

***Newly Developed Methods for Functionalization of Quaternary Carbons:  
Decarboxylative Allylation, Benzylation, and Arylation of Nitriles and the Asymmetric Baeyer–  
Villiger Oxidation of 1,3-Diketones***

By

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This manuscript is submitted to the graduate degree program in 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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Wednesday, April 11, 2012

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certifies that this is the approved version of the following dissertation:

*Newly Developed Methods for Functionalization of Quaternary Carbons:*

*Decarboxylative Allylation, Benzylation, and Arylation of Nitriles and the Asymmetric Baeyer–  
Villiger Oxidation of 1,3-Diketones*

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*Chairperson Jon A. Tunge, Ph.D.*

Date approved: April 11, 2012

## Abstract

Decarboxylative carbon–carbon bond formations have emerged as a powerful synthetic tool within the past ten years. Beginning with the seminal reports from Saegusa and Tsuji in 1980, the decarboxylative allylation (DcA) of  $\beta$ -ketoesters remained relatively uninvestigated until the independent reports from Tunge and Stoltz in 2004. As part of the body of work produced during my tenure under the mentorship of Dr. Tunge, our group in 2011 compiled a comprehensive report published in Chemical Reviews highlighting the advancements of the DcA reaction. In addition, our group has also investigated the decarboxylative benzylation (DcB) of  $\beta$ -ketoesters and the reaction has shown to be an efficient method for the introduction of benzyl moieties.

The enclosed dissertation thoroughly discusses my contribution to the advancement of palladium-catalyzed decarboxylative carbon–carbon bond forming reactions. As previously reported by the Tunge group, it was realized that, in addition to enolate nucleophiles derived from decarboxylation of  $\beta$ -ketoesters, various other nucleophiles were accessible via this path. In particular, my work involved the development of the palladium-catalyzed DcA, DcB, and decarboxylative arylation (DcAr) of cyanoacetic esters. Palladium-catalyzed ionization of allyl and benzyl cyanoacetic esters facilitates loss of carbon dioxide from cyanoacetate and is believed to allow access to the common intermediacy of non-stabilized metalated nitriles. In the course of our studies we discovered the DcA reaction to be regiospecific in C–C bond formation and to deliver enriched branched to linear allylation products. In addition, treatment of benzyl cyanoacetic esters with a palladium catalyst allows for access to newly benzylated acetonitrile molecules. However, in the case of furylmethyl cyanoesters choice of palladium catalyst determines the formation of benzylated and arylated products, representing the first reported examples for the addition of nitrile anions to Pd- $\pi$ -benzyl complexes.

*For Brandy, Hannah, and Mason*

*And my father Antonio Recio, Jr., who did not have to*

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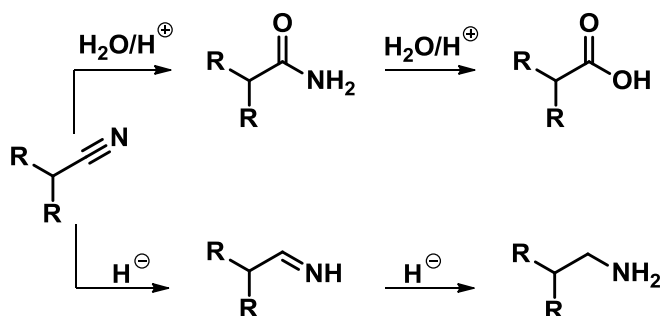
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## **Chapter I:**

### **Transition metal–catalyzed alkylation and arylation of nitriles**

### Cl.1: Synthetic relevance of nitrile functional groups

Nitrile moieties are versatile functional groups in organic synthesis that possess general synthetic accessibility and impressive reactivity.<sup>1</sup> A key feature of nitrile functionalities is manifest by their ability to be rapidly converted to both amides as well as carboxylic acids via hydrolysis. Alternatively, partial reduction to imines and further reduction results in amines (Scheme 1.1).<sup>2-4</sup> As nucleophiles, nitriles benefit from having increased nucleophilicity as a result of having a relatively high  $pK_a$  value ( $\approx 29-31$  in DMSO).<sup>5,6</sup> In addition to the minimal van

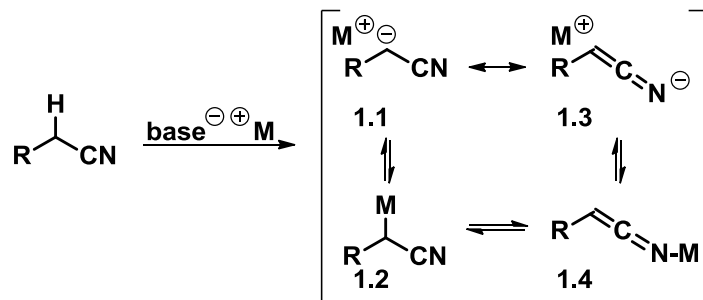


**Scheme 1.1**

der Waal radii's of the cyano moiety which possess an  $A$ -value of approximately 0.2 kcal/mol. In simplest terms, metalated nitriles are believed to exist in several potential configurations (Scheme 1.2).<sup>7</sup> Accounting for the strong electronegativity of the nitrile functionality suggests that a majority of the anionic charge remains on carbon, favoring resonance structure **1.1**. However, rationalizing the greater electronegativity of nitrogen with respect to that of carbon would suggest the ketenimine **1.3** to be the more thermodynamically favorable resonance contributor. In addition, both resonance models could exist as ion separated species as

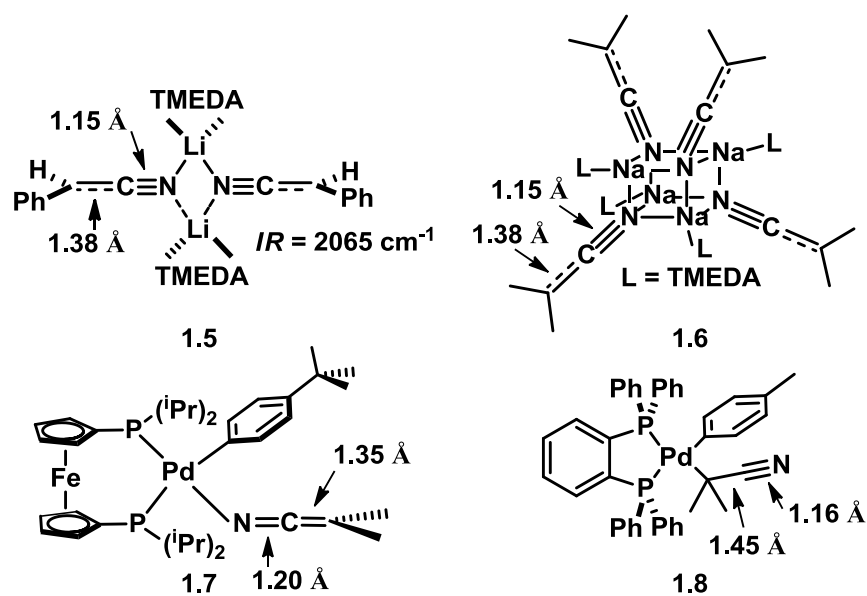


suggested by **1.1** and **1.3**, or as covalent pairs suggested by **1.2** and **1.4**. Crystallographic data suggest a minimal amount of double bond character between the  $\alpha$ -carbon and  $sp$ -hybridized



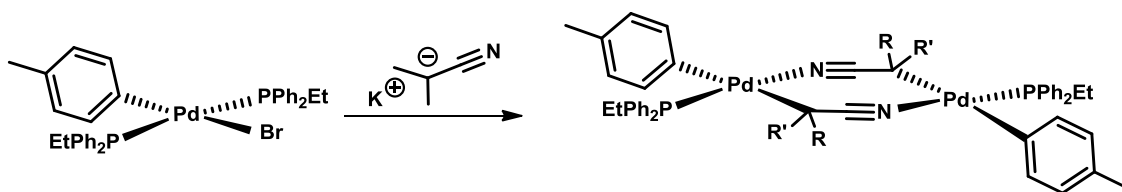
**Scheme 1.2**

carbon as represented by **1.5** and **1.6**, which have bond lengths of 1.38 Å (Figure 1.1).<sup>8</sup> In addition, the amount of elongation of the C–N triple bond associated with the lithiated and sodiated complexes is not consistent with ketenimine formation (**1.5**<sup>8</sup> and **1.6**<sup>9</sup>, Figure 1.1). This result suggests that when lithium and sodium are employed as counter ions, stabilization of the anion is due solely to an electrostatic interaction between the anionic  $\alpha$ -carbon and the elec-



**Figure 1.1**

tron withdrawing nitrile moiety. Theoretically it should be possible for the  $\alpha$ -carbanion to resonate into the nitrile moiety; however this was not observed with nitrile-stabilized carbanions until low-valent, softer transition metal<sup>10</sup> counterions were employed (**1.7** and **1.8**, Figure 1.1).<sup>11,12</sup> As a whole, literature precedent suggested that nitrile-transition metal complexes have nearly equal propensity for C-, and N-bound coordination.<sup>10</sup> However, elegant mechanistic studies performed by Hartwig and co-workers revealed that the mode of nitrile coordination could be greatly influenced via careful choice of ligand.<sup>11,12</sup> As shown in Figure 1.1, employment of a more sterically bulky electron rich ligand favors N-bound coordination of the nitrile as represented by crystallographic data revealing a bond length consistent with ketenimine formation. In addition, use of a less hindered phosphine-based ligand favors the formation of the C-ligated nitrile. Last, another mode of complexation is shown in Figure 1.2, the  $\mu^2$ -C,N coordination was observed when more labile monodentate ligands were utilized (figure 1.2).<sup>11</sup>



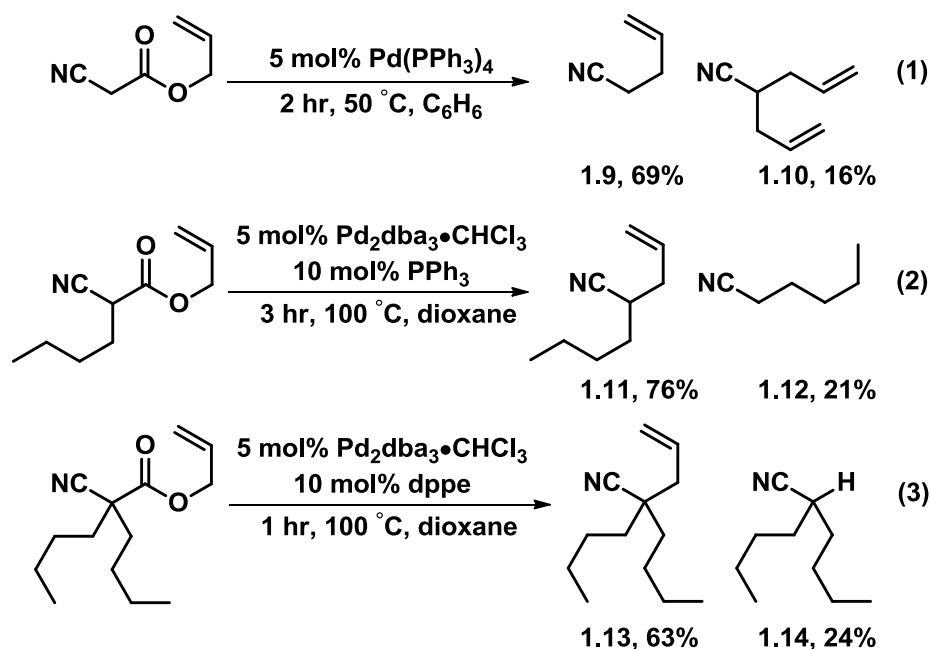
**Figure 1.2**

Having a better understanding of the potential modes of reactivity for metallated nitriles allows for more accurate interpretation of literature precedent and laboratory results. It is well known that there is an abundance of work detailing the allylic alkylation and arylation of distabilized nucleophiles (ie. malononitriles, cyanoacetates, etc.),<sup>13-23</sup> however the direct

functionalization of acetonitrile moieties has received far less investigation. For this reason, the focus of the remainder of this chapter is to highlight the recent advancements involving the transition metal–catalyzed alkylation and arylation of carbanions that are stabilized by a single nitrile moiety.

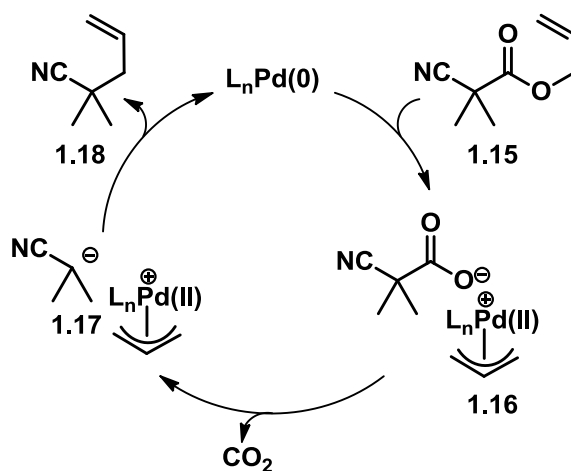
## CI.2: Transition metal–catalyzed alkylation of nitriles

The first decarboxylative allylation of cyanoacetic esters was reported by Saegusa in 1980.<sup>24,25</sup> Saegusa’s seminal work detailed the generation of nitrile-stabilized carbanions under formally neutral conditions. Preliminary studies from Saegusa revealed that treatment of allyl cyanoacetate with  $\text{Pd}(\text{PPh}_3)_4$  provided a mixture of mono- (**1.9**, eq. 1, Scheme 1.3), and diallylated (**1.10**, eq. 1, Scheme 1.3) products. It should be noted that the  $\text{pK}_\text{a}$  values of the conjugate acids of nitrile-stabilized carbanions range from 30–33 in DMSO.<sup>6</sup> Typically lithiated



Scheme 1.3

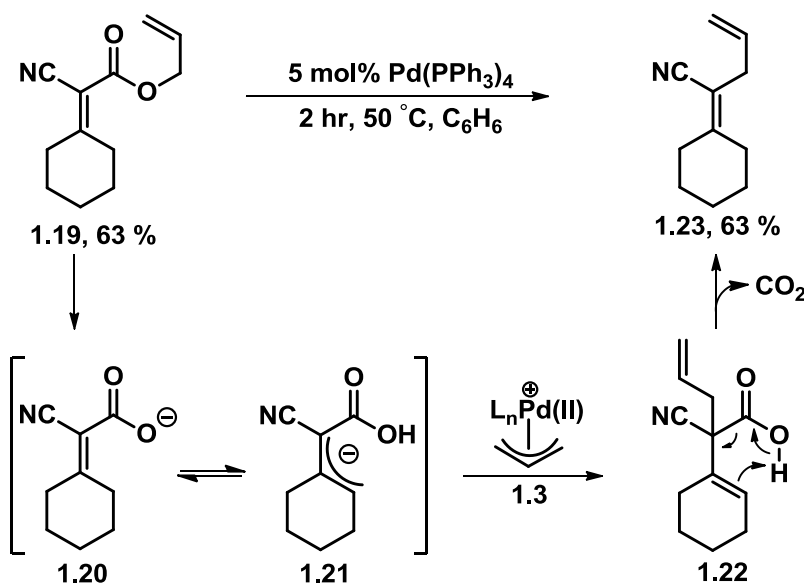
amine bases or hydroxide and heat are required to generate nitrile anions. However under the conditions reported by Saegusa and later Tsuji,<sup>26</sup> nitrile-stabilized carbanions were formed via decarboxylation. In a similar fashion, Tsuji reported the decarboxylative coupling of tertiary allyl cyanoacetates (eq. 2, Scheme 1.3). Despite obtaining 76% of the target monoallylated product, Tsuji obtained 21% of the protonated byproduct **1.12** (Scheme 1.3) as well. In an effort to circumvent the protonation product, Tsuji and coworkers reported the decarboxylative allylation of tertiary cyanoacetic esters employing  $\text{Pd}_2\text{dba}_3$  and  $\text{dppe}$  (eq. 3, Scheme 1.3).<sup>26</sup> Despite modification of the substrate and reaction conditions, a mixture of completing allylation and protonation products were obtained. A proposed catalytic cycle for the decarboxylative coupling of nitriles is as follows (Scheme 1.4): treatment of allyl cyanoacetate **1.15** with a palladium (0) catalyst results in ionization of the allyl ester moiety revealing both the electrophilic palladium- $\pi$ -allyl complex **1.16** and the pro-nucleophile nitrile carboxylate species. Loss of  $\text{CO}_2$  generates the nitrile-stabilized carbanion nucleophile **1.17** which upon recombination with the Pd- $\pi$ -allyl complex regenerates the Pd- catalyst and delivers the allyl-



**Scheme 1.4**

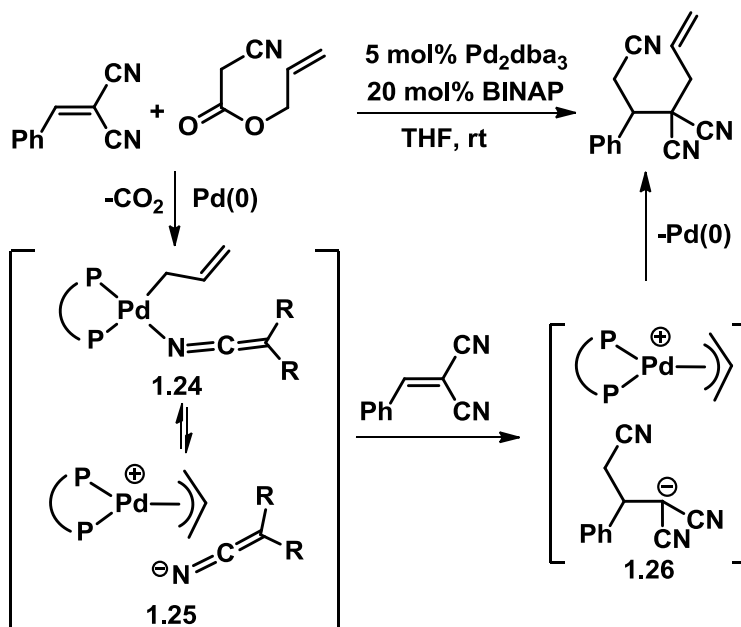
ated product **1.18**. It should be mentioned that this is believed to be the mechanism for the decarboxylative coupling of quaternary nitriles. However, if there is an accessible proton in the  $\alpha$ -position or vinylic to the  $\alpha$ -position as suggested in Scheme 1.5, literature precedent suggests that C–C bond formation takes place before loss of  $\text{CO}_2$ .<sup>26,27</sup>

Treatment of **1.19** with  $\text{Pd}(\text{PPh}_3)_4$  promotes the decarboxylative allylation of a vinyl anion, however the reaction likely proceeds via proton transfer from the vinylic carbon to the carboxylate (**1.20**→**1.21**, Scheme 1.5). Exposure of the allyl anion **1.21** to the palladium- $\pi$ -allyl complex likely generates intermediate **1.22** which can then undergo decarboxylative protonation to deliver the observed allylated product **1.23** (Scheme 1.5).<sup>27</sup> Of course it is certainly feasible that allylation takes place at the  $\gamma$ -carbon which could then undergo sigmatropic rearrangement to generate intermediate **1.22**.<sup>28</sup>



Scheme 1.5

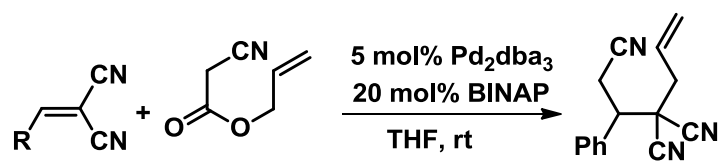
Recently, Yamamoto and coworkers reported a palladium-catalyzed interceptive decarboxylative allylation with benzylidene malononitrile moieties (Scheme 1.6).<sup>29</sup> Treatment of allyl cyanoacetate with a BINAP ligated palladium catalyst in presence of benzylidene malononitrile resulted in insertion of the Michael acceptor between the nitrile-stabilized carbanion and the electrophilic Pd- $\pi$ -allyl complex, resulting in the formation of **1.26** (Scheme 1.6). As shown in Scheme 1.6, loss of CO<sub>2</sub> reveals two equilibrating intermediates, the Pd(II)-ligated  $\sigma$ -allyl, N-bound ketenimine **1.24**<sup>30,31</sup> or the solvent separated Pd- $\pi$ -allyl complex and nitrile anion as suggested by **1.25**.<sup>32</sup> Subsequent  $\beta$ -nucleophilic addition of acetonitrile to ethylidene malononitrile generates the ion pair suggested by **1.26** which combined to form the  $\beta$ -acetonitrile- $\alpha$ -allylated product (Scheme 1.6). A brief investigation of the ethylidene malononitrile scope revealed that both electron rich (entries 1 and 2, Table 1.1) as well as polyaromatic (entry 4), heteroaromatic, and alkyl moieties were tolerated under the reaction



**Scheme 1.6**

conditions nitrile scope revealed that both electron rich (entries 1 and 2, Table 1.1) as well as polyaromatic (entry 4), heteroaromatic, and alkyl substituents were tolerated under the reaction conditions providing products in good yield. However, the reaction employing the electron deficient benzylidene malononitrile was problematic, resulting in only 35% yield (entry 3, Table 1.1).

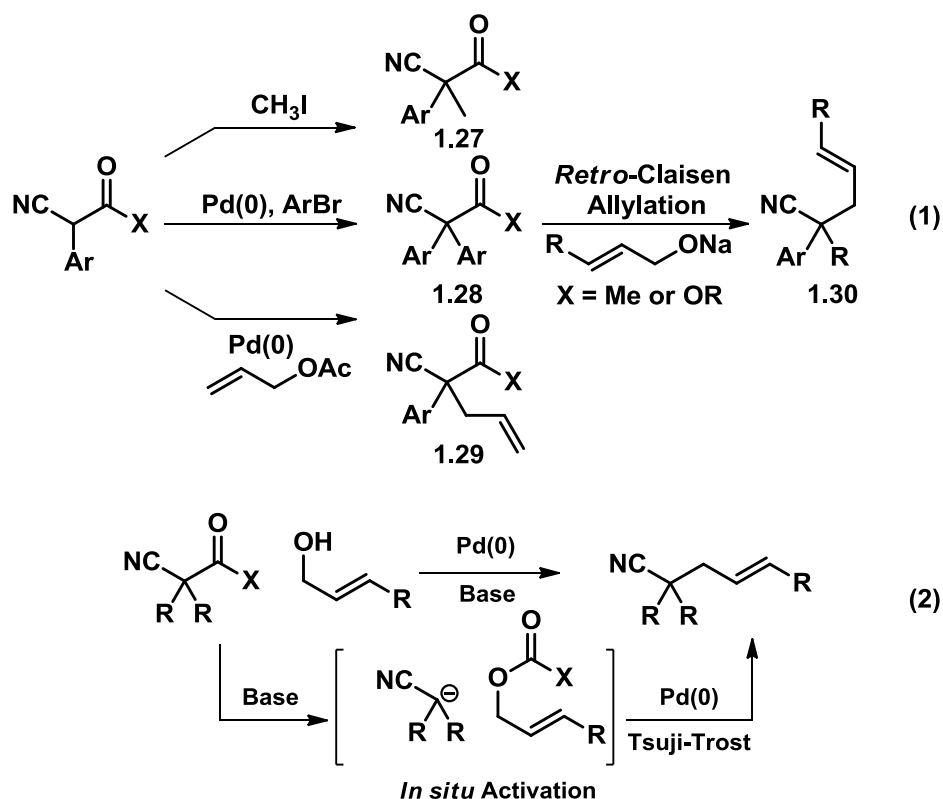
**Table 1.1: Interceptive decarboxylative coupling of allyl cyanoacetate**



Entry	R	Time	Yield
(1)	4-Me-C <sub>6</sub> H <sub>4</sub>	3.5	76
(2)	3-MeO-C <sub>6</sub> H <sub>4</sub>	4.0	68
(3)	4-Cl-C <sub>6</sub> H <sub>4</sub>	6	35
(4)	2-naphthyl	3	83
(5)	2-thienyl	4.5	70
(6)	cyclopropyl	4.5	75

In addition to a report from Recio and Tunge for the palladium-catalyzed decarboxylative allylation of nitriles in 2009,<sup>33</sup> Grenning and Tunge reported an alternative method for the allylation of nitriles in 2011 (Scheme 1.7).<sup>34</sup> The method involved the *retro*-Claisen activation of phenylacetone nitrile carbanions followed by palladium-catalyzed allylation. As shown in Scheme 1.7, broad substrate scope was shown via the decarboxylative allylation (DaA) of aryl, alkyl (**1.27**), diary (**1.28**), and aryl, allyl (**1.29**) cyanoacetone compounds (eq. 1, Scheme 1.7). The authors propose that treatment of the acyl nitrile compounds with allyl alkoxide moieties induces the *retro*-Claisen formation of a nucleophilic nitrile carbanion and an allyl

acetate (X= Me, Scheme 1.7) or carbonate (X = OEt, Scheme 1.7) species which can undergo a subsequent Tsuji-Trost allylation upon exposure to palladium (eq. 2, Scheme 1.).<sup>32,35</sup> The bimolecular deacylative allylation showcases the versatility of the reaction via the facile activation of both pronucleophilic and proelectrophilic coupling partners. As shown in Table 1.2, both  $\alpha$ - alkyl, and  $\alpha$ -allyl phenylacetonitriles smoothly undergo allylation via retro-Claisen



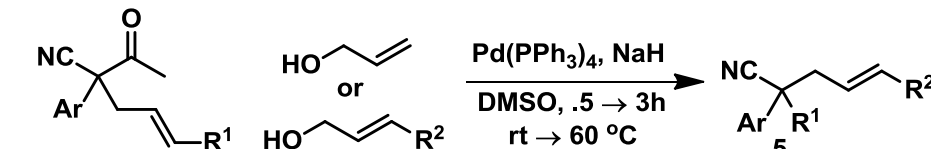
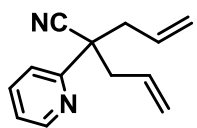
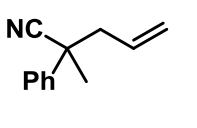
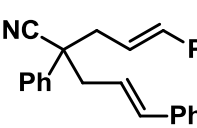
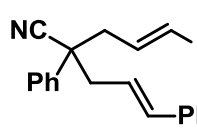
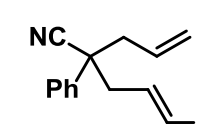
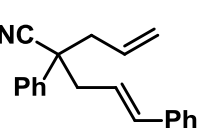
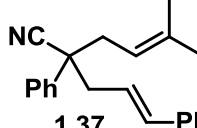
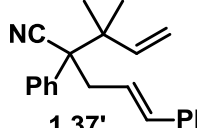
**Scheme 1.7**

activation from allyl alcohol. It should also be noted that heteroaromatic, polyaromatic, and electron rich aromatic (not shown) nitriles were allylated in good yield. In addition, the reaction scope was extended to include allyl alcohol moieties that provide linear and branched products (Table 1.2). What is particularly interesting is the ratio of linear to branched

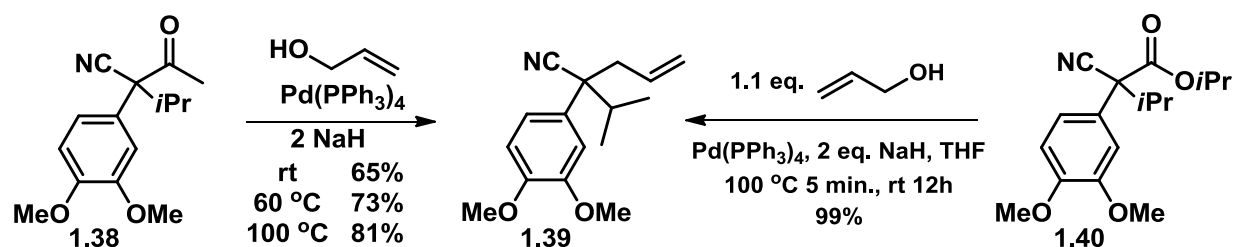


selectivities observed when employing cinnamyl alcohol **1.35** and prenyl alcohol **1.37** and **1.37'** (Table 1.2). When cinnamyl alcohol was utilized, the linear product was obtained exclusively (**1.35**, Table 1.2). However, when switching to the prenyl moiety, a 1:1 mixture of linear and branched products was observed. This result likely suggests that the DaA involving the cinnamyl alcohol proceeds via an outer-sphere mechanism (ie. sodiated nitrile) generating the linear product via nucleophilic attack at the least hindered position of the electrophile.<sup>32,35</sup> The selectivity observed with the reaction utilizing the prenyl alcohol suggests the sodiated nitrile potentially undergoes a transmetalation to the palladated nitrile.<sup>30,31,33</sup> The transmetalation facilitates competing outer- and inner-sphere mechanisms for C–C bond formation. This mode of reactivity will be discussed in depth in chapter 2 (See section CII.4). The DaA method has proven to be an efficient protocol for obtaining 1,6 heptadiene nitriles, substrates that have

**Table 1.2: Deacylative allylation of cyanoacetone derivatives**

			
R <sup>1</sup> = Ph or H	HO-CH <sub>2</sub> -CH=CH-R <sup>2</sup>	R <sup>1</sup> = Ph	HO-CH <sub>2</sub> -CH=CH-R <sup>2</sup>
 <b>1.31</b> 92%	 <b>1.32</b> 74%	 <b>1.35</b> , 3 h, 81%	 <b>1.36</b> , 3 h, 70%
 <b>1.33</b> 94%	 <b>1.34</b> 92%	 <b>1.37</b>	 <b>1.37'</b>
		71%, 60:40 <i>l:b</i>	

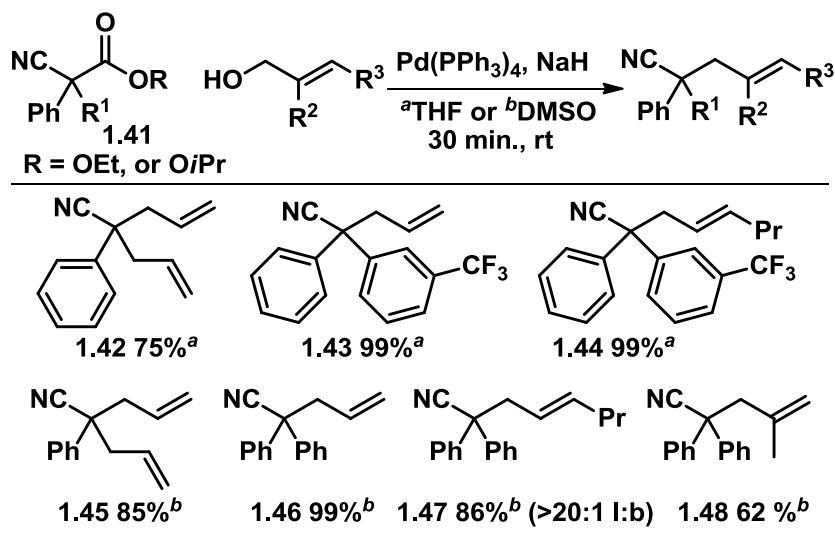
broad application in cycloisomerization reactions. Palladium-catalyzed allylic alkylation of the nitrile ketones followed by DaA with various allyl alkoxide moieties provided the 1,6 heptadiene products.



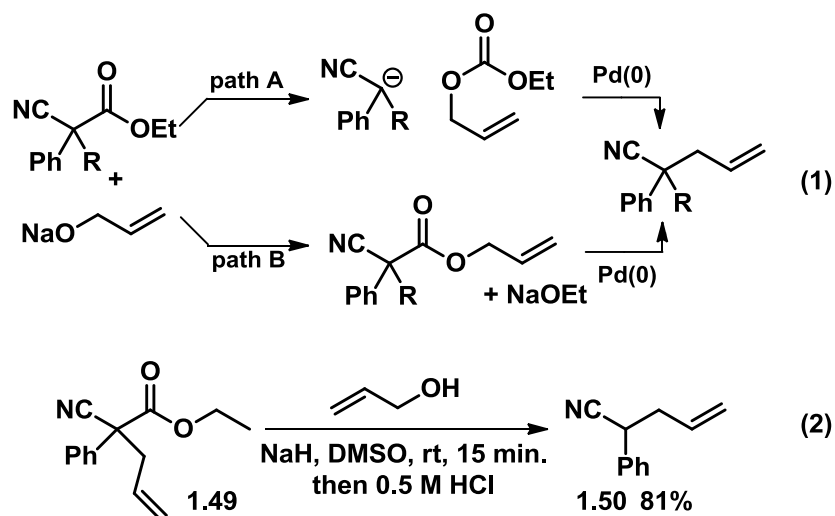
**Scheme 1.8**

In addition to utilizing the cyanoacetone derivatives, Grenning and Tunge were able to extend the DaA method to the more accessible cyanoesters **1.41** (Table 1.3). As showcased by the bifurcated approach to the synthesis of **1.39** which is an intermediate in the synthesis of verapamil via Nelson's protocol.<sup>36</sup> It should be noted that the acetonitrile ester (**1.40**, Scheme 1.) is synthesized via Hartwig's<sup>16</sup> arylation of isopropyl cyanoacetate followed by alkylation. This synthetic modification was seen as an improvement over the needed acylation of phenylacetonitriles required to obtain the cyanoacetone starting material **1.38** (Scheme 1.8). As suggested in Scheme 1.8, retro-Claisen allylation of **1.40** looks to be the optimal method for obtaining the allylated nitrile precursor **1.39**. In addition to the synthesis of precursor **1.39**, Table 1.3 details the scope of the retro-Claisen allylation from ethyl and isopropyl cyanoacetates. As shown diaryl- (**1.43**, **1.44**, **1.46**, **1.47**, **1.48**), and aryl, allyl (**1.42** and **1.45**) cyanoacetates smoothly undergo C–C bond formation via activation from allyl alkoxide derivatives.

Table 1.3: Deacylative allylation of ethyl and isopropyl cyanoacetate



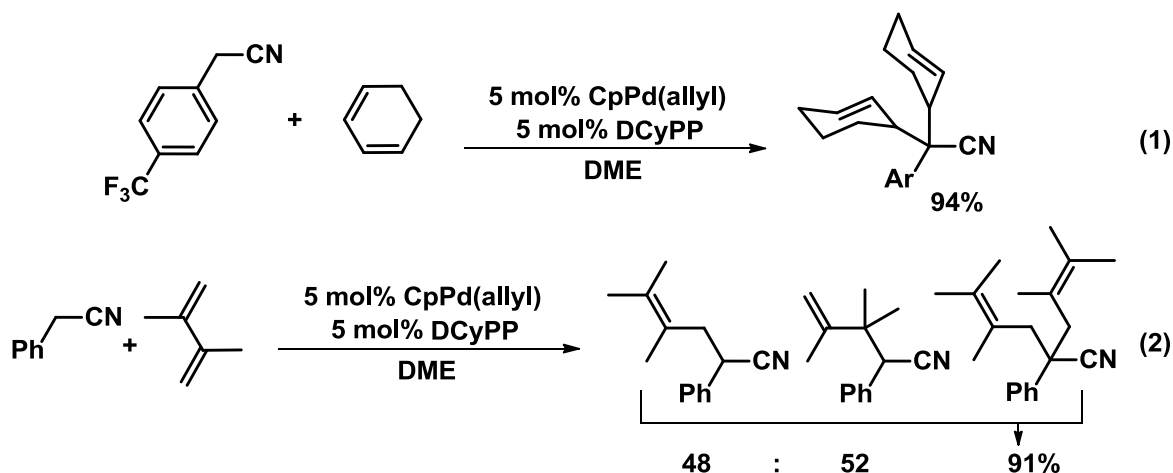
Last, given that the decarboxylative allylation of phenylacetonitriles has been reported<sup>24,26,33</sup> and is the focus of the next chapter; it was feasible to speculate that rather than a retro-Claisen allylation reactive pathway (**path A**, eq. 1, Scheme 1.9), a transesterification followed by decarboxylative allylation pathway was responsible for C–C bond formation (**path B**



Scheme 1.9

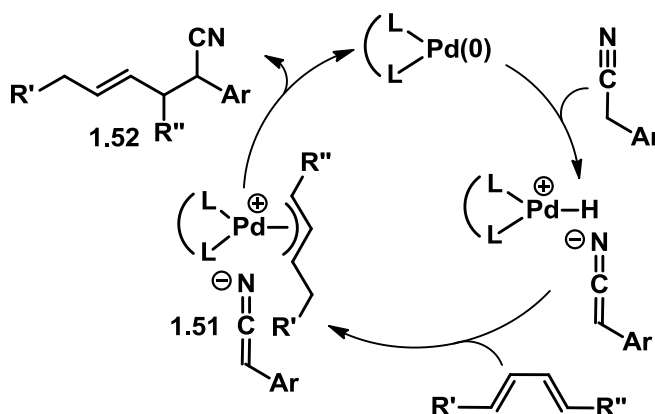
eq. 1, Scheme 1.9). A simple control reaction was performed to determine which reaction pathway was operative (eq. 2, Scheme 1.). Treatment of **1.49** with allyl alkoxide in absence of palladium revealed only the protonated allyl phenylacetonitrile **1.50**. This result confirmed that retro-Claisen activation (**path A**) was indeed the path to C–C bond formation and that the  $pK_a$  of phenylacetonitrile is lower than ethoxide in DMSO.<sup>5,6</sup>

Hartwig and coworkers also reported the allylation of nitriles, however did so via a slightly different reactive manifold (Scheme 1.10).<sup>37</sup> Taking advantage of the lower  $pK_a$  of phenylacetonitrile, exposure to a palladium (0) catalyst generates a nitrile-stabilized carbanion. As shown in Scheme 1.10 treatment of 4-trifluoromethyl phenylacetonitrile with 1,3 cyclohexadiene in the presence of dicyclohexylphosphinopropane (DCyPP) ligated CpPd(allyl) lead to formation of the diallylated product (eq. 1, Scheme 1.10). In addition, subjecting phenylacetonitrile and 2,3-dimethylbutadiene to identical reaction conditions resulted in a mixture of mono- and diallylated products. Even more interesting, is the observed ratio of



**Scheme 1.10**

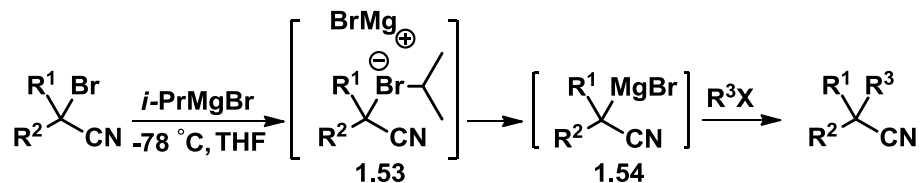
linear and branched products. This result provided another potential example of competing inner- and outer-sphere C–C bond forming mechanisms (see section CII.4).<sup>30,31</sup> The reaction is proposed to proceed via the catalytic cycle in Scheme 1.11. Exposure of the Pd(0) catalyst to the phenylacetonitrile derivative generates a nitrile-stabilized carbanion and a palladium hydride species. Regioselective hydropalladation allows for Pd- $\pi$ -allyl formation as suggested by **1.51**. Nucleophilic attack of the Pd- $\pi$ -allyl complex produces the product **1.52** and regenerates the palladium catalyst.



**Scheme 1.11**

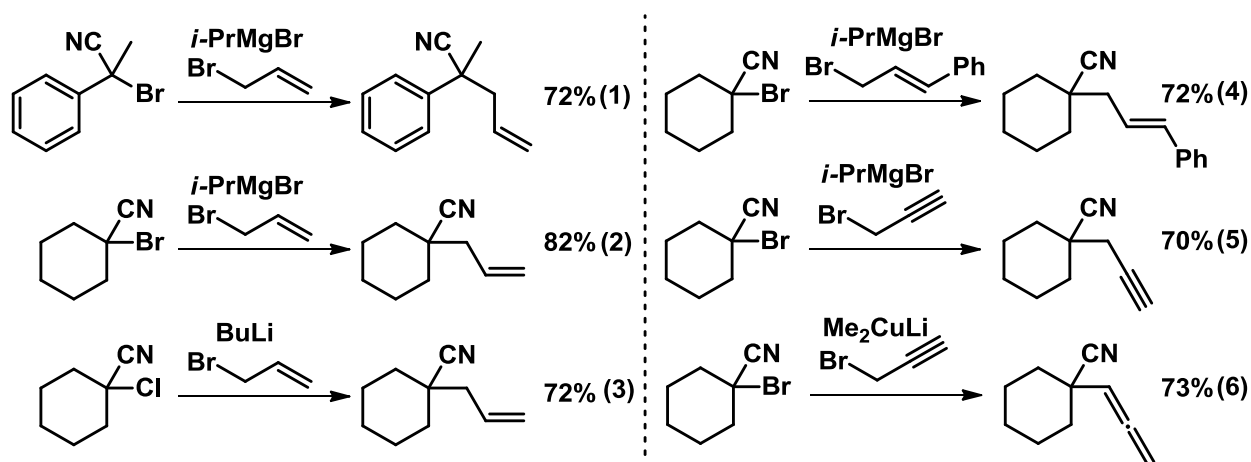
In a different reactive manifold, Fleming and coworkers developed a halogen–metal exchange with  $\alpha$ -halonitriles as an alternative to the traditional use of amide base for the generation of metalated nitriles (Scheme 1.12).<sup>38,39</sup> As shown in Scheme 1.12, Fleming takes advantage of an extremely fast halogen–metal exchange to obtain the magnesiated nitrile **1.54**; the process likely proceeds via bromate intermediate **1.53** which upon collapse and exposure to the electrophile generates the quaternarized nitrile product. A brief look at the scope of the reaction revealed that the method was quite efficient for the allylation of nitriles as shown in

Scheme 1.13. Subjecting  $\alpha$ -bromonitriles to isopropyl magnesium bromide and allyl bromide either sequentially, or *in situ* lead to the formation of the allylated nitriles (eq. 1 and 2, scheme



**Scheme 1.12**

1.13). The  $\alpha$ -chloronitriles worked more efficiently when butyl lithium was employed. In addition, incorporating cinnamyl bromide into the reaction conditions lead to the formation of cinnamylated nitriles (eq. 4, Scheme 1.13). It should also be noted that the linear product was



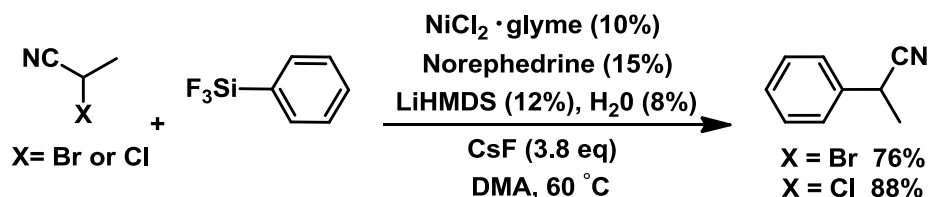
**Scheme 1.13**

formed exclusively. Another interesting example was the regioselectivity observed via modification of the metalating reagent. Treatment of cyclohexyl bromonitrile with isopropyl magnesium bromide and propargyl bromide lead to the  $\text{S}_{\text{N}}2$  alkylation product (eq. 5, Scheme 1.13). However, simple modification of the reaction conditions with  $\text{Me}_2\text{CuLi}$  reagent resulted

in the  $S_N2'$  alkylation product (eq.6, Scheme 1.13). Fleming suggests that the change in the regiochemistry for the alkylation can be attributed to the precoordination of the cuprate with the alkynyl moiety of the propargyl bromide. In addition, the coordination allows for a more classical reductive elimination of the C-bound cuprate and allenyl moiety. In contrast, the magnesiated nitrile reacts via a more direct displacement mechanism.

### Cl.3: Transition metal–catalyzed arylation of nitriles

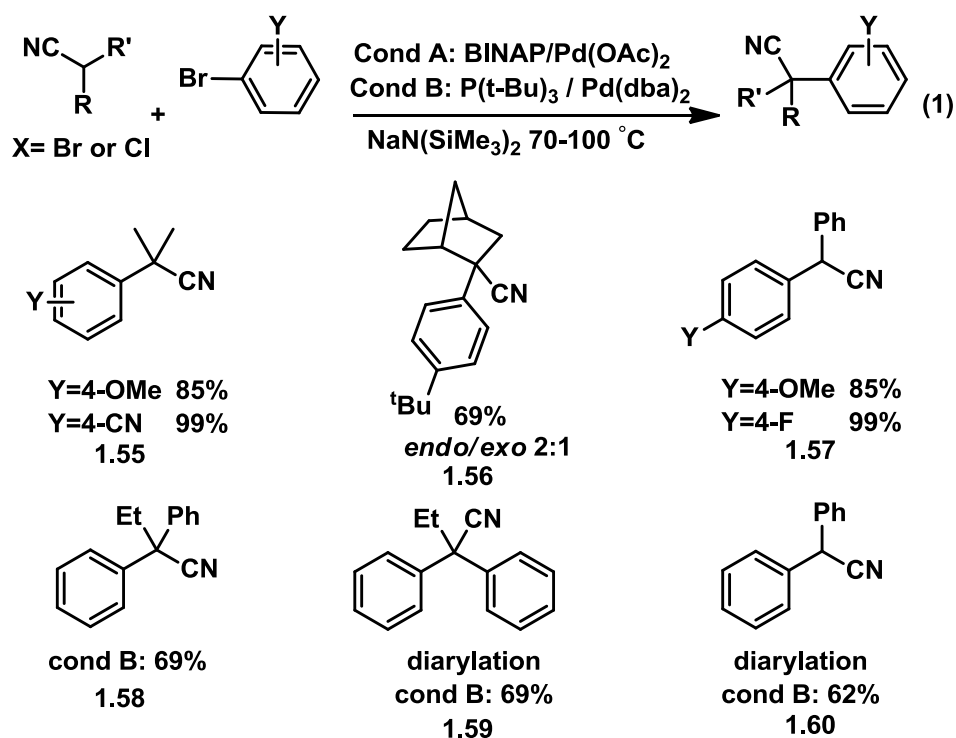
In keeping with the use of  $\alpha$ -halonitriles, Fu and coworkers reported a couple of examples of nickel-catalyzed Hiyama coupling with an aryl trifluorosilane (Scheme 1.14).<sup>40</sup> The reaction required a witch's brew of reagents that included  $\text{NiCl}_2 \cdot \text{glyme}$ , norephedrine, LiHMDS as base and CsF to activate the arylsilane. The reaction was performed in DMA at 60 °C. As shown in Scheme 1.14, the  $\alpha$ -bromo- and  $\alpha$ -chloronitriles were converted to the arylated products in good yield. It should also be noted that in a similar reactive manifold, the Lei group reported a nickel-catalyzed Suzuki type cross coupling of  $\alpha$ -bromonitriles and aryl boronic acids.<sup>41</sup>



**Scheme 1.14**

In 2002, the Hartwig group reported the  $\alpha$ -arylation of acetonitrile moieties.<sup>11,17</sup> Up until this point, carbanions stabilized by a single nitrile moiety were difficult to functionalize as

a result of their high  $pK_a$ . This inherent property of nitriles suggested that in order to develop a catalytic arylation of nitriles, a strong base would be required in addition to a ligand that could facilitate reductive elimination. Because the nitrile moiety is strongly electron withdrawing it was suggested that the reductive elimination was going to be difficult. Indeed, as discussed in the introductory paragraph Hartwig and coworkers were able to determine that electron rich bulky ligands such as BINAP and *tert*-butyl phosphine were competent for catalytic arylation. As shown in Scheme 1.15, subjecting various nitriles to either a BINAP or  $P(t\text{-Bu})_3$  ligated



**Scheme 1.15**

palladium catalyst in the presence of a strong base and heat provided mono- and diarylated nitriles (Scheme 1.15). A brief overview of the reaction scope revealed that dimethyl acetonitrile readily underwent arylation; however the yields suggest that electron poor

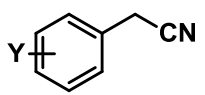
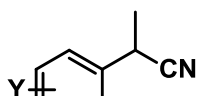
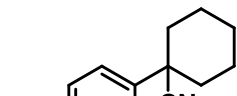
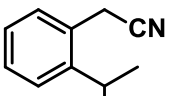
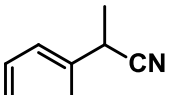
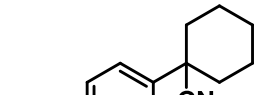
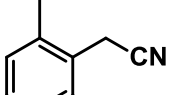
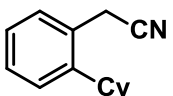
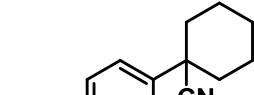


aromatic coupling partners provide optimal conversion (**1.55**, Scheme 1.15). The tertiary norbornane nitrile was also converted to the arylation product in 69% yield and with a 2:1 *endo/exo* ratio. It should also be noted that use of butyronitrile and acetonitrile required a modification in the reaction conditions to the  $P(t\text{-Bu})_3$  ligated palladium catalyst. Despite this modification, the major products were diarylation, likely stemming from the fact that the phenylacetonitrile intermediate is more activated (reduced  $pK_a$ ) toward arylation. In addition to this report, it should be noted that the Verkade group reported a protocol for the  $\alpha$ -arylation of nitriles using triaminophosphine base  $P(i\text{BuNCH}_2\text{CH}_2)_3\text{N}$  along with essentially identical catalyst conditions employed by Hartwig.<sup>42</sup> Recently, Fleming and coworkers also reported the  $\alpha$ -arylation of valeronitrile showcasing the utility of a  $\text{TMPZnCl}\cdot\text{LiCl}$  base in conjunction with the conditions reported by Hartwig.<sup>43</sup>

In a follow up to their seminal report, Hartwig and coworkers address the large amounts of diarylation observed with butyronitrile and acetonitrile derivatives (**1.58** and **1.60**, Scheme 1.15) via attenuation of the nucleophilic nitrile with trimethylsilane.<sup>44</sup> As shown in Table 1.4, treatment of various substituted and unsubstituted trimethylsilyl acetonitriles with appropriate catalytic conditions indeed afforded monosubstituted arylated products. In addition, both tertiary and quaternary nitriles were readily obtained via appropriate reaction conditions. As suggested by Hartwig, the circumvention of the large amounts of diarylation and homodimerization is likely due to the fact that silicon cyanoalkyl reagents are less basic than their alkali metal surrogates resulting in higher functional group tolerance. A brief overview of the reaction scope reveals that electron deficient aryl bromides more readily undergo C–C bond formation, however electron rich aromatics are also converted in good yield as well (**1.61**, Table

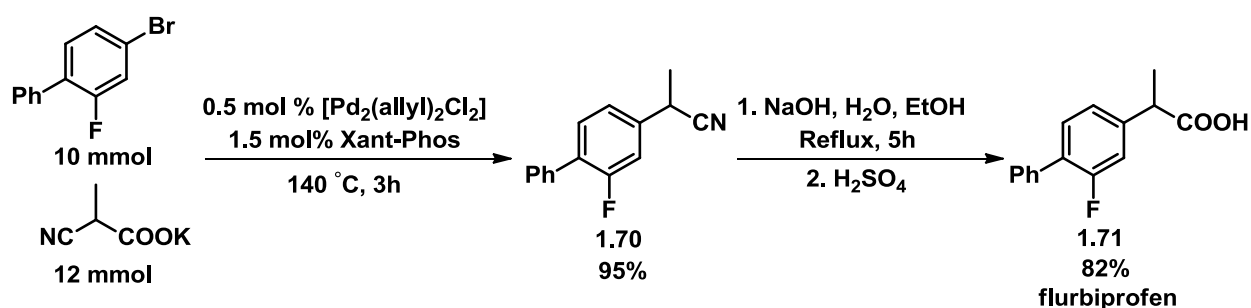
1.4). In addition, ortho substitution does not look to have a large influence on product formation as represented by **1.64** and **1.67**. The propionitrile is also smoothly arylated, albeit with slightly reduced yields. The loss in yield is potentially due to the thermodynamic favorability of formation of the styrenyl compounds via  $\beta$ -hydride elimination (**1.62**, **1.65**, **1.68**). Last, the tertiary alkyl nitriles were arylated with good yields (**1.63**, **1.66**, **1.69**).

**Table 1.4. Mild palladium-catalyzed selective monoarylation of nitriles**

$\text{ArBr} + \text{TMS}-\text{C}(\text{R}^1)(\text{R}^2)-\text{CN} \xrightarrow[\text{DMF, 90}^\circ\text{C}]{2 \text{ mol\% Pd/L 0.5 eq ZnF}_2} \text{Ar}-\text{C}(\text{R}^1)(\text{R}^2)-\text{CN}$		
R <sup>1</sup> =R <sup>2</sup> =H	R <sup>1</sup> =Me, R <sup>2</sup> =H	R <sup>1</sup> =R <sup>2</sup> =cyclohexyl
 <b>1.61</b> Y=4-NMe <sub>2</sub> 83% <sup>c</sup> Y=4-CF <sub>3</sub> 99% <sup>a</sup>	 <b>1.62</b> Y=4-OMe 71% <sup>a</sup> Y=4-CN 82% <sup>a</sup>	 <b>1.63</b> 62% <sup>a</sup>
 <b>1.64</b> 69% <sup>b</sup>	 <b>1.65</b> 60% <sup>b</sup>	 <b>1.66</b> 77% <sup>a</sup>
 <b>1.67</b> 84% <sup>b</sup>	 <b>1.68</b> 64% <sup>b</sup>	 <b>1.69</b> 84% <sup>a</sup>
<sup>a</sup> Pd <sub>2</sub> dba <sub>3</sub> /Xantphos <sup>b</sup> Pd <sub>2</sub> dba <sub>3</sub> /P( <i>t</i> -Bu) <sub>3</sub> <sup>c</sup> Pd <sub>2</sub> dba <sub>3</sub> /PhP( <i>t</i> -Bu) <sub>3</sub>		

Recently, Liu reported the palladium-catalyzed decarboxylative coupling of potassium and sodium cyanoacetate salts with aryl halides (Scheme 1.16).<sup>45</sup> The reaction involves the use of Pd<sub>2</sub>(allyl)<sub>2</sub>Cl<sub>2</sub> and Xantphos ligand at elevated temperature. It should be noted that this reaction is extremely robust and the scope of the reaction is impressively large. This method

was showcased via application to a gram scale synthesis of flurbiprofen, a nonsteroidal anti-inflammatory drug. Decarboxylative coupling of the cyanocarboxylate and aryl halide afforded the phenylacetonitrile **1.70** in nearly quantitative yield. Subsequent hydrolysis of the nitrile moiety and acidification provided the drug flurbiprofen. In the same year, Kwong reported a very similar protocol for the decarboxylative diarylation of potassium and sodium cyanoacetates.<sup>46</sup> The first arylation is initiated under conditions reported by Hartwig and a subsequent decarboxylation facilitates the second arylation.



**Scheme 1.16**

The examples above discuss the recent advancements made involving the transition metal-catalyzed alkylation and arylation of nitriles. It is important to note, that there is another important class of reactions that involve the transition metal-catalyzed activation of nitriles toward nucleophilic additions to carbonyl compounds. These methods involve the use of Cu,<sup>47-50</sup> Ru,<sup>14,51-60</sup> Rh,<sup>13,61-63</sup> Ir<sup>64</sup> and even lanthanide catalysts.<sup>20,22,65-67</sup>

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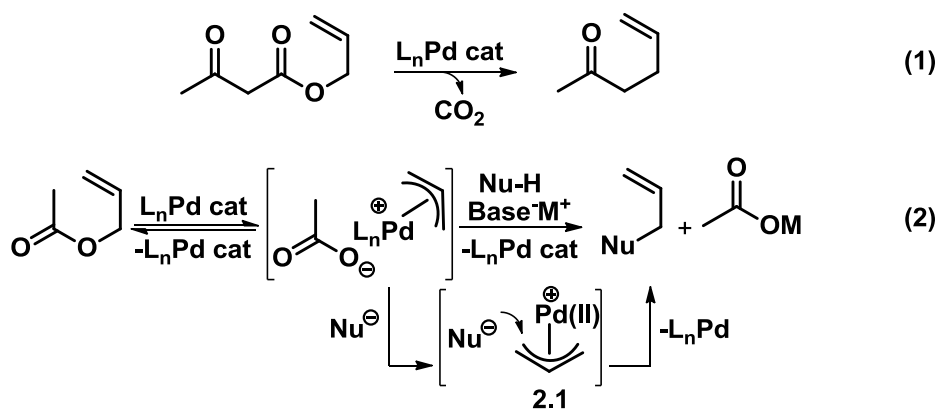
## **Chapter II.**

### **Regiospecific Decarboxylative Allylation of Nitriles**



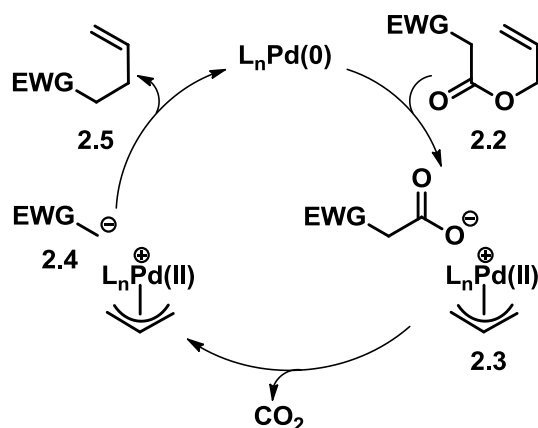
## CII.1: Introduction to the decarboxylative allylation reaction

Recently, transition metal-catalyzed decarboxylative carbon–carbon bond forming reactions have become powerful synthetic tools for organic chemists.<sup>1-8</sup> A specific subset of this class of reactions was reported by Saegusa<sup>9</sup> and Tsuji<sup>10</sup> in 1980. The reaction involved the palladium-catalyzed decarboxylative allylation (DcA) of allyl  $\beta$ -ketoester substrates (eq. 1, Scheme 2.1).<sup>9,10</sup> This methodology was likely inspired by the *Tsuji-Trost* reaction, which involves treatment of allyl acetate with a palladium catalyst in the presence of various activated nucleophiles, resulting in the production of new carbon–carbon bonds.<sup>11-14</sup> The *Tsuji-Trost* reaction proceeds via formation of a highly electrophilic Pd- $\pi$ -allyl complex **2.1** generated upon ionization of allyl acetate with a palladium catalyst.<sup>13</sup> Subsequent nucleophilic attack of the



**Scheme 2.1**

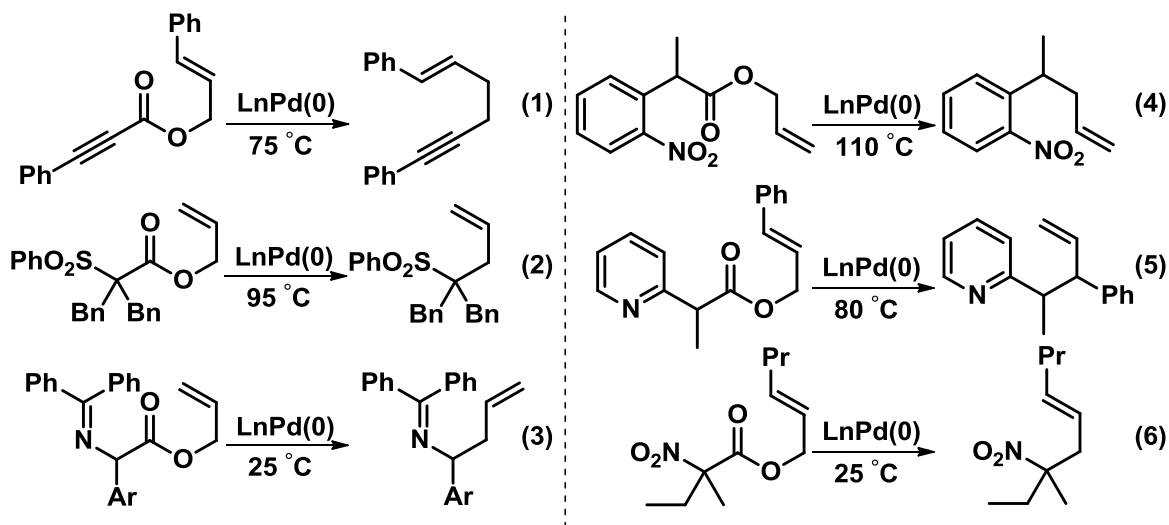
electrophilic species **2.1** results in C–C bond formation generating newly allylated products (eq. 2, Scheme 2.1). In an analogous reactive manifold, a simplified catalytic cycle for the DcA reaction proceeds as follows:<sup>9</sup> treatment of allyl ester substrate **2.2** with a palladium (0) catalyst results in ionization of the allyl ester moiety, unveiling both the palladium- $\pi$ -allyl complex **2.3**



**Scheme 2.2**

and the pro-nucleophilic carboxylate species (EWG=electron withdrawing group). Loss of  $\text{CO}_2$  generates the carbanion nucleophile **2.4** which upon recombination with the Pd- $\pi$ -allyl complex regenerates the Pd(0) catalyst and delivers the allylated product **2.5**. To this end, it is now understood that decarboxylation is largely dependent upon the  $\text{pK}_a$  of the conjugate acid of the ensuing carbanion.<sup>8</sup> In essence, the ability of the EWG group to stabilize anionic charge through resonance or inductive effects determines the ease with which  $\text{CO}_2$  is released. This reactivity represents a major difference between the decarboxylative allylation method and the *Tsuji-Trost* reaction. Traditionally, *Tsuji-Trost* reactions are performed with di-stabilized nucleophiles ( $\text{Nu-H}$  = malonate esters, acetylacetone, malononitriles, etc, eq. 2, Scheme 2.1) and require strong bases for nucleophiles with  $\text{pK}_a$  values above 16 (ie. enolates  $\text{pK}_a \approx 20$ ).<sup>13</sup> In contrast, the DcA method allowed for accessing enolate nucleophiles in the absence of base via taking advantage of the thermodynamic favorability of loss of  $\text{CO}_2$  from an  $\beta$ -keto carboxylate (**2.3**  $\rightarrow$  **2.4**, EWG =  $\text{C(O)R}$ , Scheme 2.2).<sup>8</sup> Much of the work reported by Saegusa and Tsuji addressed  $\alpha$ -allylation of enolates (EWG=  $\text{C(O)R}$ ),<sup>9,10,15</sup> however many other electron

withdrawing groups (EWG) are now known to facilitate decarboxylation upon ionization of the allyl ester moiety (Scheme 2.3).<sup>8</sup>



**Scheme 2.3**

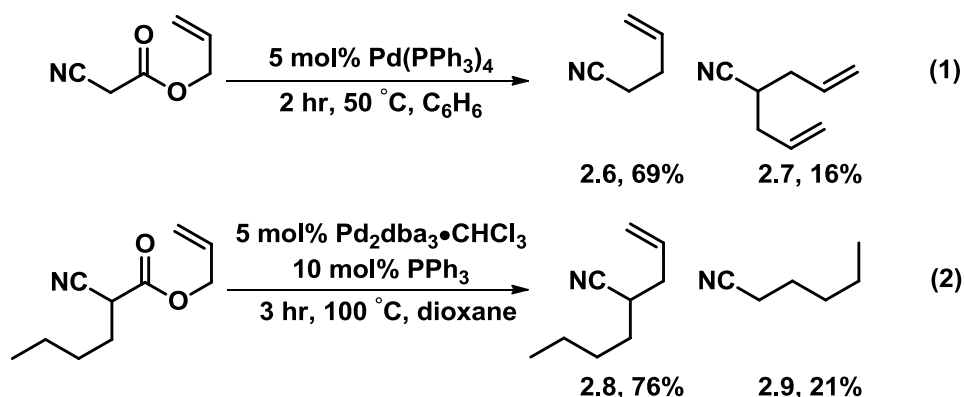
In addition to further development of the DcA of allyl  $\beta$ -ketoesters,<sup>16-19</sup> the Tunge group has also developed the DcA of various other nucleophiles (Scheme 2.3).<sup>8</sup> Phenyl propiolate esters were competent substrates for DcA as exhibited by Rayabarapu, suggesting  $sp$ -hybridized carbanions were efficient nucleophiles for C–C bond formation.<sup>20</sup> Weaver's contribution entailed the allylation of  $\alpha$ -sulfonyl carbanions (eq. 2, Scheme 2.3).<sup>21</sup> This development was significant because analogous to Rayabarapu's work it represented an example of the decarboxylative generation of carbanions being stabilized solely by inductive effects.<sup>22</sup> Waetzig reported the facile DcA of both nitroaromatic as well as heteroaromatic allyl esters (eq. 4, eq. 5, Scheme 2.3).<sup>23,24</sup> The latter reaction represents the upper limit in terms of the stability of the carbanion ( $pK_a$  of picoline  $\approx 35$ ) obtained from decarboxylation.<sup>24</sup> It should be noted that the highly basic picolinic anion was generated at relatively low temperatures and

under formally neutral conditions. In addition, Burger<sup>25</sup> and Grenning<sup>26</sup> showed that  $\alpha$ -imino carbanions as well as highly reactive, somewhat problematic, nitronate carbanions were efficiently allylated via decarboxylative coupling (eq. 3 and eq. 6, Scheme 2.3). In addition to the above stabilized nucleophiles, nitrile stabilized carbanions are coveted nucleophiles that are difficult to generate in absence of amide bases.<sup>27-29</sup> Before 2009, only two examples for the palladium-catalyzed decarboxylative allylation of nitriles had been reported.<sup>9,15</sup> Moreover, there are only a few examples in the literature for the transition metal-catalyzed decarboxylative generation of nitrile-stabilized carbanions.<sup>30-32</sup> As an alternative method for the allylation of metalated nitriles, Grenning and Tunge reported the palladium-catalyzed deacylative allylation of nitriles.<sup>33</sup> Fleming and Knochel reported that similar allylated products are obtained from Grignard reagents and  $\alpha$ -halo nitriles.<sup>34-36</sup> The next section will describe the palladium-catalyzed decarboxylative allylation of nitrile stabilized carbanions.<sup>37</sup>

## CII.2: *Decarboxylative allylation of tertiary $\alpha$ -nitrile carbanions*

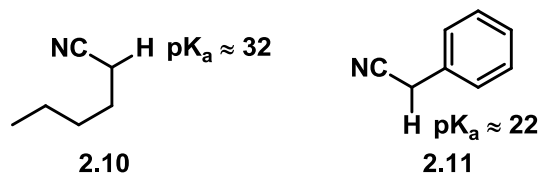
In 1980, Saegusa reported a single example of the palladium-catalyzed decarboxylative allylation of cyanoacetic esters (eq. 1, Scheme 2.4).<sup>9</sup> Saegusa employed  $\text{Pd}(\text{PPh}_3)_4$  as the catalyst to obtain the target product **2.6** in 69% yield in addition to 16% formation of the diallylated compound **2.7**. In 1987, Tsuji reported the decarboxylative allylation of tertiary cyanoacetic esters with a triphenylphosphine modified palladium catalyst in which he obtained the allylated product **2.8** in 76% yield in addition to 16% of the protonation product **2.9** (eq. 2, Scheme 2.4).<sup>15</sup> The above literature precedent suggested that competing diallylation as well as protonation products could be problematic with  $\alpha$ -protio containing substrates. With this

knowledge in hand, studies to determine catalytic conditions for the DcA of tertiary allyl cyanoacetates that circumvented the formation of both the diallylated as well as the protonation products were undertaken.



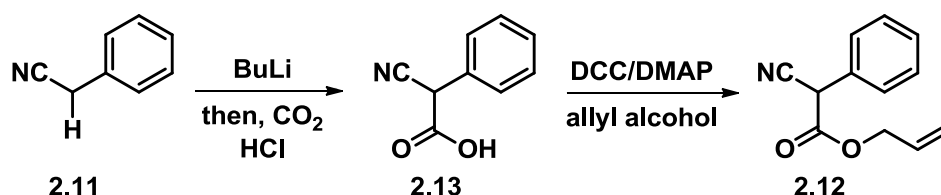
**Scheme 2.4**

Saegusa's and Tsuji's results suggest that increased  $\text{pK}_a$  of the conjugate acid of the nitrile carbanion generated via decarboxylation was leading to formation of the protonated product **2.9** (Scheme 2.4). Known  $\text{pK}_a$  values for alkyl-substituted acetonitriles **2.10** range from 30-33 in DMSO, however addition of a phenyl substituent (ie. benzyl cyanide) reduces the  $\alpha$ -nitrile  $\text{pK}_a$  to  $\approx 22$  (**2.11**, Scheme 2.5).<sup>38,39</sup> For this reason,  $\alpha$ -phenyl cyanoacetic esters were chosen initially as test substrates for DcA of nitrile stabilized carbanions.  $\alpha$ -Phenyl allyl cyanoacetate **2.12** is prepared from Steglich coupling of  $\alpha$ -phenyl cyanoacetic acid with allyl acetate



**Scheme 2.5**

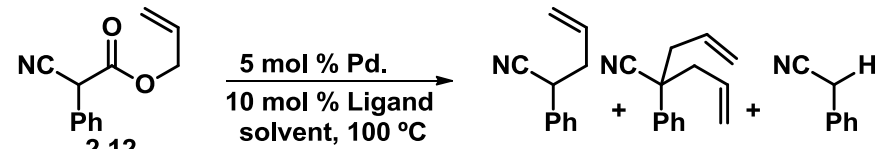
alcohol.<sup>40</sup>  $\alpha$ -Phenyl cyanoacetic acid **2.13** is prepared via lithiation of benzyl cyanide **2.11** followed by quenching with carbon dioxide and acid (Scheme 2.6).<sup>21</sup> Literature precedent suggests that  $\text{Pd}(\text{PPh}_3)_4$  and various other ligated palladium (0) sources would be effective catalysts for ionization of allyl cyanoacetic ester **2.12** (**2.2**→**2.3**, Scheme 2.2).<sup>9,10,15,21</sup> As detailed in Table 2.1, Preliminary results for the DcA of ester **2.12** utilizing a catalytic amount of  $\text{Pd}(\text{PPh}_3)_4$  in toluene at 100 °C generated the mono-allylated product **2.14** while circumventing



**Scheme 2.6**

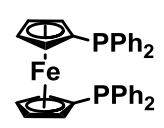
formation of the diallylated product **2.15**. However, the competing protonation product **2.16** is observed in equal amounts (entry 1, Table 2.1). A change in solvent from toluene to methylene chloride only served to introduce an equal amount of diallylated product (entry 2, Table 2.1). A switch in the source of palladium from  $\text{Pd}(\text{PPh}_3)_4$  to  $\text{Pd}_2(\text{dba})_3$  with triphenylphosphine as ligand prevents formation of the monoallylation product; instead protonation was the major product in addition to a minimal amount of the diallylated compound **2.15** (entry 3, Table 2.1). Currently, it is not clear why the use of  $\text{Pd}(\text{PPh}_3)_4$  delivers C–C bond formation while employing the precatalyst  $\text{Pd}_2(\text{dba})_3$  and triphenylphosphine does not deliver the monoallylated product **2.14**. Lack of C–C bond formation in the latter example suggests the active palladium-catalyst species forming in solution is dependent upon the initial source of palladium. A screen with a series of bidentate ligands and precatalyst  $\text{Pd}_2\text{dba}_3$  resulted in the production of monoallylated

**Table 2.1: Decarboxylative allylation of phenylacetonitrile**

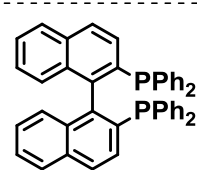


Reaction scheme: Phenylacetonitrile (2.12) reacts with 5 mol % Pd, 10 mol % Ligand, in solvent at 100 °C to yield products 2.14, 2.15, and 2.16.

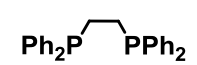
Entry	Pd source	ligand	solvent	2.14	2.15	2.16
(1)	Pd(PPh <sub>3</sub> ) <sub>4</sub>		toluene	65	-	35
(2)	Pd(PPh <sub>3</sub> ) <sub>4</sub>		CH <sub>2</sub> Cl <sub>2</sub>	40	30	30
(3)	Pd <sub>2</sub> (dba) <sub>3</sub>	PPh <sub>3</sub>	toluene	-	32	68
(4)	Pd <sub>2</sub> (dba) <sub>3</sub>	dppf	toluene	69	-	31
(5)	Pd <sub>2</sub> (dba) <sub>3</sub>	<i>rac</i> -binap	toluene	72	-	28
(6)	Pd <sub>2</sub> (dba) <sub>3</sub>	dppe	toluene	70	-	30



dppf



*rac*-BINAP



dppe

product **2.14** in addition to complete circumvention of the diallylated product **2.15** (entries 4-5, Table 2.10). Despite the various reaction conditions attempted, inhibiting the formation of the protonated product **2.16** was never achieved with the tertiary  $\alpha$ -phenyl nitrile substrates. The highest product selectivity was observed with *rac*-BINAP as ligand resulting in a 2.5 : 1 ratio of monoallylated to protonated products (entry 5, Table 2.10)

To be certain that protonation was not a result of the test substrate chosen, both cyclohexenyl- and  $\beta$ -methylallyl  $\alpha$ -phenyl cyanoacetates which are converted to products **2.17** and **2.18** respectively (Table 2.2), were subjected to the identical reaction conditions in Table 2.1. Despite modification of the substrates, similar product distributions were observed in which the diallylation products were completely eliminated however the competing protonation product persisted. Previous experiments have shown (CII.4) that the qualitative

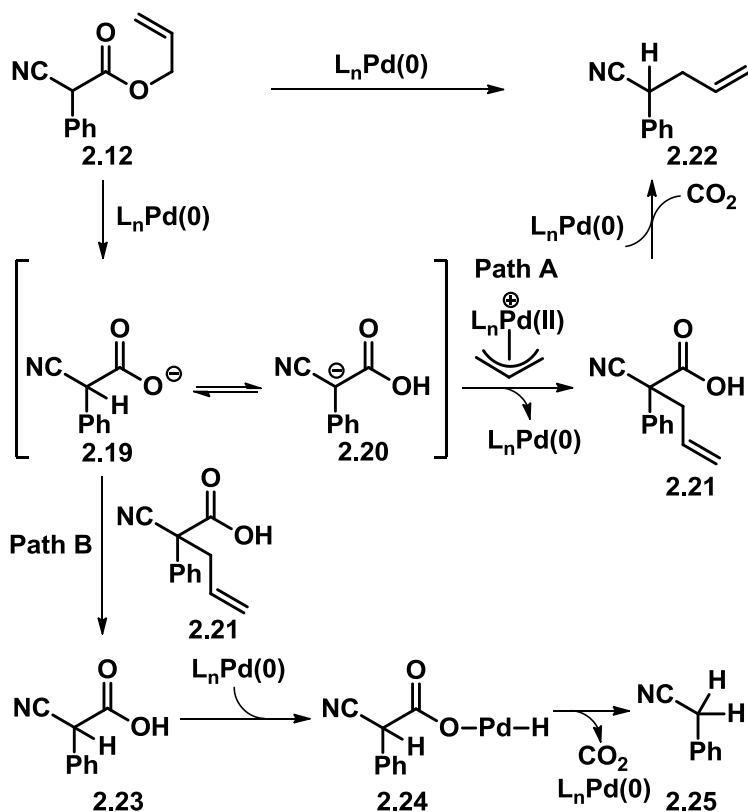
**Table 2.2: DcA of tertiary cyanoacetic esters containing substituted allyl moieties**

Entry	product	conditions	R	mono- :	di- :	protonated
(1)		A	H	<5	-	>95
(2)		B	H	50	-	50
(3)		A	Me	45	10	45
(4)		B	Me	50	-	50

\*toluene, 100 °C

rate of decarboxylation directly correlate to the  $pK_a$  of the carbanion that is formed.<sup>37</sup> It is also known that the rate of ionization of more sterically hindered allyl acetate moieties is slower with respect to unsubstituted allyl acetate.<sup>13</sup> Current literature precedent suggests, mechanistically, that protonation and C–C bond formation occur via the same reactive pathway (Scheme 2.7).<sup>41</sup> Both products are derived from carboxylate **2.19** which is obtained from palladium-catalyzed ionization of  $\alpha$ -phenyl allyl cyanoacetate **2.12**. Carboxylate **2.19** is in equilibrium via proton transfer with  $\alpha$ -anionic carboxylic acid **2.20**. Exposure of carboxylic acid **2.20** to the Pd- $\pi$ -allyl electrophile (**Path A**, Scheme 2.7) leads to the formation of  $\alpha$ -allylated carboxylic acid **2.21**. At this point, palladium-catalyzed decarboxylation of **2.21** would lead to the target mono-allylated product **2.22**. However, proton transfer from  $\alpha$ -allylated carboxylic acid **2.21** to  $\alpha$ -protio carboxylate **2.19** generates  $\alpha$ -protio carboxylic acid **2.23** (**Path B**, Scheme 2.7). Analogous to **Path A**, oxidative addition of palladium (0) catalyst into  $\alpha$ -protio carboxylic acid **2.23** as suggested by **2.24** and subsequent loss of CO<sub>2</sub> followed by reductive elimination

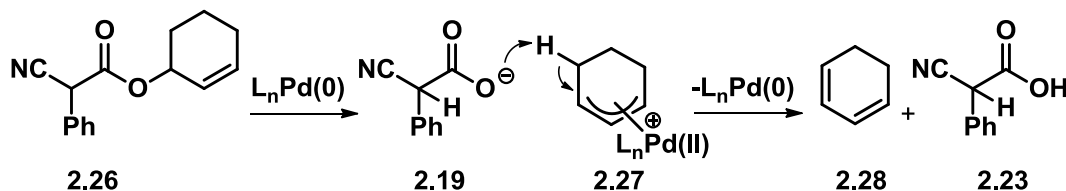




**Scheme 2.7**

delivers the protonated product **2.25** (Scheme 2.7).<sup>41</sup> In addition to the presence of  $\alpha$ -protons, substrates with allyl moieties containing acidic protons are also problematic (**2.26**, Scheme 2.8).<sup>8</sup> Ionization of the cyclohexenyl acetate moiety of ester **2.26** generates Pd- $\pi$ -allyl complex **2.27** which is susceptible to elimination, generating cyclohexadiene **2.28** and  $\alpha$ -protonic carboxylic acid **2.23** (Scheme 2.8). Compound **2.23** can then go on to form the protonation product **2.25** as shown in Scheme 2.7 (**2.24**  $\rightarrow$  **2.25**, Scheme 2.7). It was evident that circumventing the competitive formation of the protonation product is difficult. For this reason, development of the DcA of tertiary cyanoacetic esters was abandoned for the investigation into

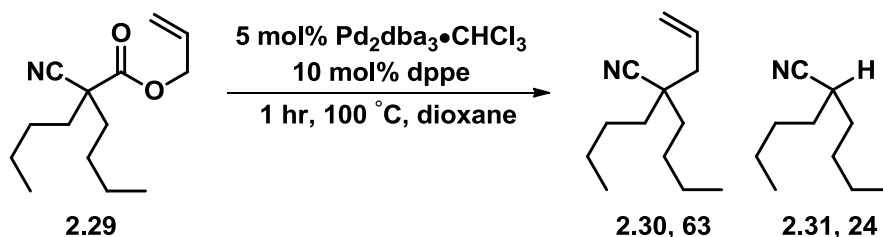
the DcA of quaternary cyanoacetic esters. The following section will detail the development of the palladium-catalyzed decarboxylative allylation of quaternary allyl cyanoacetates.<sup>37</sup>



**Scheme 2.8**

### CII.3: Decarboxylative allylation of quaternary nitriles

Decarboxylative allylation of allyl cyanoacetates containing  $\alpha$ -protio substituents is problematic due to competing formation of the protonated product (**2.25**, Scheme 2.7).<sup>15</sup> In attempt to remove the source of protonation, Tsuji reported that DcA of  $\alpha,\alpha$ -dibutyl allyl cyanoacetate **2.29** was catalyzed by diphenylphosphinoethane (dppe)-ligated palladium in toluene at 100 °C and the product **2.30** was obtained in 63% yield, however 24% of the protonated species **2.31** was also observed (Scheme 2.9).<sup>15</sup> Successful development of this



**Scheme 2.9**

methodology will allow for the generation of nitrile-stabilized anions (conjugate acid  $pK_a \approx 30$ -33)<sup>40</sup> under formally neutral conditions.<sup>9,15,30,42,43</sup> In addition, the method allows for the

functionalization of all carbon quaternary centers as well as the incorporation of nitrogen via carbon based nucleophiles.

Building on the proof of concept set forth by Tsuji,<sup>15</sup> identification of a competent palladium catalyst as well as reaction conditions selective for C–C bond formation is described. The  $\alpha,\alpha$ -dibenzyl, allyl cyanoacetate substrate **2.32** (Table 2.3) was prepared via dialkylation of the allyl cyanoacetate obtained from Steglich coupling of cyanoacetic acid and allyl alcohol (see appendix A).<sup>40</sup> The data combined in Table 2.3 was acquired via analysis of crude <sup>1</sup>H NMR spectra.<sup>37</sup> The preliminary results suggested that bidentate-ligated palladium catalysts were more selective toward C–C bond formation (**2.33**, Table 2.3) with toluene employed as solvent. The data also revealed that monodentate Pd(PPh<sub>3</sub>)<sub>4</sub> as well as the use of PPh<sub>3</sub> modified precatalyst Pd<sub>2</sub>(dba)<sub>3</sub> provided only the protonation product **2.34** (entries 1-3, Table 2.3) in thoroughly dried toluene.<sup>15,44</sup> A series of bidentate phosphine ligands with differing bite angles as well as electronic properties were screened using Pd<sub>2</sub>(dba)<sub>3</sub> as precatalyst in toluene at 100 °C (entries 4-6, Table 2.3).<sup>37</sup> Both diphosphinoferrocene (dppf) and diphosphinoethane (dppe)<sup>15</sup> were more selective toward allylation however did not successfully circumvent formation of the protonation product. In contrast, the *racemic*-binaphthylphosphino (*rac*-BINAP) ligated palladium catalyst smoothly converted the ester **2.32** to the allylated product **2.33** in addition to completely suppressing the formation of the protonated product **2.34** (entry 6, Table 2.3). Currently, it is not well understood exactly how the *rac*-BINAP ligand is able to circumvent formation of the protonated product. Nevertheless this observation is consistent with use of a *rac*-BINAP ligated palladium catalyst to prevent the formation of protonated products in the DcA of  $\alpha$ -sulfonyl esters.<sup>21</sup>

**Table 2.3: Circumventing protonation in the decarboxylative coupling of nitriles**

Reaction scheme: **2.32**  $\xrightarrow[10 \text{ mol } \% \text{ Ligand, } 100 \text{ } ^\circ\text{C}]{5 \text{ mol } \% \text{ Pd}}$  **2.33** + **2.34**

Entry	Pd source	ligand	2.33	2.34
(1)*	$\text{Pd}(\text{PPh}_3)_4$		-	-
(2)	$\text{Pd}(\text{PPh}_3)_4$		<5	>95
(3)	$\text{Pd}_2(\text{dba})_3$	$\text{PPh}_3$	<5	>95
(4)	$\text{Pd}_2(\text{dba})_3$	dppf	50	50
(5)	$\text{Pd}_2(\text{dba})_3$	dppe	61	39
(6)	$\text{Pd}_2(\text{dba})_3$	<i>rac</i> -BINAP	>95	<5

\* reaction performed in  $\text{CH}_2\text{Cl}_2$  at  $50 \text{ } ^\circ\text{C}$

dppf

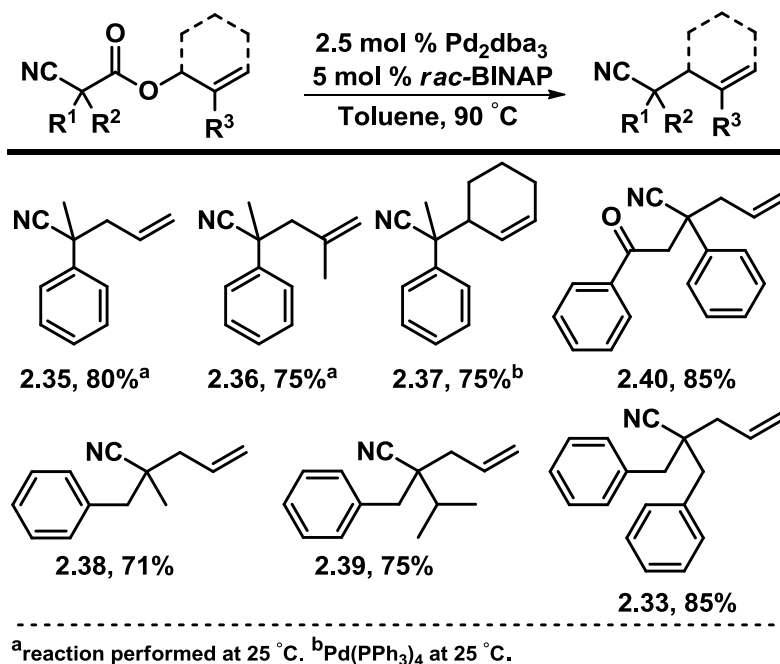
*rac*-BINAP

dppe

Having established that the *rac*-BINAP ligand promotes C–C bond formation in the absence of decarboxylative protonation, the DcA of  $\alpha,\alpha$ -disubstituted cyanoacetates is disclosed.<sup>37</sup> Literature precedent suggests that upon ionization of the allyl acetate moiety, the facility of decarboxylation is dependent upon the  $\text{pK}_a$  of the conjugate acid of the ensuing carbanion.<sup>8,37</sup> For this reason, a series of  $\alpha$ -phenyl cyanoacetates were synthesized (**2.12**, Scheme 2.6) and quaternarized via alkylation (Table 2.4).<sup>29</sup> As depicted in Table 2.4, the  $\alpha$ -phenyl,  $\alpha$ -methyl cyanoacetate containing an unsubstituted allyl moiety is converted to the allylated product **2.35** in 80% yield at  $25 \text{ } ^\circ\text{C}$ . It should be noted that this reaction is performed at room temperature, which is lower than the  $100 \text{ } ^\circ\text{C}$  required for the DcA of allyl,  $\alpha,\alpha$ -dibenzyl cyanoacetate **2.32** (Table 2.3). This observation supports the argument that decarboxylation

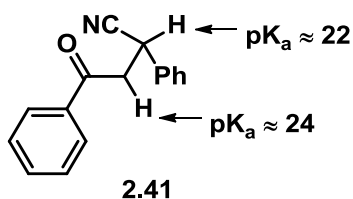
correlates with the  $pK_a$  of the conjugate acid of the forming carbanion and suggests loss of  $CO_2$  is rate-limiting.<sup>21</sup>  $\alpha$ -Phenyl,  $\alpha$ -methyl cyanoacetate substrates containing substituted allyl

**Table 2.4: Decarboxylative coupling of nitriles**

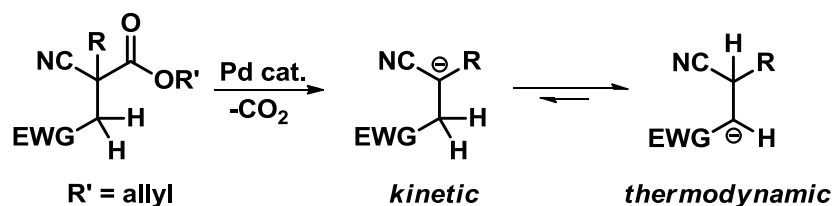


moieties also undergo C–C bond formation (**2.36**, Table 2.4), however obtaining the cyclohexenyl nitrile **2.37** required a change in catalyst from the bidentate *rac*-BINAP ligated palladium to monodentate  $Pd(PPh_3)_4$ .<sup>21</sup> Use of the *rac*-BINAP modified palladium catalyst resulted in a 50:50 mixture of the allylated product **2.37** and the protonation product (**2.28**, Scheme 2.8). In addition to the  $\alpha$ -phenyl cyanoacetate substrates, a number of  $\alpha,\alpha$ -dialkyl allyl cyanoacetates were prepared and subjected to the reaction conditions in Table 2.4. The  $\alpha$ -benzyl,  $\alpha$ -methyl allylated nitrile **2.38** is generated in 71% yield along with the more sterically encumbered  $\alpha$ -benzyl,  $\alpha$ -isopropyl allylated nitrile **2.39**, which is obtained in 75% yield. It should be noted that allylated products **2.38**, **2.39**, and **2.33** form via a nitrile stabilized

carbanion in which the conjugate acid has a  $pK_a$  value of 32.<sup>38,39</sup> This is an increase of 10 orders of magnitude from the  $\alpha$ -phenyl nitrile stabilized carbanions (Scheme 2.5).  $\alpha$ -Phenyl,  $\alpha$ -acetophenone allyl cyanoacetate undergoes C–C bond formation smoothly to produce **2.40** with minimal evidence of the protonation product **2.41** (figure 2.1). This result is interesting given that the  $pK_a$  of the conjugate acid of the carbanion generated via decarboxylation is 22, whereas the  $pK_a$  of the  $\alpha$ -acetophenone protons is 24 (figure 2.1).<sup>38,39</sup> This observation suggest that the DcA of  $\alpha,\alpha$ -disubstituted allyl cyanoacetates provided the products of regiospecific C–C bond formation. The regiospecificity of the DcA can be investigated via performing the reaction in the presence of protons containing  $pK_a$  values lower (ie more acidic) than the  $pK_a$  of the conjugate acid of the carbanion formed via decarboxylation.<sup>45</sup> If indeed the reaction is regiospecific, C–C bond formation takes place at the site of decarboxylation (**kinetic**, Scheme 2.10) and there will be no equilibration to the **thermodynamic** carbanion (Scheme 2.10). The development of regiospecific decarboxylative coupling of nitriles is detailed.

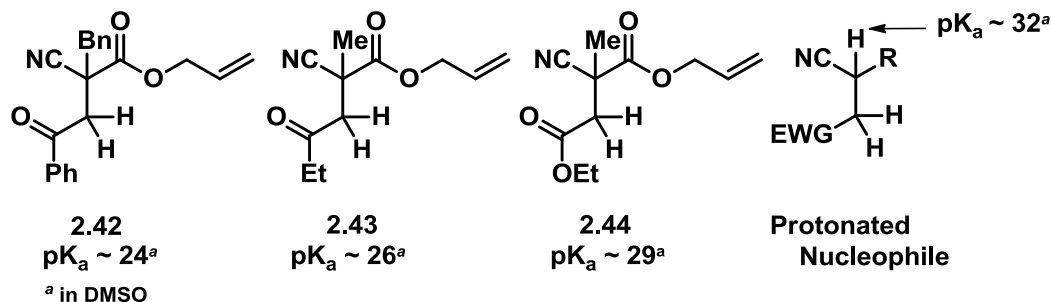


**Figure 2.1**



**Scheme 2.10**

In order to investigate the regioselectivity of the DcA reaction, a series of substrates containing protons with  $\text{pK}_a$  values lower than the  $\text{pK}_a$  of the conjugate acid of the nitrile-stabilized carbanion formed via decarboxylation were synthesized (Scheme 2.11, see appendix B). Allyl cyanoacetates containing aryl ketone (**2.42**  $\text{pK}_a=24$ , figure 2.2), alkyl ketone (**2.43**  $\text{pK}_a=26$ , figure 2.2), and ester (**2.44**  $\text{pK}_a=29$ , figure 2.2) functionalities would satisfy this requirement (**protonated nucleophile**  $\text{pK}_a=32$ , figure 2.2).<sup>38,39</sup> A brief screen of reaction



**Figure 2.2**

conditions for the regioselective decarboxylative coupling of nitriles revealed that the *rac*-BINAP ligated palladium catalyst was competent at promoting C–C bond formation and minimizing the amount of observed protonation product ( entries 1 and 3, Table 2.5).<sup>21</sup> The DcA reaction suffers a noticeable deterioration of selectivity as the  $\text{pK}_a$  of the acidic protons (**2.44**  $\text{pK}_a=29$  → **2.43**  $\text{pK}_a=26$ , figure 2.2) decreases (entry 1 → 3, Table 2.2).<sup>38,39</sup> Monodentate  $\text{Pd}(\text{PPh}_3)_4$  also

**Table 2.5: Screen of conditions for regiospecific decarboxylative coupling of nitriles**

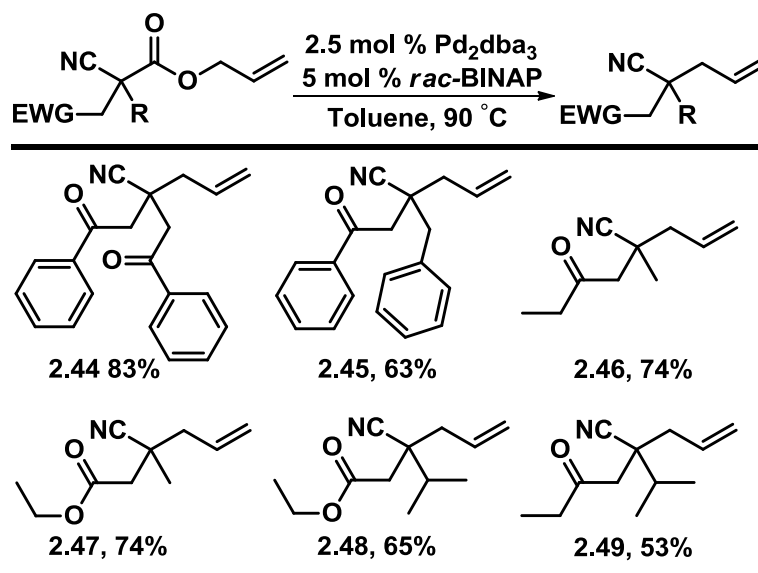
Entry	EWG	Cat.	ligand	allylation	protonation
(1)		$\text{Pd}_2\text{dba}_3$	BINAP	88	: 12
(2)		$\text{Pd}(\text{PPh}_3)_4$		50	: 50
(3)		$\text{Pd}_2\text{dba}_3$	BINAP	75	: 25
(4)		$\text{Pd}(\text{PPh}_3)_4$		50	: 50

delivered allylated nitriles, however favored formation of equal amounts of the protonated products (entries 2 and 4, Table 2.5). Having identified a palladium catalyst, a series of allyl cyanoacetates with tethered ketone and ester functionalities were subjected to the reaction conditions to further investigate the scope of regiospecific decarboxylative coupling of nitriles. As detailed in Table 2.6, products **2.46** and **2.47** containing ketone and ester substituents are allylated in 74% yield. Likewise, the substrate containing  $\alpha,\alpha$ -diacetophenone functionalities was converted to product **2.44** in 83% yield, however interchanging a single acetophenone with a benzyl substituent caused a 20% reduction in yield **2.45**. Furthermore, increasing the steric demand of the nitrile-stabilized carbanion resulted in a 53% yield of the product **2.49** (Table 2.6). It should be noted that analysis of the crude  $^1\text{H}$  NMR spectra for compounds **2.45**, **2.48**, and **2.49** suggests a higher yielding reaction, however the protonated and allylated products possess similar polarity on silica gel; so an abundance of the product is lost during purification. Based on preliminary results that suggested a regiospecific allylation of nitriles observed in Table 2.6, the limits of regiospecific C–C bond formation were further investigated to gain some



insight into the mechanism of the reaction. The investigation entailed preparation of an allyl cyanoacetate substrate with a tethered malonate functionality (**2.50**, Table 2.7). Preliminary

**Table 2.6: Regiospecific DcA of Nitriles**

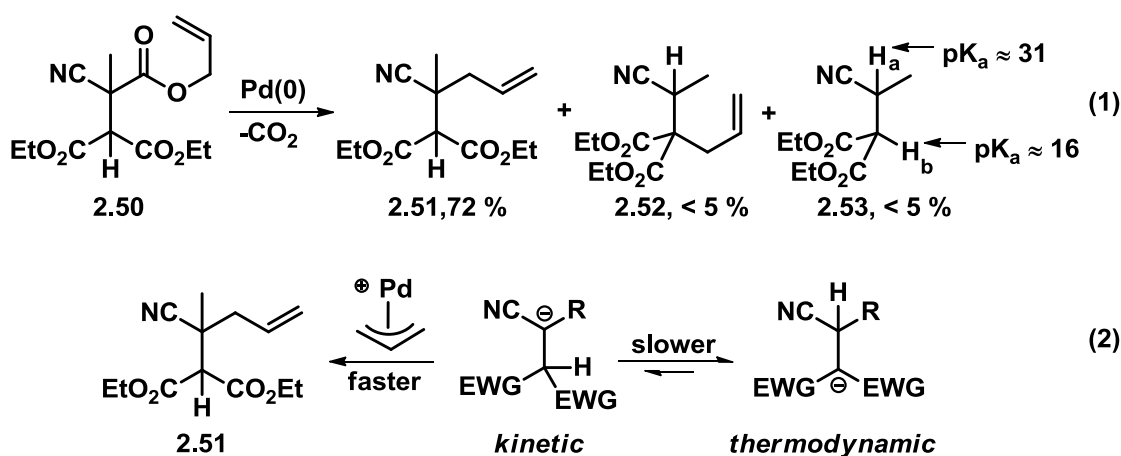


results showed formation of a 1:1 ratio of regioisomers **2.51** and **2.52** (Table 2.7). However, increasing the concentration and temperature of the reaction as well as mixing the precatalyst  $\text{Pd}_2(\text{dba})_3$  and *rac*-BINAP ligand prior to addition of the substrate delivers exclusively the product of regiospecific C–C bond formation (**2.51**, Table 2.7). Scaling-up the reaction resulted in exclusive formation of **2.51** in 72 % yield (eq. 1, Scheme 2.11). It should also be noted that neither the **2.52** nor the protonation product **2.53** was observed in the crude  $^1\text{H}$  NMR spectrum. Given the 15 orders of magnitude between the acidity of protons  $\text{H}_a$  and  $\text{H}_b$  (**2.53**, eq. 1, Scheme 2.11)<sup>38,39</sup> the result suggests that C–C bond formation is faster than equilibration between kinetic and thermodynamic carbanions formed via decarboxylation (eq. 2, Scheme 2.11). However, the observed regiospecificity of the DcA and the lack of thermodynamically

Table 2.7 Further investigation into the regiospecific decarboxylative coupling of nitriles

entry	catalyst	ligand	[M]	regiospecific	:	regioselective
(1)	Pd <sub>2</sub> dba <sub>3</sub>	BINAP	.05	50	:	50
(2) <sup>a,b</sup>	Pd <sub>2</sub> dba <sub>3</sub>	BINAP	.15	>95	:	<5

<sup>a</sup>reaction performed at 110 °C <sup>b</sup>premixed catalyst prior to addition of allyl cyanoacetate



Scheme 2.11

favorable anion equilibration suggests an alternative reaction pathway for C–C bond formation may be operative. From an application perspective, the likelihood of obtaining the allylated nitrile **2.51** from diester **2.53** via classical base-mediated methodologies would likely be kinetically and thermodynamically impossible.<sup>29</sup> The following section will detail the mechanistic studies undertaken to elucidate the mechanism of the decarboxylative coupling of nitriles.<sup>37</sup>

#### CII.4: Mechanistic studies for elucidation of the decarboxylative coupling of nitriles

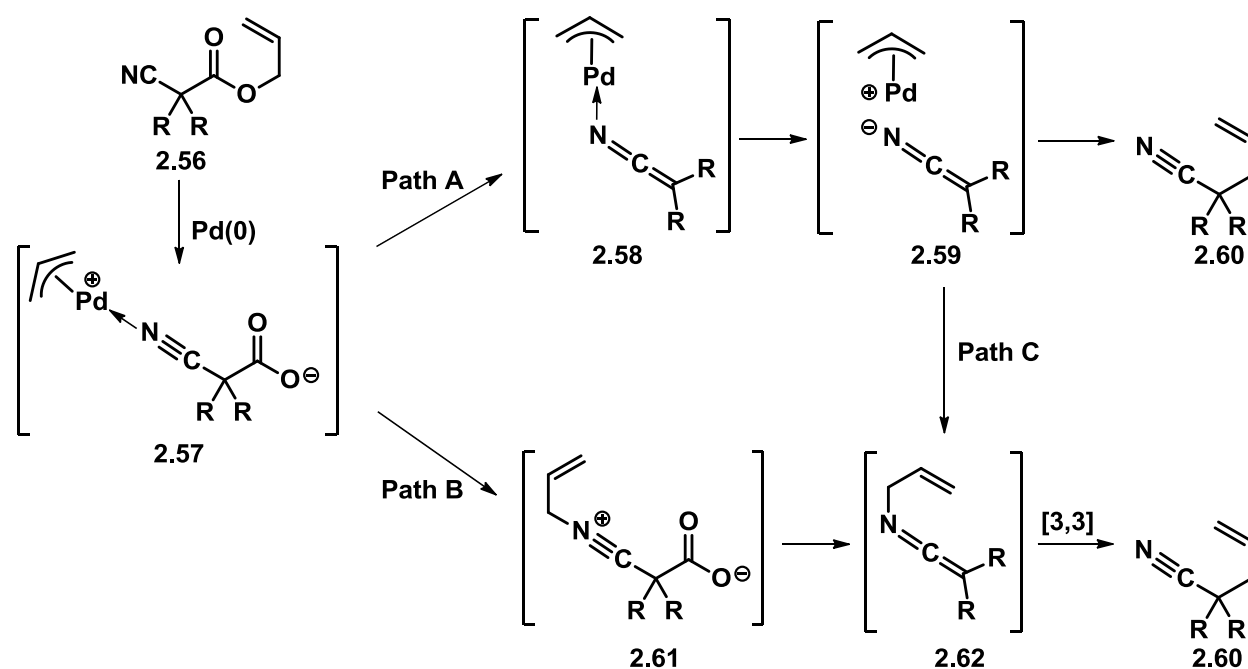
At this point, what has been determined for the decarboxylative coupling of nitriles is that C–C bond formation is regiospecific, suggesting that allylation takes place at the carbon from which CO<sub>2</sub> is released (Scheme 2.11 and Table 2.6). In addition, palladium-catalyzed decarboxylative C–C bond formation out-competes a thermodynamically favorable proton transfer (Scheme 2.11). To begin formulating a mechanistic hypothesis that includes the previous observations, a series of control experiments were performed to identify the role of palladium in decarboxylation. The control experiments depicted in Table 2.8 suggest that the decarboxylation of cyanoacetic acid is catalyzed by palladium (II) acetate.<sup>42,43</sup> Exposure of the cyanoacetic acid **2.54** to triethylamine in the absence of palladium catalyst for 15 hours at temperatures elevated above the normal reaction conditions does not convert any of the carboxylate to the protonated nitrile **2.55** (entry 1, Table 2.8). The combination of palladium acetate and triethylamine rapidly consumed the cyanoacetic acid **2.54** generating the decarboxylative protonation product **2.55** (entry 2, Table 2.8) within 5 hours. When the reaction was performed with palladium catalyst in the absence of triethylamine the cyanoacetic

**Table 2.8 Palladium-catalyzed decarboxylation**

<div><div><div><div>NC</div><div>Me</div><div>Me</div><div>C</div><div>O</div><div>OH</div></div><div>2.54</div></div><div><div>5 mol % cat.</div><div>5 mol % base</div><div>→</div></div><div><div>NC</div><div>Me</div><div>Me</div><div>C</div><div>H</div></div><div>2.55</div></div>					
entry	catalyst	base	temp (°C)	time (h)	conversion (%)
(1)	none	Et <sub>3</sub> N	115	15	<5
(2)	Pd(OAc) <sub>2</sub>	Et <sub>3</sub> N	80	5	>95
(3)	Pd(OAc) <sub>2</sub>	none	80	5	55
(4)	Pd(OAc) <sub>2</sub>	none	80	18	>95

acid was converted to the product **2.55**, albeit at a slower reaction rate (entries 3 and 4, Table 2.8). Moreover, these observations were in agreement with mechanistic studies performed by Darensbourg suggesting that metal-nitrile complexation was required for decarboxylation of cyanoacetic acid.<sup>42,43</sup>

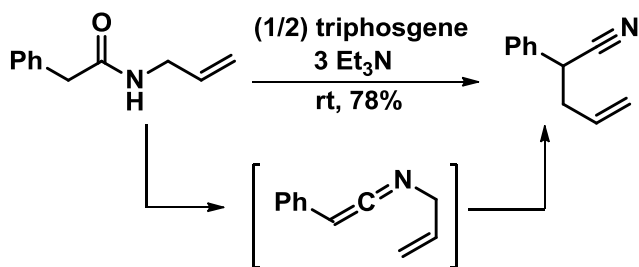
Amongst a myriad of potential reactive pathways for C-C bond formation, the data acquired to this point suggested two feasible reaction pathways for the decarboxylative coupling of nitriles. Exposure of **2.56** to the Pd(0) catalyst induces ionization of the allyl acetate moiety generating the cyanoacetate Pd(II)- $\pi$ -allyl complex **2.57** (Scheme 2.12). Subsequent



**Scheme 2.12**

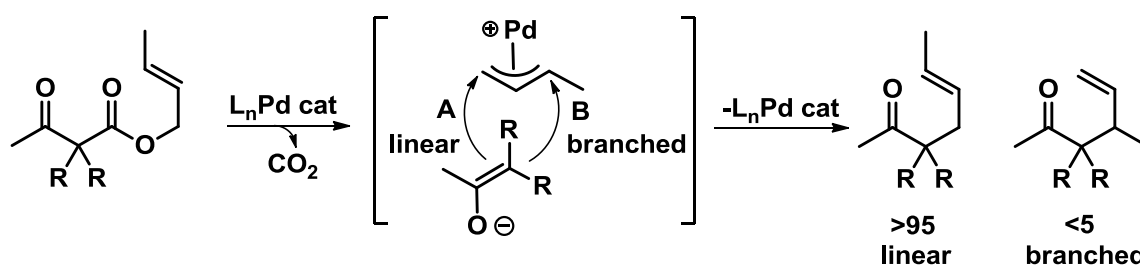
Pd(II) catalyzed decarboxylation<sup>15,46</sup> produced the N-ligated Pd(II)- $\pi$ -allyl complex **2.58** or solvated ion pair **2.59** which can recombine via the more traditional direct allylation reactive manifold to form **2.60** (path A, Scheme 2.12).<sup>13</sup> Alternatively, reductive elimination of the

palladium catalyst from **2.57** generates the *N*-allyl cyanoacetate **2.61** (path B, Scheme 2.12). Decarboxylative neutralization of **2.61** generates *N*-allyl ketenimine **2.62** which can then undergo [3,3] sigmatropic rearrangement to deliver the allylated nitrile **2.60** (path B, Scheme 2.12). Studies performed by Walters show that *N*-allyl ketenimines undergo [3,3] sigmatropic rearrangement at room temperature to form  $\alpha$ -allylated phenylacetonitriles (Scheme 2.13).<sup>47</sup> The regiospecificity of the decarboxylative coupling is rationalized via pathway B, however does not account for the increased amounts of protonation observed with other ligands (Table 2.3). The large amount of protonation observed is rationalized via path A due to the formation of more basic intermediates. Furthermore, it is feasible that both path A and Path B are operative via decarboxylation and reductive elimination of the palladium catalyst from **2.59** generating the *N*-allyl ketenimine **2.62** (path C, Scheme 2.12). To investigate the feasibility of *N*-allylation prior to C–C bond formation,<sup>48,49</sup> a series of cyanoacetate substrates with substituted allyl moieties capable of generating linear and branched products were subjected to the conditions for the decarboxylative coupling of nitriles.



**Scheme 2.13**

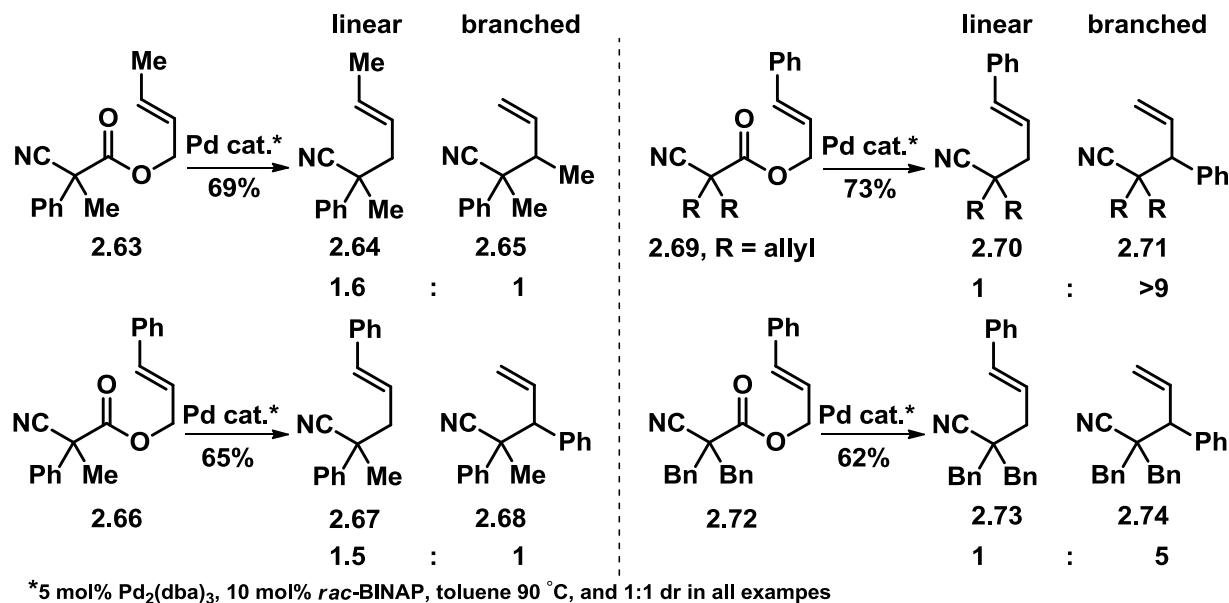
The origin of the regiospecific C–C bond formation observed with the DcA of nitriles was investigated via the synthesis of allyl cyanoacetates capable of producing linear and branched products (Scheme 2.15). Crotyl and cinnamyl functionalized cyanoacetic esters were subjected to the conditions for the decarboxylative coupling of nitriles. In order to fully appreciate the linear to branched selectivities observed in the DcA of nitriles, it should be noted that literature reported values for the linear to branched selectivities associated with DcA of ketones are in excess of 95 : 5, favoring formation of the linear product (Scheme 2.14).<sup>8</sup> Selective formation of the linear allylation product stems from the nucleophile approaching the least sterically hindered carbon of the Pd- $\pi$ -allyl complex (path A, Scheme 2.14).<sup>50</sup> Both the  $\alpha$ -phenyl, $\alpha$ -methyl crotyl cyanoacetate ester **2.63** (Scheme 2.15) as well as the  $\alpha$ -phenyl, $\alpha$ -methyl cinnamyl ester **2.66** (Scheme 2.15) are converted to the respective products in nearly a 1:1 ratio of linear to branched isomers. Taking into account that with the DcA of ketones (Scheme 2.14) the branched product is not observed by <sup>1</sup>H NMR spectra; With respect the DcA of nitriles, the increased selectivity for the formation of the branched isomer (**2.65** and **2.68**, Scheme 2.15)



**Scheme 2.14**

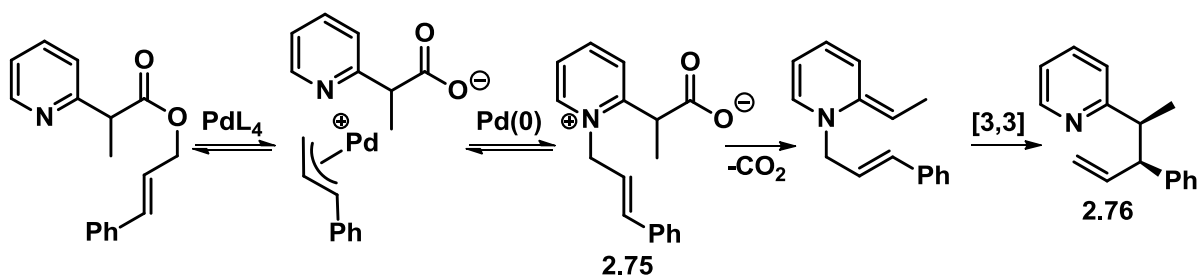
suggests that an alternative reaction pathway for allylation is operative.<sup>48,49</sup>  $\alpha$ -,  $\alpha$ -Diallyl and  $\alpha$ -,  $\alpha$ -dibenzyl cinnamyl cyanoacetates **2.69** and **2.72** (Scheme 2.15) were also subjected to the *rac*-

BINAP ligated palladium catalyst in toluene at 90 °C which resulted in increased formation of the branched isomer **2.71** and **2.74** (Scheme 2.15). This observation is consistent with studies



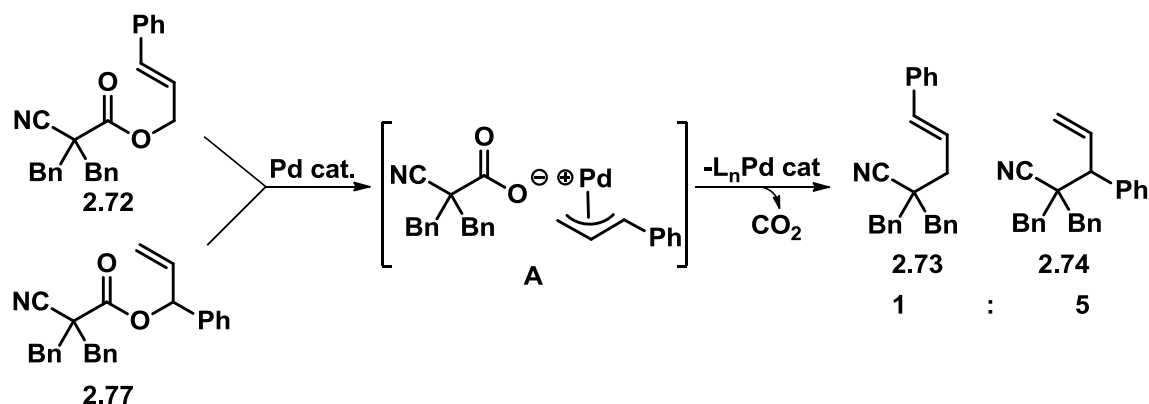
### Scheme 2.15

involving the DcA of  $\alpha$ -picolinic cinnamyl esters<sup>24</sup> in which the pyridine nitrogen is proposed to add to the least hindered position<sup>50</sup> of the Pd- $\pi$ -allyl complex generating the *N*-allylated iminium intermediate **2.75** (Scheme 2.16). Subsequent decarboxylation and [3,3]-sigmatropic rearrangement delivered exclusively the branched product **2.76** (Scheme 2.16). With respect to the decarboxylative coupling of **2.72** (Scheme 2.15), it should be noted that similar linear to branched selectivities are also obtained employing the ( $\alpha$ -phenyl) allyl substituted cyanoacetate



**Scheme 2.16**

**2.77** (Scheme 2.17). This result suggests the reaction takes place via the common intermediate **A** (Scheme 2.17) and upon ionization of the allyl acetate moiety, C-C bond formation takes place via the same reactive pathway.<sup>8</sup>

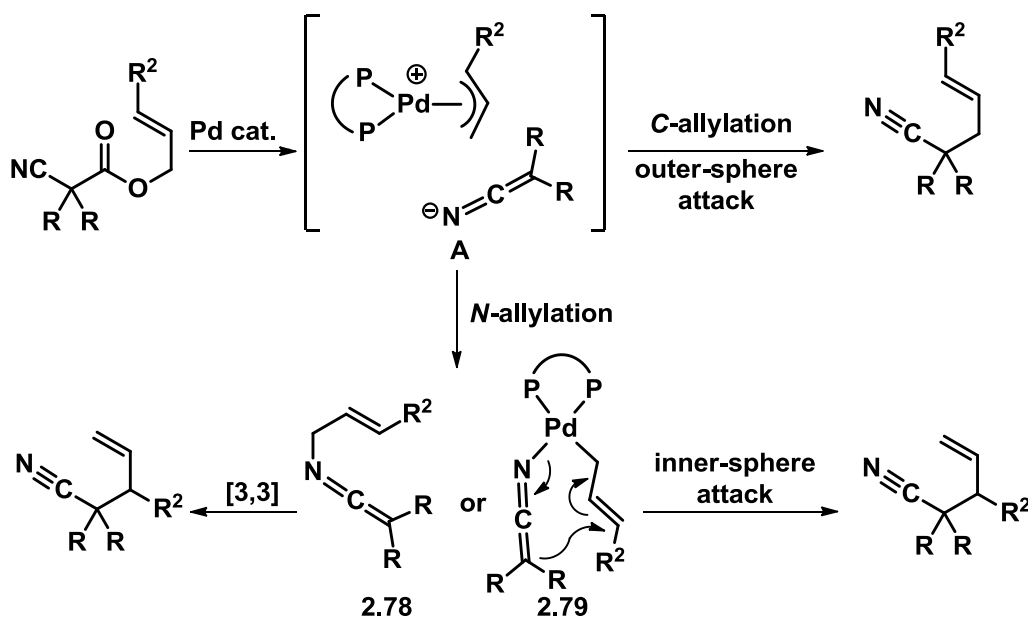


**Scheme 2.17**

Compiling all of the data to this point suggests competing kinetic *N*-allylation and *C*-allylation pathways for the decarboxylative coupling of nitriles.<sup>48,49</sup> Regiospecific C-C bond formation entails allylation of the kinetic carbanion generated via decarboxylation (eq 1., Scheme 2.11). Based on previous experiments (Scheme 2.17) it is likely that both reactive pathways originate from ion pair **A** (Scheme 2.18).<sup>8</sup> The relatively low selectivities observed for the linear and branched allylation of  $\alpha$ -phenyl cyanoacetates suggests a minimal energetic

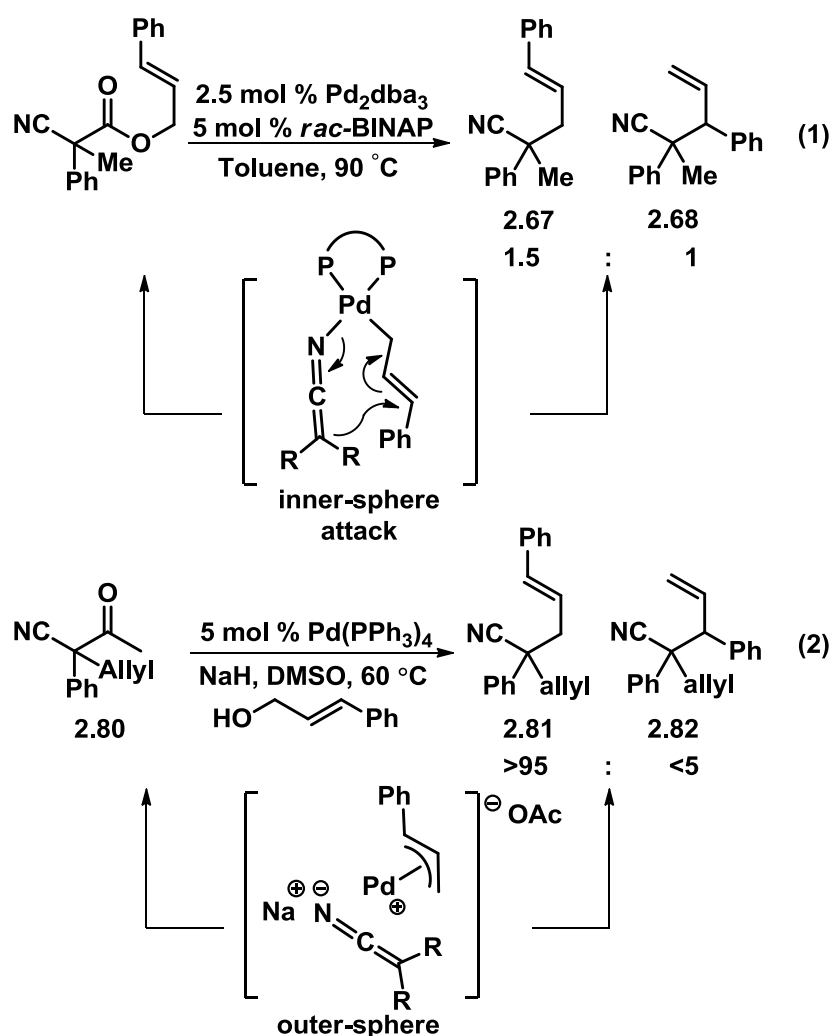


preference for *C*-allylation over *N*-allylation. In addition to the linear to branched allylation selectivities, the added stability of the  $\alpha$ -phenyl substituent makes the anion less likely to be coordinated to the metal center; as suggested by complex **2.59** (Scheme, 2.12) favoring an outer-sphere *C*-allylation pathway.<sup>33</sup> This is not the case with less stable  $\alpha,\alpha$ -dialkyl nitriles. Increased selectivity toward formation of the branched isomer suggests that bulky,  $\alpha,\alpha$ -dialkyl nitrile-stabilized carbanions favor the kinetic *N*-allylation pathway. At this point, one of two potential mechanisms is operative. Immediate reductive elimination of the palladium catalyst generates the *N*-allyl ketenimine **2.78** (Scheme 2.18) which can then undergo a [3,3] sigmatropic rearrangement to deliver the branched product. However, an inner-sphere attack involving Pd(II)-ligated  $\sigma$ -allyl, *N*-bound ketenimine complex **2.79** may also be responsible for the formation of the branched product (Scheme 2.18). The inner-sphere mechanistic rationale is in accordance with studies reported by Stoltz involving the palladium-catalyzed decarbox-



Scheme 2.18

ylative coupling of ketones.<sup>51,52</sup> In addition, studies performed by Grenning and Tunge revealed that treatment of cyanoketone **2.80** with cinnamyl alcohol in the presence of NaH and Pd(PPh<sub>3</sub>)<sub>4</sub> lead to exclusive formation of the linear allylation product **2.81** (eq. 2, Scheme 2.19).<sup>33</sup> This result suggests that the sodiated ketenimine likely undergoes an outer-sphere addition to the Pd- $\pi$ -allyl complex, resulting in exclusive formation of the linear product **2.81** (eq. 2, Scheme 2.19). However, the use of the *rac*-BINAP ligated palladium-catalyst resulted in the formation of equal amounts of linear and branched products suggesting that a inner-sphere



Scheme 2.19

reaction pathway is operative as well (eq. 1, Scheme 2.19).

In summary, development of the palladium-catalyzed decarboxylative allylation of nitriles has been detailed. This method allows for the generation of nitrile-stabilized carbanions under formally neutral reaction conditions. The reaction is regiospecific in carbon-carbon bond formation due to rapid allylation of the kinetic anion generated via palladium(II)-catalyzed decarboxylation. As a result, this method allows for the generation of allylated products not accessible via classical base-mediated methodologies. The nitrile-stabilized carbanions exhibit a heightened selectivity toward the formation of branched allylation products. This heightened selectivity in addition to the regiospecificity of C-C bond formation suggests that palladium-catalyzed decarboxylative coupling of nitriles proceeds via a competing reaction pathway. All experiments suggest that linear to branched selectivities are dependent upon the stability of the nitrile stabilized carbanion that is formed via decarboxylation.

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## Appendix A

### General Experimental:

All reactions were run in flame-dried glassware under Ar atmosphere using standard Schlenk techniques. CH<sub>2</sub>Cl<sub>2</sub> and Toluene were dried over activated alumina, and further distilled over sodium. THF was dried over sodium in the presence of benzophenone indicator. Commercially available reagents were used without additional purification unless otherwise stated. Compound purification was effected by flash chromatography using 230x400 mesh, 60 Å porosity, silica obtained from Sorbent Technologies. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were obtained on a Bruker AVIII 500 spectrometer and referenced to residual protio solvent signals (most spectra were taken using a dual <sup>13</sup>C/<sup>1</sup>H cryoprobe). Structural assignments are based on <sup>1</sup>H, <sup>13</sup>C, DEPT-135, COSY, HSQC and IR spectroscopies. Mass spectrometric analyses were run using either EI or ESI techniques.

**Synthesis of  $\alpha$ -substituted cyanoacetic acids.  $\alpha$ -phenyl, cyanoacetic acid:**<sup>1</sup> Synthesis of  **$\alpha$ -phenyl, cyanoacetic acid**: A 200 mL flame dried schlenk flask with stir bar under Ar, filled with dry THF (100mL), was charged with commercially available benzyl cyanide (31.0 mmol, 3.6mL) (commercially available propionitrile, or isovaleronitrile would be substituted for benzyl cyanide for the synthesis of the other acids) via syringe, and *n*-BuLi (18.5 mL, solution 1.6 M/Hex from Aldrich) was added dropwise over 10 minutes at room temperature. The solution was then placed in a dry ice /acetone bath and solid CO<sub>2</sub> (dryice, small amount) was added carefully. The

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<sup>1</sup> Weaver, J. D.; Tunge, J. A. *Org. Lett.* **2008**, *10*, 4657.

solution was stirred at -78 °C for 1 hr. The reaction was then quenched with NaHCO<sub>3</sub> (saturated in H<sub>2</sub>O, 125 mL) and Et<sub>2</sub>O (50 mL). The aqueous layer was isolated and ice cold EtOAc (100 mL) was added. 12M HCl was then added until pH of 2 (pH paper) was achieved. The organic layer was separated, dried over MgSO<sub>4</sub>, and reduced on rotary evaporator to yield a yellowish oil. The oil was then azeotroped with CHCl<sub>3</sub> and a white solid (3.89g, 75%) formed, and taken on as is without purification, **2-cyano-2-phenylacetic acid**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.40 (m, 2H), 7.38 – 7.33 (m, 3H), 4.91 (s, 1H), 4.68 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 168.9 (RCO<sub>2</sub>R), 129.5 (quat. Ar C), 129.32 (Ar C), 128.03 (Ar C), 115.22 (RC≡N), 43.58 (quat. C). These compounds were converted to the corresponding allyl esters by standard DCC/DMAP coupling,<sup>2</sup>

#### General procedures for the synthesis of α,α-disubstituted cyanoacetic allyl esters:

**Procedure A (synthesis of α-aryl substrates):** Synthesis of **but-3-en-2-yl 2-cyano-2-phenylpropanoate (2e)**: To a solution of but-3-en-2-yl 2-cyano-2-phenylpropanoate (0.90g, 4.2 mmol) in dry THF (0.5 M) under argon was added NaH (0.10g, 4.2 mmol). When solution became homogeneous MeI (0.6g, 4.2 mmol) was added dropwise via syringe. After 4hr, water was added to the reaction mixture and the resulting mixture was extracted with Et<sub>2</sub>O, and dried over MgSO<sub>4</sub>. The organic layer was concentrated via rotary evaporator, and the resulting residue was purified by flash chromatography over silica with Et<sub>2</sub>O/Hexanes (1:9). Fractions reduced to a clear oil, .723g, 75%.

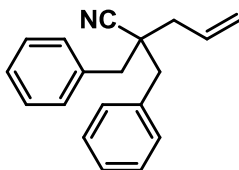
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<sup>2</sup> Neises, B., Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 522.

**Procedure B (synthesis dialkyl substrates):**<sup>1</sup> Synthesis of **allyl 2-benzyl-2-cyano-3-phenylpropanoate (1a)**: To a solution of  $\alpha$ -cyanoacetic allyl ester (0.2g, 1.6 mmol) in DMF (0.5 M) was added  $K_2CO_3$  (2.19g, 15.9 mmol) and stirred vigorously. Then benzyl bromide (1.36g, 8.0 mmol) was added and the reaction was allowed to proceed for more than 24 hrs. The reaction was then subjected to a water workup, extracted with EtOAc, and dried over  $MgSO_4$ . The product was then purified via silica chromatography with EtOAc/Hexanes (0.5:9.5) as eluent, and reduced via rotary evaporator to clear colorless oil, .270g, 56%.

**Representative procedure for decarboxylative allylations:** To a flame dried Schlenk flask with stir bar under argon was added *rac*-BINAP (0.014g, 0.023 mmol),  $Pd_2dba_3$  (0.010g, 0.011 mmol), and toluene (.05M). The mixture was then pre-heated at 90 °C (except for **2f**, realized via 5 mol %  $Pd(PPh_3)_4$ ) for 5 minutes (Note: when ligand and catalyst were not pre-mixed and heated, some of the isomerization product was observed, see Scheme 2, in paper). The reaction was then charged with **2-allyl 1,1-diethyl 2-cyanopropane-1,1,2-tricarboxylate (1n)** (.135g, 0.45 mmol) via syringe under argon. Following proper Schlenk technique, the reaction progress was monitored by TLC for consumption of starting material. The reaction was allowed to proceed at 110 °C for 17hr. Upon consumption of starting material, the reaction solution was concentrated via rotary evaporation and the residue was purified via flash chromatography over silica gel (column 23.5 cm x 2cm) with  $Et_2O$ /hexanes (1:4). TLC of fractions in  $Et_2O$ /Hexanes (1:5) gave an  $r_f \sim 0.18$ . Fractions reduced to **diethyl 2-(2-cyanopent-4-en-2-yl)malonate (2n)**, clear oil, 0.082g, 72%.

### Characterization of allylated nitriles:



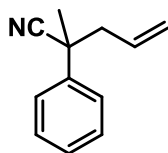
**2,2-dibenzyl-4-pentenitrile (2.33):** Clear oil, purified over silica, Et<sub>2</sub>O/Hexanes (0.1:9.9).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.29 – 7.25 (dd, *J* = 4.29, 2.95 Hz, *m*-Ar 4H), 7.22 (d, *J* = 5.9 Hz, *o*-, *p*-Ar 6H), 5.85 (m, 1H, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.24 – 5.18 (dd, 1H, *J* = 10, 1.1 Hz, CH=CH<sub>2trans</sub>), 5.14 (dd, 1H, *J* = 17.0, 1.5 Hz, CH=CH<sub>2cis</sub>), 2.85 – 2.72 (dd, 4H, *J* = 15, 20 Hz, C<sub>quat</sub>CH<sub>2</sub>C<sub>Ar-quat</sub>), 2.22 (d, 2H, *J* = 7.2 Hz, C<sub>quat</sub>CH<sub>2</sub>CH=CH<sub>2</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 135.2 (quat. Ar C), 132.0 (RHC=CH<sub>2</sub>), 130.4 (*m*-Ar CH), 128.4 (*o*-Ar CH), 127.4 (*p*-Ar CH), 122.3 (RC≡N), 120.5 (RHC=CH<sub>2</sub>), 42.8 (R<sub>1</sub>CH<sub>2</sub>C=CH<sub>2</sub>), 42.8 (2 R<sub>1</sub>CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 40.4 (quat. C).

**IR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\bar{\nu}_{\text{max}}$ : 3029, 2920, 2233, 1645, 1602, 1496, 1456, 923, 756, 702.

**HRMS** calcd for [M<sup>+</sup>] 261.1517, found 262.1574.



**2-Methyl-2-phenyl-4-pentenitrile (2.35):**<sup>3</sup> Clear oil, purified over silica, Et<sub>2</sub>O/Hexanes (0.3:9.7).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.40 – 7.36 (m, Ar 2H), 7.34 – 7.30 (m, Ar 2H), 7.27 – 7.22 (m, Ar 1H), 5.64 (m, 1H, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.10 (dd, 1H, *J* = 2.6, 1.4 Hz, 1H, CH=CH<sub>2trans</sub>), 5.09 – 5.06 (dd, 1H,

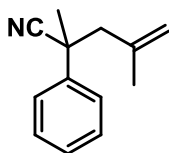
<sup>3</sup> Walters, M. A.; Hoem, A. B.; McDonough, C. S. *J. Org. Chem.* **1996**, *61*, 55-62.



$J=10, 1.5 \text{ Hz}$ ,  $\text{CH}=\text{CH}_{2\text{cis}}$ ), 2.61-2.54 (dd, 2H,  $J = 13.9, 1.2 \text{ Hz}$ ,  $\text{C}_{\text{quat}}\text{CH}_2\text{CH}=\text{CH}_2$ ), 1.65 (s, 3H,  $\text{C}_{\text{quat}}\text{CH}_3$ ).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  139.8 (quat. Ar C), 131.88 ( $\text{RHC}=\text{CH}_2$ ), 128.8 ( $m\text{-Ar CH}$ ), 127.8 ( $p\text{-Ar CH}$ ), 125.5 ( $o\text{-Ar CH}$ ), 123.1 ( $\text{RC}\equiv\text{N}$ ), 120.1 ( $\text{RHC}=\text{CH}_2$ ), 46.3 ( $\text{R}_2\text{CH}_2$ ), 42.1 (quat. C), 26.5 ( $\text{CH}_3$ ).

**IR** ( $\text{CH}_2\text{Cl}_2$ )  $\bar{\nu}_{\text{max}}$ : 3080, 2981, 2235, 1641, 1600, 1494, 1446, 995, 925, 763, 698.



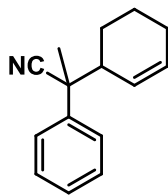
**2,4-dimethyl-2-phenyl-4-pentenitrile (2.36)**: Clear oil, purified over silica,  $\text{Et}_2\text{O}$ /Hexanes, (1.2:8.8).

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 (dd, 2H,  $J = 1.7, 1.7 \text{ Hz}$ ,  $m\text{-Ar-H}$ ), 7.33 (d, 2H,  $J = 1.5 \text{ Hz}$ ,  $o\text{-Ar-H}$ ), 7.24 (dd, 1H,  $J = 2.01, 2.01 \text{ Hz}$ ,  $p\text{-Ar-H}$ ) 4.84 (d, 1H,  $J = 1.5 \text{ Hz}$ ,  $\text{CH}_2(\text{CH}_3)\text{C}=\text{CH}_{2\text{trans}}$ ), 4.68 (d, 1H,  $J = 0.9 \text{ Hz}$ ,  $\text{CH}_2(\text{CH}_3)\text{C}=\text{CH}_{2\text{cis}}$ ), 2.56 (d, 2H,  $J = 6.05 \text{ Hz}$ ,  $\text{C}_{\text{quat}}\text{CH}_2(\text{CH}_3)\text{C}=\text{CH}_2$ ), 1.68 (s, 3H,  $\text{C}_{\text{quat}}\text{CH}_3$ ), 1.52 (s, 3H,  $\text{CH}_2(\text{CH}_3)\text{C}=\text{CH}_2$ ).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  140.1 (quat. Ar C), 140.0 (quat. vinyl  $(\text{CH}_3)\text{C}=\text{CH}_2$ ) 129.1 ( $\text{R}_2\text{C}=\text{CH}_2$ ), 127.8 ( $m\text{-Ar CH}$ ), 125.7 ( $o\text{-}, p\text{-Ar CH}$ ), 123.5 ( $\text{RC}\equiv\text{N}$ ), 116.8 ( $\text{R}_2\text{C}=\text{CH}_2$ ), 49.8 ( $\text{R}_1\text{CH}_2\text{R}_{(\text{vinylmethyl})}\text{C}=\text{CH}_2$ ), 41.5 (quat. C), 27.7 ( $\text{R}_{(\text{quat C})}\text{CH}_3$ ), 23.4 ( $\text{R}_{(\text{vinyl C})}\text{CH}_3$ ).

**IR** ( $\text{CH}_2\text{Cl}_2$ )  $\bar{\nu}_{\text{max}}$ : 3078, 2981, 2939, 2235, 1645, 1600, 1494, 1446, 1379, 900, 765, 732.

**HRMS** calcd for  $[\text{M}+\text{H}]$  186.1283, found 186.1319.



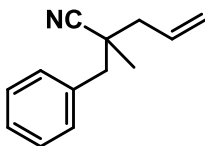
**2-(cyclohex-2-enyl)-2-phenylpropanenitrile (2.37):** Clear Oil, purified over silica, Et<sub>2</sub>O/Hex, (1.5:8.5).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) 2 diastereomers δ 7.42 – 7.35 (m, 4H, *m*-Ph-*H*), 7.34 – 7.29 (m, 4H, *o*-Ph-*H*), 7.27 – 7.21 (m, 2H, *p*-Ph-*H*), 5.88 (m, 1H, Y: R<sub>2</sub>CHCH=CHR<sub>ring</sub>), 5.80 – 5.70 (m, 1H, X: R<sub>2</sub>CHCH=CHR<sub>ring</sub>), 5.62 (ddt, 1H, *J* = 10.3, 3.8, 2.0 Hz, Y: R<sub>2</sub>CHCH=CHR<sub>ring</sub>), 5.28 (ddt, 1H, *J* = 6.0, 3.6, 1.8 Hz, X: R<sub>2</sub>CHCH=CHR<sub>ring</sub>), 2.60 (m, 1H, X: C<sub>quat</sub>(R<sub>ring</sub>)-CHCH=CHR<sub>ring</sub>), 2.50 (m, 1H, Y: C<sub>quat</sub>(R<sub>ring</sub>)-CHCH=CHR<sub>ring</sub>), 2.00 – 1.87 (m, 4H, R<sub>ring</sub>CH=CHCH<sub>2</sub>CH<sub>2</sub>R<sub>ring</sub>), 1.86 – 1.76 (m, 2H, R<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>R<sub>ring</sub>), 1.69 (s, 3H, C<sub>quat</sub>CH<sub>3</sub>), 1.65 (s, 3H, C<sub>quat</sub>CH<sub>3</sub>), 1.51 – 1.31 (m, 5H, R<sub>ring</sub>CH=CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>R<sub>ring</sub>), 1.28 – 1.20 (m, 1H, R<sub>ring</sub>CH=CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>R<sub>ring</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 139.7 (quat. Ar C), 132.0 (R<sub>(methyne)</sub>CH=CHR<sub>(methylene)</sub>), 131.2 (Ar CH), 128.7 (Ar CH), 127.7 (Ar CH), 126.0 (R<sub>(methyne)</sub>CH=CHR<sub>(methylene)</sub>), 124.8 (RC≡N), 45.6 (R<sub>3</sub>CH), 45.2 (quat. C), 25.64 (R<sub>(methyne)</sub>CH<sub>2</sub>R<sub>(methylene)</sub>), 24.53 (R<sub>(quat.)</sub>CH<sub>3</sub>), 23.9 (R<sub>(methyne)</sub>CH<sub>2</sub>R), 21.7 (R<sub>2</sub>CH<sub>2</sub>).

**IR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\bar{\nu}_{\text{max}}$ : 3028, 2939, 2862, 2233, 1650, 1600, 1494, 1446, 1026, 763, 736, 700.

**HRMS** calcd for [M+H] 212.1439, found 212.1446.



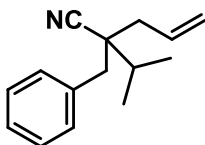
**2-Benzyl-2-methyl-4-pentenitrile (2.38):**<sup>4</sup> Clear oil, purified over silica, Et<sub>2</sub>O/Hexanes (1.5:8.5).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.39 – 7.27 (m, 5H, Ar-*H*), 5.93 (m, 1H, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.25 (d, 2H, *J* = 2.0 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 2.84 (dd, 2H, *J* = 93.3, 13.6 Hz, C<sub>quat</sub>CH<sub>2</sub>C<sub>quat</sub> Ar ), 2.34 (dd, 2H, *J* = 81.4, 7.3 Hz, C<sub>quat</sub>CH<sub>2</sub>CH=CH<sub>2</sub>), 1.28 (s, 3H, C<sub>quat</sub>CH<sub>3</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 135.3 (quat. Ar C), 132.0 (RCH=CH<sub>2</sub>), 130.3 (Ar CH), 128.4 (Ar CH), 127.3 (Ar CH), 123.5 (RC≡N), 120.26 (RCH=CH<sub>2</sub>), 44.9 (R<sub>(phenyl)</sub>CH<sub>2</sub>R<sub>(quat.)</sub> ), 43.5 (R<sub>(quat.)</sub>CH<sub>2</sub>R<sub>(vinyl)</sub>), 37.6 (quat. C), 23.5 (RCH<sub>3</sub>).

**IR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\bar{\nu}_{\max}$ : 3064, 3029, 2981, 2923, 2232, 1641, 1496, 1454, 995, 923, 759, 702.

**HRMS** calcd for [M+Na] 208.1102, found 208.1128.



**2-benzyl-2-isopropyl-4-pentenitrile (2.39):** Light yellow liquid, purified over silica, EtOAc/Hexanes (1:9).

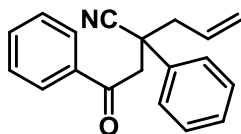
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.31 – 7.19 (m, 5H, Ph-*H*), 5.78 (m, 1H, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.22 – 5.12 (dd, 2H, *J* = 16.9, 1.4 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 2.76 (dd, 2H, *J* = 108.0, 13.8 Hz, C<sub>quat</sub>CH<sub>2</sub>Ph), 2.21 (dd, 2H, *J* = 45.3, 7.2 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 1.90 (dq, 1H *J* = 13.6, 6.8 Hz, C<sub>quat</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.04 (dd, 6H, *J* = 12.7, 6.8 Hz, C<sub>quat</sub>CH(CH<sub>3</sub>)<sub>2</sub>).

<sup>4</sup> Gao, M.; Wang, D.; Zheng, Q.; Huang, Z.; Wang, M. *J. Org.Chem.* **2007**, 72, 6060-6066.

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  134.7 (quat. Ar C), 131.0 ( $\text{RCH}=\text{CH}_2$ ), 129.3 (Ar CH), 127.3 (Ar CH), 126.2 (Ar CH), 121.7 ( $\text{RC}\equiv\text{N}$ ), 118.8 ( $\text{RCH}=\text{CH}_2$ ), 45.1 (quat. C), 37.4 (phenyl- $\text{CH}_2\text{R}$ ), 36.1 ( $\text{R}_{\text{quat}}\text{CH}_2\text{R}_{\text{vinyl}}$ ), 30.6 ( $\text{R}_3\text{CH}$ ), 16.76 ( $\text{RCH}_3$ ).

**IR** ( $\text{CH}_2\text{Cl}_2$ )  $\bar{\nu}_{\text{max}}$  : 3092, 2966, 2229, 1641, 1602, 1496, 1454, 1392, 1373, 1081, 921, 761, 702.

**HRMS** calcd for  $[\text{M}+\text{Na}]$  236.1415, found 236.1430.



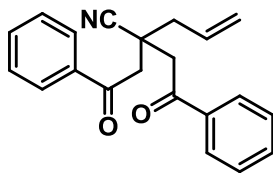
**2-(2-oxo-2-phenylethyl)-2-phenyl-4-pentenitrile (2.40)**: Clear oil, purified over silica,  $\text{Et}_2\text{O}$ /hexanes, (1:4).

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.81 (dd, 2H,  $J = 5.2, 3.3$  Hz,  $\text{COC}_{\text{quat Ar } o\text{-ArCH}}$ ), 7.52 (m, 1H,  $\text{COC}_{\text{quat Ar } p\text{-ArCH}}$ ), 7.48 (m, 2H,  $\text{COC}_{\text{quat Ar } m\text{-ArCH}}$ ), 7.43 (m, 2H,  $\text{NCC}_{\text{quat } m\text{-Ar-CH}}$ ), 7.37 (dd, 2H,  $J = 10.6, 4.9$  Hz,  $\text{NCC}_{\text{quat } o\text{-Ar-CH}}$ ), 7.26 (m, 1H,  $\text{NCC}_{\text{quat } p\text{-Ar-CH}}$ ), 5.75 (m, 1H,  $\text{CH}=\text{CH}_2$ ), 5.25 (d, 2H,  $J = 1.5$  Hz,  $\text{CH}=\text{CH}_2$ ), 3.38 (d, 2H,  $J = 17.8$  Hz,  $\text{C}_{\text{quat}}\text{CH}_2\text{CO}$ ), 2.65 (dd, 2H,  $J = 13.9, 7.9$  Hz,  $\text{C}_{\text{quat}}\text{CH}_2\text{CH}=\text{CH}_2$ ).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  194.1 ( $\text{R}_2\text{C}=\text{O}$ ), 137.9 (quat. Ar C), 136.2 (quat. Ar  $\alpha\text{-C}$ ), 133.66 (acetophenone,  $p\text{-Ar CH}$ ), 131.40 ( $\text{RCH}=\text{CH}_2$ ), 128.92 (acetophenone, Ar CH), 128.7 (acetophenone, Ar CH), 127.8 (alkyl phenyl, Ar CH), 127.9 (ArCH), 125.8 (alkyl phenyl,  $p\text{-Ar CH}$ ), 121.68 ( $\text{RC}\equiv\text{N}$ ), 120.86 ( $\text{RCH}=\text{CH}_2$ ), 46.37 ( $\alpha\text{-R}_2\text{CH}_2$ ), 45.01 ( $\text{R}_2\text{CH}_2$ ), 43.82 (quat. C).

**IR** ( $\text{CH}_2\text{Cl}_2$ )  $\bar{\nu}_{\text{max}}$  : 3062, 2239, 1689, 1641, 1596, 1579, 1494, 1448, 1218, 993, 927, 754, 690.

**HRMS** calcd for  $[\text{M}+\text{Na}]$  298.1208, found 298.1205.



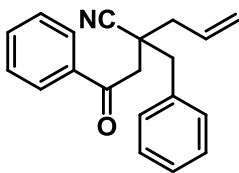
**2,2-bis(2-oxo-2-phenylethyl)-4-pentenitrile (2.44):** White solid, purified over silica, Et<sub>2</sub>O/hexanes (1:4).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.86 (dd, *J* = 8.4, 1.2, 4H, COC<sub>quat</sub> Ar *o*-ArCH), 7.51 (t, *J* = 7.4, 2H, COC<sub>quat</sub> Ar *p*-ArCH), 7.40 (t, *J* = 7.8, 4H, COC<sub>quat</sub> Ar *m*-ArCH), 5.91 (m, 1H, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.18 (dd, *J* = 18.6, 13.6, 2H, CH<sub>2</sub>CH=CH<sub>2</sub>), 3.69 (q, *J* = 18.2, 4H, 2(C<sub>quat</sub>CH<sub>2</sub>CO)), 2.75 (d, *J* = 7.4, 2H, C<sub>quat</sub>CH<sub>2</sub>CH=CH<sub>2</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 196.2 (2 C, 2(C<sub>quat</sub>CH<sub>2</sub>C(=O)Ph)), 136.4 (2 C, quat. Ar C), 133.7 (C<sub>quat</sub>CH<sub>2</sub>CH=CH<sub>2</sub>), 131.5 (4 C, *o*-Ar-C), 128.7 (2 C, *p*-Ar-C), 128.0 (4C, *m*-Ar-C), 127.9 (s), 122.4 (NCC<sub>quat</sub>), 121.3 (C<sub>quat</sub>CH<sub>2</sub>CH=CH<sub>2</sub>), 43.1 (s) 41.7 (2 C, NCC<sub>quat</sub>(CH<sub>2</sub>)<sub>2</sub>C(=O)), 40.8 (C<sub>quat</sub>CH<sub>2</sub>CH=CH<sub>2</sub>), 35.9 (NCC<sub>quat</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>).

**IR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\bar{\nu}_{\text{max}}$  : 3367, 2358, 2237, 1687, 1596, 1448, 1357, 1000, 929, 754, 688, 408.

**HRMS** calcd for [M+H] 318.1494, found 318.1471.



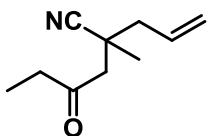
**2-benzyl-2-(2-oxo-2-phenylethyl)-4-pentenitrile (2.45):** Clear oil, purified over silica, Et<sub>2</sub>O/Hexanes, (1:4).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.80 (dd, 2H, *J* = 8.4, 1.2 Hz, COC<sub>quat</sub> Ar *o*-ArCH), 7.52 (m, 1H, COC<sub>quat</sub> Ar *p*-ArCH), 7.39 (m, 2H, COC<sub>quat</sub> Ar *m*-ArCH), 7.23 – 7.19 (m, 5H, CH<sub>2</sub>Ar-H), 5.87 (m, 1H, CH=CH<sub>2</sub>), 5.20 – 5.16 (d, 1H, *J* = 2.0 Hz, CH=CH<sub>2trans</sub>), 5.14 (d, 1H, *J* = 2.9 Hz, CH=CH<sub>2cis</sub>), 3.23 – 3.06 (dd, 4H, *J* = 40.0, 15.0 Hz, C<sub>quat</sub>CH<sub>2</sub>CO; C<sub>quat</sub>CH<sub>2</sub>Ph), 2.6 (dd, 2H, *J* = 13.9, 7.9 Hz, C<sub>quat</sub>CH<sub>2</sub>CH=CH<sub>2</sub> ).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 195.8 (R<sub>2</sub>C=O), 136.5 (quat. Ar C), 135.1 (quat. Ar α-C), 133.7 (RCH=CH<sub>2</sub>), 131.8 (ArCH), 130.4 (ArCH), 128.7 (ArCH), 128.6 (ArCH), 127.8(ArCH), 127.5 (ArCH), 122.6 (RC≡N), 120.9 (RCH=CH<sub>2</sub>), 41.5 (α-R<sub>2</sub>CH<sub>2</sub>), 41.3 (R<sub>2</sub>CH<sub>2</sub>), 40.88 (R<sub>2</sub>CH<sub>2</sub>), 39.6 (quat. C).

**IR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\bar{\nu}_{\max}$  : 3062, 2921, 2235, 1685, 1596, 1496, 1448, 1359, 1000, 752, 703.

HRMS calcd for [M+Na] 312.1364, found 312.1358.



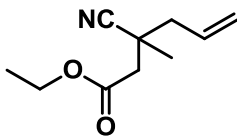
**2-allyl-2-methyl-4-oxohexanenitrile (2.46):** Clear oil, purified over silica, Et<sub>2</sub>O/Hexanes (1:3).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 5.84 – 5.73 (m, 1H, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.22 – 5.12 (dd, 2H, *J* = 16.9, 1.4 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 2.60 (dd, 2H, *J* = 77.4, 17.2 Hz, C<sub>quat</sub>CH<sub>2</sub>CO), 2.44 – 2.35 (m, 3H, COCH<sub>2</sub>CH<sub>3</sub>, C<sub>quat</sub>HCHCH=CH<sub>2</sub>), 2.32 (dd, 1H, *J* = 13.7, 7.3 Hz, C<sub>quat</sub>HCHCH=CH<sub>2</sub>), 1.36 (s, 3H, C<sub>quat</sub>CH<sub>3</sub>), 1.00 (t, 3H, *J* = 7.3 Hz, COCH<sub>2</sub>CH<sub>3</sub>).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  204.34 ( $\text{R}_2\text{C}=\text{O}$ ), 129.24 ( $\text{RCH}=\text{CH}_2$ ), 120.99 ( $\text{RC}\equiv\text{N}$ ), 118.29 ( $\text{RCH}=\text{CH}_2$ ), 46.34 ( $\alpha\text{-R}_2\text{CH}_2$ ), 40.66 ( $\text{R}_2\text{CH}_2$ ), 34.41 ( $\text{R}_{(\text{C}=\text{O})}\text{CH}_2\text{CH}_3$ ), 31.03 ( $\text{R}_{\text{quat}}\text{CH}_3$ ), 21.57 (quat. C), 5.16 ( $\text{RCH}_3$ ).

**IR** ( $\text{CH}_2\text{Cl}_2$ )  $\bar{\nu}_{\text{max}}$ : 2979, 2939, 2235, 1716, 1683, 1643, 1458, 1413, 1377, 1363, 1108, 925.

**HRMS** calcd for  $[\text{M}+\text{Na}]$  188.1051, found 188.1049.



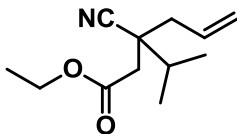
**ethyl 3-cyano-3-methyl-5-hexenoate (2.47)**: Yellowish liquid, purified over silica,  $\text{Et}_2\text{O}$ /Hexanes (1:4).

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.80 (m, 1H,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.20 (d, 1H,  $J = 9.7$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_{2\text{trans}}$ ), 5.15 (d, 1H,  $J = 16.9$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_{2\text{cis}}$ ), 4.13 (q, 2H,  $J = 7.1$  Hz,  $\text{COOCH}_2\text{CH}_3$ ), 2.57 (d, 1H,  $J = 15.7$  Hz,  $\text{C}_{\text{quat}}\text{HCHCO}$ ), 2.41 (dd, 2H,  $J = 14.7, 6.0$  Hz,  $\text{C}_{\text{quat}}\text{HCHCO}$ ,  $\text{C}_{\text{quat}}\text{HCHCH}=\text{CH}_2$ ), 2.32 (dd, 1H,  $J = 13.7, 7.3$  Hz,  $\text{C}_{\text{quat}}\text{HCHCH}=\text{CH}_2$ ), 1.38 (s, 3H,  $\text{C}_{\text{quat}}\text{CH}_3$ ), 1.22 (t, 3H,  $J = 7.2$  Hz,  $\text{COOCH}_2\text{CH}_3$ ).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  167.1 ( $\text{RCO}_2\text{R}$ ), 129.3 ( $\text{RCH}=\text{CH}_2$ ), 120.8 ( $\text{RC}\equiv\text{N}$ ), 118.9 ( $\text{RCH}=\text{CH}_2$ ), 59.0 ( $\text{ROCH}_2\text{R}$ ), 41.2 ( $\alpha\text{-R}_2\text{CH}_2$ ), 40.2 ( $\text{R}_2\text{CH}_2$ ), 32.06 ( $\text{R}_{\text{quat}}\text{CH}_3$ ), 21.9 (quat. C), 12.1 ( $\text{RCH}_3$ ).

**IR** ( $\text{CH}_2\text{Cl}_2$ )  $\bar{\nu}_{\text{max}}$ : 2981, 2939, 1735, 1643, 1448, 1417, 1371, 1348, 1201, 1029, 999, 927.

**HRMS** calcd for  $[\text{M}+\text{Na}]$  204.1000, found 204.1004.



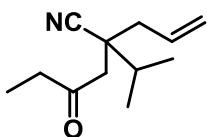
**ethyl 3-cyano-3-isopropyl-5-hexenoate (2.48):** Clear oil, purified over silica, Et<sub>2</sub>O/Hexanes (1.5:8.5).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 5.84 – 5.74 (m, 1H, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.16 (dd, 2H, *J* = 12.3, 1.4 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 4.11 (q, 2H, *J* = 7.1 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 2.59 (d, 1H, *J* = 15.6 Hz, C<sub>quat</sub>HCHCO), 2.53 – 2.46 (m, 2H, C<sub>quat</sub>HCHCO, C<sub>quat</sub>HCHCH=CH<sub>2</sub>), 2.46 – 2.40 (m, 1H, C<sub>quat</sub>HCHCH=CH<sub>2</sub>), 2.01 (dq, 1H, *J* = 13.6, 6.8 Hz, C<sub>quat</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.21 (t, 3H, *J* = 7.1 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 1.01 (dd, 6H, *J* = 11.1, 6.8 Hz, C<sub>quat</sub>CH(CH<sub>3</sub>)<sub>2</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 169.4 (RCO<sub>2</sub>R), 131.7 (RCH=CH<sub>2</sub>), 121.5 (RC≡N), 120.5 (RCH=CH<sub>2</sub>), 60.9 (ROCH<sub>2</sub>R), 43.2 (quat. C), 37.7 (α-R<sub>2</sub>CH<sub>2</sub>), 37.2 (R<sub>(quat)</sub>CH<sub>2</sub>R<sub>(vinyl)</sub>), 32.3 (R<sub>3</sub>CH), 17.8 (R<sub>(isopropyl)</sub>CH<sub>3</sub>), 14.1 (RCH<sub>3</sub>).

**IR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\bar{\nu}_{\text{max}}$  : 2977, 2358, 2235, 1737, 1641, 1465, 1444, 1373, 1195, 997, 927.

**HRMS** calcd for [M+Na] 232.1313, found 232.1306.



**2-allyl-2-isopropyl-4-oxohexanenitrile (2.49):** Clear oil, purified over silica, Et<sub>2</sub>O/Hexanes (1.5:8.5).

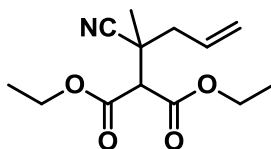
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 5.75 (m, 1H, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.10 (dd, 2H, *J* = 25.8, 13.6 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 2.64 (dd, 2H, *J* = 45.7, 17.4 Hz, C<sub>quat</sub>CH<sub>2</sub>C(=O)), 2.48 (d, 2H, *J* = 7.4 Hz, C<sub>quat</sub>CH<sub>2</sub>CH=CH<sub>2</sub>), 2.43 – 2.33 (m, 2H, C(=O)CH<sub>2</sub>CH<sub>3</sub>), 2.12 (dt, 1H, *J* = 13.6, 6.8 Hz, C<sub>quat</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.99 (m, 9H, C<sub>quat</sub>CH(CH<sub>3</sub>)<sub>2</sub>, C(=O)CH<sub>2</sub>CH<sub>3</sub>).



**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  207.2 ( $\text{R}_2\text{C}=\text{O}$ ), 132.2 ( $\text{RCH}=\text{CH}_2$ ), 121.9 ( $\text{RC}\equiv\text{N}$ ), 120.1 ( $\text{RCH}=\text{CH}_2$ ), 43.5 ( $\alpha\text{-RCH}_2\text{R}_{(\text{quat.})}$ ), 42.8 (quat. C), 37.3 ( $\alpha\text{-RCH}_2\text{CH}_3$ ), 36.8 ( $\text{R}_{(\text{quat})}\text{CH}_2\text{R}_{(\text{vinyl})}$ ), 31.7 ( $\text{R}_3\text{CH}$ ), 17.9 ( $\text{R}_{(\text{isopropyl})}\text{CH}_3$ ), 7.63 ( $\text{RCH}_3$ ).

**IR** ( $\text{CH}_2\text{Cl}_2$ )  $\bar{\nu}_{\text{max}}$  : 3080, 2972, 2939, 2878, 2231, 1720, 1641, 1460, 1413, 1375, 1365, 1110, 925.

**HRMS** calcd for  $[\text{M}+\text{H}]$  194.1545, found 194.1537.



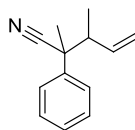
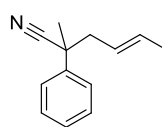
**diethyl 2-(2-cyanopent-4-en-2-yl)malonate (2.51)**: Clear oil, purified over silica,  $\text{Et}_2\text{O}$ /Hexanes (1:5).

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.88 – 5.74 (m, 1H,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.19 (dd, 2H,  $J = 28.1, 13.6$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 4.24 – 4.15 (m, 4H,  $\text{C}_{\text{quat}}\text{CH}(\text{C}=\text{O})\text{OCH}_2\text{CH}_3$ ), 3.46 (s, 1H,  $\text{C}_{\text{quat}}\text{CH}(\text{C}=\text{O})\text{OCH}_2\text{CH}_3$ ), 2.48 (dd, 2H,  $J = 106.8, 7.4$  Hz,  $\text{C}_{\text{quat}}\text{CH}_2\text{CH}=\text{CH}_2$ ), 1.45 (s, 3H,  $\text{C}_{\text{quat}}\text{CH}_3$ ), 1.23 (dt, 6H,  $J = 7.1, 2.9, 0.9$  Hz,  $\text{C}_{\text{quat}}\text{CH}(\text{C}=\text{O})\text{OCH}_2\text{CH}_3$ ).

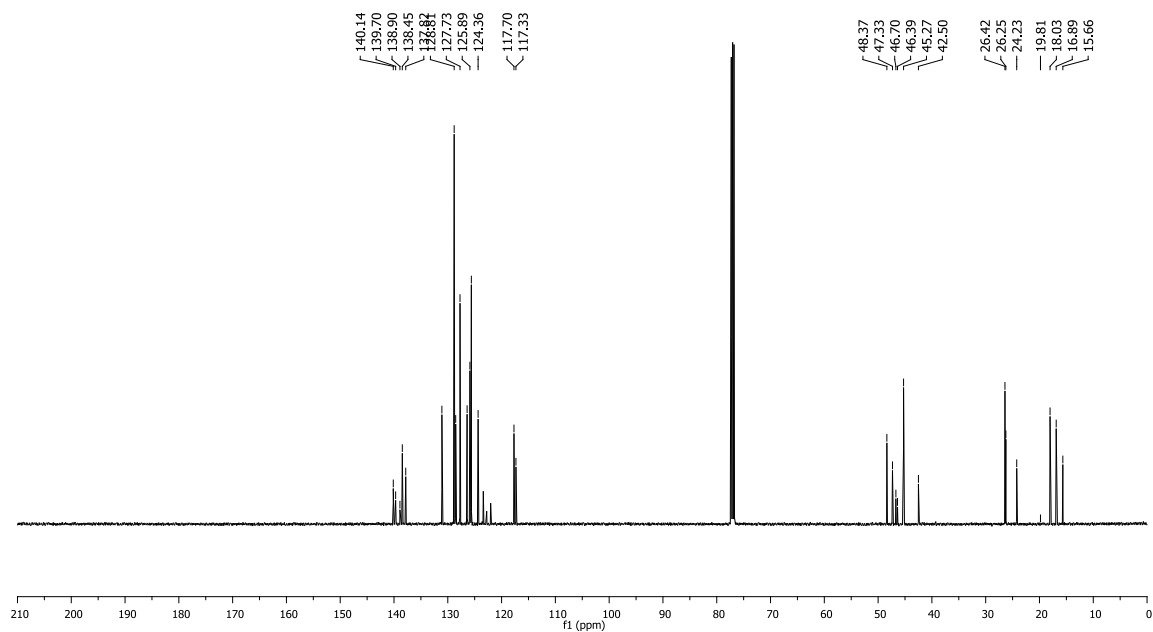
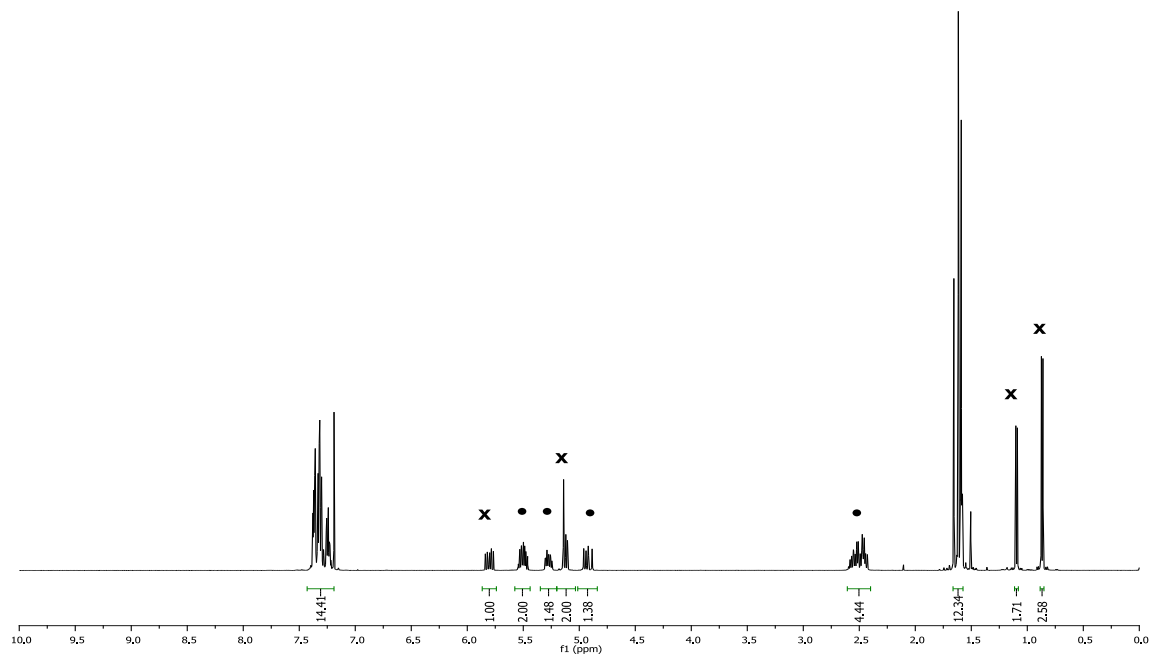
**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  164.23 ( $\text{RCO}_2\text{R}$ ), 129.1 ( $\text{RCH}=\text{CH}_2$ ), 119.78 ( $\text{RC}\equiv\text{N}$ ), 119.6 ( $\text{RCH}=\text{CH}_2$ ), 60.3 ( $\text{ROCH}_2\text{R}$ ), 54.9 ( $\text{R}_3\text{CH}$ ), 40.0 ( $\text{R}_{(\text{quat})}\text{CH}_2\text{R}_{(\text{vinyl})}$ ), 34.9 (quat. C), 20.3 ( $\text{R}_{3(\text{quat.})}\text{CH}_3$ ), 12.2 ( $\text{RCH}_3$ ).

**IR** ( $\text{CH}_2\text{Cl}_2$ )  $\bar{\nu}_{\text{max}}$  : 3082, 2983, 2941, 2239, 1755, 1735, 1643, 1465, 1446, 1369, 1305, 1272, 1224, 1178, 1155, 1031, 999, 929, 860.

**HRMS** calcd for  $[\text{M}+\text{Na}]$  276.1212, found 276.1224.



• = Linear residues    x = branched residues



**2-methyl-2-phenyl-4-hexenenitrile / (E/Z)-2-methyl-2-phenyl-4-hexenenitrile (2.64/2.65):<sup>5</sup>**

Clear oil, purified over silica, Et<sub>2</sub>O/Hexanes (1:9).

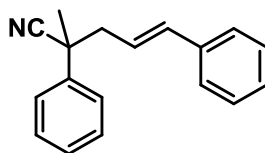
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.43 – 7.19 (m, 5H(Ph-*H*<sub>linear</sub>), 10H(Ph-*H*<sub>branched</sub>)), 5.80 (m, 1H, branched R<sub>2</sub>CHCH=CH<sub>2</sub>), 5.58 – 5.44 (m, 2H, linear CH<sub>2</sub>CH=CHCH<sub>3</sub>), 5.35 – 5.20 (m, 1H, linear CH<sub>2</sub>CH=CHCH<sub>3</sub>), 5.20 – 5.03 (m, 2H, branched R<sub>2</sub>CHCH=CH<sub>2</sub>), 5.01 – 4.84 (m, 1H, linear CH<sub>2</sub>CH=CHCH<sub>3</sub>), 2.61 – 2.40 (m, 4H, (2H Branched C<sub>quat</sub>(CH<sub>3</sub>)CHCH=CH<sub>2</sub>), (2H Linear C<sub>quat</sub>CH<sub>2</sub>CH=CHCH<sub>3</sub>)), 1.66 – 1.57 (m, 12H, (6H branched C<sub>quat</sub>CH<sub>3</sub>), (6H linear C<sub>quat</sub>CH<sub>3</sub>), 1.10 (d, 3H, *J* = 6.8 Hz, 1 diastereomer C<sub>quat</sub>(CH<sub>3</sub>)CHCH=CH<sub>2</sub>), 0.87 (d, 3H, *J* = 6.8 Hz, 1 diastereomer C<sub>quat</sub>(CH<sub>3</sub>)CHCH=CH<sub>2</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 140.1 (ArC), 139.7 (ArC), 138.9 (ArC), 138.4 (ArC), 137.8 (quat. Ar C), 131.1 (RCH=CH<sub>2</sub>), 128.8 (RCH=CHR), 128.5 (ArC), 127.7(ArC), 125.8 (Ar C), 125.6 (RC≡N), 124.4 (RCH=CH<sub>2</sub>), 117.4 (RCH=CHR), 48.3 (quat. C<sub>(branched)</sub>), 47.3 (quat. C<sub>(linear)</sub>), 46.1 (R<sub>(quat)</sub>CH<sub>2</sub>R<sub>(vinyl)</sub>), 42.5 (R<sub>2</sub>CHR<sub>(vinyl)</sub>), 26.4 (R<sub>(quat)</sub>CH<sub>3</sub>(linear)), 24.2 (R<sub>(quat)</sub>CH<sub>3</sub>(branched)), 18.0 (R<sub>(vinyl)</sub>CH<sub>3</sub>(trans)), 16.9 (R<sub>3</sub>CH<sub>3</sub>(allyl)), 15.6 (R<sub>(vinyl)</sub>CH<sub>3</sub>(cis)).

**IR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\bar{\nu}_{\max}$  : 3028, 2981, 2935, 2235, 1635, 1600, 1494, 1446, 1379, 968, 923, 759, 700.

**HRMS** calcd for [M<sup>+</sup>] 185.1204, found 185.1199.

<sup>5</sup> (a) Gaudin, J.; Millet, P. *Chem. Comm.* **2008**, 5, 588-590. (b) Yasui, H.; Yorimitsu, H.; Oshima, K. *Chem. lett.* **2007**, 36, 32-33.



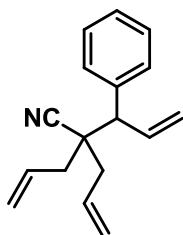
**(E)-2-methyl-2,5-diphenyl-4-pentenitrile (2.67/2.68):** Clear oil, purified over silica, Et<sub>2</sub>O/Hexanes (1:9).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.40 (dt, 4H, *J* = 8.4, 2.3, *m*-Ar-H), 7.37 – 7.30 (m, 4H, *o*-Ar-H), 7.29 – 7.13 (m, 2H, *p*-Ar-H), 6.40 (d, 1H, *J* = 15.8, CH=CHC<sub>quat</sub>Ar), 6.06 – 5.95 (m, 1H, CH<sub>2</sub>CH=CH), 2.72 (dd, 2H, *J* = 20.7, 6.8, C<sub>quat</sub>CH<sub>2</sub>CH=CH), 1.69 (s, 3H, C<sub>quat</sub>CH<sub>3</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 138.5 (C<sub>quat</sub>C<sub>quat</sub>Ar), 135.4 (CH=CHC<sub>quat</sub>Ar), 133.8 (2C, CH=CH(Ar-*m*-CH)), 127.7 (CH=CH), 127.3 (CH=CH(Ar-*p*-CH)), 126.6 (2C, C<sub>quat</sub>*m*-Ar-CH), 126.4 (2C, CH=CH(Ar-*o*-CH)), 125.1 (2C, C<sub>quat</sub>(Ar-*o*-CH)), 124.4 (C<sub>quat</sub>Ar-*p*-CH), 122.0 (CH<sub>2</sub>CH=CH), 121.9 (NCC<sub>quat</sub>CH<sub>2</sub>), 44.4 (C<sub>quat</sub>CH<sub>2</sub>CH=CH), 41.2 (NCC<sub>quat</sub>CH<sub>2</sub>), 25.1 (C<sub>quat</sub>CH<sub>3</sub>).

**IR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\bar{\nu}_{\text{max}}$ : 3028, 2979, 2235, 1598, 1494, 1446, 1260, 968, 800, 763, 748, 698.

**HRMS** calcd for [M+Na] 270.1259, found 270.1270.



**2,2-diallyl-3-phenylpent-4-enitrile (2.71):** Clear oil, purified over silica, EtOAc/Hexanes (0.5:9.5).

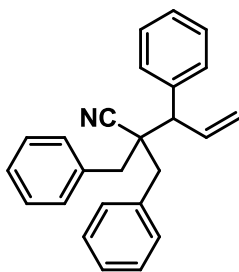
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.31 – 7.24 (m, 4H, *o*-, *m*-Ar-CH), 7.22 – 7.19 (m, 1H, *p*-Ar-CH), 6.23 (m, 1H, C<sub>quat</sub>(Ph)CHCH=CH<sub>2</sub>), 5.73 (m, 2H, C<sub>quat</sub>CH<sub>2</sub>CH=CH<sub>2</sub>), 5.20 (dd, 2H, *J* = 10.2, 1.1 Hz,

$C_{\text{quat}}CH_2CH=CH_2$ ), 5.18 – 5.13 (m, 1H,  $C_{\text{quat}}(\text{Ph})CHCH=CH_{2\text{trans}}$ ), 5.13 – 5.07 (m, 2H,  $C_{\text{quat}}CH_2CH=CH_2$ ), 5.01 (dd, 1H,  $J = 17.0, 1.5$  Hz,  $C_{\text{quat}}(\text{Ph})CHCH=CH_{2\text{cis}}$ ), 3.27 (d, 1H,  $J = 9.7$  Hz,  $C_{\text{quat}}(\text{Ph})CHCH=CH_{2\text{trans}}$ ), 2.49 (dd, 1H,  $J = 14.1, 6.5$  Hz,  $C_{\text{quat}}CH_2CH=CH_2$ ), 2.38 (dd, 1H,  $J = 14.1, 8.1$  Hz,  $C_{\text{quat}}CH_2CH=CH_2$ ), 2.10 (qd, 2H  $J = 14.3, 7.3$  Hz,  $C_{\text{quat}}CH_2CH=CH_2$ ).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  137.8 ( $\text{Ar}-C_{\text{quat}}$ ), 134.9 ( $C_{\text{quat}}(\text{Ph})CHCH=CH_2$ ) 129.6 ( $C_{\text{quat}}CH_2CH=CH_2$ ), 127.4 (5C,  $\text{Ar}-\text{CH}$ ), 126.2 ( $C_{\text{quat}}CH_2CH=CH_2$ ), 120.9 ( $\text{NCC}_{\text{quat}}$ ), 119.4 ( $C_{\text{quat}}(\text{Ph})CHCH=CH_2$ ), 118.9 ( $C_{\text{quat}}CH_2CH=CH_2$ ), 117.6 ( $C_{\text{quat}}CH_2CH=CH_2$ ), 53.0 ( $C_{\text{quat}}(\text{Ph})CHCH=CH_2$ ), 42.7 ( $\text{NCC}_{\text{quat}}R_3$ ), 36.4 (2C,  $\text{NCC}_{\text{quat}}CH_2CH=CH_2$ ).

IR ( $\text{CH}_2\text{Cl}_2$ )  $\bar{\nu}_{\text{max}}$  : 3029, 2981, 2920, 2258, 2231, 1639, 1492, 1438, 993, 923, 721, 405.

HRMS calcd for  $[\text{M}+\text{Na}]$  260.1415, found 260.1435.



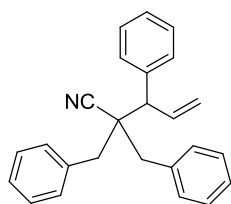
**2,2-dibenzyl-3-phenylpent-4-enenitrile (2.74):** White solid, purified over silica,  $\text{Et}_2\text{O}/\text{Hexanes}$  (0.3:9.7).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 – 6.90 (m, 15H,  $\text{Ph}-\text{H}$ ), 6.39 – 6.29 (m, 1H,  $C_{\text{quat}}(\text{Ph})CHCH=CH_2$ ), 5.30 (s, 1H  $J = 2.0$  Hz,  $\text{CH}=CH_{2\text{trans}}$ ), 5.12 (d, 1H,  $J = 16.9$  Hz,  $\text{CH}=CH_{2\text{cis}}$ ), 3.51 (d, 1H,  $J = 9.1$  Hz,  $C_{\text{quat}}(\text{Ph})CHCH=CH_2$ ), 3.06 (d, 1H,  $J = 13.8$  Hz,  $C_{\text{quat}}CH_2\text{Ph}$ ), 2.89 (d, 1H,  $J = 13.8$  Hz,  $C_{\text{quat}}CH_2\text{Ph}$ ), 2.83 – 2.70 (m, 2H,  $C_{\text{quat}}CH_2\text{Ph}$ ).

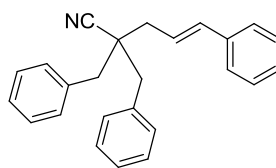
**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  139.2 (2C, quat.  $\text{C}_{\text{quat}}\text{CH}_2\text{C}_{\text{quat}}\text{Ar}$ ), 135.4 ( $\text{C}_{\text{quat}}\text{CH}(\text{C}_{\text{quat}}\text{Ar})\text{CH}_2$ ), 135.2 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ), 130.8 (6C, *o*-Ar-CH), 135.2 (ArC), 130.8 (ArC), 130.5 (ArC), 129.6(ArC), 128.5(ArC), 128.4(ArC), 127.6(ArC), 127.3 (6C, *m*-Ar-CH), 127.2 (3C, *p*-Ar-CH), 122.2 ( $\text{NCC}_{\text{quat}}$ ), 120.4 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ), 54.2 ( $\text{C}_{\text{quat}}(\text{Ph})\text{CHCH}=\text{CH}_2$ ), 47.4 ( $\text{NCC}_{\text{quat}}(\text{Ph})\text{CH}$ ), 39.9 (2C,  $\text{C}_{\text{quat}}\text{CH}_2\text{Ph}$ ).

**IR** ( $\text{CH}_2\text{Cl}_2$ )  $\bar{\nu}_{\text{max}}$  : 3029, 2927, 2231, 1600, 1496, 1454, 1029, 993, 754, 702.

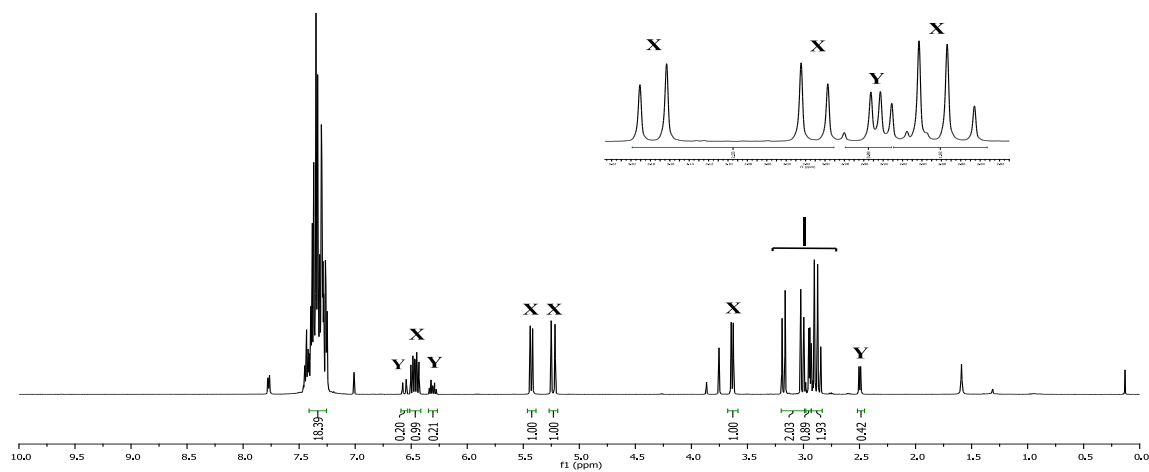
**HRMS** calcd for  $[\text{M}+\text{H}]$  338.1909, found 338.1926.

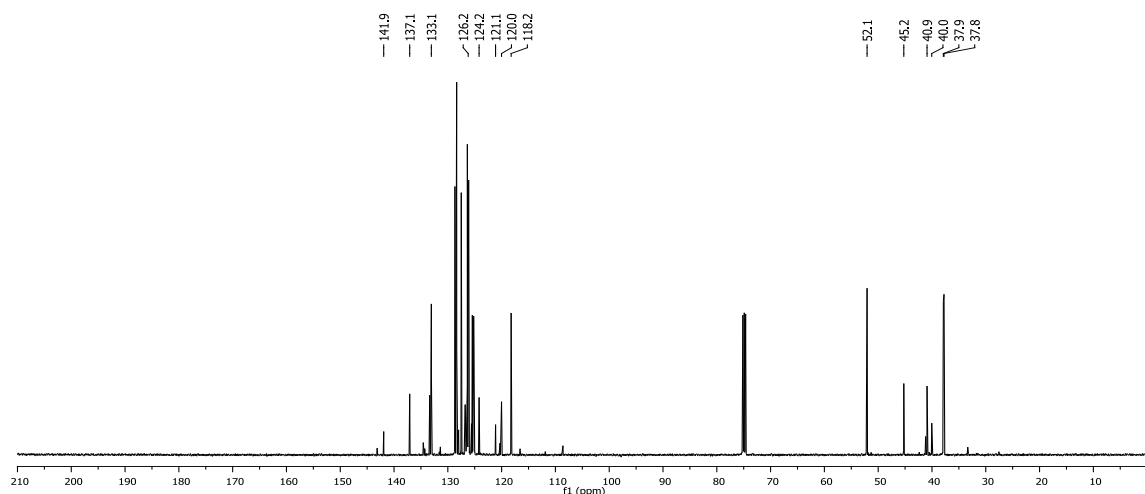


**X** = Branched product



**Y** = Linear product





**dibenzyl-3-phenylpent-4-enenitrile, (E)-2,2-dibenzyl-5-phenylpent-4-enenitrile (2.73/2.74):**

White solid, purified over silica, Et<sub>2</sub>O/Hexanes (0.3:9.7).

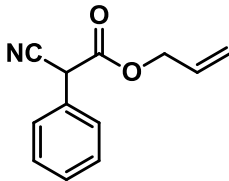
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.30 – 7.12 (m, 18H total, 15H, Ar-*H*<sub>branched</sub>, (linear 1H=.21) 15H, Ar-*H*<sub>linear</sub>), 6.65 (d, 1H, *J* = 15.7 Hz, CH<sub>2</sub>CH=CHPh), 6.49 (m, 1H, C<sub>quat</sub>(Ph)CHCH=CH<sub>2</sub>), 6.31 (dd, 1H, *J* = 14.4, 8.6 Hz, CH<sub>2</sub>CH=CHPh), 5.45 (d, 1H, *J* = 10.1, C<sub>quat</sub>(Ph)CHCH=CH<sub>2trans</sub>), 5.22 (d, 1H, *J* = 16.9 Hz, C<sub>quat</sub>(Ph)CHCH=CH<sub>2cis</sub>), 3.63 (d, 1H, *J* = 8.6 Hz, C<sub>quat</sub>(Ph)CHCH=CH<sub>2</sub>), 3.08 (dd, 2H, *J* = 83.5, 13.7 Hz, branched C<sub>quat</sub>CH<sub>2</sub>Ph), 2.73 (dd, 4H, *J* = 31.0, 17.4 Hz, linear C<sub>quat</sub>CH<sub>2</sub>Ph), 2.65 (dd, 2H, *J* = 18.2, 8.6 Hz, branched C<sub>quat</sub>CH<sub>2</sub>Ph), 2.51 (d, 2H, *J* = 7.2 Hz, linear C<sub>quat</sub>CH<sub>2</sub>CH=CHPh).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 141.9 (6C, CH=CHC<sub>quat</sub> ar), 137.1 (2C, C<sub>quat</sub>CH<sub>2</sub>C<sub>quat</sub>Ar), 133.1 (RCH=CH<sub>2</sub>, RCH=CHPh), 128.7 (12C, *m*-Ar-C), 128.3 (12C, *o*-Ar-C), 127.5 (*p*-Ar-C), 126.5 (*m*-Ar-C), 125.44 (*o*-Ar-C), 125.13 (*p*-Ar-C), 124.2 (RCH=CHPh), 121.1 (branched, NCC<sub>quat</sub>), 120.0 (linear, NCC<sub>quat</sub>), 118.23 (RCH=CH<sub>2</sub>), 52.1 (branched, C<sub>quat</sub>CH<sub>2</sub>Ph), 45.2 (C<sub>quat</sub>CH(CH<sub>2</sub>)Ph), 40.9 (linear, C<sub>quat</sub>CH<sub>2</sub>Ph), 40.0 (NCC<sub>quat</sub>), 37.8 (C<sub>quat</sub>CH<sub>2</sub>CH=CHPh).

**IR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\bar{\nu}_{\max}$  : 3029, 2927, 2231, 1600, 1496, 1454, 1029, 993, 754, 702.

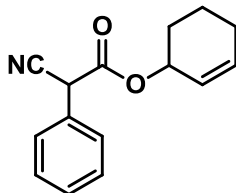
**HRMS** calcd for [M+H] 338.1909, found 338.1926.

Characterization of Allyl cyanoacetates:



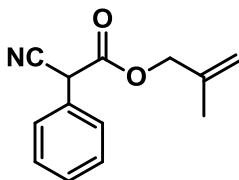
**(2.12) allyl 2-cyano-2-phenylacetate (TR1-065)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56 – 7.34 (m, 5H,  $\text{CH}_{\text{Ar}}$ ), 5.86 (ddt,  $J$  = 17.2, 10.4, 5.7 Hz, 1H,  $\text{CH}_2\text{CH}_{\text{vinyl}}$ ), 5.33 – 5.18 (m, 2H,  $\text{C(H)CH}_2$ ), 4.81 (s, 1H,  $\text{CH}_{\text{tertiary}}$ ), 4.66 (dt,  $J$  = 5.7, 1.5 Hz, 2H,  $\text{ROCH}_2$ ).



**(2.26) cyclohex-2-en-1-yl 2-cyano-2-phenylacetate**

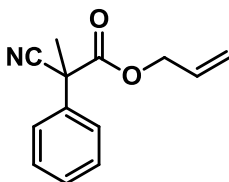
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.67 – 7.35 (m, 5H,  $\text{CH}_{\text{Ar}}$ ), 6.02 (dq,  $J$  = 14.1, 4.2 Hz, 1H,  $\text{CH}_{\text{vinyl}}$ ), 5.83 – 5.60 (m, 1H,  $\text{CH}_{\text{vinyl}}$ ), 5.31 (t,  $J$  = 4.5 Hz, 1H,  $\text{ROCH}_{\text{Cy}}$ ), 4.73 (s, 1H,  $\text{CH}_{\text{tertiary}}$ ), 2.29 – 1.94 (m, 2H,  $\text{C}_{\text{vinyl}}\text{CH}_2$ ), 1.92 – 1.47 (m, 4H,  $\text{CH}_2$ ).



**2-methylallyl 2-cyano-2-phenylacetate (TR1-126)**

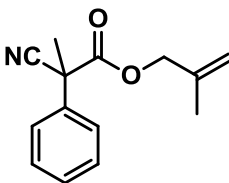


**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.57 – 7.32 (m, 5H, CH<sub>Ar</sub>), 4.95 (qd, *J* = 2.4, 1.0 Hz, 2H, C(H)CH<sub>2</sub>), 4.79 (s, 1H, CH<sub>tertiary</sub>), 4.67 – 4.52 (m, 2H, ROCH<sub>2</sub>), 1.71 (s, 3H, CH<sub>3</sub>).



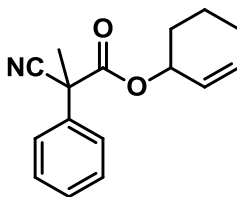
**allyl 2-cyano-2-phenylpropanoate (TR1-096)**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.64 – 7.53 (m, 2H, CH<sub>Ar</sub>), 7.51 – 7.36 (m, 3H, CH<sub>Ar</sub>), 5.94 – 5.76 (m, 1H, CH<sub>2</sub>CH<sub>vinyl</sub>), 5.35 – 5.19 (m, 2H, C<sub>vinyl</sub>CH<sub>2</sub>), 4.77 – 4.61 (m, 2H, ROCH<sub>2</sub>), 2.00 (s, 3H, CH<sub>3</sub>).



**2-methylallyl 2-cyano-2-phenylpropanoate (TR1-189)**

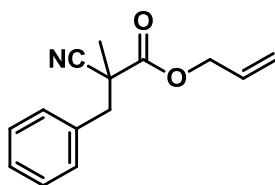
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.65 – 7.50 (m, 2H, CH<sub>Ar</sub>), 7.50 – 7.35 (m, 3H, CH<sub>Ar</sub>), 4.91 (d, *J* = 3.0 Hz, 2H, C<sub>vinyl</sub>CH<sub>2</sub>), 4.67 – 4.52 (m, 2H, ROCH<sub>2</sub>), 2.00 (s, 3H, C<sub>quat</sub>CH<sub>3</sub>), 1.66 (s, 3H, CH<sub>3</sub>).



**cyclohex-2-en-1-yl 2-cyano-2-phenylpropanoate (TR1-257)**

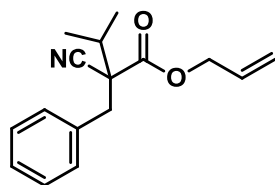
**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.52 – 7.43 (m, 2H,  $\text{CH}_{\text{Ar}}$ ), 7.40 – 7.26 (m, 3H,  $\text{CH}_{\text{Ar}}$ ), 5.99 – 5.81 (m, 2H,  $\text{CH}_{\text{vinyl}}$ ), 5.66 (ddt,  $J = 10.1, 4.0, 2.2$  Hz, 1H,  $\text{CH}_{\text{vinyl}}$ ), 5.49 (ddt,  $J = 9.7, 4.2, 2.2$  Hz, 1H,  $\text{CH}_{\text{vinyl}}$ ), 5.25 – 5.12 (m, 1H,  $\text{ROCH}_{\text{Cy}}$ ), 2.05 – 1.91 (m, 5H,  $\text{C}_{\text{vinyl}}\text{CH}_2$  and  $\text{CH}_3$ ), 1.91 – 1.43 (m, 4H,  $\text{CH}_2$ ).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  167.5, 135.8, 134.2, 129.1, 128.7, 125.7, 124.0, 123.9, 119.6, 71.2, 27.6, 24.7, 18.4.



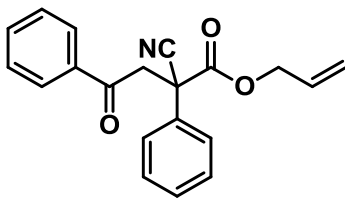
**allyl 2-cyano-2-methyl-3-phenylpropanoate (TR2-063)**

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43 – 7.25 (m, 5H), 5.85 (ddt,  $J = 16.4, 10.9, 5.8$  Hz, 1H), 5.38 – 5.22 (m, 2H), 4.65 (dd,  $J = 6.5, 2.7$  Hz, 2H), 3.27 (d,  $J = 13.6$  Hz, 1H), 3.08 (d,  $J = 13.6$  Hz, 1H), 1.65 (s, 3H).



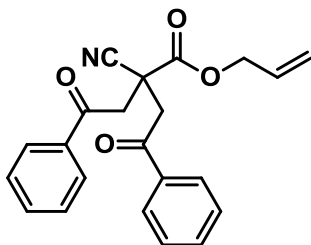
**allyl 2-benzyl-2-cyano-3-methylbutanoate (TR2-017)**

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45 – 7.24 (m, 5H), 5.70 (ddt,  $J = 17.2, 10.3, 5.8$  Hz, 1H), 5.25 – 5.14 (m, 2H), 4.57 – 4.42 (m, 2H), 3.26 – 3.17 (m, 1H), 3.14 – 3.04 (m, 1H), 2.38 (hept,  $J = 6.7$  Hz, 1H), 1.27 (d,  $J = 6.8$  Hz, 3H), 1.11 (d,  $J = 6.7$  Hz, 3H).



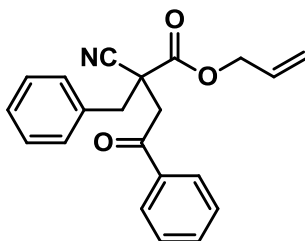
**allyl 2-cyano-4-oxo-2,4-diphenylbutanoate (TR1-198)**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 (m, 10H), 6.02 – 5.80 (m, 1H), 5.43 – 5.18 (m, 2H), 4.85 – 4.62 (m, 2H).



**allyl 2-cyano-4-oxo-2-(2-oxo-2-phenylethyl)-4-phenylbutanoate (TR1-221)**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.15 – 7.92 (m, 4H), 7.72 – 7.58 (m, 2H), 7.58 – 7.44 (m, 4H), 6.09 – 5.87 (m, 1H), 5.56 – 5.41 (m, 1H), 5.39 – 5.27 (m, 1H), 4.88 – 4.72 (m, 2H), 4.09 – 3.84 (m, 4H).

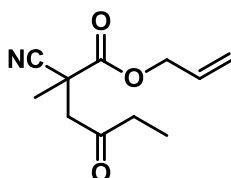


**allyl 2-benzyl-2-cyano-4-oxo-4-phenylbutanoate (TR1-228)**

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 – 7.77 (m, 2H), 7.57 – 7.49 (m, 1H), 7.44 – 7.37 (m, 2H), 7.33 – 7.22 (m, 5H), 5.74 (ddt,  $J$  = 17.3, 10.5, 5.7 Hz, 1H), 5.25 (dq,  $J$  = 17.2, 1.4 Hz, 1H), 5.17 (dq,  $J$  =

10.4, 1.2 Hz, 1H), 4.66 – 4.58 (m, 1H), 4.58 – 4.50 (m, 1H), 3.70 (d,  $J = 17.9$  Hz, 1H), 3.55 – 3.41 (m, 1H), 3.27 – 3.22 (m, 1H), 3.18 – 3.13 (m, 1H).

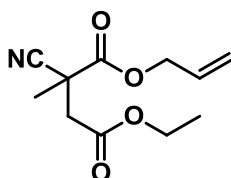
**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  194.3, 168.3, 135.3, 134.0, 133.3, 130.7, 130.1, 128.8, 128.3, 128.0, 119.2, 118.7, 67.3, 46.5, 45.1, 42.7.



**allyl 2-cyano-2-methyl-4-oxohexanoate (TR1-269)**

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.88 (ddt,  $J = 17.2, 10.4, 5.7$  Hz, 1H), 5.36 (dq,  $J = 17.2, 1.5$  Hz, 1H), 5.24 (dq,  $J = 10.4, 1.2$  Hz, 1H), 4.72 – 4.59 (m, 2H), 3.14 – 3.07 (m, 1H), 2.97 – 2.88 (m, 1H), 2.40 (q,  $J = 7.3$  Hz, 2H), 1.60 – 1.56 (s, 3H), 1.02 (t,  $J = 7.3$  Hz, 3H).

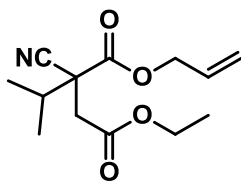
**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  205.6, 168.8, 130.8, 119.5, 119.3, 67.3, 49.2, 39.6, 35.4, 23.7, 7.4.



**1-allyl 4-ethyl 2-cyano-2-methylsuccinate (TR1-268)**

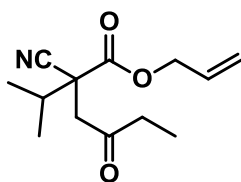
**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.88 (ddt,  $J = 17.2, 10.5, 5.7$  Hz, 1H), 5.35 (dq,  $J = 17.2, 1.4$  Hz, 1H), 5.25 (dq,  $J = 10.4, 1.2$  Hz, 1H), 4.72 – 4.61 (m, 2H), 4.13 (q,  $J = 7.1$  Hz, 2H), 2.99 (d,  $J = 17.1$  Hz, 1H), 2.77 (d,  $J = 17.1$  Hz, 1H), 1.61 (s, 3H), 1.20 (t,  $J = 7.2$  Hz, 3H).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.6, 168.4, 130.7, 119.5, 119.2, 67.4, 61.6, 41.7, 40.5, 23.8, 14.1.



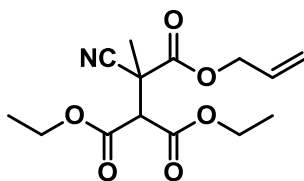
**1-allyl 4-ethyl 2-cyano-2-isopropylsuccinate (TR2-011)**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.10 – 5.89 (m, 1H), 5.46 (dt,  $J$  = 17.0, 1.4 Hz, 1H), 5.33 (dd,  $J$  = 10.0, 1.6 Hz, 1H), 4.75 (dd,  $J$  = 6.7, 2.1 Hz, 2H), 4.20 (qd,  $J$  = 7.5, 1.8 Hz, 2H), 3.12 – 2.98 (m, 1H), 2.96 – 2.80 (m, 1H), 2.17 (hept,  $J$  = 6.8 Hz, 1H), 1.29 (t,  $J$  = 7.1 Hz, 3H), 1.15 (d,  $J$  = 6.8 Hz, 3H), 1.11 (d,  $J$  = 6.8 Hz, 3H).



**allyl 2-cyano-2-isopropyl-4-oxohexanoate (TR2-009)**

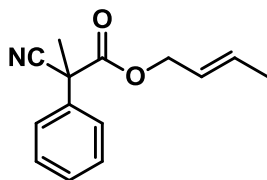
$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.05 – 5.90 (m, 1H), 5.46 (ddt,  $J$  = 17.0, 2.8, 1.5 Hz, 1H), 5.32 (ddt,  $J$  = 10.2, 2.7, 1.4 Hz, 1H), 4.73 (ddd,  $J$  = 5.6, 2.5, 1.2 Hz, 2H), 3.18 – 3.07 (m, 1H), 3.05 – 2.95 (m, 1H), 2.48 (qd,  $J$  = 7.3, 2.1 Hz, 2H), 2.11 (heptd,  $J$  = 6.8, 2.1 Hz, 1H), 1.13 (dd,  $J$  = 6.9, 2.1 Hz, 3H), 1.09 (td,  $J$  = 6.7, 3.2 Hz, 6H).



**2-allyl 1,1-diethyl 2-cyanopropane-1,1,2-tricarboxylate (TR2-008)**

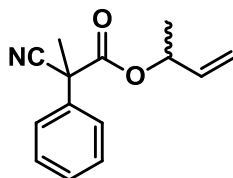
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 5.92 – 5.81 (m, 1H), 5.37 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.26 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.67 (dd, *J* = 5.8, 2.4 Hz, 2H), 4.29 – 4.13 (m, 4H), 3.95 (s, 1H), 1.66 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 167.8, 165.8, 165.2, 130.5, 119.7, 117.4, 67.8, 62.7, 62.6, 56.7, 43.4, 22.44, 14.0, 13.9.



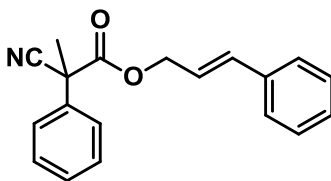
**but-2-en-1-yl 2-cyano-2-phenylpropanoate (TR2-097)**

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.56 – 7.38 (m, 2H), 5.89 – 5.77 (m, 0H), 5.64 – 5.50 (m, 0H), 4.74 (d, *J* = 3.1 Hz, 0H), 4.62 (m, 1H), 1.74 (ddq, *J* = 4.9, 2.5, 1.3 Hz, 1H), 1.57 (d, *J* = 3.6 Hz, 1H).



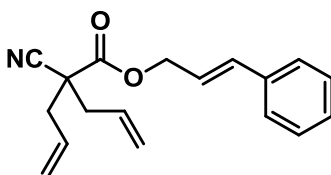
**(±)-but-3-en-2-yl 2-cyano-2-phenylpropanoate (TR1-202)**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.55 (m, 5H), 7.50 – 7.33 (m, 5H), 5.91 – 5.79 (m, 1H), 5.77 – 5.64 (m, 1H), 5.42 – 5.36 (m, 2H), 5.35 – 5.29 (m, 1H), 5.20 (dt, *J* = 10.6, 1.1 Hz, 1H), 5.08 (dtd, *J* = 12.9, 2.3, 1.1 Hz, 2H), 1.98 (s, 6H), 1.38 (dd, *J* = 6.6, 0.7 Hz, 3H), 1.29 – 1.22 (m, 3H).



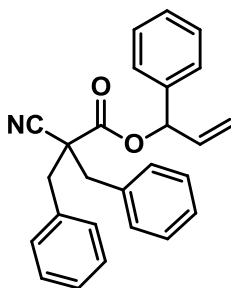
**cinnamyl 2-cyano-2-phenylpropanoate (TR1-163)**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.67 – 7.54 (m, 2H), 7.50 – 7.39 (m, 3H), 7.40 – 7.29 (m, 5H), 6.59 (dq,  $J$  = 15.9, 1.3 Hz, 1H), 6.22 (dtd,  $J$  = 16.0, 6.3, 0.9 Hz, 1H), 4.86 (dt,  $J$  = 6.0, 1.2 Hz, 2H), 2.02 (d,  $J$  = 1.0 Hz, 3H).



**cinnamyl 2-allyl-2-cyanopent-4-enoate (TR2-175)**

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46 – 7.40 (m, 2H), 7.37 (m, 1H), 7.34 – 7.29 (m, 2H), 6.73 (dt,  $J$  = 15.9, 1.3 Hz, 1H), 6.29 (dt,  $J$  = 15.8, 6.6 Hz, 1H), 5.92 – 5.79 (m, 2H), 5.29 (dq,  $J$  = 5.5, 1.3 Hz, 2H), 5.26 (t,  $J$  = 1.3 Hz, 2H), 4.87 (dd,  $J$  = 6.6, 1.4 Hz, 2H), 2.76 – 2.66 (m, 2H), 2.64 – 2.56 (m, 2H).



**1-phenylallyl 2-benzyl-2-cyano-3-phenylpropanoate (TR2-093)**

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.32 (m, 6H), 7.30 – 7.23 (m, 5H), 7.18 (m, 5H), 7.09 – 7.01 (m, 3H), 6.12 (m, 1H), 5.67 (dd, *J* = 17.2, 10.5, 5.8 Hz, 1H), 5.09 (ddd, *J* = 10.5, 2.3, 1.1 Hz, 1H), 5.00 (ddt, *J* = 17.2, 2.6, 1.3 Hz, 1H), 3.36 (dd, *J* = 13.5, 5.5 Hz, 2H), 3.14 (ddd, *J* = 16.0, 13.5, 2.0 Hz, 2H), 2.20 (m, 1H), 1.60 – 1.53 (m, 1H).

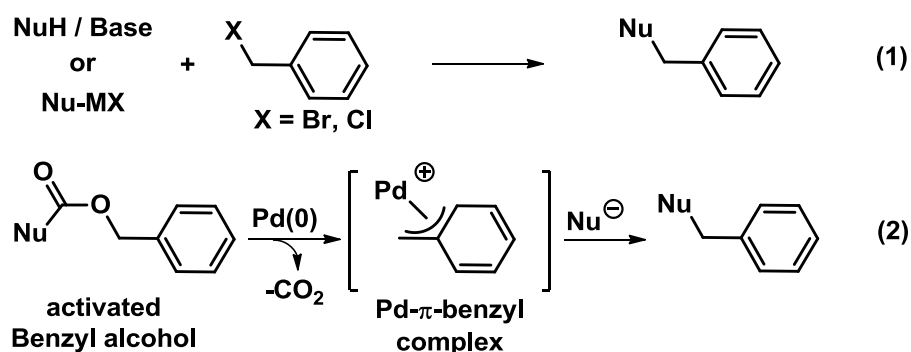


### **Chapter III.**

#### **Decarboxylative Benzylation and Arylation of Nitriles**

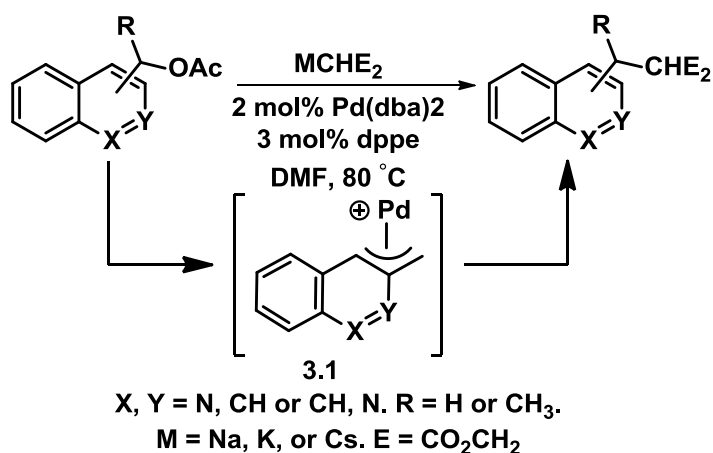
### CIII.1 Nucleophilic additions to palladium- $\pi$ -benzyl complexes

Alkylation of benzylic halides for the incorporation of aromatic moieties is ubiquitous in organic synthesis.<sup>1</sup> Despite the vast number of literature reports utilizing benzylic halides, these procedures typically require stoichiometric amounts of base<sup>2-4</sup> or organometallics,<sup>5-8</sup> in addition to necessitating expensive and difficult to handle halogenated reagents (eq. 1, scheme 3.1).<sup>9</sup> An alternative method makes use of activated benzyl alcohols that are less expensive and easier to handle than the halide variants (eq. 2, scheme 3.1). Analogous to the use of activated allyl alcohol moieties in palladium-catalyzed allylation protocols,<sup>10</sup> benzyl alcohol moieties are activated as benzyl acetates and can be utilized as benzylating reagents via the intermediacy of



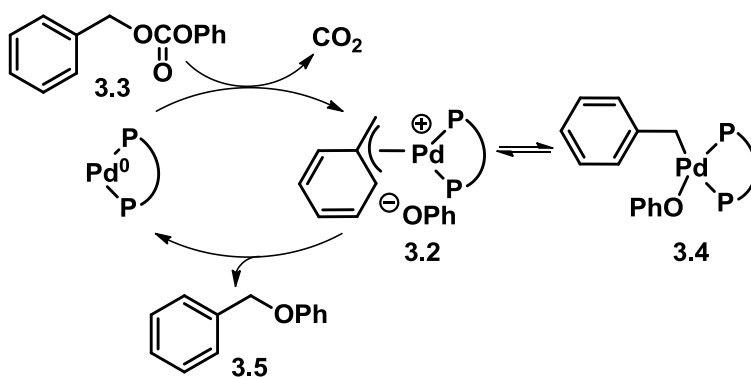
**Scheme 3.1**

Pd- $\pi$ -benzyl complexes (eq. 2, scheme 3.1).<sup>11</sup> To date, a number of examples for the addition of highly stabilized nucleophiles to benzyl acetates and carbonates have been reported.<sup>12-24</sup> Legros reported the substitution of naphthylmethyl-, and quinolylmethyl acetates with dimethylmalonate nucleophiles in presence of a Pd(0) catalyst.<sup>12,13</sup> The reaction is proposed to proceed via the electrophilic Pd- $\pi$ -naphthyl complex **3.1** (scheme 3.2). This report is significant because it suggests that palladium-catalyzed dearomatization of naphthylmethyl acetates



**Scheme 3.2**

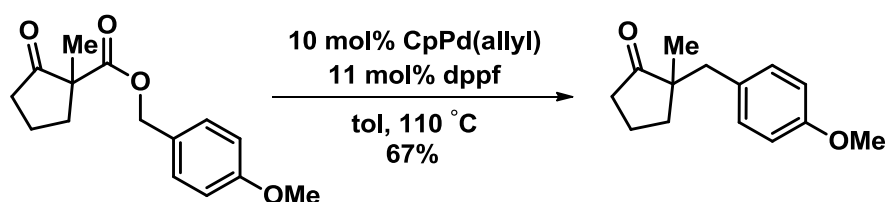
induces ionization of the benzyl acetate moiety.<sup>12</sup> The ionization leads to the formation of Pd- $\pi$ -naphthyl complexes capable of being intercepted with various nucleophiles. It should be noted that the adjacent aromatic ring compensates for the thermodynamic unfavorability of dearomatizing the naphthyl moiety. To address this issue, Kuwano reported the palladium-catalyzed ionization of benzyl carbonate moieties lacking extended conjugated systems capable



**Scheme 3.3**

of compensating for the loss of aromatization (**3.2**, scheme 3.3).<sup>14</sup> In addition to the intermolecular substitution of benzyl acetates with destabilized nucleophiles,<sup>19</sup> Kuwano has also

developed a method for the intramolecular decarboxylative etherification of benzyl aryl carbonates **3.3** that ionize upon treatment with a DPEphos ligated palladium-catalyst.<sup>18</sup> Subsequent decarboxylation reveals the relatively stabilized phenoxide anion and the  $\eta^3$ -Pd- $\pi$ -benzyl complex **3.2** which is in equilibrium with the phenol coordinated  $\eta^1$ -Pd- $\sigma$ -benzyl complex **3.4** (scheme 3.3). Reductive elimination regenerates the palladium catalyst and produces the benzylated phenol **3.5** (scheme 3.3). The catalytic cycle shown in Scheme 3.3 represents the proof of concept needed for the intramolecular decarboxylative coupling of carbon nucleophiles. In this reactive manifold, Chruma reported the decarboxylative benzylation of diphenylglycinate imines in which C-C bond formation proved to be problematic if the nucleophiles were not highly stabilized.<sup>20</sup> In another report, Torregrosa and Tunge describe the palladium-catalyzed decarboxylative naphthylmethylation, and quinolylmethylation of non-stabilized alkynes and ketones.<sup>22</sup> However, despite numerous examples of naphthyl- and quinolylmethylation, only a single example for the decarboxylative arylmethylation (ie. benzylation) of ketones is reported (scheme 3.4).



**Scheme 3.4**

Based on the above literature precedent regarding the substitution of benzyl acetate moieties via the proposed intermediate Pd- $\pi$ -benzyl complexes,<sup>12-24</sup> studies to investigate the feasibility of the decarboxylative benzylation of nitriles were initiated.<sup>25</sup> Analogous to DcA of

nitriles, it is known that treatment of benzyl cyanoacetates with an appropriate palladium catalyst generates a metallated nitrile *in situ* under formally neutral conditions.<sup>26</sup> In addition, recombination of the Pd- $\pi$ -benzyl complex and the nitrile-stabilized carbanion facilitates C–C bond formation generating a newly benzylated nitrile. Given the prevalence of nitriles<sup>27</sup> and heteroaromatic functionalities<sup>28,29</sup> in biologically relevant molecules, an investigation into the decarboxylative benzylation of electron rich and electron deficient heteroaromatic arylmethyl- as well as arylmethyl cyanoacetates is described.<sup>25</sup> It should be noted that these are the first reported examples for the addition of non-stabilized nitriles to Pd- $\pi$ -benzyl complexes.

### **CIII. 2 Decarboxylative Benzylation of Nitriles**

#### ***CIII. 2.1 Decarboxylative arylmethylation of cyanoacetates***

Nucleophilic substitution of benzyl halides is a commonly used method for the introduction of aromatic functionalities.<sup>1</sup> Given that benzyl halides are known to be toxic,<sup>9</sup> costly and difficult to handle reagents, an investigation into the feasibility of employing activated benzyl alcohols for the decarboxylative benzylation (DcB) of nitriles is detailed.<sup>25</sup> Initial studies involved identifying a metal catalyst competent for selectively promoting C–C bond formation. Current literature precedent identifies  $\alpha$ -naphthylmethyl acetate moieties as an ideal test substrate for probing the reactivity of various metal-ligand combinations (Table 3.1).<sup>12,13,22</sup> Exposure of the naphthylmethyl cyanoacetates **3.6** to the non-ligated and ligated ruthenium-catalyst in both methylene chloride and toluene did not show any consumption of the starting material (entries 1-3, Table 3.1). This observation suggests that the ruthenium-catalyst was not reactive toward ionization of the benzyl acetate moiety. Hiyama<sup>17</sup> and Tunge<sup>22</sup>

**Table 3.1 Conditions for decarboxylative arylmethylation nitriles**

entry	Ar	R	catalyst	ligand	solvent	h	°C	% conv.	3.7 : 3.8 : 3.9
(1)	$\alpha$ -naphthyl	H	$[\text{Cp}^*\text{RuCl}]_4$	none	DCM	24	45	<5	
(2)	"	"	$[\text{Cp}^*\text{RuCl}]_4$	bypridyl	DCM	24	45	<5	
(3)	"	"	$[\text{Cp}^*\text{RuCl}]_4$	bypridyl	Tol	24	110	<5	
(4)	"	"	CpPd(allyl)	BINAP	Tol	1	95	>99	30 : 35 : 35
(5)	"	"	$\text{Pd}(\text{PPh}_3)_4$	none	Tol	2	110	>99	70 : 25 : <5
(6)	$\alpha$ -naphthyl	Ph	$\text{Pd}(\text{PPh}_3)_4$	none	Tol	0.5	95	92	78 : >5 : 17
(7)	Ph	Ph	$\text{Pd}(\text{PPh}_3)_4$	none	Tol	0.5	95	99	<5 : <5 : 90
(8)	Ph	H	CpPd(allyl)	dppf	Tol	2	100	>99	15 : 30 : 15

**dppf**

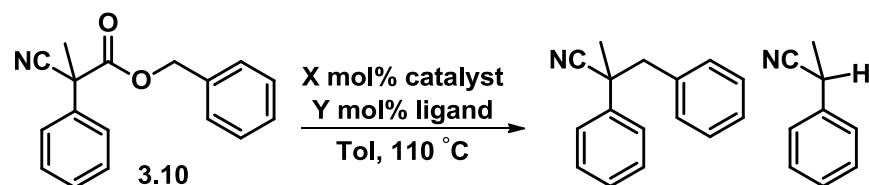
**rac-BINAP**

**bypridyl**

independently report that the combination of CpPd(allyl) and bidendate ligands were reactive catalysts toward the ionization of benzyl acetate functionalities. However, subjecting naphthylmethyl cyanoacetate to a *rac*-BINAP ligated CpPd(allyl) catalyst resulted in an equal distribution of monobenzylated (**3.7**, Table 3.1), di-benzylated (**3.8**), and protonation (**3.9**) products (entry 4, Table 3.1).<sup>14</sup> Exposure of the same substrate to  $\text{Pd}(\text{PPh}_3)_4$  in refluxing toluene generated a 2.5 : 1 ratio of **3.7** : **3.8** without any evidence of the formation of **3.9** (entry 5, Table 3.1).<sup>22</sup> Although, treatment of  $\alpha$ -phenyl, naphthylmethyl cyanoacetate with the  $\text{Pd}(\text{PPh}_3)_4$  results in the formation of a 4 : 1 ratio of monobenylation **3.7** to protonation **3.9**, with the dibenylation product **3.8** not observed (entry 6, Table 3.1). Based on the selectivity for C–C bond formation obtained with the  $\text{Pd}(\text{PPh}_3)_4$  (entry 6, Table 3.1),  $\alpha$ -phenyl benzyl cyanoacetate is examined under identical reaction conditions (entry 7, Table 3.1). Complete

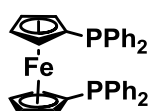
consumption of the starting material ester was observed, suggesting ionization of the acetate moiety, however the catalyst was not competent for C–C bond formation (entry 7, Table 3.1).<sup>22</sup> It should be noted that ionization of benzyl acetates involves partial dearomatization of a benzene moiety lacking an adjacent aromatic ring capable of compensating for the loss in aromaticity.<sup>19</sup> For this reason *p*-methoxyphenylmethyl cyanoacetate was treated under conditions reported by Tunge for the decarboxylative benzylation of ketones (entry 8, Table 3.1).<sup>22</sup> The results showed that dibenylation **3.8** is the major product in addition to the formation of equal amounts of **3.7** and **3.9** (entry 8, Table 3.1). Results obtained during the development of the DcA of nitriles suggest the  $\alpha$ -protio cyanoacetate substrate is likely the source of the protonated product (section 2, Chapter II). Furthermore, the observed C–C bond formation with the dppf-ligated CpPd(allyl) leads to utilization of this catalyst for the decarboxylative benzylation of the  $\alpha$ -phenyl,  $\alpha$ -methyl benzyl cyanoacetate **3.10** (Table 3.2).<sup>17</sup> A brief screen of various catalyst conditions competent for facilitating ionization of the benzyl acetate moiety in addition to promoting C–C bond formation are detailed in Table 3.2. Use of a catalytic amount of Pd(PPh<sub>3</sub>)<sub>4</sub> as reported by Tunge,<sup>22</sup> led only to the formation of the protonation product **3.12** (entry 1, Table 3.2). A similar product distribution is observed when using precatalyst Pd<sub>2</sub>(dba)<sub>3</sub> and bulky monodentate Xphos ligand (entry 2, Table 3.2).<sup>14</sup> However, switching to the dppf- ligated CpPd(allyl) catalyst led to nearly exclusive formation of the benzylated nitrile **3.11** (entry 3, Table 3.2).<sup>17</sup> These newly found reaction conditions are utilized to investigate the scope of the decarboxylative arylmethylation of nitriles. As shown in Table 3.2, treatment of 2-methylbenzyl-, and benzyl cyanoacetate with a dppf-ligated CpPd(allyl) facilitates loss of CO<sub>2</sub>, producing the benzylated nitriles **3.11** and **3.13** in 93% and

### Table 3.2 Decarboxylative benzylation of nitriles

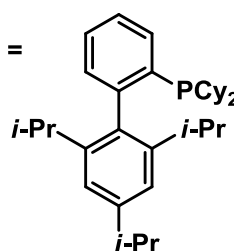


entry	X	catalyst	Y	Ligand	3.11	3.12
(1)	5	Pd(PPh <sub>3</sub> ) <sub>4</sub>		none	<5	>95
(2)	2.5	Pd <sub>2</sub> (dba) <sub>3</sub>	10	Xphos	<5	>95
(3)	10	CpPd(allyl)	11	dppf	94	6

**dppf =**



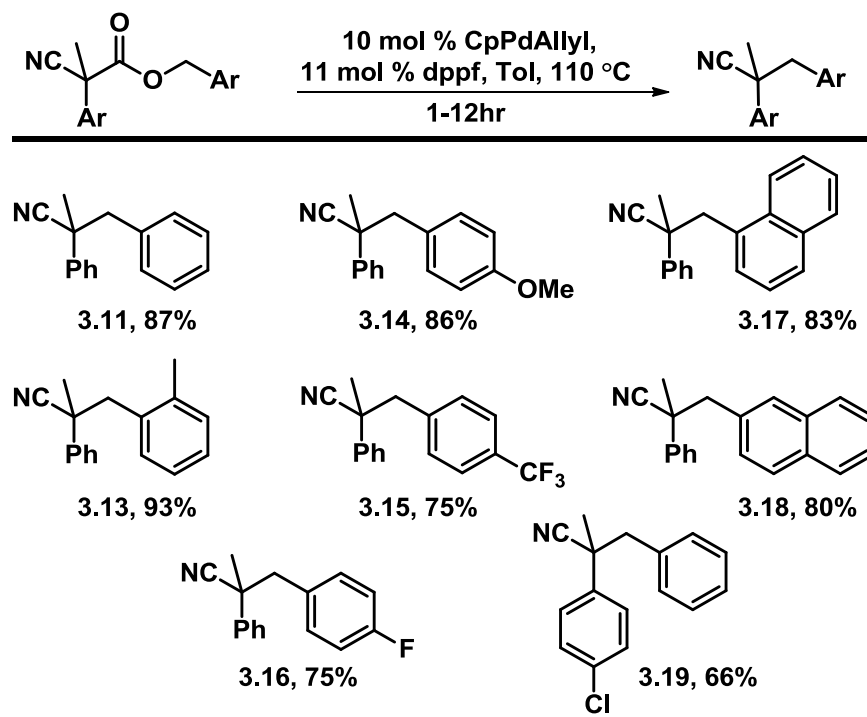
**Xphos =**



87% yield, respectively (Table 3.3). It should be noted that decarboxylative benzylation does not proceed at room temperature. As discussed in Chapter II, loss of CO<sub>2</sub> in the DcA of phenylacetonitrile-stabilized carbanions proceeds at room temperature. The needed increase in temperature for the DcB of nitriles suggests that, due to the dearomatization required, ionization of the benzyl acetate moiety is rate-limiting.<sup>26</sup> Introducing electron-withdrawing (**3.15**, **3.16**, Table 3.3), as well as electron-donating (**3.14**, Table 3.3) substituents on the benzylating coupling partner has a minimal effect on reactivity and accounts for a 10% difference in yield (**3.14**→**3.15**, Table 3.3). Arylmethyl ester substrates with extended conjugation capable of compensating for the loss of aromaticity upon ionization of the benzyl acetate moiety undergo decarboxylative coupling to produce compounds **3.17** and **3.18** in 83% and 80% yield, respectively (Table 3.3).<sup>12,13,22</sup> Last, using a *para*-chlorobenzyl nitrile nucleophile results in a minor decrease in yield as shown by compound **3.19** (Table 3.3).<sup>16</sup> To further



**Table 3.3 Decarboxylative arylmethylation of nitriles**



investigate the scope of the decarboxylative arylmethylation reaction, various  $\alpha$ -nitrile substituents are examined. Having shown the decarboxylative allylation of various phenylacetonitrile moieties,<sup>26</sup> studies employing similar functionalities for the decarboxylative arylmethylation of nitriles are detailed in Table 3.4. Exchanging a methyl substituent for an aceto-, ethyl ester functional group (**3.20**, entry 1, Table 3.4) provided the benzylated nitrile in 66% yield in addition to a substantial amount of the competing protonation product. When an isopropyl containing substrate **3.21** is subjected to the dppf-ligated Pd-catalyst, equal amounts of C–C bond formation and protonation are observed (entry 2, Table 3.4).<sup>26</sup> This deterioration of selectivity is likely due to the increased steric demand of the nitrile-stabilized carbanion containing the isopropyl unit. Introducing a  $\beta$ -methylallyl substituent (**3.22**, Table 3.4) leads to a more selective C–C bond formation, however does not completely circumvent the protonated

**Table 3.4 Scope of the decarboxylative arylmethylation of Nitriles**

$  \begin{array}{c}  \text{NC} \\    \\  \text{R}^1 \text{---} \text{C} \text{---} \text{C}(=\text{O}) \text{OCH}_2\text{Ar} \\    \\  \text{R}^2  \end{array}  \xrightarrow[24\text{hr}]{10 \text{ mol } \% \text{ CpPdAllyl}, 11 \text{ mol } \% \text{ dppf, Tol, } 110^\circ\text{C}}  \begin{array}{c}  \text{NC} \\    \\  \text{R}^1 \text{---} \text{C} \text{---} \text{CH}_2\text{Ar} \\    \\  \text{R}^2  \end{array}  +  \begin{array}{c}  \text{NC} \\    \\  \text{R}^1 \text{---} \text{C} \text{---} \text{H} \\    \\  \text{R}^2  \end{array}  $						
entry	Substrate	R <sup>1</sup>	R <sup>2</sup>	Ar	benzylation protonation	
(1) <sup>a</sup>	3.20	Ph	CH <sub>2</sub> CO <sub>2</sub> Et	Ph	67	33
(2)	3.21	Ph	CH(CH <sub>3</sub> ) <sub>2</sub>	<i>p</i> -MeOPh	50	50
(3)	3.22	Ph	CH <sub>2</sub> C(CH <sub>3</sub> )CH <sub>2</sub>	<i>p</i> -MeOPh	72	28
(4) <sup>b</sup>	3.23	Ph	C <sub>5</sub> H <sub>9</sub>	<i>p</i> -MeOPh	-	-
(5)	3.24	Bn	CH <sub>3</sub>	<i>p</i> -MeOPh	<5	>95

<sup>a</sup> isolated yield 66%. <sup>b</sup> <sup>1</sup>HNMR shows only unreacted starting material

byproduct (entry 3, Table 3.4). This observation is in accordance with studies reported by Grenning and Tunge suggesting that allylated nitrile-stabilized carbanions are competent nucleophiles for additions to Pd- $\pi$ -complexes.<sup>26,30</sup> Further investigation into the scope of this reaction reveals that a long chain aliphatic substituent renders the arylmethyl cyanoacetate **3.23** non-reactive (entry 4, Table 3.4). Additionally, dialkyl arylmethyl cyanoacetate substrate **3.24** is not activated toward C-C bond formation providing only the protonation by-product (entry 5, Table 3.4). This result is not agreement with studies performed in Chapter II detailing the decarboxylative coupling of dialkyl nitrile-stabilized anions, in which dialkyl cyanoacetates were readily allylated.<sup>26</sup>

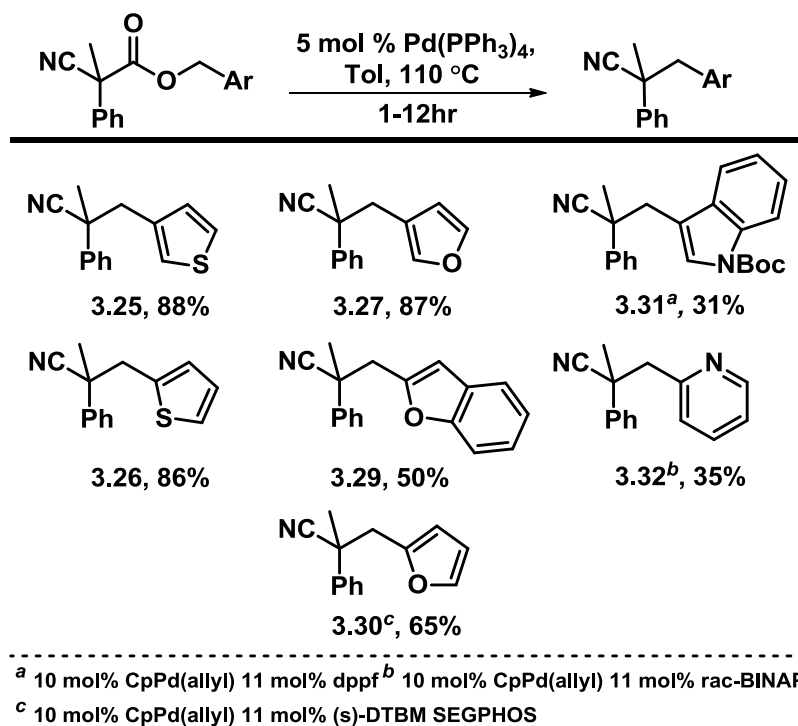
To this point, it was established that utilizing CpPd(allyl) as precatalyst and dppf as ligand generates a catalytic complex that is competent for promoting C-C bond formation and minimizing the amount of observed protonation by-product. In addition, it was determined that  $\alpha$ -phenyl nitrile-stabilized carbanions are reactive toward the Pd- $\pi$ -benzyl complexes generated upon the dearomatization/ionization of the benzyl acetate moieties. A brief

summary of the previous studies conducted in this section suggest that substituents placed on the benzyl/arylmethyl substituent likely does not affect the overall yield of the decarboxylative arylmethylation reaction. In addition, alkyl substituents other than methyl groups are tolerated, albeit in conjunction with substantial amounts of the protonation byproduct. In continuation with the investigation of the decarboxylative benzylation of nitriles, the next section details the development of the decarboxylative heteroarylmethylation of nitriles.<sup>25</sup>

### **CIII. 2.2 DcB of heteroarylmethyl cyanoacetates**

Heteroaromatic compounds such as furans, thiophenes, indoles, and pyridines are present in many active pharmaceutical ingredients as well as biologically active natural products.<sup>28,29</sup> Typically these heteroaromatic functionalities are introduced via nucleophilic<sup>31</sup> or electrophilic<sup>32</sup> aromatic substitution. Traditional metal-catalyzed cross-coupling reactions have also been employed;<sup>33</sup> however these methods typically require activation of preformed organometallic reagents and produce stoichiometric amounts of potentially hazardous metal waste. The palladium-catalyzed decarboxylative heteroarylmethylation of nitrile-stabilized carbanions serves to complement known cross-coupling methodologies via achieving C–C bond formation while generating CO<sub>2</sub> as the sole reaction by-product.<sup>34</sup> Preliminary studies identified Pd(PPh<sub>3</sub>)<sub>4</sub> as an efficient catalyst for the decarboxylative heteroarylmethylation of nitriles, these results were in accordance with studies reported by Tunge involving the decarboxylative quinolylmethylation of alkynes.<sup>22</sup> 3-, and 2-thiophenylmethyl cyanoacetates undergo Pd(PPh<sub>3</sub>)<sub>4</sub>-catalyzed coupling to provide products of heteroarylmethylated nitriles **3.25**, and **3.26** in 88% and 86% yield, respectively (Table 3.5). In addition, 3-furylmethylated

**Table 3.5 Decarboxylative Heteroarylmethylation of nitriles**



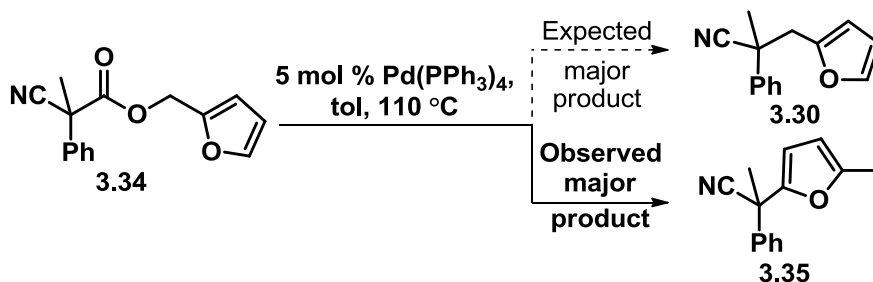
and 2-benzofuranylmethylated nitriles **3.27** and **3.29** are obtained in 87% and 50% via similar reaction conditions. The decrease in yield with the benzofuranyl product **3.29** is not currently understood; however analysis of spectral data suggests a mixture of protonation and homo-coupling of the palladated-2-methylbenzofuran moiety.<sup>35,36</sup> A similar product distribution is observed with the Boc-protected indole substrates as well, resulting in a diminished 31% yield (**3.31**, Table 3.5).<sup>20</sup> However, C–C bond formation required a change in catalyst from the  $\text{Pd(PPh}_3)_4$  to a  $\text{dppf}$ -ligated  $\text{CpPd(allyl)}$  complex. Given that pyridines are present in many pharmaceutical compounds, the  $\alpha$ -picolyl nitrile was highly coveted. Numerous attempts to synthesize a variety of picolyl cyanoacetates failed. However,  $\alpha$ -phenyl,  $\alpha$ -methyl  $\alpha$ -picolyl cyanoacetate **3.33** is obtained (appendix B) and it is determined that  $\text{Pd(PPh}_3)_4$  readily ionizes the arylmethyl acetate moiety providing exclusively the protonation product **3.12** (Table 3.6).

**Table 3.6 Decarboxylative arylmethylation from  $\alpha$ -picolyl cyanoacetates**

entry	Pd source	ligand	solvent	3.32	:	3.12
(1)	Pd(PPh <sub>3</sub> ) <sub>4</sub>	none	Tol	<5	:	>95
(2)	CpPd(allyl)	dppf	Tol	<5	:	>95
(3)	CpPd(allyl)	dppe	Tol	<5	:	>95
(4)	CpPd(allyl)	BINAP	Tol	50	:	50
(5)	CpPd(allyl)	BINAP	THF	<5	:	>95

Based on this result, a series of bidentate ligand and CpPd(allyl) combination were screened in order to determine catalytic condition for C–C bond formation. As detailed in Table 3.6, attempts with dppf- and dppe-ligated CpPd(allyl) catalyst<sup>14,22</sup> in toluene at 95 °C delivered only the protonation product, however switching to *rac*-BINAP<sup>20</sup> delivered the benzylated product **3.32** along with equal amounts of the competing protonation. Purification of the crude mixture resulted in a 35% yield of nitrile **3.32** (Table 3.5). It should be noted that simply changing the solvent from toluene to THF resulted in complete suppression of C–C bond formation. Returning to investigating the scope of the decarboxylative arylmethylation of nitriles, focus was then placed on furyl-2-methyl cyanoacetates (**3.4**, scheme 3.5). Preliminary attempts to obtain the benzylated nitrile **3.30** employing Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst resulted in formation of the decarboxylative arylation product **3.35** (scheme 3.5). As a result of this observation, Chapter III, section 3 is dedicated to identification of catalytic conditions for decarboxylative arylmethylation of nitriles. In this vein, the target method development became determination of conditions for selectively obtaining the competing benzylation and arylation products. It has

now been determined that treatment of furylmethyl cyanoacetate **3.34** with an (*S*)-DTMB-SEGPHOS (see Table 3.7) ligated palladium catalyst delivers the benzylated nitrile **3.30** in 65% yield with 11% ee (Table 3.5).



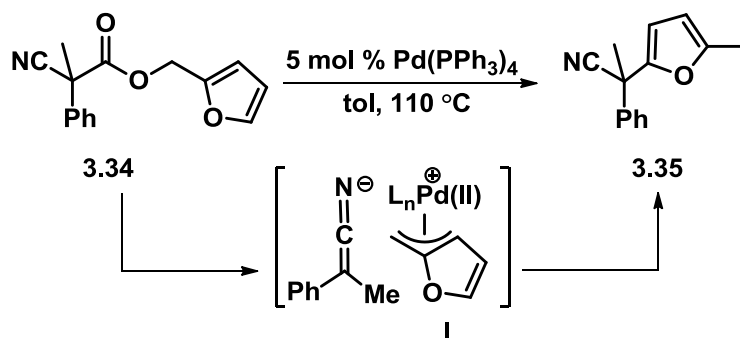
**Scheme 3.5**

To this point, it has been determined that  $\text{Pd}(\text{PPh}_3)_4$  is competent for facilitating the decarboxylative heteroarylmethylation of nitriles with substrates containing thiophenylmethyl- and furylmethyl-, and benzofurylmethyl- acetate moieties. Substrates containing indolyl- and picolyl- residues also undergo decarboxylative arylmethylation with bidentate palladium catalyst, albeit with reduced yields. Last, it was discovered that treatment of 2-methylfuryl cyanoacetates **3.34** resulted in the decarboxylative arylation of nitriles. The following section will detail the investigation into developing reaction conditions necessary for selectively obtaining the products of decarboxylative arylation and benzylation.

### CIII. 3 Decarboxylative Arylation vs. Benzylation of Nitriles

Recently, transition metal-catalyzed decarboxylative arylations have emerged as an alternative to traditional cross-coupling procedures.<sup>37-41</sup> These methods typically involve loss of  $\text{CO}_2$  to generate a metalated anion intermediate that can then be intercepted with an aryl

halide. In addition to aryl anions, there are a myriad of nucleophiles that can be generated via the loss of carbon dioxide.<sup>34,42</sup> More specifically Kwong reported the palladium-catalyzed, base-mediated decarboxylative arylation of nitrile carboxylates via aryl halides.<sup>43</sup> The reaction is proposed to proceed via transmetalation of a metalated nitrile to an aryl-palladated species, which subsequently undergoes a reductive elimination to generate the arylated nitrile. In a similar reactive manifold, Verkade,<sup>44,45</sup> Hartwig,<sup>46,47</sup> as well as Fleming and Knochel<sup>48</sup> report the palladium-catalyzed arylation of metalated nitriles. Alternatively, Fu discloses obtaining  $\alpha$ -arylnitriles via a nickel-catalyzed Hiyama-type cross-coupling reaction from  $\alpha$ -chloronitriles and aryltrifluorosilanes.<sup>8</sup> An additional report from Hartwig describes obtaining the phenyl acetonitriles from trimethylsilyl acetonitrile and aryl halides.<sup>49</sup> The above methods share two attributes: (1) the nitrile requires base activation or prefunctionalization; (2) the arylating coupling partner is either an aryl halide or preformed organometallic reagent. The decarboxylative arylation of furfuryl cyanoacetate **3.34** generates a palladated nitrile via decarboxylation as well as the arylating Pd- $\pi$ -furfuryl complex (**I**, scheme 3.6).<sup>25,50</sup> There are two examples for arylation via the intermediacy of Pd-  $\pi$ -benzyl complexes currently in the literature.<sup>51,52</sup> The following describes the palladium-catalyzed decarboxylative arylation and benzylation of furfuryl cyanoacetates.<sup>25</sup>



**Scheme 3.6**

At this point it should be noted that the arylated product **3.35** is formed when **3.34** is exposed to  $\text{Pd}(\text{PPh}_3)_4$ . As a result of the observed selectivity for the arylated product, developing the current method mainly involves screening for catalytic conditions that promoted decarboxylative benzylation of the furfuryl cyanoacetate **3.34** (Table 3.7). As detailed in Table 3.7, monodentate  $\text{Pd}(\text{PPh}_3)_4$  facilitates formation of the arylation product **3.35** (entry 1, Table 3.7). Previous studies involving the decarboxylative arylmethylation of arylmethyl cyanoacetates identified that  $\text{CpPd}(\text{allyl})$  in conjunction with bidentate ligands efficiently ionized benzyl acetate moieties.<sup>13,22</sup> However, based on the reactivity observed with  $\text{Pd}(\text{PPh}_3)_4$ , a reaction employing the more electron rich monodentate tricyclohexylphosphine ligand did not provide the benzylation product (entry 2, Table 3.7). An evaluation of the dppe-ligated Pd catalyst as reported by Kuwano<sup>14</sup> resulted in exclusive formation of the protonation product **3.12** when performed in both toluene and THF (entry 3 and 4). A modest selectivity for the formation of the benzylation product with respect to the arylation product was first observed with dppf as ligand, however the crude product mixture includes an equal amount of the protonation product.<sup>14,22</sup> As previously reported for the DcA of sulfones<sup>53</sup> and nitriles,<sup>26</sup>



**Table 3.7 Conditions for decarboxylative arylmethylation of furfuryl cyanoacetate**

entry	Pd source	ligand	solvent	3.30	:	3.35	:	3.12
(1)	Pd(PPh <sub>3</sub> ) <sub>4</sub>	none	THF	14	:	85	:	1
(2)	CpPd(allyl)	PCy <sub>3</sub>	Tol	33	:	34	:	33
(3)	CpPd(allyl)	dppe	THF	<5	:	<5	:	>90
(4)	CpPd(allyl)	dppe	Tol	<5	:	<5	:	>90
(5)	CpPd(allyl)	dppf	THF	45	:	<10	:	45
(6)	CpPd(allyl)	BINAP	THF	85	:	<5	:	10
(7)	CpPd(allyl)	BINAP	Tol	85	:	<5	:	10
(8)	CpPd(allyl)	(S) DTBM-SEGPHOS	Tol	85	:	10	:	<5
(9)	CpPd(allyl)	SEGPHOS	THF	89 <sup>a</sup>	:	11	:	trace

<sup>a</sup> Chiral stationary phase chromatography 11% ee.

dppf

*rac*-BINAP

dppe

(S) DTBM - SEGPHOS

*rac*-BINAP was the ligand of choice for circumvention of protonation product. Use of the *rac*-BINAP-ligated catalyst provided selective formation of the arylmethylated product and nearly circumvented the protonation product (entry 7, Table 3.7). Realizing that steric bulk could be the rationale for the observed switch in selectivity from arylation to benzylation products; bulky (S)-DTBM-SEGPHOS was screened and found to favor formation of the arylmethylated nitrile **3.30**, with only a trace amount of protonation (entry 9). As a result of employing the enantioenriched (S)-DTBM-SEGPHOS, **3.30** was analyzed by chiral stationary phase HPLC, however very little enantioenrichment was observed (11% ee).

Determining the conditions for both decarboxylative arylation and arylmethylation of furfuryl cyanoacetates lead to an investigation into identifying similar conditions for the thiophenyl reactant **3.36** (Table 3.8). Preliminary evaluation of reaction temperature suggested that ionization of the thiophenyl-2-methyl acetate moiety does not take place below 95 °C. It became evident that the mixture of precatalyst CpPd(allyl) and PCy<sub>3</sub> was not an active catalyst for decarboxylative coupling of arylmethyl acetates. In addition, employing the Xantphos ligand with a larger bite angle (111°)<sup>54</sup> also favored formation of the arylmethylation product **3.26**.<sup>14</sup> Last, switching to the *rac*-BINAP ligated Pd catalyst did not promote formation of the arylation

**Table 3.8 Conditions for decarboxylative arylation of 2-methylthiophenyl cyanoacetate**

Reaction scheme: 2-methylthiophenyl cyanoacetate (**3.36**) reacts with 5-10 mol% Pd and 11 mol% Ligand to yield products **3.26**, **3.37**, and **3.12**.

entry	catalyst	ligand	sol	h	°C	<b>3.26</b>	:	<b>3.37</b>	:	<b>3.12</b>
(1) <sup>a</sup>	Pd(PPh <sub>3</sub> ) <sub>4</sub>	none	THF	14	80	-	:	-	:	-
(2)	Pd(PPh <sub>3</sub> ) <sub>4</sub>	none	THF	24	95	80	:	<5	:	15
(3)	Pd(PPh <sub>3</sub> ) <sub>4</sub>	none	Tol	24	95	92	:	3	:	<5
(4) <sup>a</sup>	CpPd(allyl)	PCy <sub>3</sub>	Tol	1	95	-	:	-	:	-
(5)	CpPd(allyl)	Xantphos	Tol	1	95	50	:	<5	:	45
(6)	CpPd(allyl)	BINAP	Tol	1	95	50	:	<5	:	45

<sup>a</sup> <sup>1</sup>HNMR suggests only starting material

**Xantphos**

*rac*-BINAP

product. It should be noted, as Dewhurst has isolated a Pd- $\pi$ -furfuryl complex (**A**, figure 3.1)<sup>50</sup> and the analogous thiophenyl  $\eta^3$ -metal complexes (**B**, figure 3.1)<sup>55</sup> have also been reported, it is

Chemical structures of the catalysts are shown below:

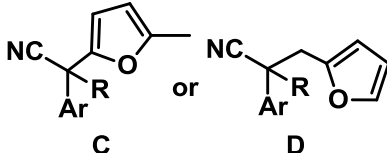
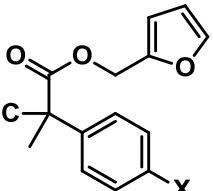
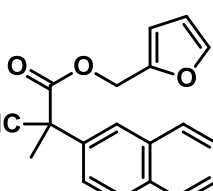
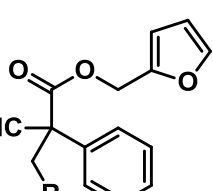
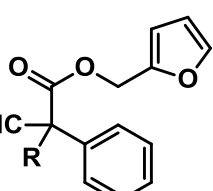
**A**: CCOC(=O)c1cc2oc3ccccc3cc2o1[Pd+](P(c1ccccc1)(c1ccccc1)c1ccccc1)[P-](c1ccccc1)(c1ccccc1)c1ccccc1.[B-](F)(F)(F)F)

**B**: C1=CC=C(S1)[Mo](C1=CC=CC=C1)C(=O)C(=O)

The conditions for selectively obtaining the products of decarboxylative arylmethylation and arylation of furfuryl cyanoacetates have been established. Table 3.7 reveals that monodentate-ligated  $\text{Pd}(\text{PPh}_3)_4$  (conditions A) facilitates decarboxylative arylation and the bidentate (S)-DTBM SEGPPOS modified Pd-catalyst (conditions B) obtained from precatalyst  $\text{CpPd}(\text{allyl})$  facilitates decarboxylative arylmethylation. Having identified these conditions, the scope of the reaction was investigated (Table 3.9). Preliminary studies involved probing the electronics of various *p*-derivatized nitrile-stabilized anions generated by decarboxylation (entries 1-7, Table 3.9). The result shown in Table 3.9 suggest that the phenylacetone nitriles substituted with electron-donating substituents (entries 3, 4, and 7) are more selective than the products obtained from *p*-chlorophenylacetone nitrile (entries 5 and 6) with respect to arylation vs. benzylation. It should be noted that the *p*-cyanophenylacetone nitrile is not reactive upon exposure to reaction conditions B, in contrast treatment of *p*-cyanophenylacetone nitrile to reaction conditions A leads to selective production of the arylated product **3.42** in 70% yield.

(entry 7). Incorporation of the more sterically demanding  $\beta$ -naphthyl nitrile results in exclusive formation of the arylation product when subjected to  $\text{Pd}(\text{PPh}_3)_4$  catalyst (conditions A, entry 8). However, exposure of the  $\beta$ -naphthyl nitrile substrate to the condition for decarboxylative

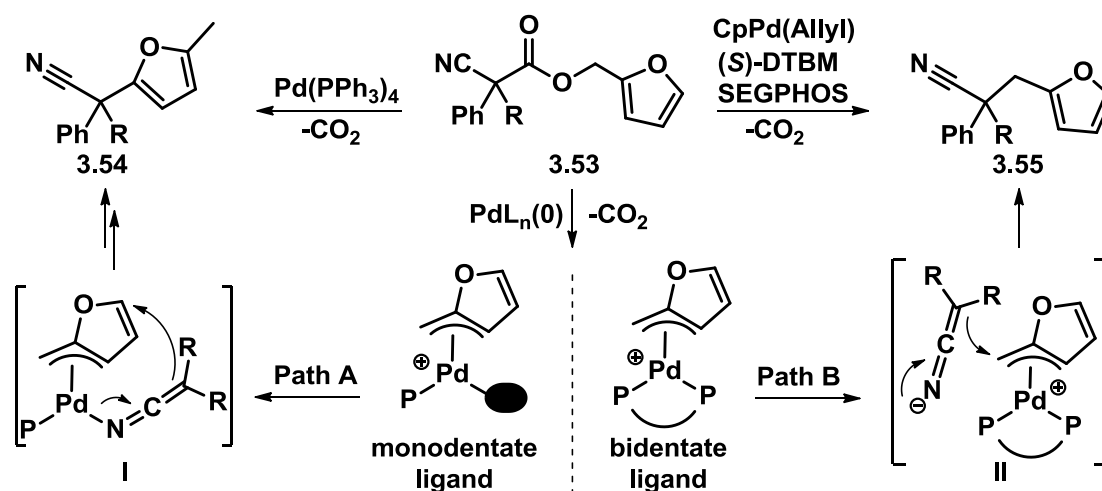
**Table 3.9 Decarboxylative arylation vs. arylmethylation of Nitriles**

substrate	cond A: 5 mol % Pd(PPh <sub>3</sub> ) <sub>4</sub> , THF, 110 °C, 12-24h cond B: 10 mol % CpPdAllyl, 11 mol % (s)-DTBM SEGPPOS, THF, 110 °C 12-24h		 C or D			
entry	substrate	Cond.	C : D <sup>a</sup>	% yield <sup>b</sup>	product	
1		X = H	A	84 : 14	86 (71)	3.35
2			B	11 : 89	83 (65)	3.30
3		X = OMe	A	>95 : <5	75 (75)	3.38
4			B	<5 : >95	69 (69) <sup>c</sup>	3.39
5		X = Cl	A	80 : 20	84 (69)	3.40
6			B	10 : 90	--- (65)	3.41
7		X = CN	A	>95 : <5	70 (70)	3.42
8			A	>95 : <5	89 (89)	3.43
9			B	16 : 84	70 (53)	3.44
10		R = Ph	A	90 : 10	--- (75)	3.45
11			B	9 : 91	86 (77)	3.46
12		R =	A	90 : 10	84 (70)	3.47
13		4-OMePh	B	<5 : >95	76 (76)	3.48
14		R = 2-Cl-5-pyridyl	A	75 : 25	65 (51)	3.49
15		R =	A	85 : 15	90 (63)	3.50
16		<i>i</i> -propyl	B	<5 : >95	71 (71)	3.51
17		R = Allyl	A	75 : 25	--- (60)	3.52

<sup>a</sup> calculated from crude HNMR, <sup>b</sup> combined yield (isolated yield major isomer)

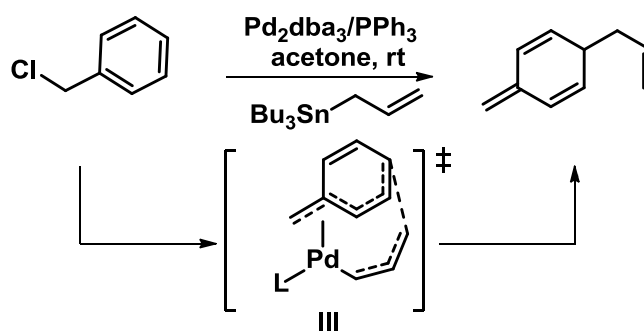
benzylation (conditions B) did not provide the same ratio of products, and the reduced yield was due to a minimal amount of the difficult to resolve protonation contaminant (entry 9, Table 3.9). In addition, only minimal changes in selectivity were observed when varying the  $\alpha$ -methyl substituent to more sterically demanding benzyl and isopropyl functionalities (entries 10-13, 15, 16). Last, substrates with functional groups capable of coordinating to the metal catalyst (entry 14, pyridine, entry 17, allyl) resulted in reduced selectivity when subjected to the reaction condition for decarboxylative arylation. It should be noted that these substrates were not competent for C–C bond formation under the reaction conditions for obtaining the arylmethylation products (conditions B, Table 3.9). With some understanding of the scope of the decarboxylative arylmethylation and arylation reaction, the current rationale for the observed selectivity will be detailed.

To address the observed selectivity for decarboxylative arylation and arylmethylation with the furfuryl cyanoacetates, a working mechanistic rationale based on literature precedent is proposed (scheme 3.7). All of the data to this point show a distinct switch in selectivity when changing from the monodentate  $\text{PPh}_3$  ligand to the bidentate bulky (S)-DTBM-SEGPHOS ligand. It is likely that both products originate from an  $\eta^3\text{-Pd-}\pi\text{-furfuryl}$  complex (scheme 3.7).<sup>50</sup> Based on literature precedent, it is feasible that the ligand-dependent selectivity observed with  $\text{PPh}_3$  originates from access to an open coordination site on the metal center (path A). The available coordination site allows for inner-sphere attack of the ketiminate nucleophile as suggested in Scheme 3.7, I. Crystallographic data characterizing an analogous palladated-keteniminate complex has been reported by Hartwig.<sup>46</sup> Moreover, mechanistic studies of an allylative dearomatization reaction performed by Lin (scheme 3.8)<sup>56</sup> suggest that an  $\eta^3\text{-Pd-}\pi\text{-benzyl}$ ,  $\eta^1\text{-}$



**Scheme 3.7**

*N*-bound ketenimine<sup>26,57,58</sup> transition state is feasible.<sup>59-61</sup> Moreover, Bao reports the dearomatization of benzyl electrophiles with allenyl stannanes likely proceeds by intermediates similar to **I**, as suggested in Scheme 3.7. With respect to the selectivity observed employing the bidentate (*S*)-DTMB-SEGPHOS ligand, lack of an available coordination site forces an outer-sphere attack (**II**, scheme 3.7) of the nitrile-stabilized carbanion resulting in formation of the arylmethylation product **3.55** (path B, scheme 3.7).



**Scheme 3.8**

The palladium-catalyzed decarboxylative arylmethylation and arylation of nitriles has been described. The method entails treatment of furfuryl cyanoacetates with monodentate  $\text{PPh}_3$  ligand to obtain arylated nitriles and bidentate (*S*)-DTMB-SEPHOS ligand to afford arylmethyated nitriles. In addition, the method represents the use of activated benzyl alcohol moieties as alternatives to benzyl halides for the benzylation and arylation of nitriles. Last, the method is another example of the functionalization of metalated nitriles generated via the loss of  $\text{CO}_2$  under formally neutral conditions.

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## Appendix B

### General information:

All reactions were performed in flame-dried glassware under Ar atmosphere using standard Schlenk techniques. All reactions run in tetrahydrofuran were performed in 5 mL Biotage microwave vials with sealable septa-caps. The THF was dried over sodium in the presence of benzophenone indicator. Toluene (tol) was dried over activated alumina and distilled over sodium. Other commercially available reagents, solvents, and catalysts were used without additional purification unless otherwise stated. CpPd(allyl) was prepared according to a literature procedure.<sup>1</sup> All imidazole carbamate benzyl esters were prepared via literature protocol.<sup>2</sup> <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on Bruker Avance 500 DRX spectrometer and were referenced to residual protio solvent signals. Compound purification was effected by flash chromatography using 230 x 400 mesh, 60 Å porosity, silica obtained from Sorbent Technologies. Structural assignments were based on <sup>1</sup>H, <sup>13</sup>C, DEPT-135, COSY, HSQC spectroscopies. Mass spectrometry was run using ESI techniques.

**Procedures for the synthesis of  $\alpha$ -phenyl cyanoacetic acid and esters:**<sup>3</sup> A 200 mL flame dried Schlenk flask under Ar was charged with commercially available benzyl cyanide (31.0 mmol, 3.6 mL) via syringe, and *n*-BuLi (18.5 mL, solution 1.6 M/Hex from Aldrich) was added dropwise over 10 minutes. The solution was then placed in a dry ice/acetone bath and solid CO<sub>2</sub> (dryice, small amount) was added carefully. The solution was stirred at -78 °C for 1 h. The reaction was then quenched with NaHCO<sub>3</sub> (saturated in H<sub>2</sub>O, 125 mL) and Et<sub>2</sub>O (50 mL). The aqueous layer was isolated and ice cold Et<sub>2</sub>O (100 mL) was added. Conc. HCl (0 °C) was then added until pH of

6 (pH paper). The organic layer was separated and reduced on rotary evaporator to yield a yellowish oil. The oil was then azeotroped with  $\text{CHCl}_3$  and a white solid formed.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 (m, 2H), 7.38 – 7.33 (m, 3H), 4.91 (s, 1H), 4.68 (s, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.9, 129.5, 129.32, 128.03, 115.2, 43.6. These compounds were converted to the corresponding benzyl<sup>4</sup> esters by standard DCC/DMAP coupling.<sup>5</sup>

### Procedure for the synthesis of $\alpha,\alpha$ -disubstituted cyanoacetic benzyl esters

**Procedure A (hetero-aromatic benzyl ester substrates in Table 3.5):**<sup>3</sup> To a solution of  $\alpha$ -substituted, benzyl cyanoacetate in dry THF (0.5 M) under argon was added NaH (1.0 eq.). When the resulting solution became homogeneous, the respective alkyl bromide (1.0 eq.) was added dropwise via syringe. After 4 h., water was added to the reaction mixture and the resulting mixture was extracted with  $\text{Et}_2\text{O}$  (2 times with twice the amount of solvent required for the reaction). The organic layer was concentrated via a rotary evaporator, and the resulting residue was purified by flash chromatography over silica with Hex/ $\text{EtOAc}$  (92:8) as eluent.

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<sup>1</sup> Komiya, S. *Synthesis of Organometallic Compounds. A Practical Guide*; John Wiley & Sons: New York, **1997**, pp 290.

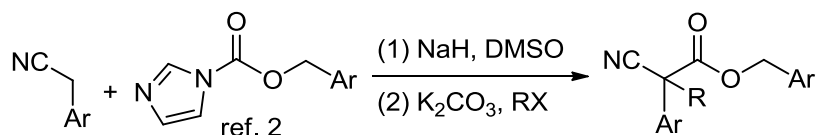
<sup>2</sup> Heller, S. T.; Sarpong, R. *Org. Lett.* **2010**, *12*, 4572.

<sup>3</sup> Recio, III, A.; Tunge, J. A. *Org. Lett.* **2009**, *11*, 630.

<sup>4</sup> Obtained via coupling with aromatic-, heteroaromatic-, and aryl-benzyl alcohols

<sup>5</sup> Neises, B., Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522.

**Procedure B (aromatic benzyl ester substrates):**<sup>3</sup> To a solution of  $\alpha$ -cyanoacetic benzyl ester, or  $\alpha$ -substituted cyanoacetic benzyl ester in DMF or DMSO (0.5 M) was added  $K_2CO_3$  (3.0 eq. Dry) and stirred vigorously. The respective electrophilic bromide (3.0 eq.) was added and the reaction was allowed to proceed for more than 12 h. The reaction was then diluted in  $CH_2Cl_2$  (3 times the volume of solvent used for the reaction). The reaction was then quenched with  $H_2O$  (5 times the volume of solvent used for the reaction). The organic layer was then washed 6 times with  $H_2O$  (5 times the volume of solvent used for the reaction) and purified via flash column chromatography using Hex/EtOAc (92:8) as eluent.



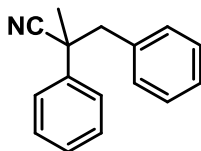
**Procedure C (substrates reported in Table 3.9):**<sup>2</sup> To a solution of the appropriate variant of benzyl cyanide (6.0 mmol), in DMSO or DMF (0.4 M) was added NaH (14.0 mmol). The solution was allowed to stir until  $H_2$  gas evolution no longer evident. The imidazole carbamate benzyl ester (9 mmol) was added and the reaction was allowed to stir for 2h. Next was added solid  $K_2CO_3$  (6.0 mmol). The flask was then charged with the alkyl halide (18.0 mmol) and stirred vigorously for 2 h. The reaction was then diluted in 30 mL  $CH_2Cl_2$  and quenched with 60 mL aqueous HCl (0.5 M). The organic layer was then washed 5 more times with 60 mL of  $H_2O$ . The compounds were purified via flash column chromatography using Hex/EtOAc (ca. 95:5) as eluent.

**Procedure for Pd-catalyzed decarboxylative benzylation and arylation:**

**Procedure D (All reaction in Tables 3.1-3.8, 3.9 entries 1 &2)**– To a flame-dried flask (Schlenk for reactions with tol or sealable microwave vial for reactions with THF) with stir bar was added the respective substrate (0.5 mmol) and placed under Ar. The catalyst (Cond. A: Table 1: 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, or Cond. B Table 1: 10 mol% CpPd(Allyl) and 11 mol% dppf ligand as denoted in Table 1 in manuscript) was then added. The flask was then charged with solvent (THF or Tol, 0.2 M) and the reaction was allowed to proceed for the amount of time noted in the manuscript (4-24h), under Ar at 110 °C. After the allotted reaction time, the solvent was reduced via rotary evaporator. All products were purified via silica gel chromatography (mobile phase for each substrate denoted below).

**Procedure E (entries 3-17 in Table 3.9):** – To a flame-dried microwave vial with stir bar was added the appropriate substrate (0.5 mmol), followed by activated (flamed with propane torch in round bottom flask) 3Å molecular sieves (0.2 g) and placed under argon. Tol or THF (0.2M) was added, the vial was sealed, and the mixture was allowed to stir vigorously at 110 °C for 0.5-1.0 h. Under Ar, the molecular sieves were filter from the solution and the catalyst (Cond. A Table 3 for arylation: 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> Cond B. Table 3 for benzylation: 10 mol% CpPd(Allyl) and 11 mol% (S)-DTBM SEGPPOS ligand) was added. The reaction was allowed to proceed for the amount time noted in the manuscript (12-24 h), under Ar at 110 °C. After the allotted reaction time, the solvent was reduced via rotary evaporator. All products were purified via silica gel chromatography (mobile phase for each substrate denoted below).

Characterization of benzylated nitriles:



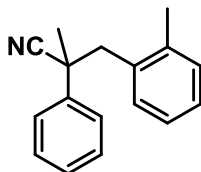
**2-methyl-2,3-diphenylpropanenitrile(3.11):<sup>6</sup>**

Clear liquid isolated via column chromatography 98:2 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.34 – 7.21 (m, 5H, R<sub>3</sub>C(q)ArH), 7.16 (dd, *J* = 5.0, 1.9 Hz, 3H, RCH<sub>2</sub>ArH), 6.98 – 6.93 (m, 2H, RCH<sub>2</sub>ArH), 3.11 – 3.02 (m, 2H, R<sub>3</sub>C(q)CH<sub>2</sub>Ph), 1.68 (s, 3H, R<sub>3</sub>C(q)CH<sub>3</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 139.7 (R<sub>3</sub>C(ArC(q))), 135.1 (R<sub>3</sub>CCH<sub>2</sub>(ArC(q))), 130.3 (R<sub>3</sub>C(ArC(*meta*))), 128.7 (R<sub>3</sub>CCH<sub>2</sub> (ArC(*ortho*))), 128.1 (R<sub>3</sub>C(ArC(*meta*))), 127.9 (R<sub>3</sub>C(ArC(*para*))), 127.4 (R<sub>3</sub>CCH<sub>2</sub> (ArC(*para*))), 125.9 (R<sub>3</sub>CCH<sub>2</sub> (ArC(*ortho*))), 123.1 (R<sub>3</sub>CN), 48.6 (R<sub>3</sub>CCH<sub>2</sub>Ph), 43.5 (CR<sub>4</sub>), 26.0 (R<sub>3</sub>C(q)CH<sub>3</sub>).

**GC/MS:** 221.1 [M<sup>+</sup>], 196.0 [M-CN], 91.0 [base peak]



**2-methyl-2-phenyl-3-(o-tolyl)propanenitrile (3.13):**

Viscous clear liquid isolated via column chromatography 97:3 Hex:EtOAc as eluent.

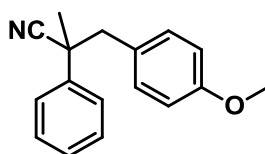
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.33 – 7.21 (m, 5H, R<sub>3</sub>C(q)ArH), 7.10 – 7.05 (m, 1H, RCH<sub>2</sub>-C(q)=C(Me)=CH(*meta*))), 7.05 – 6.99 (m, 1H, RCH<sub>2</sub>ArH(*meta*)), 6.99 – 6.94 (m, 2H, RCH<sub>2</sub>ArH), 3.11 (q, *J* = 13.9 Hz, 2H, R<sub>3</sub>C(q)CH<sub>2</sub>Ar), 1.99 (s, 3H, PhCH<sub>3</sub>), 1.74 (s, 3H, R<sub>3</sub>C(q)CH<sub>3</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 139.8 (R<sub>3</sub>C(PhC(q))), 137.5 (R<sub>3</sub>CCH<sub>2</sub>(ArC(q))), 133.4 (PhC(q)CH<sub>3</sub>), 131.1 (RCH<sub>2</sub>-C(q)=C(Me)=CH(*meta*))), 130.5 (PhC), 128.7 (PhC), 127.5 (PhC), 127.4 (PhC),

<sup>6</sup> Smith, H. A.; Bissell, R. L.; Kenyon, W. G.; MacClarence, J. W.; Hauser, C. R. *J. Org. Chem.* **1971**, *36*, 2132.

126.0 (PhC), 125.6 (PhC), 123.5 ( $R_3CN$ ), 44.6 ( $R_3CCH_2Ph$ ), 43.3 ( $CR_4$ ), 26.0 ( $R_3C(q)CH_3$ ), 19.7 (PhCH<sub>3</sub>).

**GC/MS:** 235.1 [ $M^+$ ], 210.9 [ $M-CN$ ], 105.0 [base peak]

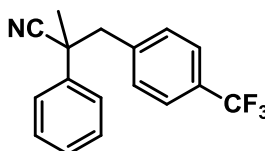


**3-(4-methoxyphenyl)-2-methyl-2-phenylpropanenitrile (3.14):**

Viscous clear liquid isolated via column chromatography 97:3 Hex:EtOAc as eluent.  **$^1H$  NMR** (500 MHz,  $CDCl_3$ )  $\delta$  7.35 – 7.19 (m, 5H,  $R_3C(q)ArH$ ), 6.85 (d,  $J$  = 8.7 Hz, 2H,  $RCH_2ArH_{(ortho)}$ ), 6.68 (d,  $J$  = 8.7 Hz, 2H,  $RCH_2ArH_{(meta)}$ ), 3.69 (s, 3H,  $CH_2ArOCH_3$ ), 3.08 – 2.94 (m, 2H,  $R_3C(q)CH_2Ar$ ), 1.66 (s,  $R_3C(q)CH_3$ ).

**$^{13}C$  NMR** (126 MHz,  $CDCl_3$ )  $\delta$  158.9 ( $CH_2ArC(q)OCH_3$ ), 139.7 ( $R_3CPhC(q)$ ), 131.4 ( $RCH_2ArCH_{(ortho)}$ ), 128.7 ( $RCH_2ArC(q)$ ), 127.8 ( $R_3CPhCH_{(meta)}$ ), 127.2 ( $R_3CPhCH_{(para)}$ ), 125.9 ( $R_3CPhCH_{(ortho)}$ ), 123.3 ( $R_3CN$ ), 113.5 ( $RCH_2ArCH_{(meta)}$ ), 55.2 ( $CH_2ArOCH_3$ ), 47.8 ( $R_3CCH_2Ar$ ), 43.7 ( $CR_4$ ), 25.9 ( $R_3C(q)CH_3$ ).

**GC/MS:** 251.2 [ $M^+$ ], 226.5 [ $M-CN$ ], 57.1 [base peak]



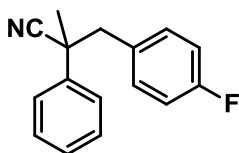
**2-methyl-2-phenyl-3-(4-(trifluoromethyl)phenyl)propanenitrile (3.15):**

Viscous clear liquid isolated via column chromatography 98:2 Hex:EtOAc as eluent.

**$^1H$  NMR** (500 MHz,  $CDCl_3$ )  $\delta$  7.40 (d,  $J$  = 8.0 Hz, 2H,  $RCH_2ArH_{(meta)}$ ), 7.32 – 7.23 (m, 5H,  $R_3C(q)ArH$ ), 7.04 (d,  $J$  = 8.0 Hz, 2H,  $RCH_2ArH_{(ortho)}$ ), 3.12 (s, 2H,  $R_3C(q)CH_2Ar$ ), 1.71 (s, 3H,  $R_3C(q)CH_3$ ).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  139.1 ( $\text{R}_3\text{C}(\text{ArC}(\text{q}))$ ), 138.8 ( $\text{R}_3\text{CCH}_2(\text{ArC}(\text{q}))$ ), 130.6 ( $\text{R}_3\text{C}(\text{ArC}(\text{m}))$ ), 128.9 ( $\text{ArCF}_3$ ), 128.2 ( $\text{ArCCF}_3$ ), 125.9 ( $\text{ArC}$ ), 125.6 ( $\text{ArC}$ ), 125.1 (q,  $J = 3.7$  Hz,  $\text{PhC}$ ), 125.0 ( $\text{ArC}$ ), 122.7 ( $\text{R}_3\text{CN}$ ), 48.2 ( $\text{R}_3\text{CCH}_2\text{Ph}$ ), 43.5 ( $\text{CR}_4$ ), 26.3 ( $\text{R}_3\text{C}(\text{q})\text{CH}_3$ ).

**GC/MS:** 290.1 [ $\text{M}^+$ ], 264.0 [ $\text{M-CN}$ ], 130.0 [base peak]

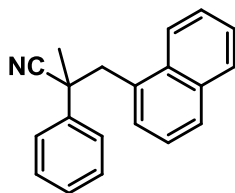


**3-(4-fluorophenyl)-2-methyl-2-phenylpropanenitrile (3.16):**

Viscous clear liquid isolated via column chromatography 97:3 Hex:EtOAc as eluent.  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 (d,  $J = 8.0$  Hz, 5H,  $\text{RCH}_2\text{ArH}$ ), 6.87 (d,  $J = 8.0$  Hz, 2H,  $\text{R}_3\text{C}(\text{q})\text{ArH}$ ), 6.83 (d,  $J = 8.0$  Hz, 2H,  $\text{RCH}_2\text{ArH}_{(\text{ortho})}$ ), 3.03 (s, 2H,  $\text{R}_3\text{C}(\text{q})\text{CH}_2\text{Ar}$ ), 1.68 (s, 3H,  $\text{R}_3\text{C}(\text{q})\text{CH}_3$ ).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.2 ( $\text{ArCF}$ ), 161.2 ( $\text{ArCF}$ ), 139.3 ( $\text{R}_3\text{CCH}_2(\text{ArC}(\text{q}))$ ), 131.8 ( $\text{R}_3\text{C}(\text{ArC}(\text{q}))$ ), 131.0 ( $\text{R}_3\text{CCH}_2(\text{ArC}_{(\text{ortho})})$ ), 129.0 ( $\text{R}_3\text{C}(\text{ArC}_{(\text{meta})})$ ), 128.0 ( $\text{R}_3\text{C}(\text{ArC}_{(\text{ortho})})$ ), 125.9 ( $\text{R}_3\text{C}(\text{ArC}_{(\text{para})})$ ), 122.8 ( $\text{R}_3\text{CN}$ ), 115.0 (d,  $J = 21.3$  Hz,  $\text{R}_3\text{CCH}_2(\text{ArC}_{(\text{meta})}\text{CF})$ ), 47.8 ( $\text{R}_3\text{CCH}_2\text{Ph}$ ), 43.6 ( $\text{CR}_4$ ), 26.1 ( $\text{R}_3\text{C}(\text{q})\text{CH}_3$ ).

**GC/MS:** 239.0 [ $\text{M}^+$ ], 214.0 [ $\text{M-CN}$ ], 109.0 [base peak]



**2-methyl-3-(naphthalen-1-yl)-2-phenylpropanenitrile (3.17):**

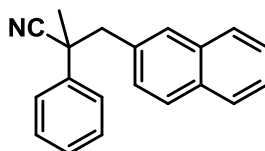
White solid isolated via column chromatography 98:2 Hex:EtOAc as eluent.



**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.78 – 7.73 (m, 2H, 5-, 8-naphthylCH), 7.70 (d, *J* = 8.2 Hz, 1H, 4-naphthylCH), 7.38 – 7.28 (m, 5H, R<sub>3</sub>C(q)PhCH), 7.28 – 7.19 (m, 4H, 2-, 3-, 6-, 7-naphthylCH), 3.68 – 3.47 (m, 2H, R<sub>3</sub>C(q)CH<sub>2</sub>(α-Naphthyl), 1.72 (s, 3H, (s, R<sub>3</sub>C(q)CH<sub>3</sub>)).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 140.0 (R<sub>3</sub>C(PhC(q))), 133.7 (R<sub>3</sub>CCH<sub>2</sub>(α-naphthylC(q))), 132.6, 131.3, 129.2, 128.9, 128.7 (R<sub>3</sub>C(q)(PhC), 128.2 (CH<sub>2</sub>-α-naphthylC), 128.0 (CH<sub>2</sub>-α-naphthylC), 126.03, 125.74 (R<sub>3</sub>C(PhC), 125.5 (CH<sub>2</sub>-α-naphthylC), 125.1 (CH<sub>2</sub>-α-naphthylC), 123.7 (R<sub>3</sub>CN), 123.5 (CH<sub>2</sub>-2-naphthylC), 43.8 (R<sub>4</sub>C(q)), 43.6 (R<sub>3</sub>C(q)CH<sub>2</sub>-β-naphthyl)), 26.0 (R<sub>3</sub>C(q)CH<sub>3</sub>).

**GC/MS:** 271.1 [M<sup>+</sup>], 141.0 [base peak]



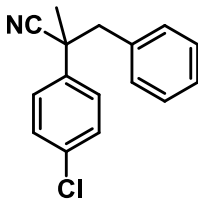
**2-methyl-3-(naphthalen-2-yl)-2-phenylpropanenitrile (3.18):**

Brown solid isolated via column chromatography 98:2 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.71 (dd, *J* = 6.1, 3.4 Hz, 1H, 5-naphthylCH), 7.66 (dd, *J* = 6.0, 3.5 Hz, 1H, 8-naphthylCH), 7.61 (d, *J* = 8.4 Hz, 1H, 4-naphthylCH), 7.43 (s, 1H, 1-naphthylCH), 7.37 (dd, *J* = 6.2, 3.2 Hz, 2H, 6-, 7-naphthylCH), 7.34 – 7.22 (m, 5H, R<sub>3</sub>C(q)ArH), 7.02 (dd, *J* = 8.4, 1.7 Hz, 1H, 3-naphthylCH), 3.31 – 3.16 (m, 2H, R<sub>3</sub>C(q)CH<sub>2</sub>-β-Naphthyl), 1.72 (s, 3H, R<sub>3</sub>C(q)CH<sub>3</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 139.6 (R<sub>3</sub>C(PhC(q))), 133.1 (R<sub>3</sub>CCH<sub>2</sub>(2-naphthylC(q))), 132.6 (2-naphthylC), 132.4, 129.4 (2-naphthylC), 128.8 (2-naphthylC), 128.3 (2-naphthylC), 128.0 (ArC), 127.8 (2-naphthylC), 127.6 (2-naphthylC), 127.5 (ArC), 126.0 (PhC), 125.9 (PhC), 125.8 (ArC), 123.2 (R<sub>3</sub>CN), 48.7 (R<sub>3</sub>C(q)CH<sub>2</sub>-β-naphthyl), 43.6 (CR<sub>4</sub>), 26.0 (R<sub>3</sub>C(q)CH<sub>3</sub>).

**GC/MS:** 271.1 [M<sup>+</sup>], 141.0 [base peak]



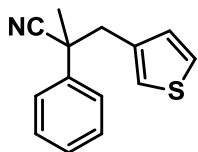
**2-(4-chlorophenyl)-2-methyl-3-phenylpropanenitrile (3.19):**

Viscous clear liquid isolated via column chromatography 97:3 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.28 – 7.14 (m, 7H), 6.94 (dd, *J* = 5.0, 1.8 Hz, 2H), 3.04 (d, *J* = 2.7 Hz, 2H), 1.67 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 138.1, 134.7, 133.9, 130.3, 128.9, 128.2, 127.4, 122.8, 48.5, 43.2, 26.1.

**GC/MS:** 255.1 [M<sup>+</sup>], 141.0 [base peak]



**2-methyl-2-phenyl-3-(thiophen-3-yl)propanenitrile (3.25):**

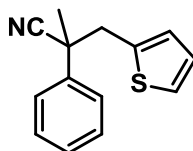
Clear liquid isolated via column chromatography 95:5 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.37 – 7.25 (m, 1H, R<sub>3</sub>C(q)PhCH<sub>(para)</sub>), 7.25 – 7.20 (m, 1H, R<sub>3</sub>C(q)PhCH<sub>(para)</sub>), 7.08 (dd, *J* = 4.9, 3.0 Hz, 1H, 5-thiophenylCH), 6.83 (dt, *J* = 2.9, 0.6 Hz, 1H, 4-thiophenylCH), 6.65 (dd, *J* = 4.9, 1.3 Hz, 1H, 2-thiophenyl CH), 3.11 (s, 2H, R<sub>3</sub>C(q)CH<sub>2</sub>(3-thiophenyl)), 1.65 (s, 3H, (s, R<sub>3</sub>C(q)CH<sub>3</sub>)).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 139.7(R<sub>3</sub>CPhC(q)) 135.4 (R<sub>3</sub>CCH<sub>2</sub>(3-thiophenylC(q)), 129.1 (R<sub>3</sub>C(PhC<sub>(meta)</sub>), 128.8 (4-thiophenylC), 128.0 (R<sub>3</sub>C(PhC(q)), R<sub>3</sub>C(PhC<sub>(ortho)</sub>), 125.8 (5-thiophenylC),

125.2 ( $R_3C(PhC_{(para)})$ ), 124.2 (2-thiophenylC), 123.4 ( $R_3CN$ ), 43.3 ( $R_4C(q)$ ), 43.0 ( $R_3C(q)CH_2$ -3-thiophenyl)), 26.2 ( $R_3C(q)CH_3$ ).

**GC/MS:** 227.1 [ $M^+$ ], 202.6 [M-CN], 97.0 [base peak]



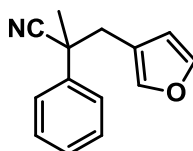
### 2-methyl-2-phenyl-3-(thiophen-2-yl)propanenitrile (3.26)

Viscous clear liquid isolated via column chromatography 97:3 Hex:EtOAc as eluent.

**$^1H$  NMR** (500 MHz,  $CDCl_3$ )  $\delta$  7.45 (d,  $J$  = 7.3 Hz, 1H, 5-thiophenylCH), 7.43 – 7.39 (m, 2H,  $R_3C(q)PhCH_{(meta)}$ ), 7.39 – 7.33 (m, 2H,  $R_3C(q)PhCH_{(ortho)}$ ), 7.15 (dd,  $J$  = 5.1, 1.1 Hz, 1H,  $R_3C(q)PhCH_{(para)}$ ), 6.93 (dd,  $J$  = 5.1, 3.5 Hz, 1H, 4-thiophenylCH), 6.84 (d,  $J$  = 3.4 Hz, 1H, 3-thiophenylCH), 3.42 (s, 2H,  $CR_3CH_2$  thiophenyl), 1.81 (s, 3H,  $R_3CCH_3$ ).

**$^{13}C$  NMR** (126 MHz,  $CDCl_3$ )  $\delta$  139.2 ( $R_3C(PhC(q))$ ), 136.5 ( $R_3CCH_2(2\text{-thiophenylC}(q))$ ), 128.9 ( $PhC_{(meta)}$ ), 128.1 (3-thiophenylC), 128.0 (4-thiophenylC), 126.8 ( $R_3C(PhC_{(ortho)})$ ), 125.9 ( $R_3C(PhC_{(para)})$ ), 125.1 (2-thiophenyl-5-C), 123.0 (RCN), 43.8 ( $CR_4$ ), 42.6 ( $RCH_2R$ ), 26.2 ( $RCH_3$ ).

**GC/MS:** 227.0 [ $M^+$ ], 202.0 [M-CN], 97.0 [base peak]



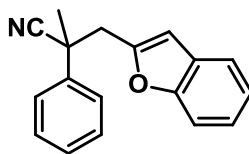
### 3-(furan-3-yl)-2-methyl-2-phenylpropanenitrile(3.27):

Clear liquid isolated via column chromatography 95:5 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.36 – 7.31 (m, 3H, ArH<sub>(meta/para)</sub>), 7.32 – 7.28 (m, 2H, ArH<sub>(ortho)</sub>), 7.27 – 7.20 (s, 1H, 2-furanyl-H), 7.08 (dq, *J* = 1.6, 0.8 Hz, 1H, 5-furanyl-H), 6.00 (dd, *J* = 1.7, 0.7 Hz, 1H, 4-furanyl-H), 2.94 (s, 2H, -CR<sub>3</sub>CH<sub>2</sub>-3-furanyl), 1.67 (s, 3H, R<sub>3</sub>CCH<sub>3</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 141.6 (ArC(q)), 140.2 (5-furanyl-C), 138.6 (3-furanyl(2-C)), 127.8 (s, ArC<sub>(ortho)</sub>), 126.9 (ArC<sub>(para)</sub>), 124.7 (ArC<sub>(meta)</sub>), 122.3 (RCN), 117.6 (3-furanyl(5-C)), 110.6 (3-furanyl(4-C)), 42.0 (CR<sub>4</sub>), 37.1 (RCH<sub>2</sub>R), 25.3 (RCH<sub>3</sub>).

**GC/MS:** 211.0 [M<sup>+</sup>], 186.1 [M-CN], 81.0 [base peak]



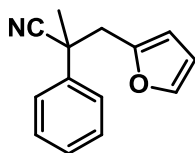
**3-(benzofuran-2-yl)-2-methyl-2-phenylpropanenitrile (3.29):**

White solid isolated via column chromatography 95:5 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.41 (d, *J* = 8.1 Hz, 2H, 2-benzofuranyl(4-,7-CH), 7.32 (t, *J* = 8.0 Hz, 2H, 2-benzofuranyl(5-,6-CH), 7.29 – 7.22 (m, 4H, R<sub>3</sub>C(PhCH) ), 7.19 (s, 1H, R<sub>3</sub>C(PhCH)), 6.42 (s, 1H, 2-benzofuranyl(3-CH)), 3.38 – 3.21 (m, 2H, CR<sub>3</sub>CH<sub>2</sub>-2-benzofuranyl), 1.76 (s, 3H, R<sub>3</sub>CCH<sub>3</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 154.7(2-benzofuranyl(2-C(q))), 152.6 (2-benzofuranyl(9-C(q))), 139.4 (R<sub>3</sub>CPhC(q)), 129.0 (2-benzofuranyl(8-C(q))), 128.3 (ArC) 128.2 (R<sub>3</sub>C(PhCH), 125.6 (R<sub>3</sub>C(PhCH), 124.0 (2-benzofuranyl(CH)), 122.9 (ArC) 122.7 (RCN), 120.9 (2-benzofuranyl(4-CH)), 111.0 (2-benzofuranyl(7-CH)), 106.0 (2-benzofuranyl(3-CH)), 42.5 (CR<sub>4</sub>), 41.2 (RCH<sub>2</sub>R), 26.3(RCH<sub>3</sub>).

**GC/MS:** 261.1 [M<sup>+</sup>], 131.0 [base peak]



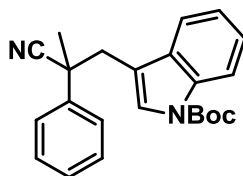
**3-(furan-2-yl)-2-methyl-2-phenylpropanenitrile (3.30):**

Viscous clear liquid isolated via column chromatography 97:3 Hex:EtOAc as eluent.

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 (m, 2H,  $\text{R}_3\text{C}(\text{PhCH}_{\text{(meta)}})$ ), 7.31 (m, 2H,  $\text{R}_3\text{C}(\text{PhCH}_{\text{(ortho)}})$ ), 7.26 (m, 1H,  $\text{R}_3\text{C}(\text{PhCH}_{\text{(para)}})$ ), 7.24 (dd,  $J = 1.8, 0.8$  Hz, 1H, 2-furanyl(5-CH)), 6.21 (dd,  $J = 3.2, 1.9$  Hz, 1H, 2-furanyl(4-CH)), 6.01 (d,  $J = 3.4$  Hz, 1H, 2-furanyl(3-CH)), 3.23 – 3.06 (m, 2H,  $\text{CR}_3\text{CH}_2$ -2-furanyl), 1.68 (s, 3H,  $\text{R}_3\text{CCH}_3$ ).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  149.7 ( $\text{R}_3\text{CCH}_2$ (2-furanyl(2-C(q)))), 142.1 ( $\text{R}_3\text{C}(\text{PhC}(\text{q})))$ , 139.6 (2-furanyl(5-C)), 128.8 ( $\text{R}_3\text{C}(\text{PhC}_{\text{(meta)}})$ ), 128.0 ( $\text{R}_3\text{C}(\text{PhC}_{\text{(ortho)}})$ ), 125.6 ( $\text{R}_3\text{C}(\text{PhC}_{\text{(para)}})$ ), 123.0 (RCN), 110.5 (2-furanyl(4-C)), 109.0 (2-furanyl(3-C)), 42.4, ( $\text{CR}_4$ ), 40.8 ( $\text{RCH}_2\text{R}$ ), 26.1 ( $\text{RCH}_3$ ).

**GC/MS:** 211.0 [ $\text{M}^+$ ], 186.6 [ $\text{M-CN}$ ], 57.1 [base peak]



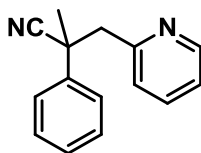
**tert-butyl 3-(2-cyano-2-phenylpropyl)-1H-indole-1-carboxylate (3.31):**

Viscous clear liquid isolated via column chromatography 97:3 Hex:EtOAc as eluent.

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.03 (d,  $J = 7.1$  Hz, 2H, 3-methylindole(4-, 7-CH)), 7.39 (d,  $J = 7.1$  Hz, 2H, 3-methylindole(6-CH)), 7.34 – 7.22 (m, 5H,  $\text{R}_3\text{CPhCH}$ ), 7.22 – 7.13 (m, 1H, 3-methylindole(2-CH)), 7.06 (dd,  $J = 6.1, 3.4$  Hz, 1H, 3-methylindole(5-CH)), 3.22 (s, 2H,  $\text{CR}_3\text{CH}_2$ -3-methyl(*N*-Boc)indole), 1.73 (s, 3H,  $\text{R}_3\text{CCH}_3$ ), 1.57 (s, 9H,  $\text{CO}_2\text{C}(\text{CH}_3)_3$ ).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  149.5 ( $\text{R}_3\text{CPhC(q)}$ ), 139.9, (ArCH), 130.7 (3-methylindole(9-C(q))), 129.2 (3-methylindole(8-C(q))), 128.9 ( $\text{R}_3\text{C(PhC}_{\text{(meta)}})$ ), 128.0 ( $\text{R}_3\text{C(PhC}_{\text{(ortho)}})$ ), 127.4 (ArC), 125.9 ( $\text{R}_3\text{C(PhC}_{\text{(para)}})$ ), 125.4 (3-methylindoleCH), 124.3 ( $\text{RCH}_2$ -3-methylindole(2-C(q))), 122.4 (RCN), 118.9 (3-methylindole(4-CH), 115.1 (3-methylindole(7-CH), 83.7 ( $\text{CO}_2\text{C(q)(CH}_3)_3$ ), 43.2 ( $\text{CR}_4$ ), 38.0 ( $\text{RCH}_2\text{R}$ ), 28.2 ( $\text{CO}_2\text{C(CH}_3)_3$ ), 26.0 ( $\text{RCH}_3$ ).

**GC/MS:** 361.2 [ $\text{M}^+1$ ], 335.8 [ $\text{M-CN}$ ], 57.1 [base peak]



**2-methyl-2-phenyl-3-(pyridin-2-yl)propanenitrile (3.32):**

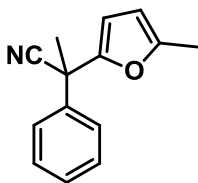
Viscous clear liquid isolated via column chromatography 97:3 Hex:EtOAc as eluent.

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.48 (d,  $J = 7.8$  Hz, 1H, 2-methyl pyridine(6-CH)), 7.52 (td,  $J = 7.7$ , 1.8 Hz, 1H, 2-methyl pyridine(5-CH)), 7.39 (m, 2H,  $\text{R}_3\text{C(PhCH}_{\text{(meta)}})$ ), 7.30 (m, 2H,  $\text{R}_3\text{C(PhCH}_{\text{(ortho)}})$ ), 7.26 (m, 1H,  $\text{R}_3\text{C(PhCH}_{\text{(para)}})$ ), 7.10 (td,  $J = 7.7$ , 1.8 Hz, 1H, 2-methyl pyridine(4-CH)), 7.06 (d,  $J = 7.8$  Hz, 1H, 2-methyl pyridine(3-CH)), 3.28 (s, 2H,  $\text{CR}_3\text{CH}_2$ -2-methyl pyridine), 1.71 (s, 3H,  $\text{R}_3\text{CCH}_3$ ).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  155.7 ( $\text{R}_3\text{CH}_2$ -2-methyl pyridyl(2-C(q))), 149.2 ( $\text{R}_3\text{CPhC(q)}$ ), 139.9 (2-methyl pyridyl(6-CH)), 136.3 (2-methyl pyridyl(4-CH)), 128.9 ( $\text{R}_3\text{C(PhC}_{\text{(meta)}})$ ), 127.9 ( $\text{R}_3\text{C(PhC}_{\text{(ortho)}})$ ), 125.7 ( $\text{R}_3\text{C(PhC}_{\text{(para)}})$ ), 124.6 (2-methyl pyridyl(3-CH)), 123.0 (2-methyl pyridyl(5-CH)), 122.3 (RCN), 50.0 ( $\text{RCH}_2\text{R}$ ), 42.9 ( $\text{CR}_4$ ), 26.1 ( $\text{RCH}_3$ ).

**GC/MS:** 222.1 [ $\text{M}^+$ ], 197.2 [ $\text{M-CN}$ ], 93.0 [base peak]

Characterization of arylated nitriles:



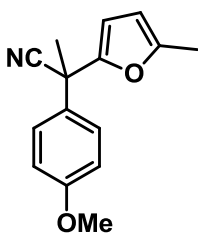
### 2-(5-methylfuran-2-yl)-2-phenylpropanenitrile

Viscous clear liquid isolated via column chromatography 97:3 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.31 (m, 2H, R<sub>3</sub>PhCH<sub>(meta)</sub>), 7.25 (m, 3H, R<sub>3</sub>PhCH<sub>(ortho/para)</sub>), 6.08 (d, *J* = 3.1 Hz, 1H, R<sub>3</sub>C-furanyl(3-CH)), 5.86 (dq, *J* = 3.1, 1.0 Hz, 1H, R<sub>3</sub>C-furanyl(4-CH)), 2.18 (s, 3H, furanylCH<sub>3</sub>), 1.94 (s, 3H, R<sub>3</sub>CCH<sub>3</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 153.3 (R<sub>3</sub>C-furanyl(2-C(q))), 149.9 (R<sub>3</sub>C-furanyl(5-C(q))), 139.3 (R<sub>3</sub>CPhC(q)), 128.9 (R<sub>3</sub>C(PhCH<sub>(ortho)</sub>)), 128.1 (R<sub>3</sub>C(PhCH<sub>(para)</sub>)), 126.0 (R<sub>3</sub>C(PhC<sub>(meta)</sub>)), 121.2 (RCN), 108.7 (R<sub>3</sub>C-furanyl(3-CH)), 106.4 (R<sub>3</sub>C-furanyl(4-CH)), 42.2 (CR<sub>4</sub>), 27.0 (RCH<sub>3</sub>), 13.6 (furnyl(5-CH<sub>3</sub>)).

**GC/MS:** 211.0 [M<sup>+</sup>], 186.6 [M-CN], 57.1 [base peak]



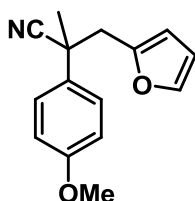
### 2-(4-methoxyphenyl)-2-(5-methylfuran-2-yl)propanenitrile

Viscous clear liquid isolated via column chromatography 98:2 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.25 (m, 2H, R<sub>3</sub>PhCH<sub>(meta)</sub>), 6.83 (m, 2H, R<sub>3</sub>PhCH<sub>(ortho)</sub>), 6.05 (d, *J* = 3.1 Hz, 1H, R<sub>3</sub>C-furanyl(3-CH)), 5.85 (dq, *J* = 3.1, 1.0 Hz, 1H, R<sub>3</sub>C-furanyl(4-CH)), 3.74 (s, 3H, CR<sub>3</sub>ArOCH<sub>3</sub>), 2.19 (s, 3H, furanylCH<sub>3</sub>), 1.92 (s, 3H, R<sub>3</sub>CCH<sub>3</sub>).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.3 ( $\text{CR}_3\text{ArC}(\text{q})\text{OCH}_3$ ), 153.2 ( $\text{R}_3\text{C-furanyl}(2\text{-C}(\text{q}))$ ), 150.3 ( $\text{R}_3\text{C-furanyl}(5\text{-C}(\text{q}))$ ), 131.3 ( $\text{R}_3\text{CPhC}(\text{q})$ ), 127.2 ( $\text{R}_3\text{C}(\text{PhCH}_{(\text{ortho})})$ ), 121.46 ( $\text{RCN}$ ), 114.1 ( $\text{R}_3\text{C}(\text{PhC}_{(\text{meta})})$ ), 108.5 ( $\text{R}_3\text{C-furanyl}(3\text{-CH})$ ), 106.3 ( $\text{R}_3\text{C-furanyl}(4\text{-CH})$ ), 55.4 ( $\text{CH}_2\text{ArOCH}_3$ ), 41.6 ( $\text{CR}_4$ ), 26.9 ( $\text{RCH}_3$ ), 13.6 ( $\text{furnyl}(5\text{-CH}_3)$ ).

**GC/MS:** 241.1 [ $\text{M}^+$ ], 216.2 [ $\text{M-CN}$ ], 226.1 [base peak].



### 3-(furan-2-yl)-2-(4-methoxyphenyl)-2-methylpropanenitrile

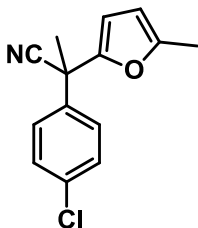
Viscous clear liquid isolated via column chromatography 98:2 Hex:EtOAc as eluent.

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 (dd,  $J = 1.8, 0.8$  Hz, 1H, 2-furanyl(5-CH)), 7.24 (m, 2H,  $\text{R}_3\text{PhCH}_{(\text{ortho})}$ ), 6.83 (m, 2H,  $\text{R}_3\text{PhCH}_{(\text{meta})}$ ), 6.21 (dd,  $J = 3.2, 1.9$  Hz, 1H,  $\text{R}_3\text{C-furanyl}(4\text{-CH})$ ), 6.02 (d,  $J = 3.2$  Hz, 1H,  $\text{R}_3\text{C-furanyl}(3\text{-CH})$ ), 3.74 (s, 3H,  $\text{CR}_3\text{ArOCH}_3$ ), 3.11 (m, 2H,  $\text{CR}_3\text{CH}_2\text{-2-furanyl}$ ), 1.65 (s, 3H,  $\text{R}_3\text{CCH}_3$ ).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.1 ( $\text{CR}_3\text{ArC}(\text{q})\text{OCH}_3$ ), 149.9 ( $\text{R}_3\text{C-furanyl}(2\text{-C}(\text{q}))$ ), 142.1 ( $\text{R}_3\text{CCH}_2(2\text{-furanyl}(5\text{-C}(\text{q}))$ ), 127.8 ( $\text{R}_3\text{CPhC}(\text{q})$ ), 126.8 ( $\text{R}_3\text{C}(\text{PhCH}_{(\text{ortho})})$ ), 123.3 ( $\text{RCN}$ ), 114.1 ( $\text{R}_3\text{C}(\text{PhC}_{(\text{meta})})$ ), 110.5 ( $\text{R}_3\text{C-furanyl}(4\text{-CH})$ ), 109.0 ( $\text{R}_3\text{C-furanyl}(3\text{-CH})$ ), 55.3 ( $\text{CR}_3\text{ArOCH}_3$ ), 41.9 ( $\text{CR}_4$ ), 40.9 ( $\text{CR}_3\text{CH}_2\text{-2-furanyl}$ ), 26.1 ( $\text{R}_3\text{CCH}_3$ ).

**GC/MS:** 241.1 [ $\text{M}^+$ ], 216.2 [ $\text{M-CN}$ ], 226.1 [base peak].



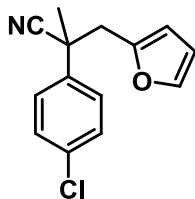


### 2-(4-chlorophenyl)-2-(5-methylfuran-2-yl)propanenitrile

Viscous clear liquid isolated via column chromatography 98:2 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.31 – 7.23 (m, 4H, R<sub>3</sub>PhCH), 6.10 (d, *J* = 3.2 Hz, 1H, R<sub>3</sub>C-furanyl(3-CH)), 5.87 (dt, *J* = 2.1, 1.0 Hz, 1H, R<sub>3</sub>C-furanyl(4-CH)), 2.19 (s, 3H, furanylCH<sub>3</sub>), 1.93 (s, 3H, R<sub>3</sub>CCH<sub>3</sub>). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 152.5 (s, R<sub>3</sub>C-furanyl(2-C(q))), 148.3 (s, R<sub>3</sub>C-furanyl(5-C(q))), 136.8 (s, CH<sub>2</sub>ArC(q)Cl), 133.1 (s, R<sub>3</sub>CPhC(q)), 128.0 (s, R<sub>3</sub>C(PhCH<sub>(ortho)</sub>)), 126.3 (s, R<sub>3</sub>C(PhC<sub>(meta)</sub>)), 119.8 (s, RCN), 107.8 (s, R<sub>3</sub>C-furanyl(3-CH)), 105.4 (s, R<sub>3</sub>C-furanyl(4-CH)), 40.8 (s, CR<sub>4</sub>), 25.8 (s, RCH<sub>3</sub>), 12.6 (s, furnyl(5-CH<sub>3</sub>)).

**GC/MS:** 245.1 [M<sup>+</sup>], 220.1 [M-CN], 230.1 [base peak].



### 2-(4-chlorophenyl)-3-(furan-2-yl)-2-methylpropanenitrile

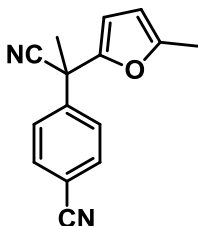
Viscous clear liquid isolated via column chromatography 98:2 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.27 (s, 4H, R<sub>3</sub>PhCH), 7.23 (dd, *J* = 1.8, 0.8 Hz, 1H, 2-furanyl(5-CH)), 6.21 (dd, *J* = 3.2, 1.9 Hz, 1H, R<sub>3</sub>C-furanyl(4-CH)), 6.02 (d, *J* = 3.2 Hz, 1H, R<sub>3</sub>C-furanyl(3-CH)), 3.13 (m, 2H, CR<sub>3</sub>CH<sub>2</sub>-2-furanyl), 1.67 (s, 3H, R<sub>3</sub>CCH<sub>3</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 149.3 (R<sub>3</sub>C-furanyl(2-C(q))), 142.3 (R<sub>3</sub>CCH<sub>2</sub>(2-furanyl(5-C(q))), 138.0 (CH<sub>2</sub>ArC(q)Cl), 134.0 (R<sub>3</sub>CPhC(q)), 129.0 (2C, R<sub>3</sub>C(PhCH<sub>(meta)</sub>)), 128.3 (ArC), 127.1 (PhCH<sub>(ortho)</sub>), 122.9

(ArC) 122.7 (RCN), 110.5 (R<sub>3</sub>C-furanyl(4-CH)), 109.2 (R<sub>3</sub>C-furanyl(3-CH)), 42.3 (CR<sub>4</sub>), 40.7 (CR<sub>3</sub>CH<sub>2</sub>-2-furanyl), 26.1 (R<sub>3</sub>CCH<sub>3</sub>).

**GC/MS:** 245.1 [M<sup>+</sup>], 220.1 [M-CN], 230.1 [base peak].



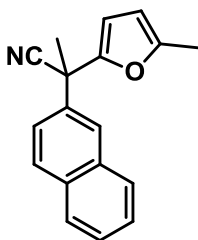
#### 4-(1-cyano-1-(5-methylfuran-2-yl)ethyl)benzonitrile

Viscous clear liquid isolated via column chromatography 85:15 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.61 (m, 2H, R<sub>3</sub>PhCH<sub>(meta)</sub>), 7.45 (m, 2H, R<sub>3</sub>PhCH<sub>(ortho)</sub>), 6.18 (d, *J* = 3.2 Hz, 1H, R<sub>3</sub>C-furanyl(3-CH)), 5.91 (m, 1H, R<sub>3</sub>C-furanyl(4-CH)), 2.18 (s, furnyl(5-CH<sub>3</sub>)), 1.95 (s, 3H, R<sub>3</sub>CCH<sub>3</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 154.0 (R<sub>3</sub>C-furanyl(2-C(q))), 148.4 (R<sub>3</sub>C-furanyl(5-C(q))), 144.4 (R<sub>3</sub>CPhC(q)), 132.8 (R<sub>3</sub>C(PhCH<sub>(meta)</sub>)), 126.8 (R<sub>3</sub>C(ArCH<sub>(ortho)</sub>)), 120.1 (RCN), 118.2 (R<sub>3</sub>ArCN), 112.4 (R<sub>3</sub>ArC(q)-CN), 109.3 (R<sub>3</sub>C-furanyl(3-CH)), 106.6 (R<sub>3</sub>C-furanyl(4-CH)), 42.3 (CR<sub>4</sub>), 26.6 (RCH<sub>3</sub>), 13.6 (furnyl(5-CH<sub>3</sub>)).

**GC/MS:** 236.1 [M<sup>+</sup>], 211.3 [M-CN], 221.1 [base peak].



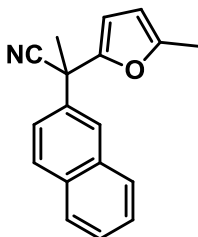
#### 2-(5-methylfuran-2-yl)-2-(naphthalen-2-yl)propanenitrile

Viscous clear liquid isolated via column chromatography 98:2 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.88 (d, *J* = 1.9 Hz, 2H, R<sub>3</sub>C-β-naphthyl(5-,8-CH)), 7.76 (m, 2H, R<sub>3</sub>C-β-naphthyl(1-,4-CH)), 7.44 (m, 2H, R<sub>3</sub>C-β-naphthyl(6-,7-CH)), 7.34 (dd, *J* = 8.7, 2.0 Hz, 1H, R<sub>3</sub>C-β-naphthyl(3-CH)), 6.12 (d, *J* = 3.2 Hz, 1H, R<sub>3</sub>C-furanyl(3-CH)), 5.87 ((dq, *J* = 3.1, 1.0 Hz, 1H, R<sub>3</sub>C-furanyl(4-CH))), 2.18 (s, 3H, furanylCH<sub>3</sub>), 2.03 (s, 3H, R<sub>3</sub>CCH<sub>3</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 153.4 (R<sub>3</sub>C-furanyl(2-C(q))), 149.9 (R<sub>3</sub>C-furanyl(5-C(q))), 136.4 (R<sub>3</sub>C-β-naphthyl(2-C(q))), 133.09 (R<sub>3</sub>C-β-naphthylC(q)), 132.8 (R<sub>3</sub>C-β-naphthylC(q)), 128.8 (R<sub>3</sub>C-β-naphthyl(5-C)), 128.3 (R<sub>3</sub>C-β-naphthyl(3-C)), 127.6 (R<sub>3</sub>C-β-naphthyl( 8-C)), 126.7 (R<sub>3</sub>C-β-naphthyl(1-, 4-C)), 125.0 (R<sub>3</sub>C-β-naphthyl(7-C)), 123.5 (R<sub>3</sub>C-β-naphthyl(6-C)), 121.2 (RCN), 108.8 (R<sub>3</sub>C-furanyl(3-CH)), 106.5 (R<sub>3</sub>C-furanyl(4-CH)), 42.4 (CR<sub>4</sub>), 26.7 (RCH<sub>3</sub>), 13.6 (furnyl(5-CH<sub>3</sub>)).

**GC/MS:** 262.0 [M<sup>+</sup>], 237.1 [M-CN], 73.0 [base peak].



### 3-(furan-2-yl)-2-methyl-2-(naphthalen-2-yl)propanenitrile

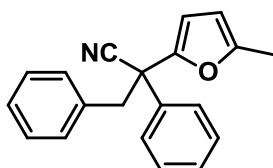
Viscous clear liquid isolated via column chromatography 98:2 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.84 (d, *J* = 2.0 Hz, 1H, R<sub>3</sub>C-β-naphthyl(5-,CH)), 7.82 – 7.74 (m, 3H, R<sub>3</sub>C-β-naphthylCH), 7.47 – 7.40 (m, 3H, R<sub>3</sub>C-β-naphthylCH), 7.22 (dd, *J* = 1.8, 0.8 Hz, 1H, 2-furanyl(5-CH)), 6.19 (dd, *J* = 3.2, 1.9 Hz, 1H, 2-furanyl(4-CH)), 6.02 (d, *J* = 3.4 Hz, 1H, 2-furanyl(3-CH)), 3.24 (m, 2H, CR<sub>3</sub>CH<sub>2</sub>-2-furanyl), 1.77 (s, 3H, R<sub>3</sub>CCH<sub>3</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 149.7 (R<sub>3</sub>CCH<sub>2</sub>(2-furanyl(2-C(q))), 142.2 (R<sub>3</sub>CCH<sub>2</sub>(2-furanyl(5-C(q))), 136.8 (R<sub>3</sub>C-β-naphthyl2-C(q))), 133.1 (R<sub>3</sub>C-β-naphthylC(q)), 132.7 (R<sub>3</sub>C-β-naphthyl(5-C)), 128.8

(R<sub>3</sub>C-β-naphthyl(3-C)), 128.2 (R<sub>3</sub>C-β-naphthyl( 8-C)), 127.6 (R<sub>3</sub>C-β-naphthyl(1-, 4-C)), 126.6 (R<sub>3</sub>C-β-naphthyl(7-C)), 124.88 (R<sub>3</sub>C-β-naphthyl(6-C)), 123.1 (RCN), 110.5 (R<sub>3</sub>C-furanyl(4-CH)), 109.1 (R<sub>3</sub>C-furanyl(3-CH)), 42.9 (CR<sub>4</sub>), 40.6 (CR<sub>3</sub>CH<sub>2</sub>-2-furanyl), 26.2 (R<sub>3</sub>CCH<sub>3</sub>).

**GC/MS:** 262.0 [M<sup>+</sup>], 237.1 [M-CN], 73.0 [base peak].



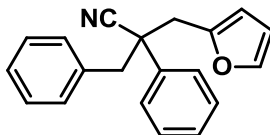
### 2-(5-methylfuran-2-yl)-2,3-diphenylpropanenitrile

Viscous clear liquid isolated via column chromatography 98:2 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.28 – 7.18 (m, 4H, PhCH<sub>(meta)</sub>), 7.14 – 7.06 (m, 6H, PhCH<sub>(ortho/para)</sub>), 6.16 (d, *J* = 3.3 Hz, 1H, R<sub>3</sub>C-furanyl(3-CH)), 5.86 (dq, *J* = 3.0, 0.9 Hz, 1H, R<sub>3</sub>C-furanyl(4-CH)), 3.65 (d, *J* = 13.3 Hz, 1H, R<sub>3</sub>CCH<sub>2</sub>furanyl), 3.31 (d, *J* = 13.3 Hz, 1H, R<sub>3</sub>CCH<sub>2</sub>-2-furanyl), 2.22 (s, 3H, furanyl(5-CH<sub>3</sub>)).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 152.1 (R<sub>3</sub>C-furanyl(2-C(q))), 147.8 (R<sub>3</sub>C-furanyl(5-C(q))), 136.2 (R<sub>3</sub>CPhC(q)), 133.7 (R<sub>3</sub>CCH<sub>2</sub>PhC(q)), 129.3 (R<sub>3</sub>CPhC<sub>(ortho)</sub>), 127.5 (R<sub>3</sub>CPhC<sub>(para)</sub>), 127.1 (R<sub>3</sub>CPhC<sub>(meta)</sub>), 126.9 (R<sub>3</sub>CCH<sub>2</sub>PhC<sub>(meta)</sub>), 126.3 (R<sub>3</sub>CCH<sub>2</sub>PhC<sub>(ortho)</sub>), 125.8 (R<sub>3</sub>CCH<sub>2</sub>PhC<sub>(para)</sub>), 118.6 (RCN), 108.7 (R<sub>3</sub>C-furanyl(3-CH)), 105.5 (R<sub>3</sub>C-furanyl(4-CH)), 48.1 (CR<sub>4</sub>), 44.1 (R<sub>3</sub>CCH<sub>2</sub>Ph )12.6 (furanyl5-CH<sub>3</sub>).

**GC/MS:** 287.2 [M<sup>+</sup>], 262.8 [M-CN], 81.0 [base peak].

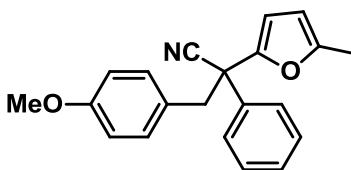


### 2-benzyl-3-(furan-2-yl)-2-phenylpropanenitrile

Viscous clear liquid isolated via column chromatography 98:2 Hex:EtOAc as eluent.

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 (m, 5H,  $\text{R}_3\text{CCH}_2\text{PhCH}$ ), 7.24 (m, 5H,  $\text{R}_3\text{CPhCH}$ ), 7.05 (dd,  $J = 7.3$ , 2.1 Hz, 1H,  $\text{R}_3\text{CCH}_2$ -2-furanyl(5-CH)), 6.29 (dd,  $J = 3.2$ , 1.9 Hz, 1H,  $\text{R}_3\text{CCH}_2$ -2-furanyl(4-CH)), 6.11 (d,  $J = 3.2$  Hz, 1H,  $\text{R}_3\text{CCH}_2$ -2-furanyl(3-CH)), 3.44 (m, 2H,  $\text{R}_3\text{CCH}_2\text{Ph}$ ), 3.31 (m, 2H,  $\text{R}_3\text{CCH}_2$ -2-furanyl).  **$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  149.6 ( $\text{R}_3\text{CCH}_2$ (2-furanyl(2-C(q))), 142.0 ( $\text{R}_3\text{CPhC(q)}$ ), 137.2 ( $\text{R}_3\text{CCH}_2$ (2-furanyl(5-CH)), 134.7 ( $\text{R}_3\text{CCH}_2\text{PhC(q)}$ ), 130.4 ( $\text{R}_3\text{CPhC}_{(\text{ortho})}$ ), 128.6 ( $\text{R}_3\text{CPhC}_{(\text{para})}$ ), 128.1 ( $\text{R}_3\text{CPhC}_{(\text{meta})}$ ), 128.0 ( $\text{R}_3\text{CCH}_2\text{PhC}_{(\text{meta})}$ ), 127.3 ( $\text{R}_3\text{CCH}_2\text{PhC}_{(\text{ortho})}$ ), 126.5 ( $\text{R}_3\text{CCH}_2\text{PhC}_{(\text{para})}$ ), 121.4 (RCN), 110.5 ( $\text{R}_3\text{C-furanyl(4-CH)}$ ), 109.1 ( $\text{R}_3\text{C-furanyl(3-CH)}$ ), 49.5 ( $\text{CR}_4$ ), 46.3 ( $\text{R}_3\text{CCH}_2\text{Ph}$ ), 38.2 ( $\text{CR}_3\text{CH}_2$ -2-furanyl).

**GC/MS:** 287.2 [ $\text{M}^+$ ], 262.8 [ $\text{M-CN}$ ], 81.0 [base peak]



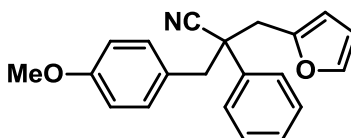
### 3-(4-methoxyphenyl)-2-(5-methylfuran-2-yl)-2-phenylpropanenitrile

Viscous clear liquid isolated via column chromatography 95:5 Hex:EtOAc as eluent.

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.24 (m, 5H,  $\text{CR}_3\text{ArH}$ ), 6.75 (d,  $J = 8.7$  Hz, 2H,  $\text{RCH}_2\text{ArH}_{(\text{ortho})}$ ), 6.64 (d,  $J = 8.7$  Hz, 2H,  $\text{RCH}_2\text{ArH}_{(\text{meta})}$ ), 6.16 (d,  $J = 3.2$  Hz, 1H,  $\text{R}_3\text{C-furnayl(4-CH)}$ ), 5.88 (m, 1H,  $\text{R}_3\text{C-furnayl(3-CH)}$ ), 3.66 (s, 3H,  $\text{CR}_3\text{CH}_2\text{ArOCH}_3$ ), 3.60 (d,  $J = 13.4$  Hz, 1H,  $\text{R}_3\text{CCH}_2$ -2-furanyl), 3.26 (d,  $J = 13.4$  Hz, 1H,  $\text{R}_3\text{CCH}_2$ -2-furanyl), 2.23 (s, 3H, furanyl(5- $\text{CH}_3$ )).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  158.9 ( $\text{CH}_2\text{ArC}(\text{q})\text{OCH}_3$ ), 153.1 ( $\text{R}_3\text{C-furanyl}(2\text{-C}(\text{q}))$ ), 149.0 ( $\text{R}_3\text{C-furanyl}(5\text{-C}(\text{q}))$ ), 137.4 ( $\text{RCH}_2\text{ArC}(\text{q})$ ), 131.4 ( $\text{R}_3\text{CPhC}(\text{q})$ ), 128.6 ( $\text{RCH}_2\text{ArCH}_{(\text{ortho})}$ ), 128.1 ( $\text{R}_3\text{C-PhC}_{(\text{ortho/para})}$ ), 126.4 ( $\text{R}_3\text{CPhC}_{(\text{meta})}$ ), 119.8 ( $\text{RCN}$ ), 113.4 ( $\text{RCH}_2\text{ArCH}_{(\text{meta})}$ ), 109.7 ( $\text{R}_3\text{C-furanyl}(3\text{-CH})$ ), 106.5 ( $\text{R}_3\text{C-furanyl}(4\text{-CH})$ ), 55.1 ( $\text{CR}_3\text{CH}_2\text{ArOCH}_3$ ), 49.8 ( $\text{CR}_4$ ), 44.4 ( $\text{R}_3\text{CCH}_2\text{Ar}$ ), 13.7 ( $\text{furanyl5-CH}_3$ ).

**GC/MS:** 317.1 [ $\text{M}^+$ ], 291.3 [ $\text{M-CN}$ ], 121.0 [base peak]



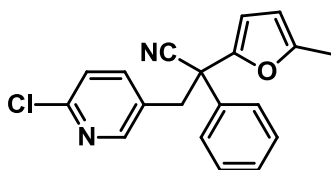
### 3-(furan-2-yl)-2-(4-methoxybenzyl)-2-phenylpropanenitrile

Viscous clear liquid isolated via column chromatography 95:5 Hex:EtOAc as eluent.

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (m, 2H,  $\text{CR}_3\text{ArH}_{(\text{meta})}$ ), 7.24 (s, 3H,  $\text{CR}_3\text{ArH}_{(\text{ortho/para})}$ ), 7.21 (dd,  $J = 1.8, 0.7$  Hz, 2H,  $\text{R}_3\text{CCH}_2\text{-2-furanyl}(5\text{-CH})$ ), 6.83 (d,  $J = 8.7$  Hz, 2H,  $\text{RCH}_2\text{ArH}_{(\text{ortho})}$ ), 6.64 (d,  $J = 8.7$  Hz, 2H,  $\text{RCH}_2\text{ArH}_{(\text{meta})}$ ), 6.17 (dd,  $J = 3.2, 1.9$  Hz, 1H,  $\text{R}_3\text{CCH}_2\text{-2-furanyl}(4\text{-CH})$ ), 5.97 (d,  $J = 3.2$  Hz, 1H,  $\text{R}_3\text{CCH}_2\text{-2-furanyl}(3\text{-CH})$ ), 3.67 (s, 3H,  $\text{CR}_3\text{CH}_2\text{ArOCH}_3$ ), 3.28 (s, 2H,  $\text{R}_3\text{CCH}_2\text{-2-furanyl}$ ), 3.15 (s, 2H,  $\text{furanyl}(5\text{-CH}_3)$ ).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  158.8 ( $\text{CH}_2\text{ArC}(\text{q})\text{OCH}_3$ ), 149.7 ( $\text{R}_3\text{C-furanyl}(2\text{-C}(\text{q}))$ ), 142.0 ( $\text{R}_3\text{C-furanyl}(5\text{-C}(\text{q}))$ ), 137.3 ( $\text{RCH}_2\text{ArCH}_{(\text{ortho})}$ ), 131.5 ( $\text{R}_3\text{CPhC}(\text{q})$ ), 128.6 ( $\text{R}_3\text{C-PhC}_{(\text{ortho})}$ ), 127.9 ( $\text{R}_3\text{C-PhC}_{(\text{para})}$ ), 126.6 ( $\text{R}_3\text{C-PhC}_{(\text{meta})}$ ), 121.5 ( $\text{RCN}$ ), 114.0 ( $\text{ArC}$ ), 113.5 ( $\text{RCH}_2\text{ArCH}_{(\text{meta})}$ ), 110.5 ( $\text{R}_3\text{C-furanyl}(4\text{-CH})$ ), 109.1 ( $\text{R}_3\text{C-furanyl}(3\text{-CH})$ ), 55.1 ( $\text{CR}_3\text{CH}_2\text{ArOCH}_3$ ), 49.7 ( $\text{CR}_4$ ), 45.5 ( $\text{R}_3\text{CCH}_2\text{Ar}$ ), 38.0 ( $\text{CR}_3\text{CH}_2\text{-2-furanyl}$ ).

**GC/MS:** 317.1 [ $\text{M}^+$ ], 291.3 [ $\text{M-CN}$ ], 121.0 [base peak]

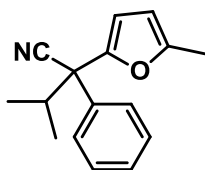


### 3-(6-chloropyridin-3-yl)-2-(5-methylfuran-2-yl)-2-phenylpropanenitrile

Viscous clear liquid isolated via column chromatography 95:5 Hex:EtOAc as eluent. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.75 (s, R<sub>3</sub>CCH<sub>2</sub>-5-pyridyl(6-CH)), 7.33 – 7.23 (m, 6H, RCH<sub>2</sub>Ar/PhH), 7.12 (dd, *J* = 2.4, 0.7 Hz, 1H, R<sub>3</sub>CCH<sub>2</sub>-5-pyridyl(6-CH)), 6.16 (d, *J* = 3.2 Hz, 1H, R<sub>3</sub>C-furnayl(4-CH)), 5.90 (dt, *J* = 3.1, 1.0 Hz, 1H, R<sub>3</sub>C-furnayl(3-CH)), 3.65 (d, *J* = 13.6 Hz, 1H, R<sub>3</sub>CCH<sub>2</sub>-5-pyridyl), 3.32 (d, *J* = 13.6 Hz, 1H, R<sub>3</sub>CCH<sub>2</sub>-5-pyridyl), 2.25 (s, 2H, R<sub>3</sub>C-2-furanyl-5-CH<sub>3</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 153.6 (R<sub>3</sub>C-furanyl(2-C(q))), 159.0 (R<sub>3</sub>C-furanyl(5-C(q))), 150.8 (R<sub>3</sub>CCH<sub>2</sub>-5-pyridyl(2-CCl)), 147.8 (R<sub>3</sub>CCH<sub>2</sub>-5-pyridyl(5-C(q))), 140.4 (R<sub>3</sub>CCH<sub>2</sub>-5-pyridyl(6-CH)), 136.4 (R<sub>3</sub>CPhC(q)), 129.4 (R<sub>3</sub>CCH<sub>2</sub>-5-pyridyl(4-CH)), 129.0 (R<sub>3</sub>CCH<sub>2</sub>-5-pyridyl(3-CH)), 128.7 (R<sub>3</sub>CPhC(meta)), 126.6 (R<sub>3</sub>CPhC(ortho)), 123.7 (R<sub>3</sub>CPhC(para)), 119.1 (RCN), 110.3 (R<sub>3</sub>C-furnayl(4-CH)), 106.8 (R<sub>3</sub>C-furnayl(3-CH)), 49.2 (CR<sub>4</sub>), 41.7 (R<sub>3</sub>CCH<sub>2</sub>Pyridyl), 13.7 (furanyl5-CH<sub>3</sub>).

**GC/MS:** 322.2 [M<sup>+</sup>], 297.2 [M-CN], 196.2 [base peak]



### 3-methyl-2-(5-methylfuran-2-yl)-2-phenylbutanenitrile

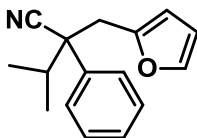
Viscous clear liquid isolated via column chromatography 98:2 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.47 (m, 2H, R<sub>3</sub>CPhCH<sub>(meta)</sub>), 7.28 (m, 2H, R<sub>3</sub>CPhCH<sub>(ortho)</sub>), 7.22 (m, 1H, R<sub>3</sub>CPhCH<sub>(para)</sub>), 6.24 (d, *J* = 3.1 Hz, 1H, R<sub>3</sub>C-furnayl(4-CH)), 5.83 (dt, *J* = 3.1, 1.0 Hz, 1H, R<sub>3</sub>C-

furnayl(3-CH)), 2.70 (hept,  $J = 6.7$  Hz, 1H,  $R_3CCH(CH_3)_2$ ), 2.19 (s, 2H,  $R_3C$ -2-furanyl-5-CH<sub>3</sub>), 1.03 (d,  $J = 6.6$  Hz, 3H,  $R_3CCH(CH_3)CH_3$ ), 0.80 (d,  $J = 6.7$  Hz, 3H,  $R_3CCH(CH_3)CH_3$ ).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  152.6 ( $R_3C$ -furanyl(2-C(q))), 149.4 ( $R_3C$ -furanyl(5-C(q))), 137.7 ( $R_3CPhC(q)$ ), 128.7 ( $R_3CPhC_{(meta)}$ ), 127.8 ( $R_3CPhC_{(ortho)}$ ), 126.4 ( $R_3CPhC_{(para)}$ ), 118.9 (RCN), 108.8 ( $R_3C$ -furnayl(4-CH)), 106.3 ( $R_3C$ -furnayl(3-CH)), 54.8 ( $R_3CCH(CH_3)_2$ ), 36.2 (CR<sub>4</sub>), 19.3 ( $R_3CCH(CH_3)CH_3$ ), 18.3 ( $R_3CCH(CH_3)CH_3$ ), 13.7 (furanyl5-CH<sub>3</sub>).

**GC/MS:** 239.1 [M<sup>+</sup>], 214.2 [M-CN], 81.0 [base peak]



### 2-(furan-2-ylmethyl)-3-methyl-2-phenylbutanenitrile

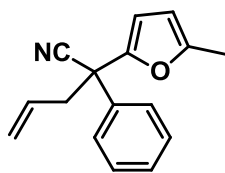
Viscous clear liquid isolated via column chromatography 98:2 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.24 (m, 5H,  $R_3CPhCH$ ), 7.11 (dd,  $J = 1.9, 0.8$  Hz, 1H,  $R_3CCH_2$ -2-furanyl(5-CH)), 6.07 (dd,  $J = 3.2, 1.9$  Hz, 1H,  $R_3CCH_2$ -2-furanyl(4-CH)), 5.74 (d,  $J = 3.2$  Hz, 1H,  $R_3CCH_2$ -2-furanyl(3-CH)), 3.40 (d,  $J = 15.0$  Hz, 1H,  $R_3CCH_2$ -2-furanyl), 3.15 (d,  $J = 15.0$  Hz, 1H,  $R_3CCH_2$ -2-furanyl), 1.22 (hept,  $J = 6.7$  Hz, 1H,  $R_3CCH(CH_3)_2$ ), 0.97 (d,  $J = 6.7$  Hz, 3H,  $R_3CCH(CH_3)CH_3$ ), 0.77 (d,  $J = 6.7$  Hz, 3H,  $R_3CCH(CH_3)CH_3$ ).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  149.9 ( $R_3CCH_2$ (2-furanyl(2-C(q))), 141.7 ( $R_3CCH_2$ (2-furanyl(5-CH)), 137.3 ( $R_3CPhC(q)$ ), 128.4 ( $R_3CPhCH_{(meta)}$ ), 127.7 ( $R_3CPhCH_{(ortho)}$ ), 126.3 ( $R_3CPhCH_{(para)}$ ), 120.8 (RCN), 110.2 ( $R_3C$ -furanyl(4-CH)), 108.6 ( $R_3C$ -furanyl(3-CH)), 53.8 ( $R_3CCH(CH_3)CH_3$ ), 36.8 (CR<sub>3</sub>CH<sub>2</sub>-2-furanyl), 36.5 (CR<sub>4</sub>), 18.8 ( $R_3CCH(CH_3)CH_3$ ), 18.6 ( $R_3CCH(CH_3)CH_3$ ).

**GC/MS:** 239.1 [M<sup>+</sup>], 214.2 [M-CN], 81.0 [base peak]





**(4-290) 2-(5-methylfuran-2-yl)-2-phenylpent-4-enenitrile**

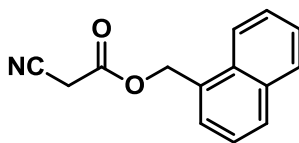
Viscous clear liquid isolated via column chromatography 98:2 Hex:EtOAc as eluent.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.34 (m, 2H, R<sub>3</sub>CPhCH<sub>(meta)</sub>), 7.30 (m, 2H, R<sub>3</sub>CPhCH<sub>(ortho)</sub>), 7.25 (m, 1H, R<sub>3</sub>CPhCH<sub>(para)</sub>), 6.13 (d, *J* = 3.2 Hz, 1H, R<sub>3</sub>C-furnayl(4-CH)), 5.86 (dt, *J* = 3.1, 1.0 Hz, 1H, R<sub>3</sub>C-furnayl(3-CH)), 5.61 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H, allyl(CH)), 5.12 (m, 2H, allyl(CH<sub>2</sub>)), 3.08 (ddt, *J* = 13.9, 7.2, 1.1 Hz, 1H, R<sub>3</sub>CCH<sub>2</sub>allyl), 2.86 (ddt, *J* = 14.0, 7.0, 1.1 Hz, 1H, R<sub>3</sub>CCH<sub>2</sub>allyl), 2.19 (s, 2H, furanylCH<sub>3</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 153.2 (R<sub>3</sub>C-furanyl(2-C(q))), 148.9 (R<sub>3</sub>C-furanyl(5-C(q))), 137.5 (R<sub>3</sub>CPhC(q)), 131.31 (Allyl(CH)), 128.79 (R<sub>3</sub>CPhCH<sub>(meta)</sub>), 128.2 (R<sub>3</sub>CPhCH<sub>(ortho)</sub>), 126.5 (R<sub>3</sub>CPhCH<sub>(para)</sub>), 120.6 (RCN), 119.8 (Allyl(CH<sub>2</sub>)), 109.3 (R<sub>3</sub>C-furnayl(4-CH)), 106.4 (R<sub>3</sub>C-furnayl(3-CH)), 47.9 (CR<sub>4</sub>), 43.4 (R<sub>3</sub>CCH<sub>2</sub>-furanyl), 13.6 (furanyl5-CH<sub>3</sub>).

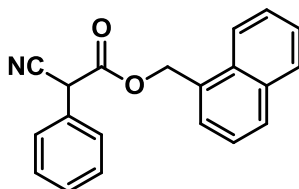
**GC/MS:** 237.2 [M<sup>+</sup>], 212.3 [M-CN], 81.0 [base peak]

Characterization of benzyl cyanoacetates:



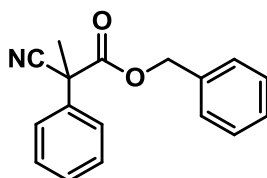
**naphthalen-1-ylmethyl 2-cyanoacetate (TR3-098)**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.06 – 7.99 (m, 1H), 7.97 – 7.89 (m, 2H), 7.66 – 7.53 (m, 3H), 7.49 (m, 1H), 5.73 (s, 2H), 3.50 (s, 2H).



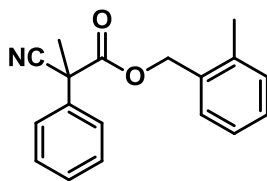
**naphthalen-1-ylmethyl 2-cyano-2-phenylacetate (TR3-183)**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.90 – 7.78 (m, 1H), 7.73 (d,  $J$  = 1.5 Hz, 1H), 7.57 – 7.46 (m, 5H), 7.43 (m, 3H), 7.40 – 7.33 (m, 2H), 5.39 (s, 2H), 4.81 (s, 1H).



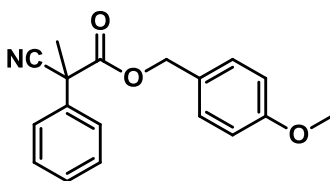
**benzyl 2-cyano-2-phenylpropanoate (TR4-189)**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60 – 7.21 (m, 5H), 5.23 (q,  $J$  = 1.7 Hz, 2H), 2.01 (s, 3H).



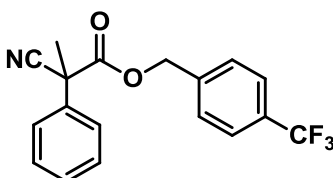
**2-methylbenzyl 2-cyano-2-phenylpropanoate (TR5-037)**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58 – 7.48 (m, 2H), 7.48 – 7.35 (m, 3H), 7.33 – 7.13 (m, 5H), 5.24 (d,  $J$  = 1.6 Hz, 2H), 2.23 (s, 3H), 2.04 – 1.96 (m, 3H).



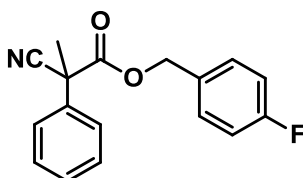
**4-methoxybenzyl 2-cyano-2-phenylpropanoate (TR4-190)**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49 (dq,  $J$  = 5.4, 1.8 Hz, 2H), 7.45 – 7.33 (m, 3H), 7.21 (dt,  $J$  = 8.6, 2.1 Hz, 2H), 6.86 (dt,  $J$  = 8.6, 2.1 Hz, 2H), 5.16 (d,  $J$  = 1.4 Hz, 2H), 3.82 (s, 3H), 1.97 (s, 3H).



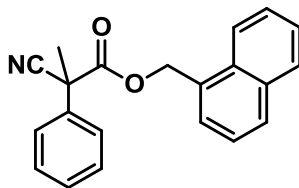
**4-(trifluoromethyl)benzyl 2-cyano-2-phenylpropanoate (TR4-205)**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58 (d,  $J$  = 8.2 Hz, 2H), 7.56 – 7.48 (m, 2H), 7.48 – 7.38 (m, 3H), 7.33 (d,  $J$  = 8.0 Hz, 2H), 5.27 (d,  $J$  = 1.4 Hz, 2H), 2.01 (s, 3H).



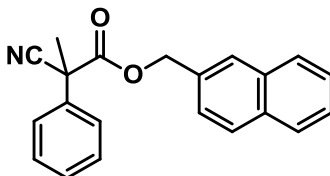
**4-fluorobenzyl 2-cyano-2-phenylpropanoate (TR4-200)**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.53 – 7.45 (m, 2H), 7.45 – 7.35 (m, 3H), 7.27 – 7.19 (m, 2H), 7.05 – 6.95 (m, 2H), 5.19 (s, 2H), 1.98 (s, 3H).



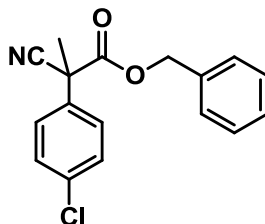
**naphthalen-1-ylmethyl 2-cyano-2-phenylpropanoate (TR5-041)**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.95 – 7.75 (m, 3H), 7.60 – 7.38 (m, 6H), 7.38 – 7.30 (m, 3H), 5.76 – 5.61 (m, 2H), 2.03 – 1.96 (m, 3H).



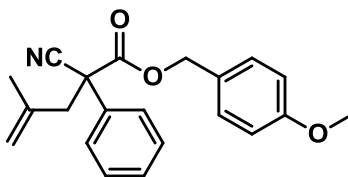
**naphthalen-2-ylmethyl 2-cyano-2-phenylpropanoate (TR4-207)**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.90 – 7.74 (m, 3H), 7.67 (d, *J* = 1.6 Hz, 1H), 7.58 – 7.47 (m, 4H), 7.44 – 7.37 (m, 3H), 7.33 (dd, *J* = 8.5, 1.7 Hz, 1H), 5.44 – 5.34 (m, 2H), 2.00 (d, *J* = 0.9 Hz, 3H).



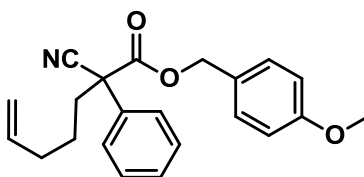
**benzyl 2-(4-chlorophenyl)-2-cyanopropanoate (JH2-130-8)**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.48 – 7.41 (m, 1H), 7.40 – 7.36 (m, 1H), 7.36 – 7.31 (m, 2H), 7.28 – 7.21 (m, 1H), 5.22 (s, 1H), 1.97 (s, 2H).



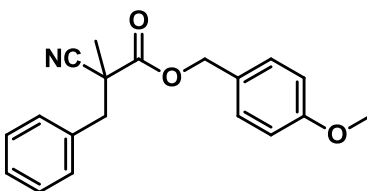
**(3.22) 4-methoxybenzyl 2-cyano-4-methyl-2-phenylpent-4-enoate (JH2-134-07)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61 – 7.52 (m, 2H), 7.45 – 7.34 (m, 3H), 7.26 – 7.17 (m, 2H), 6.90 – 6.81 (m, 2H), 5.23 – 5.08 (m, 2H), 4.94 (p,  $J$  = 1.6 Hz, 1H), 4.85 (p,  $J$  = 1.0 Hz, 1H), 3.82 (s, 3H), 3.19 (dd,  $J$  = 14.1, 1.0 Hz, 1H), 2.82 (dd,  $J$  = 14.4, 1.0 Hz, 1H), 1.65 (t,  $J$  = 1.2 Hz, 3H).



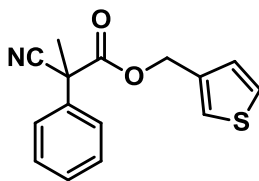
**(3.23) 4-methoxybenzyl 2-cyano-2-phenylhept-6-enoate (JH2-135-27)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 (dt,  $J$  = 5.8, 2.0 Hz, 2H), 7.44 – 7.33 (m, 3H), 7.25 – 7.15 (m, 2H), 6.90 – 6.80 (m, 2H), 5.73 (ddt,  $J$  = 16.9, 10.1, 6.6 Hz, 1H), 5.22 – 5.10 (m, 2H), 5.06 – 4.94 (m, 2H), 3.82 (s, 3H), 2.37 (ddd,  $J$  = 13.6, 10.7, 5.9 Hz, 1H), 2.19 – 2.03 (m, 3H), 1.52 (tdd,  $J$  = 11.3, 7.1, 4.7 Hz, 2H).



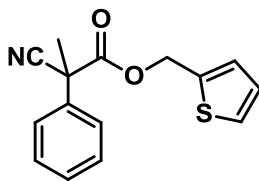
**(3.24) 4-methoxybenzyl 2-cyano-2-methyl-3-phenylpropanoate (TR5-012)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 – 7.15 (m, 7H), 6.89 (dd,  $J$  = 9.2, 2.3 Hz, 2H), 5.18 – 5.07 (m, 2H), 3.84 (s, 3H), 3.27 – 3.19 (m, 1H), 3.09 – 3.00 (m, 1H), 1.60 (s, 3H).



**thiophen-3-ylmethyl 2-cyano-2-phenylpropanoate (TR3-245)**

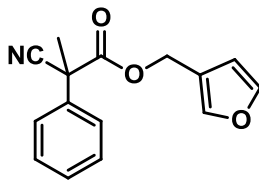
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.54 – 7.46 (m, 2H), 7.45 – 7.37 (m, 3H), 7.32 – 7.27 (m, 1H), 7.25 – 7.20 (m, 1H), 6.98 (dd, *J* = 5.0, 1.2 Hz, 1H), 5.24 (s, 2H), 1.98 (s, 3H).



**(3.36) thiophen-2-ylmethyl 2-cyano-2-phenylpropanoate (TR3-273-25)**

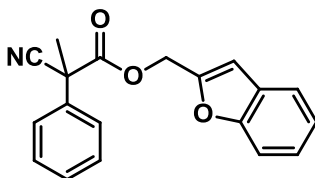
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.52 – 7.47 (m, 2H), 7.44 – 7.37 (m, 3H), 6.41 (dd, *J* = 3.2, 0.8 Hz, 1H), 6.35 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.18 (s, 2H), 1.98 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 167.7, 148.0, 143.6, 135.5, 129.1, 128.9, 125.7, 119.2, 111.5, 110.6, 60.4, 48.3, 24.83.



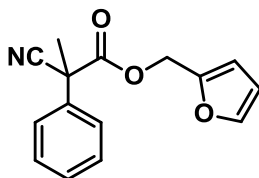
**furan-3-ylmethyl 2-cyano-2-phenylpropanoate (TR3-278)**

**<sup>1</sup>H NMR** (400 MHz, Tol) δ 7.69 – 7.60 (m, 2H), 7.32 – 7.20 (m, 3H), 7.00 (dd, *J* = 3.8, 2.1 Hz, 2H), 6.95 – 6.89 (m, 1H), 5.06 – 4.94 (m, 2H), 1.87 (s, 3H).



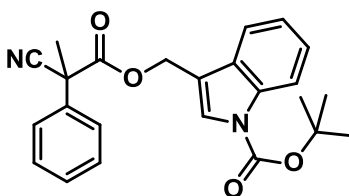
**benzofuran-2-ylmethyl 2-cyano-2-phenylpropanoate (TR3-202)**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.61 – 7.49 (m, 4H), 7.49 – 7.42 (m, 1H), 7.42 – 7.30 (m, 4H), 7.30 – 7.21 (m, 2H), 6.75 – 6.67 (m, 1H), 5.43 – 5.25 (m, 2H), 2.05 – 1.96 (m, 3H).



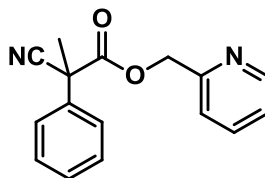
**(3.34) furan-3-ylmethyl 2-cyano-2-phenylpropanoate (TR3-208)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.64 – 7.55 (m, 1H), 7.47 – 7.33 (m, 5H), 6.41 (d, *J* = 3.2 Hz, 1H), 6.35 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.18 (s, 2H), 1.98 (t, *J* = 8.6 Hz, 3H).



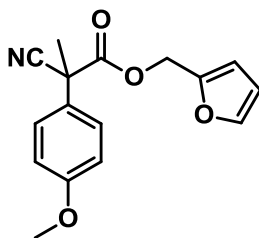
**tert-butyl 3-(((2-cyano-2-phenylpropanoyl)oxy)methyl)-1H-indole-1-carboxylate (TR4-240)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.63 (s, 1H), 7.55 – 7.30 (m, 2H), 7.44 – 7.30 (m, 5H), 7.26 – 7.15 (m, 1H), 5.46 – 5.31 (m, 2H), 1.98 (s, 3H), 1.74 (s, 9H).



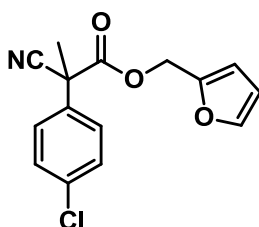
**(3.33) pyridin-2-ylmethyl 2-cyano-2-phenylpropanoate (TR2-207)**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.61 – 8.52 (m, 1H), 7.66 (td, *J* = 7.7, 1.8 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.49 – 7.38 (m, 3H), 7.27 – 7.20 (m, 1H), 7.18 (dt, *J* = 7.9, 0.9 Hz, 1H), 5.44 – 5.27 (m, 2H), 2.02 (s, 3H).



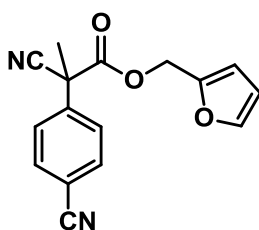
**furan-2-ylmethyl 2-cyano-2-(4-methoxyphenyl)propanoate (JH2-154-26)**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49 – 7.35 (m, 3H), 6.99 – 6.83 (m, 2H), 6.44 – 6.34 (m, 2H), 5.17 (s, 2H), 3.83 (s, 3H), 1.95 (s, 3H).



**furan-2-ylmethyl 2-(4-chlorophenyl)-2-cyanopropanoate (TR4-063)**

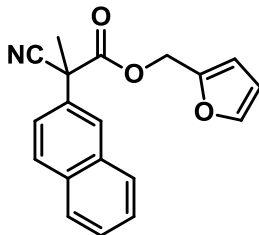
$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43 – 7.39 (m, 3H), 7.35 – 7.29 (m, 2H), 6.49 – 6.32 (m, 2H), 5.26 – 5.09 (m, 2H), 1.96 (s, 3H).



**furan-2-ylmethyl 2-cyano-2-(4-cyanophenyl)propanoate (TR4-062)**

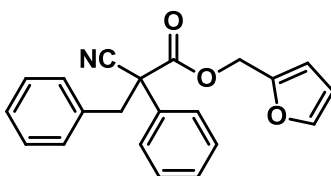
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.80 – 7.58 (m, 5H), 6.48 – 6.34 (m, 2H), 5.29 – 5.12 (m, 2H), 1.99 (s, 3H).





**furan-2-ylmethyl 2-cyano-2-(naphthalen-2-yl)propanoate (TR4-077)**

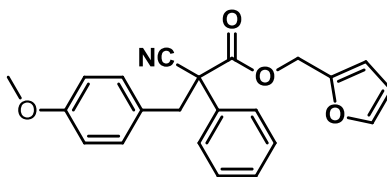
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.03 – 7.78 (m, 1H), 7.61 – 7.47 (m, 4H), 7.40 – 7.22 (m, 3H), 6.44 – 6.29 (m, 2H), 5.24 – 5.17 (m, 2H), 2.11 – 2.03 (m, 3H).



**furan-2-ylmethyl 2-cyano-2,3-diphenylpropanoate (TR4-036)**

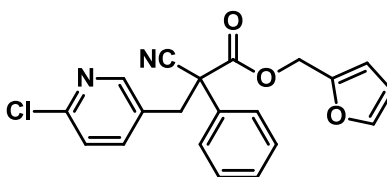
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.46 – 7.37 (m, 1H), 7.34 – 7.26 (m, 2H), 7.18 – 7.11 (m, 5H), 7.07 – 7.00 (m, 3H), 6.29 (dd, *J* = 3.3, 0.8 Hz, 1H), 6.25 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.14 – 5.00 (m, 2H), 3.63 (d, *J* = 13.6 Hz, 1H), 3.25 (d, *J* = 13.6 Hz, 1H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 167.0, 147.9, 143.5, 134.0, 133.8, 130.3, 129.1, 128.9, 128.3, 127.7, 126.4, 117.7, 111.6, 110.6, 60.3, 55.9, 44.0.



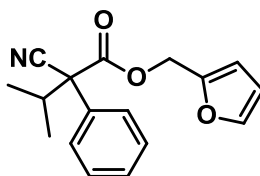
**furan-2-ylmethyl 2-cyano-3-(4-methoxyphenyl)-2-phenylpropanoate (TR5-080)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.56 – 7.47 (m, 2H), 7.42 – 7.35 (m, 4H), 7.09 – 7.02 (m, 2H), 6.81 – 6.74 (m, 2H), 6.41 – 6.32 (m, 2H), 5.22 – 5.10 (m, 2H), 3.79 (s, 3H), 3.67 (d, *J* = 13.7 Hz, 1H), 3.29 (d, *J* = 13.8 Hz, 1H).



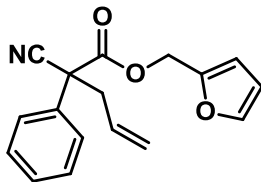
**furan-2-ylmethyl 3-(6-chloropyridin-3-yl)-2-cyano-2-phenylpropanoate (TR5-075)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.07 (d, *J* = 2.6 Hz, 1H), 7.53 – 7.34 (m, 7H), 7.21 (s, 1H), 6.44 – 6.32 (m, 2H), 5.19 (s, 2H), 3.66 (d, *J* = 14.0 Hz, 1H), 3.34 (d, *J* = 13.9 Hz, 1H).



**furan-2-ylmethyl 2-cyano-3-methyl-2-phenylbutanoate (TR4-071)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.67 – 7.57 (m, 2H), 7.46 – 7.34 (m, 3H), 7.28 (s, 1H), 6.44 – 6.30 (m, 2H), 5.24 – 5.12 (m, 2H), 2.82 (dt, *J* = 13.3, 6.7 Hz, 1H), 1.19 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).



**furan-2-ylmethyl 2-cyano-2-phenylpent-4-enoate (TR4-053-20)**

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.48 – 7.39 (m, 2H), 7.37 – 7.25 (m, 4H), 6.36 – 6.21 (m, 2H), 5.65 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.22 – 5.03 (m, 4H), 3.04 (ddt, *J* = 13.9, 7.4, 1.1 Hz, 1H), 2.78 (ddt, *J* = 13.9, 6.9, 1.1 Hz, 1H).

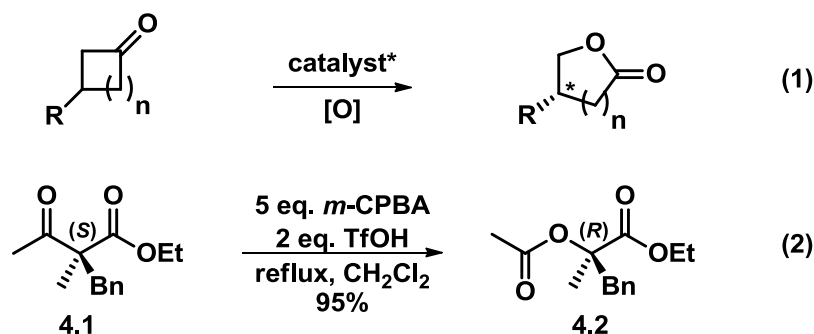
**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 166.9, 148.0, 143.6, 133.7, 130.5, 129.1, 128.9, 126.2, 121.4, 117.7, 111.6, 110.6, 60.3, 54.2, 42.2.

## **Chapter IV.**

### **Asymmetric Baeyer–Villiger Oxidation of 1,3-Diketones**

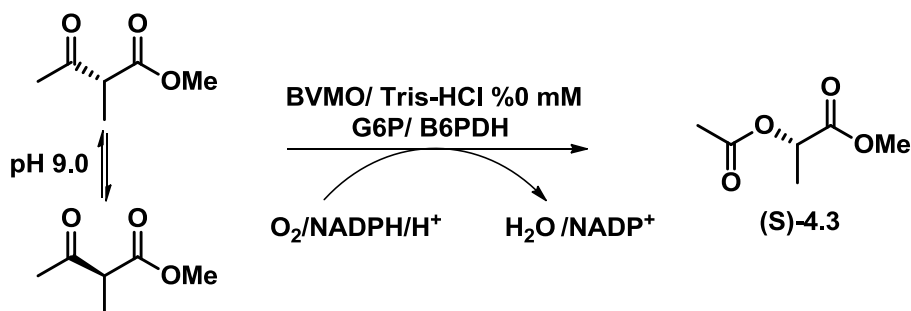
#### CIV.1: Introduction to the Asymmetric Baeyer–Villiger oxidation of Ketones

The Baeyer–Villiger<sup>1</sup> (B–V) rearrangement represents one of the most fundamental transformations for the oxidation of ketones and aldehydes in organic chemistry.<sup>2-7</sup> The reaction entails nucleophilic insertion of an oxygen atom adjacent to a carbonyl functionality producing lactones and esters. Extension of the Baeyer–Villiger methodology to include the catalytic, enantioselective oxidation of prochiral and racemic ketones was independently reported by Bolm<sup>8</sup> and Strukul<sup>9</sup> in 1994. This pioneering work has since been complemented with numerous metal complexes and organic compounds competent for inducing the catalytic, asymmetric B–V oxidation of ketones.<sup>6,7,10-17</sup> Despite the elegance of the above reports, the substrate scope is rarely extended beyond highly strained ketones (eq. 1, Scheme 4.1)<sup>4,13</sup> and the degree of enantioenrichment struggles to compete with values reported involving enzymatic systems.<sup>18-24</sup>  $\alpha,\alpha$ -Disubstituted non-enolizable  $\beta$ -ketoesters<sup>25-30</sup> have also been reported to be reactive substrates under B–V conditions, although not nearly as investigated as the Baeyer–Villiger oxidation of ketones. In addition, hydrolysis of the acyl moiety leads to the formation of  $\alpha$ -hydroxy esters.<sup>31</sup> Cristau confirms the stereospecificity<sup>32</sup> of the alkyl migration



Scheme 4.1

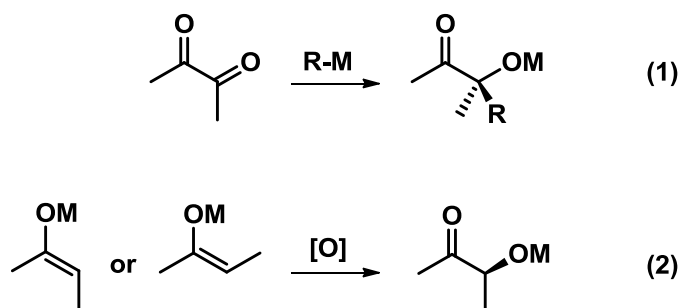
involved with the Baeyer–Villiger oxidation of enantiopure  $\alpha$ -methyl, $\alpha$ -benzyl ethyl acetoester **4.1**, which provided the  $\alpha$ -acetoxy ester product **4.2** (eq. 2, Scheme 4.1).<sup>31</sup> Measured optical rotation for **4.2** revealed the migration indeed proceeded with retention of configuration. Now it should be noted that literature precedent suggests that the Baeyer–Villiger oxidation of 1,3-dicarbonyl compounds is a well-established method for the  $\alpha$ -oxidation of esters<sup>25-31</sup> and ketones.<sup>33-36</sup> However, only a single report from Gotor described an asymmetric process that involved the Baeyer–Villiger monooxygenase-catalyzed kinetic resolution of  $\alpha$ -substituted  $\beta$ -ketoesters. This process resulted in the formation of an enantiopure secondary ester **4.3** (Scheme 4.2).<sup>37</sup> The desymmetrization depicted in scheme 4.2 reaction stems from the



**Scheme 4.2**

available enolizable  $\alpha$ -center, and enantioenriched  $\alpha$ -acetoxyesters are likely obtained via  $\alpha$ -oxidation followed by rearrangement.<sup>35,38,39</sup> In contrast, with the Cristau system (eq. 2, Scheme 4.1) or with  $\alpha,\alpha$ -disubstituted non-enolizable 1,3-diketones this mode of reactivity is not available for obtaining the  $\alpha$ -oxidized carbonyl products. In such cases, nucleophilic addition to the carbonyl moiety is required in order for the Baeyer–Villiger rearrangement to take place.

With respect to the enantioselective  $\alpha$ -oxidation of ketones, current literature protocols typically involve the addition of organometallic compounds to  $\alpha$ -diketones (eq. 1, Scheme 4.3) as well as oxidation of preformed enolate intermediates (eq. 2, Scheme 4.3). The addition of organometallic compounds to  $\alpha$ -diketones can be challenging given the requirement for regioselective addition of the reductant. These methods also typically require stoichiometric



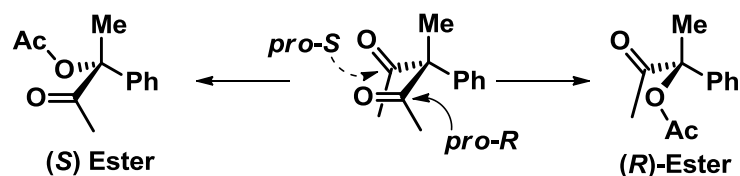
**Scheme 4.3**

amounts of preformed organometallic reagents. In addition, the oxidation of enolates can be challenging due to the requirement for the formation of a single enolate isomer in order to obtain enantioenriched products. Moreover, Rubottom-type oxidations require the prefunctionalization and resolution of a preformed enolate followed by oxidation in order to obtain enantiopure  $\alpha$ -hydroxy ketones. As a result of these synthetic challenges, it would be feasible to obtain enantioenriched  $\alpha$ -acetoxy ketones from a Baeyer–Villiger oxidation of non-enolizable 1,3-diketones (Scheme 4.4). Acetoacetone substrates are easily accessible and have



**Scheme 4.4**

been employed as starting materials in many synthetic protocols. Furthermore, the  $\alpha$ -hydroxy ketone products obtained via asymmetric B–V oxidation of 1,3-diketones would also be useful starting materials for synthetic chemists.<sup>40-45</sup> It should be noted that with traditional  $\alpha$ -oxidation of ketones, two requirements must be met in order to obtain enantiomeric excess: (1) only a single enolate isomer must be reactive, (2) only a single face of the reactive enolate isomer can be oxidized. However, with respect to the 1,3-diketones, what determines the enantioenrichment upon desymmetrization of the acetoacetone moiety is the regioselectivity of the carbonyl addition (Scheme 4.5). This will be important in the following section as the recent advancements toward the development of the asymmetric Baeyer–Villiger oxidation of  $\alpha$ -quaternary 1,3-diketones will be disclosed.



**Scheme 4.5**

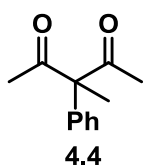
**CIV.2:** *Recent developments toward the asymmetric Baeyer–Villiger oxidation of 1,3-diketones*

Having described the benefits for developing the desymmetrization of  $\alpha$ -quaternary 1,3-diketones via B–V rearrangement, and given that the only report for asymmetric Baeyer–Villiger oxidation of 1,3-dicarbonyl compound is catalyzed by a Baeyer–Villiger monooxygenase,<sup>37</sup> the recent developments toward the chiral binaphthol phosphoric acid catalyzed Baeyer–Villiger oxidation of  $\alpha$ -quaternary 1,3-diketones is described. Based on a report from Cossy suggesting that treatment of 1,3-diketones with *m*-CPBA lead to overoxidation,<sup>46</sup> initial studies began with



determining conditions for the B–V oxidation reaction (Table 4.1). Preliminary results employing conditions analogous to those reported by Cristau resulted in exclusive formation of the overoxidized compound **4.6**.<sup>31</sup> The observed product was in line with studies reported by Cossy, in which overoxidation of  $\alpha$ -quaternary 1,3-diketones was observed when superstoichiometric amounts of *m*-CPBA were used (entry 1, Table 4.1).<sup>46</sup> A reduction in the temperature, equivalents of oxidant used, and Brönsted acid loading resulted in exclusive formation of the mono-oxidized  $\alpha$ -acetoxy ketone **4.5** (entry 2, Table 4.1). Moreover, reducing the amount of oxidant used to 1 equivalent also provided the mono-oxidized product, albeit at a lower conversion (entry 3, Table 4.1). Changing the solvent to benzene under the same reaction conditions resulted in the mono-oxidized product **4.6**, and the overoxidation product was not observed (entry 4, Table 4.1). As shown in Table 4.1, the *m*-CPBA indeed facilitates the Baeyer–Villiger oxidation in the absence of the Brönsted acid, however at a much slower rate.

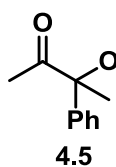
**Table 4.1: Brönsted acid and solvent screen for the Baeyer–Villiger oxidation of 1,3-diketones**



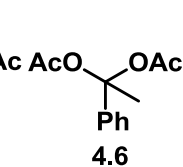
**4.4**

X mol% ( $\pm$ )-Brönsted Acid  
(Y eq. *m*-CPBA) 0.2 M

Solvent, temp °C, 24h



**4.5**



**4.6**


entry	X	Acid	Y	solvent	h	Temp	conv. %	4.5	4.6
(1)	200	TFA	5	DCM	13	45	>95	<5	>95
(2)	100	TFA	2	DCM	16	25	>95	>95	<5
(3)	100	TFA	1	DCM	15	25	60	>95	<5
(4)	200	TFA	5	Benzene	24	80	>95	>95	<5
(5)	20	BPA	1	DCM	24	25	50	>95	<5
(6)	20	BPA	2	DCM	24	35	85	>95	<5
(8)	-	None	2	DCM	24	35	55	>95	<5

<sup>a</sup> BPA-( $\pm$ )-binaphthyl phosphoric acid

At this point, it has been established that the  $\alpha$ -phenyl,  $\alpha$ -methyl substrate is competent for Baeyer–Villiger oxidation and rearrangement in presence of trifluoroacetic acid and *m*-CPBA. However, establishing a method for desymmetrization of 1,3-diketones would be difficult if not impossible under the current reaction conditions. Inspired by work published from the Ding lab in which chiral binaphthol phosphoric acids were employed to catalyze an asymmetric Baeyer–Villiger oxidation, a racemic binaphthol phosphoric acid was examined for reactivity (entry 5 and 6, Table 4.1).<sup>15,17</sup> The Binaphthol phosphoric acid proved to be competent for catalyzing the Baeyer–Villiger oxidation. Control studies also revealed that the Baeyer–Villiger oxidation takes place in the absence of added Brønsted acid, this reaction is likely catalyzed by some *meta*-chlorobenzoic acid contaminate. However, despite finding a Brønsted acid that would allow for the introduction of a chiral environment in addition to catalyzing the Baeyer–Villiger oxidation, the background oxidation was discouraging and alternative conditions for oxidation were sought.

There are a number of literature reports for the carbonate and phosphate mediated Baeyer–Villiger oxidation of 1,3-dicarbonyl moieties.<sup>25-30</sup> In addition basic amine reagents have also been employed for attenuation of the reactivity of *m*-CPBA.<sup>47</sup> Based on this precedent, a number of base mediated Baeyer–Villiger oxidations were attempted (Table 4.2). The use of DABCO was based on a report from Jorgensen in which a cinchona alkaloid was used as a proton shuttle in a catalytic oxidation reaction utilizing *m*-CPBA (entry 1, Table 4.2).<sup>47</sup> Even though superstoichiometric amounts of DABCO were utilized, the oxidized product **4.5** was never observed (entries 1 and 2, Table 4.2). In addition, attempted oxidations employing sodium carbonate as reported by Molander,<sup>27</sup> resulted in minimal conversion of **4.4** to **4.6**, even

**Table 4.2: Base-mediated Baeyer–Villiger oxidation of 1,3-Diketones**

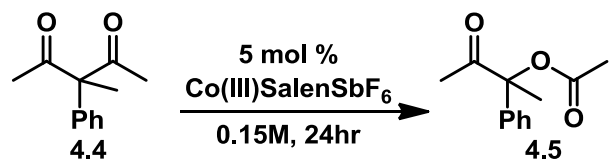
			
entry <sup>a</sup>	base	eq.	Conv. %
(1)	DBACO	1.0	<5
(2)	DBACO	2.0	<5
(3)	NaHCO <sub>3</sub>	1.5	<15

<sup>a</sup> all reactions run for 24hr prior to heating

after an extended reaction period (entry 3, Table 4.2). These results suggest that the nucleophilicity of the *m*-CPBA is not as important as the activation of the carbonyl. In keeping with the goal to develop a catalytic asymmetric Baeyer–Villiger oxidation of 1,3 diketones a series of Lewis acid and transition metal complexes were examined for reactivity.

The realm of metal–catalyzed asymmetric Baeyer–Villiger reactions has been pioneered by both Bolm<sup>3,8,10-12,14,48-54</sup> and Strukul,<sup>4,6,9,55-60</sup> however contributions from others have advanced the field as well.<sup>16, 61-64</sup> A report from Katsuki detailed the use of cationic cobalt-salen complexes<sup>65</sup> along with urea hydroperoxide (UHP) for the enantioselective Baeyer–Villiger oxidation of cyclobutanones.<sup>64</sup> Based on this report, a series of reactions utilizing the cationic cobalt-salen catalyst along with various oxidants and in different solvents is detailed in Table 4.3. It should be noted that Katsuki reported that *m*-CPBA was not a reactive oxidant with the Co-salen system; in addition the Baeyer–Villiger reaction involving *m*-CPBA in DCM proceeds in the absence of catalyst. Preliminary experiments included the use of urea hydroperoxide (UHP), *tert*-butyl hydroperoxide (TBHP), and hydrogen peroxide (HOOH) in both deuterated-DCM and

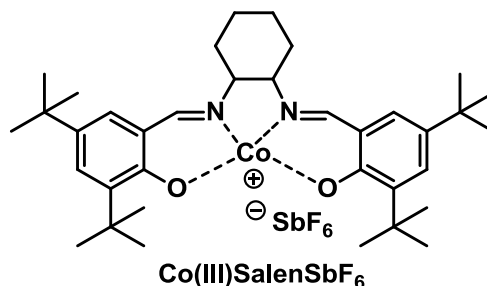
**Table 4.3: Cation Co(III)Salen SbF<sub>6</sub> for the Baeyer–Villiger oxidation of 1,3-Diketones**



entry <sup>a</sup>	Oxidant	solvent	Temp	Conversion
(1)	UHP <sup>b</sup>	d-DCM	35	<5
(2)	TBHP	d-DCM	35	<5
(3)	HOOH	d-DCM	35	<5
(4)	UHP	d-MeCN	78	<5
(5)	TBHP	d-MeCN	78	<5
(6)	HOOH	d-MeCN	78	<5
(7)	UHP	IPA	78	<5
(8)	TBHP	IPA	78	<5
(9)	HOOH	IPA	78	<5

<sup>a</sup> all reactions run for 24hr prior to heating

<sup>b</sup> UHP-Urea Hydroperoxide <sup>c</sup> TBHP-*tert*-butylhydroperoxide



MeCN as well as isopropyl alcohol (IPA). Despite performing all of these reactions at elevated temperatures and for extended periods of time, conversion from **4.4** to **4.5** was never observed (entries 1-8, Table 4.3). In addition to the cationic Co-Salen complexes, dimethyl aluminum chloride,<sup>53,54</sup> methyl magnesium bromide,<sup>52</sup> and zirconium (IV) isopropoxide<sup>51</sup> derived binaphthol catalyst as reported by Bolm were screened for reactivity (Table 4.4). As listed in Table 4.4, various combinations of oxidants and Lewis acid binaphthyl complexes did not show any activation of the 1,3-diketone **4.4** toward the Baeyer-Villiger rearrangement. In addition, use of 4 equivalents of *m*-CPBA in toluene with the zirconium binaphthol complex failed to result in any consumption of the starting material. This observation suggested that the isopropoxide is neutralizing the residual *meta*-chlorobenzoic acid contaminate in the *m*-CPBA reagent. As will be shown later in this section, the *m*-CPBA converts **4.4** to **4.5** in toluene in the absence of any catalyst. In addition to the above conditions, earlier reports from Bolm and Lopp detailed the

**Table 4.4: Screen for potential Binol Lewis acid mediated Baeyer–Villiger oxidation**

entry	X	Metal	Y	Oxidant	solvent	Temp	Conv. %
(1)	50	AlCl <sub>3</sub>	1	HOOH	Tol	110	<5
(2)	50	AlCl <sub>3</sub>	1	TBHP	Tol	110	<5
(3)	50	MgCl <sub>2</sub>	1	HOOH	DCM	60	<5
(4)	50	MgCl <sub>2</sub>	1	TBHP	DCM	60	<5
(5)	100	Zr(OiPr) <sub>4</sub>	4	TBHP	Tol	25	<5
(6)	100	Zr(OiPr) <sub>4</sub>	4	mCPBA	Tol	25	<5

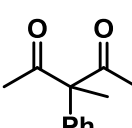
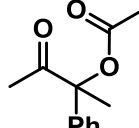
use of copper (II) acetate<sup>48</sup> and titanium (IV) isopropoxide<sup>66</sup> for the Baeyer–Villiger oxidation of ketones (Table 4.5). However despite the large number of reports for the metal-catalyzed Baeyer–Villiger reaction, none of the conditions above proved to be competent for the oxidation of  $\alpha$ -quaternary 1,3-diketones. Based on these results, and on previous experiments showing that racemic binaphthol phosphoric acid catalyzed the Baeyer–Villiger oxidation, the focus then became optimizing the binaphthol phosphoric acid catalyzed method.

**Table 4.5: Screen for potential Lewis acid mediated Baeyer–Villiger oxidation**

entry	Metal	Y	Oxidant	solvent	Conv. %
(1)	Cu(OAc) <sub>2</sub>	3	mCPBA	Benzene	<5
(2)	Cu(OAc) <sub>2</sub>	3	TBHP	Benzene	<5
(3)	Ti(OiPr) <sub>4</sub>	4	HOOH	Tol	<5
(4)	Ti(OiPr) <sub>4</sub>	4	mCPBA	Tol	<5

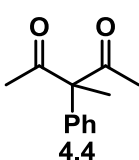
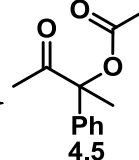
As shown in Table 4.1, it is now known that racemic binaphthol phosphoric acid catalyzes the Baeyer–Villiger oxidation of  $\alpha$ -quaternary 1,3-diketones. In addition, control studies also revealed that 1,3 diketones undergo the Baeyer–Villiger reaction when treated with *m*-CPBA in DCM solvent without any use of Brönsted acid. For this reason, preliminary studies were focused on determining the rate of the uncatalyzed reaction in order to ascertain if the reaction was even being catalyzed (Table 4.6). Analysis of the experimental results obtained from Table 4.6 suggested first and foremost that the *m*-CPBA reagent was most reactive in DCM. Studies comparing the rate of Baeyer–Villiger oxidation in DCM vs deuterated DCM revealed that much more of diketone **4.4** was converted to **4.5** in DCM (entry 1 and 2). Similarly, in the absence of Brönsted more conversion to the B–V product was observed in DCM (entry 3 and 4, Table 4.6). When comparing entry 2 to entry 4, it is clear that the reaction containing the binaphthol phosphoric acid converted **4.4** to **4.5** at a much faster rate suggesting the reaction is being catalyzed. This result was confirmed by entries 5-8, specifically comparing entry 5 and entry 8 suggested that the catalyzed reaction (entry 5) after 3 hours provided the same amount of conversion as the non-catalyzed (entry 8) reaction did after 44 hours. Entries 9-12 revealed that the Baeyer–Villiger reaction at 85 °C in dichloroethane (DCE) provided the same amount of conversion to **4.5** as the reaction performed at 35 °C in DCM (entries 5-8, Table 4.6). Last, entries 13-16 show that the similar rates of oxidation are observed when using toluene as solvent. This result will be important later in this section as the highest enantioenrichment for the asymmetric Baeyer–Villiger oxidation will be observed employing toluene as solvent. At this point, before the asymmetric variant was attempted a brief screen of other potential solvents was performed (Table 4.7). Literature precedent suggests that acti-

**Table 4.6: Measuring the background reaction with *m*-CPBA as oxidant**

<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center; margin-right: 20px;"> <b>4.4</b>  <math>\xrightarrow[\text{Solvent, temp } ^\circ\text{C, time (h)}]{\text{X mol\% } (\pm)\text{-Binaphthol Phosphoric Acid (2 eq. mCPBA) 0.2 M}}</math> </div> <div style="display: flex; gap: 20px;"> <div style="text-align: center;">   <b>4.4</b> </div> <div style="text-align: center;">   <b>4.5</b> </div> </div> </div>					
entry	X	time	temp $^\circ\text{C}$	solvent	4.4 : 4.5
(1)	50	42	25	<i>d</i> -DCM	63 : 37
(2)	50	44	25	DCM	26 : 74
(3)	None	42	25	<i>d</i> -DCM	94 : 6
(4)	None	44	25	DCM	64 : 36
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(5)	50	3	35	DCM	63 : 37
(6)	None	3	35	DCM	87 : 13
(7)	50	44	35	DCM	11 : 89
(8)	None	44	35	DCM	64 : 36
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(9)	50	3	85	DCE	50 : 50
(10)	None	3	85	DCE	90 : 10
(11)	50	44	85	DCE	14 : 86
(12)	None	44	85	DCE	75 : 25
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(13)	50	20	25	DCM	30 : 70
(14)	50	22	25	Tol	35 : 65
(15)	None	20	25	DCM	50 : 50
(16)	None	22	25	Tol	78 : 22
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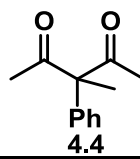
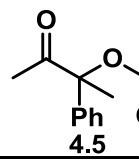
vation of ketones with binaphthol phosphoric acids proceeded well in the solvents screened in Table 4.7.<sup>15,17,67</sup> There was no real reactivity trend observed for the solvents screened, in addition toluene, benzene, and ethyl acetate seem to promote the Baeyer–Villiger oxidation more efficiently than tetrahydrofuran and 1,4-dioxane. In addition to other solvents, a screen of alternative oxidants for the binaphthol phosphoric acid catalyzed B–V reaction was performed (Table 4.8). As detailed above, 2 equivalents of *m*-CPBA in DCM in the presence of 20 mol % of the phosphoric acid resulted in 85% conversion of **4.4** to **4.5** and **4.5** was isolated in 60% yield (entry 2, Table 4.8). It should be noted, that none of the other oxidants screened provided the

**Table 4.7: Screen of solvents for the Baeyer–Villiger oxidation of 1,3-diketones**

<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;">  <p>4.4</p> </div> <div style="text-align: center; margin: 0 20px;"> <p>50 mol% (±)-Binaphthol Phosphoric Acid (2 eq. MCPBA.) 0.2 M</p> <p>Solvent, rt, 24h</p> </div> <div style="text-align: center;">  <p>4.5</p> </div> </div>		
entry	solvent	Conv. %
(1)	<i>d</i> -toluene	55
(2)	<i>d</i> -benzene	70
(3)	tetrahydrofuran	15
(4)	1,4-dioxane	25
(5)	ethyl acetate	70

$\alpha$ -acetoxy ketone **4.5**, however, the urea hydroperoxide in various solvents at elevated temperatures consistently consumed the diketone **4.4** but the product was never elucidated

**Table 4.8: Screen of oxidants for the Baeyer–Villiger oxidation of 1,3-diketones**

<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;">  <p>4.4</p> </div> <div style="text-align: center; margin: 0 20px;"> <p>X mol% (±)-Binaphthol Phosphoric Acid (Y eq. Oxidant) 0.2 M</p> <p>Solvent, temp °C, 24h</p> </div> <div style="text-align: center;">  <p>4.5</p> </div> </div>						
entry	X	Oxidant	Y	solvent	Temp	Conv. %
(1)	20	mCPBA	1	DCM	25	50
(2)	20	mCPBA	2	DCM	35	85
(3)	None	mCPBA	2	DCM	35	55
(4)	20	HOOH	2	DCM	80	>95 <sup>c</sup>
(5)	20	TBHP <sup>a</sup>	2	DCM	35	<5
(6)	20	TBHP	2	DCM	90	<5
(7)	20	UHP <sup>b</sup>	1	DCM	25	45
(8)	20	UHP	1	DCM	80	>95
(9)	None	UHP	2	DCM	80	<5
(10)	20	UHP	2	DCM	80	<5
(11)	20	UHP	2	MeCN	80	>95 <sup>c</sup>
(12)	20	UHP	2	Hexanes	80	>95 <sup>c</sup>

<sup>a</sup> TBHP-*tert*-butylhydroperoxide <sup>b</sup> UHP-Urea Hydroperoxide

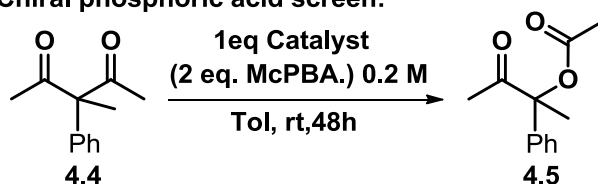
<sup>c</sup> Not the BV product



(entries 4,8, 11, and 12, Table 4.8). With defined reaction conditions competent for promoting the B–V oxidation of  $\alpha$ -quaternary 1,3-diketones, various chiral phosphoric acids were screened in order to obtain enantioenriched  $\alpha$ -acetoxy ketone **4.5** (Table 4.9). Literature precedent suggested that the (*R*)-3,3'-(9-anthracenyl) binaphthol phosphoric acid was an effective catalyst for asymmetric additions of peroxides to carbonyl compounds.<sup>15,17,67,68</sup> However, the same phosphoric acid derivative was not reactive for the Baeyer–Villiger oxidation of 1,3-diketones in toluene or DCM. It should be noted that initial experiments involving (*R*)-3,3'-(2,4,6-isopropyl Ph) binaphthol phosphoric acid were performed in DCM and resulted in minimal enantiomeric excess (7% ee, entry 2, Table 4.9). A change in solvent from DCM to toluene resulted in a rise in enantiomeric excess to 27% (entry 3, Table 4.9). Switching to the (*S*)-3,3'-(2,4,6-isopropyl Ph) binaphthol phosphoric acid provides **4.5** with 32% ee and

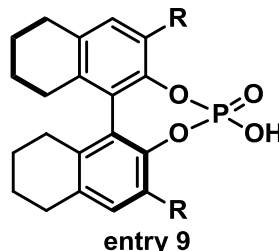
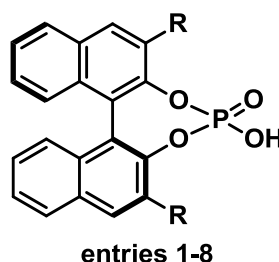
**Table 4.9: Catalyst screen for asymmetric Baeyer–Villiger oxidation**

Chiral phosphoric acid screen:



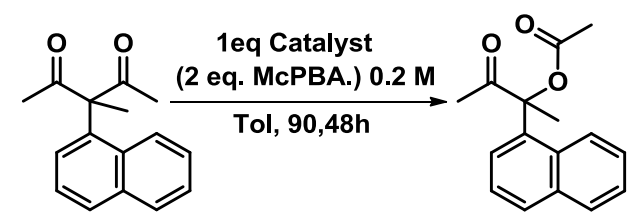
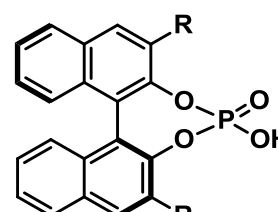
entry	( $\pm$ ) R	conv. %	ee%
(1)	( <i>R</i> ) 9-anthracenyl	<5	-
(2) <sup>a</sup>	( <i>R</i> ) 2,4,6- <i>i</i> propyl Ph	50	7
(3)	( <i>R</i> ) 2,4,6- <i>i</i> propyl Ph	50	27
(4) <sup>b</sup>	( <i>R</i> ) 2,4,6- <i>i</i> propyl Ph	50	34
(5)	( <i>S</i> ) 2,4,6- <i>i</i> propyl Ph	50	32
(6)	( <i>R</i> ) VAPOL	70	<5
(7)	( <i>R</i> ) SiPh <sub>3</sub>	50	7
(8)	( <i>R</i> ) 3,5-CF <sub>3</sub> Ph	50	3
(9)	( <i>R</i> ) 2,4,6- <i>i</i> propyl Ph	<5	27

<sup>a</sup> performed in DCM <sup>b</sup> 50 mol% catalyst performed at 0 °C



was corroborated by a distinct change in the major enantiomer observed on the HPLC chromatogram (entry 5, Table 4.9). Moreover, cooling the reaction to -15 °C resulted in a minor increase in enantiomeric excess to 32% (entry 4, Table 4.9). A recent report from Ding explained that switching from the binaphthol phosphoric acid to the hydrogenated binol phosphoric acid analog resulted in an increase in enantiomeric excess.<sup>15</sup> However an experiment employing the H8-binol-derived (H8-binol=5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol) phosphoric acid did not result in improved % ee (entry 9, Table 4.9). The remainder of the chiral binol and VAPOL derived phosphoric acids screened provided minimal to no enantioenrichment for the Baeyer–Villiger oxidation (entries 6-8, Table 4.9). Based on the analysis provided in Scheme 4.5, in order to try and improve the regioselectivity of the attack of the peroxide on the ketone moiety, an  $\alpha$ -naphthyl,  $\alpha$ -methyl 1,3-diketone<sup>69</sup> substrate was synthesized and subjected to the reaction conditions in Table 4.10. Initial experiments involved treatment of diketone **4.7** with the racemic binol phosphoric acid resulted in 30% consumption of the starting material. It should be noted that product **4.8** was never confirmed and the

**Table 4.10: Increasing the steric bulk in the  $\alpha$ -position**

			
entry	( $\pm$ )R	Conversion	
(1) <sup>a</sup>	( $\pm$ )H	30%	
(2)	( <i>R</i> ) 2,4,6- <i>i</i> propyl Ph	<5	
(3)	( <i>S</i> ) 2,4,6- <i>i</i> propyl Ph	<5	
(4)	( <i>R</i> ) 9-anthracenyl	<5	

<sup>a</sup> all reactions run for 24hr prior to heating

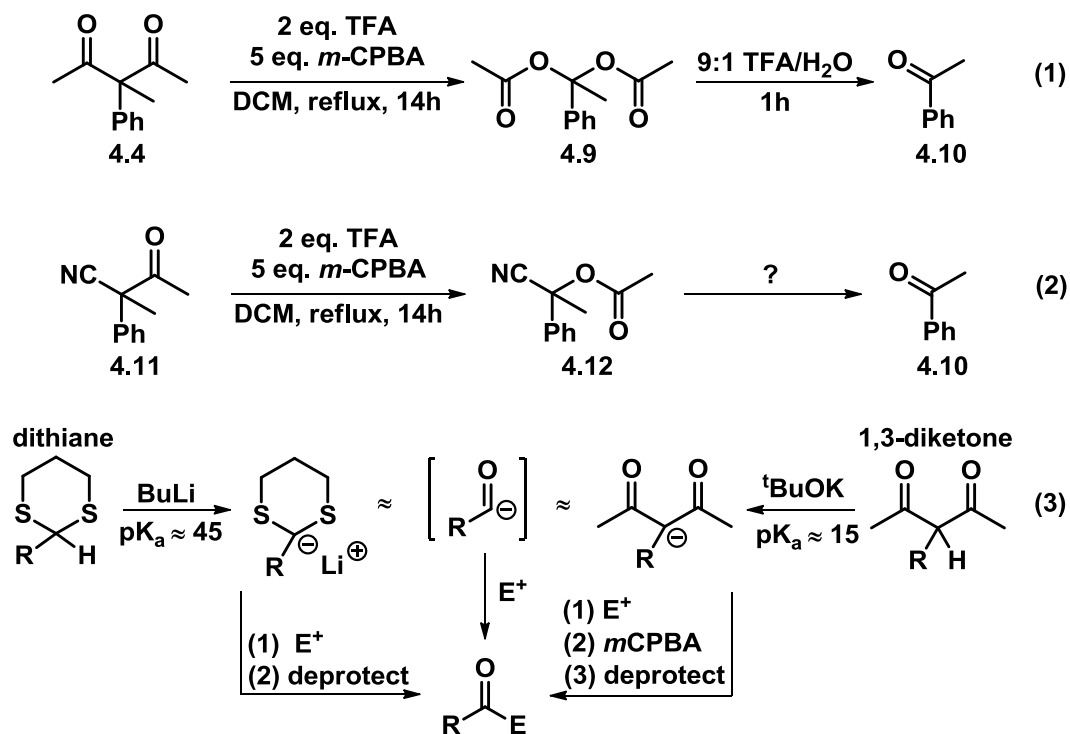
conversion is based only on consumption of the starting material **4.7**. Switching to the chiral (*R*)-3,3'-(2,4,6-isopropyl Ph) binaphthol phosphoric acid did not result in any consumption of the starting material diketone **4.7** (entry 2, Table 4.10). Currently, it is not clearly understood why the  $\alpha$ -naphthyl diketone was not as reactive as the phenyl substituted surrogate.

To this end, it has now been determined that treatment of  $\alpha$ -methyl,  $\alpha$ -phenyl 1,3-diketones with a binaphthol phosphoric acid as well as *m*-CPBA in DCM provided the Baeyer–Villiger rearrangement product  $\alpha$ -acetoxy ketone **4.5**. In addition, exposure of the  $\alpha$ -quaternary 1,3-diketone to a chiral binaphthol phosphoric acid along with *m*-CPBA resulted in minimal enantioenrichment. A change in solvent from DCM to toluene served to improve the observed enantiomeric excess. Now where the above reaction serves to provide a method for the  $\alpha$ -oxidation of ketones via the Baeyer–Villiger mono-oxidation protocol, overoxidation to the geminal acetoxy alkane **4.6** (Table 4.1) suggests that 1,3-diketones could be utilized as acyl anion equivalents. The following section details the preliminary studies involved with investigating 1,3-diketones as acyl anion equivalents.

#### **CIV.3:** *Baeyer–Villiger oxidation of 1,3-diketones: A dithiane Surrogate*

The Corey-Seebach reaction showcases the utility of 1,3-dithianes as acyl anion equivalents.<sup>70,71</sup> General synthetic accessibility and broad reactivity have made 1,3-dithianes ubiquitous in organic synthesis.<sup>72-74</sup> Despite the widespread applicability of the 1,3-dithiane, lithiated bases are required for generation of the of the acyl anion equivalent. In addition a stoichiometric amount of mercuric chloride is required for the removal of the dithiane moiety to afford the carbonyl product. As observed in Table 4.1, overoxidation of the 1,3-diketone **4.4**

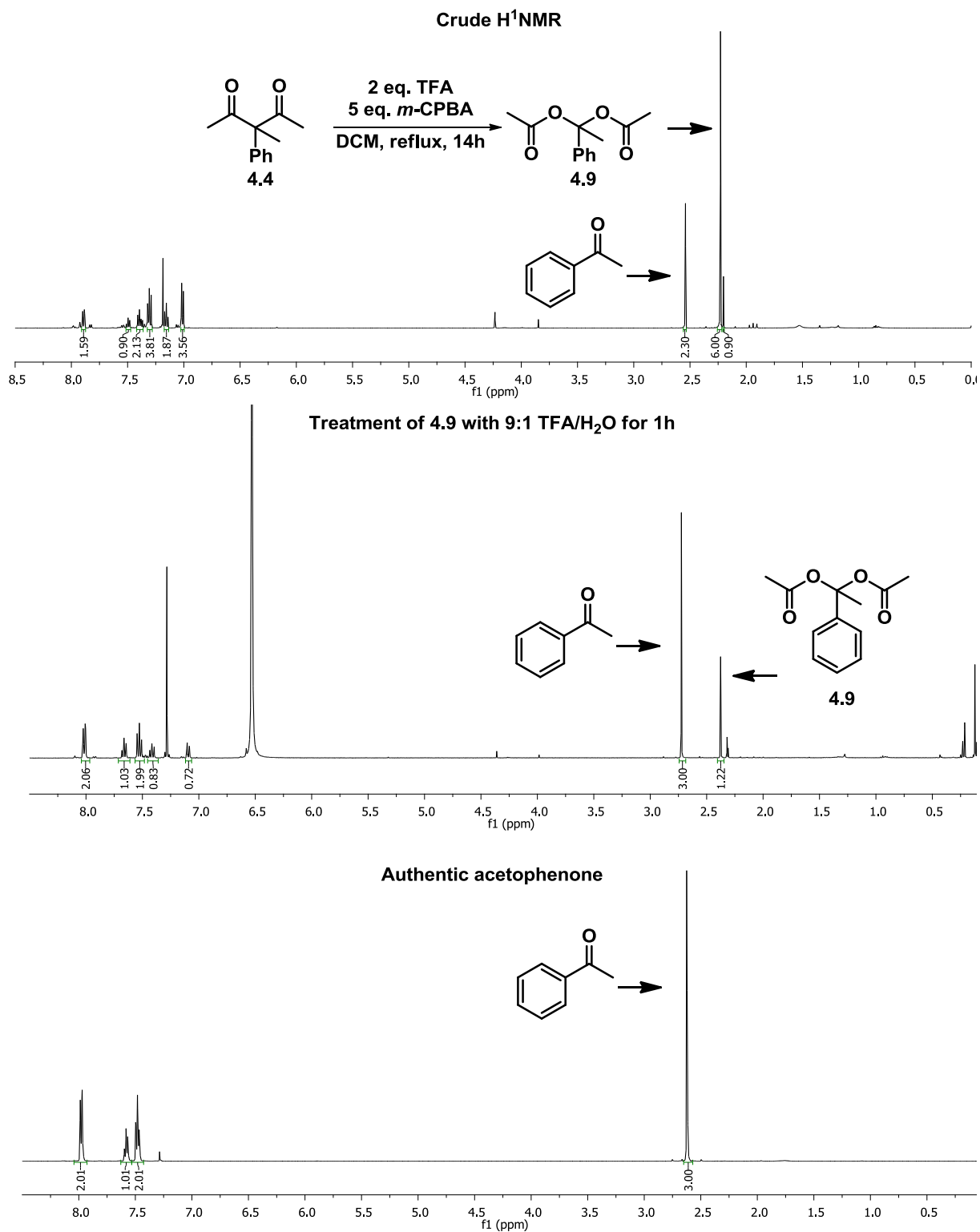
leads to the formation of geminal acetoxy alkanes **4.9** (eq. 1, Scheme 4.6).<sup>75</sup> The acetoxy diester **4.9** was then deprotected to reveal the acetophenone product **4.10** (eq. 1, Scheme 4.6).



**Scheme 4.6:**

This series of reactions suggest that it would be feasible to employ 1,3-diketones as an acyl anion equivalents. In addition, it has also been observed that the nitrile ketones **4.11** can undergo the Baeyer–Villiger oxidation under similar conditions complementing current literature precedent employing cyanohydrins as acyl anion equivalents (eq. 2, Scheme 4.6). Subsequent hydrolysis of the acyl protecting group would also deliver the acetophenone product. The advantage of using the 1,3-diketones as acyl anion equivalents is manifested in the acidity of the reactant (eq. 3, Scheme 4.6).<sup>76,77</sup> 1,3-diketone moieties can be activated toward alkylation under mildly basic conditions. In addition, acetoacetone substrates can

undergo  $\alpha$ -arylation<sup>78</sup> a reaction that has not been reported for 1,3-dithianes. As shown in equation 1 (Scheme 4.6), treatment of  $\alpha$ -phenyl,  $\alpha$ -methyl 1,3-diketones with excess trifluoroacetic acid (TFA) and superstoichiometric amounts of *m*-CPBA resulted in formation of the geminal acetoxy alkane **4.9**. As shown in Figure 4.1, crude <sup>1</sup>H NMR reveals that some of the acetophenone product is already forming. Subjecting the crude reaction mixture to aqueous TFA for 1 h shows a conversion of **4.9** to the acetophenone product (middle spectra, Figure 4.1). A comparison of the product peaks with the authentic acetophenone product (lower spectra, figure 4.1) confirms the transformation of the 1,3-diketone **4.4** into acetophenone **4.10**. This result suggests that the Baeyer–Villiger oxidation of the 1,3-dicarbonyl moieties is a complementary method to known procedures<sup>72-74,79-83</sup> for the functionalization of acyl anion equivalents (eq. 3, Scheme 4.6).



**Figure 4.1**

To conclude, it has been determined that Baeyer–Villiger oxidation of  $\alpha$ -quaternary 1,3-diketones in the presence of excess *m*-CPBA leads to the formation of geminal acetoxy alkanes. These acetoxy alkanes can then be deprotected via treatment with aqueous TFA and converted to their respective ketones. Upon determination of the scope of the reaction, this protocol could be a viable complement to known methods for generating and functionalizing acyl anion equivalents.

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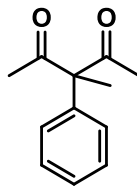
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## Appendix C:

### General information:

All reactions not performed at reflux were run in 1 dram glass scintillation vials. All reactions performed under refluxing conditions were run in 5 mL Biotage microwave vials with sealable septa-caps. THF was dried over sodium in the presence of benzophenone indicator. Toluene (Tol) was dried over activated alumina and distilled over sodium. Other commercially available reagents, solvents, and catalysts were used without additional purification unless otherwise stated.  $\alpha$ -Phenyl,  $\alpha$ -methyl acetoacetone was prepared according to a literature procedure.<sup>78</sup>  $\alpha$ -1-Naphthyl,  $\alpha$ -methyl acetoacetone was prepared according to a literature procedure.<sup>69</sup> All commercially available 3,3'-substituted binaphthol phosphoric acids were purchased from Aldrich and used without additional purification. All non-commercial 3,3'-substituted binaphthol phosphoric acids were prepared from 3,3'-substituted binaphthol according to a literature protocol.<sup>84</sup> All non-commercial 3,3'-substituted binaphthol ligands were prepared from commercially available chiral binaphthol compounds according to a literature procedure.<sup>85</sup>  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were obtained on Bruker Avance 500 DRX spectrometer and were referenced to residual protio solvent signals. Compound purification was effected by flash chromatography using 230 x 400 mesh, 60 Å porosity, silica obtained from Sorbent Technologies. Structural assignments were based on  $^1\text{H}$ ,  $^{13}\text{C}$ , DEPT-135, COSY, HSQC spectroscopies. Mass spectrometry was run using ESI techniques.

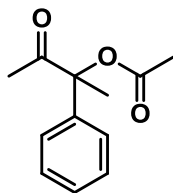
Characterization of 1,3-diketones:



**(4.4) 3-methyl-3-phenylpentane-2,4-dione<sup>78</sup>**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.38 – 7.30 (m, 1H, ArCH<sub>para</sub>), 7.28 (dd, *J* = 7.3, 1.3 Hz, 2H, ArCH<sub>meta</sub>), 7.22 – 7.13 (dd, *J* = 7.3, 1.3 Hz, 2H, ArCH<sub>ortho</sub>), 2.05 (s, 6H, RC(O)CH<sub>3</sub>), 1.71 (s, 3H, C<sub>quat</sub>.CH<sub>3</sub>).

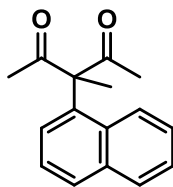
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 207.4, 138.0, 129.0, 128.0, 127.5, 70.1, 27.5, 19.6.



**(4.5) 3-oxo-2-phenylbutan-2-yl acetate**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.44 (m, 1H, ArCH<sub>para</sub>), 7.36 (dd, *J* = 7.3, 1.3 Hz, 2H, ArCH<sub>meta</sub>), 7.26 (dd, *J* = 7.3, 1.3 Hz, 2H, ArCH<sub>ortho</sub>), 2.28 (m, 3H, C<sub>quat</sub>.C(O)CH<sub>3</sub>), 1.96 (s, 3H, C<sub>quat</sub>.O<sub>2</sub>CCH<sub>3</sub>), 1.87 (s, 3H, C<sub>quat</sub>.CH<sub>3</sub>).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 203.7, 170.1, 138.5, 128.7, 128.2, 124.7, 87.5, 23.7, 22.9, 21.4.



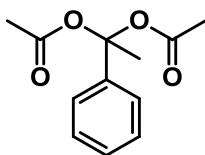
**(4.7) 3-methyl-3-(naphthalen-1-yl)pentane-2,4-dione**

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.92(m, 2H, ArCH), 7.64 (ddd,  $J = 8.5, 1.7, 0.8$  Hz, 1H, ArCH), 7.50

(m, 4H, ArCH), 2.22 (s, 6H,  $\text{RC(O)CH}_3$ ), 2.01 (s, 3H,  $\text{C}_{\text{quat.}}\text{CH}_3$ ).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  208.1, 136.0, 134.5, 131.5, 129.4, 129.3, 126.6, 125.8, 125.5,

125.3, 124.7, 70.1 ( $\text{C}_{\text{quat.}}$ ), 28.4 ( $\text{C(O)CH}_3$ ), 22.0 ( $\text{C}_{\text{quat.}}\text{CH}_3$ ).



**(4.9) 1-phenylethane-1,1-diyl diacetate<sup>75</sup>**

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.04 – 7.95 (m, 2H, ArCH), 7.44– 7.21 (m, 3H, ArCH), 2.64 (s, 3H,

$\text{C}_{\text{quat.}}\text{CH}_3$ ), 2.33 (s, 6H,  $\text{C}_{\text{quat.}}\text{O}_2\text{CCH}_3$ ).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  202.4 ( $\text{C}(\text{AcO})_2$ ), 159.2 ( $\text{O}_2\text{CCH}_3$ ), 134.2 (ArCH), 129.8 (ArCH),

128.7(ArCH), 120.1 (ArCH), 26.4 ( $\text{O}_2\text{CCH}_3$ ), 21.2 ( $\text{CH}_3$ ).



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