>
<td>No Catalyst</td>
<td>-</td>
<td>Toluene</td>
<td>-</td>
</tr>
</tbody>
</table>

**Cyclopropanation with Oxyphosphorane 3.7 and Styrene Using Optimized Conditions.** Oxyphosphorane 3.7 (0.33 g, 1.00 mmol, 1.00 equiv), styrene (0.23 mL, 2.00 mmol, 2.00 equiv) and CuSO₄ (0.096 g, 0.60 mmol, 0.60 equiv) were stirred at reflux in toluene (2 mL) for 4 h. The reaction mixture was cooled and the solution was filtered through a small pad of Celite. The solution was concentrated and purified using column chromatography (10:1...
hexanes: ethyl acetate). Three fractions were collected and isolated resulting in the cyclopropane product (0.098 g, 33%, dr > 20:1 determined by $^1$H NMR), benzil (0.065 g, 31%), and cis-dibenzoylstilbene (0.046 g, 12%). Cyclopropane 3.13: $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 7.73 (d, $J = 6.8$ Hz, 2H), 7.41-7.37 (m, 4H), 7.11-6.98 (m, 9H), 3.48 (m, 1H), 2.26 (m, 1H), 1.99 (m, 1H). MS (ESI) calcd for C$_{22}$H$_{19}$O (M+H) 299.1436, found 299.1436. This data matches previous literature data.$^{71}$ Benzil: $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 8.00 (d, $J = 7.2$ Hz, 4H), 7.68 (m, 2H), 7.54 (m, 4H). This data matches previous literature data.$^{72}$ cis-Dibenzoylstilbene: $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 7.88 (d, $J = 7.2$ Hz, 4H), 7.44 (m, 3H), 7.35 (t, $J = 7.7$ Hz, 5H), 7.24 (m, 10H); MS (ESI) calcd for C$_{23}$H$_{19}$O (M+H) 311.1436, found 311.1435. MS (ESI) calcd for C$_{23}$H$_{21}$O$_2$ (M+H) 389.1542, found 389.1541. This data matches previous literature data.$^{73}$

Attempts of Cyclopropanation with Tris(dimethylamino)phosphine-Benzil Adduct 3.18. To a suspension of benzil (0.21 g, 1.00 mmol, 1.00 equiv) in toluene (0.5 mL) at 0 °C, a solution of tris(dimethylamino)phosphine (0.18 mL, 1.00 mmol, 1.00 equiv) in toluene (0.5 mL) was added over a period of 5 min. The solution was then stirred at 0 °C for 15 min. The solution was then cooled to room temperature. Styrene (0.23 mL, 2.00 mmol, 2.00 equiv) and CuSO$_4$ (0.096 g, 0.60 mmol, 0.60 equiv) were then added to the solution with an additional 2 mL of toluene. The solution was then heated to reflux for 4 h. The desired cyclopropane product was not observed by TLC.

Attempts at Cyclopropanation with Phosphites. To a suspension of benzil (0.21 g, 1.00 mmol, 1.00 equiv) in toluene (2 mL), was added dropwise phosphite reagent (1.00 mmol, 1.00 equiv) and stirred for 30 min. Styrene (0.23 mL, 2.00 mmol, 2.00 equiv) and CuSO$_4$ (0.906
g, 0.60 mmol, 0.60 equiv) were then added and stirred at reflux for 4 h. The reaction mixture was purified by column chromatography (10:1 hexanes:ethyl acetate).

<table>
<thead>
<tr>
<th>Phosphite Reagent</th>
<th>Mass (% Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(OMe)_3</td>
<td>0.057 g (19%)</td>
</tr>
<tr>
<td>P(OEt)_3</td>
<td>0.072 g (24%)</td>
</tr>
<tr>
<td>P(OCH_2CF_3)_3</td>
<td>-</td>
</tr>
</tbody>
</table>

**Inhibition by Byproducts.** Oxyphosphorane 3.7 (0.33 g, 1.00 mmol, 1.00 equiv), styrene (0.23 mL, 2.00 mmol, 2.00 equiv), additive (1.00 mmol, 1.00 equiv) and CuSO_4 (0.096 g, 0.60 mmol, 0.60 equiv) were stirred at reflux in toluene (2 mL) for 4 h. The reaction mixture was then cooled and the solution was filtered through a small pad of Celite. The solution was then concentrated and purified using column chromatography (10:1 hexanes:ethyl acetate).

<table>
<thead>
<tr>
<th>Additive</th>
<th>Mass (% Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O=P(NMe_2)_2</td>
<td>0.015 g (5%)</td>
</tr>
<tr>
<td>O=P(OMe)_3</td>
<td>0.048 g (16%)</td>
</tr>
<tr>
<td>P(OMe)_3</td>
<td>-</td>
</tr>
</tbody>
</table>

**General Procedure A:** Oxyphosphorane 3.7 (0.33 g, 1.00 mmol, 1.00 equiv), olefin (2.00 mmol, 2.00 equiv) and CuSO_4 (0.096 g, 0.60 mmol, 0.60 equiv) were stirred at reflux in toluene (2 mL) for 4 h. The reaction mixture was then cooled and the solution was filtered through a small pad of Celite. The solution was then concentrated and purified using column chromatography (10:1 hexanes:ethyl acetate). Three fractions were collected and isolated resulting in the corresponding cyclopropane product.
General procedure A was followed giving 46 mg of compound \textbf{3.14} (15\%, \textit{dr} >10:1 determined by $^{13}$C NMR). $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 7.74 (d, $J$ = 7.7 Hz, 2H), 7.37 (t, $J$ = 7.4 Hz, 1H), 7.27 (t, $J$ = 6.9 Hz, 2H), 7.09-7.05 (m, 5H), 6.89 (m, 4H), 3.45 (m, 1H), 2.24 (m, 4H), 2.01 (m, 1H). $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 200.7, 137.9, 136.6, 136.1, 134.0, 132.2, 131.1, 129.9, 129.7, 129.5, 129.3, 129.2, 128.9, 128.8, 128.5, 128.4, 128.3, 128.2, 127.1, 44.4, 31.7, 21.4, 20.5. MS (ESI) calcd for C$_{23}$H$_{21}$O (M+H) 313.1592, found 313.1594.

General procedure A was followed giving 81 mg of compound \textbf{3.16} (26\%, \textit{dr} >20:1 determined by $^{13}$C NMR). $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 7.66 (d, $J$ = 7.2 Hz, 2H), 7.61 (d, $J$ = 14.1 Hz, 1H) 7.39-7.21 (m, 4H), 7.08-6.97 (m, 6H), 6.84 (d, $J$ = 7.5 Hz, 1H), 3.51 (d, $J$ = 6.6 Hz, 1H), 3.35-3.20 (m, 2H), 2.65 (d, $J$ = 17.7 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 201.0, 144.6, 142.2, 138.7, 134.2, 132.8, 131.8, 129.2, 128.4, 128.2, 128.1, 127.0, 126.8, 125.3, 124.9, 46.3, 42.5, 33.6, 32.2. MS (ESI) calcd for C$_{23}$H$_{19}$O (M+H) 311.1436, found 311.1435. MS (ESI) calcd for C$_{23}$H$_{19}$O (M+H) 311.1436, found 311.1435.

General procedure A was followed giving 67 mg of compound \textbf{3.17} (22\%, \textit{dr} >5:1 determined by $^{13}$C NMR). $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 7.59 (d, $J$ = 7.3 Hz, 2H), 7.31-7.19 (m, 8H), 2.11 (d, $J$ = 13.4 Hz, 2H), 1.95 (d, $J$ = 9.7 Hz, 2H), 1.70-1.68 (m, 4H), 1.56-1.53 (m, 2H), 1.39-1.30 (m, 2H), 1.01-0.98 (m, 2H); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 203.0, 139.1, 136.4, 132.7, 131.4, 128.9, 128.5, 128.1, 127.2, 43.1, 32.2, 29.7, 26.7, 25.2. MS (ESI) calcd for C$_{22}$H$_{25}$O (M+H) 305.1905, found 305.1907.
**General Procedure B:** A mixture of substituted benzil (1.00 mmol, 1.00 equiv), trimethylphosphite (0.12 mL, 1.00 mmol, 1.00 equiv), styrene (0.23 mL, 2.00 mmol, 2.00 equiv), and CuSO$_4$ (0.096 g, 0.60 mmol, 0.60 equiv) was stirred at reflux in toluene (2 mL) for 4 h. The reaction mixture was then cooled and filtered by pipette filtration through Celite and concentrated. The crude product was then purified by column chromatography (10:1 hexanes:ethyl acetate).

General procedure B was followed giving 62 mg of dimethyl substituted benzil derived cyclopropane (19%, $dr > 20:1$ determined by $^{13}$C NMR). $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 7.73 (d, $J = 8.1$ Hz, 2H), 7.29-6.98 (m, 9H), 6.88 (d, $J = 8.1$ Hz, 2H), 3.42 (dd, $J = 9.0$ Hz, 7.5 Hz, 1H), 2.34 (s, 3H), 2.24-2.19 (m, 4H), 1.93 (dd, $J = 9.0$ Hz, 5.1 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 199.8, 142.9, 137.5, 136.7, 134.9, 133.4, 130.7, 130.0, 129.3, 129.1, 129.0, 128.1, 126.4, 44.0, 31.0, 22.0, 21.4, 19.7; MS (ESI) calcd for C$_{24}$H$_{23}$O (M+H) 327.1749, found 327.1752.

General procedure B was followed giving 29 mg of dimethoxy substituted benzil derived cyclopropane (8 %, $dr > 20:1$ determine by $^{13}$C NMR). $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 7.81 (d, $J = 8.7$ Hz, 2H), 7.15-6.99 (m, 7H), 6.86-6.78 (m, 3H), 6.62 (d, $J = 8.7$ Hz, 2H), 3.81 (s, 3H), 3.69 (s, 3H), 3.37 (dd, $J = 9$ Hz, 7.2 Hz, 1H), 2.14 (dd, $J = 6.9$ Hz, 5.1 Hz, 1H), 1.90 (dd, $J = 9.3$ Hz, 5.1 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 198.6, 162.9, 158.6, 137.5, 132.3, 131.9, 131.8, 130.1, 128.9, 128.7, 128.1, 127.6, 126.4, 114.3, 114.2, 114.0, 113.6, 55.7, 55.4, 43.4, 30.8, 19.7. MS (ESI) calcd for C$_{24}$H$_{23}$O$_3$ (M+H) 359.1647, found 359.1648.
Preparation of allyl phenyl glyoxylate (3.20). To a solution of phenylglyoxylic acid (1.65 g, 11.00 mmol, 2.00 equiv) in DCM (110 mL), allyl alcohol (0.38 mL, 5.50 mmol, 1.00 equiv) and DMAP (0.067 g, 0.55 mmol, 0.10 equiv) were added. The solution was cooled to 0 °C for 15 min. DCC (2.27 g, 11.00 mmol, 2.00 equiv) was added to the mixture and stirred for 3 h. The solution was filtered and diluted with saturated NaHCO₃ (20 mL). It was extracted with DCM (3x) and dried with sodium sulfate. The solution was concentrated and purified by column chromatography (10:1 hexanes:ethyl acetate) affording 0.75 g of product (71%). ¹H NMR (CDCl₃, 360 MHz) δ 8.03 (d, J = 7.2 Hz, 2H), 7.69 (t, J = 7.5 Hz, 1H), 7.52 (m, 2H), 6.11-6.00 (m, 1H), 5.51-5.37 (m, 2H), 4.90 (d, J = 5.9 Hz, 2H). This data matches previous literature data.

Attempts at Intramolecular Cyclopropanation. To a solution of allyl phenyl glyoxalate (0.17 mL, 1.00 mmol, 1.00 equiv) in solvent (2 mL) at -78 °C, was added the phosphorus reagent (1.00 mmol, 1.00 equiv) with stirring under N₂. The solution was stirred for 30 min. A suspension of the catalyst in solvent (1 mL) was added to the mixture. The reaction mixture was stirred overnight and monitored by TLC.
<table>
<thead>
<tr>
<th>PR₃</th>
<th>Catalyst</th>
<th>Catalyst Loading</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(OMe)₃</td>
<td>CuSO₄</td>
<td>0.60 mmol</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>P(OMe)₃</td>
<td>Rh₂(OAc)₄</td>
<td>0.05 mmol</td>
<td>DCM</td>
<td>-</td>
</tr>
<tr>
<td>P(OMe)₃</td>
<td>[Ir(COD)Cl]₂</td>
<td>0.01 mmol</td>
<td>DCM</td>
<td>-</td>
</tr>
<tr>
<td>P(NMe₂)₃</td>
<td></td>
<td></td>
<td>DCM</td>
<td></td>
</tr>
<tr>
<td>P(NMe₂)₃</td>
<td>Rh₂(OAc)₄</td>
<td>0.05 mmol</td>
<td>DCM</td>
<td>-</td>
</tr>
<tr>
<td>P(NMe₂)₃</td>
<td>[Ir(COD)Cl]₂</td>
<td>0.01 mmol</td>
<td>DCM</td>
<td>-</td>
</tr>
<tr>
<td>P(NMe₂)₃</td>
<td></td>
<td></td>
<td>DCM</td>
<td>-</td>
</tr>
</tbody>
</table>

**Attempts at Cyclopropanation with α-Ketoester 3.23.** To a solution of α-ketoester 3.23 (0.037 mL, 0.20 mmol, 1.00 equiv) in DCM (0.5 mL) cooled to -78 °C, trimethyl phosphite (0.024 mL, 0.20 mmol, 1.00 equiv) was added and the mixture was stirred for 30 min. Styrene (0.023 mL, 0.20 mmol, 1.00 equiv) and a solution of the catalyst in DCM (0.5 mL) were then added. The reaction mixture was stirred for 24 h.

<table>
<thead>
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<th>Catalyst</th>
<th>Catalyst Loading</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh₂(OAc)₄</td>
<td>0.010 mmol</td>
<td>-</td>
</tr>
<tr>
<td>[Ir(COD)Cl]₂</td>
<td>0.002 mmol</td>
<td>-</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Synthesis of O-Silylated Adduct 3.26.** To a solution of benzil (2.50 g, 11.90 mmol, 1.00 equiv) in dichloromethane under N₂ was added slowly tert-butyldimethylsilyl chloride (1.79 g, 11.90 mmol, 1.00 equiv). The reaction mixture was stirred for 1 h. Tris(dimethylamino)phosphate (2.15 mL, 11.90 mmol, 1.00 equiv) was added to
the mixture and stirred for an additional 1 h. The solvent was removed under vacuum and put in a glovebox, resulting in compound 3.26 (6.14 g, 81%). $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 7.62-7.58 (m, 4H), 7.53-7.49 (m, 5H), 7.47-7.40 (m, 1H), 2.44 (d, $J$ = 10.3 Hz, 18H), 0.67 (s, 9H); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 145.3, 145.2, 135.4, 135.3, 134.0, 133.9, 133.0, 130.3, 129.8, 129.6, 129.5, 129.1, 128.9, 37.2, 25.7, 18.3, -4.2; $^{31}$P NMR (CDCl$_3$, 145 MHz) $\delta$ 35.0, -129.8, -134.6, -139.5, -144.4, -149.3, -154.2, -159.1.

Attempts at Cyclopropanation with O-Silylated Adduct 3.26. To a solution of compound 3.26 (0.13 g, 0.20 mmol, 1.00 equiv) in solvent (1 mL), styrene (0.07 mL, 0.60 mmol, 3.00 equiv) and catalyst were added and stirred at reflux for 18 h. The resulting mixture was filtered and concentrated.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Catalyst Loading</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>CuSO$_4$</td>
<td>0.120 mmol</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>Rh$_2$(OAc)$_4$</td>
<td>0.010 mmol</td>
<td>DCM</td>
<td>-</td>
</tr>
<tr>
<td>[Ir(COD)Cl]$_2$</td>
<td>0.002 mmol</td>
<td>DCM</td>
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$^-\text{Cl} + \text{O}^2\text{P(NMe}_{2}\text{)}^3 \quad \text{Synthesis of O-Silylated Adduct 3.27.}$ To a solution of benzil (2.50 g, 11.90 mmol, 1.00 equiv) in dichloromethane under N$_2$ was added slowly trimethylsilyl chloride (1.50 mL, 11.90 mmol, 1.00 equiv). The reaction mixture was stirred for 1 h. Tris(dimethylamino)phosphine (2.15 mL, 11.90 mmol, 1.00 equiv) was added to the mixture
and stirred for an additional 1 h. The solvent was removed under vacuum and put in a glovebox, resulting in compound 3.27 (4.35 g, 76%). $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 7.83-7.52 (m, 10H), 2.78 (d, $J = 10.4$ Hz, 18H), 0.242 (s, 2H). $^{31}$P NMR (CDCl$_3$, 145 MHz) $\delta$ 35.4.

![Chemical Structure](image)

**Attempts at Cyclopropanation with O-Silylated Adduct 3.27.** To a solution of Compound 3.26 (0.096 g, 0.20 mmol, 1.00 equiv) in solvent (1 mL), styrene (0.023 mL, 0.20 mmol, 1.00 equiv) and catalyst were added and stirred at reflux for 5 h. The resulting product was filtered and concentrated.

<table>
<thead>
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<th>Catalyst</th>
<th>Catalyst Loading</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
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<tr>
<td>CuSO$_4$</td>
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<td>Toluene</td>
<td>-</td>
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<td>Rh$_2$(OAc)$_4$</td>
<td>0.010 mmol</td>
<td>Acetonitrile</td>
<td>-</td>
</tr>
<tr>
<td>[Ir(COD)Cl]$_2$</td>
<td>0.002 mmol</td>
<td>Acetonitrile</td>
<td>-</td>
</tr>
<tr>
<td>Rh$_2$(OAc)$_4$</td>
<td>0.010 mmol</td>
<td>Dichloroethane</td>
<td>-</td>
</tr>
<tr>
<td>[Ir(COD)Cl]$_2$</td>
<td>0.002 mmol</td>
<td>Dichloroethane</td>
<td>-</td>
</tr>
</tbody>
</table>

**General Procedure C:** A mixture of oxyphosphorane 3.7 (0.17 g, 0.50 mmol, 1.00 equiv), alcohol (1.00 mmol, 2.00 equiv) and CuSO$_4$ (0.048 g, 0.30 mmol, 0.60 equiv) were stirred at reflux for 4h. The solution was then cooled and pipette filtered through Celite and concentrated. The product was purified by column chromatography (10:1 hexanes:ethyl acetate).
General procedure C was followed giving 54 mg of 2-methoxy-1,2-diphenylethanone (48%). $^1$H NMR (CDCl$_3$, 360 MHz) δ 8.03 (d, $J = 7.2$ Hz, 2H), 7.65-7.29 (m, 8H), 5.56 (s, 1H), 3.49 (s, 3H). This data matches previous literature data.

General procedure C was followed giving 19 mg of 2-ethoxy-1,2-diphenylethanone as a mixture with other impurities (16%). $^1$H NMR (CDCl$_3$, 360 MHz) δ 8.12-8.02 (m, 5H), 7.70-7.67 (m, 1H), 7.58-7.31 (m, 17H), 5.63 (s, 1H), 5.57 (s, 1H), 4.33 (s, 1H), 3.67-3.63 (m, 2H), 3.49 (s, 3H), 3.26-3.22 (m, 1H), 1.33-1.22 (m, 3H).

![Chemical reaction diagram]

**Attempts at N-H Insertion:** A mixture of Oxyphosphorane 3.7 (0.17 g, 0.50 mmol, 1.00 equiv), aniline (1.50 mmol, 1.50 equiv), CuSO$_4$ (0.048 g, 0.30 mmol, 0.60 equiv) were stirred at reflux in toluene (1 mL) for 4 h. The solution was cooled, filtered through a small pad of Celite, and concentrated.

<table>
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<tr>
<th>X</th>
<th>Catalyst</th>
<th>Catalyst Loading</th>
<th>Yield</th>
</tr>
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<tbody>
<tr>
<td>Br</td>
<td>CuSO$_4$</td>
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<tr>
<td>Br</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cl</td>
<td>CuSO$_4$</td>
<td>0.30 mmol</td>
<td>-</td>
</tr>
<tr>
<td>Cl</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>
References


17 Fauduet, H.; Burgada, R. *Synthesis* 1980, 642.


35 Wang, S. R. *unpublished results*.


