Palladium-catalyzed allylic alkylation via decarboxylative and

retro-Claisen C−C cleavage methods

By

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Abstract

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Presented herein is the development of new methods for Pd-catalyzed allylic alkylation with a central focus on reactions that generate molecular complexity rapidly with little waste byproduct. With this simply stated, yet challenging goal in mind, we present the decarboxylative allylation (**DcA**) of nitroalkanes and the conceptually novel deacylative allylation (**DaA**, or retro-Claisen) reaction. The main unifying themes of this research are (a) Pd-catalyzed allylation, (b) *in-situ* generation of nucleophilic and electrophilic coupling partners, and (c) "green" synthetic methods.

Regarding the former topic, **DcA** of nitroalkanes, we have developed methods for the synthesis of both tertiary and secondary allylated nitroalkanes using decarboxylation as a strategy. Carbon dioxide is the only byproduct and the organic building blocks prepared by this method are easily converted into nitrogen-containing heterocycles by functional group pairing.

The conceptually new deacylative allylation (**DaA**) reaction has been shown to be a useful method for allylation of various *in situ* generated nucleophiles. The reaction leads to similar products as can be accessed by the DcA method, but has many added benefits. For example, *both nucleophilic and electrophilic coupling partners are prepared in situ by a single retro-Claisen event.* Furthermore, DaA substrate synthesis begins from commercial/readily available active methylene nucleophiles (β-dicarbonyl compounds) and can utilize robust

methods previously developed for these compounds (e.g. Cu/Pd-catalzyed arylation, Tsuji-Trost allylation, etc.). The DaA reaction itself directly couples allylic alcohols, which is desirable due to their availability and reduced toxicity compared to other allylating agents. In terms of utility, DaA can rapidly construct 1,6-heptadienes (cycloisomerization substrates) via 1-pot 3-component coupling. We have also utilized the reaction to construct an important intermediate *en route* to the drug verapamil as well an asymmetric DaA reaction that allows formal access to (+)-hamigeran and other enantioenriched tetralone derivatives.

To my love, Laura

and my parents, James and Marilee

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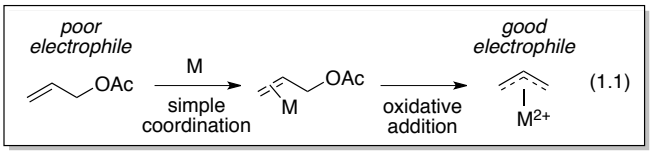
Chapter 1. Palladium-catalyzed decarboxylative allylation (DcA) of nitroalkanes[1]

1.1 Introduction to palladium-catalyzed decarboxylative allylation

The olefin (C=C) functional group is an extremely versatile functional group capable of undergoing a multitude of synthetic transformations. This diverse reactivity makes their incorporation in a given synthetic intermediate desirable. Furthermore, olefins are often considered "latent" functional groups as their reactivity requires specific conditions or catalysts for activation. Therefore alkenes are usually quite stable, a benefit when performing multi-step synthesis.

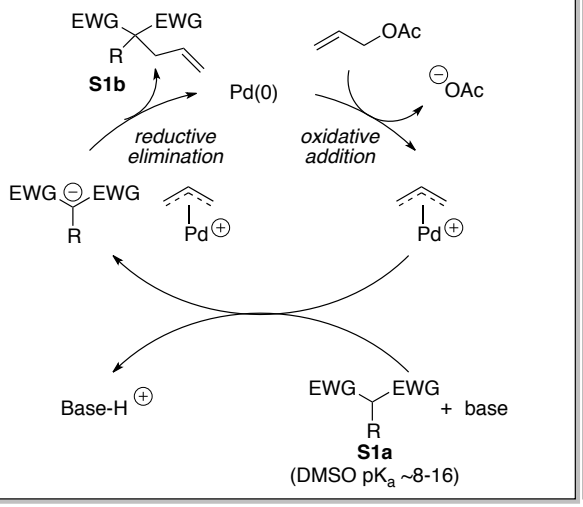


One important derivative of the olefin is the allyl motif (C=C−C). Allyl installation on a molecular scaffold can occur by both nucleophilic[2-8] (allyl anion) as well as electrophilic[9-13] (allyl cation) methods. Regarding the electrophilic sources of an allylic group, classically, allyl halide can be utilized. Though installation can be simple from the allylic halide, problems arise when considering toxicity, regioselectivity, as well as when asymmetric induction is desired. The contemporary solution to these problems is transition metal-catalyzed allylic alkylation from allylic acetates and carbonates, which are much less toxic reagents than comparable allylic halides.[9-11,13] Importantly, the reduced toxicity of alkyl acetates stems from their reduced reactivity: a metal is required to activate the allyl acetate to a metal-π-allyl complex, which are

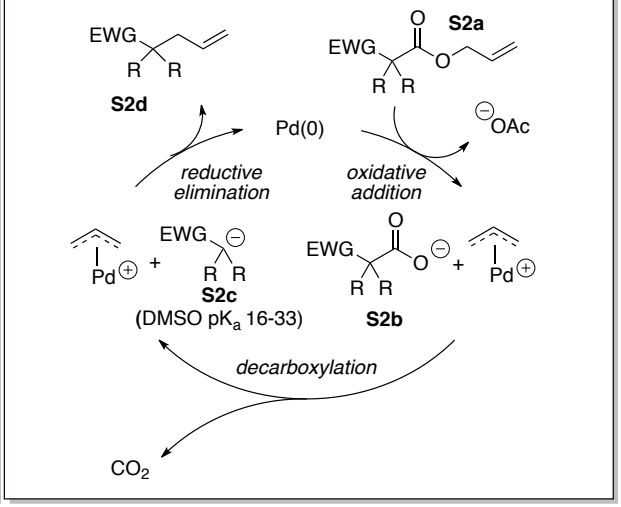
quite reactive (eq. 1). Furthermore, chiral ligands can be placed on the metal allowing for asymmetric allylic alkylation reactions.[9-11,13] Another attractive approach to access metal-π-allyl complexes is by metal-catalyzed C-H activation of simple olefins.[12]

Arguably, some of the most utilized methods for allylic alkylation are the metal-catalyzed Tsuji-Trost[9,13] and decarboxylative[10] allylation (DcA) methods. They have become mainstays in the organic chemist's toolbox for allylation of diverse nucleophiles. The Tsuji-Trost allylation, in general, is useful for the allylation of highly stabilized anions such as active methylene **S1a** as shown in Scheme 1. In this process, Pd(0), a common metal for allylic acetate activation, performs an oxidative addition on the allylic acetate transforming it into a Pd-π-allyl complex, which is a good electrophile. Concurrently, an external base deprotonates the active methylene compound **S1a**. These activated intermediates then undergo a coupling reaction to produce the desired product **S1b** as well as regenerate the Pd catalyst. This general type of reaction has been widely researched, utilized, and reviewed[9,14-16] and will not be covered in too much more detail.

Scheme 1. General mechanism of Tsuji-Trost allylation

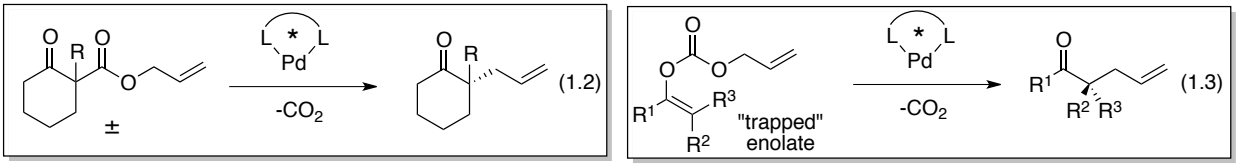


Scheme 2. General mechanism of decarboxylative allylation

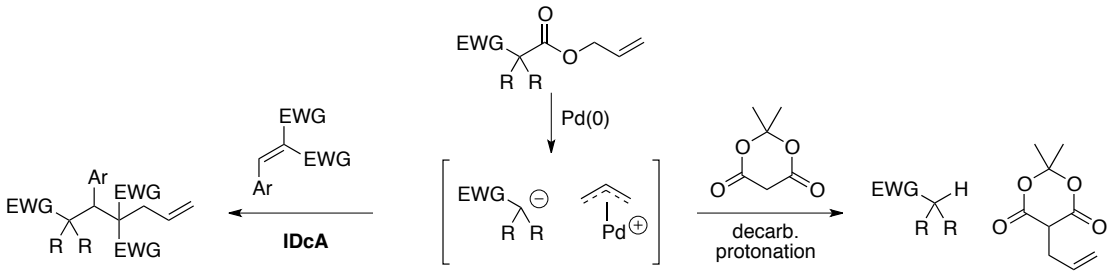


One challenge to the Tsuji-Trost allylation is its limitation to highly stabilized "active methylene" nucleophiles (DMSO pK_a values 8-16). Fortunately, it was discovered that Pd-

catalyzed decarboxylative allylation can occur on appropriately substituted allyl carboxylates to generate *less-stabilized nucleophiles* (DMSO pK_a values 16-32). Furthermore, the electrophilic coupling partner is also generated *in situ* (Scheme 2).[10] The general mechanism is as follows: an allyl α-EWG acetate (**S2a**) undergoes oxidative addition with Pd(0) generating a carboxylate **(S2b**) and a Pd-π-allyl complex. The carboxylate, substituted with an EWG, will decarboxylate to generate the active nucleophile **(S2c**). Though not necessarily a thermodynamically favorable process, decarboxylation is considered irreversible due to the loss of CO_2. Similar to the Tsuji-Trost reaction, the active nucleophile **S2c** and the Pd-π-allyl complex couple together producing the desired product **S2d** and regenerate the active catalyst. It is important to point out two unique implications of this approach to allylation: first, reactive intermediates are generated *in situ* and therefore *do not require an external base for nucleophile activation.* Secondly, this type of coupling only produces carbon dioxide as a byproduct. Thus, this approach to coupling is quite environmentally benign.



Scheme 3. Alternative reaction pathways of intermediates generated by Pd-cat. decarboxylation

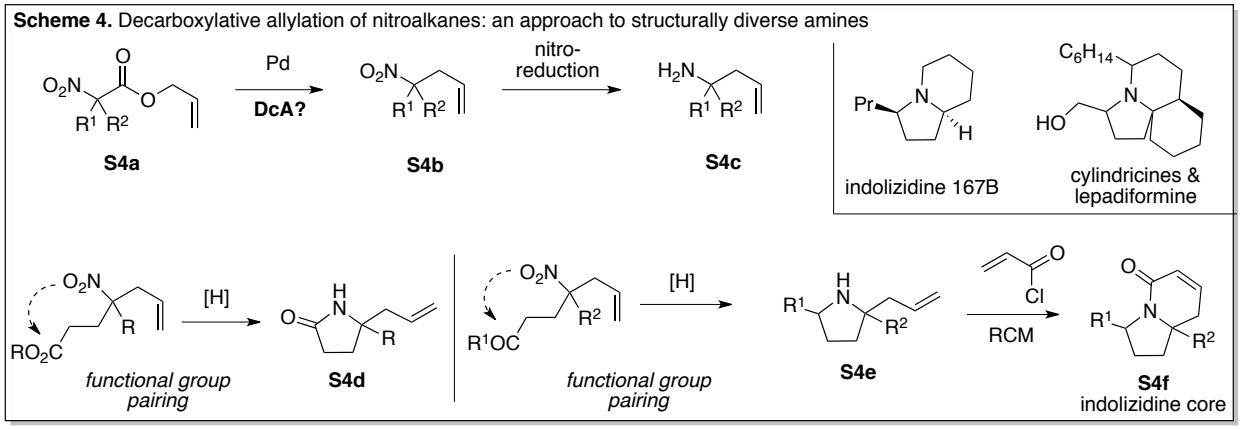


The DcA approach to coupling has yielded general allylation methods for various carbon-centered nucleophiles including ketone and ester enolates,[17,18] nitrile-stabilized anions,[19] imine anions,[20,21] and the nucleophile relevant to this dissertation, the nitronate anion.[1] Numerous

asymmetric methods have been developed for allylation of cyclic enolates (eq. 1.2) as well as "trapped" *E* or *Z* preformed acyclic enolates (eq. 1.3).[10] In addition to simple allylation, the coupling partners generated *in situ* can be funneled down alternative reaction pathways such as interceptive DcA (IDcA)[10] or protonation pathways[22] (Scheme 3). Importantly, this general approach to allylation has been extensively utilized in natural product synthesis.[10]

We have quite recently reviewed the aforementioned topics in detail.[10] In the forthcoming sections (1.2-4) my contribution to this field of research will be discussed. Specifically, the development, scope and utility of the DcA of nitroalkanes will be discussed.

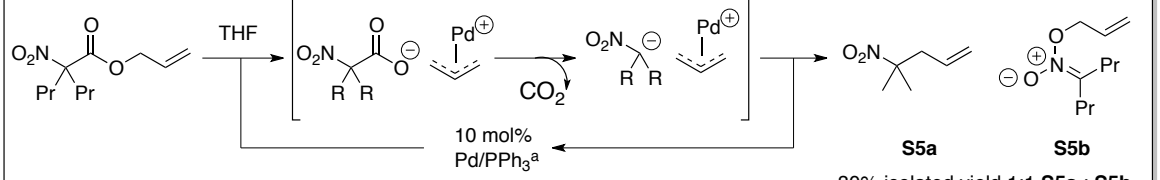
1.2 Rapid Decarboxylative allylation (DcA) of nitroalkanes



We envisioned that a DcA reaction of allyl nitroacetate would be useful as it would allow for facile nitrogen incorporation into a chemical building block (Scheme 4, **S4a** è **S4b**). Moreover, nitro groups are readily reduced, and thus, with various α-substitutions, diverse and useful homoallylic amino derivatives could quickly be prepared (**S4c-d**).[23] Aside from simple amines such as **S4c**, we envision rapid access to lactams **S4d** and cyclic amines **S4e** by functional group pairing with esters or ketones.[24] Potentially, by acrylation and ring-closing

metathesis of **S4e**, the indolizidine core could also rapidly be accessed. This is a very common core structure found in various natural products such as indolizidine 167B[25] and the cylindricine family[26] of natural products (Scheme 4, top right).

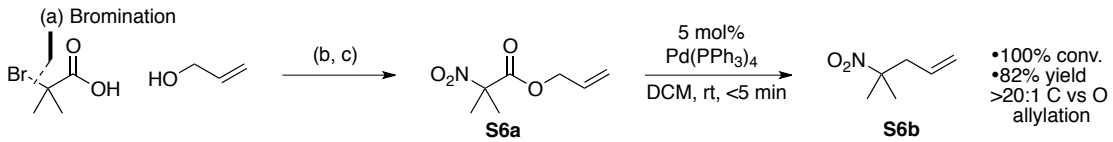
Scheme 5. Tsuji's single report of DcA of allyl nitroacetate



(a) conditions: catalyst prepared from 5 mol% Pd_2dba_3 and 10 mol% PPh_3, THF, 20 °C

Regarding the DcA reaction of allyl nitroacetates, a single result was published by Tsuji and coworkers in 1987 (Scheme 5).[27] Their conditions yielded a mixture of the desired C-allylated nitroalkane **S5a** as well as the regioisomeric O-allylated species **S5b** in 80% yield (1:1 C:O allylation) (Scheme 5). To begin improving upon Tsuji's initial result, we synthesized our own allyl nitroacetate **S6a** in 3-steps from isobutyric acid by α-bromination,[28] DCC-coupling with allyl alcohol, and Kornblum nitration[29] (Scheme 6). We were pleased to find that, by simply using the commercially available $Pd(PPh_3)_4$ in DCM, we could achieve synthesis of the desired product **S6b** in 82% yield with no detectable amount of the undesired O-allylated byproduct (Scheme 6). Interestingly, compared to other DcA reactions of allyl acetoacetates (Table 1), the reaction went unprecedentedly quick; complete conversion occurred in < 5 minutes and could visually be monitored by the effervescence of carbon dioxide.

Scheme 6. Synthesis of allyl nitroacetate **S6a** and DcA method improvement

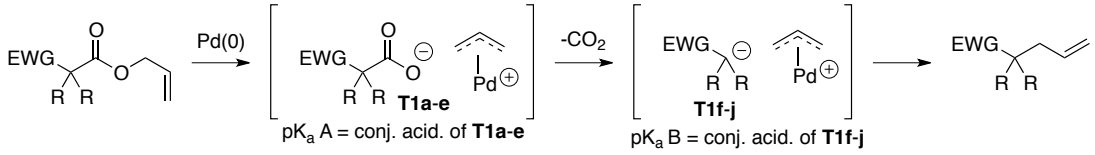


(a) From isobutyric acid, NBS, TFA, H_2SO_4 (b) DCC, DMAP (cat), allyl alcohol (c) $NaNO_2$, phloroglucinol, DMSO (Kornblum-reaction)

To help understand this dramatic rate enhancement, it is useful to compare the pK_a change and the rate of reaction between the previously studied DcA systems with the nitroacetate

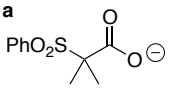
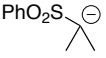
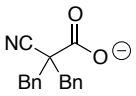
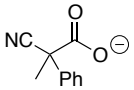
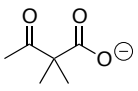
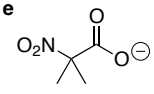
substrate. As shown in Table 1, the intermediate carboxylate (**T1a - T1e**) is always a lower pK_a than that of the corresponding decarboxylated anionic nucleophile (**T1f - T1j**). In terms of pK_a change, decarboxylation is thermodynamically uphill in energy. Interestingly, the rate of reaction and the harshness of reaction conditions required for DcA reaction to occur appears to trend with this change in pK_a such that the smaller the pK_a change, the gentler/more rapid the decarboxylative allylation will occur. For example, the decarboxylative allylation reaction requires more pressing conditions for sulfones and nitriles (**T1a-b**) than it does for ketones (**T1d**) or nitro-compounds (**T1e**), which, under the conditions we developed, is extremely rapid and chemically efficient (Scheme 6).

Table 1. Rate of reaction trends with change in pK_a



pK_a A = conj. acid. of **T1a-e**

pK_a B = conj. acid. of **T1f-j**

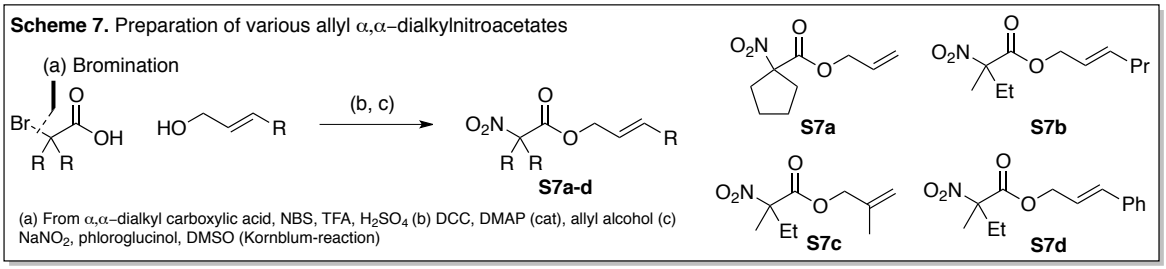
T1a-e	DMSO pK_a A	T1f-j	DMSO pK_a B	Cond. for DcA	Δ pK_a (B-A)
T1a 	~11[a]	**T1f** 	~30[b]	Pd/BINAP 95 °C, 12h	19
T1b 	~11[a]	**T1g** 	~31.3[c]	Pd/BINAP 95 °C, 12h	20.3
T1c 	~11[a]	**T1h** 	~21.8[d]	Pd/BINAP rt, 12h	10.8
T1d 	~11[a]	**T1i** 	~26.5[e]	$Pd(PPh_3)_4$ rt, 1h	15.5
T1e 	~10[a]	**T1j** 	~17.2[f]	$Pd(PPh_3)_4$ rt, <5mins	7.2

(a) the DMSO pK_a of acetic acid = 12.6 (b) based ethyl phenyl sulfone (c) based acetonitrile (d) based phenylacetonitrile (e) based on acetone (d) based on 2-nitropropane

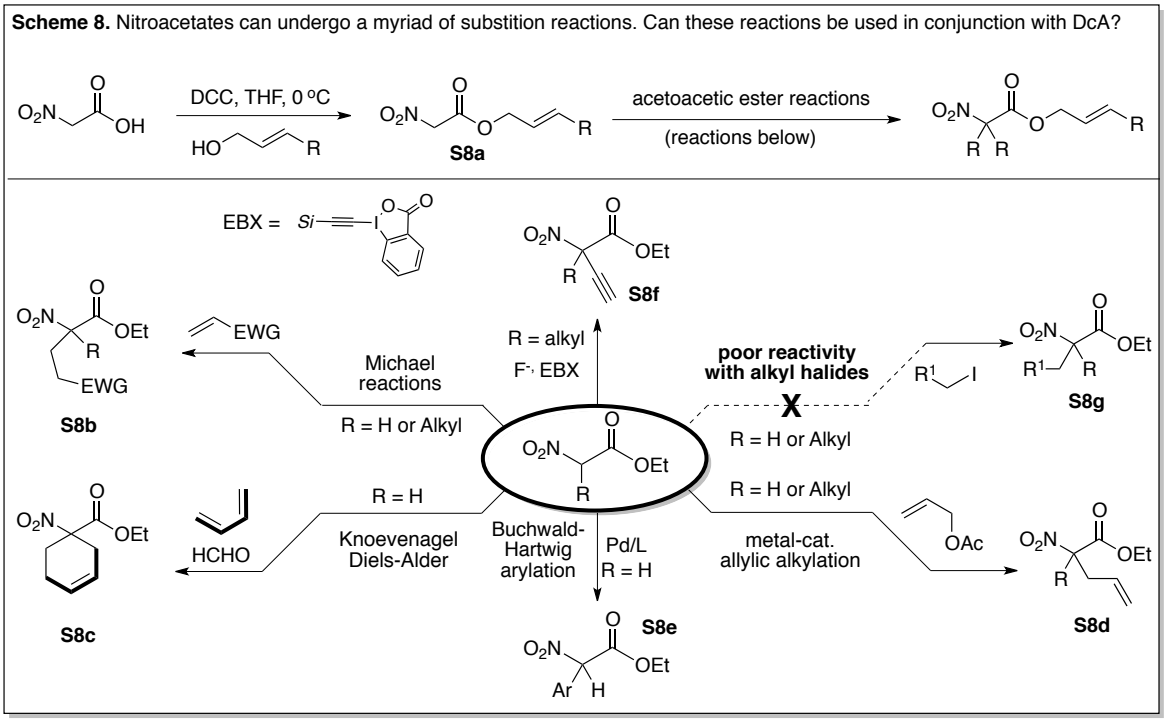
With working conditions in hand for the DcA reaction of nitroacetates, we began to test the scope of the reaction. In order to fully examine the scope, we needed a robust method for efficient access to α,α-dialkyl nitroacetates. Using the previously mentioned approach from α,α-

dialkylacetic acid (Scheme 6), we could produce a few starting materials in a stepwise fashion (Scheme 7, **S7a-d**), which was undesirable. Even more problematic was the limitation to commercially available carboxylic acid starting materials.

Scheme 7. Preparation of various allyl α,α–dialkylnitroacetates



Scheme 8. Nitroacetates can undergo a myriad of substition reactions. Can these reactions be used in conjunction with DcA?



We wished to find a common intermediate for producing diverse substrates: as shown in Scheme 8, alkyl α-nitroacetate esters undergo a myriad of unique alkyl[30] (and aryl[31]) substitution reactions and, thus, we thought that allyl nitroacetate **8a** would be a good template to begin our substrate diversification. Furthermore, nitroacetic acid can be easily prepared on multi-gram scale from nitromethane[32,33] and its DCC-coupling reaction (nitroacetic acid è **S8a**) is known.[34] Upon a literature survey, we found a diverse array of reactions that can be performed on a

nitroacetate substrate. For example, nitroacetates undergo Michael additions (**S8b**),[35,36] Knoevenagel condensations and tandem Knoevenagel/Diels-Alder reactions[37] (**S8c**) to synthesize nitroacetate substituted 6-membered rings. They have also been utilized in various metal-catalyzed reactions such as Tsuji-Trost allylations[38-42] (**S8d**), and more recently, in Pd-catalyzed Buchwald-Hartwig arylation reactions (**S8e**).[31] In a recent study by Waser, he had shown that a new reagent, EBX, can be used to transfer acetylene to a nitroacetate (**S8f**).[43] Quite surprisingly, it was interesting to discover that the classical alkylation of nitroacetates (with alkyl halides) is only sparsely reported and reactions typically occur in low yields.[39] An interesting trend in the alkylation of nitroacetate is that alkylation reactions that work well (e.g. Michael addition, Knoevenagel, Tsuji-Trost, etc) involve π*-electrophiles. The outlier is the only reaction that performs poorly: alkylation from alkyl halides, which requires σ*-orbital overlap by the nitroacetate nucleophile.

With the potential diversifying reactions outlined, it became clear that a few reactions could present some potential challenges toward substrate synthesis and, at least at first, should be avoided. That is, substrates that require a transition metal for their alkylation (or arylation) reaction might be problematic with our starting material allyl nitroacetate due to competing paths for Pd oxidative addition (Scheme 9). With that said, we thought it would be challenging to incorporate aryl groups and allyl groups via their known Pd-catalyzed methods.[31,39] We found this potential limitation to be unfortunate, yet intriguing, as aryl and allyl group incorporation would be useful and allow for more diverse couplings. In Chapter 3, our attempts, failures, and eventual successes in sequential Pd-catalysis made possible by deacylative (retro-Claisen) allylation will be discussed.[44]

Scheme 9. Some reactions in Scheme 8 could be challenging with allyl nitroacetetes

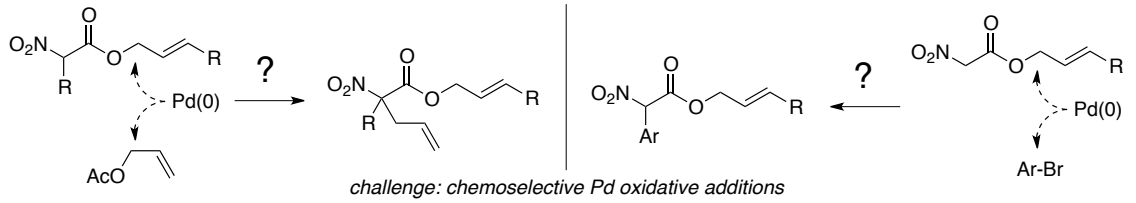
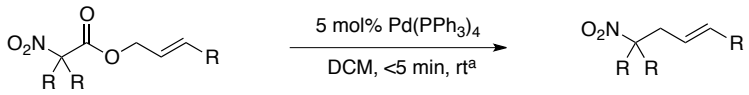
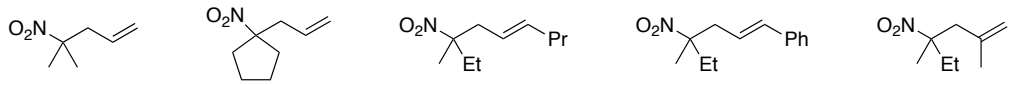


Table 2. Scope of the decarboxylative allylation reaction of allyl α,α–dialkyl nitroacetates

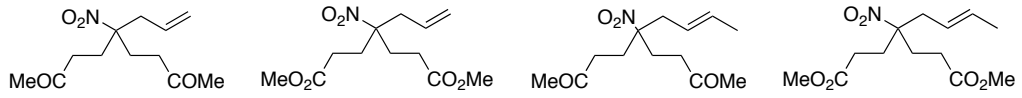


from α,α–dialkyl carboxylic acids:



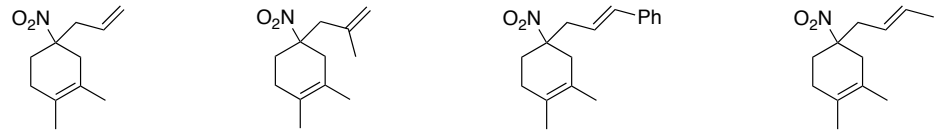
T2a, 82% **T2b**, 90% **T2c**, 87% **T2d**, ~55%[b], 87%[c] **T2e**, 81%

from allyl nitroacetate, Michael additions:



T2f, 88% **T2g**, 92% **T2h**, 94%[d] **T2i**, 99%[d]

from allyl nitroacetate, Knoevenagel/Diels-Alder:



T2j, 90% **T2k**, 91% **T2l**, 93%[c] **T2m**, 91%[e]

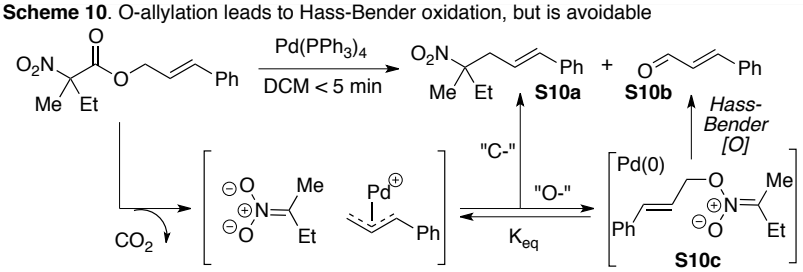
(a) standard conditions: 0.2 - 0.4 mmol scale, 0.2M in DCM (b) under standard conditions, the product was isolated as a mixture with cinnamaldehyde (c) 10 mol% $Pd(PPh_3)_4$ (d) 0.5g scale, isolated as a 4:1 mixture of crotyl isomers (e) isolated as a 5:1 mixture of crotyl isomers.

Now that the allowed transformations for substrate diversification have been outlined, the scope of the deacylative allylation will be discussed. Not surprisingly, simple dialkyl substituted nitroacetates were exceptional substrates (e.g. **T2a** and **T2b**). Substitution on the allyl moiety was generally accepted. For example, terminal alkyl (**T2c**) and aryl (**T2d**) substituted allylic nitroacetate were acceptable coupling partners. β-substitution was also acceptable, as determined by the successful DcA reaction of β-methylallyl nitroacetate **T2e**. Functionally dense allylated nitroalkanes could easily be prepared by tethering ketone (**T2f** and **T2h**) and ester (**T2g** and **T2i**) functional groups by Michael addition. Furthermore, we also took advantage of the

aforementioned Knoevenagel/Diels-Alder reaction to quickly prepare allylated nitrocyclohexenes (**T2j-m**).

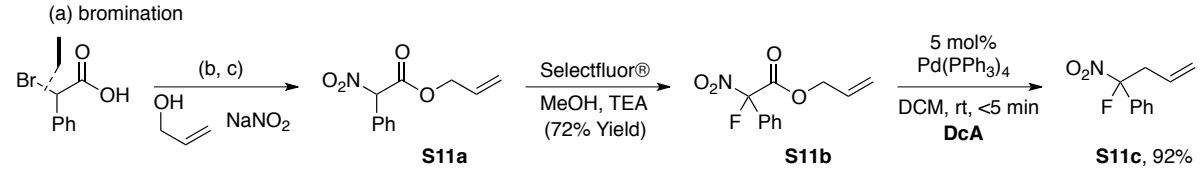
Interestingly, the cinnamyl nitroacetate required a higher-catalyst loading to give a clean reaction (e.g. Table 2, **T2d** and **T2l**). As shown in Scheme 10, when 5 mol% of Pd was utilized a 1.2 : 1 mixture of desired product **S10a** and cinnamaldehyde **S10b** was isolated (entry 1). We presume that the cinnamaldehyde is due to O-allylation, forming intermediate **S10c**, followed by Hass-Bender oxidation.[45-47] Aside from using higher catalyst loadings (entry 4), by simply increasing the reaction concentration, the desired product can be favored (entries 2-3). To explain this mechanistically, we suggest that O-allylation is reversible. At higher concentrations of Pd, reionization of the O-allylated species **S12c (**to the nitronate and Pd-π-allyl complex) occurs more efficiently than Hass-Bender oxidation, which allows for irreversible product formation by C-allylation.

Scheme 10. O-allylation leads to Hass-Bender oxidation, but is avoidable



entry	mol % Pd(0)	[substrate]	**S12a**:**S12b**
1	5	0.1M	1.2:1
2	5	0.2M	2.2:1
3	5	0.3M	4.5:1
4	10	0.1M	~10:1

Scheme 11. Decarboxylative allylation of an α–fluoronitroacetate

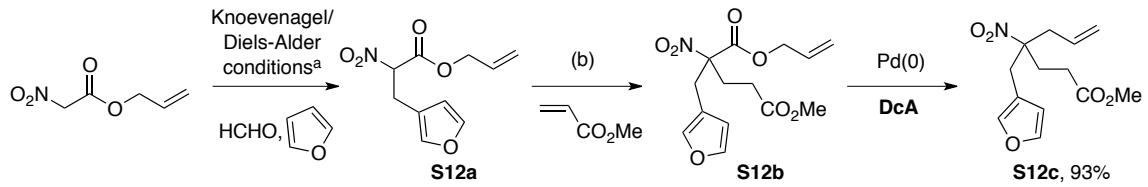


(a) From phenylacetic acid: Br_2 PCl_3 PhH, Δ (b) DCC, DMAP-cat., allyl alcohol, DCM, 1h, 82% (c) phloroglucinol, $NaNO_2$, DMF, 50% (Kornblum-reaction)

In addition to the substrates in Table 2, we prepared a few other unique allyl nitroacetates to test in the DcA reaction. As shown in Scheme 11, a fluorinated allyl nitroacetate **S11b** performed excellently in DcA providing **S11c** in near quantitative yield. Access to DcA substrate

S11b was achieved from allyl α-nitro-α-phenyl acetate **S11a**, which in turn is derived from phenylacetic acid by bromination,[48] DCC coupling with allyl alcohol, and Kornblum nitration.[43] α-Fluorination with Selectfluor yields the desired starting substrate **S11b**. In another example, substrate **S12b** was prepared by a Knoevenagel/"failed" Diels-Alder sequence with furan as the "diene" (Scheme 12). Though the reaction of allyl nitroacetate, formaldehyde, and furan lead to a product, it did not give the expected [4+2] product. Rather, it underwent an electrophilic aromatic substitution reaction to produce the monosubstituted nitroacetate **S12a**. We then performed a Michael addition (**S12b**) in excellent yield (87%) followed by the DcA reaction to produce the densely functionalized allylated nitroalkane **S12c** in near quantitative yield.

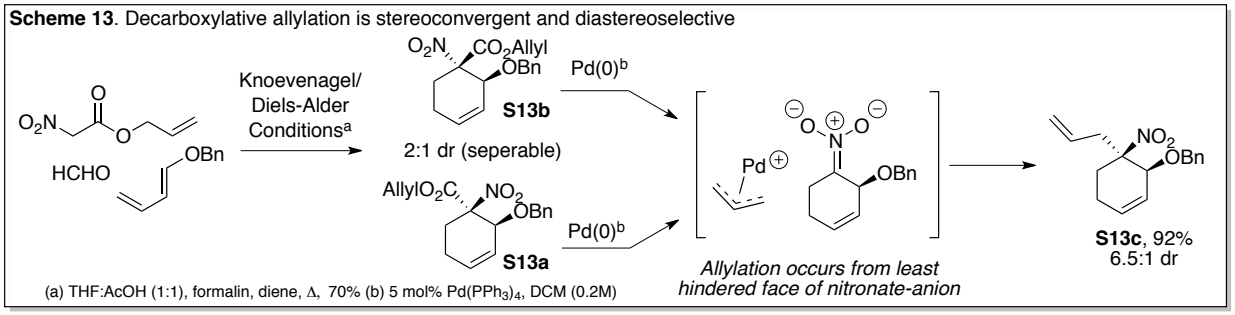
Scheme 12. Decarboxylative allylation of a functionally dense allyl nitroacetate

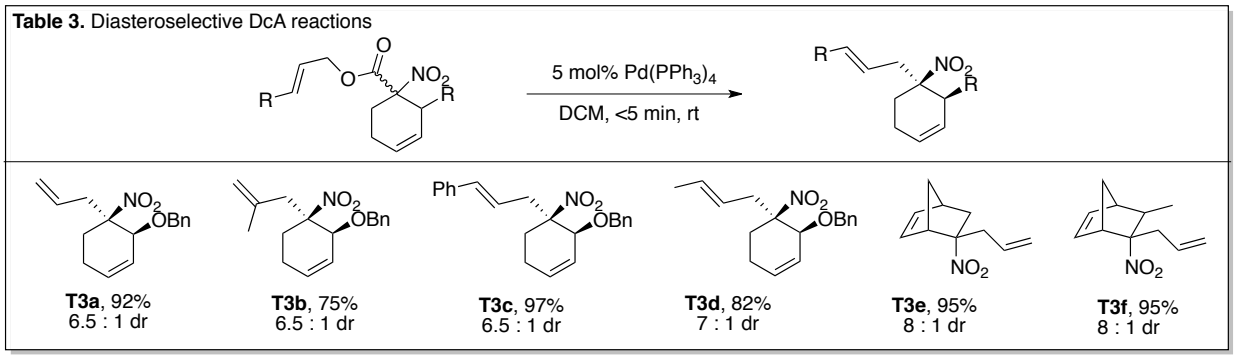


(a) THF:AcOH (1:1), formalin, furan Δ, 40% (unoptimized) (b) methyl acrylate, TBAB, DIEA, MeCN, 84%

By utilizing terminally substituted dieneophiles in the Knoevenagel/Diels-Alder reaction of allyl α-nitroacetate, we could test the diastereoselectivity of the DcA transformation (Scheme 13). Under Knoevenagel/Diels-Alder conditions we could produce a 2:1 mixture of allyl nitroacetate diastereomers **S13a/b** that were separable by chromatography. Under DcA conditions, we realized that the reaction was stereoconvergent in that both diastereomers lead to a single relative diastereomer **S13c** (6.5:1 dr). Moreover, the allylation occurred from the least hindered face (opposite of benzyloxy group), suggesting steric control in the allylation. The stereochemistry was determined by nOe studies and further confirmed by X-ray crystallography.[49] It is important to note that the poorly selective Diels-Alder reaction (2:1 dr in this case) can be resolved using this decarboxylative allylation method (**S13a/b**, 2:1 dr è **S13c**,

6.5:1 dr). The scope of this steroconvergent reaction is shown in Table 3. Simple allylic substitution (**T3a**) by DcA was well tolerated. Other benzyloxy substituted substrates performed well with a wide array of terminally substituted (**T3c-d)** as well as β-substituted allylic acetates (**T3b**) providing excellent yields (75 – 97%) and good diastereoselectivities (> 6.5:1). We also performed the Diels-Alder DcA sequence with cyclopentadiene as the dieneophile (**T3e-f**) Again, good yields and diastereoselectivities were observed with these substrates.

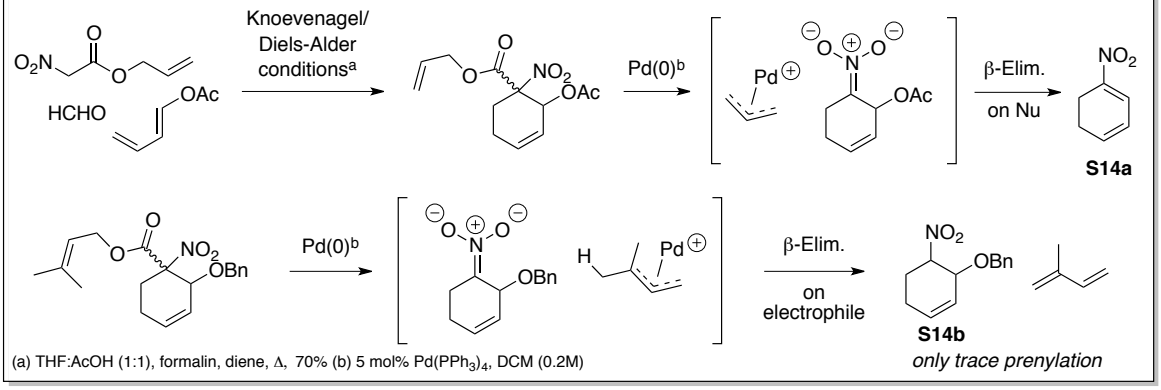




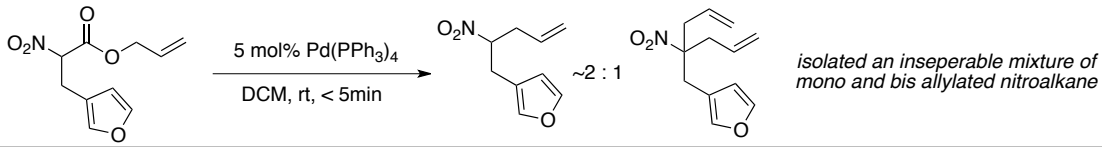
Thus far, the successes of the DcA reaction of allyl α-nitroacetates have been discussed. However, there were some general limitations. First, β-elimination is possible (Scheme 14). We witnessed (by ^{1}H NMR, 100% conv.) formation of nitroalkene **S14a** when a β-acetyloxy group was present on the nitroalkane. Thus β- (to the nitronate anion) leaving groups should be avoided. Next, prenyl nitroacetate was not a viable coupling partner due to β-elimination, producing isoprene and the undesired 2° nitroalkane **S14b**. Only a trace amount of the desired prenylated nitroalkane was formed in this reaction. In addition to elimination-type reactions, we

also found 2° allylated nitroalkane synthesis via DcA problematic due to competing over allylation (Scheme 15).

Scheme 14. β-Elimination is problematic when generating nitronate anions via DcA



Scheme 15. Preparation of 2° nitroalkanes is challenging via DcA



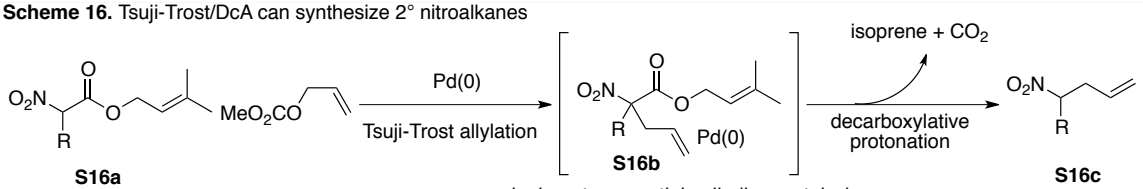
1.3 Synthesis of 2° allylated nitroalkanes from prenyl nitroacetate

The Pd-catalyzed allylation of 1° nitroalkanes (to produce 2° allylated nitroalkanes) is a known process,[42,50-53] though it is not without its downfall: excessive amounts of the nitro compound are required to avoid over-allylation to the 3° diallylated nitroalkane. This is especially undesirable when the nitroalkane to be allylated is precious.

As stated at the end of section 1.2, it was similarly challenging to prepare 2° nitroalkanes via DcA from the allyl α-monoalkylated nitroacetate due to over-allylation (Scheme 15). However, we also noticed that prenyl nitroacetates undergo β-hydrogen elimination producing 2° nitroalkanes (Scheme 14). We envisioned that we could take advantage of the prenyl nitroacetates aptitude for elimination to produce functionally dense allylated 2° nitroalkanes rapidly using a 1-pot Tsuji-Trost allylation/decarboxylative protonation of prenyl nitroacetate

sequence (Scheme 18). Furthermore, Tsuji-Trost allylation of active methylenes, such as nitroacetate, is an extremely facile process. In our approach from **S16a**, mild Tsuji-Trost allylation occurs to form **S16b**. Furthermore, over allylation is obviously avoided as the α-position is now fully substituted. From the allylated intermediate **S16b**, the same Pd catalyst from the Tsuji-Trost allylation can then remove the prenyl carboxylate via decarboxylative protonation, yielding the desired product **S16c.**

Scheme 16. Tsuji-Trost/DcA can synthesize 2° nitroalkanes

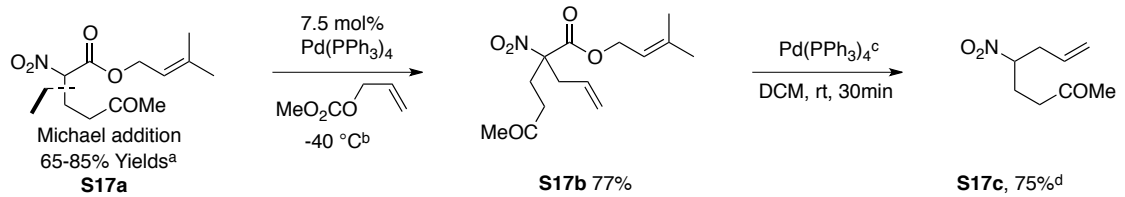


S16a **S16b** **S16c**

single-pot sequential palladium-catalysis

To test this hypothesis we prepared monoalkylated prenyl nitroacetate **S17a** by Michael-addition with MVK using a known method (Scheme 17).[35] We found that a smooth reaction between allyl methyl carbonate and **S17a** occurred producing **S17b** in 77% isolated yield [-40 °C, DCM, $Pd(PPh_3)_4$ cat.]. This compound could then be converted to the desired allylated 2° nitroalkane **S17c** by Pd-catalyzed decarboxylative protonation in 75% yield. Interestingly, about 25% of the prenylated 3° nitroalkane was also formed.

Scheme 17. Tsuji-Trost/DcA can synthesize 2° nitroalkanes



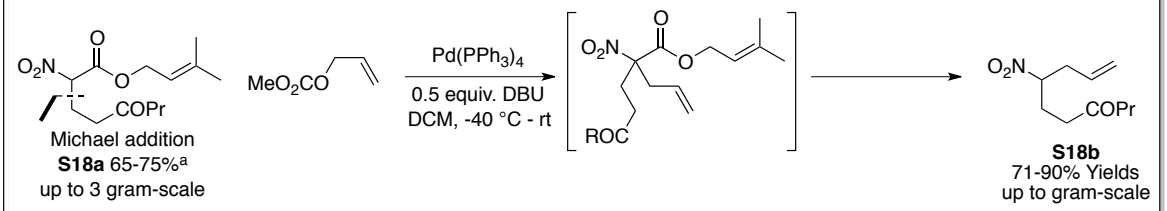
S17a **S17b** 77% **S17c**, 75%[d]

(a) prenyl nitroacetate:MVK (1 : 1.1 equiv), 5 mol% $Yb(OTf)_3$, 10 mol% NaOH and proline, H_2O (b) the reactants are added at -40 °C and the reaction is quenched at -40 °C by addition of water and extraction (c) 5 mol% $Pd(PPh_3)_4$, rt, 30min. (d) crude NMR shows a ~3:1 mixture of **S19c** and prenylated nitroalkane

On a multi-gram scale with propyl vinyl ketone, we prepared **S18a** by Michael addition (Scheme 18). We then turned to developing the 1-pot Pd-catalyzed Tsuji-Trost/decarboxylative protonation reaction. We realized that with a base additive (0.5 equiv.), the reaction went

smoother giving less of the prenylated byproduct. Under the conditions outlined in Scheme 18, we could prepare gram quantities of the 2° allylated nitroalkane **S18b** containing a pendant ketone. Moreover, this specific nitroalkane **S18b** was prepared to quickly access the indolizidine core as outlined in section 1.3 of this chapter (Scheme 20).

Scheme 18. Single pot synthesis of functionally dense 2° nitroalkane **S18b**



Michael addition
S18a 65-75%[a]
up to 3 gram-scale

S18b
71-90% Yields
up to gram-scale

(a) prenyl nitroacetate:propyl vinyl ketone (1:1.1 equiv), 5 mol% $Yb(OTf)_3$, 10 mol% NaOH and proline, H_2O

Though content with this approach to 2° nitroalkanes, scope studies were abandoned due to the discovery of an even simpler approach to these useful compounds: Tsuji-Trost/retro-Claisen condensation.[44] This reaction will be discussed in Chapter 3 of this dissertation, as retro-Claisen based methodologies became a central theme of my research.

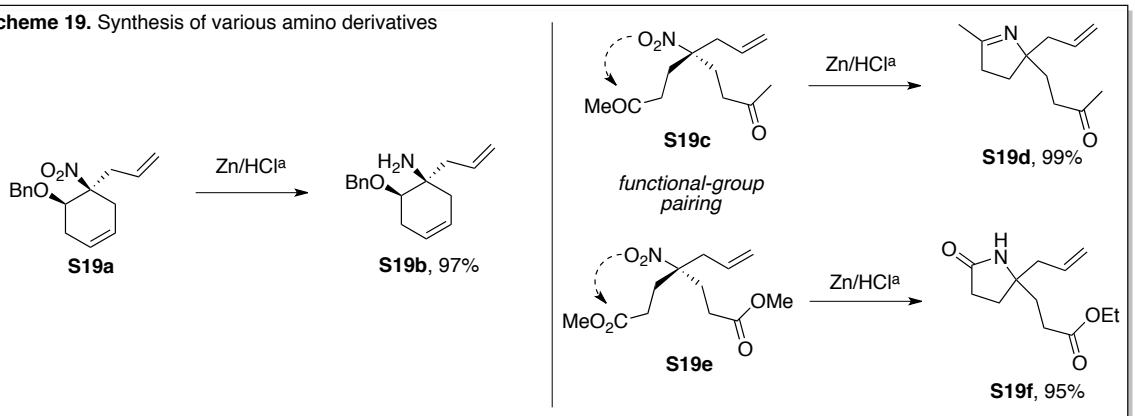
As stated, in the next section, I will outline the utility of the various 2° and 3° allylated nitroalkanes that we prepared via DcA (section 1.2) and by Tsuji-Trost/decarboxylative protonation (Section 1.3).

1.4 Nitro-group reduction to produce useful amino derivatives

Through this first chapter, I have described how various, relatively complex, allylated nitroalkanes can be prepared quickly by decarboxylative methods. In a few cases, we performed some nitro group selective reductions to give rise to homoallylic amines and derivatives thereof (Schemes 19 and 20). For example, by reduction of **S19a**, we prepared a protected 1,2-amino alcohol **(S19b**). Moreover, using a functional group pairing strategy,[24] both imines (**S19d**) and

lactams (**S19f**) can be prepared from nitro ketones (**S19c**) and esters (**S19e**) by reduction, respectively.

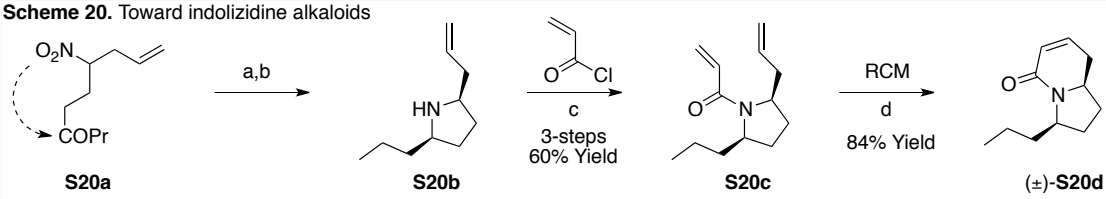
Scheme 19. Synthesis of various amino derivatives



(a) standard reaction conditions: 20 equiv. Zn dust and 40 equiv. HCl, *i*PrOH, 60 °C, 1h.

Utilizing the functionalized 2° allylated nitroalkane prepared by Tsuji-Trost/decarboxylative protonation (Scheme 18), we could utilize all appended functional groups to rapidly construct the indolizidine core as a single diastereomer and in good yield. Starting from **S20a**, reduction of the nitro group leads directly to a cyclic imine, and by further reduction using DIBAL at -40 °C, we could access the pyrollidine **S20b** as a single diastereomer. Due to challenges with this substrate's purification it was first acrylated then purified by column chromatography yielding the acrylamide **S20c**. Moreover, this was the only chromatographic event in this 3-step sequence. From **S20a**, **S20c** was prepared in 60% overall yield. Upon acrylate installation, the molecule is poised to undergo a ring-closing metathesis to synthesize the 5-6-fused ring system found in various indolizidine containing alkaloids. This is done with Grubbs' 2nd-generation catalyst yielding the desired compound **S20d** in 84% isolated yield. Overall, this sequence is rapid and generally good yielding.

Scheme 20. Toward indolizidine alkaloids



S20a **S20b** **S20c** (±)-**S20d**

(a) 20 equiv. Zn dust and 40 equiv. HCl, *i*PrOH, 60 ºC, 1h (b) 3 equiv. DIBAL, -40 °C-rt (c) 1 equiv. acryloyl chloride, 1.2 equiv. pyridine, DCM, 0 °C-rt (d) Grubbs II, Tol, 60 °C DCE

To conclude, we have developed a practical method for the rapid synthesis of a diverse array of allylated 3° nitroalkanes via decarboxylative allylation. We utilized robust methods, such as Michael addition and Knoevenagel/Diels-Adler for α-alkylation to produce structurally diverse nitro-compounds. Furthermore, nitro-group reduction along with functional group pairing can transform these compounds into various homoallylic amine derivatives. We also devised a novel single pot Tsuji-Trost/decarboxylative protonation reaction for the synthesis of 2° nitroalkanes that can be utilized to access the indolizidine core found in numerous alkaloid natural products.

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Chapter 1 appendix

Experimental methods and spectral analysis for Ch. 1 compounds.

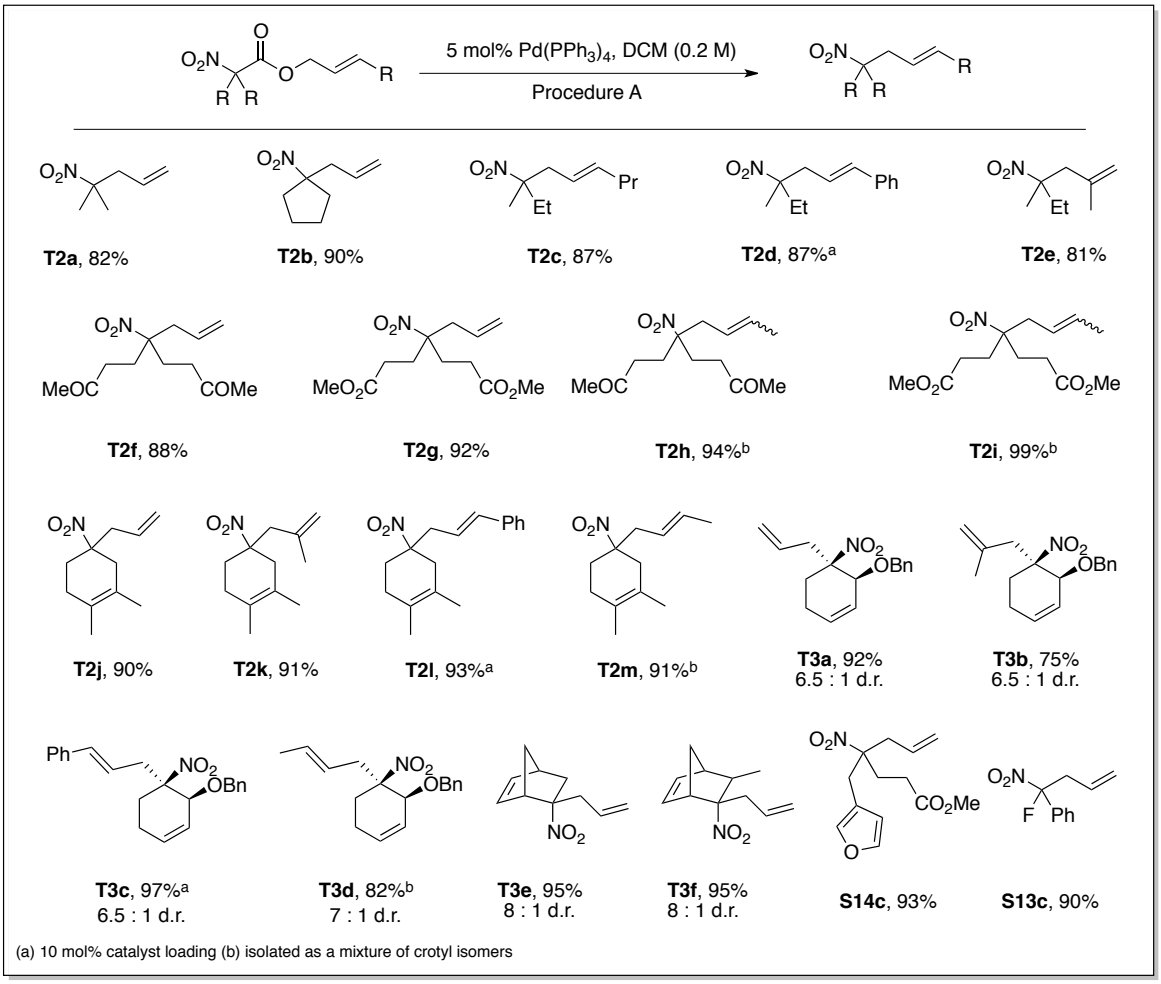
Table of contents

General information:

***Note:** Products are named after their Table or Scheme location in Chapter 1 (e.g. **T2a** = substrate **a** in **Table 2** or **S13c** = substrate **c** in **Scheme 13**). If a compound has not specifically been named and referred to in Chapter 1 text, it will be given an Appendix name (**A-1, A-2, etc.)** They are similarly named in the spectral analysis section of this appendix.

All reactions were run in flame-dried glassware. CH_2Cl_2 and Toluene were dried over activated alumina. THF was dried over sodium in the presence of benzophenone indicator. Anhydrous DMSO and DMF were purchased from Aldrich Chemical Company. Commercially available reagents were used without additional purification unless otherwise stated. Compound purification was effected by flash chromatography using 230x400 mesh, 60Å porosity silica obtained from Sorbent Technologies. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance 400 or a Bruker Avance 500 DRX spectrometer equipped with a QNP Cryoprobe and referenced to residual protio solvent signals. Structural assignments are based on ^{1}H, ^{13}C, DEPT-135, COSY, HSQC, nOe, and IR spectroscopies. Mass Spectrometry was performed using an Agilent 5890A Series II GC System.

Decarboxylative allylation of allyl nitroacetates: *General Procedure:*



(a) 10 mol% catalyst loading (b) isolated as a mixture of crotyl isomers

Procedure A:

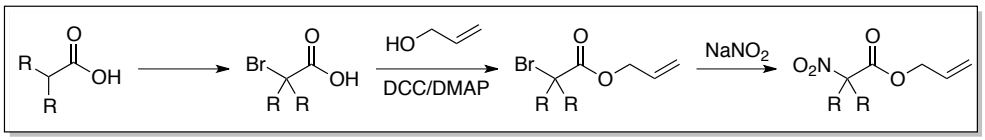
In a glove box, A flame dried 10 mL Schlenk flask equipped with a stir bar is charged with $Pd(PPh_3)_4$ (5 mol%, 0.01 mmol, 11.5 mg). The flask is removed from the glove box and attached to a Schlenk-argon line whereupon 1 mL of DCM is added. To this stirred solution, allyl nitroacetic ester (0.2 mmol) is added dropwise via syringe (1 mL disposable syringe was commonly used). The syringe is washed with DCM to ensure complete transfer. Effervescence was observed immediately upon addition of the substrate. After reaction for approximately 5 minutes, cuprous chloride (CuCl, ~5-10 mg) was added to complex the triphenylphosphine,

allowing for facile purification of product **2** by filtration of the mixture through a silica plug using 95:5 hexane:ethyl acetate as an eluent. Evaporation of solvent under reduced pressure provided compounds in >95% purity.

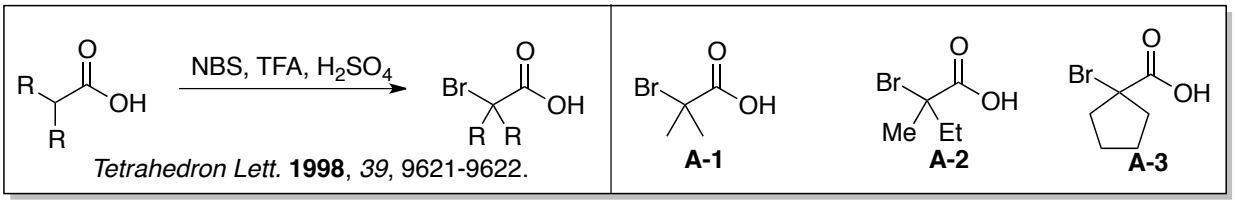
***NOTE**: 10 mol % $Pd(PPh_3)_4$ was necessary for cinnamyl esters

Preparation of various allyl nitroacetates:

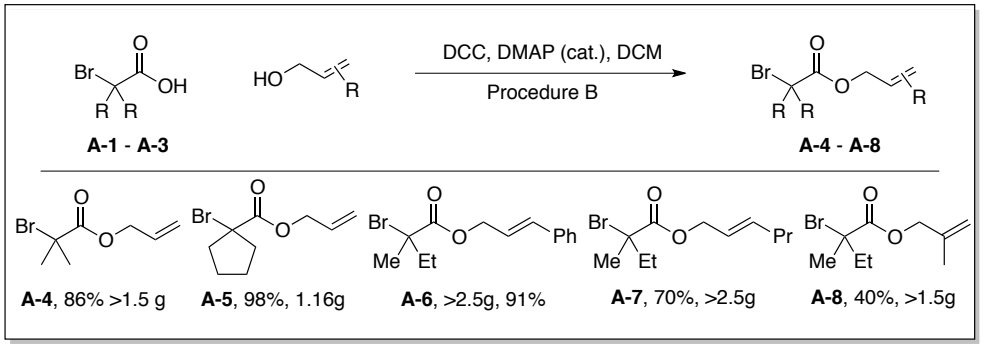
Substrate synthesis 1: from α,α-dialkyl carboxylic acids:



α-Bromination of dialkyl acetic acid:[1]



Esterification of **A-1** − **A-3** via *DCC/DMAP coupling.*



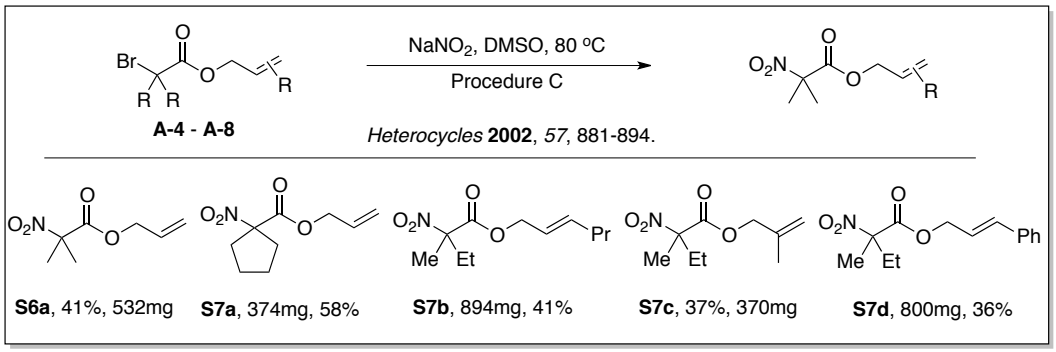
General procedure B:

In a 50-mL round-bottom flask, DCC (1.032g, 5 mmol) and DMAP (10 mol%, 0.5 mmol, 61 mg) are dissolved in ~10 mL of dry DCM. In a separate vessel mix the carboxylic acid (5 mmol) and the allyl alcohol (5 mmol) and dissolve in 10 mL of dry DCM. Add the reactants dropwise to the stirring solution of DCC/DMAP. The addition time was approximately 5 min.

Rinse the transfer vessel with 5 mL of DCM to ensure complete reactant transfer to reaction vessel. Let the reaction stir overnight (~12h).

After the allotted reaction time, Add ~2mL of 3M HCl and continue stirring for 10mins. Filter the reaction mixture through a pad of silica gel using excess DCM to ensure complete transfer. The DCM was dried over $MgSO_4$ and the solvent was evaporated yielding the desired product. The material could often be used as is, or further purified by column chromatography.

Nitration of α-Bromo acetic esters **A-4** − **A-8** *by the Kornblum-reaction:*[2]

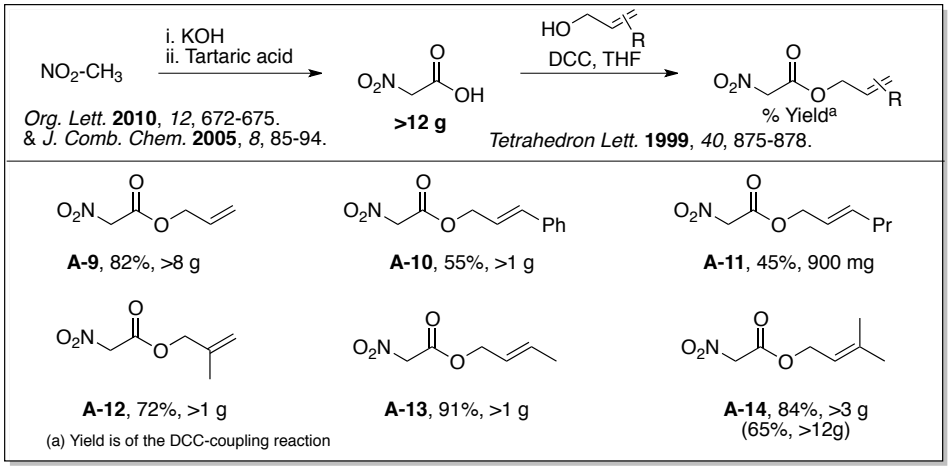


Procedure C:

A 10 mL flame-dried Schlenk flask is equipped with a stir bar and attached to an argon line. Allyl α-bromo acetate (3 mmol) is added to this flask followed by 5 mL of DMSO. To the stirring solution is added $NaNO_2$ (3.9 mmol, 268mg). The vessel is then heated at 80 °C until completion (as determined by TLC analysis, 1-3h).

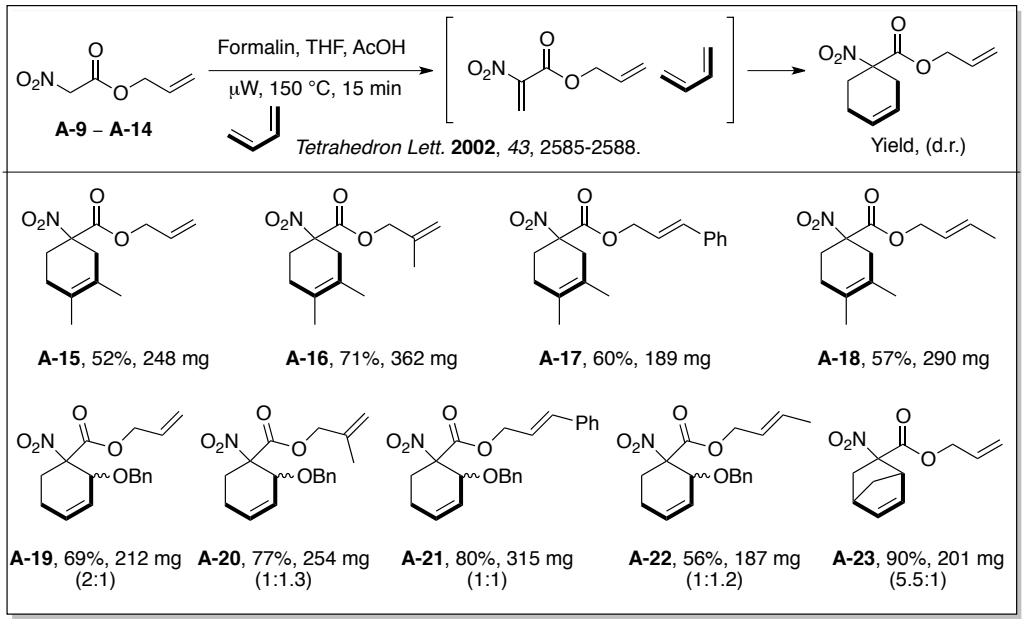
After the allotted reaction time, the reaction mixture is transferred to a seperatory funnel with the aid of 20 mL DCM. an extra 20 mL of DCM is added and the organic layer is extracted with water (2 x 20 mL). The organic layer is then brine washed (20 mL), dried over $MgSO_4$, and the volatiles are removed by rotary evaporation. The crude product residue is purified by column chromatography to yield the desired compound.

Substrate synthesis 2. Synthesis from allyl nitroacetate:[3-5]

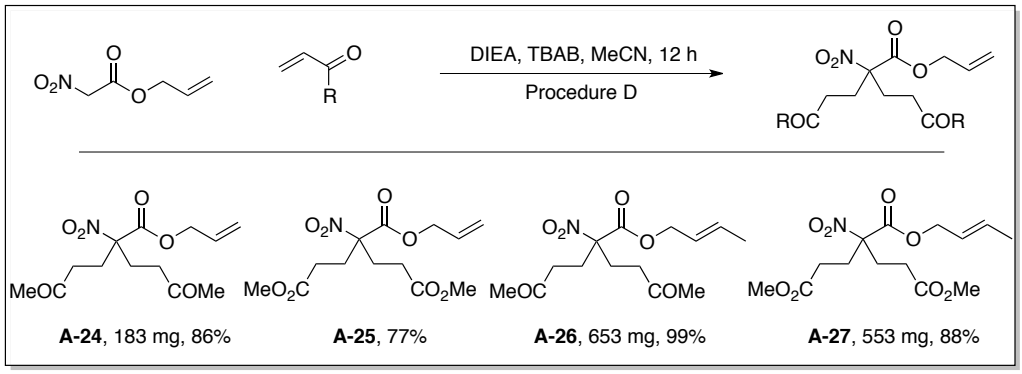


The procedure in References 3 and 4 was used to prepare nitroacetic acid. The DCC-coupling of nitroacetic acid with various alcohols was reported by Sylvain and Wagner (ref. 4)

Knoevenagel/Diels0Alder cyclization of **A-9 - A-14**:[6]



Michael addition to allyl nitroacetate **SI-14** and **SI-17**

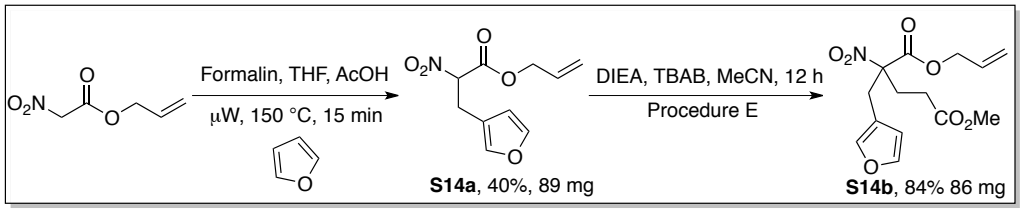


General procedure D:

In a 50 mL round bottom flask add TBAB (10 mol%, 0.3 mmol, 96 mg), DIEA (1.05 equiv., 3.1 mmol, 400 mg) and 15 mL of Dry MeCN. While stirring, add in the substrate allyl nitroacetate (3mmol) and Michael accepter (2.2 equiv., 6.6 mmol). Cap and stir the reaction mixture overnight.

After the allotted reaction time, transfer the reaction mixture to a seperatory funnel with the aid of chloroform (~20 mL) to ensure complete reaction mixture transfer. Add in ~50 mL of chloroform and extract the organic layer with sat. $NaHCO_3$ (2 x 30 mL). Wash the organic layer with brine, dry over $MgSO_4$ and evaporate off the organic layer leaving the crude, oily product residue. The reaction mixture if purified by column chromatography (15% EtOAc in hexanes).

Preparation of **S14b**:



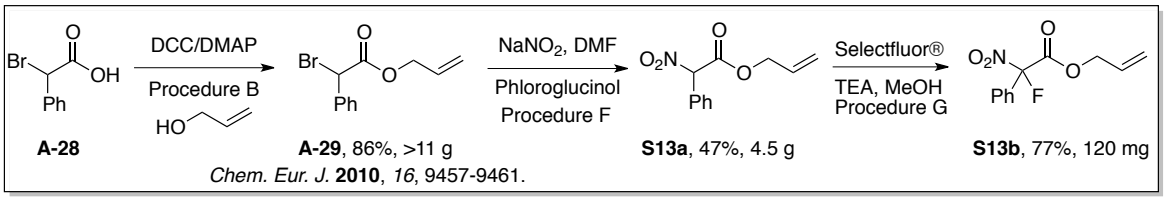
***S14b** was prepared using the method reported by Wade for performing Knoevenagel/Diels-Alder reactions.[6] Interestingly, Knoevenagel/Aromatic substitution occurred instead.

Procedure E:

In a 10 mL round bottom flask is added TBAB (10 mol%, 0.03 mmol, 10.5 mg), DIEA (1.1 equiv., 0.33 mmol, 49 mg), and 1.5 mL of MeCN. To this stirring mixture is added allyl nitroacetate **SI-32** (0.33 mmol, 75 mg) followed by methyl acrylate (1.1 equiv, 0.37 mmol, 32 mg). The reaction vessel is capped and allowed to stir overnight (12 h).

After the allotted reaction time, the mixture is transferred to a seperatory funnel with the aid of ~10 mL of chloroform. An additional 10 mL of chloroform is added and the organic layer is extracted with $NaHCO_3$ (2 x 10 mL). The organic layer is brine washed (10 mL), dried over $MgSO_4$, and the chloroform is evaporated by rotary evaporation. The crude oily residue is purified by column chromatography (15% EtOAc in hexanes) to yield 86 mg of the desired product **SI-33** (84% isolated yield).

Substrate synthesis 3: synthesis of fluorinated allyl nitroacetate **S13b**.[8]



Procedure F:

In a flame-dried 100 mL Schlenk flask equipped with a stir bar and attached to an argon line is added 50mL of phloroglucinol (1,3,5-trihydroxybenzene, 37.1 mmol, 4.7 g), $NaNO_2$ (74.2

mmol, 5.12 g) and dry DMF (~50 mL). While stirring add in allyl bromoacetete **A-29** neat and dropwise. The reaction mixture is stirred for 4h.

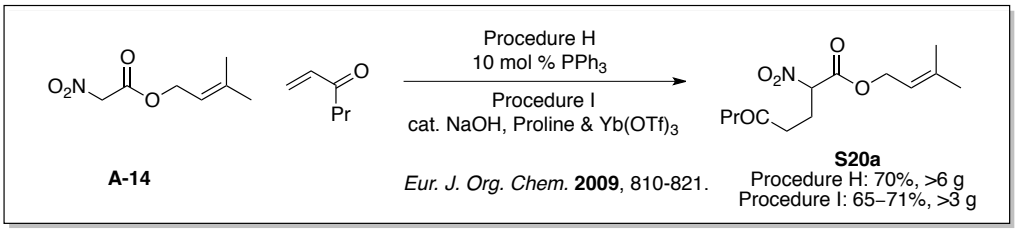
After the allotted reaction time, the reaction mixture is transferred to a seperatory funnel with the aid of 50 mL of water and hexanes to ensure complete transfer. An extra 150 mL of water is added. The water layer is extracted with hexanes (2 x 200 mL). The organic layer is extracted with brine, dried over $MgSO_4$, and the volatile organics are removed by rotary evaporation. The product is purified by column chromatography (15% EtOAc in hexanes) yielding 4.5 grams (47% yield) of the desired product **S13a**.

Procedure G:

In a 10 mL round bottom flask is added allyl nitroacetate **S13a** (0.5 mmol, 110 mg), Selectfluor® (1.5 mmol, 531 mg), and 5 mL of methanol. By Pasteur pipette, add ~5−7 drops of TEA. A rapid reaction occurs. The methanol is removed by rotary evaporation and the crude mixture is subjected to column chromatography (10% EtOAc in hexanes) to yield the pure product **S13b** (120 mg, 72% yield).

Tsuji-Trost/decarboxylative protonation sequence:

Substrate synthesis: mono-Michael addition to prenyl nitroacete:[7]



Procedure H:

In a 100 mL round bottom flask equipped with a stir bar is added triphenylphosphine (10 mol%, 3 mmol, 787 mg), prenyl nitroacetate **A-14** (30 mmol, 5.2 g) and 30 mL of THF. Propyl vinyl ketone (30 mmol, 2.95 g) is then added dropwise. The reaction is capped and allowed to stir for 12h.

After the allotted reaction time, the solvent is evaporated and the crude residue is subjected to column chromatography (5% EtOAc in hexanes) to yield the desired product.

Procedure I:

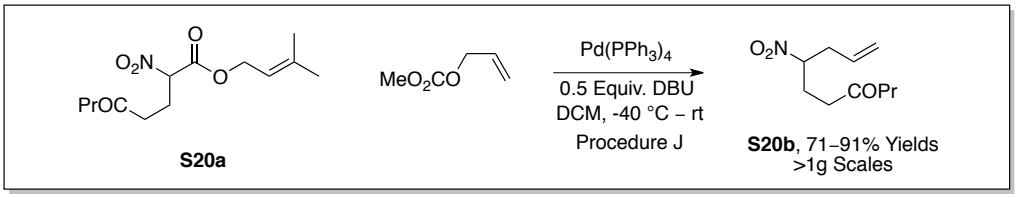
Adapted from Wennerberg's mono-Michael addition of various "malonate-type" nucleophiles.[7]

In a 50 mL round bottom flask equipped with a stir bar is added NaOH (12 mol%, 2.4 mmol, 95 mg), proline (12 mol%, 276 mg), and $Yb(OTf)_3$ (5 mol%, 1 mmol, 620 mg). 20 mL of water is added and the catalyst mixture is stirred for ~10 min. To this mixture is added prenyl nitroacetate **A-14** (20.6 mmol, 3.6 g) and propyl vinyl ketone (21 mmol, 2.15 g). The reaction mixture is then stirred for 4 h with stirring.

After the allotted reaction time, the reaction mixture is acidified with 1 M HCl (~20 mL) and transferred to a seperatory funnel with the aid of ~20 mL of $CHCl_3$ to ensure complete

transfer. The water layer is extracted with chloroform (2 x 25 mL). The organic layer is then washed with brine, dried over $MgSO_4$ and the volatiles are removed by rotary evaporation. The crude, oily product is purified by column chromatography (5 % EtOAc in hexanes).

Tsuji-Trost/decarboxylative protonation of **S20a**

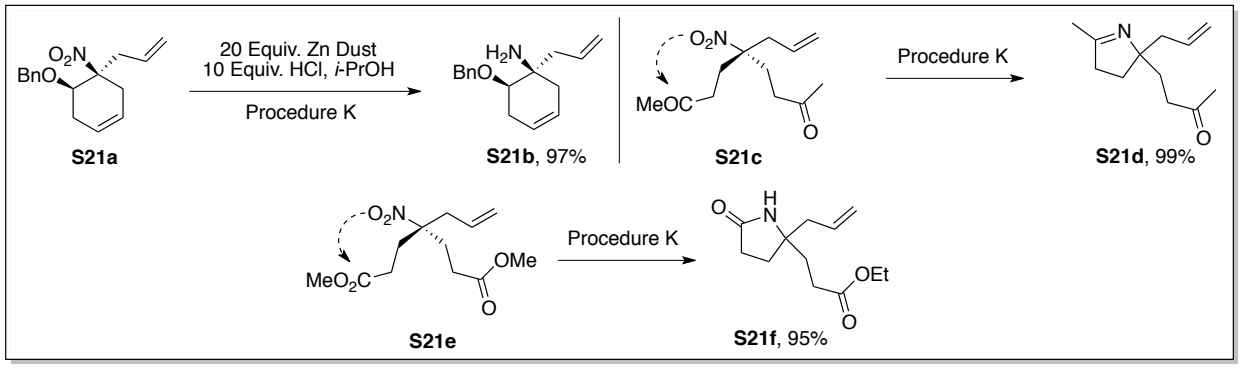


In a glove box, $Pd(PPh_3)_4$ (5 mol%, 0.33mmol, 375 mg) is charged into a 50 mL Schlenk flask. The flask is capped with a septum, removed from the glove box, and attached to a Schlenk line. Under argon, dichloromethane (20 mL) and DBU (50 mol%, 3.25 mmol, 495 mg) is added. The reaction vessel was then cooled to -40 °C and stirred. In 5 mL dichloromethane, an equimolar (6.5 mmol) mixture of allyl acetate (755 mg) and substituted prenyl acetate (1.76 g) is added dropwise over 5 min. The reaction mixture was stirred at this temperature for 15 min. and then allowed to slowly warm to room temperature where it is stirred for an additional 30 min.

After the allotted reaction time, the reaction mixture was transferred to a separatory funnel, further diluted with dichloromethane (~50 mL) and washed with 1 N HCl (25mL) followed by brine (25 mL). The organic layer was collected, dried over $MgSO_4$, evaporated, and subjected to silica gel chromatography (15:85 Et_2O:pentane) to provide 1.17 g of the desired product **S20b** (90% Yield).

Reduction of various nitro compounds:

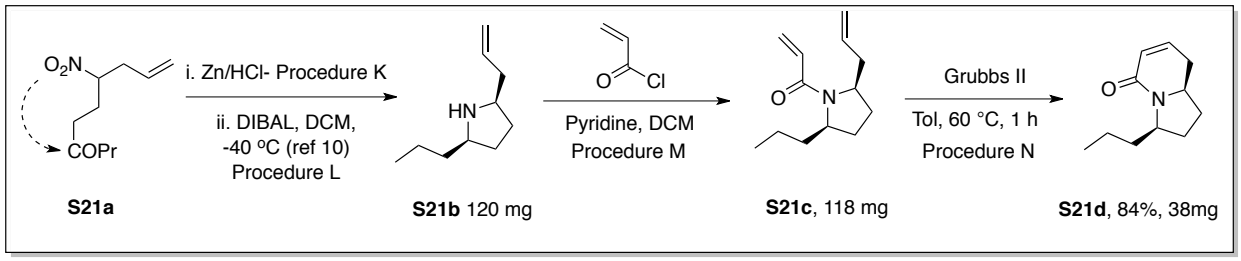
From tertiary allylated nitroalkanes



Procedure K:

In a 20 mL round bottom flask equipped with a stir bar, nitro compound (0.15 mmol) was dissolved in isopropanol (3 mL). To this solution 1 M HCl (1.5 mL) and zinc dust (190 mg, 3 mmol) was added and the mixture was stirred vigorously for 2 h at 50 ^{o}C. After cooling the mixture to room temperature, saturated K_2CO_3 (4 mL) was added and the resulting mixture was stirred for an additional 20 min. The solids were removed by filtration and the remaining solution was extracted with chloroform (3 x 20 mL). The organic layers were combined and washed with brine (1 x 20 mL), dried over anhydrous $MgSO_4$ and reduced by rotary evaporation yielding **3** in >95% purity.

Synthesis of the indolizidine core



Procedure L:

In a flame-dried 25 mL Schlenk flask equipped with a stir bar, 426mg (~0.540 mL) of neat DIBALH was added under argon using a 5 mL syringe. The used syringe was rinsed with dichloromethane (1 mL) to ensure complete DIBALH transfer. An additional 4 mL of dichloromethane was then added and the reaction vessel was cooled to -78 °C. At this temperature, a solution of substrate imine (174 mg in 3 mL of DCM) was added dropwise over a minute. After rinsing the transfer syringe with a small amount of DCM to ensure complete substrate transfer to the reaction mixture, the vessel was capped and stirred at -78 °C for 3 h. Next, the flask was removed from the dry ice acetone bath and allowed to slowly warm to room temperature. After stirring at room temperature for ~1 h, the mixture was cooled to 0 °C and 10 mL dichloromethane and 10 mL of a saturated solution of Rochelle salt was slowly added. Again the mixture was allowed to slowly warm to room temperature and stir overnight.

The resulting dichloromethane/water mixture was transferred to a separatory funnel and extracted with DCM (40 mL)/water (25 mL) followed by a brine (25 mL) wash. The organic layer was separated and dried over $MgSO_4$ and the solvent was evaporated. The 2° amine **S21b** (120 mg, 79% yield, 2-steps) was isolated as a yellow solid.

Procedure M:

In a flame-dried 10 mL Schlenk flask equipped with a stir bar was added substrate 2° amine **S21b** (100 mg, 0.76 mmol), dichloromethane (4 mL) and triethylamine (77 mg, 0.76 mmol). The mixture was stirred and cooled to 0 °C. Acryloyl chloride (69 mg, 0.76 mmol) was added as a solution in DCM (1 mL). The mixture was removed from the ice bath and slowly warmed to room temperature. After stirring at room temperature for an hour, the mixture was

transferred to a separatory funnel and extracted with dichloromethane (25 mL) and 1 N HCl (25 mL). The organic layer was dried over $MgSO_4$ and evaporated. Silica gel chromatography (25:75 EtOAc:hexanes) yielded the desired amide **S21c** (118 mg, 76% yield) as a 1:1.2 mixture of amide E/Z isomers.

Procedure N:

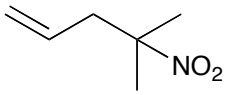
In a glove box, a flame dried 10 mL Schlenk flask was charged with Grubbs' second-generation catalyst (10.6 mg, 0.0125 mmol, 5 mol%). The vessel was capped, removed from the glove box, and 5 mL of toluene was added followed by the substrate amide **8** (52 mg). The vessel was recapped and heated at 60 °C until reaction completion was determined by TLC (~3 h).

After the allotted reaction time, the solvent was evaporated and the desired compound **S21d** (37 mg, 84% yield) was obtained via silica gel chromatography (50:50 EtOAc:hexanes).

Spectral Data:

Decarboxylative allylation products:

T2a



^{1}H NMR (500 MHz, $CDCl_3$)

δ 5.61 (m, 1H), 5.10 (m, 2H), 2.56 (d, *J* = 7.4 Hz, 2H), 1.50 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$)

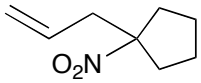
δ 130.1, 119.4, 86.7, 44.0, 24.4.

IR (Thin Film, NaCl)

Found: $\bar{\nu}$ 3090, 1650, 1537 and 1356 (NO_2) cm^{-1}.

GC-MS *m/z* (%): 83 (12) [M-NO_2], 43[base fragment].

T2b



^{1}H NMR (400 MHz, $CDCl_3$):

δ 5.70 (m, 1H), 5.17 (m, 2H), 2.74 (d, *J* = 7.2 Hz, 2H), 2.52 (m, 2H), 2.84 (m, 6H).

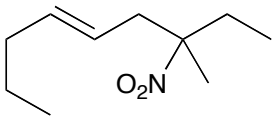
^{13}C NMR (126 MHz, $CDCl_3$):

δ 131.5, 119.88, 99.26, 43.44, 36.73, 24.21.

IR: (Thin Film, NaCl) Found: $\bar{\nu}$ 3100, 1650, 1537 and 1355 (NO_2) cm^{-1}.

GC-MS: *m/z* (%):109 (28) [M-NO_2], 67(100)[base fragment].

T2c



^{1}H NMR (400 MHz, $CDCl_3$):

δ 5.55 (m, 1H), 5.28 (m, 1H), 2.68 (dd, *J* = 13.9 Hz, 1H), 2.48 (dd, *J* = 14.2, 7.7 Hz, 1H), 2.13 – 1.94 (m, 3H), 1.86 – 1.79 (m, 1H),1.52 (s, Hz, 3H), 1.38 (q, *J* = 14.1 Hz, 2H), 0.90 (m, 6H).

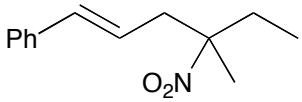
^{13}C NMR (126 MHz, $CDCl_3$):

δ 136.5, 122.4, 91.7, 42.6, 34.5, 32.4, 22.3, 21.1, 13.6, 8.3.

IR: (Thin Film, NaCl) Found: $\bar{\nu}$ 3100, 1640, 1537 and 1388 (NO_2) cm^{-1}.

GC-MS: *m/z* (%):139 (10) [M-NO_2], 55(100)[base fragment].

T2d



^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.33 (m, 5H), 6.50 (d, *J* = 15.7 Hz, 1H), 6.06 (dt, *J* = 15.2, 7.5 Hz, 1H), 2.93 (dd, *J* = 14.1 Hz, 1H), 2.71 (dd, *J* = 14.1, 7.1 Hz, 1H), 2.12 (dt, *J* = 14.1, 7.1 Hz, 1H), 1.90 (dq, *J* = 14.1, 7.4 Hz, 1H), 1.59 (s, 3H), 0.96 (t, *J* = 7.1 Hz, 3H).

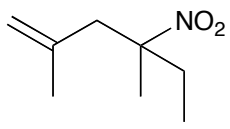
^{13}C NMR (126 MHz, $CDCl_3$):

δ 135.0, 133.5, 126.9, 126.1, 124.6, 120.7, 90.3, 41.1, 31.1, 19.8, 6.4.

IR: (Thin Film, NaCl) Found: $\bar{\nu}$ 3100 ,1537 and 1380 (NO_2), 1494, 1467, 1448, 1356, 1371(1494-1371 are aromatic).

GC-MS: *m/z* (%):173 (14) [M-NO_2], 91(100)[base fragment].

T2e



^{1}H NMR (500 MHz, $CDCl_3$)

δ 4.85 (s, 1H), 4.65 (s, 1H), 2.79 (d, *J* = 14.2 Hz, 1H), 2.40 (d, *J* =14.2 Hz, 1H), 2.03 (dq, *J* = 14.2, 7.3 Hz, 1H), 1.69 (dq, *J* = 14.2, 7.3 Hz, 1H), 1.61 (s, 3H), 1.45 (s, 3H), 0.83 (t, *J* = 14.2 Hz, 3H).

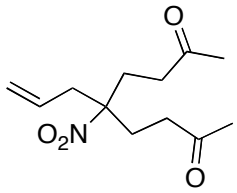
^{13}C NMR (126 MHz, $CDCl_3$)

δ 138.6, 115.7, 90.5, 46.5, 32.5, 22.3, 19.6, 7.3.

IR: (Thin Film, NaCl) Found: $\bar{\nu}$ 3100, 1655, 1537 and 1355 (NO_2) cm^{-1}.

GC-MS: *m/z* (%): 111 (10) [M-NO_2], 55(75), 69(100)[base fragment].

T2f



^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.59 – 5.49 (m, 1H), 5.13 (m, 2H), 2.59 (d, *J* = 7.3, Hz, 2H), 2.37 (t, *J* = 7.3 Hz, 2H), 2.11 (m, s, 10H).

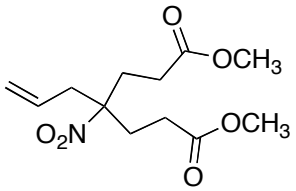
^{13}C NMR (126 MHz, $CDCl_3$)

δ 205.1, 129.2, 119.9, 91.3, 38.8, 36.5, 29.0, 28.2.

IR (Thin Film, NaCl) Found: $\bar{\nu}$ 1720, 1650, 1552 (NO_2), 1449(NO_2), 1350, 1190.

GC-MS: *m/z* (%): 195(6) [M-NO_2], 43 (100)[base fragment].

T2g



^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.56 (m, 1H), 5.19 – 5.10 (m, 2H), 3.62 (s, 6H), 2.61 (d, *J* = 7.3, 2H), 2.21 (m, 8H).

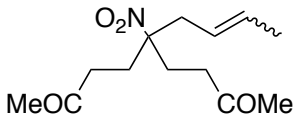
^{13}C NMR (126 MHz, $CDCl_3$):

δ 170.7, 128.4, 119.6, 90.5, 50.4, 37.9, 28.9, 26.8.

IR: (Thin Film, NaCl) Found: $\tilde{\nu}$ Found: 3031, 3002, 2954, 1667, 1639, 1539(NO_2), 1438(NO_2), 1379, 1353, 1319, 1261, 1199, 1176.

GC-MS: *m/z* (%): 226 (19) [M-NO_2], 43 (100)[base fragment].

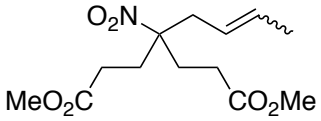
T2h



1H NMR (400 MHz, CDCl3):

δ 5.60 (dd, J = 15.1, 6.5 Hz, 1H), 5.23 (m, 1H), 2.60 (d, J = 7.3 Hz, 2H), 2.44 (t, J = 7.8 Hz, 4H), 2.17 (m, 10H), 1.69 (d, J = 6.5 Hz, 3H).

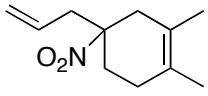
T2i



1H NMR (400 MHz, CDCl3):

δ 5.64 (m, 1H), 5.27 (m, 1H), 3.72 (s, 6H), 2.65 (m, 2H), 2.29 (m, 8H), 1.70 (d, J = 5.7 Hz, 3H).

T2j



^{1}H NMR (500 MHz, $CDCl_3$):

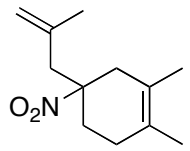
δ 5.70 – 5.52 (m, *J* = 17.5, 10.2, 7.4 Hz, 1H), 5.07 (dm, 2H), 2.70 (d, *J* = 18.2 Hz, 1H), 2.50 (m, 2H), 2.26 (m, 1H), 2.20 (d, *J* = 17.6 Hz, 1H), 2.07 – 1.89 (m, 2H), 1.89 – 1.79 (m, 1H), 1.57 (s, 3H), 1.52 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 130.6, 124.8, 121.9, 120.2, 90.2, 43.2, 38.9, 30.7, 28.5, 19.0, 18.4.

IR: (Thin Film, NaCl) Found: $\bar{\nu}$ 3082, 1643, 1539 and 1365, 1438 cm^{-1}.

T2k



^{1}H NMR (500 MHz, $CDCl_3$):

δ 4.85 (m, 1H), 4.64 (m, 1H), 2.69 (d, *J* = 17.7 Hz, 1H), 2.60 (d, *J* = 14.1 Hz, 1H), 2.49 (d, *J* = 14.1 Hz, 1H), 2.33 – 2.26 (m, 1H), 2.23 (d, *J* = 17.6 Hz, 1H), 2.03 – 1.90 (m, 2H), 1.88 – 1.80 (m, 1H), 1.63 (s, 3H), 1.57 (s, 3H), 1.52 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

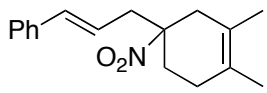
δ 138.2, 123.6, 121.0, 115.6, 89.0, 46.1, 38.3, 30.2, 27.7, 22.4, 17.8, 17.3.

IR:

(Thin Film, NaCl) Found: $\bar{\nu}$ 3090, 1640, 1537 and 1370 cm^{--1}.

GC-MS: *m/z* (%):163 (20) [M-NO_2], 107(100)[base fragment].

T2l



^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.31 (m, 5H), 6.47 (d, *J* = 15.6 Hz, 1H), 6.1 (m, 1H), 2.78 (m, 3H), 2.53 – 2.29 (m, 2H), 2.09 (s, 2H), 2.05 – 1.93 (m, 1H), 1.67 (s, 3H), 1.63 (s, 3H).

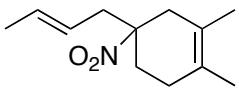
^{13}C NMR (126 MHz, $CDCl_3$):

δ 136.6, 135.0, 128.7, 127.6, 126.3, 124.8, 122.1, 121.9, 90.4, 42.6, 39.1, 30.6, 28.7, 18.9, 18.5.

IR: (Thin Film, NaCl) Found: $\bar{\nu}$ 1643, 1535, 1450, 1370 cm^{-1}.

GC-MS: *m/z* (%): 225 (11) [M-NO_2], 117(100)[base fragment].

T2m



^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.45 (m, 1H), 5.25 (m, 1H), 2.68 (d, *J* = 18.3 Hz, 1H), 2.50 – 2.37 (m, 2H), 2.27 – 2.21 (m, 1H), 2.18 (ddd, *J* = 17.6, 1.7, 0.9 Hz, 1H), 2.07 – 1.87 (m, 2H), 1.86 – 1.77 (m, 1H), 1.59 (ddt, *J* = 6.5, 1.6, 1.0 Hz, 3H), 1.56 (dd, *J* = 1.7, 0.9 Hz, 3H), 1.53 – 1.51 (m, 3H).

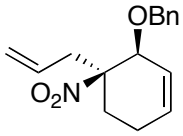
^{13}C NMR (126 MHz, $CDCl_3$):

δ 131.0, 124.8, 123.3, 121.9, 90.6, 42.4, 38.8, 30.4, 28.7, 19.0, 18.5, 18.0.

IR (Thin Film, NaCl) Found: $\bar{\nu}$ 1643, 1535, 1438, 1365 cm^{-1}.

GC-MS: *m/z* (%):163 (21) [M-NO_2], 107(100)[base fragment].

T3a



(Major diastereomer) ^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.22 (m, 5H), 5.85 (m, 1H), 5.75 (m, 1H), 5.52 (m, 1H), 5.07 (m, 2H), 4.49 (dd, *J* = 11.5, 23 Hz, 2H), 4.04 (d, *J* = 5.2, 1H), 2.64 (dd, *J* = 14.6, 6.9 Hz, 1H), 2.30 (m, 3H), 2.10 (dd, *J* = 14.6 6.9 Hz 1H), 2.97 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 135.8, 129.5, 128.3, 126.3, 125.8, 125.7, 121.8, 118.5, 89.9, 73.0, 70.1, 36.0, 22.1, 19.6.

IR: (Thin Film, NaCl) Found: $\bar{\nu}$ 2918, 2846, 1542 (NO_2), 1454 (NO_2), 1367, 1305, 1089, 1062.

GC-MS: *m/z* (%):173 (14) [M-NO_2], 91(100)[base fragment].

(Minor diastereomer) ^{1}H NMR (500 MHz, $CDCl_3$):

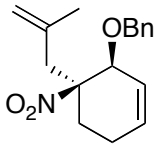
δ 7.31 – 7.14 (m, 5H), 5.88 – 5.83 (m, 1H), 5.79 – 5.73 (m, 1H), 5.53 (m, 1H), 5.07 (dd, 2H), 4.50 (q, 2H), 4.04 (d, *J* = 5.3 Hz, 1H), 2.65 (dd, *J* = 14.6, 6.9, Hz, 1H), 2.35 – 2.27 (m, 3H), 2.10

(dd, 14.6,6.9 Hz, 1H), 2.05 – 1.93 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 136.1, 134.7, 133.4, 129.9, 129.8, 128.6, 126.8, 126.6, 126.1, 126.0, 124.6, 122.2, 122.2, 119.7, 118.8, 90.4, 90.2, 73.31, 73.27, 70.4, 36.3, 35.6, 28.0, 22.5, 22.4, 20.1, 19.9, 12.4.

T3b



(Major Diastereomer) ^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.48 – 7.09 (m, 5H), 5.94 – 5.82 (m, *J* = 9.8, 4.1, 1.9 Hz, 1H), 5.82 – 5.70 (m, 1H), 4.85 (s, 1H), 4.68 (s, 1H), 4.48 (q, *J* = 11.5 Hz, 2H), 4.00 (d, *J* = 5.2 Hz, 1H), 2.74 (d, *J* = 14.6 Hz, 1H), 2.46 – 2.21 (m, 3H), 2.21 – 1.96 (m, 2H), 1.61 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 139.2, 137.8, 131.5, 128.3, 127.9, 127.8, 123.8, 116.6, 91.4, 75.5, 72.2, 41.6, 24.3, 22.6, 21.9.

IR: (Thin Film, NaCl) Found: $\tilde{\nu}$ 2918, 2846, 1654, 1542 (NO_2), 1454 (NO_2), 1089, 1062.

GC-MS: *m/z* (%): 241 (1) [M-NO_2], 91(100)[base fragment].

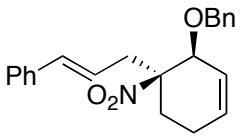
(Minor Diastereomer) ^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.41 – 7.14 (m, 6H), 5.89 – 5.80 (m, 2H), 4.88 – 4.82 (m, 1H), 4.66 (m,1H), 4.63 (d, *J* = 11.3 Hz, 1H), 4.49 (d, *J* = 11.3 Hz, 1H), 4.41 – 4.37 (m, 1H), 2.91 (d, *J* = 14.3 Hz, 1H), 2.57 (d, *J* = 14.4 Hz, 1H), 2.35 (m,1H), 2.17 – 2.10 (m, 2H), 2.09 – 2.01 (m, 1H), 1.63 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 137.7, 136.4, 129.8, 126.8, 126.2, 126.1, 123.0, 114.8, 90.3, 71.3, 69.6, 41.7, 25.2, 22.0, 21.5.

T3c



^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.21 (m, 10H), 6.38 (d, *J* = 15.7 Hz, 1H), 5.92 (m, 2H), 5.76 (m, 1H), 4.51 (q, *J* = 11.5 Hz, 2H), 4.09 (d, *J* = 5.2 Hz, 1H), 2.82 (dd, *J* = 14.7, 6.8 Hz, 1H), 2.47 (dd, *J* = 14.7, 8.2 Hz, 1H), 2.34 (m, 2H), 2.15 (dd, *J* = 12.4, 5.9 Hz, 1H), 2.02 (m, 1H).

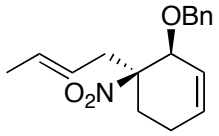
^{13}C NMR (126 MHz, $CDCl_3$):

δ 137.8, 136.5, 135.1, 131.6, 128.6, 128.3, 127.9, 127.8, 127.78, 126.4, 123.9, 121.4, 92.1, 75.0, 72.1, 37.3, 24.2, 21.8.

IR: (Thin Film, NaCl) Found: $\bar{\nu}$ 1350, 1675, 1660, 1650, 1540 (NO_2), 1440 (NO_2), 1269.

GC-MS *m/z* (%): 303 (14) [M-NO_2], 91(100)[base fragment].

T3d



^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.23 (m, 5H), 5.85 (m, 1H), 5.75 (m, 1H), 5.55 (m, 1H), 5.15 (m, 1H), 4.48 (m, 2H), 4.02 (d, *J* = 5.2 Hz, 1H), 2.56 (dd, *J* = 7.0 Hz, 1H), 2.26 (m, 3H), 2.11 (dd, 6.2 Hz, 1H), 1.97 (m, 1H), 1.58 (d, *J* = 3.5 Hz, 3H).

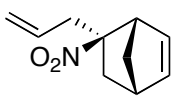
^{13}C NMR (126 MHz, $CDCl_3$):

δ 137.9, 131.5, 131.2, 128.3, 127.8, 127.7, 123.9, 122.6, 92.2, 75.1, 72.1, 36.9, 24.1, 21.6, 18.0.

IR: (Thin Film, NaCl) Found: $\bar{\nu}$ 3050, 2910, 1650, 1635, 1540 (NO_2), 1452 (NO_2), 1087, 1060.

GC-MS: *m/z* (%): 241 (1) [M-NO_2], 150 [M-NO_2-Bn^+] (5), 91(100)[base fragment].

T3e



(Major Diastereomer) ^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.27 (dd, *J* = 5.7, 3.1 Hz, 1H), 5.91 (dd, *J* = 5.7, 2.8 Hz, 1H), 5.65 (m, 1H), 5.05 (m, 2H), 3.19 (s, 1H), 2.86 (m, 2H), 2.60 (dd, *J* = 14.4, 7.0 Hz 1H), 2.20 (dd, *J* = 13.4, 3.4 Hz, 1H), 1.81 (dd, *J* = 13.4, 3.4 Hz, 1H), 1.61 (ddt, *J* = 9.2, 3.5, 1.8 Hz 1H), 1.50 (d, *J* = 9.2 Hz, 1H).

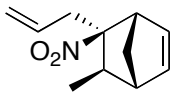
^{13}C NMR (126 MHz, $CDCl_3$):

δ 139.7, 133.7, 131.2, 119.6, 99.5, 51.4, 48.1, 45.4, 42.1, 36.4.

IR: (Thin Film, NaCl) Found: $\bar{\nu}$ 2920, 1543 (NO_2), 1454 (NO_2), 1367, 1300, 1090 cm^{-1}.

GC-MS: *m/z* (%): 133 (8) [M-NO_2], 66 (71), 91(100)[base fragment].

T3f



(Major Diastereomer) ^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.29 (dd, *J* = 5.7, 3.1 Hz, 1H), 6.02 (dd, *J* = 5.7, 2.8 Hz, 1H), 5.68 (m, 1H), 5.07 (m, 2H), 3.17 (s, 1H), 2.72 (dd, *J* = 14.6, 7.1 Hz, 1H), 2.45 (dd, *J* = 14.6, 7.1 Hz, 1H), 2.42 (s, 1H), 2.28 (q, *J* = 7.1 Hz, 1H), 1.61 (d, *J* = 9.5 Hz, 1H), 1.54 – 1.49 (m, 1H), 1.17 (d, *J* = 7.1 Hz 3H).

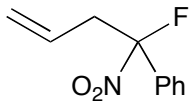
^{13}C NMR (126 MHz, $CDCl_3$):

δ 139.6, 135.3, 131.5, 119.7, 100.5, 49.5, 48.9, 44.3, 42.8, 41.1, 16.5.

IR: (Thin Film, NaCl) Found: $\bar{\nu}$ 2918, 1542 (NO_2), 1450(NO_2).

GC-MS: *m/z* (%):147 (7) [M-NO_2], 91(75), 66(100)[base fragment].

S13c



^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.59 (m, 2H), 7.39 (m, 3H), 5.65 (m, 1H), 5.21 (m, 2H), 3.31 (m, 1H), 3.29 – 3.05 (m, 7.6Hz, 1H).

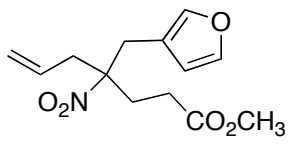
^{13}C NMR (126 MHz, $CDCl_3$):

δ 132.3(d, J_{CF} = 23.4 Hz), 129.9 (d, J_{CF} = 1 Hz), 127.8 (d, J_{CF} = 1.0 Hz), 126.3 (d, J_{CF} = 3.3 Hz), 124.3 (d, *J* = 8.6 Hz), 121.4 (d, J_{CF} = 23 Hz), 119.0 (d, J_{CF} = 242.0 Hz), 40.4 (d, J_{CF} = 21.3 Hz).

IR: (Thin Film, NaCl) Found: $\bar{\nu}$ 1645, 1539 and 1353 (NO_2), 1458, 1388, 1261, 972 (C-F) cm^1.

GC-MS: *m/z* (%):149 (71) [M-NO_2], 129 (100)[base fragment].

S14c



^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.28 (s, 1H), 6.24 (d, *J* = 3.2 Hz, 1H), 6.07 (d, *J* = 3.2 Hz, 1H), 5.65 (m, 1H), 5.16 (m, 2H), 3.62 (s, 3H), 3.24 (dd, *J* = 37.4, 15.4 Hz, 2H), 2.58 (d, *J* = 15.4, 2H), 2.44 – 2.07 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 172.3, 148.6, 142.4, 130.2, 121.3, 110.6, 109.4, 92.7, 51.9, 40.1, 33.5, 31.0, 28.5.

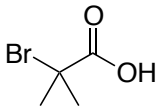
IR: (Thin Film, NaCl) Found: $\bar{\nu}$ 1540 (NO_2), 1437 (nitro NO_2).

GC-MS: *m/z* (%): 221(20) [M-NO_2], 81 (100)[base fragment].

GC-MS: *m/z* (%):149 (21) [M-NO_2], 107(100)[base fragment].

Decarboxylative allylation intermediates and substrates

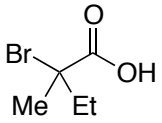
A-1



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$)δ 173.75, 61.54, 13.97.

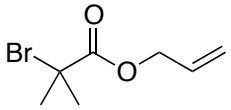
A-2



^{1}H NMR (400 MHz, $CDCl_3$):

δ 2.19 (m, 2H), 1.94 (s, 3H), 1.07 (t, *J* = 7.4 Hz, 3H).

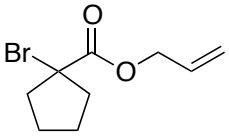
A-4



^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.94 (m, 1H), 5.39 (dm, *J* = 17.49 Hz, 1H), 5.28 (ddd, *J* = 10.5, 2.5, 1.3 Hz, 1H), 4.67 (dt, *J* = 5.6, 1.4 Hz, 2H), 1.95 (s, 6H).

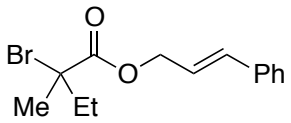
A-5



^{1}H NMR (400 MHz, $CDCl_3$):

δ 5.96 (m, 1H), 5.41 (dm, *J* = 17.16 Hz, 1H), 5.30 (dm, *J* = 9.94 Hz, 1H), 4.71 (dt, *J* = 5.6, 1.4 Hz, 2H), 2.33 (m, 3H), 2.02 (m, 2H), 1.81 (m, 2H).

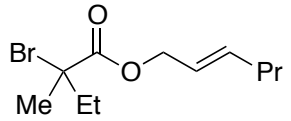
A-6



^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.43 (d, *J* = 6.94 Hz, 2H), 7.36 (t, *J* = 6.89, 2H), 7.30 (d, *J* = 7.39, 1H), 6.74 (d, *J* = 15.9 Hz, 1H), 6.33 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.87 (dd, *J* = 6.4, 1.2 Hz, 2H), 2.21 (qd, *J* = 7.3, 3.4 Hz, 2H), 1.94 (s, 3H), 1.04 (t, *J* = 7.4 Hz, 3H).

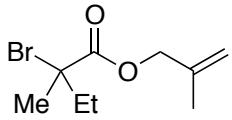
A-7



^{1}H NMR (400 MHz, $CDCl_3$):

δ 5.83 (dd, *J* = 14.5, 7.6 Hz, 1H), 5.60 (m, 1H), 4.64 (d, *J* = 6.46 Hz, 2H), 2.17 (qd, *J* = 7.3, 1.9 Hz, 2H), 2.06 (dd, *J* = 13.5, 6.7 Hz, 2H), 1.90 (s, 3H), 1.44 (m, 3H), 1.02 (t, *J* = 7.59, Hz, 3H), 0.93 (t, *J* = 7.59 Hz, 3H).

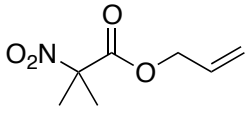
A-8



^{1}H NMR (400 MHz, $CDCl_3$):

δ 5.07 (s, 1H), 4.99 (s, 1H), 4.62 (s, 2H), 2.20 (qd, *J* = 7.3, 3.3 Hz, 2H), 1.93 (s, 3H), 1.82 (s, 3H), 1.03 (t, *J* = 7.4 Hz, 3H).

S6a



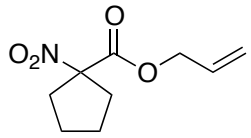
^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.90 (m, 1H), 5.35 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.30 (dd, *J* = 10.74, 1.3 Hz 1H), 4.71 (m, 2H), 1.84 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 167.44, 130.65, 119.45, 89.34, 67.04, 24.02.

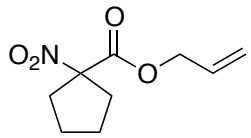
S7a



^{1}H NMR (400 MHz, $CDCl_3$):

δ 5.90 (ddt, *J* = 16.3, 10.7, 5.7 Hz, 1H), 5.35 (dm, *J* = 16.86 1H), 5.30 (dd, *J* = 10.5, 1.0 Hz, 1H), 2.72 (m, 2H), 2.42 (dt, *J* = 8.1, 5.1 Hz, 2H), 1.85 (m, 4H).

S7a



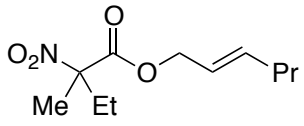
^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.89 (m, 1H), 5.34 (ddd, *J* = 17.2, 2.7, 1.4 Hz, 1H), 5.29 (dd, *J* = 10.5, 1.1 Hz, 1H), 4.70 (dt, *J* = 5.7, 1.3 Hz, 2H), 2.70 (m, 2H), 2.41 (m, 2H), 1.83 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 167.49, 130.70, 119.36, 99.57, 67.00, 36.47, 24.60.

S7b



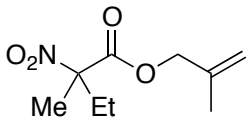
^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.73 (m, 1H), 5.46 (m, 1H), 4.56 (dd, *J* = 6.6, 0.9 Hz, 2H), 2.23 (dt, *J* = 14.9, 7.4 Hz, 1H), 2.11 (dt, *J* = 14.9, 7.4 Hz, 1H), 1.96 (apparent q, *J* = 7.38 Hz, 2H), 1.69 (s, 3H), 1.34 (m, 2H), 0.88 (t, *J* = 7.29 Hz, 3H), 0.83 (t, *J* = 7.29 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 167.33, 137.97, 122.51, 93.22, 67.23, 34.24, 29.77, 21.91, 20.72, 13.56, 8.10.

S7c



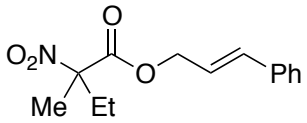
^{1}H NMR (500 MHz, $CDCl_3$):

δ 4.91 (s, 1H), 4.90 (s, 1H), 4.55 (s, 2H), 2.26 (dt, *J* = 14.9, 7.4 Hz, 1H), 2.13 (m, 1H), 1.72 (s, 3H), 1.67 (s, 3H), 0.89 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 69.64, 29.80, 20.74, 19.32, 8.10.

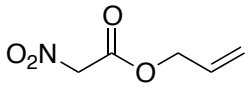
S7d



^{1}H NMR (500 MHz, $CDCl_3$3):

δ 7.42 (m, 2H), 7.36 (m, 2H), 7.30 (m, 1H), 6.69 (d, *J* = 15.9 Hz, 1H), 6.27 (dt, *J* = 15.8, 7.25, 1H), 4.87 (d, *J* = 6.54 Hz, 2H), 2.36 (dt, *J* = 14.9, 7.3 Hz, 1H), 2.24 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.80 (s, 3H), 0.95 (overlapping methyl signals, 6H).

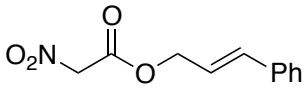
A-9



1H NMR (400 MHz, $CDCl_3$):

δ 5.94 (ddt, *J* = 16.4, 10.4, 5.9 Hz, 1H), 5.41 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.35 (d, *J* = 10.4 Hz, 1H), 5.22 (s, 2H), 4.78 (d, *J* = 5.9 Hz, 2H).

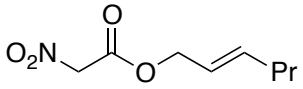
A-10



^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.43 (m, 2H), 7.35 (m, 3H), 6.74 (d, *J* = 16.1 Hz, 1H), 6.30 (dt, *J* = 16.1, 7.26 Hz, 1H), 5.23 (s, 2H), 4.94 (d, *J* = 6.7 Hz, 2H).

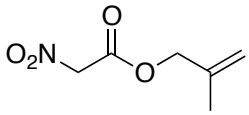
A-11



^{1}H NMR (400 MHz, $CDCl_3$):

δ 5.87 (dt, *J* = 15.74, 7.62 Hz, 1H), 5.59 (dt, *J* = 15.74, 7.62 Hz, 1H), 5.19 (s, 2H), 4.72 (d, *J* = 6.7 Hz, 2H), 2.07 (dd, *J* = 14.1, 6.8 Hz, 2H), 1.44 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).

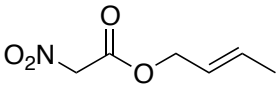
A-12



^{1}H NMR (400 MHz, $CDCl_3$):

δ 5.23 (s, 2H), 5.04 (d, *J* = 5.2 Hz, 2H), 4.70 (s, 2H), 1.80 (s, 3H).

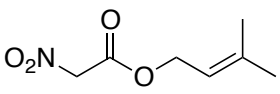
A-13



^{1}H NMR (400 MHz, $CDCl_3$):

δ 5.89 (dd, *J* = 15.2, 6.6 Hz, 1H), 5.61 (m, 1H), 5.18 (s, 2H), 4.70 (d, *J* = 6.85 2H), 1.77 (d, *J* = 6.5 Hz, 3H)

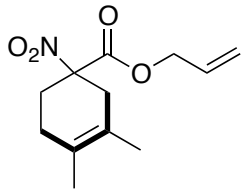
A-14



^{1}H NMR (400 MHz, $CDCl_3$):

δ 5.37 (tm, *J* = 7.56 1H), 5.18 (s, 2H), 4.77 (d, *J* = 7.4 Hz, 2H), 1.80 (s, 3H), 1.75 (s, 3H).

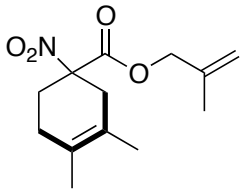
A-15



^{1}H NMR (400 MHz, $CDCl_3$):

δ 5.90 (ddd, *J* = 15.8, 10.9, 5.5 Hz, 1H), 5.37 (d, *J* = 17.54 Hz, 1H), 5.30 (d, *J* = 10.9 Hz, 1H), 4.71 (d, *J* = 5.7 Hz, 2H), 2.92 (d, *J* = 17.5 Hz, 1H), 2.76 (d, *J* = 17.1 Hz, 1H), 2.59 (m, 1H), 2.35 (m, 1H), 2.10 (s, 2H), 1.68 (s, 3H), 1.62 (s, 3H).

A-16



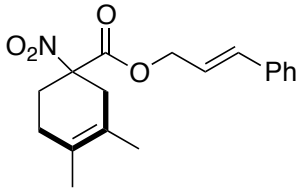
^{1}H NMR (500 MHz, $CDCl_3$):

δ 4.89 (s, 2H), 4.54 (d, *J* = 4.6 Hz, 2H), 2.83 (d, *J* = 17.5 Hz, 1H), 2.68 (d, *J* = 17.5 Hz, 1H), 2.49 (ddd, *J* = 7.5, 6.8, 1.7 Hz, 1H), 2.27 (dt, *J* = 13.88, 6.8 Hz, 1H), 2.01 (s, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 1.53 (s, 3H).

13C NMR (126 MHz, $CDCl_3$):

δ 165.87, 137.67, 123.99, 120.03, 113.04, 91.06, 68.64, 36.20, 28.09, 27.05, 18.25, 17.72, 17.52.

A-17



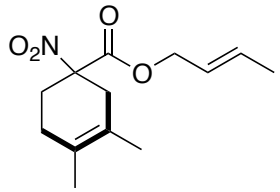
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.32 (d, *J* = 5.2, 3.4 Hz, 2H), 7.27 (m, 2H), 7.22 (m, 1H), 6.59 (d, *J* = 15.9 Hz, 1H), 6.16 (dt, *J* = 15.9, 6.5 Hz, 1H), 4.77 (dd, *J* = 6.5, 0.9 Hz, 2H), 2.84 (d, *J* = 17.7 Hz, 1H), 2.68 (d, *J* = 17.5 Hz, 1H), 2.50 (dtd, *J* = 13.76, 5.65, 1.65 Hz, 1H), 2.27 (dt, *J* = 13.76, 7.33 Hz, 1H), 2.01 (s, 2H), 1.59 (s, 3H), 1.53 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 167.00, 135.81, 135.46, 128.66, 128.38, 126.74, 124.98, 121.47, 121.06, 92.11, 67.11, 37.22, 29.10, 28.06, 18.74, 18.56.

A-18



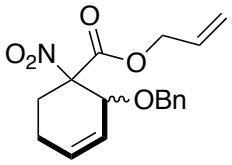
^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.74 (m, 1H), 5.47 (m, 1H), 4.54 (d, *J* = 6.12 Hz, 2H), 2.82 (d, *J* = 17.6 Hz, 1H), 2.65 (d, *J* = 17.6 Hz, 1H), 2.49 (dtd, *J* = 13.6, 5.6, 1.8 Hz, 1H), 2.23 (dt, *J* = 13.6, 8.22 Hz, 1H), 2.00 (s, 2H), 1.65 (d, *J* = 6.93 Hz, 3H), 1.59 (s, 3H), 1.54 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 167.02, 132.78, 124.93, 123.67, 121.07, 92.09, 67.23, 37.16, 29.04, 28.02, 18.72, 18.54, 17.81.

A-19 Diastereomers were separated and both are reported:



Major diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$):

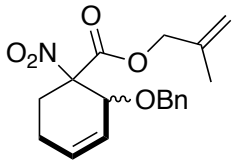
δ 7.32 (m, 5H), 5.97 (s, 2H), 5.85 (m, 1H), 5.32 (d, *J* = 17.2 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 4.72 (m, 3H), 4.67 (m, 1H), 4.59 (dd, *J* = 11.5, 3.5 Hz, 1H), 2.70 (d, *J* = 14.4 Hz, 1H), 2.51 (m, 1H), 2.32 (d, *J* = 18.9 Hz, 1H), 1.97 (m, 1H).

Minor diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.32 (m, 5 H), 5.90 (m, 3H), 5.35 (d, *J* = 17.2 Hz, 1H), 5.31 (d, *J* = 10.4 Hz, 1H), 4.73 (d, *J* = 4.7 Hz, 1H), 4.69 (m, 2H), 4.61 (q, *J* = 11.5 Hz, 2H), 2.61 (td, *J* = 12.5, 6.0 Hz, 1H), 2.53 (dd, *J* = 13.0, 6.1 Hz, 1H), 2.42 (dt, *J* = 19.4, 5.11 Hz, 1H), 1.99 (m, 1H).

A-20 Reported as a 1:1.3 mixture



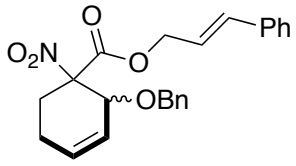
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.24 (m, 11H), 5.88 (dd, *J* = 3.9, 2.1 Hz, 1H), 5.86 (ddd, *J* = 4.5, 2.3, 1.1 Hz, 1H), 5.83 (dd, *J* = 4.6, 1.9 Hz, 1H), 4.89 (m, 3H), 4.86 (m, 1H), 4.63 (m, 4H), 4.51 (m, 4H), 4.43 (d, *J* = 12.8 Hz, 1H), 2.61 (dd, *J* = 14.5, 5.6 Hz, 1H), 2.52 (m, 1H), 2.43 (m, 2H), 2.33 (m, 1H), 2.20 (m, 1H), 1.89 (m, 2H), 1.65 (s, 3H), 1.62 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 164.82, 164.63, 138.66, 138.55, 137.44, 137.42, 130.74, 130.42, 128.42, 128.41, 127.91, 127.88, 127.64, 124.49, 123.22, 114.56, 114.31, 93.60, 93.11, 72.57, 72.02, 71.96, 70.95, 69.81, 69.73, 24.99, 23.71, 23.56, 21.64, 19.33.

A-21 Reported as a 1:1 mixture



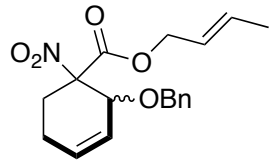
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.23 (m, 19H), 6.58 (d, *J* = 15.9 Hz, 1H), 6.54 (dt, *J* = 15.9, 1.2 Hz, 1H), 6.12 (m, 2H), 5.88 (d, *J* = 3.29 Hz, 2H), 5.86 (ddd, *J* = 4.7, 2.4, 1.3 Hz, 1H), 5.83 (dd, *J* = 4.7, 2.0 Hz, 1H), 4.75 (m, 4H), 4.65 (m, 3H), 4.51 (m, 3H), 2.60 (dd, *J* = 14.0, 5.4 Hz, 1H), 2.46 (overlapping qd/m, *J* = 12.54, 5.58 Hz, 3H), 2.31 (dt, 1H), 2.22 (m, 1H), 1.89 (m, 2H).

^{13}C NMR (126 MHz, CDCl3):

δ 164.93, 164.71, 137.45, 135.79, 135.76, 135.72, 135.51, 130.70, 130.43, 128.68, 128.62, 128.45, 128.44, 128.41, 128.32, 127.90, 127.87, 127.53, 126.76, 126.73, 124.49, 123.20, 121.51, 121.19, 93.58, 93.10, 72.57, 72.09, 71.98, 70.89, 67.19, 67.16, 25.06, 23.69, 23.56, 21.62.

A-22 Reported as a 1:1.2 mixture of diastereomers



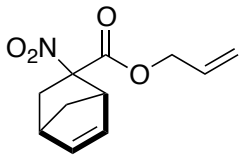
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.24 (m, 10H), 5.87 (m, 2H), 5.85 (ddd, *J* = 4.6, 2.3, 1.2 Hz, 1H), 5.82 (dd, *J* = 4.7, 1.9 Hz, 1H), 5.72 (dddd, *J* = 15.3, 12.8, 7.7, 6.6 Hz, 2H), 5.44 (m, 2H), 4.63 (m, 2H), 4.59 (s, 1H), 4.52 (m, 6H), 2.58 (dd, *J* = 5.5 Hz, 1H), 2.48 (m, 1H), 2.41 (m, 2H), 2.30 (m, 1H), 2.19 (s, 1H), 1.88 (m, 2H), 1.81 (t, *J* = 2.3 Hz, 1H), 1.65 (ddt, *J* = 6.6, 1.9, 1.0 Hz, 2H), 1.58 (ddt, *J* = 6.5, 2.0, 1.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 164.89, 164.68, 137.51, 137.48, 133.22, 132.83, 130.64, 130.37, 128.41, 128.40, 128.06, 127.88, 127.87, 127.86, 127.77, 127.56, 124.50, 123.75, 123.46, 123.27, 93.54, 93.07, 72.55, 72.11, 72.05, 71.47, 70.90, 67.30, 67.28, 57.74, 25.00, 23.65, 23.53, 21.60, 17.80, 17.74.

A-23 Major Diastereomer reported:



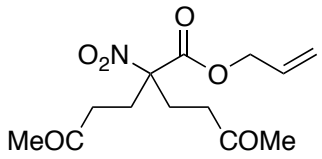
^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.36 (s, 1H), 5.92 (s, 1H), 5.81 (m, 1H), 5.26 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.21 (d, *J* = 10.5 Hz, 1H), 4.63 (d, *J* = 4.65 Hz, 2H), 3.64 (s, 1H), 2.96 (s, 1H), 2.30 (m, 2H), 2.14 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 167.82, 141.05, 132.98, 130.60, 119.43, 67.11, 51.88, 49.26, 41.72, 37.49.

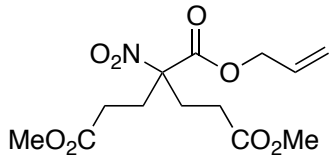
A-24



^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.91 (m, 1H), 5.38 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.33 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.70 (dt, *J* = 5.9, 1.2 Hz, 2H), 2.55 (m, 4H), 2.47 (m, 4H), 2.17 (s, 7H).

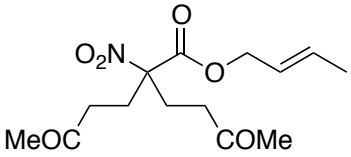
A-25



^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.91 (m, 1H), 5.38 (d, *J* = 17.2 Hz, 1H), 5.34 (d, *J* = 10.4 Hz, 1H), 4.72 (d, *J* = 5.9 Hz, 2H), 3.72 (s, 7H), 2.57 (m, *J* = 8.4, 2.1 Hz, 5H), 2.43 (m, 5H).

A-26



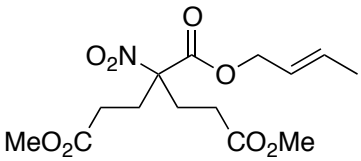
^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.77 (m, 1H), 5.50 (m, 1H), 4.54 (dt, *J* = 6.79, 2H), 2.45 (m, *J* = 7.0, 5.5, 2.4 Hz, 4H), 2.36 (m, 4H), 2.08 (s, 6H), 1.67 (dm, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 210.50, 205.63, 166.10, 133.58, 123.43, 94.47, 67.52, 37.68, 29.96, 28.45, 17.82.

A-27



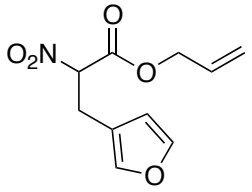
^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.83 (m, 1H), 5.55 (m, 1H), 4.63 (dt, *J* = 6.68, 1.0 Hz, 2H), 3.70 (s, 6H), 2.53 (m, 4H), 2.39 (m, 4H), 1.74 (dm, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 171.95, 165.73, 133.67, 123.33, 94.12, 67.65, 52.06, 29.56, 28.52, 17.81.

S14a



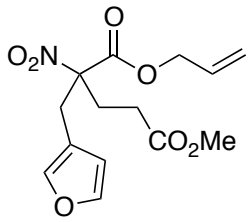
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.35 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.18 (dq, *J* = 3.23, 0.74 Hz, 1H), 5.89 (ddt, *J* = 17.1, 10.4, 5.9 Hz, 1H), 5.47 (dd, *J* = 9.5, 5.4 Hz, 1H), 5.36 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.32 (dq, *J* = 10.4, 1.1 Hz, 1H), 4.73 (d, *J* = 5.77 Hz, 2H), 3.67 (dd, *J* = 16.0, 9.5 Hz, 1H), 3.54 (dd, *J* = 16.0, 5.30 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 163.40, 147.59, 142.65, 130.30, 120.04, 110.63, 108.56, 86.25, 67.53, 29.17.

S14b



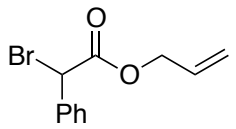
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.27 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.23 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.09 (dd, *J* = 3.2, 0.6 Hz, 1H), 5.82 (ddt, *J* = 17.1, 10.4, 5.9 Hz, 1H), 5.29 (ddd, *J* = 17.2, 2.7, 1.4 Hz, 1H), 5.24 (dq, *J* = 10.4, 1.1 Hz, 1H), 4.63 (ddd, *J* = 5.9, 2.5, 1.2 Hz, 2H), 3.62 (s, 3H), 2.39 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 171.97, 165.44, 146.77, 142.97, 130.42, 120.01, 110.69, 109.95, 94.12, 67.47, 52.00, 33.34, 28.73, 28.58.

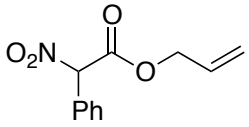
A-29



^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.58 (m, 2H), 7.39 (m, 3H), 5.92 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.40 (s, 1H), 5.34 (ddd, *J* = 17.2, 2.9, 1.5 Hz, 1H), 5.28 (ddd, *J* = 10.5, 2.4, 1.2 Hz, 1H), 4.70 (ddt, *J* = 5.6, 4.1, 1.3 Hz, 2H).

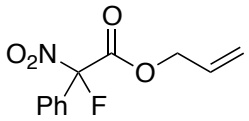
S13a



^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.52 (m, 5H), 6.22 (s, 1H), 5.91 (ddt, *J* = 16.3, 11.6, 5.8 Hz, 1H), 5.37 (dd, *J* = 16.85, 1.1 Hz, 1H), 5.31 (d, *J* = 9.91 Hz, 1H), 4.78 (m, 2H).

S13b



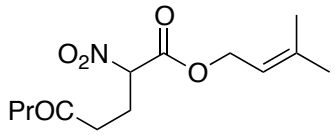
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.64 (m, 2H), 7.48 (m, 1H), 7.42 (m, 3H), 5.85 (m, 1H), 5.32 (dq, *J* = 17.29, 1.1 Hz, 1H), 5.27 (dq, *J* = 10.4, 1.1 Hz, 1H), 4.77 (d, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 160.9 (*J* = 27.49 Hz), 131.8 (*J* = 1.0 Hz), 129.74, 128.70(*J* = 1.56 Hz) , 126.49, 126.42 120.65, 112.5 (*J* = 250.6 Hz), 68.50.

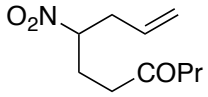
S20a



^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.35 (t, *J* = 6.7 Hz, 1H), 5.26 (dd, *J* = 8.3, 6.1 Hz, 1H), 4.75 (m, 2H), 2.60 (m, 2H), 2.49 (m, 2H), 2.40 (t, *J* = 7.3 Hz, 2H), 1.79 (s, 3H), 1.74 (s, 3H), 1.64 (dt, *J* = 14.8, 7.3 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

S20b



^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.64 (m, 1H), 5.10 (dq, *J* = 9.1, 1.3 Hz, 1H), 5.08 (m, 1H), 2.62 (m, 1H), 2.45 (m, 1H), 2.40 (m, 2H), 2.30 (q, *J* = 7.3 Hz, 2H), 2.05 (m, 2H), 0.84 (t, *J* = 7.3 HZ, 3H).

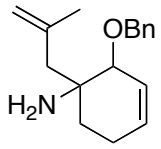
^{13}C NMR (126 MHz, $CDCl_3$):

δ 208.8, 131.2, 119.7, 87.2, 44.9, 38.1, 38.0, 26.9, 17.2, 13.7.

GC-MS: GC: single peak at 5.62. MS: [M-NO_2] Found: 153.2 (parent ion, M-NO_2, 5% of base peak), 81.1 (33% base peak), 71.1 (base peak, 100%), 67.1 (45% base peak), 43.2 (75% base peak).

Amines and derivatives thereof:

S21b



^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.26 (m, 5H), 5.78 (m, 1H), 5.72 (m, Hz, 1H), 4.84 (m, 1H), 4.65 (m, 2H), 4.48 (d, *J* = 11.5 Hz, 1H), 3.62 (s, 1H), 2.14 (d, *J* = 3.1 Hz, 2H), 2.12 – 2.06 (m, 1H), 2.05 – 1.93 (m, 1H), 1.76 (s, 3H), 1.70 (m, 1H), 1.59 (s, 2H), 1.46 (m, 1H).

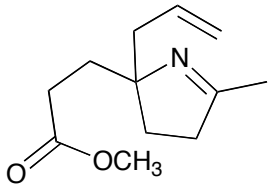
^{13}C NMR (126 MHz, $CDCl_3$)

δ 142.4, 138.8, 129.6, 128.3, 127.7, 127.6, 125.6, 115.1, 78.2, 77.3, 77.0, 76.8, 71.2, 53.3, 46.1, 31.3, 25.5, 23.2.

IR (Thin Film, NaCl) Found: υ_{max} 3070, 3031,2920,2850,1643, 1600, 1500, 1456, 1388, 1315, 1215, 1089, 1068, 1024, 891, 769, 740, 698 cm^{-1}.

HRMS: Calc. HRMS for $C_{17}H_{21}O_3N$ (M + H) 287.1521; Found (M + H) 287.1531.

S12d



^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.58 (m, 1H), 5.09 (dd, *J* = 7.29, 14.19 Hz, 2H), 2.59 (d, *J* = 7.3 Hz, 2H), 2.50 (m, 2H), 2.42 (m, 2H), 2.25 (dd, *J* = 13.8, 8.4 Hz, 1H), 2.09 (s, 3H), 2.08 – 1.98 (m, 2H), 1.96 (t, *J* = 1.5 Hz, 3H), 1.88 – 1.74 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):

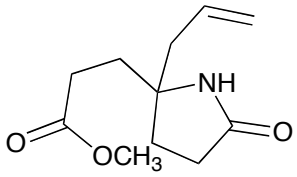
δ 206.8, 142.8, 131.0, 118.9, 76.8, 40. 7, 36.8, 30.0, 28.97, 28.89, 24.4, 11.8.

IR: (Thin Film, NaCl) Found: υ_{max} 3082, 2921, 1710, 1608, 1433, 1359, 1218, 1170,9978, 918,

775 cm^{-1}.

HRMS: Calc. HRMS for $C_{12}H_{19}ON$ (M + H) 194.1545; Found (M + H) 194.1543.

S21f



^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.88 (s, 1H), 5.78 – 5.61 (m, 1H), 5.09 (m, 2H), 3.61 (s, 3H), 2.31 (m, 4H), 2.20 (m, 2H), 1.84 (m, 4H).

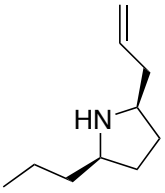
^{13}C NMR (126 MHz, $CDCl_3$):

δ 176.7, 172.7, 131.2, 118.8, 60.0, 50.9, 43.7, 33.5, 29.4, 29.1, 27.8.

IR (Thin Film, NaCl) Found: υ_{max} 3087, 2948, 1731, 1693, 1438, 1373, 1311, 1220, 1201, 1174, 773 cm^{-1}.

HRMS: Calc. HRMS for $C_{11}H_{17}O_3N$ (M + Na) 234.1106; Found (M + Na) 234.1111.

S22b



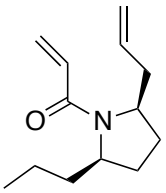
^{1}H NMR (500 MHz, CDCl3):

δ 5.74 (m, 1H), 5.03 (ddd, *J* = 17.1, 3.3, 1.5 Hz, 1H), 4.97 (d, *J* = 10.09 Hz, 1H), 3.07 (quint, *J* = 6.66 Hz, 1H), 2.99 (quint, *J* = 6.66 Hz 1H), 2.29 (dt, *J* = 13.4, 6.7 Hz, 1H), 2.21 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.82 (m, 2H), 1.52 (m, 1H), 1.38 (m, 2H), 1.29 (m, 3H), 0.87 (t, *J* = 7.11 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 135.68, 116.75, 59.36, 58.66, 40.08, 38.15, 30.86, 30.28, 20.58, 14.21.

S22c Exists as a mixture of amide E/Z isomers



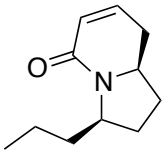
^{1}H NMR (500 MHz, CDCl3)

δ 6.48 (m, 2H), 6.43 (d, *J* = 2.7 Hz, 2H), 6.40 (d, *J* = 2.7 Hz, 1H), 5.79 (m, 2H), 5.69 (d, *J* = 2.7 Hz, 1H), 5.67 (d, *J* = 2.8 Hz, 1H), 5.14 (m, 2H), 5.07 (m, 2H), 4.19 (broad s, 1H), 4.12 (broad s, 1H), 3.99 (broad s, 1H), 3.91 (broad s, 1H), 2.78 (s, 1H), 2.43 (s, 1H), 2.18 (m, 2H), 2.07 (m, 2H), 1.96 (m, 4H), 1.86 (m, 1H), 1.78 (m, 2H), 1.73 (m, 2H), 1.64 (m, 2H), 1.38 (m, 9H), 0.97 (m, 7H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 164.53, 135.06, 134.25, 129.13, 129.02, 127.40, 117.93, 117.01, 58.39, 58.13, 57.90, 57.37, 40.81, 38.95, 38.82, 37.48, 29.31, 29.22, 28.67, 28.00, 19.88, 19.66, 14.12, 14.00.

S22d



^{1}H NMR (500 MHz, $CDCl_3$):

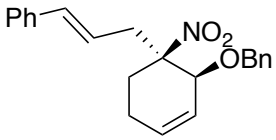
δ 6.45 (ddd, *J* = 9.6, 6.3, 2.0 Hz, 1H), 5.85 (dd, *J* = 9.7, 2.9 Hz, 1H), 3.97 (m, 1H), 3.56 (ddd, *J* = 19.0, 10.5, 4.8 Hz, 1H), 2.37 (ddd, *J* = 17.1, 6.3, 4.4 Hz, 1H), 2.01 (m, 2H), 1.82 (m, 1H), 1.74 (m, 2H), 1.61 (ddd, *J* = 19.5, 11.3, 6.8 Hz, 1H), 1.24 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H).

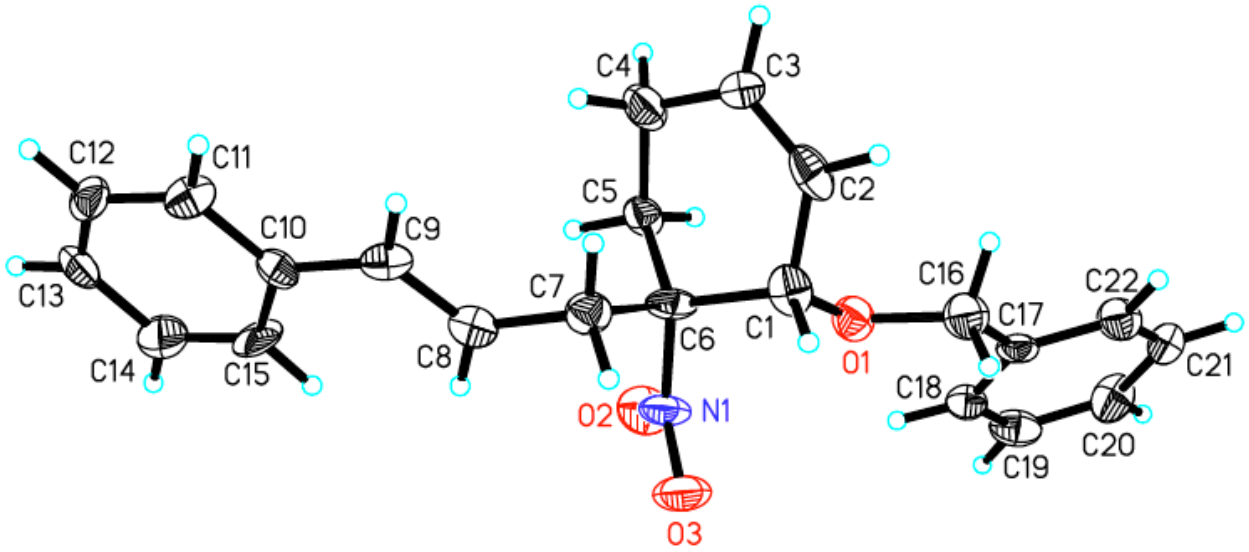
^{13}C NMR (126 MHz, $CDCl_3$):

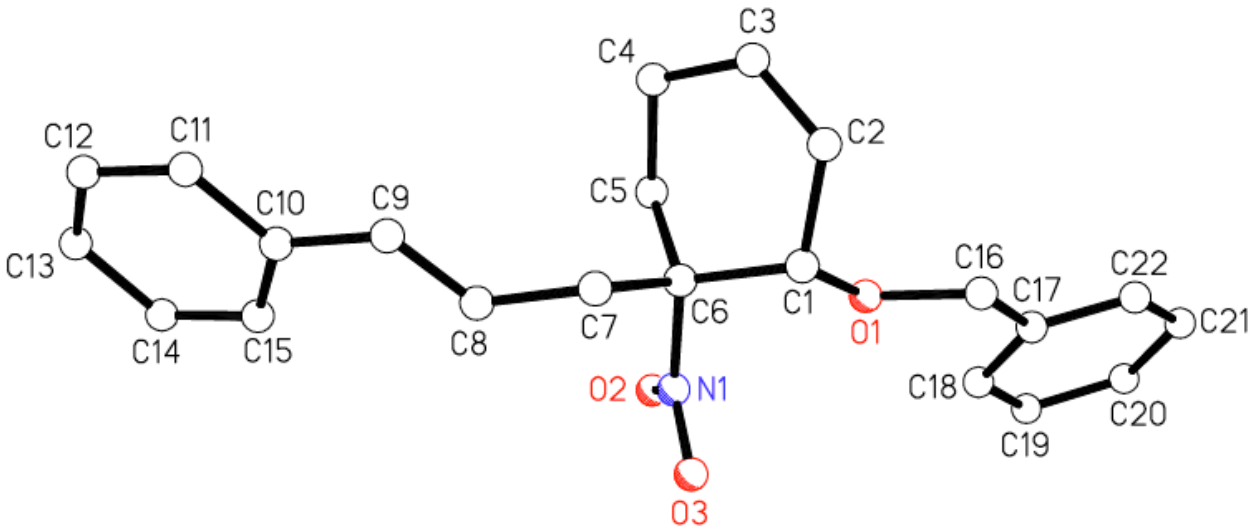
δ 163.93, 138.71, 126.77, 57.77, 56.11, 36.26, 31.10, 31.08, 27.60, 19.66, 14.12.

Crystallographic data:

Crystal structure of **T3c** obtained:







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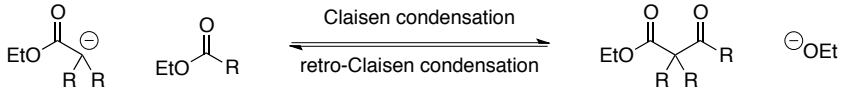
Chapter 2. Mild-functionalization/retro-Claisen: a review of synthetic tactics involving retro-Claisen condensation reactions.

2.1 Introduction to retro-Claisen condensation

The retro-Claisen condensation is a nucleophile-induced C−C cleavage reaction of β-dicarbonyl compounds (Scheme 1). The retro-Claisen condensation of α,α-dialkyl β-ketoesters was first reported by Dieckman[1,2] (1900) and mechanistic studies were reported by Adkins[3-5] in the 1930's. Synthetic strategies involving retro-Claisen condensation came sometime thereafter in the early-mid 20th century.[6] This review will focus on how the retro-Claisen cleavage reaction can be utilized to not only produce useful synthetic intermediates, but also expedite and simplify the synthesis of various complex chemical entities.

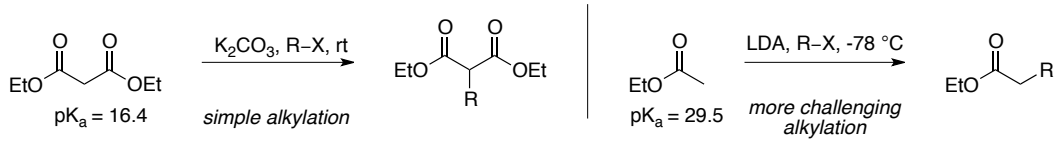
Scheme 1. The Claisen/retro-Claisen equillibrium



β-dicarbonyl compounds (active methylene compounds) and similar compounds (e.g. α-cyano or nitro esters), are an extremely useful class of chemical reactants as they can easily be utilized as nucleophilic coupling partners in various chemical reactions both classic and modern. Though complex β-dicarbonyl compounds are usually prepared by Claisen condensation, many β-dicarbonyl compounds are commercially available (e.g. acetylacetone, ethyl acetoacetate, cyanoacetic acid esters, etc.). Moreover, the relatively low pK_a of these active methylene nucleophile (DMSO pK_a 8-16) renders their functionalization simple and mild (hence the descriptor "active methylene"). For example, they can be deprotonated by mild bases, such as

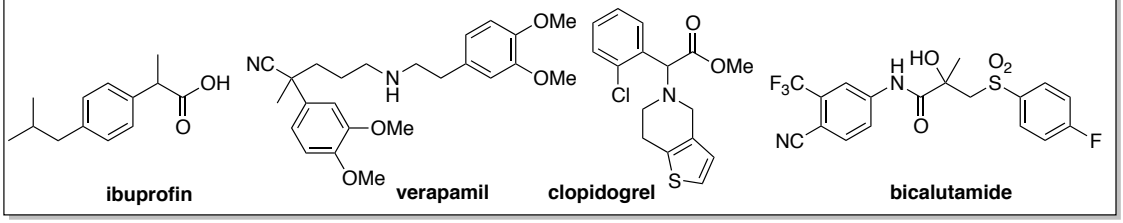
acetates, carbonates, or phosphates, and coupled with various electrophiles. To compare, mono-carbonyl compounds (such as ethyl acetate) have a much higher pK_a and require strong bases for enolate formation and functionalization. Importantly, these stronger bases are often more expensive and sensitive to moisture, both of which are undesirable qualities when considering a synthetic transformation.

Scheme 2. Generalized conditions for alkylation of malonate vs. ethyl acetate



In terms of chemical structure and therapeutics, it is arguable that α,α-functionalized mono-carbonyl compounds are much more desired than their α,α-functionalized β-dicarbonyl counterparts. For example, there are many drugs that have a single carbonyl (or carbonyl derivative, e.g. cyano) and α-substitution, for example, ibuprofen, verapamil, clopidogrel, and bicalutamide (Scheme 2).

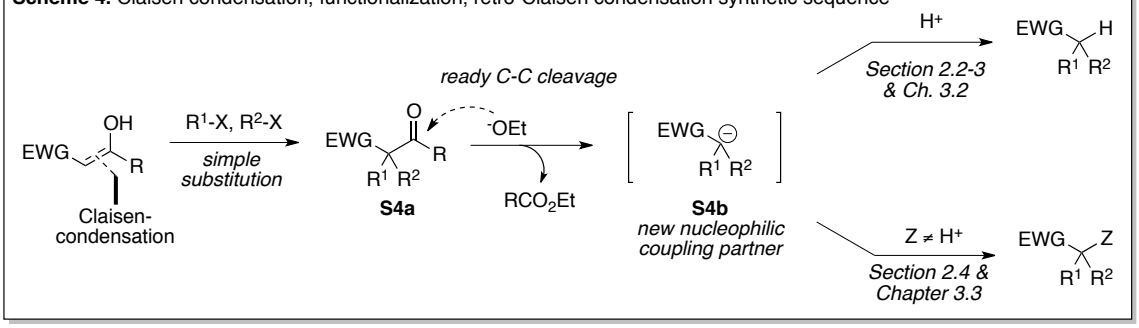
Scheme 3. Examples of important carbonyl derivatives containing α-complexity



This review will focus on how the robust reactivity of active methylene compounds can be used in tandem (1 or 2 pot reactions) with retro-Claisen condensation to prepare diverse mono-carbonyl chemical building blocks. In general, this synthetic strategy is as follows (Scheme 4): starting from a commercially available or readily available β-dicarbonyl compound, mild and diverse α,α-disubstitution occurs to give the non-enolizable β-dicarbonyl **S4a**. **S4a** can then be converted into a more relevant chemical structure by retro-Claisen condensation.

Moreover, the retro-Claisen reaction prepares another anion **S4b** (a new nucleophilic coupling partner) that can be used for further diversification. The first section of this review will focus on retro-Claisen condensation/protonation methodologies, and the latter sections, 2.4 and Chapter 3, (my contribution to this field of research), will focus on how the anion generated by retro-Claisen C−C cleavage can react with other electrophiles.

Scheme 4. Claisen condensation, functionalization, retro-Claisen condensation synthetic sequence

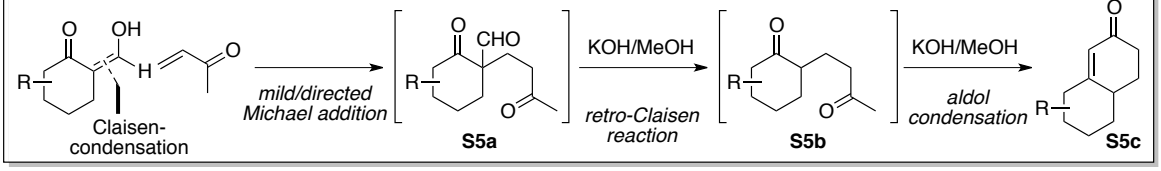


2.2 Alkylation/retro-Claisen condensation strategies

2.2.1. The Wilds-Woodward Reaction

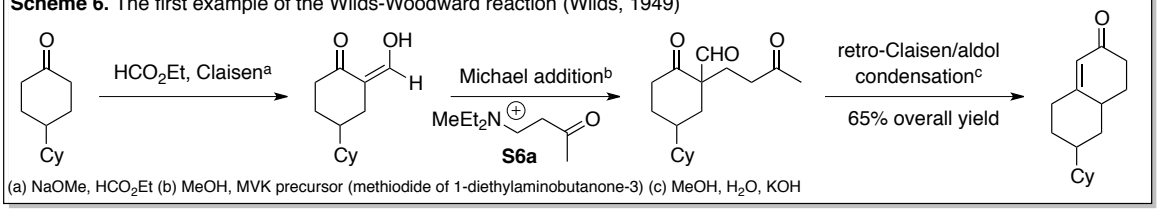
Some of the earliest use of strategic retro-Claisen condensation in synthesis was reported by Wilds in 1943.[7-9] The reaction about to be described is the Wilds-Woodward modification of the Robinson annulation. In this process, formylation via Claisen condensation allows for mild and directed Michael addition preparing **S5a**, which often does not need to isolated. Upon the addition of methanolic base, the labile aldehyde is removed (**S5b**) and aldol condensation occurs giving the desired product (**S5c**).

Scheme 5. General outline for the Wilds-Woodward modification of the Robinson annulation



The question is, why did such a modification need to be invented? The answer is quite simple: the Robinson annulation using classic conditions (alkaline) can often have limitations. For example, higher pK_a ketones, such as cyclohexanone, can be challenging to alkylate under alkaline conditions and polymerization of the methyl vinyl ketone can be problematic.[10] There are many modifications of this useful reaction that can be used to circumvent these problems,[11] with one of them being the Wilds-Woodward reaction. Regarding the Wilds-Woodward modification, by introducing the formyl group, the C-C bond formation (via Michael addition) becomes a trivial process as the pK_a of the α-carbon has been drastically altered. Furthermore, the formyl group was chosen because under the basic conditions required for the aldol condensation, the aldehyde is readily cleaved, allowing access to the Robinson annulation product.

Scheme 6. The first example of the Wilds-Woodward reaction (Wilds, 1949)

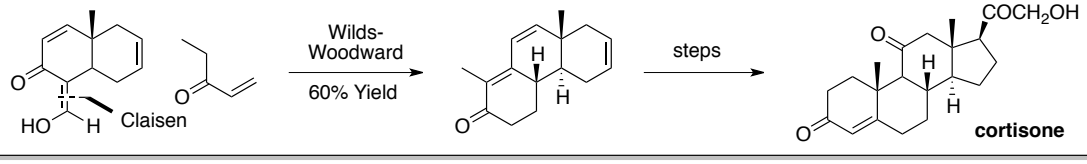


Above, it was stated that the first examples of the Wilds-Woodward reaction were published in 1943[7] and 1946.[8] However, these early publications tinkered with other cleaving groups that had various problems associated with them (e.g. challenges attaching (Claisen condensation) or detatching them (retro-Claisen cleavage). With that said, the actual first publication where the Robinson annulation was facilitated by a "traceless" formyl group was

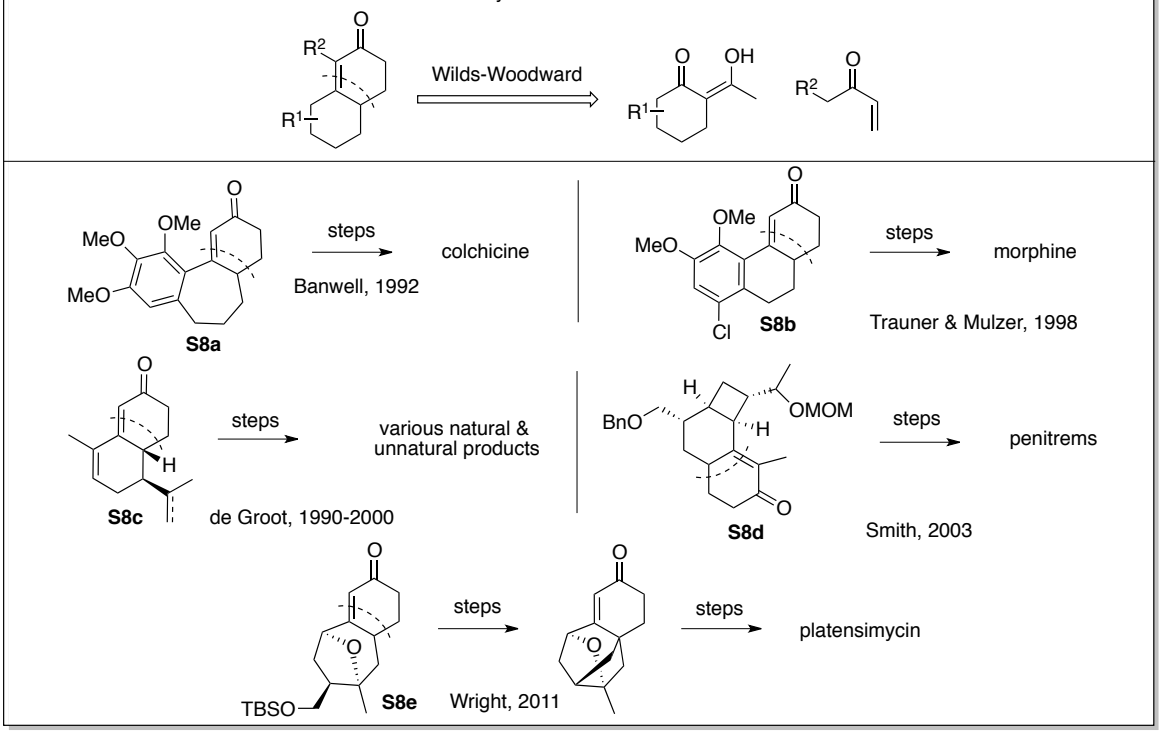
published in 1949 (Scheme 6).[9] Wilds used the reaction to construct steroid analogs lacking the C-ring. Also, he used methyl vinyl ketone generated *in situ* from the corresponding Mannich base **S4a**, as this was common practice in performing Robinson annulations at this time.[10]

The reaction commonly includes Woodward's name since he famously used it in an important step in his historic synthesis of cortisone (Scheme 7).[12] In these studies, he noted the importance of reaction conditions as well as the simplified use of methyl vinyl ketone and thus made important contributions to its development too.

Scheme 7. Woodward used Wilds' modification to synthesize cortisone (1952).



Scheme 8. Wilds-Woodward reaction in modern total synthesis

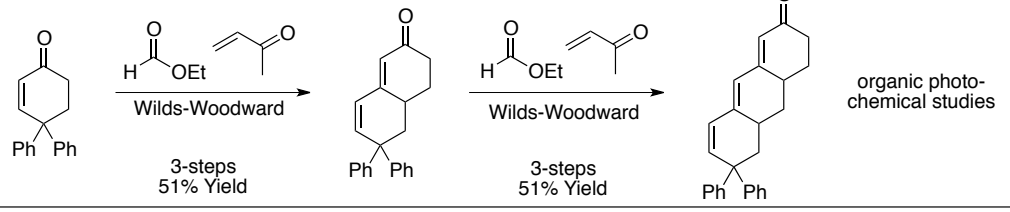


The Wilds-Woodward reaction saw much use in the steroid-synthesis heyday (ca. 1950s).[7-9,12-15] However, it saw miniminal use[16,17] in other applications until the latter part of the 20th century. As shown in Scheme 6, it has recently found use as a general strategy for the

synthesis of cyclohexane containing complex natural products.[18-24] Banwell and coworkers[18] (**S8a**) and Trauner and Mulzer[20] (**S8b**) have demonstrated the reaction's utility for synthesis of benzosubarones and tetralones, respectively. De Groot and coworkers have utilized the reaction on numerous occasions to annulate carvone and derivatives thereof (**S8c**).[19,22] Amos Smith and coworkers utilized the Wilds-Woodward reaction *en route* to penitrem alkaloids (**S8d**).[23] In Wright's use of the reaction (**S8e**),[24] he uses the newly constructed cyclic enone to perform a vinylogous enolate alkylation to construct the dense multicyclic core of platensimycin.

Aside from use in total synthesis, Zimmerman demonstrated that the reaction can be utilized in an iterative fashion to rapidly construct cyclic polyeneones (Scheme 9).[17] These molecules were then utilized in organic photochemical studies.

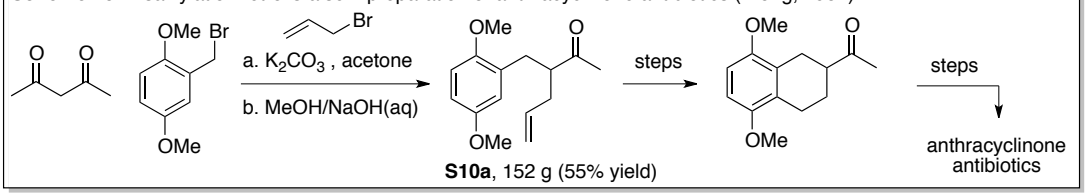
Scheme 9. Iterative Wilds-Woodward reactions (Zimmerman, 1989)



2.2.2. General alkylation/retro-Claisen condensation

Using a similar approach to the Wilds-Woodard reaction, a carbonyl can be used as a traceless, readily cleavable, activating group for alkylation of various ketone compounds.

Scheme 10. Bisalkylation/retro-Claisen: preparation of anthracyclinone antibiotics (Wong, 1982)

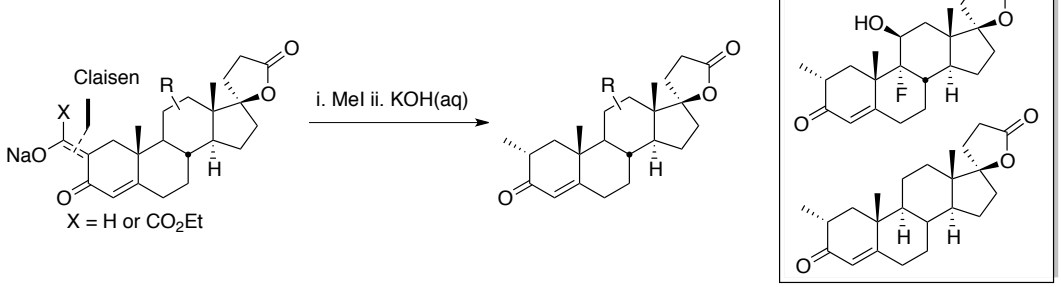


S10a, 152 g (55% yield)

We will begin with an example of bisalkylation/retro-Claisen condensation of acetylacetone to prepare an important intermediate en route to the anthracyclinone family of antibiotics (Scheme 10).[25] This is a prime example of how simple β-diketones can serve as a template for mild, sequential alkylations and by retro-Claisen reaction, prepare useful α,α-dialkyl ketones. Researches at the University of Manitoba first coupled an equivalent of a benzyl bromide derivative to acetylacetone and further quaternized the α-position with allyl bromide. This 2-step sequence was performed in a single pot. Without purification of this intermediate, the retro-Claisen reaction to **S10a** was promoted using sodium hydroxide in methanol. A single purification was performed over this 3-step sequence and 152 g (55% yield) of the desired product was isolated. An analogous approach would involve from dialkylation of acetic esters and 2-step saponification/decarboxylation (acetoacetic ester synthesis).

In another example of alkylation/retro-Claisen reaction, researches at Searle and Co. reported a simple 2-step procedure for introducing a methyl group onto the steroid core by formylation and methylation/retro-Claisen reaction (Scheme 11).[26] Moreover, the reaction occurs with complete diastereoselectivity. In addition to the formyl activating/cleaving group, the researchers reported the incorporation of an oxalyl group to promote the reaction sequence.

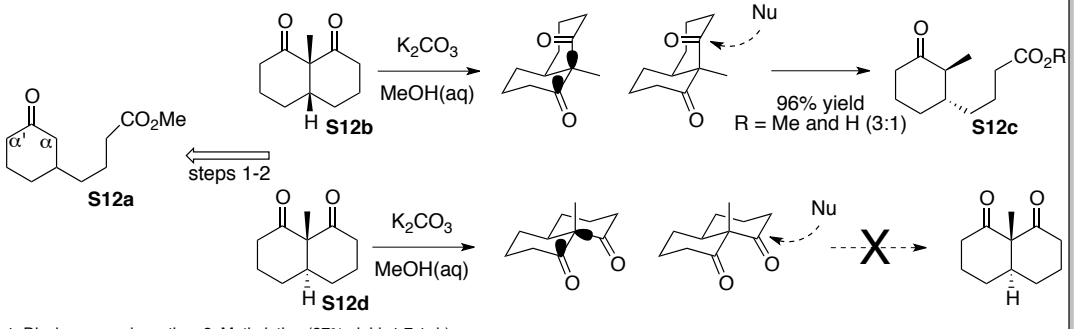
Scheme 11. Claisen/methylation/retro-Claisen of steroids (Searle and Co., 1961)

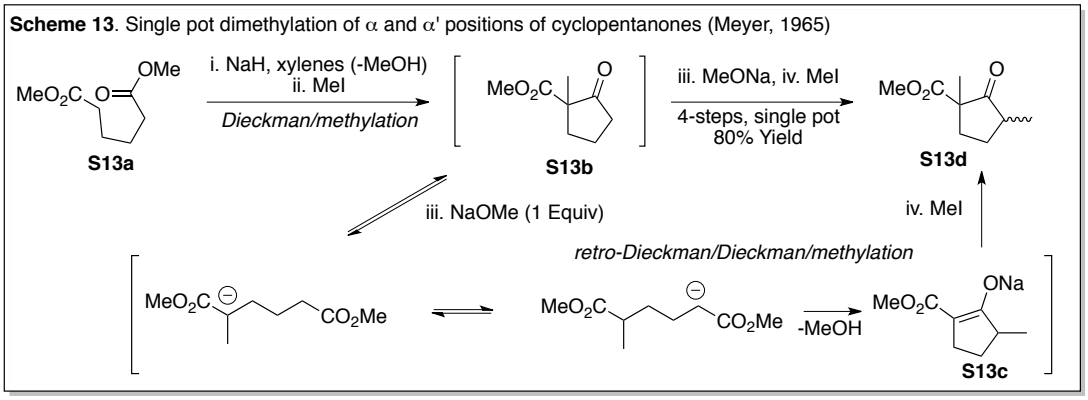


An analogous reaction to retro-Claisen condensation is the retro-Dieckman condensation. Though upon C−C cleavage, the activating group will still be tethered to the molecule and thus

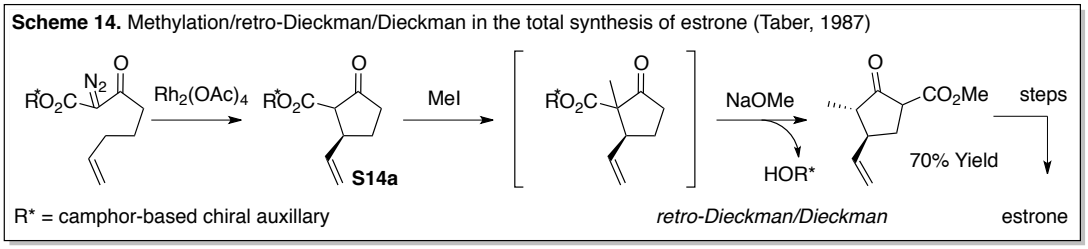
provided added functional complexity. For example, substituted cyclohexanones can be prepared by Dieckman/alkylation/retro-Dieckman as shown by Duthaler (1982).[27-29] Again, the Dieckman condensation is strategic allowing mild alkylation only at the α-position of **S12a**. One could imagine, under common ketone alkylation conditions (e.g. LDA, MeI), methylation could occur at either α- or α'-positions. Regarding the retro-Dieckman reaction, the *cis* diastereomer **S12b** underwent the C−C cleavage reaction under mild conditions (K_2CO_3, MeOH, rt) leading to *trans*-α,β-disubstituted cyclohexanone **S12c**. Interestingly, the *trans*-isomer **S12d** did not undergo retro-Dieckman condensation. This reaction dichotomy can be easily explained by the orbital orientation in each of the *cis*- and *trans*-decalin systems. In the case of the *cis*-decalin **S12b**, the pertinent orbitals are rigidly aligned to allow for rapid and mild cleavage. Conversely, in the *trans*-isomer **S12d**, the pertinent orbitals are locked perpendicular to one another, making this retro-Claisen condensation much higher in energy as no resonance stabilization would occur as the carbanion is being formed. Furthermore, as the *cis*-decalin **S12b** is prochiral, Duthaler also developed a retro-Claisen condensation based desymmetrization of this species. This is discussed in the "desymmetrization of prochiral diketones" section of this review (section 2.2.3) as there are several papers on desymmetrization of diketones via retro-Claisen condensation in the literature.

Scheme 12. Facile retro-Claisen of *cis*-decalin-1,8-diones (Duthaler, 1982)



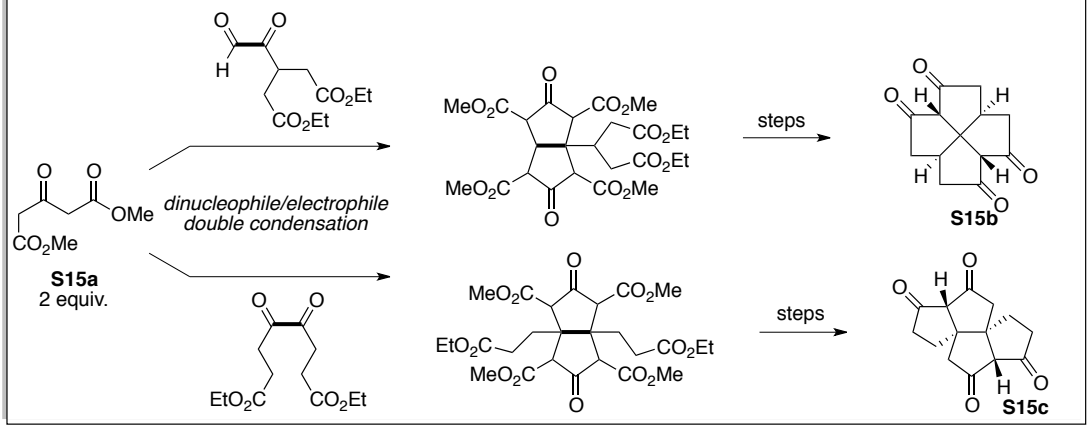


The Dieckman condensation was also used strategically to alkylate at both sides of a ketone using a series of alkylations and Dieckman/retro-Dieckman reactions.[30-33] As shown by Meyer, this can be done in a single pot and in high yield over the course of the transformation (Scheme 13).[34] Starting from dimethyl adipate **S13a** and initiated by Dieckman condensation, a β-diketone is prepared *in situ,* which is methylated by addition of methyl iodide (**S13b**). Next, a single equivalent of methoxide is added to promote a retro-Dieckman condensation, proton-transfer, and a second Dieckman condensation reaction, which gives rise to another β-diketone (**S13c**). This can again be alkylated by addition of methyl iodide leading to **S14d**. This 1-pot, multi-step sequence occurs in 80% yield on large scale.



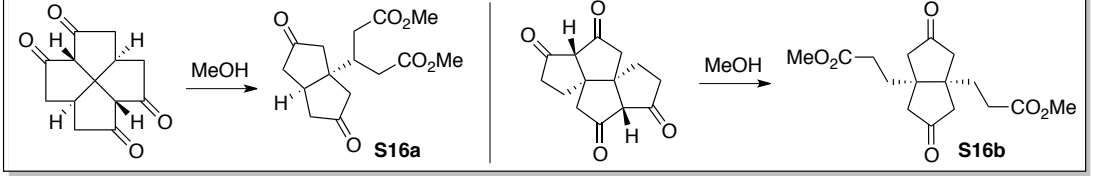
A similar Dieckman/alkylation/retro-Dieckman cascade was utilized by Taber and coworkers to prepare an important intermediate en route to estrone (Scheme 14).[35] The formal enantioenriched Dieckman substrate **S14a** was however prepared by a Rh-catalyzed C−H insertion reaction.

Scheme 15. Utiliity of β-ketoglutarate: construction of tetraquinane cores (Cook, 1982)



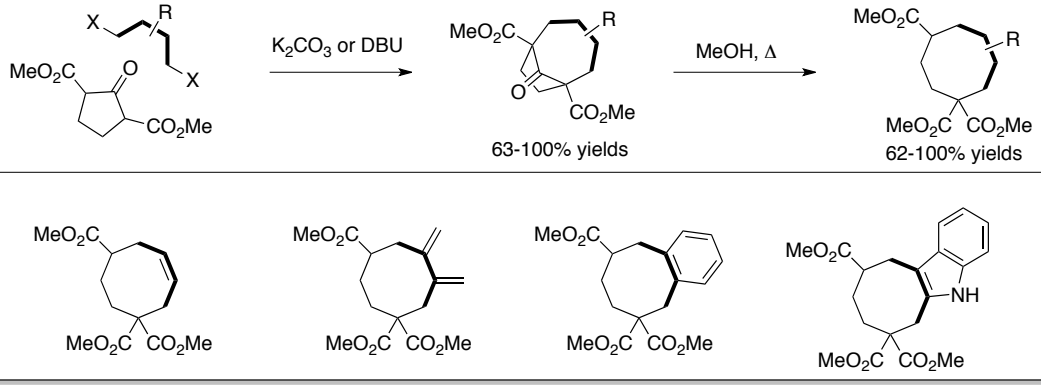
Another approach to alkylate both α- and α'-positions of a carbonyl involves starting from β-ketoglutaric esters (Scheme 15, **S15a**). These molecules function as bisnucleophiles and can couple with biselectrophiles. The central ketone can then be cleaved upon retro-Claisen condensation to prepare some interesting chemical structures. For example, in pioneering work, Cook and coworkers demonstrated that 2 equivalents of β-ketoglutarate can condense with α-keto ketones or aldehydes to synthesize fused 5-membered rings.[36-38] Upon decarboxylation and Dieckman condensation, tetraquinane cores **S15b-c** were quickly constructed. Furthermore, Cook noted that retro-Dieckman of these structures occured mildly and without the requirement of quaternarization leading to fused dicyclopentadiones **S16a-b** (Scheme 16).[38] The retro-Claisen condensation of non-quaternized β-diketones is somewhat unique as enolization can occur (see section 2.2.7 for retro-Claisen condensation of other non-quaternary β-diketones). In this case, retro-Claisen reaction is mild, presumably due to the ridged carbonyl alignment as previously discussed in Duthaler's work on *cis*-decalinones (Scheme 12).[27]

Scheme 16. β-diketone tetraquinane cores undero facile retro-Dieckman condensation (Cooke, 1982)

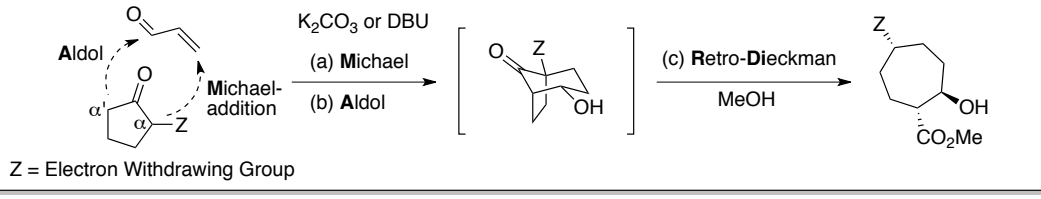


In a conceptually similar example published by the Rodriguez research group, a cyclic β-ketoglutarate derivative was coupled with 1,4-dihaloalkanes, and upon retro-Claisen reaction, ring expanded cyclooctanes were produced (Scheme 17).[39] The dialkylation was found to go in high yield using K_2CO_3 or DBU as the base. The retro-Claisen reaction then occurred in neutral refluxing methanol leading to the desired cyclooctane ring compounds. In general, β-ketoesters where the ketone is located at the bridging carbon are extremely labile due to the increased strain of bicyclic systems. This facile cleavage is well exploited and further discussed in section 2.2.4.

Scheme 17. Dianion/cation cyclization/retro-Claisen ring expanstion (Rodriguez, 2001)



Scheme 18. The **MARDi** Reaction (Rodriguez, various publications 1993-2006)

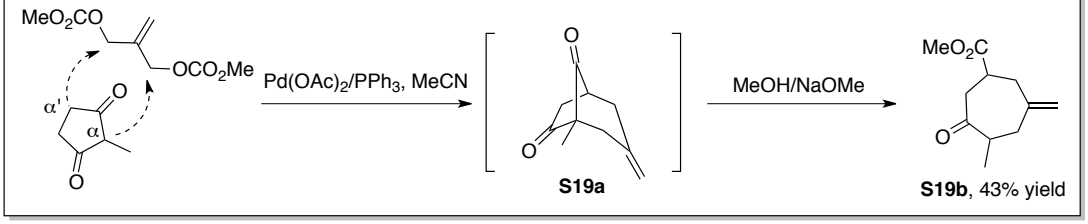


Although the reaction above was done using a cyclic β-ketoglutarate derivative, Rodriguez's major focus in annulation/retro-Claisen chemistry has involved the MARDi reaction, which doesn't require the β-ketoglutarate for formal dianion formation.[40-44] **MARDi** stands for **M**ichael-**A**ldol-**R**etro-**Di**eckman. Using the MARDi reaction, acrolein derivatives can annulate a β-ketoester at the α- and α'-positions, and undergo ring expansion via the reactions outlined in its name: Michael addition, aldol reaction, and retro-Dieckman condensation (Scheme 18). Rodriguez has published a beautiful review of this reaction and will not be

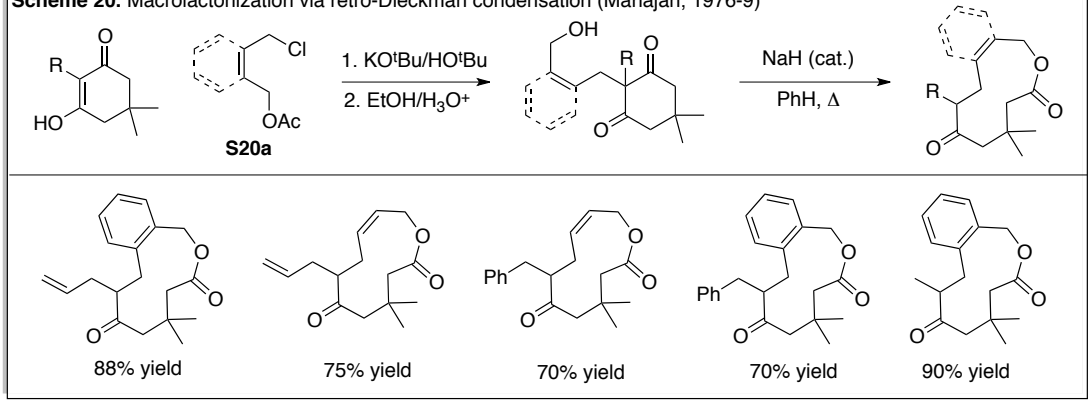
covered in nearly as much detail here.[45] Thus, I direct the reader there for the nuances of this useful transformation.

In similar vein to Rodriguez's approach to dialkylation of the α- and α'-positions of β-dicarbonyl compounds, Tenaglia has reported that a Tsuji-Trost-like annulation can occur with allyl dimethyl carbonates (Scheme 19).[46] In this process, 2-consecutive Pd-catalyzed allylations occured: the first at the more stabilized α-position and second at the less stabilized α'-position leading the annulated intermediate **S19a**. In the presence of sodium methoxide, a uniquely substituted cycloheptanone **S19b** was prepared in 43% yield over the 2-step sequence. The reaction can also proceed from the allyl diacetate though base is required and the reaction performed noticeably poorer.

Scheme 19. Pd-catalyzed dianion/cation cyclization/retro-Claisen ring expanstion (Tenaglia, 1998)



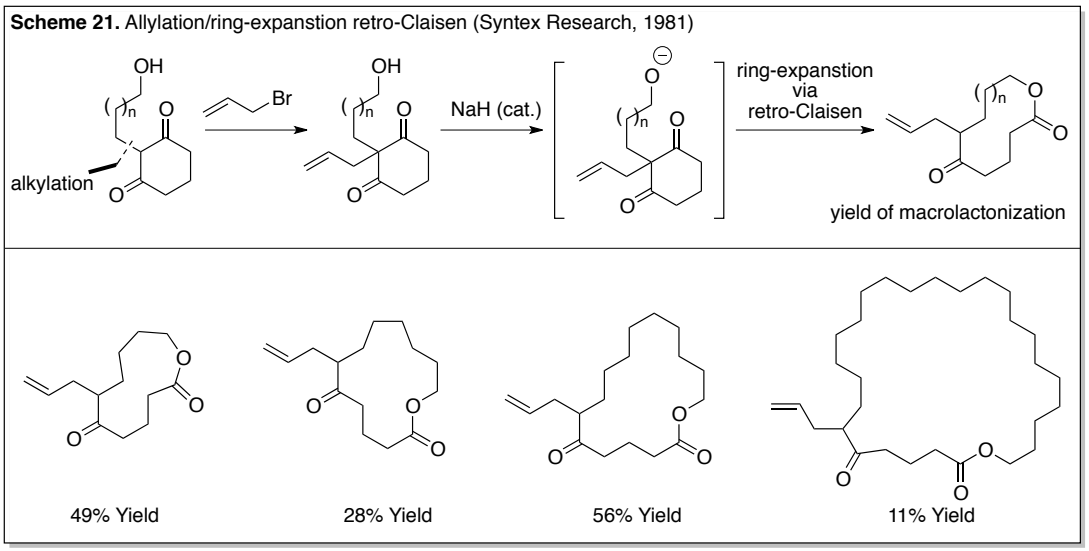
Scheme 20. Macrolactonization via retro-Dieckman condensation (Mahajan, 1976-9)



Another ring-expansion technique that complements classic approaches to macrocyclic lactones involves a retro-Claisen reaction with a pendant alcohol (Scheme 20).[47,48] Mahajan has developed an approach to 11-membered rings by alkylation followed by

macrolactonization/retro-Claisen condensation between cyclohexan-1,3-diones **S20a** and 1-chloro-4-acetoxy-*cis*-butene **S20b** derivatives (Scheme 20).

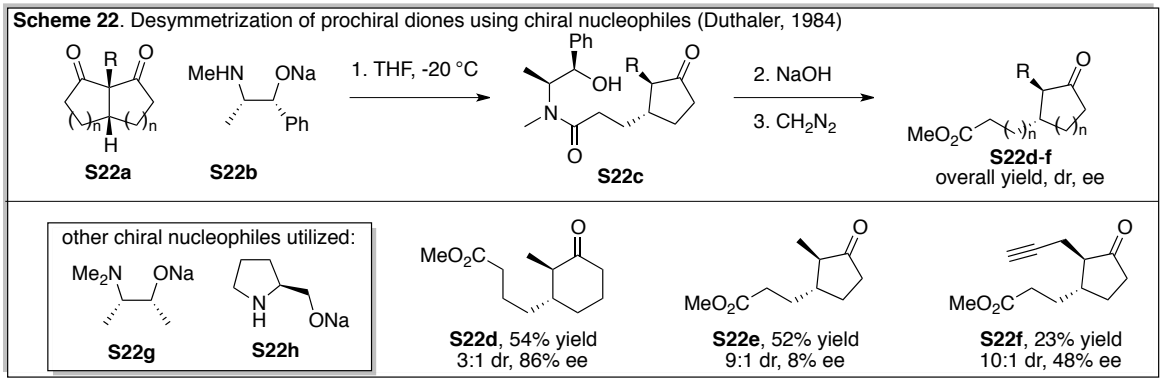
At Synthex Research Company, principles from the Mahajan's work were utilized to make various sized lactones (Scheme 21).[49] Upon quaternarization with allyl bromide (other alkylating agents had significant O-alkylation problems), the intramolecular C−C cleavage/ring-expansion occurred giving reasonable yields of various macrocyclic lactams. Normal problems with macrocyclic ring closures, such as oligomerization, kept the yield modest.



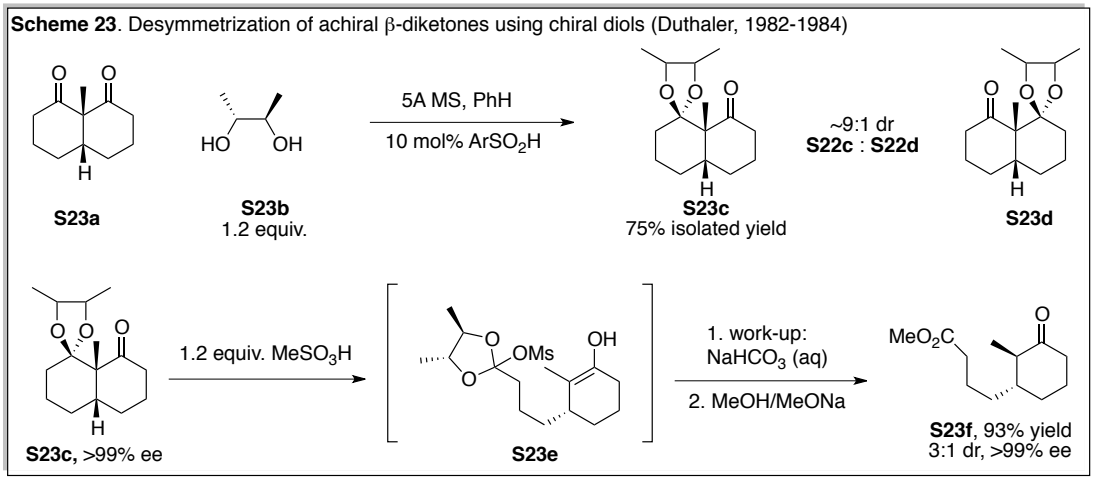
2.2.3. Desymmetrization of prochiral diketones via retro-Dieckman condensation

Above in Scheme 12, Duthaler described how prochiral decalindione **S12b** underwent facile retro-Claisen reaction leading to a *trans*-α,β-disubstituted cyclohexanone **S12c**. He was also quite interested in performing a desymmetrization of this diketone to quickly prepare enantioenriched analogs from this readily available diketone.[27-29] He envisioned two possible desymmetrizing asymmetric retro-Claisen reactions: (a) retro-Claisen condensation using chiral

bases[28] (Scheme 22) and (b) via chiral diol desymmetrization/retro-Claisen reaction (Scheme 23).[29]

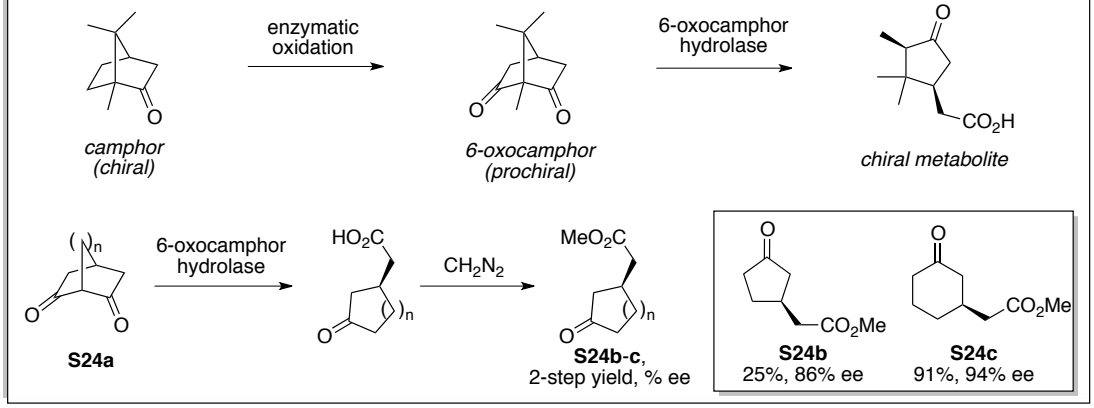


In the first approach, Duthaler and Maienfisch were able to desymmetrize the decalindione **S22a** using the sodium salt of ephedrine **S22b** as a chiral nucleophile (Scheme 22).[28] Hydrolysis of the intermediate ephedrine amide **S22c** and esterification with diazomethane lead to the desired enantioenriched dione **S22d-f**. Using this method, the enantioenriched *trans*-disubstituted cyclohexanone **S22c** was isolated in a good yield over the 3-steps (54% yield, 86% ee). Also, moderate diastereoselectivity (3:1 dr) was observed in this process. Unfortunately, only poor to modest enantioselectivity was achieved for the 5-membered ring analogs **S22d-e**. In addition to ephedrine, N-methylephedrine **S22g** and prolinol **S22h** salts were studied: they provided reasonable, but lower ee's than the ephedrine salt.

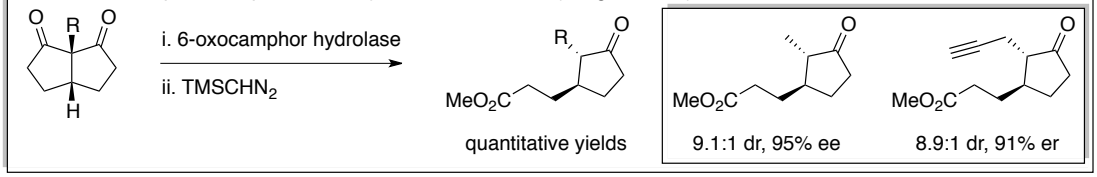


In another approach, a chiral diol condensation reaction was used to desymmetrize the prochiral dione **S23a** (Scheme 23).[29] Relatively good diastereoselectivities, which corresponds to enantioselectivity, were observed upon the condensation of decalin **S23a** with the chiral 1,2-diol **S23b**. Importantly, the unwanted diastereomer (corresponding to the unwanted enantiomer) could be removed chromatographically, giving the enantiomerically pure diastereomer **S23c** in good isolated yields (~75% yield). Upon exposure of the β-ketoacetal to an equivalent of methanesulfonic acid, an acid catalyzed retro-Claisen reaction occurred through intermediate **S23e**. Basic and alcoholic work-up then produced the enantio- and diastereo-enriched *trans*-disubstituted cyclohexanone in excellent yield and with perfect chirality transfer from the enantiopure starting material.

Scheme 24. Enzymatic desymmetrization of achiral β-diketones via retro-Claisen (Grogan, 2001)



Scheme 25. Scope development of enzymatic retro-Claisen (Grogan, 2007)



More recently, Grogan took advantage of Nature's method of converting a prochiral camphor β-diketone to a chiral metabolite using 6-oxocamphor hydrolase with other exogenous substrates (Scheme 24).[50-53] Using this enzyme, exogenous bridged β-diketones **S24a** could

undergo enzymatic retro-Claisen cleavage reaction to the enantioenriched cycloalkane **S24b-c**. The bridge was found to be quite important for asymmetry using the wild-type enzyme, potentially due to the substrate-enzyme binding and recognition mechanism, but also to prevent the enolization of the β-diketones (Bredt's rule). Nonetheless, good to excellent ee's (86−94%) were observed using the enzymatic retro-Claisen reaction. In a follow-up study,[52,53] it was reported that other substrates could participate in enzymatic retro-Claisen condensation (Scheme 25). Specifically, this method could produce enantioenriched cyclopentanones that were challenging to access using Duthaler's approach (Scheme 22).

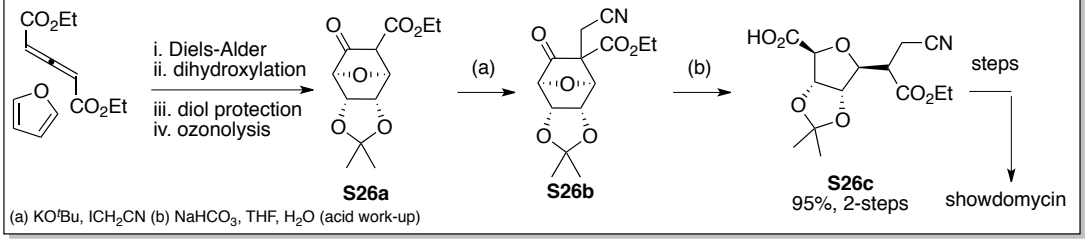
2.2.4. Pericyclization/retro-Claisen condensation reactions

The previous section focused on access to β-ketoesters by classic Claisen or Dieckman condensation methods and how they can be utilized in functionalization/retro-Claisen methodologies. β-ketoesters can be accessed by others methods too. This section will highlight how Diels-Alder and related pericyclic transformations can be utilized synergistically with retro-Claisen condensation to make useful chemical entities rapidly. In general, these cyclic β-diketo esters are considered highly reactive toward retro-Claisen C−C cleavage due to the strain from the ketone (sp^2 atom) within the bicycle. A similarly reactive comparison would be to norbornane, which has a highly reactive olefin due to strain.

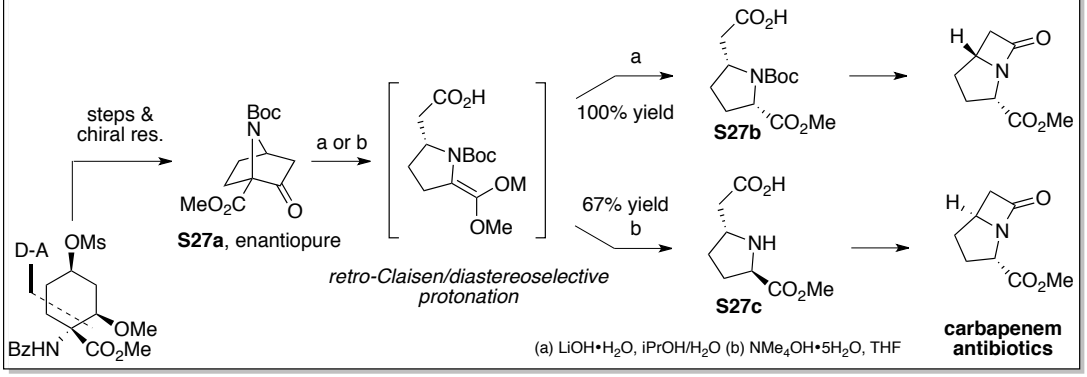
To begin, in the synthesis of showdomycin (Scheme 26), Kozikowski and coworkers utilized a Diels-Alder cyclization (between an allene derivative and furan) and a dihydroxylation to prepare the oxo-bridged cyclohexane.[54] Most importantly, these initial transformations set 4-contiguous stereocenters. The allene was chosen strategically as the dieneophile because (a) it is

electron deficient allowing for a high yielding, polarized Diels-Alder cyclization and (b) upon ozonolysis, afforded an advanced β-diketoester **S26a** that underwent mild alkylation to **S26b**. The oxo-bridged cyclohexane was converted into the tetrahydrofuran **S26c** by a mild $NaHCO_3$-catalyzed retro-Claisen reaction. From here, the complex metabolite is prepared in a few more steps. This early example utilizing pericyclization and retro-Claisen condensation in conjunction nicely demonstrates how the stereospecificity of cycloaddition and C−C fragmentation via retro-Claisen reaction can be used to create useful monocyclic compounds with complete stereocontrol around the ring.

Scheme 26. Synthesis of complex furan rings by Diels-Alder and retro-Claisen (Kozikowski, 1981)



Scheme 27. Diels-Alder and retro-Claisen: controlled synthesis of 1,5-dialkyl pyrrolidines (Avenoza and Peregrina, 2003)

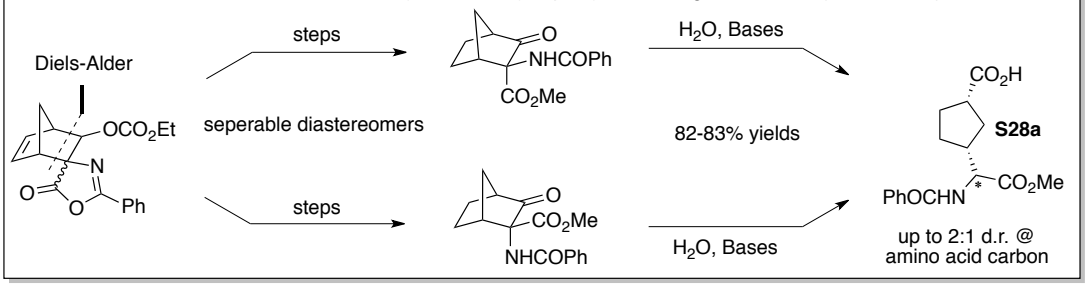


More recently, other researches have adopted the [4+2]/retro-Claisen strategy to make various complex 5-membered rings.[55-60] For example in Scheme 27,[55] Avenoza and Peregrina utilized a Diels-Alder reaction between Danishefsky's diene and an amino acid based dienophile followed by a few chemical manipulations and a chiral resolution to arrive at an amino-bridged cyclohexane containing the built-in β-ketoester **S27a**. From here, they reported that different bases could selectively form either *cis*- or *trans*-2,5-dialkylpyrrolidines by control of the

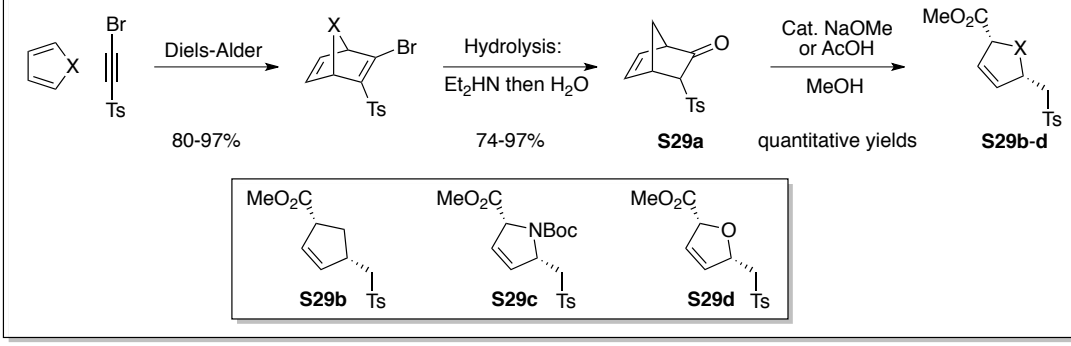
protonation in the retro-Claisen reaction. Having access to either diastereomer, the researchers could now produce various carbapenem antibiotics.

Shortly thereafter, Gelmi[56,57] and Pelligrino[58,59,61] reported that a similar [4+2]/retro-Claisen sequence could allow access to cyclopentyl containing amino acids (Scheme 28). Single enantiomers of these compounds could then be obtained by chiral resolution. Importantly, cyclopentyl amino acids have a range of interesting biological activities and this approach allows rapid access to them.

Scheme 28. Diels-Alder and retro-Claisen: synthesis of cyclopentyl containing amino acids (Gelmi, 2003)



Scheme 29. Simplified access to 1,5-*cis*-cyclopenanoids via Diels-Alder/retro-Claisen (Moreno-Vargas, Robina, 2011)



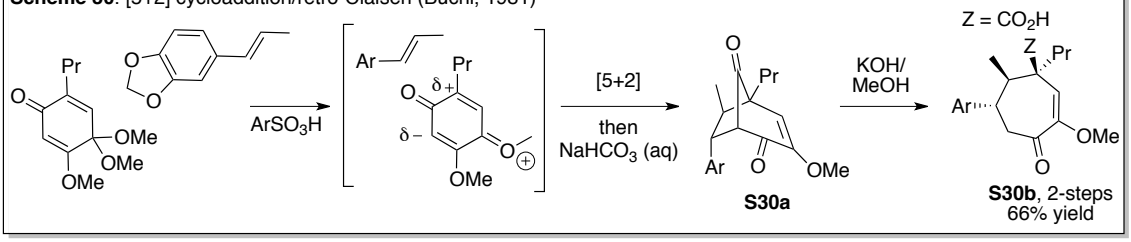
One downside to the Diels-Alder/retro-Claisen sequences outlined above is that various chemical manipulations were required to arrive at the advanced β-ketoester. An improved procedure by Moreno-Vargas involves a [4+2] cyclization between a cyclic diene and an acetylene derivative (Scheme 29).[60] Simple hydrolysis leads to a β-ketosulfonyl compound **S29a** in excellent yield. Treatment of **S29a** with acid or base commences the mild retro-Claisen

reaction to the cyclopentanoid structures **S29b-d** in quantitative yields. Also, these building blocks have a tosyl group tether for further chemical manipulation.

The previous examples had the reactive ketone within the cyclohexane ring. Depending on the substrate and reaction, the reactive carbonyl can be located at the bridging carbon, and upon retro-Claisen C−C cleavage, produce a ring expanded compounds. Some aspects of this reactivity has been discussed in the previous section where the bridgehead ketone was accessed by alkylation methods (Schemes 17−19).

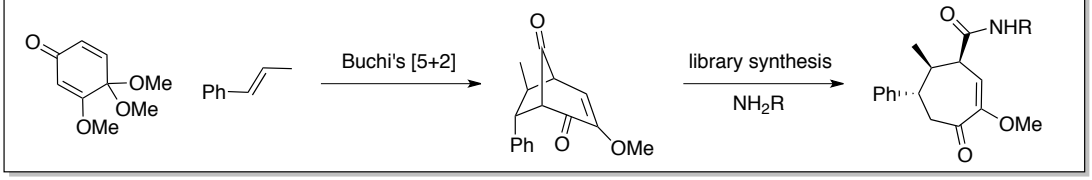
Büchi had much interest in the [5+2] cyclization between quinone ketals and olefins.[62-64] This reaction lead to highly substituted 7-membered rings with a ketone bridge (Scheme 30). By retro-Claisen cleavage, reduced-tropalones, such as **S30a**, with 3-stereocenters (from the [5+2] cyclization) could be prepared with excellent selectivity. Furthermore, by oxidation, interesting and biologically active tropolone methyl ethers could quickly be prepared. Thus, this represents a concise route to these important biologically active compounds.

Scheme 30. [5+2] cycloaddition/retro-Claisen (Buchi, 1981)



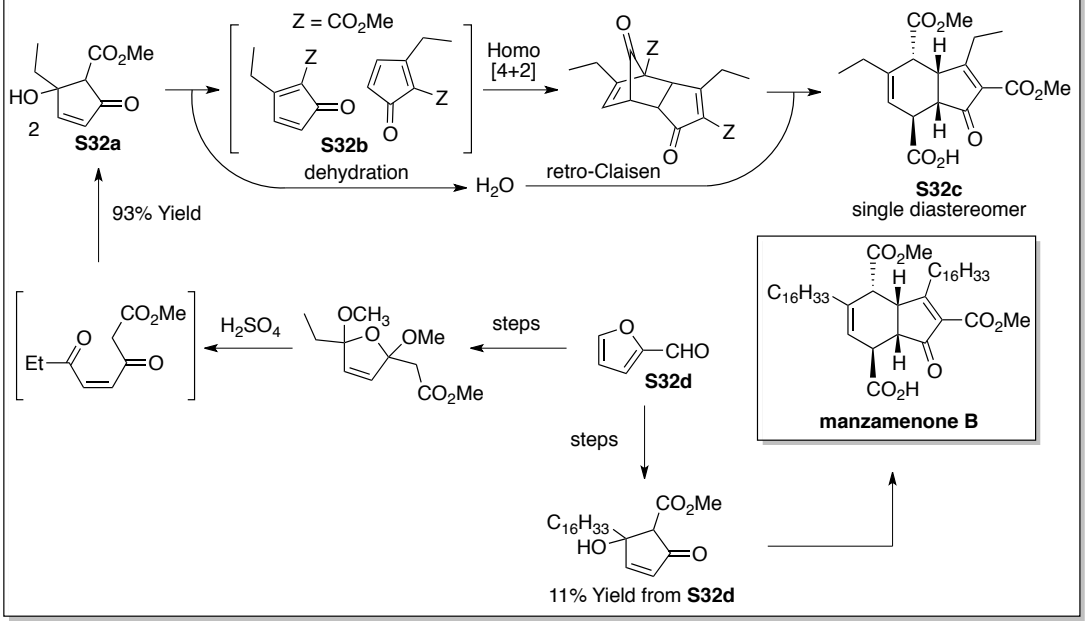
As the tropolone structure is known to be biologically active and can be prepared quickly by the aforementioned methods, researches at MIT and Boston University wished to make a library of them using Buchi's [5+2] method followed by retro-Claisen condensation with a diverse array of amines (Scheme 31).[65]

Scheme 31. [5+2] cycloaddition/retro-Claisen: application in library synthesis (Jensen, Porco, Beeler, 2009)

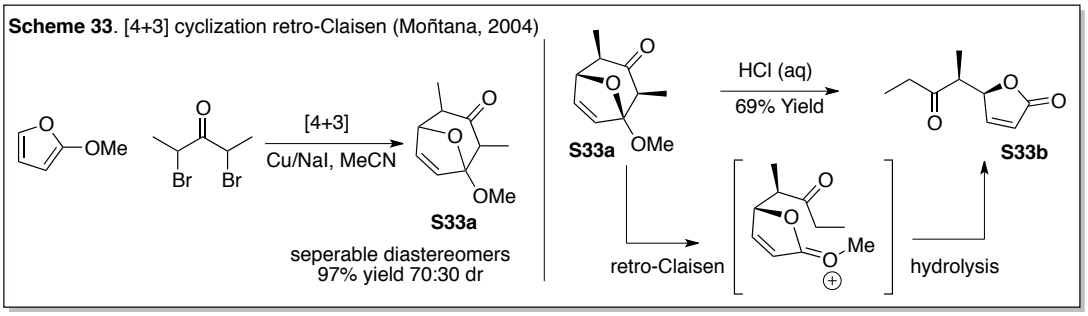


The manzamenone class of natural products are dimeric fatty-acid based compounds with a unique structure. It was proposed by the metabolite's isolator, Kobayashi,[66] and later expounded on by Whitehead,[67,68] that these dimeric natural products could arise from a homo Diels-Alder reaction of highly reactive cyclopentadienone (**S32aèb**) followed by a retro-Claisen condensation leading to the natural product (Scheme 31). Whitehead confirmed this hypothesis by making a simplified analog **S32c** as well the natural product starting from furfural **S32d**.

Scheme 32. Biomimetic approach to the manzamenone alkaloids (Whitehead, 1998-2002)



Thus far, we have covered fragmentation of bicyclic ring systems where the reactive carbonyl is in the cyclohexane ring as well as at the bridging carbon. The final location to be discussed is an acetal at the bridgehead location that can undergo retro-Claisen condensation (Scheme 33).[69]



Montaña has developed a [4+3] cyclization between 2-methoxyfuran and α,α'-dibromo acetone derivatives (Scheme 33).[69] This reaction leads to an oxo-bridging cycloheptane (**S33a**) containing an acetal at the bridgehead. Upon exposure to HCl (aq), **S33a** breaks down via retro-Claisen condensation and hydrolysis to the substituted butenolide **S33b**. Again, the stereocenters set from the cyclization are transferred to the chemical building block butenolide.

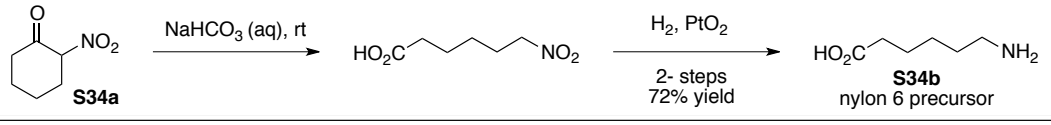
To conclude on pericyclization/retro-Claisen condensation, chemical complexity can rapidly be developed utilizing the stereospecificity of the pericyclization and transferring this information to a more useful chemical building block via retro-Claisen reaction.

2.2.5. α-Nitro-ketone alkylation/retro-Claisen condensation

Although the cleavage of α-nitroketones has been known since the early 20th century,[70] these reports didn't comment on the synthetic potential of such a C−C cleavage reaction. Synthetically useful cleavages of α-nitroketones began appearing in the 1950's and 60's.[71-75] For example, Breslow (of Hercules Inc.) reported that 2-nitrocyclohexanone **S34a** could rapidly, and in a high yield, be converted into an important synthetic intermediate **S34b** for the production of nylon 6 (Scheme 34). The sequence is as follows: an extremely mild retro-Claisen reaction occurs on nitrocyclohexanone to prepare the 6-nitrohexanoic acid, which is reduced to the nylon 6 precursor **S34b**. In general, the retro-Claisen reaction of nitro-ketones is extremely mild due to

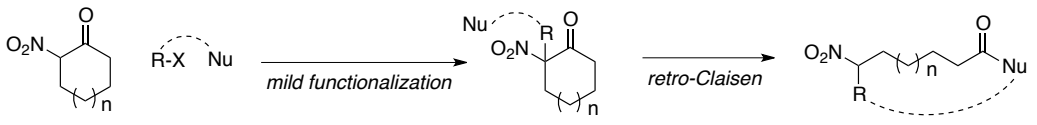
the low pK_a of the nitronate anion (pK_a = 17 in DMSO) generated by retro-Claisen. Interestingly, quaternarization of this compound was not necessary; aspects of retro-Claisen condensation of related enolizable β-ketoesters are discussed in section 2.2.7 of this chapter.

Scheme 34. An early example of α–nitroketone retro-Claisen in synthesis (Breslow, 1967)



A well-utilized strategy in organic synthesis is mild functionalization/retro-Claisen protonation of nitroketones (Scheme 35). As α-nitroketones are excellent nucleophiles, and their C−C cleavage is mild, this strategy has seen much utility.[76-80] The general strategy is outlined in Scheme 35 and is as follows: a nitroketone couples with an electrophile forming the fully substituted α-nitroketone. Next, a nucleophile (intramolecular or intermolecular) can then perform the retro-Claisen condensation to prepare (often ring-expanded in the case of retro-Dieckman condensation) diverse nitroalkanes. This reaction has been reviewed on multiple occasions,[76-80] with recent reviews by Robert Ballini, a major contributor to the development and utility of nitroketone retro-Claisen reactions and nitro group chemistry in general. To keep this review concise, only a few recent examples will be discussed herein. I direct the reader to Ballini's excellent and thorough reviews on this subject matter.

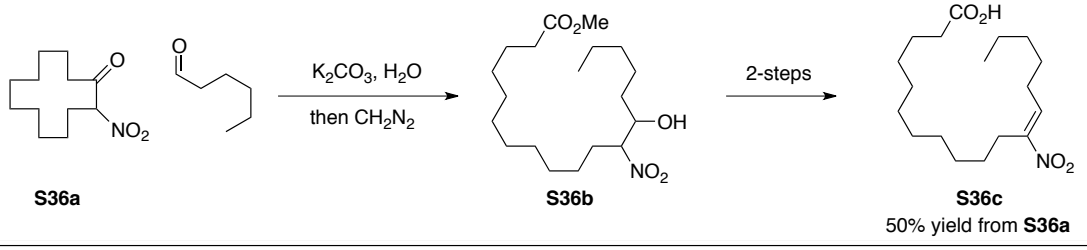
Scheme 35. Synthesis of complex nitroalkanes via functionalization/retro-Claisen



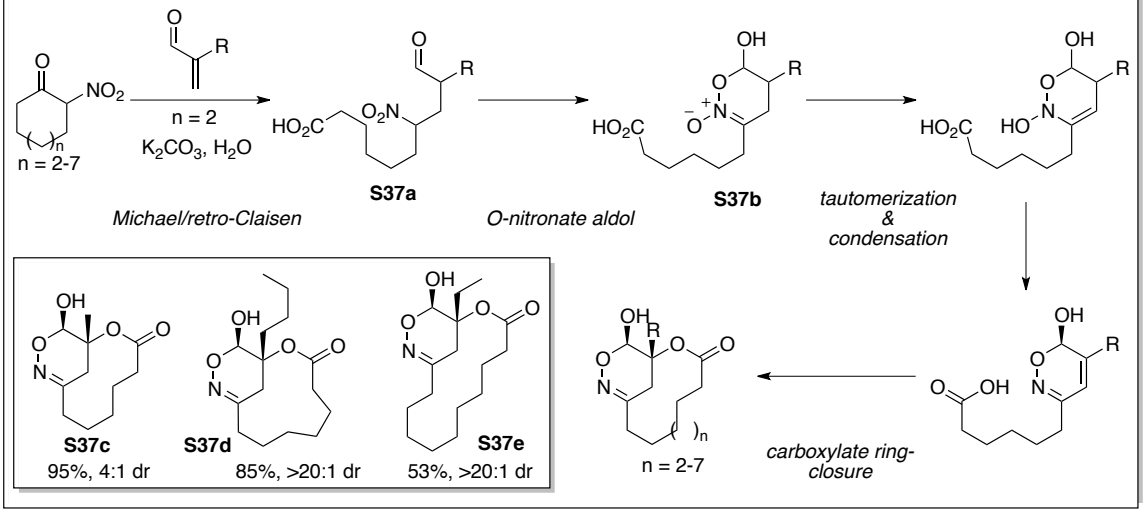
A recent example of this functionalization/retro-Claisen approach to nitroalkane synthesis was reported by Zanoni and Vidari in the improved synthesis of nitro-containing fatty acid (*E*)-12-nitrooctadec-12-enoic acid (Scheme 36).[81] Importantly, synthetic nitro-containing fatty acids

have been shown to be excellent ligands for the peroxisome proliferator-activated receptor-γ (PPARγ). Starting form 2-nitrocyclododecanone **S36a** a mild Henry/retro-Claisen sequence followed by methylation of the carboxylic acid with diazomethane allows facile access to **S36b**. From this intermediate, the desired nitro-containing fatty acid **S36c** is prepared in 2 steps by 2-consecutive hydrolysis reactions. The basis of this work (Henry/retro-Claisen) was provided by Ballini and involved the reaction of 2-nitrocyclohexane derivatives with formaldehyde in the presence of water.[77,82]

Scheme 36. Preparation of nitro-containing fatty acids via Henry/retro-Claisen condensation (Zanoni & Vidari, 2010)



Scheme 37. Michael/retro-Claisen cascade reaction of 2-nitrocycloalkanone

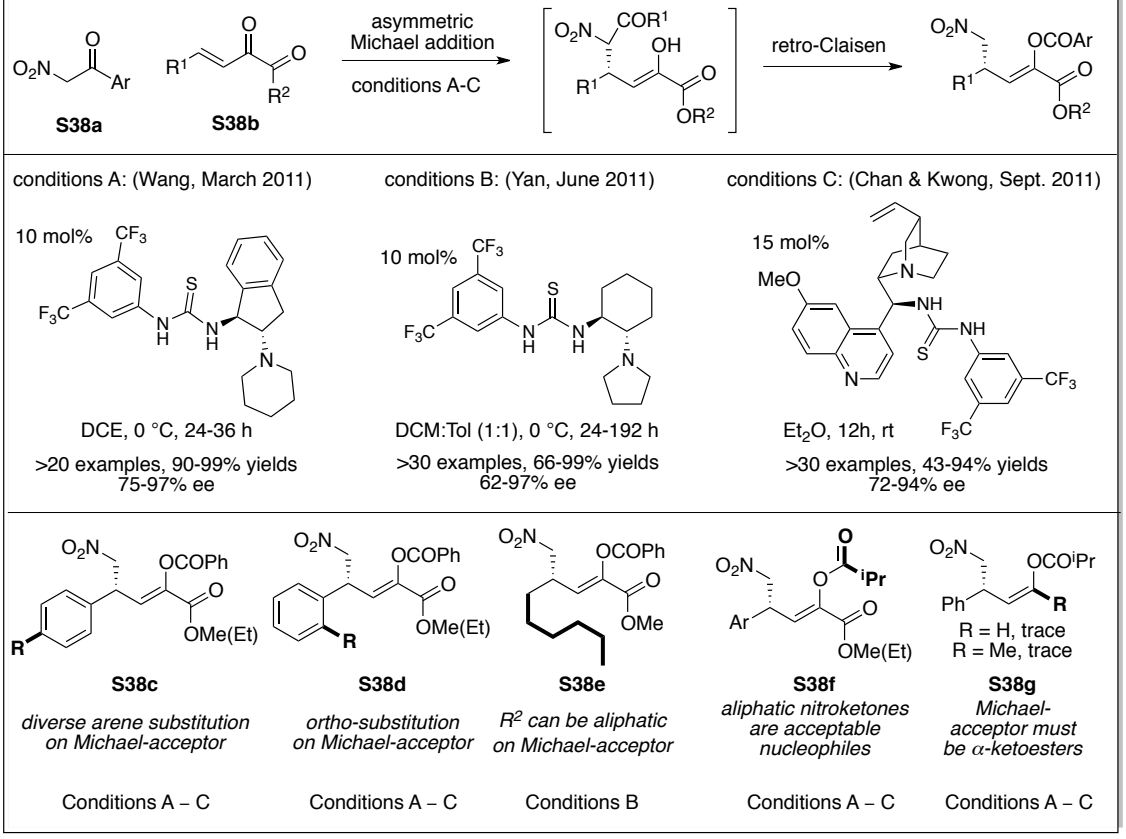


Another reaction originally reported by Ballini (and others) is the Michael addition/retro-Claisen reaction.[83] In a recent example,[84] Menéndez utilized this simple reaction to initiate a domino reaction leading to complex macrolactones in a single pot from 2-nitroalkanones and acroleins (Scheme 37). In this reaction, 2-nitrocycloalkanones are converted to **S37a** by a tandem

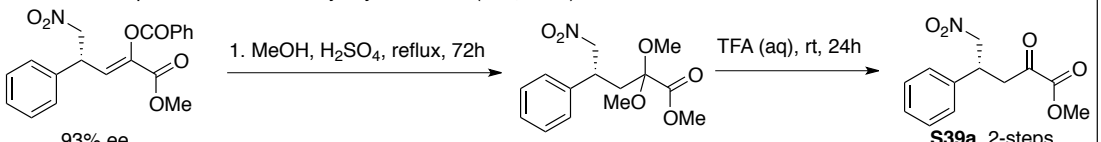
Michael/retro-Claisen reaction. Through an intramolecular O-nitronate aldol reaction followed by tautomerization, condensation and macrolactonization, products **S37c-e** are generated in good yield over this multi-step, 1-pot, synthetic sequence. In general, at least a 6-carbon tether on the nitro-containing fragment was required for the reaction, presumably due to the necessity to minimize ring strain in the macrolactone. Moreover, a β-alkyl substitution on the acrolein was also required. The R-acrolein substitution allows the linear nitroalkane to access the correct geometry for intramolecular O-nitronate aldol reaction. Following these general guidelines, various complex macrolactones (**S37c-e**) can be prepared from simple starting materials in a single pot.

In three similar studies by three different research groups,[85-87] it was reported that thiourea based organocatalysts can promote the asymmetric Michael/retro-Claisen reaction of 2-nitroacetophenone **S38a** derivatives and β,γ-unsaturated α-keto esters **S38b**. Interestingly, the reaction is extremely specific to the oxalyl derived Michael acceptor (**S38b)**; other α,β-unsaturated ketones and aldehydes failed to give a reasonable result (**S38g** could never be isolated in acceptable yields). However, using various nitroketones **S38a** and oxalyl derived Michael acceptors **S12b**, the reaction was general. Regarding the Michael acceptor, various aromatic substitution patterns (**S38c**) including *ortho***-**substitution (**S38d**) were acceptable. Moreover, the Yan group (conditions B) was able to couple aliphatic substituted Michael acceptors (**S38e**). Regarding the nitroketone, in addition to 2-nitroacetophenone derivatives (**S38a**), aliphatic nitroketones were also compatible couplings partners (**S38f**). Although the full synthetic utility was not disclosed, it was shown by Yan that the trapped enolate can be freed to the α-ketoester **S39a** under hydrolytic conditions without affecting the stereocenter (Scheme 39).

Scheme 38. Asymmetric Michael/retro-Claisen reactions



Scheme 39. Deprotection of the benzyloxy enol ether (Yan, 2011)



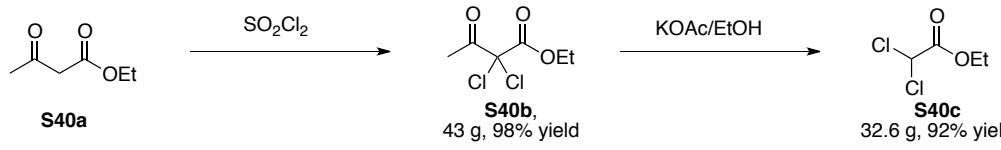
Finally, we have made our own contribution to this field of research, a Tsuji-Trost allylation/retro-Claisen of α-nitroketones.[88] However, this presented in the 3rd chapter of this dissertation.

2.2.6. C−X bond formation/retro-Claisen condensation

The previous sections have dealt with adding carbon-based electrophiles to β-dicarbonyl compounds and derivatives thereof. Heteroatomic electrophiles can also be added to active methylene nucleophiles forming a C−X bond and by retro-Claisen C−C cleavage, reveal the useful chemical building block containing a new heteroatom. Moreover, due to the nature of the C−X bond formed, where X is an electronegative atom, the retro-Claisen reaction is generally quite mild due to the anion stabilizing effect of the X-atom. The C−X bond formation/retro-Claisen condensation sequence has the same underlying principles as alkylation/retro-Claisen reaction and will be discussed in this section.

To begin, Gupta of Pfizer Inc., reported a general method for preparing α,α-dichloro acetates (Scheme 40).[89] By treating ethyl acetoacetate **S40a** with sulfonyl chloride, ethyl α,α-dichloro acetoacetate **S40b** was prepared quantitatively and on the large scale. Treatment of this compound with a mild base, such as potassium acetate, facilitated retro-Claisen condensation and upon protonation, the α,α-dichloro acetate **S40c** was made in high isolated yield.

Scheme 40. Preparation of α,α-dichloro esters by chlorination/retro-Claisen condensation (Gupta, 1973)



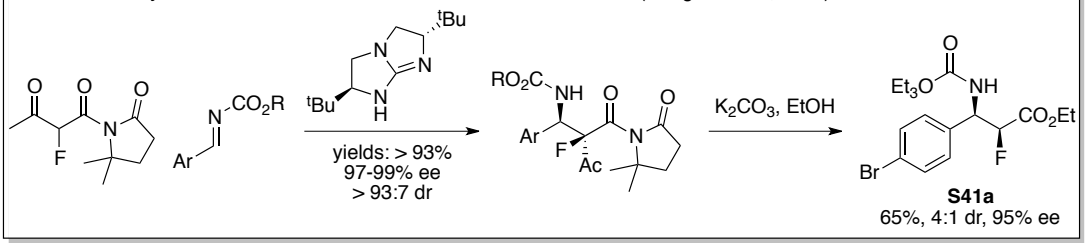
S40a

S40b, 43 g, 98% yield

S40c 32.6 g, 92% yield

C−F bond formation/retro-Claisen (e.g. with Selectfluor) can also occur on β-dicarbonyl compounds (Scheme 41). In a powerful example, C−F bond formation, asymmetric Mannich reaction and retro-Claisen condensation rapidly, enantioselectively, and diastereoselectively leads to α-fluoro-β-amino acids **S41a**.[90] This example represents how a β-ketoester can be used to its full potential by performing successive diversifying reactions.

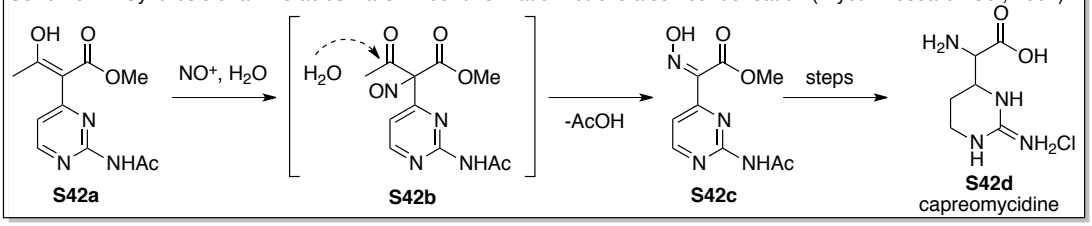
Scheme 41. Asymmetric Mannich reaction/retro-Claisen condensation (Jiang and Tan, 2011)



Though it will be discussed in a forthcoming section, Colby has another useful example of C−F bond formation/retro-Claisen condensation.[91,92] This is discussed in the section where the anions generated by retro-Claisen C−C cleavage are utilized in to make new C−C and C−X bonds (section 2.3).

In addition to halogens, nitrogen electrophiles have also been shown to couple with β-dicarboxyl species, and upon retro-Claisen condensation, prepare extremely useful α-amino carbonyl derivatives. This general structure is found in amino acids, extremely important biological building blocks.

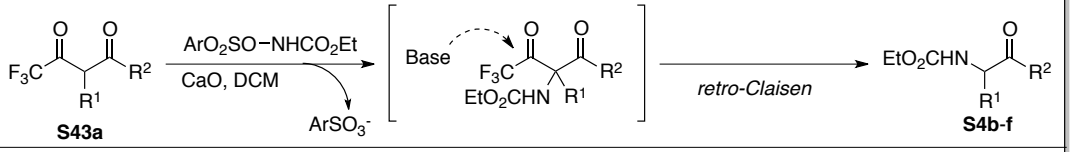
Scheme 42. Synthesis of amino acids via C–N bond formation/retro-Claisen condensation (Wyeth Research Co., 2004)

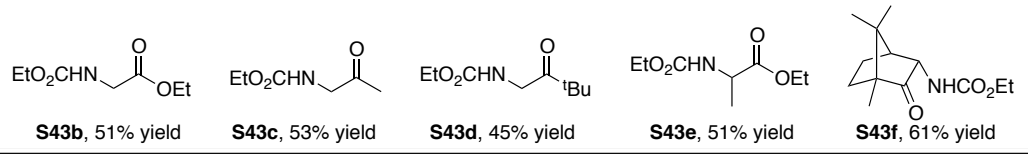


The nitrosation/retro-Claisen reaction of β-ketoesters to prepare α-oxime esters was first reported first in 1909, and reviewed in 1953.[93] This reaction was exhumed in 2004 by Wyeth, when it was used to synthesize a unique amino acid capreomycidine **S25d** (Scheme 25).[94] Treatment of the desired methyl acetoacetate **S42a** with nitrosonium ion ($NaNO_2$ and HCl) allows for C−N bond formation (**S42b**). The acetyl group is then cleaved by water leading to the desired α-oxime ester **S42c**. In 2 steps, this compound is converted to the desired amino acid,

capreomycidine **S42d**. This reaction was developed for the specific purpose of making carpreomycidine and no scope studies were performed.

Scheme 43. Synthesis of protected α-amino acetates and ketones by C-N bond formation/retro-Claisen (Pellacani, 2007)





Using a different source of electrophilic nitrogen, Pellacani demonstrated in 2007 that protected amino acid derivatives could be prepared from trifluoroacetylacetone or acetate derivatives **S43a** via C−N bond formation and retro-Claisen cleavage of the trifluoroacetyl unit *in situ* (Scheme 43).[95] They primarily focused on glycine-related amino acids (**S43a-c**), though an alanine amino acid (**S43d**) as well as camphor based amino ketone could be synthesized in good yield (**S43e**). Though no mechanism is suggested, it can be presumed to proceed by C−N bond formation followed by retro-Claisen condensation, promoted either by the CaO base or the *para*-nitrophenylsulfone (NsO^-) leaving group.

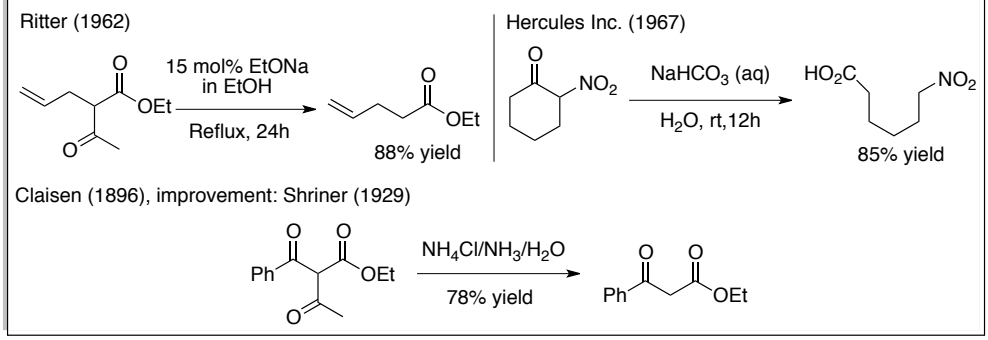
2.2.7. Retro-Claisen condensation on non-quaternary β-ketoesters

The retro-Claisen reaction of most of the examples discussed already in this review have focused on α,α-disubstituted β-dicarbonyl compounds. The retro-Claisen reaction of less substituted compounds is generally more challenging due to problematic enolization rendering the carbonyls much less reactive toward C−C cleavage. However, there are some examples of

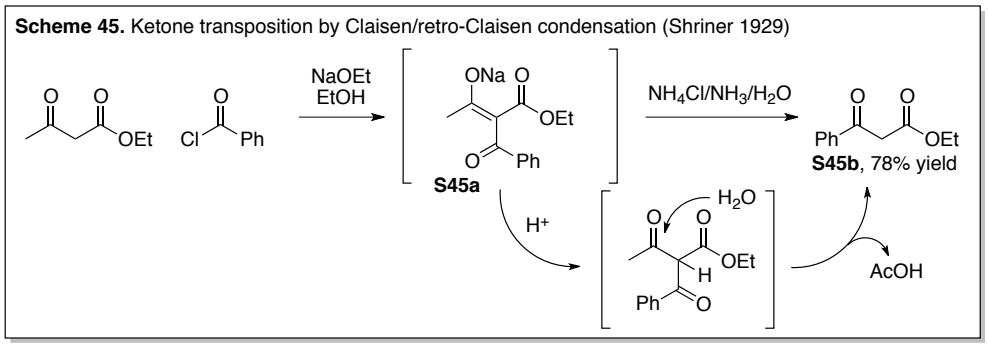
retro-Claisen condensation of mono-substituted β-dicarbonyl compounds, and they will be discussed in this section.

Early examples of this type of retro-Claisen reaction were reported by Claisen,[96] Ritter[97] and Hercules Inc.[75] (Scheme 44). Ritter and coworkers reported that a catalytic amount of ethoxide in refluxing ethanol could allow for retro-Claisen condensation to occur on an enolizable ethyl acetoacetate. To compare, fully quaternized ethyl acetoacetates undergo retro-Claisen condensation with ease.[6] Researchers at Hercules Inc. reported a mild retro-Claisen reaction for enolizable nitroketones.[75] The reaction went with a much milder base than the Ritter example, $NaHCO_3$, presumably due to the high stability of the nitronate anion generated upon retro-Claisen C−C cleavage. Claisen[96] and Shriner's[98] method for the production of ethyl benzoylacetate from the tricarbonyl also went under mild conditions again due to the high stability of the anion generated. In general, the retro-Claisen reaction is facilitated by high temperature and anion stabilization.

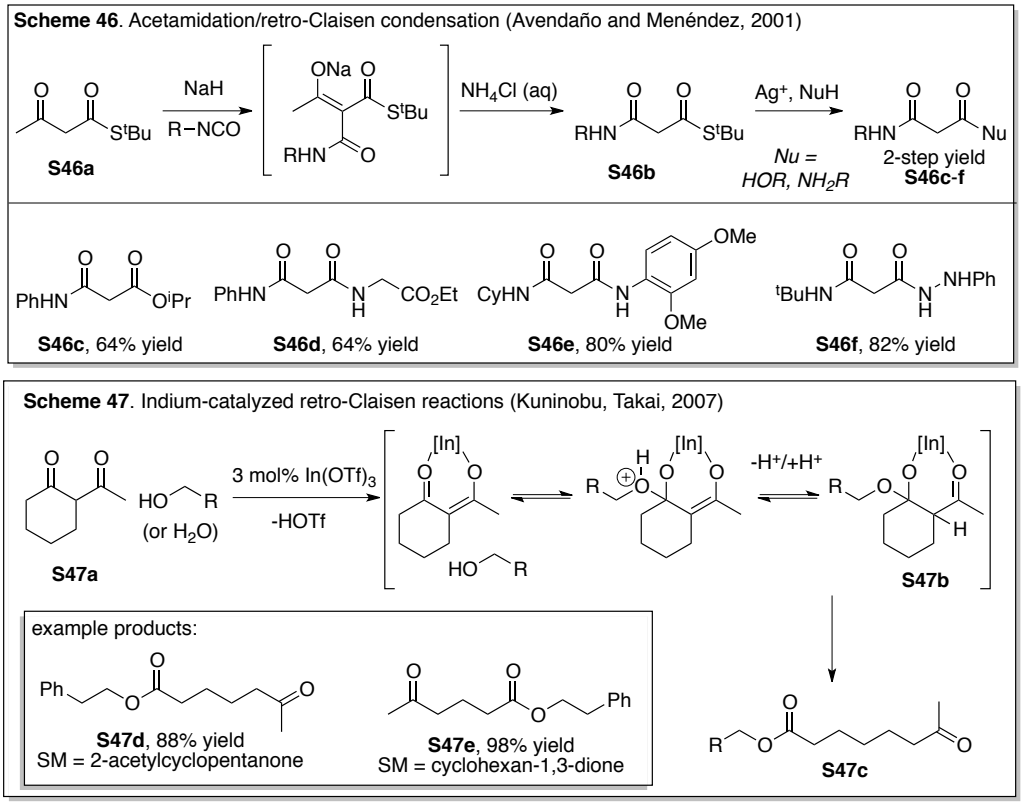
Scheme 44. Retro-Claisen condensation of various mono-substituted β-keto compounds



There are a few useful methods of acylation/retro-Claisen reaction involving intermediary tricarbonyl compounds. As introduced above, Claisen[96] and Shriner,[98] have reported a method for ketone transposition (Scheme 45) from ethyl acetoacetate and a given acyl chloride. In the presence of base, acylation occurs to the tricarbonyl compound **S45a**. Hydrolysis then removes the most electrophilic carbonyl (the acetyl unit) and yields the desired product **S45b**.



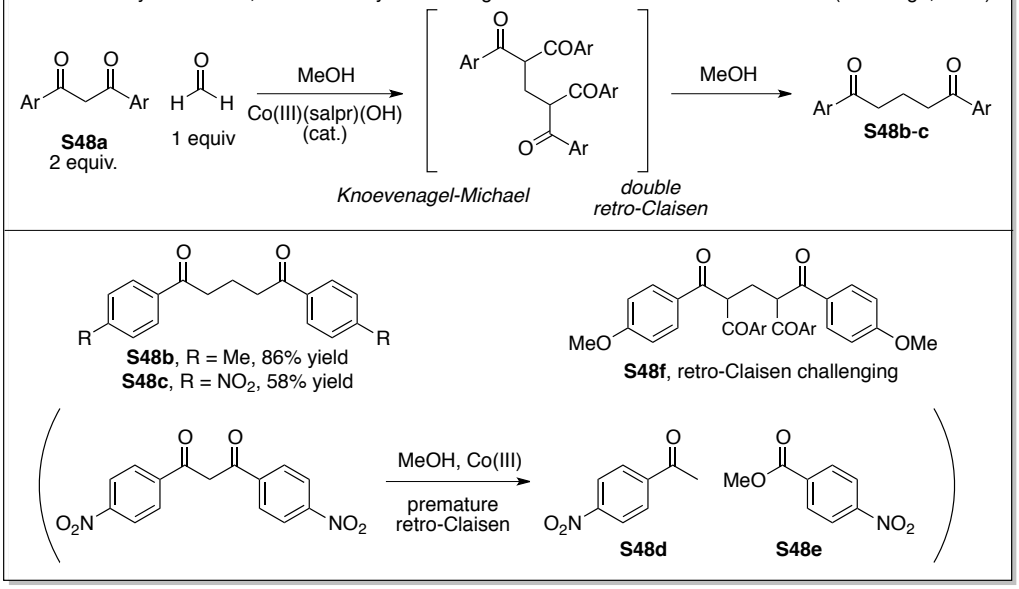
In a conceptually similar approach, β-ketothioesters could be converted to mixed thio/amide malonates **S46b** through a tricarbonyl by reaction with an isocyanate followed by retro-Claisen condensation (Scheme 46).[99] The thioester was strategically utilized to allow for late-stage diversification to mixed malonic amides and esters **S4c-f**. In general, this 2-step sequence went in good overall yield.



Using an indium catalyst, Kuninobu, Takai, and coworkers reported a very interesting retro-Claisen reaction of β-diketones (Scheme 47).[100] In this reaction, an alcohol (or water)

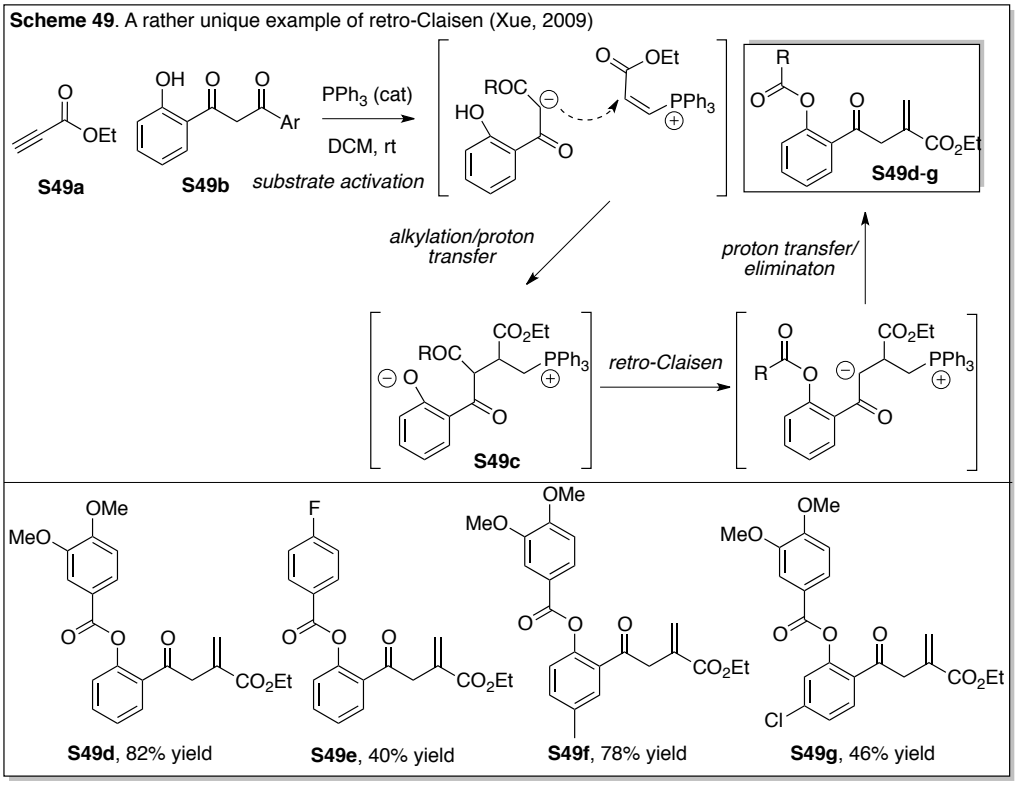
attacks the internal ketone of **S47a** selectively over the exocyclic ketone. This endocyclic nucleophilic attack is opposite to what is observed in all the other reactions presented throughout this review. This unique reactivity is presumably due to the favorable exo-enolization of the β-diketone **S47a**. Upon catalyst binding, hemiacetal formation, and proton transfer, the intermediate **S47b** is now poised to undergo retro-Claisen condensation leading the product **S47c**. A similar strategy has also been developed using $FeCl_3$ as the catalyst,[101] which is attractive since iron is very abundant and inexpensive.

Scheme 48. Synthesis of 1,5-diketones by Knoevenagel-Michael/retro-Claisen condensation (Nishinaga, 1995)



Using a cobalt catalyst, dibenzoylmethane derivatives **S48a** can undergo Knoevenagel/Michael and retro-Claisen condensation yielding symmetric 1,3-benzoylpropanes (a 1,5-diketone, Scheme 48).[102] With di-*para*-tolylmethane the reaction went smoothly to the desired product **S48b**. Using the *para*-nitrophenyl substrate the isolated yield was reasonable (**S48c**), however, premature retro-Claisen condensation of the starting material (leading to nitro substituted acetophenone **S48d** and benzoate **S48e**) was a competing reaction. Furthermore, a diketone having *para*-methoxyphenyl substitution underwent the retro-Claisen reaction too slowly, though the authors report that good yields of the Knoevenagel/Michael adduct can be

isolated with this substrate. In general, a delicate balance of reactivity is required for this reaction to progress smoothly under these reaction conditions.



A unique PPh_3-catalyzed reaction sequence coupling propiolate **S49a** and *ortho*-hydroxy containing mixed dibenzoylmethanes **S49b** involving a retro-Claisen reaction was reported by Xue (Scheme 49).[103] In this sequence, the PPh_3 activates the propiolate **S49a** by conjugate addition, the resulting anion, deprotonates the dibenzoylmethane **S49b** to activate both the starting materials for coupling. A second conjugate addition occurs as shown by the curved arrow. The resulting phosphonium ylide then deprotonates the phenol to form intermediate **S49c**, which is predisposed for retro-Claisen condensation. Through proton transfer and elimination, the product **S49d** is generated. Interestingly, electron rich benzoyl derivatives gave the best yield. For example dimethoxybenzoyl (**S49d**) vs. *para*-fluorobenzoyl (**S49e**) gave drastically different yields. This is an interesting result as retro-Claisen reaction is usually more

facile with more electrophilic carbonyls. Nonetheless, using the most effective benzoyl transfer group (3,4-dimethyoxybenzoyl), various substitution patterns (**S49f-g**) were tolerated and the reactions went in good yield.

Regarding the retro-Dieckman step of the PPh_3-catalyzed reaction above (Scheme 49), full quaternarization was likely not required due to the (a) neutral reaction conditions and the (b) favorable transition-state geometry of the acyl transfer (acyl transfer goes though a 6-membered ring). A similarly favorable 6-membered ring acyl transfer transition-state was observed in the coupling of α-nitroketones and Michael acceptors.[85-87] This was previously discussed in Scheme 38.

Finally, enolizable α-aryl β-dicarbonyl compounds also undergo retro-Claisen reaction without the requirement of quaternarization. This reaction is well-studied due to the importance of the products prepared, α-aryl monocarbonyl compounds, and the attractive synthetic route. The next section of this review will focus on this topic.

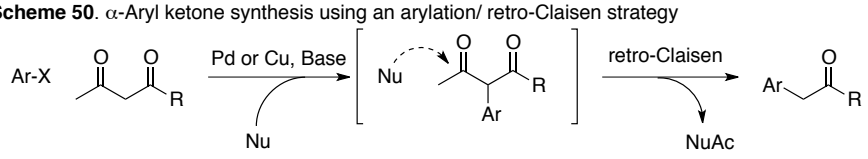
To conclude, the retro-Claisen condensation of enolizable β-dicarbonyl derivatives is less common, but can be favored using general tactics such as: (a) high temperature, (b) highly stabilized post-retro-Claisen anions, (c) Lewis acid catalysts (c) and acyl transfer through thermodynamically favorable transition-states.

2.3 Transition metal-catalyzed arylation/retro-Claisen condensation strategies

Transition metal-catalyzed enolate arylation is a heavily researched area in synthetic chemistry primarily due to the utility of α-aryl carbonyl functionality (for example, see ibuprofen, verapamil and clopidogrel in Scheme 2) but also due to the attractive retrosynthetic

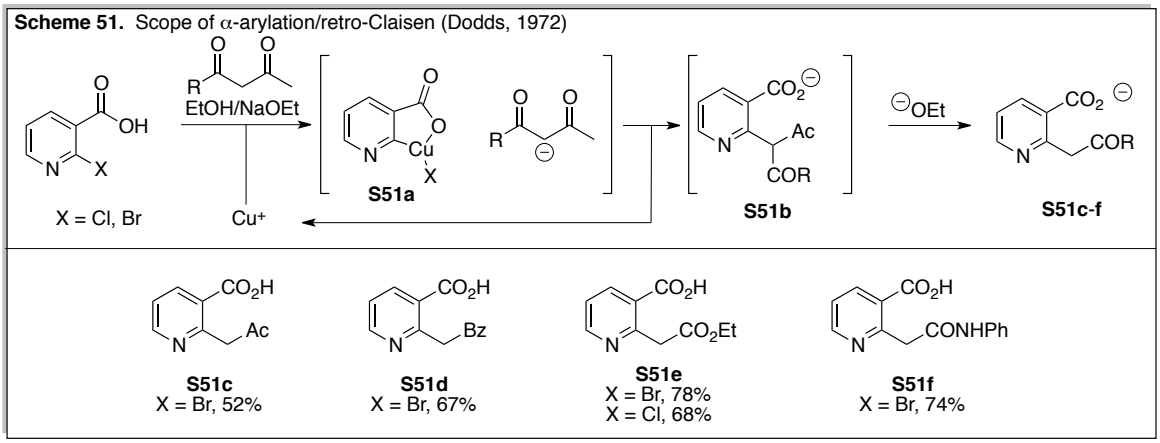
disconnection. The arylation of active methylene nucleophiles (β-dicarbonyl compounds) has been known since the early 20th century.[104] For example, the Cu-catalyzed arylation of sodium *ortho*-bromobenzoate was reported by Hurtly in 1927.[104] Active methylene compounds are commonly employed in arylation reactions due to their low pK_a's, which render their activation simple. More recently, methodologies for arylation of less stabilized monocarbonyls have been developed, however, the conditions required to do so can be challenging and require more expensive/sensitive bases and specialized catalysts.[105,106]

Scheme 50. α-Aryl ketone synthesis using an arylation/ retro-Claisen strategy



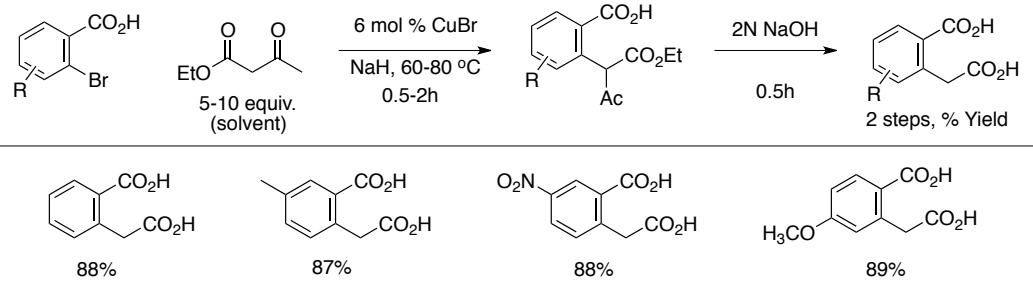
An attractive, yet underutilized, alternative strategy for the synthesis of α-aryl monocarbonyl compounds is by (a) arylation of the active methylene compound followed by (b) retro-Claisen reaction (Scheme 50). This synthetic strategy was first outlined in 1927, by Hurtley,[104] for the coupling of various active methylene compounds with *ortho*-bromobenzoic acid. Scope and method improvements were reported in 1972 and 1974 by Dodds[107] (Scheme 51) and McKillop [108,109] (Scheme 52), respectively.

Scheme 51. Scope of α-arylation/retro-Claisen (Dodds, 1972)



In these seminal papers,[104,107-109] the importance and requirement of an *ortho*-carboxylate is outlined (Scheme 15). It is suggested that the formation of a Cu-arene chelate **S51a** facilitates C−C bond formation between the picoline derivative and the active methylenes (**S51b**). In these examples, both bromo- (e.g. **S51c**) and chloro- (**S51e**) picolinic acids were viable coupling partners. Regarding the active methylene coupling partner, acetylacetone (**S51c**), dibenzoylmethane (**S51d**), ethyl acetoacetate (**S51e**) and acetoacetamide (**S51f**) were all excellent coupling partners.

Scheme 52. Method improvement for α-arylation/retro-Claisen (McKillop, 1974)

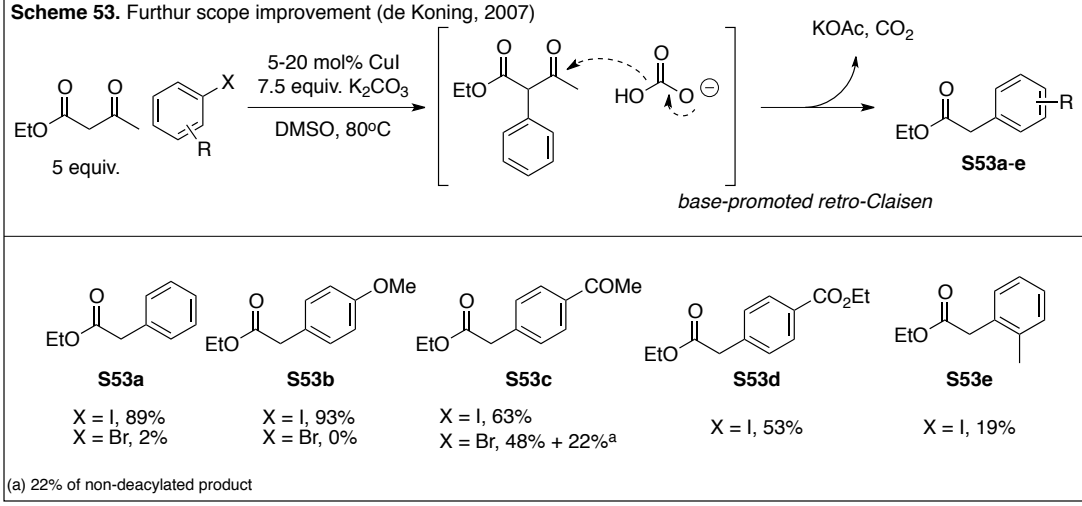


McKillop opted to use a copper(I) source rather than the Cu(0) or Cu(II) precatalyst that had been used in previous papers for the arylation/retro-Claisen reaction (Scheme 52).[108,109] He noted that the various Cu(0) or Cu(II) sources previously utilized gave irreproducible results. Moreover, ethanol and ethoxide were removed from the system to avoid concomitant formation of aryl ethyl ether byproducts. In this case, NaOH was added after the arylation reaction went to completing to promote the retro-Claisen condensation.

Cu(I)-catalyzed active methylene arylation sat dormant until the early 1990s when the importance of a polar aprotic solvent (such as DMSO) was noted by Miura.[110] It was this breakthrough that allowed de Koning to devise a Cu(I)-catalyzed method for a relatively general 1-pot arylation/retro-Claisen reaction in 2007 (Scheme 53).[111] Interestingly, as the previous retro-Claisen reactions have been water/alcohol mediated, the retro-Claisen condensation in this

sequence is thought to be base-mediated as no water or alcohol is present. Regarding the scope, the communication focuses on simple phenyl (**S53a**) and *para*-substituted aryl iodides (**S53b-d**) and bromides. Both electron rich and poor aryl iodides worked quite well (**S53a-d**), whereas electron deficient aryl bromides were the only viable coupling partners under these conditions (**S53c**). Moreover, alkyl *ortho*-substitution was not well tolerated (**S53e**). Unlike *ortho*-carboxylate substitution (Schemes 51-52), there is no potential for Cu-ion chelation with this aryl halide. Thus, only a negative steric effect is observed.

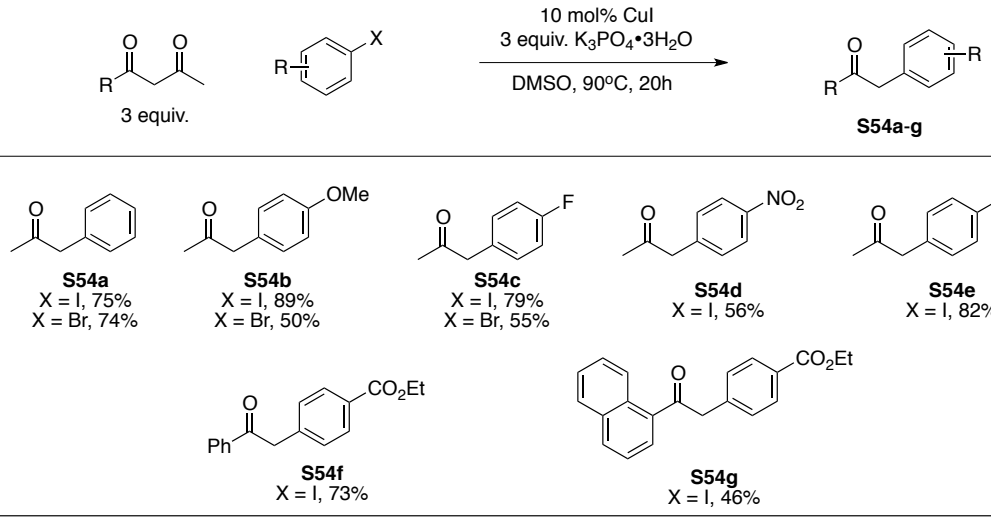
Scheme 53. Furthur scope improvement (de Koning, 2007)



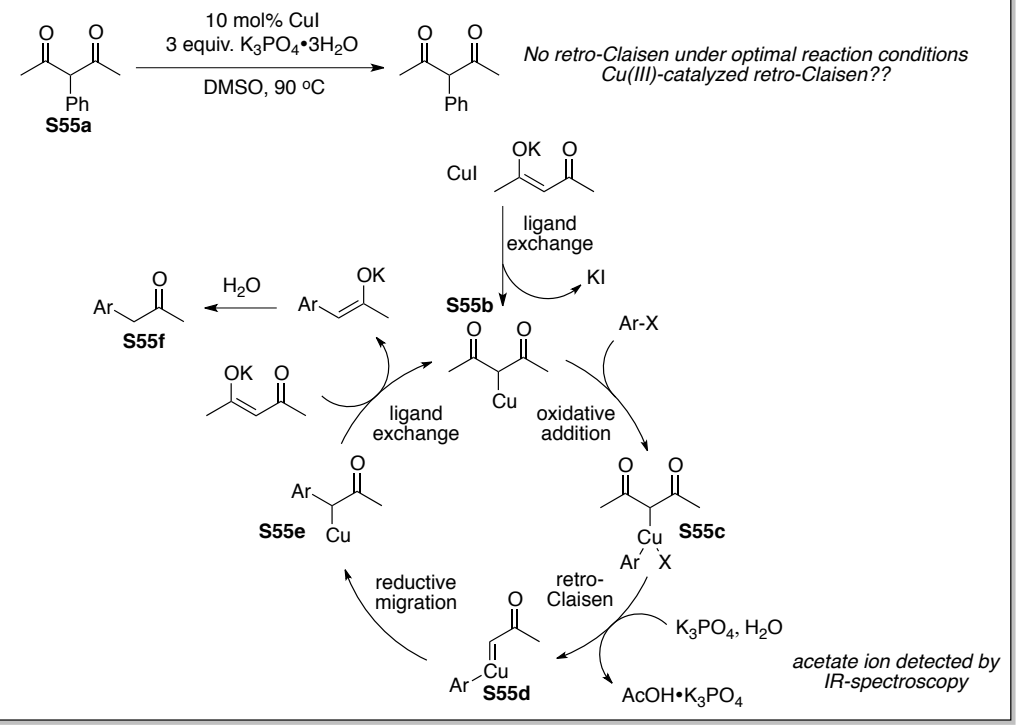
(a) 22% of non-deacylated product

In 2010, Lei further developed this Cu(I)-catalyzed arylation/retro-Claisen reaction and expanded the scope to other active methylene derivatives (Scheme 54), though he believes the reaction to proceed by a different mechanism (Scheme 55).[112] As opposed to the previously mentioned arylation of ethyl acetoacetate by de Koning (Scheme 53),[111] water is present and plays a key role in this reaction (Scheme 54). Similar to de Koning's findings, aryl iodides are better coupling partners than the corresponding bromides (**S54a-c**), though they were tolerated. He also demonstrated that chemoselective retro-Claisen reaction occurs for the acetyl group over the various benzoyl groups, allowing access to diverse aryl ketones (**S54f-g**).

Scheme 54. Cu-catalyzed arylation/retro-Claisen condensation of acetylacetone derivatives (Lei, 2010)



Scheme 55. Mechanistic insights into copper-catalyzed arylation/retro-Claisen reaction (Lei, 2010)

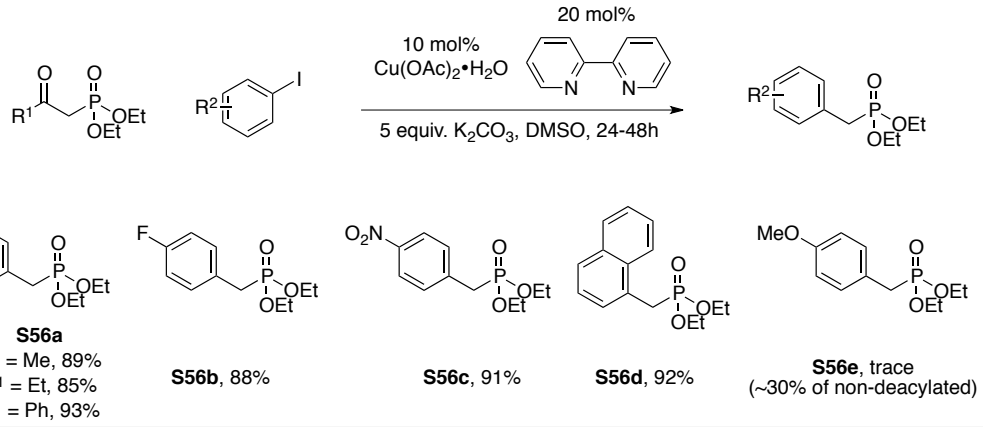


Lei and coworkers noted that phenyl acetylacetone **S55a**, the presumed intermediate in the arylation/retro-Claisen reaction presented in scheme 54, did not undergo retro-Claisen cleavage under the reaction conditions (Scheme 55, top). Moreover, it was never witnessed as a byproduct. To explain this, Lei offers the following mechanistic hypothesis (Scheme 19): the active catalyst is the Cu-acetylacetone complex **S55b**. This species undergoes oxidative addition

with the aryl halide generating **S55c**. The retro-Claisen occurs from here to generate the Cu-carbenoid **S55d**, which by reductive migration and a final ligand exchange generates the desired product **S55f** and the active catalyst. He also concluded that water performs the retro-Claisen reaction as acetate ion was detected using react-IR technologies.

Zhao has quite recently reported the arylation/retro-Claisen reaction of β-ketophosphonates leading to α-aryl phosphonates (Scheme 56).[113] However, he was limited to electron deficient aryl iodides (**S56a-d**) as *para*-iodoanisole failed to give a reasonable result (**S56e**). He did however show that various acyl derivatives could be cleaved. For example, **S56a** was prepared by arylation and retro-Claisen cleavage of an acetyl, propionyl, and a benzoyl group. As shown by **S56e**, there was a significant amount of the non-deacylated byproduct for this electron rich aromatic system. First, the retro-Claisen reaction, in this case, was potentially more challenging due to the increased pK_a of the phosphonate-stabilized anion. Moreover, this result suggests that arylation occurs before the deacylation event, and a mechanism similar to Lei's is probably not the major route to product formation, in this case.

Scheme 56. Cu-catalyzed α-arylation/retro-Claisen of β-ketophosphonates (Zhao, 2011)

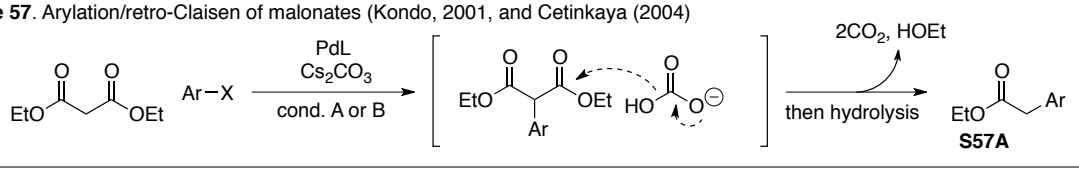


In addition to Cu-catalyzed arylation, there are also some examples of Pd-catalyzed arylation/retro-Claisen reaction in the literature too. The earliest example where tandem Pd-

catalyzed arylation/retro-Claisen cleavage was utilized to afford α-arylated mono-esters was in 2001, when Kondo and coworkers reported the coupling of aryl iodides and malonate nucleophiles followed by base induced retro-Claisen cleavage (Scheme 57).[114] This work was further elaborated by Cetinkaya and coworkers in 2004. Again, the reaction was significantly broadened and simplified by Gooβen in 2011 (Scheme 58 and 59).

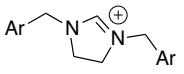
In Kondo's initial report on the arylation/retro-Claisen reaction of malonate and aryl iodides, high temperature and excessive Cs_2CO_3 were utilized to promote both reactions (Scheme 54, cond. A). Nonetheless, both electron poor (**S57a**) and electron rich (**S57b**) aryl bromides could be coupled in good yield. Cetinkaya notably extended the reaction to aryl chlorides and their conditions (cond. B) could also couple the sterically hindered 2-bromo mesitylene (**S57c**).[115] Though these initial reports were quite promising, the scope that was investigated was slim.

Scheme 57. Arylation/retro-Claisen of malonates (Kondo, 2001, and Cetinkaya (2004)



L = ^{t}BuP, aryl iodides/bromides (cond. A)
L = **S57d**, aryl iodides/bromies/chlorides (cond. B)

S57d =



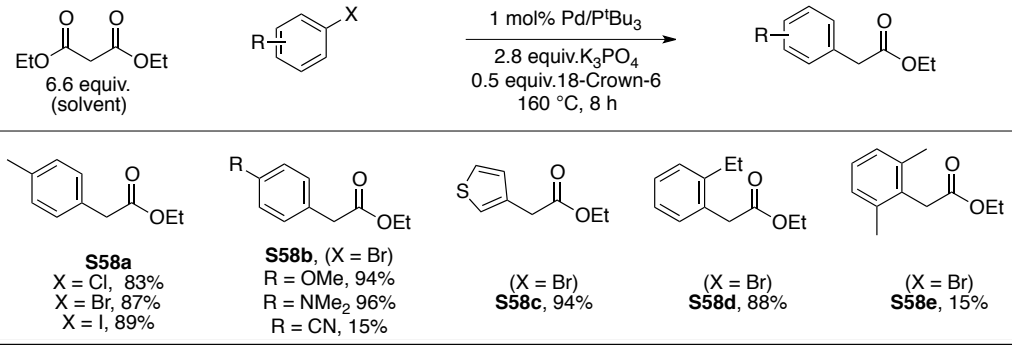
	S57a	**S57b**	**S57c**
Cond A:	X = I, 61%	X = I, 70%	-
Cond. B:	X = Cl, 92%	X = Cl, 85%	X = Br. 85%

(a) Pd/^{t}Bu$_3$ (cat), 10 equiv. Cs_2CO_3, 120 °C, DME, 45-76 h, (b) Pd/**S53X** (cat), 2 equiv. Cs_2CO_3, dioxane, 80 °C, 24 h

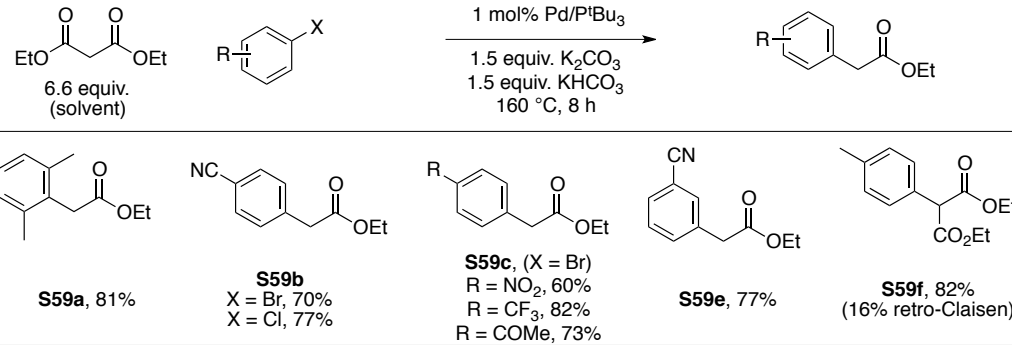
With excellent scope, Gooβen and coworkers recently reported a practical strategy for arylation/retro-Claisen condensation of ethyl malonate from diverse aryl bromides and chlorides.[116] Using the same catalyst system used by Kondo, two complimentary conditions were developed to allow both electron rich and poor haloarenes (Schemes 58 and 59, respectively) with various substitution patterns to couple cleanly and predictably.

The first conditions (Pd/^{t}Bu$_3$, K_3PO_4, 18-crown-6) coupled electron rich aryl halides with malonate nucleophiles (Scheme 58). As an electron rich aromatic is being added to the malonate, a highly reactive nucleophile for retro-Claisen condensation was required due to the heighted pK_a of aryl ester enolate anion to be generated. 18-crown-6 as an additive was found to be quite effective in promoting said cleavage reaction. As product **S58a** shows, aryl chlorides, bromides and iodides were all excellent coupling partners under these conditions. Moreover, various electron donating groups were compatible at the *para* (**S58b**) and *meta* (**S58c**) positions of the arene. Some *ortho*-substitution was tolerated (**S58d**). Unfortunately, these conditions were problematic with electron deficient and sterically encumbered aryl bromides (e.g. **S58b**, R = CN, and **S58e**). The major product in these cases was simply metal-catalyzed protodehalogenation.

Scheme 58. Conditions for arylation/retro-Claisen of electron rich haloarenes and ethyl malonate (Gooβen, 2011)



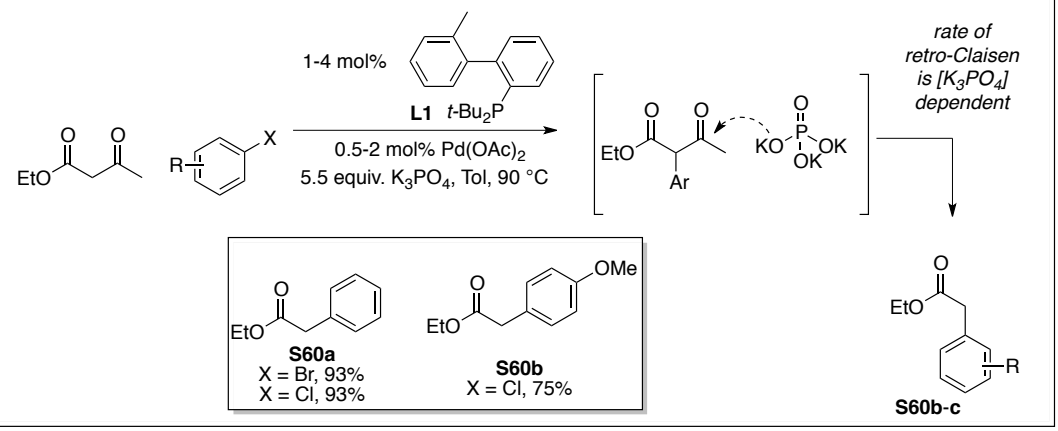
Scheme 59. Conditions for arylation/retro-Claisen of electron poor haloarenes and ethyl malonate (Gooβen, 2011)



Unwilling to allow his coupling reaction to be limited to electron rich arenes, Gooβen and coworkers went back to the drawing board and redesigned their conditions for sterically hindered

and electron poor aromatics. The employment of a milder base combination (1:1, K_2CO_3:$KHCO_3$) could promote both the arylation and the retro-Claisen cleavage of sterically demanding (**S59a**) and electron deficient substrates (**S59b-e**). As an electron deficient aryl bromide is added to the malonate, it is understandable that a milder base can promote the retro-Claisen reaction as the anion generated upon retro-Claisen condensation has added stability. This reaction was quite general with various aryl chlorides and bromides (**S59b**) as well as various electron withdrawing functional groups including cyano, nitro, trifluoromethyl and ketone EWG-groups (e.g. **S59b-c**) Interestingly, these conditions were shown to nicely promote arylation of moderately electron rich aryl bromides, however the milder base combination could not promote the retro-Claisen cleavage reaction to any appreciable level (**S59f**).

Scheme 60. Pd-catalyzed arylation/retro-Claisen of ethyl acetoacetate (de Koning, 2004)

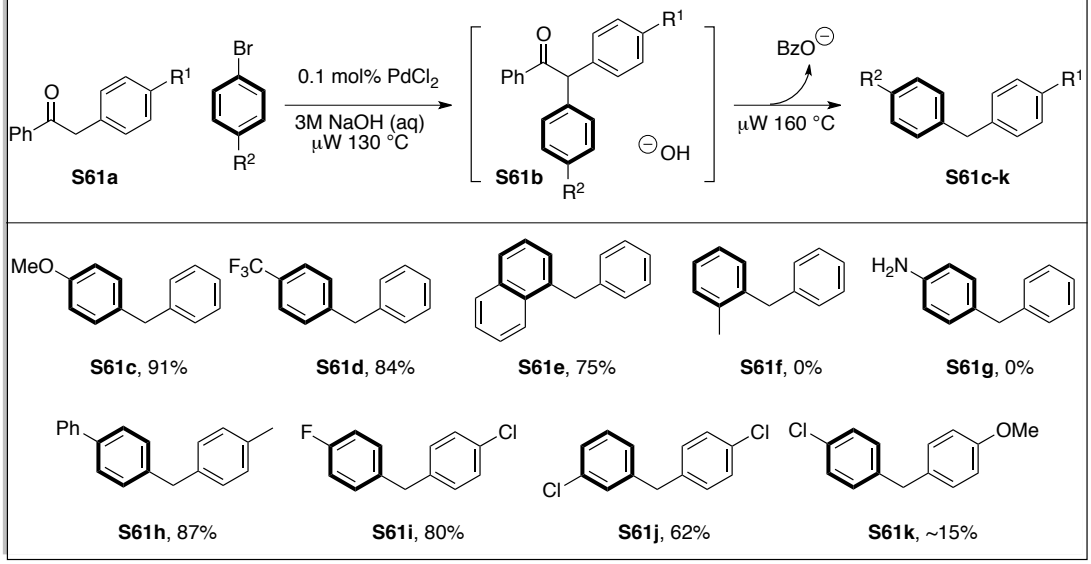


In addition to the aforementioned coupling/retro-Claisen reaction of malonate and aryl halides, α-aryl esters can be accessed by the coupling of ethyl acetoacetate with aryl chlorides and bromides, as disclosed by de Koning (Scheme 60).[117] In these examples, the state of the art (at this time) ligand was utilized. Using the tBuMePhos ligand (**L1**) reported by Fox and Buchwald in 2000, the reaction proceeds cleanly and in good yield with aryl bromides and chlorides. Regarding the retro-Claisen step, it is mediated by potassium phosphate. Moreover, the rate of retro-Claisen cleavage was seen to correspond with the concentration of phosphate,

such that as more tribasic phosphate is added, the more rapid the retro-Claisen reaction becomes. Unfortunately, a full scope study was not performed on this useful reaction.

Though not classically a "retro-Claisen" reaction as a dibenzyl anion is generated instead of an enolate or derivative thereof, the following Pd-catalyzed arylation/C−C cleavage fits nicely into this review to show that retro-Claisen C−C cleavage is not necessarily limited to enolates.[118]

Scheme 61. A Pd-catalyzed approach to diarylmethanes via retro-Claisen (Leadbeater, 2009)



It was shown by Leadbeater in 2009 that benzylphenones **S61a** can be arylated in water using ligandless $PdCl_2$ (synthesizing intermediate diaryl ketone **S61b)** and converted into diarylmethanes (**S61c-k**) via retro-Claisen condensation.[118] Regarding the aryl bromide coupling partner, electron rich (**S61c**) and poor (**S61d**) aromatics were compatible. Some *ortho*-substitution was allowed on the aryl bromide. For example, 2-napthyl bromide (**S61e**) was an excellent coupling partner, though *ortho*-methyl substitution (**S61f**) was not well-tolerated. Aromatics containg 1° amines were not compatible coupling partners as shown in the failed coupling of the aniline derivative (**S61g**). Regarding the α-aryl acetophenone **S61a**, the reaction worked best with electron withdrawing substitutions (**S61h-j**) on the aromatic ring, this further stabilizes the anion generated upon retro-Claisen condensation. Conversely, the higher pK_a *para*-

methyoxy containing benzylphenone (**S61k**) reacted poorly. Thus, the limitation does not appear to be in the retro-Claisen reaction in this case, but rather the initial Pd-catalyzed arylation. Potentially, the increased pK_a makes the active enolate more challenging to generate.

To conclude this section, there have been some extremely useful transition metal-catalyzed arylation/retro-Claisen C−C cleavage methods developed leading to α-aryl ketones and esters and even diarylmethanes. This work spans almost 100 years and is still actively being researched with major contributions published within the last year.

2.4 Methodologies based on a retro-Claisen condensation/functionalization strategy

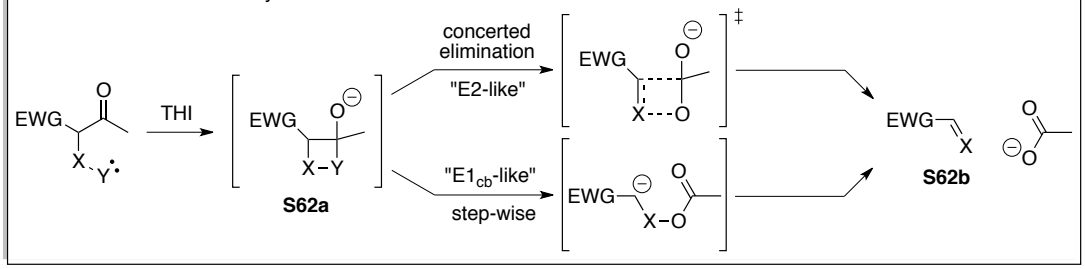
The previous sections have focused on how active methylene nucleophiles can be used as a platform for functionalization. Then, one of the carbonyls can be removed by retro-Claisen condensation/protonation. This next section will focus on how an acyl transfer event can promote further coupling reactions between the *in situ* generated anion and various electrophiles. Currently, there are two main subdivisions of this type of general reaction: acyl transfer/elimination and retro-Claisen C−C cleavage as a means to generate discrete carbanions for C−X or C−C bond formation. The former subdivision is significantly more researched and will be discussed first.

2.4.1. Retro-Claisen condensation(acyl transfer)/elimination

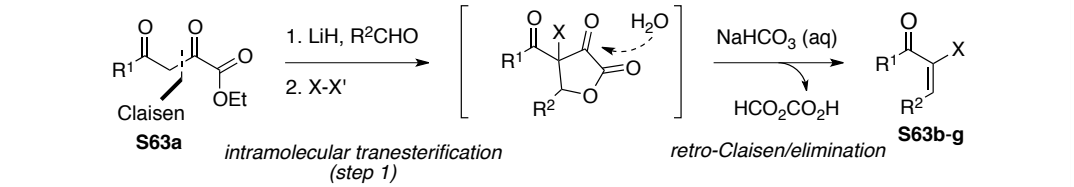
We will begin our discussion on acyl transfer/elimination with a general outline of the reaction (Scheme 62). The fundamental feature of this reaction is that an internal nucleophile,

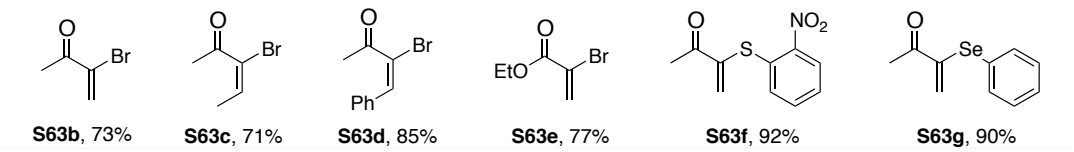
commonly in a 1,3-relationship with the acyl unit to be transferred, attacks the acyl group forming a tetrahedral intermediate **S62a** (THI). From here one of two mechanisms can be at play to reach the final elimination product **S62b**. The first possible mechanism is an "E2-like" concerted mechanism where the new π-bond forms as the leaving group is released. The second possibility involves an "$E1_{cb}$-like" mechanism, where the acyl group is transferred completely to the internal nucleophile, forming a discrete carbanion. Furthermore, this transfer also activates the internal nucleophile for elimination. Importantly, *both the anion and the leaving group are activated in situ for elimination by a single acyl transfer event*. In many of the publications about to be described, it is not always clear the exact mechanism of C−C bond fragmentation as no mechanistic studies were performed to gain insight into the reaction. However, like any common E2 vs. $E1_{cb}$ mechanistic consideration, it will depend on how stabilizing the electron withdrawing (EWG) group is and the energetics of the 4-membered ring intermediate **S62a**.

Scheme 62. Generalized acyl transfer/elimination



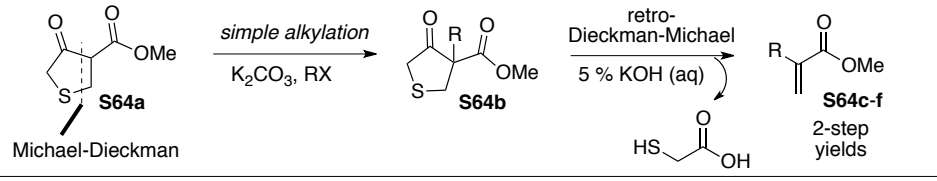
Scheme 63. Synthesis of α-hetroatom-α,β-unsaturated carbonyls (Nield, 1945 & McMurry, 1977)





Though the general reaction outline is well suited for describing most of the reactions in this section, we will begin our discussion with an outlier, as it is an early example of acetyl transfer/elimination. In 1945, Nield described an extremely simple, yet ingenious, method to prepare α-bromo vinyl ketones starting from a simple starting material, acetyl ethyl pyruvate **S63a** (Scheme 63).[119] Reaction of **S63a** with formaldehyde leads to the aldol product with subsequent transesterification to the 5-membered ring. Bromination of the β-diketone followed by retro-Claisen elimination (loss of oxalic acid) leads to the desired product **S63b**. Nield reported that the reaction worked well with other aldehydes (e.g. **S63c-d**) aside from simple formaldehyde and could also be used to prepare α-bromoacrylates (**S63e**). McMurry later utilized this method to prepare α-thio (**S63f**) and selenyl (**S63g**) containing vinyl ketones.[120]

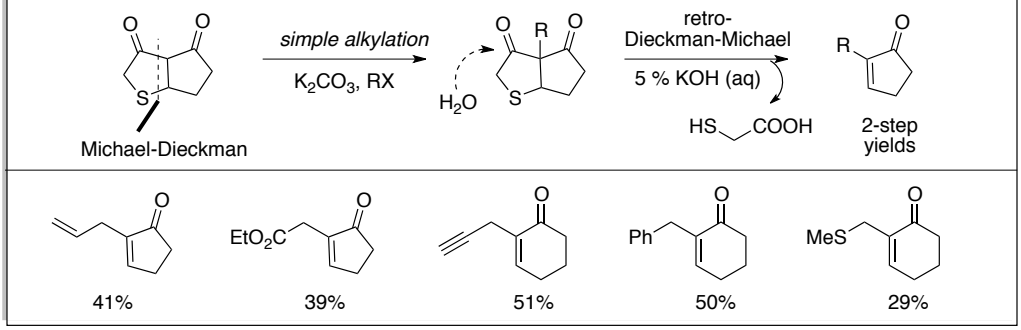
Scheme 64. Preparation of substituted acrylates via alkylation/retro-Dieckman-Michael (Baraldi, 1982)



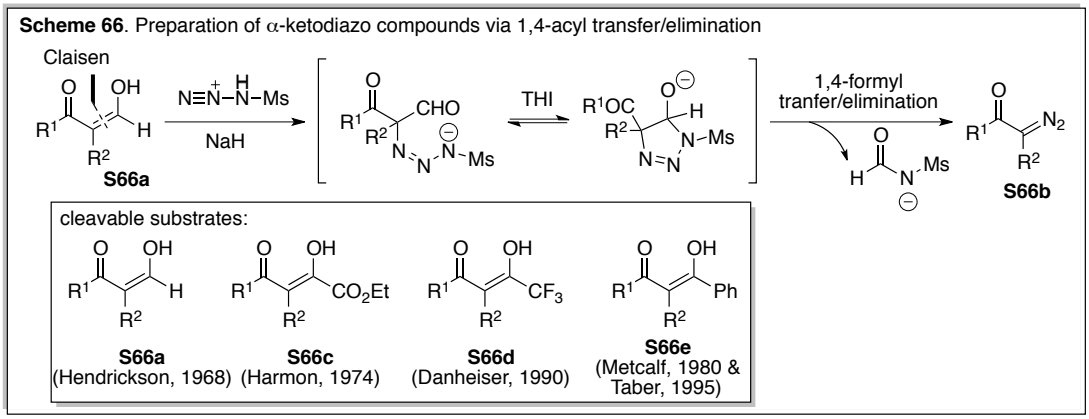
Alkylation of sp^2 carbanions is not a trivial process. Using principles from the reaction designed by Nield above, Baraldi has designed various sp^2 carbanion synthons derived from a Michael-Dieckman adduct of thioglycolate and α,β-unsaturated ketones and esters (Schemes 64-65).[121,122] For example, by treating methyl acrylate with methyl thioglycolate, a Michael-Dieckman condensation occurs yielding **S64a**. This cycloadduct can undergo mild alkylation reactions to **S64b**. Then, by treatment with dilute KOH, the retro-Dieckman-Michael reaction occurs to form the substituted acrylate (**S64c-f**) in good yields. The retro-Dieckman-Michael reaction also regenerates the thioglycolate. Aside from acrylate, other cyclic enones could also

participate in this reaction sequence (Scheme 65). Interestingly, the retro-Claisen reaction was completely chemoselective for the thioglycolate ketone.

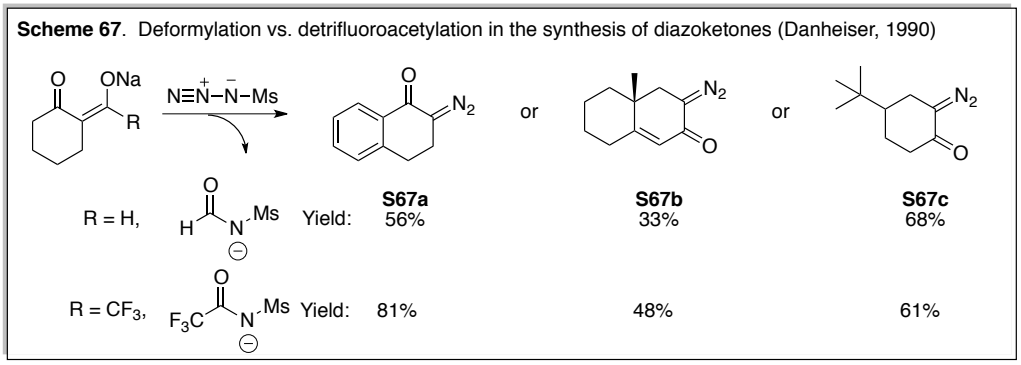
Scheme 65. Preparation of substituted cyclic eneones via alkylation/retro-Dieckman-Michael (Baraldi, 1984)



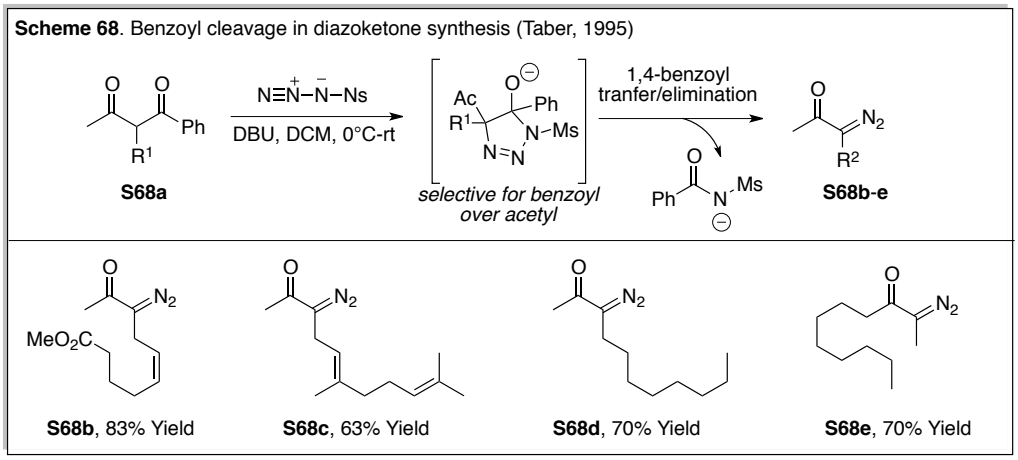
A major breakthrough in the preparation of mono-carbonyl diazo compounds was the realization that they could be prepared by an acetyl cleavage approach (Scheme 66).[123-125] Of course, the challenge of direct diazo formation of a monocarbonyl derivative is the heightened pK_a in comparison to a β-dicarbonyl compound. It was reported in the 1960's that reaction of an α-alkyl-β-formylketone **S66a** with a sulfonyl azide in the presence of base leads directly to the monocarbonyl-diazo compound **S66b**. The reaction mechanism of this transformation is as follows: nucleophilic attack of the β-formylketone ketone on the mesyl azide allows for C−N bond formation. The nucleophilic azide cyclizes onto the aldehyde to form an intermediary triazole. 1,4-formyl transfer/elimination then provides the diazo ketone and the sulfonyl formamide byproduct. This is a major area of research due to the utility of diazo compounds, and important developments have been made by Hendrickson,[123] Doyle,[126,127] Taber, [125] and Danheiser.[128] History has shown that the formyl transfer agent works reasonably well,[123] however, Danheiser improved this method by introducing the use of trifluoroacetyl as a more effective transfer agent (**S66d**).[128] Other notable cleavable substrates are the oxalyl[124] (**S66c**) and benzoyl group[127] (**S66e**) containing ketone substrates.



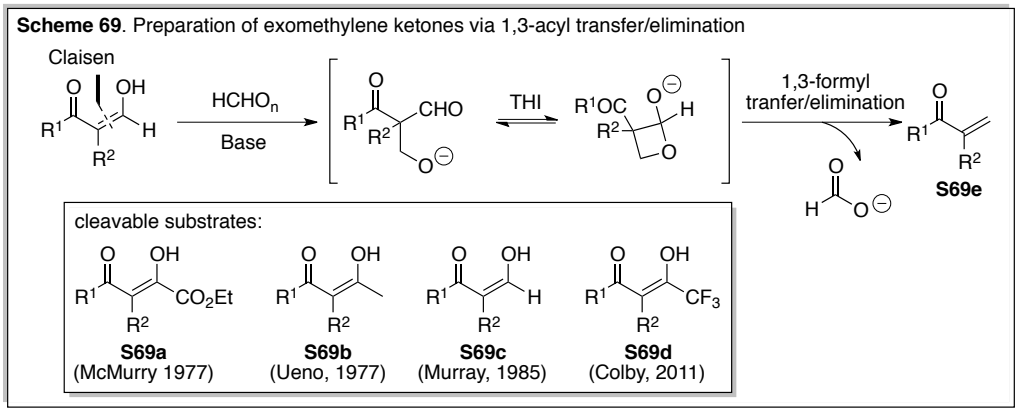
Commonly, reactions of β-trifluoroacetyl ketones (**S66d**) go smoother and in higher yield than their formyl-derived analogs due to the increased electrophilicity of the transferring ketone. For comparison purposes, Danheiser ran a series of contrast studies (Scheme 67).[128] For example, α-tetralone **S67a** and Wieland-Miescher **S67b** diazo complexes were formed in noticeably better yields starting from the trifluoroacetyl analog. However, sometimes the cleaving groups worked comparably well as in the example of the *tert*-butylcyclohexanone **S67c**.



In a rather interesting example, Taber and coworkers demonstrated that benzoylacetone derivatives underwent chemoselective cleavage at the phenyl ketone; an unexpected results since an acetyl is more electrophilic than a benzoyl group.[127] Nonetheless, unsymmetric benzoylacetone derivatives **S68a** could be converted into useful diazo ketone derivatives **S68b-e**.



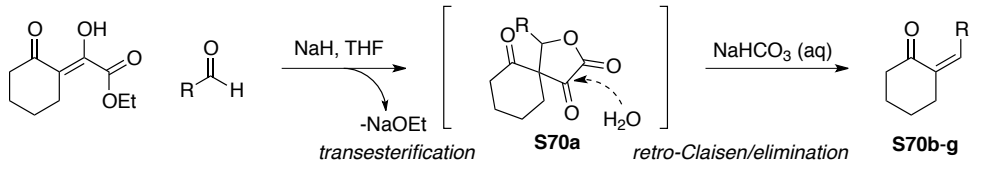
In a conceptually similar reaction, formal aldol condensation products can be made in a mild fashion from β-formyl ketones and analogs thereof (**S69a-d**) via aldol, 1,3-formyl transfer/elimination to the desired product **S69e** (Scheme 69).[120,129-131] Pioneering work on this reaction was done in the 1970's by McMurry[120] (**S69a**) and Ueno[129] (**S69bb)**. A significant improvement was published just last year by Colby and coworkers utilizing "trifluoroacetate release" as a strategy (**S69d**).[131] The deacylative (Ueno) and "trifluoroacetate release" strategy (Colby) go by the general mechanism shown in Scheme 69. However the deoxalylative strategy by McMurry is slightly unique (Scheme 70).

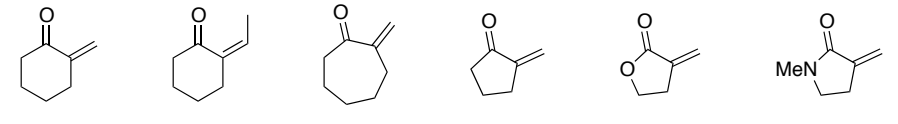


Regarding the seminal deoxalylative strategy described by McMurry,[120] the initial aldol condensation first leads to a 5-membered carbocycle **S70a** (Scheme 70) as described in the work

by Nield (Scheme 63).[119] Addition of aqueous base then allows for facile retro-Claisen/elimination transformation into the desired α,β-unsaturated carbonyl product **S70b-g**. This reaction worked best with formaldehyde as the aldol coupling partner, though other aldehydes could be utilized to form product in noticeably lower yield (e.g. **S70c**).

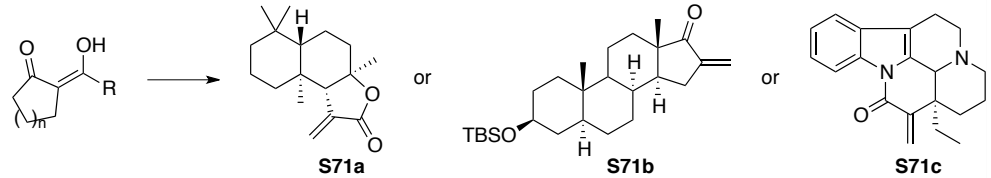
Scheme 70. Retro-Claisen/elimination of ethyloxalyic ketones (McMurry, 1977)





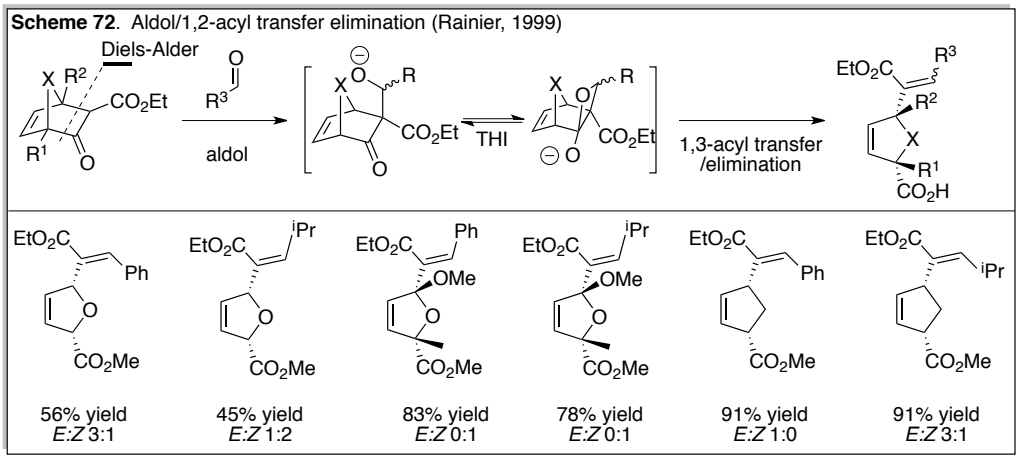
S70b, 87% **S70c**, 40% **S70d**, 72% **S70e**, "low" yield **S70f**, 83% **S70g**, 61%

Scheme 71. Comparision of deformylative vs. trifluoroacetete release exomethlene installation (Colby, 2011)

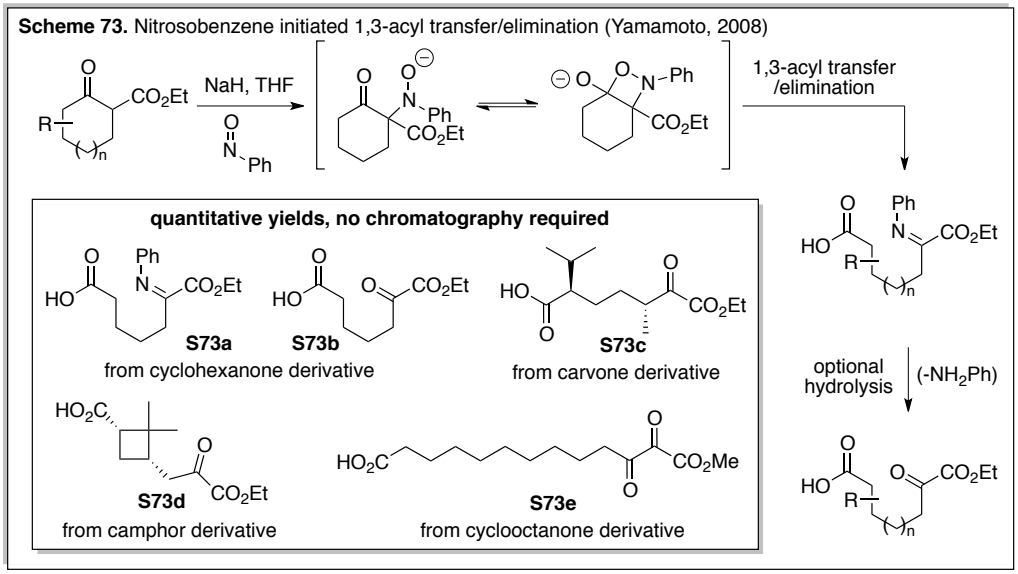


	S71a	S71b	S71c
deformylative (R = H):	28%	trace	0%
trifluoroacetete release (R = CF_3):	65%	59%	28%

Colby's contribution to this reaction was quite significant as it allows for a much more general and high yielding synthesis of the desired exomethylene ketones (Scheme 71).[131] This improvement is analogous with Danheiser's contribution to diazo ketone synthesis (Scheme 67).[128] Similar to the Danheiser publication, Colby performed a contrast study to show that 1,3-trifluoroacetyl transfer is more effective than analogous formyl transfer. For example, the trifluoroacetate release strategy was noticeably more effective than the deformylation strategy at installing exomethylene functional groups on ketone containing naturals **S71a-c**. For example, sclareolide **S71a**, a steroid derivative **S71b**, and on the eburnamonine **S71c** were all functionalized in reasonable yield. Considering that there is an adjacent quaternary center on the eburnamonine scaffold, the 26% yield of exomethyleneylated natural product is quite impressive.



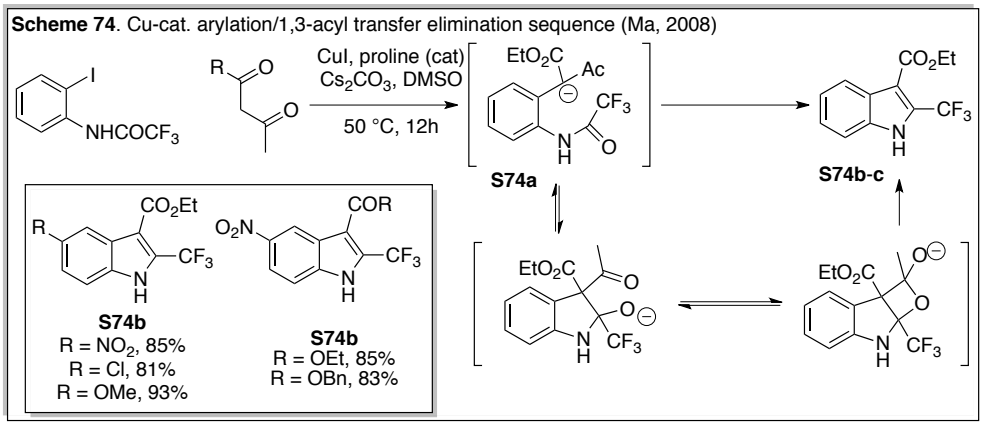
In 1999, Rainier utilized a similar reaction for the preparation of *cis*-disubstituted cyclopentanoid structures (Scheme 72).[132] Notably, he performed the aldol reaction with alkyl and aryl aldehydes, previous examples discussed mostly focused on formaldehyde as the aldol coupling partner. Moreover, he utilized a facile Diels-Alder cycloaddition to construct the β-dicarbonyl compounds that undergoes the 1,3-acyl transfer/elimination.



Yamamoto and coworkers performed a C−N bond formation on β-ketoesters followed by *in situ* 1,3-acyl transfer/elimination to construct highly functionalized α-imino (or keto upon hydrolysis) esters (Scheme 73).[133] This cleavage/elimination reaction occured with complete

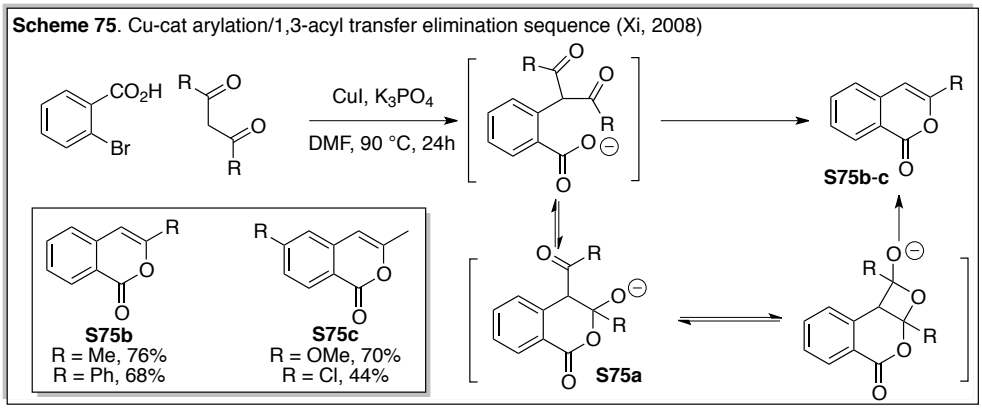
efficiency in almost all disclosed results. In addition to being able to cleave cyclic β-ketoesters (**S73a**,**e**), this cleavage strategy could be used to fragment ketone containing natural products such as carvone **S73c** and camphor **S73d**.

The final 2-examples in this section involve Cu-catalyzed arylation/retro-Claisen elimination to make aromatic compounds (Schemes 74-75).[134,135] Ma reported the coupling of N-trifluoroacetyl *ortho*-iodoaniline with acetoacetic esters producing to 2-trifluoromethylindoles.[134] In this process, the Ullman-type arylation occurs first. The α-aryl acetoacetate anion **S74a** then adds into the trifluoromethylacetyl group. Acetyl transfer/elimination then produces the desired indole product **S74b**. The reaction was generally acceptable of various electronic and substitution patterns on the aniline derivative (**S74b**). Furthermore, various alkyl acetoacetates were utilized (**S74c**).



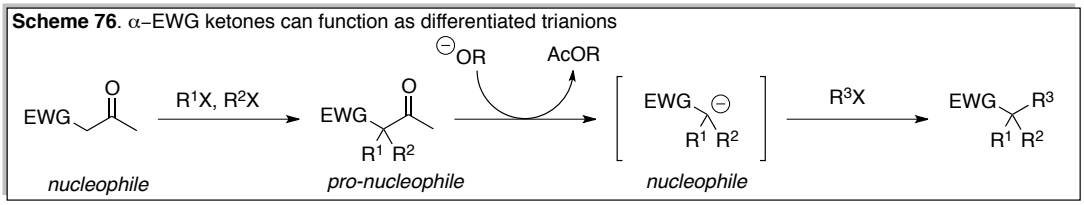
Based on the method first reported by Hurtley and fully developed by McKillop, Xi reported the preparation of isocoumarins from *ortho*-bromobenzoic acids and β-diketones via arylation/acyl transfer/elimination (Scheme 75).[135] The reaction mechanism is as follows: Following Cu-catalyzed arylation, the carboxylate attacks into the ketone giving intermediate **S75a**. Acyl transfer/elimination produces the isocoumarin **S75b**. Regarding the scope, various β-

diketones (**S75b**) were compatible nucleophiles and various substitution patterns on the bromobenzoate were generally acceptable (**S75c**).



2.4.2. Functionalization/retro-Claisen condensation/functionalization

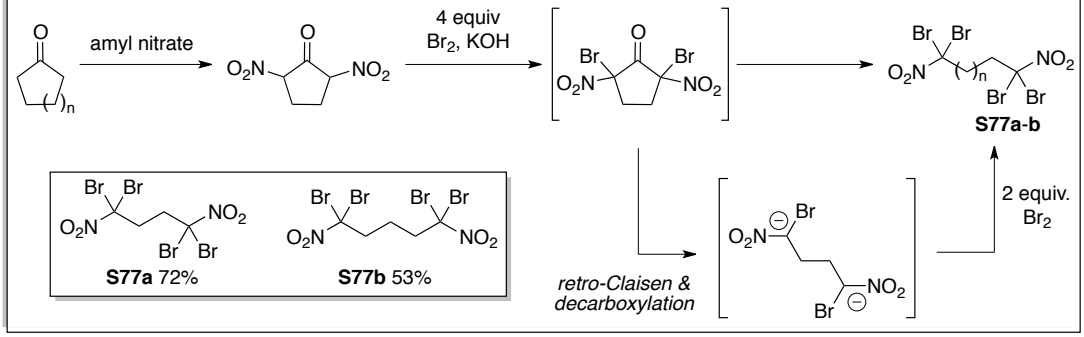
The final section of this review will focus on how a retro-Claisen C−C cleavage event can prepare an anion that can be captured with other nucleophiles in a single-pot, thus making a new C−C or C−X bond. Thus, an α-EWG ketone can function as a differentiated trinucleophile (Scheme 76). This is a relatively unexplored area of research. Furthermore, in the next chapter of this dissertation, will be presented our work in this field: deacylative allylation (**DaA**), where both nucleophile and allylic acetate electrophile are prepared *in situ* by retro-Claisen reaction and coupled together via Pd-catalysis.[88,136,137]



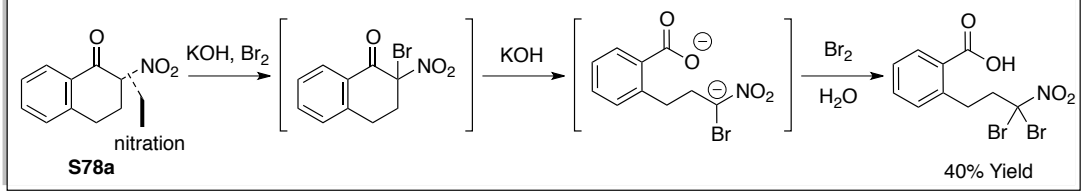
It is not surprising that the earliest examples of this type of reactivity were first discovered with α-nitroketones. Recall from section 2.2.5 that the retro-Claisen condensation of

α-nitroketones is an extremely mild C−C cleavage reaction. Furthermore, the nitronate anion is an excellent nucleophile. As reported by Klager[71] and Feuer,[72] α,α-dinitro ketones can absorb 4 equivalents of bromine leading to 1,1,4,4-dibromo-1,4-dinitrobutanes (n = 1) and derivatives thereof (Scheme 77). In this process an initial dibromination (2 equivalents) occurs to the fully substituted cyclopentanone. By retro-Claisen/decarboxylation 2-new anions are formed for further bromination (2 equivalents). This reaction worked well with various cyclic ketones including cyclopentanone and hexanone. In Feuer's article, the reaction was extended to mono-nitrated ketones, for example, of 2-nitro-α-tetralone **S78a** (Scheme 78).[72]

Scheme 77. Retro-Clasien bromination if α,α'-dinitroketones (Klager, 1955, & Feuer, 1956)

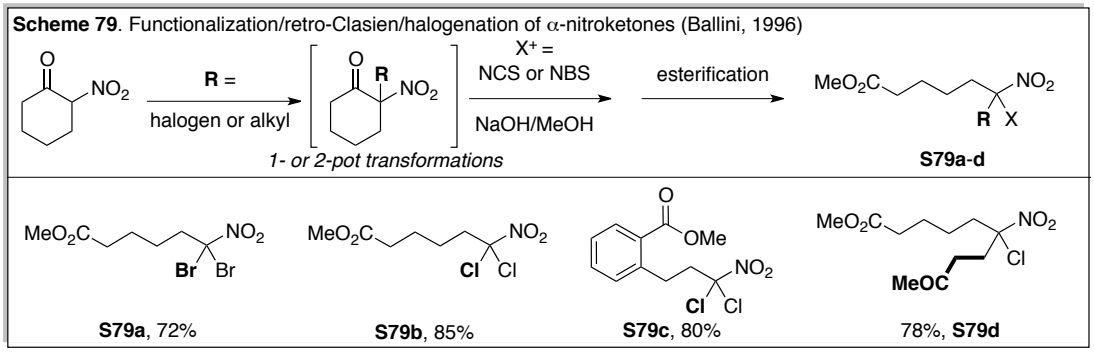


Scheme 78. Retro-Clasien bromination of α-nitroketones (Feuer, 1956)

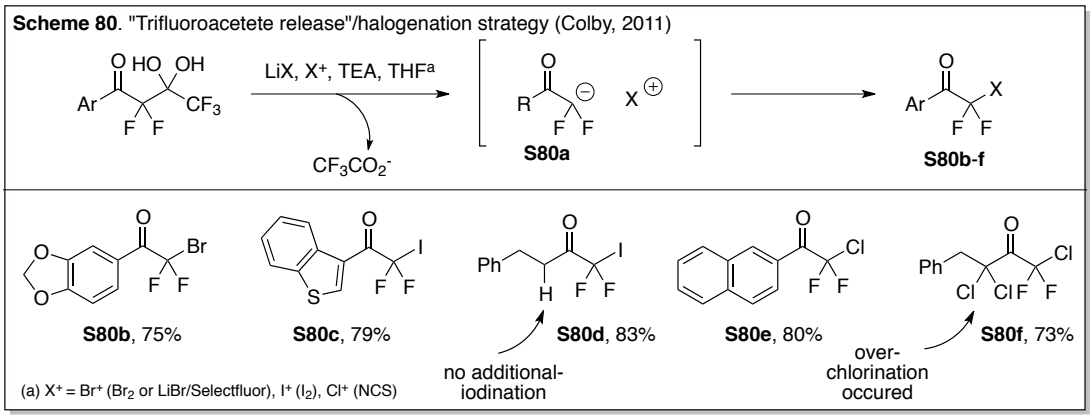


In addition to these seminal publications, Ballini developed a similar approach that not only allows retro-Claisen bromination (**S79a**), but a method for retro-Claisen chlorination **(S79b-c**) as well (Scheme 79).[138] Though most examples were performed with α-nitrocyclohexanone (**S79a-b**,**d**), 2-nitro-α-tetralone (**S79c**) could also utilized. Furthermore, Ballini also demonstrated that the reaction was not limited to the synthesis of dihaloalkanes: by alkylating (e.g. with methyl vinyl ketone) the α-nitroketone and then performing a retro-Claisen

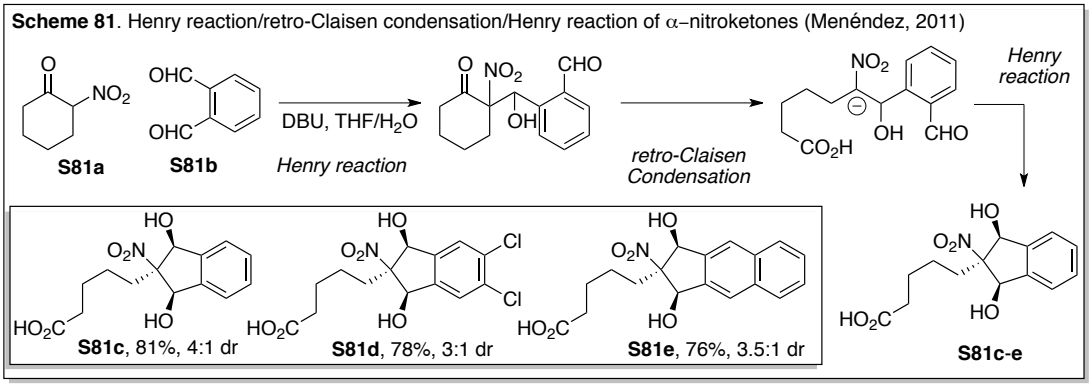
chlorination, chiral and multi-functional nitroalkanes (**S79d**) could be produced. Importantly, this represents the first example where the formal "dianion" is differentiated as the α-nitroketone is utilized in 2 distinct C−C and C−X bond formations.



Quite recently, a retro-Claisen halogenation protocol on *in situ* generated α,α-difluoro enolate anions was reported by Colby (Scheme 80). This process utilizes "trifluoroacetate release" (a specific type of retro-Claisen condensation) as a unique method to generate otherwise challenging to generate, α,α-difluoro enolate anions **S80a**. His approach allows for halogenation (bromination **S80b**, iodination **S80c-d** and chlorination **S80e-f**) of difluoro acetophenone derivatives. Iodination of α,α-difluoro acetone derivative **S80d** was successful as was chlorination (**S80f**), however, in the chlorination attempts, over-chlorination of both α- and α'-positions occurred without control.



In addition to retro-Claisen condensation/halogenation protocols, retro-Claisen condensation/C−C bond formation began appearing in late 2010[139] and early 2011.[88,91,136,140] The first examples utilized α-nitroketones as the retro-Claisen substrate of choice.[88,136,139,140] This is not surprising as α-nitroketone retro-Claisen condensation is extremely mild and nitronate anions are excellent nucleophiles.

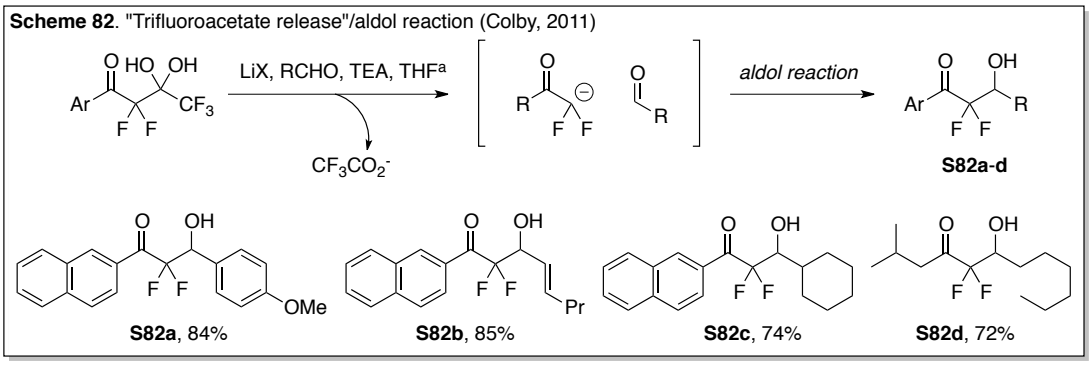


To the best of our knowledge, Menéndez and coworkers reported the first retro-Claisen C−C cleavage/C−C bond forming reaction (Scheme 81). They utilized cyclic nitroketones **S81a** as differentiated dianion equivalents to couple with dielectrophiles (phthalaldehyde derivatives **S81b**) via Henry reaction, retro-Claisen condensation and a second Henry reaction leading to the functionalized indane derivatives **S81c-e**. Within the parameters tested (cyclic nitroketones and phthalaldehyde derivatives), the reaction was generally good yielding over the 1-pot, 3-step sequence with reasonable diastereoselectivities (>3:1 dr).

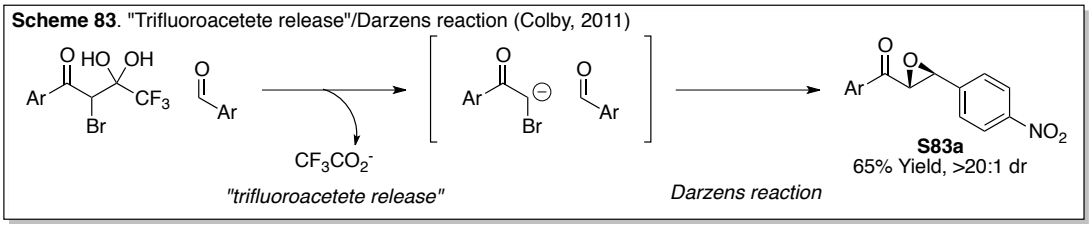
Cyclic and acyclic α-nitroketones (and other α-EWG-ketones) have also been used as differentiated dianion equivalents in Pd-catalyzed bisallyation leading to useful 1,6-heptadienes. This research was reported by us and will be discussed thoroughly in the next chapter of this dissertation.

Trifluoroacetate release is an effective method for the generation of α,α-difluoro enolate anions, as previously shown in Scheme 80. These anions can be generated *in situ* and coupled

with aldehydes leading to aldol products (Scheme 82). For example, the *in situ* generated α,α-difluoro acetophenone anions can be coupled with aromatic (**S82a**), α,β-unsaturated (**S82b**), and alaphatic aldehydes (**S82c**). α,α-Difluoro acetone based anions can also be generated and coupled with aldehydes (**S82d**). It is important to point out that in this case no α to α'-enolate transposition occurred. Recall from Scheme 80, that chlorination of α,α-difluoro acetone derivatives lead to chlorination at both α and α'-positions.



Though not fully developed, Colby demonstrated that trifluoroacetate release can be used to generate other enolates in addition to α,α-difluoro enolates (Scheme 82). α-Bromo enolates can be generated via trifluoroacetate release and undergo Darzens reactions leading to epoxide **S83a** as a single diastereomer, though this is the only example disclosed to date.



As shown throughout this section, retro-Claisen C−C cleavage is an effective technique to generate anions that can be utilized to perform further chemical reactions. Though less studied than the first sections of this review, retro-Claisen functionalization methodologies include eliminations (via acyl transfer/elimination) and C−X and C−C bond forming reactions.

2.5 Conclusions

As shown throughout this review, the retro-Claisen reaction can be used strategically in conjunction with various C−C or C−X bond forming reactions to rapidly construct chemical building blocks. The first section of this review focused on how β-dicarbonyl compounds (active methylene nuclephiles) can be utilized to perform mild α-substitution reactions. Then, one of the carbonyl groups can be removed by retro-Claisen condensation to reveal the monocarbonyl chemical building block. The ketone, in this case, is used as a readily available activating and cleaving group. The final sections of this review demonstrated how a retro-Claisen reaction can promote further chemical reaction besides simple protonation, as a new carbanion is formed. This is a powerful, yet currently under utilized strategy for the construction of useful chemical compounds. Currently, methods for retro-Claisen/elimination are in the literature where an intramolecular acetyl transfer facilitates an elimination reaction. Also presented were methods where the discrete carbanion generated upon retro-Claisen is involved in further C−X or C−C bond formation. The field of retro-Claisen/C−C bond formation is a new field of chemistry, with first publications appearing in late 2010 and early 2011.

We have also published work in the field of retro-Claisen/C−C bond formation: we have named our approach to coupling "deacylative (retro-Claisen) allylation." Our work will be presented in the next chapter of this dissertation.[88,136,141]

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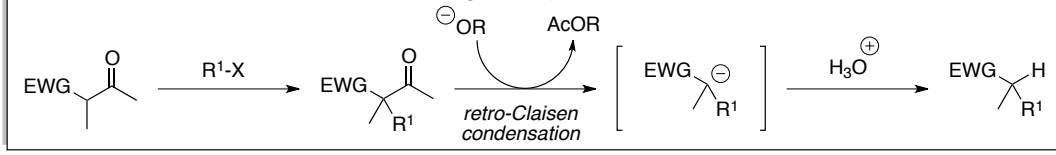
Chapter 3. Synthetic studies in retro-Claisen condensation and allylation methodologies[1-3]

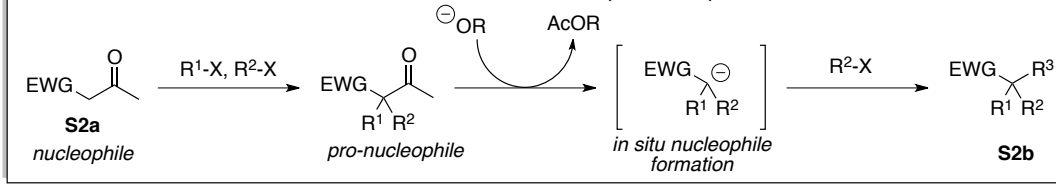
3.1 Introduction

Chapter 2 of this dissertation reviewed the utility of the retro-Claisen condensation to synthesize useful monocarbonyl chemical building blocks (Scheme 1). This approach's attractions include (a) diverse methodologies for α,α-disubstitution of active methylene compounds (e.g. simple alkylation, transition metal-catalyzed arylation, or C−X bond forming reactions), (b) commercially/readily available active methylene starting materials, and (c) mild C−C cleavage, as α,α-disubstituted active methylenes are unstable in the presence of nucleophiles (such as alkoxide) and undergo retro-Claisen condensation.

Scheme 1. α-Substitution, retro-Claisen methodologies, Chapter 2 review



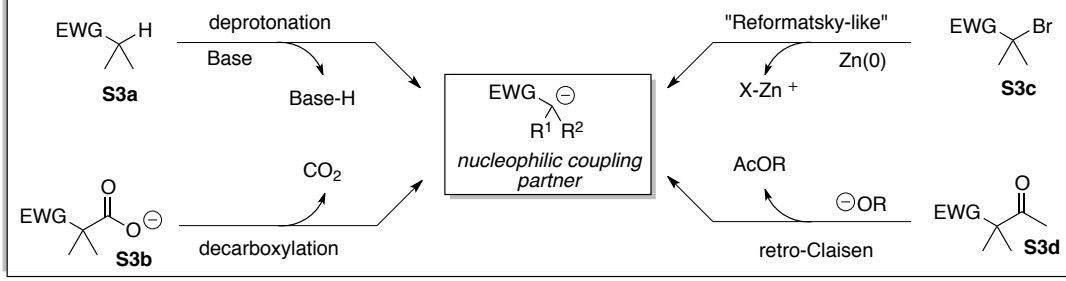
Scheme 2. α–EWG ketones can function as differentiated trinucleophiles, Chapter 2 review



In the final sections of chapter 2, we outlined how retro-Claisen can be utilized to promote further C−X or C−C bond forming reactions (Scheme 2). Essentially, this approach allows an α-EWG ketone **S2a** to be functionalized selectively up to 3-different times (twice as the active methylene nucleophile and again by retro-Claisen functionalization) leading to the quaternary compound **S2b**. Retro-Claisen C−C bond formation is a new field of research (first

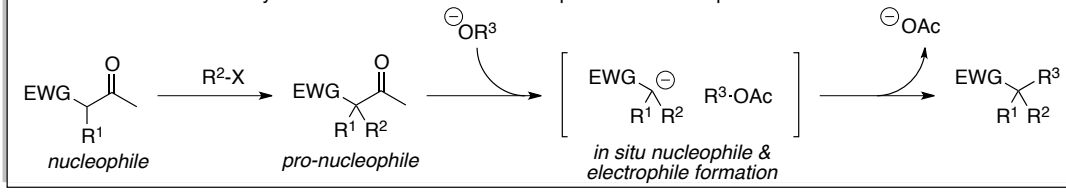
publications in late 2010 and early 2011) that holds much potential as it can generate α-EWG stabilized carbanions *in situ* for coupling. As shown in Scheme 3, other approaches to the generation of these types of nucleophilic coupling partners include (a) deprotonation (**S3a)** (b) decarboxylation (**S3b**) (c) and "Reformatsky-like" (oxidative) methods (**S3c**).

Scheme 3. Some ways to generate "enolate-type" nucleophiles



The 3rd chapter of this dissertation will focus on our contributions to the field of retro-Claisen C−C cleavage chemistry. Namely, the amalgamation of retro-Claisen condensation and palladium-catalyzed allylic alkylation methodologies, the latter has been a central theme of the Tunge research lab since its beginnings.[4-20] We have developed allylation/retro-Claisen methods that resemble the general reaction outlined in Scheme 1, where a ketone is simply used as an activating/cleaving group that can be replaced with a proton. However, the bulk of the work about to be presented in this chapter is unique and involves the *in situ* formation of both nucleophilic and electrophilic coupling partners initiated by a retro-Claisen condensation event (Scheme 4). These intermediates are then coupled back together, synthesizing a quaternary carbon.

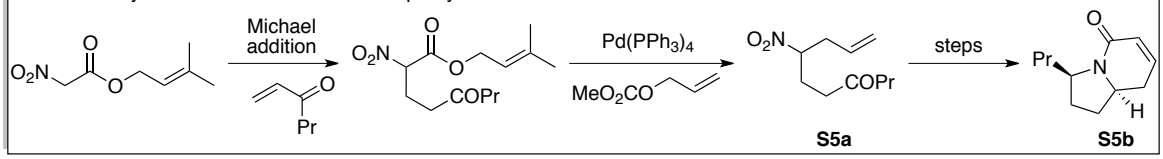
Scheme 4. retro-Claisen alkylation: *in situ* formation of nucleophiles and electrophiles



3.2 Tsuji-Trost allylation/retro-Claisen reactions[1]

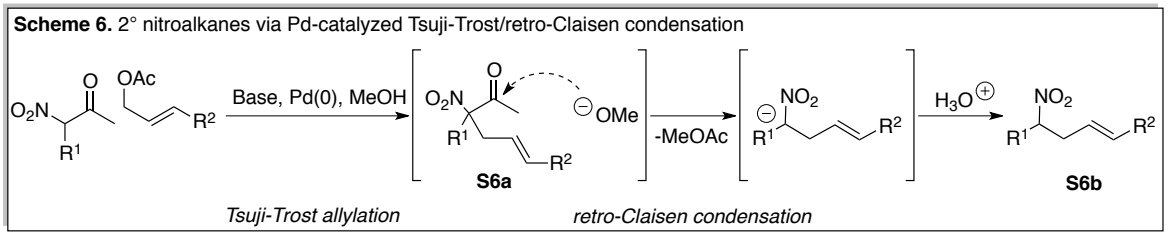
2° allylated nitroalkanes are useful synthetic building blocks.[21-28] As shown in chapter 1 and summarized in Scheme 5, we were able to efficiently convert nitroalkane **S5a** into the indolizidine core (**S5b**) rapidly.[29] **S5a** was prepared by a 2-step, 1-pot Tsuji-Trost decarboxylative protonation strategy from prenyl nitroacetate. Benefits to our approach include simple Michael addition from prenyl α-nitroacetate and the 2-step 1-pot allylation and *in situ* removal of the prenyl carboxylate via Pd catalyzed decarboxylative protonation. Throughout this sequence, reactants were utilized in equimolar fashion, which is uncommon in the preparation of 2° nitroalkanes due to challenges from over alkylations.[21-28] For example, other approaches to 2° allylated nitroalkanes by Tsuji-Trost reaction use excess (commonly 3-10 equiv.) of the 1° nitroalkane starting material.[21-28] This approach is acceptable when the 1° nitroalkane is inexpensive and commercially available, although it does produce extra waste. However, the use of excess nitroalkane is undesirable when the nitroalkane to be allylated is precious.

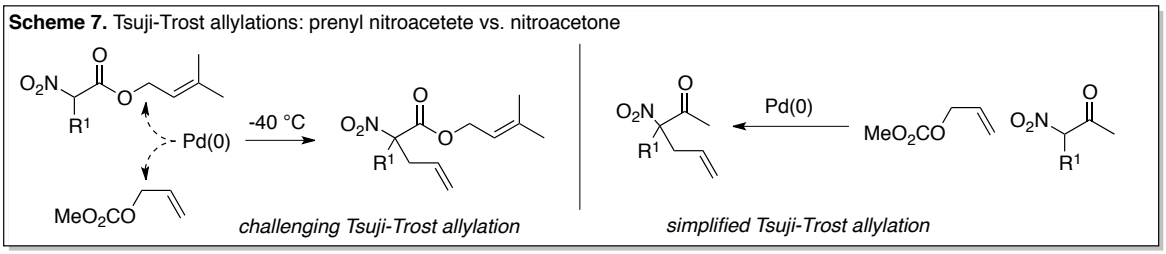
Scheme 5. Synthesis of useful amines from prenyl nitroacetete

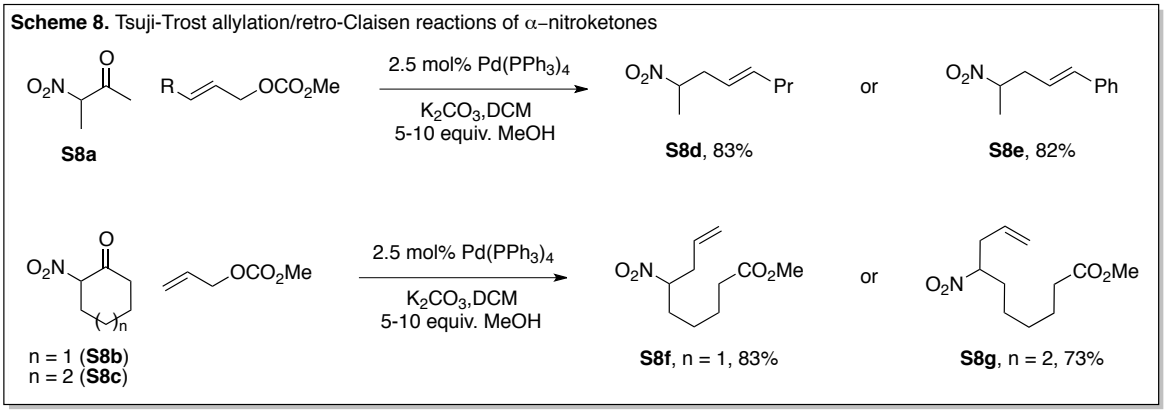


Though content with our approach to 2° allylated nitroalkanes, there were some challenges. First, the conditions for Tsuji-Trost/decarboxylative protonation were somewhat tedious, requiring cooling of the reaction mixture to -40 °C for the Tsuji-Trost allylation. If this was not done properly, often complex mixtures were isolated. Next, though waste was benign, the prenyl carboxylate group consisted of 8 atoms that did not get incorporated into the chemical building block. From an atom economy perspective, this is unattractive.[30]

As α-nitroketones are readily available[31-34] and undergo retro-Claisen condensation to the nitroalkane, we wondered if an allylation/retro-Claisen strategy could produce 2° allylated nitroalkanes with increased ease (Scheme 6). What we found most attractive about this approach was that the highly reactive (to Pd) prenyl carboxylate was now removed from the molecule, yet the increased reactivity toward alkylation was retained, as nitroketones are also active methylenes (Scheme 7). Thus, after Pd-catalyzed allylation to disubstituted α-nitroacetone **S6a** and retro-Claisen condensation, analogous 2° allylated nitroalkanes (**S6b**) should be able to be produced with added simplicity. Finally, little waste byproduct will be produced as substrates are used in equimolar fashion and the retro-Claisen condensation only produces acetate.





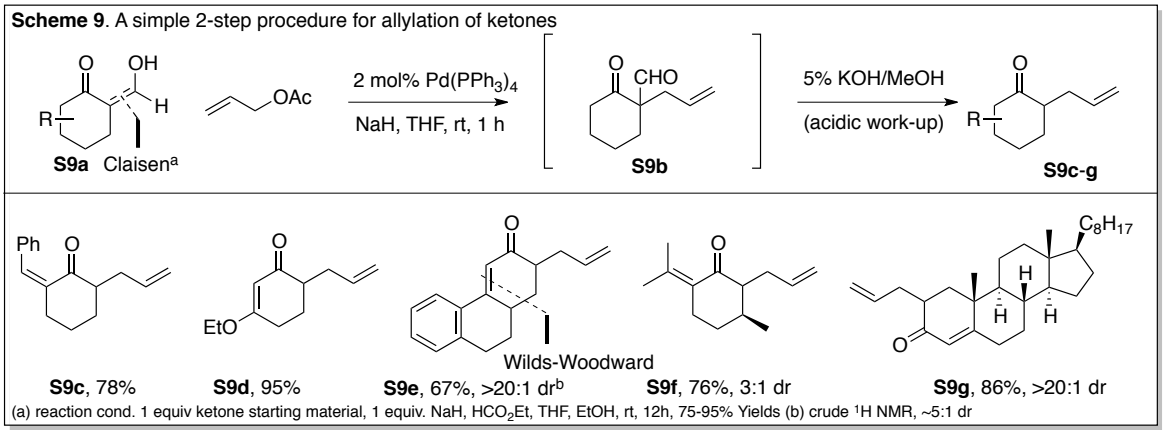


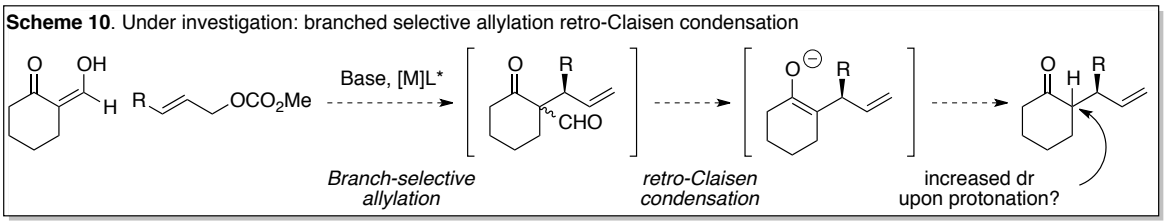
We were pleased to find that our hypothesis proved true (Scheme 8). By allowing acyclic or cyclic α-nitroketones **S8a-c** to react with an equivalent of an allylic carbonate in the presence of palladium and 5 equiv. of MeOH, various 2° allylated nitroalkanes could be produced (**S8d-g**). Regarding the allyl carbonate, simple (**S8f-g**) and terminally substituted **(S8d-e**) allylic systems were compatible. By utilizing the cyclic ketones, 2° allylated nitroalkanes with pendant methyl esters could be obtained.

In addition to the Pd-catalyzed allylation of nitroalkanes, we thought it would be useful to extend this methodology to the allylation of ketones producing tertiary centers. As ketones have a relatively high pK_a (DMSO pK_a ~25), palladium-catalyzed allylation commonly requires the use of strong bases (e.g. LDA or LiHMDS) and tedious reaction conditions (additives, cryogenic temperatures, etc.).[35-46] Other approaches to the Pd-catalyzed allylation of ketones involve using trapped enolates (e.g. silyl enol ethers)[47-50] or the decarboxylative allylation method.[47,51-56] However, in all of the above mentioned methods, over-allylation can often be an issue, so tertiary centers are considered *more challenging* to prepare than a quaternary center. With that said, branch-selective (or 1,3-disubstituted) monoallylation of ketones can occur.[36,39,48,50,51] In general, simple allyl (no branching) inclusion is best suited for the synthesis of quaternary centers, though some methods do allow for the preparation of allylated tertiary centers.[41,44-46] Another approach to allylation of enolates producing 2° allylated ketones is the combined transition metal/amine catalysis (enamine formation) method.[57,58] Unfortunately, this approach requires excess of the ketone in order to achieve monoallylation.

Inspired by the Wilds-Woodward modification of the Robinson annulation (see chapter 2), we have demonstrated that simple Claisen condensation with ethyl formate allows a Tsuji-Trost allylation/retro-Claisen condensation reaction sequence to occur. Using this approach,

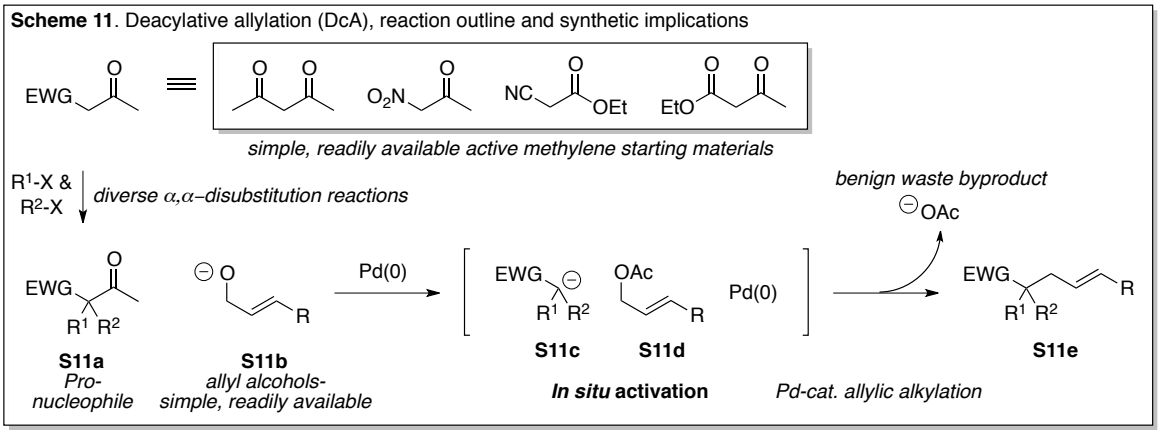
selective monoallylation of various ketone based chemical entities can be achieved under mild and simple reaction conditions using equimolar substrate ratios. The conditions are as follows: in the presence of Pd(0), the salt of the β-formyl ketone **S9a** is prepared in THF using an equivalent of NaH. Then, an equivalent of allyl acetate is added at room temperature and allowed to stir until complete consumption of starting material is observed by TLC (0.5-1h). The intermediate **S9b** undergoes retro-Claisen protonation to the desired products **S9c-g** upon the addition of dilute KOH in methanol. Using this straightforward procedure, simple ketones, such as the aldol condensation adduct (**S9c**) or the 3-ethoxy cyclohexene (**S9d**) could be monoallylated without complications. Derived from a Wilds-Woodward reaction on α-tetralone, allylated product **S9e** could be prepared by this method in good yield and diastereoselectivity. Although **S9e** was isolated as a single diastereomer, the crude NMR did show ~4:1 dr. This reaction sequence was also compatible on natural products. For example, plugone **(S9f)** and cholestenone (**S9g**) could be allylated in good yield with modest to excellent diastereoselectivity. This project is still being investigated and thus, some information is not currently known about these compounds, such as the relative stereochemistry of the diastereomers. However, this is actively being researched and will be reported in due course along with similar studies on branched selective allylation/retro-Claisen, where the retro-Claisen protonation can resolve poorly diastereoselective branched allylation (Scheme 10).





3.3 Deacylative allylation (DaA): Pd catalyzed allylic alkylation via retro-Claisen[1-3]

The retro-Claisen condensation step in the above mentioned methodologies is promoted by methanol, which generates methyl acetate (or formate) as a byproduct. If the retro-Claisen reaction on the pronucleophile **S11a** were to be promoted by an allylic alcohol **S11b**, not only would a nucleophilic coupling partner be prepared (the carbanion **S11c**), but, an allylic acetate **S11d** would also be generated *in situ*, which can be coupled to the carbanion in the presence of Pd(0), making a new C−C bond (Scheme 11). We have named this novel approach to allylic alkylation "deacylative allylation (**DaA**)."



There are many potential benefits that the DaA approach to Pd-catalyzed allylic alkylation can offer (Scheme 11). First, the DaA substrate synthesis begins from inexpensive and commercially/readily available β-dicarbonyl compounds (and similar compounds, e.g. cyanoacetic esters or α-nitroketone). Second, diverse substitution reactions that have been developed for such active methylene compounds (simple alkylations, Pd[59-64]/Cu[65-72] arylations, Tsuji-Trost allylation,[73-75] etc.) can be used for α,α-disubstitution. Third, coupling occurs directly from allylic alcohols: there are many commercially/readily available allylic alcohols and their direct application in synthesis is highly desired due to their availability and reduced toxicity (compared to allyl halides). Other approaches to the allylic alkylation using allyl alcohols usually require Lewis acid additives or acidic conditions.[76] Furthermore, due to the intermolecularity of the proposed DaA transformation, many different allylic systems can be introduced onto a scaffold at a late stage, which is ideal for "library" diversification and analog synthesis. Finally, the only byproduct of this transformation will be acetate salt, an environmentally benign material.

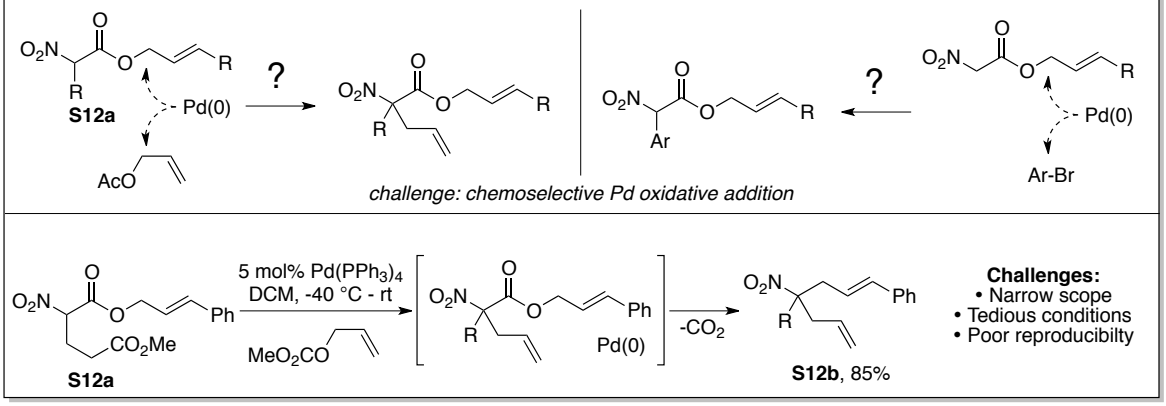
The DaA reaction hypothesis has many similarities to decarboxylative allylation (**DcA**), another contemporary approach to catalytic allyaltion.[56] DcA is an extremely useful reaction that has garnered much attention from the synthetic community,[47,51-56,77-83] including contributions

from our own lab.[4-20] The reaction has much breadth and asymmetric variants have been developed too.[56] Importantly, the reaction has seen much utility in total synthesis.[56,84-89] To compare these two methods, both DaA and DcA access similar scaffolds: quaternary allylated nucleophiles. Also, coupling partners are generated *in situ*, in the case of DcA, by decarboxylation (DaA by retro-Claisen condensation). Furthermore, the reactions are similarly "green" as the only byproduct in DcA is carbon dioxide (DaA generates acetate). Where DaA can improve on the DcA method is in the intermolecularity of the transformation and the direct coupling of allyl alcohols and readily available acetyl pronucleophiles (Scheme 11). In the realm of totally synthesis, the DcA approach often requires introduction of the allyl carboxylate moiety at a late-stage by transesterification[85,86] or allyl enol carbonate formation,[55,84,87,89] both of which add an extra synthetic manipulation into the total step count.

In the first chapter of this dissertation, I outlined how it *might* be challenging to perform Pd-catalyzed arylations[90] or Tsuij-Trost allylations[91] on allyl nitroacetate **S12a**, a DcA substrate, due to competing sites for Pd oxidative addition (Scheme 12). We even attempted, with little success, to perform such a Tsuji-Trost reaction. Interestingly, with substrate **S12a**, an allylation using allyl methyl carbonate occurred followed by DcA reaction to the 1,6-heptadiene **S12b**.[92] We were intrigued by this reaction sequence as it efficiently prepared a 1,6-heptadienes in a single pot. 1,6-heptadienes are extremely useful and well-studied substrates for cycloisomerization reactions, although most studies involve simpler substrates derived from active methylenes, amines or ethers.[93-97] Unfortunately, in our hands, substrate **S12a** was the only substrate we could perform the Tsuij-Trost/DcA sequence on. Furthermore, a search of the literature yielded a single example of 3-component bisallylation via Tsuji-Trost/DcA.[98] This reaction sequence is challenging because it requires a delicate balance of reactivity: the

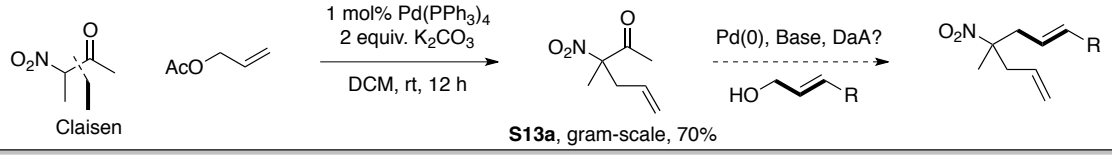
palladium catalyst must first perform oxidative addition of the allyl carbonate over the allyl nitroacetate (Scheme 12). Though allylic carbonates are usually more reactive than allyl acetate,[99] we could not extend this methodology to other substrates as complex mixtures of bisallylated nitroalkanes were isolated.

Scheme 12. Palladium catalysis on allyl nitroacetates (unpublished results)



With the challenges of one-pot Tsuji-Trost/DcA bisallylation outlined, we began contemplating surrogate procedures and substrates where the highly reactive allyl carboxylate is removed from the active methylene nitroacetate, yet an unsymmetric bisallylation can still occur leading to useful and unique 1,6-heptadienes. Our hypothesis, outlined in Scheme 13, involves Tsuji-Trost and the newly devised deacylative (retro-Claisen) allylation (Scheme 11).

Scheme 13. Simplified sequential Pd-catalysis: Tsuji-Trost/ deacylative allylation (DaA)

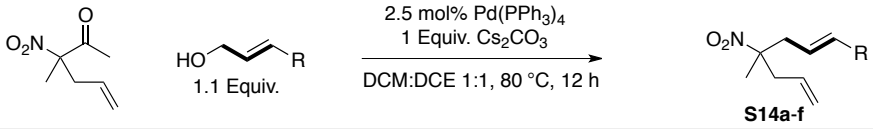


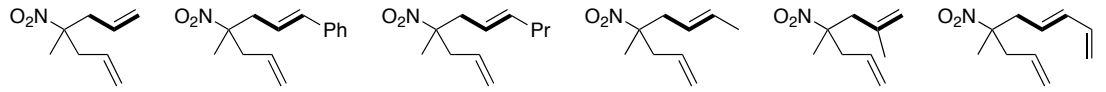
3.3.1 The development of deacylative allylation (DaA) reactions: DaA of α-nitroketones[1]

Similar to the Tsuji-Trost allylation/retro-Claisen condensation of α-nitroketones already presented in Scheme 8, we were pleased to find that, under methanol-free conditions, allylated α-

nitroketone **S13a** could easily be isolated. Thus, we have identified a simple substrate for Tsuji-Trost allylation that bears a cleavable ketone. Though the crude NMR was quite pure, we did notice a slightly reduced yield of 70% upon gram scale synthesis, presumably due the volatility of this low molecular weight molecule.

Scheme 14. Pd-catalyzed DaA of α-nitroketones





S14a, 87%, 99%[a] **S14b**, 89%[b] **S14c**, 79% **S14d**, 79%[c] **S14e**, 92% **S14f**, 78%

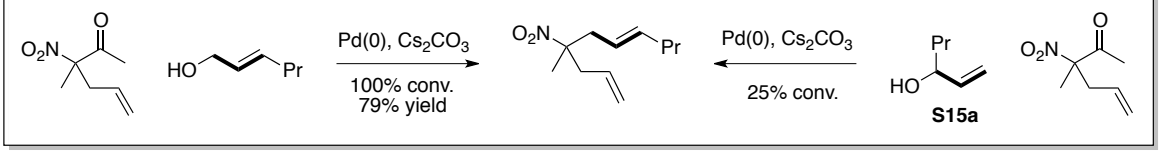
(a) 5 equiv. K_2CO_3 in lieu of Cs_2CO_3, 5 equiv. allyl alcohol (b) 10 mol% $Pd(PPh_3)_4$, (c) *E/Z* 5.6:1, *linear/branched* 3.8:1.

Having shown that the initial Tsuji-Trost is simple, we next turned to the development of the DaA reaction, which would furnish the desired 1,6-heptadiene (Scheme 14). Using 5 equiv. of both K_2CO_3 and allyl alcohol in the presence of a catalytic amount of $Pd(PPh_3)_4$ our deacylative allylation hypothesis was realized, as **S14a** was isolated in 99% yield (Scheme 14, footnote a). Unfortunately, the equivalents of allyl alcohol could not be reduced and other allylic alcohols could not be utilized with this method. Excitingly, using Cs_2CO_3 and a catalytic amount of $Pd(PPh_3)_4$, we did indeed isolated high yields of the desired deacylative allylation product with a variety of allylic alcohols in equimolar fashion (1 equiv. nitroketone, 1.1 equiv allyl alcohol, 1 equiv. Cs_2CO_3). Various commercially available allylic alcohols were viable coupling partners. For example simple allyl (**S14a**), cinnamyl (**S14b**), hexenyl (**S14c**), crotyl (**S14d**) and β-methylallyl (**S14e**) alcohol could all be coupled in good to excellent yield. Except in the case of crotyl alcohol, the allylation was completely selective for the linear product (> 20:1 dr), which is expected with a palladium catalyst. Regarding the cinnamylated product **S14b**, a 10 mol% catalyst loading was required to avoid problematic Hass-Bender oxidation.[100-102] In

addition to the commercially available allylic alcohols, we prepared a dienyl allyl alcohol and utilized it in the DaA reaction (**S14f**). **S14f** could, hypothetically, be utilized in metal-catalyzed [4+2] reactions leading to structurally interesting fused ring systems.[103-113]

Although the DaA reaction of α,α-disubstituted nitroketones is quite facile with 1° allyl alcohols, we found it challenging to promote the reaction with a 2° allyl alcohol (Scheme 15). Under the same reaction conditions utilized to couple 1° allylic alcohols cleanly, a 2° allyl alcohol **S15a** only underwent the reaction to ~25% conversion. Thus, there appears to be a steric limitation in the retro-Claisen step of this synthetic sequence.

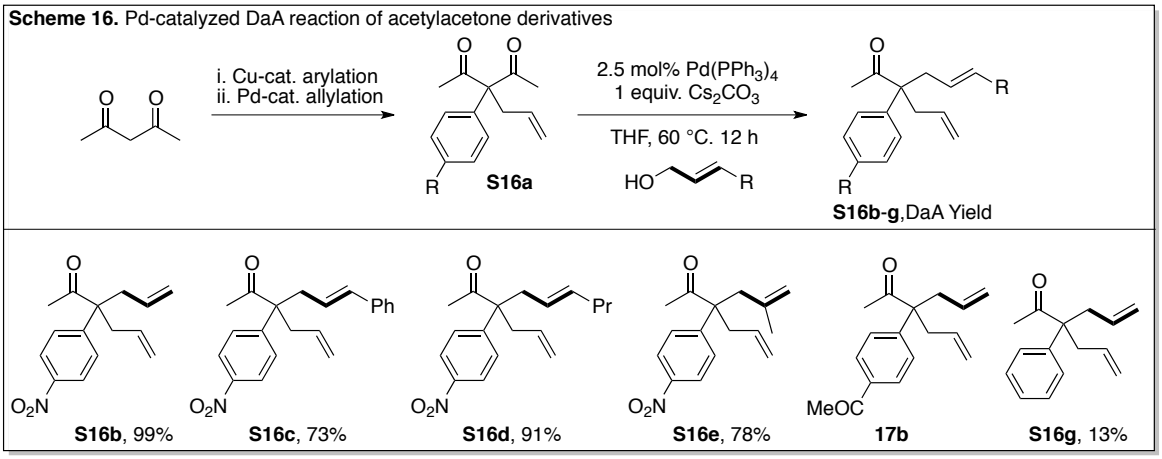
Scheme 15. 2° alcohols undergo slow retro-Claisen condensation



This 2-step Tsuji-Trost/DaA surrogate procedure has much more breadth compared to our original approach to nitro-containing 1,6-heptadienes, namely, the Tsuji-Trost/DcA attempt. The success of this approach stems from the use of nitroketones as opposed to reactive allyl nitroacetates, allowing simplified α,α-disubstitution by Pd catalyzed Tsuji-Trost allylation. In a second Pd-catalyzed event, the novel DaA reaction adds a second allyl equivalent to furnish the unsymmetric 1,6-heptadienes. Intrigued by this new approach to Pd-catalyzed allylic alkylation, we next investigated the scope of this reaction with various active methylene compounds. The next sections of this chapter will focus on other types of ketone pronucleophiles (α,α-disubstituted active methylene substrates) that can participate in the DaA reaction.

As both Tsuji-Trost and DaA allylic alkylation events utilize Pd, the final section of Chapter 3 will focus on 1-pot 3-component bisallylation leading to 1,6-heptadienes, thus fully achieving an improved 1-pot surrogate procedure for our initial hypothesis (Tsuji-Trost/DcA).

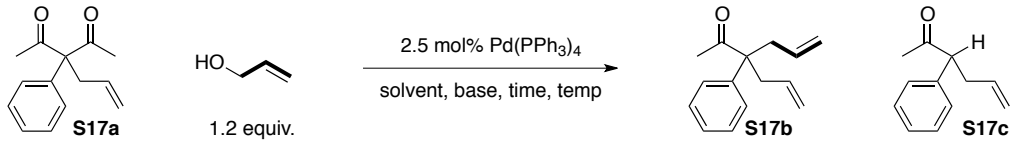
3.3.2 DaA of β-diketones: generation and allylation of enolate anions including an asymmetric variant[2,3]



The success of the DaA reaction of α,α-disubstituted nitroketones is, in large, due to the facile retro-Claisen reaction of these starting materials: retro-Claisen reaction is facile due to the high stability of the nitronate anion that is generated *in situ* (DMSO pK_a nitroalkane ~ 17). We reasoned that other highly stabilized ketone pronucleophiles could also be viable coupling partners (Scheme 16). We began improving our scope by studying the DaA reaction of α-allyl-α-aryl acetylacetone derivatives **S16a**. Importantly, these substrates are readily available by an attractive synthetic sequence: Cu-catalyzed arylation[65,66] and Pd-catalyzed Tsuji-Trost allylation.[73,74] We were pleased to see that the *para*-nitrophenyl derivative (**S16b-e**) could be coupled with similar scope to the nitroacetate derivatives disclosed above. The less electron withdrawing *para*-ketophenyl derivative could be coupled with allyl alcohol in good yield (**S16f**). Unfortunately, other alcohols with this substrate lead to complex mixtures. Furthermore, the limit of these conditions was met upon removing all electron withdrawing functionality from the phenyl ring (**S16g**). The major product in this case resulted from protonation. Thus, under

Cs_2CO_3/allyl alcohol promoted retro-Claisen conditions, Pd-catalyzed allylation requires a stabilized anion with $pK_a < 20$ (DMSO pK_a).

Scheme 17. Development of DaA for α-phenyl acetylacetone substrate **S17a**



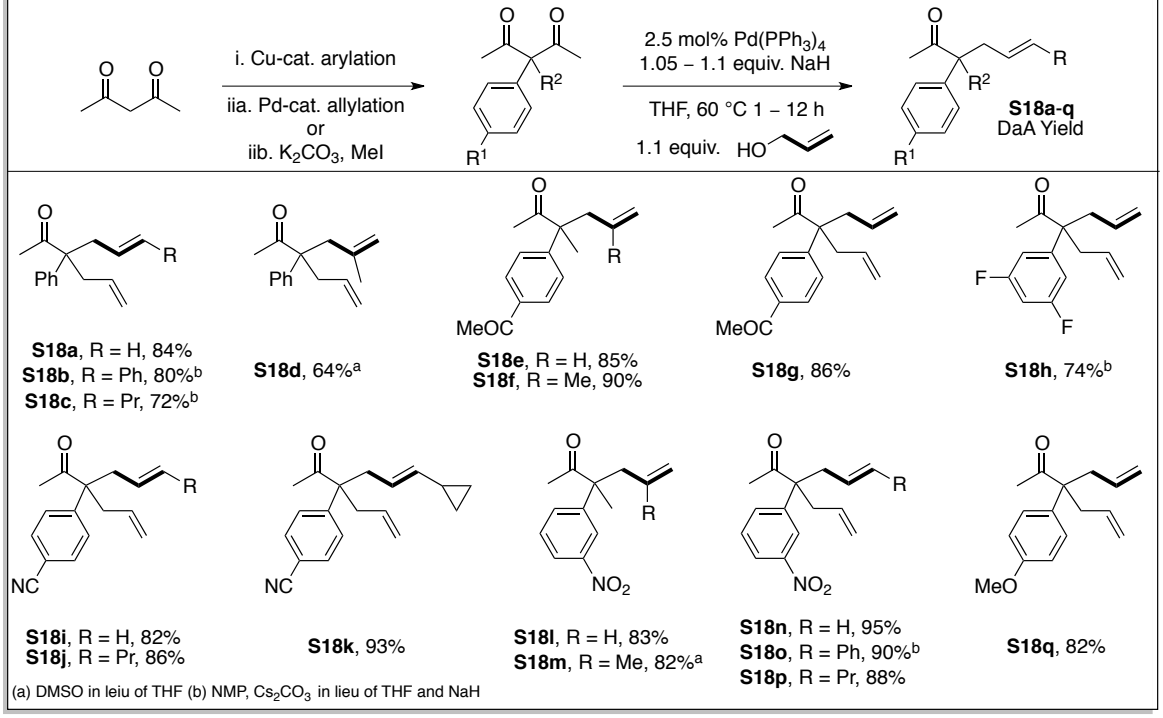
S17a 1.2 equiv. **S17b** **S17c**

entry	solvent	base	time (h)	temp. (°C)	% conv. (**S17b**:**S17c**)
1	Tol	Cs_2CO_3	15	80	25% (0:25)
2	DCE	Cs_2CO_3	15	80	0%
3	THF	Cs_2CO_3	15	80	100% (20:80)
4	CH_3CN	Cs_2CO_3	15	80	100% (70:30)
5	DMF	Cs_2CO_3	15	80	100% (75:25)
6	DMSO	Cs_2CO_3	15	80	100% (67:33)
7	NMP	Cs_2CO_3	15	80	100% (87:13)
8	NMP	^{t}BuOK	3	80	100% (82:18)
9	DMSO	NaH	3	60	100% (85:15)
10	**THF**	**NaH**	**3**	**60**	**100% (89 : 11)**

As an unsatisfactory yield of the allylated phenyl acetone **S16g** was isolated under the Cs_2CO_3/allyl alcohol DaA conditions (Scheme 16), we decided to optimize the DaA reaction for this product (Scheme 17). Starting from phenylacetylacetone derivative **S17a**, we screened different solvents and bases to increase the yield of **S17b** (**S17b** = **S16g**). Using Cs_2CO_3 as the base, various nonpolar solvents poorly promoted the desired coupling reaction (Scheme 17, entries 1-3). However, **2e** were delighted to see that the combination of Cs_2CO_3 and a polar aprotic solvent favored the desired product (entries 4-7). The best results were obtained when strong bases (such at ^{t}BuOK or NaH) were utilized in various solvents. As a complete deprotonation of allyl alcohol occurs when NaH is utilized, there are hypothetically *no protons* in solution, thus after retro-Claisen condensation, there is no chance of enolate protonation to the

undesired byproduct. Furthermore, under these conditions, retro-Claisen condensation occurred rapid, with alkoxide induced C−C cleavage complete in <1 min, as witnessed by TLC.

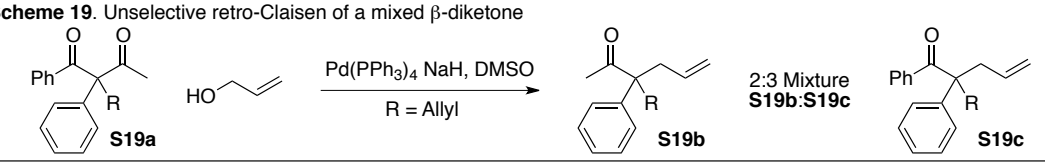
Scheme 18. Scope of the DaA reaction of α-aryl acetylacetone derivatives



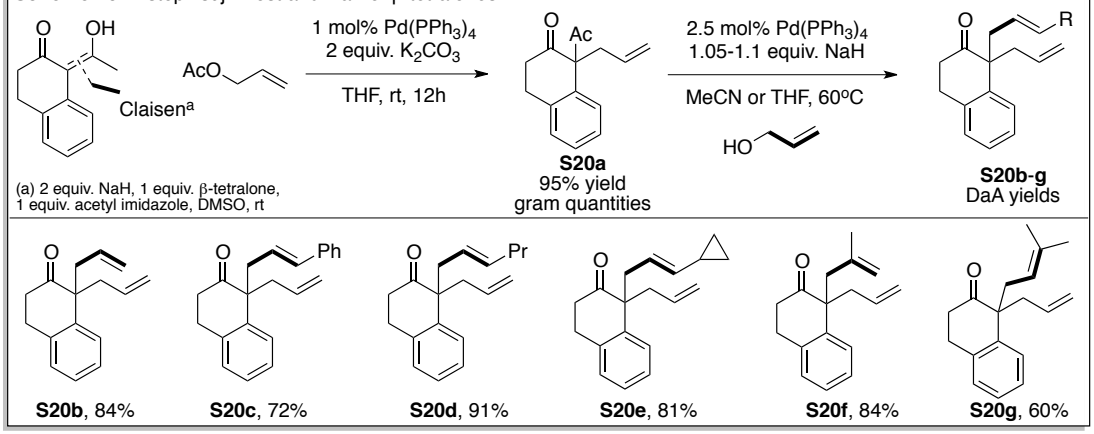
With our improved procedure in hand, we next tested the scope of the DaA reaction for the α-aryl acetylacetone derivatives (Scheme 18, **S18a-q**). The simple phenyl substituted substrate performed well with various commercially available allylic alcohols (**S18a-d**). Not surprisingly, electron withdrawing group containing substrates were excellent substrates (**S18e-p**). Furthermore, *para*- and *meta*-substitution patterns are well tolerated throughout this scope study. Though we mostly utilized commercially available allylic alcohols (e.g. allyl, cinnamyl, hexenyl, β-methylallyl), we were pleased to see that the cyclopropyl allyl alcohol was a viable coupling partner (**S18k**). This product is a unique metal catalyzed [5+2] precursor substrate.[114-121] Though we were particularly interested in the synthesis of 1,6-dienes, as Tsuji-Trost/DaA is a unique avenue for their preparation, we could also quaternize the α-aryl acetylacetone derivative by simple alkylation and perform the DaA reaction (**S18e**,**f**,**l**,**m**). Finally, we were particularly

gratified that an electron rich α-aryl acetylacetone derivative could participate in DaA (**S18q**). The enolate generated by retro-Claisen in this case has an even higher pK_a than what the reaction was developed for.

Scheme 19. Unselective retro-Claisen of a mixed β-diketone



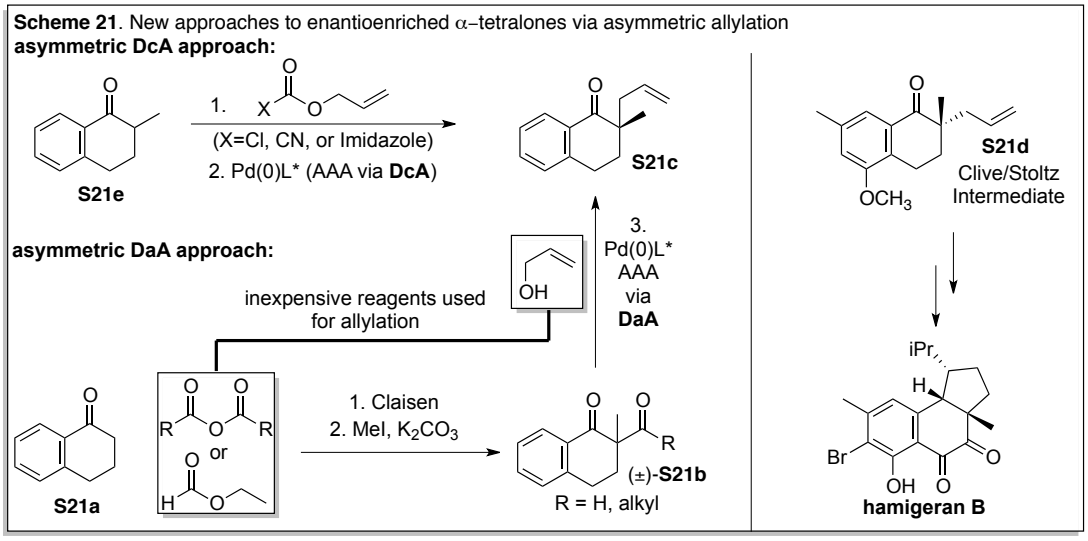
Scheme 20. 2-step Tsuji-Trost and DaA of β-tetralones



Interestingly, the benzoylacetone derivative **S19a** did not undergo selective retro-Claisen condensation. Rather a mixture of products was isolated corresponding to both benzoyl cleavage (**S19b**) and acetyl cleavage (**S19c**). However, a selective DaA reaction was observed for α-acetyl-α-allyl-β-tetralone **S20a**. Various 1,6-heptadienes could be prepared in excellent yield from β-tetralone by Claisen condensation,[31] Tsuji-Trost allylation, and DaA (Scheme 20). In addition to the previously studied allyl alcohols (**S20b-f**) we were even able to incorporate a prenyl motif by DaA reaction (**S20g**). In general, Pd-catalyzed prenylation can be challenging due to β-elimination forming isoprene.[56]

As stated previously, we were particularly gratified by the successful DaA reaction on the *para*-methoxyphenyl acetylacetone substrate due to the increased pK_a of the enolate generated upon retro-Claisen condensation (Scheme 18, **S18q**). Furthermore, we were intrigued by the

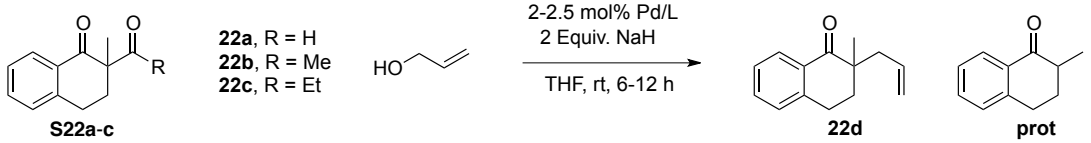
chemoselective retro-Claisen condensation observed for the β-tetralone series of substrates (Scheme 20). With these results, we felt confidant that a DaA reaction of α-tetralone would be possible (Scheme 21, **S21a è S21c)**. However, we did envision this to be more challenging as the pK_a of α-tetralone is relatively high (DMSO pK_a = 25) compared to all the other substrates examined thus far (e.g. DMSO pK_a for nitronates = 17, α-aryl acetone = 20). Importantly, the allylation of α-tetralone is a useful reaction and asymmetric variants exist in the literature.[47,52,54] For example, Clive[122,123] and Stoltz[89] have shown that allylated tetralone **S21d** can be converted rapidly into hamigeran, a biologically active natural product (Scheme 21). Stoltz's approach allows for the key quaternary stereocenter to be set by an asymmetric DcA reaction using a Pd-PHOX complex.



Previous approaches to the asymmetric allylation of tetralones have utilized allyl chloroformates (or other allyl phosgene derivatives) as the allylic source (Scheme 21, top). Compared to the reagents for allylation via the proposed retro-Claisen method (Ac_2O and allyl alcohol, Scheme 21, bottom), allyl chloroformates (or allyl phosgene derivatives) are more toxic and expensive. In our approach, following the reported procedures for Claisen condensation of

tetralones,[124,125] we envisioned being able to utilize the β-diketone to perform diverse and mild alkylation reactions followed by a stereoconvergent asymmetric retro-Claisen allylation.

Scheme 22. Development of a Pd-catalyzed retro-Claisen allylation reaction for tetralones



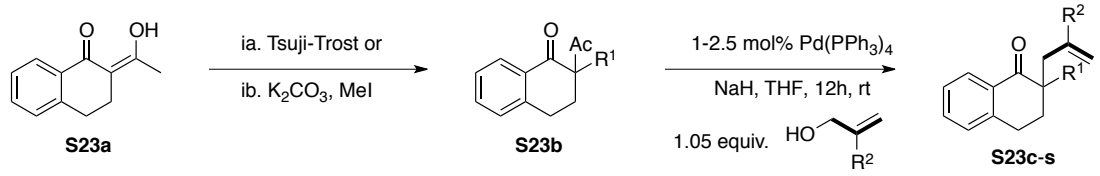
Entry	Substrate	Catalyst	22d:prot (yield 22d)
1	**22a**	2.5 mol% $Pd(PPh_3)_4$	75:25 (75% yield)
2	**22a**	2 mol% Pd/rac-BINAP	89:11 (83% yield)
3	**22b**	2.5 mol% $Pd(PPh_3)_4$	95:5 (90% yield)
4	**22c**	2.5 mol% $Pd(PPh_3)_4$	95:5 (95% yield)

(a) Scale: 0.25-0.5 mmol. Conditions: **1a-c** : allyl alcohol 1.05 : 1, 0.075 M, THF, 0 °C - rt

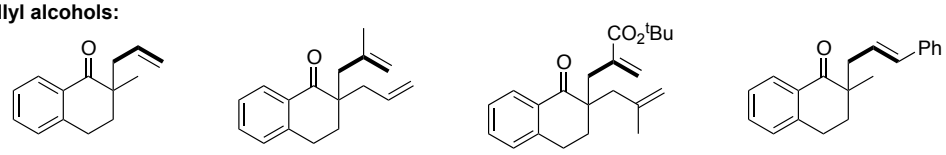
Before attempting such an asymmetric DaA transformation, we thought it would be useful to confirm that the racemic DaA reaction of α-tetralone derivatives was feasible, as this reaction has not been investigated. To begin our retro-Claisen allylation studies, we first performed a high yielding two-step Claisen condensation/methylation of α-tetralone with formyl acetate (**22a**) acetic anhydride (**22b**) and propionic anhydride (**22c**). With substrates **22a-c** in hand, the nature of the cleaving group on the Pd-catalyzed allylation reaction could be examined (Scheme 22, **S22a-c è S22d**). We found that 2 equivalents of NaH gave the best results. Potentially, an excess of NaH is required to react with any unaccounted for proton sources from the THF solvent or elsewhere that could increase the yield of the undesired protonation byproduct (**prot**). Regarding the formyl substituted reactant **S22a**, using the monodentate ligated $Pd(PPh_3)_4$ catalyst, a 75:25 mixture of the desired product **S22d** and the protonation byproduct (**prot**) was isolated. Utilizing the bidentate ligated Pd-complex (Pd-BINAP, entry 2), this ratio could be changed to favor the allylated product **S22d** (89:11 **S22d**:**prot**). The increased byproduct formation in entry 1 compared to entry 2 could possibly be due to a well known, albeit

undesired (in this case) side reaction: Pd-catalyzed allylic reduction by formate ion. This reaction prefers monodentate ligated palladium complexes as an extra coordination-site is required to accommodate the formate ion.[126-131] Using the acetyl tetralone derivative **S22b**, the reaction went cleanly to the desired product in a 90% isolated yield using $Pd(PPh_3)_4$ as a catalyst. The propanoyl substituted tetralone **S22c** was similarly effective (95% yield).

Scheme 23. Scope of the DaA reaction for acetyl tetralone derivatives

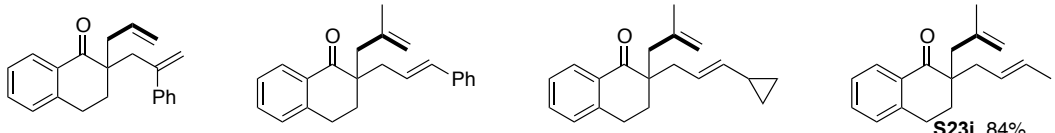


Various allyl alcohols:

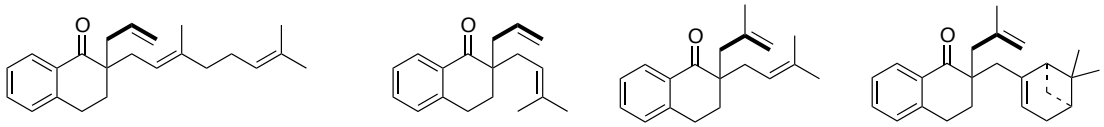


S23c, 90% | **S23d**, 68% >500 mg scale | **S2e**, 81% >500 mg scale | **S23f**, ~50% + **prot**

Substrate diversification by Tsuji-Trost allylation:

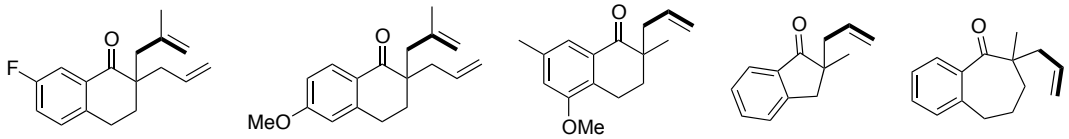


S23g, 62% | **S23h**, 77% | **S23i**, 80% | **S23j**, 84% >500 mg scale



S23k, 89% | **S23l**, 80% >500 mg scale | **S23m**, 66% >500 mg Scale | **S23n**, 95%, >500 mg scale

Diverse tetralone-core substitution:



S23o, 70% | **S23p**, 55% | **S23q**, 75% | **S23r**, 87% | **S23s**, 90% >500 mg scale

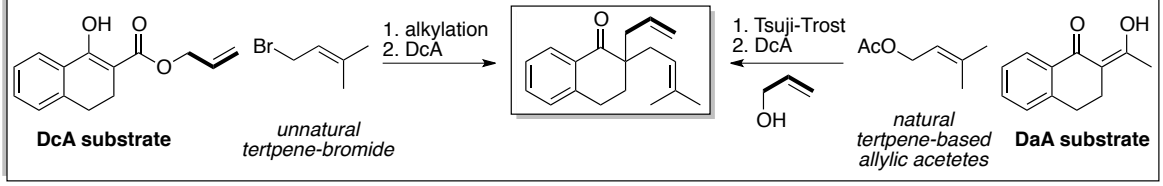
(a) standard conditions: (0.2-0.3 mmol scale) 1:1 acetyltetralone : allyl alcohol, 2 equiv. NaH, 2.5 mol% $Pd(PPh_3)_4$, NaH, 12h, 0.075M (b) 0.5-1.0 gram-scale: 1 mol% $Pd(PPH_3)_4$, 2 equiv. NaH, THF, 40°C 5-12h, 0.5M (c) Starting material was 4:1 mixture of E/Z crotyl isomers and is reflected in the product (d) standard conditions for 48h.

Having established our method for DaA reaction of the α-tetralone core, we next probed the scope of this reaction. We were pleased to see that various simple (**S23c**) and β-substituted

(**S23d-e**) allylic alcohols were viable coupling partners. Furthermore, other functional groups can be incorporated at the allyl's β-position, as demonstrated by the coupling of the acrylate derived allyl alcohol (**S23e**). Unfortunately, under these conditions, terminally substituted allylic alcohols reacted poorly (**S23f**). Though a modest ~50% yield was isolated, the remainder of the mass balance was the protonated byproduct, which in all other examples was < 5%. In addition to quaternization by methylation of the acetyl tetralone (**S23c**), starting materials could be prepared by Tsuji-Trost allylation and then undergo the DaA reaction to the 1,6-heptadienes **S23g-n**. Utilizing Tsuji-Trost allylation, β-phenylallyl (**S23g**), and its cinnamyl isomer (**S23h**) could be incorporated onto the tetralone core using their corresponding allyl acetates. A [5+2] precursor substrate could be prepared using cyclopropylallyl acetate (**S23i**) in the Tsuji-Trost reaction. Also, the crotyl group could also be installed (**S23j**) on to the tetralone core. In this case, Tsuji-Trost allylation lead to a 4:1 mixture of *E-Z* crotyl isomers and is carried through the DaA reaction. There are a number of natural allylic acetate based terpenes, such as gerenyl (**S23k**) prenyl (**S23l-m**) and (−)-myrtenyl (**S23n**) that could also be added via initial Tsuji-Trost allylation. Although a minor point, the corresponding bromides (or pseudo halides), which would be required to add such a terpene to allyl acetoacetate **S24a** (the analogous DcA substrate), are either more expensive or not commercially available (Scheme 24). Thus, the DaA approach, as it tolerates Tsuji-Trost allylation at the active methylene position, allows for the direct incorporation of these important biological building blocks on to a given scaffold without going through the unnatural and toxic bromoterpenes. Finally, the tetralone core can be substituted with electron withdrawing groups (**S23o**) or donating groups (**S23p-q**). They can also be contracted or expanded, as in the case of the indanone (**s23r**) and benzosubarone (**S23s**) based substrates, respectively. Excitingly, preparation of **S23q** represents a formal racemic total synthesis of

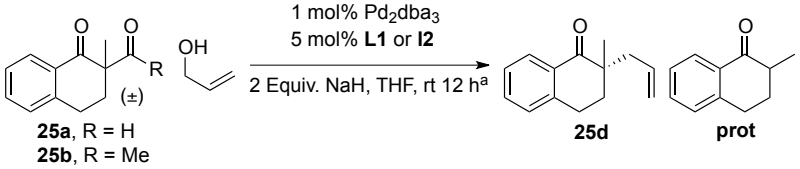
hamigeran. In many of the examples on Scheme 23, we ran the reaction on >0.5 gram scale (2-3 mmol, ~10x scale up from standard conditions) to demonstrate that useful quantities could be prepared using the DaA method. Furthermore, the catalyst loading on these scale-up reactions could easily be reduced to 1 mol%, conserving the precious Pd metal.

Scheme 24. DaA better allows allyl terpene incorporation



DcA substrate | *unnatural tertpene-bromide* | *natural tertpene-based allylic acetetes* | **DaA substrate**

Scheme 25. Development of the asymmetric DaA reaction for α-tetralones

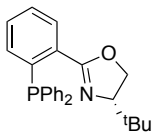


25a, R = H
25b, R = Me
25c, R = Et

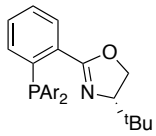
25d | **prot**

Entry	Substrate	Catalyst	**25d**:**prot** (Yield **25d**)	%ee 25d
1	**25a**	Pd/^{t}BuPHOX **L1**	89 : 11 (89% Yield)	80
2	**25b**	Pd/^{t}BuPHOX **L1**	91:9 (75% Yield)	84
3	**25c**	Pd/^{t}BuPHOX **L1**	95 : 5 (95% Yield)	80
4	**25a**	Pd/^{t}BuPHOX **L2**	90 : 10	62
5	**25b**	Pd/^{t}BuPHOX **L2**	95 : 5	58
6	**25b**[b]	Pd/^{t}BuPHOX **L2**	88 : 12 (84% Yield)	66

(a) 1.05:1 equiv. **25a**-**c**:allyl alcohol (b) 1:2 equiv. **25b**:allyl alcohol



L1



L2

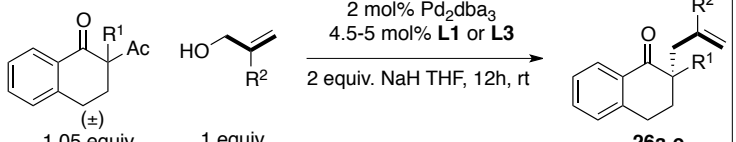
Ar = *ortho*-tolyl

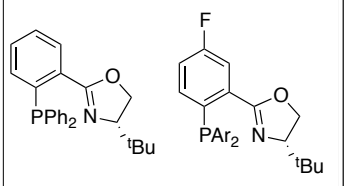
Having demonstrated that the DaA reaction of α-tetralones has wide scope, we next turned to developing the asymmetric variant (Scheme 25). We were quite pleased to find that the commercially available ^{t}BuPHOX ligand **L1** gave useful ee's with the various cleaving groups (entries 1-3, 80-84% ee). Unfortunately, none of these cleaving groups greatly affected the enantioselectivity, Another commercial ^{t}BuPHOX ligand **L2** also promoted the reaction, however with reduced ee (58-62% ee, entries 4-5). We also noticed that excess alkoxide had a

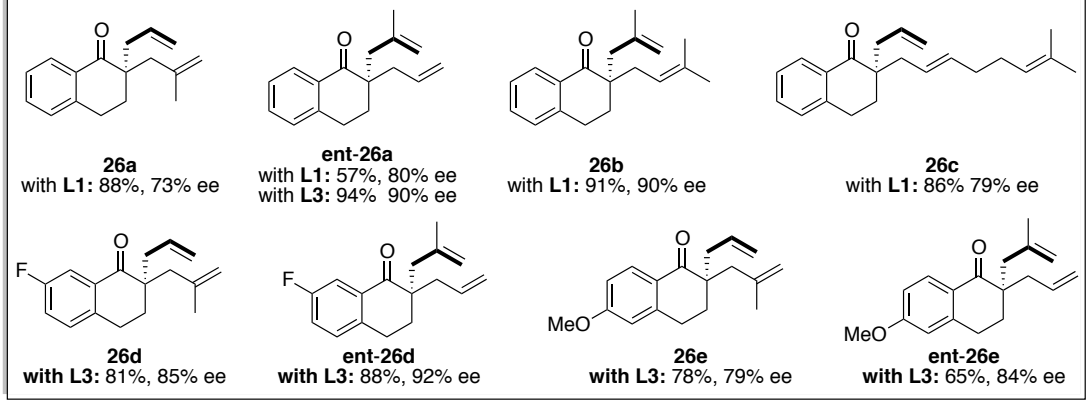
negative effective on the enantioselectivity (entry 6). Thus, in all the examples in entries 1-5, and in the next Scheme, a slight excess of the tetralone is utilized with respect to the allyl alcohol.

As shown in Scheme 26, using the commercially available ^{t}BuPHOX **L1**, or the in-house prepared fluorinated variant **L3**, good to excellent yields (57-88%) and ee's (73-92% ee) of 1,6-heptadiene tetralones could be achieved using 2-step Tsuji-Trost/asymmetric DaA. We chose to utilize ligand **L3** as fluorinated PHOX ligands have been shown (primarily by Stoltz) to be excellent at promoting asymmetric allylic alkylation reactions.[132-134] The simple tetralone core could undergo Tsuji-Trost allylation with various allylic acetates and then undergo asymmetric DaA with simple allyl alcohol or β-methylallyl alcohol **(26a-c**) producing tetralone based 1,6-heptadienes. Furthermore, the tetralone core could also withstand various electron withdrawing and donating substitution patterns (**S26d-e**). Due to the nature of the 2-step Tsuji-Trost/asymmetric DaA transformation, by interconverting the allylic substitution patterns, both enantiomers can be prepared in enantioenriched form (e.g. **S26a**,**d**,**e**/**ent-S26a**,**d**,**e**).

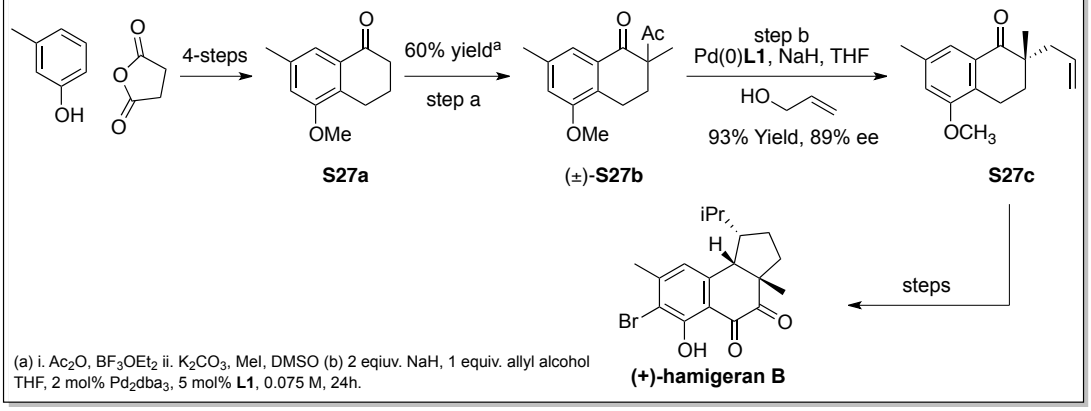
Scheme 26. Synthesis of enantioenriched 1,6-heptadienes







Scheme 27. Formal synthesis of (+)-hamigeran B using asymmetric DaA



(a) i. Ac_2O, BF_3OEt_2 ii. K_2CO_3, MeI, DMSO (b) 2 eqiuv. NaH, 1 equiv. allyl alcohol THF, 2 mol% Pd_2dba_3, 5 mol% **L1**, 0.075 M, 24h.

To further apply this new asymmetric reaction, we demonstrated that the Clive-Stoltz intermediate **S27c** for the production of (+)-hamigeran could easily be prepared in high yield and ee (Scheme 27). Starting from cresol and succinic anhydride, the required tetralone core **S27a** can be prepared by a known procedure.[135-137] From here, acetylation with acetic anhydride and quaternization with methyl iodide leads to the required starting material **S27b**. Using the conditions developed for successful asymmetric DaA, the allyl motif can be installed in 93% yield and 89% ee. This result rivals the asymmetric DcA approach utilized by Stoltz where the hamigeran precursor was isolated in 99% yield and 92% ee. However, our approach benefits from the simplified substrate synthesis via Claisen condensation (Ac_2O, BF_3□OEt_2), mild alkylation (K_2CO_3, MeI), and the direct coupling of allyl alcohol. To expound on the challenges of the DcA approach, using *Stoltz's* method (which resembled Clive's method with the exception of the allylation step), the α-methyl group was installed using highly basic enolate alkylation in the presence of HMPA. The origin of the allyl moiety was from allyl chloroformate, a toxic and sensitive phosgene derivative.

To conclude, we have thus far demonstrated that, not only can highly stabilized nitronate anions (pK_a = 17) be generated and allylated by the DaA method (section 3.3), but much less stabilized enolates (pK_a's = 20-25) can be generated and participate in this reaction. A plethora

of quaternary allylated α-aryl acetones were prepared via Cu-catalyzed arylation, alkylation, and DaA reaction starting from the simple and commercially available acetylacetone. Furthermore, over a 2-step Tsuji-Trost/DaA sequence useful 1,6-heptadienes can easily be prepared. In addition to the DaA reaction of α-aryl acetylacetone derivatives, we have demonstrated that acetylated (by Claisen condensation) α- and β-tetralones can participate in DaA. The DaA reaction generating intermediary α-tetralone enolates has culminated in an asymmetric method allowing the synthesis of enantioenriched 1,6-heptadienes as well an important intermediate *en route* to (+)-hamigeran. Due to the simplicity of this transformation, its "green" nature, and the availability of the coupling partners (allylic alcohols, acetylacetone) we envision this reaction to be a useful synthetic tool.

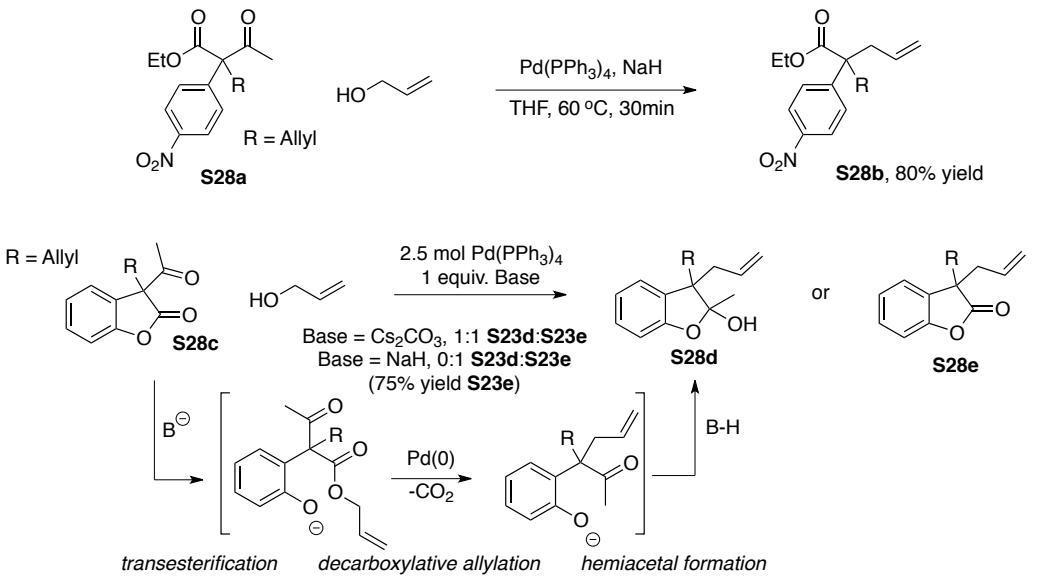
In the following sections (sections 3.3.3 - 3.3.6), we will outline the extension of the DaA reaction to other types of carbon-centered nucleophiles.

3.3.3 DaA of acetoacetate: generation and allylation of ester enolates[2]

We will begin our discussion of other nucleophiles that can be generated and allylated using DaA with ester enolates as they are quite similar to ketone enolates. As they are structurally similar with a similar pK_a, we did not put too much effort into the scope development of this reaction. What we did learn about this reaction is that retro-Claisen is, not surprisingly, chemoselective for the ketone carbonyl over the ester carbonyl when ethyl α-aryl acetoacetate **S28a** is the starting material (scheme 28, top). In this case, the DaA reaction of **S28a** and allyl alcohol produced the desired allylated product **S28b** in 80% isolated yield. Furthermore, substrate synthesis can begin from the commercially available ethyl acetoacetate

and use robust Cu-catalyzed arylation methodologies,[67] similar to that of the acetylacetone derivatives disclosed above.

Scheme 28. DaA reaction of acetoacetic ester derivatives



Using a cyclic aryl acetoacetate derivative **S28c**, the reaction was not chemoselective for the ketone over the carbonyl functionality when Cs_2CO_3 was used as the base (Scheme 2, bottom). Rather, a 1:1 mixture of products (**S28d** and **S28e**) resulting from nonselective retro-Claisen vs. transesterification was isolated. Product **S28e** was prepared by DaA reaction. The byproduct **S28d** results from transesterification of the phenyl ester to the allyl ester followed by decarboxylative allylation and hemiacetal formation. However, by switching the base from Cs_2CO_3 to NaH, a completely chemoselective retro-Claisen condensation reaction occurred and the DaA product **S28e** could be isolated in 75% yield. These few reactions outlined in Scheme 28 demonstrate the potential of the DaA reaction of acetoacetate derivatives.

3.3.4 DaA of α-aryl cyanoacetone: generation and allylation of nitrile-stabilized anions[2]

We were quite interested in extending the DaA reaction to α-aryl cyanocarbonyl derivatives **S29a** leading to allylated α-quaternary nitriles **S29b**. Not only are the starting materials **S29a** readily available by robust methods (Claisen condensation[31] or Pd-catalyzed arylation[59,60]), but **S29a** can be readily elaborated by classic alkylation,[64,138] palladium-catalyzed arylation[138] and Tsuji-Trost allylation methods.[139-141] Thus, a DaA reaction of cyanoacetones could lead to a broad array of α-quaternary nitriles. Importantly, the α-quaternary nitrile motif is found on various drug molecules[142,143] such as diphenozylate, anastrazole and verapamil, the latter which can be derived from an allylated nitrile **F1a** using a method reported by Nelson (Figure 1).[144] Thus, rapid access to this scaffold using inexpensive carbon sources is an important development. Previous methods to access allylated quaternary nitriles has involved nitrile anion alkylation (via deprotonation with strong base),[145,146] the DcA method (from allyl cyanoacetate),[14] and Reformatsky-like methods (from α-hetroatom nitriles).[147-149]

Scheme 29. A robust route to quaternary allylated-nitrile derivatives

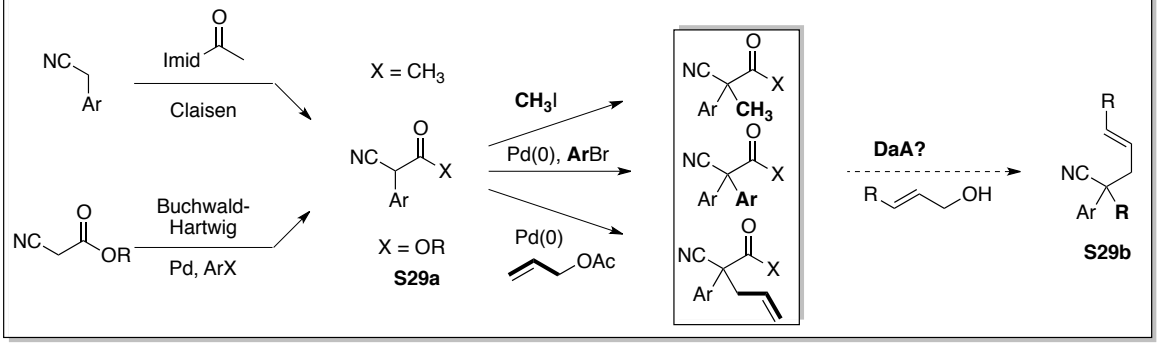
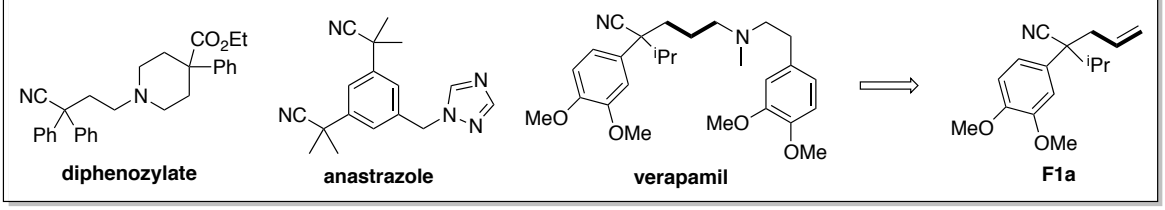
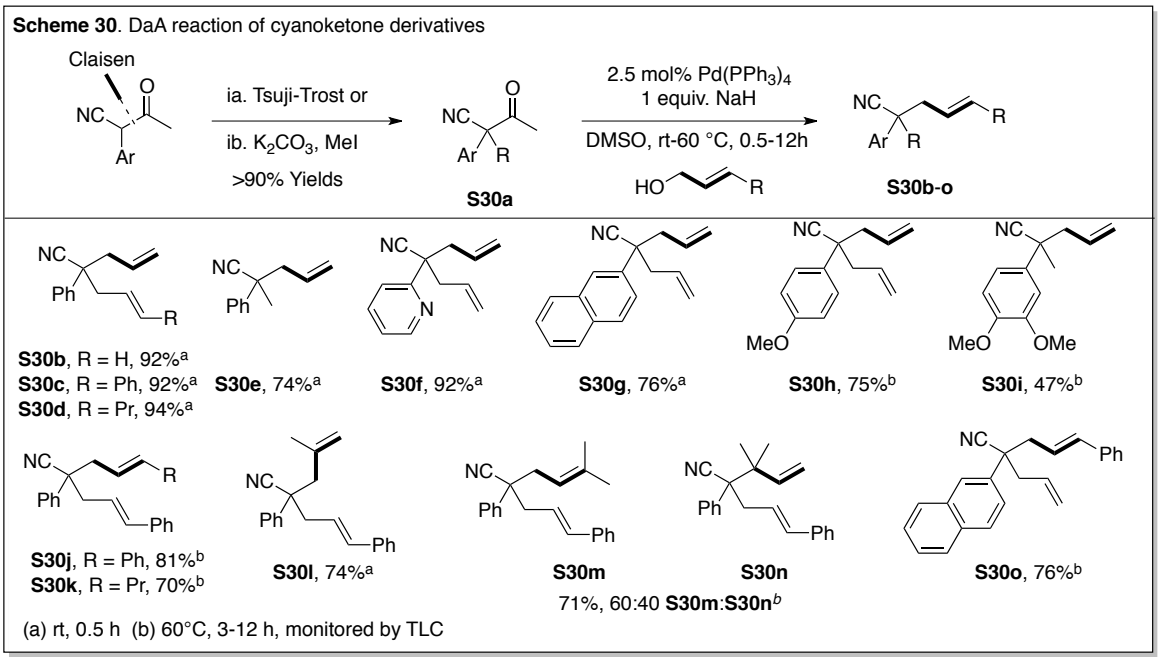


Figure 1. Quaternary nitrile-containing natural products



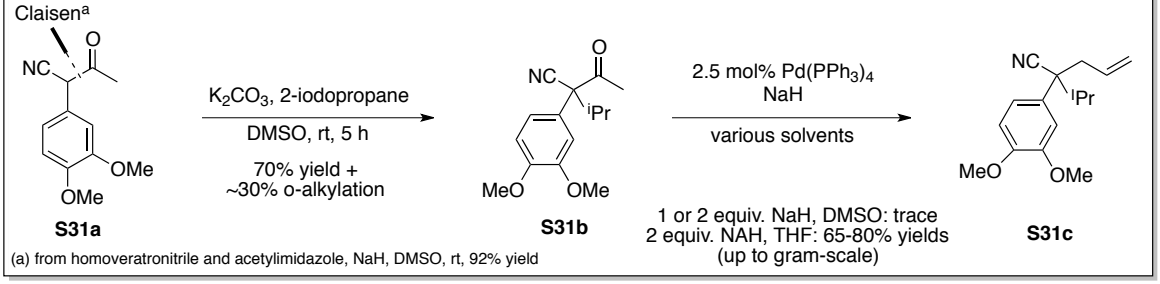


To begin, we investigated the reaction of α-aryl cyanoacetone derivatives **S30a**, prepared by Claisen condensation/alkylation starting from benzyl cyanide derivatives. Using the conditions developed for the DaA reaction for β-diketones, the reaction was quite robust and produced the desired allylated nitrile efficiently (Scheme 30). Commonly the addition of simple allyl groups occurred rapidly (<30 min.) at room temperature when DMSO was utilized as the solvent (**S30b-g**), though reaction times needed to be extended for the electron rich aromatics (**S30h-i**). Excitingly, the preparation of **S30i** represents allylation of the verapamil core, although in modest yield. In addition to simple allyl inclusion via DaA, cinnamyl (**S30j**, **o**), hexenyl (**S30k**), β-methylallyl (**S30l**), and prenyl (**S30m**) alcohols were all acceptable coupling partners. Though delighted by the incorporation of the prenyl moiety (**S30m-n**), prenylation and reverse-prenylation occurred with little selectivity. Although we focused on the rapid synthesis of 1,6-heptadienes as DaA allows a unique avenue for their preparation, in a few cases we demonstrated that alkylation under classic conditions (MeI, K_2CO_3, **S30d**,**i**) followed by DaA was also possible. In addition to the DaA reaction being chemically efficient (yields were

commonly >75%), the substrate synthesis was also quite effective: the 2-step Claisen condensation/alkylation sequence gave excellent yield of the starting substrate **S30a**. The sole exception to this was the pyridyl substrate (**S30f**, 2-steps, ~60% yield), which was a surprisingly sensitive material upon quaternization.

The ability to allylate the electron rich α-aryl nitriles (**S30h-i**) suggested that we should be able to apply this synthetic method to the production of a key intermediate *en route* to verapamil (Scheme 31). Starting from homoveratronitrile, the acetylated material **S31a** could be made in 92% yield. Alkylation with 2-iodopropane then leads to the quaternarized starting cyanoacetone **S31b** in 70% yield. Unfortunately, there was some (~30%) O-alkylation. Nonetheless, the 70% yield of **S31b** is impressive considering the simple reaction conditions sets a quaternary center adjacent to the tertiary center (isopropyl). Under the conditions utilized to couple the substrates in Scheme 30 (DMSO, NaH, cat. $Pd(PPh_3)_4$), decomposition occurred and only traces of the desired product could be isolated. However, using conditions that effectively coupled the tetralone derivatives discussed in the previous section (2 equiv. NaH, THF, cat. $Pd(PPh_3)_4$), good yields of the verapamil precursor **S31c** could be isolated. Furthermore, the reaction could be performed on gram scale, suggesting that the DaA reactions of cyanoketones are reasonably scalable. From this intermediate verapamil can be synthesized following Nelson's 3-step protocol.

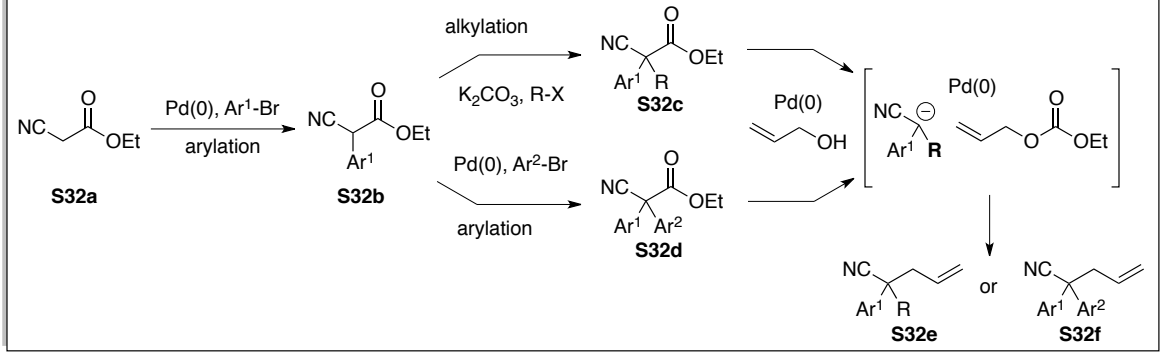
Scheme 31. Synthesis of a verapamil precursor via DaA reaction



(a) from homoveratronitrile and acetylimidazole, NaH, DMSO, rt, 92% yield

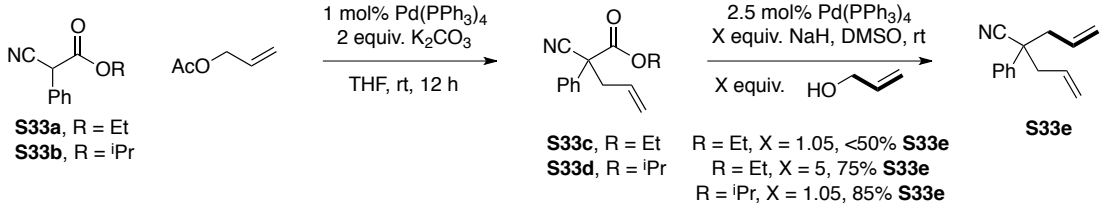
3.3.5 Retro-Claisen allylation: generation and allylation of nitrile-stabilized anions from cyanoacetic esters[2]

Scheme 32. Retro-Claisen allylation of cyanoacetic ester derivatives



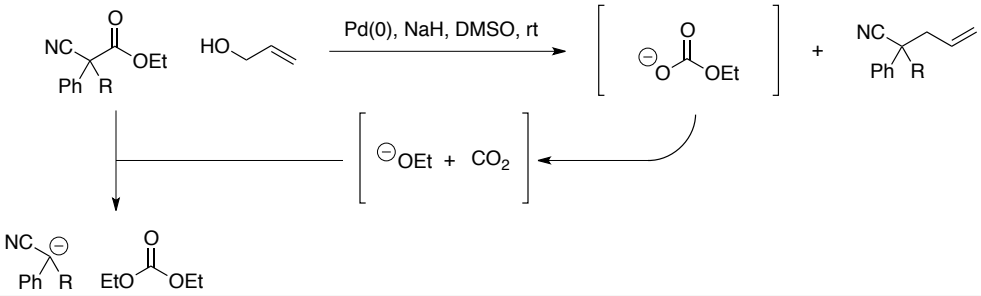
Although we were pleased with the synthesis of the various allylated nitriles via DaA of cyanoacetones, the requirement to acetylate in order to perform the DaA reaction was clearly inefficient. Furthermore, in the case of the verapamil precursor **S31c** we were displeased with the propensity for cyanoketones to undergo O-alkylation with the sterically hindered 2-iodopropane alkylating agent. With these challenges stated, we thought it might be possible to construct the same compounds starting from the readily available cyanoacetic esters **S32a** (Scheme 32). Using the robust method reported by Hartwig,[60,138] Pd-catalyzed arylation to **S32b** occurs. From here, alkylation would prepare the starting substrate **S32c**.[64] In order to access the desired quaternary allylated nitrile **S32e**, the retro-Claisen condensation would need to occur on an ester carbonyl. This C−C cleavage reaction is potentially more challenging due to the reduced electrophilicity of the ester carbonyl compared to the previously examined ketone analogues. As Hartwig also reported the bisarylation of cyanoacetic esters (**S32a è S32d**),[60,138] we envision this approach to allow us to access allylated geminal aryl nitriles **S32f**. Recall from Figure 1 that such a motif is found in many drug like molecules such as diphenozylate.[143]

Scheme 33. Pd-catalyzed retro-Claisen allylation of α-cyanoacetic esters



We began to probe the retro-Claisen allylation using substrates **S33c-d**, prepared from cyano acetic esters **S33a** or **S33b** by Hartwig's arylation method[138] and Tsuji-Trost allylation. Using the ethyl cyanoacetate derivative **S33c**, we were able to realize the reaction when excess allyl alcohol was utilized. Interestingly, when the isopropyl cyanoacetate **S33d** was utilized, the equivalents of alcohol and base could be reduced to pseudo-stoichiometric quantities. To explain this, one must consider that fact that, in the case of substrate **S33c**, ethoxide is generated over the course of the reaction, which can promote formation of an unproductive byproduct, diethyl carbonate (Scheme 34). Therefore, the excess allyl alcohol can outcompete the *in situ* generated ethoxide for retro-Claisen condensation. Allyl alcohol can be reduced to a single equivalent in the case of the isopropyl cyanoacetate **S33d** because the *in situ* generated isopropoxide cannot as easily promote the unproductive reaction, as it is a 2° alcohol.

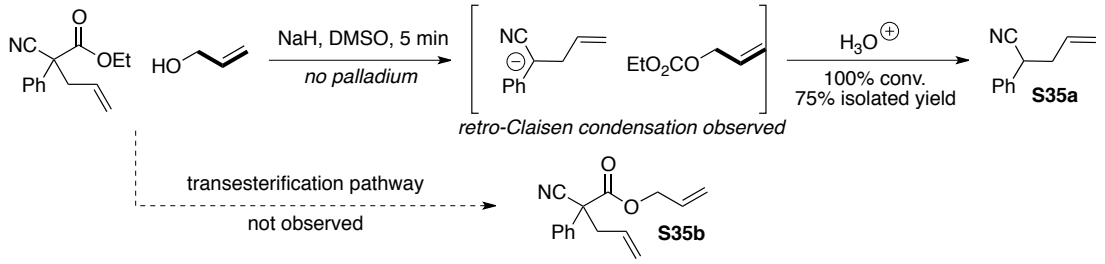
Scheme 34. Ethoxide formation promotes an unproductive reaction pathway



There was one more mechanistic question we wished to answer regarding this retro-Claisen allylation reaction: does retro-Claisen allylation occur, as we assumed in the Schemes 32-34, or can transesterification followed by DcA lead to the desired product (**S35b**, Scheme

35)? As shown in Scheme 35, in the absence of palladium, we were able to isolate the protonated nitrile **S35a**. If tranesterification/DcA were the productive reaction pathway, the experiment would have produced allyl cyanoacetate **S35b**. Thus, retro-Claisen must occur preferentially over transesterification. This result is consistent with the fact that the benzyl cyanide has a lower pK_a than that of ethanol (DMSO pK_a = 25 and 29 respectively). Thus, the nitrile-stabilized anion is a better leaving group than ethoxide.

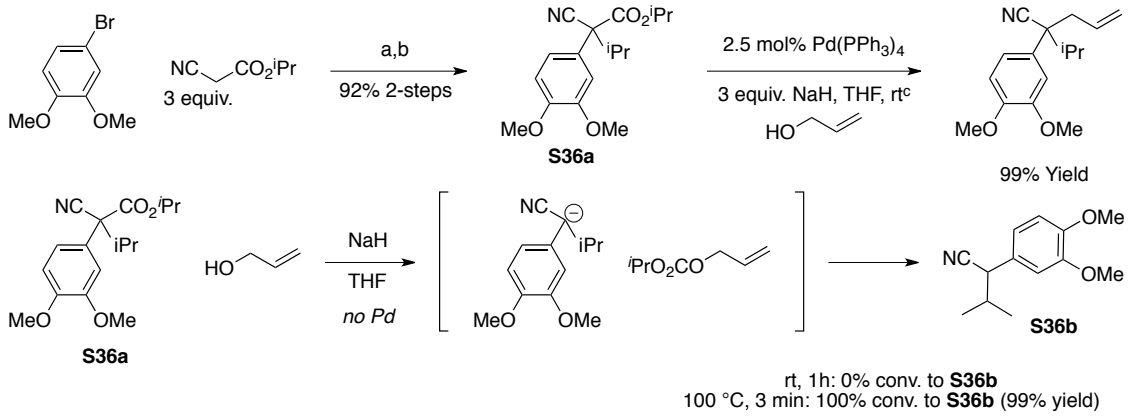
Scheme 35. Retro-Claisen occurs on cyanoacetic esters- not transesterification



Having demonstrated that the desired allylated quaternary α-aryl nitriles can be prepared by an alternate pathway starting from cyanoacetic acid derivatives, we wished to demonstrate the reaction's utility in the preparation of the previously synthesized verapamil precursor substrate (Scheme 36). The required starting substrate is prepared by the general Pd-catalyzed arylation method reported by Hartwig, followed by alkylation with 2-iodopropane. We were particularly gratified to see how efficient this sequence was: 92% yield over the 2-steps. Furthermore, no O-isopropylation was observed in this case, unlike when the analogous cyanoacetone was utilized (see Scheme 31). The verapamil precursor could be prepared from **S36a** and allyl alkoxide in 99% yield by flashing the reaction to 100 °C and stirring at room temperature for 12 h in the presence of catalytic $Pd(PPh_3)_4$. The brief heating was required to promote the C−C cleavage event: simply stirring the substrate **S36a** in the presence of alkoxide at room temperature did not promote formation of the retro-Claisen condensation product **S36b**. However, **S36b** could be

prepared with excellent chemical efficiency by briefly heating the substrate in the presence of alkoxide.

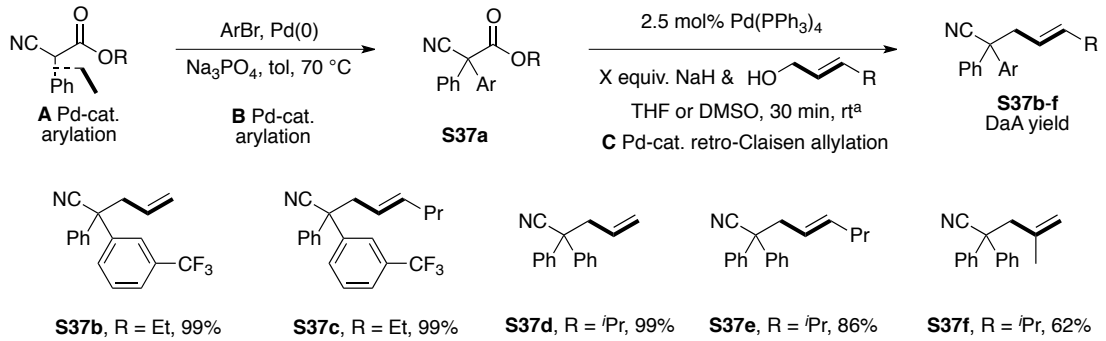
Scheme 36. Development of a Pd-catalyzed retro-Claisen allylation for a verapamil precursor



(a) Na_3PO_4, 2% $Pd(dba)_2$ 5% P^tBu_3, Tol, 100 °C, 12 h (b) 5 equiv. K_2CO_3, 5 equiv. 2-iodopropane, DMSO, rt, 1 h, (c) 1.05 equiv. allyl alcohol, flash reaction mixture to 100 °C (3 min) and leave at rt overnight

In addition to the allylated quaternary α-aryl nitriles such as the verapamil precursor (Scheme 36), we wished to extend the retro-Claisen allylation of cyanoacetic ester derivatives to α,α-diaryl nitriles, as they to are medicinally relevant structural motifs (Scheme 37).[143] We were please to see the retro-Claisen allylation worked well with various diaryl cyanoacetates **S37a** and allylic alcohols. For example, both chiral allylated diaryl nitriles **(S37b-c**) and geminal phenyl (**S37d-f**) substrates could be prepared. Regarding the allylic alcohol coupling partner, simple (**S37b**,**d**), hexenyl (**S37c**,**e**), and β-methylallyl (**S37f**) were all compatible under the reaction conditions developed. We were particularly satisfied with the substrate synthesis as it utilized 3-consecutive Pd-catalyzed transformations (two-Pd catalyzed arylations followed by retro-Claisen allylation) beginning from readily available and inexpensive cyanoacetates, aryl bromides and allyl alcohols as the carbon sources.

Scheme 37. Synthesis of α,α-diaryl-α–allyl acetonitrile derivatives by sequential Pd-catalysis



(a) if R = Et, X = 5 or if R = ^{i}Pr X = 1.1

3.3.6 Conclusions on the DaA (retro-Claisen allylation) reaction

The DaA reaction is a new approach to Pd catalyzed allylic alkylation involving a retro-Claisen condensation of an acetyl pronucleophile and an allylic alcohol. The retro-Claisen reaction generates *both nucleophilic and electrophilic coupling partners in situ,* which are coupled together in the presence of Pd. The DaA reaction is a particularly attractive choice method for the allylation of nucleophiles due to the direct coupling of commercially available allyl alcohols and readily available acetyl pronucleophiles. Regarding the origin of the acetyl-pronucleophile, they can be derived from commercially/readily available active methylene compounds by robust α-alkylation and arylation methodologies. As shown herein, we initially confirmed our hypothesis via generation of nitronate anions (DMSO pK_a ~ 17, Section 3.3.1) using allyl alcohols. The success of this reaction was hinged on the fact that retro-Claisen was facile due to the high stability of the nitronate leaving group. From these humble beginnings, we gradually extended the DaA reaction to include to α-aryl enolates (DMSO pK_a ~20, Section 3.3.2), α-tetralone enolates (DMSO pK_a = 25, Section 3.3.2) and nitrile stabilized anions (DMSO pK_a ~22-24, Sections 3.3.4 and 3.3.5).

The DaA reaction allows a unique and simple avenue for the synthesis of 1,6-heptadienes via 2-step Tsuji-Trost/DaA reaction. Thus, with all the nucleophiles investigated above, we demonstrated that these important cycloisomerization substrates can be made by the DaA method. We also developed an enantioselective DaA reaction for tetralones that culminated in the synthesis of enantioenriched 1,6-heptadienes and an important intermediate *en route* to (+)-hamigeran. Finally, the retro-Claisen allylation of α-aryl cyanoacetic esters allowed us to prepare an important intermediate *en route* to the drug verapamil. Made possible by the DaA reaction, the verapamil precursor was exclusively prepared (in 92% yield over 3-steps form commercial materials) from cyanoacetic acid, bromoveratrole, isopropyl bromide, and allyl alcohol, all of which are commercially available and inexpensive.

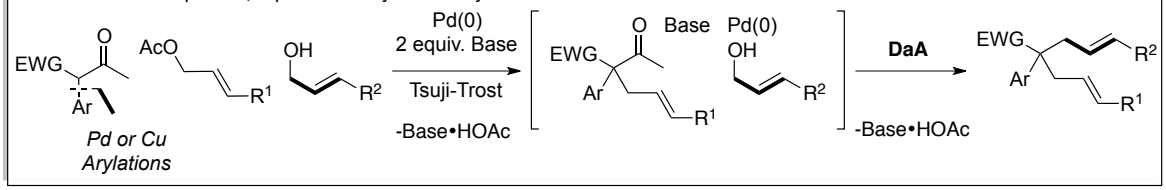
The final section of the original research section of this dissertation will demonstrate how 1,6-heptadienes can be prepared by 1-pot Pd-catalyzed Tsuji-Trost/DaA reaction.

3.4 3-component Tsuji-Trost allylation/retro-Claisen allylation: 1-pot synthesis of 1,6-heptadienes[1-3]

In the previous sections, I have described how 1,6-heptadienes can be prepared rapidly using a 2-step Tsuji-Trost allyation/DaA reaction. We have demonstrated this sequence on α-nitroketones, α-aryl-β-diketones, α- and β-tetralones, α-aryl α-cyanoacetones, and α-aryl α-cyanoacetic acid *esters*. This 2-step procedure was developed as a surrogate process to our original, 1-step attempt: the Tsuji-Trost/DcA reaction. The challenge of our original approach stems from the similarly reactive allylic acetates (or carbonates) required for such a reaction sequence. Aside from the 2-step nature of our newly devised Tsuji-Trost/DaA approach to 1,6-

dienes, allylic acetates and allyl alcohols have drastically different rates of reaction toward oxidative addition (allyl alcohols rarely form Pd-π-allyl complexes without the aid of Lewis acid additives).[76,150-154] As this 2-step sequence utilizes Pd to promote both of the reactions, we reasoned that a 1-pot Pd-catalyzed bisallylation should be possible leading to these useful 1,6-heptadienes with increased efficiency due to the differentiated reactivity of allylic acetates and alcohols toward Pd (Scheme 38). In general, this reaction should be straightforward, as the Tsuji-Trost allylation of active methylene compounds in most examples above, was rapid and high yielding. Furthermore, the 3-component coupling should require 2 equiv. of base: the first to promote the Tsuji-Trost allylation and the second, for the DaA reaction.

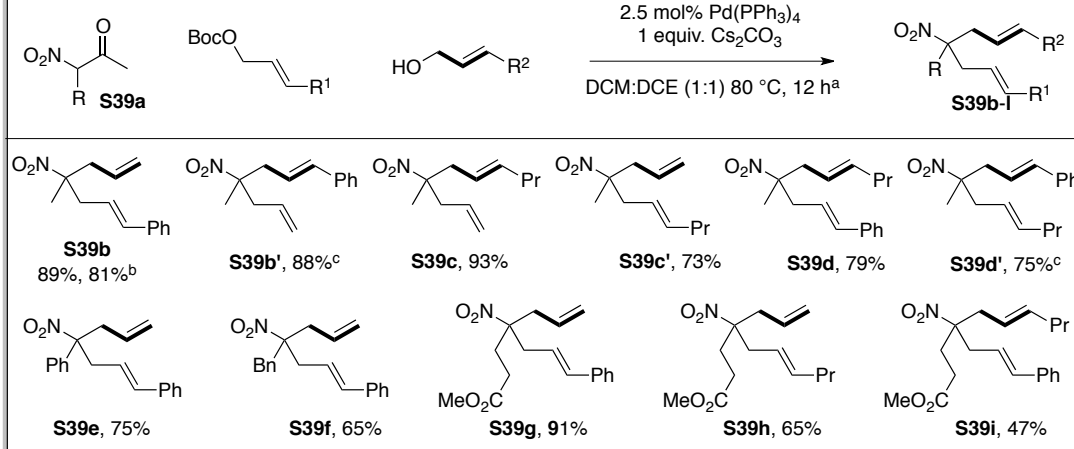
Scheme 38. 3-component, 1-pot Pd-catalyzed bisallylation



Using the conditions developed for successful DaA reaction of nitroketones [Cs_2CO_3, 2.5 mol% $Pd(PPh_3)_4$, DCM:DCE (1:1), 80 °C, 12h] the reaction was converted into a 3-component coupling with ease. The Tsuji-Trost reaction on **S39a** occurred rapidly at room temperature (<1 min) and upon heating overnight, the DaA reaction yielded the 1,6-heptadienes **S39b-l**. Though only a single equivalent of Cs_2CO_3 was utilized, the second equivalent of base is generated from the allyl *t*butyl carbonate ($^tBuCO_3^-$). Using cinnamyl carbonate and allyl alcohol, **S39b** could be prepared in high yield. The initial Tsuji-Trost reaction could also be done with cinnamyl acetate (footnote b), though an extra equivalent of base is required. Next, the reaction partners can be switched with little effect on the reaction outcome: using allyl carbonate and cinnamyl alcohol, **S39b'** is prepared in similar yield to the **S39b**. In general, the reaction partners can be switched using various allylic carbonates and alcohols (**S39b-d**, **S30b'-d'**) with little effect on the yield.

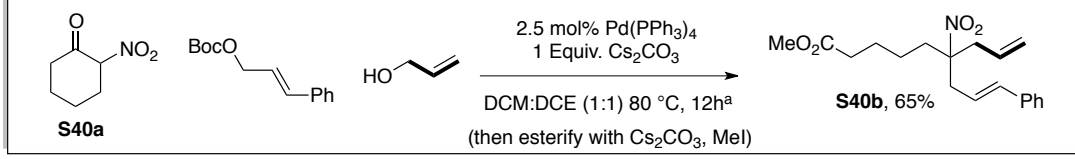
Regarding α-substitution on the nitroacetone, various aryl (**S39e**) and alkyl (**S39f-i**) substitution patterns were well tolerated. We were particularly satisfied with the coupling of the ester containing nitroketones (**S39g-i**) in the 3-component bisallylation. Not only are the nitro and ester moieties functional group paired, but this shows that the DaA reaction conditions can tolerate other electrophilic functional groups such as esters without undesired transesterification. Utilizing cyclic nitroketones such as **S40a**, 1,6-heptadienes with pendant carboxylic acids can be prepared (Scheme 40). As the 1,6-heptadiene containing the tethered carboxylate was challenging to purify, it was converted to the methyl ester **S40b** and subjected to column chromatography. In addition to bisallylation, starting from unsubstituted nitroacetone **S41a** and utilizing 2 equiv. of cinnamyl carbonate and 1 equiv. of allyl alcohol, controlled trisallylation can occur yielding **S41b** in 81% yield.

Scheme 39. Pd-catalyzed 3-component bisallylation of nitroketones

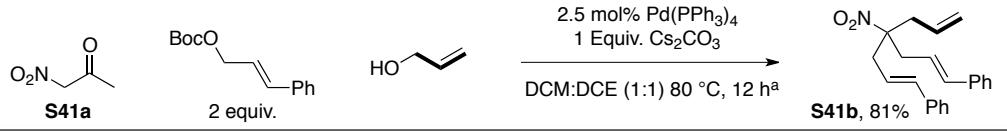


(a) 1:1:1.2 nitroacetone : allyl carbonate : allyl alcohol, 2.5 mol % $Pd(PPh_3)_4$, 1 equiv. Cs_2CO_3, DCM:DCE (1:1) 80 °C, 12 h. (b) 81% yield using 2 equiv. of Cs_2CO_3 and cinnamyl acetate. (c) 10 mol % $Pd(PPh_3)_4$

Scheme 40. 3-component bisallylation of α-nitrocyclhexanone

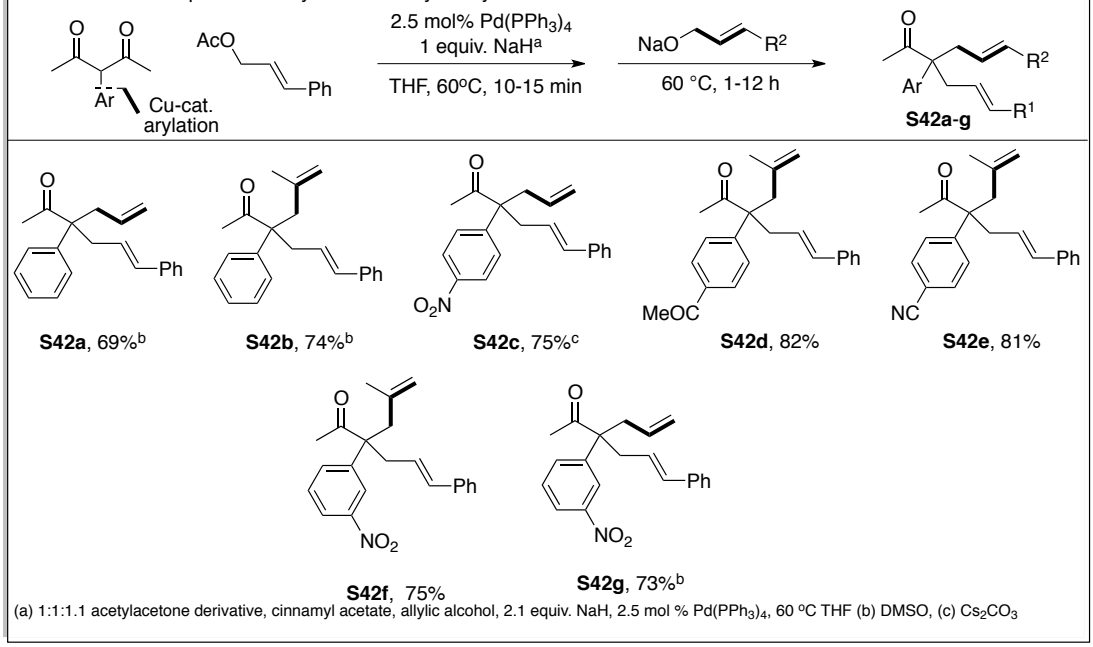


Scheme 41. Controlled triallylation of nitroacetone



We next turned to the development of the 3-component bisallylation of α-aryl acetylacetone derivatives. Though at first challenging, we realized that a lag time (10-15 min, 60 °C) was required between the Tsuij-Trost allylation and addition of the allyl alcohol for the DaA reaction as the Tsuji-Trost allylation was not as rapid as the nitroketone substrates were. Furthermore, the allyl alcohol was injected as its salt in the solvent being utilized. Nonetheless, using this adopted procedure the bisallylation could occur preparing **S42a-g**. Regarding the scope, various α-aryl acetylacetone derivatives were excellent coupling partners. Simple phenyl acetylacetone (**S42a-b**) provided the 1,6-diene in good yield. Various electron withdrawing groups on the arene ring were also tolerated at the *para*- and *meta*- positions (**S42c-g**).

Scheme 42. 3-component bisallylaiton of α-aryl acetylacetone derivatives

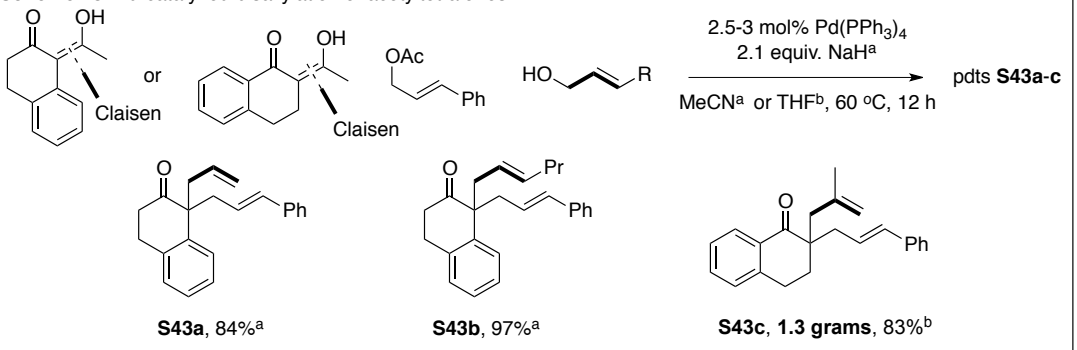


(a) 1:1:1.1 acetylacetone derivative, cinnamyl acetate, allylic alcohol, 2.1 equiv. NaH, 2.5 mol % $Pd(PPh_3)_4$, 60 ºC THF (b) DMSO, (c) Cs_2CO_3

Bisallylation of acetylated α- or β-tetralones was also possible. Using the same procedure as outlined in Scheme 42, 1,6-heptadiene β-tetralones **S43a-b** were prepared using

cinnamyl acetate and either allyl (**S43a**) or hexenyl (**S43b**) alcohol. On the >1 gram scale, we demonstrated that 1,6-diene α-tetralones could also be prepared by Pd-catalyzed bisallylation. Notably, we identified a simpler procedure for the bisallylation reaction that didn't require preformation and addition of the sodiated allyl alkoxide. Rather, both equivalents of the NaH were added at the beginning of the sequence and after Tsuji-Trost allylation was completed (~15 min., 60 °C), the reaction mixture was cooled to 0 °C, and the allyl alcohol was added dropwise into the reaction mixture. The reaction mixture is then warmed back to 60 °C to promote the DaA reaction.

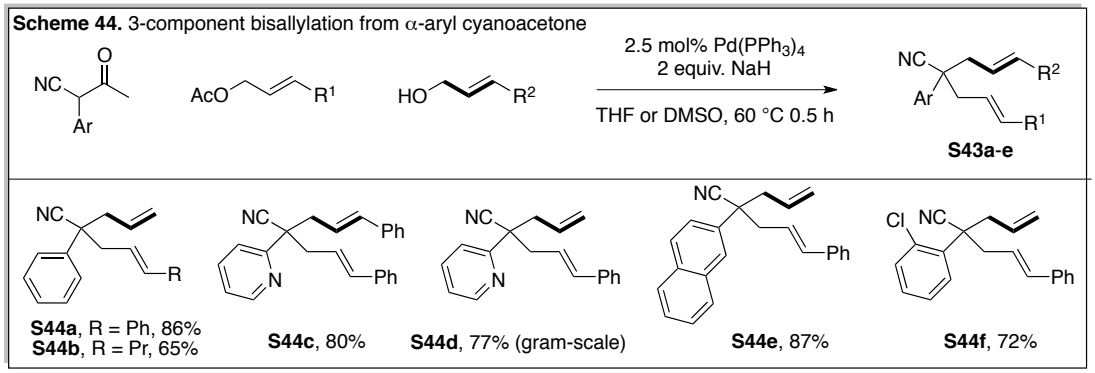
Scheme 43. Pd-catalyzed bisallylation of acetyltetralones

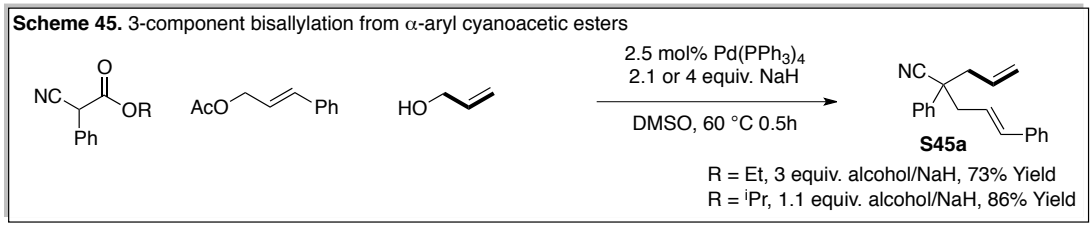


S43a, 84%[a] **S43b**, 97%[a] **S43c**, **1.3 grams**, 83%[b]

(a) same conditions as outlined in Scheme 42. (b) 3 mol% $Pd(PPh_3)_4$ 2.1 equiv. NaH, 1 equiv. allyl acetate, 1 equiv. tetralone, 60 °C 15 min (Tsuji-Trost). Then, 1.05 equiv. β–methyl allyl alcohol, 0 – 60 °C.

Finally, α-aryl cyanoketones (Scheme 44) and esters (Scheme 45) can undergo Pd-catalyzed bisallylation. The allyl alkoxide addition method was utilized that was developed for the 3-component coupling of α-aryl acetylacetone derivatives (Scheme 42). The cyanoketones were excellent coupling partners, providing good yields of the bisallylated compounds **S44a-f**. In addition to simply phenyl cyanoacetone (**S44a-b**), pyridyl (**S44c-d**), napthyl (**S44e**) and *ortho*-chlorophenyl (**S44f**) starting materials were utilized. A gram scale reaction was also performed to demonstrate that this bisallylation is reasonably scalable. As the α-aryl cyano esters are more readily available via Hartwig's method, we wished to demonstrate such a starting material could also be utilized in this Pd-catalyzed bisallylation (Scheme 45).





To conclude this section, 1,6-heptadienes can be prepared by single pot by the 3-component coupling of a mono α-substituted active methylene compound, allyl acetate (or carbonate) and an allyl alcohol. This process is made possible because of the differing reactivity of the 2 allylic systems. The palladium catalyst first couples the active methylene compound and the allyl acetate. Upon allyl alkoxide induced retro-Claisen condensation, 2 new coupling partners are generated for a second Pd-catalyzed allylic alkylation (DaA). We envision this reaction to find use amongst the organic community as it prepares unique 1,6-heptadienes using an extremely simple reaction manifold from commercially available starting materials.

3.5 Conclusions

Active methylene compounds are attractive starting materials due to their commercial/ready availability and their heightened nucleophilic tendencies. Upon α,α-disubstition of these substrates, we have demonstrated that another coupling reaction can occur by deacylative allylation (DaA). In this process, *nucleophilic and electrophilic coupling*

partners are generated in situ by a single allyl alkoxide induced retro-Claisen condensation event. In the presence of Pd, allylic alkylation occurs to a useful chemical building block. The DaA reaction is attractive due to the direct coupling of allylic alcohols, the ready availability of DaA substrates, and the minimal waste byproduct generated (only acetate).

We have demonstrated that the reaction can be utilized to generate and allylate nitronate anions, ketone and ester enolates, and nitrile-stabilized anions. This type of reaction is particularly useful in the construction of 1,6-heptadienes by 1 or 2-pot sequential Tsuji-Trost/DaA reaction. We have also demonstrated the reaction's utility in the construction of an important synthetic intermediate *en route* to verapamil from simple starting materials utilizing 2 consecutive Pd-catalyzed events (Pd-catalyzed arylation and DaA). An asymmetric DaA reaction of α-tetralone derivatives was also developed and utilized to construct enantioenriched 1,6-heptadienes as well as a precursor to (+)-hamigeran.

We envision this reaction to be of synthetic utility due to the simplicity of the transformation and the importance of the substrates that it can prepare (allylated compounds, 1,6-heptadienes).

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Chapter 3 appendix

Experimental methods and spectral analysis for Ch. 3 compounds

Table of contents

General Information:

*NOTE: Products are named after their Scheme location in Chapter 3. (e.g. **S8b** = substrate **a** in Scheme 8). If a compound has not specifically been named and referred to in Chapter 1 text, it will be given an Appendix name (**A-1, A-2, etc.)** They are similarly named in the spectral analysis section of this appendix.

All reactions were run in flame-dried glassware. Air free conditions were facilitated by the use of argon and a Schlenk line (vacuum gas manifold). CH_2Cl_2 and toluene were dried over activated alumina. THF was distilled over sodium. Anhydrous dichloroethane, acetonitrile, NMP, DMF and DMSO was purchased from Aldrich, stored in the glove box and used as is. 95% Sodium Hydride was purchased from Aldrich, stored in a glove box and used as is. 99% Cs_2CO_3 was purchased from Aldrich and used as is. >99% allyl alcohol was purchased from Aldrich and stored over 3Å-MS in a sealed tube fitted with a rubber septum. Commercially available substrates were used as is. Non-commercially available substrates were prepared by the methods described in the "Substrate preparation procedures" section of this appendix.

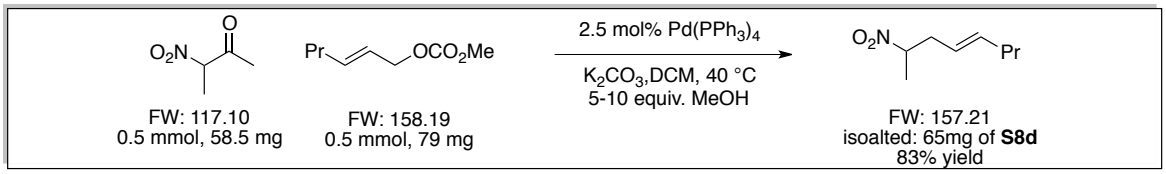
Compound purification was effected by flash chromatography using 230x400 mesh, 60Å porosity silica obtained from Sorbent Technologies and in some cases when noted, Kugelrohr distillation. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance 400 or a Bruker

Avance 500 DRX spectrometer equipped with a QNP Cryoprobe and referenced to residual protio solvent signals.

Regarding chiral resolution and ee determination, HPLC chiral resolution was performed using a Chiralcel OD-H column and hexanes/isopropyl alcohol mobile phase mixtures. Absolute configuration is assigned based on Stoltz's work, as the same ligands are utilized and the same products are prepared.[1]

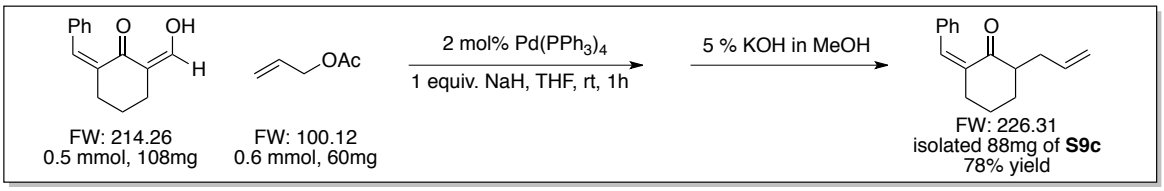
General procedures for Tsuji-Trost/retro-Claisen condensation:

1. Representative procedure for Tsuji-Trost/retro-Claisen of α-nitroketones:



In a flame-dried 10 mL Schlenk flask under argon, combine Pd(PPh3)4, (14 mg, 2.5 mol %, 0.0125 mmol), K2CO3 (138 mg, 1 mmol) and DCM (1 mL). A solution of nitroacetone (59 mg, 0.5 mmol) in DCM (1 mL), **3a**, and hexenyl *tert*-butyl carbonate (0.51 mmol, 79 mg) were added with stirring followed by 5 equivalents (80 mg) of methanol. The resulting mixture was stirred overnight at 50 °C. After cooling the mixture to room temperature, the solution was filtered through a silica gel plug with 15% EtOAc/Hexanes as eluent. Evaporation of volatiles, and subjection of the residue to column chromatography (2 mol % EtOAc/hexanes) yielded **S8d** (65 mg, 83%).

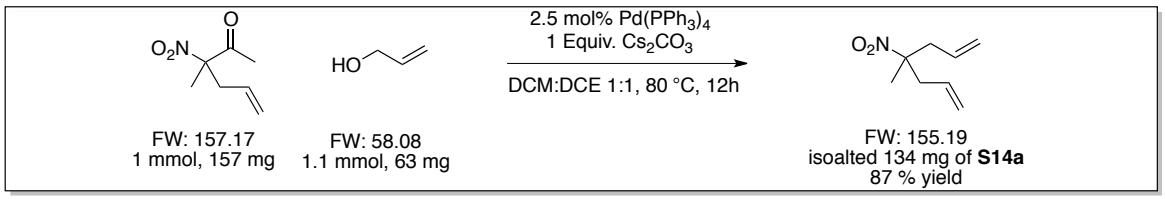
2. Representative procedure for Tsuji-Trost/retro-Claisen of β-formyl ketones:



A flame-dried 10 mL Schlenk flask equipped with a stir bar is brought into a glove box and charged with $Pd(PPh_3)_4$ (2 mol%, 0.01 mmol, 11.5 mg) and 95% NaH (1 equiv., 0.5 mmol, 12.5 mg). The flask is capped, removed from the glove box and attached to a Schlenk-argon line. 5 mL of dry THF is then added to the flask and substrate ketone (1 equiv., 0.5 mmol, 108 mg) is added neat. Allyl acetate (0.6 mmol, 60 mg) is then added and the vessel is stirred at room temperature for 1h (until completion, monitored by TLC). Once the starting material has been completely consumed, ~5 mL of 5% KOH/MeOH is added and the vessel is stirred for 15 min. The contents are then transferred to a seperatory funnel. EtOAc (~10 mL) is used to wash the reaction vessel to ensure complete transfer. An extra 10 mL of EtOAc is added to the seperatory funnel and the organic layer is extracted with 1M HCl (~15 mL) followed by brine (~15 mL). The organic layer is collected, dried over $MgSO_4$, evaporated and subjected to column chromatography (7% EtOAc in hexanes) to yield the desired product **S9c** (88 mg, 78% yield).

General procedures for deacylative (retro-Claisen) allylation:

3. Representative procedure for the DaA reaction of α-nitroketones:

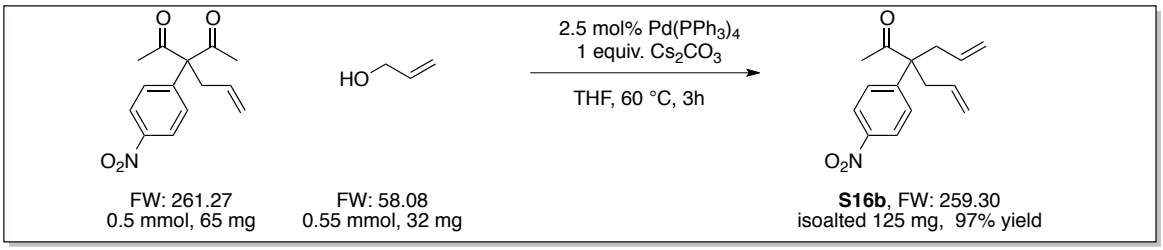


In a glove box under an argon atmosphere, a flame-dried pressure vial equipped with a

septum was charged with Pd(PPh3)4 (2.5 mol%, 14 mg, 0.0125 mmol) and Cs_2CO_3 (1 mmol, 325 mg). Anhydrous DCE (2 mL) was added and the vial was sealed. After removing the vial from the glove box, a solution of α-nitroketone (1 mmol, 157.17 mg,) and allyl alcohol (1.1 mmol, 63 mg) in dry DCM (0.5 mL) was added via syringe and the transfer vessel was washed with DCM (~0.5 mL) to ensure complete transfer of the substrates to the reaction mixture. The pressure vial was then submerged in an oil bath at 80 °C and left to stir overnight.

After the allotted reaction time, the vessel was cooled to room temperature and the resulting solution was diluted with 15% Et2O/pentane (~5 mL) and eluted through a silica plug with excess 15% Et2O/pentane (~50-75 mL). After removal of the volatiles via rotary evaporation, the crude oil was subjected to column chromatography (gradient column: 2% to 4% Et2O/pentane) yielding the desired product **S14a** (134 mg, 87% yield).

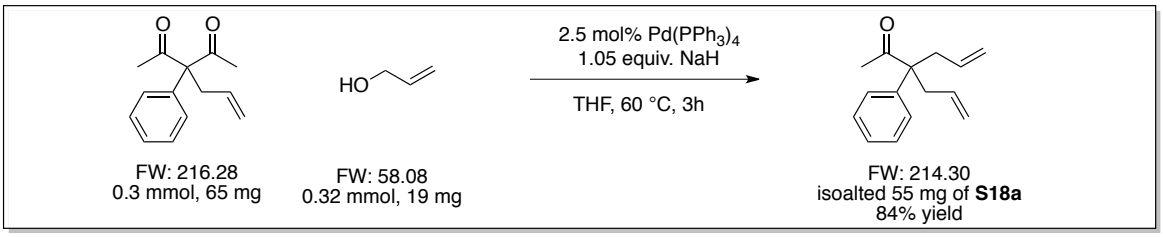
4. Representative procedure for the DaA reaction of para-nitrophenyl acetylacetone:



A flame-dried 10 mL Schlenk flask is equipped with a stir bar, brought into a glove box, and charged with an $Pd(PPh_3)_4$ (2.5 mol%, 0.0125 mmol, 14 mg) and Cs_2CO_3 (0.5 mmol, 165 mg). The flask is capped, removed from the glove box and attached to a Schlenk-argon line. 3 mL of dry THF is added to the flask and allyl alcohol (0.55 mmol, 32 mg) is added neat using a 1 mL disposable syringe. Wash the transfer syringe with the reaction mixture solvent to ensure complete transfer. The acetylacetone substrate (0.5 mmol, 65 mg) is then added neat. The vessel is capped, sealed, and heated at 60 °C overnight (12h).

After the allotted reaction time, the reaction mixture is diluted with ~5 mL of 15% EtOAc in hexanes and filtered through a silica plug. Wash the reaction vessel with the 15% EtOAc solution to ensure complete transfer to the plug. ~25 mL of the transfer solution is then used to wash the silica. The volatile organics are then removed by rotary evaporation and the oily residue is subjected to column chromatography (7% EtOAc in Hexanes) yielding the desired product **S16b** (125 mg, 97% yield).

5. Representative procedure for the DaA reaction of α-phenyl acetylacetone



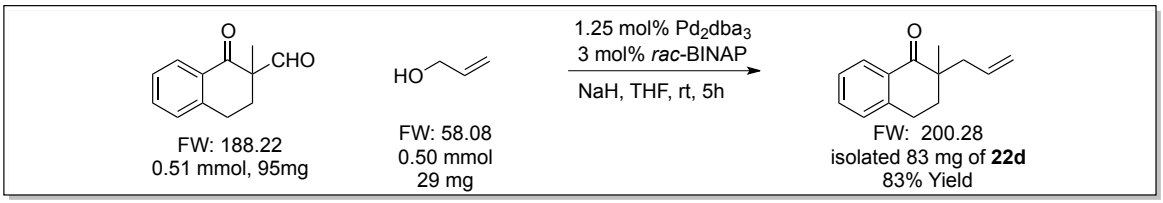
A 10 mL flame-dried Schlenk flask is equipped with a stir bar, brought into a glove box, and charged with $Pd(PPh_3)_4$ (2-3 mol %, 6-8 mg, FW:1155.57) and NaH (0.34 mmol, 8mg, FW: 24.00) in a glove box. The vessel is capped, removed from the glove box, and attached to a Schlenk-argon line. Dry, freshly distilled THF (3 mL) is added to the flask. Allyl alcohol (0.32 mmol, 19mg) is added neat using a 1 mL disposable syringe. This transfer syringe is washed with the reaction mixture to ensure complete transfer. Rapid effervescence occurs forming the alkoxide. Once H_2 effervescence ceases, the acetylacetone pronucleophile (0.3 mmol, 65 mg) is added neat dropwise to the reaction mixture using a disposable 1 mL syringe. Again, this syringe is rinsed with the reaction mixture to ensure complete transfer. The reaction is then submerged in an oil bath at 60 °C where it is left to react for the indicted time.

After the allotted reaction time, the reaction mixture is diluted with ~5 mL of 15% EtOAc in hexanes and filtered through a silica plug. Wash the reaction vessel with the 15% EtOAc solution to ensure complete transfer to the plug. ~25 mL of the transfer solution is then used to

wash the silica. The volatile organics are then removed by rotary evaporation and the oily residue is subjected to column chromatography (3% EtOAc in Hexanes) yielding the desired product **S18a** (55 mg, 84% yield).

NOTE* if DMSO or MeCN is utilized as the solvent, dilute reaction mixture with EtOAc (~20 mL total volume) and perform extractions using 1N HCl (2 x ~25 mL) followed by brine (25 mL). Dry the organic layer, evaporate the volatiles and subject to column chromatography.

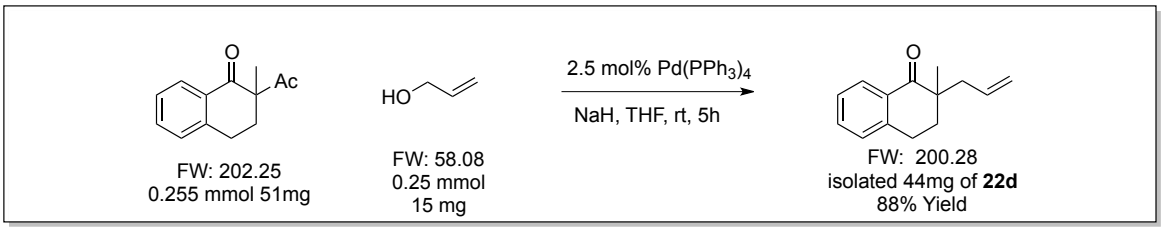
6. Representative procedure for the DaA reaction of 2-formyl α-tetralone derivatives:



Two flame-dried 10mL Schlenk flasks equipped with stir bars are flame dried and brought into a glove box. The catalyst (Pd_2dba_3, 1.25 mol % 0.0063 mmol, 5.7 mg and *rac*-BINAP, 3 mol%, 0.015 mmol, 9.5 mg) is loaded into one flask and NaH (2 equiv., 1 mmol, 25 mg) is loaded into the other. Both are capped, removed from the glove box and attached to a Schlenk argon line. 2 mL of dry THF is added to the catalyst flask, which is then stirred for 10 min at 40 °C to form the active catalyst. In the meantime, 3 mL of dry THF is added to the flask containing NaH. To the NaH containing flask is added allyl alcohol (via syringe, 0.50 mmol, 29 mg) and tetralone derivative **1a** (via syringe, 0.51 mmol, 95mg) in subsequence. Both syringes used to transfer reagents are washed with the reaction mixture solvent and reinjected. Directly after the final reagent addition, the preformed catalyst is then transferred via syringe and injected as a shot (no need to wash this syringe). The vessel is capped, wrapped in parafilm and the vessel is completely closed and allowed to react for 5h.

After the allotted reaction time as determined by TLC (5h), the reaction mixture is diluted with 15% EtOAc in hexanes and filtered through a SiO_2 Plug with excess (50-75mL) of the 15% EtOAc in hexanes solvent mixture. The solvent is evaporated and subjected to silica gel chromatography (3% EtOAc in Hexanes) to yield the pure product **22d** (83 mg, 83% yield).

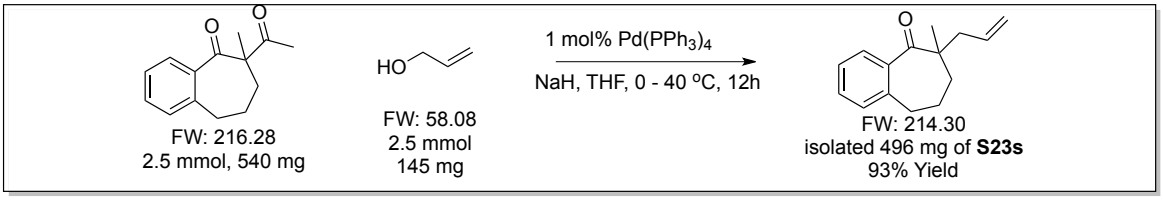
7. Representative procedure for the DaA reaction of 2-acetyl α-tetralone derivatives:



A flame-dried 10mL Schlenk flask equipped with a stir bar is brought into a glove box and charged with NaH (2 equiv. 0.50, 12mg) and $Pd(PPh_3)_4$ (2.5 mol%, 0.0063 mmol, 7.2 mg). The flask is capped, removed from the glove box and attached a Schlenk argon line. 4 mL of dry THF is added to the flask and allyl alcohol (0.25 mmol, 15 mg) and tetralone **1b** (0.255 mmol, 51 mg) are added in subsequence. Both syringes used to transfer reagents should be washed with the reaction mixture and reinjected to ensure complete transfer. The vessel is capped, wrapped in parafilm and the system is completely sealed over argon and allowed to react for 5h.

After the allotted reaction time as determined by TLC, the reaction mixture is diluted with 15% EtOAc in hexanes and filtered through a SiO_2 Plug with excess (50-75mL) of the 15% EtOAc in hexanes solvent mixture. The solvent is evaporated and subjected to silica gel chromatography (3% EtOAc in Hexanes) to yield the pure product **S22d** (44 mg, 88% yield).

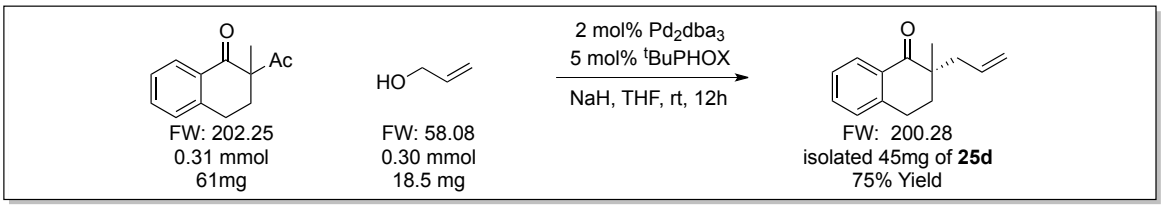
8. Representative procedure for the scale-up of the DaA reaction of 2-acetyl α-tetralone derivatives:



A flame-dried 25mL Schlenk flask equipped with a stir bar is brought into a glove box and charged with NaH (2 equiv. 5 mmol, 120 mg) and $Pd(PPh_3)_4$ (1 mol%, 0.025 mmol, 29 mg). The flask is capped, removed from the glove box and attached to a Schlenk argon line. 5 mL of dry THF is added to the flask and it is cooled in an ice-bath. Once chilled, allyl alcohol (2.5 mmol, 145 mg) and the substrate benzosubarone (2.5 mmol, 540 mg) are added consecutively. Both syringes used to transfer reagents should be washed with the reaction mixture and reinjected to ensure complete transfer of reagents. The vessel is capped, wrapped in parafilm and the system is completely sealed over argon and removed from the ice-bath. Once at room temperature the vessel is left to react in an oil bath at 40 °C for 12h.

After the allotted reaction time as determined by TLC, the reaction mixture is diluted with 15% EtOAc in hexanes and filtered through a SiO_2 Plug with excess (100 mL) of the 15% EtOAc in hexanes solvent mixture. The solvent is evaporated and subjected to silica gel chromatography (3% EtOAc in Hexanes) to yield the pure product **S23s** (496 mg, 93% yield).

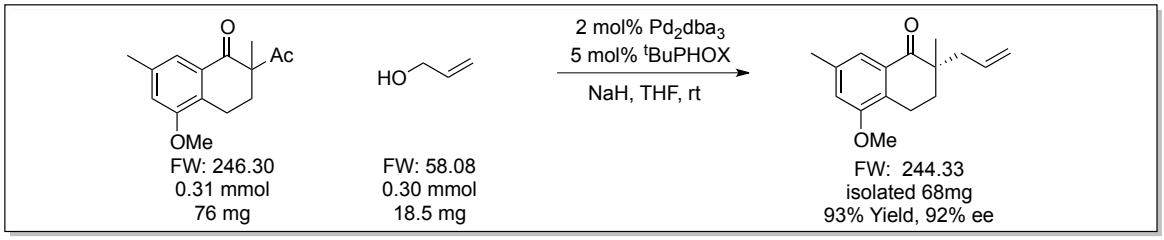
9. Representative procedure for the asymmetric DaA reaction of 2-acetyl α-tetralone derivatives:



Two flame-dried 10mL Schlenk flasks equipped with stir bars are flame dried and brought into a glove box. The catalyst (Pd_2dba_3, 2 mol % 0.005 mmol, 4.5 mg and ^{t}BuPHOX ligand, 5 mol%, 0.0125 mmol, 4.9 mg) is loaded into one flask and NaH (2 equiv. 0.50, 12mg) is loaded into the other. Both are capped, removed from the glove box and attached to a Schlenk argon line. 2 mL of dry THF is added to the catalyst flask, which is then stirred for 10 min at 40 °C to form the active catalyst. In the meantime, 3 mL of dry THF is added to the flask containing NaH. To the NaH containing flask is added allyl alcohol (via syringe, 0.30 mmol, 18.5 mg) and tetralone derivative **1a** (via syringe, 0.31 mmol, 62mg) in subsequence. Both syringes used to transfer reagents are washed with the reaction mixture solvent and reinjected. Directly after the final reagent addition, the preformed catalyst is then transferred via syringe and injected as a shot (no need to wash this syringe). The vessel is capped, wrapped in parafilm and the vessel is completely closed and allowed to react for 5h.

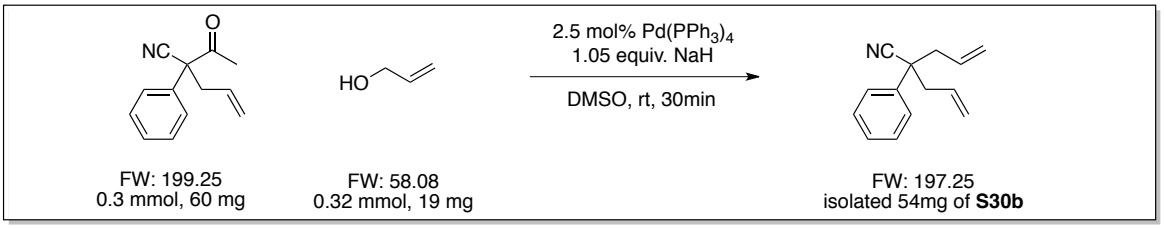
After the allotted reaction time as determined by TLC (5h), the reaction mixture is diluted with 15% EtOAc in hexanes and filtered through a SiO_2 Plug with excess (50-75mL) of the 15% EtOAc in hexanes solvent mixture. The solvent is evaporated and subjected to silica gel chromatography (3% EtOAc in Hexanes) to yield the pure product **22d** (83 mg, 83% yield, 80% ee). Using HPLC chiral resolution on a Chiralcel OD-H column, the ee was determined.

10. Representative procedure for the synthesis of the (+)-hamigeran precursor:



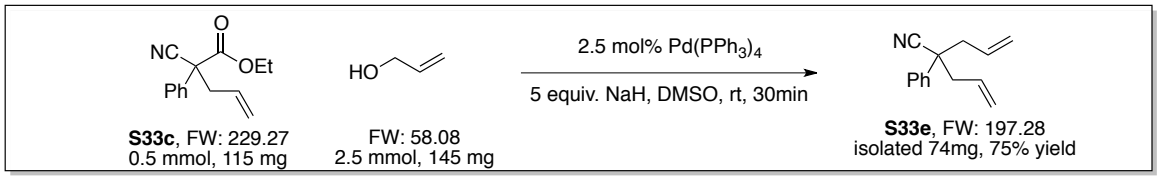
"Procedure 9" above is used to prepare the (+)-hamigeran precursor. Chiral resolution:

11. Representative procedure for the DaA reaction of α-phenyl cyanoacetone derivatives:



"Procedure 5" was used to prepare allylated nitriles via DaA.

12. Representative procedure for the retro-Claisen allylation of ethyl α-phenyl cyanoacetate derivatives:

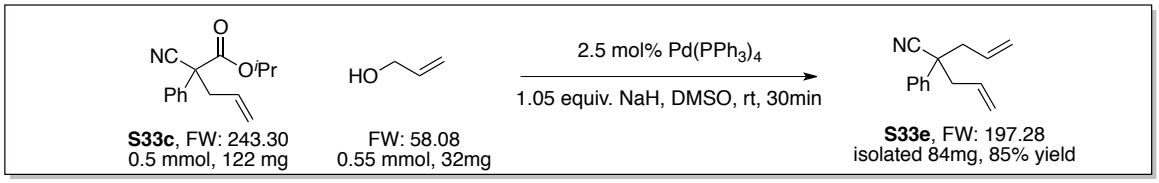


A flame-dried 10 mL Schlenk flask equipped with a stir bar is brought into a glove box and charged with $Pd(PPh_3)_4$ (2.5 mol%, 0.0125 mmol, 14 mg) and 95% NaH (0.5 mmol, 12.5 mg). 3 mL of anhydrous DMSO is added to the vessel, which is then capped, removed from the

glove box and attached to a Schlenk-argon line. Allyl alcohol (2.5 mmol, 145 mg) is dripped into the stirring reaction mixture. The substrate ethyl cyanoacetate (0.5 mmol, 115 mg) is then added neat dropwise via syringe. The vessel is then capped and stirred at rt for 30 min.

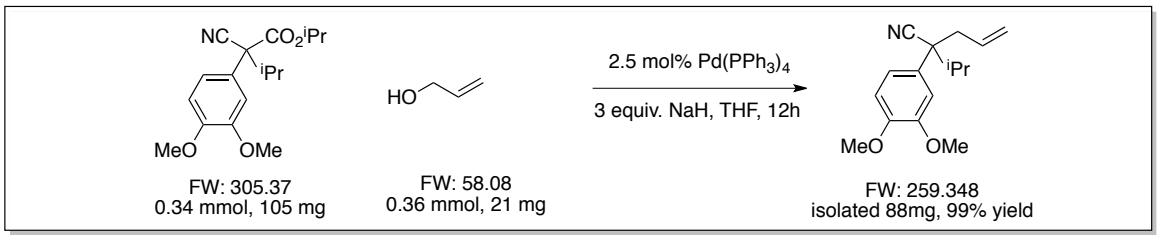
After the allotted reaction time (30 min.), the reaction mixture is transferred to a seperatory using EtOAc (total volume ~ 25 mL). The organic layer is extracted with 1N HCl (2 x 25 mL) followed by brine (25 mL). The volatile organics are removed by rotary evaporation and the oily residue is subjected to column chromatography (3 % EtOAc in hexanes) to yield the desired product **S33e** (74 mg, 75% yield).

13. Representative procedure for the retro-Claisen allylation of isopropyl α-phenyl cyanoacetate derivatives:



"Procedure 12" is utilized with the exception that the equivalents of allyl alcohol and NaH are reduced to 1.05 equiv.

14. Representative procedure for the synthesis of a verapamil precursor via retro-Claisen allylation:



A flame-dried 10 mL pressure vial is charged with NaH (0.70 mmol, 17.7 mg, 2 equiv.)

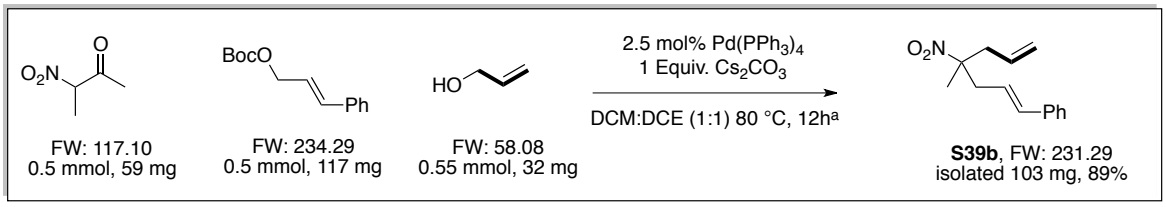
in a glove box. The vessel is capped with a rubber injectable septum capable of holding pressure (Biotage microwave vessel was used) and removed from the glove box. The vessel is connected to an argon line via needle to bleed the vessel of impending pressure from H_2 effervescence. 1.5 mL of THF is added and while stirring, a solution of allyl alcohol in 0.5 mL of THF is added. Rapid H_2 effervescence occurs. The transfer syringe is washed with an additional 0.5 mL portion of THF. The cyanoacetate substrate is then added in 0.5 mL of THF via syringe. The transfer vessel is washed with an additional 0.5 mL portion of THF. The argon bleed is removed and the vessel is placed in an oil bath at 100 °C for 10min. The vessel is then cooled to room temperature and THF solution of $Pd(PPh_3)_4$ is injected. The vessel is then stirred for 12 h.

After the allotted reaction time, the cap is removed and vessel's contents are transferred to a seperatory funnel with the aid of 2 x 5 mL portions of EtOAc. The organic layer is extracted with 0.5 M HCl and brine. The organic layer is then dried over magnesium sulfate and evaporated.

88 mg (99% Yield) of pure product is obtained by silica gel chromatography: 11-13% EtOAc in Hexanes.

General procedures for the 3-component unsymmetric bisallylation:

15. 3- component bisallylation of α-nitroketones:

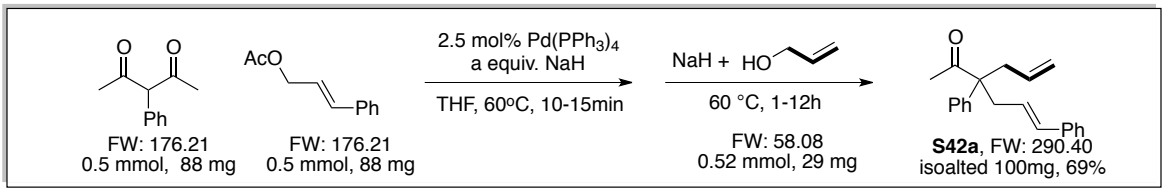


In a glove box under an argon atmosphere, a flame dried pressure vial equipped with a

septum was charged with Pd(PPh3)4 (14 mg, 0.0125 mmol) and Cs_2CO_3 (165 mg, 0.5 mmol). Anhydrous DCE (1 mL) was added and the vial sealed. After removing the vial from the glove box, a solution of α-methyl nitroacetone (58 mg, 0.5 mmol) and *tert*-butyl cinnamyl carbonate (117 mg, 0.5 mmol) in dry DCM (1 mL) was added via syringe and the transfer vessel was washed with 0.5 mL of DCM to ensure complete transfer of the substrates to the reaction mixture. Next, allyl alcohol (36 mg, 0.6 mmol) was injected via syringe and the resulting pressure vial was submerged in an oil bath at 80 °C and left to stir overnight.

After the allotted reaction time, the vessel was cooled to room temperature and the resulting solution was diluted with 15% EtOAc/hexanes (~5 mL) and eluted through a silica plug with excess 15% EtOAc/hexanes (~50-75 mL). After removal of the volatiles via rotary evaporation, the crude oil was subjected to column chromatography (gradient column: 2% EtOAc/Hexanes) yielding the pure product **S39b** as a colorless oil (103 mg, 89% Yield).

16. 3-component bisallylation of α-phenyl acetylacetone derivatives:



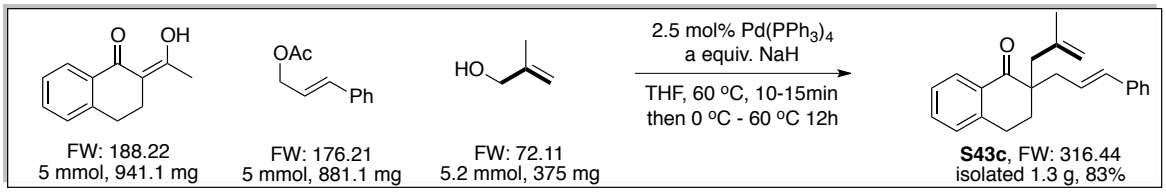
2 10 mL flame-dried Schlenk flasks equipped with stir bars are brought into a glove box. The first charged with $Pd(PPh_3)_4$ (2-3 mol%, 6-8 mg, FW:1155.57) and NaH (0.50 mmol, 12.5 mg, FW: 24.00/95% purity). The other is charged with NaH (0.55 mmol, 13.5 mg, FW: 24.00) and capped. The vessels are removed from the glove box. Outside the glove box the vessels are attached to a Schlenk apparatus. Over argon, freshly distilled THF (3 mL) is added to the reaction mixture containing Pd and stirred. α-phenyl acetylacetone (0.5 mmol, 88 mg) is added

neat to the reaction mixture. Cinnamyl acetate (0.5 mmol, 88 mg) is added neat dropwise to the reaction mixture. This transfer syringe is rinsed in the reaction mixture to ensure complete transfer of the acetate. This mixture is then submerged in an oil bath for 5-15 min. to allow the Tsuji-Trost to complete as monitored by TLC. Once complete, remove from the oil bath and allow to warm to rt.

In the mean time, the other vessel, which only contains the NaH, is charged with 2 mL of dry THF and allyl alcohol (0.52 mmol, 29 mg) is added neat dropwise. Rinse the transfer syringe in the alkoxide solution to ensure complete transfer of the substrate allyl alcohol. Transfer this alkoxide solution to the reaction mixture once the first Tsuji-Trost reaction is complete.

After the allotted reaction time as determined by TLC, work up the reaction as normal (see "procedure 3"). 100 mg of the desired product **S42a** is isolated by column chromatography (3 % EtOAc in hexanes).

17. *Improved procedure for scale-up 3-component bisallylation of α-tetralone derivatives:*

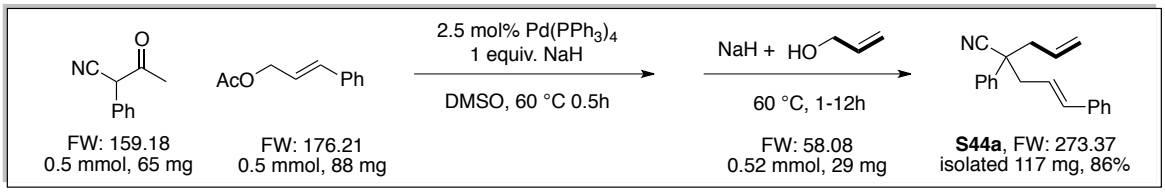


A flame-dried 25 mL Schlenk flask equipped with a stir bar is brought into a glove box and charged with NaH (2.1 equiv. 10.5 mmol, 253 mg) and $Pd(PPh_3)_4$ (3 mol%, 0.15 mmol, 173 mg). The flask is capped, removed from the glove box and attached to a Schlenk argon line. 10 mL of dry THF is then added. Acetyl tetralone (5 mmol, 940 mg) is added as a solid slowly as

effervescence occurs. Once effervescence ceases and all tetralone has been added, cinnamyl acetate (5 mmol, 880mg) is added dropwise and the mixture is heated at 60 °C for 10 min to allow the Tsuji-Trost reaction to complete (TLC analysis showed product/reagent overlap, thus mini-workup/^{1}H-NMR was used to determine reaction completion). Once the initial Tsuji-Trost reaction is complete, cool the vessel in an ice-bath and slowly drip in β-methylallyl alcohol (5 mmol, 361 mg) via syringe. Rinse the syringe with the reaction solvent and reinject to ensure complete alcohol transfer. Cap the vessel and completely seal the vessel over argon. The vessel is then heated in an oil bath at 60 °C for 12h.

After the allotted reaction time (12h), the reaction mixture is diluted with 15% EtOAc in hexanes and filtered through a pad of silica gel with excess 15% EtOAc in hexanes (100mL). The solvent is evaporated and subjected to silica gel chromatography (3% EtOAc in Hexanes) to yield the pure product **S43c** (1.3 g, 83% yield).

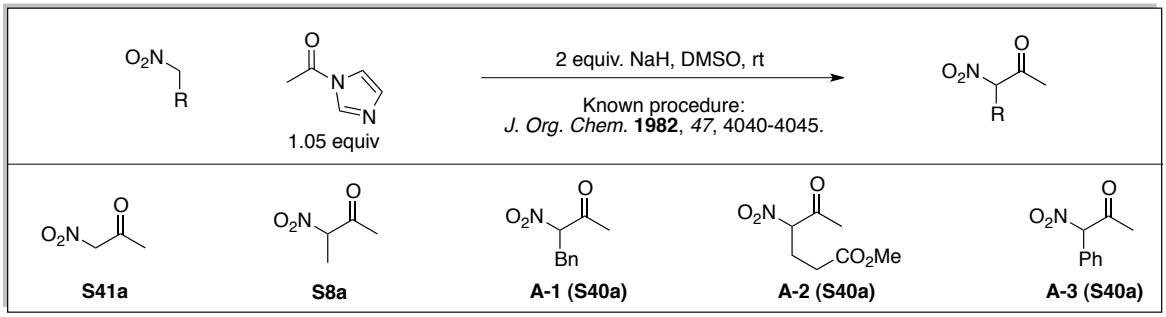
18. 3- component bisallylation of α-phenyl cyanoketone derivatives:



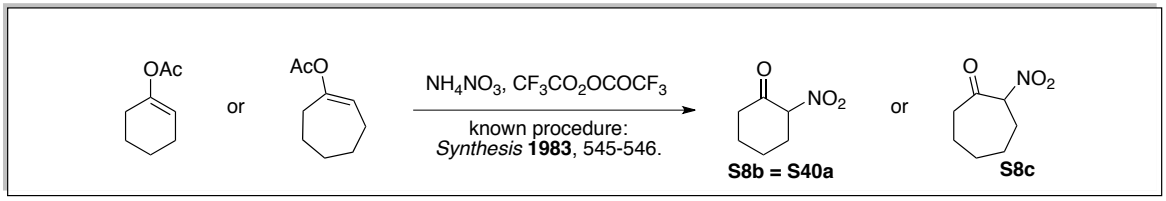
"Procedure 16" is used to prepare nitrile based 1,6-heptadienes.

Synthesis of α-nitroketones:

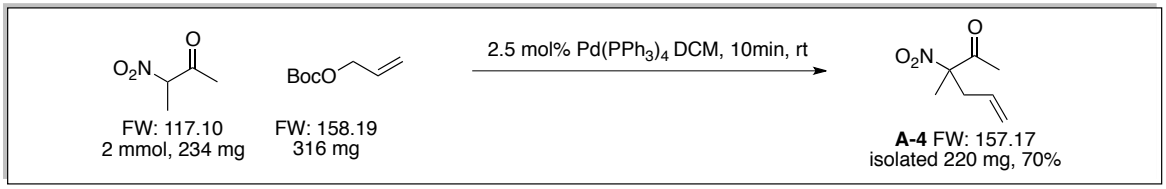
19. Synthesis of α-nitroketones from nitroalkanes:[2]



20. Synthesis of α-nitroketones from cyclic enol acetates:[3]



21. Tsuji-Trost allylation of α-nitroketones:

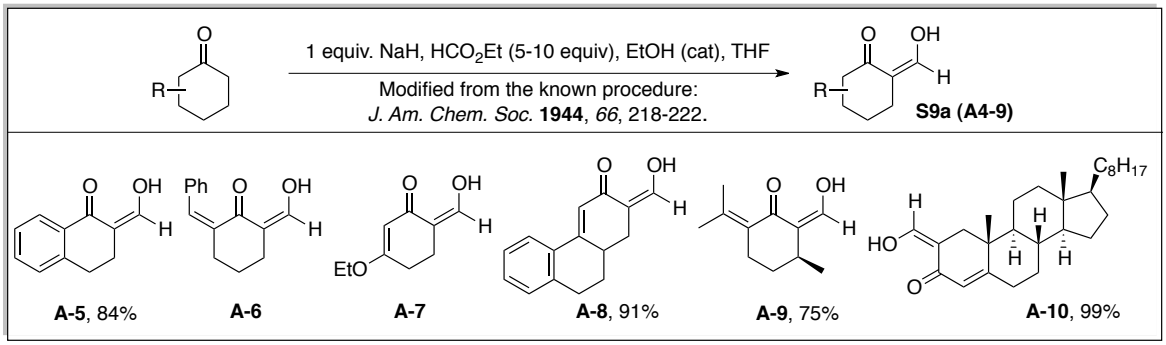


A flame-dried 10-mL Schlenk flask equipped with a stir bar is brought into a glove box and charged with $Pd(PPh_3)_4$ (2.5 mol%, 0.050mmol, 57 mg). The vessel is then capped, removed from the glove box, and attached to a Schlenk-argon line. The catalyst is then dissolved in 1 mL of anhydrous DCM. A mixture of nitroketone (234 mg, 2mmol) and allyl *tert*-butyl carbonate (234 mg, 1 mmol) is dissolved in 1 mL of DCM and injected into the reaction mixture. The

syringe is then washed with 100 μL of DCM and reinjected. Rapid effervescence ensues upon injection. The mixture is stirred for 10 min. Without reaction work-up, the mixture is put directly onto a silica gel column and eluted with EtOAc/Hexanes (3.5 % EtOAc). 220 mg of product was isolated upon evaporation (70% Yield).

Synthesis of β-carbonyl ketones:

22. Formylation of ketones by Claisen condensation:[4]

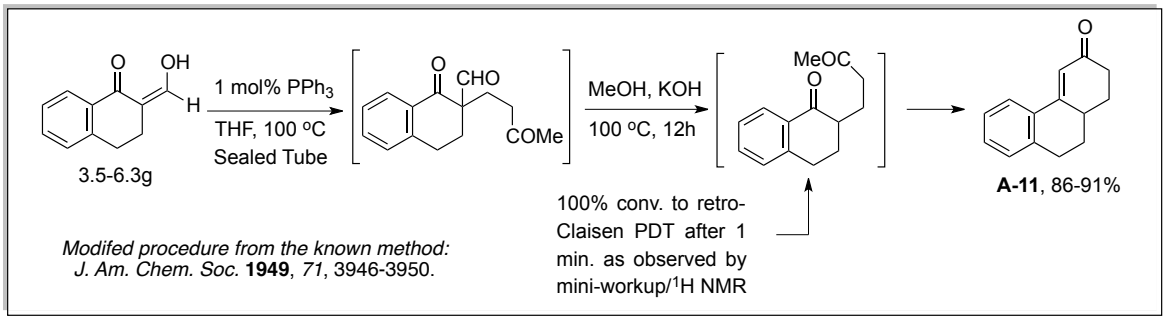


A flame-dried 500 mL Schlenk flask equipped with a stir bar is brought into a glove box and charged with 95% NaH (72 mmol, 1.82g). The vessel is capped, removed from the glove box and attached to a Schlenk-argon line. 200 mL of dry THF is added and the slurry is stirred. 1 mL of EtOH is added to the reaction vessel dropwise. The ketone (70 mmol) is loaded into a dripping funnel and dissolved in 100 mL of ethyl formate. Slowly (over 30 min.) drip the substrate mixture into the reaction vessel. After complete addition the dripping funnel is removed

and replaced with a rubber septum. The reaction mixture is left to stir over argon for 12h (do not seal, pressure builds up over time).

After the allotted reaction time, add 200 mL of water and transfer to a seperatory funnel. A small amount (~10 mL) of 1N NaOH is added to the seperatory funnel. Wash the reaction flask with 150 mL of EtOAc and transfer into seperatory funnel. Extract the water layer with 2 x 150 mL of EtOAc and discard the organic layer. The basic water layer is acidified with 1N HCl until acidic. The now acid water layer is extracted with 2 x 200 mL portions of Et_2O. The ether layer is dried over $MgSO_4$ and the volatiles are evaporated to yield the desired product. Commonly, the β-formyl ketone was of sufficient purity for direct use in the next reaction. However, purification by Kugelrohr distillation could also be performed.

*23. Synthesis of latter cyclohexanone **A-11** by Wilds-Woodward reaction:*[5]



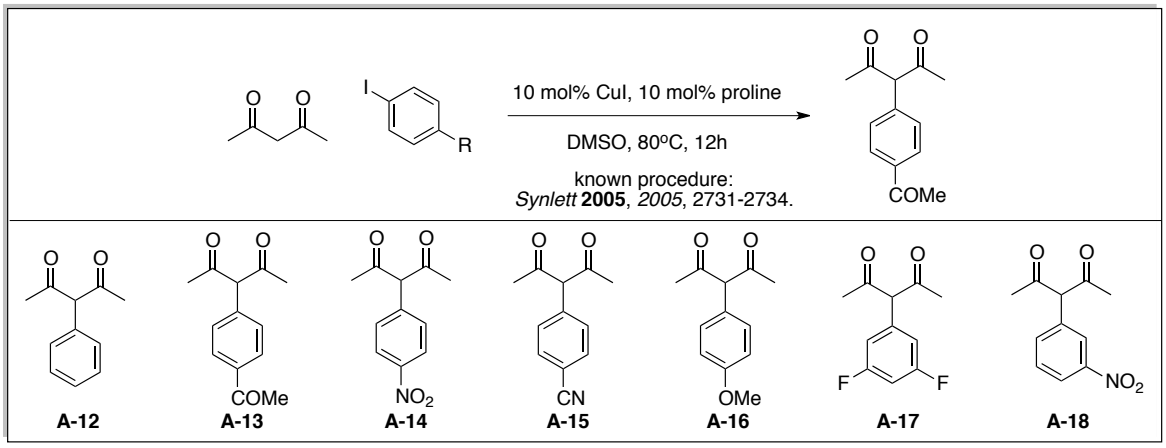
A 20 mL μW vial is equipped with a stir bar and charged with PPh_3 (1 mol% 0.2 mmol, 52 mg). β-formyl α-tetralone (20 mmol) is then added to the vessel. Methyl vinyl ketone (100 mmol, ~ 8 mL) and ~5 mL of THF are added in subsequence to the reaction vessel. The vial is then capped with a rubber septum capable of with standing moderate pressure and submerged in an oil bath at 100 °C for 30 min.

After the allotted reaction time, the contents are cooled and poured directly into a 500 mL round-bottom flask. The original vial is washed with 2 x 5 mL of MeOH to ensure complete

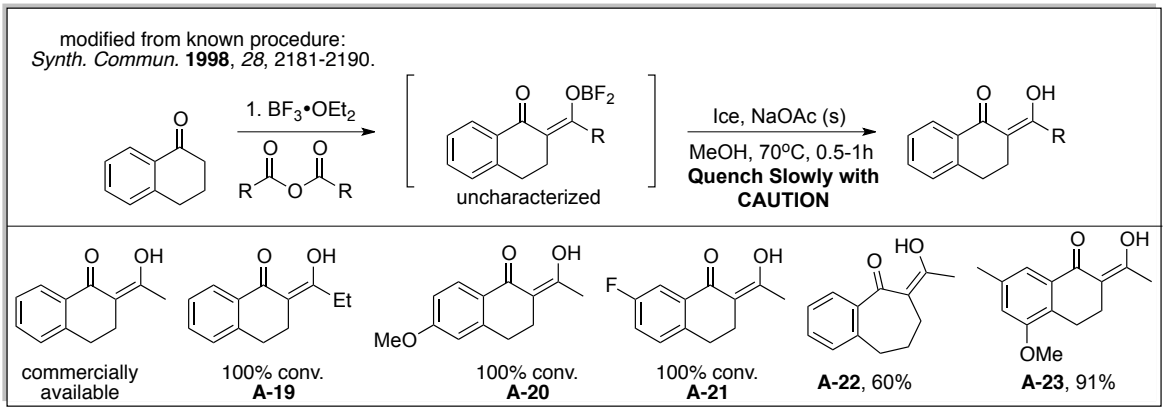
transfer to the new vessel. An additional 100 mL of MeOH and a stir bar are then added to the round-bottom flask. While stirring, a 1:1 mixture of MeOH:H_2O containing 3.33 g of KOH is poured in over 1 min. Immediately after pouring in the basic solution the reaction mixture turns dark red (NMR analysis shows complete aldehyde removal). The vessel and its contents are then refluxed over night.

After reaction overnight, cool the reaction mixture to room temperature and transfer the reaction mixture to a seperatory funnel. Wash the reaction vessel with 2 x 400 mL portions of water and 1 x 500 mL portion of EtOAc to ensure complete transfer. 1N HCl is added until the reaction mixture is acidic (~20 mL). Collect the organic layer and rewash the water layer with an addition 100 mL of EtOAc. Combine the organic layer, dry over $MgSO_4$, and evaporate. Silica gel chromatography yields the pure product (20 % EtOAc in hexanes).

24. Cu-catalyzed arylation of acetylacetone:[6]



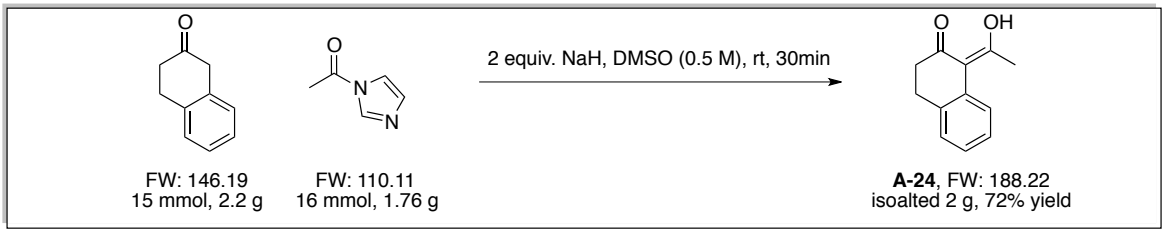
25. Synthesis of β-acetyl-diketones:[7]



A flame-dried 500 mL Schlenk flask equipped with a stir is attached to a Schlenk-argon line and α-tetralone derivative (14 mmol) is added. 25 mL of acetic anhydride is then added and the reaction mixture is stirred. Via syringe, 7.5 mL of $BF_3 \square OEt_2$ is added dropwise over 1 min. The reaction vessel is then capped and stirred 2h.

After the allotted reaction time, a large "handful" of ice is added piece by piece to quench the reaction. 40 mL of MeOH is then added to this ice slurry followed by 30 g of NaOAc. The reaction mixture is then heated at 70 °C for 45 min. The reaction mixture is then poured into a seperatory funnel. The reaction flask is then washed with 200 mL of EtOAc to ensure complete transfer. An additional 100 mL of EtOAc is added to the seperatory funnel. The organic layer is then extracted with 3 x 100 mL portions 1N HCl followed by brine (~50 mL). The organic layer is dried over $MgSO_4$, and the volatiles are removed by rotary evaporation. Residual acetic acid is removed azeotropically with toluene. Column chromatography yields the desired β-acetyl tetralone derivative.

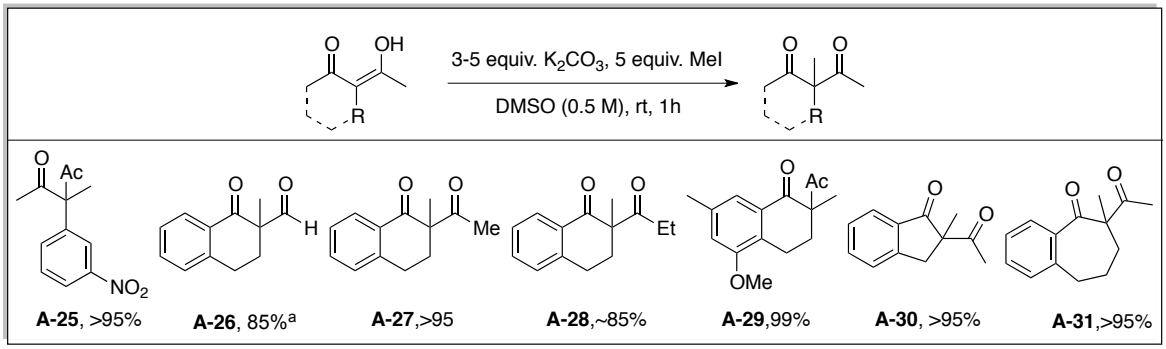
26. Synthesis of acetyl-β-tetralone:



A flame-dried 500 mL Schlenk flask equipped with a stir bar is brought into a glove box and charged with 95% NaH (30 mmol, 760 mg). The vessel is capped, removed from the glove box and attached to a Schlenk-argon line. 30 mL of anhydrous DMSO is added to the NaH and the mixture is stirred. β-Tetralone (15 mmol, 2.2g) is added neat dropwise over 5 min and H_2 effervescence occurs. An additional 5 mL of DMSO is utilized to rinse the sides of the flask. Once H_2 effervescence ceases acetyl imidazole (16 mmol, 1.76 g) is added as a solid over 5 min. Again, 5 mL of DMSO is used to rinse the sides of the flask. The reaction mixture is then stirred for 30 min.

After the allotted reaction time, The reaction mixture is Diluted with 150 mL of EtOAc followed by 150 mL of 1N HCl. The biphasic mixture is then transferred to a seperatory funnel. The water-layer is extracted by with 2 x 100 mL portions of EtOAc. The organic layers are collected, dried over $MgSO_4$, and the volatiles are removed by rotary evaporation. The crude acetylated β-tetralone **A-24** is used as is.

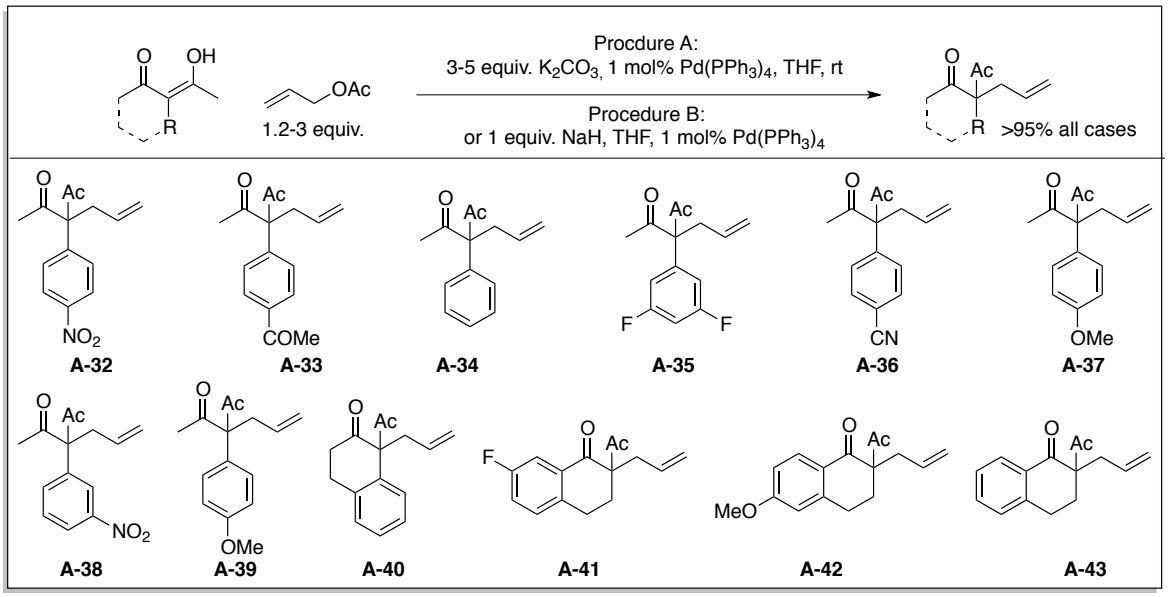
27. Methylation of β-diketones:



A 25 mL Schlenk flask equipped with is charged with K_2CO_3 (9 mmol), flame-dried and attached to a Schlenk-argon line. The β-diketone (3 mmol) is then added to the reaction vessel. 6 mL of DMSO is then added to the vessel. While stirring, 5 equiv. of MeI is added as a shot. The reaction vessel is seal and stirred at room temperature for an hour.

The reaction mixture is then diluted with EtOAc (~20 mL) and transferred to a seperatory funnel. The reaction vessel is then washed with an addition 20 mL of EtOAc to ensure complete transfer. The organic layer is then extracted with 2 x 25 mL portions of 1N HCl followed by brine (1 x 25 mL). The organic layer is dried over $MgSO_4$ and the volatiles are evaporated yielding the crude product. Silica gel chromatography yields the desired product.

28. Tsuji-Trost allylation (with allyl acetate) of β-diketones:



Procedure A:

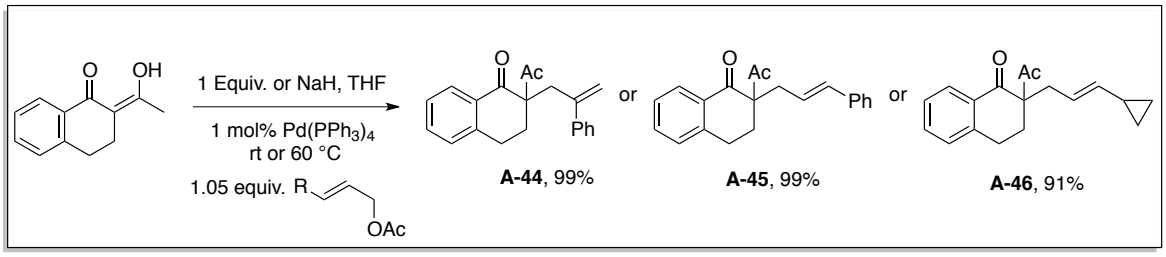
A flame-dried 25 mL Schlenk flask equipped with a stir bar and K_2CO_3 (9 mmol) is brought into a glove box and charged with $Pd(PPh_3)_4$ (1 mol%). The vessel is capped, removed from the glove box and attached to a Schlenk-argon line. 5 mL of THF is added to the flask followed by the substrate diketone (3 mmol) via syringe. The syringe is then rinsed in the reaction mixture to ensure complete transfer. Allyl acetate (often in excess as it can easily be removed by rotary evaporation) is added as a shot and the reaction mixture is stirred at room temperature until reaction completion (1-12h) as monitored by TLC. Heating to 60 °C could also be done to speed up the reactions with no noticeable effect on the yields.

Once the reaction is complete, the reaction mixture is diluted with 15% EtOAc in hexanes and filtered through a pad of SiO_2. The vessel and the silica plug are rinsed with 50-75 mL of the 15% EtOAc solution. Evaporation followed by column chromatography yields the pure compounds **A32-43**.

Procedure B:

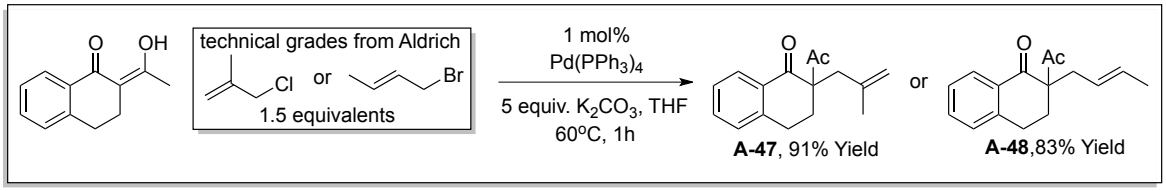
The difference in this procedure is that 1 equiv. of NaH is used in lieu of 3-5 equiv. of K_2CO_3. As a full anion is formed, this reaction is often faster and just as high yielding.

29. Tsuji-Trost allylation (with various allyl acetates) of β-diketones:



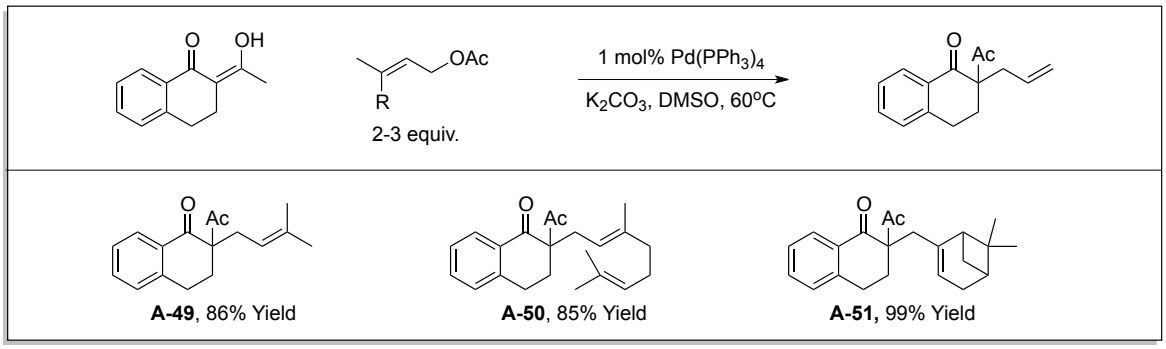
"Procedure 28B" is utilized with the exception that only a single equivalent of the allyl acetate derivative is used as these allyl acetates are nonvolatile and/or more precious.

30. Tsuji-Trost allylation (with technical grade allyl halides) of β-diketones:



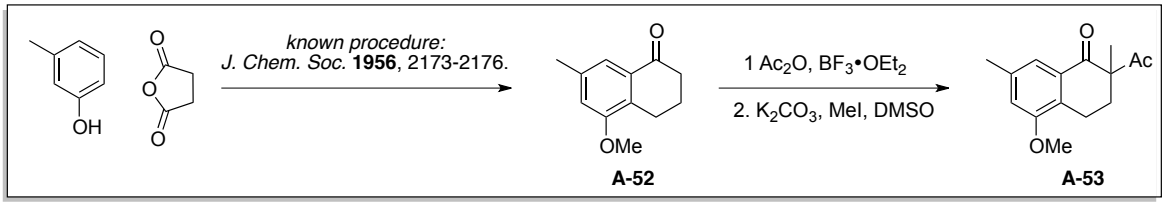
"Procedure 28A" is utilized to couple the technical grade allyl halides.

31. Tsuji-Trost allylation (with terpene allyl acetates) of β-diketones:



"Procedure 28A" is used to couple terpene-based allyl acetates. Excess of the terpene allyl acetate was required for the reaction to go to 100% conversion, presumably due to β-elimination.

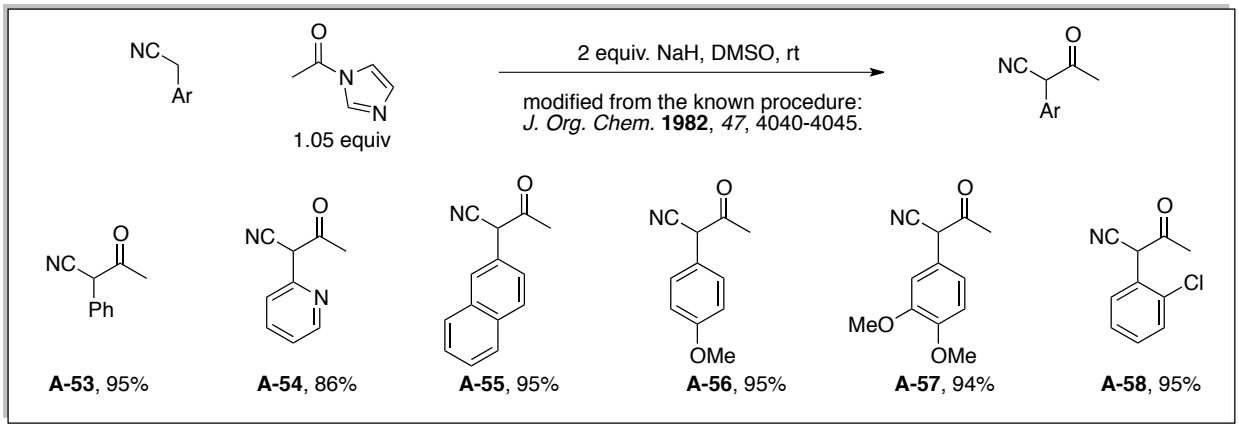
32. Synthesis of the (±)-hamigeran precursor β-diketone:[8]



From the known tetralone **A-52**, the (±)-hamigeran precursor β-diketone **A-53** is prepared using "procedures 25 and 27," respectively.

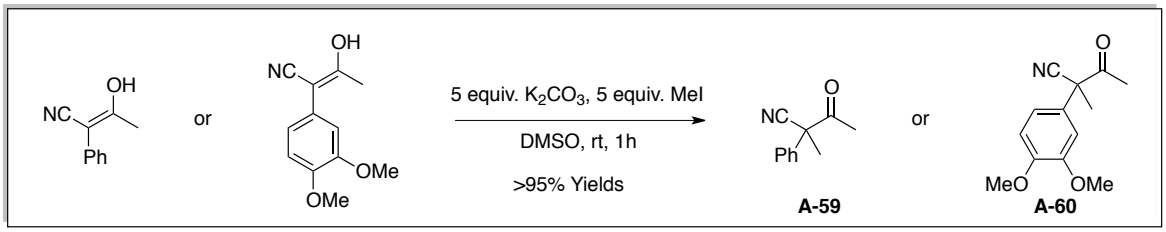
Synthesis of α-cyano ketones and esters:

33. Synthesis of α-aryl cyanoketones from benzyl cyanides:



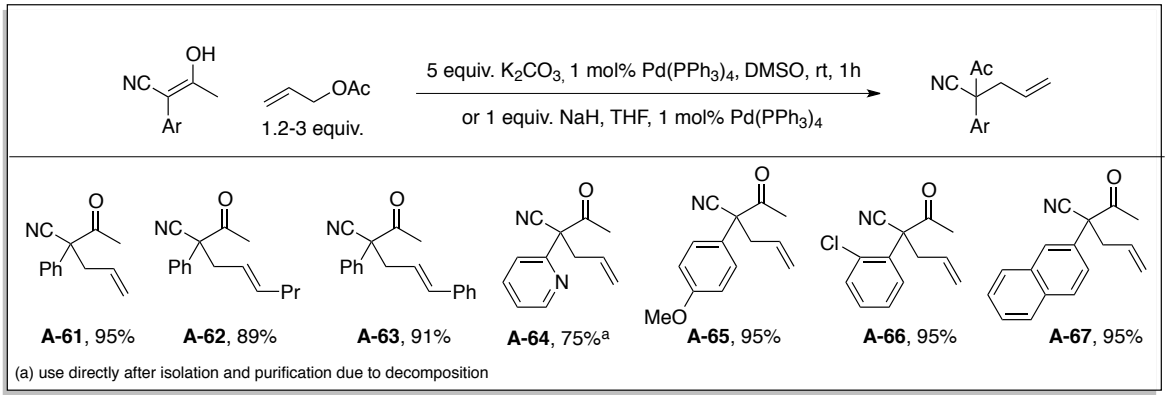
"Procedure 26," which prepared acetylated β-tetralone was utilized. In turn, this procedure was based on a reported procedure for the acetylation of nitroalkanes.

34. Methylation of α-aryl cyanoketones:



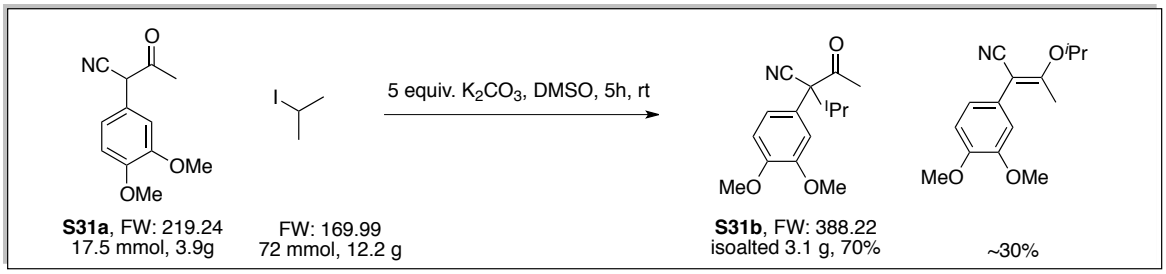
"Procedure 27" for the methylation of β-diketones was utilized without incident.

35. Tsuji-Trost allylation of α-aryl cyanoketones:



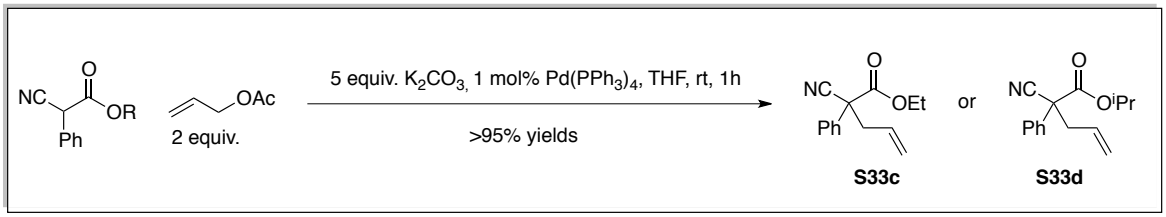
"Procedure 28," for the Tsuji-Trost allylation of β-diketones, was utilized.

36. Synthesis of cyanoketone based verapamil precursor:



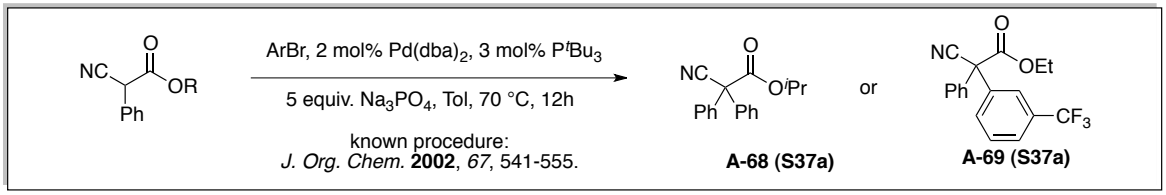
A flame-dried 50 mL Schlenk flask is charge with 10 g of K_2CO_3 (72 mmol, FW = 138). 10 mL of DMSO is added and the slurry is stirred. To this stirring mixture, acetyl homoveratronitrile (17.5 mmol, 3.9 g) is added as a solid. The sides of the vessel are washed with 10 mL DMSO. This ensures all reacts are in the solution. 2-iodopropane (72 mmol, 12.17 g) is added via syringe in a single shot. After 4 hours, the reaction is complete (monitor by NMR via aliquot removal). The reaction is transferred to a seperatory funnel and diluted with ~40 mL EtOAc. The organic layer is extracted with 2 x 50 mL portions of aqueous $NaHCO_3$ followed by brine (25 mL). The oganic layer is then dried, the volatiles are evaporated by rotary evaporation and the oily residuce is purified by gradient column chromatography, 10-15% w/v EtOAc in hexanes.

37. Tsuji-Trost allylation of cyanoacetic esters:

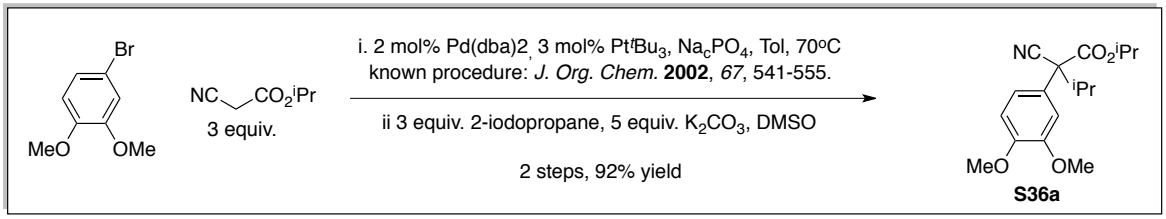


"Procedure 28" is utilized.

38. Pd-catalyzed arylations of cyanoacetic esters:[9]



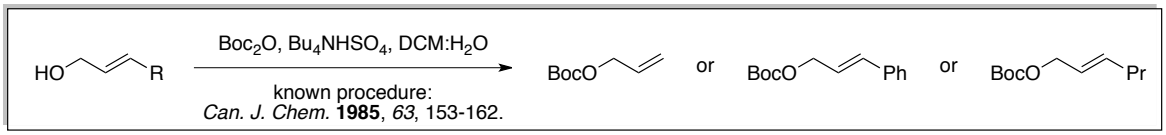
39. Synthesis of verapamil precursor substrate from cyanoacetic ester:[9]



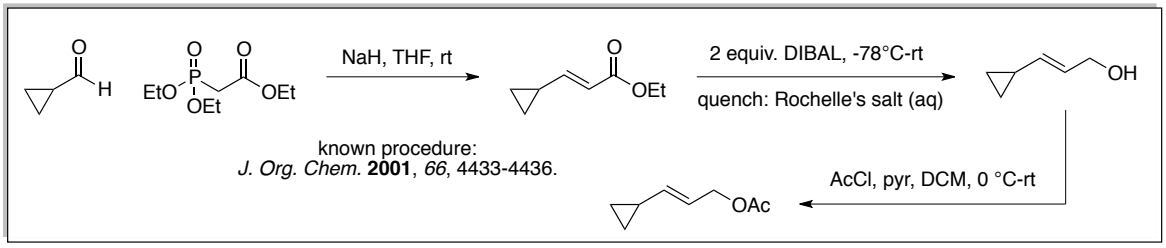
Hartwig's known coupling or aryl bromides and cyano acetate is utilized in the first step of this reaction. "Procedure 27" is used to methylate the intermediate to arrive at the quaternized starting material **S36a**.

Synthesis of allyl alcohols, acetates and carbonates:

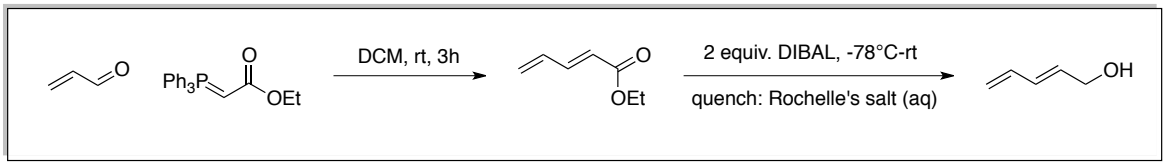
40. Synthesis of various allyl tert-butyl carbonates[10]



41. Synthesis of cyclopropylallyl alcohol and acetate:[11]

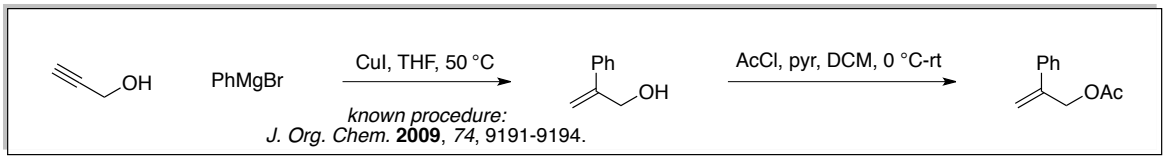


42. Synthesis of dienylallyl alcohol

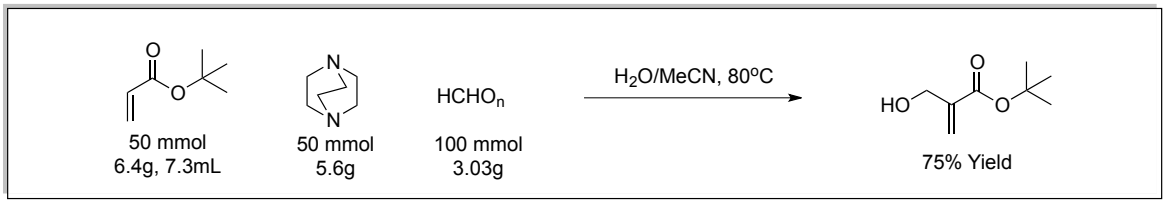


"Procedure 34" is utilized with acrolein in lieu of cyclopropyl carbaldehyde.

43. Synthesis of β-phenylallyl alcohol and acetate:[12]



44. Synthesis of Baylis-Hillman adduct allyl alcohol

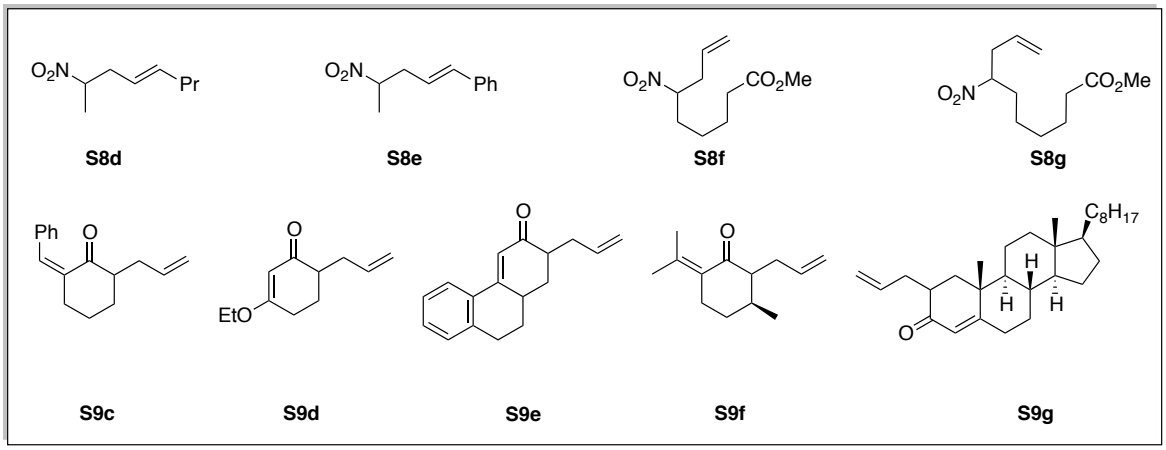


A 250 mL round-bottom flask equipped with a stir bar is charged with DABCO (50 mmol, 5.6g). 30 mL of H_2O is then added followed by paraformaldehyde (100 mmol, 3.03 g). MeCN is then added with heating at 80 °C until the reaction mixture is homogeneous (~30 mL). *Tert*-butyl acrylate(50 mmol, 6.4 g, 7.3 mL) is then added as a shot. The reaction mixture is heated for 2.5 h.

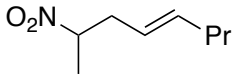
After the allotted reaction time, the reaction mixture is diluted with 100 mL of DCM and transferred to a seperatory funnel. An additional 100 mL DCM is used to wash the reaction vessel to ensure complete transfer. The DCM layer is then extracted with 100 mL of 1N HCl followed by brine (50 mL). The volatiles are removed by rotary evaporation and the crude oil is subjected to column chromatography (20% EtOAc in hexanes) to yield the desired product **A-62**.

Spectral and chromatographic data:

1. Tertiary nitroalkanes and ketones:



S8d:



^{1}H NMR (500 MHz, $CDCl_3$):

δ = 5.48 (dt, *J* = 14.4, 6.9 Hz, 1H), 1H), 5.23 (dtt, *J* = 14.5, 7.2, 1.4 Hz, 1H), 4.48 (apparent sextet, *J* = 6.7 Hz, 1H), 2.57 (dt, *J* = 14.6, 7.4 Hz, 1H), 2.37 (dt, *J* = 13.6, 6.6 Hz, 1H), 1.90 (apparent q, *J* =6.7 Hz, 2H), 1.45 (d, *J* =5.2 Hz, 3H), 1.29 (apparent sextet, *J* = 7.4 Hz, 2H), 0.81 (t, *J* =7.3 Hz, 3H).

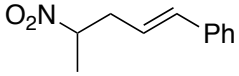
^{13}C NMR (126 MHz, $CDCl_3$):

δ = 134.3, 121.2, 81.7, 36.7, 32.9, 20.7, 16.9, 11.9.

GC-MS:

e/z: found 157.1 (M-NO2) 46 (NO_2^+).

S8e:



^{1}H NMR (500 MHz, $CDCl_3$):

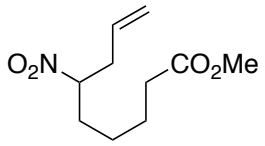
δ = 7.25 (m, 4H), 7.20 – 7.14 (m, 1H), 6.43 (d, *J* =15.8 Hz, 1H), 6.00 (dt, *J* =15.7, 7.3 Hz, 1H), 4.60 (apparent sextet, *J* = 13.4, 6.6 Hz, 1H), 2.82 (dtd, *J* = 14.7, 7.4, 1.3 Hz, 1H), 2.59 (dtd, *J* = 14.0, 7.3, 1.3 Hz, 1H) 1H), 1.52 (d, *J* =6.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ = 136.5, 134.6, 128.6, 127.8, 126.3, 122.5, 82.9, 38.5, 18.7.

GC-MS *e/z*: found 191.2 (M^+), 145.2 (M-NO2) 46 (NO_2^+).

S8f:



^{1}H NMR (500 MHz, $CDCl_3$):

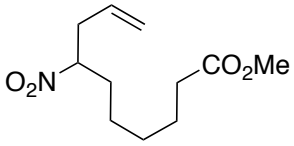
δ = 5.62 (m, 1H), 5.09 (d, *J* = 6.4 Hz, 1H), 5.08 (d, *J* = 10.5, 1H) 4.44 (m, 1H), 3.60 (s, 3H), 2.60 (dt, *J* = 15.4, 8.1 Hz, 1H), 2.42 (dt, *J* = 13.3, 6.1 Hz, 1H), 2.25 (t, *J* =7.3 Hz, 2H), 2.93 (m, 1H), 1.62 (m, 3H), 1.30 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ = 173.6, 131.4, 119.6, 87.9, 51.6, 37.9, 33.6, 32.9, 25.2, 24.2.

GC-MS *e/z*: found 157.1 (M-NO2) 46 (NO_2^+).

S8g:



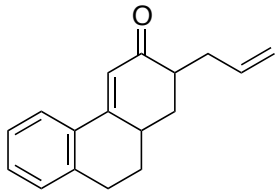
^{1}H NMR (500 MHz, $CDCl_3$):

δ = 5.63 (m, 1H), 5.08 (d, *J* = 7.5 Hz, 1H), 5.07 (d, *J* = 10.0 Hz, 1H) 4.43 (m, 1H), 3.61 (s, 3H), 2.61 (dt, *J* = 15.3, 8.1 Hz, 1H), 2.41 (dt, *J* = 13.3, 6.0 Hz, 1H), 2.23 (t, *J* =7.4 Hz, 2H), 1.92 (m, 1H), 1.66 (m, 1H), 1.55(m, 2H), 1.28 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ = 173.9, 131.5, 119.4, 88.1, 51.5, 37.9, 33.8, 33.0, 28.4, 25.4, 24.5. MS *e/z*: found 229.3 (M^+) 182.3 (M-NO2) 46.0 (NO_2^+).

S9e:



Single diastereomer, relative stereochemistry currently unknown

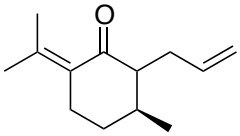
^{1}H NMR (500 MHz, CDCl3)

δ 7.70 (d, *J* = 7.9 Hz, 1H), 7.24 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 5.76 (m, 1H), 5.01 (m, 2H), 2.92 (ddd, *J* = 17.1, 12.8, 4.6 Hz, 1H), 2.87 (m, 1H), 2.72 (m, 1H), 2.63 (m, 1H), 2.36 (m, 1H), 2.15 (dt, *J* = 13.02, 4.15 Hz, 1H), 2.10 (dd, *J* = 14.12, 6.72 Hz, 1H), 1.99 (ddd, *J* = 12.6, 6.8, 4.2 Hz, 1H), 1.53 (m, 2H).

^{13}C NMR (126 MHz, CDCl3)

δ 200.93, 157.65, 139.69, 136.38, 131.23, 130.49, 129.67, 126.61, 125.28, 120.39, 116.75, 45.61, 37.59, 35.52, 33.74, 30.60, 29.99.

S9f:



Isolated at a ~3:1 mixture of diastereomers:

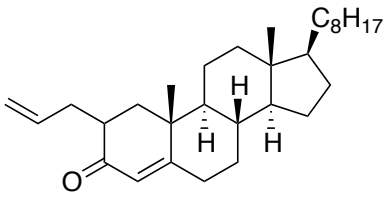
^{1}H NMR (500 MHz, CDCl3):

δ 5.69 (m, 1H), 4.93 (m, 3H), 2.50 (m, 1H), 2.41 (m, 3H), 2.27 (m, 3H), 2.00 (m, 2H), 1.83 (t, *J* = 1.4 Hz, 3H), 1.75 (m, 4H), 1.68 (s, 4H), 1.61 (m, 1H), 1.32 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 7.1 Hz, 1H).

^{13}C NMR (126 MHz, CDCl3):

δ 206.99, 206.86, 140.52, 138.47, 136.95, 136.18, 132.99, 132.44, 116.23, 115.88, 57.49, 55.84, 34.73, 33.87, 33.66, 31.15, 30.94, 30.71, 28.02, 26.93, 22.59, 22.55, 21.71, 21.51, 20.43, 14.70.

S9g:



^{1}H NMR (500 MHz, CDCl3):

δ 5.71 (m, *J* = 7.6 Hz, 1H), 5.64 (d, *J* = 1.6 Hz, 1H), 4.97 (m, 2H), 2.63 (m, 1H), 2.31 (m, *J* = 4.4 Hz, 2H), 2.20 (m, 1H), 1.98 (m, 3H), 1.76 (m, 2H), 1.12 (alaphatics, 36H).

^{13}C NMR (126 MHz, CDCl3):

δ 200.41, 170.56, 136.57, 123.50, 116.47, 56.10, 55.86, 54.19, 42.36, 41.56, 41.48, 39.62, 39.50, 39.16, 36.11, 35.75, 35.48, 33.43, 32.54, 31.98, 28.17, 28.02, 24.17, 23.82, 22.83, 22.57, 20.90, 18.64, 17.52, 11.96.

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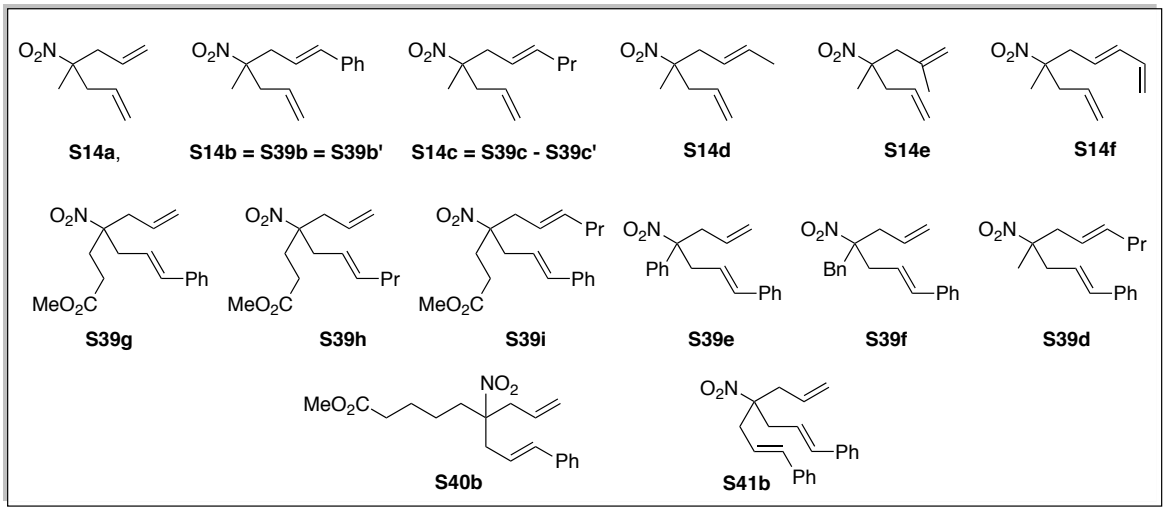
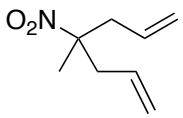
2. DaA products: nitro compounds:



S14a:



^{1}H NMR (500 MHz, $CDCl_3$):

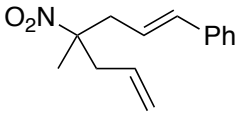
δ = 5.61 (m, 2H), 5.12 (d, *J* = 8.9 Hz, 2H), 5.09 (d, *J* = 16.3 Hz, 2H), 2.67 (dd, *J* = 14.2, 7.3 Hz, 2H), 2.48 (dd, *J* =14.2, 7.3 Hz, 2H), 1.47 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ = 128.7, 118.4, 88.3, 41.2, 19.6.

GC-MS *e/z*: found 109.2 (M-NO2) 46.0 (NO_2^+).

S14b = S39b = S39b':



^{1}H NMR (500 MHz, $CDCl_3$):

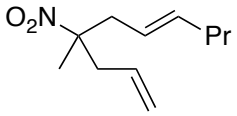
δ = 7.25 (m, 4H), 7.17 (m, 2H), 6.41 (d, *J* =15.7 Hz, 1H), 5.96 (dt, *J* = 15.3, 7.5 Hz, 1H), 5.63 (m, 1H), 5.14 (d, *J* = 9.2 Hz, 1H), 5.11 (d, *J* = 16.36 Hz, 1H) 2.83 (ddd, *J* = 14.2, 7.3, 1.3 Hz, 1H), 2.72 (dd, *J* = 14.2 7.3 Hz, 1H), 2.63 (ddd, *J* = 14.2, 7.8, 1.3 Hz, 1H), 2.52 (dd, *J* = 14.2, 7.7 Hz, 1H), 1.51 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ = 136.6, 135.4, 130.8, 128.6, 127.8, 126.3, 122.0, 120.7, 90.9, 43.5, 42.6, 22.1.

GC-MS *e/z*: found 231.2(M^+) 185.2 (M-NO2) 46.0 (NO_2^+).

S14c = S39c = S39c':

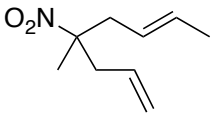


^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.60 (m, 1H), 5.47 (dt, *J* =14.6, 6.8 Hz, 1H), 5.20 (dt, *J* = 14.7, 7.3 Hz, 1H), 5.10 (d, *J* = 9.1 Hz, 1H), 5.07 (d, *J* = 16.2 Hz, 1H) 2.66 (dd, *J* = 14.2, 7.3 Hz, 1H), 2.59 (dd, *J* = 14.2, 7.3 Hz, 1H), 2.42 (m, 2H), 1.91 (apparent q, *J* = 6.6 Hz, 2H), 1.43 (s, 2H), 1.30 (apparent sextet, *J* = 7.4 Hz, 2H), 0.80 (t, *J* =7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 135.1, 129.2, 120.4, 118.6, 89.2, 41.6, 40.7, 32.8, 20.6, 20.0, 11.8.

GC-MS *e/z*: found 151.3 (M-NO2) 46.0 (NO_2^+).

S14d:



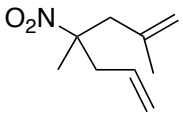
Major Diastereomer Reported

^{1}H NMR (500 MHz, $CDCl_3$):

δ = 5.59 (m, 2H), 5.49 (m, 1H), 5.22 (dtq, *J* = 14.8, 7.5, 1.6 Hz, 1H), 5.10 (d, *J* = 9.1 Hz, 1H), 5.07 (d, *J* = 15.1 Hz) 2.65 (dd, *J* = 14.4, 7.1 Hz, 1H), 2.57 (dd, *J* =14.4, 7.5 Hz, 1H), 2.42 (m, 2H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.43 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 131.4, 131.1, 123, 120, 90, 43, 42, 21, 18. MS *e/z*: found 169.2 (M^+) 123.2 (M-NO2) 46.0 (NO_2^+).

S14e:



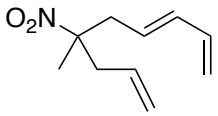
^{1}H NMR (500 MHz, $CDCl_3$):

δ = 5.60 (m, 1H), 5.11 (d, *J* = 10.1 Hz, 2H), 5.08 (d, *J* = 17.8 Hz, 1H) 4.86 (s, 1H), 4.67 (s, 1H), 2.78 (d, *J* =14.2 Hz, 1H), 2.72 (dd, *J* =14.1, 7.0 Hz, 1H), 2.41 (dd, *J* = 14.1, 7.6 Hz 1H), 2.40 (d, *J* = 14.2 Hz, 1H) 1.61 (s, 3H), 1.47 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 139.4, 130.9, 120.7, 116.7, 90.5, 47.3, 44.6, 23.4, 21.4.

GC-MS *e/z*: found 123.2 (M-NO2) 46.0 (NO_2^+).

S14f:



^{1}H NMR (500 MHz, CDCl3):

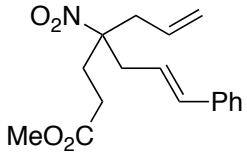
δ 6.22 (dt, *J* = 16.9, 10.3 Hz, 1H), 6.06 (dd, *J* = 15.1, 10.5 Hz, 1H), 5.60 (m, 1H), 5.45 (dt, *J* = 15.1, 7.8, Hz, 1H), 5.11 (d, *J* = 9.35 Hz, 2H), 5.08 (d, *J* = 8.4 Hz, 1H), 5.01 (d, *J* = 10.3 Hz, 1H), 2.68 (dt, *J* = 14.7, 7.2 Hz, 2H), 2.49 (dt, *J* = 22.8, 7.5 Hz, 2H), 1.46 (s, 3H).

^{13}C NMR (126 MHz, CDCl3):

δ 135.23, 135.16, 129.77, 125.02, 119.64, 116.49, 89.72, 42.38, 41.17, 20.98.

GC/MS data: 181.4 (M^+), 135.3 (M-NO_2), 67.1 (base peak).

S39g:



^{1}H NMR (500 MHz, $CDCl_3$):

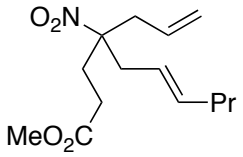
δ = 7.25(m, 4H), 7.18 (m, 2H), 6.43 (d, *J* =15.7 Hz, 1H), 5.92 (dt, *J* = 15.8, 7.5 Hz, 1H), 5.61 (m, 1H), 5.18 (d, *J* = 5.7 Hz, 1H), 5.15 (d, *J* = 14.8 Hz, 1H), 3.62 (s, 3H), 2.80 (ddd, 15.8, 7.5, 1.2 Hz, 1H), 2.72 (dd, *J* =13.9, 7.2 Hz, 1H), 2.69 (dd, *J* = 13.9, 7.6 Hz, 1H) 2.62 (dd, 14.6, 7.5 Hz, 1H), 2.27 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ = 172.4, 136.5, 135.7, 130.4, 128.6, 127.9, 126.4, 121.4, 121.1, 92.8, 51.9, 39.7, 39.1, 30.9, 28.5.

MS *e/z*: found 257.2 (M-NO2) 46.0 (NO_2^+).

S39h:



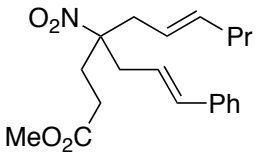
^{1}H NMR (500 MHz, $CDCl_3$):

δ = 5.57 (m, 1H), 5.52 (m, 1H) 5.16 (dt, *J* = 15.7, 7.3 Hz, 1H), 5.13 (d, *J* = 9.1 Hz, 1H), 5.12 (d, *J* = 17.6 Hz, 1H), 3.62 (s, 3H), 2.56 (m, 4H), 2.24 (m, 2H), 2.18 (m, 2H), 1.92 (apparent q, *J* = 7.0 Hz, 2H), 1.29 (apparent sextet, *J* = 7.3 Hz, 2H), 0.81 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 172.5, 137.2, 130.5, 121.6, 120.8, 92.9, 51.9, 39.5, 38.7, 34.7, 30.6, 28.5, 22.3, 13.6.

GC-MS *e/z*: found 223.3 (M-NO2) 46.0 (NO_2^+).

S39i:



^{1}H NMR (500 MHz, $CDCl_3$):

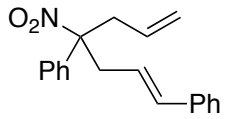
δ = 7.26 (m, 3H), 7.17 (m, 2H), 6.42 (d, *J* =15.7 Hz, 1H), 5.92 (dt, *J* = 15.7, 7.5 Hz, 1H), 5.53 (dt, *J* = 15.2, 6.9 Hz, 1H), 5.21 (dt, *J* = 15.2, 7.25 Hz, 1H), 3.62 (s, 3H), 2.78 (ddd, *J* = 14.6, 7.5, 1.2 Hz, 1H), 2.70 (ddd, *J* = 14.6, 7.5, 1.0 Hz, 1H) 2.61 (dd, *J* = 14.6, 7.3 Hz, 1H), 2.54 (dd, *J* = 14.6, 7.3 Hz, 1H) 2.29 (m, 2H), 2.23 (m, 2H), 1.94 (apparent quartet, *J* = 7.1 Hz, 2H), 1.32 (apparent sextet, *J* = 7.1 Hz, 2H), 0.82 (t, *J* =7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ = 172.5, 137.3, 136.5, 135.4, 128.6, 127.8, 126.3, 121.6, 93.1, 51.9, 38.9, 38.8, 34.6, 30.7, 28.5, 22.3, 13.6.

GC-MS *e/z*: found 299.2 (M-NO2) 46.0 (NO_2^+).

S39e:



^{1}H NMR (500 MHz, $CDCl_3$):

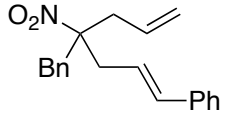
δ = 7.32 (m, 5H), 7.20 (m, 5H), 6.40 (d, *J* =15.8, 1H), 5.74 (dt, *J* = 15.8, 7.5 Hz, 1H), 5.45 (m, 1H) 5.13 (d, *J* = 6.1 Hz, 1H), 5.12 (d, *J* = 10.9 Hz, 1H), 3.29 (dd, *J* = 14.3, 7.8 Hz, 1H), 3.16 (m, 2H), 3.04 (dd, *J* = 14.0, 6.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ = 138, 136, 135, 130, 129, 128, 128, 127, 126, 125, 121, 120, 95, 39, 39.

GC-MS *e/z*: found 293.2 (M^+) 247.2 (M-NO2) 46.0 (NO_2^+).

S39f:



^{1}H NMR (500 MHz, $CDCl_3$):

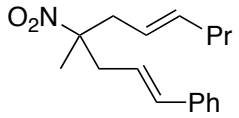
δ = 7.25 (m, 8H), 7.07 (m, 2H), 6.45 (d, *J* =15.8 Hz, 1H), 6.01 (dt, *J* = 15.8, 7.4 Hz, 1H), 5.73 (m, 1H), 5.21 (d, *J* = 10.2 Hz, 1H), 5.18 (d, *J* = 17.4 Hz, 1H), 3.20 (s, 2H), 2.84 (dd, *J* = 14.6, 7.2 Hz, 1H), 2.69 (m, 2H), 2.58 (dd, *J* = 14.6, 7.3 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ = 136.7, 135.6, 134.4, 130.9, 129.9, 128.7, 127.8, 127.6, 126.3, 122.1, 120.9, 94.3, 42.6, 39.2, 38.4.

GC-MS *e/z*: found 307.3 (M^+) 261.3 (M-NO2) 46.0 (NO_2^+).

S39d:



^{1}H NMR (500 MHz, $CDCl_3$):

δ = 7.32 – 7.12 (m, 5H), 6.40 (d, *J* =15.7 Hz, 1H), 5.96 (dt, *J* = 15.7, 7.6 Hz, 1H), 5.49 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.23 (dt, *J* = 15.2, 7.4 Hz, 1H), 2.82 (ddd, *J* = 14.4, 7.3, 1.2 Hz, 1H), 2.63 (m,

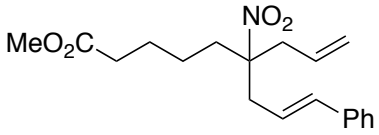
2H), 2.45 (dd, *J* = 14.2, 7.5 Hz, 1H), 1.92 (apparent quartet, *J* = 7.3 Hz, 2H), 1.49 (s, 3H), 1.36 – 1.25 (apparent sextet, *J* = 7.3 Hz, 2H), 0.82 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ = 136.9, 136.6, 135.2, 128.6, 127.7, 126.3, 122.3, 122.2, 91.2, 42.6, 42.6, 34.7, 22.3, 22.0, 13.6.

GC-MS *e/z*: found 273.3 (M^+) 227 (M-NO2) 46.0 (NO_2^+).

S40b:



^{1}H NMR (500 MHz, $CDCl_3$):

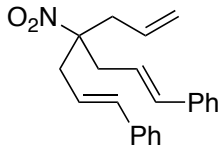
δ = 7.35 (m, 4H), 7.27 (m, 2H), 6.51 (d, *J* =15.7 Hz, 1H), 5.91 (dt, *J* = 15.7, 7.6 Hz, 1H), 5.69 (m, 1H), 5.15 (d, *J* = 5.2 Hz, 1H), 5.12 (d, *J* = 14.2 Hz, 1H), 3.60 (s, 3H), 2.74 (m, 2H), 2.64 (m, 2H), 2.25 (t, *J* =7.3 Hz, 2H), 1.97 (m, 2H), 1.67 (m, 2H), 1.35 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ = 173.6, 136.6, 135.3, 130.8, 128.6, 127.8, 126.3, 121.9, 120.6, 93.7, 51.6, 39.6, 38.9, 35.4, 33.5, 24.7, 22.9.

GC-MS *e/z*: found 331.2 (M^+) 285.2 (M-NO2) 46.0 (NO_2^+).

S41b:



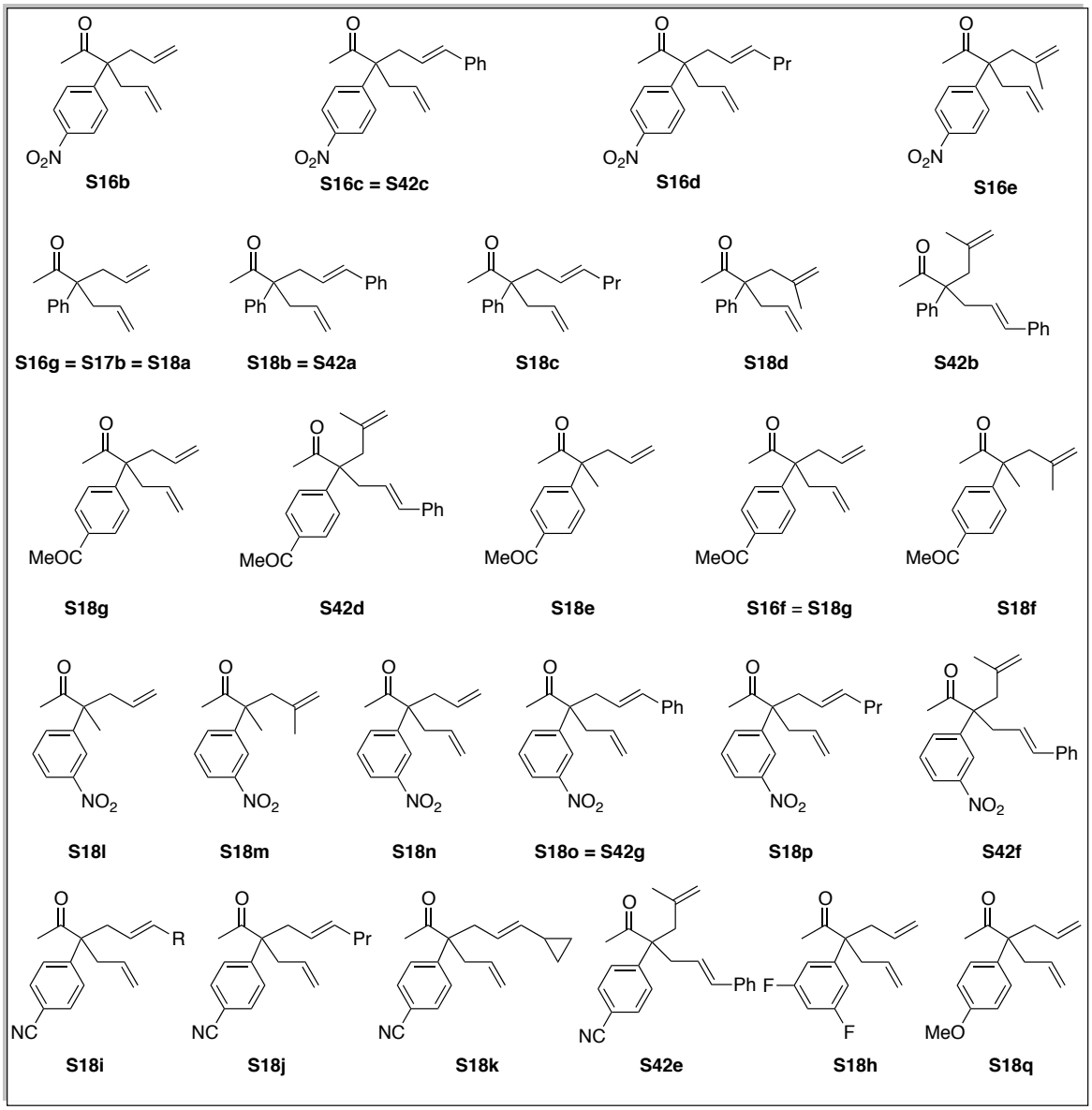
^{1}H NMR (500 MHz, $CDCl_3$):

δ = 7.25 (m, 8H), 7.18 (m, 2H), 6.45 (d, *J* =15.7 Hz, 2H), 5.98 (dt, *J* = 15.5, 7.5 Hz, 2H), 5.68 (m, 1H), 5.17 (d, *J* = 4.4 Hz, 1H), 5.15 (d, *J* = 11.9 Hz, 1H), 2.80 (dd, *J* =7.5 Hz, 1.1, 4H), 2.69 (d, *J* =7.3 Hz, 2H).

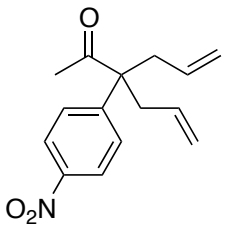
^{13}C NMR (126 MHz, $CDCl_3$):

δ = 136.6, 135.5, 130.6, 128.6, 127.8, 126.3, 121.8, 120.9, 93.6, 39.9, 39.1.

3. DaA products: ketone compounds (from acetylacetone):



S16b:



^{1}H NMR (500 MHz, $CDCl_3$):

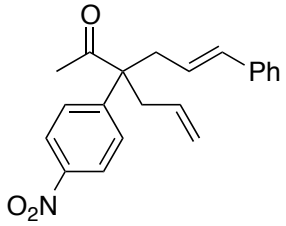
δ = 8.16 (d, *J* = 8.9 Hz, 2H), 7.30 (d, *J* = 8.9 Hz, 2H), 5.35 (m, 2H), 5.02 (s, 2H), 5.00 (d, *J* = 5.8 Hz,, 2H), 2.70 (d, *J* =7.2 Hz, 4H), 1.86 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ = 207.6, 148.7, 146.9, 132.0, 127.7, 123.9, 119.6, 59.5, 37.5, 26.5.

GC-MS *e/z*: found 259.3 (M^+) 213.3 (M-NO2) 46.0 (NO_2^+).

S16c = S42c



^{1}H NMR (500 MHz, $CDCl_3$):

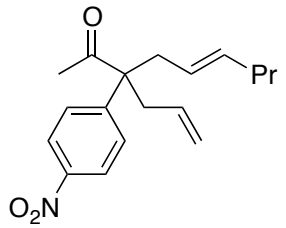
δ = 8.18 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 8.9 Hz, 2H), 7.18 (m, 6H), 6.33 (d, *J* = 15.7 Hz, 1H), 5.68 (dt, *J* = 15.7, 7.3 Hz, 1H), 5.42 (m, 1H), 5.05 (m, 2H), 2.85 (d, *J* = 5.5 Hz, 2H), 2.75 (d, *J* = 7.2 Hz, 2H), 1.91 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ = 207.6, 148.7, 147.0, 136.8, 134.4, 132.0, 128.5, 127.8, 127.6, 126.1, 124.0, 123.4, 119.7, 59.8, 37.6, 37.0, 26.5.

GC-MS *e/z*: found 289.2 (M-NO2) 46.0 (NO_2^+).

S16d:



^{1}H NMR (500 MHz, $CDCl_3$):

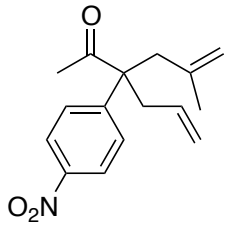
δ = 8.16 (d, *J* = 8.9 Hz, 2H), 7.29 (d, *J* = 8.9 Hz, 2H), 5.36 (m, 2H), 4.97 (m, 3H), 2.67 (m, 4H), 1.85 (s, m, 5H), 1.23 (m, 2H), 0.77 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ = 207.9, 149.0, 146.9, 135.8, 132.3, 127.8, 123.9, 123.2, 119.4, 59.8, 37.7, 36.3, 34.7, 26.58, 22.5, 13.6.

GC-MS *e/z*: found 301.2 (M^+).

S16e:



^{1}H NMR (500 MHz, $CDCl_3$):

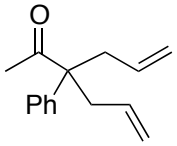
δ = 8.16 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 8.9 Hz, 2H), 5.44 (m, 1H), 5.04 (m, 2H), 4.78 (s, 1H), 4.55 (s, 1H), 2.87 (m, 1H), 2.78 (m, 2H), 2.64 (d, *J* =14.6 Hz, 1H), 1.88 (s, 3H), 1.28 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ = 207.9, 149.3, 146.8, 140.7, 132.3, 127.9, 123.8, 119.6, 116.0, 59.4, 41.2, 37.1, 26.6, 24.3.

GC-MS *e/z*: found 273.2 (M^+) 227.2 (M-NO2) 46.0 (NO_2^+).

S16g = S17b = S18a:



^{1}H NMR (500 MHz, $CDCl_3$):

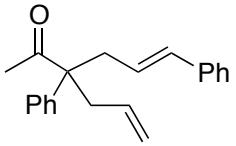
δ 7.25 (m, aromatics, 3H), 7.11 (m, aromatics, 2H), 5.37 (m, 2H), 4.98 (dd, *J* = 15.3, 6.0 Hz, 4H), 2.67 (m, 4H), 1.83 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 209.45, 141.13, 133.24, 128.81, 127.14, 126.66, 118.57, 58.93, 37.44, 26.24.

GC/MS data: 214.1 (M^+), 271.1 (M-Ac, base peak).

S18b = S42a:



^{1}H NMR (500 MHz, $CDCl_3$):

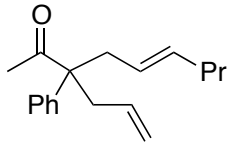
δ 7.31 (m, 2H), 7.18 (m, 9H), 6.32 (d, *J* = 15.8 Hz, 1H), 5.72 (dt, *J* = 15.7, 7.4 Hz, 1H), 5.44 (m, 1H), 5.02 (dd, *J* = 12.1, 3.57 2H), 2.80 (dd, *J* = 7.4, 1.3 Hz, 2H), 2.71 (dd, *J* = 8.4, 7.3 Hz, 2H), 1.85 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 209.46, 141.13, 137.29, 133.51, 133.19, 128.89, 128.47, 127.23, 126.68, 126.09, 125.03, 118.73, 59.31, 37.54, 36.94, 26.30.

GC/MS data: 290.2 (M^+), 247.1 (M-Ac, base peak).

S18c:



^{1}H NMR (500 MHz, $CDCl_3$):

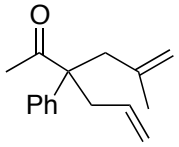
δ 7.28 (m, 2H), 7.20 (m, 1H), 7.10 (m, 2H), 5.36 (m, 2H), 4.96 (m, 3H), 2.62 (m, 4H), 1.86 (apparent quartet, *J* = 7.12, 2H), 1.82 (s, 3H), 1.25 (apparent sextet, *J* = 7.12, Hz, 2H), 0.77 (t, *J* = 7.12 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

13C NMR (126 MHz, CDCl3) δ 209.70, 141.39, 134.76, 133.54, 128.72, 127.01, 126.71, 124.26, 118.29, 59.15, 37.65, 36.03, 34.75, 26.29, 22.60, 13.60.

GC/MS data: 256.2 (M^+), 213.1 (M-Ac, base peak).

S18d:



^{1}H NMR (500 MHz, $CDCl_3$):

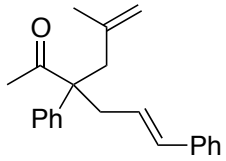
δ 7.27 (m, aromatics, 2H), 7.20 (m, aromatics, 1H), 7.14 (m, 2H), 5.48 (m, 1H), 5.01 (dd, *J* = 16.85, 7.71, 2H), 4.74 (s, 1H), 4.56 (s, *J* = 0.9 Hz, 1H), 2.84 (dd, *J* = 5.86, 5.86 Hz, 1H), 2.73 (dt, 2H), 2.59 (d, *J* = 14.4 Hz, 1H), 1.83 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 209.78, 141.89, 141.68, 133.53, 128.76, 127.14, 126.85, 118.63, 115.17, 58.80, 41.13, 36.77, 26.32, 24.15

GC/MS data: 228.2 (M^+), 185.1 (M-Ac, base peak).

S42b:



^{1}H NMR (500 MHz, $CDCl_3$):

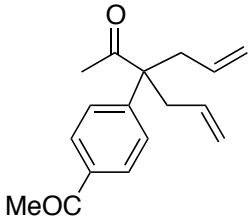
δ 7.29 (m, 2H), 7.18 (m, 8H), 6.35 (d, *J* = 15.8 Hz, 1H), 5.80 (dt, *J* = 15.8, 8.0, Hz, 1H), 4.78 (s, 1H), 4.61 (s, 1H), 2.98 (dd, *J* = 14.5, 6.4, Hz, 1H), 2.89 (dd, *J* = 14.5, 8.1 Hz, 1H), 2.78 (d, *J* = 14.5 Hz, 1H), 2.65 (d, *J* = 14.5 Hz, 1H), 1.88 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 209.84, 141.80, 141.64, 137.30, 133.60, 128.83, 128.49, 127.26, 127.22, 126.85, 126.14, 126.10, 125.26, 115.22, 59.04, 41.25, 36.25, 26.38, 24.20.

GC/MS data: 304.2 (M^+), 261.1 (M-Ac, base peak).

S18g:



^{1}H NMR (500 MHz, $CDCl_3$):

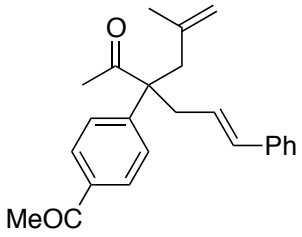
δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 5.36 (m, 2H), 5.00 (dd, *J* = 8.0, 10.2 Hz, 4H), 2.69 (d, *J* = 7.3 Hz, 4H), 2.54 (s, 3H), 1.84 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 208.43, 197.60, 146.63, 135.98, 132.61, 128.81, 127.00, 119.10, 59.33, 37.45, 26.64, 26.41.

GC/MS data: 256.1 (M^+), 114.2 (M-Ac), 173.1 (base peak).

S42d:



^{1}H NMR (500 MHz, $CDCl_3$):

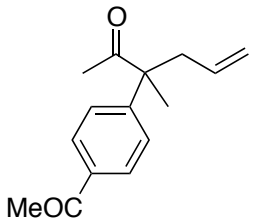
δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.17 (m, 5H), 6.36 (d, *J* = 15.8 Hz, 1H), 5.78 (dt, *J* = 15.8, 7.6 Hz, 1H), 4.80 (s, 1H), 4.61 (s, 1H), 2.99 (dd, *J* = 14.8, 6.5 Hz, 1H), 2.94 (dd, *J* = 14.8, 8.1 Hz, 1H), 2.81 (d, *J* = 14.8 Hz, 1H), 2.69 (d, *J* = 14.8 Hz, 1H), 2.56 (s, 3H), 1.85 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 208.84, 197.62, 147.19, 141.19, 137.06, 136.00, 134.04, 128.81, 128.53, 127.44, 127.20, 126.12, 124.48, 115.65, 59.45, 41.26, 36.34, 26.66, 26.54, 24.29.

GC/MS data: 346.2 (M^+), 303.2 (M-Ac, base peak).

S18e:



^{1}H NMR (500 MHz, $CDCl_3$):

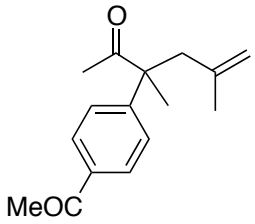
δ 7.97 (d, *J* = 8.6 Hz 2H), 7.35 (d, *J* = 8.6 Hz 2H), 5.47 (m, 1H), 5.04 (dd, *J* = 12.4, 4.3 Hz 2H), 2.71 (d, *J* = 7.3 Hz, 2H), 2.62 (s, 3H), 1.95 (s, 3H), 1.52 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 209.36, 197.62, 147.76, 135.89, 133.47, 128.81, 126.72, 118.71, 55.87, 42.26, 26.64, 26.09, 21.11.

GC/MS data: 230.1 (M^+), 188.2 (M-Ac, base peak).

S18f:



^{1}H NMR (500 MHz, $CDCl_3$):

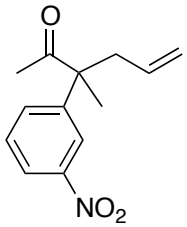
δ 7.96 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 4.80 (s,1H), 4.58 (s, 1H), 2.79 (d, *J* = 13.9, 1H), 2.69 (d, *J* = 14.0 Hz, 1H), 2.62 (s, 3H), 1.95 (s, 3H), 1.58 (s, 3H), 1.32 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 209.54, 197.63, 148.10, 141.79, 135.86, 128.71, 126.98, 115.54, 55.60, 45.56, 26.64, 26.04, 24.19, 20.65.

GC/MS data: 244.1(M^+), 201.2 (M-Ac, base peak).

S18l:



^{1}H NMR (500 MHz, $CDCl_3$):

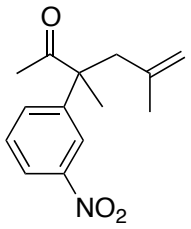
δ 8.17 (m, aromatics, 2H), 7.57 (m, aromatics, 2H), 5.48 (m, 1H), 5.07 (m, 2H), 2.73 (d, *J* = 7.6 2H), 1.98 (s, 3H), 1.58 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 208.76, 148.67, 144.64, 132.96, 132.91, 129.74, 122.26, 121.32, 119.27, 55.65, 42.33, 26.09, 21.24.

GC/MS data: 233.1 (M^+), 190.1 (M-Ac, base peak).

S18m:



^{1}H NMR (500 MHz, $CDCl_3$):

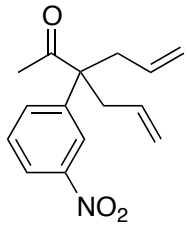
δ 8.22 (t, *J* = 2.0 Hz, 1H), 8.17 (ddd, *J* = 8.0, 2.2, 1.2 Hz, 1H), 7.61 (ddd, *J* = 7.8, 1.8, 1.2 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 4.83 (apparent quintet, *J* = 1.5 Hz, 1H), 4.57 (s, 1H), 2.83 (d, *J* = 14.1 Hz, 1H), 2.69 (d, *J* = 14.1 Hz, 1H), 1.99 (s, 3H), 1.63 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 208.97, 148.61, 145.02, 141.16, 133.19, 129.61, 122.26, 121.49, 116.02, 55.37, 45.60, 26.07, 24.29, 20.90.

GC/MS data: 247.1 (M^+), 204.1 (M-Ac, base peak).

S18n



^{1}H NMR (500 MHz, $CDCl_3$):

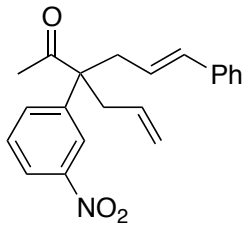
δ 8.10 (ddd, *J* = 8.1, 2.2, 1.1 Hz, 1H), 8.05 (t, *J* = 2.0 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.42 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 5.36 (m, 2H), 5.01 (m, 4H), 2.72 (d, *J* = 7.2 Hz, 4H), 1.87 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

13C NMR (126 MHz, $CDCl_3$) δ 207.83, 148.67, 143.56, 133.18, 132.04, 129.80, 122.40, 121.59, 119.60, 59.10, 37.55, 26.38.

GC/MS data: 259.1 (M^+), 216.1 (M-Ac, base peak).

S18o = S42g:



^{1}H NMR (500 MHz, $CDCl_3$):

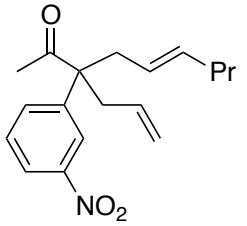
δ 8.11 (m, 2H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 7.5 1H), 7.16 (m, 5H), 6.34 (d, *J* = 15.7 Hz, 1H), 5.71 (dt, *J* = 16.2, 7.5 1H), 5.42 (m, 1H), 5.05 (m, 2H), 2.87 (d, *J* = 7.2 Hz, 2H), 2.77 (d, *J* = 7.2 Hz, 2H), 1.92 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 207.84, 148.72, 143.58, 136.84, 134.49, 133.19, 132.05, 129.87, 128.56, 127.58, 126.15, 123.48, 122.49, 121.62, 119.73, 59.47, 37.77, 36.99, 26.45.

GC/MS data: 335.2 (M^+), 292.2 (M-Ac, base peak).

S18p:



^{1}H NMR (500 MHz, $CDCl_3$):

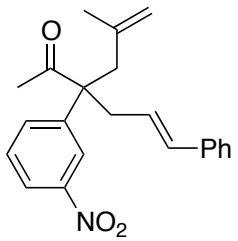
δ 8.09 (ddd, *J* = 8.1, 2.2, 1.0 Hz, 1H), 8.04 (t, *J* = 2.0 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.41 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 5.36 (m, 2H), 4.98 (m, 3H), 2.69 (d, *J* = 7.3 Hz, 2H), 2.66 (d, *J* = 7.3 Hz, 2H), 1.87 (s, 3H), 1.84 (apparent quartet, *J* = 6.9 Hz, 2H), 1.23 (apparent sextet, *J* = 6.9 Hz, 2H), 0.77 (t, *J* = 6.9, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 208.10, 148.63, 143.84, 135.84, 133.25, 132.30, 129.68, 123.14, 122.28, 121.66, 119.37, 59.36, 37.73, 36.26, 34.70, 26.45, 22.50, 13.56.

GC/MS data: 301.2 (M^+), 258.1 (M-Ac, base peak).

S42f:



^{1}H NMR (500 MHz, $CDCl_3$):

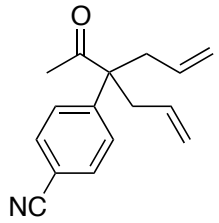
δ 8.11 (m, 2H), 7.50 (m, 2H), 7.18 (m, 6H), 6.36 (d, *J* = 15.7 Hz, 1H), 5.77 (dt, *J* = 15.7, 7.7, Hz, 1H), 4.82 (s, 1H), 4.60 (s, 1H), 3.03 (dd, *J* = 14.7, 6.7 Hz, 1H), 2.95 (dd, *J* = 14.7, 7.8 Hz, 1H), 2.84 (d, *J* = 14.7 Hz, 1H), 2.71 (d, *J* = 14.7 Hz, 1H), 1.91 (m, 3H), 1.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 208.25, 148.67, 144.08, 140.59, 136.87, 134.50, 133.40, 129.74, 128.57, 127.58, 126.14, 123.77, 122.46, 121.77, 116.09, 59.23, 41.35, 36.59, 26.50, 24.38.

GC/MS data: 349.2 (M^+), 306.1 (M-Ac, base peak).

S18i:



^{1}H NMR (500 MHz, $CDCl_3$):

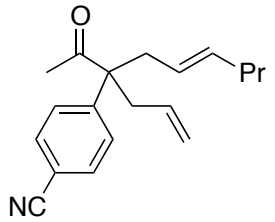
δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 5.43 (m, 2H), 5.08 (m, 4H), 2.76 (d, *J* = 7.2 Hz, 4H), 1.93 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 207.81, 146.70, 132.58, 132.14, 127.62, 119.47, 118.46, 111.29, 59.43, 37.42, 26.46.

GC/MS data: 239.1 (M^+), 196.1 (M-Ac, base peak).

S18j:



^{1}H NMR (500 MHz, $CDCl_3$):

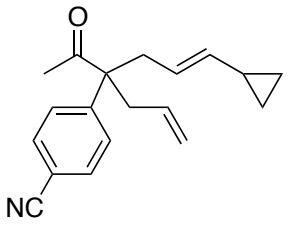
δ 7.59 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 5.37 (m, 1H), 5.31 (m, 1H), 4.96 (m, 3H), 2.64 (d, *J* = 7.3 Hz, 2H), 2.61 (d, *J* = 7.3 Hz, 2H), 1.86 (second order apparent quartet, *J* = 7.0 Hz, 1H), 1.83 (s, 3H), 1.24 (apparent sextet, *J* = 7.3 Hz, 2H), 0.77 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 208.08, 147.00, 135.68, 132.50, 132.40, 127.66, 123.24, 119.22, 118.53, 111.13, 59.68, 37.59, 36.09, 34.69, 26.52, 22.50, 13.57.

GC/MS data: 281.2 (M^+), 238.1 (M-Ac, base peak).

S18k:



^{1}H NMR (500 MHz, $CDCl_3$):

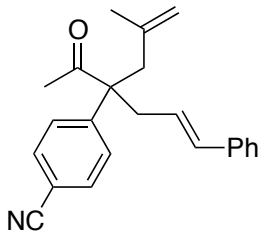
δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 5.29 (m, 1H), 4.96 (m, 4H), 2.65 (d, *J* = 7.3 Hz, 2H), 2.59 (d, *J* = 7.4 Hz, 2H), 1.85 (s, 3H), 1.22 (m, 1H), 0.58 (dd, *J* = 8.1, 2.0 Hz, 2H), 0.19 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 208.12, 146.97, 139.23, 132.50, 132.40, 127.67, 120.52, 119.23, 118.52, 111.14, 59.72, 37.59, 35.98, 26.52, 13.64, 6.60, 6.53.

GC/MS data: 279.2 (M^+), 236.1 (M-Ac, base peak).

S42e:



^{1}H NMR (500 MHz, $CDCl_3$):

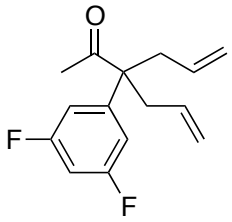
δ 7.61 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.18 (m, 7H), 6.34 (d, *J* = 15.6 Hz, 1H), 5.75 (dt, *J* = 15.6, 7.6,Hz, 1H), 4.81 (s, 1H), 4.60 (s, 1H), 2.96 (dd, *J* = 14.6, 6.7 Hz, 1H), 2.90 (dd, *J* = 14.6, 7.9 Hz, 1H), 2.79 (d, *J* = 14.6 Hz, 1H), 2.66 (d, *J* = 14.6 Hz, 1H), 1.89 (s, 3H), 1.33 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 208.25, 147.25, 140.73, 136.88, 134.37, 132.55, 128.58, 127.82, 127.58, 126.12, 123.89, 118.46, 115.94, 111.33, 59.58, 41.23, 36.39, 26.59, 24.30.

GC/MS data: 329.2 (M^+), 286.1 (M-Ac, base peak).

S18h:



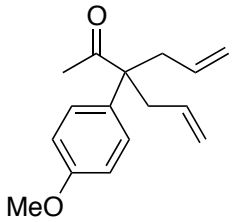
^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.67 (m, 3H), 5.35 (m, 2H), 5.01 (dd, *J* = 12.9, 3.1 Hz, 4H), 2.62 (d, *J* = 7.4 Hz, 4H), 1.87 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):δ 207.74, 163.30 (d, *J* = 249.5 Hz), 132.27, 131.16 (d, *J* = 645.5 Hz), 119.31, 109.93 (d, *J* = 19.5 Hz), 102.85 (d, *J* = 27.4 Hz), 58.89, 37.33, 26.20.

GC/MS data: 250.1 (M^+), 207.1 (M-Ac, base peak).

S18q:



^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.12 (d *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 5.47 (m, *J* = 17.1, 10.1, 7.2 Hz, 2H), 5.08 (d, *J* = 14. 8 Hz, 2H), 5.05 (d ,*J* = 6.7 Hz, 2H), 3.83 (s, 3H), 2.72 (m, 4H), 1.92 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 209.69, 158.55, 133.38, 133.05, 127.72, 118.46, 114.13, 58.19, 55.24, 37.48, 26.03.

GC/MS data: 244.1 (M^+), 201.2 (M-Ac, base peak).

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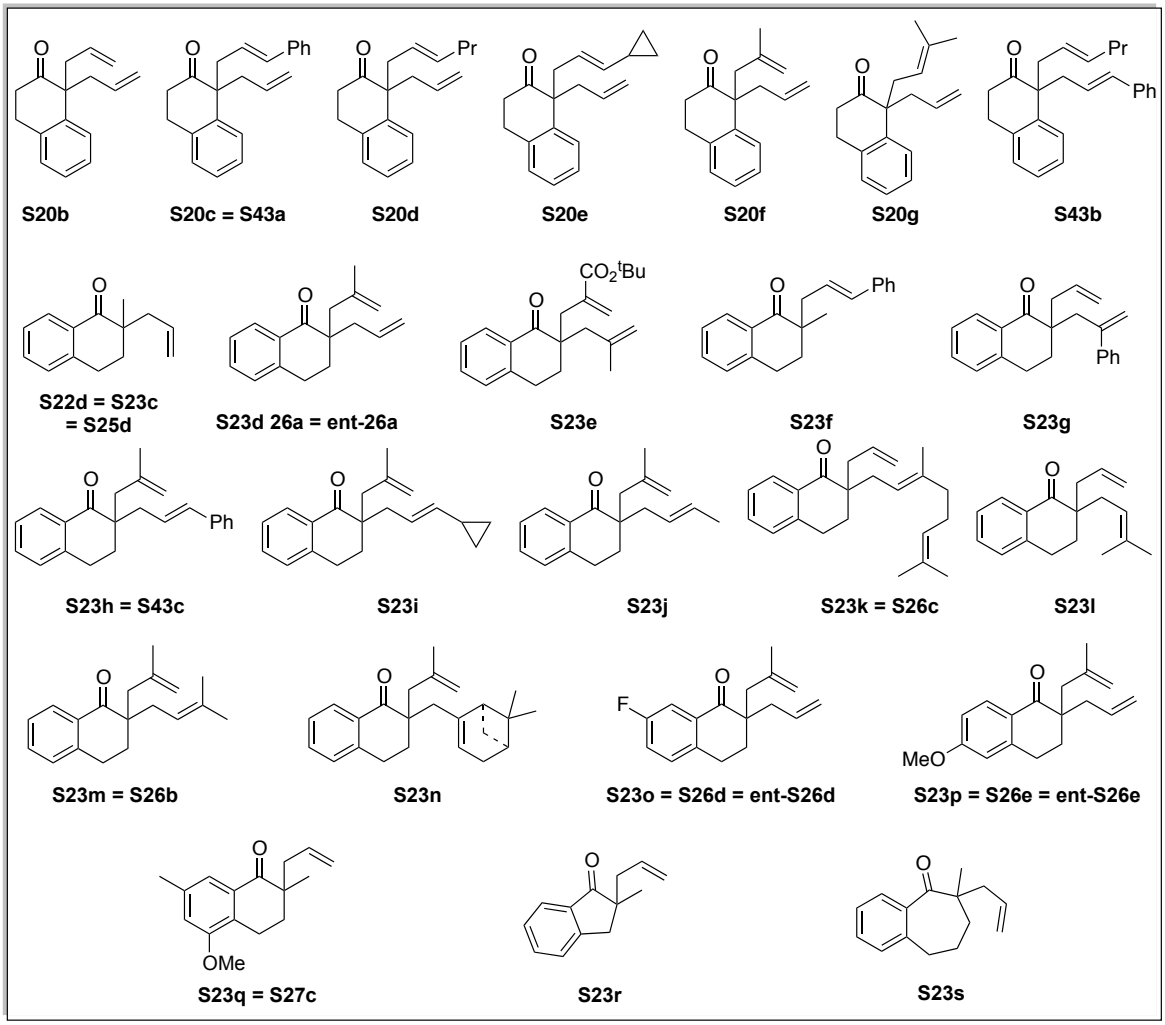
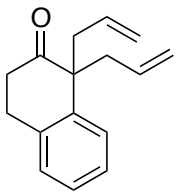
4. DaA products: ketone compounds (from tetralone):



S20b:



^{1}H NMR (500 MHz, $CDCl_3$):

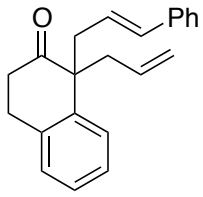
δ 7.98 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.39 (td, *J* = 7.5, 1.4 Hz, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 7.15 (m, 1H), 5.72 (m, 1H), 5.03 (d, *J* = 0.91 Hz, 1H), 5.00 (d, *J* = 4.8 Hz, 1H), 2.91 (m, 2H), 2.40 (dd, *J* = 13.8, 7.3 Hz, 1H), 2.21 (ddt, *J* = 13.8, 7.5, 1.1 Hz, 1H), 2.01 (m, 1H), 1.84 (m, 1H), 1.12 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 202.09, 143.33, 133.98, 133.08, 131.59, 128.68, 128.03, 126.64, 118.22, 44.62, 41.12, 33.35, 25.35, 21.92.

GC/MS data: 212.1 (M^+), 170.0, 128.1 (base peak).

S20c = S43a



^{1}H NMR (500 MHz, $CDCl_3$):

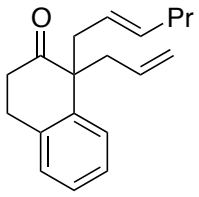
δ 7.32 (d, *J* = 7.9 Hz, 1H), 7.25 (td, *J* = 7.9, 1.4 Hz, 1H), 7.14 (m, 3H), 7.08 (m, 4H), 6.16 (d, *J* = 15.8 Hz, 1H), 5.67 (m, 1H), 5.32 (m, 1H), 4.86 (d, *J* = 17.2 Hz, 1H), 4.81 (d, *J* = 10.2 Hz, 1H), 2.85 (m, 3H), 2.77 (dd, *J* = 13.6, 8.3 Hz, 1H), 2.56 (ddd, *J* = 13.6, 6.8, 1.5 Hz, 1H), 2.51 (ddt, *J* = 13.6, 6.8, 1.1 Hz, 1H) 2.45 (ddd, *J* = 7.8, 6.5, 3.4 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 213.96, 139.07, 137.21, 137.10, 133.37, 133.27, 128.42, 128.10, 127.18, 126.99, 126.98, 126.46, 126.08, 124.86, 118.37, 56.35, 44.95, 44.53, 40.42, 27.80.

GC/MS data: 302.2 (M^+).

S20d:



^{1}H NMR (500 MHz, $CDCl_3$):

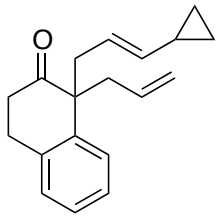
δ 7.25 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.22 (td, *J* = 7.3, 1.4 Hz, 1H), 7.12 (td, *J* = 7.3, 1.4 Hz, 1H), 7.08 (dd, *J* = 7.9, 1.1 Hz, 1H), 5.29 (m, 1H), 5.21 (dt, *J* = 15.0, 6.8 Hz, 1H), 4.90 (m, 1H), 4.83 (d, *J* = 17.3 Hz, 1H), 4.78 (d, *J* = 10.1 Hz, 1H), 2.87 (t, *J* = 6.9 Hz, 2H), 2.71 (dd, *J* = 13.6, 8.2 Hz, 1H), 2.63 (dd, *J* = 13.4, 8.3 Hz, 1H), 2.44 (td, *J* = 6.8, 2.5 Hz, 2H), 2.41 (dd, *J* = 13.4, 6.4 Hz, 1H), 2.36 (dd, *J* = 13.4, 6.4 Hz, 1H), 1.71 (m, 2H), 1.13 (apparent sextet, *J* = 7.4 Hz, 2H), 0.67 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 214.06, 139.41, 137.07, 134.52, 133.60, 127.92, 127.04, 126.81, 126.22, 124.51, 118.11, 56.28, 44.90, 44.41, 40.44, 34.57, 27.84, 22.43, 13.55.

GC/MS data: 268.2 (M^+) 268.18 (base peak).

S20e:



^{1}H NMR (500 MHz, $CDCl_3$):

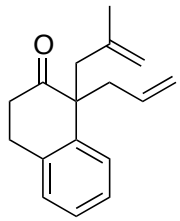
δ 7.29 (m, 3H), 7.17 (m, 2H), 7.14 (d, *J* = 7.5 Hz, 1H), 5.34 (m, 1H), 5.03 (m, Hz, 1H), 4.88 (d, *J* = 16.8 Hz, 3H), 4.83 (d, *J* = 10.0 Hz, 1H), 4.79 (dd, *J* = 15.3, 8.6 Hz, 1H), 2.94 (t, *J* = 6.9 Hz, 2H), 2.77 (dd, *J* = 13.6, 8.2 Hz, 1H), 2.66 (dd, *J* = 13.6, 8.2 Hz, 1H), 2.50 (m, 3H), 2.40 (ddd, *J* = 13.5, 6.3, 1.2 Hz, 1H), 1.13 (m, 1H), 0.53 (dd, *J* = 8.2, 2.0 Hz, 2H), 0.15 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 214.15, 139.39, 137.99, 137.18, 133.58, 127.92, 127.02, 126.81, 126.23, 121.91, 118.11, 56.39, 44.71, 44.22, 40.46, 27.82, 13.41, 6.35, 6.27.

GC/MS data: 266.1 (M^+), 223.1 (M-Ac, base peak).

S20f:



^{1}H NMR (500 MHz, $CDCl_3$):

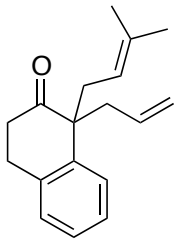
δ 7.28 (d, *J* = 7.5 Hz, 1H), 7.20 (td, *J* = 7.3, 1.3 Hz, 2H), 7.12 (td, *J* = 7.3, 1.3 Hz, 1H), 7.07 (d, *J* = 7.5, 0.7 Hz, 1H), 5.28 (m, *J* = 16.7, 10.1, 8.3, 6.4 Hz, 1H), 4.84 (d, *J* = 16.9 1H), 4.80 (d, *J* = 10.0 Hz, 1H), 2.91 (m, 2H), 2.82 (d, *J* = 13.5 Hz, 1H), 2.71 (dd, *J* = 13.5, 8.3 Hz, 1H), 2.50 (m, 3H), 2.35 (d, *J* = 13.5 Hz, 1H), 1.19 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 213.64, 141.87, 139.42, 136.76, 133.31, 128.08, 127.35, 126.71, 126.38, 118.35, 115.11, 56.17, 48.26, 46.04, 40.28, 27.80, 24.22.

GC/MS data: 240.2 (M^+), 199.2 (base peak).

S20g:



^{1}H NMR (500 MHz, $CDCl_3$):

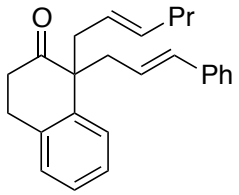
δ 7.25 (d, *J* = 7.5 Hz, 1H), 7.20 (td, *J* = 7.3, 1.4 Hz, 2H), 7.12 (td, *J* = 7.3, 1.4 Hz, 1H), 7.08 (d, *J* = 7.5, 1H), 5.29 (m, 1H), 4.83 (d, *J* = 17.4 Hz, 1H), 4.78 (d, *J* = 10.1 Hz, 1H), 4.66 (t, 7.9 Hz, 1H), 2.87 (t, *J* = 6.9 Hz, 2H), 2.73 (td, *J* = 14.8, 8.3 Hz, 2H), 2.45 (m, 3H), 2.30 (dd, *J* = 14.0, 6.5 Hz, 1H), 1.46 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (126 MHz, CDCl3):

δ 214.39, 139.57, 137.15, 134.65, 133.67, 127.89, 127.11, 126.78, 126.20, 118.95, 118.06, 56.12, 44.60, 40.34, 39.93, 27.89, 25.82, 17.72.

GC/MS data: 254.2 (M^+), 186.2 (base peak).

S43b:



^{1}H NMR (500 MHz, $CDCl_3$):

7.31 (d, *J* = 7.9 Hz, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 7.13 (m, 3H), 7.08 (m, 4H), 6.14 (d, *J* = 15.8 Hz, 1H), 5.66 (m, 1H), 5.23 (dt, *J* = 14.9, 6.8 Hz, 1H), 4.92 (dt, *J* = 14.9, 6.8 Hz 1H), 2.83 (m, 3H), 2.68 (dd, *J* = 13.5, 8.4 Hz, 1H), 2.54 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.46 (m, 3H), 1.72

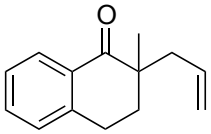
(apparent quintet, J = 7.4 Hz, 2H), 1.14 (apparent sextet, J = 7.4 Hz, 2H), 0.67 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 214.28, 139.34, 137.29, 137.15, 134.56, 133.08, 128.39, 127.99, 127.11, 127.00, 126.90, 126.31, 126.05, 125.12, 124.51, 56.62, 44.31, 44.22, 40.53, 34.58, 27.79, 22.44, 13.55.

GC/MS data: 344.2 (M^+), 301.1 (M-Ac, base peak).

S22d = S23c = S25d:



^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.97 (dd, J = 7.9, 1.1 Hz, 1H), 7.39 (td, J = 7.5, 1.4 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 5.72 (m, 1H), 5.02 (s, 1H), 5.00 (dm, J = 8.65 Hz, 1H), 2.91 (dd, J = 12.1, 5.1 Hz, 2H), 2.40 (dd, J = 13.8, 7.3 Hz, 1H), 2.21 (ddt, J = 13.8, 7.5, 1.1 Hz, 1H), 2.01 (m, 1H), 1.84 (ddd, J = 13.7, 7.1, 5.5 Hz, 1H), 1.12 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 202.09, 143.33, 133.98, 133.08, 131.59, 128.68, 128.03, 126.64, 118.22, 44.62, 41.12, 33.35, 25.35, 21.92.

Chiral Resolution: Chiracel OD-H column, mobile phose = Hexanes : 2-propanol 99.7 : 0.3, flow rate = 0.4 μL/min 18.5 mins and 20.0 mins

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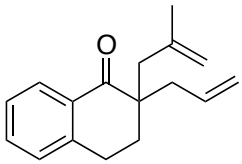
S23d = S26a = ent-S26a:



^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.98 (dd, J = 7.9, 1.1 Hz, 1H), 7.39 (td, J = 7.5, 1.4 Hz, 1H), 7.24 (t, J = 7.51 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 5.72 (m, 1H), 5.03 (dm, J = 4.61 Hz, 1H), 5.00 (dm, J = 14.02 Hz, 1H), 2.92 (m, 2H), 2.67 (d, J = 13.6 Hz, 1H), 2.44 (dt, J = 13.9, 7.03, 1.03 Hz 1H), 2.16 (m, 2H), 1.98 (ddd, J = 13.9, 8.6, 5.3 Hz, 1H), 1.90 (ddd, J = 14.0, 6.4, 5.3 Hz, 1H), 1.53 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 200.01, 142.11, 141.41, 132.87, 132.09, 130.99, 127.62, 127.09, 125.66, 117.46, 114.04, 46.66, 41.73, 39.07, 29.19, 24.14, 23.40.

Chiral Resolution: Chiracel OD-H column, mobile phose = Hexanes : 2-propanol 99.6 : 0.8, flow rate = 0.4 μL/min 6.8 mins and 7.5 mins

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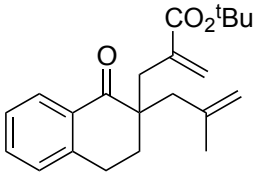
S23e:



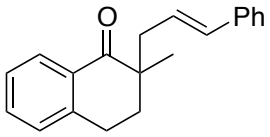
^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.96 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.38 (td, *J* = 7.51, 1.4 Hz, 1H), 7.23 (t, *J* = 7. 73 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 6.09 (d, *J* = 1.8 Hz, 1H), 5.45 (s, 1H), 4.74 (s, 1H), 4.61 (s, 1H), 3.02 (ddd, *J* = 17.0, 9.3, 4.8 Hz, 1H), 2.88 (dt, *J* = 17.05, 5.76 Hz, 1H), 2.74 (d, *J* = 13.8 Hz, 1H), 2.71 (d, *J* = 13.8 Hz, 1H), 2.61 (d, *J* = 13.4 Hz, 1H), 2.08 (m, 1H), 2.02 (d, *J* = 13.7 Hz, 1H), 1.78 (ddd, *J* = 14.0, 6.4, 4.9 Hz, 1H), 1.52 (s, 3H), 1.35 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 200.16, 166.86, 143.11, 142.40, 138.32, 133.12, 132.36, 128.61, 128.12, 126.64, 115.35, 80.62, 48.73, 43.86, 36.40, 30.24, 27.89, 25.26, 24.52.

S23f:



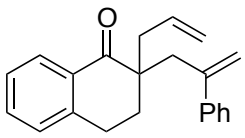
^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.00 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.39 (ddd, *J* = 7.5, 5.8, 1.4 Hz, 1H), 7.24 (m, 6H), 7.14 (m, 3H), 6.36 (d, *J* = 15.7 Hz, 1H), 6.13 (m, 1H), 2.93 (t, *J* = 6.3 Hz, 3H), 2.59 (ddd, *J* = 13.8, 7.4, 1.1 Hz, 1H), 2.35 (ddd, *J* = 13.8, 7.7, 1.1 Hz, 1H), 2.07 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.87 (dt, *J* = 13.7, 6.0 Hz, 1H), 1.17 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 202.08, 143.34, 137.40, 133.26, 133.16, 131.56, 129.72, 128.72, 128.51, 128.06, 127.16, 126.69, 126.12, 125.86, 45.21, 40.52, 33.48, 25.43, 22.13.

S23g:



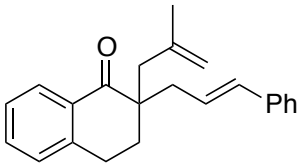
^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.80 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.35 (td, *J* = 7.5, 1.4 Hz, 1H), 7.19 (m, 8H), 7.09 (d, *J* = 7.6 Hz, 1H), 5.63 (m, 1H), 5.20 (d, *J* = 1.7 Hz, 1H), 5.03 (s, 1H), 4.96 (dm, *J* = 10.21 1H), 4.90 (dm, *J* = 17.0, 1.3 Hz, 1H), 2.95 (d, *J* = 13.9 Hz, 1H), 2.81 (m, 2H), 2.75 (d, *J* = 13.9 Hz, 1H), 2.43 (dd, *J* = 14.0, 6.7 Hz, 1H), 2.06 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.83 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 200.67, 145.51, 142.91, 134.12, 132.99, 132.15, 128.52, 128.16, 128.03, 127.26, 126.63, 126.55, 118.36, 118.11, 48.90, 39.79, 39.48, 30.41, 25.08.

S23h = S43c:



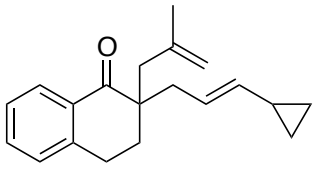
^{1}H NMR (500 MHz, $CDCl_3$)

δ 8.00 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.40 (td, *J* = 7.5, 1.4 Hz, 1H), 7.26 (m, 3H), 7.21 (t, *J* = 7.43 Hz, 2H), 7.13 (m, 2H), 6.36 (d, *J* = 15.7 Hz, 1H), 6.12 (m, 1H), 4.76 (s, 1H), 4.63 (s, 1H), 2.95 (dd, *J* = 12.3, 6.0 Hz, 2H), 2.69 (d, *J* = 13.6 Hz, 1H), 2.63 (ddd, *J* = 14.0, 7.2, 1.3 Hz, 1H), 2.31 (ddd, *J* = 14.0, 7.8, 1.1 Hz, 1H), 2.20 (d, *J* = 13.7 Hz, 1H), 1.99 (m, 2H), 1.56 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 201.13, 143.13, 142.34, 137.38, 133.47, 133.19, 132.03, 128.70, 128.51, 128.14, 127.19, 126.75, 126.14, 125.79, 115.23, 48.28, 43.02, 39.42, 30.52, 25.26, 24.46.

S23i:



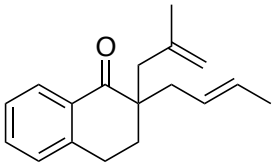
^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.98 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.38 (td, *J* = 7.5, 1.4 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 5.39 (dt, *J* = 14.9, 7.4 Hz, 1H), 4.94 (dd, *J* = 15.1, 8.6 Hz, 1H), 4.72 (dd, *J* = 2.1, 1.5 Hz, 1H), 4.61 (s, 1H), 2.90 (m, 2H), 2.66 (d, *J* = 13.6 Hz, 1H), 2.35 (ddd, *J* = 14.0, 7.1, 1.1 Hz, 1H), 2.12 (d, *J* = 13.7 Hz, 1H), 2.07 (ddd, *J* = 14.1, 7.6, 0.9 Hz, 1H), 1.92 (m, 2H), 1.54 (s, 3H), 1.28 (m, 1H), 0.58 (m, 2H), 0.24 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 201.30, 143.21, 142.65, 138.16, 133.04, 132.11, 128.64, 128.08, 126.64, 122.46, 114.91, 48.00, 42.73, 38.72, 30.03, 25.22, 24.46, 13.68, 6.56, 6.56.

S23j:



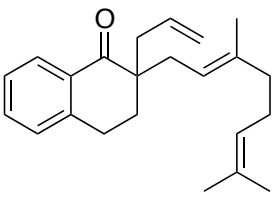
^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.98 (d, *J* = 8.14 Hz, 1H), 7.38 (td, *J* = 7.5, 1.4 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 5.41 (m, 1H), 5.33 (m, 1H), 4.73 (s, 1H), 4.60 (s, 1H), 2.91 (m, 2H), 2.66 (d, *J* = 13.7 Hz, 1H), 2.35 (dd, *J* = 14.22, 6.81 Hz, 1H), 2.10 (m, 2H), 1.92 (m, 2H), 1.59 (dd, *J* = 6.2, 1.2 Hz, 2H), 1.52 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 201.29, 143.22, 142.67, 133.07, 133.04, 132.08, 129.12, 128.64, 128.09, 126.67, 126.64, 126.05, 114.96, 114.88, 47.88, 42.75, 38.82, 30.04, 25.21, 24.46, 18.12.

S23k = S26k



^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.98 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.38 (td, *J* = 7.5, 1.4 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 5.70 (m, 1H), 5.06 (t, *J* = 7.35 1H), 4.99 (s, 1H), 4.97 (m, 2H), 2.90 (t, *J* = 6.3 Hz, 2H), 2.45 (dd, *J* = 13.9, 7.0 Hz, 1H), 2.33 (dd, *J* = 14.6, 7.0 Hz, 1H), 2.19 (m, 2H), 1.96 (m, 6H), 1.54 (s, 3H), 1.52 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 201.32, 143.27, 137.93, 134.31, 133.02, 132.01, 131.39, 128.65, 127.99, 126.60, 124.26, 119.32, 117.98, 48.58, 40.02, 39.29, 32.99, 30.39, 26.51, 25.68, 25.27, 17.71, 16.26.

Chiral Resolution: Chiracel OD-H column, mobile phase = Hexanes : 2-propanol 99.7 : 0.3, flow rate = 0.4 μL/min 26.3 mins and 27.8 mins

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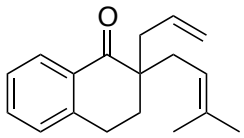
S23l:



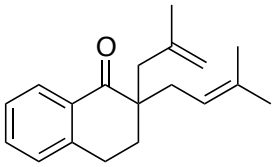
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.98 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.38 (td, *J* = 7.5, 1.4 Hz, 1H), 7.23 (t, *J* = 7.34 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 5.70 (m, 1H), 5.04 (m, 1H), 5.00 (s, 1H), 4.97 (m, 1H), 2.91 (t, *J* = 6.4 Hz, 2H), 2.46 (ddt, *J* = 14.14, 6.45, 1.45 Hz, 1H), 2.32 (dd, *J* = 14.6, 7.0 Hz, 1H), 2.19 (ddd, *J* = 14.0, 9.2, 8.2 Hz, 2H), 1.96 (t, *J* = 6.41 Hz, 2H), 1.63 (s, 3H), 1.50 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 201.30, 143.25, 134.45, 134.26, 133.02, 132.00, 128.66, 127.99, 126.60, 119.19, 118.01, 48.53, 39.27, 33.08, 30.45, 26.08, 25.23, 18.02.

S23m = S26b



^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.99 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.38 (td, *J* = 7.5, 1.4 Hz, 1H), 7.23 (t, *J* = 7.32 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 5.07 (m, 1H), 4.72 (s, 1H), 4.60 (s, 1H), 2.90 (m, 2H), 2.69 (d, *J* = 13.6 Hz,

1H), 2.30 (dd, *J* = 14.7, 6.9 Hz, 1H), 2.15 (m, 1H), 2.11 (d, *J* = 13.7 Hz, 1H), 1.93 (m, 2H), 1.64 (s, 3H), 1.53 (s, 3H), 1.51 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 201.49, 143.23, 142.74, 134.70, 133.01, 132.13, 128.62, 128.09, 126.63, 119.21, 114.84, 48.45, 42.68, 33.96, 29.97, 26.12, 25.33, 24.48, 18.08.

Chiral Resolution: Chiracel OD-H column, mobile phase = Hexanes : 2-propanol 99.7 : 0.3, flow rate = 0.4 μL/min 17.95 mins and 18.45 mins

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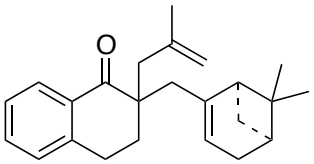
S23n:



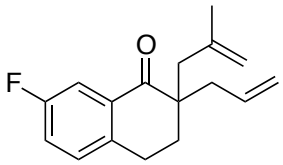
^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.97 (m, 1H), 7.38 (t, *J* = 7.6 Hz 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 5.22 (s, 1H), 4.70 (m, 1H), 4.59 (d, *J* = 6.8 Hz, 1H), 2.98 (m, 1H), 2.87 (m, 1H), 2.73 (d, *J* = 13.6 Hz, 1H), 2.37 (d, 1H), 2.03 (m, 9H), 1.51 (s, 2H), 1.18 (s, 2H), 0.77 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 201.33, 144.00, 143.19, 143.08, 143.04, 133.01, 132.97, 132.38, 128.57, 128.54, 128.10, 128.08, 126.63, 126.61, 122.59, 122.46, 114.91, 114.85, 48.93, 48.02, 47.39, 43.66, 43.62, 43.27, 42.98, 40.36, 40.22, 37.87, 31.83, 31.78, 31.67, 31.66, 29.76, 29.45, 26.40, 26.36, 25.63, 25.46, 24.62, 24.58, 21.32, 21.27.

S23o = S26d = ent-S26d



1H NMR (500 MHz, $CDCl_3$)

δ 7.64 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.11 (m, 2H), 5.70 (ddt, *J* = 17.3, 10.2, 7.3 Hz, 1H), 5.01 (m, 2H), 4.75 (s, 1H), 4.61 (s, 1H), 2.87 (m, 2H), 2.65 (d, *J* = 13.7 Hz, 1H), 2.42 (dd, *J* = 14.0, 7.1 Hz, 1H), 2.15 (m, 2H), 1.93 (m, 2H), 1.52 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 200.03, 161.68 (d, 249.9 Hz), 142.17, 138.77 (d, *J* = 2.97 Hz), 133.61, 130.48 (d, *J* = 7.03 Hz 120.55 (d, *J* = 22.21 Hz), 118.73, 115.28, 113.87 (d, *J* = 22.0 Hz), 47.49, 42.67, 39.99, 30.27, 24.49, 24.42.

Chiral Resolution: Chiracel OD-H column, mobile phase = Hexanes : 2-propanol 99.9 : 0.1, flow rate = 0.4 μL/min 9.65 mins and 10.05 mins

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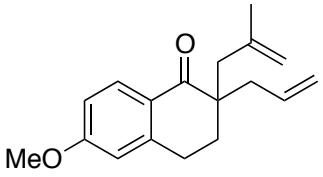
S23p = S26e = ent-S26e



^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.96 (d, *J* = 8.8 Hz, 1H), 6.76 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 5.72 (m, 1H), 5.02 (dm, *J* = 3.29 Hz 1H), 4.99 (dm, *J* = 11.31 Hz 1H), 4.73 (s, 1H), 4.61 (s, 1H), 3.78 (s, 3H), 2.88 (m, 2H), 2.67 (d, *J* = 13.6 Hz, 1H), 2.42 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.15 (m, 1H), 2.11 (d, *J* = 13.7 Hz, 1H), 1.95 (ddd, *J* = 14.0, 8.9, 5.2 Hz, 1H), 1.88 (ddd, *J* = 14.0, 8.9, 5.2 Hz 1H), 1.53 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 199.81, 163.37, 145.61, 142.65, 134.10, 130.57, 125.68, 118.34, 114.91, 113.31, 112.29, 55.42, 47.39, 42.90, 40.37, 30.20, 25.62, 24.42.

Chiral Resolution: Chiracel OD-H column, mobile phase = Hexanes : 2-propanol 99.7 : 0.3, flow rate = 1 μL/min 12.05 mins and 12.85 mins

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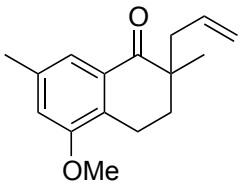
S23q = S27c



^{1}H NMR (500 MHz, $CDCl_3$)

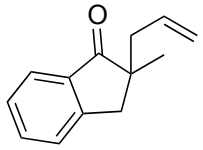
δ 7.40 (s, 1H), 6.76 (s, 1H), 5.71 (ddt, *J* = 16.6, 10.5, 7.4 Hz, 1H), 5.01 (m, 1H), 4.98 (dm, *J* = 9.53 Hz, 1H), 3.78 (s, 3H), 2.76 (m, 2H), 2.35 (dd, *J* = 13.8, 7.3 Hz, 1H), 2.30 (s, 3H), 2.18 (dd, *J* = 13.8, 7.5 Hz, 1H), 1.95 (ddd, *J* = 13.6, 7.1, 5.4 Hz, 1H), 1.80 (m, 1H), 1.09 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 202.59, 156.60, 136.79, 134.11, 132.14, 129.41, 119.60, 118.07, 115.05, 55.59, 44.28, 40.92, 32.78, 21.78, 21.53, 18.86.

Chiral Resolution: Chiracel OD-H column, mobile phase = Hexanes : 2-propanol 99.7 : 0.3, flow rate = 0.8 μL/min 14.6 mins. and 15.4 mins.

S23r:



^{1}H NMR (500 MHz, $CDCl_3$):

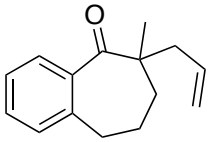
δ 7.55 (d, *J* = 7.7 Hz, 1H), 7.39 (td, *J* = 7.5, 1.1 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 5.45 (m, 1H), 4.87 (d, *J* = 17.0 Hz, 1H), 4.81 (d, *J* = 10.1 Hz, 1H), 2.97 (d, *J* = 17.2 Hz, 1H), 2.64 (d, *J* = 17.2 Hz, 1H), 2.19 (ddt, *J* = 13.6, 6.7, 1.2 Hz, 1H), 2.10 (dd, *J* = 13.7, 8.0 Hz, 1H), 1.02 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 210.81, 152.60, 135.87, 134.90, 133.89, 127.42, 126.60, 124.27, 118.36, 48.84, 42.54, 39.41, 23.81.

GC/MS data: 186.1 (M^+), 145.1 (base peak).

S23s:



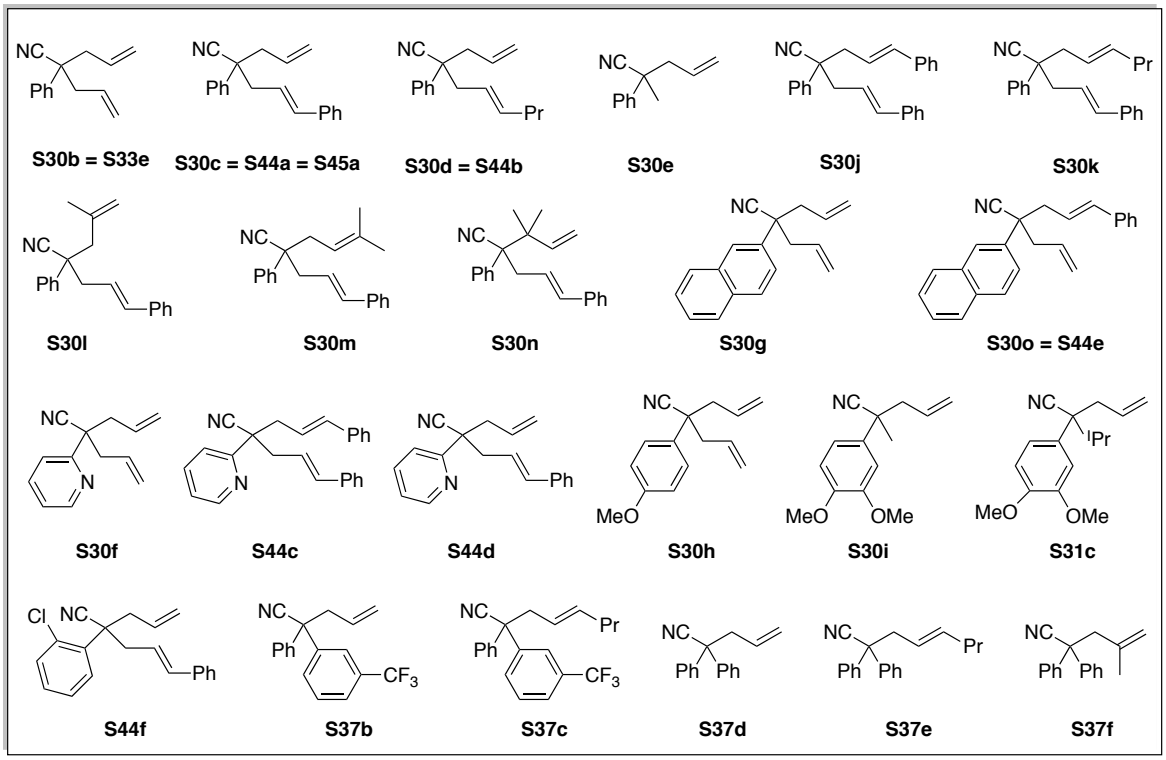
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.37 (m, 1H), 7.27 (m, 2H), 7.13 (d, J = 7.5 Hz, 1H), 5.75 (ddt, J = 16.3, 10.7, 7.5 Hz, 1H), 5.07 (m, 1H), 5.04 (ddd, J = 4.9, 2.2, 1.3 Hz, 1H), 2.80 (m, 2H), 2.34 (ddd, J = 7.1, 3.2, 2.1 Hz, 2H), 1.93 (m, 2H), 1.78 (m, 1H), 1.62 (m, 2H), 1.20 (s, 3H).

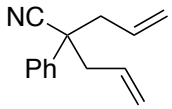
^{13}C NMR (126 MHz, $CDCl_3$):

δ 214.45, 141.58, 137.22, 133.70, 130.73, 128.40, 127.15, 126.55, 118.33, 49.11, 43.86, 34.52, 32.88, 22.79, 22.26.

5. DaA products: cyano compounds:



S30b = S33e:



^{1}H NMR (500 MHz, $CDCl_3$):

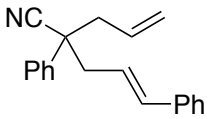
δ 7.33 (m, 4H), 7.24 (m, 1H), 5.58 (dddd, *J* = 23.6, 10.3, 7.5, 6.9 Hz, 2H), 5.08 (m, 4H), 2.63 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 137.62, 131.65, 128.84, 127.88, 126.28, 121.68, 120.20, 47.68, 44.18.

GC/MS data: 197.1 (M^+), 156.1, 129.0 (base peak).

S30c = S44a = S45a:



^{1}H NMR (500 MHz, $CDCl_3$):

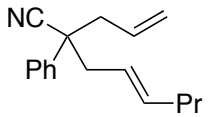
δ 7.35 (m, 4H), 7.25 (m, 1H), 7.19 (m, 5H), 7.14 (m, 1H), 6.39 (d, *J* = 15.8 Hz, 1H), 5.96 (dt, *J* = 15.3, 7.6 Hz, 1H), 5.61 (m, 1H), 5.09 (m, *J* = 9.3, 3.0, 1.6 Hz, 2H), 2.78 (m, 2H), 2.68 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 137.66, 136.71, 135.05, 131.68, 128.91, 128.52, 127.95, 127.66, 126.36, 126.30, 122.96, 121.77, 120.24, 47.98, 43.97, 43.62.

GC/MS data: 273.2 (M^+), 117.1 (base peak), 115.1, 91.1.

S30d = S44b:



^{1}H NMR (500 MHz, $CDCl_3$):

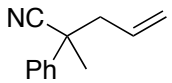
δ 7.27 (m, 6H), 5.58 (m, 1H), 5.45 (dt, *J* = 15.1, 6.9 Hz, 1H), 5.19 (dt, *J* = 15.1, 6.9 Hz, 1H), 5.07 (d, *J* = 7.9 Hz, 1H), 5.04 (s, 1H), 2.59 (m, 4H), 1.85 (apparant quartet, *J* = 7.5 Hz, 2H), 1.24 (apparent sextet, *J* = 7.5 Hz, 2H), 0.74 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 137.92, 136.56, 131.86, 128.73, 127.72, 126.33, 123.03, 121.91, 119.98, 48.05, 43.97, 43.27, 34.55, 22.33, 13.50.

GC/MS data: 239.2 (M^+), 157.1, 156.2 (base peak).

S30e:



^{1}H NMR (500 MHz, $CDCl_3$):

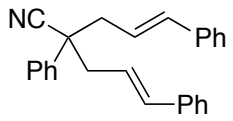
δ 7.37 (m, 2H), 7.32 (m, 2H), 7.25 (m, 1H), 5.64 (m, 1H), 5.11 (m, 1H), 5.08 (d, *J* = 8.2 Hz, 1H), 2.61 (ddt, *J* = 13.9, 6.7, 1.1 Hz 1H), 2.55 (ddt, *J* = 13.9, 7.5, 1.1 Hz, 1H), 1.65 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 139.83, 131.90, 128.89, 127.86, 125.61, 123.14, 120.20, 46.32, 42.17, 26.56.

GC/MS data: 171.1 (M^+), 130.0, 103.0, 83.0 (base peak).

S30j:



^{1}H NMR (500 MHz, $CDCl_3$):

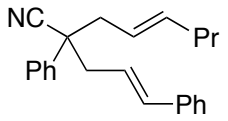
δ 7.40 (m, 2H), 7.34 (m, 2H), 7.26 (m, 2H), 7.21 (m, 7H), 7.14 (m, 2H), 6.41 (d, *J* = 15.8 Hz, 2H), 5.98 (dt, *J* = 15.7, 7.4 Hz, 2H), 2.84 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 137.72, 136.71, 135.10, 128.98, 128.53, 128.03, 127.68, 126.38, 126.32, 122.98, 121.85, 48.27, 43.43.

GC/MS data: 349.2 (M^+), 115.0, 117.1 (base peak).

S30k:



^{1}H NMR (500 MHz, $CDCl_3$):

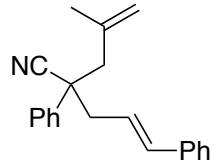
δ 7.33 (m, 4H), 7.23 (m, 6H), 7.13 (m, 1H), 6.37 (d, *J* = 15.8 Hz, 1H), 5.95 (dt, *J* = 15.7, 7.8, Hz, 1H), 5.47 (dt, *J* = 15.0, 6.9 Hz, 1H), 5.22 (dt, *J* = 15.0, 6.9 Hz, 1H), 2.76 (m, 2H), 2.60 (m, 2H), 1.87 (apparent quartet, *J* = 7.4 Hz, 2H), 1.25 (apparent sextet, *J* = 7.4 Hz Hz, 2H), 0.76 (t, *J* =7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 137.96, 136.78, 136.61, 134.85, 128.80, 128.50, 127.79, 127.59, 126.35, 123.22, 123.05, 121.99, 48.33, 43.41, 43.06, 34.57, 22.35, 13.52.

GC/MS data: 315. 2 (M^+).

S30l:



^{1}H NMR (500 MHz, $CDCl_3$):

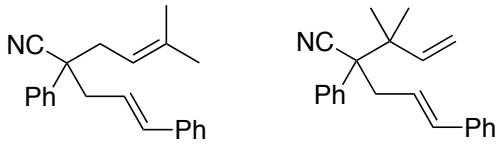
δ 7.38 (m, 2H), 7.31 (m, 2H), 7.24 (m, 1H), 7.19 (m, 4H), 7.14 (m, 1H), 6.40 (d, *J* = 15.7, Hz, 1H), 5.97 (dt, *J* = 15.7, 7.4 Hz, 1H), 4.80 (s, 1H), 4.67 (s, 1H), 2.80 (dt, *J* = 7.5, 1.1 Hz, 2H), 2.71 (d, *J* = 14.1 Hz, 1H), 2.60 (d, *J* = 14.1 Hz, 1H), 1.48 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 139.81, 137.86, 136.74, 135.05, 128.81, 128.51, 127.88, 127.63, 126.38, 126.31, 123.08, 122.09, 116.68, 47.71, 47.65, 44.87, 23.66.

GC/MS data: 287.2 (M^+), 117.1 (base peak), 91.1.

S30m & S30n:



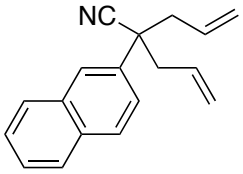
^{1}H NMR (500 MHz, $CDCl_3$):

Linear diastereomer reported.

δ 7.23 (m, 10H), 6.40 (m, 2H), 5.96 (m, 1H), 5.03 (m, 1H), 2.80 (m, 4H), 1.61 (s, 3H), 1.49 (s, 3H), 1.16 (s, 3H).

GC/MS data: 301.2 (M^+), 172.1, 117.1 (base peak), 69.1.

S30g:



^{1}H NMR (500 MHz, $CDCl_3$):

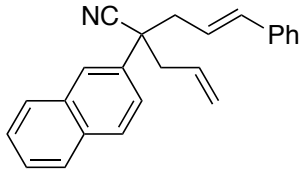
δ 7.86 (d, *J* = 1.8 Hz, 1H), 7.78 (m, 3H), 7.45 (m, 2H), 7.38 (dd, *J* = 8.7, 2.0 Hz, 1H), 5.59 (m, 2H), 5.09 (d, *J* = 17.0 Hz, 2H), 5.05 (d, *J* = 9.9 Hz, 2H), 2.74 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 134.79, 133.07, 132.65, 131.61, 128.87, 128.20, 127.56, 126.69, 126.57, 126.16, 123.08, 121.74, 120.26, 47.98, 44.11.

GC/MS data: 247.1 (M^+), 206.2, 179.1 (base peak).

S30o = S44e:



^{1}H NMR (500 MHz, $CDCl_3$):

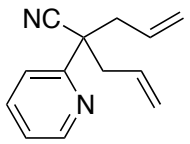
δ 7.88 (d, *J* = 1.9 Hz, 1H), 7.80 (m, 3H), 7.44 (m, 3H), 7.17 (m, 5H), 7.12 (m, 1H), 6.44 (d, *J* = 15.7 Hz, 1H), 5.97 (dt, *J* = 15.7, 7.2 Hz 1H), 5.61 (m, 1H), 5.11 (d, *J* = 17.0, 1H), 5.06 (d, *J* = 10.1 Hz 1H), 2.88 (dd, *J* = 7.4, 1.2 Hz, 2H), 2.77 (d, *J* = 7.4 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 136.64, 135.11, 134.86, 133.12, 132.70, 131.64, 128.92, 128.50, 128.23, 127.66, 127.58, 126.70, 126.59, 126.38, 126.12, 123.15, 122.90, 121.81, 120.31, 48.27, 43.98, 43.55.

GC/MS data: 323.2 (M^+), 179.0, 117.1 (base peak), 115.1, 91.1.

S30f:



^{1}H NMR (500 MHz, $CDCl_3$):

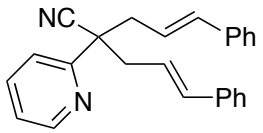
δ 8.56 (ddd, *J* = 4.8, 1.8, 1.1 Hz, 1H), 7.63 (td, *J* = 7.9, 1.8 Hz, 1H), 7.48 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.16 (ddd, *J* = 7.9, 4.8, 1.1 Hz, 1H), 5.57 (m, 2H), 5.03 (m, 4H), 2.82 (ddt, *J* = 13.7, 6.8, 1.1 Hz, 2H), 2.66 (dd, *J* = 13.7, 7.8 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 156.57, 149.69, 136.79, 131.78, 122.68, 122.18, 121.52, 120.08, 49.72, 43.17.

GC/MS data: 198.1 (M^+), 157.1 (base peak), 83.0.

S44c:



^{1}H NMR (500 MHz, $CDCl_3$):

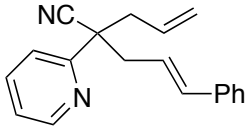
δ 8.60 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.15 (m, 13H), 6.37 (d, *J* = 15.7 Hz, 2H), 5.99 (m, 2H), 3.01 (ddd, *J* = 13.7, 7.1, 1.3 Hz, 2H), 2.88 (ddd, *J* = 13.8, 7.9, 1.1 Hz, 2H).

^{13}C NMR (126 MHz, CDCl3):

δ 156.63, 149.77, 136.94, 136.80, 134.98, 128.49, 127.59, 126.35, 123.18, 122.81, 122.27, 50.34, 42.51.

GC/MS data: 350.2 (M^+).

S44d:



^{1}H NMR (500 MHz, $CDCl_3$):

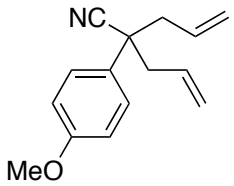
δ 8.58 (dd, *J* = 4.8, 1.8, 1H), 7.62 (td, *J* = 7.7, 1.8 Hz, 1H), 7.49 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.15 (m, 6H), 6.35 (d, *J* = 15.7 Hz, 1H), 5.97 (dt, *J* = 15.7, 7.6 Hz, 1H), 5.60 (m, 1H), 5.05 (m, 2H), 2.97 (ddd, *J* = 13.7, 7.1, 1.3 Hz, 1H), 2.86 (m, 2H), 2.71 (dd, *J* = 13.7, 7.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 156.60, 149.73, 136.86, 136.79, 134.93, 131.81, 128.48, 127.58, 126.33, 123.16, 122.75, 122.23, 121.60, 120.13, 50.03, 43.18, 42.49.

GC/MS data: 274.1 (M^+)

S30h:



^{1}H NMR (500 MHz, $CDCl_3$):

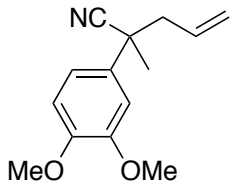
δ 7.24 (d, *J* = 9.1 Hz, 2H), 6.84 (d, *J* = 9.1 Hz, 2H), 5.58 (m, 2H), 5.07 (m, 4H), 3.74 (s, 3H), 2.59 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 159.02, 131.79, 129.57, 127.43, 121.94, 120.08, 114.10, 55.30, 46.94, 44.27.

GC/MS data: 227.1 (M^+), 186.1 (base peak).

S30i:



^{1}H NMR (500 MHz, $CDCl_3$):

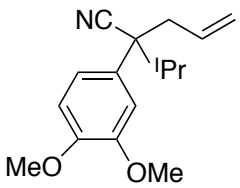
δ 6.90 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.87 (d, *J* = 2.3 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 5.64 (m, 1H), 5.09 (m, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 2.59 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.52 (dd, *J* = 13.6, 6.7 Hz, 1H), 1.63 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 149.05, 148.55, 132.32, 131.99, 123.34, 120.12, 117.72, 111.12, 109.12, 56.02, 55.95, 46.40, 41.73, 26.67.

GC/MS data: 231.1 (M^+), 190.1 (base peak).

S31c:



^{1}H NMR (500 MHz, $CDCl_3$):

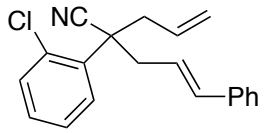
δ 6.94 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.87 (m, 2H), 5.51 (m, 1H), 5.11 (d, *J* = 16.9 Hz, 1H), 5.06 (d, *J* = 10.1 Hz, 1H) 3.92 (s, 3H), 3.90 (s, 3H), 2.85 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.63 (dd, *J* = 14.0, 6.6 Hz, 1H), 2.15 (apparent septet, *J* = 6.7 Hz, 1H), 1.22 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 148.87, 148.29, 132.34, 130.00, 121.10, 119.39, 119.02, 110.91, 109.93, 55.99, 55.87, 53.33, 42.17, 37.23, 18.81, 18.56.

GC/MS data: 259.2 (M^+), 218.2 (base peak), 138.0, 76.9.

S44f:



^{1}H NMR (500 MHz, $CDCl_3$):

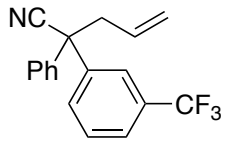
δ 7.54 (dd, *J* = 6.0, 3.5 Hz, 1H), 7.35 (dd, *J* = 6.0, 3.5 Hz, 1H), 7.19 (m, 6H), 7.14 (ddd, *J* = 9.3, 6.2, 3.3 Hz, 1H), 6.44 (d, *J* = 15.7 Hz, 1H), 5.96 (dt, *J* = 15.6, 7.4 Hz, 1H), 5.60 (m, 1H), 5.14 (d, *J* = 17.0 Hz, 1H), 5.06 (d, *J* = 10.1 Hz, 1H), 3.28 (ddd, *J* = 14.2, 7.2, 1.3 Hz, 1H), 3.20 (ddt, *J* = 14.2, 7.2, 1.0 Hz, 1H), 2.96 (ddd, *J* = 14.2, 7.7, 1.2 Hz, 1H), 2.82 (ddt, *J* = 14.2, 7.4, 1.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 136.73, 134.89, 133.24, 132.23, 132.08, 131.69, 130.79, 129.52, 128.50, 127.63, 127.28, 126.36, 123.02, 121.63, 120.12, 49.21, 40.57, 39.87.

GC/MS data: 307.1 (M^+).

S37b:

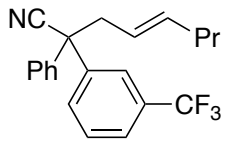


^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.57 (s, 1H), 7.51 (d, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.29 (m, 5H), 5.62 (m, 1H), 5.15 (d, *J* = 12.2 Hz, 1H), 5.12 (d, *J* = 4.6 Hz, 1H), 3.08 (m, 2H).

GC/MS data: 301.1 (M^+), 260.1 (base peak), 233.0, 190.1.

S37c:

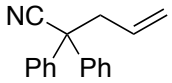


^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.56 (s, 1H), 7.49 (m,, 2H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.28 (m, 5H), 5.49 (dt, *J* = 15.1, 6.9 Hz, 1H), 5.23 (dt, *J* = 15.1, 6.9 Hz, 1H), 3.02 (m, 2H), 1.86 (apparent quartet, *J* = 7.4 Hz, 2H), 1.21 (apparent sextet, *J* = 7.4 Hz 2H), 0.72 (t, *J* = 7.4 Hz, 3H).

GC/MS data: 343.2 (M^+), 261.2 (base peak), 190.1, 165.0.

S37d:



^{1}H NMR (500 MHz, $CDCl_3$):

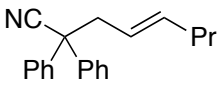
δ 7.27 (m, 10H), 5.64 (m, 1H), 5.14 (d, *J* = 17.0 Hz, 1H), 5.10 (d, *J* = 10.2, 1H), 3.07 (dt, *J* = 7.0, 1.1 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 139.74, 131.79, 128.86, 127.95, 127.06, 121.97, 120.44, 51.72, 43.95.

GC/MS data: 233.1 (M^+), 192.1, 165.1 (base peak).

S37e:



^{1}H NMR (500 MHz, $CDCl_3$):

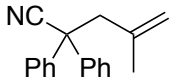
δ 7.26 (m, 10H), 5.50 (dt, *J* = 15.1, 6.9 Hz, 1H), 5.24 (dt, *J* = 15.1, 6.9 Hz, 1H), 2.99 (d, *J* = 7.0, Hz, 2H), 1.86 (apparent quartet, *J* = 7.4 Hz, 2H), 1.22 (apparent sextet, *J* = 7.4 Hz, 3H), 0.73 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 140.00, 136.83, 128.76, 127.81, 127.14, 123.15, 52.13, 42.96, 34.58, 22.30, 13.50.

GC/MS data: 275.2 (M^+), 193.1 (base peak), 165.1.

S37f:



^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.30 (m, 8H), 7.22 (m, 2H), 4.85 (s, 1H), 4.69 (s,, 1H), 3.05 (s, 2H), 1.46 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 140.32, 139.48, 128.77, 127.89, 127.10, 122.36, 117.07, 51.08, 46.90, 23.74.

GC/MS data: 247. (M^+), 192.1, 165.1 (base peak).

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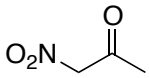
6. Characterization of synthetic intermediates:

NOTE* Compounds note explicitly given a number in Chapter 3 are given an "appendix number" in the form **A-1, A-2**, etc.

S41a:



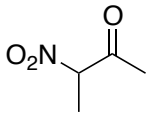
^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.25 (s, 2H), 2.25 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 193.94, 83.78, 27.46.

S8a:



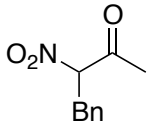
^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.24 (q, *J* = 7.1 Hz, 1H), 2.32 (s, 3H), 1.74 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 197.15, 89.36, 26.16, 14.86.

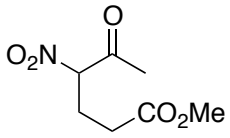
A-1 (S40a):



^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.35 (m, 5H), 7.22 (d, *J* = 7.1 Hz, 2H), 5.41 (dd, *J* = 9.4, 5.6 Hz, 1H), 3.47 (m, 2H), 2.32 (s, 3H)

A-2 (S40a):



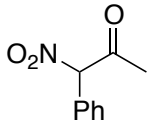
^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.29 (m, 1H), 3.64 (s, 3H), 2.40 (m, 4H), 2.27 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 196.18, 172.19, 172.15, 93.03, 52.07, 29.35, 26.79, 24.40.

A-3 (S40a)



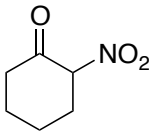
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.50 (m, 5H), 6.34 (s, 1H), 2.24 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 195.32, 130.98, 130.24, 129.52, 128.25, 97.49, 27.50.

S8b = S40a:



NMR shows cyclic nitro ketone exists as a 0.8:1 mixture ketone:enol tautaumers

^{1}H NMR (500 MHz, $CDCl_3$)

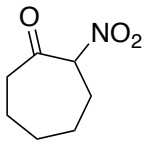
δ 13.82 (enol proton, s, 1H), 5.16 (ketone α-proton, dd, J = 11.95, 6.12 Hz, 1H), 2.60 (m, 1H), 2.51 (m, J = 6.5, 4.0, 1.4 Hz, 2H), 2.45 (m, 3H), 2.37 (m, J = 12.7, 6.9, 6.5, 2.4 Hz, 1H), 2.05 (m, J = 3.9, 2.9, 1.8 Hz, 1H), 1.98 (m, 1H), 1.70 (m, 6H).

Carbon-NMR agrees (12 unique carbon atoms)

13C NMR (126 MHz, $CDCl_3$):

δ 197.89, 172.54, 124.70, 91.83, 40.78, 31.63, 29.93, 26.44, 23.80, 22.60, 22.00, 21.18.

S8c



Interestinly, 7-membered α-nitroketone exists exclusively as the ketone (no enol tautamer).

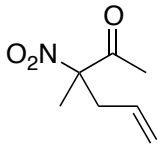
^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.34 (dd, *J* = 9.7, 3.8 Hz, 1H), 2.66 (m, 1H), 2.56 (ddd, *J* = 16.5, 10.8, 3.5 Hz, 1H), 2.28 (m, 1H), 2.15 (dddd, *J* = 14.8, 11.3, 9.7, 2.6 Hz, 1H), 1.95 (m, 1H), 1.84 (m, 2H), 1.60 (m, 2H), 1.41 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 201.16, 93.83, 41.61, 29.13, 28.99, 26.57, 23.54.

A-4:



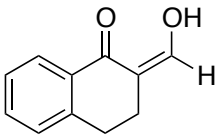
^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.55 (m, 1H), 5.16 (dm, *J* = 6.28 Hz, 1H), 5.13 (dm, *J* = 14.77 Hz, 1H), 2.90 (dd, *J* = 14.4, 7.1 Hz, 1H), 2.69 (dd, *J* = 14.4, 7.6 Hz, 1H), 2.16 (s, 3H), 1.62 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 199.11, 129.51, 121.60, 96.93, 40.19, 24.53, 20.13.

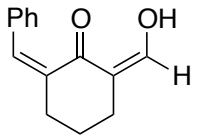
A-5:



^{1}H NMR (400 MHz, $CDCl_3$):

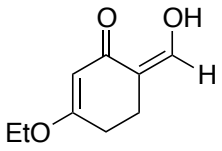
δ 14.63 (d, *J* = 6.6 Hz, 1H), 8.25 (d, *J* = 6.5 Hz, 1H), 8.00 (t, *J* = 9.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 2.93 (t, *J* = 7.12 Hz, 2H), 2.61 (t, *J* = 7.12 Hz, 2H).

A-6:



^{1}H NMR (400 MHz, $CDCl_3$) δ 14.49 (d, J = 1.7 Hz, 1H), 9.07 (d, J = 1.6 Hz, 1H), 7.66 (s, 1H), 7.43 (m, 4H), 7.34 (m, 1H), 2.74 (m, 2H), 2.51 (m, 2H), 1.78 (m, 2H).

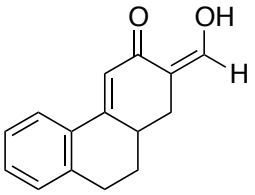
A-7:



^{1}H NMR (400 MHz, $CDCl_3$):

δ 13.93 (d, J = 10.3 Hz, 1H), 7.21 (d, J = 9.8 Hz, 1H), 5.35 (s, 1H), 3.95 (q, J = 7.14 Hz, 2H), 2.45 (m, 4H), 1.40 (t, J = 7.14 Hz, 3H).

A-8:



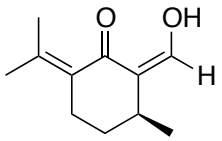
^{1}H NMR (500 MHz, $CDCl_3$)

δ 14.10 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.74 (m, 1H), 7.34 (td, *J* = 7.4, 1.3 Hz, 1H), 7.28 (m, 2H), 7.21 (d, *J* = 7.67 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 2.92 (dd, *J* = 8.5, 3.4 Hz, 2H), 2.74 (m, 1H), 2.55 (dd, *J* = 14.38, 5.51 Hz, 1H), 2.41 (td, *J* = 14.2, 1.4 Hz, 1H), 2.12 (m, 1H), 1.62 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 187.95, 168.15, 155.08, 140.27, 130.98, 130.48, 129.64, 126.75, 125.11, 119.08, 107.93, 37.46, 30.59, 30.14, 29.59.

A-9:



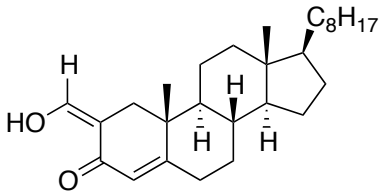
^{1}H NMR (500 MHz, $CDCl_3$):

δ 15.65 (d, *J* = 4.8 Hz, 1H), 8.43 (d, *J* = 4.7 Hz, 1H), 2.61 (m, 1H), 2.43 (m, 2H), 2.28 (s, 3H), 1.91 (s, 3H), 1.77 (m, 1H), 1.53 (m, 1H), 1.13 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 183.22, 181.62, 148.12, 125.93, 115.55, 30.26, 29.20, 24.83, 24.42, 24.33, 20.94.

A-10:



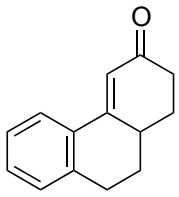
^{1}H NMR (500 MHz, $CDCl_3$):

δ 13.68 (d, *J* = 7.3 Hz, 1H), 7.29 (s,1H), 5.70 (s, 1H), 2.31 (m, 2H), 2.22 (m, 2H), 1.96 (dt, *J* = 12.7, 3.4 Hz, 1H), 1.76 (m, 2H), 1.54 (m, 1H), 1.40 (m, 5H), 1.23 (m, 7H), 1.07 (m, 8H), 0.94 (m, 8H), 0.84 (m, 4H), 0.80 (m, 9H), 0.63 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 189.32, 170.59, 165.00, 122.88, 106.59, 56.12, 55.87, 53.15, 42.38, 39.88, 39.65, 39.50, 37.55, 36.12, 35.75, 35.73, 32.57, 31.42, 28.18, 28.02, 24.24, 23.82, 22.83, 22.57, 22.36, 21.41, 18.66, 18.07, 14.08, 11.92.

A-11:



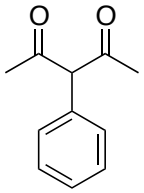
^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.25 (td, *J* = 7.5, 1.0 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 2.88 (m, 2H), 2.58 (m, 1H), 2.50 (m, 1H), 2.39 (ddd, *J* = 16.7, 14.9, 5.0 Hz, 1H), 2.13 (dtd, *J* = 12.9, 4.7, 2.6 Hz, 1H), 1.99 (m, 1H), 1.75 (dddd, *J* = 15.5, 13.2, 11.4, 4.4 Hz, 1H), 1.54 (qd, *J* = 12.8, 5.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 200.29, 158.29, 139.84, 131.31, 130.58, 129.68, 126.63, 125.22, 120.44, 37.43, 37.17, 30.58, 30.34, 30.03.

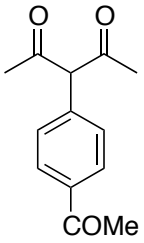
A-12



^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.39 (m, 3H), 7.19 (m, 2H), 1.92 (s, 6H).

A-13:



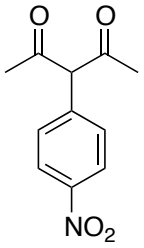
^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.01 (d, *J* = 8.10 Hz, 2H), 7.32 (d, *J* = 8.10 Hz, 2H), 2.66 (s, 3H), 1.91 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 197.66, 190.64, 142.10, 136.28, 131.47, 128.86, 114.48, 26.67, 24.20.

A-14:



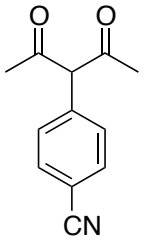
^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.29 (d, *J* = 8.85 Hz, 2H), 7.41 (d, *J* = 8.85 Hz 2H), 1.92 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 190.53, 147.36, 144.09, 132.23, 124.10, 113.68, 24.25.

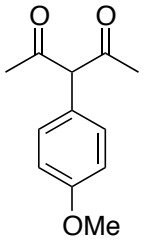
A-15:



^{1}H NMR (400 MHz, CDCl3):

δ 7.73 (d, *J* = 8.19 Hz, 2H), 7.35 (d, *J* = 8.19 Hz, 2H), 1.91 (s, 6H).

A-16:



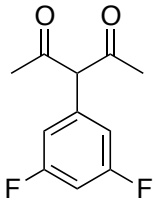
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.10 (d, *J* = 8.67 Hz, 2H), 6.94 (d, *J* = 8.67 Hz, 2H), 3.86 (s, 3H), 1.91 (s, 6H).

^{13}C NMR (126 MHz, CDCl3):

δ 191.25, 158.89, 132.14, 129.10, 114.17, 55.26, 24.17.

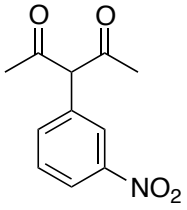
A-17:



^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.84 (tt, *J* = 8.84, 2.24 Hz, 1H), 6.76 (dd, *J* = 7.8, 2.2 Hz, 2H), 1.94 (s, 6H).

A-18:



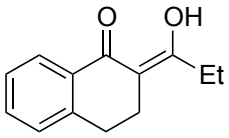
^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.25 (ddd, *J* = 8.2, 2.3, 1.2 Hz, 1H), 8.11 (t, *J* = 1.9 Hz, 1H), 7.63 (t, *J* = 7.9 Hz, 1H), 7.57 (dt, *J* = 7.74, 1.28 Hz, 1H), 1.93 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 190.83, 138.82, 137.44, 129.94, 126.02, 122.75, 113.51, 24.27.

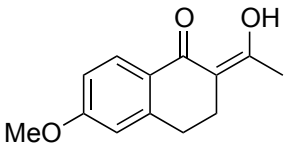
A-19:



^{1}H NMR (400 MHz, $CDCl_3$)

δ 16.36 (s, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.41 (dt, *J* = 7.4, 3.7 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 2.89 (t, *J* = 7.11 Hz, 2H), 2.65 (t, *J* = 7.11 HzHz, 2H), 2.59 (q, *J* = 7.4 Hz, 2H), 1.21 (t, *J* = 7.4 Hz, 3H).

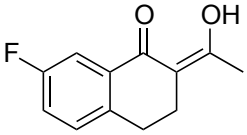
A-20:



^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.93 (d, *J* = 8.7 Hz, 1H), 6.86 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.73 (s, 1H), 3.88 (s, *J* = 2.4 Hz, 3H), 2.87 (m, 2H), 2.64 (m, 2H), 2.22 (s, 3H).

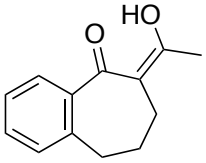
A-21:



^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.80 (dm, *J* = 9.28 Hz, 1H), 7.29 (m, *J* = 4.8 Hz, 2H), 2.98 (t, *J* = 7.4 Hz, 2H), 2.74 (t, *J* = 7.4 Hz, 2H), 2.44 (s, 3H).

A-22:



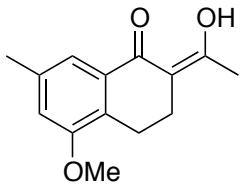
^{1}H NMR (500 MHz, $CDCl_3$):

δ 16.45 (s, 1H), 7.65 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.41 (td, *J* = 7.4, 1.5 Hz, 1H), 7.36 (td, *J* = 7.5, 1.3 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 2.71 (t, *J* = 7.0 Hz, 2H), 2.27 (s, *J* = 3.5 Hz, 3H), 2.18 (t, *J* = 6.9 Hz, 2H), 2.04 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 190.38, 188.19, 139.88, 137.49, 131.08, 128.84, 127.55, 126.70, 109.59, 31.29, 31.02, 23.78, 22.99.

A-23:



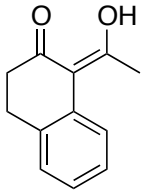
^{1}H NMR (500 MHz, $CDCl_3$):

δ 16.42 (s, 1H), 7.42 (s, 1H), 6.83 (s, 1H), 3.87 (s, 3H), 2.83 (t, *J* = 7.5 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.40 (s, 3H), 2.25 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 193.43, 177.48, 155.82, 137.03, 131.90, 126.54, 118.28, 114.77, 105.95, 55.65, 23.84, 22.31, 21.60, 20.28.

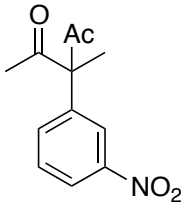
A-24:



^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.23 (m, *J* = 13.2, 7.1 Hz, 3H), 7.15 (m, 1H), 2.88 (m, 2H), 2.58 (m, 2H), 2.40 (s, 3H).

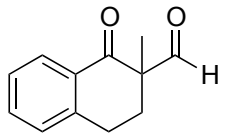
A-25:



^{1}H NMR (400 MHz, $CDCl_3$):

δ 8.25 (d, *J* = 7.8 Hz, 1H), 8.18 (m, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 2.20 (s, 6H), 1.93 (s, 3H).

A-26:



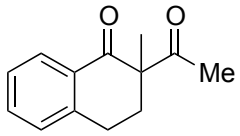
^{1}H NMR (500 MHz, $CDCl_3$):

δ 9.77 (s, 1H), 8.07 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.53 (td, *J* = 7.5, 1.4 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 3.05 (m, 2H), 2.53 (ddd, *J* = 13.7, 7.7, 5.1 Hz, 1H), 2.03 (m, 1H), 1.44 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 200.84, 197.34, 143.46, 134.10, 131.42, 128.83, 127.84, 127.02, 57.99, 29.45, 25.30, 18.55.

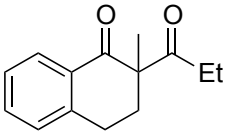
A-27:



^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.08 (d, *J* = 6.9 Hz, 1H), 7.51 (dt, *J* = 7.38, 1.35 Hz 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 1H), 3.07 (ddd, *J* = 18.07, 9.7, 4.8 Hz, 1H), 2.96 (dt, *J* = 14.0, 8.6 Hz, 1H), 2.63 (m, 1H), 2.16 (s, 3H), 1.99 (m, 1H), 1.46 (s, 3H).

A-28:



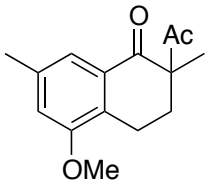
^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.08 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.50 (td, *J* = 7.5, 1.4 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 3.04 (m, 1H), 2.92 (dt, *J* = 17.4, 5.1 Hz, 1H), 2.67 (m, 2H), 2.27 (dq, *J* = 18.3, 7.2 Hz, 1H), 1.98 (ddd, *J* = 13.7, 10.0, 4.9 Hz, 1H), 1.44 (s, 3H), 1.00 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 209.54, 198.75, 143.66, 133.77, 131.86, 128.95, 127.80, 126.81, 59.79, 32.77, 32.29, 25.92, 21.18, 7.86.

A-29:



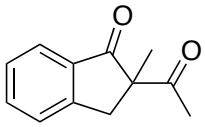
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.50 (s, 1H), 6.86 (s, 1H), 3.86 (s, 3H), 2.86 (t, *J* = 6.15 Hz, 2H), 2.60 (dt, *J* = 13.7, 5.4 Hz, 1H), 2.39 (s, 3H), 2.13 (s, 3H), 1.92 (dt, *J* = 14.1, 7.2 Hz, 1H), 1.41 (s, 3H).

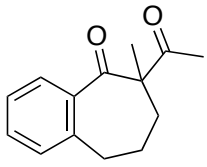
^{13}C NMR (126 MHz, $CDCl_3$):

δ 207.14, 198.96, 156.75, 137.07, 132.37, 129.71, 119.31, 115.70, 59.60, 55.61, 31.82, 26.58, 21.52, 20.43, 19.42.

A-30:



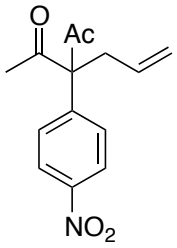
A-31:



^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.52 (d, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 2.83 (t, *J* = 6.5 Hz, 2H), 2.33 (ddd, *J* = 14.5, 9.0, 5.7 Hz, 1H), 2.11 (s, 3H), 2.03 (dt, *J* = 12.7, 6.6 Hz, 1H), 1.88 (m, 1H), 1.67 (dt, *J* = 14.2, 5.7 Hz, 1H), 1.45 (s, 3H).

A-32:



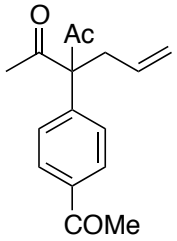
^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.18 (d, *J* = 9.04 Hz, 2H), 7.39 (d, *J* = 9.04 Hz, 2H), 5.52 (m, 1H), 5.07 (dd, *J* = 11.4, 1.5 Hz, 1H), 5.04 (m, 1H), 3.03 (dt, *J* = 7.0, 1.3 Hz, 2H), 2.09 (s, 5H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 204.02, 147.31, 143.70, 131.92, 129.51, 123.84, 119.85, 75.02, 37.88, 27.99.

A-33:



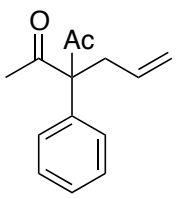
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.91 (d, *J* = 8.63 Hz, 2H), 7.31 (d, *J* = 8.63 Hz, 2H), 5.59 (m, 1H), 5.06 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.02 (dq, *J* = 10.2, 1.5 Hz, 1H), 3.01 (dt, *J* = 7.0, 1.3 Hz, 2H), 2.55 (s, 3H), 2.06 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 204.93, 197.39, 141.91, 136.57, 132.81, 128.79, 128.52, 119.18, 75.02, 37.67, 28.05, 26.66.

A-34:



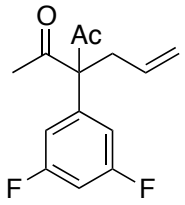
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.42 (m, 2H), 7.37 (m, 1H), 7.28 (m, 3H), 5.74 (m, 1H), 5.14 (dd, *J* = 17.1, 1.7 Hz, 1H), 5.10 (dd, *J* = 10.2, 1.7 Hz, 1H), 3.08 (dt, *J* = 7.0, 1.3 Hz, 2H), 2.14 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 206.00, 137.02, 133.64, 129.03, 128.15, 128.03, 118.56, 74.76, 37.58, 28.01.

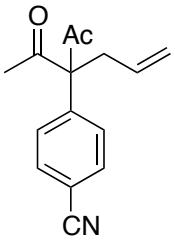
A-35:



^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.84 (m, 3H), 5.64 (m, 1H), 5.15 (m, 2H), 3.04 (d, *J* = 7.0 Hz, 2H), 2.17 (s, 6H).

A-36:



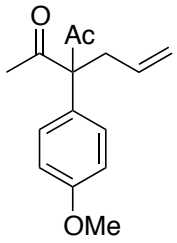
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.71 (d, *J* = 8.35 Hz, 2H), 7.42 (d, *J* = 8.35 Hz, 2H), 5.60 (m, 1H), 5.14 (dm, *J* = 12.50 Hz 1H), 5.12 (dm, *J* = 5.64 Hz 1H), 3.08 (d, *J* = 7.0 Hz, 2H), 2.16 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 204.18, 141.80, 132.49, 132.08, 129.25, 119.70, 118.19, 112.10, 75.03, 37.68, 27.98.

A-37:



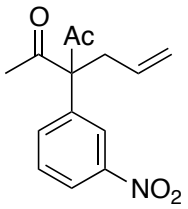
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.10 (d, *J* = 8.97 Hz, 2H), 6.85 (d, *J* = 8.97 Hz, 2H), 5.64 (m, 1H), 5.04 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.00 (dq, *J* = 10.2, 1.7 Hz, 1H), 3.75 (s, 3H), 2.96 (dt, *J* = 7.0, 1.3 Hz, 2H), 2.04 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 206.20, 159.26, 133.69, 129.20, 128.77, 118.45, 114.38, 73.99, 55.31, 37.61, 27.87.

A-38:



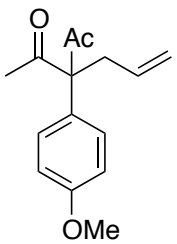
^{1}H NMR (500 MHz, $CDCl_3$)

δ 8.23 (m, 2H), 7.61 (m, 2H), 5.61 (m, 1H), 5.16 (m, 2H), 3.14 (dt, *J* = 7.0, 1.3 Hz, 2H), 2.19 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 204.08, 148.44, 138.49, 134.84, 131.79, 129.68, 123.41, 123.06, 119.96, 74.63, 37.71, 27.88.

A-39:



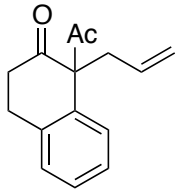
^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.19 (d, *J* = 8.91 Hz 2H), 6.94 (d, *J* = 8.91 Hz, 2H), 5.73 (m, 1H), 5.13 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.09 (dq, *J* = 10.2, 1.6 Hz, 1H), 3.84 (s, 3H), 3.05 (dt, *J* = 7.0, 1.3 Hz, 2H), 2.13 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 206.19, 159.26, 133.69, 129.20, 128.77, 118.45, 114.38, 73.99, 55.31, 37.61, 27.87.

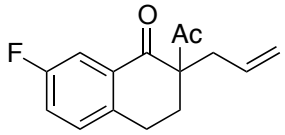
A-40:



^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.29 (m, 3H), 7.08 (m, 1H), 5.48 (m, 1H), 4.98 (m, 2H), 3.18 (m, 2H), 2.99 (dd, *J* = 13.90, 8.08 Hz, 1H), 2.89 (dd, *J* = 13.9, 5.6 Hz, 1H), 2.80 (dt, *J* = 15.0, 5.31 Hz, 1H), 2.68 (dt, *J* = 15.0, 8.31 Hz 1H), 1.92 (s, 3H).

A-41:



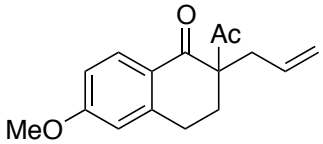
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.64 (dt, *J* = 9.0, 1.7 Hz, 1H), 7.13 (d, *J* = 1.7 Hz, 1H), 7.12 (d, *J* = 2.1 Hz, 1H), 5.62 (m, 1H), 5.06 (m, 1H), 5.03 (m, 1H), 2.96 (m, 1H), 2.81 (dt, *J* = 17.41, 4.68 Hz, 1H), 2.61 (m, 2H), 2.49 (dt, *J* = 13.9, 4.6 Hz, 1H), 2.06 (s, 3H), 1.96 (ddd, *J* = 13.9, 10.8, 5.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 205.19, 196.32, 196.30, 161.65 (*J* = 241.5 Hz), 139.44 (*J* = 3.23 Hz), 133.49, 132.53, 130.76 (*J* = 6.96 Hz), 121.38 (*J* = 22.2 Hz), 119.28, 113.60 (*J* = 22.4 Hz), 63.47, 39.00, 29.26, 27.01, 25.06.

A-42:



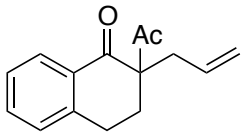
^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.05 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.66 (d, *J* = 2.5 Hz, 1H), 5.71 (m, 1H), 5.13 (m, 1H), 5.10 (m, 1H), 3.87 (s, 3H), 3.06 (dd, *J* = 11.2, 5.2 Hz, 1H), 2.87 (dt, *J* = 13.4, 8.7 Hz, 1H), 2.70 (d, *J* = 7.3 Hz, 2H), 2.56 (dt, *J* = 17.36, 4.7 Hz, 1H), 2.15 (s, 3H), 2.01 (ddd, *J* = 13.7, 10.8, 4.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 205.80, 195.71, 164.02, 146.46, 133.02, 130.42, 125.66, 118.89, 113.64, 112.36, 63.40, 55.50, 39.23, 29.22, 27.03, 26.14.

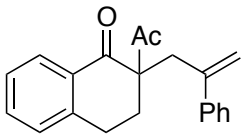
A-43:



^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.08 (d, *J* = 6.9 Hz, 1H), 7.50 (t, *J* = 6.9 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 5.73 (m, 1H), 5.15 (d, *J* = 9.4 Hz, 1H), 5.11 (m, 1H), 3.08 (m, 1H), 2.91 (dt, *J* = 17.4, 5.38 Hz, 1H), 2.71 (d, *J* = 7.6 Hz, 2H), 2.59 (dt, *J* = 14.12, 4.6 Hz, 1H), 2.15 (s, 3H), 2.08 (m, 1H).

A-44:



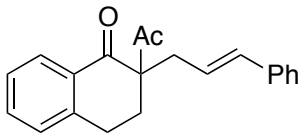
^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.00 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.46 (td, *J* = 7.5, 1.4 Hz, 1H), 7.32 (m, 4H), 7.27 (m, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 5.30 (d, *J* = 1.4 Hz, 1H), 5.14 (d, *J* = 1.1 Hz, 1H), 3.42 (d, *J* = 14.3 Hz, 1H), 3.17 (d, *J* = 14.3 Hz, 1H), 3.00 (m, *J* = 12.0, 5.0 Hz, 1H), 2.75 (m, 1H), 2.49 (ddd, *J* = 13.9, 4.7, 3.6 Hz, 1H), 2.02 (s, 3H), 1.86 (ddd, *J* = 13.9, 11.7, 5.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 204.38, 197.06, 144.44, 143.88, 142.07, 133.86, 132.04, 128.86, 128.23, 127.90, 127.55, 126.71, 126.58, 118.26, 64.52, 39.93, 29.37, 27.12, 25.82.

A-45:



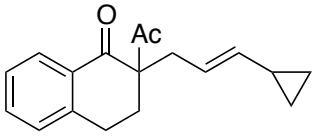
^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.01 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.42 (td, *J* = 7.5, 1.4 Hz, 1H), 7.25 (m, 3H), 7.21 (m, 3H), 7.13 (m, 2H), 6.38 (d, *J* = 15.8 Hz, 1H), 6.04 (m, 1H), 2.99 (dd, *J* = 11.0, 5.1 Hz, 1H), 2.82 (m, 2H), 2.71 (ddd, *J* = 14.1, 7.6, 1.2 Hz, 1H), 2.54 (dt, *J* = 13.8, 4.7 Hz, 1H), 2.10 (s, 3H), 2.02 (ddd, *J* = 13.8, 10.7, 5.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 205.60, 197.32, 143.80, 136.97, 133.98, 131.99, 128.99, 128.51, 127.92, 127.43, 126.80, 126.24, 124.48, 64.07, 38.34, 29.42, 27.18, 25.74.

A-46



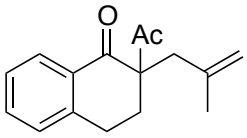
^{1}H NMR (500 MHz, $CDCl_3$)

δ 8.07 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.50 (td, *J* = 7.5, 1.4 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 5.39 (dt, *J* = 15.0, 7.4 Hz, 1H), 5.07 (dd, *J* = 15.2, 8.6 Hz, 1H), 3.08 (m, 1H), 2.91 (dt, *J* = 17.37, 4.62 Hz, 1H), 2.63 (m, 2H), 2.57 (dt, *J* = 13.8, 4.7 Hz, 1H), 2.14 (s, 3H), 2.05 (ddd, *J* = 13.8, 10.8, 5.0 Hz, 1H), 1.34 (m, 1H), 0.67 (dd, *J* = 6.9, 3.5 Hz, 2H), 0.33 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 205.73, 197.40, 143.88, 138.77, 133.83, 132.09, 128.94, 127.85, 126.69, 121.41, 64.07, 37.88, 29.06, 27.09, 25.74, 13.60, 6.63, 6.61.

A-47:



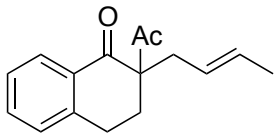
^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.08 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.50 (td, *J* = 7.5, 1.4 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 4.86 (m, 1H), 4.74 (s, 1H), 3.11 (m, 1H), 2.96 (d, *J* = 14.0 Hz, 1H), 2.90 (dt, *J* = 17.31, 4.20 Hz, 1H), 2.64 (dd, *J* = 13.9, 0.5 Hz, 1H), 2.59 (dt, *J* = 13.9, 4.4 Hz, 1H), 2.18 (s, 3H), 2.02 (ddd, *J* = 13.9, 11.4, 4.9 Hz, 1H), 1.64 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 205.83, 197.05, 143.92, 141.07, 133.92, 132.00, 128.91, 128.02, 126.70, 115.93, 63.64, 42.65, 28.73, 27.12, 25.91, 23.92.

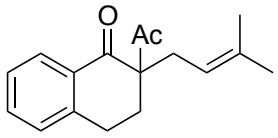
A-48:



Isolated as a 5:1 mixture of *E:Z diastereomers*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 5.55 (m, 1H), 5.34 (m, 1H), 3.08 (m, 1H), 2.90 (dt, *J* = 17.24, 5.81 Hz, 1H), 2.64 (d, *J* = 7.1 Hz, 2H), 2.57 (dt, *J* = 13.9, 4.8 Hz, 1H), 2.15 (s, 3H), 2.04 (ddd, *J* = 13.9, 10.7, 5.0 Hz, 1H), 1.66 (dd, *J* = 6.4, 1.5 Hz, 3H).

A-49



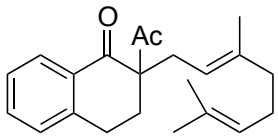
^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.08 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.49 (td, *J* = 7.5, 1.4 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 5.03 (m, 1H), 3.09 (m, 1H), 2.87 (dt, *J* = 17.5, 4.7 Hz, 1H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.59 (dt, *J* = 13.8, 4.6 Hz, 1H), 2.15 (s, 3H), 2.03 (ddd, *J* = 13.8, 11.0, 4.9 Hz, 1H), 1.70 (s, 3H), 1.64 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 205.91, 197.60, 143.94, 135.56, 133.81, 132.14, 128.93, 127.86, 126.67, 118.17, 64.29, 33.42, 28.97, 27.01, 26.00, 25.82, 18.02.

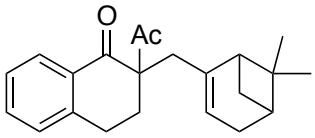
A-50:



^{1}H NMR (400 MHz, $CDCl_3$):

δ 8.08 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 6.8 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 5.04 (m, 2H), 3.10 (m, 1H), 2.88 (dt, *J* = 17.48, 4.66 Hz, 1H), 2.69 (d, *J* = 7.3 Hz, 2H), 2.57 (dt, *J* = 13.90, 4.54 Hz, 1H), 2.16 (s, 4H), 2.04 (m, 6H), 1.64 (s,s, 6H), 1.58 (s, 3H).

A-51:

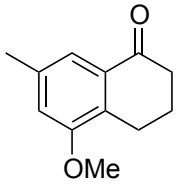


Isolated as a 1:1 mixture of diastereomers and reported as a mixture

^{1}H NMR (400 MHz, $CDCl_3$):

δ 8.06 (d, *J* = 8.1 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 7.6 Hz, 2H), 5.31 (d, *J* = 14.0 Hz, 2H), 3.10 (m, 2H), 2.87 (dt, *J* = 17.5, 4.11 Hz, 2H), 2.73 (m, 3H), 2.62 (m, 2H), 2.31 (m, 2H), 2.22 (d, 3H), 2.18 (s, 3H), 2.16 (s, 3H), 2.01 (m, 5H), 1.93 (d, *J* = 5.3 Hz, 1H), 1.25 (s, 2H), 1.24 (s, 3H), 0.83 (s, 2H), 0.78 (s, 3H).

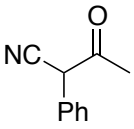
A-52:



^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.50 (s, 1H), 6.87 (s, 1H), 3.87 (s, 3H), 2.87 (t, *J* = 6.3 Hz, 2H), 2.63 (m, 2H), 2.39 (s, 3H), 2.12 (m, 2H).

A-53

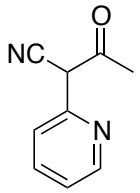


Isolated as a mixture of keto-enol tautomers

1H NMR (400 MHz, $CDCl_3$):

δ 7.44 (m, 9H), 4.70 (s, 1H), 2.37 (s, 2H), 2.29 (s, 3H).

A-54:



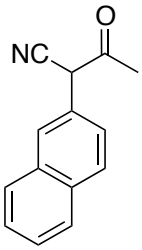
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.80 (t, *J* = 5.32 Hz, 1H), 7.72 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1H), 7.33 (dd, *J* = 8.8, 1.1 Hz, 1H), 6.90 (m, 1H), 2.34 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 192.56, 155.12, 140.49, 135.56, 120.39, 119.99, 116.18, 26.73.

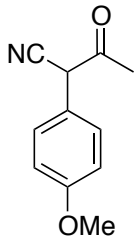
A-55:



^{1}H NMR (400 MHz, DMSO):

δ 8.09 (s, 1H), 7.89 (m, 3H), 7.82 (m, 1H), 7.49 (m, 2H), 2.40 (s, 3H).

A-56:



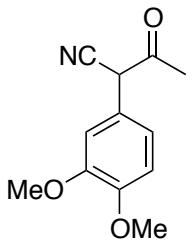
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.56 (s, 1H), 3.75 (s, 3H), 2.17 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 196.82, 160.31, 129.22, 121.47, 116.42, 115.08, 55.43, 50.74, 26.82.

A-57:



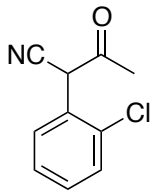
^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.89 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.75 (d, *J* = 2.2 Hz, 1H), 4.56 (s, 1H), 3.82 (s,s, *J* = 7.6 Hz, 7H), 2.18 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 196.79, 149.86, 149.84, 121.73, 120.66, 116.34, 111.71, 110.40, 56.09, 56.01, 51.09, 26.78.

A-58:



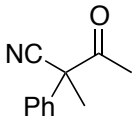
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.43 (m, 2H), 7.32 (m, 2H), 5.14 (s, 1H), 2.26 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 195.12, 133.54, 130.85, 130.34, 130.11, 128.46, 128.11, 115.49, 48.28, 27.97.

A-59:



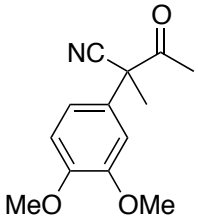
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.37 (t, *J* = 4.5 Hz, 4H), 7.32 (m, 2H), 2.19 (s, 3H), 1.74 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 198.72, 135.13, 129.58, 128.95, 125.92, 120.12, 54.29, 26.12, 23.35.

A-60:

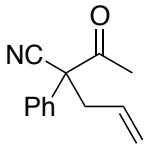


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (ddd, *J* = 8.4, 2.1, 0.8 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 1.7 Hz, 1H), 3.90 (s,s, 6H), 2.27 (s, 3H), 1.81 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 198.91, 149.65, 149.49, 127.27, 120.29, 118.49, 111.56, 108.71, 56.05, 56.00, 53.83, 25.90, 23.26.

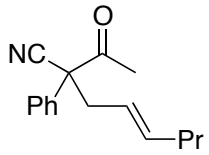
A-61:



^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.43 (m, 5H), 5.64 (m, 1H), 5.20 (m, 2H), 3.03 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.80 (dd, *J* = 14.2, 7.2 Hz, 1H), 2.30 (s, 3H).

A-62:



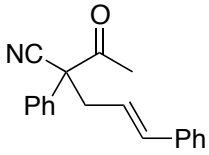
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.35 (m, 4H), 7.31 (m, 1H), 5.49 (m, 1H), 5.17 (m, 1H), 2.88 (ddd, *J* = 14.0, 7.3, 0.7 Hz, 1H), 2.63 (ddd, *J* = 14.0, 7.3, 0.8 Hz, 1H), 2.21 (s, 3H), 1.86 (q, *J* = 7.2 Hz, 2H), 1.24 (dd, *J* = 14.7, 7.4 Hz, 2H), 0.75 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 198.65, 137.27, 133.45, 129.42, 128.89, 126.42, 122.33, 119.09, 60.37, 39.63, 34.53, 27.09, 22.25, 13.48.

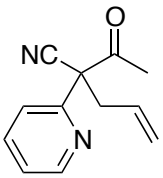
A-63:



^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.46 (m, 5H), 7.30 (m, 4H), 7.25 (m, 1H), 6.53 (d, *J* = 15.6 Hz, 1H), 6.02 (dt, *J* = 15.2, 7.5 Hz, 1H), 3.19 (dd, *J* = 14.2, 7.2 Hz, 1H), 2.93 (dd, *J* = 14.2, 7.2 Hz, 1H), 2.32 (s, 3H).

A-64:



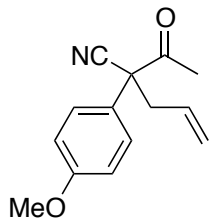
^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.65 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.82 (td, *J* = 7.8, 1.8 Hz, 1H), 7.63 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.34 (ddd, *J* = 7.6, 4.8, 1.0 Hz, 1H), 5.70 (m, 1H), 5.20 (m, 1H), 5.18 (m, 1H), 3.11 (ddt, *J* = 14.0, 7.14, 1.02 Hz, 1H), 2.97 (ddt, *J* = 14.0, 7.14, 1.02 Hz, 1H), 2.30 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 197.15, 153.45, 150.16, 137.68, 130.87, 123.59, 122.09, 120.92, 118.53, 58.96, 39.56, 27.11.

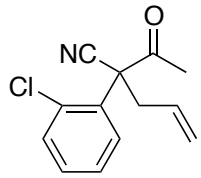
A-65:



^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.36 (d, *J* = 9.11 Hz, 2H), 6.96 (d, *J* = 9.11 Hz, 2H), 5.65 (m, 1H), 5.20 (m, 2H), 3.84 (s, 3H), 2.98 (dd, *J* = 14.2, 7.4 Hz, 1H), 2.77 (dd, *J* = 14.2, 7.0 Hz, 1H), 2.29 (s, 3H).

A-66:



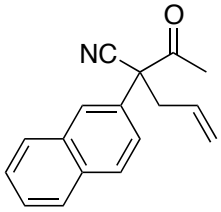
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.60 (m, 1H), 7.37 (m, 1H), 7.32 (pd, *J* = 7.4, 3.7 Hz, 2H), 5.60 (m, 1H), 5.12 (m, 1H), 5.09 (m, 1H), 3.02 (m, 2H), 2.24 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 197.97, 132.49, 132.17, 131.46, 130.67, 130.51, 130.29, 127.71, 121.02, 117.82, 58.96, 38.13, 27.15.

A-67:



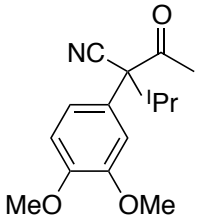
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.95 (d, *J* = 1.9 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.79 (m, 1H), 7.49 (dt, *J* = 5.5, 3.1 Hz, 2H), 7.33 (dd, *J* = 8.7, 2.1 Hz, 1H), 5.56 (m, 1H), 5.14 (ddd, *J* = 17.0, 2.8, 1.3 Hz, 1H), 5.08 (dm, *J* = 9.62 Hz, 1H), 3.01 (dd, *J* = 14.46, 7.42, 0.92 Hz, 1H), 2.83 (dd, *J* = 14.46, 7.42, 0.92 Hz, 1H), 2.23 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 198.32, 133.23, 133.08, 130.96, 130.39, 129.64, 128.26, 127.71, 127.24, 127.14, 126.48, 122.81, 120.93, 118.94, 60.05, 40.43, 27.00.

S31b:



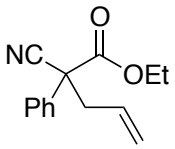
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.09 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.91 (d, *J* = 2.3 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 3.91 (s,s, 6H), 2.78 (m, 1H), 2.33 (s, 3H), 1.16 (d, *J* = 6.5 Hz, 3H), 0.78 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 199.46, 149.50, 149.40, 125.42, 119.41, 118.52, 111.32, 109.10, 66.08, 56.01, 55.95, 34.11, 28.00, 19.44, 17.64.

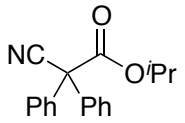
S33c:



^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.57 (d, *J* = 6.9 Hz, 2H), 7.43 (m, 3H), 5.76 (m, 1H), 5.27 (m, 2H), 4.28 (m, 2H), 3.14 (dd, *J* = 13.9, 7.3 Hz, 1H), 2.87 (dd, *J* = 13.9, 6.7 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H).

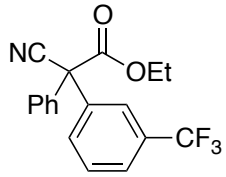
A-68



^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.42 (m, 10H), 5.19 (m, 1H), 1.33 (d, *J* = 6.2 Hz, 6H).

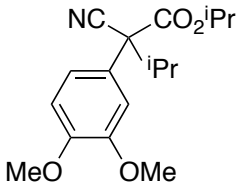
A-69:



^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.69 (d, *J* = 5.9 Hz, 2H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.44 (m, 5H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

S36a:



^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.20 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.12 (d, *J* = 2.3 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 5.06 (m, 1H), 3.92 (s,s, 6H), 2.77 (m, 1H), 1.32 (d, *J* = 6.3 Hz, 3H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.3 Hz, 4H), 0.84 (d, *J* = 6.8 Hz, 3H).

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