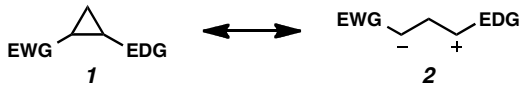
CHAPTER 1

Lewis Acid Mediated (3 + 2) Cycloadditions of Donor–Acceptor Cyclopropanes with Heterocumulenes[†]

1.1 INTRODUCTION

Donor–acceptor cyclopropanes (**1**) are those which bear an electron-donating group and an electron-withdrawing group with a vicinal relationship; these have found broad use as building-blocks in organic synthesis (Scheme 1.1.1).[1] Their reactivity is attributed to the electronic nature of these compounds, bearing substituents that polarize the cyclopropane C–C bond between them.

Scheme 1.1.1. Structural definition of donor–acceptor cyclopropanes

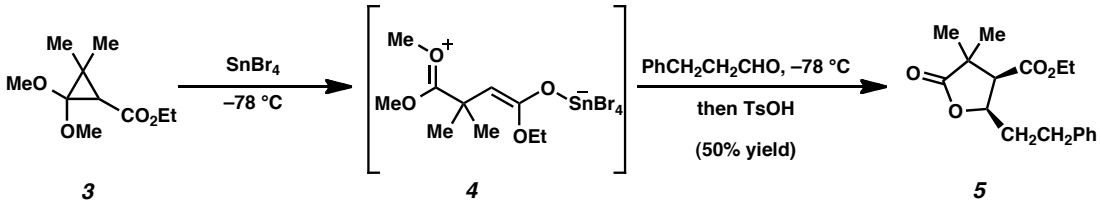


Historically, alkoxy or silyloxy substituents are among the most prevalent donor groups used in these systems. A typical example of such a system is Saigo's use of

[†] This work was performed in collaboration with Nicholas R. O'Connor and Robert A. Craig, II, graduate students in the Stoltz group. This work has been published. See: Goldberg, A. F. G.; O'Connor, N. R. O.; Craig, R. A., II; Stoltz, B. M. *Org. Lett.* **2012**, *14*, 5314–5317.

tin(IV) bromide to activate dimethoxycyclopropane **3**, which affords intermediate zwitterion **4** (Scheme 1.1.2).[2] Upon reaction with an aldehyde, followed by Brønsted acid catalyzed cyclization, lactones such as **5** are formed. In cases such as these, complete heterolysis of the reactive C-C bond results in loss of stereochemical information at those centers and any control of absolute stereochemistry must result from remote chiral centers or reagent control.

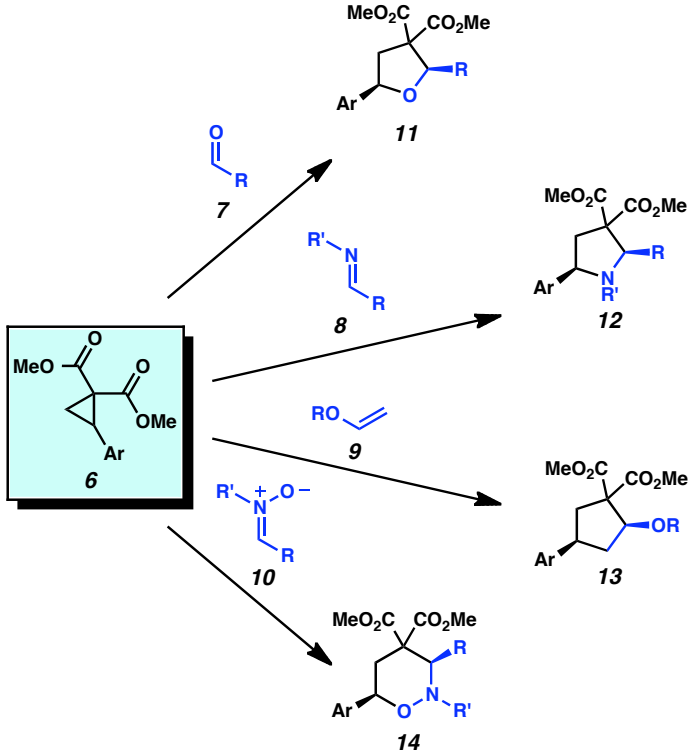
*Scheme 1.1.2. Lewis acid activation of dimethoxycyclopropane **3***



3 ***4*** ***5***

More recently, aryl-substituted cyclopropane-1,1-diesters (**6**) have proven valuable in Lewis acid promoted stereoselective 2, 3, or 4 atom ring-expansion reactions. By reaction with aldehydes (**7**),[3] imines (**8**),[4] enol ethers (**9**),[5] and nitrones (**10**),[6] an array of enantioenriched carbocycles and heterocycles (**11**–**14**) have been prepared (Scheme 1.1.3).

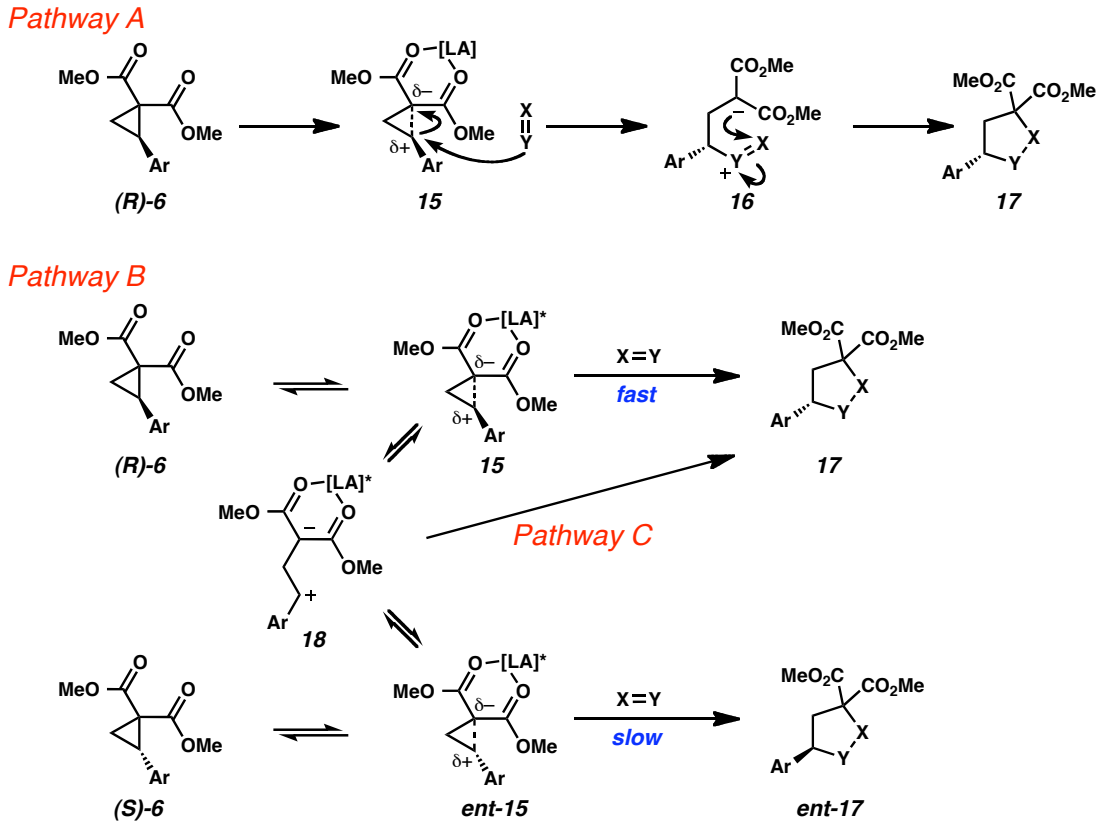
Scheme 1.1.3 Stereoselective (3 + 2) cycloadditions of donor–acceptor cyclopropanes.



There are two prevailing pathways toward enantioenriched products that have been studied in this system. First, enantioenriched starting materials have been converted stereospecifically to enantioenriched products with judicious choice of Lewis acid (Scheme 1.1.4, Pathway A). For these systems, it is generally believed that the Lewis acid activates the cyclopropane (**6**) toward nucleophilic attack without complete cleavage of the polarized C–C bond. The malonate zwitterion (**15**) then undergoes ring-closure to generate the product (**17**), with overall inversion of stereochemistry.[3b,5a,6f] Alternatively, racemic cyclopropanes have been converted to enantioenriched products by means of a dynamic kinetic asymmetric transformation (DyKAT), wherein the starting material is racemized under the reaction conditions, and one enantiomer reacts faster with a chiral Lewis acid (Scheme 1.1.4, Pathway B).[3d,4c,5b,6h] Finally, it is also possible that a discrete,

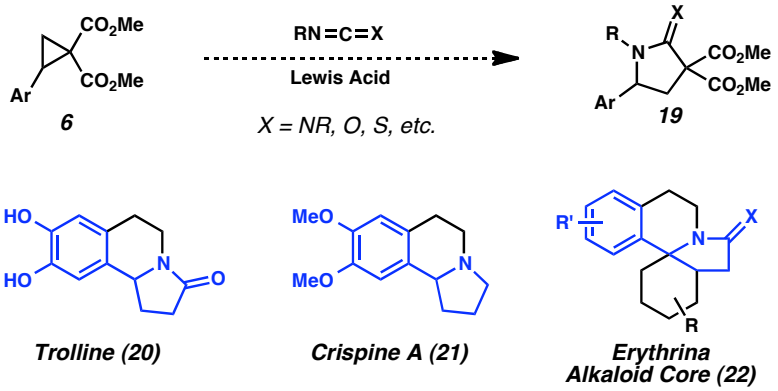
planarized zwitterion (**18**) can react with the dipolarophile in the presence of a chiral Lewis acid to effect facial selectivity.

Scheme 1.1.4. Prevailing pathways for stereoselective cyclopropane cycloadditions



Our research group has a long-standing interest in the asymmetric synthesis of chiral heterocycles.[7] We were therefore interested in examining the use of heterocumulenes with this reaction platform toward the synthesis of chiral 5-aryl substituted lactam derivatives, a structural motif found in several natural products including trolline **20**,[8] crispine A (**21**),[9] and several of the *Erythrina* alkaloids (**22**).[10,11]

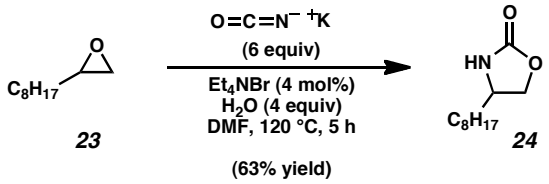
Scheme 1.1.5. Proposed (3 + 2) cycloaddition of heterocumulenes with cyclopropanes



1.2 INITIAL EFFORTS

Our initial attempts began with the investigation of potassium cyanate as a potential dipolarophile toward the synthesis of secondary γ-lactams. Swern reported the use of potassium cyanate in the synthesis of oxazolidinones from epoxides; heating of epoxides (i.e. **23**) with potassium cyanate, in the presence of a phase-transfer catalyst and water, affords oxazolidinones (i.e. **24**) in good yields (Scheme 1.2.1).[12] Notably, the inclusion of water was necessary for product formation; dimers were typically observed in the absence of water.

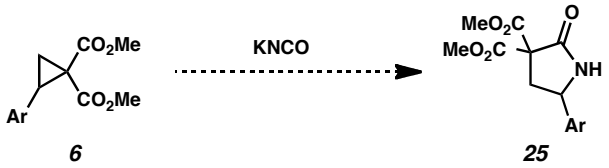
Scheme 1.2.1. Synthesis of oxazolidinones from epoxides



The use of potassium cyanate in reaction with cyclopropanes would bear certain advantages: it is readily available at low expense, and would provide direct access to γ-lactams (i.e. **25**, Scheme 1.2.2). Therefore, we began by studying the reactivity of donor–

acceptor cyclopropanes with potassium cyanate under comparable conditions to those developed by Swern.

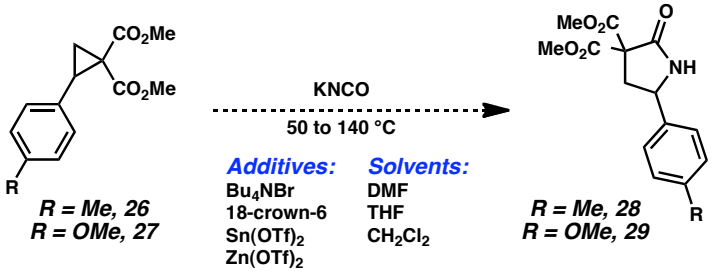
Scheme 1.2.2. Proposed synthesis of lactams using potassium cyanate



6 ***25***

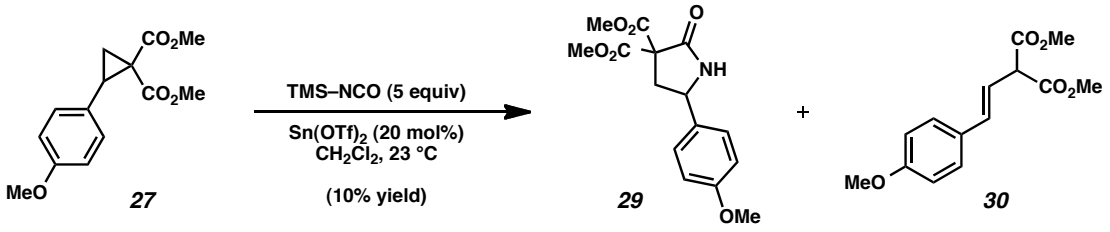
Our studies began by treatment of *para*-tolyl substituted cyclopropane **26** with potassium cyanate in several solvents in the presence of Lewis acids or phase-transfer catalysts (Scheme 1.2.3). Unfortunately, none of the desired product (**28**) was observed by LCMS. In our attempt to increase the reactivity of the cyclopropane, we examined *para*-methoxyphenyl cyclopropane **27**, and though the starting material was consumed in this case, no lactam formation was observed.

*Scheme 1.2.3. Reactivity attempts of potassium cyanate with cyclopropanes **26** and **27***



We considered that the cyclopropane may require Lewis acid activation, but the cyanate anion deactivated the Lewis acid by coordination. Therefore, we examined trimethylsilyl isocyanate as a potential alternative, using tin(II) triflate as a Lewis acid additive, and we were pleased to observe the formation of lactam **29** in 10% yield, with styrene **30** as the major side product. Having demonstrated proof-of-principle, we set out to optimize the cycloaddition reaction.

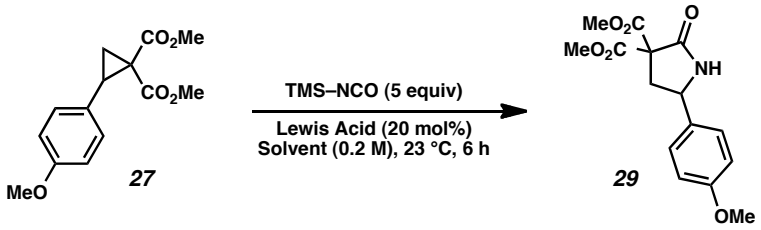
*Scheme 1.2.4. Synthesis of lactam **29** from cyclopropane **27***



1.3 REACTION OPTIMIZATION OF ISOCYANATE CYCLOADDITION

Our first course of action was to examine an array of Lewis acids and solvents in the (3 + 2) cycloaddition reaction (Table 1.3.1). In several organic solvents, the yield of lactam **29** was unimproved (entries 1–6), and most of the starting material was isomerized to styrene **30**. The use of DMSO completely halted the reaction, likely due to deactivation of the Lewis acid by coordination of solvent (entry 7). With the use of unpurified ethyl acetate, we were pleased to observe a marked improvement to 56% yield (entry 7); upon repetition of this experiment with dry, distilled ethyl acetate, the yield fell to 18%, comparable to other dry organic solvents (entry 8), suggesting that water may play a role in the reaction.[13,14] Finally, the examination of several other Lewis acids proved unfruitful in this exercise, either offering little reactivity (entries 10, 12) or complete isomerization of the cyclopropane (entry 11).

Table 1.3.1. Lewis acid and solvent screen for the (3 + 2) cycloaddition

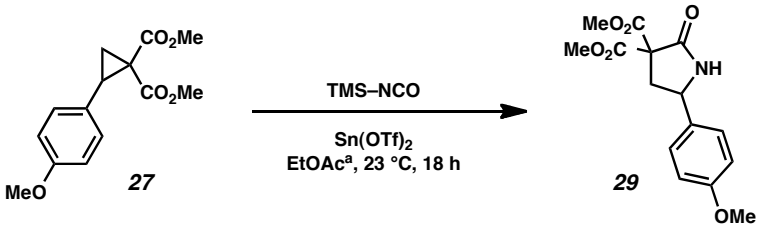


entry	Lewis Acid	Solvent	Conversion (%)	Yield of **29** (%)[a,b]
1	$Sn(OTf)_2$	CH_2Cl_2	100	23
2	$Sn(OTf)_2$	THF	56	15
3	$Sn(OTf)_2$	Et_2O	100[c]	25
4	$Sn(OTf)_2$	MeCN	97	20
5	$Sn(OTf)_2$	PhMe	60	18
6	$Sn(OTf)_2$	$CHCl_3$[d]	100	0
7	$Sn(OTf)_2$	DMSO	0	0
8	$Sn(OTf)_2$	EtOAc[d]	96[c]	56
9	$Sn(OTf)_2$	EtOAc	100[c]	18
10	$Zn(OTf)_2$[e]	CH_2Cl_2	0	0
11	$Sc(OTf)_3$	CH_2Cl_2	100	0
12	$MgBr_2 \cdot Et_2O$	CH_2Cl_2	40	15

[a] Determined by LCMS, using 1,4-dichlorobenzene as an internal standard. [b] The major side-product was typically styrene **30**. [c] 18 hour reaction time. [d] Undistilled. [e] Other unreactive Lewis acids include $Mg(OTf)_2$, $Ni(OTf)_2$, $MnCl_2$, $Sm(OTf)_3$.

We then sought to examine the effect of substrate concentration, isocyanate equivalence and Lewis acid equivalence on the outcome of the reaction (Table 1.3.2).[15] We found that lowering the equivalence of isocyanate lowered the yield of lactam **29** slightly (entries 1–3). In addition, lowering the cyclopropane concentration decreased the yield (entry 4) and decreasing the Lewis acid loading to 5 mol% shut down reactivity entirely (entry 5). However, increasing the concentration to 0.6 M at this catalyst loading restored some measure of reactivity, providing lactam in 21% yield (entry 6). Increasing the quantity of tin from our original conditions improved the yield, to the point where we observed the highest yields with stoichiometric tin (entry 10).

Table 1.3.2. Equivalence and concentration optimization.

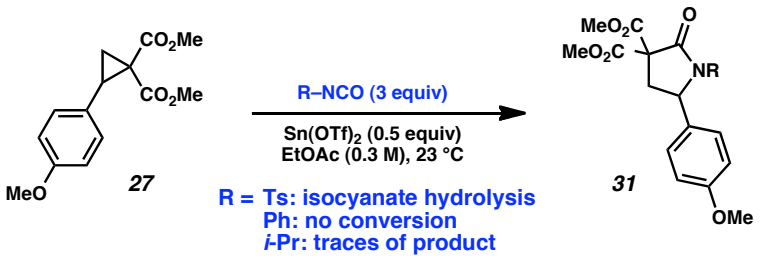


entry	Isocyanate equiv	$Sn(OTf)_2$ equiv	[*27*]	Conversion (%)	Yield of **29** (%)[b,c]
1	5	0.2	0.2 M	63	64
2	4	0.2	0.2 M	59	56
3	3	0.2	0.2 M	59	54
4	3	0.2	0.1 M	31	21
5	3	0.05	0.3 M	3[d]	0
6	3	0.05	0.6 M	23[d]	21
7	3	0.1	0.6 M	64[d]	61
8	3	0.2	0.6 M	100[d]	85 (48)[e]
9	3	0.5	0.2 M	100	93
10	3	1.0	0.2 M	100	>99

[a] Unpurified. [b] Determined by LCMS, using 1,4-dichlorobenzene as an internal standard. [c] The major side-product was typically styrene **30**. [d] 24 hour reaction time. [e] Isolated yield.

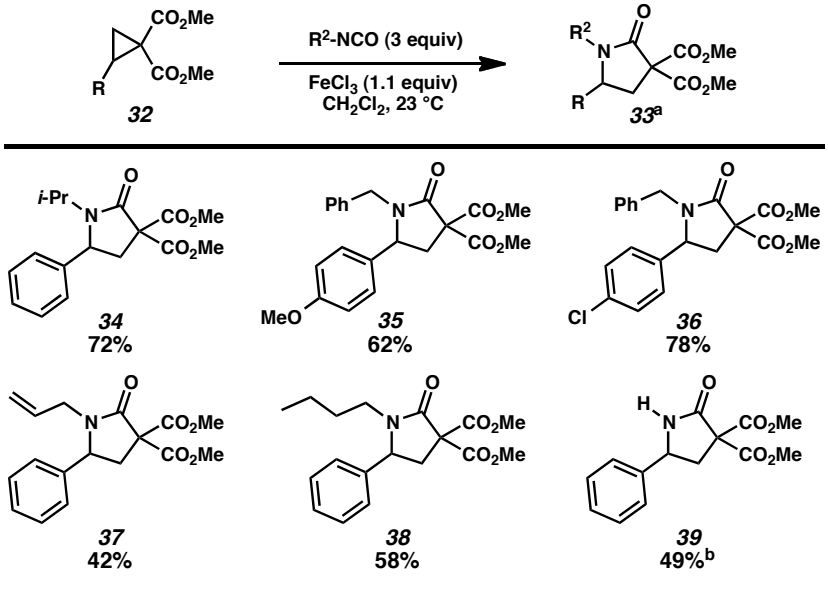
We were interested in ascertaining the compatibility of other heterocumulenes in this reaction; therefore we examined a breadth of substitution before further developing the reaction (Scheme 1.3.1). However, only with isopropyl isocyanate did we observe any trace of the desired product at room temperature. Phenyl isocyanate was found to be unreactive under the same conditions, and tosyl isocyanate was hydrolyzed quickly under the reaction conditions, presumably due to the presence of adventitious water in the unpurified solvent.

Scheme 1.3.1. Initial examination of alternative isocyanates.



The hydrolysis of tosyl isocyanate under the reaction conditions, while not surprising due to the highly electrophilic nature of the reagent, raised broader concerns about the presence of water in the reaction mixture. In addition, the poor reactivity for these substituted isocyanates prompted us to investigate stronger Lewis acids for this transformation; we sought to avoid biasing the system with an electron-rich arene. Furthermore, we returned to the use of dichloromethane, since the dry solvent was more readily accessible in our laboratory and provided comparable yields to those observed with dry ethyl acetate. A brief examination of several Lewis acids found that stoichiometric iron(III) chloride performed the desired transformation with several different alkyl-substituted isocyanates to afford lactams **34**–**39** (Scheme 1.3.2).[16]

Scheme 1.3.2. Scope of iron(III) chloride mediated (3 + 2) cycloadditions of isocyanates.

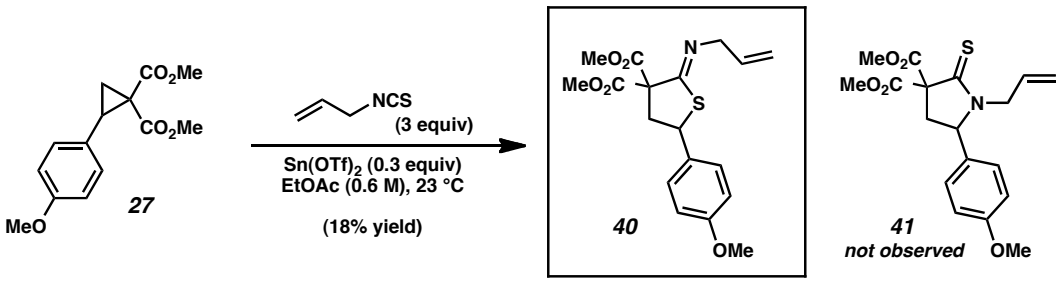


[a] Isolated yields. [b] Trimethylsilylisocyanate was used and hydrolysis of the silyl group occurred upon workup.

1.4 ISOTHIOCYANATE (3 + 2) CYCLOADDITIONS

We also examined other classes of heterocumulenes under the same conditions. We had initially found that treatment of *para*-methoxyphenyl subsituted cyclopropane (**27**) with allyl isothiocyanate in the presence of substoichiometric tin(II) triflate afforded a thioimidate (**40**) in moderate yield; thiolactam **41** was not observed under these conditions (Scheme 1.4.1).

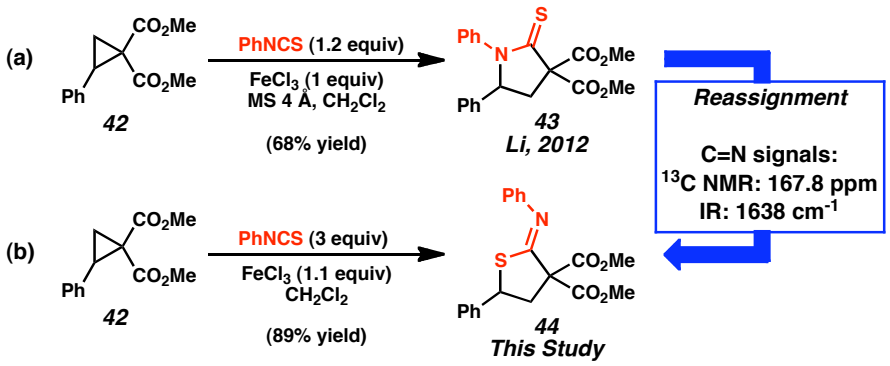
*Scheme 1.4.1. Synthesis of thioimidate **40** using allyl isothiocyanate*



Concurrent with these studies, Li and coworkers disclosed an iron(III) chloride mediated (3 + 2) cycloaddition of aryl isothiocyanates with donor–acceptor cyclopropanes to form thiolactams (e.g. **44**) rather than thioimidates (e.g. **43**, Scheme 1.4.2).[17] We suspected that the products reported by Li may have been misassigned, and decided to investigate this further. Upon comparison of the ^{13}C NMR spectrum of allyl isothiocyanate adduct **40** to the spectra of the products reported by Li, we found similar shifts in the carbonyl range for these spectra; three signals were typically observed near 160 ppm—two corresponding to the ester functionalities—and the third is consistent with a thioimidate. By contrast, a thioamide C=S ^{13}C NMR signal is expected at approximately 200 ppm.[18] Furthermore, the IR spectrum of **40** exhibited a C=N stretch at 1638 cm^{-1}, and C=S signals were not observed.[19] Although no IR spectra were included

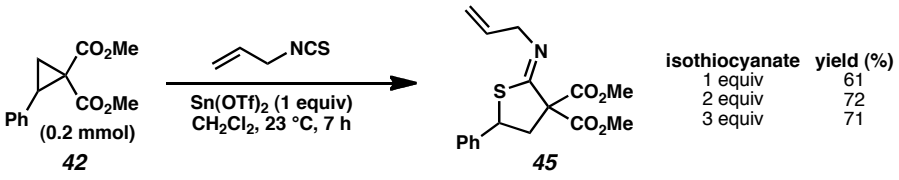
in Li's report, we reacted cyclopropane **42** with phenyl isothiocyanate under similar conditions to those reported by Li and obtained a compound with NMR spectra matching those reported (Scheme 2b). The product IR spectrum contained a C=N stretch at 1638 cm^{-1} while a C=S peak was not observed. Altogether, these data strongly support our assignment of compound **44** and Li's isothiocyanate (3 + 2) adducts as thioimidates, not thiolactams.

Scheme 1.4.2. Structural reassignment of Li's arylisothiocyanate (3 + 2) products



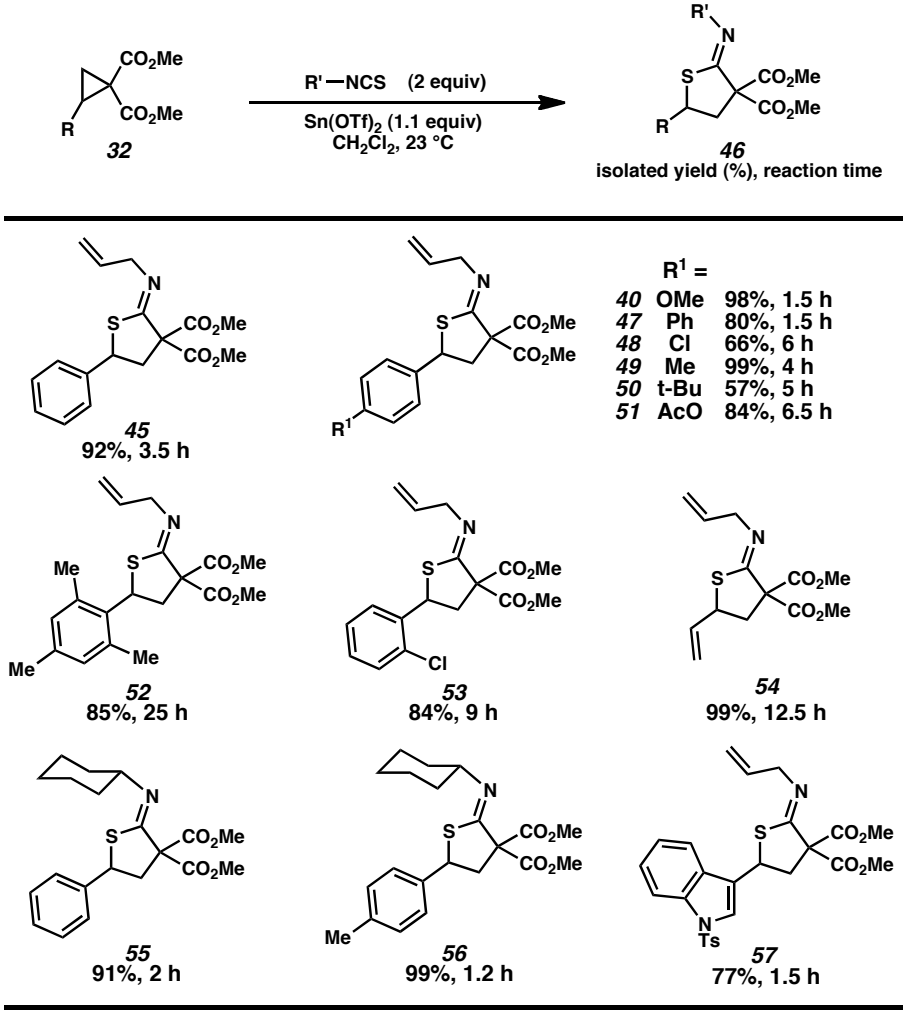
We ultimately found the use of stoichiometric Lewis acid was necessary to achieve complete conversion of the cyclopropane starting material. For the same reasons as before, we elected to perform the reaction in dry dichloromethane, and examined the necessary excess of isothiocyanate to achieve the good yields of thioimidate (Scheme 1.4.3). We found that decreasing the equivalence of allylisothiocyanate from 3 to 2 with respect to cyclopropane had no measurable impact on the reaction yield, while the use of one equivalent of isothiocyanate resulted in a lower isolated yield.

Scheme 1.4.3. Study on isothiocyanate stoichiometry in (3 + 2) cycloadditions



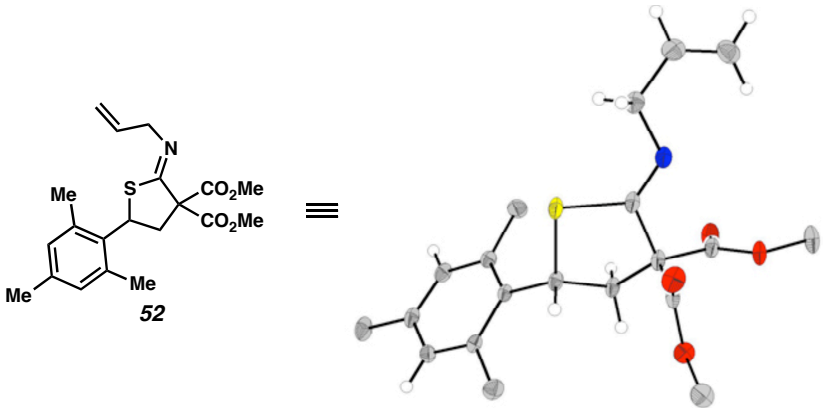
Eventually, we found that decreasing the reaction time—careful monitoring of the reaction and workup immediately upon completion—and increasing the reaction scale resulted in improved yields. Notably, the thioimidate products slowly decompose at room temperature, as observed by discoloration of the material and new signals in their NMR spectra; storage in a –20 °C freezer is necessary for prolonged storage. We then examined the substrate scope of the reaction, and found that thioimidates with electron-rich aryl substituents (**40**, **47**, **57**) were obtained with the shortest reaction times. Reactions leading to products with *ortho-* or electron-withdrawing arene substituents (**48**, **52**, **53**) were the slowest. Cyclopropanes were not limited to those with aryl substituents; a vinyl group could also be used as an electron-donating substituent, offering 5-vinylthioimidate **54** in quantitative yield. In addition, cyclohexyl isothiocyanate was also compatible under these conditions, providing thioimidates **55** and **56** in 91% and 99% yield respectively.

Scheme 1.4.4. Substrate scope of isothiocyanate (3 + 2) reaction



Notably, we were able to obtain x-ray quality crystals of mesityl-substituted product **52**, confirming our assignment of these products as thioimidates. Furthermore, the geometry of the imidate *N*-substituent was confirmed in this experiment, and the other thioimidate products were assigned as such by analogy.

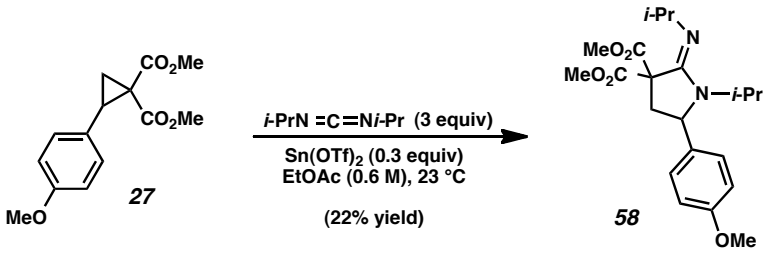
Scheme 1.4.5. Confirmation of thioimidate structure by single crystal x-ray diffraction



1.5 CARBODIIMIDE (3 + 2) CYCLOADDITIONS

Finally, we turned our attention toward (3 + 2) cycloadditions with carbodiimides. In our initial studies, we found that treatment of cyclopropane **27** with diisopropylcarbodiimide in the presence of substoichiometric tin(II) triflate afforded amidine **58**, albeit in moderate yield (Scheme 1.5.1). Akin to our studies on isocyanates and isothiocyanates, we envisioned that the use of stoichiometric tin in dry dichloromethane would improve our initial results; using wet ethyl acetate, we observed by NMR conversion of carbodiimide to a urea side product. We sought to avoid this by excluding water from the reaction mixture and limiting the excess of carbodiimide.

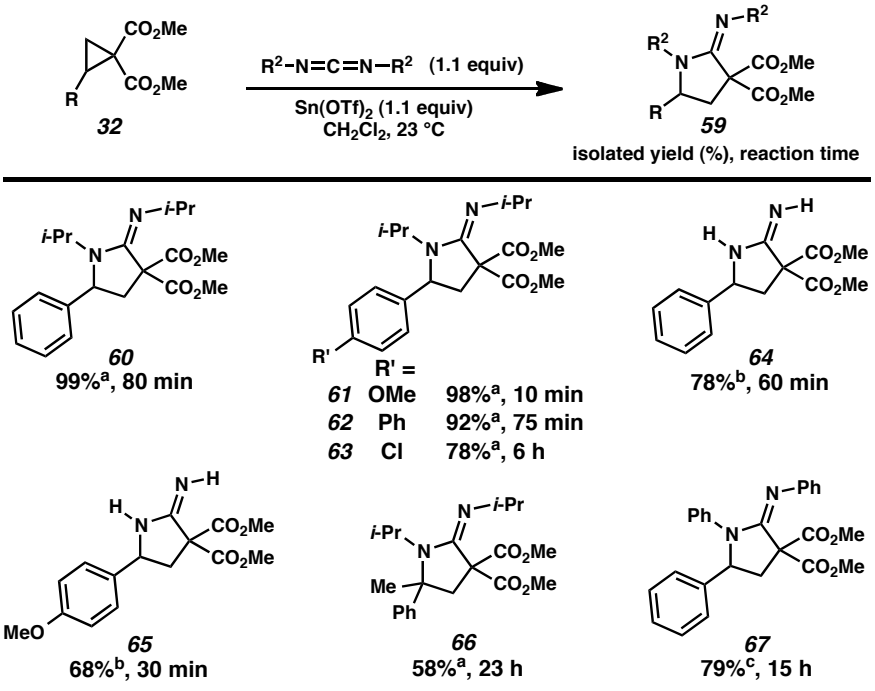
*Scheme 1.5.1. Synthesis of amidine **58** using diisopropylcarbodiimide*



We were therefore pleased to find that with only a marginal excess of carbodiimide and tin(II) triflate, we observed quantitative formation of amidine **60** (Scheme 1.5.2). In

this case, the reaction was complete in only 80 minutes, and electron rich 5-para-methoxyphenyl amidine **58** was formed in 98% yield in less than 10 minutes. Primary amidines (**64** and **65**) could also be accessed using bis(trimethylsilyl)carbodiimide. Notably, (3 + 2) reactions were possible with cyclopropanes that are unreactive with isothiocyanates. For instance, a sterically congested 5,5-disubstituted amidine **66** could be generated in 58% yield. In addition, while aryl isothiocyanates were poorly reactive in the presence of tin(II) triflate, use of diphenylcarbodiimide resulted in the formation of the corresponding amidine (**67**) in 79% yield. Overall, the shorter reaction times indicate that carbodiimides are considerably more reactive dipolarophiles than comparable isothiocyanates in these reactions.

Scheme 1.5.2. Substrate scope of carbodiimide (3 + 2) cycloaddition.

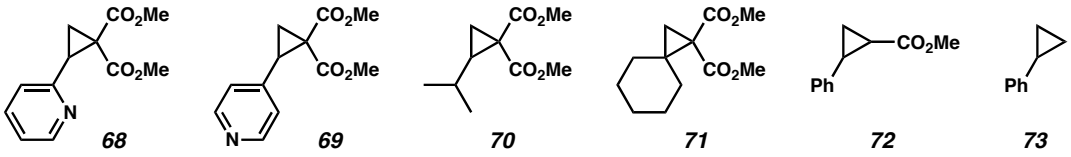


[a] diisopropylcarbodiimide was used as the dipolarophile. [b] bis(trimethylsilyl)carbodiimide was used as the dipolarophile, the silyl groups are hydrolysed upon workup. [c] diphenylcarbodiimide was used as the dipolarophile.

1.6 UNREACTIVE AND PROBLEMATIC SUBSTRATES

We found several cyclopropanes to be unreactive in the Lewis acid mediated heterocumulene (3 + 2) reaction (Scheme 1.6.1). 2- and 4-pyridyl substituted cyclopropanes (**68** and **69**) were unreactive under standard reaction conditions. We considered that the pyridyl substituent inhibited the Lewis acid; although we thought that the use of an additional equivalent of Lewis acid may restore reactivity, efforts to this end failed to generate any desired (3 + 2) adduct. We also attempted to use alkyl substituted cyclopropanes **70** and **71**, since such substrates were known to be reactive under aldehyde (3 + 2) and nitrone (3 + 3) cycloaddition conditions.[3,6] Unfortunately, these substrates did not form (3 + 2) adducts under our standard conditions with heterocumulenes. Finally, application of a cyclopropane with one or no ester substituents (**72** and **73**) failed to afford (3 + 2) adducts, suggesting that the ester moieties are necessary for coordination to the Lewis acid.

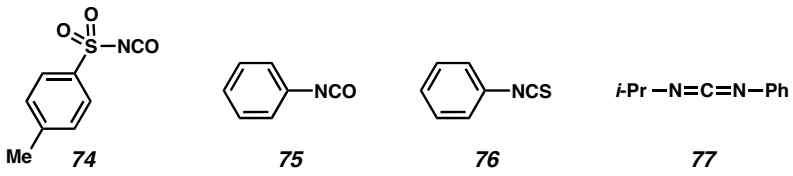
Scheme 1.6.1. Unreactive cyclopropanes in heterocumulene (3 + 2) cycloadditions



Certain heterocumulenes were also found to be unreactive under our standard conditions (Scheme 1.6.2). Tosylisocyanate (**74**) and phenylisocyanate (**75**) were unreactive under our standard conditions. Furthermore, while arylisothiocyanates (i.e. **76**) were unreactive using tin(II) triflate as the Lewis acid, these could participate in cyclopropane (3 + 2) cycloadditions with iron(III) chloride, as demonstrated by Li and coworkers.[17] Finally, unsymmetrical carbodiimide **77** was attempted in the standard

reaction conditions. We envisioned that the significant difference in reaction times between diisopropylcarbodiimide (80 min with cyclopropane **42**) and diphenylcarbodiimide (15 h) would proffer selectivity with a mixed carbodiimide (**77**), however, an inseparable mixture of constitutional isomers was produced.

Scheme 1.6.2. Problematic heterocumulenes in (3 + 2) cycloadditions



1.7 INVESTIGATIONS ON TRANSFER OF CHIRALITY

Finally, we sought to establish whether stereochemical information from the starting material is transferred to the product under the reaction conditions. We prepared enantioenriched cyclopropane (*S*)-**42** according to literature methods and subjected it to our standard reaction conditions (Scheme 1.7.1). Although treatment of this substrate with an isocyanate in the presence of iron(III) chloride resulted in complete racemization of the benzylic stereocenter (Scheme 1.7.1a), we observed transfer of chirality in the case of tin(II) triflate mediated (3 + 2) cycloadditions (Scheme 1.7.1b, c). Notably substrates that required longer reaction times resulted in increased erosion of optical activity. We were able to confirm the absolute stereochemistry of the HBr salt of (*R*)-**60** by single crystal x-ray diffraction, which revealed an inversion of configuration at the benzylic stereocenter through the course of the reaction, and also confirmed the geometry of the amidine substituent, notably it is inverted to that observed with the thioimidates (Figure 1.7.1).

Scheme 1.7.1. Reactions of enantioenriched cyclopropane ***(S)-42*** *with heterocumulenes*

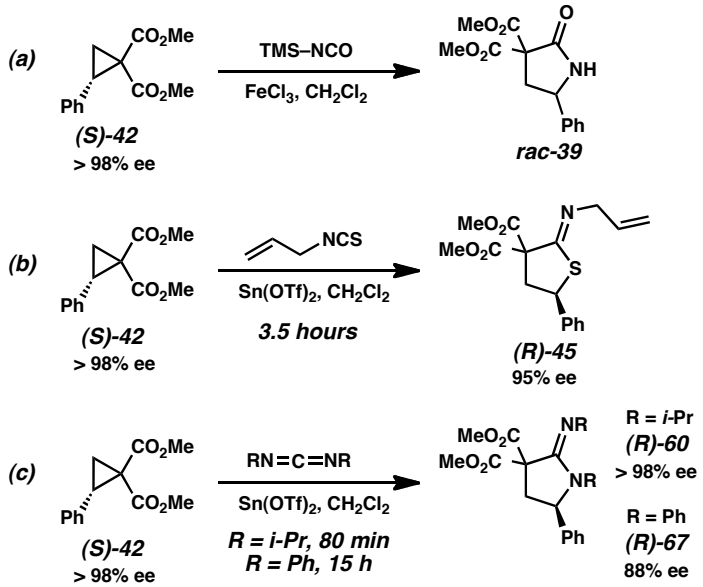
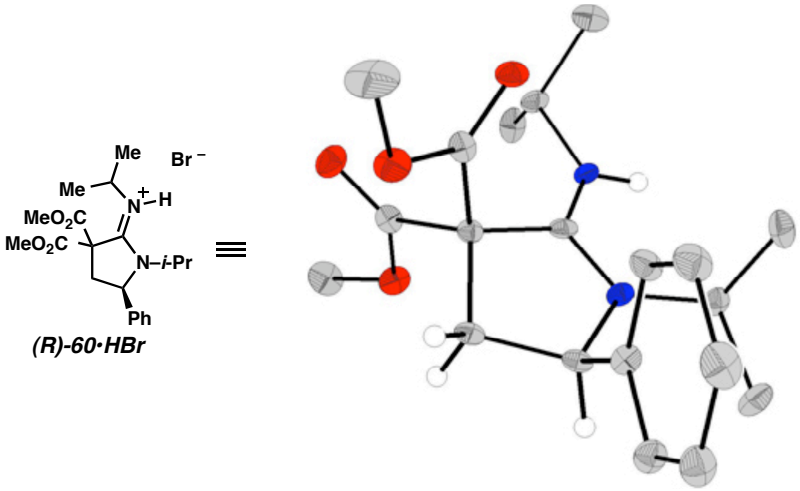


Figure 1.7.1. Determination of absolute configuration by single crystal X-ray diffraction.[20]

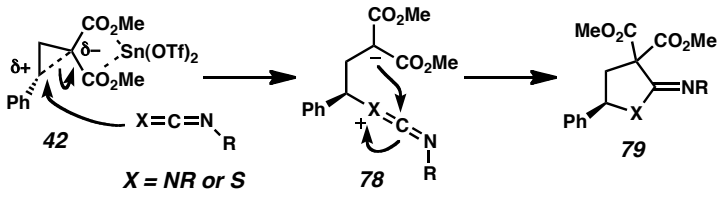


1.8 DISCUSSION OF MECHANISM

We propose that the mechanism of the isothiocyanate and carbodiimide reactions with tin(II) triflate involves a stereospecific intimate-ion pair mechanism analogous to that proposed for Johnson's (3 + 2) cycloadditions of aldehydes and donor–acceptor cyclopropanes (Scheme 1.8.1).[3b,c,6e,f,g] Our observations, including stereochemical

inversion at the benzylic position and greater reactivity of electron-rich dipolarophiles and of cyclopropanes with electron-rich aromatic substitutuents are all consistent with this mechanistic hypothesis.

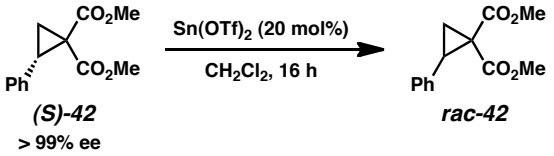
Scheme 1.8.1. Mechanism of (3 + 2) cycloaddition with carbodiimides and isothiocyanates



In the case of the iron-catalyzed isocyanate (3 + 2) cycloaddition, the dipolarophile likely reacts in a nucleophilic sense, which is corroborated by the lack of reactivity of the aryl- and sulfonyl-substituted isocyanates. However, the formation of a discrete carbocation intermediate in this case—as opposed to a contact-ion pair—is supported by the rapid racemization of the cyclopropane starting material.

Finally, the degree of interaction between the heterocumulene and the Lewis acid likely affects the course of the reaction. Whereas Johnson reported that in the presence of 0.2 equivalents of tin(II) triflate, enantioenriched cyclopropane (*S*)**-42** was completely racemized in 16 h, we found that amidine (*R)***-67** was formed in 88% ee with a reaction time of 15 h with stoichiometric Lewis acid (*vide supra*, Scheme 1.7.1).[3c] Although a direct comparison cannot be made since the cyclopropane is converted over time in the latter case, it is evident that cyclopropane racemization is attenuated in the presence of carbodiimide.

*Scheme 1.8.2. Racemization of cyclopropane (S)-**42** with catalytic tin(II) triflate*[3c]

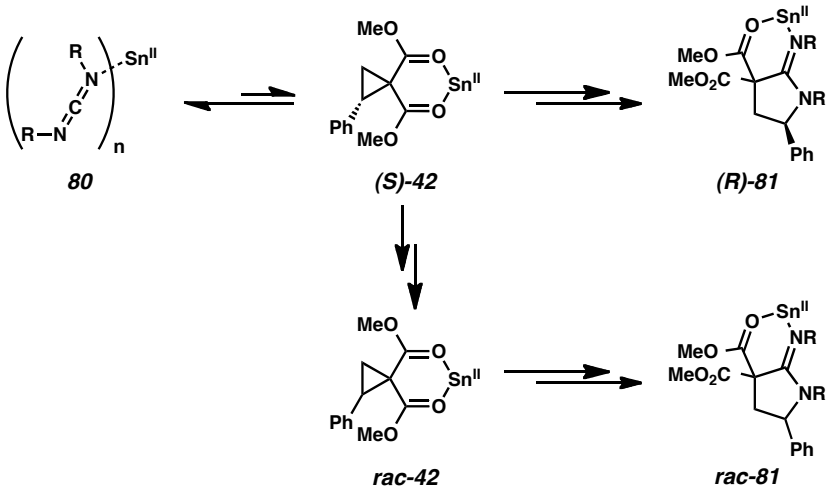


(S)-42
> 99% ee

rac-42

It is possible that an equilibrium exists between a tin–dipolarophile complex and a tin–cyclopropane complex, which would account for the mitigation of cyclopropane racemization over the extended reaction time (R = Ph, Scheme 1.8.3). Coordination of the product to the catalyst would minimize further racemization of the enantioenriched cyclopropane, and is consistent with the need for stoichiometric Lewis acid to achieve full conversion of starting material.

Scheme 1.8.3. Proposed mechanism accounting for attenuated racemization



80 ***(S)-42*** ***(R)-81***

rac-42 ***rac-81***

1.9 FUTURE DIRECTIONS

We are currently examining the extensions of this methodology, and applications toward the synthesis of natural products. These aspects of the project are discussed in Appendix 1.

1.10 CONCLUSION

In summary, we have developed a method for the (3 + 2) cycloaddition of donor–acceptor cyclopropanes with heterocumulenes. We have demonstrated a novel mode of reactivity with isothiocyanates, complementary to that previously observed with alkoxy substituted cyclopropanes. Finally, we have shown that enantioenriched starting materials may be converted to enantioenriched 5-membered heterocycles by a stereospecific process. Investigations are ongoing to develop related methodologies and to apply this method to the synthesis of natural products.

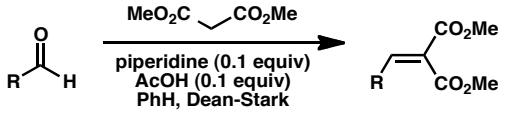
1.11 EXPERIMENTAL SECTION

1.11.1 MATERIALS AND METHODS

Unless stated otherwise, reactions were performed under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina).[21] Commercially obtained reagents were used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator. Microwave reactions were performed with a Biotage Initiator Eight 400 W apparatus at 2.45 GHz. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, or potassium permanganate, iodine, or anisaldehyde staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 126 MHz respectively), Varian 400 (at 400 MHz and 100 MHz, respectively) or on a Varian Mercury 300 (at 300 MHz) and are reported relative to $CHCl_3$ (δ 7.26 & 77.16 respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode.

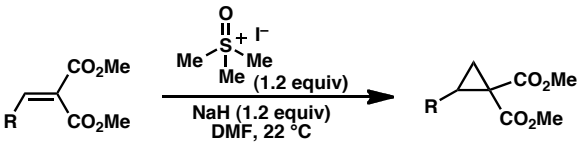
1.11.2 PREPARATIVE PROCEDURES

1.11.2.1 GENERAL AND MISCELLANEOUS EXPERIMENTAL PROCEDURES



General Procedure A. *Knoevenagel condensation*.

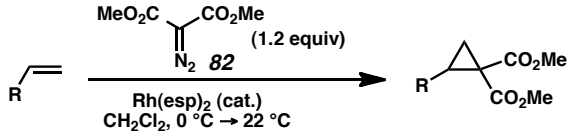
A round-bottom flask was charged with the appropriate aldehyde (14.4 mmol), followed by benzene (85 mL), dimethyl malonate (15.8 mmol), piperidine (1.44 mmol), and acetic acid (1.44 mmol). The flask was equipped with a Dean–Stark trap and condenser and the solution heated to reflux. Upon completion (as determined by TLC analysis), evaporation of the solvent gave the crude product, which was purified by silica gel column chromatography.



General Procedure B. *Corey-Chaykovsky cyclopropanation*.

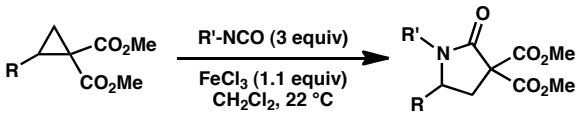
Sodium hydride (2.56 mmol, 60% dispersion in mineral oil) was suspended in anhydrous DMF (4 mL) in a flame-dried round-bottom flask under nitrogen. Trimethylsulfoxonium iodide (2.56 mmol) was added, and the solution stirred at ambient temperature for 1 hour. A solution of the appropriate benzylidene malonate (2.13 mmol) in anhydrous DMF (2 mL) was added, and the reaction mixture allowed to stir at room temperature. Upon completion (as determined by TLC analysis), the solution was poured

onto a mixture of ice and 2 M $HCl_{(aq)}$ (10 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed once with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography.



General Procedure C. *Styrene cyclopropanation.*

$Rh(esp)_2$ (0.3 mg) was added to a flame-dried round-bottom flask, which was then evacuated and backfilled with nitrogen three times. The appropriate styrene (5.0 mmol) and anhydrous dichloromethane (5 mL) were then added and the solution was stirred under nitrogen and cooled in an ice bath. A solution of diazodimethylmalonate (**82**) (6.0 mmol) in anhydrous dichloromethane (5 mL) was added dropwise over 20 minutes.[22] The reaction solution was then allowed to warm to ambient temperature. Upon completion (as determined by TLC analysis), the crude product was adsorbed onto silica gel and purified by column chromatography. When traces of the rhodium catalyst remained after chromatography (as determined by a blue discoloration), the product was dissolved in anhydrous benzene (1.5 mL) in a flame-dried round-bottom flask. A solution of tetrakis(hydroxymethyl)phosphonium hydroxide (10 μL, 1M in isopropanol) was added,[23] and the mixture was stirred at 60 °C for 12 hours. The solution was then cooled to room temperature, diluted with diethyl ether (20 mL), washed once with water and once with brine, dried over magnesium sulfate, filtered and concentrated to give the purified product.



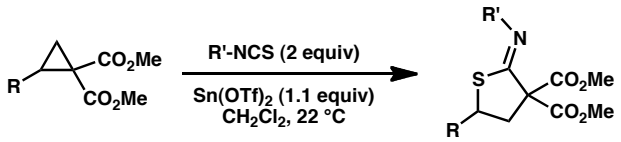
General Procedure D. *Isocyanate (3 + 2) reaction with D-A cyclopropanes.*

To a flame-dried 10 mL flask equipped with a magnetic stir bar was added iron(III) chloride (0.44 mmol) in an inert atmosphere glovebox. The flask was sealed with a Teflon septum, removed from the glovebox and placed under a nitrogen atmosphere. To an oven-dried 1 dram vial were added the appropriate cyclopropane (0.4 mmol) and isocyanate (1.2 mmol). The vial was sealed with a screw cap fitted with a Teflon septum, and this mixture was transferred to the reaction flask as a solution in anhydrous dichloromethane (1 mL + 0.33 mL rinse). The solution was then allowed to stir at ambient temperature under nitrogen. Upon consumption of the cyclopropane (as determined by TLC analysis), the reaction solution was diluted with dichloromethane, adsorbed onto Celite, and purified by silica gel column chromatography.

General Procedure E. *Isocyanate (3 + 2) reaction with D-A cyclopropanes.*

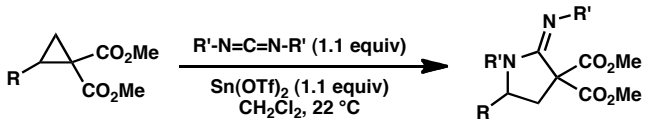
To an oven-dried 1 dram vial equipped with a magnetic stir bar was added iron (III) chloride (0.44 mmol) and oven-dried 4 Å molecular sieves (50 mg). The vial was sealed with a screw cap fitted with a rubber septum, and was placed under a nitrogen atmosphere. To a second oven-dried 1 dram vial was added the appropriate cyclopropane (0.4 mmol) and isocyanate (1.2 mmol). The vial was sealed with a screw cap fitted with a Teflon septum and this mixture was transferred to the first vial as a solution in anhydrous dichloromethane (1 mL + 0.33 mL rinse). The mixture was then allowed to

stir at ambient temperature under nitrogen. Upon consumption of the cyclopropane (as determined by TLC analysis), the reaction mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The layers were separated and the aqueous phase was washed twice with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography.



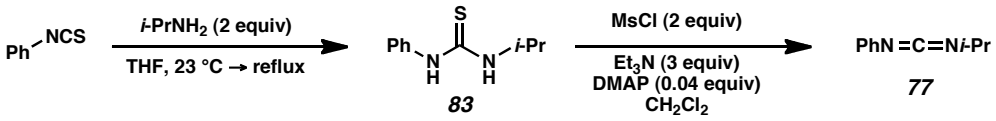
General Procedure F. *Isothiocyanate (3 + 2) reaction with D-A cyclopropanes*

To an oven-dried 1 dram vial equipped with a magnetic stir bar was added tin(II) trifluoromethanesulfonate (0.44 mmol) in an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon septum, removed from the glovebox and placed under a nitrogen atmosphere. To a separate, oven-dried 1 dram vial were added the appropriate cyclopropane (0.4 mmol) and isothiocyanate (0.8 mmol). The vial was sealed with a screw cap fitted with a Teflon septum, and the mixture was transferred to the first vial as a solution in anhydrous dichloromethane (1 mL + 0.33 mL rinse). The heterogeneous reaction mixture was then allowed to stir at ambient temperature under nitrogen. Upon consumption of the cyclopropane (as determined by TLC analysis), the reaction solution was diluted with dichloromethane (3 mL) and methanol (1 mL), adsorbed onto Celite, and purified by silica gel column chromatography. The products of this reaction were often found to be unstable during prolonged storage (~1 week) at ambient temperature; the decomposition products have not been identified.



General Procedure G. *Carbodiimide (3 + 2) reaction with D-A cyclopropanes*

To an oven-dried 1 dram vial equipped with a magnetic stir bar was added tin(II) trifluoromethanesulfonate (0.44 mmol) in an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon septum, removed from the glovebox and placed under a nitrogen atmosphere. To a separate, oven-dried 1 dram vial were added the appropriate cyclopropane (0.4 mmol) and carbodiimide (0.44 mmol). The vial was sealed with a screw cap fitted with a Teflon septum, and the mixture was transferred to the first vial as a solution in anhydrous dichloromethane (1 mL + 0.33 mL rinse). The heterogeneous reaction mixture was then allowed to stir at ambient temperature under nitrogen. Upon consumption of the cyclopropane (as determined by TLC analysis), the reaction solution was diluted with dichloromethane (3 mL) and methanol (1 mL), adsorbed onto Celite, and purified by silica gel column chromatography. The product obtained after column chromatography is an amidinium salt, which is dissolved in DCM, and washed with aqueous sodium hydroxide (0.1 M) and brine, then dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield the free amidine base.

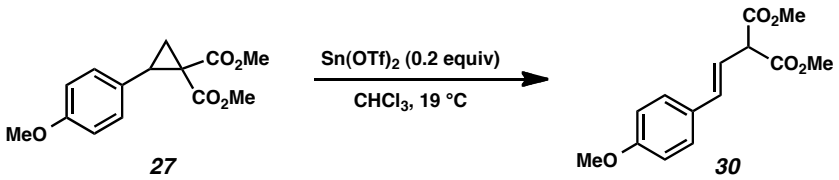


Thiourea 83. Prepared according to the method of Zhou and coworkers.[24] To a flame-dried round-bottom flask, equipped with a magnetic stir bar and fitted with a

rubber septum was added phenyl isothiocyanate (1.2 mL, 10 mmol, 1 equiv) and anhydrous THF (32 mL) under an inert atmosphere. To the stirring solution was added isopropylamine (1.64 mL, 20 mmol, 2 equiv) dropwise. The rubber septum was quickly replaced with a reflux condenser fitted with a hose adapter, connected to an inert atmosphere manifold. The resulting solution was heated to reflux with stirring for 40 min. The reaction mixture was then cooled to ambient temperature and the solvent was removed in vacuo. The residue was dissolved in ethyl acetate (60 mL) and washed with aqueous hydrochloric acid (10 mL, 1 N) and brine (10 mL), and the organic phase was dried over sodium sulfate, filtered, and concentrated in vacuo to afford crude thiourea **82** (1.89 g, 97%) as a white solid which was carried forward directly to the next step in the synthesis.

Carbodiimide 77. Prepared according to the method of Fell and Coppola.[25] To a flame-dried, round-bottom flask, equipped with a magnetic stir bar was added crude thiourea **82** (971 mg, 5 mmol, 1 equiv). The flask was sealed with a rubber septum and placed under an inert atmosphere. To the flask was added dry dichloromethane (50 mL, 0.1 M) and freshly distilled triethylamine (2.1 mL, 15 mmol, 3 equiv), followed by a dropwise addition of mesyl chloride (0.78 mL, 10 mmol, 2 equiv). Complete consumption of starting material was observed within 5 minutes, as determined by TLC. The volatiles were removed in vacuo, and a precipitate was observed. The mixture was filtered twice through SiO_2 (100 mL), eluting with dichloromethane, then purified by column chromatography on SiO_2 (10:1 hexanes:EtOAc) to afford carbodiimide **77** (332.2 mg, 41% yield) as a yellow oil: R_f = 0.81 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.20 (m, 2H), 7.21–7.02 (m, 3H), 3.80 (hept, J = 6.4 Hz, 1H), 1.35

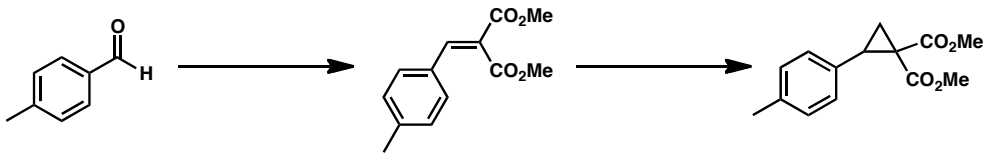
(d, J = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 136.6, 129.4, 124.7, 123.4, 50.3, 24.9; IR (Neat Film, NaCl) 3419, 3067, 2973, 2129, 1637, 1592, 1501, 1454, 1367, 1320 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{10}H_{13}N_2$ $[M+H]^+$: 161.1073, found 161.1077.



27 *30*

Styrene 30. A 1 dram vial, equipped with a magnetic stir bar, was charged with tin(II) triflate (16.7 mg, 0.04 mmol, 0.2 equiv), then cyclopropane **27** (54.1 mg, 0.2 mmol, 1 equiv) was added as a solution in chloroform (1 mL). Stirring was initiated and a heterogeneous mixture with a yellow supernatant resulted. Consumption of starting material was observed by LCMS after 35 minutes. The reaction mixture was dry-loaded onto SiO_2 (~1 mL) and purified by column chromatography on SiO_2 (3:1 hexanes:EtOAc) to afford styrene **30** as a colorless solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 7.7 Hz, 2H), 6.85 (d, J = 7.7 Hz, 2H), 6.52 (d, J = 16.0 Hz, 1H), 6.31–6.21 (m, 1H), 4.19 (d, J = 8.9 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 159.7, 134.9, 128.9, 128.0, 118.4, 114.1, 55.8, 55.4, 53.0; IR (NaCl/film) 3002, 2953, 2834, 1736, 1607, 1513, 1251, 1177, 1029 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{16}O_5$ $[M+H]^+$: 265.1071, found 265.1076.

1.11.2.2 CYCLOPROPANE CHARACTERIZATION DATA

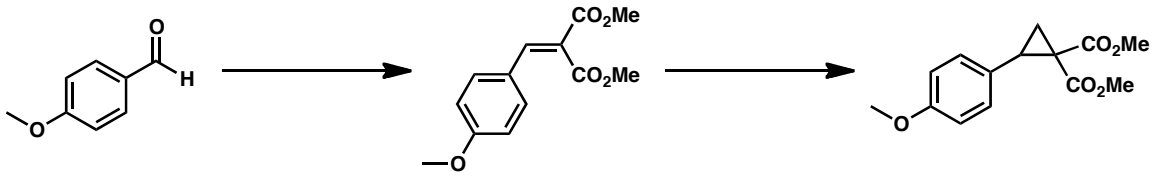


84 *26*

dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate

Benzylidene dimethylmalonate **84** was prepared according to General Method A: 30% yield. R_f = 0.19 (3:1 Heaxanes:EtOAc eluent). Characterization data matches those reported in the literature.[26]

Cyclopropane **26** was prepared according to General Method B: 77% yield. R_f = 0.60 (3:1 Hexanes:EtOAc). Characterization data matches those reported in the literature.[27]

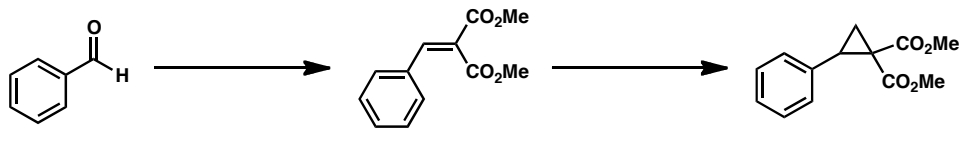


85 ***27***

dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate

Benzylidene dimethylmalonate **85** was prepared according to General Method A: 92% yield. R_f = 0.27 (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.[28]

Cyclopropane **27** was prepared according to General Method B: 95% yield. R_f = 0.40 (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.[29]

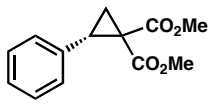


86 ***42***

dimethyl 2-phenylcyclopropane-1,1-dicarboxylate

Benzylidene dimethylmalonate **86** was prepared according to General Method A: 99% yield. R_f = 0.60 (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.[30]

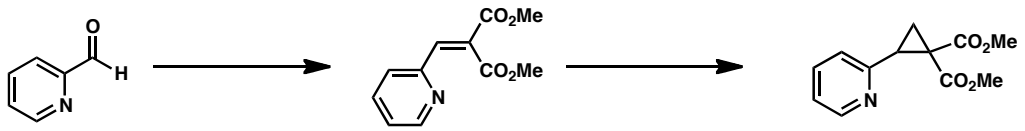
Cyclopropane **42** was prepared according to General Method B: 66% yield. R_f = 0.60 (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.[31]



(S)-42

(*S*)-dimethyl 2-phenylcyclopropane-1,1-dicarboxylate

Cyclopropane (*S*)**-42** was prepared according to the method of Davies and coworkers.[32] $[\alpha]_D^{25.0}$ -133.17° (*c* 0.99, $CHCl_3$, > 98% ee).



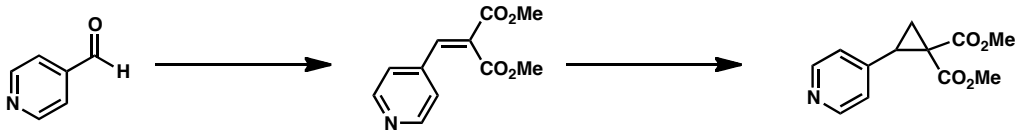
87 ***68***

dimethyl 2-(pyridin-2-yl)cyclopropane-1,1-dicarboxylate

Benzylidene dimethylmalonate **87** was prepared according to General Method A: 97% yield. R_f = 0.81 (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.[33]

Cyclopropane **68** was prepared according to General Method B, using saturated aqueous ammonium chloride in the workup instead of 2 M HCl: 95% yield. R_f = 0.30 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45–8.34 (ddd, *J* = 4.8, 1.9, 1.0 Hz, 1H), 7.62–7.53 (tdd, *J* = 7.3, 4.9, 1.1 Hz, 1H), 7.29–7.26 (dt, *J* = 7.9, 1.1 Hz, 1H),

7.12–7.05 (ddt, *J* = 7.3, 4.9, 1.1 Hz, 1H), 3.82–3.68 (m, 3H), 3.53–3.43 (m, 3H), 3.12–3.06 (ddd, *J* = 8.8, 7.4, 1.1 Hz, 1H), 2.36–2.31 (ddd, *J* = 7.4, 4.5, 1.1 Hz, 1H), 1.84–1.78 (ddd, *J* = 9.0, 4.5, 1.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 167.3, 155.4, 149.0, 136.3, 124.0, 122.0, 53.0, 52.4, 38.0, 33.0, 20.5; IR (Neat Film, NaCl) 3011, 2952, 1734, 1593, 1570, 1477, 1437, 1379, 1334, 1301, 1275, 1210, 1132, 1085, 998, 970, 924, 878, 807, 759, 749 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{14}NO_4$ $[M+H]^+$: 236.0917, found 236.0911.



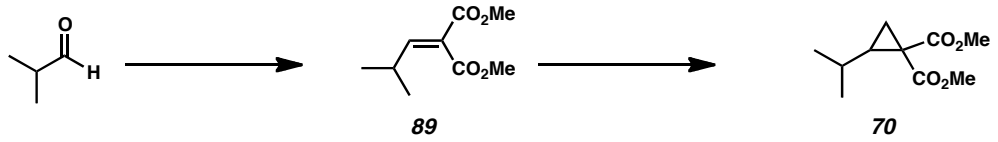
88 ***69***

dimethyl 2-(pyridin-2-yl)cyclopropane-1,1-dicarboxylate

Benzylidene dimethylmalonate **88** was prepared according to General Method A: 76% yield. R_f = 0.58 (1:1 Hexanes:EtOAc eluent); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72–8.60 (m, 2H), 7.68 (s, 1H), 7.29–7.21 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 163.8, 150.7, 140.4, 140.0, 129.9, 122.8, 53.2, 53.1; IR (Neat Film, NaCl) 2954, 1732, 1638, 1596, 1437, 1374, 1269, 1225, 1067, 813 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{12}NO_4$ $[M+H]^+$: 222.0761, found 222.0750.

Cyclopropane **69** was prepared according to General Method B: 81% yield. R_f = 0.13 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.6 Hz, 2H), 7.02 (dd, *J* = 4.4, 1.7 Hz, 2H), 3.73 (s, 3H), 3.35 (s, 3H), 3.07 (dd, *J* = 9.1, 7.9, 1H), 2.11 (dd, *J* = 8.0, 5.4 Hz, 1H), 1.71 (dd, *J* = 9.1, 5.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 166.4, 149.6, 144.1, 123.3, 53.0, 52.5, 37.7, 30.9, 18.7; IR (Neat Film, NaCl)

3029, 2954, 1732, 1601, 1437, 1335, 1282, 1212, 1133, 991, 836 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{14}NO_4$ $[M+H]^+$: 236.0917, found 236.0908.

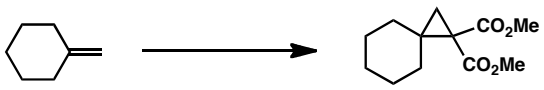


89 *70*

dimethyl 2-isopropylcyclopropane-1,1-dicarboxylate

Isopropylidene dimethylmalonate **89** was prepared according to General Method A. 94% yield. R_f = 0.30 (9:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.[34]

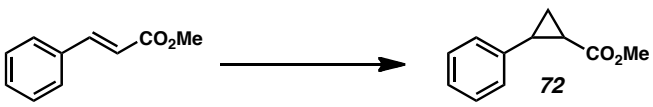
Cyclopropane **70** was prepared according to General Method B. 75% yield. R_f = 0.40 (9:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.[35]



71

dimethyl spiro[2.5]octane-1,1-dicarboxylate

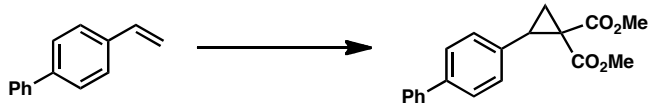
Cyclopropane **71** was prepared according to General Method C. 40% yield. R_f = 0.20 (9:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.[36]



72

methyl 2-phenylcyclopropanecarboxylate

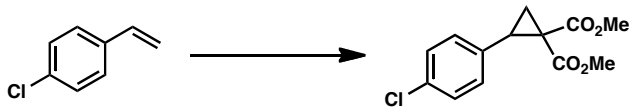
Cyclopropane **72** was prepared according to General Method B: 24% yield. $R_f = 0.6$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.[37]



90

dimethyl 2-([1,1'-biphenyl]-4-yl)cyclopropane-1,1-dicarboxylate

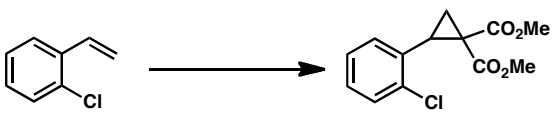
Cyclopropane **90** was prepared according to General Method C: 99% yield. $R_f = 0.48$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.[38]



91

dimethyl 2-(4-chlorophenyl)cyclopropane-1,1-dicarboxylate

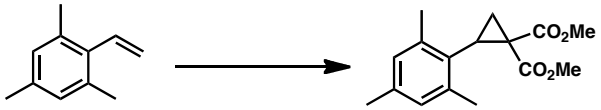
Cyclopropane **91** was prepared according to General Method C: 99% yield. $R_f = 0.53$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.[28]



92

dimethyl 2-(2-chlorophenyl)cyclopropane-1,1-dicarboxylate

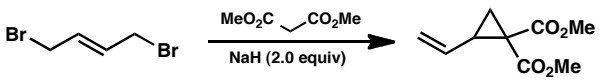
Cyclopropane **92** was prepared according to General Method C: 60% yield. $R_f = 0.50$ (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.33 (m, 1H), 7.22–7.15 (m, 2H), 7.11–7.07 (m, 1H), 3.81 (s, 3H), 3.36 (s, 4H), 2.26 (dd, *J* = 8.3, 5.2 Hz, 1H), 1.79 (dd, *J* = 9.1, 5.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 167.1, 136.6, 132.8, 129.3, 129.0, 128.9, 126.5, 53.0, 52.4, 36.5, 31.3, 19.0; IR (Neat Film, NaCl) 3001, 2953, 1732, 1483, 1435, 1377, 1331, 1288, 1219, 1131, 1055, 894, 785, 754 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{13}H_{14}{}^{35}ClO_4$ $[M+H]^+$: 269.0575, found 269.0573.



93

dimethyl 2-mesitylcyclopropane-1,1-dicarboxylate

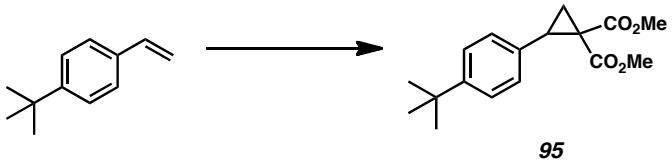
Cyclopropane **93** was prepared according to General Method C: 71% yield. $R_f = 0.40$ (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (s, 2H), 3.83 (s, 3H), 3.34 (s, 3H), 3.10–3.02 (app t, *J* = 9.3 Hz, 1H), 2.42–2.36 (dd, *J* = 8.9, 4.9 Hz, 1H), 2.32 (s, 6H), 2.22 (s, 3H), 1.97–1.89 (dd, *J* = 9.6, 4.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 168.0, 136.6, 129.2, 128.5, 52.9, 52.2, 35.3, 32.0, 24.0, 21.0; IR (Neat Film, NaCl) 2953, 2921, 1728, 1612, 1437, 1372, 1328, 1287, 1224, 1196, 1128, 1096, 1032, 1015, 992, 894, 852, 782, 718 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{21}O_4$ $[M+H]^+$: 277.1434, found 277.1420.



94

dimethyl 2-vinylcyclopropane-1,1-dicarboxylate

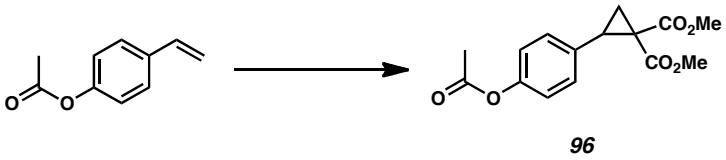
Cyclopropane **94** was prepared according to the method of Johnson and coworkers.[39]



95

dimethyl 2-(4-(*tert*-butyl)phenyl)cyclopropane-1,1-dicarboxylate

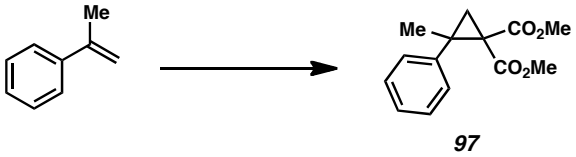
Cyclopropane **95** was prepared according to General Method C: 89% yield. $R_f = 0.50$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.[40]



96

dimethyl 2-(4-acetoxyphenyl)cyclopropane-1,1-dicarboxylate

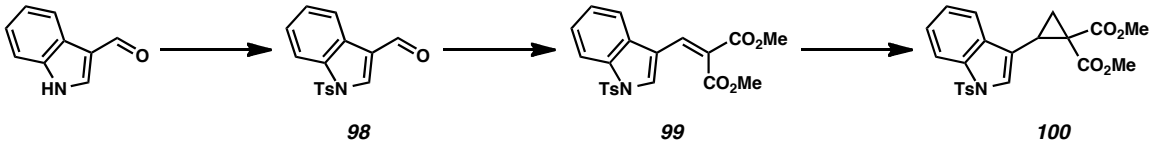
Cyclopropane **96** was prepared according to General Method C: 67% yield. $R_f = 0.30$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.[3c]



97

dimethyl 2-methyl-2-phenylcyclopropane-1,1-dicarboxylate

Cyclopropane **97** was prepared according to General Method C: 41% yield. R_f = 0.53 (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.[41]



98 *99* *100*

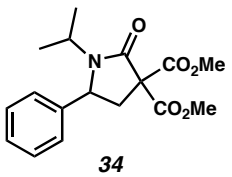
dimethyl 2-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1,1-dicarboxylate

N-Tosylindole-3-carboxaldehyde (**98**) was prepared according to literature methods from indole-3-carbodaldehyde.[42]

Benzylidene dimethylmalonate **99** was prepared according to General Method A: 75% yield. R_f = 0.20 (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.[43]

Cyclopropane **100** was prepared according to General Method B: 95% yield. R_f = 0.30 (3:1 Hexanes:EtOAc eluent).[43]

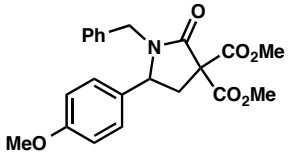
1.11.2.3 CHARACTERIZATION DATA FOR LACTAMS



34

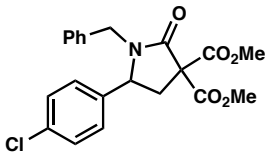
dimethyl 1-isopropyl-2-oxo-5-phenylpyrrolidine-3,3-dicarboxylate (34): Prepared according to General Method D. 72% yield. R_f = 0.46 (1:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 4.64 (t, *J* = 7.3 Hz, 1H), 3.83 (s, 3H), 3.81

(s, 3H), 3.80–3.71 (m, 1H), 3.02 (dd, *J* = 13.8, 7.7 Hz, 1H), 2.59 (dd, *J* = 13.8, 6.9 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 168.1, 167.2, 141.0, 129.0, 128.6, 127.2, 63.4, 59.7, 53.7, 53.5, 47.1, 38.4, 19.8, 19.7; IR (Neat Film, NaCl) 2954, 1735, 1703, 1495, 1457, 1434, 1367, 1342, 1259, 1218, 1130, 1090, 1065, 998, 966, 919, 894, 774 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{22}NO_5$ $[M+H]^+$: 320.1492, found 320.1490.



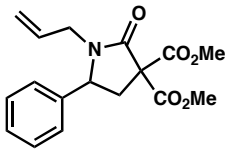
35

dimethyl 1-butyl-2-oxo-5-(4-methoxyphenyl)pyrrolidine-3,3-dicarboxylate (35): Prepared according to General Method D. 62% yield. R_f = 0.39 (1:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.23 (m, 3H), 7.08–7.02 (m, 4H), 6.94–6.87 (m, 2H), 5.11 (d, *J* = 14.5 Hz, 1H), 4.31 (t, *J* = 7.6 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.46 (d, *J* = 14.6 Hz, 1H), 2.94 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.65 (dd, *J* = 13.8, 8.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ168.1, 167.9, 167.1, 160.0, 135.5, 130.4, 128.8, 128.7, 128.6, 127.9, 114.6, 63.4, 58.3, 55.5, 53.7, 53.6, 45.2, 38.1; IR (Neat Film, NaCl) 2953, 1735, 1705, 1513, 1434, 1281, 1247 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{24}NO_6$ $[M+H]^+$: 398.1598, found 398.1581.



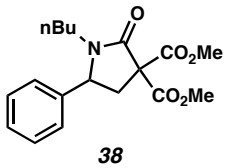
36

dimethyl 1-butyl-2-oxo-5-(4-chlorophenyl)pyrrolidine-3,3-dicarboxylate (36): Prepared according to General Method D. 78% yield. R_f = 0.41 (1:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.33 (m, 2H), 7.29–7.24 (m, 3H), 7.10–7.05 (m, 2H), 7.04–7.00 (m, 2H), 5.13 (d, *J* = 14.6 Hz, 1H), 4.33 (t, *J* = 7.6 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.46 (d, *J* = 14.6 Hz, 1H), 2.97 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.60 (dd, *J* = 13.9, 7.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 167.7, 167.2, 137.3, 135.1, 134.7, 129.5, 128.8, 128.7, 128.6, 128.0, 63.2, 58.1, 53.8, 53.7, 45.3, 37.9; IR (Neat Film, NaCl) 2953, 1736, 1708, 1435, 1242, 1204, 1090 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{21}{}^{35}ClNO_5$ $[M+H]^+$: 402.1103, found 402.1084.



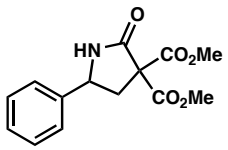
37

dimethyl 1-allyl-2-oxo-5-phenylpyrrolidine-3,3-dicarboxylate (37): Prepared according to General Method E. 42% yield. R_f = 0.52 (1:1 Hexanes:EtOAc eluent);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.29 (m, 3H), 7.24–7.18 (m, 2H), 5.71–5.52 (m, 1H), 5.12 (ddt, *J* = 10.1, 1.3, 0.7 Hz, 1H), 4.99–4.91 (m, 1H), 4.64 (t, *J* = 7.5 Hz, 1H), 4.40 (m, 1H), 3.90–3.84 (m, 3H), 3.82 (d, *J* = 0.9 Hz, 3H), 3.15–3.02 (m, 2H), 2.62 (dd, *J* = 13.8, 7.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 167.9, 166.8, 138.9, 131.0, 129.2, 128.8, 127.3, 118.9, 63.1, 59.1, 53.8, 53.6, 44.1, 38.0; IR (Neat Film, NaCl) 2953, 1735, 1707, 1433, 1245, 1214, 1070 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{20}NO_5$ $[M+H]^+$: 318.1341, found 318.1356.



38

dimethyl 1-butyl-2-oxo-5-phenylpyrrolidine-3,3-dicarboxylate (38): Prepared according to General Method E. 58% yield. R_f = 0.10 (4:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.31 (m, 3H), 7.25–7.20 (m, 2H), 4.63 (t, *J* = 7.5 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.70 (dt, *J* = 13.7, 7.9 Hz, 1H), 3.06 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.57–2.53 (m, 2H), 1.43–1.30 (m, 2H), 1.29–1.10 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 168.0, 166.9, 139.1, 129.2, 128.7, 127.1, 63.2, 59.5, 53.7, 53.6, 41.1, 38.3, 28.6, 19.8, 13.7; IR (Neat Film, NaCl) 2957, 2873, 1732, 1708, 1495, 1456, 1435, 1370, 1278, 1242, 1202, 1108, 1090, 1070, 893, 771 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{24}NO_5$ $[M+H]^+$: 334.1654, found 334.1646.



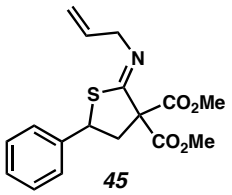
39

dimethyl 2-oxo-5-phenylpyrrolidine-3,3-dicarboxylate (39): Prepared according to General Method E. 49% yield. R_f = 0.48 (1:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.33 (m, 2H), 7.33–7.28 (m, 3H), 6.93–6.69 (bs, 1H), 4.75 (t, *J* = 7.4 Hz, 1H), 3.85 (d, *J* = 1.6 Hz, 3H), 3.77 (dd, *J* = 2.1, 0.9 Hz, 3H), 3.18 (ddt, *J* = 13.6, 7.2, 0.8 Hz, 1H), 2.63 (ddd, *J* = 13.5, 7.8, 1.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 167.5, 167.4, 140.3, 129.0, 128.4, 126.0, 63.2, 55.4, 53.7, 53.6, 40.4; IR (Neat

Film, NaCl) 3251, 2955, 1729, 1435, 1250, 1208, 1060 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{16}NO_5$ $[M+H]^+$: 278.1028, found 278.1042.

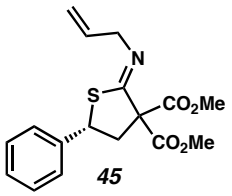
1.11.2.4 THIOIMIDATE CHARACTERIZATION DATA

Unless stated otherwise, all thioimidates were prepared according to General Method F



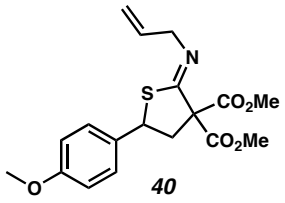
45

(*Z*)-dimethyl 2-(allylimino)-5-phenyldihydrothiophene-3,3(2*H*)-dicarboxylate (45): 92% yield. R_f = 0.45 (7:3 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.40 (m, 2H), 7.39–7.34 (m, 2H), 7.33–7.29 (m, 1H), 5.99 (ddt, *J* = 17.1, 10.4, 5.2 Hz, 1H), 5.26 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.13 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.73 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.00 (dtd, *J* = 5.5, 1.8, 0.7 Hz, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.12 (dd, *J* = 13.0, 4.9 Hz, 1H), 2.90 (dd, *J* = 13.0, 11.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 168.1, 166.0, 138.2, 134.0, 129.0, 128.5, 127.8, 116.0, 71.0, 59.8, 53.8, 53.6, 50.9, 44.3; IR (Neat Film, NaCl) 3010, 2952, 1738, 1652, 1495, 1435, 1269, 1227, 1169, 1098, 1064, 977, 921, 862, 842, 799, 765 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{20}NO_4S$ $[M+H]^+$: 334.1108, found 334.1113.



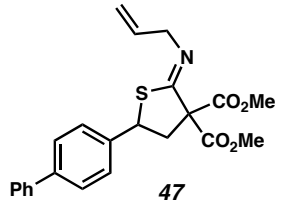
45

(*R*,*Z*)-dimethyl 2-(allylimino)-5-phenyldihydrothiophene-3,3(2H)-dicarboxylate ((*R*)-45): Characterization data is same as above; $[\alpha]_D^{25.0}$ 8.8° (*c* 0.445, $CHCl_3$, 95% ee).



40

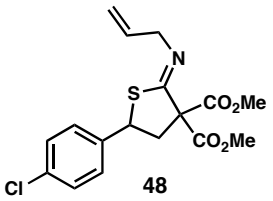
dimethyl 1-allyl-5-(4-methoxyphenyl)-2-thioxopyrrolidine-3,3-dicarboxylate (40): 98% yield. R_f = 0.49 (7:3 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.32 (m, 2H), 6.90–6.85 (m, 2H), 6.03–5.92 (m, 1H), 5.24 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.12 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.71 (dd, *J* = 11.8, 4.8 Hz, 1H), 3.99 (dt, *J* = 5.2, 1.8 Hz, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.07 (dd, *J* = 13.0, 4.9 Hz, 1H), 2.87 (dd, *J* = 13.0, 11.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 168.1, 166.5, 159.7, 134.0, 130.0, 129.0, 116.0, 114.3, 71.1, 59.7, 55.5, 53.8, 53.6, 50.6, 44.5; IR (Neat Film, NaCl) 3003, 2953, 2837, 1736, 1638, 1610, 1513, 1435, 1305, 1250, 1175, 1098, 1070, 1032, 922, 831, 792 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{22}NO_5S$ $[M+H]^+$: 364.1213, found 364.1193.



47

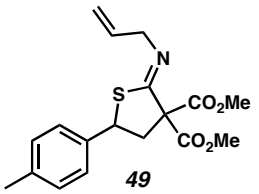
(*Z*)-dimethyl 5-([1,1'-biphenyl]-4-yl)-2-(allylimino)dihydrothiophene-3,3(2*H*)-dicarboxylate (47): 80% yield. R_f = 0.53 (7:3 Hexanes:EtOAc eluent); ^{1}H NMR (500

MHz, $CDCl_3$) δ 7.62–7.56 (m, 4H), 7.53–7.49 (m, 2H), 7.48–7.42 (m, 2H), 7.39–7.33 (m, 1H), 6.00 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.27 (dq, *J* = 17.1, 1.8 Hz, 1H), 5.14 (dq, *J* = 10.3, 1.7 Hz, 1H), 4.79 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.02 (dt, *J* = 5.2, 1.8 Hz, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 3.16 (dd, *J* = 13.0, 4.9 Hz, 1H), 2.94 (dd, *J* = 13.0, 11.7 Hz, 1H);; ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 168.0, 166.2, 141.4, 140.4, 137.0, 133.8, 128.9, 128.2, 127.6, 127.1, 116.0, 71.0, 59.6, 53.7, 53.5, 50.6, 44.2; IR (Neat Film, NaCl) 3029, 2952, 1736, 1651, 1639, 1487, 1435, 1412, 1279, 1263, 1226, 1168, 1099, 1070, 1008, 977, 920, 836, 799, 767, 738 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{24}NO_4S$ $[M+H]^+$: 410.1421, found 410.1408.



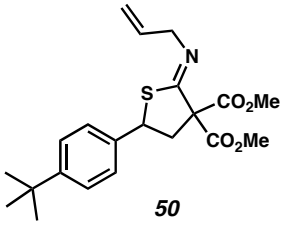
48

(*Z*)-dimethyl 2-(allylimino)-5-(4-chlorophenyl)dihydrothiophene-3,3(2*H*)-dicarboxylate (48): 66% yield. R_f = 0.49 (7:3 Hexanes:EtOAc eluent); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.19 (m, 4H), 5.97 (ddt, *J* = 17.1, 10.4, 5.1 Hz, 1H), 5.23 (dq, *J* = 17.2, 1.9 Hz, 1H), 5.12 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.69 (dd, *J* = 11.6, 4.9 Hz, 1H), 3.98 (dt, *J* = 5.1, 1.8 Hz, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.09 (dd, *J* = 13.0, 5.0 Hz, 1H), 2.82 (dd, *J* = 13.0, 11.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 167.8, 165.3, 136.7, 134.2, 133.8, 129.0, 129.0, 115.9, 70.8, 59.7, 53.7, 53.4, 50.0, 44.1; IR (Neat Film, NaCl) 2953, 1733, 1652, 1637, 1491, 1434, 1266, 1221, 1167, 1090, 1068, 1011 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{19}{}^{35}ClNO_4S$ $[M+H]^+$: 368.0718, found 368.0729.



49

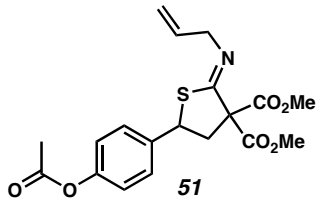
(Z)-dimethyl 2-(allylimino)-5-(p-tolyl)dihydrothiophene-3,3(2H)-dicarboxylate (49): 99% yield. R_f = 0.47 (7:3 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 7.19–7.15 (m, 2H), 5.98 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.25 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.14 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.72 (dd, *J* = 11.8, 4.8 Hz, 1H), 4.01 (dt, *J* = 5.2, 1.8 Hz, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.10 (dd, *J* = 13.1, 4.9 Hz, 1H), 2.88 (dd, *J* = 13.0, 11.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ168.2, 168.0, 138.5, 134.9, 133.7, 129.7, 127.7, 116.3, 71.1, 59.5, 53.9, 53.7, 51.1, 44.5, 21.3; IR (Neat Film, NaCl) 3011, 2952, 1737, 1652, 1639, 1515, 1435, 1278, 1269, 1257, 1228, 1169, 1071, 1018, 978, 921, 864, 848, 818, 790 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{22}NO_4S$ $[M+H]^+$: 348.1264, found 348.1254.



50

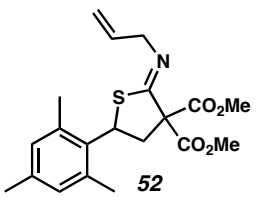
(*Z*)-dimethyl 2-(allylimino)-5-(4-(*tert*-butyl)phenyl)dihydrothiophene-3,3(2*H*)-dicarboxylate (50): 41% yield. R_f = 0.30 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.32 (m, 4H), 5.98 (ddt, *J* = 17.1, 10.4, 5.2 Hz, 1H), 5.25 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.13 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.71 (dd, *J* = 11.8, 4.9 Hz, 1H), 3.99 (dt, *J* = 5.1, 1.7 Hz, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.07 (dd, J = 13.0, 4.9 Hz, 1H), 2.90

(dd, J = 13.0, 11.8 Hz, 1H) 1.31 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 168.2, 166.3, 151.6, 135.1, 134.1, 127.5, 125.9, 116.0, 71.1, 59.8, 53.8, 53.6, 50.7, 44.3, 34.8, 31.4; IR (Neat Film, NaCl) 2955, 2904, 2868, 1737, 1652, 1639, 1509, 1435, 1363, 1280, 1267, 1227, 1168, 1111, 1070, 1016, 978, 920, 828 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{28}NO_4S$ $[M+H]^+$: 390.1734, found 390.1726.



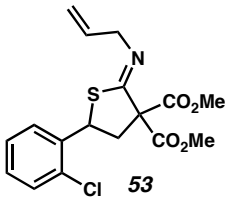
51

(*Z*)-dimethyl 5-(4-acetoxyphenyl)-2-(allylimino)dihydrothiophene-3,3(2*H*)-dicarboxylate (51): 84% yield. R_f = 0.20 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.41 (m, 2H), 7.12–7.05 (m, 2H), 5.97 (ddt, *J* = 17.2, 10.3, 5.2 Hz, 1H), 5.25 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.13 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.72 (dd, *J* = 11.6, 4.9 Hz, 1H), 3.99 (ddd, *J* = 7.0, 1.7, 1.0 Hz, 2H), 3.87 (s, 3H), 3.80 (s, 3H), 3.11 (dd, *J* = 13.1, 4.9 Hz, 1H), 2.85 (dd, *J* = 13.1, 11.6 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 168.4, 168.0, 165.8, 150.6, 135.8, 134.0, 129.0, 122.2, 116.0, 71.0, 59.8, 53.8, 53.6, 50.3, 44.5, 21.3; IR (Neat Film, NaCl) 2953, 1736, 1649, 1639, 1507, 1436, 1370, 1280, 1257, 1194, 1167, 1099, 1016, 911, 851 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{22}NO_6S$ $[M+H]^+$: 392.1162, found 392.1159.



52

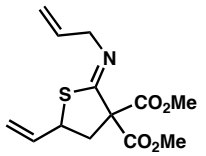
(*Z*)-dimethyl 2-(allylimino)-5-mesityldihydrothiophene-3,3(2*H*)-dicarboxylate (52): 85% yield. White, translucent crystals were obtained by slow diffusion of 1% benzene in heptane into a solution of thioimidate **52** in ethyl acetate, M.P.: 89–91 °C; R_f = 0.52 (7:3 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87–6.84 (m, 2H), 5.99 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.32 (dd, *J* = 12.5, 5.3 Hz, 1H), 5.24 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.13 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.02 (dtd, *J* = 5.2, 1.8, 0.8 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.24 (dd, *J* = 13.3, 12.5 Hz, 1H), 2.93 (dd, *J* = 13.3, 5.3 Hz, 1H), 2.46 (s, 6H), 2.25 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 168.3, 166.8, 137.9, 134.0, 130.9, 129.2, 116.0, 71.1, 59.8, 53.8, 53.6, 46.2, 40.0, 21.3, 20.9; IR (Neat Film, NaCl) 3010, 2952, 2918, 1737, 1649, 1638, 1611, 1435, 1267, 1230, 1203, 1167, 1097, 1073, 1015, 976, 921, 954, 822, 799, 774, 739 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{26}NO_4S$ $[M+H]^+$: 376.1577, found 376.1563.



53

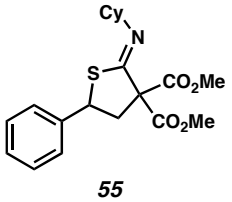
(*Z*)-dimethyl 2-(allylimino)-5-(2-chlorophenyl)dihydrothiophene-3,3(2*H*)-dicarboxylate (53): 84% yield. R_f = 0.48 (7:3 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.38 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.31 (td, *J* = 7.6, 1.4 Hz, 1H), 7.23 (td, *J* = 7.6, 1.7, 1H), 5.98 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.30–5.22 (m, 2H), 5.14 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.03 (td, *J* = 4.4, 2.0 Hz, 2H), 3.88 (s, 3H), 3.77 (s, 3H), 3.19 (dd, *J* = 13.0, 5.1 Hz, 1H), 2.84 (dd, *J* = 13.0, 11.0 Hz, 1H);; ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 168.0, 165.7, 135.8, 134.0, 133.9, 130.0, 129.5, 128.5,

127.5, 116.1, 70.6, 59.7, 53.8, 53.6, 47.0, 42.6; IR (Neat Film, NaCl) 3011, 2953, 1737, 1651, 1639, 1435, 1279, 1256, 1228, 1171, 1130, 1100, 1069, 1051, 1038, 977, 921, 760 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{19}{}^{35}ClNO_4S$ $[M+H]^+$: 368.0718, found 368.0700.



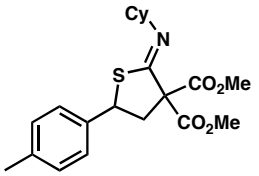
54

(*Z*)-dimethyl 2-(allylimino)-5-vinyldihydrothiophene-3,3(2*H*)-dicarboxylate (54): 99% yield. R_f = 0.45 (7:3 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.80 (ddd, *J* = 16.9, 10.0, 8.4 Hz, 1H), 5.33 (dq, *J* = 16.9, 0.8 Hz, 1H), 5.23 (ddd, *J* = 17.3, 1.8, 0.6 Hz, 1H), 5.19 (d, *J* = 10.1. 1H), 5.13 (ddd, *J* = 10.4, 1.7, 0.7 Hz, 1H), 4.22 (m, 1H), 3.98 (dd, *J* = 5.2, 2.0 Hz, 2H), 3.84 (s, 3H), 3.81 (d, *J* = 0.6 Hz, 3H), 2.97 (ddd, *J* = 13.1, 5.1, 0.8 Hz, 1H), 2.61 (dd, *J* = 13.1, 10.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 168.0, 135.7, 133.6, 118.9, 116.3, 70.5, 59.4, 53.8, 53.7, 50.3, 42.2; IR (Neat Film, NaCl) 2952, 1735, 1649, 1638, 1434, 1328, 1272, 1254, 1169, 1139, 1097, 1068, 987, 923, 859, 787, 728 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{13}H_{18}NO_4S$ $[M+H]^+$: 284.0951, found 284.0962.



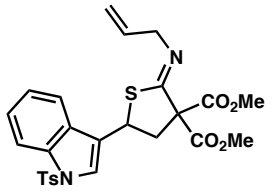
55

(*Z*)-dimethyl 2-(cyclohexylimino)-5-phenyldihydrothiophene-3,3(2*H*)-dicarboxylate (55): 91% yield. R_f = 0.40 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2H), 7.36 (ddd, *J* = 8.2, 7.1, 0.9 Hz, 2H), 7.30 (m, 1H), 4.69 (dd, *J* = 11.7, 4.9 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.08 (dd, *J* = 13.0, 4.9 Hz, 1H), 2.98 (tt, *J* = 10.1, 3.6 Hz, 1H), 2.85 (dd, *J* = 13.0, 11.7 Hz, 1H), 1.85–1.72 (m, 4H), 1.65–1.57 (m, 1H), 1.57–1.44 (m, 2H), 1.37–1.20 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 168.3, 161.5, 138.6, 128.9, 128.4, 127.8, 70.8, 67.1, 53.7, 53.4, 50.6, 44.0, 32.8, 31.7, 25.8, 24.7, 24.6; IR (Neat Film, NaCl) 2930, 2854, 1738, 1651, 1435, 1168, 1067, 973, 912, 764 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{20}H_{26}NO_4S$ $[M+H]^+$: 376.1577, found 356.1589.



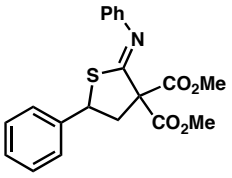
56

(*Z*)-dimethyl 2-(cyclohexylimino)-5-(*p*-tolyl)dihydrothiophene-3,3(2*H*)-dicarboxylate (56): 99% yield. R_f = 0.63 (2:1 Hexanes: EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.29 (m, 2H), 7.18–7.14 (m, 2H), 4.67 (dd, *J* = 11.8, 4.8 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.05 (dd, *J* = 13.0, 4.9 Hz, 1H), 2.98 (tt, *J* = 10.1, 3.6 Hz, 1H), 2.83 (dd, *J* = 13.0, 11.8 Hz, 1H), 2.35 (s, 3H), 1.83–1.72 (m, 4H), 1.65–1.57 (m, 1H), 1.56–1.44 (m, 2H), 1.38–1.21 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 168.3, 161.5, 138.2, 135.5, 129.6, 127.6, 70.9, 67.0, 53.6, 53.4, 50.4, 44.0, 32.8, 31.7, 25.8, 24.7, 24.5, 21.2; IR (Neat Film, NaCl) 2929, 2853, 1735, 1648, 1434, 1255, 1167, 1071, 973, 818 cm^{-1}; HRMS (APCI) *m/z* calc'd for $C_{21}H_{28}NO_4S$ $[M+H]^+$: 390.1734, found 390.1738.



57

(*Z*)-dimethyl 2-(allylimino)-5-(1-tosyl-1*H*-indol-3-yl)dihydrothiophene-3,3(2*H*)-dicarboxylate (57): 77% yield. R_f = 0.80 (1:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 168.1, 167.9, 166.2, 145.4, 135.5, 135.1, 133.6, 130.2, 128.9, 127.1, 125.5, 123.9, 123.5, 119.9, 116.3, 114.0, 77.4, 70.5, 59.7, 53.9, 53.7, 42.7, 41.7, 21.7; ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 167.9, 166.2, 145.4, 135.5, 135.1, 133.6, 130.2, 128.9, 127.1, 125.5, 123.9, 123.5, 119.9, 116.3, 114.0, 77.4, 70.5, 59.7, 53.9, 53.7, 42.7, 41.7, 21.7; IR (Neat Film, NaCl) 2953, 1738, 1639, 1447, 1372, 1275, 1175, 1126, 1095, 974, 912, 733 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{26}H_{27}N_2O_6S_2$ $[M+H]^+$: 527.1305, found 527.1298.



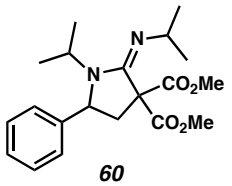
44

(*Z*)-dimethyl 5-phenyl-2-(phenylimino)dihydrothiophene-3,3(2*H*)-dicarboxylate (44): Prepared using General Method D, using phenylisothiocyanate. 89% yield. R_f = 0.60 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.37 (m, 2H), 7.36–7.31 (m, 4H), 7.30–7.27 (m, 1H), 7.16–7.11 (m, 1H), 7.05–7.01 (m, 2H), 4.76 (dd, *J* = 11.7, 4.9 Hz, 1H), 3.97 (s, 3H), 3.87 (s, 3H), 3.19 (dd, *J* = 13.1, 4.9 Hz, 1H), 2.99 (dd, *J* = 13.1, 11.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 167.9, 167.8, 151.0, 137.8,

129.1, 129.0, 128.5, 127.8, 125.3, 120.2, 71.4, 54.0, 53.8, 51.2, 43.9; IR (Neat Film, NaCl) 3030, 2952, 1735, 1638, 1593, 1486, 1434, 1268, 1224, 1170, 1063, 973, 763 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{20}H_{20}NO_4S$ $[M+H]^+$: 370.1108, found 370.1098.

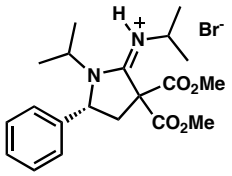
1.11.2.5 CHARACTERIZATION DATA FOR AMIDINES

All amidines were synthesized according to General Method G.



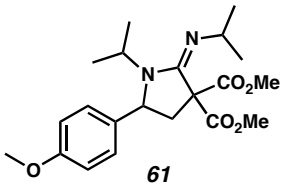
60

(*E*)-dimethyl 1-isopropyl-2-(isopropylimino)-5-phenylpyrrolidine-3,3-dicarboxylate (60): 98% yield. R_f = 0.39 (9:1 CH_2Cl_2:MeOH eluent); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.18 (m, 5H), 4.52 (t, *J* = 7.1 Hz, 1H), 3.99 (p, *J* = 6.8 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.50 (hept, *J* = 6.0 Hz, 1H), 2.95 (dd, *J* = 12.8, 7.0 Hz, 1H), 2.33 (dd, *J* = 12.8, 7.2 Hz, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.0 Hz, 3H), 1.05 (d, *J* = 5.9 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 169.2, 151.3, 143.8, 128.5, 127.8, 127.0, 60.5, 59.8, 53.1, 52.9, 51.4, 47.3, 43.4, 24.7, 24.3, 19.6, 19.2; IR (Neat Film, NaCl) 2963, 1731, 1659, 1436, 1261, 1212, 1063, 969 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{29}N_2O_4$ $[M+H]^+$: 361.2122, found 361.2018.



(R)-60·HBr

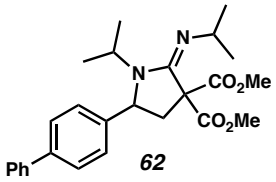
(*R*,*E*)-dimethyl 1-isopropyl-2-(isopropylimino)-5-phenylpyrrolidine-3,3-dicarboxylate (*(R)*-60•HBr): Acetyl bromide (22 μL, 0.3 mmol) was dissolved in dichloromethane (3 mL) in a 10 mL round-bottom flask. Methanol (41 μL, 1 mmol) was added to the solution and this mixture was transferred into a second flask containing a solution of amidine (*R*)-**60** (72 mg, 0.2 mmol) in dichloromethane (3 mL), prepared by the above procedure. The mixture was concentrated in vacuo and crystallized by vapor diffusion of diethyl ether into dichloromethane to produce fine colorless needles suitable for x-ray crystallography. $[\alpha]_D^{25.0}$ 8.8° (*c* 0.445, $CHCl_3$, > 98% ee).



61

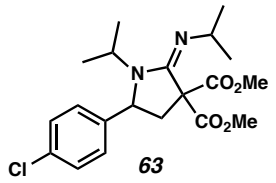
(*E*)-dimethyl 1-isopropyl-2-(isopropylimino)-5-(4-methoxyphenyl)pyrrolidine-3,3-dicarboxylate (61): 98% yield. R_f = 0.42 (9:1 CH_2Cl_2:MeOH eluent); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.16 (m, 2H), 6.89–6.79 (m, 2H), 4.50 (br t, *J* = 6.9 Hz, 1H), 4.07–3.95 (br m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.72 (s, 3H), 3.49 (p, *J* = 6.0 Hz, 1H), 2.93 (br dd, *J* = 12.8, 6.9 Hz, 1H), 2.30 (br dd, *J* = 12.9, 7.3 Hz, 1H), 1.14 (br d, *J* = 6.9 Hz, 4H), 1.11 (d, *J* = 4.3 Hz, 2H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ169.5, 169.0, 159.3, 151.6, 135.2, 128.2, 113.9, 60.7, 59.6, 55.3, 53.2, 53.0, 51.4, 47.4, 43.4, 24.5, 24.1, 19.7, 19.2.; IR (Neat Film, NaCl) 2963, 2928,

1736, 1654, 1612, 1513, 1249, 1214, 1172, 1081 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{31}N_2O_5$ $[M+H]^+$: 391.2227, found 391.2208.



62

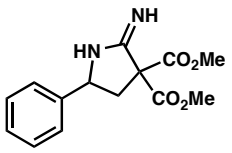
(*E*)-dimethyl 5-([1,1'-biphenyl]-4-yl)-1-isopropyl-2-(isopropylimino)pyrrolidine-3,3-dicarboxylate (62): 92% yield. R_f = 0.42 (9:1 CH_2Cl_2:MeOH eluent); ^1H NMR (500 MHz, $CDCl_3$) δ 7.63–7.53 (m, 4H), 7.47–7.38 (m, 4H), 7.37–7.32 (m, 1H), 4.59 (t, *J* = 7.1 Hz, 1H), 4.04 (hept, *J* = 6.9 Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.53 (hept, *J* = 5.9 Hz, 1H), 3.00 (dd, *J* = 12.8, 7.0 Hz, 1H), 2.37 (dd, *J* = 12.8, 7.3 Hz, 1H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.15 (d, *J* = 6.0 Hz, 3H), 1.08 (d, *J* = 5.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H);; ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 169.2, 151.4, 142.9, 140.8, 140.7, 128.9, 127.5, 127.4, 127.2, 127.1, 60.6, 59.6, 53.2, 53.0, 51.5, 47.4, 43.4, 24.7, 24.4, 19.8, 19.2; IR (Neat Film, NaCl) 2964, 1733, 1658, 1486, 1435, 1375, 1358, 1264, 1216, 1165, 1126, 1076, 1008, 973, 841, 767, 733 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{26}H_{33}N_2O_4$ $[M+H]^+$: 437.2435, found 437.2411.



63

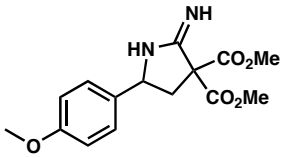
(*E*)-dimethyl 5-(4-chlorophenyl)-1-isopropyl-2-(isopropylimino)pyrrolidine-3,3-dicarboxylate (63): 78% yield. R_f = 0.40 (9:1 CH_2Cl_2:MeOH eluent); ^1H NMR (500

MHz, $CDCl_3$) δ 7.30–7.23 (m, 4H), 4.50 (t, *J* = 7.1 Hz, 1H), 4.00 (hept, *J* = 6.9 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.48 (hept, *J* = 5.9 Hz, 1H), 2.95 (dd, *J* = 12.8, 7.1 Hz, 1H), 2.27 (dd, *J* = 12.9, 7.1 Hz, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 6.0 Hz, 3H), 1.04 (d, *J* = 5.9 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 169.1, 151.2, 142.6, 133.4, 128.7, 128.3, 60.4, 59.1, 53.2, 53.0, 51.5, 47.3, 43.3, 24.7, 24.3, 19.9, 19.1; IR (Neat Film, NaCl) 2965, 1733, 1658, 1489, 1435, 1376, 1359, 1269, 1214, 1165, 1126, 1088, 1014, 974, 831 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{28}{}^{35}ClN_2O_4$ $[M+H]^+$: 395.1732, found 395.1755.



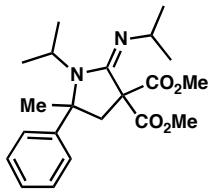
64

dimethyl 2-imino-5-phenylpyrrolidine-3,3-dicarboxylate (64): 78% yield. R_f = 0.45 (9:1 CH_2Cl_2:MeOH eluent); ^1H NMR (500 MHz, $CDCl_3$) δ7.34–7.27 (m, 3H), 7.25–7.21 (m, 2H), 4.99 (dd, *J* = 8.2, 6.9 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.10 (dd, *J* = 13.6, 7.0 Hz, 1H), 2.37 (dd, *J* = 13.6, 8.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 168.3, 160.2, 144.2, 128.6, 127.1, 126.4, 68.4, 67.4, 53.6, 53.4, 42.8; IR (Neat Film, NaCl) 3449, 3028, 1729, 1665, 1600, 1435, 1386, 1354, 1279, 1243, 1201, 1154, 1114, 1075, 765 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{17}N_2O_4$ $[M+H]^+$: 277.1188, found 277.1176.



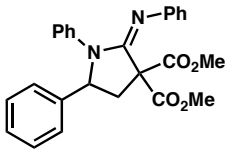
65

dimethyl 2-imino-5-(4-methoxyphenyl)pyrrolidine-3,3-dicarboxylate (65): 68% yield. R_f = 0.47 (9:1 CH_2Cl_2:MeOH eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.16 (m, 2H), 6.84 (dd, *J* = 6.8, 1.9 Hz, 2H), 4.97–4.88 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.06 (dd, *J* = 13.6, 6.9 Hz, 1H) 2.34 (dd, *J* = 13.6, 8.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 168.3, 160.1, 158.7, 136.3, 127.5, 113.9, 113.9, 67.8, 67.4, 55.4, 53.6, 53.4, 42.9; IR (Neat Film, NaCl) 3464, 3374, 3102, 2955, 2838, 1738, 1662, 1612, 1514, 1439, 1351, 1247, 1213, 1175, 1105, 1077, 1034, 831, 733 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{19}N_2O_5$ $[M+H]^+$: 307.1294, found 307.1287.



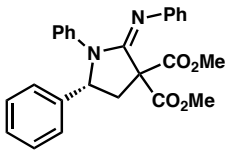
66

(*E*)-dimethyl 1-isopropyl-2-(isopropylimino)-5-methyl-5-phenylpyrrolidine-3,3-dicarboxylate (66): 58% yield. R_f =0.35 (10:1 $CHCl_3$:MeOH eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.44 (m, 2H), 7.38–7.33 (m, 2H), 7.29–7.24 (m, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 3.44 (dt, *J* = 11.8, 5.9 Hz, 1H), 3.09–2.99 (hept, *J* = 6.7 Hz, 1H), 2.83–2.72 (m, 2H), 1.61 (s, 3H), 1.35 (dd, *J* = 17.2, 6.7 Hz, 6H), 1.10 (dd, *J* = 18.8, 5.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 170.2, 148.5, 146.8, 128.3, 127.2, 126.7, 64.8, 60.3, 53.2, 53.1, 51.4, 50.5, 47.1, 24.9, 24.8, 24.5, 19.9, 19.1; IR (Neat Film, NaCl) 2963, 1731, 1654, 1375, 1251, 1217, 1090 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{31}N_2O_4$ $[M+H]^+$: 375.2278, found 375.2297.



67

(*E*)-dimethyl 1,5-diphenyl-2-(phenylimino)pyrrolidine-3,3-dicarboxylate (67): 79% yield. R_f =0.32 (10:1 CH_2Cl_2:MeOH eluent); ^{1}H NMR (400 MHz, DMSO-d6, 80 °C) δ 7.34 – 7.16 (m, 8H), 7.10 (dt, *J* = 15.2, 7.6 Hz, 5H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 2H), 5.28 (t, *J* = 7.0 Hz, 1H), 3.66 (s, 3H) 3.45 (s, 3H), 3.17 (dd, *J* = 13.0, 7.2 Hz, 1H), 3.05 (s, 1H), 2.71 (dd, *J* = 13.0, 6.9 Hz, 1H);^{13}C NMR (101 MHz, DMSO-d6, 100 °C) δ 168.5, 168.2, 152.0, 148.4, 148.3, 140.9, 129.6, 129.5, 129.4, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.2, 128.2, 128.1, 128.0, 127.7, 127.5, 127.4, 127.3, 127.2, 126.6, 125.9, 124.6, 122.0, 121.9, 120.9, 64.1, 63.1, 62.7, 55.3, 54.5, 54.3, 53.4, 52.6, 52.4, 51.9, 43.0; IR (Neat Film, NaCl) 3062, 3027, 2948, 1730, 1661, 1592, 1493, 1372, 1263, 1051 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{26}H_{25}N_2O_4$ $[M+H]^+$: 429.1809, found 429.1825.



(R)-67

(*R*,*E*)-dimethyl 1,5-diphenyl-2-(phenylimino)pyrrolidine-3,3-dicarboxylate ((*R*)-67): Characterization data same as above; $[\alpha]_D^{25.0}$ 36.7° (*c* 0.805, $CHCl_3$, 88% ee).

1.12 NOTES AND REFERENCES

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(13) A similar yield was observed with the use of 1,4-dioxane drawn from a solvent purification system collection bulb, which may be due to contamination of the solvent bulb with water.

(14) We have evidence to suggest the role of water is not to hydrolyze the trimethylsilylisocyanate to cyanic acid: in situ treatment of potassium cyanate with mild acids does not afford the desired lactam.

(15) The yields, as determined by LCMS, are inflated, likely as a result of the volatility of the internal standard. We believe the yields to be self-consistent within each

optimization table, but are not compared easily to other tables due to minor differences in experimental setup.

(16) Other Lewis acids examined included aluminum trichloride, tin(IV) chloride, indium trichloride. We also attempted to use tin(II) chloride with microwave heating, but complex reaction mixtures resulted.

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(20) Methyl and phenyl hydrogen atoms and the bromide counterion are omitted for clarity.

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