NEW DISCOVERIES IN TITANIUM AND PHOSPHORUS MEDIATED CARBONYL ADDITIONS

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Abstract

by

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A method utilizing catalytic titanocene dichloride for the conjugate reduction of $\alpha,\beta$-unsaturated carbonyls was developed and described herein. The chemoselective procedure employs an amine hydrochloride as the proton source during the catalytic modification as opposed to the difficult to handle and potentially explosive $H_2$ atmosphere. The scope of conjugated compounds includes cyclic and acyclic variations of ketones, esters, aldehydes, amides, as well as ynones, which contain an extra degree of unsaturation. Attempts to exploit the utility of titanocene-bound enolates led to the discovery of a $\text{Cp}_2\text{TiCl}_2$ accelerated organometallic formation. After a detailed investigation by Fleury, catalytic loadings of titanium as low as 1 mol% were demonstrated to be effective at catalyzing organozinc and organomagnesium reagents derived from allyl, alkyl, aryl, and vinyl species.

Subsequently, a novel phosphorus redox process was constructed en route to synthesizing amides directly from carboxylic acids. The dual role of phosphorus includes activation of the carboxylic acid for electrophilic attack while decomposing an azide to
reveal a hidden nucleophilic nitrogen source. The resultant array of amides from this process includes alkyl, aryl, and \(\alpha,\beta\)-unsaturated amides as well as lactams and dipeptides. As an application of the highly chemoselective amidation procedure, a synthesis of LY573636 was completed in 3 steps from commercially available starting materials. This unique aspect of a reagent performing two separate crucial roles was further advanced by the creation of the first Staudinger ligation catalytic in phosphine. A diverse assortment of amides and imides can be produced in moderate to excellent yields when using 10 mol\% \(\text{Ph}_3\text{P}\) and a stoichiometric reductant.

These catalytic strategies involving redox chemistry of both transition metals and phosphorus enable a fast and resourceful approach towards the construction of valuable synthetic intermediates of saturated carbonyls, homoallylic alcohols, and substituted amides from the readily accessible starting materials.
This is for my loving family, friends, and boy Milton.
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CHAPTER 1:
SINGLE ELECTRON TRANSFER (SET) REDOX CATALYSIS INVOLVING TITANIUM

1.1 Background

As chemists look to further improve, develop, and modernize new synthetic methods, several key issues at the forefront include synthetic efficiency, atom economy, and environmental friendliness. These problems remain significant when developing new synthetic routes or methods toward biologically relevant molecules of the future. In attempting to optimize synthetic efficiency, transition metal catalysis has become a preeminent tool in the rapid construction of complex molecular architectures. The employment of transition metals enables the stabilization of reactive intermediates or functional groups like enolates or alkynes, which in other ways would be difficult or impossible to handle through traditional synthetic approaches. Through further manipulation of these unstable species, atom and step economy can be increased through coupling or cascade reactions.

One such process in which transition metals have proven an advantage over conventional methods is in the area of redox catalysis. Although various metals have shown capabilities of transferring a single electron, whether through an inner- or outer-sphere type mechanism, a recent interest utilizing titanium (III) species has occurred,
especially Cp₂TiCl. Due to mild conditions, wide functional group tolerance, and enhanced chemoselectivity, several groups have employed TiIII-mediated process to invoke some remarkable C-C bond forming reactions. In sections that follow, we will discuss selected examples that highlight the utility of TiIII reagents and their role in improving current synthetic methods while developing new unique ones.

1.2 Stoichiometric Titanium

1.2.1 Reductions

1.2.1.1 Carbonyl Reductions

Despite the general utility of metal hydrides in the reduction of carbonyl derivatives, an important class of reductions involves single electron transfer (SET) reductions. Alternative procedures developed by Porta and coworkers use low-valent titanium in conjunction with a base to selectively reduce aryl aldehydes, ketones, and dicarbonyls to the corresponding alcohol chemoselectivity.¹ A demonstration of Porta’s method involving TiCl₃ and NH₃ under aqueous conditions is shown in the reduction of aromatic ketone 1.1 to the expected secondary alcohol 1.3 in quantitative yield even with the presence of a cyclopropyl group (eq 1).

\[
\begin{array}{c}
\text{O} \\
1.1 \\
\text{TiCl}_3 \text{(2 equiv)} \\
\text{MeOH, NH}_3/H_2O \\
\rightarrow \\
\begin{array}{c}
L_3\text{TiO} \\
\text{1.2} \\
\text{TIL}_3 \\
\rightarrow \\
\text{OH} \\
1.3 \\
>99\% \text{ yield}
\end{array}
\end{array}
\]

¹
The ready reducibility of aryl ketones leads to chemoselectivity in the presence of other electrophilic functionality (i.e. carboxylic acids, ketones, esters, cyano). Support of their proposed mechanism involving two-consecutive electron transfers from TiIII comes from no observed by-products resulting from a strain induced ring-opened of the cyclopropyl substituent. Interestingly when NaOH is employed instead of NH3, homocoupling of the carbonyl species is observed instead to produce diol 1.6 (eq 2).

\[
\text{NC} \quad \text{TiCl}_3 \quad \text{MeOH, NaOH/H}_2\text{O} \quad \begin{array}{c}
\text{L} \quad \text{L} \\
\text{Ar} \quad \text{CH}_3 \quad \text{CH}_3
\end{array} \quad \text{arom} \quad \text{NC} \quad \text{OH} \\
\text{1.4} \quad \text{1.5} \quad \text{75\% yield} \quad \text{1.6}
\]

In 2002, Doris expanded the titanium radical-initiated carbonyl reduction chemistry to \(\alpha,\beta\)-unsaturated carbonyls. However, when unsaturated carbonyls were subjected to 2.5 equivalents of \(\text{Cp}_2\text{TiCl}\) in the presence of a proton source (i.e. MeOH), chemoselective reduction afforded the saturated carbonyl.\(^2\) Alkyl and aryl enones as well as ynone proved viable substrates en route to producing the analogous saturated ketones (eq 3).

\[
\text{O} \quad \text{Cp}_2\text{TiCl} \quad \text{THF, MeOH, -25 \rightarrow rt} \quad \text{O} \\
\text{1.7} \quad \text{1.8} \quad \text{56\% yield}
\]

1.2.1.2 Epoxide C-O Bond Cleavage

One of the most versatile functional groups to a synthetic organic chemist is an epoxide, whose straightforward synthesis and ability to act as a functional group handle for further manipulation are desired qualities. Titanium’s capability of reducing C-O
bonds has been explored by several prominent groups, independently, in the reductive ring opening of epoxides. A seminal contribution in this area was provided by Nugent and coworkers in which they utilized epoxyselenolins to construct cyclopentane derivatives (eq 4). The rapid C-O bond cleavage produced a secondary radical, which upon cyclization resulted in a primary radical before being scavenged by another equivalent of Cp₂TiCl. Protodemetalation rendered the desired cyclopentane derivative in moderate to good yield.

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{Cp}_2\text{TiCl (2 equiv)} & \quad \text{EtO}_2\text{C} \\
1.9 & \quad \text{THF} & \quad 1.10 \\
\text{68\% yield} & \quad \text{cis:trans = 85:15}
\end{align*}
\]

In 2002, Barrero synthesized the first monocyclic triterpenoid discovered, Achilleol A, using a TiCp₂Cl–mediated reductive opening of an epoxide followed by an ensuing free-radical-mediated cyclization upon a tethered alkene. When epoxide 1.11 was treated with 2.0 equivalents of pre-generated Cp₂TiCl from a mixture of Cp₂TiCl₂ and Mn dust, in thoroughly degassed benzene at 40 °C, cyclohexanol 1.12 was obtained in 65\% yield with exo-regioisomer being favored in a 13:1 isomeric ratio (eq 5).

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{Cp}_2\text{TiCl (2 equiv)} & \quad \text{EtO}_2\text{C} \\
1.11 & \quad \text{Benzene, 40 °C} & \quad 1.12 \\
\text{65\% yield}
\end{align*}
\]
Gansäuer examined the difference between common electron transfer reagents and titanocene catalysts in the reductive opening or deoxygenation of epoxides and the ability to construct complex molecular frameworks. Although no advantage was observed using Cp₂TiCl in the deoxygenation of epoxides as compared to SmI₂ or [V₂Cl₃(THF)₆]₂[Zn₂Cl₆], differences in reactivity were observed when the reductive trapping of resulting carbon-centered radicals was examined.⁵ When epoxide 1.14 was treated with stoichiometric amounts of various single electron transfer reagents, Cp₂TiCl was the only reagent to produce the bicyclicfused furan 1.15 in 57% yield (Scheme 1.1). The use of SmI₂ or vanadium complexes resulted in deoxygenation of the epoxide 1.14 to render the alkenes 1.16 and 1.17 as the major products in their attempts.

![Scheme 1.1: Reductive Epoxide Cyclizations](image)

Titanocene’s advantage over other SET reagents to achieve cyclization instead of deoxygenation was also observed when employing alkynes as a radical trap. To illustrate, when epoxide 1.18 was subjected to 2.2 equivalents of preformed Cp₂TiCl in THF bicycle 1.19 was obtained in good to excellent yields (eq 6).
1.2.2 McMurry/Pinacol Couplings

Of the unique features that low-valent titanium possesses, the most remarkable is the aptitude to couple a substantial variety of aldehydes and ketones to make olefins in excellent yields. The titanium-mediated coupling reaction between two carbonyls is a two step process; reductive dimerization of the desired carbonyl source \(1.20\) followed by deoxygenation of the resultant 1,2-diol to bring about the olefin \(1.23\) (Figure 1.1).\(^6\)

**Step 1: Carbon-Carbon bond formation**

\[
\begin{align*}
\text{2} & \quad \text{O} \\
R^1 \quad R^2 & \quad \text{e}^- \\
1.20 & \quad \rightarrow \\
\text{2} & \quad \text{O}^M \\
R^1 \quad R^2 & \quad \rightarrow \\
1.21 & \quad \rightarrow \\
\text{M} & \quad \text{O} \\
R^1 \quad R^2 & \quad R^1 \quad R^2 \\
1.22 & \quad \rightarrow \\
\end{align*}
\]

**Step 2: Deoxygenation**

\[
\begin{align*}
\text{MO} & \quad \text{OM} \\
R^1 \quad R^2 \quad R^1 \quad R^2 \\
1.22 & \quad \rightarrow \\
\text{VR} & \quad \text{VR} \\
R^1 \quad R^2 & \quad R^1 \quad R^2 \\
1.23 & \\
\end{align*}
\]

Figure 1.1: Deoxygenation of Carbonyls

The pinacol reaction is not limited to just the use of titanium, McMurry and coworkers have shown that the dimerized diol can be isolated in high yield under the mild low-valent titanium conditions at 0 °C. While pinacol coupling of carbonyls through an intermolecular process leads to mixtures of the *threo* and *erythro* diols,
intramolecular dimerization favors a cis-diol with smaller rings (i.e. 5 and 6) while the larger rings prefer a trans-diol product (Scheme 1.2).\(^7\)

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{TiCl}_3 (15 \text{ equiv})} \xrightarrow{\text{Zn-Cu (45 equiv)}} \text{OH} \\
\text{CHO} & \xrightarrow{\text{TiCl}_3 (15 \text{ equiv})} \xrightarrow{\text{Zn-Cu (45 equiv)}} \text{OH}
\end{align*}
\]

85\% yield, \(1.25\)  
\(\text{cis:trans} = 100:0\)

80\% yield, \(1.27\)  
\(\text{cis:trans} = 25:75\)

Scheme 1.2: Selectivity During Pinacol Coupling of Aldehydes

Concurrently, McMurry,\(^8\) Mukaiyama,\(^9\) and Tyrlik\(^10\) revealed that ketones and aldehydes can be reductively coupled when treated with TiCl\(_3\) to afford alkenes. Within 15 years of its discovery in 1973, three separate reviews and over a 100 publications involving titanium-mediated coupling of carbonyls were published. McMurry later exploited the coupling between ketones and esters using titanium \textit{en route} to synthesizing cyclic ketones. When keto-ester \(1.28\) was treated with stoichiometric low-valent titanium, cycloheptanone \(1.29\) was produced in 82\% yield through dimerized of the carbonyls followed by deoxygenation (eq 7).\(^11\)

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{TiCl}_3/\text{LiAIH}_4 (5 \text{ equiv})} \xrightarrow{\text{DME, rt}} \text{C} \\
\text{CHO} & \xrightarrow{\text{TiCl}_3/\text{LiAIH}_4 (5 \text{ equiv})} \xrightarrow{\text{DME, rt}} \text{C}
\end{align*}
\]

82\% yield
1.2.3 Barbier-Type Reactions

The addition of organometallic reagents to carbonyl derivatives, remains essential to the area of organic synthesis mainly due to it being one of the primary methods for constructing carbon-carbon bonds, including allylations to yield β-hydroxy carbonyl motifs.\textsuperscript{12-14} The first stoichiometric titanium-mediated ketone allylation was reported in 1987 by Eisch using \(\eta^3\)-allyl(dicyclopentadienyl)titanium(III) (1.31). Eisch discovered that when a solution of 1.31 in toluene was treated in a 1:1 stoichiometry with acetophenone 1.30, the homoallylic alcohol 1.32 was isolated in yields greater than 70\% (Scheme 1.3).\textsuperscript{15} Interestingly, a simple modification of solvent from toluene to THF resulted in trace quantities of the carbotitanination alcohol and >75\% yield of the pinacol-coupled dimmer 1.33.

\[ \text{Cp}_2\text{Ti(\eta^3-allyl)} \quad 1.31 \]

A milder approach to this method was developed by Roy and coworkers, whose allylation of aldehydes was accomplished by using 2 equivalents of the \textit{in situ} prepared \textit{Cp}_2\text{TiCl} reagent in THF.\textsuperscript{16} With titanium(III) acting as the radical initiator, excellent yields
of the resultant homoallylic alcohol derived from aryl, alkyl, and heteroaromatic aldehydes were achieved (eq 8).

\[
\begin{align*}
\text{1.34} & \xrightleftharpoons[\text{Cp}_2\text{TiCl} (2.2\text{ equiv}), \text{allyl bromide, THF, rt, 1.5 h}]{\text{Cp}_2\text{TiCl} (2.2\text{ equiv}), \text{allyl bromide, THF, rt, 1.5 h}} \text{1.35} \quad 94\%\text{ yield}
\end{align*}
\]

1.3 Catalytic Titanium Redox Reactions

1.3.1 Carbonyl Reductions

The reduction of carbonyls to the corresponding alcohols is of significant interest to synthetic organic chemists producing primary and secondary alcohols. While remaining environmentally friendly, a catalytic procedure to accomplish this chemical modification would be of great advancement. Together, Cuerva, Gansäuer, and Oltra developed a catalytic method invoking titanocene dichloride and zinc dust to reduce ketones to the subsequent alcohols through a radical pathway. An example of their mild method can be seen in the transformation of keto-ester 1.36 to benzylic alcohol 1.37 upon treatment of 10 mol% of Cp$_2$TiCl$_2$ and zinc dust in THF with addition of H$_2$O as a mild and safe proton source (eq 9).

\[
\begin{align*}
\text{1.36} & \xrightarrow[\text{Cp}_2\text{TiCl}_2 (10\text{ mol\%}), \text{Zn}^0 (8\text{ equiv}), \text{THF/H}_2\text{O (4:1), rt, 24 hr}]{\text{Cp}_2\text{TiCl}_2 (10\text{ mol\%}), \text{Zn}^0 (8\text{ equiv}), \text{THF/H}_2\text{O (4:1), rt, 24 hr}} \text{1.37} \\
& \quad >95\%\text{ yield}
\end{align*}
\]

Under these conditions, strong bases, molecular hydrogen, or toxic reagents such as 1,4-cyclohexadiene are avoided. They also observed chemoselectivity of ketones
over esters and alkenes, aromatic substrates over aliphatics, and reduction of cyclic substrates occurring faster than acyclic variants. One could also imagine instead of protonation of the radical intermediate, an ensuing development of C-C and C-O bonds could be prepared through a cascade-coupling route. In 2006, Oltra and coworkers looked at the coupling between α,β-unsaturated enals and aldehydes to synthesize γ-lactol type intermediates. They proposed that through the use of titanocene dichloride as both a single-electron transfer agent and substrate coordinator, stereoselectivity was achieved between the ligated aldehyde and the titanium-alkoxy allyl radical intermediate 1.41 (Scheme 1.4).

Scheme 1.4: SET-Mediated Reductive Cyclization

High yields of the γ-lactols utilizing Oltra’s procedure are obtained with catalytic Cp₂TiCl₂ while observing dr’s as high as 23:1. Over the next several years, multiple groups investigated the coupling between α,β-unsaturated carbonyls and other electrophilic radical acceptors to further explore the cascade of C-C bonds that could be prepared due to catalytic titanium. The Streuff research group undertook the linking of two separate unsaturated groups through a radical coupling to synthesize a 1,6-
difunctionalized carbon framework.\textsuperscript{19} When cyclohexanone 1.44 was subjected to 10 mol\% \(\text{Cp}_2\text{TiCl}_2\), 2 equivalents of \(\text{Zn}^0\), 1.3 equivalents of \(\text{Et}_3\text{N}-\text{HCl}\), TMS-Cl, and excess acrylonitrile 1.45 in THF after 4 h at 35 °C, the alkylated cyclohexanone derivative 1.46 was isolated in 87\% yield (eq 10). Selectivity of the alkylation favored the \(\beta\)-carbon, unless alkylation at the \(\beta\)-carbon formed a second vicinal of a quaternary center, in those cases the highly substituted alkene remained unchanged and tertiary alcohol resulting from 1,2-addition was isolated in moderate to good yields (eq 11).

\[
\text{Cp}_2\text{TiCl}_2 \ (10 \text{ mol\%}), \text{Zn dust (2 equiv)} \text{TMSCl, Et}_3\text{N-HCl}
\]

![Chemical structure](image)

\[
\text{87\% yield}
\]

More recently, Streuff applied a similar approach to synthesize \(\alpha\)-hydroxy ketones in an asymmetric fashion by means of a chiral titanocene catalyst.\textsuperscript{20} Beneficially, the commercially available Brintzingers’ titanocene catalyst 1.50 provided the highest yields and \(ee\)'s when various ketonitriles were treated with 10 mol\% catalyst in the presence of zinc dust, amine hydrochloride, and trimethylsilyl chloride in THF. An array of 5- and 6-membered cyclic analogs were synthesized using this method including benzofused \(\alpha\)-hydroxy ketone 1.51 in 55\% yield with 88\% \(ee\) after a TBAF or acidic workup (eq 12).
The \(\alpha\)-hydroxy ketone motif, especially those bearing an \(\alpha\)-tertiary alcohol, is present in a wide array of biologically active natural products. For example, Sieboldine A 1.52, which has shown low micromolar activity towards acetylcholinesterase (Figure 1.2).\(^{21}\)

![Chemical structure of 1.52](image)

**Figure 1.2:** (+)-Sieboldine A

### 1.3.2 Reformatsky Reactions

Highly reactive organometallic intermediates, especially organozinc reagents, and their assembly are of upmost importance in the creation of complex synthetic intermediates towards biologically active molecules of interest. One approach to generating these reactive intermediates is through the Reformatsky reaction, wherein the zinc enolate derived from an \(\alpha\)-halo carbonyl precursor are added to various carbonyls. Early reports from Shimizu\(^{22}\) and Little\(^{23}\) independently discovered that stoichiometric titanium sources in the form of Ti\(_4\) or Cp\(_2\)TiCl could promote a Reformatsky-type addition of \(\alpha\)-halo ketones or esters to aldehydes. Shortly thereafter,
a series of catalytic advances involving a titanium mediated Reformatsky reactions were published by Cozzi, Robles and Oltra, and Ding. Cozzi’s system made use of Cp₂TiCl₂ in catalytic fashion (10 mol%), manganese as the stoichiometric reductant (3.0 equivalents), and the use of trifluoromethyl acetic anhydride (TFAA) as a scavenger. The utility of TFAA has been highlighted previously by Furstner in his development of a catalytic McMurry coupling of assorted carbonyls towards synthesizing indole derivatives. An array of electron-rich and electron-deficient aryl aldehydes as well as aliphatic aldehydes were subjected to their Reformatsky-type reaction including hexanal 1.53 which produced the respected β-hydroxy ester 1.55 in 48% yield (eq 13). Despite attempts to induce enantioselectivity through the use of chiral titanium ligands, the hydroxy esters were rendered racemic in 42-70% yield.

Robles and Oltra used a similar approach toward their titanocene-promoted Reformatsky coupling of α-halo ketones and aldehydes by also using Mn(0) as the stoichiometric reductant but instead invoking a mixture of Me₃SiCl/collidine as their titanocene-regenerating agent. Their broad scope of substrates including both alkyl and aromatic aldehydes, which both produced β-hydroxy ketones in moderate to excellent yields, as demonstrated by the reaction involving chloroacetone 1.57 and monoterpinoid citronellal 1.56 (eq 14).
Ding and coworkers investigated catalytic \( \text{Cp}_2\text{TiCl}_2 \) and zinc dust in the reaction between imines and \( \alpha \)-bromoalkanoates toward synthesizing \( \beta \)-lactam derivatives. Through a series of experiments, they proposed that the corresponding titanocene-catalyzed Reformatsky reaction with \( \text{Zn}^0 \) proceeds through a zinc enolate in the C–C bond-forming event.\(^{27}\) Following addition of various organozinc species to imines, intramolecular cyclization of the \( \beta \)-amino functional group upon the ester proceeds rapidly to yield lactams in good yields with selectivity favoring the \( \text{cis} \)-substituted variants (eq 15).\(^{28}\)

Ding also showed that 4-bromoacrolates participate in the titanium-catalyzed Reformatsky reaction, with alkyl imines producing \( \gamma \)-addition while aromatic imines rendered the \( \alpha \)-addition product. This result likely inspired several prominent research groups, including our own, to investigate the utility of low-valent titanium catalysts participating in Barbier-type reactions with carbonyl sources.
1.3.3 Barbier-Type Reactions

The ability of \( \text{Cp}_2\text{TiCl}_2 \) to mediate Barbier-type carbonyl addition reactions was further developed by Cuerva and Oltra in collaboration with Gansäuer. They observed when both aldehydes and ketones were treated with 20 mol% of pre-catalyst \( \text{Cp}_2\text{TiCl}_2 \), Mn dust, \( \text{Me}_3\text{SiCl} \), 2,4,6-collidine, and excess allyl bromide \( \text{1.62} \) that the corresponding homoallylic alcohol was isolated in high yields.\(^{29} \) When acetophenone \( \text{1.30} \) was subjected to their catalytic titanocene allylation conditions, tertiary alcohol \( \text{1.32} \) was created in 86% yield after 16 h at room temperature (eq 16). Under similar conditions, they also showed preliminary results regarding propargylation of ketones and aldehydes, as seen by 2-decanal \( \text{1.63} \) which produced the expected acetylenic secondary alcohol \( \text{1.65} \) in 80% yield (eq 17).

\[
\text{PhCO} + \text{CH}_2=CHCH=CH_2 \xrightarrow{\text{Cp}_2\text{TiCl}_2 (\text{cat.}), \text{Mn}^0} \text{PhCOCHCH=CH}_2 \quad \text{(16)}
\]

\[
\text{PhCHO} + \text{CH}_3\text{C}=\text{C}CH=\text{C}H = \text{CH}_2 \xrightarrow{\text{Cp}_2\text{TiCl}_2 (\text{cat.}), \text{Mn}^0} \text{PhCOC}H\text{C}H\text{C}H\text{C}H=\text{C}H \quad \text{(17)}
\]

Recently a detailed mechanistic study was undertaken by Rosalas and Oltra to determine how an unexpected difference in reactivity between carbonyls can produce two separate products from the titanium-promoted Barbier-type reaction of propargylic halides; \( \alpha \)-hydroxy-allenes or homopropargylic alcohols.\(^{30} \) Additionally, the first asymmetric-titanocene catalyzed Barbier-allylation was also developed. Unfortunately,
low enantioselectivities were observed when chiral Brintzinger catalyst 1.50 was employed with 3,4,5-trimethoxybenzaldehyde 1.66 and allyl bromide 1.62 (eq 18).

\[
\begin{array}{c}
\text{MeO} \quad \text{CH}=\text{O} \\
\text{MeO} \\
\ddots \\
\text{MeO}
\end{array} + \begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\ddots \\
\text{MeO}
\end{array}
\xrightarrow{\text{chiral Ti 1.50 (cat.), Mn}^0 \text{ TMSCl, Collidine, THF, rt}}
\begin{array}{c}
\text{MeO} \quad \text{OH} \\
\text{MeO} \\
\ddots \\
\text{MeO}
\end{array}
\]

(18) 50% yield, 33% ee

Although initial attempts to develop an asymmetric allylation protocol using chiral titanium 1.50 weren’t optimal, the potential for high ee’s using more effective chiral titanocene complexes remains promising. Investigations into the effects involving a higher substituted allyl bromide subunit were examined by treating similar aldehydes and ketones with prenyl bromide 1.68 instead.\(^{31}\) Although prenyl-Ti (IV) complexes have been shown to give \(\gamma\)-allylation,\(^ {32}\) under the titanium-catalyzed Barbier reaction the \(\alpha\)-addition could be isolated in 39% yield when citronellal 1.56 was subjected to the slightly modified prenylation procedure (eq 19). Interestingly, prenylation of \(\alpha,\beta\)-unsaturated or aryl aldehydes gave solely the \(\alpha\)-allylation homoallylic alcohol in excellent yields, supporting the idea of formation of a prenyl radical due to a single electron transfer from \(\text{Cp}_2\text{TiCl}\).\(^ {33}\)

\[
\begin{array}{c}
\text{CH} \quad \text{CHO} \\
\ddots \\
\text{CHO}
\end{array} + \begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\ddots \\
\text{MeO}
\end{array}
\xrightarrow{\text{Cp}_2\text{TiCl}_2 \text{(cat.) Mn dust} \text{ 2,4,6-collidine, Me}_3\text{SiCl} \text{ THF, rt}}
\begin{array}{c}
\text{MeO} \quad \text{OH} \\
\text{MeO} \\
\ddots \\
\text{MeO}
\end{array}
\begin{array}{c}
\text{MeO} \quad \text{OH} \\
\text{MeO} \\
\ddots \\
\text{MeO}
\end{array}
\]

(19) 39% yield 7:3 dr 58% yield 1:1 dr

Some extraordinary work by Fleury et al. utilizes catalytic sources of \(\text{Cp}_2\text{TiCl}_2\) in conjunction with zinc dust to activate alkyl halides to their respective organozinc
intermediate which is readily added to various carbonyl derivatives.\textsuperscript{34} The facile allylation mediated by titanium was also shown to be effective in the presence of magnesium turnings as the stoichiometric reductant metal, which in turn produced Grignard reagents instead.\textsuperscript{35} The in situ formation of these highly reactive intermediates allows various functional groups including esters and alcohols to remain unaffected during the C-C bond forming allylation event.

1.4 Conclusion

Of the selected examples highlighted in this chapter involving Cp\textsubscript{2}TiCl-catalyzed and promote chemical transformations, several methods have been used in the construction of complex molecules including natural products. Several attractive aspects of low-valent titanium-mediated reactions include their mild experimental conditions and observed chemoselectivity. The usefulness, and potential associated with Cp\textsubscript{2}TiCl-mediated reactions guarantees that titanocene(III)-based reactions will be an essential method in the toolbox of the synthetic chemist for generations to come.
CHAPTER 2:

SINGLE ELECTRON TRANSFER REDOX CHEMISTRY OF TITANIUM

2.1 Transition Metal Conjugate Reduction of $\alpha,\beta$-Unsaturated Carbonyls

2.1.1 Introduction

When performing functional group transformations in organic synthesis, selectivity remains one of the topics at the forefront of consideration. An example of this selectivity is when reducing an $\alpha,\beta$-unsaturated carbonyl compound where two possibilities exist; a 1,2- or 1,4-reduction. In recent years, a number of significant advances including the use of transition metal catalysis, were made toward the development of efficient, economical, and enantioselective protocols for achieving this transformation. As a result, various catalysts proved to facilitate the conjugate reduction of $\alpha,\beta$-unsaturated carbonyls, including palladium, rhodium, magnesium, and copper hydride complexes. Of the effective alkali and lanthanide metal-based reagents, chemoselectivity is often an issue.

Since its conception in 1997, the Green Chemistry Institute has been promoting “green chemistry” through its twelve principles that include catalysis, energy efficiency, and atom economy. Through the use of transition metals in a catalytic fashion, potentially several of these framework ideals can be addressed. Among the various
methods in which conjugate reduction of carbonyl derivatives takes place, a single
electron transfer-type process invoking catalytic loadings of a redox transition metal has
yet to be accomplished.\textsuperscript{2} The expansion of such a method would enable the controlled
Barbier-type reduction of $\alpha,\beta$-unsaturated carbonyl derivatives \textit{en route} to be
implemented in the context of cascade bond forming reactions potentially including
reductive alkylation, aldol, or cyclization reactions.

2.1.2 Titanocene-Catalyzed Conjugate Reductions

In efforts to find an efficient, transition metal complex that could catalyze the
conjugate reduction of $\alpha,\beta$-unsaturated carbonyl derivatives, we were inspired by
titanocene derivatives due to their propensity to undergo redox SET processes. Based
mainly on the elegant work by Gansäuer and coworkers, we speculated that a conjugate
reduction could be achieved through a metal-ketyl intermediate, where catalytic
turnover is facilitated by the addition of a proton source and a mild reducing metal, such
as zinc or manganese.\textsuperscript{29,31,48-51} When subjecting enone \textbf{2.1a} to 5 mol\% of Cp$_2$TiCl$_2$, zinc
dust, and Et$_3$N-HCl, we were delighted to see the 1,4-reduction product \textbf{2.2a} in 57%
yield (eq 20).\textsuperscript{52} The observation that we were able to achieve 10-fold catalyst turnover
yields potential for the use of Cp$_2$TiCl$_2$ as an efficient, transition metal complex for
conjugate reduction of $\alpha,\beta$-unsaturated carbonyls. It is important to note that in the
absence of Cp$_2$TiCl$_2$, none of the desired saturated ketone was observed.
After evaluating various catalytic sources of titanium, including TiCl₄, we identified Cp₂TiCl₂ as optimal due to the substantially higher yields, ease of handling, and reproducibility.²,⁵³,⁵⁴ Efforts to reduce the catalyst loading led to an increase in reaction time, lower yield, and increase in pinacol coupling by-products. These results are consistent with a finite lifetime of the proposed in situ generated active catalyst Cp₂TiCl. Through our examination of various solvents, it was discovered that solvent selection was crucial to the catalytic conjugate reduction. Other than DCM, THF also provided the reduced product, but with less reliable results. A screen of proton sources revealed that Et₃N·HCl provided the best overall results in relation to alcohols and organic acids. Employing manganese in place of zinc also resulted in longer reaction times.

Having established our optimal reagents, we turned our attention toward determining the amount of zinc dust and Et₃N·HCl needed to achieve an efficient reduction of enone 2.1a (Table 2.1, entry 1). Decreasing the amount of zinc dust to 1.1 equiv resulted in a dramatic decrease in the yield of ketone 2.2a to 33% (entry 2). Most notably was the inefficiency of the reduction, leading to an increase in side reactions rendering a 37% yield based on recovered enone 2.1a. The use of 2.5 equivalents of zinc dust and 5 equivalents of Et₃N·HCl, resulted in a 60% yield of 2.2a (entry 3).
TABLE 2.1

OPTIMIZATION STUDIES IN THE REDUCTION OF ENONE 2.1A

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. of Zn dust</th>
<th>Equiv. of Et&lt;sub&gt;3&lt;/sub&gt;N·HCl</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>5</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>5</td>
<td>33 (37)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>3.2</td>
<td>27 (42)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conditions: enone (1 mmol), Cp<sub>2</sub>TiCl<sub>2</sub> (5 mol%), Zn<sup>0</sup>, and Et<sub>3</sub>N·HCl in DCM (0.05 M) at rt for 6 h. <sup>b</sup>Isolated yields. Yields based on recovered starting material.

Efforts to reduce the amount of Et<sub>3</sub>N·HCl from 5 equivalents to 2.1 equivalents resulted in a meager 27% yield of 2.2a (entry 4). For those experiments that resulted in low isolated yields of ketone 2.2a, the major by-product observed occurred from a pinacol coupling process.<sup>55,56</sup> Having minimized the homo-radical coupling by-products to provide 60% of 2.2a, we moved forward with these optimized conditions of 5 mol% Cp<sub>2</sub>TiCl<sub>2</sub>, 2.5 equivalents of Zn<sup>0</sup>, and 5 equivalents of Et<sub>3</sub>N·HCl in DCM.

2.1.2.1 Reduction of Ketones

With optimized conditions in hand, we turned our attention toward evaluating the scope of the titanium-catalyzed conjugate reduction on a series of α,β-unsaturated ketones. In general, the 1,4-reduction products 2.2 were obtained in good to excellent yields. β-aryl enones (Table 2.2, entries 1-4) all gave the corresponding saturated ketones in excellent yield despite whether the aryl ring was electron neutral (entry 1) or
electron deficient (entries 2-4). \( \beta \)-alkyl enones (entries 5-7) provided the corresponding ketones in good to excellent yields. Additionally, acyclic (entries 1-5) and cyclic (entries 6 and 7) enones performed equally well in the reduction sequence. Interestingly, when the conjugate reduction of \( \beta \)-alkyl substituted enones was performed under the optimized conditions involving \( \text{CH}_2\text{Cl}_2 \) and \( \text{Et}_3\text{N-HCl} \), only decomposition of the starting enone was observed. However, by exchanging the solvent from \( \text{CH}_2\text{Cl}_2 \) to THF, and the proton source to collidine\-HCl, an excellent yield of the desired saturated ketones was obtained (entries 5-7). Despite the proposed formation of an allylic radical prior to trapping an additional \( \text{Cp}_2\text{TiCl} \), cyclopropyl enone \( 2.1f \) underwent conjugate reduction in 57\% yield (entry 5). Failure to observe any of the corresponding ring opened by-product resulting from a strain-driven ring expansion of a cyclopropane system indicated a rapid sequestration of the allylic radical by another SET. An alternative reduction pathway of \( 2.1f \) involves ring opening of the cyclopropyl ring follow by a rapid ring closure before reacting with another \( \text{Cp}_2\text{TiCl} \). Attempts to reduce \( \alpha,\beta \)-unsaturated substrates with electron rich aromatic rings at the \( \beta \)-position failed to produce any saturated ketones, resulting in quantitative recovery of the enone.
<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th><strong>Substrate</strong></th>
<th><strong>Product</strong></th>
<th><strong>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</strong></th>
</tr>
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<td><img src="image" alt="2.1b" /></td>
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<td>96</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="2.1c" /></td>
<td><img src="image" alt="2.2c" /></td>
<td>99</td>
</tr>
<tr>
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<td><img src="image" alt="2.1d" /></td>
<td><img src="image" alt="2.2d" /></td>
<td>91 (98)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="2.1e" /></td>
<td><img src="image" alt="2.2e" /></td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="2.1f" /></td>
<td><img src="image" alt="2.2f" /></td>
<td>57&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="2.1g" /></td>
<td><img src="image" alt="2.2g" /></td>
<td>95&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>1.44</td>
<td><img src="image" alt="2.2h" /></td>
<td>90&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conditions: enone (1 mmol), Cp₂TiCl₂ (5 mol%), Zn dust (2.5 mmol) and Et₃N·HCl (5 mmol) in CH₂Cl₂ (0.05 M) for 6 h at rt.  
<sup>b</sup>Yields calculated by 400 MHz <sup>1</sup>H NMR to an internal standard (naphthalene).  
<sup>c</sup>Yields in parentheses based on recovered starting material.  
<sup>d</sup>THF and collidine-HCl was used in place of CH₂Cl₂ and Et₃N·HCl.
2.1.2.2 Reduction of Aldehydes

Upon observing a variety of results involving the conjugate reduction of ketones, we next investigated the scope of more electrophilic \( \alpha,\beta \)-unsaturated aldehydes. We were pleased to see that when cinnamaldehyde \( 2.1i \) was subjected to our optimized conditions hydrocinnamaldehyde \( 2.2i \) was produced in 78\% yield (table 2.3, entry 1).

**TABLE 2.3**

<table>
<thead>
<tr>
<th>Entry(^a)</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[\text{2.1i} ]</td>
<td>[\text{2.2i} ]</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>[\text{2.1j} ]</td>
<td>[\text{2.2j} ]</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>[\text{2.1k} ]</td>
<td>[\text{2.2k} ]</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>[\text{2.1l} ]</td>
<td>[\text{2.2l} ]</td>
<td>41</td>
</tr>
</tbody>
</table>

\(^a\)Conditions: enal (1 mmol), \( \text{Cp}_2\text{TiCl}_2 \) (5 mol\%), Zn dust (2.5 mmol) and \( \text{Et}_3\text{N-HCl} \) (5 mmol) in \( \text{CH}_2\text{Cl}_2 \) (0.05 M) for 12 h at rt. \(^b\)Yields calculated by 400 MHz \( ^1\text{H} \) NMR to an internal standard (naphthalene).

\( \beta \)-Aryl enals with an electron withdrawing substituent (entries 2-4) all gave the corresponding saturated aldehyde in moderate to good yield. As compared to the
enones, saturated aldehydes were produced in slightly lower yields, most likely due to
the propensity of aldehydes to oxidize easily and dimerize faster. Interestingly enal 2.1k
that contains a para-substituted formyl group on the β-aryl ring, reduced to the
aldehyde 2.2k in 75% yield without the formation of any side-products involving pinacol
coupling of the benzaldehyde (entry 4). Attempts to subject alkyl enals to conjugate
reduction conditions led to a mixture of unidentifiable by-products.

2.1.2.3 Reduction of Enoates, Enamides, and Ynones.

To further establish the efficacy of this catalytic transition metal-catalyzed
conjugate reduction, we subjected enoates, enamides, and ynones to our optimized
conditions. Aromatic enoates (table 2.4, entries 1-2) were reduced to the analogous
saturated esters in good yields. In spite of enoates sluggish reactivity, yields based on
recovers starting material were near quantitative (entry 2). Based on reactivity,
unsubstituted enamides are also applicable to the 1,4-conjugate reduction conditions,
although in slightly lower yield than enoates (entry 3). To further expand the utility of
this method, we modified the α,β-unsaturated carbonyl to include an alkyne instead of
an alkene. Ynones (2.1p and 2.1q) proved to be viable substrates by providing the
(corresponding fully saturated carbonyl compounds in good yields (entries 4-5) using 10
mol% Cp₂TiCl₂, zinc dust, and Et₃N·HCl in CH₂Cl₂. Interestingly no enones resulting from a
partial 1,4-conjugate reduction were isolated during the reactions of ynones.
TABLE 2.4
TITANIUM-CATALYZED CONJUGATE REDUCTION OF ESTERS, AMIDES, AND YNONES

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Structural Formula" /></td>
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</tr>
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<td>2</td>
<td><img src="image" alt="Structural Formula" /></td>
<td><img src="image" alt="Structural Formula" /></td>
<td>56 (&gt;99)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Structural Formula" /></td>
<td><img src="image" alt="Structural Formula" /></td>
<td>35 (76)&lt;sup&gt;c&lt;/sup&gt;</td>
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<td><img src="image" alt="Structural Formula" /></td>
<td><img src="image" alt="Structural Formula" /></td>
<td>55&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Structural Formula" /></td>
<td><img src="image" alt="Structural Formula" /></td>
<td>40&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conditions: carbonyl (1 mmol), Cp₂TiCl₂ (5 mol%), Zn dust (2.5 mmol) and Et₃N·HCl (5 mmol) in CH₂Cl₂ (0.05 M) for 16 h at rt. <sup>b</sup>Yields calculated by 400 MHz ¹H NMR to an internal standard (naphthalene). <sup>c</sup>Yields in parentheses based on recovered starting material. <sup>d</sup>Cp₂TiCl₂ (10 mol%), Zn dust (5 equiv.), and Et₃N·HCl (10 equiv.).

2.1.2.4 Chemoselectivity

To evaluate the chemoselectivity of the catalytic conjugate reduction protocol, a series of competition studies were performed between α,β-unsaturated carbonyls of varying electronics (Table 2.5). Treatment of a 1:1 mixture of enone 2.1a and enoate 2.1r to catalytic Cp₂TiCl₂ in the presence of zinc dust and Et₃N·HCl provided a 53% yield...
of the 1,4-reduced enone $2.2a$ and 95% yield of recovered unreacted enoate $2.1r$ (entry 1). Likewise, subjection of enal $1.34$ and enoate $2.1r$ to identical conditions resulted in the selective 1,4-reduction of $1.34$ to afford saturated aldehyde $2.2i$ in 76% yield and again recovered enoate $2.1r$ in near quantitative yield (entry 2). We also demonstrated that 1,4-reduction of $\alpha,\beta$-unsaturated aldehyde $1.34$ (73% yield) is achieved selectively in the presence of enone $2.1a$ by a slight modification of 2.5 equivalents of zinc dust to 1.5 equivalents and 5.0 equivalents of Et$_3$N-HCl to 3.0 equivalents (entry 3). Finally, a chemoselective reduction of electron deficient enone $2.1e$ in the presence of electron rich enone $2.1s$ provided 78% yield of $2.2e$ and 87% of $2.1s$. Attempts to reduce acyclic enone $2.1a$ in the presence of cyclic enone $2.1h$ failed leading primarily to decomposition of both starting materials and pinacol coupling by-products.
### Table 2.5
CHEMOSELECTIVITY IN THE CONJUGATE REDUCTION

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Substrate I</th>
<th>Substrate II</th>
<th>Product Yield (%)</th>
<th>Yield of II (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate I" /></td>
<td><img src="image2" alt="Substrate II" /></td>
<td>53 (2.2a)</td>
<td>95 (2.1r)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate I" /></td>
<td><img src="image4" alt="Substrate II" /></td>
<td>76 (2.2i)</td>
<td>95 (2.1r)</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td><img src="image5" alt="Substrate I" /></td>
<td><img src="image6" alt="Substrate II" /></td>
<td>73 (2.2i)</td>
<td>91 (2.1a)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate I" /></td>
<td><img src="image8" alt="Substrate II" /></td>
<td>78 (2.2e)</td>
<td>87 (2.1s)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conditions: Substrate I (1 mmol), Substrate II (1 mmol), Cp₂TiCl₂ (5 mol%), Zn dust (2.5 mmol) and Et₃N·HCl (5 mmol) in CH₂Cl₂ (0.05 M) for 10 h at rt.  
<sup>b</sup>Zn dust (1.5 equiv.) and Et₃N·HCl (3 equiv.).

2.1.2.5 Diastereoselectivity

We next sought to examine the diastereoselectivity observed in the conjugate reduction of a chiral α,β-unsaturated ketone. We identified enone 2.1t as ideally suited under our optimized set of conditions to examine the stereochemical outcome of the resulting protonation event. However, when enone 2.1t was subjected to the titanium-catalyzed conjugate reduction conditions, a meager 1.3:1 ratio of diastereomers was formed in which the all equatorial substituted ketone 2.2t was slightly favored (eq 21).
Efforts to improve selectivity at lower temperatures (0 °C) provided a similar diastereomeric ratio of cis:trans isomers with a diminished overall yield. Attempts to examine the stereoselectivity at the β-carbon of α,β-unsaturated carbonyl substrates by the reduction, 3,5-dimethyl-2-cyclohexen-1-one (2.1u) was subjected to the reaction conditions. Unfortunately, reduction of the corresponding trisubstituted olefin proved unsuccessful leading to an inseparable complex mixture of by-products.

![Chemicalreaction](attachment:image.png)

(21)

\[ \text{Ph}^\text{Me} \underset{\text{Cp}_2\text{TiCl}_2 (5 \text{ mol\%})}{\text{Zn, Et}_3\text{N}+\text{HCl (5 equiv.), CH}_2\text{Cl}_2} \text{Me} \]

2.1t

59% yield (71% brsm)

cis/trans = 1.3:1

2.1.3 Summary

Based on work by Gansäuer and others utilizing titanocene in various single electron transfer redox processes, a possible catalytic cycle for the titanocene-catalyzed conjugate reduction involves initial reduction of the precatalyst Cp₂TiCl₂ to generate the active reducing species Cp₂TiCl by zinc dust (Scheme 2.1). Two successive single electron transfers to unsaturated carbonyl 2.1h provides the bis-titanium(IV)-bound intermediate 2.3. Protonation of the titanium alkoxide and allyl motifs by an amine hydrochloride produces the saturated ketone 2.2h and the initial precatalyst Cp₂TiCl₂. A second reduction of Cp₂TiCl₂ with zinc dust regenerates the active titanium (III) catalyst to complete the catalytic cycle.
Scheme 2.1: Proposed Catalytic Cycle.

In conclusion, we have demonstrated the ease with which an inexpensive titanocene catalyst, Cp₂Ti⁴Cl₂, can be used as an efficient catalyst for the conjugate reduction of α,β-unsaturated carbonyl derivatives. A series of α,β-unsaturated ketones, aldehydes, esters, unsubstituted amides, and yrones underwent chemoselective conjugate reduction by utilizing a catalytic quantity of titanocene with a stoichiometric amount of zinc dust. Several generalizations can be made through the development of this catalytic titanium conjugate reduction method *en route* to saturated carbonyl compounds. First, the efficiency of the reduction was highly dependent upon the catalyst loading and type of titanium catalyst. It should also be noted that reactions performed with greater than 10 mol% titanocene, or at concentrations greater than 1 M, had detrimental effects on the yield while increasing the amount of pinacol coupling products. Also, α,β-unsaturated substrates with β-aryl rings substituted with electron
withdrawing groups provided the reduced products in excellent yields, whereas those containing electron-donating substituents failed to undergo reduction.

Although electron-rich systems were poorer substrates under the optimized conditions, the catalytic reduction process has two potential areas for exploration in the future. The first inquiry would involve installing chiral ligands on various titanium complexes to explore whether an asymmetric protocol could be established. Investigations directed toward the development of a catalytic asymmetric reduction of α,β-unsaturated carbonyl derivatives would further enhance the use of titanium mediated redox catalysts by means to synthesizing complex intermediates or natural products. Another area of exploitation, which would aid in synthesizing molecules of increasing complexity, is the titanium-bound intermediates for use in cascade carbon-carbon or carbon-heteroatom bond-forming reactions.

2.2 Transition Metal C-X Activation and Addition to Carbonyls

2.2.1 Introduction

Organometallic intermediates, especially organozinc and organomagnesium, are essential reagents towards the construction and assembly of biologically active natural products and derivatives thereof. Although known for their aptitude in generating various carbon-carbon and carbon-heteroatom bonds, Grignard and organozinc compounds have also established their importance in transition metal catalyzed cross-couplings reactions. Thus, creation of new and improved methods in which these synthetically versatile compounds are produced is vital component toward synthetic
efforts of structurally complex frameworks. Although the most direct way to generate these organometallic reagents is oxidative insertion of Zn\(^0\) or Mg\(^0\) into C–X bonds,\(^{64-66}\) this method has several drawbacks including the exothermic process involved with magnesium turnings and lack of compatibility when utilizing zinc dust due to its lower reduction potential.\(^{67-69}\) Therefore, recent methods have focused their attention on a mild activation procedure towards the generation of these highly desired intermediates. One significant advance is Knochel’s use of LiCl to accelerate oxidative insertion into C–X bond likely due its operational simplicity and ready availability of LiCl.\(^{70}\) Other complexes including Cu\(^{1}\),\(^{71}\) Pd\(^{II}\),\(^{72}\) Ni\(^{II}\),\(^{73}\) Mn\(^{II}\),\(^{74}\) In\(^{III}\),\(^{75}\) Fe\(^{III}\),\(^{76}\) Al\(^{III}\),\(^{77}\) and Co\(^{II}\)\(^{78}\) have shown the ability to facilitate organozinc formation, while the formation of Grignard reagents derived from 2-chloropyridines employ the use of FeCl\(_2\), MgBr\(_2\) and ethylbromide.\(^{79}\) Ideally, a universal method for the formation of both organozinc and organomagnesium reagents under mild reaction conditions would constitute a significant advance. We hypothesized that commercially available Cp\(_2\)TiCl\(_2\) could activate various alkyl halides via a single electron transfer process, which would be followed by a transmetallation event to generate the appropriate organozinc or organomagnesium reagent.\(^{23,27,34,35,80,81}\)

2.2.2 Discovery and Optimization of Titanocene Catalyzed Allylation of Carbonyls

Cascade reactions, in which high atom economy is obtained through rapid construction of several components *en route* to complex intermediates, has become an increasingly important tool to the synthetic community.\(^{82}\) Albert Einstein once said “The significant problems we face today cannot be solved at the same level of thinking we
were at when we created them.” As chemists continue to improve and discover new methods in which C-C and C-X bonds are created in a complex molecular framework, a balance between utility and “greenness” has to be considered. Waste generation, toxicity of reagents, benign solvent choice, purification steps/technique, and use of a catalyst instead of stoichiometric reagents are fundamental concepts to be evaluated when solving future problems.\(^{83}\) Having discovered a catalytic, single electron transfer process for the conjugate reduction of \(\alpha,\beta\)-unsaturated carbonyls,\(^{52}\) we were interested in exploiting a highly-reactive intermediate along the reduction pathway. Captivatingly, the proposed bis-titanocene-bound enolate intermediate could be utilized in a cascade alkylation via a single or double electron pathway with the desired electrophile. Initial screenings of various electrophilic components (e.g. MeI, acrolein, BnBr, PhCN) resulted in only saturated ketone 2.2a and recovered starting material. Conversely, when enone 2.1a was treated with 10 mol% of \(\text{Cp}_2\text{TiCl}_2\), zinc dust (2.5 equiv), and excess allylbromide (1.62, 5 equiv) in THF, homoallylic alcohol 2.4 was isolated in quantitative amounts with no observed \(\beta\)-alkylation (eq 22).

\[
\begin{align*}
\text{Ph} & \text{CH} & \rightarrow & \text{HO} & \text{Ph} \\
2.1a & \xrightarrow{\text{Cp}_2\text{TiCl}_2 (10 \text{ mol%}), \text{zinc dust (2.5 equiv)}} & \text{allylbromide 1.62 (6 equiv), -60 \rightarrow rt \rightarrow 55^\circ C} & 2.4 & 99\% \text{ yield} \\
& & & \left[ \begin{array}{c} \text{Ph} \\
\text{CH} \\
\text{O} \\
\text{Ph} \\
\end{array} \right] & 2.5 & \text{not observed}
\end{align*}
\]

Subsequent work in the group by Lauren Fleury led us to hypothesize that \(\text{Cp}_2\text{TiCl}_2\) activated the C-X bond for Zn insertion to generate a highly reactive allylzinc species.\(^{34}\) Additional studies conducted by Fleury found that the titanium loading could be reduced to 1 mol% and the amount of Zn(0) to 1.2 equivalents. The substrate scope
proved to be inclusive of various carbonyls including aldehydes, ketones, and esters (Table 2.6).\textsuperscript{34} Aromatic and alkyl aldehydes produced homoallylic alcohols in good to excellent yields after only 5 minutes (entries 1-5). Interestingly, when cinnamaldehyde \textbf{1.34} was subjected to the optimized allylation conditions, the alcohol \textbf{1.35} resulting from 1,2-addition was observed (entry 4). Ketones also provided the more substituted homoallylic alcohols in admirable yields regardless of the carbonyl bearing electronic rich or electron poor substituents (entries 6-8). Its worth mentioning that even enones containing an unprotected phenol still underwent rapid allylation to provide \textbf{2.9e} in 97% yield (entry 7). Even the allylation of esters was accomplished in the presence of Cp\textsubscript{2}TiCl\textsubscript{2} (1 mol\%) and zinc dust to produce bis-homoallylic alcohol \textbf{2.9f} in good yield (entry 9).
### TABLE 2.6

**ALLYLATIONS OF ALDEHYDES, KETONES, AND ESTERS**

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-CF₃-C₆H₄ (2.8a)</td>
<td>H</td>
<td><img src="image" alt="2.9a" /></td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>4-CO₂Me-C₆H₄ (2.8b)</td>
<td>H</td>
<td><img src="image" alt="2.9b" /></td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>4-MeO-C₆H₄ (2.8c)</td>
<td>H</td>
<td><img src="image" alt="2.9c" /></td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>C₆H₅CH=CH (1.34)</td>
<td>H</td>
<td><img src="image" alt="1.35" /></td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>c-hexyl (2.8d)</td>
<td>H</td>
<td><img src="image" alt="2.9d" /></td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>4-CF₃-C₆H₄·CH=CH (2.1e)</td>
<td>Me</td>
<td><img src="image" alt="2.9e" /></td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>2-OH-3-OMe-C₆H₃·CH=CH (2.8e)</td>
<td>Me</td>
<td><img src="image" alt="2.9e" /></td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>c-C₃H₅CH=CH (2.1f)</td>
<td>Me</td>
<td><img src="image" alt="2.11" /></td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>4-OMe-C₆H₄·CH=CH (2.8f)</td>
<td>OEt</td>
<td><img src="image" alt="2.9f" /></td>
<td>87&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Fleury’s Conditions:<sup>34</sup> carbonyl (1.0 mmol), Cp₂TiCl₂ (1 mol%), zinc dust (1.2 mmol) and allylbromide (1.2 mmol) in THF (0.1 M) for 5-20 min at rt. <sup>b</sup>Isolated yields. <sup>c</sup>Reaction time of 3 h.
2.2.2.1 Mechanistic Investigations

Driven by the fundamental importance of alkylation chemistry to the field of synthetic organic chemistry, we sought to gain insight into the mechanism and ultimate efficiency of allylzinc formation (Table 2.7).\textsuperscript{34} Initially, Fleury investigated the temperature affect on the formation and reactivity of the allylzinc species. Similar to previously reported results, alkylation of aldehyde 2.8g proceeds swiftly to generate alcohol 2.9g at room temperature. Although alcohol 2.9g can be obtained in excellent yields at temperatures as low as -20 °C, attempts to perform alkylation in the absence of titanium for an extended period of time (> 48 h) failed to produce any homoallylic alcohol 2.9g. Even though allylzinc reagents are known to react with carbonyls at -78 °C, Fleury observed no titanocene-catalyzed metatllation at -40 °C.\textsuperscript{34} Even at -78 °C, addition of 1 equivalent of PCy\textsubscript{3} phosphine to help accelerate C-X activation only provided trace amounts of homoallylic alcohol 2.9g. It wasn’t until at -40 °C that catalytic phosphine (5 mol%) accelerated the rate of allylbromide metatllation to create homoallylic alcohols (entries 7-9). Regardless of the ligands on phosphorus (trialkyl, triaryl, or bisphosphine) and their vast difference in cone angle, improved metatllation was observed when used in catalytic amounts. Predictably, Fleury also observed a distinct difference in the effect of a phosphine additive when the basicity was investigated.\textsuperscript{34} Her head-to-head comparison between Ph\textsubscript{3}P and nBu\textsubscript{3}P at various additive loadings highlighted nBu\textsubscript{3}P’s inability to assist in metatllation at lower temperatures resulting in isolated yields of the desired alcohol less than 42%.
TABLE 2.7

TEMPERATURE AND PHOSPHINE EFFECTS

\[
\begin{align*}
2.8g & \xrightarrow{\text{Cp}_{2}TiCl_2 (1 \text{ mol\%), Zn dust,}} \xrightarrow{\text{THF, additive, temperature}} 2.9g \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry(^a)</th>
<th>Additive</th>
<th>Temperature (°C)</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>23</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>0</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-20</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-40</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>-78</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>1 eq. PCy(_3)</td>
<td>-78</td>
<td>&lt;10</td>
</tr>
<tr>
<td>7</td>
<td>5 mol% PCy(_3)</td>
<td>-40</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>5 mol% PPh(_3)</td>
<td>-40</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>5 mol% dppp</td>
<td>-40</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

\(^a\)Fleury's Conditions: \(^{34}\) aldehyde 2.8g (0.4 mmol), \(\text{Cp}_2\text{TiCl}_2\) (1 mol\%), zinc dust (1.0 mmol) and bromide 1.62 (1.0 mmol) in THF (0.1 M) at indicated temperature for 20 min. \(^b\)Isolated yields

Recent work from Wilson et al. illustrated the utility of phosphine additives in zinc acetylide additions to aldehydes and ketones when synthesizing propargyl alcohols (Figure 2.1).\(^{84}\) The scope of the carbonyl appears broad, including aryl and alkyl substrates whether cyclic or acyclic in nature. Diversity on the alkynylidene backbone (i.e. alkyl, aryl, electron-rich, electron-deficient) seems to have little effect on the C-C bond forming step.\(^{84}\) Based upon the isolation of a bis-phosphine ligated dinuclear zinc acetylide complex (Figure 2.2) and Fleury’s phosphine additive results, we speculate
phosphines playing a role in both the metallasition event and perhaps the C-C bond forming transition state.

![Chemical reaction diagram](image)

**Figure 2.1: Zinc Acetylide Additions to Carbonyls**

![Phosphine-Ligated Zn-Acetylide Dimer](image)

**Figure 2.2: Phosphine-Ligated Zn-Acetylide Dimer**

2.2.3 Various Highly Reactive Organometallics

While Cp₂TiCl₂ proved effective at catalyzing the formation of allylzinc and allyl Grignard reagents (Table 2.8, entry 1),³⁵ unactivated alkyl bromides proved less efficient. As previously shown, the addition of phosphine additives led to an overall
increase in metallation, yield, and efficiency of these organometallics. In general, alkyl and aryl bromides metallated well in the presence of \( \text{Cp}_2\text{TiCl}_2 \), phosphine, and Mg turnings to produce allylic alcohol in acceptable to good yields (entries 2-7). \(^{35}\)

**TABLE 2.8**

ACTIVATION OF VARIOUS ORGANOMETALLICS

<table>
<thead>
<tr>
<th>Entry(^a)</th>
<th>( R )</th>
<th>Phosphine</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H(_2)C=CHCH(_2)Br (1.62)</td>
<td>-</td>
<td>Ph(\text{-CH=CHCH}_2\text{Br})(2.4)</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>( n\text{BuBr} ) (2.15b)</td>
<td>dppp</td>
<td>Ph(\text{-CH=CHCH}_2\text{Br})(2.16b)</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>(CH(_3))(_2)CHBr (2.15c)</td>
<td>dppe</td>
<td>Ph(\text{-CH=CHCH}_2\text{Br})(2.16c)</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>PhCH(_2)Br (2.15d)</td>
<td>dppp</td>
<td>Ph(\text{-CH=CHCH}_2\text{Br})(2.16d)</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>Ph(_2)CHBr (2.15e)</td>
<td>dppe</td>
<td>Ph(\text{-CH=CHCH}_2\text{Br})(2.16e)</td>
<td>39</td>
</tr>
<tr>
<td>6</td>
<td>PhBr (2.15f)</td>
<td>dppp</td>
<td>Ph(\text{-CH=CHCH}_2\text{Br})(2.16f)</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>CH(_2)=CHBr (2.15g)</td>
<td>dppp</td>
<td>Ph(\text{-CH=CHCH}_2\text{Br})(2.16g)</td>
<td>49</td>
</tr>
</tbody>
</table>

\(^a\)Fleury’s Conditions\(^{15}\): enone 2.1a (0.4 mmol), \( \text{Cp}_2\text{TiCl}_2 \) (1 mol%), magnesium turnings (1.0 mmol) and bromide (1.0 mmol) in THF (0.1 M) for 1 h at rt. \(^b\) Isolated yields
The metallation and subsequent carbonyl addition reaction involving alkyl bromides \textit{2.15b} and \textit{2.15c} provided alcohols \textit{2.16b} and \textit{2.16c} in 41\% and 24\% respectively in the presence of magnesium and bisphosphine dppp or dppe. Treatment of benzyl bromides \textit{2.15d} or \textit{2.15e} with catalytic titanocene, Mg\textsuperscript{0} turnings, a bidentate phosphine, and enone \textit{2.1a} produced the corresponding allyl alcohols in satisfactory yields (entries 4-5)\textsuperscript{35}. Even the Cp\textsubscript{2}TiCl\textsubscript{2} catalyzed metallation proved effective for aryl and vinyl bromides illustrated by bromobenzene \textit{2.15f} and vinyl bromide \textit{2.15g} (entries 6 and 7). Fleury noted that in general, metallation of unactivated alkyl bromides was more efficient using Mg\textsuperscript{0} than zinc dust and bisphosphines dppp and dppe had a tendency to give comparable results regardless of the alkyl halide. Although yields are moderate, this method highlights a new approach to generating highly reactive organometallic intermediates through the use of titanocene dichloride\textsuperscript{35}.

Based on our observations thus far, a possible mechanism begins with initial reduction of the precatalyst Cp\textsubscript{2}TiCl\textsubscript{2} by the reductant metal to give the active catalyst Cp\textsubscript{2}TiCl (Scheme 2.2). Cp\textsubscript{2}TiCl then metallates the appropriate alkyl halide to yield R-TiCp\textsubscript{2}Cl \textit{2.17}, which is followed by another reduction to Ti(III) complex \textit{2.18}. Transmetallation to the more reactive MX\textsubscript{2} forms reagent \textit{2.19} and regeneration of active titanium (III) catalyst Cp\textsubscript{2}TiX. The ensuing addition of \textit{2.19} to the carbonyl \textit{2.1a}–\textit{2.8} affords metal alkoxide \textit{2.20}. Although the exact role of phosphorus is unknown, one possibility involves a stabilizing effect on titanium (III) intermediates while increasing the reactivity of \textit{2.19}. 

40
Scheme 2.2: Proposed Catalytic Cycle Ti-Catalyzed Allylation

2.2.4 Intramolecular Allylation Variants

Given the prevalence of small carbocyclic ring systems in a variety of biologically active natural products, including daphniyunnine A (2.21) and pleocarpenone (2.22) exploration of an intramolecular titanocene-catalyzed metallation carbonyl addition protocol would provide ready access to these molecular architectures (Figure 2.3).
Figure 2.3: Carbocyclic Natural Products

To test this hypothesis, our initial experiments involved the use of allylbromide 2.23a en route to the synthesis of 5-membered cyclopentanol 2.24a. Once in hand, 2.23a was subjected to substoichiometric amount of Cp₂TiCl₂ (2 mol%) and zinc dust in CH₂Cl₂ at room temperature (Table 2.9, entry 1). However, no cycloalkanol was observed (entry 1). Exchange of CH₂Cl₂ for the more polar CHCl₃ also failed to produce the desired homoallylic alcohol, resulting in nearly quantitative recovery of starting material 2.23a (entry 2). When allylation of acetophenone derivative 2.23a was performed in CH₃CN and NMP, cyclopentanol 2.24a was produced in 48% and 36% yield respectively (entries 3 and 4). In each case, 2.24a is isolated exclusively as the syn diastereomer as determined by 2-D ¹H NMR and nOe correlations. Interestingly, when allylbromide 2.23a was treated with 2 mol% titanocene in THF, cyclopentanol 2.24a was produced in 94% after a mere 10 minutes at room temperature (entry 5).⁸⁸ Having optimized solvent choice to THF, our focus turned towards the choice of reductant metal and additives.
TABLE 2.9

INTRAMOLECULAR ALLYLATION OF 2.23A

![Chemical structure and reaction scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Additive (mol%)</th>
<th>Reductant (equiv)</th>
<th>Yield of 2.24a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>-</td>
<td>Zn (2.5)</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>CHCl₃</td>
<td>-</td>
<td>Zn (2.5)</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CN</td>
<td>-</td>
<td>Zn (2.5)</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>NMP</td>
<td>-</td>
<td>Zn (2.5)</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>-</td>
<td>Zn (2.5)</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>-</td>
<td>Mg (2.5)</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>-</td>
<td>In (2.0)</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>PPh₃</td>
<td>Zn (2.5)</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>DPPP (5 mol%)</td>
<td>Zn (2.5)</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Conditions: 2.23a (0.5 mmol), Cp₂TiCl₂ (2 mol%), reductant metal (1.25 mmol), and additive in solvent (0.05 M) for 10-60 min at rt. NR = No reaction.
The use of Mg(0) turnings in place of zinc dust offered only recovered ketone 2.23a, whereas indium metal gave the cyclopentanol in moderate yield (60%) as seen in entries 6 and 7. Although Fleury showed that phosphine additives accelerate the transmetallation event from an allyltitanium to an allylzinc species at low temperatures, this was not the case for intramolecular allylations. Addition of 5 mol% of PPh₃ to the optimized conditions lead to a reduction in isolatable yield of alcohol 2.24a (entry 8) while the use of bisphosphine dppp completely inhibited the intramolecular allylation (entry 9). Having settled upon the optimal conditions of 2 mol% Cp₂TiCl₂, Zn⁰ as a reductant metal, and THF as a solvent, the formation of various sized carbocycles was examined. In a similar fashion to the 5-membered version, the 6-membered carbocycles were achieved by the intramolecular allylation of ketone 2.23b to produce homoallylic alcohol 2.24b in 94% yield (eq 23).

![Chemical Reaction](image)

Likewise, cycloheptanol 2.24c was obtained in moderate yield after only 10 minutes by subjection of methyl ketone 2.23c to our optimized conditions (53%, Scheme 2.3). Conversely, when the catalytic titanocene allylation of 2.23c was stirred for prolong periods (i.e. > 1 h) bridged bicycle c-2.24c, resulting from intramolecular transesterification of the methyl ester residing syn to the newly formed homoallylic alcohol, is isolated in 93% yield. It’s important to note that the diastereoselectivity
was excellent in each case shown, providing the \textit{syn} diastereomer in \(\geq 99:1\) even in the case of the 7-membered carbocycle \textbf{2.24c} and bicyclic carbocycle \textit{c-2.24c}.

![Scheme 2.3: Synthesis of Cycloheptanols](image)

After successfully synthesizing a series of cyclic and bicyclic carbocycles, our sights focused on establishing a titanocene-catalyzed intramolecular metallation/allylation procedure towards the assembly of nitrogen heterocycles.\textsuperscript{91-93} Upon treatment of sulfonamide \textbf{2.23d} with \(\text{Cp}_2\text{TiCl}_2\) (2 mol\%) and zinc dust, pyrrolidine homoallylic alcohol \textbf{2.24d} was produced in 34\% yield with complete \textit{syn} selectivity (eq 24).

\[
\begin{align*}
\text{Ts} & \quad \text{O} & \quad \text{Ph} \\
\text{2.23d} & \quad \text{Cp}_2\text{TiCl}_2 \quad \text{(2 mol\%)} & \quad \text{zinc dust, THF, rt} \\
\rightarrow & \quad \text{Ts} & \quad \text{N} & \quad \text{Ph} \\
\text{2.24d} & \quad \text{O} & \quad \text{Ph} & \quad \text{OH} & \quad \text{(24)}
\end{align*}
\]

34\% yield, \(dr > 99:1\)

Attempts to increase the isolatable yield of pyrrolidine \textbf{2.24d} by increasing catalyst loading, reaction times, or temperature failed. However, when extending this
method to ketone 2.23e, under our optimized conditions, sulfonyl piperidine 2.24e was isolated in 98% yield (eq 25).

\[
\begin{align*}
\text{TsN} & \quad \text{Br} \quad \text{Ph} \\
\text{O} & \\
\text{Cp}_2\text{TiCl}_2 (2 \text{ mol}%) \\
\text{Zn}^0, \text{THF, rt} \\
\rightarrow \\
\text{TsN} & \quad \text{Oh} \quad \text{Ph}
\end{align*}
\]

(25)

98% yield, \( dr >99:1 \)

An increase in the carbon tether length bolster yields of desired \( N \)-heterocycle 2.24e above 95%. Again, in each example reported thus far, exceptional levels of diastereoselectivity were observed in the formation of 2.24d and 2.24e. These results compliment conventional methods for the intramolecular alkylation of ketones.\(^{94,95}\)

Recently, allenes have gained interest due to their reactivity in transition metal-catalyzed reactions.\(^ {96,97} \) To provide rapid access to these important subunits, our intramolecular substrates were modified to incorporate a propargyl bromide functional group. Accordingly, treatment of propargyl bromide 2.25a under the optimal titanocene-catalyzed metallation conditions generated allene 2.26a in 88% yield after only 15 minutes at room temperature (eq 26). As anticipated, the alkylation of 2.25a proceeded with exclusive \( S_22' \) selectivity to furnish a cyclopentanol containing an exocyclic allene. It is noteworthy that longer reaction times with cycloalkanol 2.26a resulted in isomerization and decomposition to various by-products.
Lengthening the carbon tether allowed access to 6-membered cycloalkanols possessing a similar allene subunit. Accordingly, this was observed when phenyl ketone 2.25b was treated with 2 mol% of Cp₂TiCl₂ in the presence of zinc dust to provide cyclohexyl-substituted allene 2.26b in 77% yield (eq 27). In a similar manner to intramolecular titanocene-catalyzed allylation of allyl bromide 2.23c, the alkylation of methyl ketone 2.25c ensued under identical conditions to provide seven-membered allene-bearing carbocycle analogs, shown by the isolation of 2.26c in 35% yield (eq 28). Development of the intramolecular carbonyl addition reaction to involve propargyl bromides further expands the utility of this method to construct carbinols with a functional group handle in the form of an alkene or exocyclic allene for further manipulations.³⁰

The high level of observed diastereoselectivity in the intramolecular alkylation cases is rationalized by invoking a chair-like transition state similar to that which is generally accepted in the allylation of carbonyl substrates (Scheme 2.4).³⁸ The anti-selectivity in the intramolecular allylations of 2.23a towards the production of
cyclopentanols is inherent by examining the two envelope transition states 2.27 and 2.28. Transition state 2.27, wherein the R group of the carbonyl resides in the more favorable pseudo-equatorial position, is preferred compared to 2.28, which has the occurrence of a large transannular diaxial interactions between said R group and the axial ester.$^{94}$

![Chemical reaction scheme]

Scheme 2.4: Diastereoselectivity in Intramolecular Substrates.

2.2.5 Summary

This titanocene-catalyzed metallation protocol compliments existing approaches toward the creation of highly-reactive organometallic reagents. This titanocene-catalyzed reductive transmetallation of alkyl halides showed excellent regio-, chemo-, and diastereoselectivity in the fabrication of homoallylic alcohols and carbocyclic substrates. One of the most attractive aspects of our method is its simplistic approach, a highly desired trait when constructing complex synthetic intermediates quickly.
2.3 Conclusions

The utility of transition metal-catalyzed methods has begun to establish roots as the synthetic chemists choice to construct complex synthetic intermediates rapidly. Their ability to make various disconnects, which remain inaccessible through current methods represents one of the most significant synthetic advances of the last 50 years. The reliability of these processes inspire researchers to continually explore and innovate new ways in which transition metals can be used.

The first section in this chapter introduced a titanocene-catalyzed conjugate reduction of $\alpha,\beta$-unsaturated carbonyls. As demonstrated earlier, the chemoselective reduction of enones, enals, enoates, and ynone are made possible through the use of a stoichiometric reductant (i.e. zinc) and amine hydrochloride as the proton source. Although with the lack of observed diastereoselectivity, attempts to exploit a titanium-bound enolate lead to the discovery of high reactive organozinc reagents via a titanium transmetallation and their subsequent addition to various carbonyls. Types of organometallics accelerated by the use of catalytic titanocene dichloride include alkyl, allyl, aryl, benzyl, and vinyl species with additions to ketones, esters, and amides. Subsequent work led to the discovery that phosphine additives had beneficial effects on the rate of organozinc and organomagnesium formation.
CHAPTER 3:
REDOX PHOSPHORUS CHEMISTRY

3.1 Introduction

A major challenge facing synthetic chemists in attempts to maximize synthetic efficiency as we enter the 21st century is the poor atom economy resulting from stoichiometric formation of high molecular weight by-products in some of the most fundamental chemical transformations. Significant importance remains on rendering current methods, metal-mediated and metal-free, catalytic while optimizing atom and step economy.

Phosphorus-mediated reactions are widely sought-after for their synthetic ease and reproducibility while remaining chemoselective in complex synthetic situations, in spite of stoichiometric waste formation. As a result of their inherent utility in C-C and C-heteroatom bond formations, recent efforts have focused on the development of catalytic variants to optimize synthetic efficiency. In this chapter, phosphorus-mediated transformations will be discussed highlighting their function to make various C-C, P-C, and C-N bonds as well as current approaches to modify them catalytic in phosphorus.
3.2 Stoichiometric Redox Phosphorus Reactions

3.2.1 Michaelis-Arbuzov

A common method for the formation of carbon-phosphorus bonds is the Michaelis-Arbuzov rearrangement.\(^9\) Despite various names for this rearrangement, including the Arbuzov reaction,\(^1\) this procedure has been exploited in the synthesis of various organophosphorus derivatives including phosphine oxides and phosphonates. The rearrangement was originally discovered by the German chemist Michaelis\(^1\) in 1898, in which a trivalent phosphorus species 3.1 is reacted with an alkyl halide 3.2, rendering an oxidized phosphorus(V) intermediate 3.4 as the desired product and a subsequent new alkyl halide 3.5 (Figure 3.1).

![Chemical reaction diagram](image)

**Figure 3.1: Michaelis-Arbuzov Reaction**

The generally accepted mechanism begins with nucleophilic attack of the trivalent phosphorus reagent on the alkyl halide, to provide a phosphonium salt intermediate. Once one of the alkyl groups is eliminated thermally through an attack by the conjugate nucleophile, the end result is formation of a new alkyl halide and strong P=O bond, a net gain of 32 kcal/mol.\(^1\) Employment of this procedure with \(\alpha\)-halogenated carbonyls as your electrophilic source is an alternative route to synthesizing \(\beta\)-carbonyl phosphonate derivatives. \(\beta\)-carbonyl phosphonates are key
synthetic intermediates in the construction of both biologically active drugs and molecules through a Horner–Wadsworth–Emmons olefination (eq 29).\(^{103}\)

\[
\begin{align*}
\text{(EtO)}_2P & + R\text{O}X \xrightarrow{\Delta} \text{(EtO)}_2PO \xrightarrow{\text{Et}} R + \text{Et}X \quad (29)
\end{align*}
\]

One drawback to the Michaelis-Arbuzov reaction is elevated reaction conditions required for phosphonate formation to occur, which can result in substrate decomposition of side-reactions between the newly formed alkyl halide \(3.5/3.9\) and the original phosphite \(3.1/3.6\). This presence of various polar pentavalent phosphorus species also often complicates product purification.

3.2.2 Wittig

Prior to 1950, olefinations were limited to procedures of ketones and aldehydes due to positional selectivity or isomeric rearrangements of the alkenes.\(^{104}\) In 1953, Wittig and Geissler\(^{105}\) developed an efficient, simple, and general method where phosphonium ylides reacted with aldehydes or ketones rendering the anticipated olefin without previously described issues (Scheme 3.1).

Scheme 3.1: Wittig Olefination

52
Since the 1960’s, mechanistic investigations led to the development of modifications that allowed synthetic chemists to modify and control $E/Z$ selectivity of the Wittig reaction, to the point where it has become one if not the most well known methods for carbonyl olefination.\textsuperscript{106} Since it’s establishment, the Wittig reaction and its variants thereof, have proven their reliability with often high levels of $E$- or $Z$-selectivity in the synthesis of complex fragments despite the formation of stoichiometric amounts of phosphine oxide waste. As the chemical community attempts to become more environmentally friendly, reactions proceeding with poor atom economy, such as the Wittig reaction, require improvements.

3.2.3 Staudinger-Type Reactions

3.2.3.1 The Staudinger Reduction

The innovation of organophosphorus ylides and their impact on the field of organophosphorus chemistry precedes Wittig’s discovery in the early 1950’s. An earlier observation and study, completed by Hermann Staudinger in 1919, examined the reactivity between phosphines and azides to produce phosphorus aza-ylide type intermediates (3.20/3.21), also known as iminophosphoranes.\textsuperscript{107} These pentacovalent phosphorus intermediaries were hydrolyzed to render the reduced azide as an amine and stoichiometric formation of the phosphine oxide (eq 30).

\[
\begin{align*}
PPh_3 & \xrightarrow{\text{RN}_3 (3.19)} \xrightarrow{-\text{N}_2} \xleftarrow{\text{H}_2\text{O}} \xrightarrow{\text{3.20}} \xleftrightarrow{\text{3.21}} \xrightarrow{\text{3.22}} \xleftarrow{\text{3.17}} \text{R–NH}_2 + \text{Ph}_3\text{PO} \end{align*}
\]
The synthetic versatility of the azide functional group is evident in cycloaddition reactions,\textsuperscript{108} but more importantly they can also act as a ‘protected amine.’ This concealed amine functionality is only revealed when decomposed with a phosphine via the Staudinger reduction, thus highlighting the utility of an azide to act as a ‘hidden’ amine functional group. This protecting group method has been exploiting in several total synthesis including Stemoamide, where Williams and coworkers installed an azide initially which could be carried through their multistep synthesis unaffected until the amine functional is unmasked to do a nucleophilic acyl substitution upon a pendant ester (eq 31).\textsuperscript{109}

\begin{equation}
\text{\begin{align*}
\text{3.23} & \xrightarrow{\text{PPh}_3 (6.5 \text{ equiv})} \text{THF:H}_2\text{O} (100:1) \text{ reflux, 48 h, 87\% yield} \text{3.24} \\
\end{align*}}
\end{equation}

3.2.3.2 Staudinger Ligation

To further expand the utility of the Staudinger process, modifications began to exploit the reactivity of these interesting iminophosphorane-type intermediates prior to hydrolysis. The pioneering work done by Vilarrasa and coworkers highlighted the ability of the nitrogen on the iminophosphorane can be acylated whether through an inter- or intramolecular process.\textsuperscript{110-114} Though originally carboxylic acids were shown to react
with stoichiometric amounts of preformed iminophosphorane to produce amides, the duration and reaction conditions inspired a modification to the carbonyl motif (eq 32).\textsuperscript{110} Based on several subsequent experiments, Vilarrasa proposes an initial amidation mechanism that involves protonation of the phosphazene species rendering a phosphonium salt intermediate.

\[
\text{PhCOOH} \xrightarrow{\text{PPh}_3, \text{PhN}_3 \text{ 3.27a, C}_6\text{H}_6} \xrightarrow{\text{reflux}, 5 \text{ d}, 96\% \text{ yield}} \text{PhCONHPh} \quad (32)
\]

Substitution of a more electrophilic acylating reagent (i.e. ester or anhydride) to react with an “aza-ylide” allowed access to amides under mild conditions without prolonged reaction periods (eq 33).\textsuperscript{112} This approach also permitted the formation of often difficult to synthesize large-membered lactams. When 3.30 is subjected to tri-\(n\)-butyl phosphine under high dilution conditions, 14-membered amide 3.31 is formed in 82% yield with less than 2% dimerization by-products (eq 34).\textsuperscript{113}

\[
\begin{align*}
\text{PhCOOCl} & \xrightarrow{n\text{Bu}_3\text{P}, \text{BnN}_3 \text{ 3.27b, C}_6\text{H}_6} \text{PhCONHPh} \\
(33) & \quad 92\% \text{ yield}
\end{align*}
\]

When constructing various C-N amide bonds, such as those in peptides, the most popular synthetic intermediate is the activated carbonyl. Vilarrasa initially demonstrated
the coupling between α-azido esters and amino acid derivatives with trialkylphosphines through an intermolecular pathway. The resulting dipeptides were obtained under mild conditions with minimal epimerization at valuable stereocenters.\textsuperscript{114} Several years later an inspiring “traceless-ligation” approach was developed by Raines as an alternative to native chemical ligation. Implementing phosphinobenzenethiol 3.33 as a coupling agent between activated carbonyls in the form of thioesters and azidopeptide fragments, various dipeptides were produced in excellent yields (Scheme 3.2).\textsuperscript{115}

![Scheme 3.2: Traceless Peptide Ligation](image)

Even with the advantages associated with this ligation method, taking into account viewpoints from the economic and environmental side of chemistry, a strong desire remains to develop variations to improve the efficiency of these aforementioned redox-phosphorus based modifications.
3.3 Catalytic Redox Phosphorus Chemistry

3.3.1 Wittig

Since its discovery almost 60 years ago, the Wittig reaction remains a widely utilized method by synthetic organic chemists for the assembly of olefins.\textsuperscript{116} Like many of the phosphorus-mediated reactions employed by chemists, the Wittig is intrinsically wasteful with stoichiometric phosphine oxide by-products. Thus, the implementation of a catalytic variant remains essential as chemists seek to improve the atom economy of popular transformations. The groundbreaking development of an olefinic alternative to using phosphine was discovered by Shi and Huang. Through the use of 20 mol\% tributylarsine, the Wittig-type olefination procedure was rendered catalytic by triphenyl phosphite acting as the stoichiometric reductant. The proposed reaction pathway begins with attack of the alkyl arsine upon 3.41 followed by deprotonation to form arsin ylide. Upon olefination, tributylarsine is regenerated upon reduction of the arsine oxide by triphenyl phosphite. This process likely inspired groups to examine other olefination protocols that could be rendered catalytic in phosphorus (eq 35).\textsuperscript{117}

\begin{equation}
\begin{array}{c}
\text{3.40} \\
\text{3.41}
\end{array}
\rightarrow
\text{3.42}
\end{equation}

\text{80\% yield}
\text{E:Z = 99:1}

The inherent toxicity of using arsenic coupled with stoichiometric formation of triphenyl phosphate implores a less toxic alternative to a catalytic olefination procedure. The first example of a catalytic Wittig reaction was reported by O’Brien at the University
of Texas at Arlington. The O’Brien group employed silanes as a reductant to recycle the phosphate oxide by-product back to the active phosphate catalyst. Under their optimal conditions containing a catalyst loading of 10 mol% with 1.1 equivalents of Ph₂SiH₂, aldehyde 2.8g was transformed into α,β-unsaturated ketone 2.1b in 74% yield with an observed E:Z selectivity of >95:5 (eq 36).¹¹⁸

![Chemical Reaction Image]

3.3.2 Appel

An important role as a synthetic chemist involves the ability to construct new C-C and C-X bonds. One of the first routes to accomplishing such processes is through nucleophilic substitution of an electrophilic component. The functional group conversion from an alcohol to a better leaving group remains a popular first step to this reaction. One method in which primary and secondary alcohols are converted to their respected halogenated variants is through the use of halophosphonium salts popularized by Appel in the mid-1970s.¹¹⁹ While these reagents can furnish high yields of alkyl halides from the corresponding alcohols under relatively mild conditions, the creation of stoichiometric phosphine oxide by-products can complicate purification. In hopes of addressing this major problem with phosphine-mediated reactions, Denton and coworkers investigated the use of a stoichiometric reductant to shuttle the
phosphine oxide 3.17 by-product back into the active chlorophosphonium salt form 3.46 (Scheme 3.3).

Scheme 3.3: Catalytic Appel Catalytic Cycle

They discovered that oxalyl chloride was a proficient reductant for the regeneration of the halophosphonium salt for their phosphine-catalyzed construction of alkyl chlorides. An overwhelming advantage to using oxalyl chloride as a stoichiometric reductant yields only CO, CO$_2$, and HCl as by-products of the reaction.$^{120}$ Under their optimized conditions of 15 mol% of triphenylphosphine oxide, cinnamyl alcohol 3.50 was converted to cinnamyl chloride 3.51 in 83% yield after 7 h at room temperature (eq 37). Shortly thereafter, a bromination variant was developed using a slightly modified procedure with either oxalyl bromide or the combination of oxalyl chloride/bromide source (i.e. LiBr or NaBr).$^{121}$ When 2-cyclohexenol 3.52 was treated with 15 mol% Ph$_3$P=O, (COCl)$_2$, and LiBr in CHCl$_3$ for 5 h, allylic bromide 3.53 was obtained in 73% yield (eq 38).
Concurrently, van Delft and coworkers developed an alternative to the catalytic Appel reaction employing silanes as the stoichiometric reductant instead of oxalyl chloride.\textsuperscript{122} After a well-designed rate-comparison study of an assortment of phosphine oxides, they settled upon cyclic phosphine \textbf{3.55} in conjunction with diethyl bromomalonate \textbf{3.56} and diphenylsilane in CH\textsubscript{3}CN to convert alcohol \textbf{3.54} to bromide \textbf{3.57} in 82\% yield (eq 39).

\begin{equation}
\text{PhCH(OH)} + \text{BrCH(}CO\text{Et}_2)_{3.56}, \text{Ph}_2\text{SiH}_2, \text{CH}_3\text{CN, reflux, 19 h} \\
\text{BrCH(CO}_2\text{Et})_{3.56}, \text{Ph}_2\text{SiH}_2, \text{CH}_3\text{CN, reflux, 19 h} \quad (39)
\end{equation}

\textbf{3.3.3 Mitsunobu Reaction}

The Mitsunobu reaction, in which primary and secondary alcohols undergo nucleophilic displacement, is another widely popular substitution reaction.\textsuperscript{123} Originally developed in 1967 by Professor Oyo Mitsunobu,\textsuperscript{124} the method was created to substituted alcohols under mild yet stereospecific conditions utilizing a phosphine reagent. Much like the Wittig reaction, the Mitsunobu typically suffers from product isolation and purification issues due to phosphine oxide and dihydrohydrazine by-products. A catalytic Mitsunobu variant must address the issue of stoichiometric
hydrazine use and/or phosphine. The first organocatalytic Mitsunobu approach, discovered by Toy and coworkers, employed 10 mol% dimethyl azodicarboxylate, Ph₃P, and diacetoxyiodobenzene with various carboxylic acids to synthesize an array of esters. Even chiral ester 3.64, derived from carboxylic acid 3.27b and chiral α-hydroxy ester 3.63, is created in 65% yield without loss of optical purity (eq 40).

![Chemical Reaction Image](image)

In their catalytic cycle, diacetoxyiodobenzene 3.58 is used as a mild and selective stoichiometric oxidant to shuttle the dihydrohydrazine by-product 3.62 back to the active azodicarboxylate form 3.59 (Scheme 3.4). It should be highlighted that Toy’s catalytic Mitsunobu procedure still is stoichiometric in phosphine.

![Scheme 3.4: Organocatalytic Mitsunobu Catalytic Cycle](image)

More recently, current investigations out of the O’Brien group have demonstrated the capability of rendering the Mitsunobu reaction catalytic in phosphine...
as well. By applying 20 mol% of 3-methyl-1-phenylphospholane-1-oxide 3.44 with 4-nitro benzoic acid 3.27b, benzyl alcohol 3.65, diisopropyl azodicarboxylate, and phenylsilane in toluene for 24 h at 80 °C produced benzyl benzoate 3.66 in 63% yield (eq 41).

\[
\begin{align*}
\text{O}_2\text{N} & \quad (\text{iPrO}_2\text{CN})_2, \text{PhSiH}_3 \\
& \quad \text{Toluene, 80 °C, 24 h} \\
\text{O} & \quad \text{63% yield}
\end{align*}
\]

With the abundant use of the Mitsunobu reaction in both industrial and the academia settings, the ability to afford catalytic versions in either organoazo or phosphine reagents constitute as significant advances to the field of synthetic organic chemistry. One of the most challenging aspects in the future would be the development of a dual-catalytic Mitsunobu procedure. One would implement catalytic amounts of both azo and phosphine while balancing the presence of both a selective reducing and oxidizing agent for each catalyst.

3.3.4 Staudinger Reduction

Over the last decade several new advancements have surfaced to circumvent the issues associated with phosphorus-mediated reactions. One approach to overcoming the purification problems associated with these reactions is through immobilization of the phosphorus source. Inspired by other recent phosphorus applications rendered catalytic, focus is turned towards tackling the original organophosphorus reaction developed nearly a century ago; the Staudinger reduction of azides. In the Staudinger
reduction, hydrolysis of the iminophosphorane-type intermediate provides the reduced azide (i.e. amine). One major challenge that arose when the van Delft group attempted to extend a catalytic version of the Staudinger reduction was the identification of a stoichiometric reductant that would be compatible with water. To address this issue, they investigated the direct reduction of the “aza-ylide” intermediate 3.68 to regenerate the phosphine catalyst 3.67 and produce a silyl-amine derivative 3.69. An aqueous workup would then yield the desired amine (Scheme 3.5).126 Under their optimal conditions, numerous alkyl and aryl azides are reduced efficiently to the analogous amine by using 5 mol% of dibenzophosphole 3.55 and 1.5 equivalents of PhSiH₃ in refluxing 1,4-dioxane including aryl azide 3.70 with a pendant carboxylic acid group at the para-position in quantitative yield (eq 42).

Scheme 3.5: Proposed P=N Reduction Catalytic Cycle

Ph₂SiH₃, dioxane, reflux

99% yield
3.4 Conclusion

Over the last 120 years, the development of several phosphorus-mediated procedures has advanced the field of synthetic chemistry. As shown above, the synthetic versatility of the discussed transformations remains indispensable to the synthetic chemist. With the development of catalytic variants, distinct advantages over its stoichiometric counterpart are addressed, particularly in terms of waste production. Through current explorations, the research area of organophosphorus chemistry will continue to generate new means and tools for the construction of complex synthetic targets and biologically relevant molecules.
CHAPTER 4:

REDOX PHOSPHORUS CHEMISTRY *EN ROUTE* TO NEW C-C AND C-N BONDS

4.1 Phosphorus Redox Chemistry Utilizing Carboxylic Acids

4.1.1 Introduction

The interconversion of carboxylic acid derivatives through nucleophilic acyl substitutions represents one of the most fundamental transformations in synthetic organic chemistry.\textsuperscript{127} Functionalization of these derivatives is prevalent in many fields, including the construction of biologically active natural products through macrocyclizations or fragment couplings.\textsuperscript{128-130} Despite the recent developments in transition metal-catalyzed\textsuperscript{131-133} acyl substitutions, the most widely-utilized strategies for functionalization involves the dehydration of carboxylic acids via an activated acyl intermediate.\textsuperscript{124,134-137} Unfortunately, difficulties with product purification, harsh/caustic reagents, generally acidic conditions, and poor atom economy of the dehydration process are several of the drawbacks to this approach. Therefore, the development of alternative routes that avoid these complications have been investigated.\textsuperscript{138-140} Given the widespread commercial availability of various carboxylic acids, a method that enables the direct acyl substitution while maintaining a high level of chemoselectivity, requiring minimal or no product purification would constitute a significant advance.
4.1.2 Phosphite-Modified Staudinger Ligation

4.1.2.1 Introduction

Given the inherent functional group compatibility issues and the practical challenges associated with conventional methods, we sought to develop a protocol for the direct functionalization of carboxylic acids that proceeds in the presence of nucleophilic (e.g. RH₂, ROH) and electrophilic functionality (e.g. RCHO, R₁C(O)R₂). The addition of in situ generated azal-ylides to carboxylic acid derivatives has proven to be an effective strategy for amide bond formation. Vilarrasa, Raines, and Bertozzi are a select few who have successfully applied this method in the acyl substitution of carboxylic acid derivatives. Recently, the Staudinger ligation has gained recognition, especially in biological sciences, due to its ability to tether bioactive probes to molecules of interest for further study of metabolic functions as well as the construction of peptide building blocks.

Two of the most influential advances in the Staudinger ligation include Raines’ use of phosphinothiol in the ligation of thioesters and azides en route to dipeptides through an intramolecular acylation event (Scheme 4.1) and Bertozzi’s synthesis of glycoproteins from esters bearing a tethered phosphine and glycosidic azides to study glycosyltransferase activity (Scheme 4.2). Separately, Vilarrasa demonstrated the ligation of carboxylic acids and azides via an acyl selenide (Scheme 4.3).
Scheme 4.1: Raines’ Alternative to Native Peptide Ligation

Scheme 4.2: Use of Glycosyl Azides by Bertozzi
Scheme 4.3: Staudinger Ligation of an Acyl Selenide

Although these methods exhibit broad reactivity scope, the inability to use carboxylic acids directly and the stoichiometric phosphine oxide waste generated, prompted us to seek an alternative ligation strategy. We speculated that a Staudinger-type ligation utilizing carboxylic acids directly would lead to C–N bond formation through a rearrangement of intermediate phosphite ylide 4.20 to produce phosphoryl imide 4.21. The construction of amides through this route is contingent on a bifunctional chlorophosphite reagent that activates both carboxylic acids 4.19 and azides 4.14 through an intermediate ester aza-ylide 4.20. The dual activation behavior of the chlorophosphite permits the direct acyl substitution of carboxylic acids in the presence of additional electrophilic and nucleophilic functionality.
Scheme 4.4: Proposed Dual Activation of Carboxylic Acids and Azides

Upon hydrolysis, the primary amide 4.23 is produced in conjunction with the water-soluble phosphoric acid 4.22 by-product. Beneficially, the resultant phosphoric acid is effortlessly removed through a basic workup, thus simplifying purification.

4.1.2.2 Identification of Conditions

To evaluate our hypothesis involving the utility of a chlorophosphite to mediate a Staudinger-like ligation process, we originally examined the coupling of anisic acid 4.19a with benzyl azide 3.27b using commercially available diethyl chlorophosphite (eq 43). Although we were uncertain whether the electron-deficient phosphite ester would decompose an azide, use of an electron-rich carboxylic acid should be beneficial. Upon treatment of carboxylic acid 4.19a with Et₃N, ClP(OEt)₂, and azide 3.27b in 1,4-dioxane at 80 °C, benzyl amide 4.23a in produced in 35% yield. We also observed formation of anhydride 4.25 and the corresponding phosphonate ester 4.24 in 31% and 10% respectively under these conditions. These by-products seem to indicate a sluggish O-to-N acyl migration or azide decomposition.¹⁴₈
Motivated by this initial result, we directed our efforts toward evaluating the nature of the amine base, solvent choice, and equivalents of azide on this phosphite modified Staudinger ligation. For a direct comparison, anisic acid 4.19a, benzyl azide 3.27b, and Cl(PEt)2 were treated with various higher boiling, aprotic solvents in order to effect the O-to-N acyl transfer (Table 4.1). When exchanging dioxane for toluene (PhMe), we observed a decrease in the yield of amide 4.23a (entry 1). However, a simple change from toluene to xylenes increased the yield to 38% (entry 2). After assessing several polar solvents (i.e. THF, acetonitrile, DMF, and DMSO) that failed to provide the desired amide in good yield, chlorobenzene (PhCl) produced benzyl amide 4.23a in the highest yield (entry 3). Predictably the concentration of the reaction proved crucial; with higher concentrations leading to a decrease in the isolatable yield of 4.23a (entries 4 and 5). When evaluating the nucleophilicity and steric hindness of the amine base, we discovered that substitution of Et3N for DBU, DABCO, iPr2NH, or DMAP led to inferior yields of the benzyl amide (entries 6-9). The use of Et3N and diethyl chlorophosphite in PhCl also proved effective at ligating the more electron-deficient azide, para-toluenesulfonylazide 4.14b (entry 10). Seeing that acylsulfonamide 4.23b
could be produced in comparable yield to benzyl amide 4.23a (41% yield), we next sought to evaluate what effect changing the ligands on phosphorus would have on this new ligation technique.

### TABLE 4.1

IDENTIFICATION OF BASE AND SOLVENT

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>R</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn (3.27b)</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>PhMe</td>
<td>16 (4.23a)</td>
</tr>
<tr>
<td>2</td>
<td>Bn (3.27b)</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>xylenes</td>
<td>38 (4.23a)</td>
</tr>
<tr>
<td>3</td>
<td>Bn (3.27b)</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>PhCl</td>
<td>40 (4.23a)</td>
</tr>
<tr>
<td>4</td>
<td>Bn (3.27b)</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>PhCl (0.5 M)</td>
<td>21 (4.23a)</td>
</tr>
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<td>5</td>
<td>Bn (3.27b)</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>PhCl (2.0 M)</td>
<td>23 (4.23a)</td>
</tr>
<tr>
<td>6</td>
<td>Bn (3.27b)</td>
<td>DBU</td>
<td>PhCl</td>
<td>31 (4.23a)</td>
</tr>
<tr>
<td>7</td>
<td>Bn (3.27b)</td>
<td>DABCO</td>
<td>PhCl</td>
<td>&lt;5 (4.23a)</td>
</tr>
<tr>
<td>8</td>
<td>Bn (3.27b)</td>
<td>iPr&lt;sub&gt;2&lt;/sub&gt;NH</td>
<td>PhCl</td>
<td>17 (4.23a)</td>
</tr>
<tr>
<td>9</td>
<td>Bn (3.27b)</td>
<td>DMAP</td>
<td>PhCl</td>
<td>10 (4.23a)</td>
</tr>
<tr>
<td>10</td>
<td>Ts (4.14b)</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>PhCl</td>
<td>41 (4.23b)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions conducted using 0.3 mmol of azide, 0.39 mmol of 4.19a, 0.39 mmol of ClP(OEt<sub>2</sub>)<sub>2</sub>, and 0.39 mmol of base in the refluxing solvent indicated for 12 h.<br><sup>b</sup>Isolated yield.

In our optimization studies, we were intrigued by the effect of varying the alkoxy ligands on the phosphite coupling reagent would have on amide bond-formation. We
started by examining a series of bidentate ligand scaffolds, including catechol [CIP(cat)],
binol [CIP(bin)], 2,2-dimethylpropane-1,3-diol [CIP(dmp-ol)], and pinacol [CIP(pin)]
derived chlorophosphites (Table 4.2).

**TABLE 4.2**

**CHLOROPHOSPHITE LIGATION EFFECT**

![Chemical structure]  

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^1$</th>
<th>$CIP(OR_2)_2$</th>
<th>Acid/Azide (equiv)</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ts (4.14b)</td>
<td>CIP(cat)</td>
<td>1.3/1.0</td>
<td>69 (4.23b)</td>
</tr>
<tr>
<td>2</td>
<td>Ts (4.14b)</td>
<td>CIP(pin)</td>
<td>1.3/1.0</td>
<td>96 (4.23b)</td>
</tr>
<tr>
<td>3</td>
<td>Ts (4.14b)</td>
<td>CIP(dmp-ol)</td>
<td>1.3/1.0</td>
<td>89 (4.23b)</td>
</tr>
<tr>
<td>4</td>
<td>Ts (4.14b)</td>
<td>CIP(bin)</td>
<td>1.3/1.0</td>
<td>20 (4.23b)</td>
</tr>
<tr>
<td>5</td>
<td>Bn (3.27b)</td>
<td>CIP(cat)</td>
<td>1.3/1.0</td>
<td>48 (4.23a)</td>
</tr>
<tr>
<td>6</td>
<td>Bn (3.27b)</td>
<td>CIP(pin)</td>
<td>1.3/1.0</td>
<td>63 (4.23a)</td>
</tr>
<tr>
<td>7</td>
<td>Bn (3.27b)</td>
<td>CIP(pin)</td>
<td>1.0/3.0</td>
<td>59 (4.23a)</td>
</tr>
</tbody>
</table>

$^a$Reactions conducted on a 0.3 mmol scale at 0.2 M for 12 h using the stoichiometry of 4.19a and 3.27b/4.14b indicated, with CIP(OR)$_2$ and Et$_3$N in equal molar amounts to 4.19a.  $^b$Isolated yield.

The first bidentate chlorophosphite ligand examined was CIP(cat), which when used to ligate anisic acid 4.19a, azide 4.14b, and Et$_3$N improved the yield of tosyl amide
4.23b (entry 1) to 69% yield compared to (EtO)$_2$P. Oddly, a simple modification to the ligand backbone to the more sterically hindered CIP(pin) or CIP(dmp-ol) improved the yield of amide 4.23b to 96% and 89%, respectively (entries 2 and 3). Interestingly, when a seven-membered ring phosphite CIP(bin) was employed, 4.23b was obtained in a mere 20% yield (entry 4). This low yield may be due to the lack of rigidity in a seven-membered bidentate backbone, supported by the observance of 1,1'-bi-2-naphthol during reactions utilizing CIP(bin). When using CIP(cat) and CIP(pin) (entries 5 and 6) with acid 4.19a and azide 3.27b, a similar trend was observed in the amount of amide 4.23a being produced. Changes to the relative stoichiometry of acid 4.19a and azide 3.27b/4.14b proved significant to the overall efficiency of the coupling event. When an excess of azide relative to acid 4.19a was used, the yield of 4.23a dropped slightly to 57% (entry 7). An increase in the ratio of acid to azide, regardless of the chlorophosphite source, had a negative effect on the yield of amide 4.23 while increasing the degradation of the starting materials. Based on these findings, we settled upon the optimized conditions of CIP(pin), Et$_3$N, PhCl, and a 1.3/1 stoichiometric ratio of acid to azide.

4.1.2.3 Synthesis of Amides

With optimized conditions for C–N bond construction in hand, we turned our attention toward determining the structural tolerability of various carboxylic acids components with para-toluenesulfonyl azide (Table 4.3). In general, aryl and aliphatic carboxylic acids provided the corresponding amides in moderate to excellent yields.
Furthermore, it appears electronic factors of the carboxylic acid have minimal effect on the ligation event of this method. Assessment of other aryl carboxylic acids, such as benzoic acid (3.26a), gave an excellent yield of the desired amide 4.23c (entry 1).

TABLE 4.3

SYNTHESIS OF ARYL AND ALKYL ACYL SULFONAMIDES

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylic Acid</th>
<th>Amide Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>phenyl carboxylic acid</td>
<td>phenyl NHTs amide</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>4.19f</td>
<td>4.23h</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>4.19g</td>
<td>4.23i</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>4.19h</td>
<td>4.23j</td>
<td>94</td>
</tr>
</tbody>
</table>
TABLE 4.3 (CONTINUED)

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Carboxylic Acid</th>
<th>Amide Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>( nC_7H_{15} )COOH</td>
<td>( nC_7H_{15} )CONHTs</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>( \text{Cyclohexanecarboxylic acid} ) ( 4.19j )</td>
<td>( \text{Cyclohexylcarboxamide} ) ( 4.23i )</td>
<td>80&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>( \text{Acetic acid} ) ( 4.19k )</td>
<td>( \text{Acetamide} ) ( 4.23m )</td>
<td>56&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions conducted using 0.3 mmol of TsN<sub>3</sub> \( 4.14b \), 0.39 mmol of \( 4.19 \), 0.39 mmol of ClIP(pin), and 0.39 mmol of Et<sub>3</sub>N in PhCl (0.2 М) for 12 h.<sup>b</sup>Isolated yield.<sup>c</sup>Reaction employed NaH in place of Et<sub>3</sub>N.

Electron deficient benzoic acid derivatives proceeded to full conversion providing the corresponding amides in yields up to 96% (entries 2-5). Nitriles (entry 3) and aryl halides in \( 4.19d \) and \( 4.19e \) did not adversely affect the formation of amides \( 4.23e, 4.23f, \) and \( 4.23g \) (entries 3-5). Notably, pyrrole-2-carboxylic acid \( 4.19f \) gets converted to the related amide \( 4.23h \) in 81% lending utility to the use of unprotected \( N \)-heterocyclic substrates \textit{en route} to synthesizing amides (entry 6). Even various aliphatic carboxylic acids, when subjected to the optimized ligation conditions, produce alkyl amides in great yields. Ligation of cinnamic acid \( 4.19g \) and tosyl azide \( 4.14b \) with ClIP(pin) provided the \( N \)-sulfonyl cinnamidamide \( 4.23i \) in exceptional yield (93% yield) without observation of the 1,4-adduct resulting from a \([3,3]\)-rearrangement (entry 7).<sup>150,151</sup> Primary alkyl carboxylic acids underwent C–N coupling to afford amides in comparable yields to cinnamic acid as seen by the use of phenyl acetic acid \( 4.19h \) and octanoic acid \( 4.19i \) (entries 8 and 9). The amidation reaction also proved tolerant to sterically
challenging α-substituted aliphatic acids. The presence of cyclohexyl and t-butyl substituents on acids 4.19j and 4.19k did not hinder the O-to-N acyl migration, furnishing amides 4.23l and 4.23m in 80% and 56% yield respectively (entries 10 and 11). For these carboxylic acids, NaH was used in place of Et₃N, resulting in slightly higher yields. In addition, the conversion of pivalic acid 4.19k to amide 4.23m would indicate that the reaction does not proceed through a ketene intermediate.¹⁵²

We next turned our attention toward determining azide compatibility (Table 4.4). Although the ligation of anisic acid 4.19a with BnN₃ (3.27b) proceeded in 63% yield, employing electron deficient benzoic acid derivative 4.19b gave amide 4.23n in 85% yield (entry 1). MsN₃ (4.14c) gave comparable results to TsN₃ (4.14b) as demonstrated by the formation of sulfonamide 4.23o in 76% yield (entry 2). Despite the relative instability of acyl azides,¹⁵³ we were pleased to see that treatment of benzoyl azide 4.14d with acid 4.19g provided imide 4.23p in 77% yield (entry 3). Even the somewhat unstable and difficult to handle aryl azides reacted smoothly under the optimized conditions. Ligation of phenyl azide (3.27a) and acid 4.19a yielded acylated aniline 4.23q in excellent yield (entry 4). This utility can be highlighted as a complementary method for the synthesis of protected anilines, a dominant substructure in many biologically active natural products and pharmaceutical agents.¹⁵⁴,¹⁵⁵ The versatility of both the carboxylic acid and azide components employing this ligation strategy shows great promise in constructing various amide derivatives using commercially available carboxylic acids and synthetically distinct azides.
TABLE 4.4
COMPATABILITY OF VARIOUS AZIDES

\[ R^1\text{OH} \xrightarrow{\text{R}_3\text{N}_2 \text{(4.14), CIP(pin), Et}_3\text{N}} \] PhCl 12 h, 80→130 °C \[ \rightarrow R^1\text{NHR}^2 \]

<table>
<thead>
<tr>
<th>Entry(^a)</th>
<th>Azide</th>
<th>Acid</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH₂N₃ (3.27b)</td>
<td>4.19b</td>
<td><img src="image" alt="" /></td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>CH₃SO₂N₃ (4.14c)</td>
<td>4.19g</td>
<td><img src="image" alt="" /></td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>4-MeO-C₆H₄-C(O)N₃ ((4.14d))</td>
<td>4.19g</td>
<td><img src="image" alt="" /></td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>C₆H₅N₃ (3.27a)</td>
<td>4.19a</td>
<td><img src="image" alt="" /></td>
<td>89</td>
</tr>
</tbody>
</table>

\(^a\)Reactions conducted using 0.3 mmol of azide 4.14/3.27, 0.39 mmol of 4.19, 0.39 mmol of CIP(pin), and 0.39 mmol of Et₃N in PhCl (0.2 M) for 12 h. \(^b\)Isolated yield. \(^c\)Reaction employed NaH in place of Et₃N and run at 80 °C.

4.1.2.4 Intramolecular Ligations

Lactams are critical substructures in many biologically active natural products and chemotherapeutics.\(^{156-159}\) To access this substructure, we chose to evaluate our method in the context of a direct intramolecular coupling between carboxylic acids and azides. Thus, ligation of carboxylic acid 4.26 bearing a pendant benzyl azide with CIP(pin) and Et₃N led to an excellent yield (87%) of the benzo-fused lactam 4.27 (eq 44).
Emboldened by this result, we examined the importance of the benzo-fused backbone and rigidity \textit{en route} to synthesizing lactams. To test this, acyclic azido acid 4.28 was subjected to the intramolecular amidation conditions. Upon treatment of 4.28 with NaH and CIP(pin) in PhCl, lactam 4.29 was produced in only a slightly lower yield (eq 45). The use of NaH in lieu of Et$_3$N led to a better isolatable yield of amide 4.29. Unlike the conditions required for the formation of 4.27, reflux temperatures were necessary to furnish the amide 4.29 derived from alkyl substituted carboxylic acid 4.28.

Of the various lactam ring sizes, one of the most popular is the β-lactam that consists of a four-membered cyclic core. Attempts to synthesize these motifs initially raised concern when examining the ring strain associated with β-lactams and our elevated temperature conditions required for O-to-N acyl transfer. Much to our surprise, when cinnamic acid derivative 4.30 was subjected to the chlorophosphite conditions, β-lactam 4.31 was created in 86% yield despite the presence of an exocyclic double bond (eq 46).\textsuperscript{160,161}
Considering the importance and role that β-lactams play in the design of new antibiotics, we were pleased to find the formation of such strained heterocycles occurred with relative ease by employing our modified chlorophosphite Staudinger ligation. Utilizing the standard Staudinger ligation to produce lactams is inefficient due to the insolubility of the resultant phosphonium carboxylate salt in the required solvents.\textsuperscript{113}

4.1.2.5 Synthesis of Peptides

Amide bonds are prevalent in various fields including chemical biology, where the synthesis of peptides remains of the upmost importance. Peptides play several roles from being small molecule drugs to ligands in asymmetric catalysis reactions.\textsuperscript{162,163} More recently, the Staudinger ligation has become a powerful alternative to the “native chemical ligation” approach toward the synthesis of peptide fragments\textsuperscript{164,165} by addressing the limitations associated with the need for a cysteine residue at the site of ligation.\textsuperscript{166,167} To evaluate our method for the derivatization of amino acids and the construction of optically active dipeptides, a collection of \textit{N}-protected amino acids \textbf{4.32} was assembled and ligated with various functionalized azides \textbf{4.14} (Table 4.5). In general, CIPPh\textsubscript{2} and NaH proved superior when synthesizing dipeptides. It’s noteworthy that the diphenylphosphinic acid generated instead of the pinacol phosphinic acid is
removed through an aqueous workup as in the optimized conditions. To test whether
amino acids would behave similarly to aromatic and alkyl carboxylic acids, Cbz-alanine
(4.32a) was treated with BnN₃ (3.27b) and Ph₂PCL in PhCl, which ultimately provided Cbz
amino amide 4.33a in 60% yield (entry 1).

TABLE 4.5
SYNTHESIS OF AMINO ACID DERIVATIVES AND DIPEPTIDES

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino Acid</th>
<th>Azide</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cbz-Ala-OH</td>
<td>BnN₃</td>
<td>MeCNHBnz</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>Fmoc-Phe-OH</td>
<td>TsN₃</td>
<td>PhCNHfomoc</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>Fmoc-Ala-OH</td>
<td>Gly-N₃</td>
<td>MeCNHfomoc</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>Fmoc-Phe-OH</td>
<td>Gly-N₃</td>
<td>PhCNHfomoc</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>Fmoc-Ile-OH</td>
<td>Gly-N₃</td>
<td>PhCNHfomoc</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>Fmoc-Cys(Trt)-OH</td>
<td>Gly-N₃</td>
<td>Ph₃CSCNHBnz</td>
<td>73</td>
</tr>
</tbody>
</table>
### TABLE 4.5 (CONTINUED)

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Amino Acid</th>
<th>Azide</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fmoc-Trp(Boc)-OH</strong>&lt;sup&gt;4.32f&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fmoc-Pro-OH</strong>&lt;sup&gt;4.32g&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fmoc-Trp(Boc)-OH</strong>&lt;sup&gt;4.32f&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Ph[2]CO₂H NHFmoc</td>
<td>Phe-N₃&lt;sup&gt;(4.14e)&lt;/sup&gt;</td>
<td>Ph[2]NHFmoc CO₂Et&lt;sub&gt;Et&lt;/sub&gt;</td>
<td>71 (Fmoc-Phe-Phe-OEt)</td>
</tr>
<tr>
<td><strong>Fmoc-Phe-OH</strong>&lt;sup&gt;4.32b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>N-Fmoc[6]CO₂H</td>
<td>Phe-N₃&lt;sup&gt;(4.14e)&lt;/sup&gt;</td>
<td>N-Fmoc[6] CO₂Et&lt;sub&gt;Et&lt;/sub&gt;</td>
<td>83 (Fmoc-Pro-Phe-OEt)</td>
</tr>
<tr>
<td><strong>Fmoc-Pro-OH</strong>&lt;sup&gt;4.32g&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions conducted using 0.3 mmol of azide 6, 0.39 mmol of 23, 0.39 mmol of Cl₃PPh₃, and 0.39 mmol of NaH in PhCl (0.2 M) for 12 h. <sup>b</sup>Isolated yield.

Attempts to increase the yield of 4.33 using the more reactive sulfonfyl azide 4.14b was successful by ligation of Fmoc-protected phenylalanine 4.32b with tosyl azide 4.14b to assemble N-acyl sulfonamide 4.33b (entry 2). Various Fmoc-protected amino acids were subjected to the peptide ligation conditions with the azido ester derivative of glycine 4.14a. Ligation of Fmoc-protected alanine and phenylalanine provided Fmoc-Ala-Gly-OEt 4.33c and Fmoc-Phe-Gly-OEt 4.33d with Gly-N₃ 4.14a in 88% and 87% respectively (entries 3 and 4). Substitution on the amino acid side chain did not adversely effect the amidation reaction as illustrated by the coupling of Fmoc-isoleucine.
4.32d and azido glycine 4.14a to yield dipeptide 4.33e in 51% yield (entry 5). Interestingly, the trityl sulfide in Fmoc-cysteine 4.32e did not hinder the formation of dipeptide 4.33f, which proceeded in a respectable yield (73%). Various other protecting groups were tolerated under the amidation conditions, as seen by the treatment of the N,N-diprotected tryptophan with Gly-N₃ 4.14a to provided dipeptide 4.33g in 78% yield. Intriguingly, the most efficient dipeptide formation occurred when utilizing cyclic amino acid Fmoc-Pro-OH 4.32g, which lacks a free N-H bond. Perhaps the lack of this bond prohibits the nitrogen from ligating to phosphorus, minimizing degradation of various intermediates. Importantly, the C–N bond formation proceeded without loss of optical purity as determined by comparing the optical rotations to literature values.

To further probe this modified Staudinger ligation, numerous dipeptides containing two chiral centers were synthesized by employing a chiral azide. In general, various Fmoc-protected amino acids ligated efficiently with the azido ester derivative of phenylalanine 4.14e (entries 9-11). Attempts to couple fully protected Trp-Phe 4.32f with Phe-N₃ 4.14e led to only a modest yield of Fmoc-Trp(Boc)-Phe-OEt 4.33i likely due to a sterically encumbered transition state (entry 9). In light of this result, ligation between the smaller phenylalanine amino acid 4.32b with azido phenylalanine ester 4.14e gave Fmoc-Phe-Phe-OEt in 71% yield without loss of optical purity (entry 10). Similarly, coupling of Fmoc-proline 4.32g with azide 4.14e proceeded in excellent yield of dipeptide 4.33k in 83% (entry 11). In each case, C–N bond formation provided the optically active dipeptide with dr of > 90:10 as determined through ¹H NMR spectroscopy.¹⁵²
4.1.2.6 Chemoselectivity

A frequent problem encountered with Staudinger ligations involving an activated carboxylic acid and nucleophilic azide is the presence of other electrophilic and nucleophilic functional groups. Our method was specifically designed to address this issue through an intramolecular acylation event in the presence of other nucleophiles and electrophiles. In our hands, an unprotected hydroxyl group tethered to benzoic acid 4.19i did not inhibit formation of amide 4.23r, which occurred in 64% yield without competitive intermolecular esterification on the intermediate ester phosphite or phosphazine (eq 47). Electrophilic carbonyl derivatives remained unaffected during the C–N coupling event, as demonstrated by the conversion of para-formyl benzoic acid 4.19m and acetophenone-substituted acid 4.19n to their matching amides 4.23s and 4.23t in 60% and 82% yield respectively (eq 48 and 49).
Interestingly, neither the Schmidt rearrangement\textsuperscript{368} product resulting from addition of azide to the electrophilic aldehyde/ketone or imine formation due to competitive aza-Wittig reactions\textsuperscript{169} at the carbonyl carbon were observed. As observed by the addition of BnN$_3$ (3.27b) and chlorophosphite to benzoic acid derivative 4.19o, location of the electrophilic component possessed some importance (eq 50). The problematic substrate led to a low yield of the corresponding amide 4.23u while also resulted in a mixture of unidentifiable side products. This is likely a consequence of the proximal carbonyl attacking the intermediate ester phosphite or attack upon carbonyl by the phosphazene.

![Chemical Reaction](image)

Although lower yields of the amides 4.23s, 4.23t, and 4.23u were obtained, no competitive nucleophilic or electrophilic by-products were isolated. To evaluate whether 4.19l-o were non-optimal substrates, an intermolecular carboxylic acid chemoselectivity in the phosphite-mediated ligation was examined. By probing a series of competition experiments between carboxylic acid 4.19a and a carbonyl additive 2.8c/1.30/4.34 perhaps a better understanding of selectivity could be established (Table 4.6). Treatment of 4.19a and 4.14b with ClP(pin) and Et$_3$N in the presence of anisaldehyde 2.8c led to an excellent yield of amide 4.23b (93%) while recovering back 94% of aldehyde 2.8c (entry 1). An alterative pathway through which amide 4.23b is formed involves a Schmidt rearrangement of aldehyde 2.8c with azide 4.14b. Although
this mechanism cannot be ruled out, it appears unlikely in light of previous reports by Aubé indicating a migratory preference of carbon bearing groups over hydrogen.\textsuperscript{170} Exchanging aldehyde 2.8c for acetophenone (1.30) or methyl benzoate (4.34) had no detrimental affect to the ligation of acid 4.19a and tosyl azide. In fact N-acyl amide 4.23b was obtained in 93% and 92% yield respectively while recovering 1.30 and 4.34 in near quantitative amounts (entries 2 and 3).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Entry}\textsuperscript{a} & \textbf{Carbonyl Additive} & \textbf{Yield of 4.23b (\%)}\textsuperscript{b} & \textbf{Yield of Recovered Additive (\%)}\textsuperscript{b} \\
\hline
1 & \includegraphics[width=0.2\textwidth]{4.19a} & 93 & 94 \\
2 & \includegraphics[width=0.2\textwidth]{1.30} & 93 & >99 \\
3 & \includegraphics[width=0.2\textwidth]{4.34} & 92 & 93 \\
\hline
\end{tabular}
\caption{CHEMOSELECTIVITY OF ELECTROPHILIC CARBONYLS}
\end{table}

\textsuperscript{a}Reactions conducted using 0.3 mmol of azide 4.14b and 0.39 mmol each of 4.19a, 2.8c/1.30/4.34, CIP(pin), and Et\textsubscript{3}N in PhCl (0.2 M) for 12 h. \textsuperscript{b}Isolated yield.
4.1.2.7 Competitive Amidation Between Azides and Amines

In any synthetic strategy, whether it be in natural product or designed materials synthesis, chemoselectivity is of paramount importance.\textsuperscript{171-173} The acyl migration from the proposed ester aza-ylide intermediate \textbf{4.20} was designed to activate the carbonyl \textit{in situ} and tolerate the presence of unprotected electrophilic and nucleophilic character. To evaluate chemoselectivity between the azide nitrogen and other nucleophilic functional groups, carboxylic acid \textbf{4.19a} was treated with NaH, CIP(pin), tosyl azide \textbf{4.14b}, and 1 equivalent of benzenesulfonamide \textbf{4.35} (eq 51). Sulfonamide \textbf{4.23b}, derived from azide \textbf{4.14b}, was produced in 79\% yield while recovering additive \textbf{4.35} nearly quantitatively. Despite a slightly lower yield of tosyl amide \textbf{4.23b}, treatment of acid \textbf{4.19a} under the same conditions (i.e. 1 equiv of TsN$_3$, CIP(pin), and NaH) gave comparable results (eq 52).

\[
\begin{align*}
\text{PhCOOH} & \xrightarrow{\text{TsN$_3$, CIP(pin), NaH, PhCl}} \text{PhCONHts} + \text{PhSO$_2$NH$_2$} \quad \text{(51)} \\
\text{TsN$_3$, CIP(pin), NaH, PhCl} & \rightarrow \text{PhCONHts} \quad \text{(52)}
\end{align*}
\]

To examine a more nucleophilic counterpart, Fmoc-Pro \textbf{4.32g} was treated with azido glycine \textbf{4.14a}, NaH, CIPPh$_2$, and methyl glycine \textbf{4.36} (eq 53). Amide \textbf{4.33h}, a result from intramolecular ligation involving azide \textbf{4.14a}, was obtained in a 5:1 ratio with
amide 4.33l, arising from an acyl substitution of the phosphite ester or a transamidation reaction with amine 4.36.

When compared to previously reported results involving competitive ligation of thioesters, Raines observed a similar ratio for azide ligation (azide/amine = 3:1).\textsuperscript{174} Based on the apparent chemoselectivity for azide 4.14a over amine 4.36 in the ligation step, we hypothesized that our phosphite-mediated acyl substitution strategy would enable the coupling of peptides using unprotected amino acids. Surprisingly, treatment of proline (4.37) with NaH, Ph₂PCl, and azido glycine ester 4.14a furnished the crucial peptide bond of the isolated cyclic dipeptide c-Pro-Gly 4.38 in 62% yield (eq 54). Any opportunity to avoid the standard conventional and tedious protection/deprotection procedure in peptide synthesis would be considered a substantial advancement to assembly of peptides and peptide bonds.\textsuperscript{175-177}
4.1.2.8 Application Towards the Total Synthesis of LY573636

To evaluate the synthetic utility of our modified Staudinger-igation toward the synthesis of chemotherapeutic agents, we targeted the sulfonamide linkage in the promising anti-tumor agent LY573636 4.42 (Scheme 4.5).\textsuperscript{178} Although its mode of action is unknown, initial results show \textbf{4.42} induces apoptosis though a mitochondrial mechanism not used by other anti-cancer drugs.\textsuperscript{179,180} What makes \textbf{4.42} an excellent synthetic target is its selectivity towards various cancer cell lines in the low micromolar range (3-7 \textmu M). The process group at Lilly constructs the crucial sulfonamide linkage using an activated carbonyl species in the form of either a carbonyl imidazole or acid chloride of \textbf{4.19p}.

\[
\begin{align*}
\text{Br-S-S-Cl} & \quad \xrightarrow{\text{NH}_2\text{OH, THF}} \quad \text{Br-S-S-NH}_2 \\
\textbf{4.39} & \quad \text{96\% yield} & \quad \textbf{4.40}
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} \\
\text{4.19p} & \quad \xrightarrow{(\text{COCl})_2, \text{pyridine, PhMe}} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} \\
\textbf{4.41} & \quad \xrightarrow{\textbf{4.40, Et}_3\text{N, DMAP}} & \quad \text{isopropyl acetate} & \quad \text{89\% over 2 steps} & \quad \textbf{4.42} & \quad \text{LY573636}
\end{align*}
\]

Scheme 4.5: Yates and Coworkers Route to LY573636.

An alternative approach using our Staudinger ligation method would support an additional route not reliant upon carbonyl preactivation compared to the existing four-step synthesis of \textbf{4.42}, reported by Yates and coworkers. In contrast, our synthesis of LY573636 began with thiophene sulfonyl azide \textbf{4.44}, which was accomplished in 45%
yield through sulfonylation of bromothiophene 4.43 followed by nucleophilic displacement of chloride by NaN₃ (Scheme 4.6).¹⁸¹

![Scheme 4.6: Modified Staudinger Ligation Approach to LY573636](image)

Treatment of commercially available carboxylic acid 4.19p and azide 4.44 with CIP(pin) and Et₃N in PhCl provided LY573636 4.42 in near quantitative yield (97% yield). By employing a chlorophosphite modified Staudinger ligation approach, total step count and purification steps can be reduced by at least one. This efficient, rapid, and chemoselective route toward the synthesis of heterocyclic sulfonamides is an ideal approach for structure activity relationship (SAR) studies. With the ability to quickly screen various sulfonamide-containing biologically active molecules, it will be easier to identify new and improved highly potent pharmaceutical agents.¹⁸²-¹⁸⁴

4.1.2.9 Proposed Mechanism

Our hypothesis for a proposed mechanism involves initial attack of the carboxylate of 4.45 upon the chlorophosphite (Scheme 4.7). This phosphite ester 4.46
formation is likely the cause for the high levels of chemoselectivity and observed reactivity of the intramolecular, nucleophilic acyl substitution of carboxylic acid 4.45. Evidence of 4.46 formation is observed by precipitation of either Et$_3$N·HCl or NaCl in PhCl. When the chlorophosphite is omitted from the reaction conditions, quantitative recovery of carboxylic acid 4.45 and azide 4.47 occurs. Following formation of 4.46, the electron deficient phosphorus decomposes azide 4.47 generating phosphazide 4.48, which simultaneously activates both the carboxylic acid and azide motif for the emergent acyl substitution event. Based on the findings by Bertozzi and Bergman, and independently by Raines, involving esters and thioesters respectively, one acyl substitution pathway involves attack of the azide motif upon phosphorus, followed quickly with a retro-[2+2] and expulsion of N$_2$ to provide ester aza-ylide 4.50. This aza-ylide intermediate is setup perfectly to undergo the [1,3]-acyl migration from oxygen to the basic ylide nitrogen (Scheme 4.7, path a).$^{185-187}$ The elevated temperatures required for C–N bond formation to occur is consistent with a high energy transition state such as a 4-exo-trig cyclization, in spite of the formation of a strong P=O bond.$^{188-190}$ This supports the observations regarding lower boiling solvents, which failed to produce the desired amides.$^{191,192}$
Alternatively, if aza-ylide formation is relatively slow, one could envision a six-membered transition state where the azide nitrogen attacks the activated carbonyl instead to provide acyl phosphoryl triazene 4.55.\(^{193}\) Nucleophilic attack of the amide nitrogen upon phosphorus with followed by a similar retro-[2+2] to lose nitrogen gas resulting in phosphoramidate intermediate 4.52 (path b). Dephosphorylation via hydrolysis or nucleophilic attack and ligand exchange on phosphorus produces the desired amide 4.57. Although it is unclear whether the acyl substitution event is occurring via an ester aza-ylide 4.50 (path a) or directly from a phosphazide-type intermediate 4.54 (path b), it is plausible that both pathways function under the reaction conditions to provide amide 4.57. Along with a proposed mechanism, several
preliminary mechanistic conclusions can be concluded about our modified Staudinger ligation.

Although an intermolecular aza-ylide addition to another phosphite ester 4.46 or a ketene intermediate cannot be entirely ruled out, these pathways remain unlikely due to the lack of crossover carbonyl by-products isolated from the explored chemoselective reactions. The observed chemoselectivity for carboxylic acid and azide functional groups as shown is likely an outcome of initial O–P bond formation which precedes intramolecular acyl migration; a net overall dual activation through the use of phosphorus.

Several comparisons can be drawn between the previously mentioned mechanistic studies on the Staudinger ligation by Bertozzi/Bergman\textsuperscript{194} or Raines\textsuperscript{174} and our observations. Initially, it was speculated that the yield of amide 4.57 would improve if zwitterionic intermediates 4.48 and 4.50 were stabilized by the use of more polar solvents. Our findings support this hypothesis by observing that PhCl (40\%) proved superior to PhMe (16\%) in the formation of amide 4.57 (Table 4.1). An under-explored aspect of the Staudinger ligation pertains to the geometry around phosphorus, as influenced by the mono- or bi-dentate ligand scaffolds. By employing a series of different phosphites in the ligation of acid 4.19a and azide 4.14b, an intriguing correlation between the bite angle at phosphorus and the isolatable yield of amide 4.23b is observed (Table 4.2). Chlorophosphites bearing diol ligands that form five- and six-membered ring chelates produced superior yields compared to larger chelates or two separate labile ligands. Reaction efficiency increased when going from CIP(OEt)\textsubscript{2} and
CIP(bin) to CIP(pin) and CIP(dmp-ol) indicating that a decreased bite angle around phosphorus promotes aza-ylide formation through an improved lone pair accessibility needed for azide attack. Another rational for this increase in reactivity of pinacol and dimethylpropanediol ligands is due to fewer decomposition pathways through elimination or substitution on the ligand.

4.1.2.10 Summary

Among the several advantages of the phosphite-modified amidation protocol described herein, the ability to conduct acyl substitution on carboxylic acids directly without need for pre-activation is an improvement from conventional methods. In our case, the chloride anion (e.g. Et₃N·HCl or NaCl), phosphinic acid by-products, and unreacted carboxylic acid are easily removed from the crude material through an aqueous workup.

Overall, the method presented herein allows for rapid access to a diverse assortment of amides through direct functionalization of carboxylic acids and azides by a dual-activating chlorophosphite reagent. This procedure complements existing amide-bond forming technology by virtue of the chemoselective intramolecular acyl transfer from oxygen to nitrogen. The appealing roles the phosphite plays to unmask the hidden electrophilicity of carboxylic acids and the nucleophilicity of azides in a controlled fashion is capable of influencing the assembly of biologically active natural products and complex synthetic targets containing peptides, amides, or lactams bonds.
4.1.3 Phosphine-Catalyzed Amidation of Carboxylic Acids

4.1.3.1 Introduction

The Staudinger-type ligation of carboxylic acid derivatives (e.g. acid chlorides, anhydrides, acyl selenides and thioesters) and azides has evolved into a preeminent strategy for the construction of amide C–N bonds (Figure 4.1). However, the overall synthetic efficiency becomes limited due to stoichiometric formation of by-products (e.g. \( \text{R}_3\text{P} = \text{O} \)). Therefore, a phosphine-catalyzed Staudinger ligation that directly couples carboxylic acids and azides would reduce the formation of undesired by-products while avoiding the need for additional preactivation steps.

\[
\begin{align*}
\text{O} & \quad \text{R}^1 \quad \text{Z} + \text{R}^2 \quad \text{N}_3 \quad \text{L}_3\text{P} \quad (1-3 \text{ equiv}) \\
& \quad \text{(-N}_2\text{)} \rightarrow \text{O} & \quad \text{R}^1 \quad \text{Z} \quad \text{L} \quad \text{PL}_2 \quad \text{H}_2\text{O} \\
& \quad \text{NR}_2 \quad - & \quad \text{O} & \quad \text{R}^1 \quad \text{NH} \quad \text{R}^2 + \text{O} & \quad \text{PL}_3
\end{align*}
\]

\( Z = \text{Cl, OR, SeR, SR, OC(O)R; L = aryl, alkyl} \)

**Figure 4.1: Conventional Activation for Staudinger Ligations**

The implementation of a catalytic Staudinger ligation has several challenges associated with it including identification of an appropriate phosphine/reductant combination that would enable catalyst turnover. Unlike the conventional Staudinger ligation wherein \( \text{R}_3\text{P}=\text{O} \) is generated by hydrolysis of an amidophosphonium salt, a catalytic variant would require oxygen transfer from the carboxylic acid to the phosphorus under anhydrous conditions (Figure 4.2).
Inspired by recent work involving the development of redox phosphine catalyzed transformations,\textsuperscript{118,122,126,202} silanes caught our attention as a mild reductant for phosphine oxides.\textsuperscript{203,204} We hypothesized that the aza-ylide intermediate reacts with the carboxylic acid 4.19b in an acid/base fashion to produce the crucial activated phosphonium carboxylate 4.62 \textit{in situ} towards the C–N bond forming event (Scheme 4.8).

![Scheme 4.8: Proposed Phophonium Carboxylate-Type Intermediate](image)

With the P\textsuperscript{iii}/P\textsuperscript{v} redox cycle mediated by the silane reductant, compatibility with the carboxylic acid, azide, and amide product is crucial. Based on recent work by van Delft and coworkers, the biggest trepidation would be minimization of aza-ylide
reduction while still enabling catalytic turnover.\textsuperscript{126} Competitive aza-ylide reduction would hinder formation of the activated phosphonium carboxylate salt and the resulting amide bond-forming event.

4.1.3.2 Optimization of Amidation

The initial choice to examine catalytic PPh\textsubscript{3} and Ph\textsubscript{2}SiH\textsubscript{2} in the ligation of carboxylic acids with azides is based on the slower reduction rate of the resulting aza-ylide derivative as highlighted previously. Hence, treatment of trifluoromethyl benzoic acid \textbf{4.19b} and benzyl azide (\textbf{3.27b}) with 10 mol\% PPh\textsubscript{3} and Ph\textsubscript{2}SiH\textsubscript{2} provided the corresponding benzyl amide \textbf{4.23n} in 25% yield (eq 55).

\begin{center}
\begin{tikzpicture}
\begin{scope}[scale=0.8]
\node[draw,shape=circle] (a) at (0,0) {$4.19b$};
\node[draw,shape=circle] (b) at (3,0) {$4.23n$};
\node at (1.5,0) {25\% yield};
\node at (1.5,-0.5) {80\% based on recovered azide};
\node[align=center] at (2.5,-1) {eq 55};
\draw[->] (a) to node[above]{$\text{BnN}_3, \text{PPh}_3$ (10 mol\%), \text{PhMe}$rt\rightarrow 60 \, ^\circ \text{C}, 18 \, h$} (b);
\end{scope}
\end{tikzpicture}
\end{center}

Although the isolated yield of \textbf{4.23n} was low, an 80\% yield was achieved based on recovered \textbf{4.19b}. This result indicated that PPh\textsubscript{3} underwent at least 1.5 turnovers, lending evidence in support of our hypothesis that the Staudinger ligation could be rendered catalytic in phosphine. Initially, it is presumed that amide formation is occurring through a phosphonium carboxylate-type intermediate \textbf{4.62} (Scheme 4.8). Embolden by this initial result, we focused our attention on examining various silanes and their capability to couple acid \textbf{4.19b} with BnN\textsubscript{3} \textbf{3.27b} (Table 4.7). Although alkoxy silanes are known to efficiently reduce phosphine oxides, employment of (MeO)\textsubscript{3}SiH or (EtO)\textsubscript{2}MeSiH failed to provide amide \textbf{4.23n} in more than trace quantities (entries 1 and
Unfortunately, the use of ClSiH provided similar results to alkoxy silanes in formation of amides with and without additional base being present (entry 3). Intriguingly, an exchange of PhSiH for PhSiH led to a dramatic improvement in the isolatable yield of 4.23n (entry 4). A slight increase in the amount of azide 3.27b further increased the yield up to near quantitative amounts (entry 5).

**TABLE 4.7**

**EFFECT OF VARIOUS SILANES UPON AMIDATION**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv of Azide</th>
<th>Silane</th>
<th>Equiv of Silane</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>(MeO)SiH</td>
<td>1.0</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>(EtO)MeSiH</td>
<td>1.0</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>ClSiH</td>
<td>1.0</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>PhSiH</td>
<td>1.0</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>PhSiH</td>
<td>1.0</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>PhSiH</td>
<td>0.5</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>1.2</td>
<td>PhSiH</td>
<td>1.5</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>1.2</td>
<td>PhSiH</td>
<td>2.0</td>
<td>50</td>
</tr>
</tbody>
</table>

Reactions Conditions: 4.19b (0.30 mmol), PPh (10 mol%), 3.27b (indicated), and RSiH (indicated) in PhMe (0.3 M) for 18 h. Isolated yield. NR = no reaction.

Interestingly, attempts to reduce or increase the amount of PhSiH led to a significant reduction in the yield of 4.23n. This observation supports our hypothesis that minimizing competitive iminophosphorane reduction is critical for the creation of a
catalytic Staudinger ligation (entries 6-8). Although carboxylic acids and free amines have previously been shown to ligate in the presence of excess PhSiH₃, a modification to include benzyl azide 3.27b, cinnamic acid 4.19g, PPh₃ (10 mol%), and PhSiH₃ in DMF produced only trace quantities of desired amide 4.26a (eq 56).²⁰⁶

\[
\begin{align*}
\text{4.19g} & \xrightarrow{\text{PPh₃ (10 mol%), BnN₃ 3.27b, PhSiH₃ (4 equiv), DMF, rt}} \text{4.26a} \\
& \text{<5% yield}
\end{align*}
\]

We next turned our attention toward examining the nature of phosphorus-based catalyst and its catalytic loading. Unfortunately, reducing the amount of PPh₃ to 5, 2, or 1 mol% resulted in a lower yield of amide 4.23n and longer reaction times (Table 4.8, entries 1-3). Modifications to the electronic nature of the phosphorus-based catalyst by employing the more electron rich aryl phosphate (4-MeOC₆H₄)₃P or more basic trialkyl phosphine (nBu3P) provided benzyl amide 4.23n in 64% and 45% yields respectively. As expected, dibenzophosphole 3.55 and phospholane oxide 3.44 failed to supply 4.23n in a yield above 65% likely due to competitive P=N reduction (entries 6 & 7).¹¹⁸,¹²⁶
### TABLE 4.8

PHOSPHORUS CATALYST OPTIMIZATION

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Catalyst</th>
<th>Mol% of Catalyst</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph₃P</td>
<td>5%</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>Ph₃P</td>
<td>2%</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>Ph₃P</td>
<td>1%</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>(4-MeOC₆H₄)₃P</td>
<td>10%</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>nBu₃P</td>
<td>10%</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="3.56" /></td>
<td>10%</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="3.45" /></td>
<td>10%</td>
<td>48</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions Conditions: **4.19b** (0.30 mmol), phosphorus source (indicated), BnN₃ (0.36 mmol), and PhSiH₃ (1 equiv) in PhMe (0.3 M) for 18 h. <sup>b</sup>Isolated yield.

Throughout this study, we discovered that the reaction efficiency was highly solvent dependent. Performing the phosphine-catalyzed ligation between carboxylic acids and azides in a solvent other than PhMe proved inferior (Table 4.9). Substituted of the high-boiling hydrocarbon solvent for halogenated variations (e.g. DCE and PhCl) failed to produce benzyl amide **4.23n** in yields above 51% (entries 1 and 2). Not surprisingly, the use of polar protic solvents (i.e. MeOH) failed to provide any reaction
likely due to a competitive process with the reductant. Employment of CH₃CN or DME
gave moderate yields of the desired amide 4.23n in 43% and 58% yield respectively. Use
of highly polar solvents DMF or DMSO gave poor yields of amide 4.23n, a result of
destabilization upon the proposed phosphonium carboxylate-type intermediate 4.62.
Having established our optimized conditions of 10 mol% of PPH₃, 1.0 equivalent of
PhSiH₃, and toluene, we focused our attention toward the variability of the carboxylic
acid and azide motifs.

TABLE 4.9

ASSESSMENT OF VARIOUS SOLVENTS

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Solvent</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCE</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>PhCl</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>CH₃CN</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>DME</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>DMSO</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions Conditions: 4.19b (0.30 mmol), PPH₃ (10 mol%), 3.27b (0.36 mmol), and PhSiH₃ (1 equiv) in solvent (0.3 M) for 18 h. <sup>b</sup>Isolated yield. NR = no reaction.
4.1.3.3 Synthesis of Amides

Overall, treatment of various carboxylic acids 4.19 and diverse azides with PPh₃ (10 mol%) and PhSiH₃ provided good to excellent yields of amides 4.26 (Table 4.10). In our initial examination of aromatic carboxylic acids, benzoic acid 3.26a ligated extremely well with 3.27b to produce benzamide 4.26b in 94% yield (entry 1). Modification of the electronics of the aryl ring had little effect on the C-N bond-forming step. Electron rich aryl rings, such as anisic acid 4.19a, formed the analogous benzyl amide in great yield (entry 2). Electron deficient benzoic acid derivatives provided excellent isolatable yields of the corresponding benzyl amides as seen by the ligation of 4-bromobenzoic acid (4.19q) and 4-cyanobenzoic acid (4.19c) with benzyl azide 3.27b to generate benzyl amides 4.26d and 4.26e in 95% and 97% respectively (entries 3 & 4). Oddly, strong electron withdrawing groups (i.e. nitro) produced the corresponding amide in lower yields (entry 5). Alkyl carboxylic acids also effortlessly converted to their corresponding amides directly (entries 6-8). Interestingly, α,β-unsaturated acid cinnamic acid 4.19g underwent amidation with exclusive 1,2-addition without observing 1,4-addition or [3,3]-rearranged by-products. Other aliphatic acids 4.19j and 4.19k proceeded simply to the resultant amides 4.26g and 4.26h in moderate yields (88% and 61% yield respectively). It is noteworthy that the amidation of pivalic acid 4.19k proceeds in moderate yield of amide 4.26h, indicating that a ketene-type mechanism is not plausible.¹⁵²
### TABLE 4.10
COMPATIBILITY OF ASSORTED CARBOXYLIC ACIDS

![Chemical Reaction Image]

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Carboxylic Acid</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.26a</td>
<td>4.26b</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>4.19a</td>
<td>4.26c</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>4.19q</td>
<td>4.26d</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>4.19c</td>
<td>4.26e</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>4.19r</td>
<td>4.26f</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>4.19g</td>
<td>4.26a</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>4.19j</td>
<td>4.26g</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>4.19k</td>
<td>4.26h</td>
<td>61</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conditions: 3.26a/4.19 (0.30 mmol), 3.27b (0.36 mmol), PPh₃ (10 mol%), and PhSiH₃ (0.30 mmol) in PhMe (0.3 M) for 18 h. <sup>b</sup>Isolated yield.
Having established the scope of viable carboxylic acids, we turned our attention toward the compatibility of various azides with our catalytic Staudinger ligation reaction (Table 4.11). Treatment of cinnamyl azide 4.14f with trifluoromethyl benzoic acid 4.19b produced cinnamyl amide 4.26i in 94% yield (entry 1). Additionally, azides attached to a pendant heteroaromatic group also were feasible substrates as demonstrated by the formation of amide 4.26j from carboxylic acid 4.19b and furfural azide 4.14g (entry 2). Even aliphatic azides 4.14h produced the desired alkyl amide in impeccable yields (entry 3). In addition to the benzyl, allyl, and alkyl azides, we sought to examine the effectiveness of aryl and acyl azides in the PPh$_3$-catalyzed Staudinger ligation. Ligation of aryl azide 4.14i with cinnamic acid 4.19g gave the N-acyl aniline 4.26l in 80% yield (entry 4). Moreover, the difficult to handle acyl azide 4.14d did undergo conversion to imide 4.23p with the cinnamic acid in a mere 35% yield (86% based on recovered acid, entry 5).$^{153}$ Attempts to increase the yield of 4.23p through longer reaction times or lower temperatures led primarily to decomposition of azide 4.14d and diminished yield of imide 4.23p.
TABLE 4.11

EXPLORATION OF VARIOUS AZIDES UNDER CATALYTIC CONDITIONS

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylic Acid</th>
<th>Azide</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F₃C₄H₂CO₂H</td>
<td>4.14f</td>
<td>4.26i</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>F₃C₄H₂CO₂H</td>
<td>4.14g</td>
<td>4.26j</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>F₃C₄H₂CO₂H</td>
<td>4.14h</td>
<td>4.26k</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>MeO₂C₄H₂</td>
<td>4.14i</td>
<td>4.26l</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>MeO₂C₄H₂</td>
<td>4.14d</td>
<td>4.23p</td>
<td>35 (86)²</td>
</tr>
</tbody>
</table>

⁹Conditions: 4.19 (0.30 mmol), 4.14 (0.36 mmol), PPh₃ (10 mol%), and PhSiH₃ (0.30 mmol) in PhMe (0.3 M) for 18 h. bIsolated yield. cYield based on recovered starting material.

Given the pervasiveness of the lactam motif in chemotherapeutics,¹⁵⁶,¹⁵⁷,²⁰⁷ and the critical role lactamizations play in the construction of biologically active natural products,¹⁵₈,¹⁵⁹,²⁰₈ this phosphine-catalyzed Staudinger ligation provides a powerful tool for their construction. One of the major drawbacks to previous Staudinger ligation methods is the inability to generate lactams efficiently without prior activation of the
carbonyl. Presumably this is due to the insolubility of the resultant intramolecular phosphonium carboxylate intermediate.\textsuperscript{113} Contrary to their results, the catalytic Staudinger ligation method preceded effortlessly in the intramolecular ligation of carboxylic acid 4.26 with 10 mol\% PPh\textsubscript{3} and PhSiH\textsubscript{3} to produce benzofused lactam 4.27 in 77\% yield (eq 57).

![Chemical Reaction Image]

4.1.3.4 Synthesis of Peptides

Several alternative approaches to the “native chemical ligation” method to synthesizing peptides have recently been developed.\textsuperscript{165} Many of these new techniques, including the Staudinger ligation, address the inherent need for a cysteine residue at the terminal site of the ligation partner. With cysteine being the second least naturally abundant amino acids at 1.7\%, new and improved procedures are in high synthetic demand. Although initially uncertain whether the catalytic Staudinger ligation could become applicable to synthesize peptides, concerns did arise regarding the use of amino acids. A potential problem when utilizing α-amino acids is their ability to racemize under various conditions including elevated temperatures. To evaluate our catalytic method, we examined the coupling of Cbz-protected alanine 4.32\textsubscript{a} with azido glycine ethyl ester 4.14\textsubscript{a} to generate dipeptide 4.33\textsubscript{a} (Table 4.12, entry 1).
TABLE 4.12

CHIRAL DIPEPTIDE SYNTHESIS

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino Acid</th>
<th>Dipeptide Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;H&lt;/sub&gt; NHCbz</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;H&lt;/sub&gt; NHCbz</td>
<td>59 (Cbz-Ala-Gly-OEt)</td>
</tr>
<tr>
<td></td>
<td>Cbz-Ala-OH 4.32a</td>
<td>Cbz-Ala-OH 4.32a</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;H&lt;/sub&gt; NHCbz</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;H&lt;/sub&gt; NHCbz</td>
<td>59 (Cbz-Phe-Gly-OEt)</td>
</tr>
<tr>
<td></td>
<td>Cbz-Phe-OH 4.32h</td>
<td>Cbz-Phe-OH 4.32h</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CO&lt;sub&gt;H&lt;/sub&gt; NFMoc</td>
<td>CO&lt;sub&gt;H&lt;/sub&gt; NFMoc</td>
<td>60 (Fmoc-Pro-Gly-OEt)</td>
</tr>
<tr>
<td></td>
<td>Fmoc-Pro-OH 4.32g</td>
<td>Fmoc-Pro-OH 4.32g</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;H&lt;/sub&gt; NHCbz</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;H&lt;/sub&gt; NHCbz</td>
<td>50 (Cbz-Trp-Gly-OEt)</td>
</tr>
<tr>
<td></td>
<td>Cbz-Trp-OH 4.32i</td>
<td>Cbz-Trp-OH 4.32i</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Conditions: 4.32 (0.30 mmol), 4.14a (0.36 mmol), PPh<sub>3</sub> (10 mol%), and PhSiH<sub>3</sub> (0.30 mmol) in PhMe (0.3 M) for 16 h. <sup>b</sup>Isolated yield.

When N-Cbz-protected alanine 4.32a was subjected to the optimized catalytic Staudinger ligation conditions, dipeptide 4.33a resulted in 59% yield. Additional β-carbon substituents failed to hinder the C-N bond forming step as seen by using Cbz-phenylalanine 4.32h with azide 4.14a to synthesize dipeptide 4.33m in similar yield (entry 2). Each dipeptide synthesized retained all optical activity as determined by optical rotation and comparison to known values. By modifying the protecting group
from N-Cbz to N-Fmoc, Fmoc-Pro-Gly dipeptide 4.33h is created in 60% yield from the corresponding Fmoc-proline 4.32g (entry 3). Interestingly, the use of N-Cbz-protected tryptophan 4.32i, which contains a free indole N–H, did not impede the formation of peptide 4.33n (entry 4), unlike the chlorophosphite modified Staudinger ligation procedure. These results herein highlight the ability of our phosphine-catalyzed Staudinger ligation procedure to construction optically enriched dipeptide fragments rapidly.

4.1.3.5 Chemoselectivity

Speculation of the importance of a tight ion pair in the proposed phosphonium carboxylate intermediate led us to examine chemoselectivity issues during the carboxylic acid and azide ligation event. We initially investigated the PPh₃-catalyzed Staudinger ligation in the presence of additional carbonyl electrophiles. Thus, upon treatment of acid 4.19n, bearing a 4-acetyl group, with catalytic PPh₃ and PhSiH₃ afforded amide 4.26m in 71% yield (Scheme 4.9). It is important to note that neither the imine or amides, resulting from a competitive aza-Wittig reaction¹⁶⁹ or Schmidt-type rearrangement¹⁶₈ respectively were observed in the reaction of keto acid 4.19n.
A similar result occurred when carboxylic acid 4.19s was treated with benzyl azide 3.27b to produce benzyl amide 4.26n in excellent yield (91% yield). The observed chemoselectivity for carboxylic acids over the esters indicates a contrasting mechanism than that of the intra/intermolecular carbonyl addition of an iminophosphorane proposed by Bertozzi and Raines.\(^{174,194}\) In addition, methyl benzoate derivative 4.63 gave only trace quantities of benzofused lactam 4.27 (< 10% yield) perhaps due to inefficient catalyst turnover under our anhydrous conditions (eq 58).

4.1.3.6 Mechanistic Investigations

To gain further insight into the reaction mechanism, and importance of the proposed phosphonium carboxylate intermediate, Wilson examined the effect of
carboxylic acid structure and Brönsted acidity on the rate of amidation (Figure 4.3). In general, her observations indicate that while steric and electronics affect the amide bond formation step, carboxylic acid pKa also played an important role in the rate of conversion. Support for these were observed when electron deficient acid 4.19b exhibiting a faster rate of benzamide formation than electron rich acid 4.19a, while hindered acids o-tolyl 4.19t and mesityl acid 4.19u formed amides slower than more sterically accessible acids like 3.26a and 4.19j (Graph 1).
Figure 4.3: Absolute Rate of Amide Formation.
Interestingly, the least acidic cyclohexane acid \textbf{4.19j} underwent amidation the fastest indicating a correlation between the rate of amidation and ionic character of the phosphonium carboxylate. If the strength of the phosphonium carboxylate covalent bond affects the rate of acyl substitution, then more nucleophilic carboxylates should proceed faster. This would indicate that promotion of a tight ion pair between the phosphonium ion and the carboxylate increases the reaction rate. The faster consumption of acid \textbf{4.19j} (Graph 2) in comparison to formation rate of amide \textbf{4.19a} suggests that acyl substitution leading to C–N bond formation, and not phosphonium carboxylate generation, is rate determining. Based on these observations, a possible mechanism for the redox phosphine-catalyzed Staudinger ligation involves initial reduction of azide \textbf{4.63} by PPh$_3$ to yield aza-ylide \textbf{3.21}. Deprotonation of carboxylic acid \textbf{4.64} by the aza ylide provides the phosphonium carboxylate \textbf{4.65}. An equilibrium exists between the tight ion pair and the partially covalent P–O bond in \textbf{4.66}, which activates the carboxylate for nucleophilic acyl substitution. Nucleophilic attack of the nitrogen upon the activated carboxyl leads to formation of amide \textbf{4.67} and Ph$_3$P=O \textbf{3.17}. Reduction of the phosphine oxide by a silane regenerates your active PPh$_3$ catalyst thus completing the catalytic cycle (Scheme 4.10).
Scheme 4.10: Proposed Catalytic Cycle.

The ability of polar, aprotic solvent like PhMe to promote the formation of a tight ion pair, indicates that intermediate 4.65 is crucial for nucleophilic acyl substitution. Given the propensity for silanes to reduce iminophosphoranes, an alternative mechanistic pathway where reduction of azaylide 3.21 by the silane to yield silyl amine 4.68 and regeneration of your phosphine catalyst A nucleophilic acyl substitution of an activated silyl ester intermediate by the silyl amine 4.68 would produce the desired amide 4.67. This pathway only seems feasible when the rate of iminophosphorane reduction is faster than deprotonation of acid 4.64 by ylide 3.21. Attempts at pre-formation of the silane ester derived from trifluoromethyl benzoic acid 4.19b and Ph₂HSiCl followed by addition of PPh₃ (10 mol%) and azide 3.27b failed to provide more than 20% of amide 4.23n (eq 59).
4.1.3.7 Summary

In conclusion, the first phosphine-catalyzed Staudinger-type ligation has been developed that enables the direct conversion of carboxylic acids to amides while avoiding complications associated with preactivation and isolation due to stoichiometric phosphine oxide. This method allows for access to an assortment of amides through the direct functionalization of carboxylic acids utilizing azides. This catalytic method constitutes a conceptually new approach toward amide bond formations by use of a phosphine mediated intramolecular acyl migration from oxygen to nitrogen. The impact of this catalytic Staudinger ligation upon on the assembly of biologically active natural products that contain amide, lactam, and peptide linkages will solidify its place in the synthetic chemist’s toolbox.

4.1.4 Phosphate Esterification of Carboxylic Acids

4.1.4.1 Introduction

The reactivity of phosphorus (III) reagents with various carbonyl derivatives is well established despite recent inquiries to further improve upon these synthetic methods. Phosphorus (V) reagents, such as diphenyl and dialkoxy phosphoryl reagents, also have long been known for their ability to interconvert alcohols and carboxylic acids
into derivatives thereof.\textsuperscript{209-211} Of particular interest is phosphorylcyanide and its ability to produce activated carbonyls in the form of acyl cyanides from carboxylic acids.\textsuperscript{212,213} These carboxylic acid derivatives have found application in general synthetic strategies toward a wide array of biologically active natural products and peptide synthesis.\textsuperscript{214} To examine whether other heteroatoms are transferable from phosphorus, we explored the reactivity between carboxylic acids and a modified phosphoryl reagent containing an alkoxide ligand (Figure 4.4, $Z = \text{O}, R^2 = \text{O}$).

![Chemical structure](image)

**Figure 4.4:** Proposed Heteroatom Transfer From Phosphorus

4.1.4.2 Synthesis of Benzyl Esters

When benzoic acid **3.26a** is treated with phosphate **4.72a** and DBU in refluxing dioxane for 18 h, benzyl benzoate **4.73a** is afforded in 83% yield (eq 60). Inspired by this initial result, the compatibility of various carboxylic acids to participate in esterification were investigated. In general, alkyl and aryl carboxylic acids provided the corresponding ester in good to excellent yields regardless of steric and electronic factors (Table 4.13).
### TABLE 4.13

**SCOPE OF CARBOXYLIC ACID IN ESTERIFICATION**

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^{1}$</th>
<th>$R^{2}$</th>
<th>Product</th>
<th>Yield (%)$^{b}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-Cl-C$_6$H$_4$ (4.19d)</td>
<td>OMe (4.72a)</td>
<td>4.73b</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>2-I-C$_6$H$_4$ (4.19e)</td>
<td>CN (4.72b)</td>
<td>4.73c</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>4-CF$_3$-C$_6$H$_4$ (4.19a)</td>
<td>CN (4.72b)</td>
<td>4.73d</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>2,6-(CH$_3$)$_2$-C$_6$H$_3$ (4.19v)</td>
<td>CN (4.72b)</td>
<td>4.73e</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>PhCH=CH (4.19g)</td>
<td>CN (4.72b)</td>
<td>4.73f</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>MeCH=CH (4.19w)</td>
<td>CN (4.72b)</td>
<td>4.73g</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>PhCH$_2$ (4.19h)</td>
<td>CN (4.72b)</td>
<td>4.73h</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>tBu (4.19k)</td>
<td>CN (4.72b)</td>
<td>4.73i</td>
<td>67</td>
</tr>
</tbody>
</table>
Electron deficient carboxylic acids, when treated with phosphates 4.72a or 4.72b, produce halogenated benzoates in good to excellent yields (entries 1-3). Interestingly, sterically hindered 2,6-dimethylbenzoic acid 4.19v produced benzyl benzoate 4.73e in 71% yield when treated with phosphate 4.72b and DBU in dioxane (entry 4). α,β-unsaturated acids also proved viable substrates, affording benzyl esters 4.73f and 4.73g in 74% and 64% respectively when subjected to 4-cyanobenzyl diphenylphosphinate 4.72b and DBU in dioxane. Interestingly, no by-products resulting from 1,4-addition were isolated from the reactions of enoic acids. Various α-substituted alkyl carboxylic acids also participated in the acyl-substitution event to afford benzoates 4.73h, 4.73i, and 4.73j in yields ranging from 53-72% (entries 7-9). Heteroaromatic acids possessing unprotected N-H bond esterified under our conditions to afford ester 4.73k in near quantitative yield (entry 10). Having established the broad scope of carboxylic

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>nC$<em>7$H$</em>{15}$ (4.19i)</td>
<td>CN (4.72b)</td>
<td><img src="image" alt="4.73j" /></td>
<td>53 (93)</td>
</tr>
<tr>
<td>10</td>
<td>2-pyrrole (4.19f)</td>
<td>CN (4.72b)</td>
<td><img src="image" alt="4.73k" /></td>
<td>98</td>
</tr>
</tbody>
</table>

*Conditions: Phosphate 4.72 (1 equiv), carboxylic acid 4.19 (1 equiv), and DBU (1.1 equiv) in dioxane (5 mL) for 18 h at 100 °C. Unpublished results. *Isolated yield. *Yield based on recovered starting material.
acids that react with benzyl phosphinates, we turn our attention toward examination of various transferability alkoxide ligands.

Preliminary results involving esterification of anisic acid 4.19a with various phosphate derivatives 4.72 are summarized in Table 4.14. Generally, acceptable to good yields of the desired esters can be obtained after heating acid 4.19a in the presence phosphate 4.72 and DBU for 18 h. Electron-rich and electron-poor benzyl alkoxides transfer forming the desired C-O ester bond in good to excellent yields. Functional groups attached to phosphinates do not hinder acyl substitution of carboxylic acids. Phosphinate 4.72c, containing a pendant nitro group, produces benzoate 4.73l in 83% yield when subjected to anisic acid and DBU. Benzyl alkoxides containing halogens also are tolerated, affording esters in yields above 66% (entries 2-4). Even phosphinates containing ester and cyano groups ligate with acid 4.19a to give benzoates 4.73p and 4.73q in 63% and 94% yield respectively (entries 5 and 6). Electron rich phosphinates 4.72a proceeded to esterify 4-methoxybenzoic acid in 73% yield (88% yield based on recovered 4.19a) after 18 h (entry 7). Interestingly, initial modification of the alkoxide group from aryl to allyl proved rewarding as shown by the formation of allylic benzoate 4.73s in 60% yield using phosphinate 4.72h (entry 8). It’s noteworthy that carboxylic acid derived aniline 4.19x is a viable substrate producing benzyl ester 4.73t in good yield without observing of any N-acyl substituted by-products (eq 61).
TABLE 4.14
VARIOUS ALKOXIDE LIGANDS ON PHOSPHINATES

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-O_2N-C_6H_4</td>
<td>4.73l</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>(4.72c)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4-F_3C-C_6H_4</td>
<td>4.73m</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>(4.72d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3,5-(F_3C)_2-C_6H_3</td>
<td>4.73n</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>(4.72e)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4-Cl-C_6H_4</td>
<td>4.73o</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>(4.72f)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4-MeO_2C-C_6H_4</td>
<td>4.73p</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>(4.72g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4-NC-C_6H_4</td>
<td>4.73q</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>(4.72b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4-MeO-C_6H_4</td>
<td>4.73r</td>
<td>73 (88)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>(4.72a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CH_3CH=CH</td>
<td>4.73s</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>(4.72h)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Conditions: Phosphate 4.72 (1 equiv), carboxylic acid 4.19a (1 equiv), and DBU (1.1 equiv) in dioxane (5 mL) for 18 h at 100 °C. Unpublished results. <sup>b</sup>Isolated yield. <sup>c</sup>Yield based on recovered starting material.
4.1.4.3 Summary

The ability of various alkoxy groups to transfer from phosphorus to synthesize numerous carboxylic acid derivatives was deemed successful when employing benzyl and allyl phosphinate reagents. The ability of phosphorus (V) reagents to activate carboxylic acids in situ highlights nucleophilic acyl substitution reactions without prior pre-activation of the carbonyl. Future exploration into other transferable groups (i.e. nitrogen, carbon, etc) in conjunction with mechanistic studies would develop a better understanding of phosphorus’ ability to synthesize carbonyl analogs through nucleophilic acyl substitution pathways.

4.2 Conclusion

A major issue with numerous phosphorus-mediated reactions is poor atom economy. The stoichiometric formation of phosphorus (V) waste also can cause purification issues. The influential works by several prominent research groups have focused significant efforts to solving this problem with an efficient and reliable procedure.
The first portion of this chapter is devoted toward our development of a chlorophosphite-modified Staudinger ligation between unactivated carboxylic acids and azides. With current synthetic routes toward amides utilizing harsh, toxic, or caustic reagents. One of the advances associated with our chlorophosphite modified Staudinger ligation involves high chemoselectivity of the carboxylic acid over more electrophilic functionality. Despite formation of a phosphinic acid by-product, analytically pure products can be obtained following a simple aqueous workup.

With a desire to minimize the formation of stoichiometric phosphine waste led us to examine a catalytic system in which the phosphine oxide by-product could be recycled. Our resulting phosphine-catalyzed Staudinger ligation produced amides, lactams, and peptides in good to excellent yields by employing 10 mol% PPh₃ and PhSiH₃. With successfully catalyst turnover, we observed a reduction in wasteful by-products formed and minimal purification issues associated with them. Additional experiments to fully elucidate the mechanism of the catalytic-phosphine Staudinger ligation would expand the utility of the phosphonium carboxylate-type intermediate to subsequent aza-ylide reactions. Future objectives involve exploiting phosphorus’ dual abilities to active carboxylic acids *in situ* while revealing the latent nucleophilic nitrogen of an azide in a late stage total synthesis. Demonstration of this unique dual role would highlight the significance of these methods as an alternative to conventional amidation procedures.
CHAPTER 5:

EXPERIMENTAL PROCEDURES

5.1 General Materials and Methods

All solvents and reagents were ACS reagent grade, obtained from commercial sources, and used without further purification unless otherwise stated. Acetonitrile (CH$_3$CN), dimethylformamide (DMF), toluene (PhMe), tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$) and diethyl ether (Et$_2$O) were degassed with argon, passed through a column of molecular sieves, and stored under argon. Chlorobenzene (C$_6$H$_5$Cl) was distilled over CaH$_2$, stored over 4 Å molecular sieves, and degassed thoroughly prior to use. All reactions were carried out in oven-dried glassware under argon unless otherwise specified.

$^1$H nuclear magnetic resonance (NMR) spectra were obtained at either 300, 400, 500 or 600 MHz. $^{13}$C NMR were obtained at 100, 125 or 150 MHz. Chemical shifts are reported in parts per million (ppm, $\delta$), and referenced from the solvent or tetramethylsilane (TMS). Coupling constants are reported in Hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; comp, complex; app, apparent; hom, higher order multiplet; and br, broad. Infrared (IR) spectra were obtained using a Thermo Electron Nicolet 380 FT-IR using a
silicon (Si) crystal in an attenuated total reflectance (ATR) tower and reported as wavenumbers (cm\(^{-1}\)). High and Low resolution electrospray ionization (ESI) measurements were made with a Bruker MicroTOF II mass spectrometer. Analytical thin layer chromatography (TLC) was performed using EMD 250 micron 60 F254 silica gel plates, visualized with UV light (254 nm lamp) and stained with either p-anisaldehyde, ceric ammonium nitrate (CAN) or potassium permanganate (KMnO\(_4\)) solutions. Flash column chromatography was performed according to Still’s procedure (Still, W. C.; Kahn, M.; Mitra, A. J. Org. Chem. 1978, 43, 2923) using EMD 40-63 μm 60Å silica gel. Melting points were determined in capillary tubes using am Electrothermal Mel-Temp apparatus and are uncorrected.

5.2 Synthetic Procedures From Chapter 2

5.2.1 General

The following compounds were purchased from a commercial source and used without further purification unless noted: 1.34, 1.44, 2.1o, 2.1u. The following compounds were prepared following previously reported literature procedures: 2.1g\(^{215}\) and 2.1f.\(^{216}\) Zn\(^{(0)}\) dust was rinsed with 1M HCl, filtered and washed thoroughly with water, acetone and ether and dried under vacuum. 2.1e and 2.1n was prepared by Fleury.\(^{35}\)
5.2.2 Synthesis of Substrates and Reagents

**Triethylamine hydrochloride (Et₃N-HCl).** An oven dried round bottom flask equipped with a magnetic stirrer at 0 °C was charged with triethylamine (3.04 g, 30 mmol, 4.22 mL) and MeOH (20 mL). To the solution was added acetyl chloride (2.59 g, 33 mmol, 2.34 mL) slowly over 10 min. After stirring for an additional 30 min at 0 °C, volatiles were concentrated under reduced pressure until precipitate began to appear. Et₂O (50 mL) was added to the resulting slurry followed by vacuum filtration. The fluffy white solid was collected to yield 3.49 g (85%) of triethylamine hydrochloride.

**Collidine hydrochloride (Col-HCl).** An oven dried round bottom flask equipped with a magnetic stirrer at 0 °C was charged with acetyl chloride (4.71 g, 60 mmol, 4.3 mL) in MeOH (41 mL). To the solution was added collidine (5.0 g, 41.3 mmol, 5.5 mL) in MeOH (82 mL) over 30 min. After stirring for an additional 30 min at 0 °C, volatiles were removed under reduced pressure until precipitation occurred. To the resulting slurry was added Et₂O (150 mL) followed by filtration to afford 6.96 g (quantitative yield) of collidine hydrochloride as a white solid.

**Representative procedure for the Horner-Wadsworth-Emmons olefination to provide \(\alpha,\beta\)-unsaturated ketones:** An oven dried round bottom flask equipped with a magnetic stirrer and reflux condenser was charged with the desired aldehyde (10 mmol), acetylmethylene triphenylphosphorane (11 mmol) and THF (40 mL). The resulting solution was heated to reflux and stirred for 12 h. The mixture was allowed to cool to room temperature by removal of the oil bath and concentrated under reduced pressure.
to afford a slushy solid. The residue was washed with Et₂O (3 x 30 mL) and the combined organic fractions concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc to give the α,β-unsaturated ketone.

![2.1a](image)

**(E)-4-Phenylbut-3-en-2-one (2.1a).** Following the representative general procedure, olefination of benzaldehyde (2.8g) was performed on 19.8 mmol scale, refluxing for 12 h. Purification by column chromatography eluting with hexanes/EtOAc (2:1) provided 2.56 g (88%) of **2.1a** as a white solid whose ¹H NMR spectral data was consistent with literature values.²¹⁷

¹H NMR (400 MHz, CDCl₃) δ 7.60-7.47 (comp m, 2 H), 7.41 (m, 4 H), 6.73 (d, J = 16.0 Hz, 1 H), 2.40 (s, 3 H). mp = 41 °C.

![2.1c](image)

**(E)-Methyl 4-(3-oxobut-1-en-1-yl)benzoate (2.1c).** Following the representative general procedure, olefination of methyl 4-formylbenzoate (2.8b) was performed on 7.0 mmol scale, refluxing for 12 h. Purification by column chromatography eluting with
hexanes/EtOAc (2:1) provided 1.0 g (72%) of 2.1c as a white solid whose \textsuperscript{1}H NMR spectra was consistent with literature values.\textsuperscript{218}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 8.08 (d, \( J = 8.5 \), 2 H), 7.60 (d, \( J = 8.5 \), 2 H), 7.52 (d, \( J = 16.5 \) Hz, 1 H), 6.76 (d, \( J = 16.5 \) Hz, 1 H), 3.90 (s, 3 H), 2.43 (s, 3 H). mp = 119-120 °C.

\begin{center}
\textbf{2.1d}
\end{center}

\textbf{(E)-4-(4-Chlorophenyl)but-3-en-2-one (2.1d).} Following the representative general procedure, olefination of 4-chlorobenzaldehyde was performed on 6.6 mmol scale, refluxing for 12 h. Purification by column chromatography eluting with hexanes/EtOAc (5:1) provided 1.02 g (86%) of 2.1d as a white solid whose \textsuperscript{1}H NMR spectral data was consistent with literature values.\textsuperscript{218}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.49 (d \( J = 8.0 \), 2 H), 7.45 (d, \( J = 16.0 \) Hz, 1 H), 7.37 (d, \( J = 8.6 \), 2 H), 6.69 (d, \( J = 16.0 \) Hz, 1 H), 2.38 (s, 3 H). mp = 50 °C.

\begin{center}
\textbf{2.1e}
\end{center}

\textbf{(E)-4-(4-(Trifluoromethyl)phenyl)but-3-en-2-one (2.1e).} Following the representative general procedure, olefination of 4-(trifluoromethyl)benzaldehyde (2.8a) was performed on 6.2 mmol scale, refluxing for 12 h. Purification by column
chromatography eluting with hexanes/EtOAc (2:1) provided 1.26 g (95%) of 2.1e as a white solid whose $^1$H NMR spectral data was consistent with literature values.$^{219}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.67 (m, 4 H), 7.53 (d, $J = 16.4$ Hz, 1 H), 6.78 (d, $J = 16.4$ Hz, 1 H), 2.44 (s, 3 H). mp = 55 °C

![2.1s](image)

**(E)-4-(4-Methoxyphenyl)-3-buten-2-one** (2.1s). Following the representative general procedure, olefination of 4-methoxybenzaldehyde (2.8c) was performed on 5 mmol scale, refluxing for 12 h. Purification by column chromatography eluting with hexanes/EtOAc (4:1) provided 0.69 g (79%) of 2.1s as a clear solid whose $^1$H NMR spectral data was consistent with literature values.$^{218}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50 (d, $J = 7.0$, 2 H), 7.46 (d, $J = 16.0$ Hz, 1 H), 6.93 (d, $J = 9.0$, 2 H), 6.61 (d, $J = 16.5$ Hz, 1 H), 3.82 (s, 2 H), 2.35 (s, 3 H). mp = 69-70 °C.

**Representative general procedure for Wittig olefination reactions to provide $\alpha,\beta$-unsaturated esters:** An oven dried round bottom flask equipped with a magnetic stirrer and reflux condenser was charged with the desired aldehyde (6.2 mmol), ethoxycarbonylmethylene triphenylphosphorane (6.5 mmol) and dry THF (25 mL). The solution was heated to reflux and stirred for 12 h. The mixture was allowed to cool to room temperature by removal of the oil bath and concentrated under reduced pressure.
to afford a slushy solid. This solid was washed thoroughly with Et₂O (3 x 20 mL), the combined organics evaporated and residue purified by column chromatography, eluting with hexanes/EtOAc to give the required α,β-unsaturated ester.

![Image of 2.1m](image)

**(E)-Ethyl 3-(4-chlorophenyl)acrylate (2.1m).** Following the representative general procedure, olefination of 4-chlorobenzaldehyde was performed on 6.6 mmol scale, refluxing for 12 h. Purification by column chromatography eluting with hexanes/EtOAc (5:1) provided 1.27 g (92%) of **2.1m** as a clear oil whose **1**H NMR spectral data was consistent with literature values.²²⁰

**1**H NMR (400 MHz, CDCl₃) δ 7.65 (d, J = 16.2 Hz, 1 H), 7.43 (d, J = 8.4, 2 H), 7.35 (d, J = 8.6 Hz, 2 H), 6.40 (d, J = 16.0 Hz, 1 H), 4.24 (q, J = 7.2 Hz, 2 H), 1.32 (t, J = 7.2 Hz, 3 H).

![Image of 2.1r](image)

**Ethyl cinnamate (2.1r).** Following the representative general procedure, olefination of benzaldehyde (2.8g) was performed on 7.92 mmol scale, refluxing for 12 h. Purification by column chromatography eluting with hexanes/EtOAc (4:1) provided 1.11 g (80%) of **2.1r** as a clear oil whose **1**H NMR spectral data was consistent with literature values.²²⁰
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.70 (d, $J = 16.0$ Hz, 1 H), 7.53 (m, 2 H), 7.40 (m, 3 H), 6.45 (d, $J = 16.0$ Hz, 1 H), 4.28 (q, $J = 7.2$ Hz, 2 H), 1.35 (t, $J = 7.2$ Hz, 3 H).

**Representative general procedure for the synthesis of α,β-unsaturated aldehydes:** An oven dried round bottom flask equipped with a magnetic stirrer was charged with the desired α,β-unsaturated ester (1.9 mmol) and toluene (20 mL) and cooled to -78 °C. To the cooled solution was added diisobutylaluminium hydride (1.0 M DIBALH in DCM, 9.5 mL, 9.5 mmol). The mixture was allowed to stir at -78 °C for 3 h. The mixture is quenched with saturated aqueous Rochelle’s salt and stirred at room temperature for 4 h. The aqueous layer was extracted with Et$_2$O (3 x 40 mL), the combined organics were dried (MgSO$_4$), concentrated under reduced pressure, and used without purification. To the crude residue was added DMSO (2 mL), DCM (2 mL), and N,N-diisopropylethylamine (775 mg, 6 mmol, 1 mL) then cooled to 0 °C. To the mixture was added SO$_3$-pyridine (955 mg, 6 mmol) portion wise and stirred at room temperature for approx 3 h. The slurry was diluted with water (10 mL) before extraction with DCM (3 x 15 mL). The combined organic layers were washed with water (20 mL), saturated aqueous NaCl solution (20 mL), dried (MgSO$_4$), and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with hexanes/EtOAc to give the title α,β-unsaturated aldehyde.
(E)-3-(4-Chlorophenyl)acrylaldehyde (2.1j). Following the representative general procedure, reduction of enoate (2.1m) was performed on 1.92 mmol scale. Purification by column chromatography eluting with hexanes/EtOAc (4:1) provided 264 mg (79% over 2 steps) of 2.1j as a white solid whose $^1$H NMR spectral data was consistent with literature values.$^{221}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.71 (d, $J$ = 7.6 Hz, 1 H), 7.60-7.35 (comp m, 5 H), 6.71 (dd, $J$ = 16.0, 8.0 Hz, 1 H). mp = 60-61 °C.

(E)-4-(3-Oxoprop-1-en-1-yl)benzaldehyde (2.1k). Following the representative general procedure, reduction of enoate (2.1n) was performed on 1.50 mmol scale, using 10 eq of DIBALH. Purification by column chromatography eluting with hexanes/EtOAc (2:1) provided 173 mg (65% over 2 steps) of 2.1k as a white solid whose $^1$H NMR spectral data was consistent with literature values.$^{222}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.76 (d, $J$ = 7.6 Hz, 1 H), 7.69 (m, $J$ = 4 H), 7.51 (d, $J$ = 16.4 Hz, 1 H), 6.78 (dd, $J$ = 16.0, 7.6 Hz, 1 H). mp = 97-98 °C.
\[
\begin{align*}
\text{(E)-3-(4-(Trifluoromethyl)phenyl)acrylaldehyde (2.1l).} \\
\end{align*}
\]
Following the representative general procedure, reduction of enoate (2.1e) was performed on 1.43 mmol scale. Purification by column chromatography eluting with hexanes/EtOAc (2:1) provided 140 mg (40\% over 2 steps) of 2.1l as an off-white solid whose \(^1\)H NMR spectral data was consistent with literature values.\(^{221}\)
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.1 (s, 1 H), 9.78 (d, \(J = 7.6\) Hz, 1 H), 7.96 (d, \(J = 8.4\) Hz, 2 H), 7.74 (d, \(J = 8.0\) Hz, 2 H), 7.53 (d, \(J = 16.0\) Hz, 1 H), 6.82 (dd, \(J = 16.0, 7.2\) Hz, 1 H). mp = 57-58 °C.

**Representative general procedure for the synthesis of \(\alpha,\beta\)-unsaturated ynones:** An oven dried round bottom flask equipped with a magnetic stirrer was added phenyl acetylene (1.32 g, 13 mmol, 1.43 mL) and dry THF (12 mL) and cooled to -78 °C. \(n\)-Butyl lithium (13.65 mmol, 1.05 equiv) was added drop wise followed by starting aldehyde (14.3 mmol, 1.1 equiv) in THF (5 mL) before allowed to warm to room temperature, and stirred for 1 h. The mixture was diluted with water (25 mL), the layers separated, and the aqueous layer extracted with Et\(_2\)O (3 x 25 mL). The combined organic layers were washed with saturated aqueous NaCl solution (25 mL), dried (MgSO\(_4\)), and concentrated under reduced pressure. The resulting residue was used without purification. The crude residue was diluted with DMSO (22 mL), DCM (22 mL). \(N,N\)-diisopropylethylamine (8.40 g, 65 mmol, 10.74 mL) was added, and the resulting mixture cooled to 0 °C. SO\(_3\)-pyridine
(8.28 g, 52 mmol) was added portion wise and the resultant slurry stirred at room temperature until complete consumption of starting material by TLC (approx 2 h). The slurry was diluted with water (100 mL) and extracted with DCM (3 x 35 mL). The combined organic layers were washed with water (80 mL), saturated aqueous NaCl solution (80 mL), dried (MgSO₄), and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with hexanes/EtOAc to give the desired α,β-unsaturated ynone.

![Image](2.1p)

**1,3-Diphenylprop-2-yn-1-one (2.1p).** Following the representative general procedure conversion of benzaldehyde (2.8g) was performed on 5.0 mmol scale. Purification by column chromatography eluting with hexanes/EtOAc (3:1) provided 732 mg (71% over 2 steps) of 2.1p as a yellowish solid whose ¹H NMR spectral data was consistent with literature values.²²³

¹H NMR (400 MHz, CDCl₃) δ 7.71 (dt, J =1.2, 7.2 Hz, 2 H), 7.65 (t, J = 7.2 Hz, 1 H), 7.60-7.40 (comp m, 7 H). mp = 44-45 °C.

![Image](2.1q)
**1-Cyclohexyl-3-phenylprop-2-yn-1-one (2.1q).** Following the representative general procedure conversion of cyclohexylcarboxaldehyde (2.8d) was performed on 5.0 mmol scale. Purification by column chromatography eluting with hexanes/EtOAc (3:1) provided 700 mg (67% over 2 steps) of 2.1q as a clear low-melting point solid whose \(^1\)H NMR spectral data was consistent with literature values.\(^{224}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.65-7.30 (comp m, 5 H), 2.52 (m, 1 H), 2.10-1.10 (comp m, 10 H).

![2.1b](image)

**(E)-Chalcone (2.1b).** An oven dried round bottom was charged with magnesium turnings (608 mg, 25 mmol) and dry THF (19 mL) followed by the slow addition of bromobenzene (4.0 g, 25.5 mmol, 2.69 mL) in THF (6 mL). The resulting mixture was stirred until the magnesium was fully consumed (approx 2 h). A solution of cinnamaldehyde 1.34 (3.15 g, 23.8 mmol, 3 mL) in THF (30 mL) was then added over 1 h, and stirred for an additional 2 h. The mixture was diluted with saturated aqueous NH\(_4\)Cl (100 mL), followed by exaction of the aqueous layer with DCM (3 x 50 mL). The combined organic layers were dried (MgSO\(_4\)) and concentrated under reduced pressure. To the residue was added DMSO (15 mL), DCM (15 mL), and diisopropylethylamine (13 g, 100 mmol, 7 equiv, 17 mL) before being cooled to 0 °C. To the cooled mixture was added SO\(_3\)-pyridine (9.2 g, 57 mmol, 4 equiv). The resulting slurry was stirred at room temperature for 8 h before dilution with water (50 mL) and extracted with Et\(_2\)O (3 x 50
mL). The combined organic layers were washed with water (60 mL), saturated aqueous NaCl solution (50 mL), saturated CuSO₄ solution (50 mL), dried (MgSO₄), and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with hexanes/EtOAc (2:1) to give 2.1 g (70%) of 2.1b as a yellowish solid whose ¹H NMR spectral data was consistent with literature values.²²⁵

¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, J = 8.4 Hz, 2 H), 7.83 (d, J = 16.0 Hz, 1 H), 7.70-7.45 (comp m, 6 H), 7.43 (m, 3 H). mp = 53-54 °C.

(E)-2-Benzylidene-6-methylcyclohexanone (2.1t). An oven dried round bottom equipped with a stirbar was added freshly distilled diisopropylamine (703 mg, 6.95 mmol, 0.98 mL, 1.2 equiv) and dry THF (15 mL) before being cooled to 0 °C. To the flask was added n-butyl lithium (7.06 mmol, 1.22 equiv) slowly. The resulting solution was stirred at 0 °C for 15 min before being cooled to -78 °C. To the cold mixture was added a solution of cyclohexanone 2.2h (568 mg, 5.79 mmol, 0.60 mL, 1 equiv) in dry THF (10 mL) over 30 min before allowed to warm up to -5 – 0 °C over 1.75 h. To the solution was added methyl iodide (1.0 g, 7.06 mmol, 0.45 mL) in THF (5 mL) drop wise. After stirring for 1 h, 1 M HCl solution (30 mL) is added, followed by extraction of the aqueous layer with DCM (3 x 50 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The crude residue was purified by column
chromatography eluting with hexanes/EtOAc (4:1) to give 171 mg (26%) of 2-methyl cyclohexanone as a clear oil whose $^1$H NMR spectral data was consistent with literature values.$^{226}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 2.40 (m, 2 H), 2.30 (m, 1 H), 2.08 (m, 2 H), 1.95-1.60 (comp m, 3 H), 1.40 (dt, $J = 12.4$, 3.2 Hz, 1 H), 1.04 (d, $J = 7.6$ Hz, 3 H).

An oven dried vial and stir bar containing 2-methyl cyclohexanone (171 mg, 1.52 mmol) was added freshly distilled benzaldehyde 2.8g (242 mg, 2.28 mmol, 0.23 mL), MeOH (1 mL), and 10% NaOH (2 mL). The resulting mixture was stirred rapidly for 12 h before being diluted with water (15 mL), followed by extraction of the aqueous layer with EtOAc (3 x 20 mL). The combined organic layers were dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography eluting with hexanes/EtOAc (4:1) to give 110.6 mg (36%) of 2.1t as an off white solid whose $^1$H NMR spectral data was consistent with literature values.$^{227}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.45-7.28 (comp m, 6 H), 3.01 (m, 1 H), 2.68 (m, 1 H), 2.49 (m, 1 H), 2.10 (m, 1 H), 1.89 (m, 1 H), 1.80-1.50 (comp m, 2 H), 1.21 (d, $J = 6.8$ Hz, 3 H).

**Representative Procedure for catalytic titanium reduction:** A mixture of Cp$_2$TiCl$_2$ (2.6 mg, 0.010 mmol, 5 mol%), zinc dust (33.5 mg, 0.51 mmol, 2.5 equiv), and triethylamine hydrochloride (1.0 mmol, 5 equiv) was stirred in CH$_2$Cl$_2$ (1.5 mL) for 10 min. A solution of $\alpha,\beta$-unsaturated carbonyl (0.205 mmol, 1 equiv) in CH$_2$Cl$_2$ (2.5 ml) was then added via syringe over listed time. The reaction was stirred until starting material consumed as
monitored by TLC (p-anisaldehyde). The mixture was quenched with saturated aqueous
NH₄Cl (10 ml). The solution was passed through celite, extracted with Et₂O (3 x 10 ml),
and the combined organic fractions were washed with saturated aqueous NaCl (30 ml),
dried (MgSO₄) and concentrated under reduced pressure. The crude residue was
purified by flash chromatography, eluting with hexanes/EtOAc to give the desired
saturated carbonyl.

![2.2a](image)

**4-Phenylbutan-2-one (2.2a).** Reduction of 2.1a was performed on 0.137 mmol
scale while being added over 24 h. Purification by flash chromatography eluting with
hexanes/EtOAc (2:1) provided 12.5 mg (60%) of 2.2a as an oil whose $^1$H NMR spectra
were consistent with literature values.$^{232}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.29 (t, $J$ = 7.6 Hz, 2 H), 7.20 (m, 3 H), 2.91 (t, $J$ = 7.2 Hz, 2 H),
2.77 (t, $J$ =7.6 Hz, 2 H), 2.15 (s, 3 H).

![2.2b](image)

**1,3-Diphenylpropan-1-one (2.2b).** Reduction of 2.1b was performed on 0.24
mmol scale while being added over 6 h. Purification by flash chromatography eluting
with hexanes/EtOAc (2:1) provided 48.2 mg (96%) of 2.2b as an oil whose $^1$H NMR
spectra were consistent with literature values.$^{233}$
1H NMR (400 MHz, CDCl3) δ 7.97 (d, J = 8 Hz, 2 H), 7.57 (t, J = 7.6 Hz, 1 H), 7.56 (t, J = 8 Hz, 2 H), 7.40-7.15 (comp m, 5 H), 3.32 (t, J = 8 Hz, 2 H), 3.10 (t, J = 8 Hz, 2 H).

![Methyl 4-(3-oxobutyl)benzoate (2.2c)](image)

**Methyl 4-(3-oxobutyl)benzoate (2.2c).** Reduction of 2.1c was performed on 0.235 mmol scale while being added over 6 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 47.6 mg (99%) of 2.2c as an oil whose 1H NMR spectra were consistent with literature values.234

1H NMR (400 MHz, CDCl3) δ 7.96 (d, J = 8 Hz, 2 H), 7.25 (d, J = 8 Hz, 2 H), 3.9 (s, 3 H), 2.95 (t, J = 7.6 Hz, 2 H), 2.77 (d, J = 7.6 Hz, 2 H), 2.15 (s, 3 H).

![2.2d](image)

**4-(4-Chlorophenyl)butan-2-one (2.2d).** Reduction of 2.1d was performed on 0.342 mmol scale while being added over 6 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 56.8 mg (91%, 98% with recovered starting material) of 2.2d as an oil whose 1H NMR spectra were consistent with literature values.235

1H NMR (400 MHz, CDCl3) δ 7.25 (d, J = 8 Hz, 2 H), 7.11 (d, J = 8 Hz, 2 H), 2.87 (t, J = 7.2 Hz, 2 H), 2.74 (d, J = 7.6 Hz, 2 H), 2.14 (s, 3 H).
4-(4-(Trifluoromethyl)phenyl)butan-2-one (2.2e). Reduction of 2.1e was performed on 0.2334 mmol scale while being added over 6 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 46.1 mg (91%) of 2.2e as an oil whose $^1$H NMR spectra were consistent with literature values.$^{236}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.54 (d, $J$ = 8 Hz, 2 H), 7.29 (d, $J$ = 8 Hz, 2 H), 2.96 (t, $J$ = 7.2 Hz, 2 H), 2.79 (d, $J$ = 7.6 Hz, 2 H), 2.16 (s, 3 H).

4-Cyclopropylbutan-2-one (2.2f). Reduction of 2.1f was performed on 0.454 mmol scale using collidine·HCl and THF while being added over 6 h. Purification by flash chromatography eluting with hexanes/EtOAc (4:1) provided 29 mg (57%) of 2.2f as an oil whose $^1$H NMR spectra were consistent with literature values.$^{237}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 2.55 (t, $J$ = 7.2 Hz, 2 H), 2.15 (s, 3 H), 1.49 (q, $J$ = 7.2 Hz, 2 H), 0.70 (comp m, 1 H), 0.44 (m, 2 H), 0.05 (m, 2 H).
**4-(tert-Butyl)cyclohexanone (2.2g).** Reduction of **2.1g** was performed on 0.164 mmol scale using collidine-HCl and THF while being added over 10 min. Purification by flash chromatography eluting with hexanes/EtOAc (4:1) provided 23 mg (95%) of **2.2g** as an oil whose $^1$H NMR spectra were consistent with commercially available authentic samples.

$^1$H NMR (400 MHz, CDCl$_3$) δ 2.50-2.20 (comp m, 4 H), 2.09 (m, 2 H), 1.47 (m, 3 H), 0.93 (s, 9 H).

![2.2h]

**Cyclohexanone (2.2h).** Reduction of **1.44** was performed on 0.52 mmol scale using collidine-HCl and THF while being added over 10 min. Purification by flash chromatography eluting with hexanes/EtOAc (4:1) provided 45.9 mg (90%) of **2.2h** as an oil whose $^1$H NMR spectra were consistent with commercially available authentic samples.

$^1$H NMR (400 MHz, CDCl$_3$) δ 2.33 (t, $J = 6.4$ Hz, 4 H), 1.86 (p, $J = 5.2$ Hz, 4 H), 1.72 (m, 2 H).

![2.2i]
3-Phenylpropanal (2.2i). Reduction of 1.34 was performed on 0.397 mmol scale while being added over 6 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 41.3 mg (78%) of 2.2i as a clear oil whose $^1$H NMR spectra were consistent with literature values.²²⁸

$^1$H NMR (400 MHz, CDCl₃) δ 9.84 (t, $J = 1.2$ Hz, 1 H), 7.31 (t, $J = 7.6$ Hz, 2 H), 7.22 (m, 3H), 2.98 (t, $J = 8.0$ Hz, 2 H), 2.80 (comp m, 2 H).

![2.2j](image)

3-(4-Chlorophenyl)propanal (2.2j). Reduction of 2.1j was performed on 0.30 mmol scale while being added over 6 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 25.8 mg (49%) of 2.2j as an oil whose $^1$H NMR spectra were consistent with literature values.²²⁹

$^1$H NMR (400 MHz, CDCl₃) δ 9.78 (s, 1 H), 7.24 (d, $J = 8$ Hz, 2 H), 7.09 (d, $J = 8$ Hz, 2 H), 2.91 (t, $J = 7.6$ Hz, 2 H), 2.74 (t, $J = 7.6$ Hz, 2 H).

![2.2k](image)

4-(3-Oxopropyl)benzaldehyde (2.2k). Reduction of 2.1k was performed on 0.312 mmol scale while being added over 6 h. Purification by flash chromatography eluting
with hexanes/EtOAc (2:1) provided 38 mg (75%) of 2.2k as a yellow oil whose \(^1\)H NMR spectra were consistent with literature values.\(^{230}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.96 (s, 1 H), 9.80 (t, \(J = 1.2\) Hz, 1 H), 7.80 (d, \(J = 7.6\) Hz, 2 H), 7.34 (d, \(J = 7.6\) Hz, 2 H), 3.01 (t, \(J = 7.6\) Hz, 2 H), 2.83 (t, \(J = 7.6\) Hz, 2 H).

![2.2l](image)

**3-(4-(Trifluoromethyl)phenyl)propanal (2.2l).** Reduction of 2.1l was performed on 0.30 mmol scale while being added over 6 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 25 mg (41%) of 2.2l as an oil whose \(^1\)H NMR spectra were consistent with literature values.\(^{231}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.80 (t, \(J = 1.2\) Hz, 1 H), 7.53 (d, \(J = 8\) Hz, 2 H), 7.29 (d, \(J = 8\) Hz, 2 H), 2.99 (t, \(J = 7.2\) Hz, 2 H), 2.80 (t, \(J = 7.2\) Hz, 2 H).

![2.2m](image)

**Ethyl 3-(4-chlorophenyl)propanoate (2.2m).** Reduction of 2.1m was performed on 0.137 mmol scale while being added over 1 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 19.7 mg (68%) of 2.2m as an oil whose \(^1\)H NMR spectra were consistent with literature values.\(^{230}\)
$^1$H NMR (400 MHz, CDCl$_3$) δ 7.22 (d, J = 8.4 Hz, 2 H), 7.10 (d, J = 8.4 Hz, 2 H), 4.09 (q, J = 7.2 Hz, 2 H), 2.89 (t, J = 8 Hz, 2 H), 2.56 (t, J = 8 Hz, 2 H), 1.20 (t, J = 7.2 Hz, 3 H).

Methyl 4-(3-ethoxy-3-oxopropyl) benzoate (2.2n). Reduction of 2.1n was performed on 0.128 mmol scale while being added over 4 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 16.9 mg (56%, quantitative with recovered starting materials) of 2.2n as a yellowish oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.97 (dt, J = 8.2, 1.8 Hz, 2 H), 7.28 (bdt, J = 8.2, 2 H), 4.13 (q, 7.1 Hz, 2 H), 3.91 (s, 3 H), 3.01 (t, 7.8 Hz, 2 H), 2.65 (t, 7.5 Hz, 2 H), 1.24 (t, 7.2 Hz, 3 H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 172.8, 167.3, 146.3, 130.1, 128.6, 60.8, 52.3, 35.7, 31.2, 14.5.

IR (neat) 3011, 2927, 1723, 1612, 1436, 1281, 1180, 1110 cm$^{-1}$.

HRMS (ESI$^+$); Calc’d for C$_{13}$H$_{16}$O$_4$Na: 259.0941; found: 259.0933.

3-Phenylpropanamide (2.2o). Reduction of 2.1o was performed on 0.136 mmol scale while being added over 1 h. Purification by flash chromatography eluting with 5%
MeOH in DCM provided 7.1 mg (35%, 76% with recovered starting materials) of 2.2o as an oil whose $^1$H NMR spectra were consistent with literature values.$^{238}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50-7.15 (m, 5 H), 5.6 (br s, 2 H), 2.96 (t, $J$ = 8 Hz, 2 H), 2.54 (t, $J$ = 8 Hz, 2 H).

![Image of 2.2q](image)

**1-Cyclohexyl-3-phenylpropan-1-one (2.2q).** Reduction of 2.1q was performed on 0.187 mmol scale while being added over 5 h. Purification by flash chromatography eluting with hexanes/EtOAc (4:1) provided 16.2 mg (40%) of 2.2q as an oil whose $^1$H NMR spectra were consistent with literature values.$^{239}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.35 (d, $J$ = 8.4 Hz, 2 H), 7.17 (t, $J$ = 7.2 Hz, 3 H), 2.86 (t, $J$ = 7.6 Hz, 2 H), 2.73 (t, $J$ = 7.6 Hz, 2 H), 2.40-0.90 (comp m, 11 H).

![Image of syn-2.2t and anti-2.2t](image)

**2-Benzyl-6-methylcyclohexanone (2.2t).** Reduction of 2.1t was performed on 0.0984 mmol scale while being added over 5 h. Purification by flash chromatography eluting with hexanes/EtOAc (4:1) provided 11.7 mg (59%, 71% based on recovered starting materials) of 2.2t as an off-white solid in a 1.3:1 mixture of syn/anti
diastereomers whose $^1$H NMR spectra were consistent with literature values.$^{240}$ mp = 53-54 °C

**syn-2.2t:** $^1$H NMR (400 MHz, CDCl$_3$) δ 7.45-7.10 (comp m, 5 H), 3.35-3.0 (m, 2 H), 2.80-1.20 (m, 8 H), 1.00 (d, $J = 6.4$ Hz, 3 H).

**anti-2.2t:** $^1$H NMR (400 MHz, CDCl$_3$) δ 7.45-7.10 (comp m, 5 H), 3.35-3.0 (m, 2 H), 2.80-1.20 (m, 8 H), 1.12 (d, $J = 6.8$ Hz, 3 H).

![Diagram of chemical structure](image)

**(E)-Dimethyl 2-(4-bromobut-2-en-1-yl)-2-(2-oxo-2-phenylethyl)malonate (2.23a).** Dimethyl malonate (2.31 g, 17.5 mmol, 2.0 mL) was added drop wise to a slurry of NaH (290 mg, 7 mmol) in THF (35 mL, 0.2 M) at 0 °C. The mixture was allowed to warm to room temperature by removal of the ice bath, then bromoacetophenone (1.39 g, 7 mmol) was added slowly and stirring continued for an additional 8 h. The resulting solution was diluted with saturated aqueous NH$_4$Cl (50 ml) and CH$_2$Cl$_2$ (30 ml), the layers were separated, and the aqueous phase extracted with CH$_2$Cl$_2$ (3 x 30 ml). The combined organic fractions were washed with saturated aqueous NaCl (60 ml), dried (MgSO$_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc (3:1) to give 1.44 g (5.75 mmol, 82%) of dimethyl 2-(2-oxo-2-phenylethyl)malonate as a white solid whose $^1$H NMR spectral data was consistent with literature values.$^{241}$
$^1$H NMR (400 MHz, CDCl$_3$) δ 8.00 (d, $J = 8.4$ Hz, 2 H), 7.58 (t, $J = 5.6$ Hz, 1 H), 7.48 (t, $J = 7.2$ Hz, 2 H), 4.10 (t, $J = 7.2$ Hz, 1 H), 3.80 (s, 6 H), 3.65 (d, $J = 6.8$ Hz, 2 H); mp = 71-72 °C.

Dimethyl 2-(2-oxo-2-phenylethyl)malonate (400 mg, 1.6 mmol) was added to a slurry of NaH (64 mg, 1.6 mmol) in THF (6 mL, 0.25 M) at 0 °C. The mixture was allowed to warm to room temperature by removal of the ice bath, stirred for 15 min, then 1,4-dibromo-2-butene (1.03 g, 4.8 mmol) was added in one portion. The resulting solution was stirred for 4 h then diluted with saturated aqueous NH$_4$Cl (10 ml) and DCM (10 ml). The layers were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 15 ml). The combined organic fractions were washed with saturated aqueous NaCl (30 ml), dried (MgSO$_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc (3:1) to give 387 mg (1.0 mmol, 62%) of 2.23a as a clear, colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.98 (d, $J = 8$ Hz, 2 H), 7.61 (t, $J = 7.6$ Hz, 2 H), 7.50 (t, $J = 7.2$ Hz, 1 H), 5.70 (m, 2 H), 3.84 (d, $J = 2$ Hz, 2 H), 3.78 (s, 6 H), 3.69 (s, 2 H), 2.90 (d, $J = 2$ Hz, 2 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 196.6, 170.8, 136.4, 133.6, 131.2, 130.0, 128.7, 128.2, 55.4, 53.0, 41.5, 36.0, 32.1;

IR (neat) 3059, 3029, 2953, 2844, 1737, 1687, 1597.5, 1448, 1281, 1207, 1058, 973 cm$^{-1}$; HRMS (ESI$^+$); Calc’d for C$_{27}$H$_{20}$BrO$_5$: 383.0489; found: 383.0461 (M+1).
\[
\text{MeO}_2\!\!\text{C}-\text{CO}_2\text{Me} \quad \overset{1. \ \text{NaH, THF}}{\longrightarrow} \quad \text{MeO}_2\!\!\text{C}-\text{CO}_2\text{Me} \\
\quad \overset{2. \ \text{Ph} \!\!\text{O} \!\!\text{ketene Cl}}{\longrightarrow} \quad \begin{array}{c}
\text{Ph} \!\!\text{C} \!\!\text{O} \\
\text{Ph}
\end{array} \\
\quad \overset{1. \ \text{NaH, THF}}{\longrightarrow} \quad \text{MeO}_2\!\!\text{C}-\text{CO}_2\text{Me} \\
\quad \overset{2. \ \text{Br} \!\!\text{alkene Br}}{\longrightarrow} \quad \begin{array}{c}
\text{Br} \!\!\text{C} \!\!\text{C} \!\!\text{O} \\
\text{Ph}
\end{array} \\
\]

\((E)\)-Dimethyl 2-(4-bromobut-2-en-1-yl)-2-(3-oxo-3-phenylpropyl)malonate (2.23b). Following a similar procedure listed above for the synthesis of dimethyl 2-(2-oxo-2-phenylethyl)malonate, dimethyl 2-(3-oxo-3-phenylpropyl)malonate was produced as a clear oil in 75\% yield (594 mg, 2.25 mmol) whose \(^1\text{H}\) NMR spectra were consistent with literature values.\(^{242}\)

\(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.96 (d, \(J = 6.4\) Hz, 2 H), 7.56 (t, \(J = 6.0\) Hz, 1 H), 7.47 (t, \(J = 8.0\) Hz, 2 H), 3.73 (s, 6 H), 3.58 (t, \(J = 7.6\) Hz, 1 H), 3.10 (t, \(J = 7.2\) Hz, 2 H), 2.36 (q, \(J = 7.2\) Hz, 2 H).

Following a similar allylation procedure listed above for the synthesis of 2.23a, dimethyl 2-(3-oxo-3-phenylpropyl)malonate (206 mg, 0.78 mmol) was allylated with 1,4-dibromo-2-butene to yield 2.23b as a clear low-melting point solid in 48\% yield (150 mg, 0.38 mmol).

\(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.96 (d, \(J = 8\) Hz, 2 H), 7.59 (t, \(J = 7.2\) Hz, 1 H), 7.48 (t, \(J = 8\) Hz, 2 H), 5.76 (m, 2 H), 3.91 (d, \(J = 7.2\) Hz, 2 H), 3.75 (s, 6 H), 3.03 (t, \(J = 7.6\) Hz, 2 H), 2.72 (d, \(J = 7.2\) Hz, 2 H), 2.33 (t, \(J = 6.8\) Hz, 2 H);

\(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 198.9, 171.4, 136.8, 133.4, 131.1, 129.6, 128.8, 128.2, 57.3, 52.8, 37.1, 33.9, 32.4, 27.7;

IR (neat) 3003, 2954, 1731, 1687, 1448, 1210, 1079, 973.7, 740 cm\(^{-1}\);

HRMS (ESI\(^+\)); Calc’d for C\(_{18}\)H\(_{22}\)BrO\(_5\): 397.0645; found: 397.0640 (M+1).
(E)-Dimethyl 2-(4-bromobut-2-en-1-yl)-2-(4-oxopentyl)malonate (2.23c). To a cold solution of pent-4-yn-1-ol (1.48 g, 17.6 mmol, 1.64 mL) and triethylamine (2.18 g, 21.4 mmol, 3.0 mL) in CH₂Cl₂ (60 mL, 0.3 M) was added methanesulfonyl chloride (2.46 g, 21.4 mmol, 1.66 mL) drop wise at 0 °C. The mixture was allowed to warm to room temperature by removal of the cooling bath and stirred for 4 h. The resulting solution was diluted with saturated aqueous NH₄Cl (50 ml) and CH₂Cl₂ (40 ml) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 30 ml), and the combined organic fractions were dried (MgSO₄) and concentrated under reduced pressure. The crude residue was added slowly to a solution of NaH (1.43 g, 35.7 mmol) and dimethyl malonate (5.89 g, 44.6 mmol, 5.1 mL) in THF (71 mL, 0.25 M) at room temperature and stirred for 8 h. The resulting solution was quenched with saturated aqueous NH₄Cl (80 ml), the layers were separated and the aqueous phase extracted with CH₂Cl₂ (3 x 90 ml). The combined organic fractions were dried (MgSO₄) and concentrated under reduced pressure. Lindlar’s catalyst (195 mg, 10 mg/mmol) was added to the crude residue and EtOAc (65 mL) was added to the flask at room temperature. The solution was purged with H₂ before being placed under 1 atmosphere of H₂ and stirred for 8 h at room temperature. The heterogeneous mixture was filtered, washed with EtOAc (120 mL), and the filtrate concentrated under reduced pressure. The
crude material was then diluted with DMF (5 mL) and added to a mixture of CuCl (800 mg, 8.1 mmol) and PdCl₂ (238 mg, 1.34 mmol) in DMF/H₂O (6.3:1, 0.2 M) that was stirred under 1 atmosphere of O₂ for 30 min. The mixture was stirred at 45 °C for 14 h then diluted with water (100 mL), the layers separated, and the aqueous phase extracted with CH₂Cl₂ (3 x 50 ml). The combined organic fractions were washed sequentially with water (3 x 30 mL) and saturated aqueous NaCl (100 mL), then dried (MgSO₄) and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc (1:1) to give 756 mg (20%) of dimethyl 2-(4-oxopentyl)malonate as a clear oil.

¹H NMR (400 MHz, CDCl₃) δ 3.75 (s, 6 H), 3.38 (t, J = 7.6 Hz, 1 H), 2.48 (t, J = 7.2 Hz, 2 H), 2.15 (s, 3 H), 2.00-1.80 (m, 2 H), 1.60 (m, 2 H);

¹³C NMR (100 MHz, CDCl₃) δ 208.2, 169.9, 52.8, 51.7, 43.3, 30.1, 28.4, 21.6;

IR (neat) 2957, 1735, 1437, 1251, 1153 cm⁻¹;

HRMS (ESI⁺); Calc’d for C₁₀H₁₇O₅: 217.1071; found: 217.1057 (M+1).

Following a similar allylation procedure listed above for the synthesis of 2.23a, dimethyl 2-(4-oxopentyl)malonate (294 mg, 1.36 mmol) was allylated with 1,4-dibromo-2-butene rendering 2.23c as a clear oil in 89% yield (421 mg, 1.21 mmol).

¹H NMR (400 MHz, CDCl₃) δ 5.77 (m, 2 H), 3.91 (d, J = 7.2 Hz, 2 H), 3.73 (s, 6 H), 2.67 (s, J = 7.2 Hz, 2 H), 2.45 (t, J = 7.2 Hz, 2 H), 2.14 (s, 3 H), 1.84 (m, 2 H), 1.47 (m, 2 H);

¹³C NMR (100 MHz, CDCl₃) δ 208.1, 171.5, 130.9, 129.8, 57.8, 52.8, 43.5, 35.5, 32.6, 32.2, 30.2, 18.3;

IR (neat) 3000, 2954, 1734, 1436, 1205, 1090, 973 cm⁻¹;
HRMS (ESI⁺); Calc’d for C\textsubscript{14}H\textsubscript{22}BrO\textsubscript{5}: 349.0645; found: 349.0641 (M+1).

\[
\begin{align*}
\text{Ph} & \text{-OH} \quad \text{Ph} & \text{-CO NH Ts} \\
\text{Et}_3\text{N}, \text{TsCl}, \text{CHCl}_3 & \quad 2. \text{SO}_3\text{-Pyridine,} \\
& \quad \text{DMSO/DCM} \\
\text{diisopropylethylamine} & \quad \text{K}_2\text{CO}_3, \text{CH}_3\text{CN} \\
\text{Br} & \quad \text{Ph} & \text{-} & \text{N Ts} & \text{-} & \text{Br} \\
\text{2.23d}
\end{align*}
\]

\begin{itemize}
\item \textit{(E)-N-(4-Bromobut-2-en-1-yl)-4-methyl-N-(2-oxo-2-\text{phenylethyl})benzenesulfonamide (2.23d).} To a solution of 2-amino-1-phenylethanol (775 mg, 5.65 mmol) and triethylamine (1.16 g, 11.51 mmol, 1.6 mL) in CHCl\textsubscript{3} (1.2 mL) at 0 °C was added drop wise a solution of tosyl chloride (1.2 g, 6.2 mmol) in CHCl\textsubscript{3} (2 mL). Reaction was stirred for 4 h before being diluted with water (10 ml) and CH\textsubscript{2}Cl\textsubscript{2} (10 ml) and the layers were separated. The aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 10 ml), and the combined organic fractions were washed with saturated aqueous NaCl (60 ml), dried (MgSO\textsubscript{4}), filtered, and concentrated under reduced pressure. The crude residue was used in the subsequent step without purification. The crude \textit{N}-tosyl amino alcohol (828 mg, 2.84 mmol) was dissolved in DMSO:DCM (1:1, 0.2 M) and cooled in an ice bath. Diisopropylethylamine (1.22 g, 9.94 mmol, 1.64 mL) was added followed by portion wise addition of sulfur trioxide pyridine complex (1.58 g, 9.94 mmol). The ice bath was removed and the solution was warmed to room temperature and stir for 6 h. The mixture was poured into cold saturated aqueous NH\textsubscript{4}Cl (20 ml) and DCM (20 ml) before the layers were separated. The aqueous layer was extracted with DCM (3 x 25 ml), and the combined organic fractions were washed several times with H\textsubscript{2}O (3 x 40 mL) followed by washing with saturated aqueous NaCl (30 ml), dried (MgSO\textsubscript{4}), filtered, and
\end{itemize}
concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc (1:1) to give 730 mg (85% over two steps) of 4-methyl-N-(2-oxo-2-phenylethyl)benzenesulfonamide as an off-white solid whose $^1$H NMR spectral data was consistent with literature values.$^{243}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.90-7.70 (comp m, 4 H), 7.60 (t, $J = 5.6$ Hz, 1 H), 7.48 (t, $J = 7.6$ Hz, 2 H), 7.29 (d, $J = 8.4$ Hz, 2 H), 5.64 (s, 1 H), 4.47 (d, $J = 4.4$ Hz, 2 H), 2.41 (s, 3 H); mp = 105-107 °C.

To an oven-dried vial was added $N$-tosyl amino ketone (400 mg, 1.38 mmol), K$_2$CO$_3$ (580 mg, 4.14 mmol), 1,4-dibromo-2-butene (1.18 g, 5.52 mmol), and acetonitrile (9.2 mL, 0.15 M) before being capped and heated to reflux for 2-3 hr. The solution was cooled to room temperature before addition of water (20 ml). The aqueous layer was extracted with DCM (3 x 30 ml), and the combined organic fractions were dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc (2:1) to give 214 mg (0.506 mmol, 37%) of **2.23d** as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.91 (d, $J = 3.2$ Hz, 2 H), 7.77 (d, $J = 3.2$ Hz, 2 H), 7.61 (t, $J = 6.8$ Hz, 1 H), 7.48 (t, $J = 8$ Hz, 2 H), 7.30 (d, 2 H), 5.70 (m, 2 H), 4.74 (s, 2 H), 3.93 (d, $J = 6.4$ Hz, 2 H), 3.82 (d, $J = 6.4$ Hz, 2 H), 2.44 (s, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 193.9, 143.7, 136.8, 134.9, 133.9, 131.4, 129.7, 129.5, 128.9, 128.0, 127.6, 52.1, 49.2, 31.1, 21.7;

IR (neat) 3062, 2974, 2867, 1702, 1598, 1340, 1158, 1066, 990 cm$^{-1}$;

HRMS (ESI$^+$); Calc’d for C$_{19}$H$_{21}$BrNO$_3$S: 422.0420; found: 422.0407 (M+1).
\[ \text{Ts-} \text{NH}_2 \xrightarrow{1. \text{CHCl}_3, \text{Alumina}} \text{Ph} \xrightarrow{2. \text{K}_2\text{CO}_3, \text{CH}_3\text{CN}} \text{Ph} \]

\((E)-N-(4\text{-Bromobut}-2\text{-en-1-yl})-4\text{-methyl-N-}-(3\text{-oxo}-3\text{-phenylpropyl})\text{benzenesulfonamide } (2.23\text{e}). \) \(p\)-Toluenesulfonamide (0.5 g, 2.9 mmol) was dissolved in minimal amount of chloroform (2 mL) before adding neutral alumina (0.55g, 1.1 w/w) to the flask. A solution of 1-phenylprop-2-en-1-one (460 mg, 3.5 mmol) was added followed by heating to 45 °C for 48 hr. The reaction was cooled to room temperature, filtered through celite, rinsed with chloroform (30 mL), and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc (3:1) to give 730 mg (84%) of 4-methyl-\(N\)-(3-oxo-3-phenylpropyl)benzenesulfonamide as a white solid whose \(^1\text{H} \) NMR spectral data was consistent with literature values.\(^{244}\)

\(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.87 \((d, J = 8.4 \text{ Hz}, 2 \text{ H})\), 7.78 \((d, J = 8.4 \text{ Hz}, 2 \text{ H})\), 7.59 \((t, J = 8.8 \text{ Hz}, 1 \text{ H})\), 7.47 \((t, J = 8.0 \text{ Hz}, 2 \text{ H})\), 7.30 \((d, J = 8.0 \text{ Hz}, 2 \text{ H})\), 5.22 \((\text{br t}, J = 6 \text{ Hz}, 1 \text{ H})\), 3.36 \((q, J = 5.2 \text{ Hz}, 2 \text{ H})\), 3.22 \((t, J = 6.0 \text{ Hz}, 2 \text{ H})\), 2.44 \((s, 3 \text{ H})\); mp = 99-101 °C.

Following a similar allylation procedure for the synthesis of 2.23d, 220 mg (0.50 mmol, 35%) of 2.23e were prepared as a clear, colorless solid.

\(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.94 \((d, J = 7.2 \text{ Hz}, 2 \text{ H})\), 7.21 \((d, J = 8.4 \text{ Hz}, 2 \text{ H})\), 7.60 \((t, J = 7.6 \text{ Hz}, 1 \text{ H})\), 7.49 \((t, J = 6.4 \text{ Hz}, 2 \text{ H})\), 7.32 \((d, J = 8 \text{ Hz}, 2 \text{ H})\), 5.75 \((m, 2 \text{ H})\), 3.86 \((\text{comp}, 4 \text{ H})\), 3.51 \((t, J = 4.4 \text{ Hz}, 2 \text{ H})\), 3.38 \((t, J = 3.2 \text{ Hz}, 2 \text{ H})\), 2.46 \((s, 3 \text{ H})\);
$^1$H NMR (400 MHz, CDCl$_3$) δ 8.00 (d, $J = 6.4$ Hz, 2 H), 7.58 (t, $J = 6$ Hz, 1 H), 7.49 (t, $J = 6.4$ Hz, 2 H), 4.22 (t, $J = 2$ Hz, 2 H), 3.91 (s, 2 H), 3.76 (s, 6 H), 3.16 (t, $J = 2$ Hz, 2 H), 0.86 (s, 9 H), 0.05 (s, 6 H);
¹³C NMR (100 MHz, CDCl₃) δ 196.8, 169.9, 136.4, 133.6, 128.7, 128.2, 82.4, 79.8, 77.4, 77.1, 76.8, 54.8, 53.2, 51.8, 41.2, 25.8, 23.8, 18.4, -4.8;

IR (neat) 2955, 2931, 2858, 1743, 1688, 1598, 1436, 1207, 1079 cm⁻¹;

HRMS (ESI⁺); Calc’d for C₂₃H₃₃O₆Si: 433.2041; found: 433.2014 (M+1).

A solution of dimethyl 2-[(4-[(tert-butyldimethylsilyl)oxy]but-2-yn-1-yl)-2-(2-oxo-2-phenylethyl)malonate (200 mg, 0.46 mmol) in DCM (14 mL, 0.03M) was cooled to 0 °C before portion wise addition of triphenylphosphine dibromide (215 mg, 0.50 mmol). The solution was then allowed to warm up to room temperature slowly and stirred for 8 h before being diluted with saturated aqueous NH₄Cl (15 ml) and separation of the layers. The aqueous layer was extracted with DCM (3 x 20 ml) and the combined organic fractions were dried (MgSO₄), filtered, and then concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc (3:1) to give 83 mg (47%) of 2.25a as a clear oil.

¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, J = 8.4 Hz, 2 H), 7.61 (t, J = 7.6 Hz, 1 H), 7.50 (t, J = 8 Hz, 2 H), 3.91 (s, 2 H), 3.83 (t, J = 2.4 Hz, 2 H), 3.77 (s, 6 H), 3.19 (t, J = 2 Hz, 2 H);

¹³C NMR (100 MHz, CDCl₃) δ 197.0, 170.2, 136.7, 133.7, 128.8, 128.3, 83.1, 79.3, 55.1, 53.3, 41.4, 24.6 14.9;

IR (neat) 3008, 2954, 2923, 1740, 1686, 1435, 1208 cm⁻¹;

HRMS (ESI⁺); Calc’d for C₂₁H₂₁BrO₅Na: 403.0152; found: 403.0154 (M+Na).
Dimethyl 2-(4-bromobut-2-yn-1-yl)-2-(3-oxo-3-phenylpropyl)malonate (2.25b).

Following a similar procedure listed above for the formation of 2-(4-((tert-butyldimethylsilyl)oxy)but-2-yn-1-yl)-2-(2-oxo-2-phenylethyl)malonate, 548 mg (1.23 mmol, 77% yield) of dimethyl 2-(4-((tert-butyldimethylsilyl)oxy)but-2-yn-1-yl)-2-(3-oxo-3-phenylpropyl)malonate was produced as a clear oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.97 (d, $J$ = 7.2 Hz, 2 H), 7.57 (t, $J$ = 5.6 Hz, 1 H), 7.46 (t, $J$ = 8 Hz, 2 H), 4.25 (t, $J$ = 2 Hz, 2 H), 3.74 (s, 6 H), 3.04 (m, 2 H), 2.96 (t, $J$ = 2 Hz, 2 H), 2.50 (m, 2 H), 0.92 (s, 9 H), 0.08 (s, 6 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 198.7, 170.6, 136.7, 133.2, 128.7, 128.1, 82.4, 79.1, 56.4, 52.9, 51.8, 33.8, 27.2, 25.9, 24.4, 18.3, -5.1;

IR (neat) 2955, 2930, 2858, 1738, 1690, 1448, 1254, 1207, 1079, 838 cm$^{-1}$;

HRMS (ESI$^+$); Calc’d for C$_{24}$H$_{35}$O$_6$Si: 447.2197; found: 447.2197 (M+1).

Following a similar alkylation procedure for the synthesis of 2.25a, 141 mg (0.36 mmol, 79%) of 2.25b was prepared as a clear oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.96 (d, $J$ = 8 Hz, 2 H), 7.57 (t, $J$ = 7.2 Hz, 1 H), 7.47 (t, $J$ = 7.6 Hz, 2 H), 3.84 (t, $J$ = 2.4 Hz, 2 H), 3.74 (s, 6 H), 3.06 (t, $J$ = 6.4 Hz, 2 H), 2.95 (t, $J$ = 2.4 Hz, 2 H), 2.48 (t, $J$ = 7.6 Hz, 2 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 198.6, 170.5, 136.6, 133.3, 128.7, 128.2, 82.0, 78.8, 56.4, 53.0, 33.8, 27.4, 24.6, 14.7;
IR (neat) 3060, 3006, 2955, 2869, 2237, 1734, 1686, 1598, 1448, 1211, 1072 cm⁻¹;

HRMS (ESI⁺); Calc’d for C₁₈H₂₀BrO₅: 395.0489; found: 395.0478 (M+1).

**Dimethyl 2-(4-bromobut-2-yn-1-yl)-2-(4-oxopentyl)malonate (2.25c).** Following a similar alkylation procedure listed above for 2-(4-((tert-butyldimethylsilyloxy)but-2-yn-1-yl)-2-(2-oxo-2-phenylethyl)malonate, dimethyl 2-(4-((tert-butyldimethylsilyloxy)but-2-yn-1-yl)-2-(4-oxopentyl)malonate (185 mg, 0.46 mmol) was produced as a clear oil in 48% yield.

¹H NMR (400 MHz, CDCl₃) δ 4.24 (t, J = 2 Hz, 2 H), 3.72 (s, J = 6 H), 2.86 (t, J = 2 Hz, 2 H), 2.44 (t, J = 7.6 Hz, 2 H), 2.12 (s, 3 H), 1.99 (m, 2 H), 1.45 (m, 2 H), 0.88 (s, 9 H), 0.08 (s, 6 H);

¹³C NMR (100 MHz, CDCl₃) δ 207.9, 170.6, 81.9, 79.3, 56.9, 52.8, 51.8, 43.5, 31.6, 29.9, 25.8, 23.2, 18.3, 18.3, -4.9;

IR (neat) 2955, 2931, 2857, 1743, 1689, 1599, 1436, 1207, 1091 cm⁻¹;

HRMS (ESI⁺); Calc’d for C₂₀H₃₄O₆SiNa: 421.2017; found: 421.2012 (M+Na).

Following a similar allylation procedure for the synthesis of 2.25a, 41.3 mg (0.119 mmol, 35%) of 2.25c was prepared as a clear oil.

¹H NMR (400 MHz, CDCl₃) δ 3.87 (t, J = 2.4 Hz, 2 H), 3.75 (s, 6 H), 2.90 (t, J = 2.4 Hz, 2 H), 2.48 (t, J = 7.2 Hz, 2 H), 2.15 (s, 3 H), 2.00 (m, 2 H), 1.47 (m, 2 H);
$^{13}$C NMR (100 MHz, CDCl$_3$) δ 208.1, 170.6, 82.3, 78.5, 57.1, 53.1, 43.6, 31.8, 30.1, 23.5, 18.4, 15.0;

IR (neat) 2955, 2373, 2345, 1736, 1719, 1439, 1205 cm$^{-1}$;

HRMS (ESI$^+$); Calc’d for C$_{14}$H$_{20}$BrO$_5$: 347.0489; found: 347.0484 (M+1).

(E)-3-Methyl-1-phenylhexa-1,5-dien-3-ol (1.35). A clean, oven dried 4 dram screw cap vial was charged with Cp$_2$TiCl$_2$ (3.7 mg, 0.015 mmol, 10 mol %) and zinc dust (24.5 mg, 0.375 mmol, 2.5 equiv) under an atmosphere of N$_2$ at room temperature. THF (1.5 mL) was added via syringe and the slurry stirred for 10 min or until the solution had turned from red to green. Once a green color persisted, the mixture was cooled down to -60 °C followed by addition of a solution containing enone 2.1a (0.15 mmol, 1 equiv), allylbromide (90.8 mg, 0.75 mmol, 5 equiv) in THF (1.5 ml). The reaction was stirred for 10 min at -60 °C until allowed to slowly warm up to room temperature over 1 h. The mixture was stirred for an additional 2 h before being quenched with saturated aqueous NaHCO$_3$ (10 ml). The aqueous layer was extracted with Et$_2$O (3 x 15 ml), and the combined organic fractions were washed with saturated aqueous NaCl (15 ml), dried (MgSO$_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc (2:1) to give 1.35 (27.9 mg, 0.149 mmol, 99% yield) as a clear oil whose $^1$H NMR spectral data was consistent with literature values.$^{245}$
$^1$H NMR (400 MHz, CDCl$_3$) δ 7.45-7.20 (m, 5 H), 6.60 (d, $J = 16.0$ Hz, 1 H), 6.31 (d, $J = 16.0$ Hz, 1 H), 5.85 (comp m, 1 H), 5.17 (m, 2 H), 2.50-2.30 (m, 2 H), 1.79 (br s, 1 H), 1.40 (s, 3 H).

**Representative general procedure for the intramolecular allylation of ketones.** A clean, oven dried 4 dram screw cap vial was charged with Cp$_2$TiCl$_2$ (1.2 mg, 5 μmol, 5 mol %) and zinc dust (16.3 mg, 0.25 mmol, 2.5 equiv) under an atmosphere of N$_2$ at room temperature. THF (0.9 mL) was added via syringe and the slurry stirred for 10 min or until the solution had turned from red to green. A solution of ketone (0.1 mmol, 1 equiv) in THF (0.2 ml) was then added via syringe drop wise. The reaction was stirred for 20 min or until all starting material was consumed as monitored by TLC ($\rho$-anisaldehyde or KMnO$_4$). The mixture was diluted with saturated aqueous NH$_4$Cl (2 ml) and DCM (2 ml) and the layers were separated. The aqueous layer was extracted with DCM (3 x 4 ml), and the combined organic fractions were washed with saturated aqueous NaCl (15 ml), dried (MgSO$_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc to give the desired cyclic alcohol.
Dimethyl-3-hydroxy-3-phenyl-4-vinylcyclopentane-1,1-dicarboxylate (2.24a).

Allylation of (E)-dimethyl 2-(4-bromobut-2-en-1-yl)-2-(2-oxo-2-phenylethyl)malonate (2.23a) was performed on a 0.1 mmol scale at room temperature for 1 h. Purification by flash chromatography eluting with hexanes/EtOAc (3:1) provided 28.6 mg (94%) of 2.24a as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.50 (d, $J = 8.8$ Hz, 2 H), 7.38 (t, $J = 7.6$ Hz, 2 H), 7.29 (t, $J = 7.4$ Hz, 1 H), 5.67 (m, 1 H), 5.11 (m, 2 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.14 (m, 1 H), 2.69 (comp, 4 H), 2.28 (s, 1 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.17, 143.4, 134.1, 128.3, 127.2, 125.2, 118.6, 83.3, 53.8, 53.2, 53.1, 50.1, 36.8;

IR (neat) 3520, 3027, 2954, 2925, 1732, 1446, 1264 cm$^{-1}$;

HRMS (ESI$^+$); Calc’d for C$_{17}$H$_{20}$O$_3$Na: 327.1203; found: 327.1191 (M+Na); mp = 96-97 °C.

$^1$H NMR and $^{13}$C NMR spectra for opposite diastereomer do not match the isolated compound leading to determination of opposite syn/anti stereochemistry.\(^8\)

\[\text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \]
\[\text{Ph} \quad \text{OH} \]
\[2.24b\]

Dimethyl-4-hydroxy-4-phenyl-3-vinylcyclohexane-1,1-dicarboxylate (2.24b).

Allylation of (E)-dimethyl 2-(4-bromobut-2-en-1-yl)-2-(3-oxo-3-phenylpropyl)malonate (2.23b) was performed on a 0.1 mmol scale at room temperature for 6 h. Purification by
flash chromatography eluting with hexanes/EtOAc (2:1) provided 29.9 mg (94%) of 2.24b as a clear crystalline white solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40-7.15 (comp, 5 H), 5.52 (m, 1 H), 5.08 (m, 2 H), 3.76 (s, 3 H), 3.72 (s, 3 H), 2.92 (m, 1 H), 2.40-2.15 (comp, 4 H), 1.95 (m, 1 H), 1.90-1.75 (comp, 2 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.7, 171.9, 147.4, 137.2, 128.5, 127.0, 124.8, 117.7, 73.9, 53.0, 52.9, 44.4, 37.0, 30.3, 29.9, 26.8;

IR (neat) 3525, 3024, 2954, 1731, 1446, 1251 cm$^{-1}$;

HRMS (ESI$^+$); Calc’d for C$_{18}$H$_{22}$O$_5$Na: 341.1359; found: 341.1359 (M+Na); mp = 84-85 °C.

Dimethyl-4-hydroxy-4-methyl-3-vinylcycloheptane-1,1-dicarboxylate  (2.24c).

Allylation of (E)-dimethyl 2-(4-bromobut-2-en-1-yl)-2-(3-oxo-3-phenylpropyl)malonate (2.23c) was performed on a 0.11 mmol scale at room temperature for 10 min. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 15.8 mg (53%) of 2.24c as a thick clear oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.92 (m, 1 H), 5.07 (m, 2 H), 5.08 (m, 2 H), 3.74 (s, 3 H), 3.70 (s, 3 H), 2.49 (m, 1 H), 2.25-1.95 (m, 4 H), 1.80-1.50 (comp m, 4 H), 1.16 (s, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.2, 172.8, 139.72, 115.5, 73.1, 57.1, 52.7, 52.4, 48.3, 44.5, 34.9, 32.2, 30.1, 19.8;
IR (neat) 3535, 2955, 2929, 1731, 1456, 1233 cm⁻¹;

HRMS (ESI⁺); Calc’d for C₁₄H₂₃O₅: 271.1540; found: 271.1563 (M+1).

Methyl-5-methyl-7-oxo-9-vinyl-6-oxabicyclo[3.2.2]nonane-1-carboxylate (c-2.24c). Allylation of (E)-dimethyl 2-(4-bromobut-2-en-1-yl)-2-(3-oxo-3-phenylpropyl)malonate (2.23c) was performed on a 0.11 mmol scale at room temperature for 1 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 24.3 mg (93%) of c-2.24c as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 5.83 (m, 1 H), 5.05 (m, 2 H), 3.79 (s, 6 H), 2.57 (m, 1 H), 2.38 (comp, 2 H), 2.20-1.70 (comp m, 6 H), 1.29 (s, 3 H);

¹³C NMR (100 MHz, CDCl₃) δ 172.8, 171.8, 138.6, 116.0, 84.0, 77.3, 53.0, 43.4, 39.6, 32.4, 30.6, 28.1, 20.4;

IR (neat) 2979, 2952, 1744, 1729, 1450, 1272, 1054 cm⁻¹;

HRMS (ESI⁺); Calc’d for C₁₃H₁₈O₄Na: 261.1097; found: 261.1079 (M+Na); mp = 97-98 °C.
3-Phenyl-1-tosyl-4-vinylpyrrolidin-3-ol (2.24d). Allylation of (E)-N-(4-bromobut-2-en-1-yl)-4-methyl-N-(2-oxo-2-phenylethyl)benzenesulfonamide (2.23d) was performed on a 0.1 mmol scale at room temperature for 24 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 29.9 mg (38%) of 2.24d as an off-white solid whose $^1$H NMR spectral data was consistent with literature values.\(^{246}\)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J = 8$ Hz, 2 H), 7.40-7.27 (comp m, 7 H), 5.57 (m, 1 H), 5.18 (dt, $J = 10.8$, 1.2 Hz, 1 H), 5.02 (dt, $J = 17.6$, 1.6 Hz, 1 H), 3.76 (dd, $J = 7.6$, 9.2 Hz, 1 H), 3.70 (d, $J = 11.6$ Hz, 1 H), 3.60 (d, $J = 11.6$ Hz, 1 H), 3.45 (dd, $J = 10.8$, 9.6 Hz, 1 H), 3.14 (m, 1 H), 2.46 (s, 3 H), 1.75 (d, $J = 1.2$ Hz, 1 H); mp = 170-172 °C.

![2.24e](image)

4-Phenyl-1-tosyl-3-vinylpiperidin-4-ol (2.24e). Allylation of (E)-N-(4-bromobut-2-en-1-yl)-4-methyl-N-(3-oxo-3-phenylpropyl)benzenesulfonamide (2.23e) was performed on a 0.1 mmol scale at room temperature for 1 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 35 mg (98%) of 2.24e as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.72 (d, $J = 6.8$ Hz, 2 H), 7.45-7.15 (comp, 7 H), 5.43 (m, 1 H), 5.08 (d, $J = 10.8$ Hz, 1 H), 4.95 (d, $J = 17.6$ Hz, 1 H), 3.85-3.70 (comp m, 2 H), 3.04 (m, 1 H), 2.80-2.60 (comp, 2 H), 2.47 (s, 3 H), 2.18 (m, 1 H), 1.80 (dt, $J = 14$, 2.4 Hz, 1 H), 1.65 (d, $J = 2$ Hz, 1 H);
$^{13}$C NMR (100 MHz, CDCl$_3$) δ 152.1, 146.0, 143.8, 134.4, 133.6, 130.0, 128.7, 127.9, 127.4, 124.7, 119.0, 73.0, 47.2, 45.6, 42.3, 39.4, 21.8;

IR (neat) 3509, 3059, 3030, 2925, 2864, 1339, 1162, 925 cm$^{-1};$

HRMS (ESI$^+$); Calc’d for C$_{20}$H$_{24}$NO$_3$S: 358.1471; found: 358.1461 (M+1); mp = 143-144 °C.

![Chemical structure](image)

**Dimethyl-3-hydroxy-3-phenyl-4-vinylidenecyclopentane-1,1-dicarboxylate (2.26a)**  
Alkylation of dimethyl 2-(4-bromobut-2-yn-1-yl)-2-(2-oxo-2-phenylethyl)malonate (2.25a) was performed on a 0.1 mmol scale at room temperature for 30 min. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 26.6 mg (88%) of 2.26a as a thick clear oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.49 (d, J = 7.2 Hz, 2 H), 7.36 (t, J = 8.4 Hz, 2 H), 7.27 (m, 1 H), 4.81 (m, 2 H), 3.83 (s, 3 H), 3.73 (s, 3 H), 3.58 (m, 1 H), 3.14 (m, 1 H), 2.87 (d, J = 14 Hz, 1 H), 2.75-2.50 (m, 2 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 203.6, 173.2, 144.5, 128.2, 127.4, 125.9, 109.6, 83.6, 80.5, 58.7, 53.4, 53.2, 51.2, 37.9;

IR (neat) 3509, 3001, 2955, 2924, 1957, 1739, 1687, 1448, 1207 cm$^{-1};$

HRMS (ESI$^+$); Calc’d for C$_{17}$H$_{18}$O$_5$Na: 325.1046; found: 325.1067 (M+Na).
**Dimethyl-4-hydroxy-4-phenyl-3-vinylidenecyclohexane-1,1-dicarboxylate**

(2.26b). Alkylation of dimethyl 2-(4-bromobut-2-yn-1-yl)-2-(3-oxo-3-phenylpropyl)malonate (2.25b) was performed on a 0.1 mmol scale at room temperature for 30 min. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 24.4 mg (77%) of 2.26b as a white solid.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.47 (d, \(J = 8.8\) Hz, 2 H), 7.45 (t, \(J = 6.4\) Hz, 2 H), 7.30 (m, 1 H), 4.76 (m, 2 H), 3.78 (s, 3 H), 3.73 (s, 3 H), 3.11 (d, \(J = 13.6\) Hz, 1 H), 2.68 (m, \(J = 14\) Hz, 1 H), 2.60-2.30 (m, 2 H), 2.20-1.85 (m, 3 H);

\(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 204.7, 171.3, 143.5, 128.3, 127.7, 126.1, 104.1, 78.1, 73.8, 55.3, 52.8 52.7, 35.8, 33.9, 28.1;

IR (neat) 3504, 3057, 2955, 2373, 2245, 1961, 1736, 1439, 1254 cm\(^{-1}\);

HRMS (ESI\(^+\)); Calc’d for C\(_{18}\)H\(_{26}\)O\(_5\)Na: 339.1203; found: 339.1201 (M+Na); mp = 120-121 °C.

**Dimethyl-4-hydroxy-4-phenyl-3-vinylidenecycloheptane-1,1-dicarboxylate**

(2.26c). Alkylation of dimethyl 2-(4-bromobut-2-yn-1-yl)-2-(4-oxopentyl)malonate
(2.25c) was performed on a 0.1 mmol scale at room temperature for 6 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 11.6 mg (35%) of 2.26c as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 4.83 (m, 2 H), 3.71 (s, 6 H), 2.99 (d, J = 14 Hz, 1 H), 2.61 (d, J = 14 Hz, 1 H), 2.20 (m, 1 H), 1.85 (comp m, 3 H), 1.76 (s, 1 H), 1.64 (m, 2 H), 1.35 (s, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 206.7, 172.5, 106.9, 78.0, 73.2, 57.6, 52.4, 52.2, 41.7, 35.8, 32.3, 30.0, 20.14;

IR (neat) 3510, 2953, 1953, 1732, 1436, 1244, 1203 cm$^{-1}$;

HRMS (ESI$^+$); Calc’d for C$_{14}$H$_{20}$O$_3$Na: 291.1203; found: 291.1216 (M+Na); mp = 46-47 °C.

**Determination of stereoselectivity in the intramolecular allylations:** $^1$H NMR and $^{13}$C NMR spectral data of 2.24d was consistent with literature reported values.$^{246}$ $^1$H NMR and $^{13}$C NMR spectral data for 2.24a does not match literature known values for the anti-diastereomer leading to determination of syn stereochemistry. Below are observed nOEs marked with arrows for 2.24a in comparison to literature values for anti-diastereomer of 2.24a and closely related syn- and anti-compound.$^{88,94}$
The relative stereochemistry of compounds 2.24b, 2.24c, c-2.24c, and 2.24e was tentatively assigned based on the structure of allylic alcohols 2.24a and 2.24d. Utilizing 1D nOe $^1\text{H}$ NMR spectroscopy, we observed the key nOes marked with arrows. The syn-assignment is consistent with closely related structures of previously reported metal catalyzed allylations.\textsuperscript{88,94,247,248}

![Chemical Structures](image)

5.3 Synthetic Procedures From Chapter 4

5.3.1 General

Reagents 4.19a, 4.19b, 4.19e, 4.19f, 4.19g, 4.19h, 4.19k, 4.19n, 4.19o, 4.19p, 4.19t, 4.19u, amino acids 4.32a-l, 4.43, 4.35, and 1,3,5-trimethoxybenzene were purchased and used without purification. Additives 2.8c, 1.30, and 4.34 were purchased and distilled prior to use. Carboxylic acids 4.19c,\textsuperscript{249} 4.19d,\textsuperscript{249} 4.19j,\textsuperscript{249} 4.19l,\textsuperscript{250,251} 4.19m,\textsuperscript{252} 4.19q,\textsuperscript{249} 4.19s,\textsuperscript{249} and 4.26\textsuperscript{253} were prepared following known literature procedures. Azides 3.27a,\textsuperscript{257} 3.27b,\textsuperscript{254} 4.14a,\textsuperscript{258} 4.14b,\textsuperscript{255} 4.14c,\textsuperscript{255} 4.14d,\textsuperscript{256} 4.14e,\textsuperscript{259} 4.14f,\textsuperscript{126} 4.14g,\textsuperscript{265} 4.14h,\textsuperscript{264} and 4.14i\textsuperscript{266} were also prepared according to known protocols. Diethyl chlorophosphite [ClP(OEt)$_2$] and diphenylchlorophosphine (ClPPh$_2$) were purchased and distilled prior to use. The following chlorophosphites were
prepared following known literature procedures and distilled prior to use: catechol chlorophosphite \([\text{ClP(cat)}]\),\(^{260}\) binol-chlorophosphite \([\text{ClP(bin)}]\),\(^{261}\) dimethyl-propandiolchlorophosphite \([\text{ClP(dmp-ol)}]\),\(^{262}\) and pinacol chlorophosphite \([\text{ClP(pin)}]\).\(^{263}\) Silanes \(\text{Ph}_2\text{SiH}_2\), \((\text{MeO})_3\text{SiH}\), \((\text{EtO})_2\text{MeSiH}\), \(\text{Cl}_3\text{SiH}\), \(\text{PhSiH}_3\) and phosphines triphenylphosphine, tris(4-methoxy)phenylphosphine, and tri-\(n\)-butylphosphine were purchased from commercial sources and used without further purification. Phosphine \(3.55\)^{122} and phosphine oxide \(3.44\)^{118} were prepared following known literature procedures.

5.3.2 Synthesis of Substrates and Reagents

\[
\begin{align*}
\text{Ph}-\text{CH}=(\text{O})-\text{CH}-(\text{N}_3) & \xrightarrow{10\% \text{ NaOH, MeOH}} \text{Ph}-\text{CH}=\text{CH}-\text{CO} \quad \text{(4.30)}
\end{align*}
\]

\((E)-2-(\text{Azidomethyl})-3\text{-phenylacrylic acid (4.30).} \) To a solution of \((E)\)-methyl 2-(azidomethyl)-3-phenylacrylate (427 mg, 1.84 mmol)\(^{267,268}\) in MeOH (3.7 mL, 0.5 M) was added 10% aqueous NaOH solution (3.7 mL, 0.5 M) and the resulting solution stirred for 8 h. The mixture was washed with DCM (3 x 15 mL) and the aqueous layer acidified to a pH of 1-2 with 5% aqueous HCl and re-extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried (MgSO\(_4\)), and concentrated under reduced pressure to yield 365 mg (98%) of \textbf{4.30} as fluffy, off-white crystals.
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 11.91 (br s, 1 H), 8.13 (s, 1 H), 7.60-7.30 (m, 5 H), 4.24 (s, 2 H);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.7, 146.9, 133.9, 130.2, 129.9, 129.0, 125.9, 46.7;

IR (neat) 3057, 2953, 2823, 2118, 2089, 1671, 1617, 1448, 1323, 1221;

HRMS (ESI) m/z 226.0583 [C10H9N3O2Na (M+Na) requires 226.0587]; m.p = 128-130 °C.

**5-Bromothiophene-2-sulfonyl azide (4.44).** To a solution of 5-bromothiophene-2-sulfonyl chloride 4.39 (1.04 g, 3.99 mmol\(^{181}\)) in 3:1 acetone/water (16 mL, 0.3 M) was added NaN\(_3\) (649 mg, 9.98 mmol) and the resulting slurry stirred for 12 h. The solution was then diluted with H\(_2\)O (25 mL), the layers separated, and the aqueous phase extracted with pentane (3 x 20 mL). The combined organic fractions were dried (MgSO\(_4\)) and concentrated under reduced pressure. The resulting crude mixture was purified by flash chromatography eluting with hexanes/EtOAc (5:1) to provide 487 mg (45% over 2 steps) of 4.44 as a low melting-point off-white solid.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.58 (d, J = 4 Hz, 1 H), 7.20 (d, J = 4 Hz, 1 H);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 138.6, 135.1, 131.2, 124.0;

IR (neat) 2989, 2901, 2130, 1395, 1379, 1166, 1056, 1022 cm\(^{-1}\);

HRMS (ESI - negative ion mode) m/z 268.8858 [C4H4BrN3O2S2 (M+2) requires 268.8934].
Representative procedure for the ligation of carboxylic acids and azides: To a solution of carboxylic acid (0.39 mmol) in chlorobenzene (1 mL) was added Et₃N (54.4 µl, 0.39 mmol) at room temperature. The mixture was then cooled to 0 °C and CIP(pin) (71.2 mg, 0.39 mmol) was added drop wise with rapid stirring. The resulting slurry was allowed to warm to room temperature by removal of the cooling bath, and stirred for an additional 15 min. A solution of azide (0.30 mmol) in chlorobenzene (0.5 mL) was then added drop wise, and stirring continued for 1 h. The mixture was heated to 80 °C and for an additional 2 h, then heated to 130 °C and stirred until complete consumption of the carboxylic acid was observed by TLC (ca. 10 h).

Purification Method A - Aqueous Workup: The solution was diluted with EtOAc (5 mL) and saturated aqueous NaHCO₃ (10 mL), the layers were separated, and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried (MgSO₄) and concentrated under reduced pressure. The resulting residue provided the desired amide in >95% purity by NMR.

Purification Method B - Flash Chromatography: The crude mixture was purified directly by flash chromatography eluting with hexanes/EtOAc in the indicated ratio to give the corresponding amide.
**N-Benzyl-4-methoxybenzamide (4.23a).** Ligation of 4.19 with BnN$_3$ (3.27b) was performed on 0.3 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 46 mg (63%) of 4.23a as a white solid whose $^1$H NMR spectra were consistent with literature values.$^{269}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J = 8.8$ Hz, 2 H), 7.40-7.28 (m, 5 H), 6.93 (d, $J = 8.8$ Hz, 2H), 6.36 (br s, 1 H), 4.64 (d, $J = 5.6$ Hz, 2 H), 3.85 (s, 3 H); mp = 130-131 °C.

**4-Methoxy-N-tosylbenzamide (4.23b).** Ligation of 4.19 with TsN$_3$ (4.14b) was performed on 0.3 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 95.4 mg (96%) of 4.23b as an off-white solid whose $^1$H NMR spectra were consistent with literature values.$^{271}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.04 (d, $J = 8$ Hz, 2 H), 7.83 (d, $J = 6.8$ Hz, 2 H), 7.35 (d, $J = 8$ Hz, 2 H), 6.89 (d, $J = 9.2$ Hz, 2 H), 5.21 (br s, 1 H), 3.83 (s, 3 H), 2.43 (s, 3 H); m.p = 176-177 °C.
**N-Tosylbenzamide (4.23c).** Ligation of 3.26 with TsN₃ (4.14b) was performed on 0.2 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 51.4 mg (93%) of 4.23c as a white solid whose ¹H NMR spectra were consistent with literature values.²⁷¹

¹H NMR (400 MHz, CDCl₃) δ 8.8 (br s, 1 H), 8.08 (d, J = 8.4 Hz, 2 H), 7.81 (d, J = 7.6 Hz, 2 H), 7.62 (t, J = 8 Hz, 1 H), 7.49 (t, J = 6.4 Hz, 2 H), 7.39 (d, J = 7.2 Hz, 2 H), 2.46 (s, 3 H); m.p = 138-139 °C.

**N-Tosyl-4-(trifluoromethyl)benzamide (4.23d).** Ligation of 4.19b with TsN₃ (4.14b) was performed on 0.3 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 83 mg (81%) of 4.23d as a white solid whose ¹H NMR spectra were consistent with literature values.²⁷²

¹H NMR (400 MHz, CD₃OD) δ 8.03 (d, J = 8 Hz, 2 H), 7.95 (d, J = 8 Hz, 2 H), 7.73 (d, J = 8 Hz, 2 H), 7.37 (d, J = 7.6 Hz, 2 H), 2.41 (s, 3 H); m.p = 173-175 °C.
**4-Chloro-N-tosylbenzamide (4.23f).** Ligation of **4.19d** with TsN$_3$ (4.14b) was performed on 0.2 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 56.3 mg (91%) of **4.23f** as a white solid whose $^1$H NMR spectra were consistent with literature values.$^{272}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.8 (br s, 1 H), 8.03 (d, $J = 8$ Hz, 2 H), 7.74 (d, $J = 8.8$ Hz, 2 H), 7.42 (d, $J = 8$ Hz, 2 H), 7.36 (d, $J = 7.6$ Hz, 2 H), 2.45 (s, 3 H); m.p = 169-172 °C.

\[
\text{\includegraphics[width=0.5\textwidth]{4.23f.png}}
\]

**N-Tosyl-1H-pyrrole-2-carboxamide (4.23h).** Ligation of **4.19f** with TsN$_3$ (4.14b) was performed on 0.30 mmol scale, with a reaction time of 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 47.8 mg (60%) of **4.23h** as a tan solid whose $^1$H NMR spectra were consistent with literature values.$^{273}$

$^1$H NMR (300 MHz, d$_6$-DMSO) $\delta$ 11.97 (br s, 1 H), 11.72 (br s, 1 H), 7.85 (d, $J = 5.1$ Hz, 2 H), 7.41 (d, $J = 5.1$ Hz, 2 H), 7.11 (br s, 1 H), 7.00 (br s, 1 H), 6.14-6.11 (m, 1 H), 2.38 (s, 3 H); m.p = 160 °C.

\[
\text{\includegraphics[width=0.5\textwidth]{4.23h.png}}
\]

**N-Tosylcinnamamide (4.23i).** Ligation of **4.19g** with TsN$_3$ (4.14b) was performed on 0.3 mmol scale, with a reaction time of 14 h. Purification by flash chromatography
eluting with hexanes/EtOAc (1:1) provided 88 mg (96%) of 4.23i as a yellowish/white solid whose $^1$H NMR spectra were consistent with literature values.$^{272}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.42 (br s, 1 H), 8.01 (d, $J = 8.4$ Hz, 2 H), 7.71 (d, $J = 15.6$ Hz, 1 H), 7.46 (m, 2 H), 7.4-7.25 (m, 5 H), 6.54 (d, $J = 16$ Hz, 1 H), 2.38 (s, 3 H); m.p = 119-120 °C.

![4.23j](image)

2-Phenyl-$N$-tosylacetamide (4.23j). Ligation of 4.19h with Ts$_3$N (4.14b) was performed on 0.25 mmol scale, with a reaction time of 14 h, using NaH instead of Et$_3$N. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 69 mg (94%) of 4.23j as a white solid whose $^1$H NMR spectra were consistent with literature values.$^{271}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.10 (br s, 1 H), 7.84 (d, $J = 6.8$ Hz, 2 H), 7.25-7.18 (m, 5 H), 7.11 (d, $J = 6.8$ Hz, 2 H), 3.53 (s, 2 H), 2.37 (s, 3 H); m.p = 148-149 °C.

![4.23k](image)

$N$-Tosyloctanamide (4.23k). Ligation of 4.19i with Ts$_3$N (4.14b) was performed on 0.2 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 55 mg (91%) of 4.23k as a white solid.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.72 (br s, 1 H), 7.96 (d, $J = 8.4$ Hz, 2 H), 7.36 (d, $J = 8$ Hz, 2 H), 2.45 (s, 3 H), 2.25 (t, $J = 7.6$ Hz, 2 H), 1.56 (m, 2 H), 1.23-1.12 (m, 8 H), 0.86 (t, $J = 6.8$ Hz, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.7, 145.3, 135.6, 129.8, 128.6, 36.51, 31.7, 29.0, 28.9, 24.5, 22.7, 21.9, 14.2;

IR (neat) 3431, 3054, 2952, 2198, 1720, 1437, 1280, 1114, 1031;

HRMS (ESI) $m/z$ 298.1458 [C$_{15}$H$_{24}$NO$_3$S (M+1) requires 298.1471]; m.p = 69-70 °C.

![Diagram of N-Tosylcyclohexanecarboxamide](image)

**N-Tosylcyclohexanecarboxamide (4.23l).** Ligation of 4.19j with TsN$_3$ (4.14b) was performed on 0.3 mmol scale, with a reaction time of 14 h, using NaH instead of Et$_3$N. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 68 mg (80%) of 4.23l as a white solid whose $^1$H NMR spectra were consistent with literature values.$^{271}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.94 (d, $J = 8$ Hz, 2 H), 7.84 (br s, 1 H), 7.34 (d, $J = 8.4$ Hz, 2 H), 2.44 (s, 3 H), 2.16 (m, 1 H), 1.9-1.5 (m, 6 H), 1.5-1.0 (m, 6 H); m.p = 184-185 °C.

![Diagram of N-Tosylpivalamide](image)

**N-Tosylpivalamide (4.23m).** Ligation of 4.19k with TsN$_3$ (4.14b) was performed
on 0.25 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 36 mg (56%) of 4.23m as a white solid whose \(^1\)H NMR spectra were consistent with literature values.\(^\text{271}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.33 (br s, 1 H), 7.95 (d, \(J = 8\) Hz, 2 H), 7.34 (d, \(J = 8\) Hz, 2 H), 2.45 (s, 3 H), 1.16 (s, 9 H); m.p. = 168-170 °C.

![Structure of 4.23n](image)

\(N\)-benzyl-4-(trifluoromethyl)benzamide (4.23n). Ligation of 4.19c with BnN\(_3\) (3.27b) was performed on 0.3 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 71 mg (85%) of 4.23n as an off-white solid whose \(^1\)H NMR spectra were consistent with literature values.\(^\text{270}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.92 (d, \(J = 8\) Hz, 2 H), 7.70 (d, \(J = 8\) Hz, 2 H), 7.5-7.2 (m, 5H), 6.42 (br s, 1 H), 4.66 (d, \(J = 5.6\) Hz, 2 H); m.p. = 169-171 °C.

![Structure of 4.23p](image)

\(E\)-\(N\)-Cinnamoyl-4-methoxybenzamide (4.23p). Ligation of 4.19g with azide 4.14d was performed on 0.25 mmol scale, with a reaction time of 14 h, heating to only 80°C and using NaH instead of Et\(_3\)N. Purification by flash chromatography eluting with
hexanes/EtOAc (1:1) provided 54 mg (77%) of 4.23p as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$), δ 7.73 (d, $J = 15.6$ Hz, 1 H), 7.60-7.30 (m, 7 H), 6.90 (d, $J = 9.2$ Hz, 2 H), 6.54 (d, $J = 15.6$ Hz, 1 H), 3.90 (s, 3 H);

$^{13}$C NMR (100 MHz) δ 178.6, 163.9, 156.7, 142.3, 134.9, 131.3, 130.1, 129.1, 128.1, 121.9, 121.0, 114.4, 55.7;

IR (neat) 3264, 3056, 3027, 1658, 1624, 1576, 1510, 1244;

HRMS (ESI) m/z 282.1133[C$_{17}$H$_{15}$NO$_3$ (M+1) requires 282.1125]; mp = 153-154 °C.

![4.23q](image)

4-Methoxy-$N$-phenylbenzamide (4.23q). Ligation of 4.19a with PhN$_3$ (3.27a) was performed on 0.231 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 58 mg (89%) of 4.23q as a white solid whose $^1$H NMR spectra were consistent with literature values.\textsuperscript{274}$^1$H NMR (400 MHz, CDCl$_3$) δ 7.87 (d, $J = 6.8$ Hz, 2 H), 7.70 (br s, 1 H), 7.63 (d, $J = 8$ Hz, 2 H), 7.38 (t, $J = 8$ Hz, 2 H), 7.17 (t, $J = 6.4$ Hz, 1 H), 6.99 (d, $J = 8$ Hz, 2 H), 3.89 (s, 3 H); mp = 175 °C.

![4.23u](image)
2-Benzoyl-N-benzylbenzamide (4.23u). Ligation of 4.19o with BnN₃ (3.27b) was performed on 0.3 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 31.7 mg (34%) of 4.23u as a white solid.

¹H NMR (400 MHz, CDCl₃) 7.49-7.46 (m, 2 H), 7.38-7.25 (m, 9 H), 7.24-7.18 (m, 2 H), 4.85 (d, J = 15 Hz, 1 H), 4.01 (d, J = 15 Hz, 1 H);

¹³C NMR (100 MHz, CDCl₃) δ 167.9, 149.0, 138.2, 138.1, 132.9, 130.3, 129.7, 128.8, 128.6, 128.5, 128.3, 127.1, 126.4, 123.6, 122.8, 91.8, 43.0;

IR (neat) 3054, 2986, 1711, 1362, 1265, 909 cm⁻¹;

HRMS (ESI) m/z 338.1121 [C₂₁H₁₇NO₂Na (M+Na) requires 338.1151; mp = 145-147 °C.

![Structure 4.42](image)

N-((5-Bromothiophen-2-yl)sulfonyl)-2,4-dichlorobenzamide (4.42). Ligation of 4.19p with azide 4.44 was performed on 0.20 mmol scale, with a reaction time of 12 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 91 mg (97%) of 4.42 as an off-white solid whose ¹H NMR and ¹³C NMR spectra were consistent with literature values.¹⁷₈

¹H NMR (400 MHz, d⁶-DMSO) δ 7.53 (d, J = 8.4 Hz, 1 H), 7.51 (d, J = 8.4 Hz, 1 H), 7.37 (dd, J = 8.4, 2 Hz, 1 H), 7.34 (d, J = 4 Hz, 1 H), 7.17 (d, J = 4 Hz, 1 H);

¹³C NMR (100 MHz, d⁶-DMSO) δ 169.7, 148.1, 138.5, 133.9, 131.9, 131.5, 130.5, 130.0,
129.6, 127.2, 116.0;

IR (neat) 3494, 3094, 3004, 2420, 2156, 1709, 1584, 1340, 1267, 1127, 1078, 967;

HRMS (ESI) m/z 413.8422 and 435.8245 \([\text{C}_{11}\text{H}_{7}\text{BrCl}_{2}\text{NO}_{3}\text{S}_{2} (\text{M}+1)]\) requires 413.8440 and \([\text{C}_{11}\text{H}_{6}\text{BrCl}_{2}\text{NNaO}_{3}\text{S}_{2} (\text{M}+\text{Na})]\) requires 435.8242; mp = 148-150 °C.

**General procedure for the intramolecular Staudinger ligation.** To a solution of azido acid (0.39 mmol) in chlorobenzene (1.5 mL) was added Et\(_3\)N (54.4 µl, 0.39 mmol) at room temperature. The mixture was then cooled to 0 °C and ClIP(pin) (71.2 mg, 0.39 mmol) was added drop wise with rapid stirring. The resulting slurry was allowed to warm to room temperature by removal of the cooling bath, and stirred for an additional 1.5 h. The mixture was heated to 80 °C for an additional 2 h, then heated to 130 °C and stirred until complete consumption of the carboxylic acid was observed by TLC (ca. 10 h).

![4.27](image_url)

**Isoindolin-1-one (4.27).** Ligation of 4.26 was performed on 0.39 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:2) provided 45.2 mg (87%) of 4.27 as a white solid whose \(^1\)H NMR spectra were consistent with literature values.\(^{275}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.88 (d, \(J = 7.2 \text{ Hz}, 1 \text{ H}\)), 7.70-7.40 (m, 4H), 4.48 (s, 2H); mp = 176
151-152 °C.

3-Benzylpyrrolidin-2-one (4.29). Ligation of 4.28 was performed on 0.20 mmol scale, with a reaction time of 14 h, using NaH instead of Et₃N. Purification by flash chromatography eluting with EtOAc provided 22.6 mg (64%) of 4.29 as a tan solid whose ¹H NMR spectra were consistent with literature values.²⁷⁶

¹H NMR (300 MHz, CDCl₃) δ 7.32-7.20 (m, 5 H), 6.70 (br s, 1 H), 3.31-3.18 (m, 3 H), 2.72-2.60 (m, 2 H), 2.18-2.07 (m, 1 H), 1.89-1.77 (m, 1 H); mp = 111 °C.

(E)-3-Benzylideneazetidin-2-one (4.31). Ligation of 4.30 was performed on 0.25 mmol scale, with a reaction time of 14 h, using NaH instead of Et₃N. Purification by flash chromatography eluting with hexanes/EtOAc (1:2) provided 32.2 mg (86%) of 4.31 as an off-white solid whose ¹H NMR spectra were consistent with literature values.²⁷⁷

¹H NMR (400 MHz, CDCl₃) δ 7.50-7.30 (m, 5 H), 7.02 (s, 1 H), 6.13 (br s, 1 H), 4.21 (t, J = 1.2 Hz, 2 H); mp 158-160 °C.
General procedure for peptide ligation. To a solution of amino acid (0.26 mmol) in chlorobenzene (0.8 mL) was added NaH (10.4 mg, 0.26 mmol) at room temperature. The mixture was cooled to 0 °C and then CIPPh$_2$ (57.4 mg, 0.26 mmol) was added drop wise with rapid stirring. The resulting slurry was allowed to warm to room temperature by removal of the cooling bath, and stirred for an additional 15 min. A solution of azide (0.20 mmol) in chlorobenzene (0.2 mL) was then added drop wise, and stirring continued for 1 h. The mixture was heated to 80 °C and stirred until complete consumption of the carboxylic acid was observed by TLC (ca. 14 h).

![Structure](image)

(S)-Benzyl (1-(benzylamino)-1-oxopropan-2-yl)carbamate (4.33a) [Cbz-Ala-NHBn]. Ligation of 4.32a with BnN$_3$ (3.27b) was performed on 0.25 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 46.5 mg (60%) of 4.33a as a fluffy white solid whose $^1$H NMR spectra were consistent with literature values.$^{278}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.55-7.20 (m, 10 H), 6.52 (br s, 1 H), 5.40 (br d, $J = 4.8$ Hz, 1 H), 5.06 (s, 2 H), 4.43 (m, 2 H), 4.28 (m, 1 H), 1.41 (d, $J = 7.2$ Hz, 3 H);

[$\alpha$]$_D^{20} = -7.5$ (c 0.69, CHCl$_3$), [known: [$\alpha$]$_D^{22} = -8.1$ (c 1.3, CHCl$_3$)]; mp = 138 °C.
(S)-(9H-Fluoren-9-yl)methyl (1-(4-methylphenylsulfonamido)-1-oxo-3-phenylpropan-2-yl)carbamate (4.33b) [Fmoc-Phe-NHTs]. Ligation of 4.32b with TsN₃ (4.14b) was performed on 0.2 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:2) provided 76 mg (70%) of 4.33b as a white flakey solid.

¹H NMR (400 MHz, CDCl₃) δ 9.55 (br s, 1 H), 7.84 (d, J = 8 Hz, 2 H), 7.78 (d, J = 7.2 Hz, 2 H), 7.51 (m, 2 H), 7.45-6.95 (m, 10 H), 6.90 (d, J = 3.6 Hz, 2 H), 5.36 (br s, 1 H), 4.51 (br m, 1 H), 4.33 (m, 2 H), 4.13 (br m, 1 H), 2.95 (dd, J = 18.8, 5.2 Hz, 2 H), 2.40 (s, 3 H);

¹³C NMR (100 MHz, CDCl₃) δ 169.7, 156.5, 145.3, 143.8, 143.5, 141.4, 135.8, 135.3, 129.7, 129.4, 128.9, 128.6, 128.0, 127.3, 125.3, 120.2, 67.8, 56.3, 47.1, 38.1, 21.8;

IR (neat) 3331, 3029, 2922, 2471, 1947, 1712, 1681, 1520, 1418;

HRMS (ESI) m/z 563.1614[C₃₁H₂₈N₂NaO₅S (M+Na) requires 563.1611];

[α]D²⁰ = −10.6 (c 0.66, CHCl₃); mp = 222 °C.

(S)-Ethyl 2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)acetate (4.33c) [Fmoc-Ala-Gly-OEt]. Ligation
of 4.32c with azide 4.14a was performed on 0.20 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:2) provided 70 mg (88%) of 4.33c as a clear flakey crystals whose $^1$H NMR spectra were consistent with literature values.\textsuperscript{279}

$^1$H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 7.76 (d, $J = 7.6$ Hz, 2 H), 7.59 (d, $J = 7.2$ Hz, 2 H), 7.40 (t, $J = 7.2$ Hz, 2 H), 7.31 (t, $J = 7.6$ Hz, 2 H), 6.73 (br s, 1 H), 5.54 (br d, $J = 7.6$ Hz, 1 H), 4.41 (d, $J = 6.8$ Hz, 2 H), 4.33 (m, 1 H), 4.20 (m, 3 H), 4.03 (d, $J = 4.4$ Hz, 2 H), 1.42 (d, $J = 6.8$ Hz, 3 H), 1.27 (t, $J = 7.2$ Hz, 3 H);

$[\alpha]_d^{20}$ = $-9.5$ (c 1.05, CHCl\textsubscript{3}), [known: $[\alpha]_d^{25}$ = $-16.4$ (c 1.1, CHCl\textsubscript{3})]; mp = 163-164 °C.

\[
\text{Ph} \quad \begin{array}{c}
\hat{O} \\
\hat{\text{NHFmoc}} \\
\hat{\text{CO}_2\text{Et}}
\end{array}
\begin{array}{c}
\text{(S)-Ethyl} \\
\text{2-((2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)acetate (4.33d) [Fmoc-Phe-Gly-OEt]. Ligation of 4.32b with azide 4.14a was performed on 0.2 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:2) provided 82 mg (87%) of 4.33d as a white fluffly solid whose $^1$H NMR spectra were consistent with literature values.}\textsuperscript{282}
\end{array}
\]

$^1$H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 7.77 (d, $J = 8$ Hz, 2 H), 7.55 (t, $J = 7.2$ Hz, 2 H), 7.41 (t, $J = 7.6$ Hz, 2 H), 7.35-7.0 (m, 7 H), 6.22 (br s, 1 H), 5.27 (br s, 1 H), 4.55-4.27 (comp m, 3 H), 4.19 (m, 3 H), 3.95 (m, 2 H), 3.12 (br d, $J = 3.6$ Hz, 2 H), 1.28 (t, $J = 7.2$ Hz, 3 H);

$[\alpha]_d^{20}$ = $-10.7$ (c 0.94, CHCl\textsubscript{3}), [known: $[\alpha]_d^{20}$ = $-14.2$ (c 1.02, CHCl\textsubscript{3})]; mp = 184-185 °C.

180
HPLC (CHIRALCEL OD-H, hexane:iPrOH = 9:1, 0.5 mL/min, detect 254 nm).

Ethyl 2-((2S,3S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylpentanamido)acetate (4.33e) [Fmoc-Ile-Gly-OEt]. Ligation of 4.32d with azide 4.14a was performed on 0.2 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 45 mg (51%) of 4.33e as a clear flakey crystals whose $^1$H NMR spectra were consistent with literature values.$^{280,281}$

$^1$H NMR (400 MHz, CHCl$_3$) δ 7.77 (d, $J$ = 7.2 Hz, 2 H), 7.59 (d, $J$ = 6 Hz, 2 H), 7.41 (t, $J$ = 7.2 Hz, 2 H), 7.32 (t, $J$ = 7.2 Hz, 2 H), 6.42 (br s, 1 H), 5.40 (br d, $J$ = 8 Hz, 1 H), 4.41 (m, 2 H), 4.30-4.15 (m, 3 H), 4.15-3.90 (m, 2 H), 1.93 (br m, 1 H), 1.54 (br m, 1 H), 1.40-1.05 (m, 4 H), 1.04-0.70 (m, 6 H);

[α]$_D^{20}$ = −11.9 (c 0.61, CHCl$_3$), [known: [α]$_D^{20}$ = −16.7 (c 0.67, CHCl$_3$)]; mp = 178-179 ºC.
(R)-Ethyl 2-{2-{((9H-fluoren-9-yl)methoxy)carbonyl}amino}-3-(tritylthio)propanamido)acetate (4.33f) [Fmoc-Cys(Trt)-Gly-OEt]. Ligation of 4.32e with azide 4.14a was performed on 0.2 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 98 mg (73%) of 4.33f as an off-white solid whose $^1$H NMR spectra were consistent with literature values.$^{284}$

$^1$H NMR (400 MHz, CHCl$_3$) $\delta$ 7.77 (t, $J = 7.6$ Hz, 2 H), 7.60 (d, $J = 6.4$ Hz, 2 H), 7.45 (d, $J = 8$ Hz, 6 H), 7.40 (m, 2 H), 7.30 (t, $J = 7.2$ Hz, 8 H), 7.21 (m, 3 H), 6.37 (br s, 1 H), 5.03 (br d, $J = 7.6$ Hz, 1 H), 4.42 (m, 2 H), 4.22 (comp m, 3 H), 3.95 (m, 2 H), 3.83 (m, 1 H), 2.71 (m, 2 H), 1.27 (t, $J = 7.2$ Hz, 3 H);

[α]$_D^{20}$ = +10 (c 0.74, MeOH), [known: [α]$_D^{20}$ = +34.7 (c 0.1, MeOH)]; mp = 80-82 °C.

(S)-tert-Butyl 3-{2-{((9H-fluoren-9-yl)methoxy)carbonyl}amino}-3-{(2-ethoxy-2-oxoethyl)amino}-3-oxopropyl)-1H-indole-1-carboxylate (4.33g) [Fmoc-Trp(Boc)-Gly-OEt]. Ligation of 4.32f with azide 4.14a was performed on 0.2 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc
(1:1) provided 95 mg (78%) of 4.33g as a yellowish solid whose $^1$H NMR spectra were consistent with literature values.\textsuperscript{285}

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.17 (d, $J = 7.2$ Hz, 1 H), 7.77 (d, $J = 7.6$ Hz, 2 H), 7.65 (br d, 1 H), 7.54 (m, 3 H), 7.40 (t, $J = 7.2$ Hz, 2 H), 7.35-7.20 (m, 4 H), 6.35 (br s, 1 H), 5.62 (br s, 1 H), 4.61 (m, 1 H), 4.42 (m, 2 H), 4.21 (comp m, 3 H), 3.92 (m, 2 H), 3.23 (comp m, 2 H), 1.64 (s, 9 H), 1.28 (t, $J = 7.2$ Hz, 3 H);

[$\alpha$]$^D_{20}$ = $-10.4$ (c 1.09, CHCl$_3$), [known: [$\alpha$]$^D_{20}$ = $-10.3$ (c 1.11, CHCl$_3$)]; mp = 80-83 °C.

![Chemical structure](image)

**(R)-(9H-Fluoren-9-yl)methyl 2-((2-ethoxy-2-oxoethyl)carbamoyl)pyrrolidine-1-carboxylate (4.33h)** [Fmoc-Pro-Gly-OEt]. Ligation of 4.32g with azide 4.14a was performed on 0.2 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:2) provided 76 mg (90%) of 4.33h as a white crystalline solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.77 (d, $J = 6.8$ Hz, 2 H), 7.57 (m, 2 H), 7.40 (t, $J = 7.2$ Hz, 2 H), 7.31 (t, $J = 7.2$ Hz, 2 H), 7.08 (br s, 1 H), 4.55-4.10 (comp m, 6 H), 4.10-3.70 (m, 2 H), 3.50 (m, 2 H), 2.50-1.80 (comp m, 4 H), 1.25 (t, $J = 7.2$ Hz, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.0, 169.8, 156.3, 144.0, 141.5, 127.9, 127.2, 125.2, 120.5, 67.8, 61.6, 60.6, 47.4, 41.5, 31.2, 28.7, 24.7, 23.7, 14.3;

IR (neat) 3329, 3065, 2979, 2893, 1747, 1712, 1536, 1415, 1335, 1197, 1118, 759;

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HRMS (ESI) m/z 445.1744 [C_{24}H_{26}N_2NaO_5 (M+Na) requires 445.1734];

[α]_D^{20} = -52 (c 1.0, CHCl_3); mp = 95 °C.

tert-Butyl 3-((S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-((S)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-oxopropyl)-1H-indole-1-carboxylate (4.33i) [Fmoc-Trp(Boc)-Phe-OEt]. Ligation of 4.32f with azide 4.14e was performed on 0.15 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:2) provided 40.5 mg (38%) of 4.33i as a thick clear oil.

^1H NMR (400 MHz, CDCl_3) δ 8.16 (br d, J = 6.8 Hz, 1 H), 7.78 (d, J = 7.6 Hz, 2 H), 7.65 (d, J = 6.4 Hz, 1 H), 7.60-7.47 (m, 3 H), 7.41 (m, 2 H), 7.37-7.23 (comp m, 4 H), 7.14 (d, J = 6.8 Hz, 3 H), 6.90 (br s, 1 H), 6.19 (d, J = 7.6 Hz, 1 H), 5.52 (br d, J = 7.2 Hz, 1 H), 4.71 (q, J = 7.2 Hz, 1 H), 4.51 (br d, J = 4.8 Hz, 1 H), 4.39 (dq, J = 13.2, 6 Hz, 2 H), 4.30-3.95 (comp m, 4 H), 3.27 (m, 1 H), 3.12 (m, 1 H), 3.00 (comp m, 2 H), 1.64 (s, 9 H), 1.18 (t, J = 7.2 Hz, 3 H);

^13C NMR (100 MHz, CDCl_3) δ 170.6, 170.3, 155.9 149.5, 143.8, 141.4, 135.6, 135.5, 130.3, 129.2, 128.7, 128.5, 127.8, 127.2, 125.2, 125.1, 124.8, 124.7, 122.9, 120.1, 119.0, 115.5, 83.7, 67.7, 61.7, 55.0, 53.4, 47.3, 38.1, 28.4, 28.2, 14.0;

IR (neat) 3314, 3063, 2979, 2932, 2113, 1713, 1536, 1452, 1368, 1256, 1222, 1159, 1087, 760;
HRMS (ESI) m/z 724.3025 [C_{42}H_{43}N_{3}NaO_{7} (M+Na) requires 724.2993];

[\alpha]_{D}^{20} = +25.4 (c 0.70, CHCl_{3}).

![Chemical Structure](image)

(S)-Ethyl 2-(((S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)-3-phenylpropanoate (4.33j) [Fmoc-Phe-Phe-OEt]. Ligation of 4.32b with azide 4.14e was performed on 0.2 mmol scale, heating to 130°C with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 80 mg (71%) of 4.33j as a yellowish solid.283

$^1$H NMR (400 MHz, CHCl$_3$) $\delta$ 7.78 (d, $J$ = 7.2 Hz, 2 H), 7.54 (t, $J$ = 6.8 Hz, 2 H), 7.42 (t, $J$ = 7.2 Hz, 2 H), 7.29 (m, 5 H), 7.19 (m, 5 H), 6.98 (m, 2 H), 6.24 (d, $J$ = 6 Hz, 1 H), 5.30 (br m, 1 H), 4.76 (q, $J$ = 6.8 Hz, 1 H), 4.44 (comp m, 2 H), 4.30 (m, 1 H), 4.25-4.00 (comp m, 3 H), 3.05 (comp m, 4 H), 1.22 (t, $J$ = 7.2 Hz, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.0, 170.4, 156.0, 143.9, 141.5, 135.8, 129.6, 129.4, 129.0, 128.7, 128.0, 127.4, 127.3, 127.2, 125.3, 125.2, 120.2, 67.3, 61.8, 56.1, 53.6, 47.3, 38.6, 38.2, 14.3;

IR (neat) 3582, 3289, 2920, 2351, 1947, 1729, 1713, 1643, 1536, 1503, 1453;

HRMS (ESI) m/z 563.2540 [C$_{35}$H$_{35}$N$_{2}$O$_{5}$ (M+1) requires 563.2540];

[\alpha]_{D}^{20} = +15 (c 0.987, CHCl$_3$), [known: [\alpha]_{D}^{20} = +18 (c 0.97, CH$_2$Cl$_2$)]; mp = 170-171 °C.
(R)-(9H-Fluoren-9-yl)methyl 2-(((S)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (4.33k) [Fmoc-Pro-Phe-OEt]. Ligation of 4.32g with azide 4.14e was performed on 0.15 mmol scale, with a reaction time of 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:2) provided 64 mg (83%) of 4.33k as a thick yellow-tinted oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.79 (d, $J = 6.8$ Hz, 2 H), 7.70-7.45 (m, 2 H), 7.45-6.90 (m, 9 H), 4.83 (br s, 1 H), 4.50-4.20 (m, 3 H), 4.20-3.90 (m, 2 H), 3.44 (m, 2 H), 3.10 (ddd, $J = 6.8$, 14, 61.2 Hz, 2 H), 2.40-1.50 (m, 4 H), 1.40-1.00 (m, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.4, 171.2, 156.3, 144.1, 141.5, 136.3, 129.5, 128.7, 128.5, 128.0, 127.3, 125.4, 120.2, 68.0, 61.7, 61.5, 53.5, 53.0, 47.4, 38.1, 28.2, 24.7, 14.6;

IR (neat) 3319, 3028, 2976, 2889, 2361, 2340, 1738, 1703, 1686, 1417, 1351, 1195, 1118;

HRMS (ESI) m/z 535.2209 [C$_{31}$H$_{32}$N$_2$NaO$_5$ (M+Na) requires 535.2203];

$[^\alpha]_D^{20} = -35$ (c 0.986, CHCl$_3$).
**Representative procedure for the competition experiments between carboxylic acid**

**4.19a and carbonyl additive 2.8c in the synthesis of amide 4.23b.** To a solution of **4.19a** (59.3 mg, 0.39 mmol) in chlorobenzene (1 mL) was added Et$_3$N (54.4 µl, 0.39 mmol) at room temperature. The mixture was then cooled to 0 °C and CIp(pin) (0.39 mmol) was added drop wise with rapid stirring. The resulting slurry was allowed to warm to room temperature by removal of the cooling bath, and stirred for an additional 15 min. A solution of azide **4.14b** (59.1 mg, 0.30 mmol) and **2.8c** (40.8 mg, 0.30 mmol) in chlorobenzene (0.5 mL) was then added drop wise, and stirring continued for 1 h. The mixture was heated to 80 °C and for an additional 2 h, then heated to 130 °C and stirred for 10 h. The resulting crude mixture was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to provide 85.1 mg (93%) of **4.23b** and 38.2 mg (94%) of recovered **2.8c**.

**Representative procedure for catalytic phosphine ligation of acids and azides.**

Triphenylphosphine (7.9 mg, 0.03 mmol) and a solution of azide (0.36 mmol) in PhMe (0.5 mL) were added sequentially to a mixture of carboxylic acid (0.30 mmol) and PhSiH$_3$ (32 mg, 0.30 mmol) in PhMe (0.5 mL) at room temperature. The reaction was heated in an oil bath at the indicated temperature and stirred until complete consumption of azide was observed by TLC (ca. 18 h). The mixture was allowed to cool to room temperature by removal of the oil bath and concentrated under reduced pressure. The crude mixture was purified by flash chromatography eluting with hexanes/EtOAc in the indicated ratio to provide amide.
**N-Benzyl-4-(trifluoromethyl)benzamide (4.23n).** Ligation of 4.19b with 3.27b was performed on 0.3 mmol scale, and stirred at 60 °C for 21 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 82 mg (98%) of 4.23n as an off-white solid whose \(^1\text{H} \) NMR spectra were consistent with literature values.\(^{270}\)

\(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \(\delta \) 7.92 (d, \( J = 8 \text{ Hz} \), 2 H), 7.70 (d, \( J = 8.0 \text{ Hz} \), 2 H), 7.50-7.20 (m, 5H), 6.42 (br s, 1 H), 4.66 (d, \( J = 5.6 \text{ Hz} \), 2 H); mp = 169-171 °C.

**N-Benzylbenzamide (4.26b).** Ligation of 3.26a with 3.27b was performed on 0.30 mmol scale, and stirred at reflux for 19 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 60 mg (94%) of 4.26b as a white solid whose \(^1\text{H} \) NMR spectra were consistent with literature values.\(^{131}\)

\(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \(\delta \) 7.80 (d, \( J = 8 \text{ Hz} \), 2 H), 7.51 (t, \( J = 7.2 \text{ Hz} \), 1 H), 7.45-7.27 (m, 7 H), 6.38 (br s, 1 H), 4.67 (d, \( J = 5.6 \text{ Hz} \), 2 H); mp = 100-102 °C.
**N-Benzyl-4-methoxybenzamide (4.26c).** Ligation of 4.19a with 3.27b was performed on 0.30 mmol scale, and stirred at reflux for 46 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 57 mg (79%) of 4.26c as a white solid whose $^1$H NMR spectra were consistent with literature values.$^{269}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J = 8.8$ Hz, 2 H), 7.40-7.28 (m, 5 H), 6.93 (d, $J = 8.8$ Hz, 2H), 6.36 (br s, 1 H), 4.64 (d, $J = 5.6$ Hz, 2 H), 3.85 (s, 3 H); mp = 130-131 °C.

![4.26a](image)

**N-Benzylcinnamamide (4.26a).** Ligation of 4.19g with 3.27b was performed on 0.3 mmol scale, and stirred at reflux for 14 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 68 mg (95%) of 4.26a as a white solid whose $^1$H NMR spectra were consistent with literature values.$^{286}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71 (d, $J = 15.6$ Hz, 1 H), 7.50 (m, 2 H), 7.40-7.27 (m, 7 H), 6.43 (d, $J = 15.6$ Hz, 1 H), 5.89 (br s, 1 H), 4.60 (d, $J = 5.6$ Hz, 2 H); mp = 108-110 °C.

![4.26i](image)

**N-Cinnamyl-4-(trifluoromethyl)benzamide (4.26i).** Ligation of 4.19b with 4.14f was performed on 0.3 mmol scale, and stirred at reflux for 21 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 70 mg (76%) of 4.26i as a
yellowish/white solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.93 (d, $J = 8.4$ Hz, 2 H), 7.70 (d, $J = 8.4$ Hz, 2 H), 7.45-7.20 (m, 6 H), 6.64 (d, $J = 16.0$ Hz, 1 H), 6.30 (comp m, 2 H), 4.27 (m, 2 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.2, 136.4, 133.2, 128.8, 128.1, 127.6, 126.6, 126.0, 125.9, 125.8, 125.7, 125.0, 42.5;

IR (neat) 3311, 3070, 2914, 1945, 1638, 1545, 1328;

HRMS (ESI) $m/z$ 306.1137 [C$_{17}$H$_{15}$F$_3$NO (M+1) requires 306.1100]; $mp = 133-134 \degree C$.

\[ \text{N-(Furan-2-ylmethyl)-4-(trifluoromethyl)benzamide (4.26j).} \]

Ligation of 4.19b with 4.14g was performed on 0.3 mmol scale, and stirred at reflux for 21 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 63 mg (78%) of 4.26j as a white/yellow solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.91 (d, $J = 8.8$ Hz, 2 H), 7.71 (d, $J = 8.8$ Hz, 2 H), 7.40 (m, 1 H), 6.48 (br s, 1 H), 6.35 (comp m, 2 H), 4.67 (d, $J = 5.6$ Hz, 2 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.4, 151.1, 142.8, 137.6, 133.3, 127.7, 125.8, 122.6, 111.0, 108.2, 37.3;

IR (neat) 3345, 3069, 2931, 1641, 1549, 1336, 1121;

HRMS (ESI) $m/z$ 270.0767 [C$_{13}$H$_{11}$F$_3$NO$_2$ (M+1) requires 270.0736]; $mp = 127-129 \degree C$.  

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\(N\)-(4-Methoxyphenyl)cinnamamide (4.26l).\) Ligation of 4.19g with 4.14i was performed on 0.3 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 60 mg (80\%) of 4.26l as a white solid whose \(^1\)H NMR spectra were consistent with literature values.\(^{287}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.77 (d, \(J = 15.6\) Hz, 1 H), 7.60-7.28 (m, 8 H), 6.91 (d, \(J = 8.8\) Hz, 2 H), 6.55 (d, \(J = 15.6\) Hz, 1 H), 3.81 (s, 3 H); mp = 156-157 °C.

\((E)-N\)-Cinnamoyl-4-methoxybenzamide (4.23p).\) Ligation of 4.19g with 4.14d was performed on 0.30 mmol scale, and stirred at 80 °C for 36 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 30 mg (35\%) of 4.23p as a white solid.

\(^1\)H NMR (400 MHz, CDCl\(_3\)). \(\delta\) 7.73 (d, \(J = 15.6\) Hz, 1 H), 7.60-7.30 (m, 7 H), 6.90 (d, \(J = 9.2\) Hz, 2 H), 6.54 (d, \(J = 15.6\) Hz, 1 H), 3.90 (s, 3 H);

\(^{13}\)C NMR (100 MHz) \(\delta\) 178.6, 163.9, 156.7, 142.3, 134.9, 131.3, 130.1, 129.1, 128.1, 121.9, 121.0, 114.4, 55.7;

IR (neat) 3264, 3056, 3027, 1658, 1624, 1576, 1510, 1244;

HRMS (ESI) m/z 282.1133 [C\(_{17}\)H\(_{15}\)NO\(_3\) (M+1) requires 282.1125]; mp = 153-154 °C.
**Isoindolin-1-one (4.27).** Triphenylphosphine (7.9 mg, 0.03 mmol) was added to a mixture of 4.26 (53.1 mg, 0.30 mmol) and PhSiH$_3$ (32 mg, 0.30 mmol) in PhMe (0.5 mL) at room temperature. The reaction was heated to reflux, stirred for 20 h, then allowed to cool to room temperature by removal of the oil bath. The crude mixture was concentrated under reduced pressure and purified by flash chromatography eluting with hexanes/EtOAc (1:2) to provide 31 mg (77%) of 4.27 as a white solid whose $^1$H NMR spectra were consistent with literature values.$^{238}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.88 (d, $J = 7.2$ Hz, 1 H), 7.70-7.40 (m, 4H), 4.48 (s, 2H); mp = 151-152 °C.

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**Methyl 4-(benzylcarbamoyl)benzoate (4.26n).** Ligation of 4.19s with 3.27b was performed on 0.30 mmol scale, and stirred at reflux for 17 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 73.5 mg (91%) of 4.26n as a white solid whose $^1$H NMR spectra were consistent with literature values.$^{288}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.07 (d, $J = 6.8$ Hz, 2 H), 7.86 (d, $J = 6.8$ Hz, 2 H), 7.40-7.20 (m, 5 H), 6.75 (br s, 1 H), 4.63 (d, $J = 5.6$ Hz, 2 H), 3.92 (s, 3 H); mp = 149-151 °C.
Representative procedure for the ligation of \( \alpha \)-amino acids and azido glycerinate

4.14a. Triphenylphosphine (7.9 mg, 0.03 mmol) and a solution of 4.14a (46.5 mg, 0.36 mmol) in PhMe (0.5 mL) were added sequentially to a mixture of 4.32 (0.30 mmol) and PhSiH\(_3\) (32 mg, 0.30 mmol) in PhMe (0.5 mL) at room temperature. The reaction was heated in an oil bath at the indicated temperature and stirred until complete consumption of 4.14a was observed by TLC (ca. 18 h). The mixture was allowed to cool to room temperature by removal of the oil bath and concentrated under reduced pressure. The crude mixture was purified by flash chromatography eluting with hexanes/EtOAc in the indicated ratio to provide 4.33.

![Chemical Structure](image_url)

(S)-Ethyl 2-[(benzoyloxy)carbonyl]amino)propanamido)acetate [Cbz-Ala-Gly-OEt] (4.33c). Ligation of 4.32a with 4.14a was performed on 0.20 mmol scale, and stirred at 80 °C for 20 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:2) provided 36 mg (59%) of 4.33a as a white solid whose \(^1\)H NMR spectra were consistent with literature values.\(^{289a}\)

\[^1\]H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.38 (comp m, 5 H), 6.55 (br s, 1 H), 5.31 (br s, 1 H), 5.15 (dd, \( J = 11.6, 8.8 \) Hz, 2 H), 4.32 (m, 1 H), 4.25 (q, \( J = 7.6 \) Hz, 2 H), 4.05 (d, \( J = 4.8 \) Hz, 2 H), 1.43 (d, \( J = 7.2 \) Hz, 3 H), 1.31 (t, \( J = 7.2 \) Hz, 3 H);
\[ \alpha_d^{20} = -17 \, (c \, 1.02, \text{EtOH}), \text{[known: } \alpha_d^{23} = -19.3 \, (c \, 1.00, \text{EtOH})\text{]; } \text{mp} = 97-98 \, ^\circ \text{C}. \]

HPLC (CHIRALCEL OD-H, hexane:iPrOH = 9:1, 0.5 mL/min, detect 254 nm, lit values \( t_R = 28.7 \, (L), 36.2 \, (D) \))\(^{289b}\)

(S)-Ethyl 2-(2-((benzyloxy)carbonyl)amino)-3-phenylpropanamido)acetate

\([\text{Cbz-Phe-Gly-OEt}] \, (4.33m)\). Ligation of 4.32h with 4.14a was performed on 0.30 mmol scale, and stirred at 60 \( ^\circ \text{C} \) for 22 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 68.6 mg (59\%) of 4.33m as an off-white solid whose \( ^1\text{H} \) NMR spectra were consistent with literature values.\(^{289}\)

\( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta 7.45-7.10 \) (comp m, 10 H), 6.31 (br s, 1 H), 5.32 (br s, 1 H), 5.09 (m, 2 H), 4.49 (m, 1 H), 4.21 (q, \( J = 7.2 \) Hz, 2 H), 3.95 (comp m, 2 H), 3.10 (d, \( J = 7.6 \) Hz, 2 H), 1.28 (t, \( J = 7.2 \) Hz, 3 H);

\[ \alpha_d^{20} = -16 \, (c \, 0.995, \text{EtOH}), \text{[known: } \alpha_d^{25} = -17 \, (c \, 1.0, \text{EtOH})\text{]; } \text{mp} = 107-108 \, ^\circ \text{C}. \]
(S)-Ethyl 2-(2-(((benzyloxy)carbonyl)amino)-3-(1H-indol-3-yl)propanamido)acetate [Cbz-Trp-Gly-OEt] (4.33n). Ligation of 4.32i with 4.14a was performed on 0.30 mmol scale, and stirred at 80 °C for 22 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:2) provided 63.2 mg (50%) of 4.33n as a tan/brown solid whose $^1$H NMR spectra were consistent with literature values.$^{289}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.20-6.9 (comp m, 10 H) 6.30 (br s, 1 H), 5.65-5.30 (m, 2 H), 5.11 (m, 2 H), 4.80-4.45 (m, 2 H), 4.14 (q, $J$ = 7.2 Hz, 2 H), 3.88 (comp m, 2 H), 3.30 (m, 2 H), 1.24 (t, $J$ = 7.2 Hz, 3 H);

$\left[\alpha\right]_D^{20} = +8.6$ (c 0.50, CHCl$_3$), [known: $\left[\alpha\right]_D^{25} = +2.9$ (c 0.23, CHCl$_3$)]; mp = 68-70 °C.

**Representative procedure for the synthesis of phosphinates 4.72.** An oven dried round bottom flask was added diphenylphosphine oxide (1.85 mmol, 1 equiv), alkyl halide (1.85 mmol, 1 equiv), K$_2$CO$_3$ (510 mg, 3.69 mmol, 2.0 equiv), 18-crown-6 (24 mg, 0.093 mmol, 5 mol%), and acetone (20 mL, 0.1 M). The resulting mixture was heated in an oil bath at reflux until complete consumption of starting materials was observed by TLC (ca. 12 h). The mixture was allowed to cool to room temperature by removal of the oil bath and diluted with H$_2$O (20 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL), dried (MgSO$_4$), and concentrated under reduced pressure. The crude mixture was purified by flash chromatography eluting with hexane:EtOAc ratio to provide 4.72.
4-Methoxybenzyl diphenylphosphinate (4.72a). Following the general procedure alkylation of diphenylphosphine oxide with 1-(bromomethyl)-4-methoxybenzene on 2.967 mmol scale, purification by flash chromatography eluting with 100% EtOAc furnished 486 mg (48%) of 4.72a as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.82 (m, 4 H), 7.52 (tq, $J = 7.6$, 1.6 Hz, 2 H), 7.49 (m, 4 H), 7.29 (d, $J = 8.4$ Hz, 2 H), 6.87 (d, $J = 8.8$ Hz, 2 H), 5.00 (d, $J = 6.8$ Hz, 2 H), 3.81 (s, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 132.3, 132.2, 131.9, 131.8, 130.0, 128.7, 128.6, 114.1, 66.4, 55.49;

$^{31}$P NMR (128 MHz, CDCl$_3$) $\delta$ 33.1;

IR (neat) 3056, 2961, 1613, 1513, 1438, 1226, 1129;

HRMS (ESI) $m/z$ 361.0980 [C$_{20}$H$_{20}$O$_3$P (M+1) requires 361.0964]; mp = 68–70 °C.

4-Cyanobenzyl diphenylphosphinate (4.72b). Following the general procedure alkylation of diphenylphosphine oxide with 4-(bromomethyl)benzonitrile on 1.85 mmol scale, purification by flash chromatography eluting with 100% EtOAc furnished 154 mg (25%) of 4.72b as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.83 (m, 4 H), 7.65 (d, $J = 8.0$ Hz, 2 H), 7.56 (tq, $J = 7.6$, 1.6 Hz, 2 H), 7.48 (comp m, 6 H), 5.12 (d, $J = 7.6$ Hz, 2 H);
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 141.8, 132.7, 132.6, 132.5, 131.8, 131.7, 131.6, 130.3, 128.9, 128.8, 128.1, 118.7, 65.3;

$^{31}$P NMR (128 MHz, CDCl$_3$) $\delta$ 34.5;

IR (neat) 3057, 2228, 1438, 1222, 1130, 1014;

HRMS (ESI) $m/z$ 334.1005 [C$_{20}$H$_{17}$NO$_3$P (M+1) requires 334.0991]; mp = 105-106 °C.

![4.72d](image)

**4-(Trifluoromethyl)benzyl diphenylphosphinite (4.72d).** Following the general procedure alkylation of diphenylphosphine oxide with 1-(bromomethyl)-4-(trifluoromethyl)benzene on 1.255 mmol scale, purification by flash chromatography eluting with 100% EtOAc furnished 216 mg (46%) of **4.72d** as a clear oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.85 (m, 4 H), 7.60 (d, $J = 8.4$ Hz, 2 H), 7.55 (t, $J = 7.2$ Hz, 2 H), 7.48 (comp m, 6 H), 5.13 (d, $J = 7.2$ Hz, 2 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 132.6, 132.5, 131.9, 131.8, 128.9, 128.8, 128.0, 125.7, 125.6, 65.5;

$^{31}$P NMR (128 MHz, CDCl$_3$) $\delta$ 34.1;

IR (neat) 3059, 1620, 1439, 1327, 1226, 1165, 1066, 1013;

HRMS (ESI) $m/z$ 377.0942 [C$_{20}$H$_{17}$F$_3$O$_3$P (M+1) requires 377.0913].
3,5-Bis(trifluoromethyl)benzyl diphenylphosphinate (4.72e). Following the general procedure alkylation of diphenylphosphine oxide with 1-(bromomethyl)-3,5-bis(trifluoromethyl)benzene on 1.52 mmol scale, purification by flash chromatography eluting with 100% EtOAc furnished 291 mg (43%) of 4.72e as clear crystals.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.82 (comp m, 7 H), 7.55 (m, 2 H), 7.47 (comp m, 4 H), 5.18 (d, $J = 8.0$ Hz, 2 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 139.1, 139.0, 132.8, 131.8, 131.7, 131.5, 130.1, 129.0, 128.8, 128.0, 122.5, 122.4, 122.3, 64.8;

$^{31}$P NMR (128 MHz, CDCl$_3$) δ 34.9;

IR (neat) 3060, 1624, 1439, 1366, 1279, 1130, 1019;

HRMS (ESI) m/z 445.0794 [C$_{21}$H$_{16}$F$_6$O$_2$P (M+1) requires 445.0787]; mp = 40-41 °C.

4-Chlorobenzyl diphenylphosphinate (4.72f). Following the general procedure alkylation of diphenylphosphine oxide with 1-(bromomethyl)-4-chlorobenzene on 2.43 mmol scale, purification by flash chromatography eluting with 100% EtOAc furnished 397 mg (51%) of 4.72f as an off-white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.82 (m, 4 H), 7.53 (tq, $J = 7.2$, 1.2 Hz, 2 H), 7.45 (comp m, 4
H), 7.30 (m, 4 H), 5.02 (d, J = 6.8 Hz, 2 H);

^{13}C\text{ NMR (100 MHz, CDCl}_3\text{) }\delta \text{ 135.1, 135.0, 134.3, 132.5, 132.4, 132.0, 131.9, 131.8, 130.6, 129.4, 128.9, 128.8, 128.7, 65.7;}

^{31}P\text{ NMR (128 MHz, CDCl}_3\text{) }\delta \text{ 33.8;}

IR (neat) 3056, 1492, 1438, 1222, 1130, 1008, 993;

HRMS (ESI) m/z 343.0670 [C_{19}H_{17}ClO_3P (M+1) requires 343.0649]; mp = 61-62 °C.

![Methyl 4-(((diphenylphosphoryl)oxy)methyl)benzoate (4.72g)](image)

**Methyl 4-(((diphenylphosphoryl)oxy)methyl)benzoate (4.72g).** Following the general procedure alkylation of diphenylphosphine oxide with methyl 4-(bromomethyl)benzoate on 1.09 mmol scale, purification by flash chromatography eluting with 100% EtOAc furnished 201 mg (50%) of **4.72g** as a white solid.

^{1}H\text{ NMR (400 MHz, CDCl}_3\text{) }\delta \text{ 8.02 (d, J = 8.4 Hz, 2 H), 7.84 (m, 4 H), 7.55 (t, J = 7.2 Hz, 2 H), 7.46 (comp m, 6 H), 5.12 (d, J = 7.2 Hz, 2 H), 3.93 (s, 3 H);}

^{13}C\text{ NMR (100 MHz, CDCl}_3\text{) }\delta \text{ 166.9, 141.5, 132.6, 132.5, 131.9, 131.8, 130.5, 130.0, 128.9, 128.7, 127.5, 65.7, 52.4;}

^{31}P\text{ NMR (128 MHz, CDCl}_3\text{) }\delta \text{ 34.1;}

IR (neat) 3035, 2949, 1717, 1436, 1281, 1217, 1130, 1110;

HRMS (ESI) m/z 367.1092 [C_{21}H_{20}O_4P (M+1) requires 367.1094]; mp = 85-87 °C.
(E)-But-2-en-1-yl diphenylphosphinate (4.72h). Following the general procedure alklylation of diphenylphosphine oxide with (E)-1-bromobut-2-ene on 5.0 mmol scale, purification by flash chromatography eluting with hexanes:EtOAc (1:1) furnished 146 mg (11%) of 4.72h as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.87 (m, 4 H), 7.53 (m, 2 H), 7.46 (comp m, 4 H), 5.70 (comp m, 2 H), 4.67-4.45 (tt, $J = 6.4,1.2$ Hz, 2 H), 1.74-1.56 (dq, $J = 6.4, 1.2$ Hz, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 132.5, 132.3, 131.9, 131.8, 131.3, 129.7, 128.7, 128.6, 126.3, 126.2, 125.5, 125.4, 65.7, 17.9;

$^{31}$P NMR (128 MHz, CDCl$_3$) δ 32.9;

IR (neat) 3056, 3025, 2359, 2339, 1591, 1440, 1216, 1129, 963, 696;

HRMS (ESI) $m/z$ 273.1047 [C$_{16}$H$_{18}$O$_2$P (M+1) requires 273.1039]; mp = 42-43 °C.

Representative procedure for the esterification of carboxylic acids. An oven dried vial containing a stir bar was added carboxylic acid (0.10 mmol, 1 equiv), phosphinate 4.72 (0.10 mmol, 1 equiv), DBU (0.11 mmol, 1.1 equiv), and 1,4-dioxane (1 mL, 0.1 M). The resulting mixture was heated in an oil bath at 100 °C until consumption of starting materials was observed by TLC (ca. 18 h). The mixture was allowed to cool to room
temperature by removal of the oil bath and concentrated under reduced pressure. The crude mixture was purified by flash chromatography eluting with hexanes/EtOAc in the indicated ratio to provide 4.73.

![4.73a](image)

**4-Methoxybenzyl benzoate (4.73a).** Esterification of 3.26a with 4.72a was performed on 0.092 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 18.5 mg (83%) of 4.73a as a white solid whose $^1$H NMR spectra were consistent with literature values. \(^\text{290}\)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.06 (d, $J = 8.0$ Hz, 2 H), 7.56 (t, $J = 8.0$ Hz, 1 H), 7.48-7.35 (m, 4 H), 6.93 (d, $J = 6.8$ Hz, 2 H), 5.32 (s, 2 H), 3.83 (s, 3 H); mp = 40 °C.

![4.73b](image)

**4-Methoxybenzyl 4-chlorobenzoate (4.73b).** Esterification of 4.19d with 4.72a was performed on 0.093 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 19 mg (74%) of 4.73b as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.00 (d, $J = 8.4$ Hz, 2 H), 7.45-7.35 (comp m, 4 H), 6.92 (d, $J = 8.8$ Hz, 2 H), 5.30 (s, 2 H), 3.83 (s, 3 H);
$^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.9, 159.9, 139.6, 131.3, 130.4, 128.9, 128.0, 114.2, 67.0, 55.5;

IR (neat) 2955, 2836, 1718, 1612, 1515, 1270, 1248, 1093;

HRMS (ESI) m/z 299.0462 [C$_{15}$H$_{13}$ClNaO$_3$ (M+Na) requires 299.0445]; mp = 35-36 ℃.

![4-Cyanobenzyl 2-iodobenzoate (4.73c)](image)

**4-Cyanobenzyl 2-iodobenzoate (4.73c).** Esterification of 4.19e with 4.72b was performed on 0.10 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 32.0 mg (88%) of 4.73c as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, $J$ = 8.0 Hz, 1 H), 7.85 (d, $J$ = 8.0 Hz, 1 H), 7.69 (d, $J$ = 8.0 Hz, 2 H), 7.58 (d, $J$ = 8.4 Hz, 2 H), 7.43 (t, $J$ = 7.6 Hz, 1 H), 7.19 (t, $J$ = 7.2 Hz, 1 H), 5.42 (s, 2 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.2, 141.7, 140.9, 133.2, 132.7, 131.3, 128.8, 128.2, 118.7, 112.1, 94.4, 66.3;

IR (neat) 2900, 2221 1728, 1649, 1449, 1370, 1250;

HRMS (ESI) m/z 385.9664 [C$_{15}$H$_{10}$NiNaO$_2$ (M+Na) requires 385.9648]; mp = 109-110 ℃.

![F$_3$C](image)

**4.73d**
**4-Cyanobenzyl 4-(trifluoromethyl)benzoate (4.73d).** Esterification of **4.19b** with **4.72b** was performed on 0.091 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 15.1 mg (55%) of **4.73d** as an off-white solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.20 (d, $J = 8$ Hz, 2 H), 7.73 (comp m, 4 H), 7.56 (d, $J = 8.4$ Hz, 2 H), 5.45 (s, 2 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.2, 141.0, 132.7, 130.4, 128.6, 125.9, 125.8, 125.7, 125.6, 118.6, 112.5, 66.2;

IR (neat) 3080, 2924, 2853, 2230, 1725, 1410, 1327, 1277, 1121;

HRMS (ESI) $m/z$ 328.0538 [C$_{16}$H$_{10}$F$_3$NNaO$_2$ (M+Na) requires 328.0556]; mp = 74-75 °C.

![4.73e](image)

**4-Cyanobenzyl 2,6-dimethylbenzoate (4.73e).** Esterification of **4.19v** with **4.72b** was performed on 0.095 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 17.8 mg (71%) of **4.73e** as an off-white solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.69 (d, $J = 8.4$ Hz, 2 H), 7.56 (d, $J = 8.0$ Hz, 2 H), 7.22 (t, $J = 8.0$ Hz, 1 H), 7.04 (d, $J = 7.6$ Hz, 2 H), 5.41 (s, 2 H), 2.29 (s, 6 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.6, 141.0, 135.2, 133.2, 132.6, 129.8, 129.0, 127.8, 118.7, 112.4, 65.8, 19.9;
IR (neat) 2926, 2229, 1721, 1265, 1246, 1113;

HRMS (ESI) m/z 288.0991 [C_{17}H_{15}NNaO_2 (M+Na) requires 288.0995]; mp = 64-65 °C.

![4-Cyanobenzyl cinnamate](image)  
**4-Cyanobenzyl cinnamate (4.73f).** Esterification of **4.19g** with **4.72b** was performed on 0.109 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 21.1 mg (74%) of **4.73f** as a thick yellow oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.76 (d, \(J = 16.4\) Hz, 1 H), 7.70 (d, \(J = 8.0\) Hz, 2 H), 7.54 (m, 4 H), 7.41 (comp m, 3 H), 6.50 (d, \(J = 16.0\) Hz, 2 H), 5.31 (s, 2 H);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 166.7, 146.2, 141.6, 134.3, 132.6, 130.9, 129.2, 128.5, 128.4, 118.8, 117.3, 112.2, 65.3;

IR (neat) 3030, 2925, 2228, 1714, 1636, 1308, 1161;

HRMS (ESI) m/z 286.0841 [C_{17}H_{13}NNaO_2 (M+Na) requires 286.0838].

![4.73g](image)

**{(E)-4-Cyanobenzyl but-2-enolate (4.73f).}** Esterification of **4.19w** with **4.72b** was performed on 0.134 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 17.2 mg (64%) of **4.73f** as a
white solid.

$^{1}$H NMR (400 MHz, CDCl$_3$) δ 7.66 (d, $J = 8.4$ Hz, 2 H), 7.46 (d, $J = 8.4$ Hz, 2 H), 7.07 (comp
m, 1 H), 5.91 (dq, $J = 15.6$, 2.4 Hz, 1 H), 5.22 (s, 2 H), 1.91 (dd, $J = 7.2$, 1.6 Hz, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.1, 146.3, 141.8, 132.6, 128.4, 122.1, 118.8, 112.1, 64.9,
18.3;

IR (neat) 3070, 2946, 2229, 1721, 1655, 1443, 1309, 1262, 1173;

HRMS (ESI) $m/z$ 224.0689 [C$_{12}$H$_{11}$NNaO$_2$ (M+Na) requires 224.0682]; mp = 35 °C.

4-Cyanobenzyl 2-phenylacetate (4.73h). Esterification of 4.19h with 4.72b was
performed on 0.093 mmol scale, and stirred at reflux for 18 h. Purification by flash
chromatography eluting with hexanes/EtOAc (2:1) provided 16.7 mg (72%) of 4.73h as a
white solid.

$^{1}$H NMR (400 MHz, CDCl$_3$) δ 7.63 (d, $J = 8.4$ Hz, 2 H), 7.45-7.20 (comp m, 7 H), 5.18 (s, 2
H), 3.71 (s, 2 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.3, 141.3, 132.5, 129.4, 128.8, 128.3, 127.5, 118.7,
112.1, 65.5, 41.5;

IR (neat) 3063, 3031, 2927, 2229, 1739, 1496, 1454, 1242, 1148;

HRMS (ESI) $m/z$ 274.0843 [C$_{16}$H$_{13}$NNaO$_2$ (M+Na) requires 274.0838]; mp = 47 °C.
4-Cyanobenzyl octanoate (4.73j). Esterification of 4.19i with 4.72b was performed on 0.090 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 12.2 mg (53%, 93% yield with recovered starting material) of 4.73j as a clear oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.66 (d, $J$ = 8.4 Hz, 2 H), 7.46 (d, $J$ = 8.0 Hz, 2 H), 5.17 (s, 2 H), 2.39 (t, $J$ = 7.6 Hz, 2 H), 1.66 (m, 2 H), 1.29 (comp m, 8 H), 0.88 (t, $J$ = 7.6 Hz, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.6, 141.7, 132.6, 128.5, 118.8, 112.1, 65.0, 34.4, 31.8, 29.4, 29.0, 25.1, 22.8, 14.3;

IR (neat) 2928, 2856, 2229, 1739, 1647, 1159;

HRMS (ESI) m/z 282.1462 [C$_{16}$H$_{21}$NNaO$_2$ (M+Na) requires 282.1465].

4-Cyanobenzyl pivalate (4.73i). Esterification of 4.19k with 4.72b was performed on 0.095 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 13.9 mg (67%) of 4.73i as a clear oil whose $^1$H NMR spectra were consistent with literature values.$^{291}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.65 (d, $J$ = 8.4 Hz, 2 H), 7.44 (d, $J$ = 8.0 Hz, 2 H), 5.16 (s, 2 H), 1.26 (s, 9 H).
4-Cyanobenzyl 1H-pyrrole-2-carboxylate (4.73k). Esterification of 4.19f with 4.72b was performed on 0.095 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 21 mg (98%) of 4.73k as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.19 (br s, 1 H), 7.67 (d, $J = 8.0$ Hz, 2 H), 7.51 (d, $J = 8.0$ Hz, 2 H), 7.00 (t, $J = 3.6$ Hz, 2 H), 6.30 (q, $J = 3.2$ Hz, 1 H), 5.37 (s, 2 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 160.8, 141.8, 132.6, 128.3, 123.8, 122.2, 118.8, 116.2, 112.2, 111.0, 64.9;

IR (neat) 3314, 2235, 1685, 1556, 1454, 1407, 1305, 1167;

HRMS (ESI) m/z 249.0626 [C$_{13}$H$_{10}$N$_2$NaO$_2$ (M+Na) requires 249.0634]; mp = 141-142 °C.

4-Nitrobenzyl 4-methoxybenzoate (4.73l). Esterification of 4.19a with 4.72c was performed on 0.089 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 21.3 mg (83%) of 4.73l as a yellowish-white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.25 (d, $J = 8.8$ Hz, 2 H), 8.06 (d, $J = 8.8$ Hz, 2 H), 7.61 (d, $J =
8.4 Hz, 2 H), 6.95 (d, J = 9.2 Hz, 2 H), 5.44 (s, 2 H), 3.88 (s, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.0, 164.0, 147.8, 143.9, 132.0, 128.4, 124.0, 122.0, 114.0, 65.1, 55.7;

IR (neat) 2965, 1705, 1600, 1521, 1346, 1251, 1186;

HRMS (ESI) m/z 310.0696 [C$_{15}$H$_{13}$NNaO$_{5}$ (M+Na) requires 310.0686]; mp = 135-136 °C.

![Image](image_url)

4-(Trifluoromethyl)benzyl 4-methoxybenzoate (4.73m). Esterification of 4.19a with 4.72d was performed on 0.140 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 29.5 mg (68%) of 4.73m as a white solid whose $^1$H NMR spectra were consistent with literature values.$^{292}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.04 (d, J = 8.8 Hz, 2 H), 7.65 (d, J = 8.0 Hz, 2 H), 7.56 (d, J = 8.4 Hz, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 5.40 (s, 2H), 3.89 (s, 3 H); mp = 52-53 °C.

![Image](image_url)

3,5-Bis(trifluoromethyl)benzyl 4-methoxybenzoate (4.73n). Esterification of 4.19a with 4.72e was performed on 0.094 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 33.5
mg (94%) of **4.73n** as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.04 (d, $J = 9.2$ Hz, 2 H), 7.90 (br s, 2 H), 7.87 (br s, 1 H), 6.95 (d, $J = 8.8$ Hz, 2 H), 5.44 (s, 2 H), 3.88 (s, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.0, 164.0, 139.1, 132.0, 128.2, 124.7, 122.3, 122.0, 121.8, 114.0, 64.9, 55.7;

IR (neat) 3051, 2922, 1708, 1610, 1287, 1268, 1172, 1125;

HRMS (ESI) $m/z$ 401.0598 [C$_{17}$H$_{12}$F$_6$NaO$_3$ (M+Na) requires 401.0583]; mp = 84-85 °C.

![Image of 4-Chlorobenzyl 4-methoxybenzoate](4.73o)

**4-Chlorobenzyl 4-methoxybenzoate (4.73o).** Esterification of **4.19a** with **4.72f** was performed on 0.141 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 26 mg (66%) of **4.73o** as a white solid whose $^1$H NMR spectra were consistent with literature values.$^{293}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.02 (d, $J = 9.2$ Hz, 2 H), 7.43-7.31 (m, 4 H), 6.92 (d, $J = 8.8$ Hz, 2 H), 5.31 (s, 2 H), 3.87 (s, 3 H); mp = 81-83 °C.

![Image of 4-(Methoxycarbonyl)benzyl 4-methoxybenzoate](4.73p)

**4-(Methoxycarbonyl)benzyl 4-methoxybenzoate (4.73p).** Esterification of **4.19a** with **4.72g** was performed on 0.095 mmol scale, and stirred at reflux for 23 h.
Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 17.9 mg (63%) of 4.73p as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.05 (comp m, 4 H), 7.50 (d, $J = 8.0$ Hz, 2 H), 6.93 (d, $J = 9.2$ Hz, 2 H), 5.40 (s, 2 H), 3.93 (s, 3 H), 3.87 (s, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.0, 166.2, 163.8, 141.6, 132.0, 130.1, 130.0, 127.8, 122.4, 113.9, 65.8, 55.7, 52.4;

IR (neat) 2948, 1731, 1705, 1607, 1277 1103;

HRMS (ESI) m/z 323.0902 [C$_{17}$H$_{16}$NaO$_5$ (M+Na) requires 323.0890]; mp = 69-70 °C.

4-Cyanobenzyl 4-methoxybenzoate (4.73q). Esterification of 4.19a with 4.72b was performed on 0.141 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 35.6 mg (94%) of 4.73q as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.04 (d, $J = 8.8$ Hz, 2 H), 7.69 (d, $J = 6.4$ Hz, 2 H), 7.55 (d, $J = 6.8$ Hz, 2 H), 6.94 (d, $J = 9.2$ Hz, 2 H), 5.39 (s, 2 H), 3.88 (s, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.1, 163.9, 141.9, 132.6, 132.0, 128.3, 122.1, 118.8, 114.0, 112.1, 65.4, 55.7;

IR (neat) 2923, 2223, 1708, 1605, 1276, 1254, 1163;

HRMS (ESI) m/z 290.0800 [C$_{16}$H$_{13}$NNaO$_3$ (M+Na) requires 290.0788]; mp = 127-128 °C.
4-Methoxybenzyl 4-methoxybenzoate (4.73r). Esterification of 4.19a with 4.72a was performed on 0.095 mmol scale, and stirred at reflux for 42 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 19.0 mg (73%, 88% with recovered starting material) of 4.73r as a clear oil whose $^1$H NMR spectra were consistent with literature values.$^{294}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.02 (d, $J = 8.8$ Hz, 2 H), 7.39 (d, $J = 8.4$ Hz, 2 H), 6.92 (comp m, 4 H), 5.38 (s, 2 H), 3.86 (s, 3 H), 3.83 (s, 3 H).

(E)-But-2-en-1-yl 4-methoxybenzoate (4.73s). Esterification of 4.19a with 4.72h was performed on 0.0764 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 9.4 mg (60%) of 4.73s as a clear oil whose $^1$H NMR spectra were consistent with literature values.$^{295}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.01 (d, $J = 8.8$ Hz, 2 H), 6.92 (d, $J = 8.8$ Hz, 2 H), 5.95-5.55 (comp m, 2 H), 4.80 (d, $J = 2$ Hz, 2 H), 3.87 (s, 3 H), 1.76 (m, 3 H).
**4-Cyanobenzyl 2-amino-5-nitrobenzoate (4.73t).** Esterification of 4.19x with 4.72b was performed on 0.089 mmol scale, and stirred at reflux for 18 h. Purification by flash chromatography eluting with hexanes/EtOAc (1:1) provided 18.9 mg (71%) of 4.73t as a yellow solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.87 (d, $J = 2.4$ Hz, 1 H), 8.16 (d, $J = 9.2$ Hz, 1 H), 7.71 (d, $J = 8.0$ Hz, 2 H), 7.56 (d, $J = 8.0$ Hz, 2 H), 6.70 (d, $J = 9.2$ Hz, 1 H), 5.42 (s, 2 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.5, 155.1, 140.9, 132.8, 129.8, 129.0, 128.7, 118.7, 116.6, 112.6, 108.7, 65.8;

IR (neat) 3406, 3346, 2225, 1698, 1625, 1326, 1254;

HRMS (ESI) $m/z$ 298.0821 [C$_{15}$H$_{12}$N$_3$O$_4$ (M+1) requires 298.0822]; mp = 233 °C (decomposed).
APPENDIX A:

SELECTED $^1$H- AND $^{13}$C-NMR SPECTRA
Ts
N
Br
Ph
2.23 d
2.25b
Br
MeO
MeO\_2 C
MeO\_2 C
C
O
Ph

![Chemical Structure](image)

**SI setup**

**C13-set-up**

222
H1 setup

2.24a

C13

227
H_1 setup

[C]_3 setup

MeO_2C-CO_2Me

2.26c

Ph \cdot OH
$$\text{Ph}_3\text{P} - \text{O} - \text{CN} \quad 4.72\text{b}$$
Ph₂PO₂⁻CO₂Me

4.72g
REFERENCES


(10) Tyrlik, S.; Wolochowicz, I. Application of transition metal complexes with low oxidation states in organic synthesis I: New synthesis of olefins from


270


1986, 27, 2409–2410.

(43) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G. Selective reduction of α,β-
unsaturated esters in the presence of olefins. *Tetrahedron Lett.* 1987, 28,
5287–5290.

(44) Tsuda, T.; Fujii, T.; Kawasaki, K.; Saegusa, T. Copper (I)-catalysed conjugate
reduction of α,β-unsaturated carbonyl compounds by lithium aluminium

(45) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. A convenient, efficient
method for conjugate reductions using catalytic quantities of Cu (I). *Tetrahedron

Asymmetric Conjugate Reduction of α,β-Unsaturated Esters Using a Chiral

(47) Fujita, Y.; Fukuzumi, S.; Otera, J. Sml₂-promoted conjugate reduction of α,β-
unsaturated esters and ketones studied in comparison with Mukaiyama-
2124.

(48) Gansäuer, A.; Pierobon, M.; Bluhm, H. Stereoselective synthesis of tri- and
tetrasubstituted olefins by tandem cyclization addition reactions featuring

(49) Gansäuer, A.; Bluhm, H.; Rinker, B.; Narayan, S.; Schick, M.; Lauterbach, T.;
Pierobon, M. Reagent-controlled stereoselectivity in titanocene-catalyzed
epoxide openings: reductions and intermolecular additions to alpha,beta-

Gansäuer, A.; Barchuk, A.; Keller, F. Elucidation of the mechanism of
titanocene-mediated epoxide opening by a combined experimental and

(51) Gansäuer, A.; Barchuk, A.; Keller, F.; Schmitt, M.; Grimme, S.; Gerenkamp,
M.; Mück-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. Mechanism of titanocene-
mediated epoxide opening through homolytic substitution. *J. Am. Chem.

(52) Kosal, A. D.; Ashfeld, B. L. Titanocene-catalyzed conjugate reduction of


(85) Boonsombat, J.; Zhang, H.; Chuhtai, M. J.; Hartung, J.; Padwa, A. A general
synthetic entry to the pentacyclic strychnos alkaloid family, using a [4 + 2]-


(96) López, F.; Mascareñas, J. L. Allenes as three-carbon units in catalytic
cycloadditions: new opportunities with transition-metal catalysts. Chem.

(97) Yu, S.; Ma, S. Allenes in catalytic asymmetric synthesis and natural product

(98) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. Palladium-catalyzed carbonyl
allylation by allylic alcohols with stannous chloride. J. Am. Chem. Soc. 1992,
114, 2577–2586.


(101) Michaelis, A.; Kaehne, R. Ueber das Verhalten der Jodalkyle gegen die


(103) Lee, K.; Wiemer, D. F. Reaction of diethyl phosphorochloridite with
enolates: a general method for synthesis of β-keto phosphonates and α-

(104) Takeda, T., ed. Modern Carbonyl Olefination: Methods and Applications.

(105) Wittig, G.; Geissler, G. Zur Reaktionsweise des Pentaphenyl-phosphors und

(106) Maryanoff, B. E.; Reitz, A. B. The Wittig olefination reaction and
modifications involving phosphoryl-stabilized carbanions. Stereochemistry,

(107) Staudinger, H.; Meyer, J. Uber neue organische Phosphorverbindungen III.
635–646.

diversity of a unique class of compounds. Angew. Chem. Int. Ed. 2005, 44,
5188–5240.


281


(218) Stern, T.; Rückbrod, S.; Czekelius, C.; Donner, C.; Brunner, H. A Selective and


(228) Sabitha, G.; Nayak, S.; Bhikshapathi, M.; Yadav, J. S. Palladium Hydroxide Catalyzed Isomerization of Primary Allylic Alcohols to Aldehydes:


289


290


(269) Liu, C.; Liao, S.; Li, Q.; Feng, S.; Sun, Q.; Yu, X.; Xu, Q. Discovery and


