PALLADIUM-CATALYZED DECARBOXYLATIVE ALLYLATIONS OF ESTER ENOLATE EQUIVALENTS
AND
PALLADIUM-CATALYZED CYCLIZATIONS VIA CO$_2$ AND SILYL ACTIVATION

by

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Submitted to the graduate degree program in Department of Chemistry and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Jon A. Tunge, Chairperson

Date approved: June 3, 2014
Abstract

Yamuna Ariyarathna

Department of Chemistry, June 2014

The University of Kansas

Palladium-catalyzed decarboxylative allylation (DcA) has received much attention as an alternative C–C bond formation method to traditional metal-catalyzed cross-coupling reactions. Among various nucleophilic partners that undergo DcA, ester enolates are reported to be difficult to allylate and often demand harsher conditions. Herein we report the development of a mild and fast method that provides access to various types of α-allylated amides and esters via decarboxylative allylation of ester enolate equivalents. These amide and ester products undergo further transformations such as hydrolysis, reduction and nucleophilic addition reactions without pre-functionalization. Also enantioselective DcA and diastereoselective DcA of α,α-disubstituted amide enolates are extensively studied and reported.

Rapid and efficient synthesis of complex molecules via multicomponent reactions (MCR) is a viable alternative method to time- and resource-consuming stepwise synthesis. In general, multicomponent reactions assemble three or more different reactive components into a multisubstituted product in a one-pot, batch-wise process. Also, this process allows the formation of multiple new bonds in a single operation. Herein we report the development of one-pot, three-component and four-component double decarboxylative allylation reactions to produce α- and γ-allylated amides. In these MCRs, benzylic amide enolates exhibited remarkable success over alkyl amide enolates due to stability differences between two nucleophiles.

In the progress of transition metal catalyzed allylation reactions, it is of great interest to activate allylic alcohols in situ to obtain π-allyl intermediates instead of using pre-activated allyl sources. Due to the inherently poor leaving ability of the hydroxyl group several attempts to activate allyl alcohols have...
been made using Lewis acids such as Ti(OPr')₄, BEt₃, BPh₃, and SnCl₂. Compared to these methods, activation of allyl alcohol using CO₂, an inexpensive and readily available gas, is an economical choice. CO₂ activates the allylic alcohol in 2-(1-hydroxyallyl)phenol substrate allowing formation of π-allyl palladium intermediate followed by intramolecular etherification to synthesize benzopyrans. Furthermore, we report a successful attempt to activate allyl alcohols by an adjacent silyl group to obtain benzopyrans.
To

my mother and my late father
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<td>Ar</td>
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<td>PHOX</td>
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Chapter 1

Palladium-Catalyzed Decarboxylative Allylation (DcA) of Ester Enolate Equivalents
1.1 Introduction to palladium-catalyzed DcA

Among all the alkyl groups that can be introduced into an organic molecule, the allyl group is among the most resourceful, allowing several different synthetically important transformations such as ozonolysis, epoxidation, dihydroxylation, hydroboration, and olefin metathesis. An electrophilic allyl group can be introduced into a molecule via an allyl halide, which is often toxic and creates regio- and stereo-selectivity issues. Transition metal-catalyzed allylation of organic molecules via allyl esters or allyl carbonates provides an alternative solution to these issues. In this regard, the synthetic applicability of Tsuji–Trost allylation has been increasing over the past few decades (Scheme 1.1).

Scheme 1.1 Tsuji–Trost allylation

In general, Tsuji–Trost allylation permits the allylation of highly stabilized active methylene nucleophiles (DMSO pKₐ 8-16). Scheme 1.2 shows a general mechanism for the Tsuji–Trost allylation. The coordination of the Pd(0) catalyst to the allyl substrate (1.1.1) facilitates the nucleophilic displacement of the leaving group to generate a palladium σ-allyl complex. The mode of attack of nucleophile on palladium-σ-allyl intermediates is based on the pKₐ of the pronucleophile. In 1996, Trost and Van Vranken recognized 2 classes of nucleophiles. (1) Stabilized or “soft” carbon nucleophiles; enolates and those derived from pronucleophiles with pKₐ’s < 25 and (2) unstabilized or “hard” nucleophiles; derived from pronucleophiles with pKₐ’s > 25.
The difference in these 2 classes of nucleophiles is that “soft” nucleophiles undergo outer sphere attack on the π-allyl moiety with net retention of stereochemistry while “hard” nucleophiles first attack the palladium center before reductive elimination, resulting in inversion of stereochemistry. Both “soft” and “hard” nucleophiles have received much attention in asymmetric catalysis. However recent studies demonstrate that the border-line value (pKₐ 25) of these two classes of nucleophiles is shifted to higher values (pKₐ 32) (Scheme 1.3). Broadening the scope of “soft” nucleophiles, Trost and co-workers were able to “soften” the 2-alkylpyridine derived nucleophiles (otherwise a “hard” nucleophile; pKₐ 34) by coordinating BF₃ to the pyridine nitrogen (Scheme 1.3A). To study whether these nucleophiles behave as “soft” nucleophiles, 2-methyl pyridine was reacted with a chiral, non-racemic allyl substrate. Net retention of stereochemistry (single diastereomer, 94% ee) was observed in the product, suggesting an external attack of the nucleophile on palladium π-allyl intermediate. Further they have demonstrated that more acidic heterocyclic substrates undergo allylic alkylation without pre-functionalization or activation (Scheme 1.3B).
Scheme 1.3 Allylic alkylations of “soft” nucleophiles with higher $pK_a$ values

Recently Walsh and co-workers reported that diaryl methane derivatives ($pK_a$ 32) behave as “soft” nucleophiles in palladium-catalyzed allylic alkylation reactions (Scheme 1.3C).\textsuperscript{23} Given these few examples; the Tsuji–Trost allylation reaction still faces some limitations with less stabilized nucleophiles. In this regard, palladium-catalyzed decarboxylative allylic alkylation proved to be more effective in allylating less stabilized nucleophiles ($pK_a$ up to 32).\textsuperscript{27,28} In 1982, Tsuji and co-workers reported that palladium-catalyzed allylic alkylation of allyl carbonates could take place under neutral conditions.\textsuperscript{27} Use of allyl carbonate strategically obviated the need of a base to deprotonate the pro-nucleophile, by producing an alkoxide after oxidative addition and decarboxylation. This strategy was further exploited by tethering the allyl moiety to the pronucleophile in forms of allyl esters, allyl carbonates or enol carbonates. Scheme 1.4 shows a general mechanism for palladium-catalyzed decarboxylative alkylation (DcA). Coordination of the Pd(0) catalyst to the allyl moiety facilitates the oxidative addition to produce a palladium $\pi$-allyl intermediate and carboxylate 1.1.4. Upon decarboxylation the carboxylate will expose the active nucleophile, which then couple with palladium $\pi$-allyl intermediate to generate the product.
However Tunge and co-workers have shown that the mechanism of decarboxylative allylation reactions can be different based on the substitution pattern on α-carbon of the nucleophile. They observed that α-protio malonate derivatives undergo a proton transfer to the carboxylate allowing allylation before decarboxylation.

Various types of nucleophilic partners have been used in decarboxylative allylation reactions. Among them β-keto esters, nitriles, nitro-alkanes, sulfones and amino acid derivatives are few examples. Few literature examples are reported for the decarboxylative allylation of ester enolate equivalents.

1.2 Background of palladium-catalyzed DcA of ester enolate equivalents.

While the α-allylation of ketone enolates has received significant attention, preparation of α-allylic esters via decarboxylative allylation is comparatively difficult and demands harsher conditions.

In 1987 Tsuji reported the decarboxylative allylation of β-keto carboxylic esters and substituted malonate derivatives (Scheme 1.5).
During the course of study they observed a smooth decarboxylation-allylation for the β-keto carboxylic esters where the carbanion formed is stabilized by a ketone group. Allyl esters of malonic acid showed a slow reaction producing mixtures of products. However in refluxing conditions of dioxane or DMF, substituted malonate esters underwent DcA. When compared to the β-keto carboxylic esters, substituted diallyl malonate esters are less reactive and often result in protonation of the enolate in considerable amounts.

After a long silence in ester enolate DcA chemistry, in 2007, Ohta and co-workers reported a palladium-catalyzed decarboxylative allylation of diallyl malonates (Scheme 1.6). Among the investigated substrates, α-phenyl substituted diallyl malonates underwent DcA under milder conditions. Solvent screening of the reaction shows that the reaction could be carried out in number of different organic solvents including, 1,4-dioxane, THF, DCM, toluene and acetone giving excellent yields. During further screenings of phosphine ligands it was observed that the DcA is feasible with both mono- and bidentate ligands but no reaction was observed with electron-deficient phosphite ligands.
Scheme 1.6 Decarboxylative allylation of diallyl malonates

However, during the course of study, no reaction was observed for the \( \alpha, \alpha \)-dialkyl substituted substrates. This observation shows the dependence of the rate of DcA reaction on the stability of the enolate. Enantioselective DcA was attempted using Trost ligands, \((R)\)-BINAP, \((R, S)\)-Josiphos, and \((S)\)-iPr-PHOX ligands. In all the instances a low yield and racemic mixtures were observed due to the difficulty of achieving an enolate selectivity i.e. \( O(Z) \) or \( O(E) \). When chiral non-racemic substrates (83\% ee) were subjected to the same reaction conditions, only racemic products were observed.

Miller and co-workers have overcome the diminished reactivity of unsubstituted malonate esters towards DcA, reported by Tsuji and co-workers,\(^{31}\) by employing allyl 2,2,2-trifluoroethyl malonates.\(^{43}\) Replacement of allyl methyl malonate \((1.2.1)\) with electron withdrawing trifluoroethyl malonate \((1.2.3b)\) improves the stability of ester enolate and facilitates the decarboxylation (Scheme 1.7).

Scheme 1.7 DcA of allyl methyl malonate vs. trifluoroethyl malonate

In 2010, Tunge and co-workers reported DcA of aryl ester enolates in the form of dihydrocoumarin derivatives.\(^{29}\) Not only do these 3-carboxydihydrocoumarin derivatives undergo DcA under ambient
conditions, they also show a high diastereoselectivity (Scheme 1.8). The high cis selectivity of α-protio malonate derivatives and high trans selectivity of α-methyl malonate derivatives were explained by two different DcA mechanisms where one pathway involves decarboxylation after allylation while the other pathway involves decarboxylation prior to allylation. $^1$H NMR spectroscopic studies showed that the α-protio malonate derivatives undergo decarboxylation after allylation. Further, the cis selectivity was determined by a subsequent substrate controlled protonation step. In the case of α-methyl derivatives, where there is no possibility for allylation before decarboxylation, they undergo decarboxylation first. Then the trans selectivity will be determined by a substrate-controlled allylation step.

Scheme 1.8 Diastereoselective DcA of aryl ester enolates

1.3 Asymmetric DcA of ester enolate equivalents

Stereocontrolled allylation of ester enolate equivalents was not documented until Trost and co-workers reported asymmetric allylic alkylations of 2-acylimidazole-derivatives where geometric selection
of enolate was achieved via preformed (Z)-enol carbonates. The choice of imidazole derivatives over alkyl esters not only increased the electrophilicity of acyl ketone, facilitating decarboxylation, but also allowed the synthesis of carboxylic acid derivatives via secondary transformations. However the imidazole leaving group must be activated by alkylation before any nucleophilic substitution. During the course of study, isomerically pure (Z)-enol carbonates were synthesized via base mediated O-acylation of 2-acyl imidazole enolates and subjected to asymmetric alkylation in different solvents. While the reaction successfully proceeded in several organic solvents like toluene, THF and dioxane with several TROST ligands, the highest enantioselectivity and yield were observed with dioxane and Anden-Phenyl Trost ligand (Scheme 1.9).

Scheme 1.9 Asymmetric DcA of imidazole enol carbonates

A variety of acyclic (1.2.5) and cyclic (1.2.6, 1.2.8) allyl carbonates underwent asymmetric DcA affording products in high enantio- and diastereoselectivity. Mild reaction conditions tolerated the alkynes (1.2.7) and heteroaromatic (1.2.8) substituents as well. Interestingly, Trost and co-workers extended the chemistry towards the synthesis of Cetiedil, a drug that is used clinically for the treatment of vascular diseases in its racemic form, in high yield and ee. A series of further transformations were carried out on acyl imidazole products demonstrating that they could be converted into carboxylic acids, amides, ketones and alkyl esters (Scheme 1.10). Even though the described method provides access to
enantioenriched carboxylic acid derivatives, it is still a requirement to find an ester enolate surrogate that undergoes nucleophilic substitution without prior activation.

Scheme 1. Further transformations of acyl imidazoles; synthesis of Cetiedl

More recently, parallel to our work in this area, Trost and co-workers reported asymmetric DcA of N-acetyl benzoxazolinone-derived enol carbonates. They have demonstrated that the resulting allylated amide product can be converted into carboxylic acid, ester, thioester, or alcohol under mild conditions without a significant loss of enantiopurity (Scheme 1.1). Regarding the substrate scope, substitutions of allyl carbonates at the internal, allylic and terminus served best by increasing enantioselectivity. Good regioselectivities (linear:branched) were reported with terminally substituted allyl carbonates. However β,β-disubstituted enols and longer alkyl chains exhibited a minor decrease in selectivity. However α-aryl or α,α-disubstituted substrates were not reported. Moreover Trost’s strategic ‘enolate trapping’ in to enol carbonate method requires the relatively difficult generation of the allyl enol carbonates.
Hence we envisioned the importance of developing a methodology, which would start from simple diester substrates to form $\alpha$-quaternary centers. The next subtopics will cover the author’s contribution in this area.

1.4 Palladium-catalyzed decarboxylative allylations of ester enolate equivalents

One of the key considerations of this project was to identify different ester enolate equivalents that would facilitate $\alpha$-allylation of $\alpha,\alpha$-disubstituted esters/equivalents and further transformations (Scheme 1.12). For example, aryl esters (1.3.3) and thiophenol esters (1.3.6) can be readily substituted by amines, alcohols and thiols to produce a vast range of carboxylate derivatives.$^{50-58}$

Evans and co-workers have shown that the acyl pyrroles (1.3.4) undergo further synthetic transformations with hydride and Grignard reagents to provide pyrrole carbinols.$^{59,60}$ Weinreb amide and
oxazolidinone (1.3.7 and 1.3.8) derivatives are well known excellent precursors for carbonyl derivatives.\textsuperscript{61-66}

Further we envisioned that these β-oxo esters are readily available from Meldrum’s acid through a few simple synthesis steps. For example, our first substrate was synthesized as shown in Scheme 1.13. Commercially available phenyl malonic acid (1$\$/g) was converted into phenyl Meldrum’s acid via acid-catalyzed acetone protection. Simple alkylation and nucleophilic ring opening of Meldrum’s acid using allyl alcohol was followed by the synthesis of the acyl chloride.

Scheme 1.13 Synthesis of acyl pyrroles

Use of pre-prepared lithium pyrrolide proved to be successful for the nucleophilic substitution of the acyl chloride. The synthesized acyl pyrrole ester was subjected to the decarboxylative allylation conditions. To our delight 1.3.1 underwent decarboxylative allylation quickly and cleanly with 10 mol\% of Pd(PPh\textsubscript{3})\textsubscript{4} within 25 minutes at room temperature (Table 1.1, entry 1). Furthermore, it was found that the reaction could be carried out in THF solvent (entry 2) or with other palladium sources such as Pd\textsubscript{2}dba\textsubscript{3} and CpPd(allyl) in the presence of dppf ligand (Table 1.1, entries 3-4). Excellent yields and high reaction rates were observed in all the instances.

Without further screening tests, we selected 10 mol\% of Pd(PPh\textsubscript{3})\textsubscript{4} in benzene as optimized reaction conditions.
1.5 Further transformations of acyl pyrroles

Having identified optimized conditions for successful α-allylation, we were interested in further transformations of acyl pyrroles. Evans, Fu, and Arai have shown that N-acyl pyrroles undergo acyl substitution with water, alcohols and amines to produce acids, esters and amid es. As expected, the acyl pyrrole products are excellent precursors for further derivatization (Scheme 1.14). For example, the use of MeLi as nucleophile resulted in rapid formation of tertiary alcohol (1.3.10) in excellent yield.

Scheme 1.14 Further transformations of acyl pyrroles

Likewise, primary alcohol (1.3.11) could be readily prepared by NaBH₄ reduction and the carboxylic acid (1.3.12) resulted from hydrolysis in the presence of lithium peroxide. These results demonstrate that
acyl pyrroles undergo further synthetic transformations to furnish synthetically important intermediate functionalities without pre-activation or pre-functionalization. Having established a successful method for decarboxylative $\alpha$-allylation of an acyl pyrrole, we chose to investigate the enantioselectivity of the reaction.

1.6 Enantioselective DcA of ester enolates

Enantioselective decarboxylative allylation is an important process where one can achieve an enantioenriched product via stereoconvergence, starting from a chiral racemic stereogenic substrate. In 2004, Tunge and co-workers reported asymmetric decarboxylative allylation of ketone enolates with high levels of asymmetric induction.\(^{34}\) A possible explanation for the stereoinduction is shown in Scheme 1.15.

Scheme 1.15 Asymmetric DcA of ketone enolates

Decarboxylative ionization of chiral racemic substrate forms a meso Pd \(\pi\)-allyl complex (1.3.13), which would lead to racemic mixture of products in the absence of a chiral non-racemic palladium catalyst.\(^{69}\) However at this point asymmetric allylation is possible with the help of a chiral non-racemic ligand. Such ligands can create a rate difference between nucleophilic attacks of the electrophile in favor
to one face over the other i.e. facial selectivity. Also the chiral ligands can influence the site of the nucleophilic attack on intermediate 1.3.13 to generate either 1.3.14 or 1.3.15.

However, the enantioselectivity of the DcA of α-substituted acyclic β-keto esters (1.3.16) is largely determined by the geometric preference of the enolate. Stoltz and Trost have utilized cyclic β-keto esters (1.3.17) and enol carbonates (1.3.18), where the enolate is forced to achieve a single geometry. In the case of acyclic β-keto esters, lack of geometric preference is detrimental to the enantioselectivity of the product. A comparison is shown in Scheme 1.16.

Scheme 1.16 Enantioselective DcA of cyclic, acyclic β-keto esters and enol carbonates

Enantioselective DcA of ester enolates has been already discussed in section 1.2, Scheme 1.9. However, up to date there are no reports of asymmetric allylation of ester enolates of acyclic α,α-disubstituted substrates. Hence we started our studies on asymmetric allylation of α,α-disubstituted acyclic di-ester substrates.

First, the racemic acyl pyrrole di-ester substrate (Table 1.2, 1.3.1) was subjected to asymmetric DcA conditions. The ligands of choice were QUINAP, BINAP, TROST and PHOX ligands. These chiral ligands are known for the asymmetric induction in DcA reactions. Direct separation of the products on
chiral HPLC and chiral GC were not successful due to the appearance of several other byproducts which we believe arise due to the side reactions with iPrOH or thermal decomposition respectively. Hence we envisioned that a product obtained from a secondary transformation of the acyl pyrrole substrate would be much better candidate for the chromatographic separations. Therefore acyl pyrrole was reacted with an excess amount of MeLi to obtain a tertiary alcohol (1.3.3) and enantiomeric separation was carried out on a chiral GC (CHIRALDEX B-DM column, 107 °C – 115 °C at 0.1 °C/min). Obtained results are shown in table 1.2.

Table 1.2 Attempted asymmetric DcA of acyl pyrroles

<table>
<thead>
<tr>
<th>entry</th>
<th>Ligand</th>
<th>solvent</th>
<th>temp / °C</th>
<th>yield%</th>
<th>ee%</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>(S)-QUINAP</td>
<td>Benzene</td>
<td>rt</td>
<td>93</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>(S)-QUINAP</td>
<td>Benzene</td>
<td>10</td>
<td>92</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>(R)-BINAP</td>
<td>Benzene</td>
<td>rt</td>
<td>85</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>(S,S)-DACH-Ph Trost</td>
<td>Benzene</td>
<td>rt</td>
<td>94</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>(S)-iPr-PHOX</td>
<td>Benzene</td>
<td>rt</td>
<td>97</td>
<td>5</td>
</tr>
</tbody>
</table>

Acyl pyrrole substrate (1.3.1) was allowed to react with palladium and chiral non-racemic ligands such as (S)-QUINAP, (R)-BINAP, (S)-iPr-PHOX and (S,S)-DACH-Ph Trost ligands in benzene solvent at room temperature to obtain good to excellent conversions. However, in all the cases a low enantioselectivity was observed (entries 1-5). Relatively higher ee was obtained using (S)-QUINAP (entry 1, 11% ee), however lowering the temperature to 10 °C further reduced the ee to 7%.
Next the other ester enolates were tested towards asymmetric DcA (table 1.3). First the thiophenol diester substrate was reacted with Pd$_2$dba$_3$ catalyst and two chiral ligands (entries 1-2). In both cases a low conversion was observed. However no enantioselectivity was observed. Further studies were done using indoles, substituted pyrrole, succinimide, and phenol enolates (entries 3-7). Lack of enantioselectivity was observed throughout the study. The Weinreb amide enolate exhibited a sluggish reactivity at lower temperatures with bulky chiral ligands (entries 8, 9).

After these failed attempts to achieve asymmetric DcA for $\alpha,\alpha$-phenyl,methyl substituted diester substrates, we turned our attention to other substitutions at the $\alpha$ position. Table 1.3, entry 10 shows the reactivity of $\alpha$-methyl-$\alpha$-ethyl substituted acyl pyrrole diester substrate with several different chiral ligands. None of the products showed any enantioselectivity, probably due to almost identical energy of O(Z) and O(E) enolates. Further, $\alpha$-mono substituted substrates (entry 11,12) were subjected to asymmetric DcA reaction conditions, however we did not observe any selectivity. Thus far the reactions were carried out at room or elevated temperatures.

Hence we turned our attention to performing the reactions at lower temperatures in different solvents (Table 1.4). Gratifyingly, in THF at -40 °C the enantioselectivity elevated to 24%, the highest ee obtained so far (entry 1). Encouraged by the result, further solvent screenings were carried out. Changing the solvent in to DME caused a decrease in the ee (entry 2) but toluene increased it up to 49% ee giving 90% yield (entry 3). With a 1:1 mixture of toluene and hexane as the solvent decreased the ee to 38% (entry 4) as well as dioxane (entry 5). Our attempt to reduce the temperature to -78 °C led to low consumption of the starting material even after 24 hours. Hence according to obtained results, the highest ee was recorded with toluene solvent at -40 °C.
Table 1.3 Asymmetric DcA of ester enolate equivalents

![Diagram](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>ligand</th>
<th>er</th>
<th>entry</th>
<th>substrate</th>
<th>ligand</th>
<th>er</th>
<th>temp.</th>
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<tbody>
<tr>
<td>1</td>
<td>PhS</td>
<td>(S)-QUINAP</td>
<td>1:1</td>
<td>10</td>
<td>(R,R)-Anden-Phenyl Trost</td>
<td>(S,S)-DACH-Ph Trost</td>
<td>1:1</td>
<td>at 80°C</td>
</tr>
<tr>
<td>2</td>
<td>PhS</td>
<td>(S)-Bu-PHOX</td>
<td>nd</td>
<td>11a</td>
<td>(R,R)-Anden-Phenyl Trost</td>
<td>(S)-Bu-PHOX</td>
<td>1:1</td>
<td>at 80°C</td>
</tr>
<tr>
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<td>1:1</td>
<td>12a</td>
<td>(R,R)-Anden-Phenyl Trost</td>
<td>(S)-Bu-PHOX</td>
<td>1:1</td>
<td>at 80°C</td>
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<td>nd</td>
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<td>at 80°C</td>
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<tr>
<td>5</td>
<td>NC</td>
<td>(S)-QUINAP</td>
<td>1:1</td>
<td></td>
<td>(S)-QUINAP</td>
<td>(S)-Bu-PHOX</td>
<td>1:1</td>
<td>at 80°C</td>
</tr>
<tr>
<td>6</td>
<td>NC</td>
<td>(S)-Bu-PHOX</td>
<td>1:1</td>
<td></td>
<td>(S)-Bu-PHOX</td>
<td>(R)-BINAP</td>
<td>1:1</td>
<td>at 80°C</td>
</tr>
<tr>
<td>7</td>
<td>NC</td>
<td>(S)-Bu-PHOX</td>
<td>1:1</td>
<td></td>
<td>(S)-Bu-PHOX</td>
<td>(R)-BINAP</td>
<td>1:1</td>
<td>at 110°C</td>
</tr>
<tr>
<td>8a</td>
<td>NC</td>
<td>(R,R)-Anden-Phenyl Trost</td>
<td>nd</td>
<td></td>
<td>(R,R)-Anden-Phenyl Trost</td>
<td>nd at -40°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9a</td>
<td>NC</td>
<td>(S)-Bu-PHOX</td>
<td>nd</td>
<td></td>
<td>(S)-Bu-PHOX</td>
<td>nd at rt and 80°C</td>
<td></td>
<td></td>
</tr>
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</table>

lc=low conversion *in toluene
These results are explained by the lack of geometric preference in formation of reactive enolate by decarboxylation. Hence we envisioned that a substrate modification could be useful for achieving a single geometry. Our attempts towards diastereoselective DcAs of oxazolidinone enolates will be discussed in the next section.

### 1.7 Diastereoselective DcA of ester enolates

Synthesis of enantiomerically pure compounds using chiral auxiliaries has received much attention during last few decades. Among all the chiral auxiliary controlled reactions asymmetric alkylations, aldol and Diels-Alder reactions are highly developed.\(^{72-78}\) When performing a chiral auxiliary controlled synthetic transformation, there are three major issues to address.

1) Facile introduction of readily available chiral auxiliary \((X_c)\) in to the substrate.

2) Incorporated \(X_c\) must provide a strong reinforcement for both selective enolization process and enolate distereoface selection process.
3) Easy and mild cleavage without racemization of the newly formed stereocenters.

Up to date a myriad of nitrogen-based chiral auxiliaries have been designed, synthesized and applied in number of synthetic transformations. A nitrogen based chiral auxiliary can be introduced in to a prochiral molecule either by condensation with a carboxy acid or by nucleophilic displacement of carboxylic acid derivative. Among the latter mentioned types, oxazolidinone derivatives are one of the most utilized chiral auxiliaries. First developed by the Evans group and later several other structural variants were developed by several other groups (Scheme 1.17). Evans and co-workers were able to achieve a highly stereoselective enolization ($Z:E >100$) by incorporating a chiral auxiliary in to the prochiral substrate.

Scheme 1.17 Structural variations of N-acyloxazolidinones

![Structural variations of N-acyloxazolidinones](image)

Hence we envisioned the incorporation of a chiral auxiliary into the substrate would provide a better control of enolate geometry. However thus far the reported oxazolidinone chemistry is restricted to the formation of tertiary stereocenters. To our knowledge, there are no reports of formation of quaternary centers using oxazolidinone auxiliaries. For the same reason, there are no reported data for the allylation of $\alpha,\alpha$-phenyl,methyl disubstituted substrates, a relatively close assessment would be a comparison of allylations of $\alpha$-methyl and $\alpha$-phenyl substituted oxazolidinone substrates. As shown in Scheme 1.18 several research groups have observed highly diastereoselective $\alpha$-allylations of substrate 1.3.19 (dr 98:2) and 1.3.20 (dr 92:8) indicating almost complete Z-selectivity.
Scheme 1.18 α-allylation of ethyl- and benzyl-oxazolidinones

With these insights, we planned to combine the following strategies.

1) Chiral auxiliary mediated stereoselective formation of enolate by decarboxylation.

2) Palladium catalyzed enolate allylation.

Hence we started our studies towards chiral auxiliary mediated decarboxylative allylations of oxazolidinone enolates, mainly focusing on formation of quaternary centers.

Several acyl oxazolidinone substrates were synthesized and subjected to the conditions for decarboxylative allylation. Gratifyingly, all of them underwent decarboxylative allylation within 30 minutes, giving good yields of products (Table 1.5).

While the yields are good, the use of chiral auxiliaries only led to modest improvement in stereocontrol, with the maximum diastereoselectivity being 85:15. Nonetheless, this is the highest stereoselectivity achieved for the decarboxylative allylation of acyclic β-oxo esters. Our attempts to separate the diastereomers through column chromatography were not fruitful, even with several different solvent systems and stationary phases. However in one case, the major diastereomer of 1.3.23 could be obtained diastereopure in 53% yield by recrystallization and X-ray crystallographic analysis proved the stereochemical outcome of the reaction (Figure 1.1). The observed stereochemistry is most easily explained based on an inner-sphere allylation based on Evans chiral auxiliary model.96–88
Table 1.5 Diastereoselective DcA of chiral enolates

![Diastereoselective DcA of chiral enolates](image)

Even though the thiazolidinethione (1.3.26) and oxazolidinethione (1.3.27) structural variants of the Evans auxiliary have proven to be highly selective in alkylation reactions, we did not observe any...
improvement in the selectivity of DcA reactions utilizing these auxiliaries. Further screening tests were carried out in order to increase the selectivity (Table 1.6). Substrate 1.3.28 was screened with four different solvents. According to the results, toluene and benzene have almost identical effect on selectivity (left, entry 1 and 4) while THF had a detrimental effect on the diastereoselectivity (left, entry 3). Substrate 1.3.29 was also screened against five different solvents. In that case the highest dr was also observed with toluene (right, entry1).

Table 1.6 Solvent and catalyst loading

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<th>entry</th>
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</tr>
<tr>
<td>2</td>
<td>CD$_2$Cl$_2$</td>
<td>76:24</td>
</tr>
<tr>
<td>3</td>
<td>D-THF</td>
<td>57:43</td>
</tr>
<tr>
<td>4</td>
<td>C$_6$D$_6$</td>
<td>79:21</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>entry</th>
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<th>X mol%</th>
<th>dr</th>
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<tbody>
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<td>1</td>
<td>D-Toluene</td>
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<td>79:21</td>
</tr>
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<td>2</td>
<td>CD$_2$CN</td>
<td>10</td>
<td>58:42</td>
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<td>4</td>
<td>CD$_2$Cl$_2$</td>
<td>10</td>
<td>67:33</td>
</tr>
<tr>
<td>5</td>
<td>C$_6$D$_6$</td>
<td>10</td>
<td>62:38</td>
</tr>
<tr>
<td>6</td>
<td>C$_6$D$_6$</td>
<td>5</td>
<td>77:23</td>
</tr>
<tr>
<td>7</td>
<td>C$_6$D$_6$</td>
<td>1</td>
<td>78:22</td>
</tr>
<tr>
<td>8</td>
<td>D-Toluene</td>
<td>1</td>
<td>78:22</td>
</tr>
</tbody>
</table>

ratio based on $^1$H NMR of crude material

When we reduce the catalyst loading, a slight improvement of diastereoselectivity was observed (right, entries 5 -7). However when considering the overall results, substrate 1.3.29 showed the highest selectivity when reacted with 10 mol% of Pd(PPh$_3$)$_4$ in toluene. Next the selectivity was studied with different palladium catalysts (Table 1.7). Pd$_2$dba$_3$ with dppf ligand did not show any improvement of dr in benzene or toluene (entry 1 and 2). However one interesting observation is shown in entry 3. The reaction
of 1.3.29 with Pd$_2$dba$_3$ and BINAP was monitored for 6 hours. After first 25 minutes of the reaction an excellent dr (96:4) was observed with 10% conversion of the reactant to the product. After 2 hours, the reaction reached 33% of conversion and the selectivity had declined to 81:19. The selectivity was further reduced as it approached complete conversion. At this point we speculate that one of the diastereomers of starting diesterbsubstrate is more reactive and cause higher enolate selectivity than the other.

### Table 1.7 Palladium catalyst screening

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>temp.</th>
<th>solvent</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5% Pd$_2$dba$_3$,10% dppf,</td>
<td>rt</td>
<td>C$_6$D$_6$</td>
<td>75:25</td>
</tr>
<tr>
<td>2</td>
<td>2% Pd$_2$dba$_3$, 4% dppf,</td>
<td>rt</td>
<td>Tol-</td>
<td>76:24</td>
</tr>
<tr>
<td>3</td>
<td>2% Pd$_2$dba$_3$, 4% (rac)-BINAP,rt</td>
<td>D-Tol</td>
<td>96:04 (25 min,10% conv.) 81:19 (2 h, 34% conv.) 77:23 (6 h, 75% conv.)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2% Pd$_2$dba$_3$, 8% XPhos,</td>
<td>rt</td>
<td>D-Tol</td>
<td>lc</td>
</tr>
<tr>
<td>5</td>
<td>2% Pd$_2$dba$_3$, 8% XPhos,</td>
<td>110 °C</td>
<td>D-Tol</td>
<td>67:33</td>
</tr>
</tbody>
</table>

Ratio based on $^1$H NMR spectroscopy of crude material, lc=low conversion

Further, changing the ligand to XPhos and heating the reaction to 110 °C did not help to increase the selectivity. More screening tests were carried out on substrate 1.3.30 (Table 1.8). Reduction of the catalyst loading (entries 1-3) or use of other catalyst systems like Pd$_2$dba$_3$ with dppf ligand (entry 6) was not able to increase the selectivity. Addition of BF$_3$•OEt$_2$ affected the conversion (entry 7). Next we analyzed the effect of temperature and chiral ligand on the DcA of the same substrate (Table 1.9). Since benzene has a freezing point around 10 °C, further temperature screenings were carried out in toluene.
The diastereoselectivity observed for toluene at room temperature was 78:22 (table 1.9, entry 5). The reaction temperature was reduced to -25 °C and this resulted in a decrease in selectivity to 68:32 (entry 1).

Table 1.8 Catalyst loading

<table>
<thead>
<tr>
<th>entry</th>
<th>X mol%</th>
<th>Pd(0)</th>
<th>M</th>
<th>solvent</th>
<th>t/min.</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>Pd(PPh₃)₄</td>
<td>0.06</td>
<td>C₆D₆</td>
<td>5</td>
<td>75:25</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>Pd(PPh₃)₄</td>
<td>0.06</td>
<td>C₆D₆</td>
<td>60</td>
<td>72:28</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Pd(PPh₃)₄</td>
<td>0.06</td>
<td>C₆D₆</td>
<td>120</td>
<td>74:26</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>Pd(PPh₃)₄</td>
<td>0.01</td>
<td>C₆D₆</td>
<td>10</td>
<td>76:24</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>Pd(PPh₃)₄</td>
<td>0.03</td>
<td>D-Tol</td>
<td>10</td>
<td>78:22</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>Pd₂dba₂, dpff</td>
<td>0.03</td>
<td>C₆D₆</td>
<td>15</td>
<td>80:20</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>Pd(PPh₃)₄, BF₃•OEt₂</td>
<td>0.03</td>
<td>D-Tol</td>
<td>960</td>
<td>lc</td>
</tr>
</tbody>
</table>

ratio based on ¹H NMR spectroscopy of crude material, lc=low conversion

The selectivity was further reduced when the temperature was lowered to -40 °C (entry 2). To bring further facial discrimination to the Pd π-allyl complex we introduced chiral non-racemic ligands to the reaction. Both the enantiomers were tested (entry 4 and 5) and found a slight increase of dr with (S,S)-Anden-Phenyl Trost ligand. In this case both the substrate and the reagent are chiral and both cause a facial bias. In matched cases, both components have the same facial bias; they reinforce the facial selectivity leading to an increased selectivity. With that; the highest dr observed for the DcA reaction was 87:13.
1.8 Substrate scope of DcA of ester enolate equivalents

Having shown that acyl pyrroles and acyl oxazolidinones undergo efficient decarboxylative allylation, we became curious whether other ester/amide enolate equivalents would participate in decarboxylative allylation (Table 1.10). Indeed, other amide enolates such as pyrrole-2-carbonitrile (1.3.31), indole (1.3.32), and indole-5-carbonitrile (1.3.33) undergo high-yielding allylation in just 10-15 minutes at room temperature. While somewhat less reactive, a Weinreb amide enolate (1.3.34) underwent allylation with Pd$_2$dba$_3$ in the presence of dppf ligand at 80 °C in high yield. A phenyl ester enolate also underwent decarboxylative allylation in high yield (1.3.35), while an aryl thioester enolate provided product in only moderate yield (57%, 1.3.36). Lastly, it was found that the method could be successfully applied toward the allylation of α,α-dialkyl substrates (1.3.37 and 1.3.38). Interestingly, while the α,α-diallyl acyl pyrrole (1.3.37) underwent decarboxylative coupling in THF solvent under ambient
conditions, significantly harsher conditions were required for the allylation of \(\alpha\)-methyl-\(\alpha\)-ethyl acyl pyrrole amide enolate (1.3.38). Nonetheless, each product was isolated in high yield.

Next the substrate scope of decarboxylative allylation of phenyl ester enolates was examined using easily substituted dimethylphenyl esters (Table 1.11). Among \(\alpha\)-monosubstituted phenolic ester substrates, an \(\alpha\)-phenyl phenolic ester (1.3.39) underwent allylation smoothly with \(\text{Pd(PPh}_3\text{)}_4\) in 15 minutes under ambient conditions while \(\alpha\)-methyl substituted phenolic esters (1.3.40 and 1.3.41) required elevated temperatures and longer reaction times.

Table 1.10 DcA of ester enolate equivalents

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3.2</td>
<td>C(_6)H(_6), RT, 0.03M, 10 mol% Pd(PPh(_3))(_4)</td>
<td>97%</td>
</tr>
<tr>
<td>1.3.31</td>
<td>C(_6)H(_6), 80 °C, 0.03M, 10 mol% Pd(PPh(_3))(_4), 10 mol% dppf, rt</td>
<td>81%</td>
</tr>
<tr>
<td>1.3.32</td>
<td>Benzene, rt</td>
<td>99%</td>
</tr>
<tr>
<td>1.3.33</td>
<td>Toluene, 110 °C, 0.03M, 10 mol% Pd(PPh(_3))(_4)</td>
<td>96%</td>
</tr>
<tr>
<td>1.3.34</td>
<td>THF, rt, 0.03M, 5 mol% Pd(_2\text{dba}_3), 10 mol% dppf, 110 °C</td>
<td>89%</td>
</tr>
<tr>
<td>1.3.35</td>
<td>Toluene, 110 °C, 0.03M, 10 mol% Pd(PPh(_3))(_4)</td>
<td>99%</td>
</tr>
<tr>
<td>1.3.36</td>
<td>Benzene, rt</td>
<td>57%</td>
</tr>
<tr>
<td>1.3.37</td>
<td>Benzene, rt</td>
<td>99%</td>
</tr>
<tr>
<td>1.3.38</td>
<td>Toluene, 110 °C, 0.03M, 10 mol% Pd(PPh(_3))(_4)</td>
<td>98%</td>
</tr>
</tbody>
</table>

In addition, \(\alpha,\alpha\)-dialkyl phenolic esters gave good yields under the reported reaction conditions (1.3.42 and 1.3.43). Lastly, various allyl functionalities including cinnamyl (1.3.41), \(\beta\)-methallyl (1.3.43) and hexenyl (1.3.45 and 1.3.46) are well tolerated under the reaction conditions.
1.9 Conclusion

In conclusion, we have developed a rapid, high yielding method for the synthesis of \( \alpha \)-allylated ester equivalents. A wide range of different ester enolates and ester enolate equivalents undergo catalytic allylation under conditions that are conducive to decarboxylative enolate formation. Importantly, the method allows the construction of quaternary carbon centers, although there remains significant room for improvement of the stereoselectivity.
1.10 References


1.11 Methodology and compound characterization

All reactions were run in flame dried glassware under Argon atmosphere. Commercially available reagents and anhydrous benzene were used without further treatment. Compound purification was effected by flash chromatography using 230x400 mesh, 60Å porosity, silica obtained from Sorbent Technologies. The $^1$H and $^{13}$C NMR spectra were obtained on a Bruker Avance 400 or Bruker Avance 500 DRX spectrometer in CDCl$_3$ unless otherwise indicated and are referenced to the residual solvent peak CDCl$_3$ at $\delta$ 7.26 and $\delta$ 77.16 in $^1$H and $^{13}$C NMR respectively. Multiplicities are reported as follows: singlet (s), doublet (d), broad singlet (bs), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), multiplet (m). Structural assignments were based on $^1$H, $^{13}$C, DEPT-135, COSY, HSQC, and FT-IR spectroscopies. Mass spectrometry was run using ESI techniques. Synthesis of diester compounds was achieved by nucleophilic ring opening of substituted Meldrum’s acid by allyl alcohol, acid chloride formation in refluxing SOCl$_2$, followed by nucleophilic substitution at the carbonyl group with corresponding amine, lithium pyrrolide, thiol or alcohol.

Synthesis of lithium pyrrolide

In a flame dried Schlenk tube under argon, freshly distilled pyrrole (1g, 14.9 mmol, 1.0 eq.) in anhydrous ether (25 mL) was cooled to -20 °C and n-BuLi (9.3 mL, 14.9 mmol, 1.0 eq.) was added in batches (0.5 mL). The resulting solution was warmed to room temperature and stirring was continued for 4 hours. The white precipitate of lithium pyrrolide was filtered, washed with ether, dried under an inert atmosphere and
stored in a glove box. The same procedure was followed to prepare lithium indolide except the indolide was prepared at -78 °C.

**Transformations of 1.3.2:**

![Chemical Structure](image)

**2,3-dimethyl-3-phenylhex-5-en-2-ol (1.3.10)**

In a flame dried Schlenk flask under argon, MeLi (1 mL, excess) was added to a solution of 2-methyl-2-phenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (50 mg, 0.21 mmol, 1.0 eq.) in THF (1 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature, quenched with water (10 mL) and extracted with EtOAc (3x10 mL). The solution was then dried over anhyd. MgSO₄ and concentrated in vacuo. The residue was purified via flash chromatography using 5% EtOAc and Hexane to obtain colorless oil (40 mg, 93%).

**1H NMR** (500 MHz, CDCl₃) δ 7.33 (dt, J = 8.4, 1.7 Hz, 2H), 7.28–7.23 (m, 2H), 7.18–7.13 (m, 1H), 5.41 (m, 1H), 4.98 (m, 1H), 4.84 (dd, J = 10.2, 0.8 Hz, 1H), 3.09 (dd, J = 14.2, 5.0 Hz, 1H), 2.25 (dd, J = 14.3, 8.5 Hz, 1H), 1.30 (d, J = 0.6 Hz, 3H), 1.12 (s, 3H), 1.02 (s, 3H)

**13C NMR** (126 MHz, CDCl₃) δ 143.1, 135.9, 128.9, 127.7, 126.1, 117.1, 74.7, 48.3, 39.7, 25.9, 25.5, 21.2

**FT-IR** (CH₂Cl₂) ν max cm⁻¹ 3366, 3448, 2985, 1637, 1375, 908, 702

Calcd. HRMS for C₁₄H₂₀OLi (M+Li) – 211.1674, found 211.0926
In a flame dried Schlenk flask under argon, NaBH$_4$ (9.5 mg, 0.25 mmol, 2.0 eq.) was added to a solution of 2-methyl-2-phenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (30 mg, 0.13 mmol, 1.0 eq.) in THF (1 mL) at 0 °C. The solution was stirred 4 hours at 0 °C and overnight at room temperature. Saturated K$_2$CO$_3$ (2 mL) was slowly added to the reaction mixture and then the aqueous layer was extracted with EtOAc (3x10mL). The organic layer was then dried over anhyd. MgSO$_4$ and concentrated in vacuo. The residue was purified via flash chromatography using 5% EtOAc and Hexane to obtain colorless oil (17 mg, 76%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.35–7.24 (m, 4H), 7.18–7.14 (m, 1H), 5.52 (m, 1H), 4.95 (m, 2H), 3.68 (dd, $J = 10.9$, 2.1 Hz, 1H), 3.54 (dd, $J = 10.8$, 5.4 Hz, 1H), 2.49 (dd, $J = 13.9$, 6.6 Hz, 1H), 2.34–2.25 (m, 1H), 1.27 (s, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 144.6, 134.5, 128.5, 126.7, 126.3, 117.6, 71.8, 43.2, 42.9, 21.9

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3396, 2920, 1027, 906, 692

Calcd. HRMS for C$_{12}$H$_{17}$O (M+H) – 177.1279, found 177.1333

A flame dried Schlenk flask under argon, was charged with 2-methyl-2-phenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (50 mg, 0.21 mmol, 1.0 eq.) in THF (2mL) and H$_2$O (0.5 mL). The solution was cooled to 0 °C and H$_2$O$_2$ (30% in H$_2$O, 0.1 mL) followed by LiOH•H$_2$O (44 mg, 1 mmol, 5.0 eq.) were added. The
reaction mixture was stirred overnight at room temperature. To workup, Na$_2$S$_2$O$_3$ (0.7 M, 1mL) and NaHCO$_3$ (0.5 N, 2 mL) were added and THF was removed in vacuo. The aqueous layer was acidified 2M HCl (monitored by pH papers) and extracted with EtOAc (3x10mL). The solvent was removed in vacuo and the residue was purified via flash chromatography using 5%-15% EtOAc and Hexane to obtain colorless oil (34 mg, 85%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.44–7.33 (m, 4H), 7.29 (m, 1H), 5.64 (m, 1H), 5.16–5.04 (m, 2H), 2.84 (dd, $J = 13.8$, 7.4 Hz, 1H), 2.71 (dd, $J = 13.8$, 7.1 Hz, 1H), 1.59 (s, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 181.8, 142.4, 133.7, 128.5, 127.1, 126.2, 118.7, 49.7, 43.5, 22.2

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3076, 1697, 1446, 1277, 918

Calcd. HRMS for C$_{12}$H$_{14}$O$_2$Na (M+Na) 213.0892, found 213.0823

Representative procedure for Palladium catalyzed DcA:

![Diagram of 2-methyl-2-phenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one]

2-methyl-2-phenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one

In a flame dried Schlenk flask under argon, Pd(PPh$_3$)$_4$ (40.8 mg, 0.035 mmol, 0.10 eq.) and anhydrous benzene (9 mL, 0.04 M) was added to the allyl 2-methyl-3-oxo-2-phenyl-3-(1H-pyrrol-1-yl)propanoate (100 mg, 0.35 mmol, 1.0 eq.) and stirred for 25 minutes at room temperature. The reaction solution was concentrated in vacuo and the residue was purified via flash chromatography using 5% EtOAc and Hexane to obtain colorless oil (81 mg, 97%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.28 (dt, $J = 9.7$, 1.9 Hz, 2H), 7.23–7.15 (m, 3H), 6.92–6.87 (m, 2H), 5.97 (d, $J = 2.4$ Hz, 2H), 5.48 (m, 1H), 4.99–4.94 (m, 1H), 4.88 (m, $J = 17.0$, 3.2, 1.4 Hz, 1H), 2.81 (dd, $J = 13.7$, 8.0 Hz, 1H), 2.71 (dd, $J = 13.7$, 6.6 Hz, 1H), 1.60 (s, 3H)
13C NMR (126 MHz, CDCl3) δ 172.7, 142.3, 132.1, 128.1, 126.2, 124.8, 119.6, 118.1, 110.8, 51.0, 44.0, 23.6

FT-IR (CH2Cl2) νmax cm⁻¹ 3020, 1704, 1494, 1465, 1213, 1155, 700, 503

Calcd. HRMS for C16H17NO (M⁺) – 239.1310, found 239.1245

The above representative procedure was followed starting with 55 mg’s (0.16 mmol) of oxazolidinone allyl ester to obtain colorless oil in 88% yield (42 mg) as a mixture of diastereomers (85:15 dr).

Major isomer - 1H NMR (500 MHz, CDCl3) δ 7.23 (dd, J = 10.4, 4.8 Hz, 3H), 7.17–7.04 (m, 3H)- Ar-H major and minor are overlapped, 5.56 (m, 1H), 5.07–4.93 (m, 2H), 4.49–4.41 (m, 1H), 4.13–3.99 (m, 2H), 3.25 (dd, J = 13.7, 8.1 Hz, 1H), 2.58 (dd, J = 13.8, 6.5 Hz, 1H), 2.35 (m, J = 13.9, 7.0, 3.4 Hz, 1H), 1.53 (s, 3H), 0.86 (d, J = 7.1 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H)

13C NMR (126 MHz, CDCl3) δ 175.6, 151.4, 143.3, 133.9, 128.1, 126.4, 125.5, 118.6, 62.8, 60.1, 52.9, 43.2, 28.4, 24.4, 18.3, 14.7

Minor- 1H NMR (500 MHz, CDCl3) δ Ar-H are overlapped with major isomer, 5.54–5.44 (m, 1H-overlapped with major isomer), 5.07–4.97 (m, overlapped with major isomer, 4.12–3.99 (m, overlapped with major isomer), 2.93 (dd, J = 13.8, 8.3 Hz, 1H), 2.53 (dd, J = 13.8, 6.4 Hz, overlapped with major isomer), 1.64 (s, 3H), 0.79 (d, J = 6.9 Hz, 6H - overlapped with major isomer).

13C NMR (126 MHz, CDCl3) δ 142.8, 134.2, 118.4, 63.1, 59.9, 52.9, 44.5, 28.6, 23.1, 18.1, 14.9

FT-IR (CH2Cl2) νmax cm⁻¹ 3055, 2975, 1689, 1598, 1380, 703
Calcd. HRMS for C_{18}H_{23}NO_{3}Na (M+Na) – 324.1576, found 324.1541

(4S)-4-(tert-butyl)-3-(2-methyl-2-phenylpent-4-enoyl)oxazolidin-2-one (1.3.22)

The above representative procedure was followed starting with 75 mg’s (0.21 mmol) of oxazolidinone allyl ester to obtain pale yellow oil in 83% yield (55 mg) as a mixture of diastereomers (84:16 dr).

Major isomer - $^1$H NMR (500 MHz, CDCl$_3$) δ 7.29–7.20 (m, 3H), 7.15–7.06 (m, 2H + minor isomer), 5.73 (m, 1H), 5.12 (m, 1H), 5.08–5.02 (m, 1H), 4.43 (dd, $J = 7.4, 1.4$ Hz, 1H), 4.10–4.01 (m, 2H), 3.71–3.55 (m, 1H), 2.67 (m, 1H), 1.47 (s, 3H), 0.87 (s, 9H + minor isomer)

Minor isomer - $^1$H NMR (500 MHz, CDCl$_3$) δ 7.27–7.15 (Ar-H - overlapped with major isomer), 5.51–5.42 (m, 1H), 4.94 (s, 1H), 4.93–4.90 (m, 1H), 4.52 (dd, $J = 7.4, 1.6$ Hz, 1H), 4.32 (dd, $J = 7.6, 1.4$ Hz, 1H), 4.14 (dd, $J = 9.3, 1.4$ Hz, 1H), 2.74 (dd, $J = 13.8, 8.1$ Hz, 1H), 2.48 (dd, $J = 13.8, 6.5$ Hz, 1H), 1.75 (s, 3H), 0.89 (tBu – overlapped with major isomer)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 175.7, 174.8, 152.6, 152.0, 144.1, 142.3, 134.4, 134.1, 128.6, 128.3, 128.1, 127.2, 126.4, 125.5, 125.2, 119.0, 118.3, 64.9, 53.4, 52.9, 42.9, 41.6, 35.9, 35.8, 27.5, 26.1, 25.7, 20.1

FT-IR (CH$_2$Cl$_2$) $v_{\text{max}} \text{ cm}^{-1}$ 3060, 2973, 1690, 1590, 1370, 700

Calcd. HRMS for C_{19}H_{25}NO_{3}Na (M+Na) – 338.1732, found 338.1701
The above representative procedure was followed starting with 70 mg’s (0.15 mmol) of oxazolidinone allyl ester to obtain white solid in 88% yield (64 mg) as a mixture of diastereomers (38:62 dr). After recrystallization the major isomer was isolated in 53% yield (<5:95 dr).

$^1$H NMR (500 MHz, CDCl$_3$) Ar-H major isomer + minor isomer $\delta$ 7.30–7.22 (m, 4H), 7.22–7.17 (m, 6H), 7.17–7.12 (m, 7H), 7.10 (m, 3H), 6.93 (dd, $J = 8.3, 1.1$ Hz, 1H), 6.90–6.86 (m, 2H), 5.39 (m, 1H), 5.31 (m, 1H), 5.29–5.18 (m, 1H), 4.96–4.83 (m, 3H), 4.69 (d, $J = 6.2$ Hz, 1H), 4.54 (d, $J = 7.3$ Hz, 1H), 4.20–4.10 (m, 3H), 3.03 (dd, $J = 13.8, 7.2$ Hz, 1H), 2.63 (dd, $J = 13.7, 8.0$ Hz, 1H), 2.51 (dd, $J = 13.8, 7.2$ Hz, 1H), 2.41–2.35 (m, 1H), 1.46 (s, 3H), 1.44 (s, 2H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 175.7, 175.2, 151.3, 150.9, 142.7, 142.1, 139.9, 139.7, 138.6, 138.5, 134.4, 134.0, 129.1×3, 128.9, 128.8, 128.7×2, 128.6, 128.0×2, 127.7×2, 127.1, 126.3×2, 125.7, 125.6, 118.4, 118.1, 65.4, 65.1, 58.7, 57.9, 52.7, 52.6, 52.5, 51.9

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3060, 2977, 1789, 1681, 1600, 1496, 1242, 918, 700

Calcd. HRMS for C$_{28}$H$_{27}$NO$_3$Na (M+Na) – 448.1889, found 448.1931
The above representative procedure was followed starting with 100 mg’s (0.25 mmol) of oxazolidinone allyl ester to obtain colorless oil in 87% yield (76 mg) as a mixture of diastereomers (26:74 dr).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ Ar-H major isomer + minor isomer 7.29–7.20 (m, 6H), 7.20–7.17 (m, 4H), 7.17–7.12 (m, 2H), 7.12–7.07 (m, 3H), 5.64 (m, 1H), 5.55–5.48 (m, minor), 5.10–4.93 (m, 2H + minor), 4.70–4.62 (m, 1H + minor), 4.00–3.93 (m, 2H + minor), 3.40–3.26 (m, 2H + minor), 3.00–2.95 (m, minor), 2.68–2.55 (m, 1H + minor), 2.50 (dd, $J = 13.1, 10.8$ Hz, 1H, major), 1.65 (s, minor), 1.56 (s, 3H, major)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 175.8, 175.5, 150.8, 143.2, 142.6, 135.8, 135.6, 134.1, 133.9, 129.5, 129.4, 129.0, 128.9, 128.2, 128.2, 127.3, 127.28, 126.4, 125.6, 125.5, 118.8, 118.5, 65.9, 65.8, 57.3, 57.0, 52.8, 52.7, 44.2, 42.7, 37.9, 37.8

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3026, 2977, 1789, 1681, 1236, 700

Calcd HRMS for C$_{22}$H$_{24}$NO$_3$ (M+H) – 350.1756, found 350.1743
1-(2-methyl-2-phenylpent-4-enoyl)-1H-pyrrole-2-carbonitrile (1.3.31)

The above representative procedure was followed starting with 80 mg’s (0.26 mmol) of pyrrol allyl ester to obtain colorless oil in 81% yield (56 mg).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.40–7.22 (m, 3H), 7.22–7.10 (m, 3H), 6.81 (dd, \(J = 3.6, 1.4\) Hz, 1H), 6.53 (dd, \(J = 3.4, 1.4\) Hz, 1H), 5.94 (t, \(J = 3.5\) Hz, 1H), 5.50 (m, 1H), 5.03–4.97 (m, 1H), 4.86 (m, 1H), 2.85–2.70 (m, 2H), 1.63 (s, 3H)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 172.7, 142.1, 132.3, 129.5, 127.9, 125.9, 125.6, 125.1, 119.8, 113.4, 112.3, 104.4, 52.7, 44.8, 24.4

FT-IR (CH\(_2\)Cl\(_2\)) \(\nu_{\text{max}}\) cm\(^{-1}\) 3057, 2200, 1725, 1450, 1150, 725

Calcd. HRMS for C\(_{17}\)H\(_{16}\)N\(_2\)ONa (M+Na) – 287.1160, found 287.1161

1-(1H-indol-1-yl)-2-methyl-2-phenylpent-4-en-1-one (1.3.32)

The above representative procedure was followed starting with 100 mg’s (0.3 mmol) of indole allyl ester to obtain colorless oil in 99% yield (86 mg).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.51 (dd, \(J = 8.4, 0.6\) Hz, 1H), 7.39 (d, \(J = 7.7\) Hz, 1H), 7.33–7.26 (m, 3H), 7.21 (dd, \(J = 6.2, 5.2\) Hz, 3H), 7.18 (m, 2H), 6.79 (d, \(J = 3.9\) Hz, 1H), 6.21 (d, \(J = 3.6\) Hz, 1H), 5.52 (m, 1H), 4.98–4.86 (m, 2H), 2.88 (dd, \(J = 13.7, 7.9\) Hz, 1H), 2.77 (dd, \(J = 13.7, 6.7\) Hz, 1H), 1.66 (s, 3H)
$^{13}$C NMR (126 MHz, CDCl$_3$) δ 174.7, 143.8, 136.5, 133.3, 129.5, 129.2, 127.3, 126.2, 125.8, 125.0, 123.7, 120.5, 119.1, 117.2, 108.2, 52.8, 45.3, 24.7

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3068, 2989, 1704, 1539, 1494, 1379, 1321, 1207, 1145, 931, 767

Calcd. HRMS for C$_{20}$H$_{19}$NOLi (M+Li) – 296.1627, found 296.1648

1H NMR (500 MHz, CDCl$_3$) δ 8.58 (d, $J = 8.7$ Hz, 1H), 7.73 (d, $J = 1.1$ Hz, 1H), 7.53 (dd, $J = 8.7, 1.6$ Hz, 1H), 7.31 (dt, $J = 9.7, 1.8$ Hz, 2H), 6.91 (d, $J = 3.9$ Hz, 1H), 6.27 (d, $J = 4.4$ Hz, 1H), 5.50 (m, 1H), 4.98–4.92 (m, 1H), 4.87 (m, 1H), 2.82 (m, 2H), 1.66 (s, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 174.9, 143.1, 138.4, 132.8, 129.5, 128.2, 127.6, 125.7, 125.2, 119.6, 119.5, 117.9, 107.7, 107.0, 53.1, 45.0, 24.6

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3058, 2875, 2360, 1751, 1639, 1512, 1249, 1116, 916, 698

Calcd. HRMS for C$_{21}$H$_{18}$N$_2$OLi (M+Li) – 321.1579, found 321.1531

1-(2-methyl-2-phenylpent-4-enoyl)-1H-indole-5-carbonitrile (1.3.33)

The above representative procedure was followed starting with 80 mg’s (0.22 mmol) of indole allyl ester to obtain colorless oil in 96% yield (70 mg).
N-methoxy-N,2-dimethyl-2-phenylpent-4-enamide (1.3.34)

The above representative procedure was followed starting with 80 mg’s (0.29 mmol) of Weinreb amide allyl ester to obtain white solid in 89% yield (67 mg).

\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \delta 7.25 (m, 2H), 7.21–7.10 (m, 3H), 5.49 (m, 1H), 5.01–4.91 (m, 2H), 3.03 (s, 3H), 2.90 (dd, } J = 13.6, 8.1 \text{ Hz, 1H), 2.60–2.50 (m, 4H), 1.45 (s, 3H) } \]

\[ ^13C \text{ NMR (126 MHz, CDCl}_3 \delta 177.0, 144.8, 134.5, 128.2, 126.2, 125.9, 118.1, 58.9, 49.9, 43.1, 33.3, 22.9 } \]

FT-IR (CH\textsubscript{2}Cl\textsubscript{2}) ν\textsubscript{max} cm\textsuperscript{-1} 3064, 2935, 1654, 1490, 1379, 999, 698

Calcd HRMS for C\textsubscript{14}H\textsubscript{20}NO\textsubscript{2} (M+H) – 234.1494 found 234.1520

2,5-dimethylphenyl 2-methyl-2-phenylpent-4-enoate (1.3.35)

Above representative procedure was followed starting with 75 mg’s (0.29 mmol) of allyl diester to obtain colorless oil in 89% yield (67 mg).

\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \delta 7.40 (d, } J = 7.9 \text{ Hz, 2H), 7.35–7.16 (m, 5H), 6.95 (d, } J = 7.7 \text{ Hz, 1H), 6.82 (d, } J = 7.6 \text{ Hz, 1H), 6.61 (s, 1H), 5.64 (m, 1H), 5.14–4.98 (m, 2H), 2.91 (dd, } J = 13.8, 7.4 \text{ Hz, 1H), 2.73 (dd, } J = 13.8, 6.9 \text{ Hz, 1H), 2.20 (s, 3H), 1.80 (s, 3H), 1.65 (s, 3H) } \]
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.9, 146.9, 140.3, 134.4, 131.5, 128.6, 126.5, 126.3, 124.9, 124.6, 124.4, 123.9, 119.8, 116.6, 47.7, 41.3, 20.0, 18.6, 13.3

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3078, 2980, 1735, 1598, 1508, 1492, 1240, 1198, 1128, 925, 700

Calcd. HRMS for C$_{20}$H$_{23}$O$_2$ (M+H) – 295.1698, found 295.1670

![S-phenyl 2-methyl-2-phenylpent-4-enethioate (1.3.36)](image)

S-phenyl 2-methyl-2-phenylpent-4-enethioate (1.3.36)

Above representative procedure was followed starting with 100 mg’s (0.3 mmol) of thio phenol allyl ester to obtain colorless oil in 57% yield (48 mg).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.40–7.21 (m, 10H), 5.55–5.43 (m, 1H), 5.07–4.95 (m, 2H), 2.77 (m, 2H), 1.61 (s, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 202.5, 141.6, 134.8, 133.4, 129.1, 128.6, 128.3, 127.4, 127.2, 118.8, 57.1, 43.7, 22.7

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3058, 2985, 1780, 1697, 1440, 952, 703

Calcd. HRMS for C$_{18}$H$_{19}$OS (M+H) – 283.1157, found 283.1202
2,2-diallyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (1.3.37)

The above representative procedure was followed starting with 75 mg’s (0.27 mmol) of pyrrol allyl ester to obtain colorless oil in 99% yield (63 mg).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.41–7.38 (m, 2H), 6.21–6.18 (m, 2H), 5.62 (m, 3H), 5.05–4.94 (m, 6H), 2.53 (d, $J = 7.4$ Hz, 6H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.2, 132.6, 120.2, 119.4, 112.2, 51.7, 39.2

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3072, 2941, 1704, 1637, 1467, 1284, 1255, 1103, 921, 736

Calcd HRMS for C$_{15}$H$_{20}$NO (M+H) – 230.1545, found 230.1539

2-ethyl-2-methyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (1.3.38)

The above representative procedure was followed starting with 150 mg’s (0.64 mmol) of pyrrol allyl ester to obtain pale yellow oil in 98% yield (120 mg).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50–7.44 (m, 2H), 6.31–6.24 (m, 2H), 5.80–5.65 (m, 1H), 5.11–4.97 (m, 2H), 2.71 (dd, $J = 14.1$, 7.0 Hz, 1H), 2.43 (dd, $J = 14.1$, 7.7 Hz, 1H), 2.08–1.92 (m, 1H), 1.79 (m, 1H), 1.39 (s, 3H), 0.89 (t, $J = 7.5$ Hz, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.4, 132.1, 119.2, 117.7, 110.9, 47.7, 42.6, 31.3, 22.2, 7.8

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 2966, 2949, 1760, 1664, 1517, 1463, 1163, 919, 734
Calcd HRMS for C\textsubscript{12}H\textsubscript{18}NO (M+H) – 192.1388, found 192.1443

\[
\begin{array}{c}
\text{O} \\
\text{Ph} \\
1.3.39
\end{array}
\]

2,5-dimethylphenyl 2-phenylpent-4-enoate (1.3.39)

The above representative procedure was followed starting with 150 mg’s (0.46 mmol) of diester to obtain colorless oil in 95% yield (123 mg).

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.38–7.33 (m, 2H), 7.32–7.27 (m, 2H), 7.26–7.21 (m, 1H), 6.96 (d, \(J = 7.7\) Hz, 1H), 6.83 (d, \(J = 8.4\) Hz, 1H), 6.63 (s, 1H), 5.76 (m, 1H), 5.15–4.97 (m, 2H), 3.83 (dd, \(J = 8.8, 6.8\) Hz, 1H), 2.90 (m, 1H), 2.56 (m, 1H), 2.19 (s, 3H), 1.79 (s, 3H)

\textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 170.6, 147.9, 137.1, 135.7, 134.1, 129.7, 127.7, 127.1, 126.6, 125.8, 125.7, 121.1, 116.3, 50.4, 36.2, 19.8, 14.5

FT-IR (CH\textsubscript{2}Cl\textsubscript{2}) \(\nu_{\text{max}}\) cm\textsuperscript{-1} 3070, 2920, 1755, 1508, 1454, 1242, 1134, 1110, 918

Calcd. HRMS for C\textsubscript{10}H\textsubscript{12}O\textsubscript{2} (M+H) – 281.1542, found 281.1497
2,5-dimethylphenyl 2-methylpent-4-enoate (1.3.40)

The above representative procedure was followed starting with 200 mg’s (0.76 mmol) of diester, 5 mol% of Pd$_2$dba$_3$ and 10 mol% of dpff in toluene to obtain pale yellow oil in 97% yield (161 mg).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.02 (d, $J = 7.7$ Hz, 1H), 6.87 (d, $J = 8.4$ Hz, 1H), 6.71 (s, 1H), 5.79 (m, 1H), 5.13–5.01 (m, 2H), 2.73 (m, 1H), 2.56–2.48 (m, 1H), 2.30–2.24 (m, 1H), 2.24 (d, $J = 3.4$ Hz, 3H), 2.05 (s, 3H), 1.26 (d, $J = 7.0$ Hz, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 174.4, 149.1, 136.9, 135.3, 130.8, 126.7, 122.3, 117.3, 39.4, 37.8, 20.9, 16.8, 15.9

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3072, 2869, 1753, 1623, 1510, 1244,1114, 918

Calcd. HRMS for C$_{14}$H$_{19}$O$_2$ (M+H) – 219.1385, found 219.1384

(E)-2,5-dimethylphenyl 2-methyl-5-phenylpent-4-enoate (1.3.41)

The above representative procedure was followed starting with 150 mg’s (0.44 mmol) of diester, 5 mol% of Pd$_2$dba$_3$ and 10 mol% of dpff in toluene to obtain yellow oil in 92% yield (119 mg).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.30 (dd, $J = 5.3$, 3.4 Hz, 2H), 7.24 (dd, $J = 10.3$, 4.9 Hz, 2H), 7.17–7.13 (m, 1H), 7.01 (d, $J = 7.7$ Hz, 1H), 6.86 (d, $J = 7.5$ Hz, 1H), 6.67 (s, 1H), 6.44 (d, $J = 15.8$ Hz, 1H), 6.19
(dt, \( J = 15.7, 7.2 \text{ Hz}, 1\text{H} \)), 2.90–2.75 (m, 1H), 2.66 (m, 1H), 2.43 (m, 1H), 2.19 (s, 3H), 2.03 (s, 3H), 1.31 (d, \( J = 7.0 \text{ Hz}, 3\text{H} \))

\(^{13}\text{C NMR (126 MHz, CDCl}_3\)) δ 174.4, 149.1, 137.3, 136.9, 132.6, 130.8, 128.6, 127.3, 126.1, 122.4, 39.9, 37.1, 20.8, 16.9, 15.8

FT-IR (CH\(_2\)Cl\(_2\)) \( \nu_{\text{max}} \text{ cm}^{-1} \) 3033, 2975, 2933, 1755, 1506, 1456, 1377, 1247, 1143, 1114, 968

Calcd. HRMS for C\(_{20}\)H\(_{22}\)O\(_2\)Na (M+Na) – 317.1518, found 317.1529

\[
\begin{align*}
\text{\includegraphics[width=0.2\textwidth]{image}}
\end{align*}
\]

**2,5-dimethylphenyl 2-allyl-2-methylpent-4-enoate (1.3.42)**

The above representative procedure was followed starting with 150 mg’s (0.47 mmol) of diester, 5 mol% of Pd\(_2\)dcp, and 10 mol% of dppf in toluene to obtain colorless oil in 95% yield (120 mg).

\(^1\text{H NMR (400 MHz, CDCl}_3\)) δ 7.12 (d, \( J = 7.6 \text{ Hz}, 1\text{H} \)), 6.96 (d, \( J = 7.6 \text{ Hz}, 1\text{H} \)), 6.79 (s, 1H), 5.90 (m, 2H), 5.24–5.13 (m, 4H), 2.59 (m, 2H), 2.42 (m, 2H), 2.34 (s, 3H), 2.16 (s, 3H), 1.34 (s, 3H)

\(^{13}\text{C NMR (126 MHz, CDCl}_3\)) δ 173.8, 148.3, 135.7, 132.5, 129.8, 125.6, 121.3, 117.6, 44.9, 41.8, 20.6, 19.9, 15.0

FT-IR (CH\(_2\)Cl\(_2\)) \( \nu_{\text{max}} \text{ cm}^{-1} \) 3076, 2983, 1751, 1641, 1510, 1242, 1199, 1116, 1000, 919

Calcd. HRMS for C\(_{17}\)H\(_{23}\)O\(_2\) (M+H) – 259.1698, found 259.1711
The above representative procedure was followed starting with 100 mg’s (0.32 mmol) of diester, 5 mol% of Pd$_2$dba$_3$ and 10 mol% of dppf in toluene to obtain colorless oil in 93% yield (81 mg).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.01 (d, $J = 7.7$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 6.74 (s, 1H), 5.86–5.74 (m, 1H), 5.15–5.04 (m, 2H), 4.87–4.82 (m, 1H), 4.73 (d, $J = 0.9$ Hz, 1H), 2.55 (dd, $J = 13.9$, 5.6 Hz, 2H), 2.29 (m, 2H), 2.23 (s, 3H), 2.07 (s, 3H), 1.73 (s, 3H), 1.24 (s, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 175.2, 149.3, 141.9, 136.7, 133.7, 130.9, 126.6, 126.5, 122.2, 118.8, 114.9, 46.5, 45.9, 44.0, 24.4, 21.6, 20.9, 16.1

FT-IR (CH$_2$Cl$_2$) $\nu_{max}$ cm$^{-1}$ 3072, 2985, 2919, 1750, 1644, 1507, 1454, 1244, 1194, 1115, 897

Calcd. HRMS for C$_{18}$H$_{25}$O$_2$ (M+H) – 273.1855, found 273.1848

The above representative procedure was followed starting with 100 mg’s (0.28 mmol) of diester to obtain colorless oil in 99% yield (86 mg).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.35 (dt, $J = 3.0$, 1.7 Hz, 2H), 7.33–7.28 (m, 2H), 7.24–7.19 (m, 1H), 6.94 (d, $J = 7.7$ Hz, 1H), 6.81 (d, $J = 7.7$ Hz, 1H), 6.62 (s, 1H), 5.60–5.50 (m, 1H), 5.14–5.00 (m, 2H), 2.96
(dd, J = 14.2, 7.8 Hz, 1H), 2.82 (dd, J = 14.2, 6.6 Hz, 1H), 2.24 (dd, J = 14.3, 7.1 Hz, 1H), 2.20 (s, 3H), 2.10 (m, 1H), 1.76 (s, 3H), 0.83 (t, J = 7.4 Hz, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.8, 149.2, 141.5, 136.6, 133.4, 130.8, 128.5, 127.0, 126.9, 126.7, 126.5, 122.1, 118.5, 53.9, 37.9, 26.4, 20.9, 15.6, 8.4

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3076, 2979, 1737, 1598, 1508, 1496, 1242, 1188, 1118, 923, 702

Calcd. HRMS for C$_{21}$H$_{24}$O$_2$Na (M+Na) – 331.1674, found 331.1682

The above representative procedure was followed starting with 100 mg’s (0.25 mmol) of diester to obtain colorless oil in 99% yield (87 mg).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.40 (d, J = 8.0 Hz, 2H), 7.36 (t, J = 7.7 Hz, 2H), 7.26 (t, J = 7.2 Hz, 1H), 6.99 (d, J = 7.7 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H), 6.68 (s, 1H), 5.54 (dt, J = 13.9, 6.8 Hz, 1H), 5.23 (dt, J = 14.5, 6.7 Hz, 1H), 2.97 (dd, J = 14.1, 7.7 Hz, 1H), 2.80 (dd, J = 14.1, 6.6 Hz, 1H), 2.30–2.23 (m, 4H), 2.18–2.12 (m, 1H), 1.95 (q, J = 7.1 Hz, 2H), 1.82 (s, 3H), 1.39–1.29 (m, 2H), 0.85 (m, 6H)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 174.0, 149.2, 141.8, 136.6, 134.6, 130.8, 128.4, 126.8, 126.5, 124.5, 122.1, 54.2, 36.6, 34.8, 26.5, 22.6, 20.9, 15.6, 13.6, 8.3

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3020, 2958, 2927, 2871, 1508, 1750, 1203, 1151, 1108, 804, 698

Calcd. HRMS for C$_{24}$H$_{30}$O$_2$Na (M+Na) – 373.2144, found 373.2149

(E)-2,5-dimethylphenyl 2-ethyl-2-phenyloct-4-enoate (1.3.45)
(E)-2,5-dimethylphenyl 2-methyl-2-phenyloct-4-enolate (1.3.46)

The above representative procedure was followed starting with 100 mg’s (0.26 mmol) of diester to obtain colorless oil in 82% yield (72 mg).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.47–7.42 (m, 2H), 7.40–7.33 (m, 2H), 7.27 (dt, $J = 3.9, 1.7$ Hz, 1H), 7.00 (d, $J = 7.7$ Hz, 1H), 6.87 (d, $J = 7.6$ Hz, 1H), 6.67 (s, 1H), 5.52 (dt, $J = 14.8, 6.7$ Hz, 1H), 5.39–5.22 (m, 1H), 2.92 (dd, $J = 13.9, 7.4$ Hz, 1H), 2.70 (dd, $J = 13.7, 6.9$ Hz, 1H), 2.26 (s, 3H), 1.95 (q, $J = 7.0$ Hz, 2H), 1.86 (s, 3H), 1.67 (s, 3H), 1.40–1.29 (m, 2H), 0.85 (t, $J = 7.4$ Hz, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 174.5, 149.4, 143.1, 136.8, 135.2, 130.9, 128.6, 127.1, 126.8, 126.5, 125.2, 122.3, 50.4, 42.5, 34.9, 22.8, 22.7, 21.1, 15.8, 13.9

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 2968, 2920, 1749, 1502, 1430, 1238, 1110, 692

Calcd. HRMS for C$_{23}$H$_{28}$O$_2$ (M+Na) – 359.1987 found 359.1989
Structure 1.3.24
Table 1. Crystal data and structure refinement for C28H27NO3.

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<tr>
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<td>1.000 and 0.661</td>
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<td>Full-matrix least-squares on (F^2)</td>
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<td>R indices (all data)</td>
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Table 2. Atomic coordinates (x x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for C28H27NO3. U(eq) is defined as one third of the trace of the orthogonized U^ij tensor.

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Table 3. Bond lengths [Å] and angles [°] for C28H27NO3.

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C(3)-H(3B) 0.9900
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C(4)-C(9) 1.535(5)
C(4)-C(5) 1.546(5)
C(7)-C(8) 1.528(5)
C(7)-H(7A) 0.9900
C(7)-H(7B) 0.9900
C(8)-C(16) 1.546(4)
C(8)-H(8) 1.0000
C(9)-H(9A) 0.9800
C(9)-H(9B) 0.9800
C(9)-H(9C) 0.9800
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C(11)-C(12) 1.398(6)
C(11)-H(11) 0.9500
C(12)-C(13) 1.375(8)
C(12)-H(12) 0.9500
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C(13)-H(13) 0.9500
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C(16)-C(17) 1.525(4)
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C(17)-C(22) 1.398(6)
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C(23)-C(24) 1.394(5)
C(24)-C(25) 1.390(6)
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C(26)-H(26) 0.9500
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C(6)-N-C(8) = 110.2(3)
C(5)-N-C(8) = 118.6(2)
C(2)-C(1)-H(1A) = 127(3)
C(2)-C(1)-H(1B) = 124(3)
H(1A)-C(1)-H(1B) = 106(4)
C(1)-C(2)-C(3) = 125.1(4)
C(1)-C(2)-H(2) = 118(2)
C(3)-C(2)-H(2) = 117(2)
C(2)-C(3)-C(4) = 114.0(3)
C(2)-C(3)-H(3A) = 108.8
C(4)-C(3)-H(3A) = 108.8
C(2)-C(3)-H(3B) = 108.8
C(4)-C(3)-H(3B) = 108.8
H(3A)-C(3)-H(3B) = 107.7
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C(11)-C(12)-H(12)  120.6
C(14)-C(13)-C(12)  120.7(4)
C(14)-C(13)-H(13)  119.6
C(12)-C(13)-H(13)  119.6
C(13)-C(14)-C(15)  119.9(4)
C(13)-C(14)-H(14)  120.0
C(15)-C(14)-H(14)  120.0
C(14)-C(15)-C(10)  121.1(4)
C(14)-C(15)-H(15)  119.4
C(10)-C(15)-H(15)  119.4
C(17)-C(16)-C(23)  112.6(3)
C(17)-C(16)-C(8)   111.4(2)
C(23)-C(16)-C(8)   112.1(3)
C(17)-C(16)-H(16)  106.8
C(23)-C(16)-H(16)  106.8
C(8)-C(16)-H(16)   106.8
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C(18)-C(17)-C(16)  122.6(3)
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C(19)-C(18)-H(18)  119.9
C(17)-C(18)-H(18)  119.9
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Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å\(^2\times 10^3\)) for C28H27NO3. The anisotropic displacement factor exponent takes the form: \\
\[-2\delta^2[h^2 a^2 U_{11} + \ldots + 2hk a^* b^* U_{12}]\]

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Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for C28H27NO3.

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<th></th>
<th>x</th>
<th>y</th>
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Table 6. Torsion angles [°] for C28H27NO3.

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<td>C(8)-N-C(5)-O(3)</td>
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<td>C(6)-N-C(8)-C(16)</td>
<td>98.5(3)</td>
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C(5)-N-C(8)-C(16) -78.0(3)
O(1)-C(7)-C(8)-N 25.8(3)
O(1)-C(7)-C(8)-C(16) -94.9(3)
C(9)-C(4)-C(10)-C(11) -168.1(4)
C(5)-C(4)-C(10)-C(11) -42.0(5)
C(3)-C(4)-C(10)-C(11) 72.9(4)
C(9)-C(4)-C(10)-C(15) 13.9(5)
C(5)-C(4)-C(10)-C(15) 140.0(3)
C(3)-C(4)-C(10)-C(15) -105.1(4)
C(15)-C(10)-C(11)-C(12) 0.1(6)
C(4)-C(10)-C(11)-C(12) -178.0(4)
C(10)-C(11)-C(12)-C(13) -0.3(8)
C(11)-C(12)-C(13)-C(14) 1.8(8)
C(12)-C(13)-C(14)-C(15) -3.0(7)
C(13)-C(14)-C(15)-C(10) 2.8(6)
C(11)-C(10)-C(15)-C(14) -1.3(6)
C(4)-C(10)-C(15)-C(14) 176.8(3)
N-C(8)-C(16)-C(17) -61.7(4)
C(7)-C(8)-C(16)-C(17) 51.5(4)
N-C(8)-C(16)-C(23) 171.1(2)
C(7)-C(8)-C(16)-C(23) -75.7(3)
C(23)-C(16)-C(17)-C(18) 33.7(4)
C(8)-C(16)-C(17)-C(18) -93.3(4)
C(23)-C(16)-C(17)-C(22) -149.1(3)
C(8)-C(16)-C(17)-C(22) 83.9(4)
C(22)-C(17)-C(18)-C(19) -1.5(5)
C(16)-C(17)-C(18)-C(19)  175.7(3)
C(17)-C(18)-C(19)-C(20)  0.8(5)
C(18)-C(19)-C(20)-C(21)  0.0(5)
C(19)-C(20)-C(21)-C(22)  0.2(6)
C(20)-C(21)-C(22)-C(17)  -1.0(5)
C(18)-C(17)-C(22)-C(21)  1.7(5)
C(16)-C(17)-C(22)-C(21)  -175.6(3)
C(17)-C(16)-C(23)-C(28)  57.2(4)
C(8)-C(16)-C(23)-C(28)  -176.2(3)
C(17)-C(16)-C(23)-C(24)  -123.5(3)
C(8)-C(16)-C(23)-C(24)  3.1(4)
C(28)-C(23)-C(24)-C(25)  0.9(5)
C(16)-C(23)-C(24)-C(25)  -178.3(3)
C(23)-C(24)-C(25)-C(26)  -1.4(6)
C(24)-C(25)-C(26)-C(27)  1.8(6)
C(25)-C(26)-C(27)-C(28)  -1.7(6)
C(26)-C(27)-C(28)-C(23)  1.3(5)
C(24)-C(23)-C(28)-C(27)  -0.9(5)
C(16)-C(23)-C(28)-C(27)  178.5(3)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for C28H27NO3 [Å and °].

<table>
<thead>
<tr>
<th>D-H...A</th>
<th>d(D-H)</th>
<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
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<tr>
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<td>1.00</td>
<td>2.53</td>
<td>3.315(3)</td>
<td>135.4</td>
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</table>
Symmetry transformations used to generate equivalent atoms:

#1 x-1/2,-y+3/2,-z
Chapter 2

One-pot, Three-component DcA of Ester Enolate Equivalents
2.1 Palladium-catalyzed multicomponent reactions

Rapid and efficient synthesis of complex molecules via multicomponent reactions (MCR) is a viable alternative method to time- and resource-consuming stepwise synthesis.\textsuperscript{1–4} In general, multicomponent reactions assemble three or more different reactive components into a multi-substituted product in a one-pot, batch-wise process. The reagents or catalysts are not considered as components unless they contribute to the product structure. Also this process allows the formation of multiple new bonds in a single operation.\textsuperscript{5–8} Here the starting materials react in a sequence of elementary steps rather than in one step. MCRs are ideal for library synthesis of complex molecules. A number of products can be synthesized from only a few starting materials because different reactive components can be introduced to the reaction mixture independent of each other. Many MCRs are one-pot processes starting with readily available or easily accessible reagents. That makes MCRs economical in terms of time and resources.\textsuperscript{1–8}

The first report of MCRs was done by Laurent and Gerhardt in 1838.\textsuperscript{9} Later, Strecker reported the synthesis of α-aminocyanides using ammonia, carbonyl compounds and hydrogen cyanide.\textsuperscript{10} Three decades later, classical MCR chemistry started to flourish with several recognized reactions. Some of them; Mannich,\textsuperscript{11} Hantzsch,\textsuperscript{12} Ugi,\textsuperscript{13,14} and Biginelli\textsuperscript{15} are well known for the synthesis of amino-compounds or heterocyclic compounds. As a modern and efficient tool in organic synthesis, transition-metal-catalyzed methods are well established for synthesizing heterocyclic compounds.\textsuperscript{16,17} Among other transition-metal-catalyzed methods for the synthesis of heterocyclic compounds, palladium-catalyzed methods are highly developed and the chemistry has been utilized in one-pot MCRs. Here palladium catalysis and other synthetic transformations; such as condensations, additions, cycloadditions take place within the same reaction vessel. Palladium-catalyzed MCRs are feasible under mild reaction conditions. Also palladium is compatible with many polar functional groups, and high degrees of chemo-, regio-, and stereoselectivity are observed. Most of the palladium catalyzed MCRs are based on carbopalladation of allenes, alkynes or carbon monoxide, Heck type reactions, and Sonogashira coupling reactions.\textsuperscript{16–18}
Most of the palladium-catalyzed, multicomponent methods, to produce styryl or \( \alpha,\beta \)-unsaturated ketones are based on carbopalladation of allenes with aryl, heteroaryl, vinyl halides or aroyl-Pd intermediates. Grigg and co-workers reported the multicomponent synthesis of heterocyclic compounds using allenes, and 4-hydroxycoumarins as reactive substrates (eq. 1).\(^{19}\)

\[
\begin{align*}
| & \quad + & \quad \text{Ar}-I & \quad \begin{array}{c}
\text{OH} \\
\text{MeCN, 80 °C, 20 h} \\
(65 - 97 \%)
\end{array} & \quad \begin{array}{c}
\text{OH} \\
\text{Ar}
\end{array} & \quad \begin{array}{c}
\text{TFA}, \text{CHCl}_3 \\
\text{rt}
\end{array} & \quad \begin{array}{c}
\text{Ar} \\
\text{O}
\end{array} \\
\ &= \quad + & \quad \text{Ar}-I & \quad \begin{array}{c}
\text{OH} \\
\text{MeCN, 80 °C, 20 h} \\
(65 - 97 \%)
\end{array} & \quad \begin{array}{c}
\text{OH} \\
\text{Ar}
\end{array} & \quad \begin{array}{c}
\text{TFA}, \text{CHCl}_3 \\
\text{rt}
\end{array} & \quad \begin{array}{c}
\text{Ar} \\
\text{O}
\end{array}
\end{align*}
\]

Mechanistically, the oxidative addition of palladium into aryl iodide followed by carbopalladation of allene produce the Pd \( \pi \)-allyl intermediate which then undergo C–allylation or O–allylation followed by Claisen rearrangement and subsequent acid-catalyzed cyclization to furnish the desired product. As shown in eq. 1, cyclized product was achieved in two steps. A one-pot procedure is also reported. The same group extended the concept to four-component, 1,3-dipolar cycloaddition reaction to produce isoquinoline derivatives (eq. 2).\(^{20}\)

\[
\begin{align*}
| & \quad + & \quad \text{PhCO}_2\text{Me} & \quad \begin{array}{c}
\text{H}_2\text{N} \\
\text{C}_6\text{H}_{12}\text{CO}_2\text{Me}
\end{array} & \quad \begin{array}{c}
\text{Ar} \\
\text{O}
\end{array} & \quad \begin{array}{c}
\text{N} \\
\text{H}
\end{array} & \quad \begin{array}{c}
\text{Ph} \\
\text{CO}_2\text{Me}
\end{array} & \quad \begin{array}{c}
\text{O} \\
\text{N}
\end{array}
\end{align*}
\]

2-Iodo benzaldehyde, \( N \)-methyl maleimide, phenylalanine methyl ester and allene reacted under palladium-catalyzed conditions and the authors observed the desired product in a mixture of epimers in good yield. The four-component cascade begins either with the oxidative addition of palladium into aryl iodide followed by allene insertion or with the condensation of amine into the aldehyde forming an imine. The rest of the first mentioned pathway involves: condensation of amine into the aldehyde, nucleophilic
attack into the Pd $\pi$-allyl intermediate and cycloaddition to produce the desired product. The latter mentioned pathway undergoes cycloaddition prior to the oxidative addition and allene insertion. These four-component reactions result in overall molecular complexity with formation of five new bonds, two rings, and four stereocenters.

The Ugi four-component reaction between an aldehyde, an amine, a carboxylic acid, and an isocyanide allows the preparation of $\alpha$-acylamino acyl derivatives. The combination of Ugi-chemistry with Heck coupling allows the development of palladium-catalyzed multicomponent reactions to synthesize polysubstituted heterocycles. Umkehrer and co-workers reported the Ugi-Heck reaction for the synthesis of indole-2-ones. Here, in one-pot fashion, the product of the Ugi-reaction participates in a cyclic carbopalladation reaction (eq. 3).

$$\begin{align*}
\text{Ugi 4-CR} & \quad \text{Heck} \\
\begin{array}{c}
\text{Br} \\
\text{NH}_2 \\
\cdots \text{Ph} \\
\text{COOH} \\
\text{NC} \text{Ph} \\
\text{O}
\end{array} & \quad \begin{array}{c}
Pd(OAc)_{2}, PPh_3 \\
\text{MeCN} \\
16 \text{~h}
\end{array}
\end{align*}$$

Sonogashira coupling reactions have been used in several multicomponent reactions. Muller and co-workers developed a one-pot, four-component reaction to synthesize annelated and substituted pyridines. An electron poor (hetero) aryl halide, a terminal propargyl alcohol, an enamine, and ammonium chloride were used to perform coupling-isomerization-enamine addition-cyclocondensation sequence (eq. 4). After the palladium-catalyzed coupling reaction of aryl halide and terminal alkyne, the product undergoes isomerization to furnish chalcones. The enamine addition to chalcones results in formation of 1,5-diketones, which undergo cyclocondensation in the presence of ammonia to furnish the desired pyridine products.
Several research groups have utilized palladium-catalyzed Michael addition/Tsuji-Trost allylation cascade to synthesize $\gamma$-allylated cyclic $\beta$-keto esters, nitro alkanes, and diphenylglycinate products.\textsuperscript{23-26} Even though the pro-electrophile and pro-nucleophile are introduced to the reaction mixture by one tethered molecule, these interceptive decarboxylative allylation reactions are considered to be ‘three-component’. More details will be discussed in the next chapter.

In this regard, we were able to develop palladium-catalyzed one-pot, multicomponent reactions for the synthesis of $\alpha$-, and $\gamma$-allylated acyl pyrroles. These reactions operate through a double decarboxylative allylation/Michael addition sequence.

### 2.2 One-pot, three-component DcA of ester enolate equivalents

In chapter 1 we introduced the development of a mild and fast method that provides access to various types of $\alpha$-allylated amides and esters via decarboxylative allylation of ester enolate equivalents. These amide and ester products undergo further transformations such as hydrolysis, reduction and nucleophilic addition reactions without pre-functionalization. The step-wise synthesis of acyl pyrroles is shown in Scheme 2.1. First, $\alpha,\alpha$-disubstituted Meldrum’s acid derivative (2.2) was synthesized from phenyl malonic acid (2.1).\textsuperscript{27} The Meldrum’s acid derivative was then subjected to subsequent nucleophilic ring opening, acyl chloride formation and nucleophilic substitution reactions to synthesize acyl pyrrole diester \textit{i.e.} DcA substrate (1.3.1). The DcA substrate (1.3.1) was deliberately planned in such a way that both the pro-nucleophile \textit{i.e.} acyl pyrrole, and the pro-electrophile \textit{i.e.} the allyl ester, are tethered in the same molecule.
Scheme 2.1 Step-wise and one-pot syntheses of acyl pyroles

Most of the synthetic steps were required for the tethering process of these two moieties. Hence we envisioned that, independent introduction of the enolate and the allyl moiety into the reaction mixture would be helpful to overcome additional tethering steps. Therefore we became interested in developing a multicomponent method.

In a multicomponent reaction, three or more starting materials react to form a single product via a cascade of elementary chemical reactions.\textsuperscript{4,28} The product contains portions of all the components. However a catalyst or other additive, which facilitates the reaction, is not considered as a component unless it contributes to the product structure. A one-pot, multicomponent reaction does not require extensive manipulation, such as isolation of each intermediate and re-exposure to new reagents in each step of the reaction. Also multicomponent reactions are effective in terms of time, resources, and effort. Additionally, any of the components of the reaction can be varied independently of all the other components. However, the presence of several reactive functional groups in the same pot can increase side reactions. Therefore, it was vital to choose proper reactive components that would produce desired enolates, or $\beta$-oxo carboxylates, and Pd $\pi$-allyl complexes while minimizing the number of side reactions.
2.3 Meldrums acid; *in situ* formation of β-oxo carboxylates

In 1908, Meldrum’s acid was first reported by A. N. Meldrum, which he discovered from condensation of malonic acid with acetone in the presence of acetic anhydride and sulfuric acid (Scheme 2.2).29 However the structure was incorrectly assigned as a carboxylic acid (2.4). 40 years later, Davidson and Bernhard correctly assigned the structure as 2,2-dimethyl-1,3-dioxan-4,6-dione (2.3).30 Structural variants of Meldrum’s acid can be prepared by condensing un-, mono- or di-substituted malonic acid with ketones (aliphatic or aromatic) or aryl aldehydes. However alkyl aldehydes have been found to be ineffective towards condensation.27

Scheme 2.2 *Meldrum’s acid formation and structure*

Meldrum’s acid has pKₐ of 4.83 (in water), comparatively as strong as acetic acid (pKₐ 4.76 in water) and more acidic than acyclic malonate esters (pKₐ 13 in water). The high acidity of Meldrum’s acid can be explained by the stability of the resultant anion (Scheme 2.3). The cyclic nature of the acid provides a rigid configuration allowing π-orbitals to overlap.

Scheme 2.3 Stability of the anion
Meldrum’s acid derivatives are valuable synthetic intermediates in organic synthesis due to their ability to undergo the following two types of reactions.\textsuperscript{31}

1) Reaction with an electrophile at the position 5 leaving the ring intact

2) Reactions with nucleophiles at positions 4 and 6 causing ring opening

Reactions such as acylation with acid chlorides, mono- or di-alkylation, or condensation with an aldehyde to form methylene derivatives are a few examples of first category.\textsuperscript{27} These derivatives have been widely used in preparation of 1,3 dicarbonyl compounds,\textsuperscript{32,33} malonic ester synthesis,\textsuperscript{34} conjugate additions and Diels-Alder reactions.\textsuperscript{35} We were interested in the second category of the above reactions. Knowing that positions 4 and 6 of the Meldrum’s acid are susceptible to nucleophilic attack, we started investigating different types of nucleophiles that would facilitate the \textit{in situ} formation of $\beta$-oxo carboxylates (Scheme 2.4).

\textbf{Scheme 2.4 Nucleophilic attack at positions 4 and 6}

As shown in Scheme 2.4, Meldrum’s acid furnish malonic acid, (2.5) and malonate diester (2.6) via simple hydrolysis,\textsuperscript{29} and nucleophilic attack of methoxide anion\textsuperscript{36} respectively. However these two
reactions could not be utilized in our allylation reaction, because we speculated that the protonation would dominate the allylation under these conditions. Interestingly at high temperatures, solvolysis of Meldrum’s acid with phenols furnishes monoaryl esters (2.7). Monoester formation with other alcohols such as EtOH, MeOH, iPrOH, BuOH and allyl alcohol is also reported (Table 2.1). These alcohol nucleophiles also demand high heat conditions. Hence we turned our attention to nitrogen-based nucleophiles.

Table 2.1 Alcohol as nucleophiles

<table>
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<th>entry</th>
<th>ROH</th>
<th>yield %</th>
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<tr>
<td>1</td>
<td>EtOH</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>4-NO$_2$C$_6$H$_4$OH</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>i-PrOH</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>t-BuOH</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>PhOH</td>
<td>34</td>
</tr>
</tbody>
</table>

In 1978, McNab reported that nitrogen nucleophiles, such as aniline react with Meldrum’s acid to produce monoamides of malonic acid. The nucleophilic attack of aniline on the C4 or C6 position triggers the ring opening of Meldrum’s acid followed by acetone elimination. They further observed the decarboxylation of the product to generate amides. In 1990, Svetlik and coworkers reported the synthesis of substituted oxygen-bridged tetrahydro-2-pyridones (2.12) using 4-(2-hydroxyphenyl)but-3-en-2-one (2.10), Meldrum’s acid and ammonium acetate (Scheme 2.5). The consecutive reactions involved in the synthesis are: (a) Michael addition of Meldrum’s acid carbanion, (b) aminal formation, (c) cyclization by acetone and carbon dioxide expulsion. In their synthesis, they cleverly incorporated the Meldrum’s acid into the molecule so that nucleophilic attack of nitrogen can occur on the C4 or C6
Two other research groups have applied the same strategy for the synthesis of 2-pyridones (2.14 and 2.16).\textsuperscript{41,42} Recently Huang and coworkers reported a three component, one-pot reaction with Meldrum’s acid, benzaldehyde and heterocyclic ketene aminal (2.17) to afford tetrahydropyridine-fused 1,3-diazaheterocycle (2.19) in good yield.\textsuperscript{43}

Scheme 2.5 *Nitrogen nucleophiles in synthesis of tetrahydro-2-pyridones*

With this information we envisioned that the use of nitrogen based nucleophiles would eventually lead to the *in situ* formation of the desired amide enolates or amide carboxylates.\textsuperscript{42,44,45} However, nitrogen nucleophiles are known to undergo *N*-allylation in the presence of metal-\(\pi\)-allyl complexes.\textsuperscript{46–55} Therefore our next objective was to identify a nitrogen-based nucleophile, which does not undergo *N*-allylation under decarboxylative conditions, and would thus be compatible with other reactants.
2.4 Allylic amination

Direct mono-allylation of amine nucleophiles is known to be difficult due to the formation of dialkylated products.\textsuperscript{56} A traditional way of overcoming this problem is to apply Gabriel synthesis, which uses potassium phthalimide, a \textit{–NH}_2-synthon, as the nucleophile (eq. 1).\textsuperscript{57-59} However, the removal of phthalimide group from the product without affecting, if present, other hydrolyzable groups such as nitriles and esters is often a problem.\textsuperscript{60,61}

\[
\text{Br} + \text{KN} \xrightarrow{\text{EtOH reflux}} \text{N} \xrightarrow{\text{eq. 1}} \text{O}
\]

Trost and coworkers have shown that anionic phthalimides undergo asymmetric allylation under palladium catalyzed reaction conditions (eq. 2 and 3).\textsuperscript{62,63} As shown in equation 2, high enantioselectivity was obtained using a bulky ammonium cation and a relatively nonpolar dichloromethane solvent. In a separate study, they reported that phthalimides undergo \textit{N}-allylation under the reaction conditions as shown in eq.3.\textsuperscript{38} Both products are formed via amination of the Pd \textpi-allyl complexes. Hence we envisioned that the use of anionic phthalimide in our decarboxylative one-pot, three-component reaction would trigger \textit{N}-allylation rather than formation of the enolate.
Lithium salts of di-tert-butylimino-dicarbonates,\textsuperscript{64} and sodium salts of tosyl amides\textsuperscript{65} have been reported to undergo N-allylation.\textsuperscript{53} Heterocyclic amines are also known to undergo allylation in the presence of Pd \( \pi \)-allyl complexes.\textsuperscript{54,66–68} Trost and co-workers shown that (bis)indole lactams undergo asymmetric allylic alkylation in the presence of cyclopentenyl carbonate.\textsuperscript{69} In 2005, Tunge and coworkers reported allylation of several heterocyclic amines under decarboxylative conditions.\textsuperscript{70} In the course of their study, they synthesized a variety of tertiary carbamates including those derived from anilines, cyclic and acyclic amines.

**Table 2.2 DcA of hetero-aromatic amines**

<table>
<thead>
<tr>
<th>entry</th>
<th>Reactant</th>
<th>product</th>
<th>yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{morpholine} )</td>
<td>( \text{morpholine-N} )-allyl carbamate</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>( \text{pyrrolidine} )</td>
<td>( \text{pyrrolidine-N} )-allyl carbamate</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>( \text{aniline-N} )</td>
<td>( \text{aniline-N} )-allyl carbamate</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>( \text{bisindole lactam} )</td>
<td>( \text{bisindole lactam-N} )-allyl carbamate</td>
<td>81 (1:1.6)</td>
</tr>
<tr>
<td>5</td>
<td>( \text{amine} )</td>
<td>( \text{amine} )-allyl carbamate</td>
<td>-</td>
</tr>
</tbody>
</table>

Under the decarboxylative conditions, morpholine and pyrrolidine allyl carbamates underwent \( N \)-allylation quickly and cleanly. Interestingly the scope of proelectrophiles revealed cyclic, acyclic, aryl-
substituted, and alkyl-substituted allyl substrates yielded aminated product. The study was extended to heteroaromatic amines (Table 2.2). Interestingly allylic carbamates of pyrazole (entry 1), imidazole (entry 2), triazole (entry 3), and benzotriazoles (entry 4) underwent decarboxylative allylation while the allylic carbamate of pyrrole underwent elimination to form cyclohexadiene and pyrrole (entry 5). It could be concluded that allylation of pyrrolide under the reaction conditions was slow. Hence we assumed that if we employ lithium pyrrolide in our three-component reaction, it would react selectively with Meldrum’s acid and lead us to the formation of the desired enolate rather than N-allylated by-product.

2.5 One-pot, three-component Decarboxylative Allylation; reactive partners

In the midst of designing and developing a multicomponent reaction, the first challenge was to identify proper reactive partners.

1) Source of β-oxo carboxylates

Meldrum’s acid was chosen as the source of β-oxo carboxylates for a few important reasons. Meldrum’s acid is a known source for 1,3-dicarbonyl compounds and it is known to react with nucleophiles, providing access to β-oxo carboxylates. Also it has a unique ring-opening pattern, which expels easily removable acetone and carbon dioxide as its only byproducts. Preparation of un-, mono-, and di-subsisted Meldrum’s acid, starting from malonic acid, is easy and high yielding. In addition, malonic acid is a commercially available inexpensive reagent.

2) Nucleophile

One of the major challenges was to identify a nucleophile that preferentially reacts with Meldrum’s acid instead of Pd π-allyl complex. Knowing that Pd π-allyl complexes are soft electrophiles, we envisioned that choice of a hard nucleophile would prevent the undesired N-allylation reactions. Previously we have shown that (Table 1.3.1) pyrrole amide enolates undergo quick and efficient
decarboxylative allylation. Therefore we envisioned that the nucleophilic attack of lithium pyrrolide on Meldrum’s acid would provide us with the desired pyrrole amide enolates to undergo allylation. Even though moisture free conditions are required, preparation, handling and storage of lithium pyrrolide is not difficult. The white, powder-like solid of lithium pyrrolide can be stored in a glovebox for months without affecting its reactivity. Also we have already shown the synthetic importance of acyl pyroles as an intermediate structure (Scheme 1.3.2).

3). Allyl source

Allyl halides, allyl acetates, and allyl carbonates are the obvious choices for making Pd π-allyl complexes. The latter two are either commercially available or easily synthesized from allyl alcohols.

Scheme 2.2.1 Choice of components for one-pot allylation

Thus, we started our study towards developing the one-pot, three-component reaction with Meldrum’s acid, lithium pyrrolide, and different allyl sources (Scheme 2.2.1). A plausible mechanism is shown in Scheme 2.2.2. Simultaneous formation of β-oxo carboxylate and Pd π-allyl complex are the starting points of the reaction sequence. Nucleophilic attack of lithium pyrrolide on the C4 or C6 positions of Meldrum’s acid generates β-oxo carboxylate (2.20) via acetone exclusion. Oxidative addition, facilitated by coordination of the palladium catalyst to the alkene followed by expulsion of the leaving group forms the Pd π-allyl complex. Next, palladium-catalyzed decarboxylation of β-oxo carboxylate generates the amide enolate (2.21) and the subsequent allylation forms the desired acyl
pyrrole product (1.3.2). Though an exclusive formation of acyl pyrrole product (1.3.2) is anticipated, there are several possibilities of formation of undesired byproducts (Scheme 2.2.3).

Scheme 2.2.2 Acyl pyrrole formation via three-component coupling

Scheme 2.2.3 Desired product and possible byproducts

Formation of byproducts not only lowers the yield (1.3.2) but also challenges the isolation and purification of the desired product. Byproduct 2.22, which is formed via protonation of the in situ
generated pyrrolamide enolate, is commonly observed in DcA chemistry. If enough moisture, or/and a proton source is present, there is the possibility of protonation of lithium pyrrolide to generate pyrrole. We speculated that the formation of byproduct 2.23 is possible, but unlikely due to the hard-soft mismatch of lithium pyrrolide and Pd π-allyl complex. Moreover, Tunge and coworkers reported that the allylic carbamate of pyrrole underwent elimination to form cyclohexadiene and pyrrole under DcA conditions. The potential byproduct, β-acyl carboxylic acid (2.24), is expected to undergo decarboxylation in the presence of palladium, which would form 2.22. With this point of view, 2.22 is the major byproduct we expect to observe during our studies.

In the next section we will discuss the development of the one-pot, three-component DcA of benzylic enolates.

2.6 One-pot, three-component coupling of benzylic enolates

During our initial studies, α-phenyl substituted Meldrum’s acids were preferentially studied. Phenyl substitution in an amide substrate lowers the pKₐ by ca. 7-8 units. A comparison between the pKₐ of the two types of amides is shown in Scheme 2.2.4. The enolate formed after decarboxylation of phenyl-substituted substrates is more stable than that of unsubstituted or alkyl-substituted substrates.

Scheme 2.2.4 pKₐ of amides: proton vs phenyl

Phenyl substituted Meldrum’s acid derivatives were synthesized according to the reported literature. Following Meldrum’s original procedure, phenyl malonic acid was reacted with acetone, acetic anhydride
and sulfuric acid to obtain α-phenyl Meldrum’s acid.29 Then a methylation was carried out to obtain the α,α-disubstituted Meldrum’s acid (Scheme 2.1).

As a control experiment, we reacted α-methyl-α-phenyl Meldrum’s acid, lithium pyrrolide and allyl bromide in THF at room temperature without any catalysts (Scheme 2.2.5). Excitingly we isolated a 16% combined yield that contained a mixture of desired product (1.3.2), and protonated byproduct (2.27). Spectroscopic analysis showed significant byproduct (2.27) formation. The reaction did not reach a full conversion under the conditions, unconsumed Meldrum’s acid was observed in the crude reaction mixture. The presence of protonated byproduct (2.27) and allylated product (1.3.2) was an indication of in situ formation of the enolate. With this data we turned our attention to the catalytic formation of acyl pyrroles by replacing allyl bromide with allyl acetate. Repeating the reaction with 10 mol% of Pd(PPh₃)₄ in THF we isolated 73% yield containing the desired product (1.3.2), and the protonated enolate byproduct (2.27, Scheme 2.2.6). Spectroscopic analysis showed significant formation of the desired product (1.3.2) over the byproduct (2.27).

Scheme 2.2.5 One-pot, three-component allylation; control experiment

Scheme 2.2.6 Catalytic formation of acyl pyrroles

91
With the observations of these preliminary reactions, we sought to improve the yields by optimizing the reaction conditions. The optimal conditions should offer following aspects; (a) complete conversion of the starting material, and (b) less byproduct formation. Different solvents and palladium catalysts were screened and crude reaction mixtures were analyzed by $^1$H NMR spectroscopy (Table 2.2).

Table 2.2 *Optimization of the conditions for one-pot, three-component allylation*

<table>
<thead>
<tr>
<th>entry</th>
<th>Catalyst</th>
<th>solvent</th>
<th>R</th>
<th>% conversion$^a$</th>
<th>2.26 : 2.27$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^c$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>CD$_2$Cl$_2$</td>
<td>CH$_3$</td>
<td>7:1</td>
<td>73</td>
</tr>
<tr>
<td>2$^c$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>THF</td>
<td>CH$_3$</td>
<td>4:1</td>
<td>71</td>
</tr>
<tr>
<td>3$^c$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>D-Tol</td>
<td>CH$_3$</td>
<td>4:1</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>1,4-Dioxane</td>
<td>CH$_3$</td>
<td>10:1</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>1,4-Dioxane, 3 ÅMS</td>
<td>CH$_3$</td>
<td>1:1</td>
<td>34</td>
</tr>
<tr>
<td>6$^d$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>1,4-Dioxane</td>
<td>CH$_3$</td>
<td>4:1</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>Pd$_2$dba$_3$, dppf</td>
<td>1,4-Dioxane</td>
<td>CH$_3$</td>
<td>2:1</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>Pd$_2$dba$_3$, BINAP</td>
<td>1,4-Dioxane</td>
<td>CH$_3$</td>
<td>0.3:1</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>Pd$_2$dba$_3$, P'Bu$_3$</td>
<td>1,4-Dioxane</td>
<td>CH$_3$</td>
<td>2:1</td>
<td>96</td>
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<tr>
<td>10</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>1,4-Dioxane</td>
<td>OCH$_3$</td>
<td>&gt;95:&lt;5</td>
<td>99</td>
</tr>
<tr>
<td>11</td>
<td>Pd$_2$dba$_3$, ANDEN-Ph Trost</td>
<td>1,4-Dioxane</td>
<td>OCH$_3$</td>
<td>1:1</td>
<td>95</td>
</tr>
<tr>
<td>12</td>
<td>CpPdallyl, ANDEN-Ph Trost</td>
<td>1,4-Dioxane</td>
<td>OCH$_3$</td>
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<td>54</td>
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<tr>
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<td>1,4-Dioxane</td>
<td>OCH$_3$</td>
<td>60:1</td>
<td>85</td>
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</table>

*Reactions were carried out with 10 mol% of Pd(0) catalyst in 0.3 M solutions $^b$based on the crude $^1$H NMR, $^c$started at -78°C and brought to rt $^d$at 60°C. $^a$ based on conversion% of starting Meldrum’s acid to product and by-product.

The substrates; Meldrum’s acid (1 eq.), lithium pyrrolide (1.2 eq.), and cinnamyl acetate (1.2 eq.) were subjected to the catalytic conditions in several different solvents, such as CD$_2$Cl$_2$, THF, toluene-d$_8$ and
1,4-dioxane (entries 1-4). Spectroscopic analyses of crude reaction mixtures revealed the presence of desired product (2.26), protonated byproduct (2.27) and starting Meldrum’s acid (2.28). Initially the reactions were started at -78°C and allowed to reach to room temperature over 16 hours of time. At this temperature, CD₂Cl₂ and THF lead to the formation of a mixture of products (7:1 and 4:1) with approximately 70% conversions (entries 1 and 2). No improvement was observed with toluene (entry 3). Next, the reaction with 1,4-dioxane was performed at room temperature and an improvement of both selectivity (10:1) and conversion was observed (78%, entry 4). Yet the results did not reach our expectations.

Since we observed a considerable amount of protonated byproduct, we were concerned about the dryness of the solvents and glassware. Commercially available anhydrous solvents were kept under an inert atmosphere and precautions were taken when handling the solvents and drying glassware. Introduction of 3 Å molecular sieves, to adsorb any moisture, did not diminish the byproduct formation, however it did reduce the amount of product and conversion to 34% (entry 5). Next we heated the reaction mixture to 60°C and observed an almost complete conversion. But the mixture still contained considerable amount of byproduct (entry 6). Other Pd(0) sources such as Pd₂dba₃, Pd(dba)₂ and CpPd(allyl) appeared to improve conversion and as well as protonation (entries 7-9). With these results Pd(PPh₃)₄ remained as the best catalyst.

At this point, we were interested in using an external base to deprotonate the byproduct 2.27 or use cinnamyl methyl carbonate as the allyl source. After the decarboxylation, cinnamyl methyl carbonate generates methoxide anion as a byproduct and that will serve as a base to deprotonate the byproduct 2.27 or remove the sources of protons. The substrates were subjected to reaction conditions with cinnamyl methyl carbonate and nearly complete conversion of Meldrum’s acid to the desired product with a small amount of byproduct was observed (entry 10). Other catalyst systems appeared to promote protonation (entries 11-13). With these results we concluded that 10 mol% of Pd(PPh₃)₄, 1,4-dioxane, cinnamyl
methyl carbonate and ambient temperature as optimized reaction conditions for the one-pot, three-component DcA reaction.

With the optimized reaction conditions, we investigated several other \( \alpha, \alpha \)-disubstituted Meldrum’s acid substrates and allyl methyl carbonates (Table 2.3). We were pleased to see that phenyl substituted Meldrum’s acid substrates and a range of allyl carbonates were capable of undergoing DcA to form the corresponding products.

Under the optimized reaction conditions, \( \alpha \)-methyl-\( \alpha \)-phenyl Meldrum’s acid underwent three-component coupling with methyl cinnamyl carbonate (2.26) giving 70\% yield (Table 2.3). The scope of Meldrum’s acid was investigated by substituting \( \alpha \)-position with methyl, allyl and benzyl groups. Interestingly all three substrates underwent decarboxylative allylation with methyl cinnamyl carbonate giving good yields of 2.26, 2.31, and 2.36 respectively. Two other allyl reagents; allyl methyl carbonate, and hexenyl methyl carbonate furnished the coupling product in excellent yields (1.3.2 and 2.29). Similarly \( \alpha \)-allyl-\( \alpha \)-phenyl Meldrum’s acid was subjected to the optimized reaction conditions with allyl (2.30), hexenyl (2.32), \( \beta \)-phenyl allyl (2.33), and 4-methoxy-cinnamyl carbonate (2.34). In all the instances we observed the coupled product in high yields (70-85\%). Also \( \alpha \)-phenyl-\( \alpha \)-benzyl Meldrum’s acid furnished the desired product with five different allyl substrates (2.35 - 2.40). Notably minimal byproduct formation was observed. Next, we turned our attention towards the reactivity of \( \alpha, \alpha \)-dialkyl substituted Meldrum’s acid substrates.
Table 2.3 *One-pot, three-component DcA of benzylic enolates*

<table>
<thead>
<tr>
<th>Structure</th>
<th>Reaction</th>
<th>Yield</th>
</tr>
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<tbody>
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<td><img src="image" alt="Yield 1.3.2" /></td>
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<td><img src="image" alt="Structure Reaction" /></td>
<td><img src="image" alt="Yield 2.26" /></td>
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<tr>
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<td><img src="image" alt="Structure Reaction" /></td>
<td><img src="image" alt="Yield 2.29" /></td>
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<td><img src="image" alt="Yield 2.40" /></td>
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</table>
2.7 One-pot, three-component coupling of dialkyl enolates

Decarboxylative allylations of α-dialkyl ester enolate substrates are known to be difficult. In 1987, Tsuji and coworkers reported DcA of an α-butyl diallyl malonate substrate under harsh conditions. However they reported a 76% yield of the product and a 2% yield of protonated byproduct. Later Ohta and coworkers reported DcA for α-phenyl diallyl malonates but they could not achieve DcA for the α,α-dialkyl diallyl malonate substrates. Similar behavior was also observed throughout our investigation of DcA of α,α-dialkyl Meldrum’s acid substrates. For example, α-methyl-α-benzyl Meldrum’s acid under optimized reaction conditions afforded the product with low conversion (eq. 4). In lieu of this result we proceeded to optimize the reaction (Table 2.4).

First, α-methyl-α-benzyl Meldrum’s acid, lithium pyrrolide, and cinnamyl methyl carbonate were allowed to react with 10 mol% of Pd(PPh₃)₄ in 1,4-dioxane (entry 1). After overnight stirring at room temperature, 80% conversion was observed with a 3:1 ratio of desired product (2.42) to protonated byproduct (2.43). Lithium pyrrolides that are substituted at the 2, 5 positions with groups such as nitrile (entry 2), ethyl (entry 3), and methyl (entry 4) did not furnish the desired product. Almost no conversion was observed. Based on these results unsubstituted lithium pyrrolide stands as the best nucleophile for the three-component reaction. Several other catalyst systems were tested at room temperature and at slightly elevated temperatures. CpPd(allyl) and Pd₂dba₃ catalysts in the presence of dppf ligand at room temperature and at 40 °C only provided low conversions (50-67%) and high levels of protonation (entries 5 - 8). However the dppe ligand caused an increase in conversion to 71% and a decrease in protonation (entry 9). Lastly heating the reaction to 40 °C improved the conversion and product ratio (entry 10).
Next, large-scale reactions were pursued with the optimized conditions depicted in entry 10 (Table 2.5). Scaling up from small scale to large scale proved problematic. The first scaled up experiment gave an isolated yield of 47%, which contained a mixture of product and byproduct (2.43) in a 5 to 1 ratio. The reaction conditions, which include concentration, number of equivalents, temperature, reaction vessel, and source of solvent were maintained in both small and large-scale reactions. However the observed difference in conversion and product selectivity between small-scale and large-scale reactions cannot be exactly explained. Allyl methyl carbonate and α-methyl-α-benzyl Meldrum’s acid furnished 52% of
mixture of products (2.41). \( \alpha, \alpha \)-dimethyl Meldrum’s acid with cinnamyl methyl carbonate (2.43) and allyl methyl carbonate (2.44) furnished the products in lower yields. In these cases the byproduct was volatile.

Table 2.5 One-pot, three-component coupling of dialkyl enolates

```
\[
\text{\textscarce} R^1 \text{Li} + \text{\textscarce} R^2 \text{OCH}_3 \rightarrow \text{\textscarce} \text{O} + \text{\textscarce} \text{O} + \text{\textscarce} R^1 R^2 + \text{\textscarce} \text{O}
\]

\[
\begin{array}{c}
47\% (5:1) \\
52\% (6:1) \\
32\%
\end{array}
\]

However, under the optimized conditions, \( \alpha \)-methyl-\( \alpha \)-allyl Meldrum’s acid furnished the desired product in 40\% yield and a mixture of products (2.45) and the protonation byproduct could not be separated via vacuum or chromatographic methods.

2.8 Other nucleophiles in one-pot, three-component DcA

Attempted, but failed reactions with other nucleophiles in the three-component coupling reaction are shown in scheme 2.3.1. The ratios and the conversions are based on \(^1\text{H}\) NMR spectroscopic analysis of the crude reaction mixture. Lithium phenoxide and phenols furnished the protonated byproduct and/or low conversions at room and elevated temperatures (eq. 5 - 9). As shown in eq. 10 cyclohexanone protected \( \alpha, \alpha \)-dialkyl Meldrum’s acid was subjected to the standard reaction conditions to obtain a poor conversion (eq. 10). Interestingly lithium indolide afforded a mixture of desired product and protonated
byproduct as shown in eq. 11 and 12. However employing an external base with indole did not yield any product.

Scheme 2.3.1 Other nucleophiles in one-pot, three-component DcA

\[
\begin{align*}
\text{Scheme 2.3.1 Other nucleophiles in one-pot, three-component DcA} \\
\end{align*}
\]
2.9 Conclusion

In conclusion, we have developed a successful one-pot, three-component double decarboxylative allylation of benzylic enolates using less expensive and commercially available starting materials. The resulting acyl pyrrole products are important synthetic intermediates that can undergo further transformations without prior activation. Even though our attempts to employ dialkyl enolates were not fruitful due to inherent poor stability, the chemistry of benzylic enolates was successful.
2.10 References


2.11 Methodology and compound characterization

All reactions were run in flame-dried glassware under Argon atmosphere. Commercially available reagents and anhydrous benzene were used without further treatment. Compound purification was effected by flash chromatography using 230x400 mesh, 60Å porosity, silica obtained from Sorbent Technologies. The $^1$H and $^{13}$C NMR spectra were obtained on a Bruker Avance 400 or Bruker Avance 500 DRX spectrometer in CDCl$_3$ unless otherwise indicated and are referenced to the residual solvent peak CDCl$_3$ at $\delta$ 7.26 and $\delta$ 77.16 in $^1$H and $^{13}$C NMR respectively. Multiplicities are reported as follows: singlet (s), doublet (d), broad singlet (bs), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), multiplet (m). Structural assignments were based on $^1$H, $^{13}$C, DEPT-135, COSY, HSQC, and FT-IR spectroscopies. Mass spectrometry was run using ESI techniques. Lithium pyrrolide (section 1.5), substituted Meldrum’s acid$^{27,29}$ and allyl methyl carbonates$^{34}$ were synthesized according to the literature procedures.

Representative procedure for one-pot, three-component DcA:

**Synthesis of 2-methyl-2-phenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (1.3.2)**

\[
\begin{align*}
\text{Ph} & \quad \text{Li} \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}
\]

In a flame dried Schlenk tube, lithium pyrrolide (0.6 mmol, 44 mg, 1.2 eq.) was added to a solution of Meldrum’s acid (0.5 mmol, 117 mg, 1.0 eq.) and anhydrous 1,4-Dioxane (2.5 ml, 0.2 M). The reaction mixture was stirred for a minute. Then Pd(PPh$_3$)$_4$ (0.05 mmol, 58 mg, 10 mol%) and allyl methyl carbonate (0.6 mmol, 70 mg, 1.2 eq.) were added. After stirring overnight at room temperature, the solution was concentrated in vacuo and the crude material was purified via flash chromatography using
2% - 5% EtOAc and Hexane to obtain colorless oil (90% yield). Note - freshly prepared lithium pyrrolide and highly anhydrous conditions are required.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.28 (dt, \(J = 9.7, 1.9\) Hz, 2H), 7.23–7.15 (m, 3H), 6.92–6.87 (m, 2H), 5.97 (d, \(J = 2.4\) Hz, 2H), 5.48 (m, 1H), 4.99–4.94 (m, 1H), 4.88 (m, \(J = 17.0, 3.2, 1.4\) Hz, 1H), 2.81 (dd, \(J = 13.7, 8.0\) Hz, 1H), 2.71 (dd, \(J = 13.7, 6.6\) Hz, 1H), 1.60 (s, 3H)

\(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 172.7, 142.3, 132.1, 128.1, 126.2, 124.8, 119.6, 118.1, 110.8, 51.0, 44.0, 23.6

FT-IR (CH\(_2\)Cl\(_2\)) \(\nu\) max cm\(^{-1}\) 3020, 1704, 1494, 1465, 1213, 1155, 700, 503

Calcd. HRMS for C\(_{16}\)H\(_{17}\)NO (M+) – 239.1310, found 239.1245

![Chemical structure](image)

\((E)-2\)-methyl-2,5-diphenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (2.26)

The above representative procedure was followed to obtain colorless oil in 70% yield.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.38–7.34 (m, 2H), 7.31–7.20 (m, 7H), 7.19–7.15 (m, 1H), 6.99–6.95 (m, 2H), 6.24 (d, \(J = 15.8\) Hz, 1H), 6.06–6.03 (m, 2H), 5.96–5.88 (m, 1H), 3.03–2.96 (m, 1H), 2.90 (m, 1H), 1.72 (s, 3H)

\(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 173.8, 143.3, 137.3, 134.1, 129.2, 128.5, 127.3, 126.2, 125.9, 124.9, 120.7, 111.9, 52.5, 44.6, 24.5

FT-IR (CH\(_2\)Cl\(_2\)) \(\nu\) max cm\(^{-1}\) 3020, 2364, 1703, 1467, 1290, 1099, 970, 744, 696, 597

Calcd. HRMS for C\(_{22}\)H\(_{22}\)NO (M+H) – 316.1701, found 316.1681
(E)-2-methyl-2-phenyl-1-(1H-pyrrol-1-yl)oct-4-en-1-one (2.29)

The above representative procedure was followed to obtain colorless oil in 92% yield.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37–7.30 (2 H, m), 7.28–7.18 (9 H, m), 6.99–6.89 (2 H, m), 6.04–5.96 (2 H, m), 5.33–5.07 (2 H, m), 2.83 (1 H, dd, $J = 13.6$, 7.8), 2.70 (1 H, dd, $J = 13.0$, 6.1), 1.86 (2 H, dt, $J = 7.4$, 3.8), 1.62 (3 H, s), 1.26 (2 H, dt, $J = 14.6$, 7.4), 0.80 (3 H, t, $J = 7.4$)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.9, 144.0, 135.6, 129.3, 127.3, 125.9, 124.4, 120.8, 111.9, 52.7, 43.7, 34.9, 25.4, 22.7, 13.8

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 2948, 2366, 1704, 1463, 1286, 1093, 964, 742, 700

Calcd. HRMS for C$_{19}$H$_{23}$NO (M+) – 281.1780, found 281.1741

2-allyl-2-phenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (2.30)

The above representative procedure was followed to obtain colorless oil in 70% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.35 (2 H, t, $J = 7.5$), 7.27 (1 H, dd, $J = 10.5$, 4.3), 7.21 (2 H, dd, $J = 8.3$, 1.1), 6.93 (2 H, s), 6.06–5.99 (2 H, m), 5.55–5.39 (2 H, m), 5.08–4.99 (2 H, m), 4.91 (2 H, dd, $J = 17.0$, 1.2), 2.86 (4 H, d, $J = 7.3$)
\[^1^3\text{C} \text{NMR} \text{ (126 MHz, CDCl}_3\text{)} \, \delta \text{ } 172.9, 142.0, 132.7, 129.3, 127.7, 126.5, 120.6, 119.7, 112.1, 55.8, 40.3\]

\[\text{FT-IR (CH}_2\text{Cl}_2\text{)} \, \nu_{\text{max}} \text{ cm}^{-1} 3072, 2351, 1703, 1463, 1325, 1282, 1101, 921, 740, 696\]

Calcd. HRMS for C\(_{18}\)H\(_{20}\)NO (M+H) – 266.1545, found 266.1500

\[
\begin{array}{c}
\text{Ph} \quad O \\
\text{Ph} \quad \text{Ph} \\
\end{array}
\]

\(\text{(E)-2-allyl-2,5-diphenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (2.31)}\)

The above representative procedure was followed to obtain colorless oil in 83% yield.

\[^1^H \text{NMR} \text{ (500 MHz, CDCl}_3\text{)} \, \delta \text{ } 7.38 \text{ (2 H, dd, } J = 10.3, 4.7\text{), } 7.33-7.28 \text{ (1 H, m), } 7.27-7.22 \text{ (4 H, m), } 7.22-7.16 \text{ (3 H, m), } 6.95 \text{ (2 H, s), } 6.22 \text{ (1 H, d, } J = 15.8\text{), } 6.07-6.02 \text{ (2 H, m), } 5.85-5.76 \text{ (1 H, m), } 5.54 \text{ (1 H, m), } 5.09-5.05 \text{ (1 H, m), } 4.95 \text{ (1 H, dd, } J = 17.0, 1.7\text{), } 3.04-2.98 \text{ (2 H, m), } 2.92 \text{ (2 H, d, } J = 7.7\text{)}\]

\[^1^3\text{C} \text{NMR} \text{ (126 MHz, CDCl}_3\text{)} \, \delta \text{ } 172.9, 142.1, 137.4, 134.5, 132.7, 129.4, 128.7, 127.7, 127.5, 126.5, 126.4, 124.3, 120.7, 119.7, 112.1, 56.2, 40.4, 39.8\]

\[\text{FT-IR (CH}_2\text{Cl}_2\text{)} \, \nu_{\text{max}} \text{ cm}^{-1} 3028, 1706, 1460, 1294, 1097, 970, 748, 694\]

Calcd. HRMS for C\(_{24}\)H\(_{24}\)NO (M+H) – 342.1858, found 342.1837
(E)-2-allyl-2-phenyl-1-(1H-pyrrol-1-yl)oct-4-en-1-one (2.32)

The above representative procedure was followed to obtain colorless oil in 85% yield.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.31–7.24 (2 H, m), 7.22–7.17 (1 H, m), 7.13 (2 H, dt, $J$ = 8.4, 1.8), 6.87 (2 H, s), 5.97–5.92 (2 H, m), 5.37 (1 H, m), 5.19 (1 H, dt, $J$ = 15.0, 6.8), 5.03 (1 H, m), 4.97–4.93 (1 H, m), 4.85 (1 H, m), 2.77 (3 H, dd, $J$ = 17.0, 7.4), 1.81 (2 H, q, $J$ = 7.1), 1.28–1.14 (2 H, m), 0.75 (3 H, t, $J$ = 7.4)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.0, 142.3, 135.9, 132.9, 129.2, 127.5, 126.5, 123.6, 120.6, 119.4, 111.9, 56.0, 40.7, 38.8, 34.9, 22.7, 13.8

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 2958, 1704, 1461, 1292, 1101, 970, 746, 700

Calcd. HRMS for C$_{21}$H$_{26}$NO (M+H) – 308.2014, found 308.2000

2-allyl-2,4-diphenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (2.33)

The above representative procedure was followed to obtain colorless oil in 83% yield.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.24 (3 H, d, $J$ = 14.8), 7.20–7.15 (1 H, m), 7.15–7.08 (6 H, m), 6.80 (2 H, s), 5.97–5.92 (2 H, m), 5.48–5.29 (1 H, m), 5.10 (1 H, d, $J$ = 1.6), 4.93–4.86 (1 H, m), 4.67 (1 H, d, $J$ = 0.8), 4.55 (1 H, m), 3.35 (2 H, dt, $J$ = 43.4, 10.6), 2.84–2.66 (2 H, m)
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 172.7, 145.2, 142.6, 142.2, 132.7, 129.0, 128.1, 127.5, 127.2, 126.8, 120.6, 119.6, 112.0, 56.7, 40.7, 40.1

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3089, 2372, 1697, 1471, 1288, 1101, 904, 742, 698

Calcd. HRMS for C$_{24}$H$_{23}$NONa (M+Na) – 364.1677, found 364.1697

![Image](image_url)

(E)-2-allyl-5-(4-methoxyphenyl)-2-phenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (2.34)

The above representative procedure was followed to obtain colorless oil in 74% yield.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 (2 H, t, $J$ = 7.5), 7.29 (1 H, dd, $J$ = 8.4, 6.2), 7.24 (2 H, dd, $J$ = 5.5, 3.1), 7.16–7.11 (2 H, m), 6.95 (2 H, s), 6.83–6.74 (2 H, m), 6.15 (1 H, d, $J$ = 15.8), 6.06–6.00 (2 H, m), 5.66 (1 H, dt, $J$ = 15.4, 7.5), 5.53 (1 H, m), 5.06 (1 H, dd, $J$ = 10.2, 1.4), 4.94 (1 H, dd, $J$ = 17.0, 1.4), 3.77 (3 H, s), 3.04–2.94 (2 H, m), 2.94–2.85 (2 H, m)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 172.9, 159.2, 142.2, 133.9, 132.8, 130.3, 129.3, 127.7, 127.5, 126.6, 121.9, 120.7, 119.7, 114.1, 112.1, 56.3, 55.5, 40.4, 39.8

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 2945, 2354, 1701, 1606, 1512, 1463, 1290, 1249, 1170, 1101, 1031, 966, 740, 703

Calcd. HRMS for C$_{25}$H$_{26}$NO$_2$ (M+H) – 372.1964, found 372.1952
The above representative procedure was followed to obtain colorless oil in 86% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.34–7.26 (3 H, m), 7.16–7.06 (5 H, m), 6.97 (2 H, s), 6.60–6.54 (2 H, m), 6.07–6.04 (2 H, m), 5.69 (1 H, m), 5.15–5.08 (1 H, m), 4.95 (1 H, dd, $J$ = 17.0, 1.8), 3.47 (1 H, d, $J$ = 13.5), 3.35 (1 H, d, $J$ = 13.5), 2.81 (2 H, d, $J$ = 7.1)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 172.8, 142.1, 136.3, 132.9, 130.8, 129.2, 128.0, 127.7, 126.9, 126.9, 120.8, 119.9, 112.2, 57.2, 42.2, 39.3

FT-IR (CH$_2$Cl$_2$) $v_{\text{max}}$ cm$^{-1}$ 3028, 2364, 1701, 1463, 1284, 1101, 1074, 887, 734, 694

Calcd. HRMS for C$_{22}$H$_{22}$NO (M+H) – 316.1701, found 316.1697

The above representative procedure was followed to obtain colorless oil in 79% yield.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37–7.28 (4 H, m), 7.28–7.20 (9 H, m), 7.20–7.08 (6 H, m), 6.98 (2 H, s), 6.63 (2 H, dd, $J$ = 7.8, 1.3), 6.21 (1 H, d, $J$ = 15.8), 6.09–6.06 (2 H, m), 6.06–5.97 (1 H, m), 3.52 (1 H, d, $J$ = 13.5), 3.40 (1 H, d, $J$ = 13.5), 2.94 (2 H, d, $J$ = 7.1)

114
\[^{13}\text{C} \text{ NMR (}126 \text{ MHz, CDCl}_3\text{)} \delta 172.8, 142.1, 137.4, 136.3, 134.8, 130.8, 129.3, 128.7, 128.1, 127.8, 127.6, 126.9, 126.4, 124.5, 120.8, 112.3, 57.6, 42.3, 38.8 \]

\[
\text{FT-IR (CH}_2\text{Cl}_2\text{)} \nu_{\text{max}} \text{ cm}^{-1} 3024, 2354, 1704, 1465, 1290, 1078, 744, 696
\]

Calcd. HRMS for C\(_{28}\)H\(_{26}\)NO (M+H) – 392.2014, found 392.2013

\[
\text{(E)-2-benzyl-2-phenyl-1-(1H-pyrrol-1-yl)oct-4-en-1-one (2.37)}
\]

The above representative procedure was followed to obtain colorless oil in 90% yield.

\[^1\text{H} \text{ NMR (}500 \text{ MHz, CDCl}_3\text{)} \delta 7.32–7.25 (3 \text{ H, m}), 7.15–7.10 (1 \text{ H, m}), 7.10–7.04 (4 \text{ H, m}), 6.95 (2 \text{ H, s}), 6.58–6.53 (2 \text{ H, m}), 6.06–6.01 (2 \text{ H, m}), 5.39–5.30 (1 \text{ H, m}), 5.30–5.20 (1 \text{ H, m}), 3.44 (1 \text{ H, d, } J = 13.5), 3.31 (1 \text{ H, d, } J = 13.4), 2.74 (2 \text{ H, d, } J = 6.8), 1.91 (2 \text{ H, q, } J = 6.8), 1.33–1.23 (2 \text{ H, m}), 0.83 (3 \text{ H, t, } J = 7.4)
\]

\[^{13}\text{C} \text{ NMR (}126 \text{ MHz, CDCl}_3\text{)} \delta 173.0, 142.3, 136.5, 136.2, 130.9, 129.1, 127.9, 127.6, 127.0, 126.7, 123.8, 120.8, 112.1, 57.5, 42.5, 37.8, 35.1, 22.8, 13.8
\]

\[
\text{FT-IR (CH}_2\text{Cl}_2\text{)} \nu_{\text{max}} \text{ cm}^{-1} 2962, 2360, 1703, 1460, 1286, 1108, 970, 744, 692
\]

Calcd. HRMS for C\(_{25}\)H\(_{28}\)NO (M+H) – 358.2171, found 358.2160
2-benzyl-2,4-diphenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (2.38)

The above representative procedure was followed to obtain colorless oil in 86% yield.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.22–7.12 (8 H, m), 7.09–7.01 (3 H, m), 6.98 (2 H, t, $J$ = 7.5), 6.84 (2 H, s), 6.43 (2 H, d, $J$ = 7.4), 6.00–5.95 (2 H, m), 5.19 (1 H, d, $J$ = 1.3), 4.89 (1 H, d, $J$ = 0.9), 3.44 (1 H, d, $J$ = 13.6), 3.41–3.33 (2 H, m), 3.23 (1 H, d, $J$ = 13.6)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.4, 145.3, 143.1, 141.9, 136.4, 130.9, 128.7, 128.0, 127.4, 127.0, 126.8, 126.4, 120.7, 119.2, 111.9, 57.7, 40.8

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3058, 2368, 1703, 1596, 1463, 1290, 1101, 898, 742, 696

Calcd. HRMS for C$_{29}$H$_{26}$NO (M+H) – 392.2014, found 392.2013

(E)-2-benzyl-5-(4-nitrophenyl)-2-phenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (2.39)

The above representative procedure was followed to obtain colorless oil in 86% yield.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.20–8.08 (2 H, m), 7.35 (5 H, dd, $J$ = 16.4, 8.1), 7.15 (5 H, dd, $J$ = 15.6, 7.6), 6.98 (2 H, s), 6.62 (2 H, d, $J$ = 6.7), 6.22 (2 H, s), 6.10 (2 H, d, $J$ = 1.9), 3.55 (1 H, d, $J$ = 13.5), 3.41 (1 H, d, $J$ = 13.6), 3.11–2.98 (1 H, m), 2.98–2.87 (1 H, m)
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 172.5, 147.0, 143.7, 141.7, 135.9, 132.8, 130.6, 130.1, 129.4, 128.3, 128.0, 127.2, 126.9, 126.9, 124.2, 120.8, 112.6, 57.7, 42.6, 39.4

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3072, 2351, 3062, 2360, 1778, 1739, 1706, 1598, 1514, 1340, 1280, 1076, 1035, 948, 744, 700

Calcd. HRMS for C$_{28}$H$_{25}$N$_2$O$_3$ (M+H) – 437.1865, found 437.1827

\[ \text{PhO} \]
\[ \text{N} \]
\[ \text{OCH}_3 \]

\[ \text{(E)-2-benzyl-5-(4-methoxyphenyl)-2-phenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (2.40)} \]

The above representative procedure was followed to obtain colorless oil in 93% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.39–7.26 (3 H, m), 7.22–7.09 (7 H, m), 6.98 (2 H, s), 6.87–6.77 (2 H, m), 6.65–6.59 (2 H, m), 6.15 (1 H, d, $J = 15.8$), 6.10–6.05 (2 H, m), 5.94–5.82 (1 H, m), 3.78 (3 H, s), 3.51 (1 H, d, $J = 13.5$), 3.40 (1 H, d, $J = 13.5$), 2.93 (2 H, d, $J = 7.2$)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 172.9, 159.3, 142.2, 136.3, 134.1, 130.8, 130.3, 129.2, 128.0, 127.8, 127.5, 126.9, 122.1, 120.8, 114.1, 112.2, 57.6, 55.5, 42.4, 38.7

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3037, 2354, 1703, 1604, 1512, 1471, 1290, 1249, 1176, 1035, 966, 744, 702

Calcd. HRMS for C$_{29}$H$_{28}$NO$_2$ (M+H) – 422.2120, found 422.2118
2-benzyl-2-methyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (2.41)

The above representative procedure was followed with 5 mol% Pd$_2$dba$_3$ and 13 mol% of dppe at 40 °C to obtain colorless oil in 52% yield (6:1).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.50–7.48 (2 H, m), 7.20–7.16 (3 H, m), 6.91 (2 H, dd, $J$ = 7.0, 2.1), 6.29 (2 H, dd, $J$ = 3.4, 1.3), 6.26–6.24 (byp, m), 5.80–5.64 (1 H, m), 5.10–4.98 (2 H, m), 3.39–3.33 (byp, m), 3.29 (1 H, d, $J$ = 13.7), 3.22–3.12 (1 H, m), 2.99 (1 H, d, $J$ =13.8), 2.82 (1 H, dd, $J$ = 14.1, 6.9), 2.78–2.72 (byp, m), 2.37 (1 H, dd, $J$ = 14.3, 7.7), 1.34 (3 H, s), 1.29 (byp, d, $J$ = 6.9)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.9, 136.7, 133.1, 130.2, 129.2, 128.7, 128.5, 127.1, 126.8, 120.7, 119.4, 119.2, 113.4, 112.5, 49.8, 45.6, 44.1, 40.7, 39.9, 23.7, 17.9

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 2933, 2351, 1701, 1463, 1288, 1261, 1101, 1076, 889, 742

Calcd. HRMS for C$_{17}$H$_{20}$NO (M+H) – 254.1545, found 254.1520

(E)-2-benzyl-2-methyl-5-phenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (2.42)

The above representative procedure was followed with 5 mol% Pd$_2$dba$_3$ and 13 mol% of dppe at 40 °C to obtain colorless oil in 47% yield (5:1).
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.54–7.49 (2 H, m), 7.27–7.24 (5 H + CDCl\(_3\), m), 7.22–7.15 (5 H, m), 6.97–6.90 (2 H, m), 6.38–6.23 (3 H, m), 6.15–6.05 (1 H, m), 3.38–3.27 (1 H + byp α-H, m), 3.17 (byp benzylic H, dd, \(J = 13.8, 6.7\)), 3.06 (1 H, d, \(J = 13.8\)), 2.97 (1 H, dd, \(J = 14.2, 6.8\)), 2.76 (byp benzylic H, dd, \(J = 13.6, 7.6\)), 2.50 (1 H, dd, \(J = 14.2, 8.1\)), 1.40 (3 H, s), 1.29 (byp, d, \(J = 6.9\))

\(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 173.9, 139.1, 137.3, 136.7, 134.3, 130.2, 129.2, 128.7, 128.7, 128.5, 127.6, 127.1, 126.8, 126.4, 124.8, 120.7, 119.2, 113.4, 112.6, 50.1, 45.8, 43.3, 40.7, 39.9, 23.8, 17.9

FT-IR (CH\(_2\)Cl\(_2\)) \(\nu_{\text{max}}\) cm\(^{-1}\) 2930, 2349, 1699, 1460, 1277, 1259, 1101, 1067, 890, 740

Calcd. HRMS for C\(_{23}\)H\(_{24}\)NO (M+H) – 330.1858 found 330.1865

The above representative procedure was followed with 5 mol% Pd\(_2\)dba\(_3\) and 13 mol% of dppe at 40 °C to obtain colorless oil in 47% yield (5:1).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.23 (2 H, d, \(J = 4.3\)), 7.21 (1 H, s), 7.19–7.11 (1 H, m), 6.30 (1 H, d, \(J = 15.7\)), 6.26–6.24 (byp, H, m), 6.24–6.22 (2 H, m), 6.08 (1 H, dd, \(J = 15.4, 7.8\)), 2.65 (2 H, dd, \(J = 7.5, 1.2\)), 1.44 (6 H, s)

\(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 175.1, 137.3, 133.9, 129.2, 128.6, 128.4, 128.2, 127.5, 127.2, 126.5, 125.1, 120.8, 118.4, 112.2, 56.9, 44.8, 26.5, 24.1

Calcd. HRMS for C\(_{17}\)H\(_{18}\)NO (M-H) – 252.1388 found 252.1325
2,2-dimethyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (2.44)

The above representative procedure was followed with 5 mol% Pd$_2$dba$_3$ and 13 mol% of dppe at 40 °C to obtain colorless oil in 28% yield.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.45-7.36 (2 H, m), 6.27-6.20 (2 H, m), 5.78-5.63 (1 H, m), 5.12-4.92 (2 H, m), 2.53 (2 H, d, $J$ = 7.3), 1.41 (6 H, d, $J$ = 1.3)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.9, 132.1, 119.4, 117.7, 110.9, 44.4, 43.3, 25.3

2-allyl-2-methyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (2.45)

The above representative procedure was followed with 5 mol% Pd$_2$dba$_3$ and 13 mol% of dppe at 40 °C to obtain colorless oil in 40% yield (2.5:1).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.46-7.43 (m, 2H), 7.37-7.31 (m, 1H), 6.33-6.29 (m, 1H), 6.29-6.24 (m, 2H), 5.81-5.65 (m, 2H), 5.14-4.97 (m, 5H), 2.68 (m, 2H), 2.63-2.54 (m, byp), 2.46 (m, 2H), 2.33-2.20 (m, 1H), 1.40 (s, 3H), 1.30 (d, $J$ = 6.9 Hz, 1H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 174.1, 173.9, 173.8, 134.9, 132.9, 120.5, 119.2, 117.7, 113.3, 112.2, 48.3, 43.6, 38.4, 38.0, 29.8, 23.6, 17.5
Chapter 3

One-pot, Four-component Interceptive DeA of Ester Enolate Equivalents
3.1 A brief introduction to four-component reactions

Four-component reactions are capable of condensing four reactive components into a complex product in a single reaction. The time and resource effectiveness of these reactions have attracted many synthetic organic chemists to employ them in library synthesis. The Ugi reaction, named after Ivar Karl Ugi, is one of the well-known four component coupling reactions.\(^1\)\(^-\)\(^4\) In a single reaction vessel, a ketone or an aldehyde, an amine, an isocyanide, and a carboxylic acid react in a sequence of elementary reactions such as imine formation, nucleophilic addition, and Mumm rearrangement\(^5\) to produce a bis-amide product.\(^1\)\(^-\)\(^4\) New combinations of Ugi reactions and other known reactions are also reported. Ugi-Diels-Alder,\(^6\) Ugi-Smiles,\(^7\) Ugi-Buchwald-Hartwig,\(^8\) and Ugi-Heck\(^9\) are few of them. Asinger,\(^10,11\) Reissert-Ugi,\(^12,14\) and Bucherer-Bergs\(^15\) reactions are other known reactions that use isonitrile as one of the four components. Transition metal catalysis is incorporated into the four-component reactions through Buchwald-Hartwig or Heck coupling reactions. Therefore we were interested in developing a method to incorporate DcA chemistry into four-component reaction. Herein we report the development of a one-pot, four-component decarboxylative allylation reaction via tandem Michael addition and allylation reactions.

3.2 One-pot, four-component interceptive DcA of ester enolate equivalents

In chapter 2 we disclosed the development of a one-pot, three-component DcA reaction, where \textit{in situ} generated \(\beta\)-oxo carboxylates underwent decarboxylation and allylation to afford the desired acyl pyrrole products (Scheme 3.2, eq. 1). In this chapter we will discuss the interception of the three-component DcA reaction with a Michael acceptor. A possible mechanistic pathway for the four-component DcA reaction is shown in Scheme 3.2. Simultaneous formation of Pd \(\pi\)-allyl complex and \(\beta\)-oxo carboxylate are the starting points of the reaction sequence. Oxidative addition, facilitated by coordination of the palladium catalyst to the alkene followed by expulsion of the leaving group forms the Pd \(\pi\)-allyl complex.
Scheme 3.1 *Multi-component DcA*

\[
\begin{align*}
\text{R}_1 \text{Ph} & \quad \text{CN} \quad \text{CN} \\
\quad & \quad \text{NC} \quad \text{cn} \\
\quad & \quad \text{Pd(0)} \\
\quad & \quad \text{Pd(0)} \\
\end{align*}
\]

Scheme 3.2 *A Possible mechanism for the four-component IDcA*

Nucleophilic attack of lithium pyrrolide on the C4 or C6 positions of Meldrum’s acid generates β-oxo carboxylate (2.20) via acetone exclusion. Palladium-catalyzed decarboxylation of β-oxo carboxylate generates the amide enolate (2.21) and the subsequent Michael addition of the enolate forms the second
nucleophilic species (3.1). Importantly, electron poor dienophiles such as benzylidene malononitrile have a higher electrophilicity than Pd π-allyl complexes.\textsuperscript{16–18} Hence we presumed that the enolate (2.21) would undergo Michael addition to form intermediate 3.1 rather than allylation.

### 3.3 Background of interceptive decarboxylative allylation (IDcA)

In 1989, Tsuji and co-workers reported the synthesis of spiro[4.4]nonanones via palladium-catalyzed intramolecular Michael addition of ketone enolates to tethered enones (Scheme 3.3).\textsuperscript{19} In the course of study 2-allyloxyacarbonylcyclopentanone (3.3), which has both a Michael acceptor and the pro-nucleophile tethered in to the same molecule, was subjected to decarboxylative coupling conditions. The reaction was expected to proceed via decarboxylative π-allyl-enolate formation (A) followed by Michael addition to the enone (B). The newly formed enolate would (B) then undergo allylation to furnish the desired spirocyclic product (3.8). However, along with the desired intercepted product (3.8) a mixture of byproducts was observed.

**Scheme 3.3 Interceptive decarboxylative allylation of ketone enolates**

![Scheme 3.3](image)

Protonation, allylation and dehydrogenation of the enolate intermediate A furnished the byproducts 3.4, 3.5, and 3.6,\textsuperscript{20,21} while the Michael addition followed by protonation and β-hydride elimination of
palladium enolate B furnished the byproducts 3.7 and 3.9. The desired product (3.8) is formed by tandem Michael addition and allylation of Pd π-allyl enolate intermediate B. The ratios of the products varied according to the reaction conditions (Table 3.1).

Table 3.1 Reaction conditions for Interceptive DcA

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd (mol%)</th>
<th>R</th>
<th>solvent</th>
<th>temp. °C</th>
<th>3.4</th>
<th>3.5</th>
<th>3.6</th>
<th>3.7</th>
<th>3.8</th>
<th>3.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)₂(5), PPh₃(10)</td>
<td>H</td>
<td>THF</td>
<td>40</td>
<td>7</td>
<td>-</td>
<td>4</td>
<td>65</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂(5), PPh₃(10)</td>
<td>H</td>
<td>THF</td>
<td>80</td>
<td>5</td>
<td>12</td>
<td>-</td>
<td>16</td>
<td>46</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh₃)₄(7)</td>
<td>H</td>
<td>THF</td>
<td>rt</td>
<td>-</td>
<td>31</td>
<td>-</td>
<td>16</td>
<td>31</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh₃)₄(7)</td>
<td>H</td>
<td>MeCN</td>
<td>rt</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>84</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh₃)₄(2)</td>
<td>H</td>
<td>THF</td>
<td>80</td>
<td>-</td>
<td>22</td>
<td>-</td>
<td>18</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Pd(PPh₃)₄(7)</td>
<td>Me</td>
<td>THF</td>
<td>80</td>
<td>-</td>
<td>6</td>
<td>-</td>
<td>13</td>
<td>65</td>
<td>-</td>
</tr>
</tbody>
</table>

During the catalyst screening, they found that Pd(OAc)₂ and PPh₃ ligand facilitated the tandem Michael-allylation reaction in low yields (entries 1 and 2). Changing the catalyst to Pd(PPh₃)₄ increased the yield of desired product (3.8) up to 31%. However, the same amount of the protonated product was also observed (entry 3). The presence of acetic acid in the reaction mixture would be a possible reason for the formation of protonated byproduct in Pd(OAc)₂ and PPh₃ catalyst system. Reaction in acetonitrile furnished only the Michael-protonation byproduct (entry 4). Raising the temperature to 80 °C increased the yield up to 48% (entry 5) and a methyl substituted allyl substrate furnished the desired product in 65% yield. Even though the yields are modest, Tsuji and co-workers revealed an interesting concept in allylation chemistry, which has been further explored by several other research groups.

A decade after Tsuji’s first report, Yamamoto resurfaced the interceptive allylation chemistry by utilizing benzyldiene and furylmethylidene malononitrile derivatives as Michael acceptors in an intermolecular β-acetonation reaction (eq. 3).²²
The reaction proceeded in the presence of a catalytic amount of \( \text{Pd(PPh}_3\text{)}_4 \) in THF under ambient conditions. Several electron deficient Michael acceptors were tested and revealed that activated olefins bearing two nitrile groups (3.10) are most effective in the tandem addition-allylation reactions. Olefins (3.11), which have nitrile and carboxy ethyl ester groups as electron withdrawing groups furnished the desired product along with a minute formation of Michael addition-protonation product. Furthermore they have reported that other olefins such as ethyl acrylates (3.12) diethyl malonates (3.13) and simple olefins (3.14) were not able to furnish the desired product. The most plausible explanation for the difference in reactivity of these olefins is the concept of ‘steric inhibition of resonance’ proposed by Boeckman.\(^{22,23}\)

The cyano group, which is small and axially symmetric, has the ability to be in plane with the olefin \( \pi \)-system exerting an effect upon the LUMO energy level. Having no rotational requirement for overlap itself, it provides much less disruption for the ester overlap (3.11). However when two ester groups are introduced, steric interactions are such that they are not often both in plane with the olefin. Michael acceptors with two nitrile groups (3.10), where both groups contribute to the reduction of LUMO energy, are most effective in interceptive allylation chemistry. Scheme 3.4 shows the substrate scope of the tandem Michael addition-allylation reaction. Benzyldiene- (3.41), furylidene- (3.15), 3-methoxy benzyldiene (3.16), and naphthyledene (3.17) malononitriles worked well under the decarboxylative conditions giving good yields (69-91%) after <5 hours at room temperature. However benzyldiene cyano-acrylates required longer reaction times (15-24 h) and furnished the Michael-allylation adduct in 63% yield and the simple Michael adduct in 25% yield.
The reported chemistry was limited to (arylidene)malononitriles because they could not isolate (alkylmethylidene)malononitriles in acceptable yields. Therefore a one pot three component reaction with alkyl aldehyde, malononitrile and allyl acetoacetate was designed, so that the \textit{in situ} formed (alkylmethylidene)malononitrile can be used in the next step without isolation. Under the palladium-catalyzed conditions, cyclohexenecarbaldehyde, isobutyraldehyde, and \textit{n}-hexenaldehyde furnished the desired product in 74\%, 63\% and 48\% yields respectively. The mechanism proposed by Yamamoto and co-workers, is shown in Scheme 3.5, where oxidative addition, decarboxylation, Michael addition and allylation occur in a sequence. According to the proposed mechanism, decarboxylation of \(\beta\)-keto carboxylate (A) occurs right after the oxidative addition to produce intermediate palladium enolates (B-E). However Tunge and co-workers propose an alternative mechanism (Scheme 3.5, right) for the IDcA reaction based on their observation of growth and disappearance of carboxylic acid for \(\alpha\)-unsubstituted substrates.\textsuperscript{24,25} According to the proposed mechanism oxidative addition, enolate formation by proton transfer, Michael addition, and allylation occur prior to the decarboxylation.
In 2005, Tunge and co-workers reported the ruthenium-catalyzed interceptive decarboxylative allylation of ketone enolates.\textsuperscript{26} Benzyldiene malononitriles and the Knoevenagel adduct of benzaldehyde and Meldrum’s acid underwent tandem Michael addition-allylation with allyl $\beta$-keto esters (Scheme 3.6). During the investigation, they observed that benzyldiene malononitrile ($E = -9.42$)\textsuperscript{16} and benzyldiene malononitriles with a $p$-acetyl substituent underwent smooth IDcA to furnish the three-component product (3.21, and 3.22), while $p$-hydroxybenzylidene malononitrile ($E \sim -10.8$)\textsuperscript{16} furnished only the simple allylation product. This indicates that the substituent on phenyl group plays a major role in the electronics of the Michael acceptor. In addition, they have shown that Meldrum’s acid adduct (3.23) and $\alpha$-cyanocoumarin (3.24) are sufficiently electrophilic ($E > -10$) to intercept the allylation. An interesting observation was made when ruthenium catalyzed conditions furnished the branched product (3.25) in 89% yield, while palladium catalyzed conditions selectively formed the linear product in 80% yield, demonstrating the catalyst-controlled regioselectivity of the reaction.\textsuperscript{27–30}
Scheme 3.6 IDcA of allyl β-keto esters

Enantioselective interceptive decarboxylative allylation is an interesting process to construct quaternary stereocenters via α-functionalization. In 2010, Stoltz and co-workers reported the asymmetric, palladium-catalyzed tandem Michael addition-allylation reaction of keto enolates (Table 3.2). Table 3.2 illustrates the substrate scope of the reaction. In the study, cyclic β-ketoesters (cyclohexanone and piperidinone) and benzylidene malononitriles were subjected to asymmetric decarboxylative conditions. Interestingly they observed moderate diastereoselectivities and good to excellent enantioselectivities. Asymmetric transformation tolerated the small alkyl groups such as methyl (entry 1), ethyl (entry 2), benzyl (entry 3) and small alkyl chains (entry 4) in the α-position, however they observed a reduction in yield with benzyl and small alkyl chains due to enolate allylation (entries 3 and 4). Electron rich benzylidene malononitriles (entries 6-8) caused a reduction in overall yield.
Also, α-cyanoacetates and Meldrum’s acid adducts caused a reduction of yield and selectivity under the reaction conditions. Alkylidene Michael acceptors proved to be ineffective in the reaction and only furnished enolate allylation product. In addition to cyclohexanone, piperidinone substrates furnished three component coupling product in high selectivity (entry 5).

The proposed mechanistic rationale for the asymmetric IDcA is shown in Scheme 3.7. It proposes that in the first step, the oxidative addition of the chiral palladium catalyst to the β-keto allylic substrate and decarboxylation generates allyl Pd-enolate intermediate A. The chiral environment of intermediate A allows one of the enolate faces (re or si) to react with the Michael adduct to generate intermediate B, the second nucleophilic species and a π-allyl palladium complex. A chiral non-racemic PHOX ligand provides the facial selectivity of the π-allyl palladium complex. The nucleophilic attack of intermediate B on π-allyl palladium complex generates the desired product.
Arylidene malononitriles have been used to intercept the palladium catalyzed decarboxylative allylation reactions of keto enolates (as we already discussed above) as well as other palladium-catalyzed nucleophilic allylation reactions.

In 2009, Churma and co-workers reported the interceptive tandem Michael addition-allylation reactions of 2-azaallyl anions\textsuperscript{33} as an extension to their previous study on decarboxylative allylations of the same anion.\textsuperscript{34} In the course of their study, diphenylglycinate imines and benzylidene malononitriles were subjected to palladium-catalyzed reaction conditions and quantitative formation of intercepted product was observed albeit with no diastereoselectivity (Scheme 3.8). A range of imines and benzylidene malononitriles were tested under the standard conditions. The results demonstrate that the interceptive DcA reaction proceeds smoothly with imines and benzylidene malononitriles with electron withdrawing aryl groups (3.26). Michael acceptors (3.27 and 3.28) and imines (3.29) with electron rich aryl groups caused lower yields. In addition, the regioisomeric allylation product (3.31) was also observed with substrates with electron rich aryl substituent on the azaallyl anion intermediate (3.29). The homo allylic imine byproduct 3.30 was barely detected with arylidene malononitrile substrates. However an alkylidene
malononitrile with $t$-butyl group (i.e. $R_2 = t$-butyl) led to the formation of byproduct 3.30 via non-interceptive decarboxylative allylation. The proposed catalytic cycle is shown in Scheme 3.9.

Scheme 3.8 Interceptive DcA of imines with benzylidene malononitriles

According to the proposed mechanism by Churma and co-workers, the oxidative addition of the palladium catalyst to the C–O bond generates intermediate A and this intermediate then undergoes decarboxylation to generate $N$-ligated 2-azaallyl Pd(II) intermediate B. Michael addition of the intermediate B leads to the formation of a second palladacycle, which generates the desired product via reductive elimination. Two other side reactions are possible with the intermediate B. It could undergo simple allylation to furnish the byproduct 3.30. Alternatively, it could be protonated, however protonation of the intermediate B was not observed even in the presence of H$_2$O. Based on this observation, Churma and co-workers suggest that protonation is prevented by the tight coordination of $\alpha$-amino anion to the metal center in the intermediate B.
Scheme 3.9 *Interceptive decarboxylative allylation of imino esters- proposed mechanism*

Scheme 3.10 *IDcA of nitrogen based nucleophiles*

**Tunze**

\[
\text{TsN} - \text{O} + \text{NC} - \text{CN} \xrightarrow{5 \text{ mol}\% \text{ Pd}^{2+} \text{db}a_3} \text{N} - \text{Ph} \text{CN} - \text{CN} \xrightarrow{11 \text{ mol}\% \text{ Anden-Ph} \text{ Trost ligand}} \text{DCl, rt} \rightarrow \text{TsN} - \text{Ph} \text{CN} - \text{CN}
\]

90%, >99:1 dr, 99% ee

**Tunze**

\[
\text{TsN} - \text{O} + \text{NC} - \text{CN} \xrightarrow{5 \text{ mol}\% \text{ Pd(PPh}_3)_4} \text{N} - \text{Ph} \text{CN} - \text{CN} \xrightarrow{\text{THF, rt}} \text{TsN} - \text{Ph} \text{CN} - \text{CN}
\]

2,4-trans, 87%, 1:19 dr

**Yamamoto**

\[
\text{EtO} - \text{N} - \text{O} - \text{CN} \xrightarrow{5 \text{ mol}\% \text{ Pd(PPh}_3)_4} \text{N} - \text{Ph} \text{CN} - \text{CN} \xrightarrow{\text{THF, rt}} \text{EtO} - \text{N} - \text{Ph} \text{CN} - \text{CN}
\]

91%

**Knight**

\[
\text{TsN} - \text{O} + \text{NC} - \text{CN} \xrightarrow{5 \text{ mol}\% \text{ Pd}_{2+} \text{db}a_3 \cdot \text{CHCl}_3} \text{N} - \text{Ph} \text{CN} - \text{CN} \xrightarrow{20 \text{ mol}\% \text{ PPh}_3} \text{THF, 40°C} \rightarrow \text{TsN} - \text{Ph} \text{CN} - \text{CN}
\]

95%
In addition to the above example, several other studies have been reported concerning the IDcA of benzylidene malononitriles with other nitrogen-based nucleophiles (Scheme 3.10).

Tunge and co-workers utilized vinyl benzoxazinanones (eq. 4) and vinyl oxazinanones (eq. 5) in the interceptive synthesis of highly substituted vinyl piperidines and dihydroquinolines.\textsuperscript{35,36} Yamamoto and Knight reported similar palladium catalyzed decarboxylation and conjugate addition of allyl carbamates and vinyloxazolidinones to benzylidene malononitriles.\textsuperscript{37-39}

However, there are no reports of interceptive decarboxylative allylations of ester enolate equivalents.

### 3.4 One-pot, four component IDcA of ester enolate equivalents

As an extension of our one-pot, three-component decarboxylative allylation reaction (Scheme 3.1, eq. 1), we started developing a one-pot, four-component reaction by introducing electron-poor Michael acceptors to the reaction (eq. 2). 1.2 equivalents of lithium pyrrolide, 1.0 equivalent of Meldrums acid, 1.2 equivalents of benzylidene malononitrile and 1.2 equivalents of methyl cinnamyl carbonate were simultaneously added and allowed to react overnight under three-component coupling reaction conditions (eq. 8).

\[
\begin{align*}
\text{Ph} & \quad \text{CN} \\
\text{N} & \quad \text{Ph} \\
\text{OCH}_3 & \quad \text{NC}
\end{align*}
\quad +
\begin{align*}
\text{Ph} & \quad \text{CN} \\
\text{Ph} & \quad \text{CN} \\
\text{Ph} & \quad \text{OCH}_3
\end{align*}
\rightarrow
\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\quad (8)
\]

Even though Tsuji,\textsuperscript{19} Yamamoto,\textsuperscript{22} and Tunge,\textsuperscript{26} have reported successful interceptive DcA with Pd(PPh\textsubscript{3})\textsubscript{4} catalyst, after the overnight reaction we did not observe any product formation. Next according to Stoltz’s\textsuperscript{31} conditions the same starting components were reacted with Pd\textsubscript{2}dba\textsubscript{3} and dppe ligand at 40 °C. However these conditions did not lead to any product formation either. At this point we speculated that the bulkier allyl source was problematic and decided to use an unsubstituted allyl source. Gratifyingly the
reaction exhibited 58% conversion and we were able to isolate a mixture of desired four-component product (3.32) and starting Meldrum’s acid (Table 3.3, entry 1). Almost identical $R_f$ values made isolation of the product from the starting Meldrum’s acid impossible. Hence it was important to achieve a full conversion of Meldrum’s acid. High temperatures (60 °C) led to a low conversion and decomposition of the reaction mixture to some extent (entry 2) while reaction at 100 °C caused total decomposition (entry 3). At this point it is not clear whether decomposition happened before or after the product formation. NMR spectroscopic detection of byproducts was difficult as the NMR was cluttered with many proton signals. However, the starting Meldrum’s acid was not detected, which may be due to the decarboxylicative formation of ketenes at this temperature. Next, a ligand screening was done using dppm and dppp. Those bi-dentate ligands were chosen as they possess lower (dppm~72°) and higher (dppp~91°) bite angles than that of dppe (~86°). However both ligands led to 50% conversion (entries 4 and 5). Next, we performed a reaction at room temperature, and obtained a higher conversion (entry 6). Large-scale reactions were performed under these conditions, however the isolation of the product via column chromatography was problematic as it was inseparable from Meldrum’s acid. Our attempts to isolate the product using several different solvent systems such as EtOAc/hexane, EtOAc/pentane, Et₂O/hexane, and DCM/hexane were not successful. Use of an alumina stationary phase proved unsuccessful. Hence we attempted to consume the remaining Meldrum’s acid by adding 0.5 equivalents of lithium pyrrolide to the reaction. At this point we expected to observe the byproduct formed by protonation of the enolate. By converting the Meldrum’s acid to the protonation byproduct, which is much less polar than the four-component product, we expected better separation conditions for column chromatography.

To our delight, instead of forming the byproduct the formed enolate underwent tandem Michael addition, allylation to afford the four-component product. Encouraged by the result we added two more batches of lithium pyrrolide (0.3 equivalents each) until we observed a complete conversion of Meldrum’s acid. This whole process took three days to achieve an almost full conversion. During the experiments we observed a low diastereoselectivity, which was expected under the reaction conditions.
Having identified the standard reaction conditions we started to investigate the substrate scope of the reaction (Table 3.4). Several research groups have successfully used benzylidene malononitriles in interceptive reactions.\(^{19,22,26,31}\) Similar to their observations, we were able to conduct a successful interceptive DcA reaction using benzylidene malononitrile. After three days, a 76% of mixture of two diastereomers in low selectivity (2:3) was isolated (entry 1, 3.32). These diastereomers were inseparable by column chromatography. However the isolation was feasible utilizing recrystallization. Gratifyingly we isolated 28% of the minor diastereomer and the X-ray crystallographic structure determination revealed the relative stereochemistry of the four-component product (Figure 3.1).
Next, substituted benzylidene malononitriles were also subjected to the standard reaction conditions. Even though electron-donating groups such as \( p \)-methoxy and \( p \)-methyl reduce the electrophilicity of the Michael acceptor we observed good yields of four-component products (entries 2 and 3). This reduction in electrophilicity could be attributed to the slight reduction of the yield. This observation suggests that both Michael acceptors are more electrophilic than that of the Pd \( \pi \)-allyl complex (E~10). The diastereomers of both products (3.33 and 3.34) were not isolable by chromatographic methods or recrystallization. A Michael acceptor with an electron withdrawing \( o \)-CF\(_3\) group caused further reduction of the yield (entry 5, 3.36). This reduction may be due to the steric reasons rather than electronic reasons. Next the tolerance of the arylidene malononitrile substituted with heteroaromatic groups was investigated. Furylidene malononitrile (entry 4) and benzofurylidene malononitrile (entry 6) successfully tolerated the reaction conditions and furnished the four-component product (3.35 and 3.37) in good yields. In the latter case, separation of both diastereomers was possible via column chromatographic methods. However \( N \)-methyl pyrrole furnished the product in a lower yield and produced an inseparable mixture of diastereomers (entry 7, 3.38). An \( \alpha \)-allyl substituted substrate was also produced (entry 8, 3.39).
The substrates that were unsuccessful (except v, ix and x) in the four-component IDcA reaction are shown in Scheme 3.12. Even though we included naphthylidene malononitrile (v) in this category, it underwent successful Michael addition and allylation to furnish the four-component coupling product in 63% yield, however the product was inseparable from an unknown minor impurity (>10%). Repeated chromatographic methods or recrystallization were not able to produce the pure product. A benzylidene malononitrile with a strong electron withdrawing NO₂ group (vi) caused decomposition of the reaction mixture. Even though Tunge and co-workers successfully intercepted the ketone allylation process with Meldrum’s acid adducts (vii), under the standard conditions the pyrrole amide enolate did not undergo
Michael addition. Both Meldrum’s acid adduct (vii) and ethoxymethylene malononitrile (viii) furnished the protonated byproduct as the major product.

Scheme 3.12 Unsuccessful substrates in four-component IDcA reaction

Synthesis and isolation of alkylidene malononitriles (ix and x) were not successful due to the instability of the products. The attempted four-component coupling with a chiral palladium catalyst (Pd$_2$dba$_3$, (s)-$^1$Bu-PHOX) failed due to the low conversion of the starting Meldrum’s acid. As we have already discussed in chapter 3, alkyl Meldrum’s acids were not successful in three-component decarboxylative allylation. Therefore they were not investigated in this study.

3.5 Conclusion

In conclusion, we have developed a four-component interceptive decarboxylative allylation method to synthesize $\alpha$-quaternary acyl pyrrole substrates. However the reaction proceeds with $\alpha$-aryl substituted
substrates such as α-phenyl Meldrum’s acid and arylidene malononitriles. In some cases, the diastereomers of formed four-component products are isolable via chromatography or recrystallization. This synthetic strategy allows for the use of Meldrum’s acid as an acylating reagent. Further the observed byproducts CO₂, MeOH and acetone are volatile and easily removable. Since the reported methodology facilitates the interceptive decarboxylative alkylation readily for benzylic enolates, there is room for the future expansion to the alkyl enolates.
3.6 References


3.7 Methodology and compound characterization

All reactions were run in flame dried glassware under Argon atmosphere. Commercially available reagents and anhydrous benzene were used without further treatment. Compound purification was effected by flash chromatography using 230x400 mesh, 60Å porosity, silica obtained from Sorbent Technologies. The $^1$H and $^{13}$C NMR spectra were obtained on a Bruker Avance 400 or Bruker Avance 500 DRX spectrometer in CDCl$_3$ unless otherwise indicated and are referenced to the residual solvent peak CDCl$_3$ at $\delta$ 7.26 and $\delta$ 77.16 in $^1$H and $^{13}$C NMR respectively. Multiplicities are reported as follows: singlet (s), doublet (d), broad singlet (bs), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), multiplet (m). Structural assignments were based on $^1$H, $^{13}$C, DEPT-135, COSY, HSQC, and FT-IR spectroscopies. Mass spectrometry was run using ESI techniques. Lithium pyrrolide (section 1.5), substituted Meldrum’s acid$^{41,42}$ and allyl methyl carbonates$^{43}$ were synthesized according to the literature procedures.

Representative procedure for one-pot, four-component IDcA reaction:

Synthesis of 2-allyl-2-(2-methyl-3-oxo-1,2-diphenyl-3-(1H-pyrrol-1-yl)propyl)malononitrile (3.32)

In a glove box a flame dried Schlenk tube was charged with lithium pyrrolide (0.51 mmol, 37.5 mg, 1.2 eq.), Meldrum’s acid (0.43 mmol, 100 mg, 1.0 eq.) and anhydrous 1,4-Dioxane (4.3 mL, 0.1 M). The reaction mixture was stirred for a minute and added Pd$_2$dba$_3$ (0.021 mmol, 19.7 mg, 5 mol%) and dppe (0.056 mmol, 22.3 mg, 13 mol%) followed by benzylidene malononitrile (0.43 mmol, 66.3 mg, 1.0 eq.) and stirred for another minute. Then added allyl methyl carbonate (0.51 mmol, 59.2 mg, 1.2 eq.). The reaction was allowed to stir overnight at room temperature. A 0.1 mL was withdrawn from the reaction
mixture for $^1$H NMR spectroscopy. Next a second portion of lithium pyrrolide (0.21 mmol, 15.7 mg, 0.5 eq.) was added and stirred for another 8 hours and another 0.1 mL was withdrawn from the reaction mixture for $^1$H NMR spectroscopy. After 8 hours a third portion of lithium pyrrolide (0.13 mmol, 9.4 mg, 0.3 eq.) was added to the reaction mixture and stirred overnight. After overnight reaction $^1$H NMR was taken. The last portion of lithium pyrrolide (0.3 eq.) was added to the reaction mixture and stirred for another day or until $^1$H NMR shows a complete consumption of Meldrum’s acid. Then the reaction mixture was concentrated in vacuo and the crude mixture was purified via flash chromatography using 5% EtOAc and Hexane to obtain a white solid (76% yield). The solid product was then recrystallized using EtOAc and Hexane to obtain the minor diastereomer as white crystals (28% yield).

Mixture of diastereomers of 3.32

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.73 (s, 1H), 7.58 (s, 2H), 7.49 (s, 5H), 7.41–7.33 (m, 3H), 7.12–7.02 (m, 4H), 7.02–6.96 (m, 1H), 6.95–6.89 (m, 2H), 6.84 (d, $J$ = 2.0, 2H), 6.66 (s, 1H), 6.08–6.05 (m, 2H), 6.05–5.97 (m, 3H), 5.89 (m, 1H), 5.44 (d, $J$ = 10.1, 1H), 5.34 (dd, $J$ = 20.5, 13.6, 2H), 5.19 (dd, $J$ = 16.9, 1.0, 1H), 4.59 (s, 1H), 4.57 (s, 1H), 2.70 (dd, $J$ = 13.8, 8.0, 1H), 2.61 (dd, $J$ = 13.9, 6.4, 1H), 2.52 (s, 3H), 2.44–2.34 (m, 2H), 1.60 (s, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.6, 173.5, 139.1, 137.3, 134.6, 134.1, 133.5, 129.9, 129.7, 129.3, 129.1, 129.0, 128.92, 128.9, 128.8, 128.6, 128.4, 127.9, 127.8, 126.8, 123.6, 123.2, 121.6, 121.4, 116.6, 115.9, 115.8, 114.9, 112.6, 112.5, 56.5, 55.9, 55.8, 55.7, 44.3, 43.4, 39.8, 39.2, 26.2, 19.2

Calcd. HRMS for C$_{26}$H$_{24}$N$_3$O (M+H) – 394.1919, found 394.1906

Minor diastereomer of 3.32

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.73 (s, 1H), 7.17 (dd, $J$ = 8.8, 2.9 Hz, 1H), 7.13–6.94 (m, 7H), 6.94–6.89 (m, 2H), 6.66 (s, 1H), 6.09–6.04 (m, 2H), 5.99 (dd, $J$ = 17.3, 7.3 Hz, 1H), 5.38 (dd, $J$ = 49.1, 13.6 Hz, 2H), 4.59 (s, 1H), 2.65 (m, 2H), 2.51 (s, 3H)
mixture of diastereomers of 3.32

minor diastereomer of 3.32
$^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.4, 138.9, 133.3, 128.8, 128.7, 128.5, 128.3, 127.7, 126.6, 123.3, 121.2, 116.4, 115.7, 112.4, 56.3, 55.6, 43.2, 39.6, 19.0

2-allyl-2-(1-(4-methoxyphenyl)-2-methyl-3-oxo-2-phenyl-3-(1H-pyrrol-1-yl)propyl)malononitrile

(3.33)

The above representative procedure was followed to obtain a pale yellow solid in 66% yield in 1:1.4 diastereomeric ratio.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.57 (s, 3H), 7.49 (s, 3H), 7.40 (t, $J$ = 7.8, 1H), 7.16 (d, $J$ = 7.6, 1H), 7.12–6.98 (m, 4H), 6.91 (d, $J$ = 1.8, 2H), 6.90–6.85 (m, 2H), 6.83 (s, 2H), 6.77–6.40 (m, 2H), 6.06 (d, $J$ = 1.8, 1H), 6.02 (dd, $J$ = 3.5, 2.4, 2H), 5.98 (d, $J$ = 6.6, 1H), 5.89 (td, $J$ = 16.7, 6.7, 1H), 5.43 (d, $J$ = 10.2, 1H), 5.34 (dd, $J$ = 21.1, 13.6, 2H), 5.20 (d, $J$ = 16.9, 1H), 4.53 (s, 1H), 4.50 (s, 1H), 3.82 (d, $J$ = 1.3, 3H), 3.67 (d, $J$ = 1.3, 2H), 2.70 (dd, $J$ = 13.8, 7.9, 1H), 2.62 (dd, $J$ = 13.4, 5.9, 1H), 2.49 (s, 2H), 2.41 (d, $J$ = 7.1, 2H), 1.59 (s, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.7, 173.5, 160.1, 159.5, 139.2, 137.3, 135.8, 129.8, 129.7, 129.1, 129.0, 128.9, 128.8, 127.9, 126.7, 125.8, 125.3, 123.3, 123.2, 121.5, 121.4, 116.6, 116.0, 115.9, 115.0, 114.4, 114.1, 113.6, 112.5, 112.4, 55.9, 55.8, 55.7, 55.4, 55.3, 55.2, 44.3, 43.3, 39.9, 39.2, 26.2, 19.1

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3020, 2933, 1703, 1612, 1583, 1512, 1467, 1297, 1280, 1182, 1095, 902, 744

Calcd. HRMS for C$_{27}$H$_{25}$N$_3$O$_3$Na (M+Na) – 446.1844, found 446.1883
2-allyl-2-(2-methyl-3-oxo-2-phenyl-3-(1H-pyrrol-1-yl)-1-(p-tolyl)propyl)malononitrile (3.34)

Above representative procedure was followed to obtain a white solid in 67% yield in 1:1.4 distereomeric ratio.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.57 (s, 3H), 7.49 (s, 3H), 7.37 (d, $J = 5.0$ Hz, 1H), 7.15 (t, $J = 9.1$ Hz, 3H), 7.02 (dt, $J = 6.5$, 5.7 Hz, 4H), 6.91 (d, $J = 1.7$ Hz, 2H), 6.83 (s, 2H), 6.06 (s, 2H), 6.01 (d, $J = 1.8$ Hz, 2H), 5.94–5.84 (m, 1H), 5.47–5.25 (m, 3H), 5.19 (d, $J = 15.7$ Hz, 1H), 4.54 (d, $J = 2.6$ Hz, 1H), 4.52 (d, $J = 2.8$ Hz, 1H), 2.65 (m, 2H), 2.50 (d, $J = 2.7$ Hz, 2H), 2.39 (d, $J = 7.2$ Hz, 2H), 2.36 (d, $J = 2.4$ Hz, 3H), 2.16 (d, $J = 2.3$ Hz, 2H), 1.59 (d, $J = 2.7$ Hz, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.7, 173.6, 139.3, 139.2, 138.5, 137.4, 134.5, 130.9, 130.3, 129.8, 129.7, 129.1, 129.0, 128.9, 127.9, 127.8, 126.8, 123.42, 123.4, 121.6, 121.4, 116.6, 116.0, 115.9, 114.9, 112.5, 112.4, 56.3, 55.9, 55.8, 44.3, 43.4, 41.0, 39.9, 39.2, 26.2, 21.3, 21.1, 19.2

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 2923, 1701, 1514, 1467, 1298, 1091, 1076, 902, 736, 702

Calcd. HRMS for C$_2$H$_{23}$N$_3$ONa (M+Na) – 430.1895, found 430.1906
2-allyl-2-(1-(furan-2-yl)-2-methyl-3-oxo-2-phenyl-3-(1H-pyrrlo-1-yl)propyl)malononitrile (3.35)

The above representative procedure was followed to obtain a white solid in 53% yield in 1:1 diastereomeric ratio. One of the diastereomers was isolated in 33% yield.

Mixture of diastereomers of 3.35

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.58–7.51 (m, 2H), 7.51–7.43 (m, 4H), 7.22–7.08 (m, 7H), 6.94–6.90 (m, 2H), 6.87 (s, 2H), 6.51–6.47 (m, 1H), 6.42 (dd, $J = 3.3$, 1.8 Hz, 1H), 6.10–5.96 (m, 8H), 5.91–5.79 (m, 1H), 5.46 (dd, $J = 10.2$, 1.0 Hz, 1H), 5.41–5.34 (m, 2H), 5.23 (dd, $J = 16.9$, 1.3 Hz, 1H), 4.74 (s, 1H), 4.57 (s, 1H), 2.79–2.73 (m, 2H), 2.50 (s, 3H), 2.37 (d, $J = 7.3$ Hz, 2H), 1.72 (s, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.2, 172.8, 148.4, 146.9, 143.3, 142.8, 138.9, 136.6, 130.0, 129.8, 129.1, 128.9, 128.5, 128.2, 126.0, 123.8, 123.6, 121.5, 121.2, 115.9, 115.4, 114.7, 114.4, 113.1, 112.7, 112.6, 112.3, 111.2, 110.4, 56.4, 55.6, 51.9, 50.6, 43.7, 43.4, 38.6, 38.4, 24.0, 18.6

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3153, 2954, 1699, 1498, 1467, 1307, 1149, 1091, 1080, 900, 736, 702

Calcd. HRMS for C$_{24}$H$_{22}$N$_3$O$_2$ (M+H) – 384.1712, found 384.1697

One diastereomer of 3.35

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.22–7.10 (m, 6H), 6.94–6.90 (m, 2H), 6.09–6.06 (m, 2H), 6.05–5.97 (m, 3H), 5.42 (m, 2H), 4.57 (s, 1H), 2.81–2.74 (m, 2H), 2.50 (s, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.2, 146.9, 143.3, 138.9, 129.1, 128.9, 128.2, 126.0, 123.6, 121.2, 115.9, 115.4, 113.1, 112.7, 110.4, 55.6, 51.9, 43.4, 38.6, 18.6
2-allyl-2-(2-methyl-3-oxo-2-phenyl-3-(1H-pyrrol-1-yl)-1-(2-(trifluoromethyl)phenyl)propyl)malononitrile (3.36)

The above representative procedure was followed to obtain a white solid in 39% yield from a mixture of diastereomers (1:1.5).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.88–7.81 (m, 3H), 7.66–7.62 (m, 1H), 7.61–7.53 (m, 3H), 7.45 (s, 2H), 6.86 (s, 1H), 6.04 (t, $J = 2.5$ Hz, 2H), 5.78 (m, 1H), 5.54 (s, 1H), 5.35–5.17 (m, 2H), 2.78 (dd, $J = 13.6$, 7.6 Hz, 1H), 1.99 (m, 1H), 1.50 (s, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 172.7, 137.5, 133.8, 132.7, 130.1, 129.5, 129.3, 128.7, 123.4, 121.7, 115.7, 113.8, 112.4, 56.1, 49.3, 43.6, 41.1, 25.7

2-allyl-2-(1-(benzofuran-2-yl)-2-methyl-3-oxo-2-phenyl-3-(1H-pyrrol-1-yl)propyl)malononitrile (3.37)

The above representative procedure was followed to obtain a white solid in 76% yield in 1:1.4 diastereomeric ratio. Two diastereomers were isolated in 44%, and 27% yield via column chromatography.
Major diastereomer of 3.37

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.60 (d, \(J = 7.5\), 3H), 7.52 (d, \(J = 7.2\), 4H), 7.38–7.31 (m, 1H), 7.28 (d, \(J = 7.4\), 1H), 6.91 (s, 1H), 6.87 (s, 2H), 6.08–5.97 (m, 2H), 5.86 (m, 1H), 5.36 (d, \(J = 10.1\), 1H), 5.22 (d, \(J = 16.8\), 1H), 4.87 (s, 1H), 2.45 (d, \(J = 7.0\), 2H), 1.82 (s, 3H)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 172.7, 154.3, 151.0, 136.5, 130.2, 129.9, 128.3, 127.7, 125.3, 124.0, 123.7, 121.7, 121.4, 114.4, 114.3, 112.6, 111.7, 109.3, 56.3, 50.9, 43.7, 38.2, 23.9

FT-IR (CH\(_2\)Cl\(_2\)) \(\nu_{\max}\) cm\(^{-1}\) 3163, 1701, 1475, 1454, 1299, 1097, 1076, 991, 937, 904, 746, 707

Calcd. HRMS for C\(_{28}\)H\(_{23}\)N\(_3\)O\(_2\)Na (M+Na) – 456.1688, found 456.1694

Minor diastereomer of 3.37

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.36 (d, \(J = 8.2\), 1H), 7.32 (d, \(J = 7.5\), 1H), 7.22 (dd, \(J = 7.3\), 1.0, 1H), 7.18 (dd, \(J = 9.4\), 4.4, 2H), 7.11 (t, \(J = 7.5\), 1H), 7.04 (t, \(J = 7.8\), 2H), 7.01–6.96 (m, 1H), 6.94 (d, \(J = 2.2\), 2H), 6.40 (s, 1H), 6.14–6.07 (m, 2H), 6.07–5.99 (m, 1H), 5.48 (d, \(J = 10.1\), 1H), 5.39 (d, \(J = 16.9\), 1H), 4.72 (s, 1H), 2.83 (d, \(J = 7.3\), 2H), 2.60 (s, 3H)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 173.0, 154.7, 149.6, 138.5, 129.1, 128.7, 128.3, 126.9, 126.0, 125.1, 123.8, 123.2, 121.3, 121.1, 115.8, 115.3, 112.8, 111.3, 110.0, 55.6, 52.4, 43.4, 38.4, 18.8
2-allyl-2-(2-methyl-1-(1-methyl-1H-pyrrol-2-yl)-3-oxo-2-phenyl-3-(1H-pyrrol-1-yl)propyl)malononitrile (3.38)

The above representative procedure was followed to obtain a white solid in 35% yield in 1:1.7 diastereomeric ratio.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.51 (dd, $J = 23.7, 17.5, 5$H), 7.12 (q, $J = 6.7, 2$H), 7.03 (d, $J = 8.0, 1$H), 6.92–6.85 (m, 4H), 6.67 (d, $J = 1.4, 2$H), 6.33–6.28 (m, 1H), 6.19–6.12 (m, 2H), 6.09 (d, $J = 1.7, 1$H), 6.04 (d, $J = 1.6, 2$H), 6.04–5.92 (m, 2H), 5.84 (td, $J = 16.8, 6.7, 1$H), 5.46–5.29 (m, 3H), 5.20 (d, $J = 16.9, 1$H), 4.75 (s, 1H), 4.59 (s, 1H), 3.67 (s, 3H), 3.08 (s, 2H), 2.71 (dd, $J = 13.5, 7.7, 1$H), 2.57 (dd, $J = 13.3, 6.1, 1$H), 2.48–2.36 (m, 3H), 2.28 (dd, $J = 13.2, 5.9, 1$H), 1.62 (s, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 174.0, 173.8, 138.7, 137.1, 129.9, 129.5, 129.0, 128.9, 128.6, 128.2, 126.3, 124.9, 123.4, 123.3, 123.2, 123.1, 123.0, 121.6, 121.3, 116.6, 115.7, 115.6, 114.0, 112.7, 112.6, 110.8, 110.2, 108.2, 107.8, 56.7, 56.1, 43.5, 42.9, 41.2, 40.8, 34.6, 33.9, 24.9, 18.7

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3159, 1699, 1465, 1290, 1091, 989, 902, 740

Calcd. HRMS for C$_{25}$H$_{24}$N$_4$ONa (M+Na) – 419.1848, found 419.1859
2-allyl-2-(1,2-diphenyl-2-(1H-pyrrole-1-carbonyl)pent-4-en-1-yl)malononitrile (3.39)

The above representative procedure was followed to obtain a white solid of one diastereomer in 31% yield from a 1:1 mixture of diastereomers.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.87 (s, 1H), 7.59 (s, 1H), 7.53 (t, $J$ = 6.9 Hz, 3H), 7.39 (m, 5H), 7.23 (t, $J$ = 5.7 Hz, 3H), 6.02 (s, 2H), 5.99–5.87 (m, 1H), 5.54 (m, 1H), 5.38 (d, $J$ = 10.1 Hz, 1H), 5.22 (d, $J$ = 16.9 Hz, 1H), 4.93 (d, $J$ = 10.2 Hz, 1H), 4.59 (s, 1H), 4.46 (d, $J$ = 16.9 Hz, 1H), 2.68 (d, $J$ = 7.2 Hz, 2H), 2.40 (m, 2H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.3, 137.7, 134.5, 133.5, 132.4, 130.9, 130.0, 129.75, 129.7, 129.6, 129.4, 128.9, 128.8, 128.2, 127.6, 123.4, 121.5, 120.8, 116.3, 114.6, 112.5, 60.1, 54.1, 44.52, 42.6, 39.9

FT-IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ cm$^{-1}$ 3089, 2923, 1733, 1641, 1440, 1276, 1166, 1124, 993, 937, 702

Calcd. HRMS for C$_{28}$H$_{29}$N$_4$O (M+NH$_4$) – 437.2341, found 437.2217
Crystal structure of minor diastereomer of 3.32
Table 1. Crystal data and structure refinement for C26H23N3O

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Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for C26H23N3O. U(eq) is defined as one third of the trace of the orthogonalized U^ij tensor.

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Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters ($\AA^2 \times 10^3$) for C26H23N3O. The anisotropic displacement factor exponent takes the form: $-2\mathbf{h}^2 \mathbf{a}^* \mathbf{b}^* U_{11} + ... + 2 \mathbf{h} \mathbf{k} \mathbf{a}^* \mathbf{b}^* U_{12}$

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Table 5. Hydrogen coordinates ($x \times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^{-3}$) for C26H23N3O.

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Table 6. Torsion angles [*] for C26H23N3O.

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C(7)-C(6)-C(17)-C(18)  47.30(13)
C(5)-C(6)-C(17)-C(18)  67.48(13)
C(22)-C(17)-C(18)-C(19)  1.15(17)
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C(6)-C(17)-C(22)-C(21)  178.00(11)
C(20)-C(21)-C(22)-C(17)  -0.66(19)
C(26)-N(3)-C(23)-C(24)  -0.60(13)
C(7)-N(3)-C(23)-C(24)  -175.54(10)
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C(23)-C(24)-C(25)-C(26)  -0.50(14)
C(24)-C(25)-C(26)-N(3)  0.12(13)
C(23)-N(3)-C(26)-C(25)  0.28(13)
C(7)-N(3)-C(26)-C(25)  174.63(11)

Symmetry transformations used to generate equivalent atoms:
Chapter 4

Palladium-Catalyzed Cyclizations via CO$_2$ and Silyl Activation
4.1 Brief introduction to palladium-catalyzed cyclizations via CO₂ catalysis

The first part of this chapter discusses the development of a project that concerns the synthesis of benzopyrans via cyclization (eq. 1). In the progress of decarboxylative allylation reactions, it is of great interest to activate allylic alcohols in situ to obtain π-allyl palladium intermediates instead of using pre-activated allyl carbonates. Due to the inherent low leaving group ability of the hydroxyl group, several attempts to activate allyl alcohol have been made using Lewis acids such as Ti(OPr)₄,¹–⁷ BEt₃,⁸–¹⁸ and SnCl₂.¹⁹ Compared to these attempts to activate allylic alcohols, CO₂ becomes an economical choice, being an inexpensive and a readily available gas. CO₂ activates the allylic alcohol in 1-(1-hydroxyallyl)naphthalenol substrates (4.1) allowing cyclization of π-allyl palladium intermediate to synthesize benzopyrans (4.2). The next sub section discusses the importance of in situ activation of allyl alcohols and different methods of achieving such activation.

4.2 In situ activation of allyl alcohols

Palladium-catalyzed C–C, C–N, and C–O bond formation via Tsuji-Trost allylation and decarboxylative allylation are well established and widely applied methods in synthetic organic chemistry.²⁰–²³ During the allylation process it is vital to generate the palladium π-allyl complexes using pre-functionalized allyl sources. In general allyl halides,²⁰,²⁴,²⁵ esters,²⁶–³⁵ carbonates,³⁶–⁴⁴ carbamates,⁴⁵–⁴⁷ phosphates⁴⁸–⁵⁰ and other related derivatives⁵¹–⁵³ have been used to generate the palladium π-allyl complexes (Scheme 4.1). From an atom-economical and environmental point of view, the direct application of allyl alcohol is more desirable instead of using pre-functionalized allyl substrates.
Scheme 4.1 *Different allyl substrates in generation of palladium π-allyl complex*

\[
\text{Nu} \quad \text{(Nu)} \quad \text{Pd(0)} \\
\downarrow \\
X \quad \text{Pd(0)} \\
\downarrow \\
\text{Pd-π-allyl} \\
\text{Pd(0)} \\
\downarrow \\
\text{AcO} \quad \text{AcO} \\
\text{(AcO)} \\
\text{Pd(0)} \\
\downarrow \\
\text{Pd(0)} \\
\end{align*}

**Direct use of allyl alcohol**

The direct use of allyl alcohol as an allylating reagent has been limited, mainly due to the low leaving group ability of the nonactivated hydroxyl group. Despite this challenging condition, several research groups have successfully employed unactivated allyl alcohol in palladium-catalyzed allylation reactions without any activators.\(^{5,19,54-70}\) In 1970, Manyik and co-workers reported palladium catalyzed allylic amination of unactivated allyl alcohols in the presence of Pd(acac)\(_2\) and PPh\(_3\) in mild conditions.\(^{63}\) Later, two other research groups, Chauvin and Bergbreiter, directly utilized allyl alcohol in allylation reactions of β-keto esters and malonates; however these reactions required harsher conditions.\(^{61,62}\) More recently Yoshifuji and co-workers developed a catalytic allylation method using palladium complexes bearing bulky diphosphinidenecyclobutane (DPCB) ligands.\(^{55,56,58}\) However the substrate scope was limited and rather harsh conditions were required. Considering these disadvantages research groups focused on in
Situ activation of allyl alcohol by incorporating stoichiometric amounts of Lewis acids such as Ti(OPr)i4, 7,71,72 BEt3, 8–18 and SnCl2.19 These additives make hydroxyl a better leaving group, allowing allylations under milder conditions.

**Activation by Ti(OPr)i4**

The first disclosure of direct allylic alcohol amination via Ti(OPr)i4 activation was reported by Yang and co-workers.3 In the course of their study allyl alcohol and aniline were subjected to catalytic amounts of Pd(OAc)2 and PPh3 and Ti(OPr)i4 to furnish mono- and di-allylated anilines (Table 4.1). It is important to note that the use of molecular sieves improved the yield of the reaction. Some of the results are shown in Table 4.1. Both electron donating (entries 1) and electron withdrawing (entry 2) substituents were tested and a slight decrease in the yield with electron withdrawing groups was observed. However, better electron-donating groups (entries 3 and 4) caused a reduction in the observed yield. Importantly the best yield and selectivity was observed with the 2,4-dimethyl substituted substrates (entry 5). It suggests that

![Table 4.1 Allylic amination via C–O bond activation of Ti(OPr)i4](image)

<table>
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<th>R</th>
<th>yield % (4.3:4.4)</th>
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<td>4-Me</td>
<td>76 (87:13)</td>
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<tr>
<td>2</td>
<td>4-Cl</td>
<td>70 (87:13)</td>
</tr>
<tr>
<td>3</td>
<td>4-OMe</td>
<td>56 (91:9)</td>
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<tr>
<td>4</td>
<td>3,5-OMe</td>
<td>67 (87:13)</td>
</tr>
<tr>
<td>5</td>
<td>2,4-Me</td>
<td>82 (90:10)</td>
</tr>
</tbody>
</table>
moderately nucleophilic anilines are better candidates for the reaction. Nomura and co-workers showed that it was possible to utilize Ti(OPr')₄ in allylic etherifications as well.¹² Ti(OPr')₄ will ultimately produce titanium dioxide (TiO₂) as a byproduct. Moreover, because the reagent is highly moisture sensitive, storage and usage must be done under moisture free conditions. Therefore it is important to find a convenient C–O activating reagent other than Ti(OPr')₄.

**Activation by boron-based reagents**

Several research groups have paid attention to activate the allyl C–O bond using boron-based reagents. Tamaru and co-workers extensively studied the usage of BEt₃ as a Lewis acid in allylation reactions and they demonstrated that sub-stoichiometric amounts of BEt₃ accelerates the palladium-catalyzed allylation of amines,¹⁵ active methylene compounds,⁸ indoles,¹⁶ aliphatic aldehydes¹³ and o-hydroxypropiophenones.¹⁴

Table 4.2 Direct use of allyl alcohol in enantioselective allylation

<table>
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<th>entry</th>
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<th>R²</th>
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<td>5-OMe</td>
<td>Bn</td>
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However an asymmetric version did not emerge until Trost and co-workers published their work on C–3 selective allylation of indoles using trialkylboranes.\textsuperscript{18} This interesting study shows that C–3 alkyl substituted indoles undergo palladium-catalyzed enantioselective, and C–3 selective allylation in the presence of a stoichiometric amount of 9-BBN (Table 4.2).

Clearly the study showed a substituent effect on the reactivity. A substrate with an electron-withdrawing group did not furnish the desired allylated product (entry 1). In contrast, electron rich indoles and indoles with electron donating substituents at the 4-, 5-, and 6-positions underwent the expected allylation. Moreover, substrates with electron withdrawing groups at the 7-position did not undergo allylation due to steric prevention of formation of the boron-nitrogen bond. Even though there have been interesting applications developed, disadvantages of the method are the use of stoichiometric amounts of expensive boron reagents and formation of borinic acids as byproducts.

\textit{Activation by SnCl\textsubscript{2}}

Musayama and co-workers showed that the C–O bond activation could be achieved using SnCl\textsubscript{2}.\textsuperscript{19} After a brief investigation of reaction conditions, they were able to achieve allylic amination in the presence of catalytic amounts of Pd(PPh\textsubscript{3})\textsubscript{4}, and stoichiometric amounts of SnCl\textsubscript{2}, and triethyl amine (Table 4.3). Substituted allyl alcohols, primary, and secondary amines tolerated the reaction conditions. However, they have reported that carbon nucleophiles such as dimethyl malonate or ethyl cyanoacetate did not undergo allylation under these conditions. Furthermore, the reaction was inhibited by the slightest presence of moisture. We speculate that the formation of Sn(OH)Cl and HCl in the presence of water would prevent the Lewis acidic activity of SnCl\textsubscript{2} and promote amine protonation.
Table 4.3 Allylic amination via SnCl₂ activation

\[
\text{\begin{align*}
\text{OH} & + \text{NH(Bn)}_2 & \xrightarrow{2 \text{ mol}\% \text{Pd}(\text{PPh}_3)_4, 2 \text{ eq. SnCl}_2, 2 \text{ eq. Et}_3\text{N}} & \xrightarrow{\text{THF}} \text{N(Bn)}_2 \\
\text{no SnCl}_2 + \text{no NEt}_3 & \text{rt} & \text{nr} \\
\text{SnCl}_2 + \text{NEt}_3 & \text{rt} & 24\% \\
\text{SnCl}_2 + \text{NEt}_3 & 50 ^\circ\text{C} & 78\% \\
\text{SnCl}_2 + \text{no NEt}_3 & 50 ^\circ\text{C} & 43\%
\end{align*}}
\]

4.3 In situ activation of allyl alcohols via CO₂

In 1996, Yamamoto and co-workers identified the effect of CO₂ in palladium-catalyzed allylic amination reactions (eq. 2).²⁵ The reaction did not proceed in the absence of palladium catalyst or CO₂ under ambient conditions.

\[
\text{\begin{align*}
\text{OH} & + \text{NH(Et)}_2 & \xrightarrow{0.6 \text{ mol}\% \text{Pd}(\text{PPh}_3)_4, \text{CO}_2 (g) 1 \text{ atm}} & \xrightarrow{\text{rt}} \text{N(Et)}_2 \\
70-80 \% & \text{no solvent} & 96\% & \text{in acetone}
\end{align*}}
\]

The introduction of CO₂ gas into the reaction mixture allowed the allyl C–O bond activation via formation of allyl hydrogen carbonates (Scheme 4.2). The nucleophilic attack of the allyl alcohol on CO₂ could form the allyl hydrogen carbonate and it then could undergo oxidative addition to generate the Pd π-allyl complex and the bicarbonate anion. The formed bicarbonate could undergo decarboxylation to generate hydroxide anion, facilitating the deprotonation of the pro-nucleophile. Formation of the nucleophile would lead to the product formation.
In contrast to the conditions used for amines, active methylene compounds required high pressure conditions to undergo allylation. The yield of the allylated product was low at the normal pressure of carbon dioxide while the reaction performed under 20 or 30 atm of CO₂ pressure furnished the product in higher yields (eq. 3). It is noteworthy to mention that the allylations performed under high temperatures and high catalyst loading conditions furnished the product without CO₂ catalysis.

\[
\text{Nu} + \text{O} + \text{H} \xrightarrow{0.6 \, \text{mol\% Pd(PPh₃)₄}} \xrightarrow{\text{rt}} \text{CO}_2 \xrightarrow{1\, \text{atm}} 22\% \\text{CO}_2\text{Et}\]

Perhaps due to the acquired high-pressure condition, CO₂ was not utilized as an activator for allylation reactions for a long period of time. In 2013, Tunge and co-workers resurfaced the CO₂ chemistry and they were able to perform the allylation chemistry under normal pressure conditions. In the course of their study they were able to allylate nitoralkanes (eq. 4) and nitriles (eq. 5) under the shown conditions (unpublished results). In contrast to Yamamoto’s observation, reactions that were performed in high temperatures, such as 80 and 90 °C, still required CO₂ catalysis to undergo allylation.
The choice of CO₂ as an activator outshines other Lewis acids in several ways: (a) CO₂ is an inexpensive and a readily available gas, (b) storage and handling is not difficult, (c) allylation is possible under normal pressure conditions, and (d) the only byproduct observed is water. For these reasons, we suggest that CO₂ is a better activator than other Lewis acids.

4.4 Background of synthesis of benzopyrans (chromenes)

The chromene ring system is frequently found in many biologically important molecules (Figure 4.1).⁷³–⁷⁶ Chromenes have been isolated from fungi (4.5, 4.10) and plant sources (4.6, 4.7, 4.8, 4.9) and have been identified as antioxidants (4.5), anti-inflammatory agents (4.5, 4.6), antibacterial agents (4.6, 4.10), insecticides (4.7), and antifungal agents (4.8, 4.9).⁷⁷–⁸³

Figure 4.1 Chromenes; biologically active molecules
Because of the interesting biological activities of chromenes, several synthetic methods, such as photocatalytic, organocatalytic, Brønsted acid-catalyzed, ring closing metathesis, oxa-Michael addition to Bayliss-Hillman intermediates, o-quinone methide formation via oxidation of phenols or benzoazines, electrochemical methods, selenium or palladium resin based methods, Claisen rearrangement methods, and Wittig cyclizations have been reported. Herein we discuss a few methods that use similar types of substrates to those used in our work.

In 2002, Sinou and co-workers reported the synthesis of 2-phenyl-2H-chromene via palladium catalysis (Scheme 4.3). Starting from salicyaldehyde, a chain extension and unsaturation was done using a Wittig reaction. Next, phenol group protection, reduction of the carboethoxy group, oxidation of the allyl alcohol, Grignard addition, and acetylation followed by deprotection of the phenol group furnished the substrate for palladium-catalyzed cyclization. The cyclization provided a 34% overall yield of 2-phenyl-2H-chromene. However they may have saved additional reduction and oxidation steps if they used (triphenylphosphoranylidene)acetaldehyde in the first Wittig step instead of (carbethoxymethylene)triphenylphosphorane reagent.

Scheme 4.3 Synthesis of 2-phenyl-2H-chromene; Sinou approach
Jong and co-workers used a gold-catalyzed endo-cyclization approach for the chromene synthesis (Table 4.4). A series of salicyaldehyde-derived diols were subjected to the standard reaction conditions and high yields of chromene formation were observed. Both electron donating (4.11) and withdrawing substituents (4.12) at the position para to the nucleophilic phenol group furnished the product; however an electron deficient substrate required less reaction time (4.12). Furthermore, this substrate underwent cyclization under ambient conditions, where other substrates failed to do so. Highly substituted phenols (4.13) and naphthols (4.14) tolerated the reaction conditions. Incorporation of the dioxolane moiety caused decomposition of the products (4.15). Substitutions on vinyl group (4.16) are also tolerated. Although the mechanistic details are not discussed, authors speculate that the gold-complex may serve as either an π-acid by activating the alkene, or a Lewis acid by ionizing the alcohol.

Table 4.4 Chromene synthesis via gold-catalyzed endo-cyclization; Jong approach

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO</td>
<td>R1</td>
<td>4.11, 20 h, 74%</td>
<td></td>
</tr>
<tr>
<td>O2N</td>
<td>R1</td>
<td>4.12, 5 h, 91%</td>
<td></td>
</tr>
<tr>
<td>Br</td>
<td>R1</td>
<td>4.13, 20 h, 72%</td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>R1</td>
<td>4.14, 0.5 h, 73%</td>
<td></td>
</tr>
<tr>
<td>O2</td>
<td>R1</td>
<td>4.15, 1 h, 0%</td>
<td></td>
</tr>
<tr>
<td>Br</td>
<td>R1</td>
<td>4.16, 2 h, 53%</td>
<td></td>
</tr>
</tbody>
</table>

In 2010, Rueping and co-workers reported a chiral Brønsted acid-mediated enantioselective allylic alkylation reaction for the synthesis of chromenes.90 The substrate scope of the reaction is shown in Table 4.5. Both electron-donating (entries 1 and 2) and electron-withdrawing substituents (entries 3-5) in the para position of the vinylic aryl group led to the formation of chromenes in high yields and selectivity. In contrast, when a meta chloro group was introduced to the vinylic aryl group, no reaction was observed at -
78 °C. However raising the temperature to -48 °C led to excellent yield and good selectivity. In addition, both electron-donating (entries 4 and 5) and electron-withdrawing substituents (entry 6) on the aryl group tolerated the reaction conditions well.

The observed high selectivity depends on chiral contact ion-pair catalysis, where a chiral organic counteranion and an allylic carbocation facilitate the selective allylic substitution. Regarding the reaction mechanism, one can postulate that this reaction might produce a vinyl o-quinone methide intermediate and go through an oxa-6π electrocyclization. Because those types of reactions require high temperature conditions, the authors eliminate the electrocyclization pathway when considering the applied low temperature conditions. Several experiments have been conducted to support the idea of an allylic cation intermediate. An enantiopure (ee > 99%) substrate formed a racemic product with achiral catalyst while the same substrate with a chiral catalyst formed a product with 92 % ee, as in the case of the racemic substrate with a chiral catalyst.

Table 4.5 Brønsted acid-catalyzed asymmetric allylic substitution; Rueping approach

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Me</td>
<td>4-Me-Ph</td>
<td>84</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Me</td>
<td>4-OMe-Ph</td>
<td>91</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>Me</td>
<td>4-Br-Ph</td>
<td>80</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>5-Me</td>
<td>Me</td>
<td>4-F-Ph</td>
<td>82</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>4-MeO</td>
<td>Me</td>
<td>4-Cl-Ph</td>
<td>83</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>5-F</td>
<td>Me</td>
<td>4-Me-Ph</td>
<td>94</td>
<td>92</td>
</tr>
</tbody>
</table>
These observations suggest that the chiral substrate loses its chiral information when making the intermediate. The loss of enantiopurity during the reaction excludes the $S_{N2'}$ type substitution. Based on these observations, the authors propose that the Brønsted acid protonates the allyl alcohol and dehydrates it to form a chiral contact ion pair of phosphoramidate anion and allyl cation. The phenolic OH group is deprotonated by the anion and regenerates the chiral catalyst while forming the cyclized product. In the next section, we will discuss our attempts to synthesize chromenes via CO$_2$ activation of allyl alcohols.

4.5 Palladium-catalyzed cyclizations via CO$_2$ activation

The retrosynthetic plan for the palladium and CO$_2$-catalyzed synthesis of chromene is shown in Scheme 4.4 and the following aspects were taken into consideration (a) intramolecular allylic etherification via intermediate A, which possesses both Pd π-allyl complex and phenolate (b) Pd π-allyl complex formation via CO$_2$ activation of an allyl OH group (c) substrate (4.1) synthesis via Grignard addition of vinyl group to 2-hydroxy-1-naphthaldehyde.

Scheme 4.4 Synthesis of chromenes; retrosynthetic plan

Intermolecular decarboxylative allylic etherification has been reported to occur with Pd$^{101-103}$ Rh$^{104}$ Ru$^{105-107}$ and Fe-based$^{108}$ catalysts. Hence we expected a similar but intramolecular transformation with our substrate.
Similar to Yamamoto’s mechanism, we also expect the mechanism to start with \( \text{CO}_2 \) activation. Nucleophilic attack of the allyl alcohol on \( \text{CO}_2 \) would form the allyl hydrogen carbonate (C) and it would then undergo oxidative addition to generate the Pd \( \pi \)-allyl complex (\text{syn}-A, \text{anti}-B) and a bicarbonate anion. The formed bicarbonate can deprotonate phenol. Formation of the phenolate would then lead to the allylic etherification.

With this in mind, substrate 4.1 was subjected to palladium and \( \text{CO}_2 \) catalyzed conditions (Table 4.6).

Scheme 4.5 \textit{Plausible mechanism; Pd and CO}_2\textit{catalysis}

Interestingly the first set of conditions we tried furnished the desired cyclized product with an almost complete conversion (entry 1). Further investigations were carried out to identify other suitable solvents, low temperatures and higher concentrations. We felt that it was worthy but not necessary to identify other easily removable, less expensive solvents to perform the reactions. Three other solvents, toluene, acetonitrile and THF were tested, but lower conversions were observed under refluxing conditions (entries 2-4). Longer reaction times may provide us with a full conversion, however we declined to do so due to the high temperatures required. In addition, entry 2 was refluxed in toluene for 4 hours, but only 82% conversion was observed. Therefore DMSO was chosen as the standard solvent. The temperature
was lowered by 20 degrees and the concentration of the reaction was raised to 0.2 M and no polymeric products were observed (entry 7). Therefore the conditions depicted in entry 8 were selected as the standard reaction conditions. The control experiments indicate the necessity of Pd and CO$_2$ for the cyclization (entries 9 and 10).

As expected 1-(1-hydroxyallyl)naphthalen-2-ol substrate (4.1) was an excellent precursor for the reaction.

Table 4.6 Pd- and CO$_2$-catalyzed cyclization; investigation of the conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>X mol%</th>
<th>solvent</th>
<th>Z (M)</th>
<th>Y (°C)</th>
<th>CO$_2$</th>
<th>Conversion %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>DMSO-d$_6$</td>
<td>0.06</td>
<td>80</td>
<td>yes</td>
<td>&gt;95</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>Tol-d$_8$</td>
<td>0.06</td>
<td>110</td>
<td>yes</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>CD$_3$CN</td>
<td>0.06</td>
<td>80</td>
<td>yes</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>THF-d$_8$</td>
<td>0.06</td>
<td>60</td>
<td>yes</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>DMSO-d$_6$</td>
<td>0.06</td>
<td>60</td>
<td>yes</td>
<td>&gt;95</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>DMSO-d$_6$</td>
<td>0.1</td>
<td>60</td>
<td>yes</td>
<td>&gt;95</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>DMSO-d$_6$</td>
<td>0.2</td>
<td>60</td>
<td>yes</td>
<td>&gt;95</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>DMSO-d$_6$</td>
<td>0.2</td>
<td>60</td>
<td>yes</td>
<td>&gt;95</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>DMSO-d$_6$</td>
<td>0.2</td>
<td>60</td>
<td>no</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>DMSO-d$_6$</td>
<td>0.2</td>
<td>60</td>
<td>no</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

conversion based on $^1$H NMR spectroscopic analysis of crude reaction mixture

It furnished the product (4.2) in 96% yield in the milligram scale and 81% in the gram scale reaction (Table 4.7). Even though a full conversion was observed in the crude reaction mixture, low isolated yields
were obtained with 7-methyl-2H-chromene (4.17) and 2H-chromene. The high volatility of the products accounted for the low yield of these two products.

Table 4.7 Pd- and CO₂-catalyzed cyclization

<table>
<thead>
<tr>
<th>Reaction Product</th>
<th>Yield (volatile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.17</td>
<td>62%</td>
</tr>
<tr>
<td>4.18</td>
<td>50%</td>
</tr>
<tr>
<td>4.2</td>
<td>96%</td>
</tr>
<tr>
<td>(81% in 1.5 g scale)</td>
<td></td>
</tr>
</tbody>
</table>

When a substitution was introduced to the α-position of the allyl alcohol, the reaction proceeded without CO₂ activation (4.19 and 4.20 in Scheme 4.6). However high temperatures were required. A similar observation was made when substrates were substituted with electron withdrawing groups (4.21 and 4.22).

Scheme 4.6 Cyclization without CO₂ catalysis

---

*Based on ¹H NMR spectroscopic analysis*
Also highly substituted allylic substrates (Scheme 4.7, 4.23) underwent cyclization without CO₂ catalysis. Next 1,5-hydroxyl substrates were subjected to the reaction conditions and β-hydride elimination with alkyl-substituted substrates (4.24) and successful cyclization with phenyl-substituted substrates (4.25) were observed.

Scheme 4.7 Cyclization without CO₂ catalysis; more substrates

Our plan to synthesize Puuphedione via Pd and CO₂-catalyzed cyclization (Figure 4.2) was deemed not fruitful as we observed an almost 1:1 formation of the desired product and the β-hydride eliminated byproduct in our model studies (4.26 in Scheme 4.7).
Figure 4.2 Synthesis of Puupehedione via Pd and CO$_2$-catalyzed cyclization

Table 4.8 Attempted but failed interceptive etherification

<table>
<thead>
<tr>
<th>entry</th>
<th>substrates</th>
<th>conditions</th>
<th>entry</th>
<th>substrates</th>
<th>conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A and D</td>
<td>CpPdallyl, dppe, DMSO, 120 °C</td>
<td>10</td>
<td>A and D</td>
<td>Pd(PPh$_3$)$_4$, C$_6$D$_6$, 80 °C</td>
</tr>
<tr>
<td>2</td>
<td>A and D</td>
<td>Pd(PPh$_3$)$_4$, DMSO, 120 °C</td>
<td>11</td>
<td>A and D</td>
<td>Pd$_2$dba$_3$, Trost ligand, DMSO, 120 °C</td>
</tr>
<tr>
<td>3</td>
<td>A and D</td>
<td>Pd(PPh$_3$)$_4$, DCM, rt</td>
<td>12</td>
<td>A and F</td>
<td>Pd$_2$dba$_3$, BINAP, DMSO, 120 °C</td>
</tr>
<tr>
<td>4</td>
<td>A and D</td>
<td>Pd(PPh$_3$)$_4$, D-toluene, rt</td>
<td>13</td>
<td>A and E</td>
<td>Pd$_2$dba$_3$, BINAP, DMSO, 120 °C</td>
</tr>
<tr>
<td>5</td>
<td>A and D</td>
<td>Pd(PPh$_3$)$_4$, DMSO, 80 °C</td>
<td>14</td>
<td>B and F</td>
<td>Pd$_2$dba$_3$, BINAP, DMSO, 80 °C, CO$_2$</td>
</tr>
<tr>
<td>6</td>
<td>A and D</td>
<td>Pd(PPh$_3$)$_4$, D-THF, 65 °C</td>
<td>15</td>
<td>B and G</td>
<td>Pd$_2$dba$_3$, BINAP, DMSO, 80 °C, CO$_2$</td>
</tr>
<tr>
<td>7</td>
<td>A and D</td>
<td>Pd(PPh$_3$)$_4$, D-toluene, 110 °C</td>
<td>16</td>
<td>C and D</td>
<td>Pd$_2$dba$_3$, Trost ligand, DMSO, 60 °C, CO$_2$</td>
</tr>
<tr>
<td>8</td>
<td>A and D</td>
<td>Pd(PPh$_3$)$_4$, CD$_2$Cl$_2$, 40 °C</td>
<td>17</td>
<td>C and F</td>
<td>Pd$_2$dba$_3$, Trost ligand, DMSO, 60 °C, CO$_2$</td>
</tr>
<tr>
<td>9</td>
<td>A and D</td>
<td>Pd(PPh$_3$)$_4$, dioxane, 110 °C</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Next, we tried to intercept the etherification step with several Michael acceptors. Table 4.8 summarizes all the conditions and the substrates that failed in the interceptive etherification reaction. In all cases, we did not observe the intercepted product.

4.6 Palladium-catalyzed cyclizations via silyl activation

During the course of study we observed that the substrates with a silyl protected phenol group underwent allylic etherification without CO₂ catalysis. This observation made us speculate about another mode of activation of hydroxyl groups. Hence we assume that the silyl group activates the hydroxyl via a hypervalent silyl intermediate (Figure 4.3). As the conditions depicted in Table 4.9 illustrate, at 80 °C, the reaction furnished the desired product in almost full conversion (Table 4.9, entry 2). The control experiment (entry 3) did not lead to the formation of the desired product. A few substrates were subjected to these standard conditions and observed good to excellent yields (Table 4.10). The high volatility of some of the products affected the overall isolated yield (4.27, 4.17, 4.18).

Figure 4.3 Allylic etherification via silyl activation

![Figure 4.3 Allylic etherification via silyl activation](image-url)
Table 4.9 Reaction conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>X mol%</th>
<th>Y °C</th>
<th>Conversion %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>60</td>
<td>&gt;95 (4 hr)</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>80</td>
<td>&gt;95 (2hr)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>80</td>
<td>&lt;5 (2hr)</td>
</tr>
</tbody>
</table>

Conversion is based on crude ¹H NMR spectroscopic analysis

Table 4.10 Allylic etherification via silyl activation

In the future we would like to extend the chemistry to enantioselective cyclizations using substrates 4.28 and 4.29 (Scheme 4.8).

Scheme 4.8 Future directions
4.7 Conclusion

Herein we disclosed two methods to activate allylic hydroxyl group using CO$_2$ and adjacent silyl groups. The substrate scope has not been adequately studied at this point; more studies will be disclosed in the future.
4.8 References


4.5 Methodology and characterization

All reactions were run in flame-dried glassware under Argon atmosphere. Commercially available reagents and anhydrous solvents were used without further treatment. Compound purification was effected by flash chromatography using 230x400 mesh, 60Å porosity, silica obtained from Sorbent Technologies. The $^1$H and $^{13}$C NMR spectra were obtained on a Bruker Avance 400 or Bruker Avance 500 DRX spectrometer in CDCl$_3$ unless otherwise indicated and are referenced to the residual solvent peak CDCl$_3$ at $\delta$ 7.26 and $\delta$ 77.16 in $^1$H and $^{13}$C NMR respectively. Multiplicities are reported as follows: singlet (s), doublet (d), broad singlet (bs), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), multiplet (m). Structural assignments were based on $^1$H, $^{13}$C, DEPT-135, COSY, HSQC, and FT-IR spectroscopies. Mass spectrometry was run using ESI techniques.

Representative procedure (A) for the synthesis of 2H-chromenes via Pd and CO$_2$ catalysis;

Synthesis of 3H-benzo[f]chromene (4.2)

In a flame dried Schlenk flask under argon, Pd(PPh$_3$)$_4$ (43 mg, 0.037 mmol, 0.05 eq.) and anhydrous DMSO (3.75 mL, 0.2 M) were added to 1-(1-hydroxyallyl)naphthalen-2-ol (4.1, 150 mg, 0.75 mmol, 1.0 eq.). The reaction was bubbled with CO$_2$ gas using a balloon for 5 minutes and then stirred for 1 hour at 60 °C. The reaction mixture was concentrated in vacuo and the crude material was purified via flash chromatography using 5% EtOAc and hexane to obtain pale yellow solid (131 mg, 96%).
Representative procedure (B) for the synthesis of 2H-chromenes via silyl activation;

Synthesis of 3H-benzo[f]chromene (4.2)

![Chemical structure of 3H-benzo[f]chromene (4.2)](image)

In a flame dried Schlenk flask under argon, Pd(PPh\(_3\))\(_4\) (37 mg, 0.032 mmol, 0.05 eq.) and 3.2 mL anhydrous DMSO (3.2 mL, 0.2 M) were added to 1-(2-(tert-butyldimethylsilyl)oxy)naphthalen-1-yl)prop-2-en-1-ol (200 mg, 0.64 mmol, 1.0 eq.) and then stirred for 2 hours at 80 °C. The reaction mixture was concentrated in vacuo and the crude material was purified via flash chromatography using 5% EtOAc and hexane to obtain pale yellow solid (108 mg, 93%).

3H-benzo[f]chromene (4.2)

The representative procedure (A) was followed to obtain a white solid in 96% yield in mmol scale and 81% yield in gram scale.

The representative procedure (B) was followed to obtain a white solid in 93% yield.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.93 (d, \(J = 8.4\) Hz, 1H), 7.75 (d, \(J = 8.2\) Hz, 1H), 7.65 (d, \(J = 8.8\) Hz, 1H), 7.48 (m, 1H), 7.35 (m, 2H), 7.14 (d, \(J = 9.9\) Hz, 1H), 7.07 (d, \(J = 8.8\) Hz, 1H), 5.92 (dt, \(J = 9.9, 3.9\) Hz, 1H), 4.88 (dd, \(J = 3.9, 1.7\) Hz, 2H)
$^{13}$C NMR (126 MHz, CDCl$_3$) δ 152.5, 133.9, 130.1, 129.5, 128.7, 126.8, 123.7, 121.5, 121.1, 120.4, 117.8, 115.5, 65.4

![Image of 7-methoxy-2H-chromene](image)

**7-methoxy-2H-chromene**

The representative procedure (B) was followed to obtain pale yellow oil in 86% yield.

$^1$H NMR (500 MHz, CDCl$_3$) δ 6.86 (d, $J = 8.3$ Hz, 1H), 6.42 (dd, $J = 8.3$, 2.5 Hz, 1H), 6.40-6.35 (m, 2H), 5.63 (dt, $J = 9.8$, 3.6 Hz, 1H), 4.79 (dd, $J = 3.6$, 1.8 Hz, 2H), 3.77 (s, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 160.7, 155.4, 127.3, 124.3, 118.9, 115.8, 107.1, 101.8, 65.7, 55.5

![Image of 7-methyl-2H-chromene](image)

**7-methyl-2H-chromene**

The representative procedure (A) was followed to obtain colorless oil in 62% yield.

The representative procedure (B) was followed to obtain colorless oil in 60% yield.

$^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.16-7.08 (m, 2H), 6.89 (dd, $J = 7.6$, 1.8 Hz, 1H), 6.66 (dd, $J = 7.6$, 0.9 Hz, 1H), 6.43 (d, $J = 9.8$ Hz, 1H), 5.78 (dt, $J = 10.1$, 3.3 Hz, 1H), 4.72 (q, $J = 2.9$ Hz, 2H), 2.20 (s, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 157.8, 142.3, 127.6, 127.4, 121.2, 120.9, 118.4, 116.8, 65.7, 22.5
**2H-chromene**

The representative procedure (A) was followed to obtain colorless oil in 50% yield.

The representative procedure (B) was followed to obtain colorless oil in 45% yield.

\[^1\text{H} \text{NMR (400 MHz, DMSO-}	ext{d}_6\text{)} \delta 7.22-7.12 (m, 1H), 7.02-6.86 (m, 2H), 6.73-6.65 (m, 2H), 5.88 (m, 1H), 5.35-5.17 (m, 2H)\]

\[^{13}\text{C NMR (126 MHz, CDCl}_3\text{)} \delta 157.8, 129.3, 128.6, 127.4, 122.2, 121.9, 119.4, 114.2, 63.7\]

**2-phenyl-2H-chromene**

The representative procedure (A) was followed at 100 °C, without CO\textsubscript{2} to obtain colorless oil in 81% yield.

\[^1\text{H} \text{NMR (500 MHz, CDCl}_3\text{)} \delta 7.48-7.44 (m, 2H), 7.40-7.36 (m, 2H), 7.35-7.33 (m, 1H), 7.11 (m, 1H), 7.01 (dd, } J = 7.4, 1.6 \text{ Hz, 1H}), 6.87 (m, 1H), 6.79 (d, } J = 8.1 \text{ Hz, 1H}), 6.54 (dd, } J = 9.8, 1.5 \text{ Hz, 1H}), 5.92 (dd, } J = 3.3, 2.0 \text{ Hz, 1H}), 5.80 (dd, } J = 9.8, 3.4 \text{ Hz, 1H})\]

\[^{13}\text{C NMR (126 MHz, CDCl}_3\text{)} \delta 153.3, 140.9, 133.9, 133.8, 129.6, 128.8, 128.5, 127.2, 126.7, 124.9, 124.1, 121.4, 121.3, 116.1, 77.4\]
Characterization data of starting materials;

\[
\text{1-}(2-((\text{tert-butyldimethylsilyl})\text{oxy})-4\text{-methoxyphenyl})\text{prop-2-en-1-ol}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.24-7.17 (m, 1H), 6.51 (dd, \(J = 8.5, 2.5\) Hz, 1H), 6.39 (d, \(J = 2.5\) Hz, 1H), 6.09 (m, 1H), 5.45 (m, 1H), 5.30 (dt, \(J = 17.2, 1.6\) Hz, 1H), 5.18 (dt, \(J = 10.5, 1.6\) Hz, 1H), 3.77 (s, 3H), 2.31 (d, \(J = 4.8\) Hz, 1H), 1.02 (s, 9H), 0.28 (d, \(J = 6.5\) Hz, 6H)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 160.0, 154.0, 139.8, 128.4, 125.7, 114.5, 106.0, 105.5, 70.0, 55.4, 25.9, 18.4, -3.9

\[
\text{1-}(2-((\text{tert-butyldimethylsilyl})\text{oxy})\text{phenyl})\text{prop-2-en-1-ol}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.36-7.29 (m, 1H), 7.20-7.12 (m, 1H), 6.96 (m, 1H), 6.82 (dd, \(J = 8.1, 1.0\) Hz, 1H), 6.11 (m, 1H), 5.50 (m, 1H), 5.31 (dt, \(J = 17.2, 1.6\) Hz, 1H), 5.19 (dt, \(J = 10.5, 1.6\) Hz, 1H), 2.45 (d, \(J = 5.0\) Hz, 1H), 1.02 (s, 9H), 0.28 (d, \(J = 4.2\) Hz, 6H)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 153.0, 139.6, 132.9, 128.6, 127.7, 121.5, 118.5, 114.7, 70.5, 25.9, 18.4, -3.9×2
2-(1-hydroxyallyl)phenol

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.24-7.15 (m, 1H), 7.02 (dd, $J = 7.5$, 1.6 Hz, 1H), 6.93-6.81 (m, 2H), 6.15 (m, 1H), 5.39 (dt, $J = 6.5$, 1.4 Hz, 1H), 5.34 (dt, $J = 17.2$, 1.3 Hz, 1H), 5.30-5.23 (m, 1H), 2.60 (s, 1H)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 155.7, 138.0, 129.6, 127.7, 125.4, 120.1, 117.4, 116.6, 76.6

1-(1-hydroxyallyl)naphthalen-2-ol

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.85 (s, 1H), 7.80-7.68 (m, 3H), 7.45 (m, 1H), 7.32 (m 1H), 7.13 (dd, $J = 8.9$, 2.3 Hz, 1H), 6.27-6.15 (m, 2H), 5.37 (m, 1H), 5.27 - 5.20 (m, 1H), 2.84 (s, 1H)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.5, 154.4, 153.5, 136.9, 134.7, 131.3, 130.2, 129.5, 129.0, 128.8, 128.7, 126.9, 123.1, 121.5, 121.1, 120.4, 119.9, 119.7, 116.5, 115.2, 72.9

1-(2-((tert-butyldimethylsilyl)oxy)naphthalen-1-yl)prop-2-en-1-ol
$^1$H NMR (500 MHz, CDCl$_3$) δ 8.24 (d, $J$ = 8.7 Hz, 1H), 7.76 (d, $J$ = 7.6 Hz, 1H), 7.69 (d, $J$ = 8.9 Hz, 1H), 7.49-7.41 (m, 1H), 7.34 (m, 1H), 7.11-7.03 (m, 1H), 6.35-6.27 (m, 1H), 6.18 (m, 1H), 5.26 (dt, $J$ = 17.2, 1.7 Hz, 1H), 5.17 (dt, $J$ = 10.5, 1.8 Hz, 1H), 3.14 (d, $J$ = 6.4 Hz, 1H), 1.06 (s, 9H), 0.31 (d, $J$ = 4.9 Hz, 6H)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 150.9, 140.1, 132.4, 129.9, 129.6, 128.6, 126.4, 124.5, 124.2, 123.8, 120.3, 114.7, 69.6, 26.1, -3.5, -3.6

![Diagram of 1-(2-((tert-butyldimethylsilyl)oxy)-4-methylphenyl)prop-2-en-1-ol]

1-(2-((tert-butyldimethylsilyl)oxy)-4-methylphenyl)prop-2-en-1-ol

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.18 (d, $J$ = 7.8 Hz, 1H), 6.77 (d, $J$ = 7.6 Hz, 1H), 6.63 (s, 1H), 6.13-6.06 (m, 1H), 5.46 (t, $J$ = 5.0 Hz, 1H), 5.30 (dt, $J$ = 17.2, 1.3 Hz, 1H), 5.20-5.14 (m, 1H), 2.29 (s, 3H), 1.01 (s, 9H), 0.27 (d, $J$ = 5.4 Hz, 6H)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 152.9, 139.7, 138.7, 130.0, 127.5, 122.2, 119.3, 114.5, 70.4, 25.9, 21.4, 18.4, -3.8

![Diagram of 2-(1-hydroxy-1-phenylallyl)phenol]

2-(1-hydroxy-1-phenylallyl)phenol

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$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.22 (s, 1H), 7.44-7.30 (m, 5H), 7.23-7.16 (m, 1H), 6.91-6.87 (m, 1H), 6.84 (dd, $J = 7.8$, 1.7 Hz, 1H), 6.81-6.76 (m, 1H), 6.41 (dd, $J = 17.1$, 10.5 Hz, 1H), 5.39 (d, $J = 10.6$ Hz, 1H), 5.17 (d, $J = 17.1$ Hz, 1H), 2.97 (s, 1H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 156.0, 143.6, 141.5, 129.6, 128.8, 128.5, 128.2, 127.1, 119.4, 117.8, 115.6, 82.3

![Chemical structure](image)

**$(E)-2$-(2-hydroxy-4-phenylbut-3-en-2-yl)phenol**

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 10.76 (s, 1H), 7.85 (dd, $J = 16.7$, 8.8 Hz, 2H), 7.73 (dd, $J = 17.2$, 8.4 Hz, 2H), 7.43-7.38 (m, 2H), 7.38-7.31 (m, 2H), 7.14 (dd, $J = 8.9$, 1.3 Hz, 1H), 6.97-6.76 (m, 2H), 2.69 (s, 1H), 2.12 (s, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 154.7, 136.3, 131.4, 130.2, 129.0, 128.8, 128.5, 126.9, 125.7, 125.0, 122.3, 120.9, 80.1, 28.4

![Chemical structure](image)

**2-(cyclohex-1-en-1-yl(hydroxy)methyl)phenol**
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.04 (s, 1H), 7.22-7.13 (m, 1H), 6.95 (dd, $J = 7.5$, 1.4 Hz, 1H), 6.90-6.78 (m, 2H), 5.84 (q, $J = 3.6$ Hz, 1H), 5.30 (s, 1H), 2.34 (d, $J = 2.8$ Hz, 1H), 2.13-2.05 (m, 2H), 2.04-1.90 (m, 2H), 1.60 (m, 4H)

![Chemical structure](image)

$\text{(E)-2-(3-hydroxy-3-phenylprop-1-en-1-yl)phenol}$

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.48-7.41 (m, 2H), 7.40-7.36 (m, 3H), 7.33-7.28 (m, 1H), 7.12 (m, 1H), 6.95 (d, $J = 15.7$ Hz, 1H), 6.91-6.87 (m, 1H), 6.77 (dd, $J = 8.1$, 1.0 Hz, 1H), 6.42 (dd, $J = 15.9$, 6.6 Hz, 1H), 5.42 (dd, $J = 6.4$, 2.4 Hz, 1H), 5.02 (s, 1H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 153.1, 142.8, 133.3, 129.0, 128.8, 127.9, 127.8, 126.5, 125.1, 123.8, 121.1, 116.0, 75.6

![Chemical structure](image)

$\text{(E)-2-(3-hydroxybut-1-en-1-yl)phenol}$

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.37 (dd, $J = 7.7$, 1.5 Hz, 1H), 7.13 (m, 1H), 6.95-6.87 (m, 1H), 6.84-6.75 (m, 2H), 6.28 (dd, $J = 16.0$, 6.4 Hz, 1H), 5.01 (s, 1H), 4.52 (m, 1H), 1.39 (d, $J = 6.4$ Hz, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 152.7, 135.4, 128.8, 127.7, 123.9, 121.1, 115.9, 69.4, 23.6

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2-(1-hydroxyallyl)-4-nitrophenol

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.83 (s, 1H), 8.11 (dd, $J = 9.0$, 2.7 Hz, 1H), 7.98-7.94 (m, 1H), 6.96 (d, $J = 9.0$ Hz, 1H), 6.12 (m, 1H), 5.50 (d, $J = 6.5$ Hz, 1H), 5.46-5.36 (m, 2H)

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 161.8, 136.7, 125.6, 125.4, 124.0, 118.5, 118.0, 76.3