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# One-pot Heteroconjugate addition-diels-alder reactions and acetate-catalyzed aldol reactions of α-silyl nitriles

Carly Mueller
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One-Pot Heteroconjugate Addition-Diels–Alder Reactions and Acetate-Catalyzed Aldol Reactions of α-Silyl Nitriles

By

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Honors Thesis

In

Program In Biochemistry and Molecular Biology
University of Richmond
Richmond, VA

Spring 2014

Advisor: Dr. C. Wade Downey

This thesis has been accepted as part of the honors requirements

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*Acknowledgments*

I would like to acknowledge my research advisor Dr. C. Wade Downey. You have been an incredible and supportive mentor over these last four years, both in and out of the classroom and lab. You've not only instilled within me a value for organic chemistry and for research, but you've also taught me the important balance between persistence and moving forward. I'd also like to thank the other members of my lab, who showed me that being surrounded by genuine people is invaluable and important for any life successes. Finally, thanks to Ana Neferu, Christina Vivelo, Smaranda Craciun, Brian C. Southall, Stephanie Corsi, Eric W. Etchill, and Ryan J. Sault for starting a project I was able to pick up and produce successful results immediately upon joining the lab.

**Abstract:**

**I.** A one-pot three-step Diels–Alder reaction sequence of ethyl propiolate and thiols can be performed to produce high yields of complex bicyclic products. A KO*t*-Bu-catalyzed thioconjugate addition of thiols to enoates, oxidation of the generated thioenoate by *m*CPBA, and Li-catalyzed Diels–Alder addition of cyclopentadiene occur in situ, without any purification of intermediates.

**II.** Stereoselectivity of the Diels–Alder product was examined by utilizing a chiral sulfone substrate. It was determined that these substrates were unable to provide significant stereochemical control.

**III.** Silylation of 3-phenylpropionitrile is achieved at the α-position with trimethylsilyl trifluoromethanesulfonate and trialkylamine base. Catalyzed by tetrabutylammonium acetate (2.5 mol%), the silylated nitrile reacts in a crossed aldol reaction with a variety of aldehydes to produce β-hydroxynitriles after desilylation.

**Chapter 1:** *One-Pot Three-Step Conjugate Addition-Oxidation-Diels–Alder Reactions of Ethyl Propiolate and Aliphatic Thiols*

## I. Introduction

One-pot reactions are utilized in organic synthesis as a means of saving resources and time. These methods involve multistep reactions performed in one flask. In other words, a reaction with a single reagent is run to completion, at which time a second reagent is added, initiating the next step to a multistep reaction, and so forth, without purification between steps. This complex sequence can often result in undesirable side reactions and byproducts, and as a result one-pot reactions are more difficult to control than typical reactions. However, successful completion of a complex one-pot reaction is extremely favorable, as it provides eco-efficient and cost-effective techniques.[1] As a result, in recent years there has been a significant increase in interest for one-pot reactions.

Unsaturated esters, such as enoates (Figure 2) and ynoates, are typically used as a substrates in conjugate addition reactions.[2] Ynoates are considerably more active conjugate acceptors than enoates due to the sp hybridization of the β carbon and their linear structure, both of which make the molecule more accessible to nucleophiles.[2] Enoates, however, have received the majority of attention in literature. This is most likely due to the achiral product that results from the single conjugate addition on an ynoate. One-pot sequences of conjugate additions can overcome this limitation by selectively forming a single geometric isomer. This control could lead to stereocontrol in later reaction steps. Ynoate esters (Figure 1) such as ethyl propiolate are excellent candidates

for substrates in one-pot reactions due to their known ability to act as bisacceptors in the presence of excess nucleophile.[3]

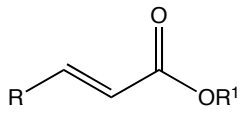



***Figure 1.*** General Structure of an Enoate Ester

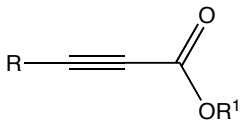



***Figure 2.*** General Structure of an Ynoate Ester

Thiols have been shown to reliably react in conjugate additions with ethyl propiolate with stereochemical control under specific reaction conditions.[4] Amine-catalyzed conjugate addition of thiols to ethyl propiolate proceeds through an allenolate intermediate, as shown in Figure 3. Under kinetic control, the allenolate intermediate (compound 1 in Figure 3a) shows selectivity for *Z*-thioenoates due to difficulty of protonation on the same face as the bulky thioether group. However, when reaction conditions are thermodynamically controlled, the reaction equilibrates towards the more stable *E*-thioenoate (Figure 3b).[3]

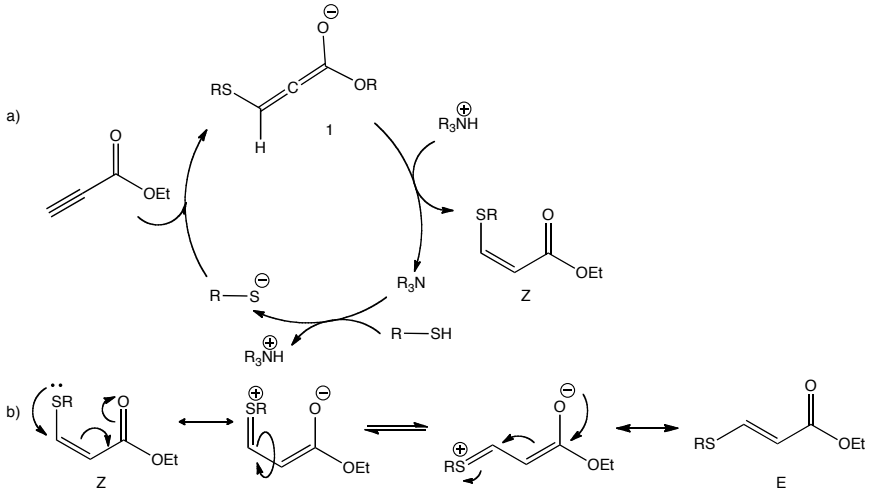



***Figure 3.*** Mechanism of Conjugate Addition of Thiols to Ethyl Propiolate: a) Generation of the Z isomer; b) Equilibration to the E isomer

In the presence of a Lewis acid, both ynoate and enoate electrophiles have the ability to react in a Diels–Alder cycloaddition.[5] When there is an electron-withdrawing group present on the dienophile, the reaction works particularly well and is useful in producing bicyclic products. Stereoselectivity of ynoate Diels–Alder products, which is particularly difficult to achieve due to their linear geometry,[6] could be indirectly controlled by a stereoselective conversion of ynoates to enoates prior to the Diels–Alder reaction.

The goal of this project was to utilize a one-pot reaction sequence to synthesize densely functionalized, stereochemically controlled complex bicyclic systems.[3] The reaction was initiated with a conjugate addition to ethyl propiolate, and followed by a Diels–Alder reaction. Similar strategies have been performed in the literature to synthesize biologically active compounds.[7]

## II. Previous Work

In previous research, the Downey group has determined the optimal conditions for the conjugate addition of thiols to ethyl propiolate (Figure 4).[2] Low temperatures favor selectivity for the Z isomer, while higher temperatures favor the E isomer.

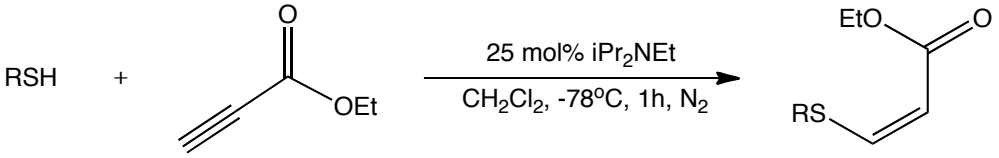



**Figure 4.** *Optimized Conjugate Addition of Thiols to Ethyl Propiolate*

Utilization of this substrate alone in a Diels–Alder reaction has been unsuccessful due to the lone pairs on the sulfur, which gives the enoate, as a whole, less electron-withdrawing characteristics. It has been shown in the Downey group, though, that

removing the lone pairs through oxidization of the enoate generates a dienophile with sufficient electron-withdrawing qualities. Utilizing this dienophile intermediate between the conjugate addition and Diels–Alder steps requires a more complex three-step one-pot sequence as opposed to a simpler, two-step reaction.[2] Optimized production of *Z*-sulfones was achieved via the oxidation of Z-thioenoates with *m*CPBA (meta-chlorobenzoic acid), the mechanism of which is proposed in Figure 5.[2]

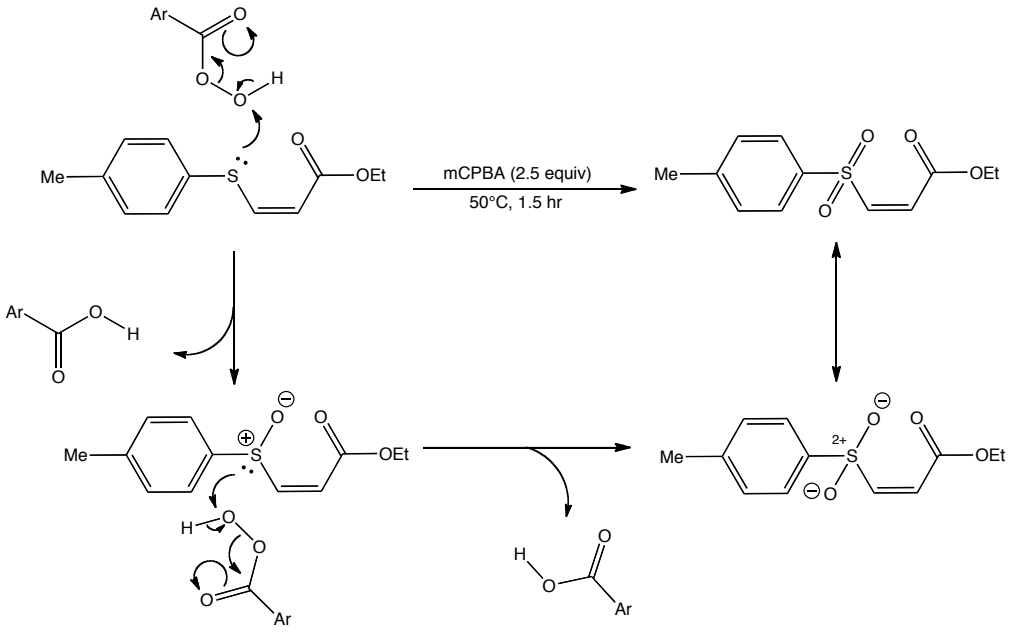



***Figure 5.*** *Mechanism of Thioenoate Oxidation by mCPBA (Ar = m-chlorophenyl)*

Additional byproducts were formed when the conjugate addition and oxidation steps were attempted in a one-pot reaction due to amine left over from the addition step. The addition of a Lewis acid, $LiClO_4$, has been shown to control the presence of these byproducts (Figure 6).[2]

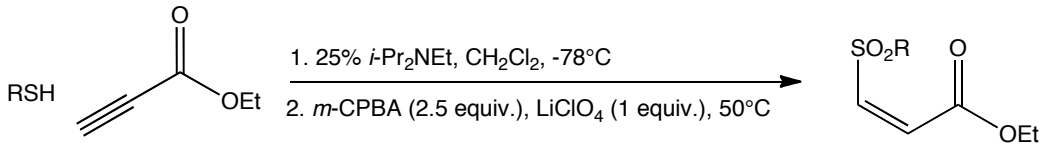



***Figure 6.*** *Optimized One-Pot Addition-Oxidation To Z-Enoates*

The *Z*-sulfone that formed from the addition and oxidation steps reacted more readily in the Diels–Alder cycloaddition, and optimal conditions for the one-pot three-step reaction were determined (Figure 7).

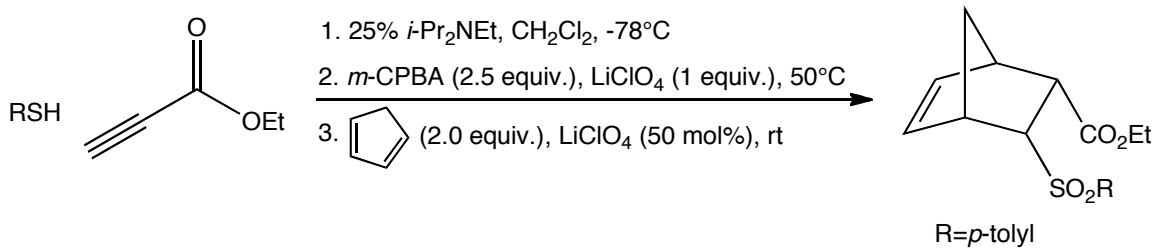


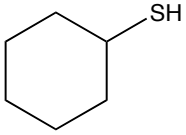
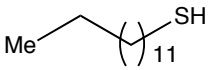
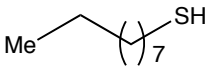

***Figure 7.*** *Optimal Conditions for the One-Pot Three-Step Sequence*

A variety of aromatic thiols were tested for their conjugate addition to ethyl propiolate under the previously discussed reaction conditions by the researchers in the Downey Group. Products were obtained in high yields and selectivity.

## III. Results and Discussion

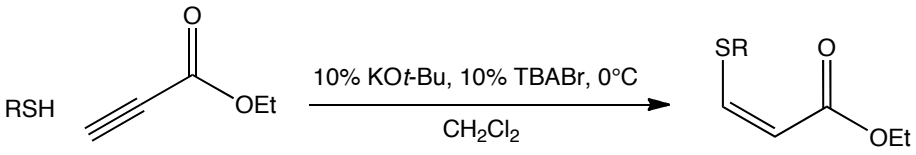
The current work focuses on extending the scope for the one-pot reaction sequence to include aliphatic thiols. When examined under the initially proposed reaction conditions used in the one-pot reaction sequence with aromatic thiols, aliphatic thiols did not produce promising results. Table 1 shows a summary of the thiols utilized and their respective yields and isomer selectivity. Only cyclohexanethiol gave reproducible results (entry 1) after the conjugate addition to ethyl propiolate, and those results were significantly inferior to yields and selectivity obtained by using aromatic thiols as the substrate.

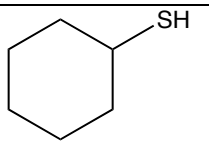
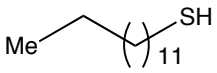
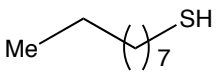
***Table 1.*** *Conjugate Addition for Aliphatic Thiols under Previously Proposed Conditions*

| Entry | Thiol | Z:E | Yield Z+E (%) |
|---|---|---|---|
| 1 |  | 6:1 | 67 |
| 2 |  | Irreproducible | |
| 3 |  | Irreproducible | |

It was found that replacing *i*Pr$_2$NET in the conjugate addition step with a stronger base, KO*t*-Bu, produced significantly better results. Tetrabutylammonium bromide (TBABr) was required to homogenize the reaction mixture due to the insolubility of KO*t*-Bu in methylene chloride. The large aliphatic groups on the tetrabutylammonium ion allow TBABr to not only be soluble in organic solvents but also to allow for the *tert*-butoxide and allenolate ions to be brought into solution as well.[2] Altering the temperature from -78°C to 0°C was also required to accomplish solubility of KO*t*-Bu (Table 2). Unfortunately, the consequence of the higher temperature resulted in lower isomer selectivity than the aromatic thiols.

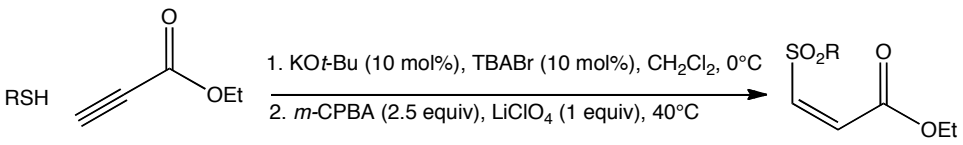
***Table 2.*** *Conjugate Addition Results with Aliphatic Thiols*

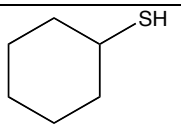
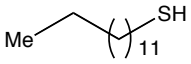
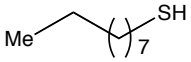



| Entry | Thiol | Z:E | Yield Z (%) |
|---|---|---|---|
| 1 |  | 4.7:1 | 90 |
| 2 |  | 3.5:1 | 81 |
| 3 |  | 4.1:1 | 88 |

With the conjugate addition optimized, the reaction of aliphatic thiols in first the one-pot addition-oxidation sequence and then in the one-pot three-step sequence was attempted. When performed immediately after the optimized conjugate addition step, oxidation did not require any additional modification from the conditions employed for aromatic thiols (Table 3). The yields of the isolated *Z*-sulfones, while reproducible, were not as high as those obtained from the aromatic thiol reactions.

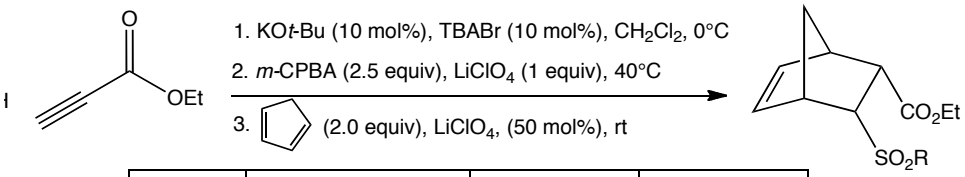
***Table 3.*** *One-Pot Conjugate Addition-Oxidation Results with Aliphatic Thiols*

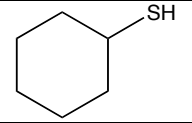
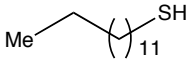
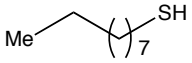



| Entry | Thiol | Diastereomer Ratio | Yield Endo (%) |
|---|---|---|---|
| 1 |  | 4:1 | 60 |
| 2 |  | 3:1 | 51 |
| 3 |  | 3:1 | 58 |

The Diels–Alder step was successfully performed in the one-pot fashion under the same conditions as the aromatic thiols. However the yields obtained were significantly decreased (Table 4).

***Table 4.*** *One-Pot Three-Step Reaction with Aliphatic Thiols*




| Entry | Thiol | Diastereomer Ratio | Yield Endo (%) |
|---|---|---|---|
| 1 |  | 74:26 | 47 |
| 2 |  | 81:19 | 51 |
| 3 |  | 84:16 | 57 |

## IV. Conclusion and Future Work

This project effectively extended the scope of the one-pot three-step conjugate addition-oxidation-Diels–Alder sequence established previously by the Downey research group to include aliphatic thiols. This furthers our ability to produce a densely functionalized bicyclic product that can be easily synthesized from commercially available, inexpensive starting materials.

Some later work born of this project examined chiral ynoates in an attempt to control stereochemistry in the product. The products in the project described above are racemic, so determining conditions that would allow for stereochemical control would be an improvement of the scope of this reaction.

# **Chapter 2:** Stereochemical Control of a One-Pot Three-Step Diels–Alder Reaction using Chiral Substrates

## I. Chiral Sulfones

Stereochemical control in organic reactions is important in order for procedures to be translated into other areas, such as the medical field, due to the vastly different behaviors between two different isomers. In an attempt to control the stereochemistry of the Diels-Alder reaction with sulfones described in Chapter 1, a sulfone with a chiral center was first generated and then utilized as a substrate (Figure 8).

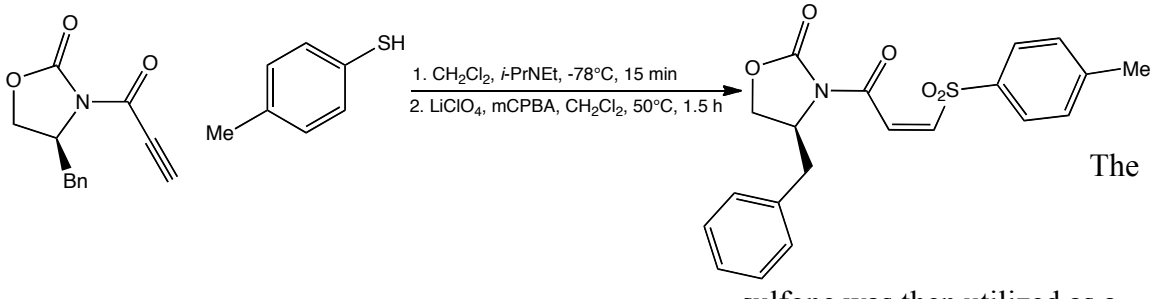
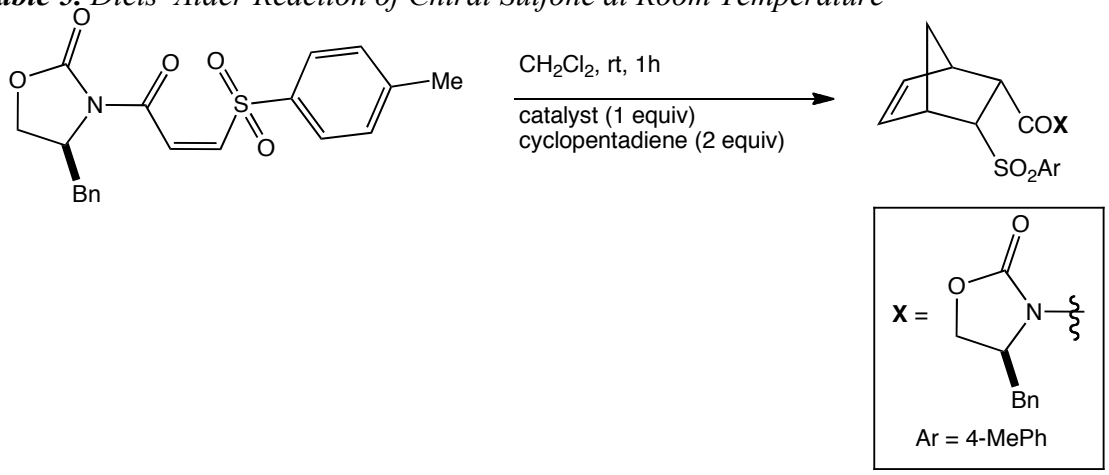



***Figure 8.*** *Generating a Chiral Sulfone Substrate*

The sulfone was then utilized as a

substrate in a Diels–Alder reaction with the goal of eventually completing a one-pot three-step sequence similar to that performed in the reactions of Chapter 1. A variety of different catalysts were tested at room temperature, the results of which are summarized in Table 5. Diastereomeric Ratios for **the 8 different isomers** were examined for the chiral sulfone product. The main isomer was consistently set to 100, and successful values would have been accomplished with a maximum percentage of isomer presence of 100.

***Table 5.*** *Diels–Alder Reaction of Chiral Sulfone at Room Temperature*




| **Catalyst** | **Conversion (%)** | **dr** |
|---|---|---|
| None | 63 | 100:379:382:406:156:370 |
| $LiClO_4$ | 74 | 100:136:190:144:134 |
| $ZnBr_2$ | 98 | 100:39:30:22:9 |
| $MgBr_2 \bullet OEt_2$ | 100 | 100:45:41:53:44 |
| $Yb(OTf)_3$ | 93 | 100:30:91:50:70 |
| $In(OTf)_3$ | 58 | 100:412:352:409:398 |
| $BF_3 \bullet OEt_2$ | No Rxn | ND |
| $TiCl_4$ | 100 | 100:67:89:81:68 |

Various catalysts were then tried at cooler temperatures of -78°C and 0°C in an attempted to generate better isomer selectivity. The results of these reactions are summarized in Tables 6 and 7.

***Table 6.*** *Diels–Alder Reaction at -78°C*

| **Catalyst** | **Conversion (%)** | **dr** |
|---|---|---|
| $ZnBr_2$ | No reaction | _____ |
| $MgBr_2 \bullet OEt_2$ | 76 | 100:71:39:39:42 |

***Table 7.*** *Diels–Alder Reaction at 0°C*

| **Catalyst** | **Conversion (%)** | **dr** |
|---|---|---|
| $ZnBr_2$ | 74 | 100:39:35:22:18 |
| $MgBr_2 \bullet OEt_2$ | 100 | 100:77:14:25:11 |
| $TiCl_4$ | 84 | 100:65:111:72 |

Lower temperature seemed to have no significant effect on the diastereomeric ratio or the conversion to product. Cooling the temperature down to -78°C resulted in lower conversion rates and less selective isomer ratios.

## II. Conclusion and Future Work

The goal of this project was to determine a way to contrive stereoselectivity of the product in the one-pot three-step Diels-Alder reaction described in Chapter 1. It was hoped that utilizing a chiral sulfone substrate would promote this stereoselectivity, however this was not determined.

**Chapter 3:** *Activation of α-Silyl Nitriles by Catalytic Acetate and Addition to Aldehydes: A Nitrile Aldol Reaction*

## I. Introduction

The aldol reaction is one of the most frequently employed carbon-carbon bond forming strategies.[8] Taking two simple molecules and combining them to form a complex product with two new stereocenters makes the aldol reaction a powerful tool in organic synthesis. The mechanism of the reaction involves an attack by a nucleophilic enolate at a carbonyl carbon to produce a β-hydroxy carbonyl compound.[8] An example of such a reaction is that of acetaldehyde in the presence of a base (Figure 9). During this reaction, the enolate anion of the acetaldehyde undergoes a nucleophilic addition onto the carbonyl group of another molecule of acetaldehyde.[8] An alkoxide anion intermediate forms, which can then be protonated to produce the β-hydroxy carbonyl product, which is also known as an aldol. In this reaction, two molecules of the same compound are behaving as both a nucleophilic enolate anion and as an electrophilic carbonyl group.

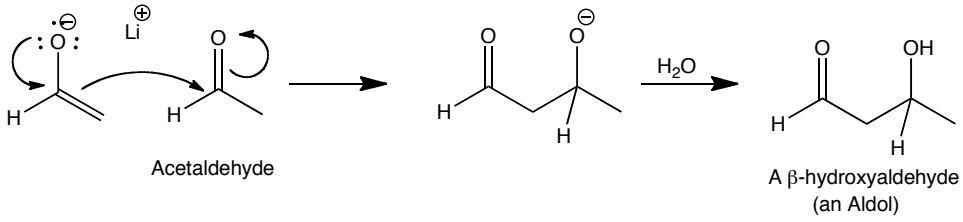



***Figure 9.*** An aldol reaction of acetaldehyde under basic conditions.

Under more basic, vigorous reaction conditions, an aldol condensation may occur, where the aldol product can react further with a hydroxide ion in a reversible deprotonation (Figure 10). In this scenario, the aldol product undergoes net loss of water and becomes an α,β-unsaturated carbonyl compound. Aldol condensations are favored at

high temperature and under extremely basic reaction conditions.[9] At lower temperatures and in more mildly basic environments, the β-hydroxy carbonyl product of an aldol reaction can be favored.

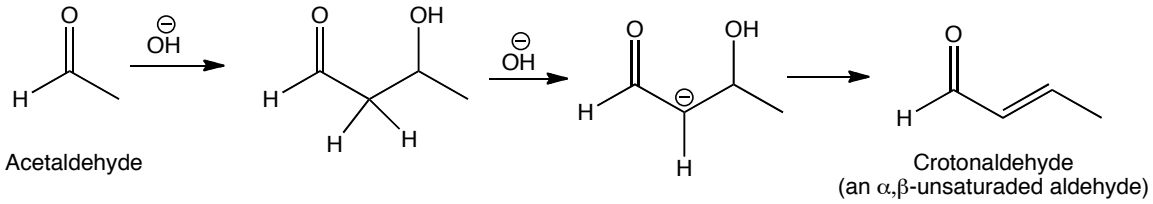



***Figure 10.*** An aldol condensation of acetaldehyde under basic conditions.

The aldol reaction works most predictably when the same molecule is behaving as both nucleophilic enolate and electrophilic carbonyl, as is the case in the mechanisms of Figure 9 and Figure 10. Crossed aldol reactions, which occur between two different carbonyl compounds, are more difficult to control.[9] This is due to the ability of each carbonyl compound to either act as a nucleophilic enolate or an electrophilic carbonyl, and the subsequent formation of four different initial products. A crossed aldol reaction can be controlled, however, when one of the carbonyl compounds lacks α- hydrogen atoms. Aromatic aldehydes are one such class of molecule that has potential usefulness in this reaction.[9] Additionally, aldehydes exhibit greater electrophilicity than ketones, resulting in a greater likelihood that the ketone will behave as the enolate anion, thus limiting the possible number of products (Figure 11).

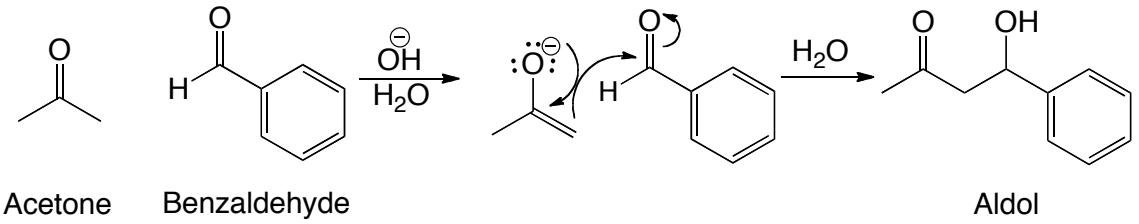



***Figure 11.*** A crossed aldol reaction of acetone and benzaldehyde

Previous work in the literature has demonstrated that aldehydes are able to successfully partake in crossed aldol reactions via silylation of an enol ether prior to the crossed aldol addition.[10] A "trapping" of the aldol anion intermediate as a silylated ether prevents the reverse reaction from occurring (Figure 12). This variation is called the "Mukaiyama aldol reaction." The pre-formation of the enol ether further allows the aldol reaction itself to take place under mild conditions, and avoids resorting to extremely basic or acidic conditions. The variant in Figure 12 is catalyzed by the fluorine source present in tetrabutylamonium fluoride, which removes the silicon from the enolate and activates the molecule toward attacking the aldehyde.

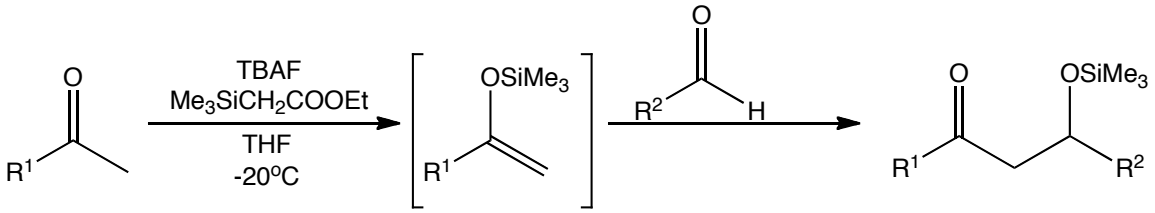



***Figure 12.*** Fluoride-catalyzed aldol reaction between an enol silyl ether and an aldehyde

Nitriles, or compounds that contain a carbon-nitrogen triple bond, could be substituted for the nucleophilic ketone in a crossed aldol reaction. Although oxygen is more electronegative than nitrogen, when the carbon and nitrogen are bonded by a triple bond, the dipole moment between the two atoms becomes approximately equal to the dipole moment present on a carbonyl. Previous research has demonstrated that cerium-mediated nitrile aldol reactions afford high yields of β-hydroxynitriles.[11] Anhydrous cerium chloride has been shown to activate the carbonyl on the aldehyde of these reactions by initiating a partial positive charge (Figure 13). However, extremely basic reaction conditions are still necessary in order to activate the nitrile as a nucleophile, which can then attack at the aldehyde carbonyl.

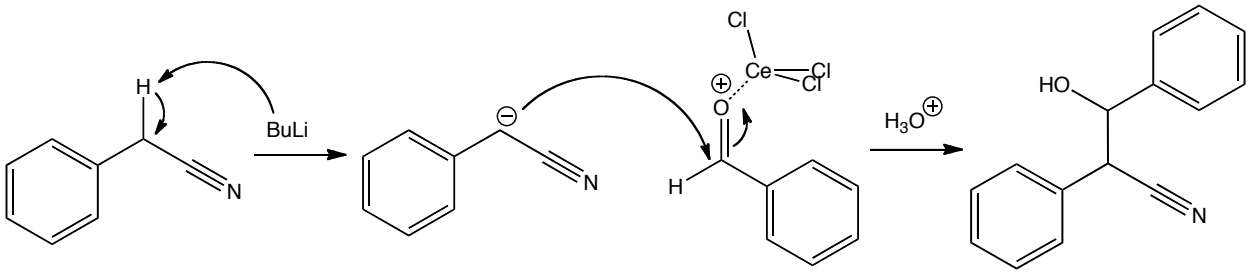



***Figure 13.*** A cerium-mediated nitrile aldol reaction

The Shaw group at UC-Davis has reported silylation of triple bond-containing compounds with TMSOTf. In Figure 14A,[12] the conditions that permit terminal silylation of alkynes are depicted, and in Figure 14B,[13] *C*-silylation of a nitrile is illustrated.

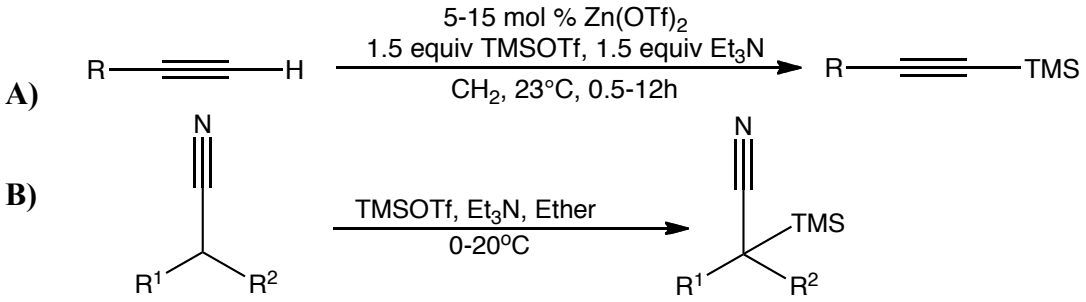



***Figure 14.*** *A)* Silylation of terminal alkynes employing TMSOTf and catalytic quantities of $Zn(OTf)_2$ and *B)* Silylation of nitriles at the α-carbon.

The Shaw group has attempted to silylate 3-phenylpropionitrile with the intention of using the product in a crossed aldol reaction with various aldehydes. They were able to generate a 78% yield of silylated nitrile in the presence of TMSOTf and $Et_3N$ (Figure 15).

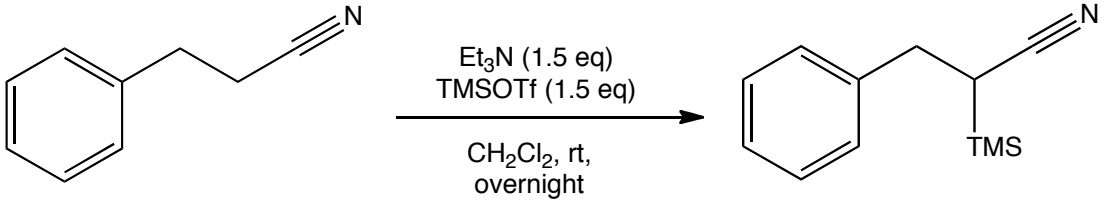



***Figure 15.*** Silylation of 3-phenylproprionitrile

The silylated nitrile was tested as a reactant with benzaldehyde in a crossed aldol reaction under various reaction conditions. It was shown that the solvents DMF, $CH_3CN$, THF, toluene, and DMSO were able to produce the β-hydroxynitrile product in the presence of a nucleophilic catalyst. The best product outcome they obtained was 71% yield using catalytic amounts of cinchonidine in DMF.[14]

The researchers involved in the Downey group have had a long history with TMSOTf reactions,[15] and have recently worked with reactions of TMSOTf and nitrones.[16] This historic interest in TMSOTf and a newer interest in nitrogen-containing compounds have led to a collaboration with the Shaw group on the chemistry involved in the crossed aldol addition of silylated 3-phenylpropionitrile with various aldehydes. The research aims were first to optimize the silylation of the proposed nitrile, and then to develop the crossed aldol addition with various aldehydes.

## II. Results and Discussion

The collaborative efforts with the Shaw research group began with the optimization of the α-silylation of 3-phenylpropionitrile. It was discovered that the nitrile exhibited conversion to the silylated nitrile when in the presence of Hunig's base, trimethylsilyl trifluoromethanesulfonate (TMSOTf), and methylene chloride in additon to the conditions utilized by the Shaw group. The proposed mechanism for the reaction first involves the silylation of the nitrile at the nitrogen, which generates a positive charge (Figure 16). This facilitates deprotonation of the α-carbon by Hunig's base. The nucleophilic nitrile derivative will attack an additional molecule of TMSOTf, leading to the silylation of the nitrile at the α-carbon position. The resulting carbocation will allow

an additional molecule of Hunig's base to attack the TMS on the nitrogen, restoring the molecule as a nitrile. These reaction conditions were tested at a variety of temperatures, the results of which are summarized in Table 8. The best conversion (35%) was obtained when run at room temperature for 16 hours.

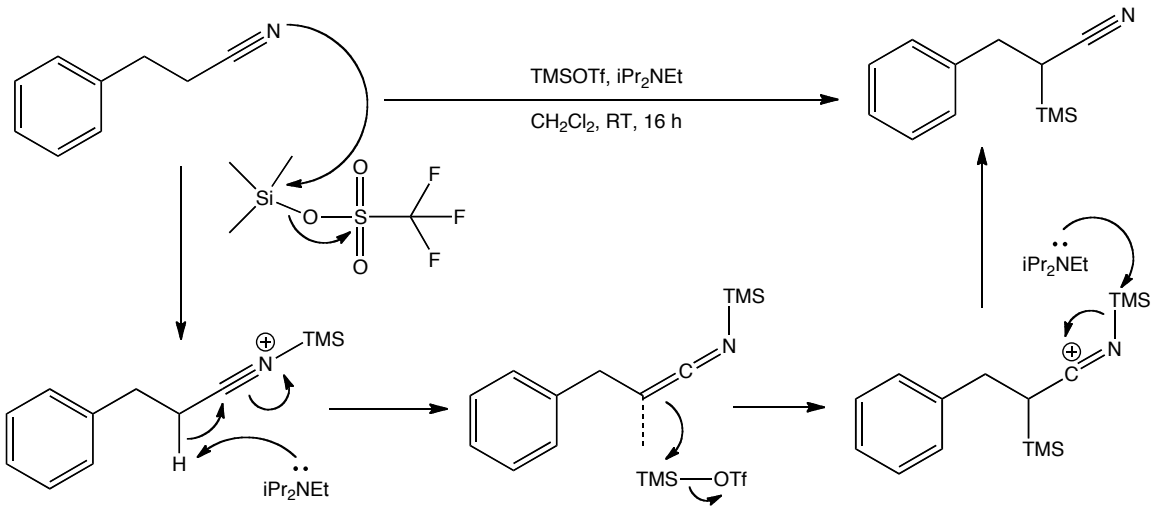
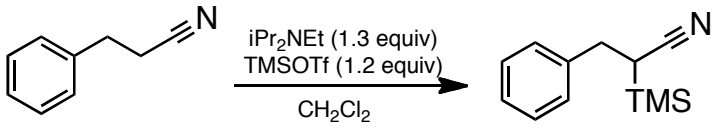



***Figure 16.*** Proposed mechanism for optimized α-silylation of 3-phenylpropionitrile.

***Table 8.*** α-Silylation optimization for 3-phenylpropionitrile.




| Time (hr) | Temp (°C) | Conv. (%) |
|---|---|---|
| 1 | RT | 12.5 |
| 1 | 0 | 0 |
| 1 | -78 | 0 |
| 16 | RT | 35 |

We next optimized the effect of the stoichiometry of Hunig's base and TMSOTf in the reaction. At 1.7 equivalents for each, we were able to obtain a 90% conversion and an 85% yield for the silylated nitrile (Figure 17). Other bases examined included triethylamine and *n*-butyllithium, which resulted in 54% conversion and 65% yield, respectively. Accordingly, the conditions described in Figure 17 were utilized for the remainder of this project.

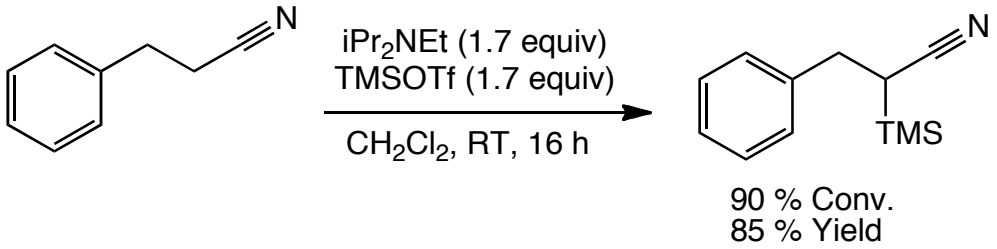
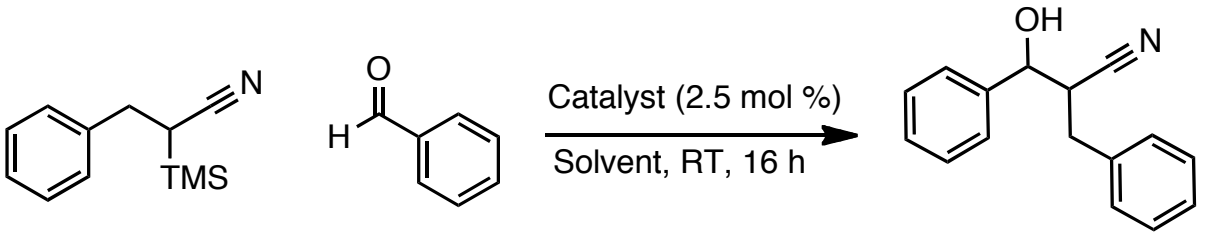



***Figure 17.*** Optimized stoichiometry to produce the silylated nitrile

Optimization of the crossed aldol reaction of the α-silylated nitrile with various aldehydes was then examined. In order to determine ideal conditions for the reaction, benzaldehyde, a common non-enolizable aldehyde, was utilized as the electrophile. A number of catalysts and solvents were screened, the best of which are summarized in Table 9. The optimal catalytic conditions were determined to consist of a catalytic amount (2.5 mol%) of tetrabutylammonium acetate (TBA acetate), with toluene as solvent at room temperature for one hour. These conditions afforded 82% conversion to the β-hydroxynitrile.

***Table 9.*** Successful catalytic combinations in the production of a β-hydroxynitrile




| Catalyst | Solvent | Conversion (%) | Desilylated: Product |
|---|---|---|---|
| TBA acetate | toluene | 82 | 1:4.6 |
| TBA acetate | THF | 73 | 1:1.3 |
| TBA acetate | CPME | 69 | 1:1.5 |
| TBA acetate | DMF | 60 | 1:1.5 |
| TBA acetate + $Pd(OAC)_2$ | toluene | 51 | 1:1 |
| $Pd(OAC)_2$ | toluene | 14 | 1:0.7 |
| TBAF | THF | 56 | 1:1.3 |
| TBAF + $MgSO_4$ | toluene | 83 | 1:1.2 |
| KOtBu + TBABr | DMF | 80 | 1:4.3 |
| KOtBu + TBABr | CPME | 64 | 1:1.4 |
| KOtBu | ether | 43 | 1:0.8 |
| Li(OAC) + TBABr | DMF | 71 | 1:2.5 |
| Na Benzoate | DMF | 67 | 1:2 |
| Cu(OAC) | DMF | 62 | 1:1 |
| $PPh_3$ | CPME | 12 | 1:1 |

Some problems were encountered during the optimization phase. In particular, a reversion back to the desilylated 3-phenylpropionitrile was consistently observed. For this reason, the desilylated nitrile to product ratio became an important factor in our determination of which conditions yielded the most promising results. In addition to affording high conversion to product, the optimized conditions discussed above yielded the best desilylated to product ratio, which ultimately became the determining factor for optimization. Although the combination of KO*t*Bu and TBABr in DMF produced 83% conversion of the α-silyl nitrile, the desilylated to product ratio was significantly poorer than with TBA acetate and toluene (Table 9).

As depicted in the proposed mechanism in Figure 18, it is believed the desilylated nitrile is forming as a result of accidental protonation of the enimine anion by an unknown source, most likely immediately following the desilylation of the nitrile by the acetate. Protonation and resoration of the nitrile disrupts the reaction by preventing a nucleophilic attack on the aldehyde. The most likely proton sources are undesirable $H_2O$ present in the solvent or hygroscopic catalyst source, another nitrile, or the catalyst itself, which is enolizable when silylated. Lowering the catalyst loading of the hygroscopic acetate allowed for control of the amount of unwarranted water and enolizable silylated catalyst present in the reaction.

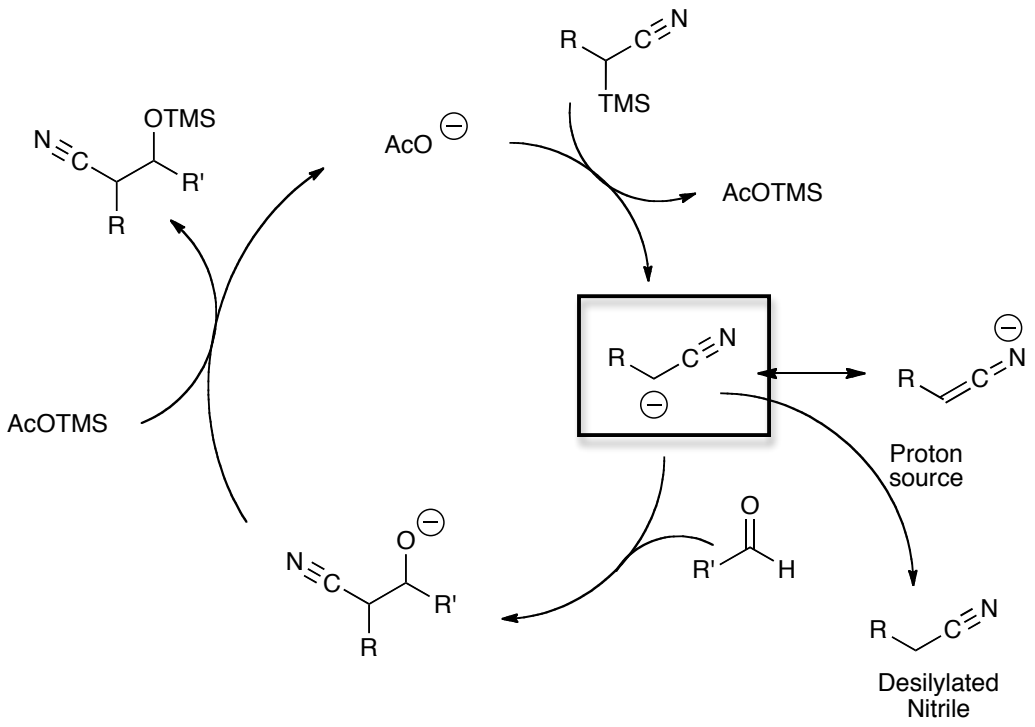


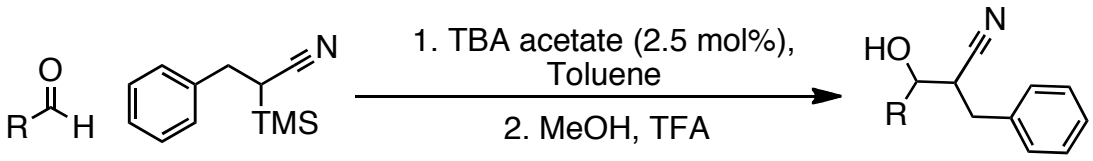

***Figure 18.*** Proposed mechanism for the production of β-hydroxy nitrile by a crossed aldol reaction.

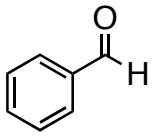
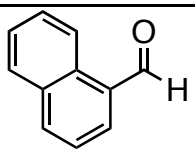
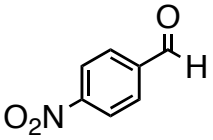
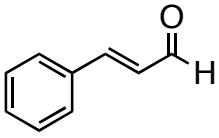
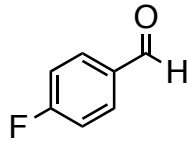
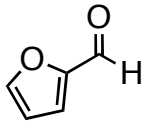
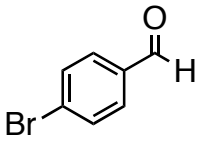
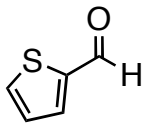
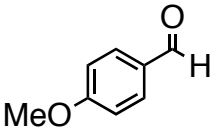
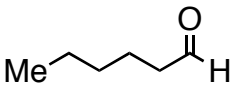
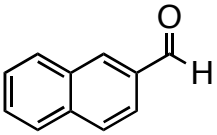
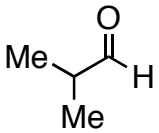
The order of addition was also critical to preventing the reversion to desilylated nitrile. Addition of the aldehyde to the reaction mixture must occur before addition of the acetate. If the aldehyde is added after the catalyst, a complete reversion to the desilylated nitrile is observed before addition to the aldehyde can occur.

Workup is achieved through catalyst removal via a silica plug, and deprotection is performed using MeOH and trifluoroacetic acid (TFA). Deprotection simplifies purification, since the original product mixture contains both free OH and O-silylated products.

Addition to several different aldehydes by silylated 3-phenylpropionitrile has been achieved. The aldehydes with aromatic rings attached to the carbonyl have the highest yields. These results are summarized in Table 10. Yields observed by the addition

of isobutyraldehyde and cinnamaldehyde were particularly low (33 %) due to the presence of hydrogens on the α-carbon of the aldehyde, which can act as a proton source and result in reversion back to the original, desilylated nitrile.




| Aldehyde | Yield (%) | Aldehyde | Yield (%) |
|---|---|---|---|
|  | 89 |  | 80 |
|  | 87 |  | TBD |
|  | 83 |  | 90 |
|  | 88 |  | 76 |
|  | 77 |  | 33 |
|  | 86 |  | 33 |

The current method is an improvement upon previous nitrile aldol reactions for several reasons. First, nitrile aldol reactions described in the literature are often reversible. The silylation of the oxygen on the β carbon makes this product more stable by preventing a base from attacking the β-hydroxyl group, which would provoke a

reversion to starting material (Figure 19). In this reaction, it is only after the mildly basic acetate is removed from the environment that the TMS is removed from the product via deprotection.

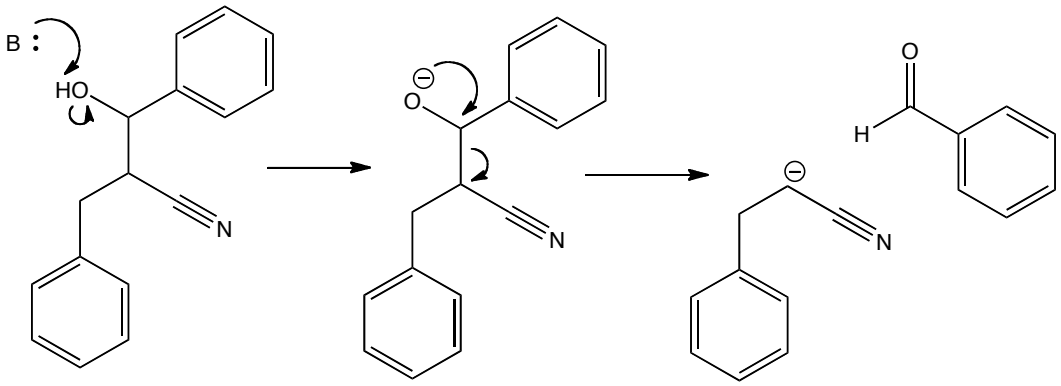



***Figure 19.*** *Base-Mediated Retro-Aldol Reaction of β-Hydroxy Nitriles*

The reaction discussed here further improves on reactions in the literature by avoiding the use of dangerous bases, such as *n*-butyllithium. Not only are such bases highly flammable and extremely reactive with ambient water vapor, but they also require reaction temperatures as low as -78°C and reaction times as long as three days. The conditions utilized in this paper are mild and reactions quickly reach completion.

To further establish the applicability of this reaction, it is imperative to demonstrate the ability of other silylated nitriles to undergo the reaction. Alice Lee, ’16, is currently working to synthesize other α-silyl nitriles, and to demonstrate their ability to react with benzaldehyde under the proposed conditions. The hope is for eventual expansion to other electrophile classes will follow.

## III. Conclusion and Future Work

In collaboration with Jared T. Shaw's research group at UC-Davis, an α-silylated 3-phenylpropionitrile has been synthesized. A crossed aldol reaction of the nitrile with various aldehydes to generate a β-hydroxynitrile product has also been optimized. This nitrile aldol reaction improves upon past methods by introducing a silylated oxygen at the β position, which prevents the reverse reaction from occurring. Furthermore, we have managed to control a nitrile aldol reaction under mild conditions and have avoided resorting to dangerous bases or catalysts.

# **Chapter 4:** *Experimental*

## I. *One-Pot Reaction of Ethyl Propiolate Experimental Section*

**General Information.** Reactions were carried out under an atmosphere of nitrogen with a septum cap in oven-dried glassware with magnetic stirring. $CH_2Cl_2$ was purified by passage through a bed of activated alumina.[17] *i*-$Pr_2NEt$ was distilled and stored in a Schlenk flask under inert atmosphere. Cyclopentadiene was cracked and distilled from dicyclopentadiene, stored at -20 °C, and used within two weeks of distillation. All other chemicals were used as received. Purification of reaction products was carried out by flash chromatography using silica gel (230-400 mesh). Analytical thin layer chromatography was performed on silica gel plates. Visualization was accomplished with UV light and phosphomolybdic acid stain, followed by heating. Infrared spectra were recorded on an FT-IR spectrometer. $^1H$ NMR spectra were recorded on a 500 MHz spectrometer or 300 MHz spectrometer, and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.28 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, sx = sextet, sp=septet, m = multiplet, b = broad; coupling constant(s) in Hz; integration). Proton-decoupled $^{13}C$ NMR spectra were recorded on a 125 MHz spectrometer or 75 MHz spectrometer, and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). High-resolution mass spectra were obtained by electrospray ionization. Melting points were determined using a capillary melting point apparatus.

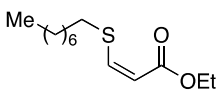
**General Procedure A.** *Alkoxide-Mediated Heteroconjugate-Addition of Thiol Nucleophiles to Ethyl Propiolate*

To an oven-dried round-bottomed flask under $N_2$ atmosphere was added the KO*t*-Bu (22.7 mg, 0.20 mmol), $CH_2Cl_2$ (4.0 mL), and thiol (2.0 mmol). To the heterogeneous mixture was added tetrabutylammonium bromide (65.2 mg, 0.20 mmol) and the reaction

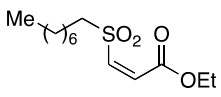
mixture became homogenous. After cooling to -78 °C, the mixture was treated with ethyl propiolate (203 μL, 196 mg, 2.0 mmol) and stirred for 1 h. The mixture was passed through a column of silica (2 cm x 1 cm) with $Et_2O$. The solvent was removed in vacuo and the residue was purified by column chromatography (0-10% EtOAc/hexanes).

**General Procedure B.** *Two-Step Alkoxide-Mediated Heteroconjugate-Addition-Oxidation Sequence*

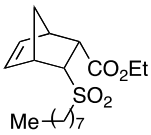
To an oven-dried round-bottomed flask under $N_2$ atmosphere was added the KO*t*-Bu (23.3 mg, 0.21 mmol), $CH_2Cl_2$ (4.0 mL), and thiol (2.0 mmol). To the heterogeneous mixture was added tetrabutylammonium bromide (64.5 mg, 0.20 mmol) and the reaction mixture became homogenous. After cooling to 0 °C, the mixture was treated with ethyl propiolate (203 μL, 196 mg, 2.0 mmol) and stirred for 1 h. Under ambient atmosphere, *meta*-chloroperbenzoic acid (*m*CPBA) (1121 mg, 5.0 mmol, 77% purity) was added, followed by cold $CH_2Cl_2$ (20 mL). After 5 min, $LiClO_4$ (213.0 mg, 2.0 mmol) was added and the reaction mixture was warmed to room temperature, then stirred at reflux (40 °C) for 1.5 h. The mixture was diluted with 40 mL of $Et_2O$, then washed with 20 mL 1M NaOH solution (2x), 20 mL 1M HCl solution (1x), 20 mL 1M $Na_2S_2O_3$ solution (1x) and 20 mL water (1x). The organic layer was dried over $MgSO_4$. After filtration, the solvent was removed in vacuo and the residue was purified by column chromatography (5-20% EtOAc/hexanes).




**Ethyl 3-(octylthio)acrylate** When General Procedure B was followed using octanethiol (348 mL, 293 mg, 2.0 mmol), the title compound was prepared as a colorless oil as a mixture of the *Z* and *E* isomers (430 mg, 88% yield): IR (film) 2924, 2854, 2697, 1568, 1372, 1208, 1159, 1034, 797 $cm^{-1}$; HRMS (ESI, TOF): Exact mass calcd for $C_{13}H_{24}O_2SNa$ $[M+Na]^+$, 267.1395. Found 267.1404. ***Z* isomer:** $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 10.0 Hz, 1H), 5.86 (d, *J* = 10.0 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 2.77 (t, *J* = 7.5 Hz, 1H), 1.74-1.68 (m, 2H), 1.46-1.39 (m, 2H), 1.36-1.26 (m, 8H), 1.31 (t, *J* = 7.1, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 166.7, 150.3, 113.0, 60.0, 36.1, 31.8, 30.3, 29.1 (double intensity), 28.5, 22.6, 14.4, 14.0; ***E* isomer:** $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 15.0 Hz, 1H), 5.76 (d, *J* = 15.3 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.81 (t, *J* = 7.5 Hz, 1H), 1.73-1.67 (m, 2H), 1.46-1.39 (m, 2H), 1.36-1.26 (m, 8H), 1.30 (t, *J* = 7.2, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 165.4, 146.9, 113.7, 60.1, 32.0, 31.8, 29.1, 29.0, 28.8, 28.6, 22.6, 14.3, 14.0.




**Ethyl 3-(octylsulfonyl)acrylate** When General Procedure B was followed using 1-octanethiol (348 mL, 293 mg, 2.0 mmol), the title compound was prepared as a colorless oil (321 mg, 58% yield): IR (film) 2923, 2847, 1733, 1468, 1342, 1313, 1227, 1158, 1127, 1022, 789, 736 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.63 (d, *J* = 11.9 Hz, 1H), 6.59 (d, *J* = 11.6 Hz, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.26-3.22 (m, 2H), 1.89-1.82 (m, 2H), 1.49-1.43 (m, 2H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.38-1.26 (m, 8H), 0.91 (t, *J* = 6.9 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 163.5, 136.1, 134.1, 62.2, 55.6, 31.7, 29.0, 28.9, 28.4, 22.6, 22.0, 14.0, 13.9; HRMS (ESI, TOF): Exact mass calcd for $C_{13}H_{25}O_4S$ $[M+H]^+$, 277.1468. Found 277.1464.



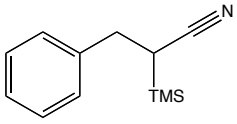

***cis*,*endo*-Ethyl 3-(octylsulfonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate** To an oven-dried round-bottomed flask under $N_2$ atmosphere was added the KO*t*-Bu (22.2 mg, 0.20 mmol), $CH_2Cl_2$ (4.0 mL), and octanethiol (348 mL, 293 mg, 2.0 mmol). To the heterogeneous mixture was added tetrabutylammonium bromide (64.6 mg, 0.20 mmol) and the reaction mixture became homogenous. After cooling to 0 °C, the mixture was treated with ethyl propiolate (203 μL, 196 mg, 2.0 mmol) and stirred for 1 h. Under ambient atmosphere, *meta*-chloroperbenzoic acid (*m*CPBA) (1.12 g, 5.0 mmol, 77% purity) was added, followed by cold $CH_2Cl_2$ (20 mL). After 5 min, $LiClO_4$ (211.2 mg, 2.0 mmol) was added and the reaction mixture was warmed to room temperature, then stirred at reflux (40 °C) for 1.5 h. The mixture was allowed to cool to room temperature, and then cyclopentadiene (330 mL, 265 mg, 4.0 mmol) and more $LiClO_4$ (211.7 mg, 2.0 mmol) were added. The flask was sealed and the mixture was stirred overnight. The mixture was diluted with 40 mL of $Et_2O$, then washed with 20 mL 1M NaOH solution (2x), 20 mL 1M HCl solution (1x), 20 mL 1M $Na_2S_2O_3$ solution (1x) and 20 mL water (1x), and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (5-15% EtOAc/hexanes). The product was isolated as a pale yellow oil (199 mg, 58% yield): IR (film) 2923, 2852, 1737, 1464, 1315, 1246, 1182, 1134, 1121, 1063, 1041, 908, 727, 648 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 5.3, 2.8 Hz, 1H), 6.33, (dd, *J* = 5.3, 2.8 Hz, 1H), 4.20 (dq, *J* = 11.0, 7.2 Hz, 1H), 4.11 (dq, *J* = 11.0, 7.2 Hz, 1H), 3.93 (dd, *J* = 10.0, 3.4 Hz, 1H), 3.51 (bs, 1H), 3.41 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.27 (bs, 1H), 3.23-3.13 (m, 2H), 1.90-1.80 (m, 2H), 1.56 (dt, *J* = 8.7, 1.9 Hz, 1H), 1.48-1.41 (m, 2H), 1.29 (t, *J* = 7.2 Hz 3H), 1.38-1.26 (m, 9H), 0.91 (t, *J* = 6.9 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 170.4, 137.5, 132.2, 65.9, 60.8, 55.0, 49.0, 47.6, 46.2 (double intensity), 31.6, 29.0, 28.9, 28.5, 22.5, 21.3, 13.94, 13.87; HRMS (ESI, TOF): Exact mass calcd for $C_{18}H_{31}O_4S$ $[M+H]^+$, 343.1938. Found 343.1930.

## II. *Aldol Reaction of α-Silyl Nitriles Experimental Section*

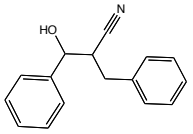
**General Information:** Reactions were carried out under an atmosphere of nitrogen with a septum cap in oven-dried glassware with magnetic stirring. Toluene was purified by passage through a bed of activated alumina.[17] Tetrabutylammonium acetate was stored in a desiccator. TMSOTf was transferred to a Schlenk Flask under inert atmosphere for storage after opening. *i*-$Pr_2NEt$ was distilled and stored in a Schlenk flask under inert atmosphere. All other chemicals were used as received. Purification of reaction products was carried out by flash chromatography using silica gel (230-400 mesh). Analytical thin layer chromatography was performed on silica gel plates. Visualization was accomplished with UV light and phosphomolybdic acid stain. Infrared spectra were recorded on an FT-IR spectrometer. $^1H$ NMR spectra were recorded on a 500 MHz spectrometer or 300 MHz spectrometer, and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.28 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, sx = sextet, sp=septet, m = multiplet, b = broad; coupling constant(s) in Hz; integration). Proton-decoupled $^{13}C$ NMR spectra were recorded on a 125 MHz spectrometer or 75 MHz spectrometer, and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). High-resolution mass spectra

were obtained by electrospray ionization. Melting points were determined using a capillary melting point apparatus.

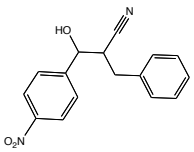
**General Procedure for Acetate-Catalyzed Aldol Reactions of α-Silyl Nitriles.** To an oven-dried round-bottomed flask under $N_2$ atmosphere was added 3-phenyl-2-(trimethylsilyl)propanenitrile (203 mg), aldehyde (1.00 mmol), toluene (10 mL), and TBA Acetate (7.5 mg). The reaction was stirred at room temperature for one hour. The mixture was passed through a column of silica (2 cm x 1 cm) with $Et_2O$. The solvent was removed in vacuo. The residue was purified by column chromatography (5-20% EtOAc/hexanes).




**3-phenyl-2-(trimethylsilyl)propanenitrile** To a 50-mL oven-dried round-bottomed flask under $N_2$ was added $CH_2Cl_2$, 3-phenylpropionitrile, *i*-$Pr_2NEt$, and TMSOTf. The reaction was capped and left to stir at room temperature for 16 h. Solvent was reduced to about 2mL in vacuo. An extraction was performed with 50 mL $Et_2O$ and $H_2O$. The organic layer was dried with $MgSO_4$. The drying agent was filtered off, and the solvent was removed in vacuo. The residue was purified by column chromatography (1-20% EtOAc/hexanes). The product was isolated as a yellow solid. mp: 28-33°C; $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.33 (m, 2H), 7.33 – 7.25 (m, 3H), 2.91 – 2.80 (m, 2H), 2.08 (dd, *J* = 10.5, 4.9 Hz, 1H), 0.27 (s, 9H).

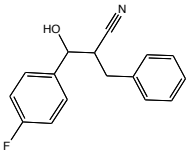



**2-Benzyl-3-hydroxy-3-phenylpropanenitrile** The title compound was prepared according to the General Procedure, using benzaldehyde (102 μL, 1.00 mmol). The product was isolated as a colorless solid. mp: 71-86°C; IR (film) 3746, 3435, 3066, 3021, 2354, 2242, 1597, 1490, 1455, 1321, 1210, 1179, 1067, 1027, 908, 765, 730, 697, 623, 610 $cm^{-1}$; $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.48 – 7.24 (m, 20H), 4.82 (d, *J* = 6.5 Hz, 1H), 4.78 (d, *J* = 5.0 Hz, 1H), 3.52 (s, 2H), 3.20 (ddd, *J* = 9.9, 6.6, 4.5 Hz, 1H), 3.07 (ddd, *J* = 9.2, 6.1, 4.9 Hz, 1H), 3.03 – 2.90 (m, 3H), 2.86 (dd, *J* = 13.8, 10.0 Hz, 1H).; $^{13}$C NMR (126 MHz, $CDCl_3$) δ 140.3, 139.8, 136.8, 136.8, 129.2, 129.0, 128.9, 128.9, 128.9, 128.8, 128.8, 127.4, 127.3, 126.7, 126.2, 119.8, 119.7, 77.5, 77.3, 77.0, 73.2, 72.9, 43.3, 42.6, 35.3, 34.1; HRMS (ESI) exact mass calcd for $C_{26}H_{19}ON_2$ [M+$NH_4$] 255.149, found 255.148.

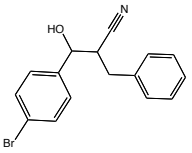



**2-Benzyl-3-hydroxy-3-(4-nitrophenyl)propanenitrile** The title compound was prepared according to the General Procedure, using 4-nitrobenzaldehyde (152 mg, 1.00 mmol). The product was isolated as a yellow oil. IR (film) 3439, 3066, 3026, 2919, 2861, 2371, 2242, 1597, 1517, 1497, 1450, 1345, 1071, 1013, 910, 857, 720, 698, 602 $cm^{-1}$; $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 2.0 Hz, 1H), 8.26 (d, *J* = 2.2 Hz, 2H), 8.24 (d, *J* = 1.9 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.62 – 7.55 (m, 2H), 7.42 – 7.23 (m, 9H), 4.99 (dd, *J* = 6.7, 3.5 Hz, 1H), 4.93 (q, *J* = 2.3, 1.8 Hz, 1H), 3.10 – 3.07 (m, 2H),

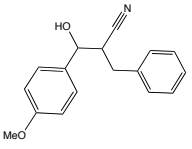
3.04 – 2.91 (m, 1H), 2.80 (d, *J* = 3.8 Hz, 1H), 2.76 (d, *J* = 4.3 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 148.2, 148.1, 147.4, 146.8, 136.2, 136.0, 129.1, 128.9, 128.9, 127.6, 127.5, 127.0, 124.0, 123.9, 120.0, 119.0, 118.5, 77.3, 77.2, 77.0, 76.8, 72.3, 71.5, 43.0, 42.4, 35.3, 33.9.



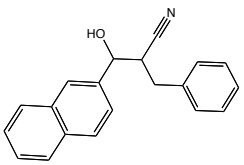

**2-Benzyl-3-(4-fluorophenyl)-3-hydroxypropanenitrile** The title compound was prepared according to the General Procedure, using 4-fluorobenzaldehyde (106 μL, 1.00 mmol). The product was isolated as a yellow wax. IR (film) 3422, 3061, 3021, 2919, 2371, 2242, 1980, 1601, 1509, 1450, 1294, 1223, 1157, 1063, 1014, 908, 840, 729, 699, 649, 610; $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.44 – 7.29 (m, 9H), 7.29 – 7.21 (m, 4H), 7.09 (dtd, *J* = 8.6, 6.1, 2.2 Hz, 4H), 4.78 (dd, *J* = 13.0, 5.6 Hz, 2H), 3.38 – 3.24 (m, 2H), 3.16 (ddd, *J* = 9.8, 6.6, 4.6 Hz, 1H), 3.06 – 2.89 (m, 4H), 2.84 (dd, *J* = 13.8, 9.9 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.8, 163.7, 161.9, 161.8, 136.7, 136.7, 136.4, 136.3, 135.9, 135.8, 129.1, 129.0, 128.9, 128.8, 128.5, 128.4, 128.0, 127.9, 127.4, 127.4, 119.7, 119.6, 115.8, 115.7, 115.6, 115.6, 72.5, 72.0, 43.4, 42.7, 35.2, 34.1.




**2-Benzyl-3-(4-bromophenyl)-3-hydroxypropanenitrile** The title compound was prepared according to the General Procedure, using 4-bromobenzaldehyde (185 mg, 1.00 mmol). The product was isolated as a white wax. IR (film) 3435, 3025, 2919,2247,1593, 1488, 1455, 1397, 1071, 1030, 1009, 907, 819, 730, 698, 648, 631, 627, 622, 612, 607 $^{cm-1}$; $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.53 (t, *J* = 8.1 Hz, 4H), 7.42 – 7.19 (m, 13H), 4.80 – 4.68 (m, 2H), 3.31 (s, 2H), 3.14 (ddd, *J* = 10.6, 6.6, 4.6 Hz, 1H), 3.05 – 2.89 (m, 4H), 2.83 (dd, *J* = 13.9, 9.9 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 139.5, 139.0, 136.6, 136.6, 131.9, 131.9, 129.1, 129.0, 128.9, 128.9, 128.4, 127.9, 127.5, 127.4, 122.8, 122.6, 119.7, 119.5, 72.5, 72.0, 53.6, 43.2, 42.5, 35.2, 34.0; HRMS (ESI) exact mass calcd for $C_{16}H_{18}ON_2$ [M+$NH_4$] 333.0597, found 333.0589.

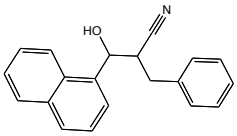



**2-Benzyl-3-hydroxy-3-(4-methoxyphenyl)propanenitrile** The title compound was prepared according to the General Procedure, using 4-anisaldehyde (113 μL, 1.00 mmol). The product was isolated as a white solid. Mp: 70-74°C; IR (film) 3448, 2932, 2839, 2362, 2242, 1606, 1513, 1459, 1303, 1248, 1175, 1030, 907, 834, 726, 698, 668, 649; $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.21 (m, 12H), 6.94 (dq, *J* = 8.7, 3.2 Hz, 3H), 4.74 (t, *J* = 6.5 Hz, 2H), 3.82 (d, *J* = 1.6 Hz, 5H), 3.18 (ddd, *J* = 9.8, 6.7, 4.6 Hz, 1H), 3.07 – 2.99 (m, 2H), 2.99 – 2.80 (m, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 159.2, 159.3, 177.0, 136.9, 132.5, 132.1, 129.2, 129.0, 128.8, 128.8, 127.9, 127.5, 127.3, 127.2, 120.0, 120.0, 119.9, 114.2, 114.2, 76.9, 72.8, 72.6, 55.4, 55.4, 43.3, 42.7, 35.3, 34.3; HRMS (ESI) exact mass calcd for $C_{17}H_{21}O_2N_2$ [M+$NH_4$] 285.1598, found 285.1589.

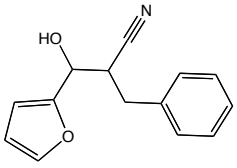



**2-Benzyl-3-hydroxy-3-(naphthalen-2-yl)propanenitrile** The title compound was prepared according to the General Procedure, using 2-naphthaldehyde (156 mg, 1.00 mmol). The product was isolated as

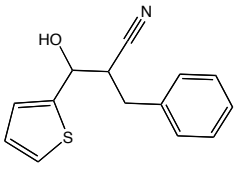
a white wax. IR (film) 3435, 3057, 3025, 2362, 2247, 1601, 1490, 1446, 1361, 1272, 1125, 1076, 1036, 905, 854, 814, 726, 699, 646, 621; $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 7.89 (tdd, *J* = 14.5, 8.0, 2.7 Hz, 8H), 7.57 (ddd, *J* = 22.9, 7.1, 2.7 Hz, 5H), 7.48 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.42 – 7.30 (m, 6H), 7.30 – 7.22 (m, 4H), 4.96 (d, *J* = 6.5 Hz, 1H), 4.89 (d, *J* = 5.1 Hz, 1H), 3.63 – 3.45 (m, 2H), 3.29 (ddd, *J* = 10.6, 6.5, 4.5 Hz, 1H), 3.15 (dt, *J* = 9.3, 5.8 Hz, 1H), 3.03 – 2.85 (m, 4H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 137.9, 137.4, 136.9, 136.9, 133.6, 133.5, 133.2, 133.2, 129.2, 129.1, 128.9, 128.8, 128.8, 128.7, 128.3, 128.3, 127.9, 127.4, 127.3, 126.7, 126.6, 126.6, 126.1, 125.7, 124.1, 123.7, 120.0, 120.0, 73.2, 73.0, 43.2, 42.6, 35.4, 34.1; HRMS (ESI) exact mass calcd for $C_{20}H_{21}ON_2$ [M+$NH_4$] 305.1648, found 305.1651.




**2-Benzyl-3-hydroxy-3-(naphthalen-1-yl)propanenitrile** The title compound was prepared according to the General Procedure, using 1-naphthaldehyde (136 μL, 1.00 mmol). The product was isolated as a pale yellow wax. IR (film) 3433, 3058, 3023, 2370, 2253, 1600, 1494, 1451, 1065, 1022, 986, 908, 800, 779, 728, 699, 626, 614; $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 8.03 – 7.98 (m, 1H), 7.97 – 7.82 (m, 4H), 7.81 – 7.77 (m, 1H), 5.73 (d, *J* = 5.7 Hz, 1H), 5.48 (d, *J* = 3.5 Hz, 1H), 3.44 (ddd, *J* = 10.2, 5.8, 4.7 Hz, 1H), 3.25 (td, *J* = 7.7, 3.5 Hz, 1H), 3.22 – 3.07 (m, 2H), 3.07 – 2.86 (m, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 137.0, 136.8, 136.0, 135.3, 133.9, 133.8, 130.2, 129.6, 129.3, 129.3, 129.2, 129.2, 129.1, 129.1, 129.1, 129.0, 128.9, 128.9, 128.8, 128.8, 128.7, 128.7, 128.7, 127.5, 127.2, 126.7, 126.6, 126.0, 125.8, 125.6, 125.3, 124.8, 123.9, 122.5, 121.6, 120.2, 119.3, 70.0, 68.3, 42.4, 41.4, 36.1, 33.3, 1.1; HRMS (ESI) exact mass calcd for $C_{20}H_{21}ON_2$ [M+$NH_4$] 305.1648, found 305.1649.

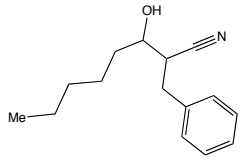



**2-benzyl-3-(furan-2-yl)-3-hydroxypropanenitrile** The title compound was prepared according to the General Procedure, using 2-Furanaldehyde (83 μL, 1.00 mmol). The product was isolated as a deep yellow oil. IR (film) 3421, 3030, 2910, 2362, 2247, 1957, 1608, 1497, 1455, 1228, 1146, 1067, 1030, 1011, 746, 700, 618, 591; $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 7.45 (dd, *J* = 13.0, 1.8 Hz, 2H), 7.42 – 7.34 (m, 4H), 7.34 – 7.25 (m, 5H), 6.47 (dd, *J* = 7.8, 3.3 Hz, 2H), 6.41 (ddd, *J* = 7.0, 3.4, 1.8 Hz, 2H), 4.83 (dd, *J* = 22.5, 6.0 Hz, 2H), 3.44 – 3.26 (m, 2H), 3.15 – 2.91 (m, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 152.69, 152.47, 142.89, 142.79, 136.62, 136.55, 129.19, 129.11, 128.87, 128.81, 127.40, 127.33, 119.55, 119.50, 110.67, 108.60, 108.23, 66.98, 66.89, 66.87, 40.57, 40.25, 34.99, 34.04.

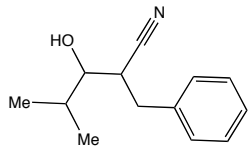



**2-Benzyl-3-hydroxy-3-(thiophen-2-yl)propanenitrile** The title compound was prepared according to the General Procedure, using 2-thiophenecarboxaldehyde (92 μL, 1.00 mmol). The product was isolated as a pale yellow oil. IR (film) 3436, 3108, 3086, 3060, 3026, 2924, 2359, 2338, 2245, 1809, 1602, 1497, 1455, 1439, 1391, 1307, 1235, 1178, 1125; $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.34 (m, 6H), 7.34 – 7.25 (m, 6H), 7.15 (dt, *J* = 3.5, 0.9 Hz, 1H), 7.13 (dt, *J* = 3.5, 1.0 Hz, 1H), 7.05 (td, *J* = 5.4, 3.6 Hz, 2H), 5.06 (dd, *J* = 9.6, 6.0 Hz, 2H), 3.26 (ddd, *J* = 9.4, 6.7, 4.9 Hz, 1H), 3.17 (ddd, *J* = 9.3, 5.9, 5.2 Hz, 1H), 3.14 – 3.07 (m, 1H), 3.07 – 2.89 (m, 4H); $^{13}$C NMR (126 MHz,

$CDCl_3$) δ 143.7, 143.2, 136.6, 136.6, 129.2, 129.1, 128.9, 128.8, 127.4, 127.3, 127.1, 127.1, 126.0, 125.9, 125.8, 125.4, 119.5, 119.5, 69.4, 69.2, 43.5, 43.0, 35.2, 34.3.




**2-Benzyl-3-hydroxyoctanenitrile** The title compound was prepared according to the General Procedure, using hexanal (123 μL, 1.00 mmol). The product was isolated as green oil. IR (film) 3453, 3030, 2931, 2856, 2371, 2238, 2144, 1606, 1495, 1455, 1250, 1125, 1029, 947, 849, 743, 698, 620, 601 $cm^{-1}$; $^1H$ NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.33 (m, 4H), 7.33 – 7.27 (m, 6H), 3.77 (ddd, *J* = 8.9, 5.3, 3.0 Hz, 1H), 3.67 (ddd, *J* = 8.2, 4.8, 3.1 Hz, 1H), 3.14 – 3.01 (m, 3H), 2.96 – 2.88 (m, 2H), 2.85 (ddd, *J* = 8.7, 6.8, 3.0 Hz, 1H), 2.48 (s, 2H), 1.83 – 1.68 (m, 2H), 1.68 – 1.53 (m, 3H), 1.52 – 1.42 (m, 1H), 1.42 – 1.21 (m, 10H), 0.93 (dt, *J* = 10.5, 6.7 Hz, 6H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 137.1, 137.0, 129.0, 129.0, 128.8, 128.8, 127.2, 71.0, 70.4, 41.5, 41.3, 35.7, 35.3, 34.4, 34.3, 31.6, 31.5, 25.3, 25.1, 22.5, 22.5, 21.8, 14.0, 14.0; HRMS (ESI) exact mass calcd for $C_{15}H_{25}ON_2$ [M+$NH_4$] 249.1961, found 249.1961.




**2-Benzyl-3-hydroxy-4-methylpentanenitrile** The title compound was prepared according to the General Procedure, using isobutyraldehyde (91 μL, 1.00 mmol). The product was isolated as pale yellow oil. IR (film) 3453, 3025, 2962, 2923, 2874, 2242, 1601, 1497, 1455, 1388, 1254, 1130, 1060, 1030, 1006, 836, 746, 699, 621 $cm^{-1}$; $^1H$ NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.27 (m, 9H), 3.62 (p, *J* = 3.2 Hz, 1H), 3.29 – 3.22 (m, 1H), 3.19 – 3.11 (m, 2H), 3.05 – 2.96 (m, 2H), 2.96 – 2.86 (m, 2H), 2.37 – 2.30 (m, 1H), 2.30 – 2.22 (m, 1H), 2.10 (heptd, *J* = 6.8, 4.2 Hz, 1H), 1.93 (dp, *J* = 8.1, 6.6 Hz, 1H), 1.06 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 137.2, 137.1, 129.2, 129.0, 128.8, 128.7, 127.2, 127.2, 120.4, 119.7, 75.8, 75.2, 38.9, 38.8, 35.9, 34.1, 32.8, 31.0, 19.7, 19.0, 18.5, 15.5.

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