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DEVELOPMENT OF A PHOSPHORUS (III)-MEDIATED ASYMMETRIC REDUCTIVE C-N AND C-O BOND FORMING METHOD

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by

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ABSTRACT

Synthetic methods leading to the formation of carbonyl derivatives with α-heterofunctionality are valuable for the synthesis of important molecular targets. The research described in this thesis details the development of a new nonmetal approach to the preparation of α-heterofunctionalized carbonyl derivatives from readily available and bench-stable precursors. Specifically, the method involves the direct reductive coupling of diverse α-ketoesters with a range of protic pro-heteronucleophiles (i.e. O-H, N-H, and S-H derivatives) under the action of tris(dimethylamino)phosphorus to yield the corresponding α-alkoxy, -amino-, and -thio esters. More than thirty assorted examples of this reaction demonstrate the broad scope of reactivity. Mechanistically, the reductive coupling is believed to be initiated by a formal [4+1] cycloaddition of the trivalent phosphorus compound with the α-dicarbonyl substrate to give a 10-P-5 dioxaphospholene intermediate (i.e. a Ramirez reaction). Subsequent decomposition of this pentacoordinate intermediate via protonolysis and displacement by the heteronucleophile then yields the target product with concomitant formation of water-soluble hexamethylphosphoramidate as the sole by-product. By employing a stereochemically defined phosphorus triamide, a stereoselective reaction sequence yields optically active α-heterofunctionalized carbonyl derivatives with enantiomeric excesses approaching 98% ee. In short, the method described serves as a mild and selective route for the preparation of α-heterofunctionalized carbonyl derivatives, representing a useful complement to known protocols.
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Chapter 1

α-Heterofunctionalized Carbonyl Compounds: Utility and Preparation

Carbonyl compounds bearing α-heterofunctional activity have been the focus of intense synthetic interest, both as synthons for the preparation of complex targets and as targets in their own right. This chapter describes the utility of these valuable compounds and outlines the diverse synthetic approaches to their preparation, providing the historical context for the reductive coupling methodology that is the topic of this thesis.

1.1 – Targets Illustrating Utility of α-Heteroatom Functionalized Compounds

α-Heterofunctionalized carbonyl derivatives are valuable for the synthesis of a broad range of molecular targets. Consequently, methods for forming C-X (X = N, O, S, etc.) bonds are vital for organic chemists. For instance, heterofunctionalization of carbonyls plays an important role in the key ring-closing step in the Merck synthesis of the β-lactam antibiotic thienamycin, which is used for treatment of skin and other types of infections (Scheme 1.1). An eight-step synthesis starting from diethyl 3-oxopentanedioate (1) results in the formation of diazo compound 2. Ring closing of diazo compound 2 is performed via a rhodium-catalyzed intramolecular N-H insertion reaction resulting in carbapenam 3, ultimately leading to thienamycin (4).
Recently, non-natural carbonyl compounds with α-heteroatom functionality have proven to be important pharmaceuticals (Figure 1.1). This facet is best exemplified by Plavix (5), an α-amino ester anti-platelet drug commercialized by Bristol-Meyers Squibb for treatment of ischemic strokes, heart attacks, and artherosclerosis.\textsuperscript{3,4} In 2010, Plavix had $4.6 billion in retail sales and over 25 million prescriptions.\textsuperscript{5} The commercial route to Plavix hinges on the construction of the α-C-N bond.

The value of α–heterofunctionalized carbonyl compounds in the pharmacopeia is also illustrated by Keppra (levetiracetam) (6), another highly prescribed drug displaying an α-amino amide moiety (Figure 1.1). Keppra is an anti-epileptic drug commercialized by UCB Pharma accounting for $241 million in retail sales in 2010.\textsuperscript{5,6} As illustrated by these two examples, α-heterofunctionalized carbonyl derivatives are valuable targets and synthetic methods for their preparation remain of intense interest.
1.2 – Methods for Achieving α-Heterofunctionalization

Numerous bond disconnection strategies have been investigated for the preparation of α-heterofunctionalized carbonyl compounds. The most obvious route for the synthesis of these compounds stems from the “direct” construction of the C-X linkage. Within this purview, three broad classes of reactions can be defined according to the change in oxidation state of the carbonyl substrate during functionalization (Scheme 1.2):

1.) Oxidative processes, involving conversion of an α-C–H unit of the carbonyl substrate into the corresponding α-C–X moiety with a formally electrophilic heteroatomic reagent (X⁺);

2.) Redox-neutral processes, wherein a prefunctionalized carbonyl substrate bearing a leaving group (LG) undergoes displacement at the α-position with a heteroatom nucleophile (X⁻);

3.) Reductive processes, where the α-carbon in a +2 oxidation state (e.g. C=Y, where Y is N₂ or O) is reduced to form a new carbon-heteroatom single bond.
In the following sections, examples illustrating each of these approaches to α-functionalization are described, and the relative merits and drawbacks of each are discussed.

**Scheme 1.2**

1.2.1 - Oxidative Methods for Achieving α-Heterofunctionalization

Oxidation of an α-C–H position of a carbonyl derivative to the corresponding α-C–X analogue is usually a two-step process requiring enolization of the carbonyl substrate 7 under either acidic or basic conditions (Scheme 1.3). By conversion to the enol(ate) 8, the latent nucleophilic reactivity of the carbonyl substrate is unmasked. Subsequent exposure to an electrophilic heteroatomic reagent then leads smoothly to the α-heterofunctionalized product 9.
Scheme 1.3

This approach is exemplified in the classical methods for α-halogenation of carbonyl compounds. In acetic acid, ketones and aldehydes undergo equilibrium formation of the enol tautomer (8, R = H). In the presence of the electrophilic halogenating reagent Br₂, this reactive enol can be trapped resulting in isolation of the α-monobrominated derivative. Alternatively, the carbonyl compound can be deprotonated in a stoichiometric fashion with a strong base like lithium diisopropylamide (LDA), then treated with a halogenating reagent to give the brominated product (cf. Scheme 1.3, X = Br).

A similar approach is evidenced in the α-oxidation of carbonyl compounds by the Rubottom protocol (Scheme 1.4). Formed by deprotonation of carbonyl compound and trapping with a silylating reagent, silylenol ether reacts with an electrophilic per oxyacid to give α-silyloxy ketone via rearrangement of silyloxy epoxide. Relying on the regioselectivity of enolization, the newly formed α-C–O bond can be installed with positional selectively in a predictable manner. Moreover, stereoselective variants of the Rubottom oxidation have been developed yielding configurationally defined α-oxygenation products, further extending the utility of the method in target oriented synthesis.
There has also been success in forming α-C-N bonds via electrophilic nitrogen compounds. For example, in 1999, Evans and Johnson reported a catalytic enantioselective amination of silylenol ethers using copper(II) Lewis acids, leading to a newly formed α-C-N bond. Silylenol ether 15 was reacted with azo-imide 16 in the presence of catalyst 17 and trifluoroethanol in THF, resulting in α-amination product 18 in 93% yield and 98% ee (Scheme 1.5). Although these copper catalysts were effective in providing high enantioselectivity in this amination process, the reaction is limited in scope – only azodicarboxylate derivatives have been shown to serve as nitrogen electrophiles.

Recent advances in the area of α-heterofunctionalization have been driven by developments in the emerging field of organocatalysis. In the presence of a homochiral
secondary amine 19, the nucleophilic character of the carbonyl compound 20 is engendered by equilibrium conversion to an enamine 21; subsequent reaction in situ with electrophilic reagents (X\(^+\)) and iminium ion 22 leads to the overall \(\alpha\)-functionalized species 23 (Scheme 1.6).\(^{14}\) Importantly, the use of homochiral amine organocatalysts permits the enantioselective preparation of \(\alpha\)-heterofunctionalized compounds. A wide range of heteroelectrophiles have been shown to participate in this reactivity. One significant drawback to this approach stems from the fact that aldehyde substrates undergo enamine formation more readily under typical conditions, and the heteroatom electrophile scope is limited due to the inherent electronegativity of atoms such as O, N, S, etc.

**Scheme 1.6**
1.2.2 – Redox-Neutral α-Heterofunctionalization

As an alternative to the oxidative methods noted above, redox-neutral methods have also been developed for the formation of α-C-X bonds (Scheme 1.7). The most conventional approach to redox-neutral synthesis of C-X bonds exploits the natural polarization of the C-X linkage – carbon is electropositive with respect to the majority of heteroatoms of synthetic interest (i.e. N, O, and S). Consequently, exposure of heteroatomic nucleophiles (X−) to carbonyl α-electrophiles results in functionalized product 25. Fundamentally, these nucleophilic displacement reactions are of an S_N2 type (via transition state 26), and as a result access to stereodefined products 25 may arise from stereospecific displacement of an appropriate optically active electrophile 24.

Scheme 1.7

An interesting stereoselective extension of the displacement methodology has been demonstrated in a substrate-controlled, redox-neutral α-C-X functionalization method involving α-haloesters. Specifically, Koh and Durst have demonstrated that (R)-pantolactone esters 27 of racemic α-halo carboxylic acids undergo nucleophilic attack by
sodium aryloxides to produce \( \alpha \)-aryloxy esters 28 in isolated yields from 55-76\% and up to a 95:5 \( dr \) \((S):(R)\) (Scheme 1.8).\(^{15}\)

**Scheme 1.8**

The stereoselectivity of this reaction arises from the differing rates at which the two diastereomers of the starting \( \alpha \)-halo ester 27 react with the oxygen nucleophile. Under the basic reaction conditions, isomerization of the \( \alpha \)-stereocenter rapidly interconverts diastereomers \((2R)-27\) and \((2S)-27\) (Scheme 1.9). Differential rates of nucleophilic displacement at these diastereomeric substrates result in predominant formation of the \((S)\)-isomer of product 28 via \( S_N^2 \) substitution. A conformational effect in which the pantolactone auxiliary blocks backside approach of the nucleophile in \((2S)-27\) is believed to be responsible for the observed stereoselection.
Despite the utility in promoting high selectivity in the aforementioned α-C-O bond forming method, the use of chiral auxiliaries as a general strategy for stereoselection suffers from additional synthetic steps required for both addition and removal of the stereocontrol element. Consequently, alternative strategies based on a catalytic enantioselective process have been sought. One such approach involves asymmetric attack on a prochiral α-electrophilic carbonyl compound or a related synthetic surrogate. This umpolung-type reactivity is best exemplified by the behavior of nitrosoalkenes, potent electrophiles that may be prepared in solution via elimination from an α-halo oxime. Recently, a substrate-controlled, stereoselective variant of this chemistry has been reported for C-C and C-N functionalization. Additionally, a catalytic asymmetric C-S functionalization variant of this method has been developed using thiols as nucleophiles. To this end, α-chlorooxime 29 was treated with sodium bicarbonate in dichloromethane to form nitrosoalkene 30. Presumably by coordination to the chiral amine catalyst 31 through hydrogen bonding, nitrosoalkene 30 reacted with thiophenol to give chiral α-sulfenyl ketone 32 in a 94:6 er and 86% yield (Scheme 1.10).
Although this chemistry has shown success in \( \alpha \)-C-S functionalization, extension to the analogous \( \alpha \)-C-N and \( \alpha \)-C-O bond forming modes has been unsuccessful.

**Scheme 1.10**

![Scheme 1.10](image)

**1.2.3 - Reductive Methods for Achieving \( \alpha \)-Heterofunctionalization**

The third method for promoting \( \alpha \)-heterofunctionalization involves the formation of a new \( \alpha \)-C-X at a \( C_{sp}^3 \) center in product 34 by reductive bond formation from an \( \alpha \)-C\(^{sp2}\) carbonyl starting material 33 (Scheme 1.11). This bond forming scheme is particularly attractive since the conversion of achiral starting materials into chiral products offers the possibility of either substrate- or reagent-controlled stereoselection.
A recent manifestation of this α-C-X bond forming mode has involved carbenoid insertion chemistry (Scheme 1.12).\textsuperscript{18} Formed commonly from decomposition of diazo precursors, metallocarbenoids undergo insertion of the divalent carbon center into an unactivated X-H bond. The reaction is initiated by formation of metallocarbenoid intermediate 37 from diazo compound 35 with a metal catalyst 36 and release of nitrogen gas. The mechanism by which metallocarbenoid 37 then undergoes insertion into an H-X bond has been the matter of significant study, and results indicate that either of two possibilities may prevail depending on the precise nature of reactants.\textsuperscript{19} In the first case, a concerted process involving a three-center, two electron transition structure 38 has been posited. Alternatively, a more polar, stepwise pathway proceeding via an initial proton transfer as in complex 39 may ultimately produce product 40.
Although transition metal-facilitated X-H insertion chemistry has been known for decades,\textsuperscript{20,21} within the last ten years there have been major advances in stereoselective metallocarbenoid insertion chemistry. For example, Fu and Maier reported in 2006 an effective enantioselective, intermolecular O-H insertion reaction employing a chiral copper(I) catalyst.\textsuperscript{22} The catalyst that offered the best selectivity was a copper(I)/bisazaferrocene complex \textbf{41}, formed \textit{in situ} from copper(II) triflate, providing high enantioselectivity (up to 98\% ee) of the $\alpha$-alkoxy ester product (Scheme 1.13). In comparison to alternative stoichiometric methods for $\alpha$-oxygenation (\textit{e.g.} Rubottom oxidation), the metallocarbenoid insertion approach offers a one-step, catalytic process for the enantioselective preparation of $\alpha$-C-O bonds with good atom economy.

\textbf{Scheme 1.13}

A computational study of this chemistry by Yu \textit{et al.}\textsuperscript{23} elucidated both the overall mechanism of this transformation as well as a rationale for the stereoselection. Figure 1.2 shows the favored ylidic transition state \textbf{42} of the copper-catalyzed O-insertion transformation with a chiral chelating ligand (Zhou’s\textsuperscript{24} chiral spirobox ligand \textbf{43}) related
to the one employed by Fu. Calculations suggest that a stepwise mechanism involving a water-assisted 1,2-hydride shift (Figure 1.2, top left) is favored over concerted direct O-H insertion via a three-member transition structure. In terms of stereoselectivity, the preferred conformation of the transition state is (R)-42 as opposed to (S)-42. This preference arises from steric repulsion of the substrate phenyl group with the ligand phenyl groups in (S)-39; this steric interaction is absent in (R)-42 (Figure 1.2).²³

![Figure 1.2 – Calculated Ylide Transition State Model²³](image)

Metallocarbenoid chemistry can also be utilized for α-C-N bond formation.²⁵,²⁶ For example, in 2012, Zhou et al.²⁷ developed a copper catalyst that promoted excellent enantioselectivity (up to 98% ee) for insertion of α-diazoesters into anilines. A synthesis of the herbicide (R)-flamprop-M-isopropyl²⁸ (44) illustrates the utility of the method (Scheme 1.14): isopropyl α-diazopropionate (45) and 3-chloro-4-fluoroaniline (46) react
in the presence of 1 mol% Cu-(S<sub>a</sub>,S<sub>s</sub>)-47 giving insertion product 48 in 97% yield and 98% ee, which following benzoylation gave the target 44 in excellent yield.

Scheme 1.14

This example shows the potential for a wide application of this chemistry in synthesizing certain target molecules in organic synthesis, especially α-amino acid derivatives. However, the metallocarbenoid chemistry relies on the use of highly reactive diazo compounds that can be explosive if not handled with care. Additionally, diazo substrates are not widely and readily available from commercial vendors; rather, they must be prepared in sometimes step-intensive synthetic sequences from parent carbonyl compounds by either diazo transfer or hydrazone derivatization.
1.3- Overview and Outlook

In summary, the utility of $\alpha$-heterofunctionalized carbonyl compounds has spawned a large number of strategies for their preparation. Despite the depth of literature in this area, there continue to be opportunities for the development of new and practical methods for the construction of valuable $\alpha$-heterofunctionalized targets. For instance, methods delivering rapid and direct access to stereodefined $\alpha$-alkoxy and -amino carbonyl derivatives starting from widely available and bench-stable precursors under mild conditions would be a welcome contribution to this area. The chemistry detailed in subsequent chapters of this thesis offers such possibilities.
Chapter 2

Organophosphorus Redox Chemistry and Its Synthetic Applications

This chapter outlines several practical synthetic methods that employ organophosphorus compounds as reagents. The goal of this survey is to highlight the general reactivity features that underpin the diversity of reactions enabled by these phosphorus reagents and provide key precedents for the coupling method described in the subsequent chapters.

2.1 – Common Redox States of Organophosphorus Compounds

Organic phosphorus derivatives are commonly employed as reactants and reagents in organic synthesis, and their utility derives from the diversity of a structures and oxidations states available (Figure 2.1). Canonical octet-filled organophosphorus compounds are trivalent with a stereochemically active lone pair. These compounds of phosphorus in its +3 oxidation state, colloquially termed “phosphines”, serve in organic chemistry as strong nucleophiles and Lewis bases. Quaternization of the phosphorus center leads to the formation of phosphonium ions. The reactivity of these species, as will be discussed in greater depth below, depends in large part on the nature of the substitution. Organophosphorus compounds that possess greater than eight formal valence electrons in their primary coordination spheres are also well known. Both pentacoordinated compounds (phosphoranes) and tetracoordinated compounds with phosphorus-element multiple bonds (e.g. phosphine oxides, phosphorus ylides) are examples of hypervalent species of phosphorus in its +5 oxidation state. The ability of the
phosphorus center to support both the +3 and +5 oxidation states with concomitant accommodation of between three and five ligands serves as the fundamental basis for the useful reactivity of organophosphorus reagents in synthesis.

Figure 2.1 – Common Organic Phosphorus Derivatives

2.2 – Synthetic Methods Based on Organophosphorus Redox Processes

Synthetic methods mediated by phosphorus reagents hold particular significance in organic chemistry. In most cases, the strongly nucleophilic character of electron-rich trivalent phosphorus compounds is harnessed for reaction. This fundamental reactivity is further augmented by the significant driving force arising from facile formation of a very strong phosphorus-oxygen multiple bond (BDE$_{P=O}$ = 110 kcal/mol). The following sections highlight some of the landmark developments in this area that exploit these basic reactivity features.

2.2.1 – Olefination of Carbonyl Compounds – Wittig Chemistry

The most venerable of all organophosphorus-mediated organic reactions is the synthesis of olefins developed by Georg Wittig (Nobel laureate 1979). In its most basic application, the Wittig olefination involves the preparation of a C=C bond by reaction of a phosphorus ylide with a carbonyl derivative. Proceeding first via nucleophilic addition
of the ylide 49 to the carbonyl 50 via the intermediacy of a betaine 51, the driving force inherent in the formation of a P=O bond ultimately results in decomposition of an intermediate oxaphosphetane 52 with extrusion of the olefinic product 53 (Scheme 2.1). Numerous synthetic variants of this reaction have been developed to address issues of olefin configuration and other practical issues, but in each of these methods the thermodynamic driving force for the formation of a phosphorus(V) species is responsible for the observed reactivity.32

Scheme 2.1

2.2.2 – Halogenation of Alcohols – Appel Chemistry

Scheme 2.2 displays a well-known pathway in which a bond forming event is coupled to the production of a phosphine oxide. As outlined, the scheme illustrates reactivity wherein SN2 substitution of an incoming nucleophile towards alkoxyphosphonium species 54 leads to direct displacement of the phosphine oxide 55, forming product 56.

Scheme 2.2
One embodiment of this basic reactivity paradigm is the Appel reaction (Scheme 2.3). Alkoxyphosphonium salt 59 is generated upon reaction of phosphine 57 with a halogenating reagent 58 (e.g. carbon tetrachloride, carbon tetrabromide), followed by attack of alcohol 60 after deprotonation by 59. The resulting phosphonium 61 is attacked by the halide anion, producing alkyl halide 62 with concomitant formation of phosphine oxide by-product 63.

Scheme 2.3

In 2011, Denton et al. developed a catalytic Appel reaction (Scheme 2.4). In this work, alcohol 64 was converted to alkyl halide 65 using oxalyl chloride (67) as a consumable stoichiometric reagent in order to regenerate the halophosphonium salt 68 from a catalytic amount of phosphine oxide 66. Carbon monoxide and carbon dioxide gases are released as side products, eliminating stoichiometric amounts of phosphine oxide waste.
The Appel reaction is an efficient strategy for the formation of alkyl halides from alcohols, and catalytic developments in this chemistry show that there is value in dedicating time into research on phosphorus-mediated bond forming reactions that may be able to compete with transition metal-promoted processes.

### 2.2.3 – Dehydrative Etherification – Mitsunobu Chemistry

The Mitsunobu reaction is another bond forming method involving $S_{N}2$ substitution on an alkoxyphosphonium ion with an external nucleophile. Specifically, the Mitsunobu reaction involves the substitution of primary or secondary alcohols with an acidic pronucleophile ($pK_a < 15$) in the presence of a dialkyl azodicarboxylate and a triaryl- ortrialkylphosphine (Scheme 2.5). Mechanistically, phosphine 69 reacts with azodicarboxylate species 70 to give a betaine, which deprotonates alcohol 71. Alkoxide attack of 72 at the phosphorus atom of 73 releases the anionic hydrazinedicarboxylate species 74, which deprotonates the pronucleophile 75. Finally, nucleophilic attack by 75
at the electrophilic carbon of 76 via S_N2 substitution, results in a newly formed C-C, C-N, C-S, C-X, or C-O bond in product 77, along with phosphine oxide 78 and acyl hydrazine 79 by-products.\textsuperscript{30}

\textbf{Scheme 2.5}

An example of the utility of the Mitsunobu reaction arises in the total synthesis of (+)-zampanolide (83), where tetrazolo sulfide 82 was isolated in 95\% yield from primary alcohol 80 and thiotetrazole 81 (Scheme 2.6).\textsuperscript{36}

The Mitsunobu reaction provides a way to form a variety of new bonds through the production of a phosphine oxide. This reaction is limited to the use of pronucleophiles with pKa values of less than 15 in order to have sufficient deprotonation to activate the nucleophile for attack. There is also accumulation of acyl hydrazine 79 and phosphine oxide 78 by-products that can be an inconvenience when this reaction is run on a large scale.
Scheme 2.6

The reactivity of four- and five-coordinate phosphorus compounds discussed in this chapter has been advantageous for a variety of bond forming events. The next chapter details unconventional condensation reactions mediated by five-coordinate phosphorus compounds and how this reactivity could lead to new method for a wide variety of bond forming methods.
A Formal [4+1]-Cycloaddition Route to Phosphorus(V) Intermediates: The Ramirez Reaction

This chapter details the reduction of 1,2-dicarbonyl substrates by trivalent phosphorus reductants. The reaction is considered a [4+1]-cycloaddition that yields reactive five-coordinate phosphorus compounds. Structural analysis of these adducts and their reactive properties towards electrophilic compounds are discussed.

3.1 – Formation and Structure of Phosphorus(V) Compounds via Ramirez Chemistry

Some unconventional approaches exist for the preparation of oxyphosphorane and oxyphosphonium compounds. For instance, it was discovered by Fausto Ramirez that the addition of diacetyl (84) to trimethylphosphite (85) underwent an oxidative/reduction reaction (diacetyl = oxidant, trimethylphosphite = reductant) to give a cyclic unsaturated oxyphosphorane 86 that was isolated in quantitative yield (Scheme 3.1). This reaction was later given the name the Ramirez reaction.

Scheme 3.1
The extent of this redox reaction of a trivalent phosphorus species with 1,2-dicarbonyl substrates is not limited to the use of trialkylphosphite compounds. Ramirez and Burgada\textsuperscript{32} reported that hexamethylphosphorous triamide successfully undergoes condensation with \(\alpha\)-dicarbonyl substrates. Burgada assigned structure 89 for the adduct formed in the reaction of tris(dimethylamino)phosphine (87) with diethyl oxomalonate (88) (Scheme 3.2).\textsuperscript{39}

**Scheme 3.2**

\[
\begin{array}{c}
\text{Me}_2\text{N}^+\text{P}^\equiv\text{NMe}_2 \quad \text{O} \quad \text{OC}_{2}\text{H}_5 \\
\quad + \quad \text{C}_2\text{H}_5\text{O} \quad \text{OC}_{2}\text{H}_5 \quad \rightarrow \quad \text{Me}_2\text{N}^+\text{P}^\equiv\text{NMe}_2 \\
\text{87} \quad \text{88} \quad \text{89}
\end{array}
\]

In addition to the formulation of the condensation product as a pentavalent dioxaphospholene like 89, it was recognized that a zwitterionic tetravalent oxyphosphonium complex 90 may also be a viable valence depiction (Figure 3.1).\textsuperscript{40}

**Figure 3.1 – Zwitterionic Ramirez Adduct 90**

In 1968, Ramirez reported a single-crystal X-ray diffraction study focused on the stereochemistry of oxyphosphoranes.\textsuperscript{41} It was observed that the phospholene ring is in the
apical-equatorial plane of the trigonal bipyramid 91 (Figure 3.2). The N-P-O and P-N-C bonds are capable of distorting and the substituents on the phosphorus atom are crowded because of short nonbonded distances.\textsuperscript{41}

![Diagram of an Oxyphosphorane Complex](image)

**Figure 3.2** – Crowding Sites of an Oxyphosphorane Complex (Arrows Depict Sites Where Crowding Occurs)

Because of this crowding, different types of amino substituents on the phosphine can affect whether a cyclic (pentacoordinate) or acyclic (tetracoordinate) phosphorus(V) intermediate is favored. For example, Ramirez reported that when reacting phenanthrenequinone (92) with acyclic tris(dimethylamino)phosphine (93), zwitterionic oxyphosphonium 94 is favored (Scheme 3.3a). However, reacting the same substrate with a cyclic aminophosphine 95 resulted in cyclic oxyphosphorane 96 (Scheme 3.3b).\textsuperscript{41}
3.2 – Mechanistic Details of the Ramirez Reaction

The mechanistic course for the formation of phosphorus(V) compounds via the Ramirez reaction is speculative, but two possible pathways have been postulated that result in the formation of the observed phosphorus(V) products. The first mechanism is based on a kinetic study by Ogata and Yamashita$^{42}$ on the reactivity of trialkyl phosphites towards benzil. It was reported that the reaction of a trialkyl phosphite 97 with neat benzil (98) is an irreversible process initiated through nucleophilic attack of the phosphite on one of the carbonyl carbons of benzil, resulting in zwitterionic compound 99. Next, the negatively charged oxygen atom undergoes nucleophilic attack on the phosphorus atom to form zwitterionic phosphonium species 100. The negatively charged oxygen atom of 100 then forms a σ-bond with phosphorus to give oxyphosphorane product 101 (Scheme 3.4).
Scheme 3.4

The second proposed mechanism is believed to proceed simply through a concerted [4+1] cycloaddition of the trivalent phosphorus compound 102 with α-dicarbonyl compound 103 to give hypervalent phosphorus intermediate 104 (Scheme 3.5).

Scheme 3.5

Experimental evidence in support of a stepwise mechanistic pathway stems from the reaction of benzil with trialkylphosphites. It was determined that this reaction is a second order process dependent on the concentrations of both the phosphite and dicarbonyl substrate (eq 1).

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

This observation suggests that both trialkyl phosphite and benzil are involved in the rate determining step, which is posited to be the initial nucleophilic attack of the phosphite on the carbonyl carbon of benzil. It is further argued that attack at the carbonyl
carbon (cf. Scheme 3.4) is favored over attack of the carbonyl oxygen (cf. Scheme 3.5) because the enthalpy of activation in the rate determining step is within the range commonly seen for nucleophilic additions to carbonyl compounds. Utilizing data from a temperature screen in dioxane, it was calculated that the energy of activation for this process is 8.41 kcal/mol and the entropy of activation is -47.5 eu. The calculated entropy of activation is much different than that of a typical Diels-Alder-type mechanism (−30 eu), so a concerted [4+1] cycloaddition was ruled out.

3.3 – Reactivity of Phosphorus(V) Intermediates Formed via Ramirez Chemistry

The reactivity of the phosphorus(V) addition products like 104 (cf. Scheme 3.5) has been the subject of little interest. Treatment of dioxaphospholene 105 with three equivalents of diacetyl (84) resulted in the formation of condensation product 106 in 88% yield (Scheme 3.6). This reactivity indicates the nucleophilicity of the dioxaphospholene of type 105 with respect to carbon-based electrophiles. This method then serves as an interesting way to promote the formation of new C-C bonds via condensation of 105 with ketones, aldehydes, and ketenes, providing an alternative method to the use of a Lewis acid/transition metal catalyzed or classic base promoted enolate condensation of carbonyl compounds.
The proposed mechanism of this condensation reaction involves the enolate reactivity of dioxaphospholene compounds like 105 (cf. Scheme 3.6) on an electrophilic species. One particular report\textsuperscript{46} by Ramirez suggests that aldehyde 108 undergoes nucleophilic attack from dioxaphospholene species 107 to give the overall condensation product 109 (Scheme 3.7). This mechanism is assumed for the reactivity of ketones (cf. Scheme 3.6) as well as ketenes\textsuperscript{47} but utilizing this reactivity for the formation of C-X bonds has not been reported.

Based on Ramirez’s studies, we envision the possibility of utilizing this enolate reactivity of oxyphosphoranes as a means to $\alpha$-heterofunctionalization of 1,2-dicarbonyl substrates. The following chapter presents results on $\alpha$-heterofunctionalization of 1,2-dicarbonyl substrates using dioxaphospholene compounds like 105 (cf. Scheme 3.6) and acidic oxygen and nitrogen pronucleophiles, providing a new method for direct $\alpha$-
heterofunctionalization with unactivated X-H compounds in the absence of transition metal complexes.
Chapter 4

Development of a Phosphorus(III)-Mediated Reductive Coupling Reaction

This chapter details the discovery and optimization of a potential broadly applicable method for the synthesis of α-heterofunctionalized carbonyl derivatives by the direct reductive coupling of α-ketoesters and acidic oxygen and nitrogen pronucleophiles. A mechanistic rationale for the observed reactivity, as well as opportunities for further expansion of the method are discussed.

4.1 – Background and Reaction Discovery

In conjunction with the information obtained from Ramirez’s studies, an isolated result reported by Burgada attracted our attention about the enolate reactivity of an oxyphosphorane towards an acidic pronucleophile and provides precedent as to how oxyphosphoranes might be leveraged to form new α-C-O and α-C-N bonds. It was observed that the use of one equivalent of tris(dimethylamino)phosphine along with one equivalent of methyl benzoylformate (110) in methanol resulted in the formation of α-methoxy ester 111 (Scheme 4.1).

Scheme 4.1
Mechanistically, this transformation can be rationalized by invoking a formal [4+1]-cycloaddition to give oxyphosphorane 114 through reduction of the 1,2-dicarbonyl substrate 113 by trisaminophosphine 112 (Scheme 4.2). In the presence of the protic solvent methanol, protonation of 112 would generate alkoxyphosphonium ion 115 and alkyl/aryloxide 116. S_N2 substitution on the activated alkoxyphosphonium species 115 by alkyl/aryloxide 116 would then result in formation of α-alkoxy/aryloxy carbonyl compound 117 with expulsion of the corresponding phosphorus triamide.\textsuperscript{49-52}

**Scheme 4.2**

![Scheme 4.2 diagram]

The formation of the α-methoxy ester 111 (cf. Scheme 4.1) from Burgada’s report is analogous to the X-H insertion chemistry of the transition metal series (cf. Scheme 1.12). The reaction achieves α-heterofunctionalization with unactivated X-H compounds via phosphorus(V) intermediates, suggesting the possibility of a new α-heterofunctionalization method without using transition metals that rely on decomposition of unstable diazo substrates.
4.2 - Optimization of the Reaction Conditions

In order to define optimal conditions for the observed reductive coupling reactivity noted above, the effect of the trivalent phosphorus reagent was examined. Commercially available trialkyl phosphines, phosphites, and tris(amo)phosphines were evaluated for the desired reactivity by addition to a methylene chloride solution of methyl benzoylformate (118) and p-cresol (119) at ambient temperature for one hour. As shown in Table 4.1, simple phosphines are ineffective at promoting the desired reaction; starting material was recovered after the addition of both tricyclohexyl- and triphenylphosphine (Entries 1 and 2). In the case of phosphites, both trimethyl- and triphenylphosphite provided trace amounts of the reductive coupling product 120 as a minor component of a

Table 4.1 – Phosphine Screen for Reductive α-Heterofunctionalization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phosphorus Compound</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph₃P, Ph</td>
<td>No Reaction</td>
</tr>
<tr>
<td>2</td>
<td>C₁₀H₉₆, P₃, C₁₀H₉₆</td>
<td>No Reaction</td>
</tr>
<tr>
<td>3</td>
<td>PhO₃P, OPh</td>
<td>Small amount of product in complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>MeO₂P, OMe</td>
<td>Small amount of product in complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>Me₃N₂P, NMe₂</td>
<td>Product isolated in 75% yield</td>
</tr>
</tbody>
</table>
complex mixture as determined by NMR analysis of the crude reaction mixture (Entries 3 and 4). By contrast, the addition of tris(dimethylamino)phosphine, which had been previously used by Burgada,\textsuperscript{48} to a solution of $\alpha$-dicarbonyl substrate 118 and phenolic pronucleophile 119 provided the coupling product 120 in 75\% isolated yield at room temperature (Entry 5). We believe the electron-donating characteristics of the amine ligands on the phosphine are placing more electron density on the phosphorus atom, which makes the trisaminophosphine a better reductant for the reduction of the $\alpha$-dicarbonyl substrate 118. Additionally, the amine ligands could be stabilizing the cationic charge on the phosphorus atom of the open, dipolar form of the phosphorus intermediate (cf. Figure 3.1).

A survey of reaction solvents under otherwise identical conditions indicated that the coupling reaction can be conducted successfully in a broad range of solvents. For instance, tetrahydrofuran, dimethylformamide, acetonitrile, dichloromethane, and toluene all gave moderate to excellent yields of the desired product 121 (Table 4.2), with the more polar solvents offering slightly better results.
Table 4.2 – Solvent Screen for Phosphine-Mediated α-Heterofunctionalization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tetrahydrofuran</td>
<td>99%</td>
</tr>
<tr>
<td>2</td>
<td>Dimethylformamide</td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td>Acetonitrile</td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td>Dichloromethane</td>
<td>81%</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>74%</td>
</tr>
</tbody>
</table>

One complication observed during the course of this survey involved the propensity for the tris(dimethyamino)phosphorus reagent to undergo ligand exchange with the protic pronucleophile. Specifically, the formation of phosphoramidite compounds of the type 122 was observed as a competing process (Scheme 4.2). This process is problematic insofar as oxygenated trivalent phosphorus compounds were shown to be ineffective reagents for reductive coupling (cf. Table 4.1). This deleterious background reaction could be largely eliminated by initiating the reaction at low temperature (−78 °C) and warming to room temperature prior to workup. Under these conditions, reliably high yields of the desired reductive coupling product could be achieved.
Based on the results of our initial studies, we decided to use tris(dimethylamino)phosphine in tetrahydrofuran in order to test the scope of nucleophiles capable of undergoing this transformation. We initiated our survey of the reaction scope with various phenols of different steric and electronic properties (Table 4.3).

**Table 4.3 – Racemic Aryl Oxygen Nucleophile Scope**

<table>
<thead>
<tr>
<th>Phenol Structure</th>
<th>Product Structure</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![PhO]</td>
<td>![PhO]</td>
<td>93%</td>
</tr>
<tr>
<td>![PhO]</td>
<td>![PhO]</td>
<td>87%</td>
</tr>
<tr>
<td>![PhO]</td>
<td>![PhO]</td>
<td>96%</td>
</tr>
<tr>
<td>![PhO]</td>
<td>![PhO]</td>
<td>91%</td>
</tr>
<tr>
<td>![PhO]</td>
<td>![PhO]</td>
<td>99%</td>
</tr>
<tr>
<td>![PhO]</td>
<td>![PhO]</td>
<td>60%</td>
</tr>
<tr>
<td>![PhO]</td>
<td>![PhO]</td>
<td>63%</td>
</tr>
<tr>
<td>![PhO]</td>
<td>![PhO]</td>
<td>89%</td>
</tr>
</tbody>
</table>
Results with oxygen nucleophiles show that successful $\alpha$-functionalization of methyl benzoylformate (118) in moderate to high yields is possible. Good results obtained from the use of $o$-, $m$-, and $p$- cresol as pronucleophiles ($pK_a = 10.28$, $10.08$, and $10.19$, respectively) show that steric hindrance does not have a significant effect on the reaction yields (123-125). The reaction can successfully be carried out using both electron-rich (less acidic) and electron-deficient (more acidic) pronucleophiles such as 4-methoxy-, 2-bromo-, and 4-nitrophenol (126, 127, and 128, respectively). We attribute the modest decrease in observed yield for 4-nitrophenol to solubility issues. Carboxylic acids are also viable coupling partners; acetic acid ($pK_a = 4.8$) and benzoic acid ($pK_a = 4.2$) formed the desired product in good yields (129 and 130, respectively).

In addition to aryloxy nucleophiles, aliphatic oxygen pronucleophiles in a similar $pK_a$ range were also screened in order to broaden the oxygen nucleophile scope (Table 4.4). Propargyl alcohol ($pK_a = 13.5$) and 2,2,2-trifluoroethanol ($pK_a = 12.5$) gave the desired products (131 and 132, respectively) in 60% yield, but using ethanol ($pK_a = 15.9$) resulted in transesterification of the methoxy ester to the ethoxy ester along with the desired $\alpha$-ethoxy functionalization 133, indicating $\alpha$-alkoxy products can be accessed by this method, but an excess of the pronucleophile may be necessary because of the undesired reactivity towards the ester moiety.
In order to expand the reactivity of this method, we also screened acidic nitrogen pronucleophiles beginning with \( p \)-toluenesulfonamide \( (\text{pK}_a = 11) \), which provided a 70\% yield of the desired product 134 when reacted with methyl benzoyleformate. Numerous other acidic nitrogen pronucleophiles varying in steric bulk and acidity were shown to successfully undergo the desired transformation (Table 4.5).
Secondary sulfonamides displayed good to excellent yields from 82% to 93% (135-139). Nitrogen heterocycles such as phthalimide (pK$_a$ = 9), imidazole (pK$_a$ = 14.5), and pyrazole (pK$_a$ = 14) gave the desired products in yields of 83%, 81%, and 32% (140, 141, & 142, respectively). Unfortunately, reactions with simple alkyl- and arylamines did not result in the desired coupling products. These results and limitations are largely consistent with those observed in the Mitsunobu reaction, suggesting additional opportunities for nucleophilic partners based on a rough pK$_a$ analysis.
4.4 - Substrate Scope

The scope of the coupling methodology with respect to α-dicarbonyl substrate was next probed. Substrates containing various electron-donating and electron-withdrawing substituents on the phenyl ring were subjected to the reaction conditions (Table 4.6). Both electron-donating and electron-withdrawing groups on the phenyl group afford good to excellent yields ranging from 70% to 95% (143-148). These results suggest that the success of the coupling reaction is not largely dependent upon the electronic character of the reactive carbon center.

Table 4.6 – Ring-Substituted Aryl Substrate Scope

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>143</td>
<td>H</td>
<td>85</td>
</tr>
<tr>
<td>144</td>
<td>CF₃</td>
<td>95</td>
</tr>
<tr>
<td>145</td>
<td>F</td>
<td>91</td>
</tr>
<tr>
<td>146</td>
<td>Cl</td>
<td>85</td>
</tr>
<tr>
<td>147</td>
<td>Br</td>
<td>70</td>
</tr>
<tr>
<td>148</td>
<td>OMe</td>
<td>85</td>
</tr>
</tbody>
</table>

In an effort to broaden the reactivity of our methodology and to explore whether aryl substitution is required to be adjacent to the reactive center, we screened various alkyl dicarbonyl substrates under optimized reaction conditions (Table 4.7). The reaction of methyl pyruvate (149) and 2-bromophenol with tris(dimethylamino)phosphine in THF
resulted in a 50% isolated yield of the desired product 150. Under these conditions, the competitive formation of a phosphoramidite 122 (cf. Scheme 4.2) by direct reaction of

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Nucleophile</th>
<th>Product (% Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>149</td>
<td>Br-CH₂OH</td>
<td>150 50%</td>
</tr>
<tr>
<td>149</td>
<td>NH₂</td>
<td>151 60%</td>
</tr>
<tr>
<td>152</td>
<td>Br-CH₂OH</td>
<td>153 74%</td>
</tr>
<tr>
<td>154</td>
<td>Br-CH₂OH</td>
<td>155 70%</td>
</tr>
<tr>
<td>156</td>
<td>Br-CH₂OH</td>
<td>157 75% (3 h instead of 1 h)</td>
</tr>
<tr>
<td>156</td>
<td>OH-CH₂OH</td>
<td>158 84% (3 h instead of 1 h)</td>
</tr>
</tbody>
</table>
the phenol with tris(dimethylamino)phosphine limits the degree of success using methyl pyruvate as the substrate. This suggests that while alkyl substituted α-dicarbonyl substrates are indeed viable coupling partners, they are generally less reactive that the corresponding aryl-substituted analogues.

The competitive ligand exchange at phosphorus is less pronounced for non-oxygen pronucleophiles. Employing p-toluenesulfonamide as pronucleophile, the coupling reaction with methyl pyruvate (149) as substrate gave the desired product 151 in 60% yield, a modest increase in yield with respect to the phenol. Ethyl pyruvate (152) and ethyl 2-oxo-4-phenylbutyrate (154) also resulted in desired products 153 and 155 in 74% and 70% yields, respectively. Finally, ethyl 3-methyl-2-oxobutyrate (156) provided the desired product 157 in 75% yield in the presence of 2-bromophenol and product 158 in 84% yield in the presence of 4-methoxyphenol (reaction time of 3 hours instead of 1 hour).

In summary, the reductive coupling method described above is successful with a wide range of oxygen and nitrogen nucleophiles. Moreover, the use of both alkyl and aryl α-dicarbonyl substrates allows for the preparation of a structurally diverse palette of α-alkoxy and α-amino carboxylic acid derivatives in a single step from readily available and bench-stable precursors. These observations suggest that the current method could be considered a useful complement to metallocarbenoid chemistry for the preparation of valuable α-heterofunctionalized carbonyl compounds.
4.5 - Inducing Enantioselectivity via Ramirez Chemistry

The next step in expanding the utility of our α-C-X functionalization method was to control the absolute stereochemistry of the final product. Our analysis of this challenge centered on ways in which the putative pentavalent dioxaphospholene intermediate might be desymmetrized. We envisioned two distinct modes by which the stereoselectivity of the reaction might be controlled, both of which hinge on a stereo-defining protonation of the dioxaphospholene (Scheme 4.3). In a first approach, we considered the possibility of facially-selective protonation of the key dioxophospholene 159 by a chiral proton source. Stereospecific displacement of the resultant oxyphosphonium 160 with nucleophile would then lead to product 161 with defined configuration. Alternatively, a reagent-controlled approach employing homochiral phosphorus reductants might also lead to a stereodefining proton that would lead on to product. Experiments probing both of these possibilities are detailed below.

![Scheme 4.3](image-url)

Two possible approaches for stereo-defining protonation:

- Use of a chiral proton source
- Use of an asymmetric phosphine
4.5.1 – Utility of a Catalytic Chiral Proton Source

The potential use of a chiral proton source is interesting because it opens up the possibility of developing a catalytic variant of the reaction. Under an idealized scenario, only a catalytic amount of the chiral proton source 162, in conjunction with the commercially available tris(dimethylamino)phosphine (87), would be necessary in order to facilitate the reaction. Ideally, the reaction would proceed through formation of the Ramirez adduct 163 followed by a stereodefining protonation step that would produce oxyphosphonium species 164. The generated conjugate base of the chiral acid 165 will deprotonate the pronucleophile 166 in solution and regenerate the chiral proton source 1162 (Scheme 4.4). The nucleophile will then attack the oxyphosphonium species 164 in a stereospecific manner to yield an excess of one enantiomer of the desired product 167.

Scheme 4.4

Experiments performed in order to test the feasibility of this stereoselective reaction were largely discouraging. Three separate trials were run with different catalyst loadings of (1S)-(+) -10-camphorsulfonic acid (168) or BINOL-phosphoric acid (169) in a reaction mixture consisting of methyl benzoyleformate and 2-bromophenol in THF. The
solution was cooled to $-78\, ^\circ \text{C}$ and the phosphine was added dropwise over 0.5 h (Table 4.8). At substoichiometric acid loadings (10 and 50 mol%), only racemic coupling product was isolated from the reaction mixture. At these concentrations, we suppose that racemic background coupling outcompetes the desired stereoselective transformation. Increasing the concentration of chiral acid to a stoichiometric amount resulted in a loss of coupling reactivity, presumably due to rapid decomposition of the phosphorus compound by the acidic reagent.

Table 4.8 – The Effect of Chiral Acid Catalyst Concentration

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Amount</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>118</td>
<td>10%</td>
<td>Racemic (91% yield)</td>
</tr>
<tr>
<td>118</td>
<td>50%</td>
<td>Racemic (88% yield)</td>
</tr>
<tr>
<td>118</td>
<td>1.1 equiv.</td>
<td>Starting Mat.</td>
</tr>
<tr>
<td>168</td>
<td>10%</td>
<td>Racemic (87% yield)</td>
</tr>
<tr>
<td>168</td>
<td>50%</td>
<td>Racemic (89% yield)</td>
</tr>
<tr>
<td>168</td>
<td>1.1 equiv.</td>
<td>Starting Mat.</td>
</tr>
</tbody>
</table>

The order and rate of addition did not appear to affect the transformation significantly. Slow addition of tris(dimethylamino)phosphine to a solution of a-dicarbonyl substrate, carboxylic acid pronucleophile, and ($1S$)-($+)-10-camphorsulfonic acid as a chiral proton source over the course of two hours at $-78\, ^\circ \text{C}$ did not result in any
observed stereoselectivity in the isolated coupling product. Finding no leads on the opportunity to develop a catalytic reaction via a chiral proton source, we set our sights on inducing stereoselectivity via phosphines bearing chiral amine ligands.

4.5.2 – Utilizing Asymmetric Phosphines for Enantioselectivity

The idea behind the use of an asymmetric phosphine is to produce an oxyphosphorane intermediate 170 that will allow for selective protonation of the substrate. Upon completion of the protonation step, a stereospecific substitution of the nucleophile onto the substrate 171 will yield the desired product 172 enantioselectively (Scheme 4.5).

Scheme 4.5

Our initial study of asymmetric phosphines involved the use of phosphines 173 and 174 in order to facilitate the stereoselective reaction of m-cresol or p-toluenesulfonamide towards methyl benzoylformate in various solvents (Table 4.9). The results displayed in Table 4.9 indicate that substitution on the phosphorus reagent is
tolerated and coupling in acceptable chemical yield is observed. Notably, chromatographic analysis of the coupling product on a chiral stationary phase indicates that the coupling reaction does indeed proceed stereoselectively, albeit in modest optical yield. The solvent did not seem to affect the degree of stereoselection to a significant degree.

Table 4.9 – Initial Results on Enantioselectivity Using a Homochiral Phosphine

<table>
<thead>
<tr>
<th>Nucleophile-H</th>
<th>Phosphine</th>
<th>Solvent (temp)</th>
<th>% Yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>174</td>
<td>MeCN (-40 °C)</td>
<td>86</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>173: R = 'Pr</td>
<td>THF (-78 °C)</td>
<td>74</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>174: R = OMe</td>
<td>THF (-78 °C)</td>
<td>78</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>174</td>
<td>PhMe (-78 °C)</td>
<td>70</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>174</td>
<td>PhMe (-78 °C)</td>
<td>30</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>
Concerned that stereoselectivity of the coupling product may be eroded \textit{in situ} by a subsequent racemization event, a more acidic pronucleophile was tested that would hopefully eliminate any phenoxide conjugate base present in solution. Benzoic acid was chosen as the pronucleophile to react with methyl benzoylformate in the presence of asymmetric phosphine 174 (Table 4.10, Entry 1). The use of benzoic acid resulted in the highest enantioselectivity (74\% yield and 40\% \textit{ee}) we were able to observe up to this point in our research.
Table 4.10 – Improved Enantioselectivity Using Benzoic Acids and Asymmetric Phosphines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Acid 1" /></td>
<td>78% yield, 40% ee (PhMe)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Acid 2" /></td>
<td>74% yield, 98% ee (THF)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Acid 3" /></td>
<td>78% yield, 44% ee (PhMe)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Acid 4" /></td>
<td>71% yield, 40% ee (PhMe)</td>
</tr>
</tbody>
</table>

Based on this result, we decided to test more acidic benzoic acids that contained electron-withdrawing substituents. Gratifyingly, 3,5-dinitrobenzoic acid gave excellent selectivity with 98% ee and a yield of 74% in toluene (Entry 2). Interestingly, 4-nitrobenzoic acid (Entry 3) provided a yield of 78%, but the enantioselectivity was significantly lower than with the dinitrobenzoic acid species with 44% ee in tetrahydrofuran.
In an attempt to find a trend based on acidity of the benzoic acid substituents, 4-fluoro-, 4-chloro-, and 4-bromobenzoic acids were tested giving product yields of 71%, 98%, and 85%, respectively. As for the stereoselectivity of the reaction, 4-fluorobenzoic acid resulted in 40% ee, 4-chlorobenzoic acid gave 60% ee, and 4-bromobenzoic acid gave 80% ee (Entry 4). These results seemed to be based on the deactivation/withdrawing trends of the halogen substituents on the aromatic ring. The fluorine-substituted ring, being the least deactivated \( \sigma_{\text{para}} = 0.15 \), is the least acidic of the halogenated benzoic acids and provides the lowest enantiomeric excess, whereas the more acidic bromine-substituted benzoic acid \( \sigma_{\text{para}} = 0.26 \) provided the highest enantiomeric excess. This trend did not follow with 4-nitrophenol, which is more acidic than 4-bromophenol and showed lower enantioselectivity. This result indicates that further screening of benzoic acids is needed in order to determine what specifically is governing selectivity.

### 4.6 - Ligand Recovery

Since the chemistry reported so far has only succeeded in a stoichiometric sense, it was important to find a way to recycle valuable reagents used in the reaction in order to reduce the cost and amount of waste produced preparing the phosphorus reagent. We found that upon purification of the final product, the phosphoric triamide could also be isolated cleanly via column chromatography. Once isolated, the phosphoric triamide \textbf{181} was treated with 1 M HCl in tetrahydrofuran and heated to 80 °C for three hours in order to recover the diamine ligand \textbf{182} and produce phosphoric acid (\textbf{183}) as a by-product (Scheme 4.6).
The diamine ligand 182 was isolated cleanly in quantitative yield and can be reused in order to make the asymmetric phosphine. Until a catalytic system is developed, recovering the ligand provides an efficient process that avoids accumulation of phosphoric triamide 181 waste.

4.7 - Conclusion and Future Work

Our research has been dedicated to finding reactivity of the main group elements that is comparable to the catalytic reactivity of the transition metals. Specifically, developing an enantioselective, phosphorus(III)-mediated α-functionalization method that can compete with, and possibly supplant, the use of transition metals could open new avenues to understanding and developing more methodologies with the p-block elements analogous to the transition metal series. Finding stoichiometric reactivity in the p-block elements that result in the same overall transformation as a transition metal-catalyzed process is the first step in reshaping the role of the main group block elements in catalysis, and the work discussed in this thesis has accomplished this initial step by taking advantage of known phosphorus chemistry that promotes new C-X bonds.
In order to expand this research to a more general and attractive procedure, future work will involve reacting various conditions such as phosphines, chiral acids, and nucleophiles with complex substrates. There is also literature precedence involving the reduction of phosphine oxides with diarylsilanes, resulting in the trivalent phosphine species. The use of a silane in our methodology could lead to a catalytic reaction where a substoichiometric amount of the asymmetric phosphoric triamide could be reduced to the active trivalent phosphine *in situ*, followed by regeneration of the phosphorus triamide after the reductive α-heterofunctionalization reaction is completed. Testing our methodology with the formation of other bonds like α-C-C bonds could expand its utility since C-C bond formation is the essence of organic chemistry. Additionally, testing intramolecular α-heterofunctionalization reactions could also help increase the value of our method.

Overall, if a novel catalytic α-functionalization process is developed in the p-block series, and this success translates to other processes such as hydrogenations and cross-couplings, than these methods could serve as useful complements to the transition-metal processes, leading to more efficient ways to synthesize valuable synthetic targets.
Chapter 5

Experimental Section

General Notes
All solvents were degassed by sparging with argon, dried by passage over activated alumina column, and stored under argon prior to use. All glassware used was dried in a 120 °C oven and purged under nitrogen before use. All reagents used are commercially available from TCI, Sigma-Aldrich, and Alfa-Aesar. NMR data was collected on Bruker Avance 300, 360, and 400 MHz instruments. Spectra were referenced internally to residual protiated solvent (chloroform: $^1$H $\delta$ 7.26 ppm, $^{13}$C $\delta$ 77.2 ppm). Mass spectrometric measurements were performed at The Huck Institute of the Life Sciences – Proteomics and Mass Spectrometry Core Facility. All yields reported are isolated yields unless stated otherwise.

**General Procedure A** In a dried 25 mL round bottom flask, 164 mg (1 mmol) of 1,2-dicarbonyl compound was added to THF (10 mL, 0.1 M). The oxygen nucleophile (cf. Tables 3.3 and 3.4) (1.05 mmol) was added and the solution was stirred at ambient temperature under a nitrogen atmosphere until all reagents dissolved. The reaction mixture was placed in a -78 °C dry-ice/acetone bath and the mixture was stirred for 15 min. Tris(dimethylamino)phosphine (0.20 mL, 1.05 mmol) was added dropwise to the cold solution. Upon complete addition of the phosphine, the dry-ice bath was removed and the solution was warmed to ambient temperature over 0.5 h. Once the starting
material was consumed (monitored via TLC), the reaction mixture was concentrated and dissolved in 50 mL of ethyl acetate. The organic layer was washed sequentially with 10% NaOH (5 x 30 mL) and dilute (~2%) brine (5 x 30 mL) to remove HMPA and excess phenol. The organic layer was dried over anhydrous sodium sulfate, concentrated in vacuo, and the product was isolated via column chromatography (10% ethyl acetate in hexanes) unless otherwise stated.

**Analytical Data**

General procedure A was followed giving 238 mg of compound 123 (93% yield). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.59 (d, 2H, $J = 7.6$ Hz), 7.40-7.28 (m, 3H), 7.18-7.13 (m, 1H), 7.07 (t, 1H, $J = 1.2$ Hz), 6.86 (t, 1H, $J = 7.4$ Hz), 6.71 (d, 1H, $J = 8.1$ Hz), 5.63 (s, 1H), 3.66 (s, 3H), 2.34 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 171.1, 156.0, 136.3, 131.6, 129.4, 129.2, 128.1, 127.4, 127.2, 122.0, 112.5, 79.0, 53.0, 16.9; MS (ESI) calcd for C$_{16}$H$_{20}$NO$_3$ (M+NH$_4^{+}$) 274.1443, found 274.1455.

General procedure A was followed giving 222 mg of compound 124 (87% yield). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.66 (d, 2H, $J = 7.8$ Hz), 7.49-7.39 (m, 3H), 7.22 (t, 1H, $J = 7.7$ Hz), 6.88-6.79 (m, 3H), 5.72 (s, 1H), 3.78 (s, 3H), 2.33 (s, 3H); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 170.6, 157.4, 139.8, 135.6, 129.4, 129.0, 128.8, 127.1, 122.8, 116.5, 112.1, 78.6, 52.6, 21.6; MS (ESI) calcd for C$_{16}$H$_{20}$NO$_3$ (M+NH$_4^{+}$) 274.1443, found 274.1428.
General procedure A was followed giving 245 mg of compound 125 (96% yield). $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.62 (d, 2H, $J = 7.9$ Hz), 7.45-7.35 (m, 3H), 7.07 (d, 2H, $J = 8.6$ Hz), 6.89 (d, 2H, $J = 8.6$ Hz), 5.66 (s, 1H), 3.75 (s, 3H), 2.30 (s, 3H); $^{13}$C NMR (CDCl$_3$, 90 MHz) δ 170.7, 155.2, 135.6, 131.2, 130.1, 129.0, 128.8, 127.1, 115.5, 78.9, 52.6, 20.6; MS (ESI) calcd for C$_{16}$H$_{20}$NO$_3$ (M+NH$_4$) 274.1443, found 274.1433.

General procedure A was followed giving 247 mg of compound 126 (91% yield). $^1$H NMR (CDCl$_3$, 360 MHz) δ 7.61 (d, 2H, $J = 7.4$ Hz), 7.42 (d, 3H, $J = 7.5$ Hz), 6.95 (d, 2H, $J = 9.1$ Hz), 6.85 (d, 2H, $J = 9.1$ Hz), 5.61 (s, 1H), 3.78-3.76 (m, 6H); $^{13}$C NMR (CDCl$_3$, 90 MHz) δ 170.6, 154.7, 151.4, 135.7, 129.0, 128.8, 127.1, 116.9, 114.7, 79.7, 55.6, 52.6; MS (ESI) calcd for C$_{16}$H$_{20}$NO$_4$ (M+NH$_4$) 290.1392, found 290.1387.

General procedure A was followed giving 317 mg of compound 127 (99% yield). $^1$H NMR (CDCl$_3$, 360 MHz) δ 7.70 (d, 2H, $J = 7.3$ Hz), 7.62 (d, 1H, $J = 7.9$ Hz), 7.48-7.41 (m, 3H), 7.24 (t, 1H, $J = 7.9$ Hz), 6.94-6.86 (m, 2H), 5.74 (s, 1H), 3.76 (s, 3H); $^{13}$C NMR (CDCl$_3$, 90 MHz) δ 169.9, 153.8, 135.0, 133.8, 129.1, 128.8, 128.4, 127.0, 123.2, 114.7, 113.2, 79.4, 52.7; MS (ESI) calcd for C$_{16}$H$_{17}$NO$_3$Br (M+NH$_4$) 338.0392, found 338.0390.
General procedure A was followed giving 172 mg of compound 128 (60% yield). $^1$H NMR (CDCl$_3$, 300 MHz) δ 8.18 (d, 2H, $J = 7.1$ Hz), 7.58-7.54 (m, 2H), 7.42 (d, 3H, $J = 2.2$ Hz), 6.98 (d, 2H, $J = 7.1$ Hz), 5.73 (s, 1H), 3.72 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 169.7, 162.4, 142.7, 134.5, 130.0, 129.5, 127.5, 126.4, 115.8, 79.2, 53.4; MS (ESI) calcd for C$_{15}$H$_{17}$N$_2$O$_3$ (M+NH$_4$) 305.1137, found 305.1137.

General procedure A was followed (Without aqueous wash) giving 116 mg of compound 129 (63% yield). $^1$H NMR (CDCl$_3$, 360 MHz) δ 7.50-7.41 (m, 5H), 5.97 (s, 1H), 3.75 (s, 3H), 2.22 (s, 3H); $^{13}$C NMR (CDCl$_3$, 90 MHz) δ 170.3, 169.3, 133.8, 129.3, 128.8, 127.7, 74.5, 52.6, 20.7; MS (ESI) calcd for C$_{11}$H$_{16}$NO$_4$ (M+NH$_4$) 226.1079, found 226.1071.

General procedure A was followed giving 340 mg of compound 130 (89% yield). $^1$H NMR (CDCl$_3$, 360 MHz) δ 8.18 (d, 2H, $J = 7.1$ Hz), 7.65-7.60 (m, 3H), 7.52-7.44 (m, 5H), 6.23 (s, 1H), 3.79 (s, 3H); $^{13}$C NMR (CDCl$_3$, 90 MHz) δ 169.3, 165.9, 134.0, 133.5, 130.0, 129.4, 129.3, 128.9, 128.5, 127.7, 74.9, 52.7; MS (ESI) calcd for C$_{16}$H$_{18}$NO$_4$ (M+NH$_4$) 288.1236, found 288.1230.
**Aliphatic Nucleophiles**

General procedure A was followed giving 131 mg of compound **131** (60% yield). $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 7.46-7.38 (m, 2H), 7.37-7.34 (m, 3H), 5.21 (s, 1H), 4.29 (d, 1H, $J = 16.1$ Hz), 4.14 (d, 1H, $J = 16.1$ Hz), 3.71 (s, 3H), 2.49 (s, 1H); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 170.7, 135.4, 129.1, 128.8, 127.6, 78.6, 78.5, 75.8, 56.2, 52.4; MS (ESI) calcd for C$_{13}$H$_{16}$NO$_3$ (M+NH$_4$) 222.1130, found 222.1113.

General procedure A was followed giving 149 mg of compound **132** (60% yield). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.60-7.41 (m, 5H), 5.11 (s, 1H), 4.04-3.78 (m, 2H), 3.76 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 170.4, 135.1, 129.8, 129.3, 127.9, 81.8, 66.6 (q, $^{1}J_{CF} = 34.8$ Hz), 53.0; MS (ESI) calcd for C$_{11}$H$_{15}$NO$_3$F$_3$ (M+NH$_4$) 266.1004, found 266.0999.

General procedure A was followed, but ethanol was used as a solvent, giving 119 mg of compound **133** (57% yield). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.50-7.47 (m, 2H), 7.41-7.34 (m, 3H), 4.89 (s, 1H), 4.25-4.15 (m, 2H), 3.66-3.51 (m, 2H), 1.35-1.21 (m, 6H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 171.5, 137.2, 129.0, 128.5, 128.0, 127.6, 65.7, 61.6, 15.6, 14.5; MS (ESI) calcd for C$_{12}$H$_{17}$O$_3$ (M+H) 209.1178, found 209.1181.
**General Procedure B** In a dried 25 mL round bottom flask, methyl benzoylformate (164 mg, 1.0 mmol) was added to THF (10 mL, 0.1 M) under a nitrogen atmosphere. The nitrogen nucleophile (cf. Table 3.5) (1.05 mmol) was added and the solution was stirred at ambient temperature until all reagents dissolved. The flask was placed in a -78 °C dry-ice/acetone bath and the mixture was stirred for 15 min. Tris(dimethylamino)phosphine (0.20 mL, 1.1 mmol) was added dropwise via syringe to the cold solution. Upon complete addition of the phosphine, the dry-ice bath was removed and the solution was warmed to ambient temperature over 0.5 h. Once the starting material was consumed (monitored via TLC), the solution was concentrated and dissolved in 50 mL of ethyl acetate. The organic layer was washed with dilute (~2%) brine (5 x 30 mL) to remove HMPA. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo*, and the product was isolated via column chromatography (10% ethyl acetate in hexanes) unless stated otherwise.

**Analytical Data**

General procedure B was followed giving 223 mg of compound 134 (70% yield). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.66 (d, 2H, $J = 9.0$ Hz), 7.30-7.21 (m, 7H), 5.80 (d, 1H, $J = 7.0$ Hz), 5.09 (d, 1H, $J = 7.5$ Hz), 3.59 (s, 3H), 2.41 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 171.0, 144.0, 137.3, 135.7, 129.9, 129.2, 129.0, 127.6, 127.5, 59.8, 53.4, 21.9; MS (ESI) calcd for C$_{16}$H$_{18}$NO$_4$S (M+H) 320.0957, found 320.0946.
General procedure B was followed giving 349 mg of compound 135 (93% yield). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.73 (d, 2H, $J = 7.8$ Hz), 7.33-7.29 (m, 5H), 7.23 (bs, 2H), 5.75 (s, 1H), 3.55 (s, 3H), 3.29-3.13 (m, 2H), 2.42 (s, 3H), 1.43-1.42 (m, 1H), 0.98-0.91 (m, 2H), 0.80-0.76 (m, 1H), 0.62 (t, 3H, $J = 14.6$ Hz); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 170.4, 143.4, 136.9, 134.2, 129.6, 129.0, 128.9, 128.8, 127.3, 62.8, 52.1, 46.0, 32.7, 21.6, 19.8, 13.5; MS (ESI) calcd for C$_{20}$H$_{26}$NO$_4$S (M+H) 376.1583, found 376.1567.

General procedure B was followed giving 352 mg of compound 136 (89% yield). $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 7.59 (d, 2H, $J = 8.2$ Hz), 7.23 (d, 2H, $J = 8.2$ Hz), 7.16-7.09 (m, 4H), 7.05-7.01 (m, 2H), 6.93-6.87 (m, 4H), 6.16 (s, 1H), 3.71 (s, 3H), 2.40 (s, 3H); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 171.1, 143.6, 137.0, 135.8, 133.7, 133.0, 129.9, 129.3, 128.7, 128.5, 128.4, 128.3, 128.0, 65.4, 52.5, 21.7; MS (ESI) calcd for C$_{22}$H$_{22}$NO$_4$S (M+H) 396.1270, found 396.1274.

General procedure B was followed giving 406 mg of compound 137 (85% yield). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.72 (d, 2H, $J = 8.1$ Hz), 7.34 (s, 3H), 7.30 (d, 2H, $J = 8.1$ Hz), 7.16 (bs, 2H), 5.74 (s, 1H), 3.62-3.57 (m, 1H), 3.51 (s, 3H), 3.38-3.34 (m, 1H), 3.28-3.24 (m, 1H), 2.78-2.74 (m, 1H), 2.42 (s, 3H), 0.75 (s, 9H), -0.15 (d, 6H, $J = 4.4$ Hz); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 170.1, 143.7, 136.4, 134.3, 129.6, 129.1, 129.0, 128.9, 127.4, 62.7, 62.3, 52.1, 47.1, 25.9, 21.6, 18.2, -5.4; MS (ESI) calcd for C$_{24}$H$_{36}$NO$_5$SSi (M+H) 478.2083, found 478.2076.
General procedure B was followed giving 306 mg of compound 138 (85% yield). $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.73 (d, 2H, $J = 8.3$ Hz), 7.32-7.28 (m, 5H), 7.20-7.18 (m, 2H), 5.79 (s, 1H), 5.43-5.36 (m, 1H), 4.74 (d, 2H, $J = 15.8$ Hz), 3.87 (qd, 2H, $J = 16.7, 6.2$ Hz), 3.59 (s, 3H), 2.42 (s, 3H); $^{13}$C NMR (CDCl$_3$, 90 MHz) δ 170.4, 143.5, 137.0, 134.8, 133.8, 129.6, 129.1, 128.8, 128.8, 127.4, 116.5, 62.7, 52.2, 48.3, 21.6; MS (ESI) calcd for C$_{19}$H$_{22}$NO$_4$S (M+H) 360.1270, found 360.1278.

General procedure B was followed giving 336 mg of compound 139 (82% yield). $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.61 (d, 2H, $J = 7.5$ Hz), 7.23 (d, 2H, $J = 7.7$ Hz), 7.18-7.16 (m, 3H), 7.12-7.11 (m, 2H), 7.02 (m, 3H), 6.88-6.66 (m, 2H), 5.79 (s, 1H), 4.64 (d, 1H, $J = 16.3$ Hz), 4.42 (d, 1H, $J = 16.3$ Hz), 3.55 (s, 3H), 2.38 (s, 3H); $^{13}$C NMR (CDCl$_3$, 90 MHz) δ 170.4, 143.5, 137.4, 136.9, 133.4, 129.5, 129.3, 128.8, 128.7, 127.9, 127.7, 127.4, 126.7, 63.1, 52.2, 49.3, 21.5; MS (ESI) calcd for C$_{23}$H$_{24}$NO$_4$S (M+H) 410.1426, found 410.1422.

General procedure B was followed giving 245 mg of compound 140 (83% yield). $^1$H NMR (CDCl$_3$, 360 MHz) δ 7.84-7.82 (m, 2H), 7.70-7.67 (m, 2H), 7.55 (d, 2H, $J = 7.5$ Hz), 7.35 (d, 3H, $J = 7.5$ Hz), 6.03 (s, 1H), 3.80 (s, 3H); $^{13}$C NMR (CDCl$_3$, 90 MHz) δ 168.6, 167.1, 134.5, 134.3, 131.8, 129.8, 128.7, 128.6, 123.7, 55.8, 53.1; MS (ESI) calcd for C$_{17}$H$_{14}$NO$_4$ (M+H) 296.0923, found 296.0912.
General procedure B was followed without performing column chromatography. Purification was accomplished by washing with 10% NaOH followed by water/brine to give 174 mg of compound 141 (81% yield). $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 7.51 (bs, 1H), 7.31-7.20 (m, 4H), 7.05-6.95 (m, 3H), 5.86 (s, 1H), 3.71 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 169.5, 134.5, 129.8, 129.7, 129.0, 128.2, 128.1, 127.9, 127.7, 53.5; MS (ESI) calcd for C$_{12}$H$_{13}$N$_2$O$_2$ (M+H) 217.0977, found 217.0961.

General procedure B was followed without performing column chromatography. Purification was accomplished by washing with 10% NaOH followed by water/brine (10x) to give 69 mg of compound 142 (32% yield). $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 7.57 (s, 1H), 7.40 (m, 6H), 6.27 (s, 1H), 5.26 (s, 1H), 3.79 (s, 3H); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 169.5, 140.0, 133.9, 129.5, 129.3, 129.2, 128.5, 106.1, 67.9, 53.0; MS (ESI) calcd for C$_{12}$H$_{13}$N$_2$O$_2$ (M+H) 217.0977, found 217.0957.

**Substrate Scope**

General procedure A was followed giving 223 mg of compound 143 (78% yield). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.61 (d, 2H, $J = 6.3$ Hz), 7.543-7.35 (m, 3H), 6.94 (d, 2H, $J = 4.6$ Hz), 6.82 (d, 2H, $J = 4.6$ Hz), 5.57 (s, 1H), 4.26-4.14 (m, 2H), 3.73 (s, 3H), 1.21 (t, 3H, $J = 7.1$ Hz); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 170.1, 154.5, 151.4, 135.7, 128.8, 128.7, 127.0, 116.8, 114.6, 79.6, 61.5, 55.5, 14.0; MS (ESI) calcd for C$_{17}$H$_{19}$O$_4$ (M+H) 287.1283, found 287.1285.
General procedure A was followed giving 336 mg of compound 144 (95% yield). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.73 (d, 2H, $J = 8.3$ Hz), 7.65 (d, 2H, $J = 8.3$ Hz), 6.91 (d, 2H, $J = 9.1$ Hz), 6.82 (d, 2H, $J = 9.1$ Hz), 5.62 (s, 1H), 4.26-4.13 (m, 2H) 3.72 (s, 3H), 1.22 (t, 3H, $J = 7.2$ Hz); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 169.5, 154.9, 151.1, 139.8, 135.6 (q, $^1J_{CF} = 1.3$ Hz), 130.4, 127.4, 122.5, 116.9, 114.7, 79.0, 61.9, 55.5, 14.0; MS (ESI) calcd for C$_{18}$H$_{21}$NO$_4$F$_3$ (M+NH$_4$) 372.1423 found 372.1414.

General procedure A was followed giving 276 mg of compound 145 (91% yield). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.56-7.52 (m, 2H) 7.06 (t, 2H, $J = 8.7$ Hz), 6.88 (d, 2H, $J = 6.9$ Hz), 6.80 (d, 2H, $J = 6.9$ Hz), 5.51 (s, 1H), 4.22-4.14 (m, 2H), 3.72 (s, 3H), 1.18 (t, 3H, $J = 7.2$ Hz); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 170.0, 163.0 (d, $^1J_{CF} = 247.7$ Hz), 153.0 (d, $^2J_{CF} = 312.4$ Hz), 131.7 (d, $^3J_{CF} = 3.3$ Hz), 129.0 (d, $^4J_{CF} = 8.2$ Hz), 116.9, 115.8, 115.6, 114.7, 79.0 61.7, 55.6, 14.0; MS (ESI) calcd for C$_{17}$H$_{21}$NO$_4$F (M+NH$_4$) 322.1455, found 322.1440.

General procedure A was followed giving 272 mg of compound 146 (85% yield). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.50 (d, 2H, $J = 8.3$ Hz), 7.33 (d, 2H, $J = 8.3$ Hz), 6.87 (d, 2H, $J = 8.9$ Hz), 6.78 (d, 2H, $J = 8.9$ Hz), 5.50 (s, 1H), 4.26-4.14 (m, 2H), 3.70 (s, 3H), 1.17 (t, 3H, $J = 7.2$ Hz); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 169.7, 154.7, 151.2, 134.8, 134.3, 128.9, 128.4, 116.9, 114.7, 78.9, 61.7, 55.6, 14.0; MS (ESI) calcd for C$_{17}$H$_{21}$NO$_4$Cl (M+NH$_4$) 338.1159, found 338.1152.
General procedure A was followed giving 256 mg of compound 147 (70% yield). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.49 (d, 2H, $J = 8.3$ Hz), 7.43 (d, 2H, $J = 8.3$ Hz), 6.87 (d, 2H, $J = 7.7$ Hz), 6.78 (d, 2H, $J = 7.7$ Hz), 5.48 (s, 1H), 4.22-4.09 (m, 2H), 3.70 (s, 3H), 1.17 (t, 3H, $J = 1.3$ Hz); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 169.6, 154.7, 151.1, 134.8, 131.8, 128.7, 123.0, 116.8, 114.6, 78.9, 61.7, 55.5, 14.0; MS (ESI) calcd for C$_{17}$H$_{21}$NO$_4$Br (M+NH$_4$) 382.0654, found 382.0625.

General procedure A was followed giving 267 mg of compound 148 (85% yield). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.47 (d, 2H, $J = 8.7$ Hz), 6.91-6.85 (m, 4H), 6.80-6.73 (m, 2H), 5.47 (s, 1H), 4.23-4.10 (m, 2H), 3.77 (s, 3H), 3.71 (s, 3H), 1.19 (t, 3H, $J = 7.1$ Hz); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 170.3, 160.0, 154.5, 151.4, 128.6, 127.8, 116.9, 114.6, 114.1, 79.3, 61.5, 55.6, 55.3, 14.1; MS (ESI) calcd for C$_{18}$H$_{21}$O$_5$ (M+H) 317.1389, found 317.1393.

General procedure A was followed giving 137 mg of compound 150 (50% yield). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.54 (d, 1H, $J = 7.9$ Hz), 7.20 (t, 1H, $J = 7.6$ Hz), 6.86 (t, 1H, $J = 7.6$ Hz), 6.79 (d, 1H, $J = 7.9$ Hz), 4.76 (q, 1H, $J = 7.9$ Hz), 3.75 (s, 3H), 1.68 (d, 3H, $J = 7.9$ Hz); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 172.1, 154.3, 133.7, 128.4, 123.1, 114.9, 113.1, 74.1, 52.4, 18.6; MS (ESI) calcd for C$_{10}$H$_{15}$NO$_3$Br (M+NH$_4$) 276.0235, found 276.0230.
General procedure B was followed with no aqueous wash giving 154 mg of compound 151 (60% yield). $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.73 (d, 2H, $J = 8.2$ Hz), 7.30 (d, 2H, $J = 8.2$ Hz), 5.29 (d, 1H, $J = 7.2$ Hz), 3.98 (q, 1H, $J = 7.2$ Hz), 3.55 (s, 3H), 2.43 (s, 3H), 1.39 (d, 3H, $J = 7.2$ Hz); $^{13}$C NMR (CDCl$_3$, 90 MHz) δ 172.7, 143.7, 136.8, 129.7, 127.2, 52.6, 51.5, 21.6, 19.8; MS (ESI) calcd for C$_{11}$H$_{19}$N$_2$O$_4$S (M+NH$_4$) 275.1066, found 275.1062.

General procedure A was followed giving 202 mg of compound 153 (74% yield). $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.56 (d, 1H, $J = 7.9$ Hz), 7.24-7.20 (m, 1H), 6.86 (t, 1H, $J = 7.9$ Hz), 6.76 (d, 1H, $J = 8.2$ Hz), 4.61 (t, 1H, $J = 6.0$ Hz), 3.76 (s, 3H), 2.11-2.04 (m, 2H), 1.14 (t, 3H, $J = 7.5$ Hz); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 172.1, 154.9, 134.1, 128.8, 123.1, 114.5, 113.1, 79.1, 52.7, 26.7, 10.1; MS (ESI) calcd for C$_{11}$H$_{17}$NO$_3$Br (M+NH$_4$) 290.0392, found 290.0378.

General procedure A was followed giving 254 mg of compound 155 (70% yield. $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.62 (d, 1H, $J = 7.8$ Hz), 7.35-7.22 (m, 6H), 6.91 (t, 1H, $J = 7.8$ Hz), 6.75 (d, 1H, $J = 8.2$ Hz), 4.66-4.63 (m, 1H), 4.27-4.22 (m, 2H), 3.01-2.95 (bs, 2H), 2.47-2.32 (m, 2H), 1.33-1.26 (m, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 171.6, 154.8, 141.1, 134.1, 129.1, 128.9, 126.6, 123.2, 114.4, 113.1, 78.0, 61.9, 54.0, 34.9, 31.7, 14.6; MS (ESI) calcd for C$_{18}$H$_{23}$NO$_3$Br (M+NH$_4$) 380.0861, found 380.0852.
General procedure A was followed (3 h instead of 1 h reaction time) giving 225 mg of compound 157 (75% yield). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.57 (d, 1H, $J = 6.3$ Hz), 7.20 (t, 1H, $J = 5.9$ Hz), 6.86 (t, 1H, $J = 6.3$ Hz), 6.73 (d, 1H, $J = 9.4$ Hz), 4.44 (d, 1H, $J = 5.0$ Hz), 4.26 (q, 2H, $J = 7.1$ Hz), 2.42-2.36 (m, 1H), 1.29-1.24 (m, 3H), 1.19-1.14 (m, 6H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 171.1, 155.0, 134.0, 128.7, 122.8, 113.9, 113.0, 82.7, 61.6, 32.3, 19.3, 18.0, 14.6; MS (ESI) calcd for C$_{13}$H$_{21}$NO$_3$Br (M+NH$_4$) 318.0705, found 318.0694.

General procedure A was followed (3 h instead of 1 h reaction time) giving 212 mg of compound 158 (84% yield). $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 6.89-6.82 (m, 4H), 4.30-4.21 (m, 3H), 3.77 (s, 3H), 2.32-2.26 (m, 1H), 1.27 (t, 3H, $J = 7.1$ Hz), 1.13-1.09 (m, 6H); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 171.6, 154.4, 152.5, 116.5, 114.6, 82.8, 60.9, 55.6, 31.7, 18.6, 17.8, 14.2; MS (ESI) calcd for C$_{14}$H$_{24}$NO$_4$ (M+NH$_4$) 270.1705, found 270.1697.

Asymmetric Reaction Data

General Procedure C  In a dried 25 mL round bottom flask, methyl benzoyleformate (82 mg, 0.5 mmol) was added to THF or PhMe (5 mL, 0.1 M). The substituted benzoic acid (cf. Table 3.10) (0.53 mmol) was added and the solution was stirred at ambient temperature until all reagents were dissolved. The flask was placed in a -78 °C dry-ice/acetone bath and the mixture stirred for 15 min. Chiral phosphine 174 (235 mg, 0.55 mmol) was added in one portion to the cold solution. The reaction was stirred at -78 °C for 0.5 h, and was to warmed to 0 °C and held at this temperature until
completion. Once the starting material was consumed (monitored via TLC), the solution was concentrated, and the product was isolated via column chromatography (10% ethyl acetate in hexanes).

General procedure C was followed giving 100 mg of compound 175 (74% yield and 40% ee). HPLC conditions: CHIRALPAK® AD-H (4.6 mm x 250 mm), 7% IPA/hexanes, flow rate = 0.9000 mL/min; t₁ 7.032 min., t₂ 7.727 min.; ¹H NMR (CDCl₃, 360 MHz) δ 8.18 (d, 2H, J = 7.1 Hz), 7.65-7.60 (m, 3H), 7.52-7.44 (m, 5H), 6.23 (s, 1H), 3.79 (s, 3H); ¹³C NMR (CDCl₃, 90 MHz) δ 169.3, 165.9, 134.0, 133.5, 130.0, 129.4, 129.3, 128.9, 128.5, 127.7, 74.9, 52.7; MS (ESI) calcd for C₁₆H₁₈NO₄ (M+NH₄) 288.1236, found 288.1230; MS (ESI) calcd for C₁₆H₁₈NO₄ (M+NH₄) 288.1236, found 288.1230.

General procedure C was followed in PhMe giving 133 mg of compound 176 (74% yield and 98% ee). HPLC conditions: CHIRALPAK® AD-H (4.6 mm x 250 mm), 10% IPA/hexanes, flow rate = 0.5000 mL/min; t₁ 22.736 min., t₂ 25.798 min.; ¹H NMR (CDCl₃, 360 MHz) δ 9.26-9.22 (m, 3H), 7.60-7.59 (m, 2H), 7.50-7.49 (m, 3H), 6.28 (s, 1H), 3.81 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 168.8, 162.4, 149.1, 133.3, 133.0, 130.4, 130.2, 129.6, 128.3, 123.3, 76.7, 53.5; MS (ESI) calcd for C₁₆H₁₂N₂O₄Na (M+Na) 383.0491, found 383.0498.
Genera

general procedure C was followed in THF giving 123 mg of compound 177 (78% yield and 44% ee). HPLC conditions: CHIRALPAK® AD-H (4.6 mm x 250 mm), 10% IPA/hexanes, flow rate = 0.5000 mL/min; t₁ 13.498 min., t₂ 15.307 min.; ¹H NMR (CDCl₃, 300 MHz) δ 8.60 (s, 4H), 7.72-7.70 (m, 2H), 7.60-7.59 (m, 3H), 6.22 (s, 1H), 3.80 (s, 3H); ¹³C NMR (CDCl₃, 90 MHz) δ 168.8, 164.1, 134.6, 133.3, 131.2, 129.7, 129.1, 129.0, 127.8, 123.7, 75.6, 52.9; MS (ESI) calcd for C₁₆H₁₃NO₆Na (M+Na) 338.0641, found 338.0642.

General procedure C was followed in PhMe giving 102 mg of compound 178 (71% yield and 40% ee). HPLC conditions: CHIRALPAK® AD-H (4.6 mm x 250 mm), 7% IPA/hexanes, flow rate = 0.5000 mL/min; t₁ 16.077 min., t₂ 17.670 min.; ¹H NMR (CDCl₃, 300 MHz) δ 8.43-8.14 (m, 2H), 7.61-7.57 (m, 2H), 7.46-7.44 (m, 3H), 7.15 (t, 2H, J = 8.7 Hz), 5.92 (s, 1H), 3.78 (s, 3H); ¹³C NMR (CDCl₃, 90 MHz) δ 167.5, 167.0 (d, ¹¹J₉₀ = 391.7 Hz), 164.7, 133.8, 132.6 (d, ³¹J₉₀ = 9.4 Hz), 129.4, 129.0, 127.7, 125.4 (⁴¹J₉₀ = 3.1 Hz), 115.7 (d, ²¹J₉₀ = 22.0 Hz), 75.0, 52.8; MS (ESI) calcd for C₁₆H₁₇NO₄F (M+NH₄⁺) 306.1142, found 306.1158; MS (ESI) calcd for C₁₆H₁₇NO₄F (M+Na) 306.1142, found 306.1158.

General procedure C was followed in THF giving 149 mg of compound 179 (98% yield and 60% ee). HPLC conditions: CHIRALPAK® AD-H (4.6 mm x 250 mm), 7% IPA/hexanes, flow rate = 0.5000 mL/min; t₁ 18.891 min., t₂ 19.842 min.; ¹H NMR (CDCl₃, 300 MHz) δ 8.08 (d, 2H, J = 8.6 Hz), 7.70-7.58 (m, 2H), 7.49-7.34 (m, 5H), 6.18 (s, 1H), 3.77 (s, 3H); ¹³C NMR
(CDCl₃, 90 MHz) δ 169.2, 165.1, 142.4, 140.1, 133.8, 131.4, 129.5, 129.0, 128.9, 127.7, 75.1, 52.8; MS (ESI) calcd for C₁₆H₁₃O₄ClNa (M+Na) 327.0400, found 327.0405.

General procedure C was followed in PhMe giving 150 mg of compound 180 (86% and 80% ee). HPLC conditions: CHIRALPAK® AD-H (4.6 mm x 250 mm), 8% IPA/hexanes, flow rate = 0.9000 mL/min; t₁ 6.683 min., t₂ 7.377 min.; ¹H NMR (CDCl₃, 300 MHz) δ 8.01 (d, 2H, J = 6.8 Hz), 7.63-7.57 (m, 4H), 7.49-7.44 (m, 3H), 6.18 (s, 1H), 3.77 (s, 3H); ¹³C NMR (CDCl₃, 90 MHz) δ 169.1, 165.2, 133.7, 131.9, 131.5, 129.5, 128.9, 128.8, 128.1, 127.7, 75.1, 52.8; MS (ESI) calcd for C₁₆H₁₃O₄BrNa (M+H) 349.0075, found 349.0070.

**Ligand Recovery** The mobile phase of the column mentioned in general procedure C was increased to 100% EtOAc in order to remove excess benzoic acid from the column. Once the benzoic acid was removed, the mobile phase was increased to 10% MeOH in DCM and the phosphoric triamide 181 was eluted. To phosphoric triamide 181 (25 mg, 0.05 mmol) in THF (1 mL) was added 1M HCl(aq) (0.2 mL, 0.2 mmol) in a sealed NMR tube. The reaction mixture was heated at 80 °C for 3 h (or until ³¹P NMR indicated complete conversion to phosphoric acid). The aqueous solution was placed into a separatory funnel and basified with 10% NaOH to pH 14. The aqueous layer was extracted five times with diethyl ether and the combined organic layers were dried over sodium sulfate and concentrated in vacuo to provide the diamine ligand 157 (18 mg, 100%) as a white solid.
Preparation of (1R, 2R)-N,N'-bis(4-Methoxybenzyl)-cyclohexane-1,2-diamine (182) Racemic cyclohexanediamine was resolved with L-(-)-tartaric acid to form (R,R)-1,2-Diammoniumcyclohexane mono-(+)-tartrate following Jacobsen’s procedure.\(^5\) The tartrate salt (7.00 g, 26.00 mmol) was added to distilled water (122 mL) at rt. Potassium carbonate (7.3 g, 53 mmol) was added to the aqueous suspension, followed by the addition of 61 mL of ethanol. Methanesulfonic acid (0.21 mL, 3.2 mmol) was added to 122 mL of dichloromethane along with 4-methoxybenzaldehyde (6.1 mL, 53 mmol). The resulting organic solution was added to the aqueous suspension and stirred at ambient temperature for 12 h. The bilayer mixture was then heated at reflux for 1 h, followed by solvent removal via rotary evaporation. The residue was dissolved in 31 mL of methanol and cooled to 0 °C. Sodium borohydride (2.21 g, 58.4 mmol) was added in one portion and the solution was heated at reflux for 1 h once gas evolution ceased. The solvent was evaporated, and the residue was dissolved in 50 mL of 1 M NaOH and extracted three times with 1:1 EtOAc/hexanes. Purification of the crude mixture via column chromatography (20% EtOAc/hexanes, then 1:1:0.1 EtOAc:hexanes:Et\(_3\)N) afforded the chiral diamine as a white solid (4.74 g, 51% yield).\(^5\)\(^8\)\(^1\)H NMR (CDCl\(_3\), 360 MHz) \(\delta\) 7.25 (d, 4H, \(J = 8.6\) Hz), 6.87 (d, 4H, \(J = 8.6\) Hz), 3.86 (d, 2H, \(J = 7.1\) Hz), 3.83 (s, 6H), 3.61 (d, 2H, \(J = 7.1\) Hz), 2.26-2.16 (m, 4H), 1.76-1.73 (m, 3H), 1.28-1.22 (m, 3H), 1.06-1.04 (m, 2H); \(^13\)C NMR (CDCl\(_3\), 90 MHz) \(\delta\) 158.5, 133.3, 129.2, 113.7, 60.7, 55.3, 50.2, 31.5, 25.1; MS (ESI) calcd for C\(_{22}\)H\(_{31}\)N\(_2\)O\(_2\) (M+H) 355.2386, found 355.2376.
Preparation of (3aR, 7aR)-1,3-bis(4-Methoxybenzyl)-N,N-dimethylhexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-amine (174) The title compound was prepared by a modification of the procedure reported by Alexakis. The diamine ligand (4.74 g, 13.4 mmol) was placed in a flame dried, 25 mL reaction flask previously purged under nitrogen. Tris(dimethylamino)phosphine (3.05 mL, 16.8 mmol) was added to the diamine and the vessel was heated to 150 °C and stirred under nitrogen for 96 h. The excess tris(dimethylamino)phosphine was removed under high vacuum for 24 h. The sealed vessel was then placed in 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 an off-white/yellow solid (5.15 g, 90% yield). 

\[ \text{H NMR (CDCl}_3, 360 \text{ MHz}) \delta 7.28 (d, 4H, J = 7.8 \text{ Hz}), 6.86 (d, 4H, J = 7.8 \text{ Hz}), 4.18-3.96 (m, 3H), 3.82-3.73 (m, 7H), 2.99-2.94 (m, 1H), 2.71 2.65 (m, 1H), 2.55-2.53 (d, 7H, J = 7.2 \text{ Hz}), 1.92-1.85 (m, 2H), 1.70 (m, 2H), 1.35-1.17 (m, 4H), 0.94-0.90 (m, 2H); \]

\[ \text{^31P NMR (CDCl}_3, 145 \text{ MHz}) \delta 119.7; \]

\[ \text{^13C NMR (CDCl}_3, 90 \text{ MHz}) \delta 158.2 (2), 133.9 (d, J_{CP} = 6.3 \text{ Hz}), 133.7 (d, J_{CP} = 4.0 \text{ Hz}), 133.6, 129.3 (d, J_{CP} = 2.9 \text{ Hz}), 129.0, 113.4 (2), 66.9 (d, J_{CP} = 3.6 \text{ Hz}), 66.2 (d, J_{CP} = 8.7 \text{ Hz}), 55.2 (2), 50.5 (d, J_{CP} = 33.1 \text{ Hz}), 47.5 (d, J_{CP} = 11.0 \text{ Hz}), 38.1, 37.9, 31.0, 30.4, 24.7, 24.4; \]

\[ \text{MS (EI) calcd for [C}_{24}H_{34}O_{2}N_{3}P]^{+} 427.2387, \text{ found 427.2383}. \]
References


7. This approach can be distinguished from “indirect” methods for the preparation of heterofunctionalized carbonyl compounds, whereby nucleophilic addition of an acyl anion equivalent to a C=X double bond results in formation of the target product. Examples of this mode of reactivity include acyloin condensation, Strecker-type synthesis, etc.


29. The IUPAC naming convention for these trivalent phosphorus derivatives suggests “phosphane” is the preferred nomenclature; however, in this thesis we use the commonly employed “phosphine.”


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