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One-pot reactions of ethyl propiolate

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Title of Project __ ONE-POT REACTIONS OF ETHYL PROPIOLATE

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ONE-POT REACTIONS OF ETHYL PROPIOLATE

by

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Honors Thesis

in

Department of Chemistry
University of Richmond
Richmond, VA

March 28, 2013

Advisor: Prof. C. Wade Downey

To my parents Maria and Marcel, and my sister Laura

Mulţumesc!

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Abstract

Through an efficient one-pot reaction sequence, ethyl propiolate can be transformed into a complex, usefully functionalized bicyclic product. Thioconjugate addition yielding *Z*-selective enoates has been developed for both aromatic thiols (trialkylamine-catalyzed) and aliphatic thiols (KO*t*-Bu-catalyzed). The oxidation of the thioenoates thus generated is followed by Li-catalyzed oxidation to sulfones using *m*CPBA, and Li-catalyzed Diels–Alder addition of cyclopentadiene. These subsequent steps are performed in situ, without any purification of intermediates. The yields obtained using the described synthesis are acceptable for a one-pot three-step sequence. Preliminary conjugate addition results with alcohols and amines as nucleophiles are also presented.

1. Introduction

One-pot reactions represent an improvement over classical synthetic sequences because they avoid using toxic and expensive material usually associated with purification procedures, as well as loss of products and time during the purification process. Figure 1 [1] summarizes the basic principle of a one-pot reaction sequence: upon reacting the starting material A with reagent R_1, product B is formed, which is then treated in the same flask with reagent R_2 to form product C. Additional reagents are added successively in the same flask if more than two steps are involved in the one-pot synthetic procedure.

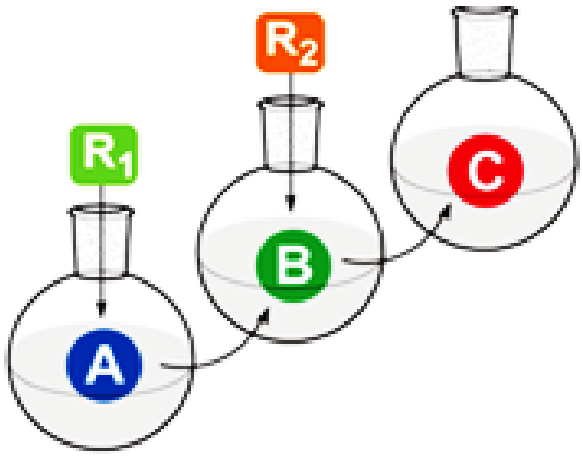


Figure 1.[1] *Basic Principle of One-Pot Reactions*

In this sequence, reaction mixtures become increasingly complex, resulting in side reactions and associated byproducts. This aspect makes the method harder to control and creates difficulties in the development process. Therefore, historically one-pot sequences have seldom been employed in synthesis development, but the current trend toward increasingly efficient and environmentally friendly synthetic procedures has led to a significant resurgence of interest.[2]

Ynoate esters (Figure 2) such as ethyl propiolate are known to act as one-pot bisacceptors in the presence of an excess of a single nucleophile,[3] which makes them excellent candidates to serve as substrates for one-pot reactions.

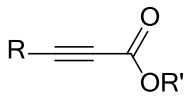


Figure 2. *General Structure of an Ynoate Ester*

Ynoates typically undergo conjugate addition reactions under basic conditions. Base-catalyzed conjugate addition involves the addition of a nucleophile to the β carbon of α,β-unsaturated carbonyl compounds, through the general mechanism presented in Figure 3a. Unsaturated esters, particularly enoates, have often been used as conjugate addition substrates[4] (Figure 3b). Ynoates are significantly more active conjugate acceptors than enoates, because the carbon being attacked by the nucleophile has a greater electrophilic character due to its sp hybridization, and its linear structure renders it more accessible sterically. However, they have attracted considerably less attention in literature, in part because a single conjugate addition leads to an achiral product. This aspect can be compensated in a one-pot sequence by their ability to selectively form one geometric isomer during conjugate addition, which can lead to stereocontrol in subsequent reaction steps.

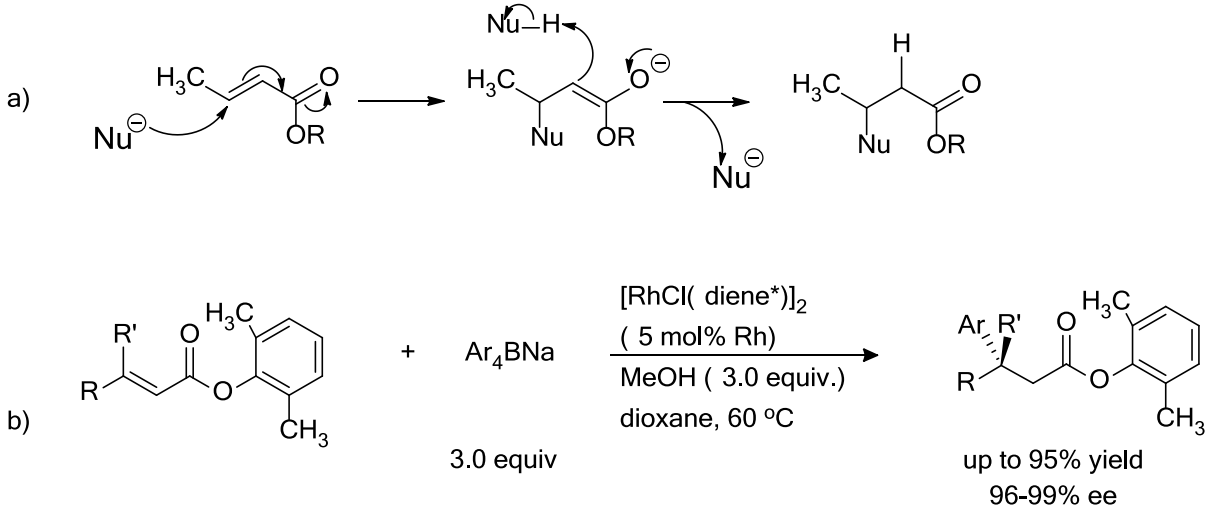


Figure 3. *a) General Mechanism of Conjugate Addition; b) A Recent Literature Example[5] of a Conjugate Addition with Enoates*

When thiols are employed as nucleophiles, either geometric product can be favored under different reaction conditions.[6]

Figure 4 shows the mechanism proposed for the amine-catalyzed conjugate addition of thiols to ethyl propiolate, which proceeds through an allenolate intermediate. Selectivity toward *Z*-thioenoates is achieved under kinetic control, when the allenolate intermediate (compound **1** in Figure 4a) is attacked more easily on the side opposite to the bulky thioether group. Under thermodynamic control, equilibration to the more stable *E*-thioenoate occurs (Figure 4b).

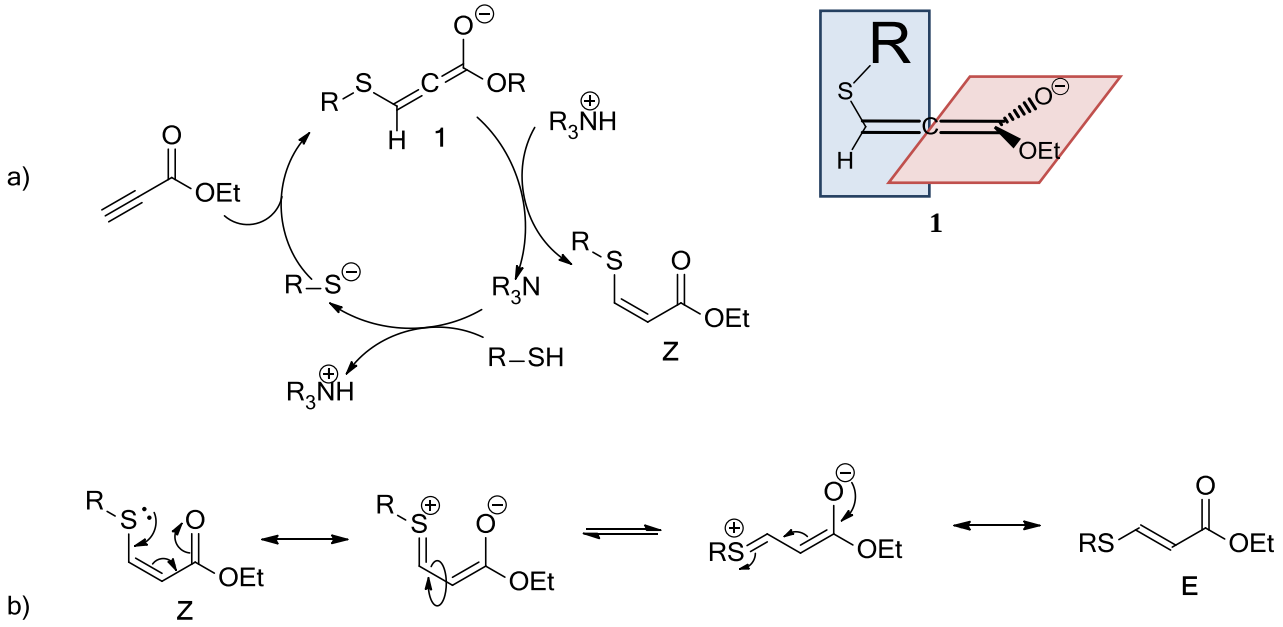


Figure 4. *Mechanism of Conjugate Addition of Thiols to Ethyl Propiolate: a) Generation of the Z isomer; b) Equilibration to the E isomer*

Both ynoate and enoate electrophiles can undergo Diels–Alder cycloaddition, especially in the presence of Lewis acid catalysts.[7] The reaction works best when electron-withdrawing groups are present on the dienophile, and is particularly useful for synthesizing bicyclic products, which are otherwise very hard to synthesize (Figure 5). Because ynoates have a linear geometry, stereocontrol of their Diels–Alder products is very hard to achieve.[8] Stereoselectivity might be indirectly controlled through stereoselective transformation of ynoates to enoates prior to the Diels-Alder reaction.

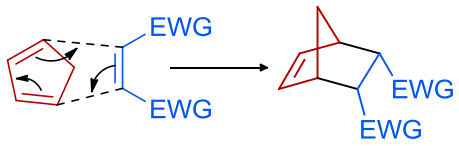


Figure 5. *A Generic Diels–Alder Reaction (EWG=electron-withdrawing group)*

The current project aims to synthesize densely functionalized, completely controlled stereochemically complex bicyclic systems in a one-pot fashion, starting with a conjugate addition to ethyl propiolate, followed by a Diels–Alder reaction. Similar strategies have been used in the literature to synthesize biologically active compounds.[9] In addition, bicyclic systems of similar structure have been employed as precursors for biologically active compounds (Figure 6).[10]

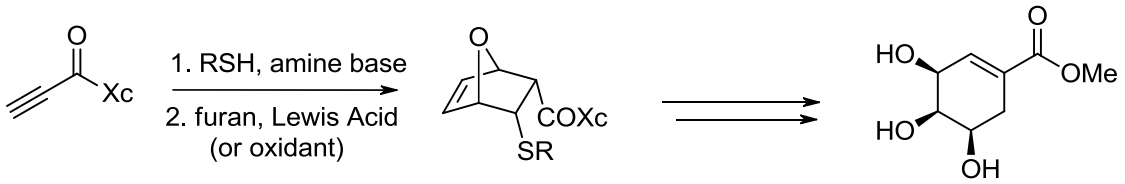


Figure 6. *One Application for Compounds of Similar Structure: Synthesis of (+)-Methyl 5-epi-Shikimate*[10]

2. Previous Work

Previous work in the Downey group has led to the optimization of reaction conditions for the conjugate addition of thiols to ethyl propiolate (Figure 7). Selectivity toward *Z*-enoates was achieved under kinetic control (Figure 4a) by using very low temperatures. Increasingly higher temperatures were found to significantly lower the selectivity of the reaction because the thermodynamic equilibrium (Figure 4b) favors the E isomer.

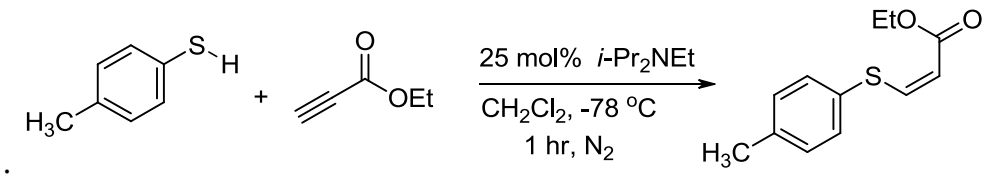


Figure 7. *Optimized Conjugate Addition of Thiols to Ethyl Propiolate*

Attempts to use this enoate as a substrate in a Diels–Alder reaction have consistently proven unsuccessful, probably because the lone pairs on sulfur prevent the enoate from being sufficiently electron-withdrawing. To overcome this issue, the enoate has to be oxidized to remove the lone pairs and enhance the electron-withdrawing character of the dienophile. This involves an intermediate step between the conjugate addition and the Diels–Alder steps, which in turn requires a more complex three-step one-pot sequence instead of a two-step version.

The oxidation of *Z*-thioenoates with *m*CPBA has been optimized to yield *Z*-sulfones. The optimal experimental conditions and the mechanism proposed are presented in Figure 8.

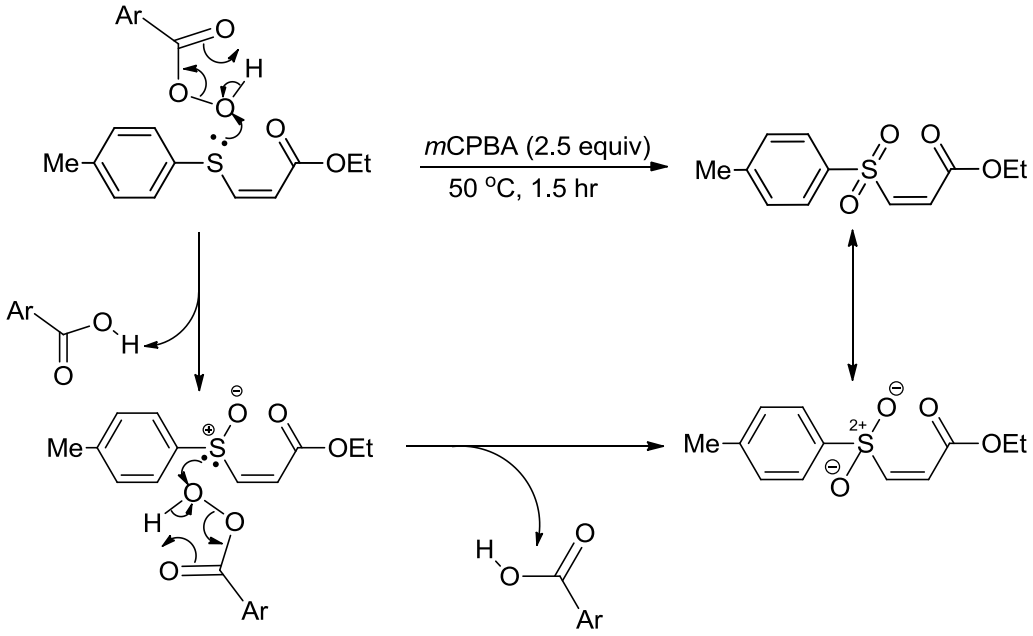


Figure 8. *Mechanism of Thioenoate Oxidation by mCPBA (Ar = m-chlorophenyl).*

While the reaction was carried out with *m*CPBA alone when purified enoate was used, when the addition and oxidation steps were attempted in a one-pot fashion, residual amine left after the addition step led to the formation of unidentified byproducts. This problem was solved by the addition of a Lewis acid, $LiClO_4$, to sequester the amine. In this manner, the optimized conditions for the one-pot addition-oxidation process shown in Figure 9 proved successful.

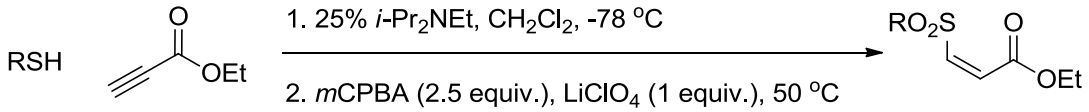


Figure 9. *Optimized One-Pot Addition-Oxidation of Z-Enoates*

As expected, the *Z*-sulfones participated more easily in the Diels–Alder cycloaddition than the Z-thioenoates obtained after the conjugate addition step. With these results in hand, proof of principle of the one-pot three-step sequence was established (Figure 10).

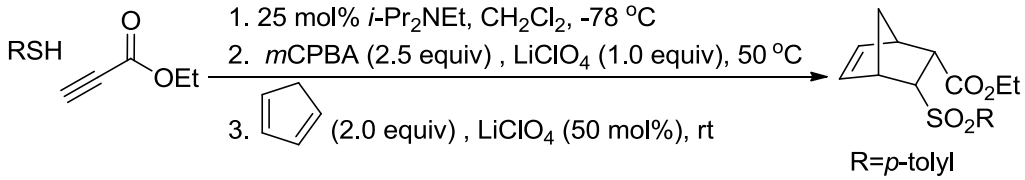


Figure 10. *Proof of Principle of the One-Pot Three-Step Sequence*

The current work focuses on establishing the scope of thiol substrates that can undergo this one-pot reaction sequence. [11]

3. Results and Discussion[i]

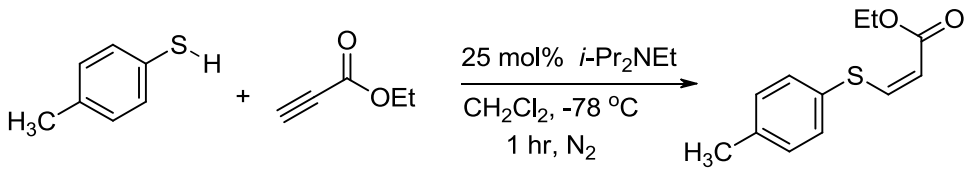
3.1. Scope of Aromatic Thiols as Nucleophiles[ii]

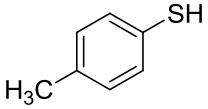
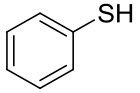
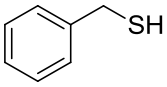
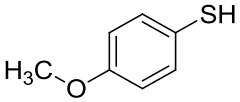
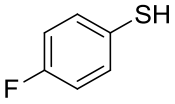
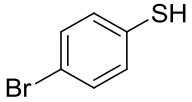
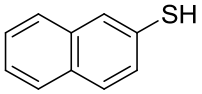
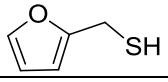
Initial efforts focused on establishing the scope of conjugate addition, because it was expected that a variety of thiols should react according to the mechanism in Figure 4. Aromatic

[i] Unless otherwise noted, work was performed without collaboration
[ii] Work performed with Smaranda Craciun and Christina A. Vivelo

thiols were subjected to the previously established conditions and reacted with very good yields and selectivities to produce *Z*-thioenoates, as can be seen in Table 1.

Table 1. *Scope of Conjugate Addition with Aromatic Substrates*

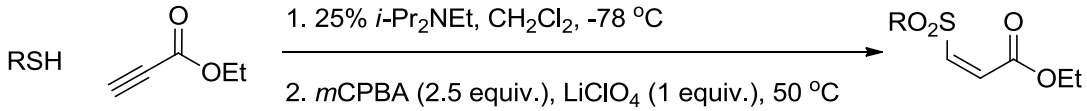


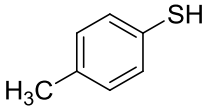
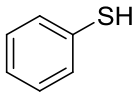
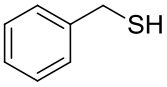
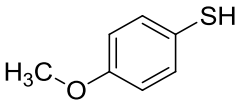
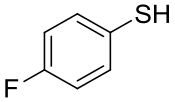
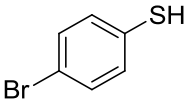
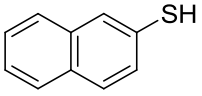
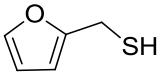
Entry	Thiol	Z:E	Yield (Z+E)
1		10:1	99%
2		12:1	94%
3		5:1	96%
4		15:1	95%
5		6:1	97%
6		8:1	86%
7		11:1	91%
8		8:1	91%

Among aromatic thiols, the presence of activating groups (entries 1 and 4) usually enhanced yields and selectivities, while deactivating groups (entries 5 and 6) lowered selectivities. The lowest selectivity for the *Z*-enoate was obtained for benzyl mercaptan (entry 3), probably because the thiol group is connected to a sp^3 carbon, which renders the lone pairs on sulfur more available to participate in resonance and form the *E*-enoate (see Figure 4b).

Once the conjugate addition was carried out successfully, the scope of the two-step, one-pot addition-oxidation reaction was investigated. Most aromatic thiols reacted with very good yields. The substrates with deactivated aromatic rings (entries 5 and 6) proved to be less reactive, probably due to deactivation of the thiolate, but not to a point where the reaction could not be applied. For example, *p*-bromothiophenol (entry 6) required a higher reflux temperature to achieve full conversion, which is why dichloromethane was replaced with 1,2-dichloroethane as solvent. The selectivity for *Z*-sulfones is usually similar to that obtained after the conjugate addition step, suggesting that thermodynamic equilibration is not an issue under these conditions.

Table 2. *One-Pot Addition-Oxidation for Aromatic Thiols*

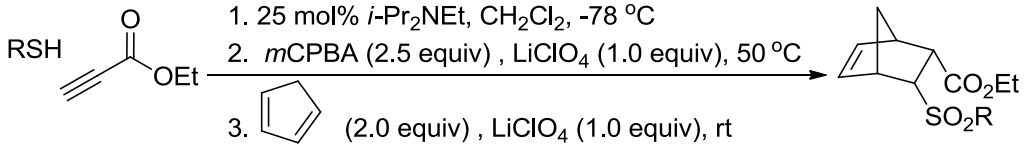


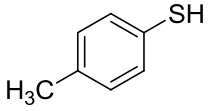
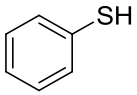
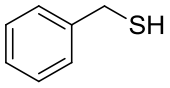
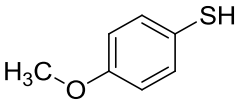
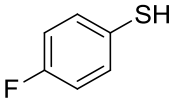
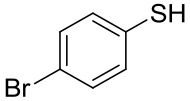
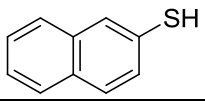
Entry	Thiol	Z:E	Yield Z (%)
1		8:1	81
2		12:1	71
3		5:1	64
4		10:1	90
5		10:1	70
6		3:1	51*
7		10:1	84
8		Mostly E	Decomposition

** 1,2-dichloroethane used as solvent; 2nd step at 83 °C*

With the thiols for which the one-pot addition-oxidation process has been successfully optimized, the one-pot three-step procedure was attempted, including the final Diels–Alder cycloaddition with cyclopentadiene. As the results summarized in Table 3 show, the sequence can be applied successfully to many aromatic thiols, although *p*-bromothiophenol (entry 6) required minor additional optimization, as shown for the oxidation step. Similar to the aromatic thiols, benzyl mercaptan (entry 3) also worked with acceptable yields and selectivities.

Table 3. *One-Pot Three-Step Reaction with Aromatic Thiols*



Entry	Thiol	$LiClO_4$ in Step 2 (equiv)	$LiClO_4$ in Step 3 (equiv)	Diastereomer Ratio	Yield Endo (%)
1		0.5	-	76:24	81
2		1.0	1.0	70:30	75
3		0.5	1.0	76:24	67
4		1.0	1.0	87:13	81
5		1.0	1.0	76:24	56
6		1.0	1.0	71:29	57*
7		1.0	1.0	80:20	60

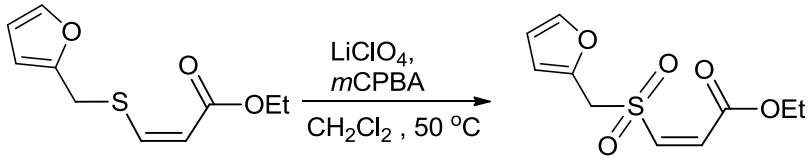
** 1,2-dichloroethane used as solvent; 2nd step at 83 °C*

It is worth noting that for *p*-toluenethiol and *p*-bromothiophenol (entries 1 and 6), the yields obtained after the one-pot three-step sequence are actually the same as or greater than the yields obtained after only the first two steps (Table 2, entries 1 and 6). While purifying the reactions using aqueous extraction (see Appendix), significant emulsions appeared after the two-step process, which might have led to substantial loss of product. This issue is avoided in the three-step one-pot process, where the entire oxidation product is present to undergo the Diels–Alder step.

3.2 Attempts with Furfuryl Thiol

The use of 2-furfuryl thiol was also attempted under the established addition-oxidation conditions. As the results above show, it worked satisfactorily in the conjugate addition reaction (Table 1, entry 8), but the addition-oxidation sequence proved particularly challenging (Table 2, entry 8). Because the initial conjugate addition step was shown to work successfully, problems likely occur during the oxidation step or during the one-pot process. Table 4 summarizes a series of attempts to optimize the reaction sequence for this substrate. As entry 1 shows, the purified thioenoate quickly equilibrates to a mixture favoring the *E*-sulfone under oxidation conditions, even if the oxidizing agent is added at -78 °C. Entries 2, 3, and 4 show that the oxidation products decompose in the presence of amine. Decomposition is avoided if the reaction is stopped after a shorter time (entry 5) but oxidation remains incomplete under these conditions. When more oxidizing agent is added (entry 6), the reaction is not stereoselective. The conclusion drawn from these attempts has been that unfortunately furfuryl thiol is not suited for the purposes of the current project.

Table 4. *Experiments with Furfuryl Thiol*



Entry	Equiv $LiClO_4$	Equiv mCPBA	Equiv iPr_2NEt	Time (h)	Result
1	1	2.5*	-	1	Z:E=1:3
2	1	1	0.25	1.5	Decomposition
3	1	2.5*	0.25*	1.5	Decomposition
4	-	2.5	0.25**	2	Decomposition
5	-	2.5*	0.25**	1	Z:E:Z sulfoxide=1:3:0.1
6	-	3	0.25**	2.5	Z:E=1.18:1

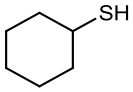
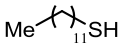
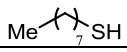
*Added at -78 °C
** Base already present from the enoate generated in situ by conjugate addition

3.3 Aliphatic Thiols[iii]

The one-pot reaction sequence successfully accomplished for aromatic thiols, we focused on extending the scope of the process to aliphatic thiols. The early results with benzyl mercaptan (Table 3, entry 3) mentioned above showed promise for this new series of substrates. However, for cyclohexanethiol, octanethiol, and dodecanethiol, initial results were discouraging, in that they did not seem compatible with the previously established conditions for the conjugate addition reaction (Table 5). Under the standard reaction conditions, only cyclohexanethiol gave reproducible results (entry 1), albeit with yield and *Z*:*E* selectivity that were significantly inferior to those obtained with aromatic thiols.

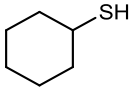
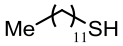
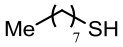
[iii] Work performed with Carly J. Mueller

Table 5. *Conjugate Addition for Aliphatic Thiols under Previous Conditions*

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

Even though conjugate addition results indicated that a problem was already present, we also subjected the aliphatic substrates to the one-pot addition-oxidation conditions. Table 6 shows that cyclohexanethiol and dodecanethiol (entries 1 and 2) decompose under these conditions, and octanethiol reacts only under slightly modified conditions, and with an extremely low yield (entry 3).

Table 6. *One-Pot Addition-Oxidation for Aliphatic Thiols under Previous Conditions*

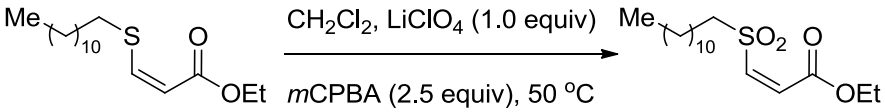
Entry	**Thiol**	**Z:E**	**Yield Z (%)**
1		-	Decomposition
2		-	Decomposition
3		3:1	22*

** with CF_3CO_2H as catalyst instead of $LiClO_4$*

Next, we concentrated on optimizing the oxidation step of purified dodecyl thioenoate. As Table 7 shows, the oxidation step is much less problematic than the conjugate addition step. However, under standard reaction conditions, *m*CPBA is not able to completely oxidize the thioenoate to the sulfone; instead, small amounts of *Z*-sulfoxide are always present (entries 1, 2, 3). The problem was resolved by replacing $LiClO_4$ with CF_3CO_2H, but the trade-off was a lower

selectivity toward the *Z*-sulfone (entry 4). Overall, these results showed promise, assuming that the conjugate addition step would be improved.

Table 7. *Experiments with Dodecyl Thioenoate*

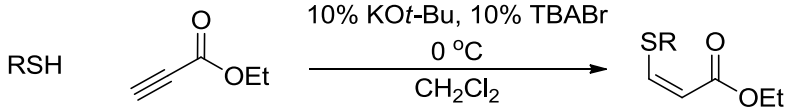


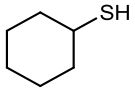
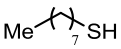
Entry	Equiv mCPBA	Time (h)	Result
1	2.5	2	Z:E:Z sulfoxide = 5:1:0.7
2	2.5	4	Z:E: Z sulfoxide = 6:1:0.5
3	3.5	2	Z:E:Z sulfoxide = 5:1:0.1
4	3.5*	2	Z:E = 3:1 ; 52% yield Z

** with CF_3CO_2H as catalyst instead of $LiClO_4$*

Indeed, aliphatic thiols were ultimately rendered effective reaction partners by replacing the amine base in the conjugate addition step with a stronger base, KO*t*-Bu. Because KO*t*-Bu is not soluble in methylene chloride, tetrabutylammonium bromide (TBABr) was added to homogenize the reaction mixture. Unlike potassium cation, the large tetrabutylammonium ion is soluble in organic solvents due to its large nonpolar regions, so that the *tert*-butoxide and allenolate ions may also be brought into solution. However, even in the presence of TBABr, KO*t*-Bu was still insoluble at -78 °C, so conjugate addition reactions were carried out at 0 °C instead. As Table 8 shows, a cost of using higher temperatures included lower geometric selectivities compared to aromatic thiols due to advanced equilibration toward the *E*-thioenoate, as shown in Figure 4b. Still, both selectivities and yields were a clear improvement compared to previous results with trialkylamine catalysts.

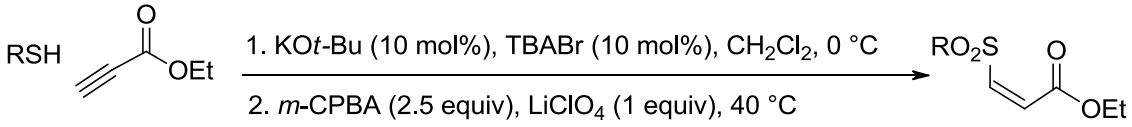
Table 8. *Conjugate Addition Results with Aliphatic Thiols*

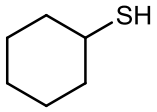
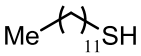
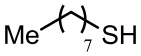


Entry	Thiol	Z:E	Yield Z (%)
1		4.7:1	90
2		3.5:1	81
3		4.11:1	88

With these modified conditions, the one-pot addition-oxidation sequence was again attempted, this time with significantly more success (Table 9). If employed after the modified conjugate addition step, the oxidation step did not require any modification from the conditions employed for aromatic thiols. The geometric selectivities were not significantly lower than after the conjugate addition step, suggesting again that equilibration toward the more stable *E*-sulfone is not a significant issue under these conditions. However, the yields of the isolated *Z*-sulfones, while still acceptable, were lower when compared to aromatic thiols. This result is surprising considering that the oxidation step is identical, but may be explained by the even more significant emulsions that occurred during aqueous extractions of aliphatic thiols than aromatic thiols (see Appendix). If this explanation is true, it provides further motivation for carrying out the entire synthetic procedure in a one-pot fashion, because this aqueous workup would not occur until after the cycloaddition.

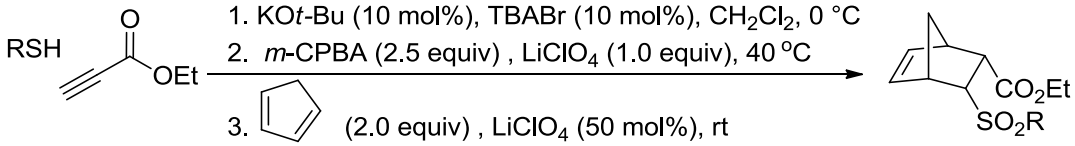
Table 9. *One-Pot Conjugate Addition – Oxidation Results with Aliphatic Thiols*

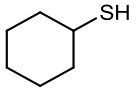
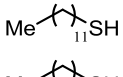
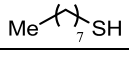


Entry	Thiol	Z:E	Yield Z (%)
1		3.5:1	60
2		3.1:1	51
3		4.0:1	58

Once the one-pot addition-oxidation sequence was proven to work successfully, the Diels–Alder step was also performed in a one-pot fashion with no difficulties. The Diels–Alder step was performed identically as with aromatic thiols, according to the conditions mentioned in Table 10. The yields were slightly lower than for aromatic thiols, but still acceptable for a three-step process.

Table 10. *One-Pot Three-Step Reaction with Aliphatic Thiols*



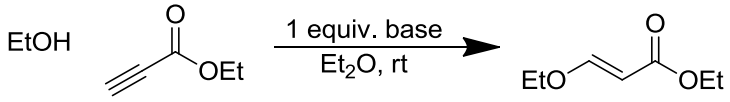
Entry	Thiol	Diastereomer Ratio	Yield Endo (%)
1		74:26	47
2		81:19	51
3		84:16	57

3.4 Expansion of Nucleophile Scope to Alcohols

Although still in the early stages of development, current work focuses on expanding the scope of conjugate additions to ethyl propiolate to include alcohols and amines as nucleophiles. Our initial efforts have focused on optimizing the experimental conditions for conjugate addition by alcohols, in order to optimize the conversion and the selectivity toward the thermodynamically favored *E*-enoate. The choice of catalyst and solvent, as well as the amount of catalyst required, were investigated.

Based on previous success with thiol nucleophiles, tertiary amines seemed to be well suited candidates. We surveyed several tertiary amines as base catalysts, using ethanol as nucleophile. The results are presented in Table 11. Hunig's base, the catalyst used throughout previous efforts with thiols as nucleophiles, proved to be unsuited for these new types of nucleophiles (entries 1 and 2). Instead, *N*-methylmorpholine, *N*-methyldicyclohexylamine, and triethylamine all seemed to efficiently catalyze this reaction (entries 3, 4, 6). Because selectivity was the primary driving force of this project, triethylamine was chosen for further studies.

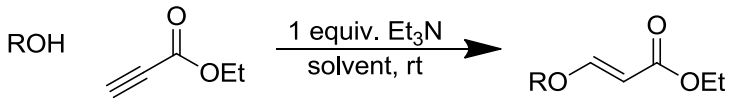
Table 11. *Catalyst Choice Optimization*



Entry	R_3N	Reaction Time (h)	Conversion (%)	E:Z Ratio
1	Hunig's Base	24	10	N/D
2	Hunig's Base	48	10	N/D
3	N-methylmorpholine	48	100	5.4:1
4	N-methyldicyclohexyl amine	48	100	1.8:1
5	2,6-lutidine	24	0	-
6	**Triethyamine**	**24**	**89**	**17:1**

Next, we tested different solvents using both ethanol and phenol as substrates. Table 12 shows that ethanol usually gave higher selectivities while phenol gave higher conversions in otherwise identical conditions. All solvents proved to be well suited for this reaction, but we chose methylene chloride for further study in order to match the conditions employed during the projected subsequent one-pot steps, which are expected to be similar to those employed for the thiol experiments described above.

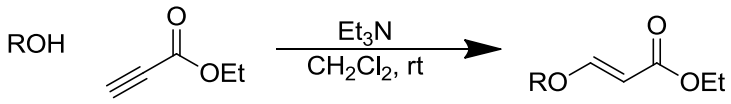
Table 12. *Solvent Choice Optimization*



Entry	Solvent	Conversion (%)		E:Z Ratio	
		Ethanol	Phenol	Ethanol	Phenol
1	Ether	89	100	>20:1	14:1
2	**Methylene Chloride**	**100**	**100**	**>20:1**	**13:1**
3	Tetrahydrofuran	81	100	20:1	20:1
4	Toluene	100	100	>20:1	10:1

Having discovered a suitable catalyst and solvent, we performed investigations to minimize the amount of catalyst used (Table 13). Ethanol proved to react satisfactorily regardless of the amount of catalyst present, but phenol did not tolerate very small amounts of catalyst. Because a general procedure was sought for a potential wide variety of alcohols, we decided to use a molar ratio of 25% for subsequent studies, even though results with ethanol suggested that some substrates may require less catalyst.

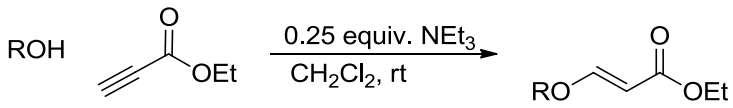
Table 13. *Catalyst Loading Optimization*



Entry	Equiv NEt_3	Conversion (%)		E:Z Ratio	
		Ethanol	Phenol	Ethanol	Phenol
1	1	100	100	>20:1	13:1
2	0.50	99	100	>20:1	>20:1
3	**0.25**	**97**	**99**	**>20:1**	**15:1**
4	0.10	94	9	>20:1	6:1

Under these optimized conditions, we moved on to testing the scope of the conjugate addition reaction with respect to a variety of alcohols. Unfortunately, among the examples attempted so far (Table 14), ethanol and phenol (entries 1 and 2) remain the most efficient substrates. Menthol and cinnamyl alcohol (entries 6 and 8) are almost completely unreactive. Allyl alcohol (entry 3) completely reacted under these conditions, but the products were unidentified. Methanol, isopropanol, and 4-methoxybenzyl alcohol (entries 4, 6, 7) did not react completely, and the products formed were unidentified. Alternative explanations for the reaction products involve the presence of rotamers or competition with transesterification reactions. Additional studies to confirm the exact identity of the products are pending.

Table 14. *Scope of Conjugate Addition for Alcohols*



Entry	Alcohol	Conversion	E:Z Ratio	Alternative Explanation
1	Ethanol	100%	>20:1	
2	Phenol	100%	13:1	
3	Allyl Alcohol	100%	N/D	
4	4-Methoxy Benzyl Alcohol	N/D	N/D	Rotamers, Transesterification
5	Menthol	<10%	N/D	
6	Methanol	N/D	N/D	Rotamers, Transesterification
7	Isopropanol	N/D	N/D	Rotamers, Transesterification
8	Cinnamyl Alcohol	0%	-	
9	Ethylene Glycol	100%	N/D	Double Addition, Transesterification
10	Propanediol	100%	N/D	Double Addition, Transesterification
11	Butanediol	100%	N/D	Double Addition, Transesterification

Similarly, for ethylene glycol, 1,3-propanediol and 1,4-butanediol (entries 9, 10, 11), ^{1}H NMR spectroscopic studies were not conclusive with respect to the identity of the products obtained. Likely fates of this reaction involve initial formation of the monoaddition product followed either by a second addition of the other nucleophilic group to the enoate, or by intramolecular transesterification (Figure 11). Probably more than one of these products is

present in the product mixture. Our attempts to drive the reaction completely in one direction by adding a variety of Lewis acids as catalysts proved unsuccessful[iv].

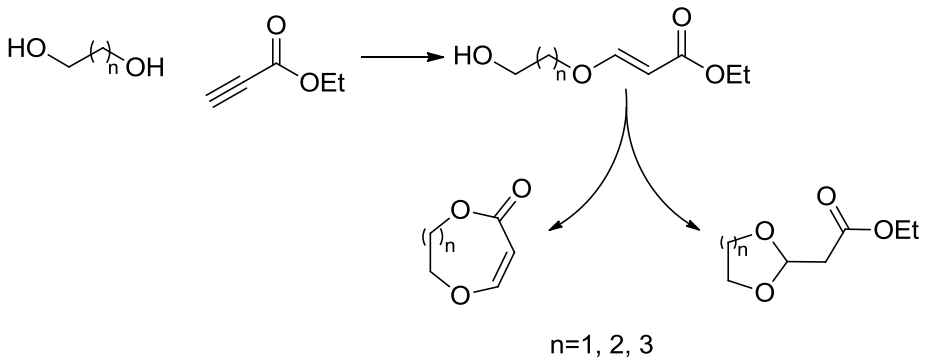
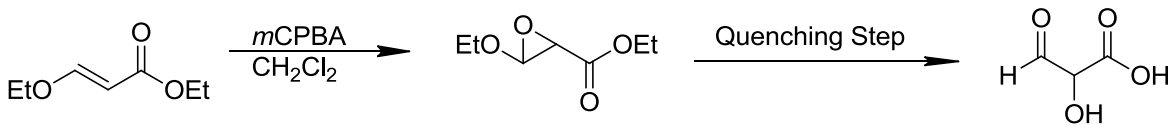


Figure 11. *Possible Pathways of Conjugate Addition of Diols with Ethyl Propiolate*

Because our goal is to develop a one-pot reaction sequence similar to that employed for thiols, we next attempted the oxidation of the purified conjugate addition product. Early oxidation results did not encounter significant success however (Table 15). We anticipated that the enoate π bond would undergo epoxidation, but no epoxide was isolated, possibly because hydrolysis occurred under aqueous workup to produce an α-hydroxy-β-aldocarboxylic acid. In most cases, both in the presence or absence of $LiClO_4$, a mixture of products whose structure is still somewhat uncertain has been obtained (entries 1 and 6). Only in the presence of $LiClO_4$ and after quenching with hydrochloric acid could a single product be formed in acceptable conversions (entries 3 and 4), but its identity has not been established.

[iv] Lewis acids attempted include $LiClO_4$, $Zn(OTf)_2$, $MgBr_2 \cdot OEt_2$, $NaSbF_6$, $ZnBr_2$, $Sn(OTf)_2$, $Yb(OTf)_3$, $In(OTf)_3$

Table 15. *Oxidation of Enoate Intermediate with mCPBA*



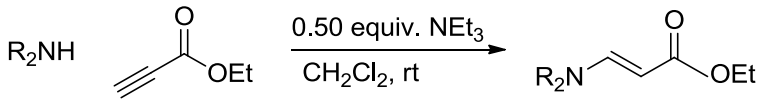
Entry	Equiv *m*CPBA	Equiv $LiClO_4$	Quenching Step	Results
1	1.5	-	-	Mixture of Products
2	1.5	-	1N HCl	Mixture of Products
3	1.5	1	1N HCl	60% Conversion
4	1.5*	1	1N HCl	84% Conversion
5	2.5	1	1N HCl	Mixture of Products
6	2.5	1	Saturated $NaHCO_3$	Mixture of Products

** Reaction was refluxed at 50 °C*

3.5 Expansion of Nucleophile Scope to Amines

Under the optimized conditions determined for alcohols, we decided to also investigate the scope of conjugate addition of amines to ethyl propiolate. Preliminary results (Table 16) show that the reaction works best with secondary amines (entries 1, 2, 3, 7, 8). Aliphatic amines work better than aromatic amines, as illustrated by the fact that the reaction with diphenylamine (entry 3) did not go to completion even after stirring overnight.

Table 16. *Preliminary Scope of Conjugate Addition with Amines as Nucleophiles*



Entry	Amine	Conversion	E:Z ratio	Yield (%)	Observations
1	Pyrrolidine	100%	>20:1	84	
2	Piperidine	100%	>20:1	66	
3	Diphenylamine	91%	>20:1	-	No change after longer reaction time
4	Aniline	100%	N/D	-	Mixture of unidentified products
5	Acetanilide	N/D	N/D	-	Mixture of unidentified products
6	Benzylamine	N/D	N/D	-	Unclear NMR Data
7	Diethylamine	100%	20:1	81	
8	Morpholine	100%	9:1	70	

4. Conclusions and Future Directions

A conjugate addition-oxidation-Diels–Alder sequence of reactions for a wide variety of thiols and ethyl propiolate was successfully developed in a one-pot fashion. In this manner, a densely functionalized bicyclic product can be synthesized easily and efficiently from commercially available, inexpensive starting materials.

Comparing the yields of the one-pot sequence with an equivalent step-by-step sequence validates the effectiveness of the one-pot process. As seen in Table 3 (entry 1), the yield for *p*-toluenethiol is 81%, while the equivalent step-by-step synthesis resulted in a combined yield of 66% (Figure 12). This fact confirms that the increasing complexity of the one-pot reaction mixture is outweighed by any potential loss of products in the purification process after each reaction step.

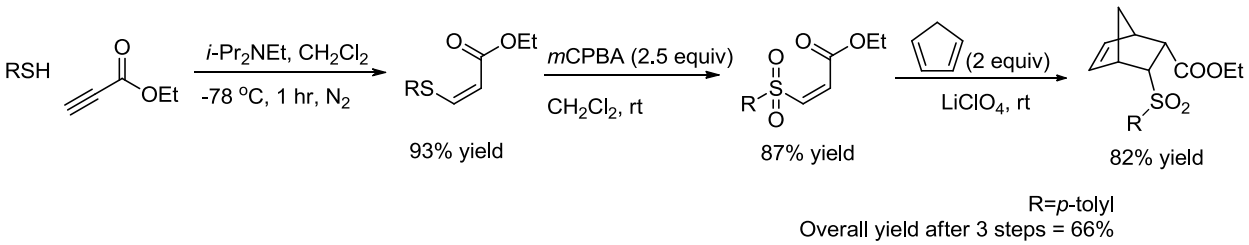


Figure 12. *Equivalent Step-by-Step Sequence*

The efficiency trade-off between the two synthetic procedures also favors the one-pot sequence, even if the process proposed requires an additional equivalent of Lewis acid ($LiClO_4$) to deactivate the residual amine after the conjugate addition step. This aspect is significantly outweighed by avoiding the use of large amounts of reagents and solvents during purifications after each step involved in the step-by-step sequence, as well as the time-economical convenience of the one-pot process.

Expansion of several dimensions of the scope of the one-pot sequence of reactions is underway in the Downey group. Very early results obtained by replacing thiols with other nucleophiles have been presented here. Some aspects of this work show promising results. Work by other members of the Downey group focuses on replacing ethyl propiolate with chiral ynoates generated in situ, in order to introduce optical activity in the products. Another planned direction of this project involves expanding the scope of dienes used in the Diels–Alder step.

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[10] Takahashi, T.; Iyobe, A.; Arai, Y.; Koizumi, *Synthesis* **1989**, 189-191.
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One-Pot Reactions of Ethyl Propiolate

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Appendices

1) Experimental

General. 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.[1] *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. ^{1}H 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. *Amine-Mediated Heteroconjugate-Addition of Thiol Nucleophiles to Ethyl Propiolate*

To an oven-dried round-bottomed flask under N_2 atmosphere was added the thiol (2.0 mmol), CH_2Cl_2 (3.3 mL) and diisopropylethylamine (87 μL, 65 mg, 0.50 mmol). The homogenous mixture was allowed to stir for 15 minutes in a dry ice/acetone bath at -78 °C. Ethyl propiolate (203 μL, 196 mg, 2.0 mmol) was added dropwise and the reaction mixture was allowed to stir at

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-78°C for 1 h, then it 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. *Alkoxide-Medated 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 C. *Two-Step Amine-Mediated Heteroconjugate-Addition-Oxidation Sequence*

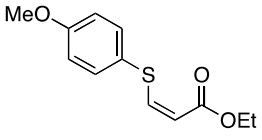
To an oven-dried round-bottomed flask under N_2 atmosphere was added the thiol (2.0 mmol), CH_2Cl_2 (3.3 mL) and diisopropylethylamine (87 μL, 65 mg, 0.50 mmol). The homogenous mixture was allowed to stir for 15 minutes in a dry ice/acetone bath at -78 °C. Ethyl propiolate (203 μL, 196 mg, 2.0 mmol) was added dropwise and the reaction mixture was allowed to stir at -78°C for 1 h. Under ambient atmosphere, $LiClO_4$ (213 mg, 2.0 mmol) and CH_2Cl_2 (13.3 mL) were added. After 15 min, *meta*-chloroperbenzoic acid (*m*CPBA) (1345 mg, 6.0 mmol, 77% purity) was added. 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 (5-30% EtOAc/hexanes).

General Procedure D. *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).

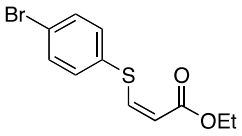
General Procedure E. *Amine-Mediated Heteroconjugate-Addition of Alcohol or Amine Nucleophiles to Ethyl Propiolate*

To an oven-dried round-bottomed flask under N_2 atmosphere was added CH_2Cl_2 (3.0 mL), the nucleophile (2.0 mmol), ethyl propiolate (203 μL, 196 mg, 2.0 mmol), and triethylamine (140 μL, 102 mg, 1.00 mmol). The homogenous mixture was allowed to stir at room temperature for 1 h. The solvent was removed in vacuo and the residue was purified by column chromatography (5-15% EtOAc/hexanes).

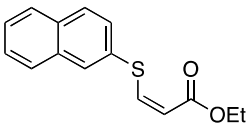


Ethyl 3-((4-methoxyphenyl)thio)acrylate (1c) The title compound was prepared according to General Procedure A, using *p*-methoxythiophenol (279 μL, 220 mg, 2.00 mmol) as the thiol nucleophile. The product was isolated as a yellow oil as a mixture of the *Z* and *E* isomers (453 mg, 95% yield): IR (film) 2972, 1692, 1592, 1566, 1492, 1287, 1245, 1206, 1157, 1027, 828, 797, 701 cm^{-1}; HRMS (ESI, TOF): Exact mass calcd for $C_{12}H_{14}O_3SNa$ $[M+Na]^+$, 261.0561. Found 261.0563. ***Z* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.46-7.43 (m, 2H), 7.19 (d, *J* = 10.3 Hz, 1H), 6.93-6.90 (m, 2H), 5.86 (d, *J* = 10.0 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6; 160.1, 151.6, 133.5, 126.9, 114.9, 112.7, 60.3, 55.4, 14.4; ***E* isomer:** ^1H

NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 15.1 Hz, 1H), 7.44-7.41 (m, 2H), 6.97-6.95 (m, 2H), 5.52 (d, *J* = 14.7 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 2 H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) peaks below detection limit.

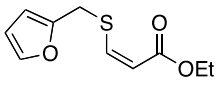


Ethyl 3-((4-bromophenyl)thio)acrylate (1e) The title compound was prepared according to General Procedure A, using *p*-bromothiophenol (379 mg, 2.00 mmol) as the thiol nucleophile. The product was isolated as a yellow oil as a mixture of the *Z* and *E* isomers (494 mg, 86% yield): mp: 43-49 °C; IR (film) 2979, 2928, 1689, 1581, 1473, 1386, 1371, 1229, 1185, 1173, 1055, 1033, 1007, 829, 817, 798 cm^{-1}; HRMS (ESI, TOF): Exact mass calcd for $C_{11}H_{11}O_2SBrNa$ $[M+Na]^+$, 308.9561, 310.9540. Found 308.9553, 310.9528. ***Z* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.33-7.31 (m, 2H), 7.16 (d, *J* = 10.0 Hz, 1H), 5.91 (d, *J* = 10.0 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 148.5, 135.3, 132.5, 132.4, 122.5, 114.0, 60.4, 14.4; ***E* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 15.0 Hz, 1H), 7.52-7.48 (m, 2H), 7.32-7.28 (m, 2H), 5.64 (d, *J* = 15.0 Hz, 1H), 4.14 (q, *J* = 6.9 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) peaks below detection limit.

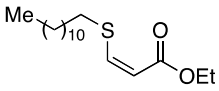


Ethyl 3-(naphthalen-2-ylthio)acrylate (1f) The title compound [2] was prepared according to General Procedure A, using 2-naphthylthiol (320 mg, 2.00 mmol) as the thiol nucleophile. The product was isolated as a yellow oil as a mixture of the *Z* and *E* isomers (470, 91% yield): mp: 34-37 °C IR (film) 2981, 2928, 1696, 1567, 1371, 1213, 1165, 1133, 1033, 799, 746, 668 cm^{-1}; HRMS (ESI, TOF): Exact mass calcd for $C_{15}H_{14}O_2SNa$ $[M+Na]^+$, 281.0612. Found 281.0625. ***Z* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (bs, 1H), 7.90-7.80 (m, 3H), 7.58-7.52 (m, 3H), 7.39 (d, *J* = 10.0 Hz, 1H), 5.99 (d, *J* = 10.0 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 149.5, 133.6, 133.4, 132.7, 130.2, 129.2, 128.2, 127.8, 127.6, 127.0, 126.8, 113.7, 60.4, 14.4; ***E* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (bs, 1H), 7.86-7.79 (m, 3H), 7.76-7.72 (m, 1H), 7.64 (dd, *J* = 1.9, 8.4 Hz, 1H), 7.50-7.44 (m, 2H), 5.72 (d, *J* = 15.1 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) peaks below detection limit.

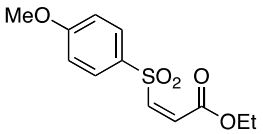
[2] *Z* isomer: Kabir, M. S.; Namjoshi, O. A.; Verma, R.; Polanowski, R.; Krueger, S. M.; Sherman, D.; Rott, M. A.; Schwan, W. R.; Monte, A.; Cook, J. M. *Bioorg. Med. Chem.* **2010**, *18*, 4178-4186. The *E* isomer is known but no synthesis is reported.



Ethyl 3-((furan-2-ylmethyl)thio)acrylate (1h) The title compound was prepared according to General Procedure A, using furfuryl mercaptan (200 μL, 226 mg, 2.0 mmol) as the thiol nucleophile. The product was isolated as a yellow oil as a mixture of the *Z* and *E* isomers (386 mg, 91% yield): IR (film) 2972, 1692, 1529, 1209, 1161, 1030, 1010, 935, 798, 733 cm^{-1}; HRMS (ESI, TOF): Exact mass calcd for $C_{10}H_{12}O_3SNa$ $[M+Na]^+$, 235.0405. Found 235.0407. ***Z* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.38 (m, 1H), 7.17 (d, *J* = 10.3 Hz, 1H), 6.35-6.31 (m, 1H), 6.28-6.26 (m, 1H), 5.88 (d, *J* = 10.3 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.95 (s, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 148.2, 142.71, 142.70, 113.7, 110.6, 108.2, 60.2, 31.6, 14.3; ***E* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 15.0, 1H), 7.40-7.39 (m, 1H), 6.36-6.34 (m, 1H), 6.31-6.29 (m, 1H), 5.88 (d, *J* = 15.0 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.05 (s, 2H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 150.7, 149.3, 145.3, 114.9, 110.7, 108.5, 60.3, 29.0, 14.3.

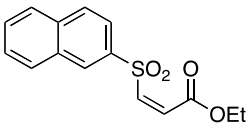


Ethyl 3-(dodecylthio)acrylate (1j) When General Procedure B was followed using 1-dodecanethiol (480 mL, 406 mg, 2.0 mmol), the title compound was prepared as a colorless oil as a mixture of the *Z* and *E* isomers (487 mg, 81% yield): IR (neat) 2922, 2852, 1701, 1569, 1458, 1369, 1207, 1160, 1034, 954, 797 cm^{-1}; HRMS (ESI, TOF): Exact mass calcd for $C_{17}H_{32}O_2SNa$ $[M+Na]^+$, 323.2021. Found 323.2010. ***Z* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 10.0 Hz, 1H), 5.86 (d, *J* = 10.3 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 2.77 (t, *J* = 7.2 Hz, 1H), 1.73-1.66 (m, 2H), 1.46-1.39 (m, 2H), 1.35-1.27 (m, 16H), 1.31 (t, *J* = 7.2, 3H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 150.3, 112.9, 59.9, 36.0, 31.9, 30.3, 29.6 (double intensity), 29.5, 29.4, 29.3, 29.1, 28.4, 22.6, 14.3, 14.0; ***E* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 15.3 Hz, 1H), 5.76 (d, *J* = 15.0 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.81 (t, *J* = 7.2 Hz, 1H), 1.73-1.66 (m, 2H), 1.46-1.39 (m, 2H), 1.35-1.27 (m, 16H), 1.30 (t, *J* = 7.1, 3H), 0.90 (t, *J* = 6.9 Hz, 3H);

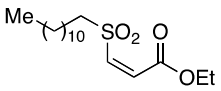


Ethyl (*Z*)-3-((4-methoxyphenyl)sulfonyl)acrylate (2c) The title compound was prepared from *p*-methoxythiophenol (245 μL, 279 mg, 2.0 mmol) using General Procedure C, the title compound was isolated as a white solid (487 mg, 90% yield): mp: 74-77 °C; IR (film) 2977, 2841, 1734, 1682, 1595, 1577, 1498, 1301, 1260, 1144, 1087, 1022, 833, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87-7.84 (m, 2H), 6.99-6.96 (m, 2H), 6.49 (d, *J* = 11.6 Hz, 1H), 6.43 (d, *J* = 11.6 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 164.1,

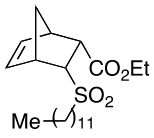
135.5, 130.8, 130.5, 114.6, 62.0, 55.8, 14.0; HRMS (ESI, TOF): Exact mass calcd for $C_{12}H_{14}O_5SNa$ $[M+Na]^+$, 293.0460. Found 293.0461.



Ethyl (*Z*)-3-(naphthalen-2-ylsulfonyl)acrylate (2f) The title compound was prepared from 2-naphthylthiol (321 mg, 2.0 mmol) using General Procedure C, the title compound[3] was isolated as a white solid (488 mg, 84% yield): mp: 40-42 °C; IR (film) 2904, 2847, 1736, 1369, 1342, 1319, 1237, 1150, 1128, 1072, 1021, 860, 750, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (bs, 1H), 8.05-7.99 (m, 3H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.73-7.64 (m, 2H), 6.61 (d, *J* = 11.6 Hz, 1H), 6.55 (d, *J* = 11.6 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 136.3, 135.5, 135.2, 132.2, 131.9, 130.2, 129.7, 129.6, 129.5, 128.0, 127.7, 122.7, 62.2, 14.0; HRMS (ESI, TOF): Exact mass calcd for $C_{15}H_{14}O_4SNa$ $[M+Na]^+$, 313.0511. Found 313.0511.



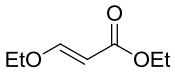
Ethyl 3-(dodecylsulfonyl)acrylate (2j) When General Procedure D was followed using 1-dodecanethiol (244 μL, 232 mg, 2.0 mmol), the title compound was prepared as a white solid (339 mg, 51% yield): mp: 25-27 °C; IR (film) 2922, 2854, 1735, 1466, 1342, 1315, 1228, 1129, 1023, 788, 723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.62 (d, *J* = 11.6 Hz, 1H), 6.59 (d, *J* = 11.9 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.25-3.21 (m, 2H), 1.88-1.81 (m, 2H), 1.49-1.41 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 2H), 1.36-1.26 (m, 16H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 136.1, 134.1, 62.2, 55.6, 31.9, 29.6 (double intensity), 29.5, 29.3, 29.2, 29.0, 28.4, 22.7, 22.0, 14.1, 13.9; HRMS (ESI, TOF): Exact mass calcd for $C_{17}H_{32}O_4SNa$ $[M+Na]^+$, 355.1919. Found 355.1911.



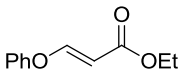
***cis*,*endo*-Ethyl 3-(dodecylsulfonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (9)** To an oven-dried round-bottomed flask under N_2 atmosphere was added the KO*t*-Bu (22.2 mg, 0.20 mmol), CH_2Cl_2 (4.0 mL), and dodecanethiol (480 μL, 406 mg, 2.0 mmol). To the heterogeneous mixture was added tetrabutylammonium bromide (71.4 mg, 0.22 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) (1120 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

[3] Compound is known but no synthesis is reported

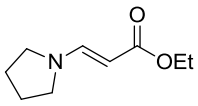
the reaction mixture was warmed to room temperature, then stirred at reflux (40 °C) for 1.5 h. The mixture was allowed to cool to room temperature, and then cyclopentadiene (330 μL, 265 mg, 4.0 mmol) and more $LiClO_4$ (213.0 mg, 2.0 mmol) were added. The flask was sealed and the mixture was stirred 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 white solid (407 mg, 51% yield): mp: 28-30 °C; IR (film) 2923, 2853, 1741, 1466, 1316, 1290 1181, 1133, 1121, 1096, 1063, 1040, 872, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d 6.54 (dd, *J* = 5.3, 2.8 Hz, 1H), 6.33, (dd, *J* = 5.6, 2.8 Hz, 1H), 4.20 (dq, *J* = 10.9, 7.2 Hz, 1H), 4.11 (dq, *J* = 10.9, 7.2 Hz, 1H), 3.93 (dd, *J* = 9.7, 3.1 Hz, 1H), 3.51 (bs, 1H), 3.41 (dd, *J* = 10.0, 3.1 Hz, 1H), 3.27 (bs, 1H), 3.23-3.12 (m, 2H), 1.90-1.78 (m, 2H), 1.55 (dt, *J* = 8.7, 1.9 Hz, 1H), 1.48-1.41 (m, 2H), 1.29 (t, *J* = 7.2 Hz 3H), 1.37-1.26 (m, 17H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 137.5, 132.3, 65.9, 61.1, 55.2, 49.1, 47.8, 46.2, 31.9, 29.6 (double intensity), 29.5, 29.3 (double intensity), 29.1, 28.6, 22.6, 21.4, 14.1, 14.0; HRMS (ESI, TOF): Exact mass calcd for $C_{22}H_{39}O_4S$ $[M+H]^+$, 399.2564. Found 399.2570.



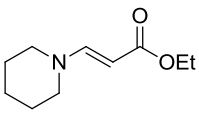
Ethyl (E)-3-(ethoxy)acrylate To an oven-dried round-bottomed flask under N_2 atmosphere was added the phenol (189.6 mg, 2.01 mmol), CH_2Cl_2 (3.0 mL), ethanol (115μL, 90.7 mg, 1.97 mmol), ethyl propiolate (203 μL, 196 mg, 2.0 mmol), and triethylamine (70 μL, 50.8 mg, 0.50 mmol). The mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo and the residue was purified by column chromatography (5% EtOAc/hexanes). The product was isolated as a yellow oil (196 mg, 78% yield): ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J*=12.8 Hz, 1H), 5.20 (d, *J*=12.8 Hz, 1H), 4.18 (q, *J*=7.2 Hz, 2H), 3.92 (q, *J*=7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H).



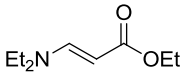
Ethyl (*E*)-3-(phenoxy)acrylate The title compound was prepared according to General Procedure E, using phenol (189.6 mg, 2.01 mmol) as the alcohol nucleophile. The product was isolated as a yellow oil (379 mg, 98% yield): ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J*=12.2 Hz, 1 H), 7.40 (t, *J*=8.0 Hz, 2H), 7.21 (t, *J*=7.5 Hz, 1H), 7.10 (d, *J*=8.8 Hz, 2 H), 5.57 (d, *J* = 12.2 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2 H), 1.31 (t, *J* = 7.2 Hz, 3 H**.**



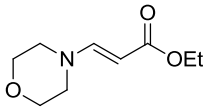
Ethyl (*E*)-3-(N-pyrrolidinyl)acrylate The title compound was prepared according to General Procedure E, using pyrollidine (165 μL, 143 mg, 2.01 mmol) as the amine nucleophile. The product was isolated as a yellow oil (286 mg, 84% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J*=13.1Hz, 1H), 4.50 (d, *J*=13.1 Hz, 1H), 4.15 (t, *J*=7.2 Hz, 2H), 3.28 (bs, 4H), 1.95 (bs, 4 H), 1.29 (t, *J* = 7.2 Hz, 3 H).



Ethyl (*E*)-3-(N-morpholinyl)acrylate The title compound was prepared according to General Procedure E, using piperidine (150 μL, 129 mg, 1.51 mmol) as the amine nucleophile. The product was isolated as a yellow oil (182 mg, 66% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J*=13.1Hz, 1H), 4.64 (d, *J*=13.1 Hz, 1H), 4.15 (q, *J*=7.2 Hz, 2H), 3.20 (bs, 4H), 1.59-1.66 (m, 6 H), 1.28 (t, *J* = 7.2 Hz, 3 H).



Ethyl (*E*)-3-(N-diethylamino)acrylate The title compound was prepared according to General Procedure E, using diethylamine (210 μL, 148 mg, 2.02 mmol) as the amine nucleophile. The product was isolated as a yellow oil (278 mg, 81% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J*=13.1Hz, 1H), 4.59 (d, *J*=13.1 Hz, 1H), 4.15 (q, *J*=7.2 Hz, 2H), 3.20 (q, *J*=7.2 Hz, 4H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.70 (t, *J* = 7.2 Hz, 6 H).



Ethyl (*E*)-3-(N-morpholinyl)acrylate The title compound was prepared according to General Procedure E, using morpholine (175 μL, 174 mg, 2.00 mmol) as the amine nucleophile. The product was isolated as a yellow oil (260 mg, 70% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J*=12.8Hz, 1H), 4.72 (d, *J*=12.8Hz, 1H), 4.16 (q, *J*=7.2 Hz, 2H), 3.73 (t, *J*=4.8 Hz, 4H), 3.23 (t, *J* = 4.8 Hz, 4 H).

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4) List of Abbreviations or Symbols

E	entgegen
Et	ethyl
HRMS	High-Resolution Mass Spectroscopy
i-Pr	*iso*-propyl
IR	Infrared Spectroscopy
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
NOESY	Nuclear Overhauser Effect Spectroscopy
NMR	Nuclear Magnetic Resonance
p	para
R	generic organic group
rt	room temperature
t-Bu	*tert*-butyl
Z	zusammen