DISSERTATION

APPLICATION OF METALLACYCLES FOR THE SYNTHESIS OF SMALL MOLECULES

Submitted by

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ABSTRACT

APPLICATION OF METALLACYCLES FOR THE SYNTHESIS OF SMALL MOLECULES

A method for the nickel-catalyzed hydrocarboxylation of styrene derivatives has been developed that affords exclusively the branched carboxylic acids in moderate to excellent yields. The reaction scope is tolerant of a variety of electron-deficient ortho-, meta-, and para-styrene analogues containing ester, ketone, nitrile, and halide functionalities. The reaction is remarkably efficient, proceeding well with as little as 1 mol% $Ni(acac)_2$ and 2 mol% Cs_2CO_3.

A system for carbon dioxide sequestration and release in organic polymers has been investigated. Although evidence supporting successful carbon dioxide fixation has been found, the envisioned system is not a practical means of sequestration and release.

A rapid approach for the synthesis of Abyssomicin C has been developed utilizing the desymmetrization of *meso*-dimethylglutaric anhydride. Closely modeled after Sorensen's synthesis, our route bypasses the more inefficient beginning steps to intercept the completed synthesis at the Diels-Alder precursor.

DEDICATION

To my parents, without their continual love and support this work would not have been possible.

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LIST OF ABBREVIATIONS

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dppp	1,3-bis(diphenylphosphino)propane
cod	cyclooctadiene
Cy	cyclohexyl
acac	acetylacetonate
KHMDS	Potassium bis(trimethylsilyl)amide
bipy	bipyridine
DCC	N,N'-Dicyclohexylcarbodiimide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
DMA	N,N-dimethylacetamide
PVA	poly(vinyl alcohol)
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DMSO	dimethylsulfoxide
DMF	N,N-dimethylformamide
NMP	N-methyl-2-pyrrolidinone
Pyr	Pyridine
LDA	lithium diisopropylamide
TBS	tert-butyldimethylsilyl
BBN	9-borabicyclo[3.3.1]nonane
HMPA	hexamethylphosphoramide
TMEDA	N,N,N’,N’-tetramethylethylenediamine
HMPT	hexamethylphosphorous triamide
DMPU	N,N-dimethyl propylene urea
nbd	norbornadiene
DMP	Dess Martin periodinane
IBX	ortho-iodoxybenzoic acid
Gln	Glutamine
Glu	Glutamic acid
Tf	trifluoromethanesulfonyl

CHAPTER 1

THE DEVELOPMENT OF CARBON DIOXIDE FIXATION METHODOLOGY

1.1 Introduction

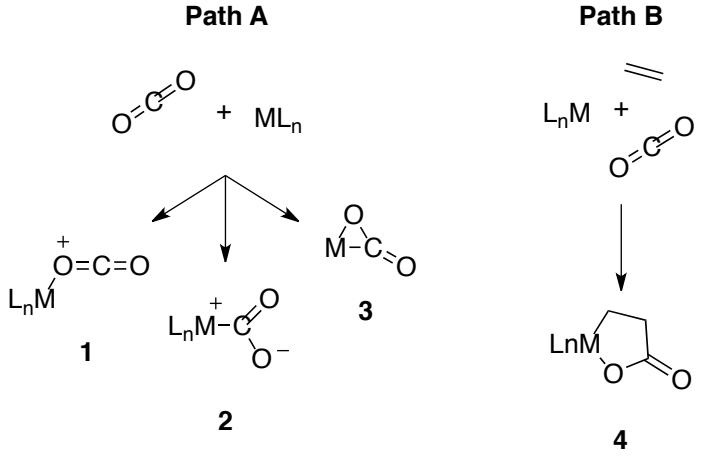
Organic reactions which promote the formation of carbon-carbon bonds remain some of the most important and widely used chemical processes. Although a wide variety of methods for C-C bond formation exist, selective and efficient transformations exploiting readily available and inexpensive starting materials are highly valued. The use of transition metals to catalyze these processes has greatly increased the selectivity and efficiency of established methods and has allowed for the development of powerful new reaction manifolds.[1]

An important methodology for C-C bond formation that takes advantage of transition metals utilizes carbon dioxide as a C1 feedstock. Carbon dioxide is perhaps the most readily available, inexpensive, non-toxic, and inherently renewable source of carbon, making it an extremely attractive starting material for organic synthesis. Not surprisingly, its utilization as a C1 source has seen a resurgence in recent years.[2] In part, this resurgance is attributed to the development of transition metal chemistry in contemporary organic chemistry.[3]

One advantage of using transition metals as catalysts is their ability to activate carbon dioxide via several binding modes.[4] As shown in Scheme 1, path **A** shows that the metal can afford Lewis acid complexation (η^1) with the carbonyl

oxygen (**1**) or by side-on coordination through either a single bond (η^1) to the central carbon (**2**) or two bond (η^2) complexation with the carbon and oxygen in arrangement **3**. X-ray crystal structures of well characterized metal-CO_2 complexes display side-on coordination modes. Two significant examples are $[Rh(diars)_2(Cl)(\eta^1\text{-}CO_2)]$[5] and Aresta's complex $[Ni(\eta^2\text{-}CO_2)(PCy_3)_2]$[6]. Additionally, transition metals can lead to the formation of bonds with carbon dioxide and an unsaturated organic substrate. This process culminates in the formation a metallacycle via the insertion of carbon dioxide (Scheme 1, path B).

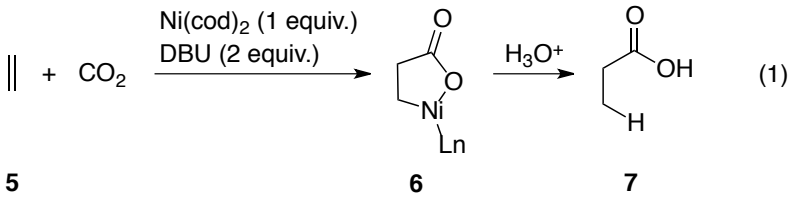
Scheme 1.



1.1.1 Stoichiometric approaches for the fixation of CO_2

Metallacycles involved in carbon dioxide activation have been known for over 20 years. The laboratories of Heinz Hoberg provided the foundation for our understanding of reactivity by demonstrating the isolation of metallacycles formed from nickel, carbon dioxide, and a variety of simple alkenyl and alkynyl π-systems (eq. 1).[7] As these studies only described the isolation of metallacycles

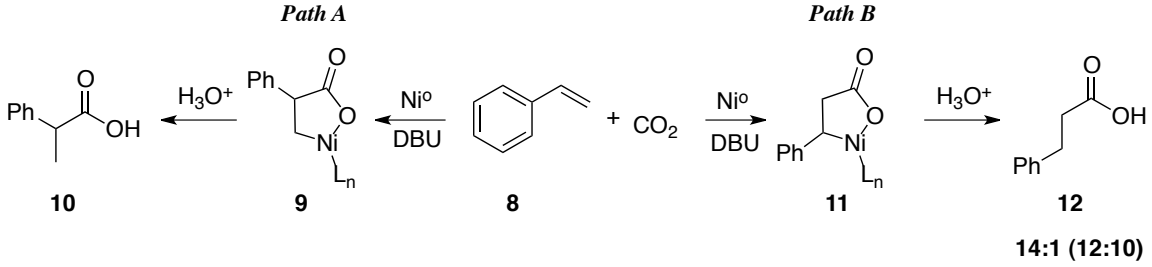
and the reaction with acid to provide the corresponding carboxylic acid, the synthetic utility of these transformations remained largely unexplored.



5 **6** **7**

With substitution in the alkene components, regioisomers can be formed, which are derived from insertion of CO_2 at either site of the activated olefin (Scheme 2). When the phenyl substituent of styrene is bonded α to the carbonyl in the metallacycle **9** (Scheme 2, Path A), the branched carboxylic acid **10** is obtained. When the phenyl (Ph) group is bonded α to the metal center as in **11**, (Scheme 2, Path B), the linear carboxylic acid is produced. Interestingly, a marked preference for the formation of the linear acid (**12**) versus the branched acid (**10**) is generally observed. This preference is thought to be influenced by electronic factors at the metal center.

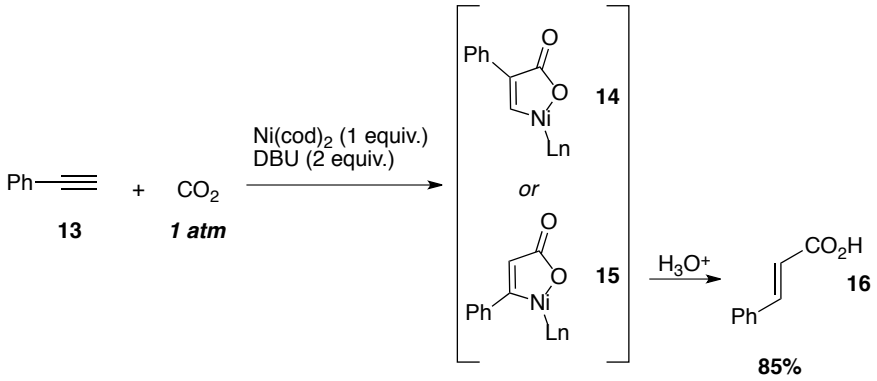
Scheme 2.



Although Hoberg pioneered transition-metal mediated CO_2 activation and established the synthesis of simple carboxylic acids, further investigations by Saito and Yamamoto expanded upon this body of work to access unsaturated

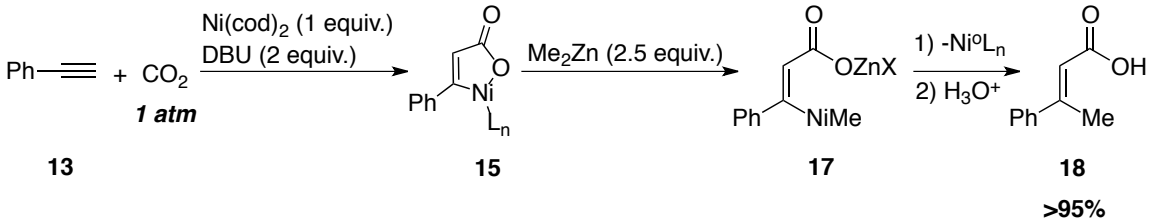
acids. This method utilizes stoichiometric nickel(II), 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU), carbon dioxide, and a variety of alkyne, diyne, and enyne reactants (Scheme 3).[8] These investigations addressed some of the pitfalls of the early studies of Hoberg, which commonly required high pressures of carbon dioxide and a large excess of alkene. In the reports of Saito and Yamamoto, the basic ligand DBU was required for reactivity and regioselectivity. In addition, product selectivity in favor of the linear regioisomer **16** with electron-deficient alkynes suggests a preference for metallacycle **15**.

Scheme 3.



Mori intercepted Hoberg-type metallacycle intermediates with the addition of diorganozinc reagents to provide β-substituted carboxylic acids (Scheme 4).[9] These reagents transform metallacycle **15** by transmetallation to yield zinc carboxylate **17**. Reductive elimination from the alkenyl nickel intermediate **17** allows for an additional C-C bond to be formed, providing the trisubstituted alkene **18** with excellent regioselectivity.

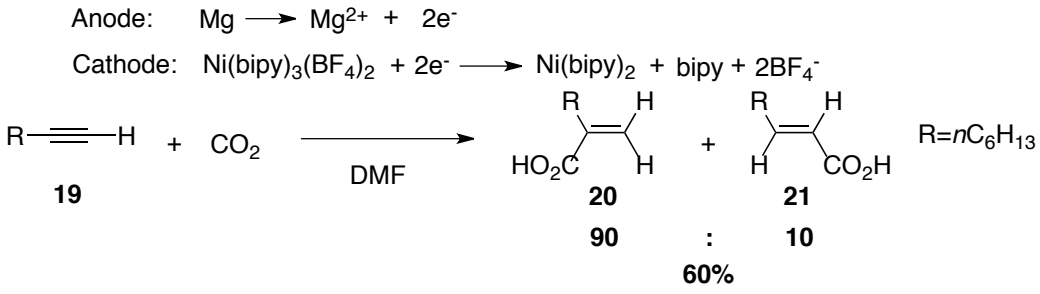
Scheme 4.



This methodology is compatible with alkynes, dienes, and allenes and allows for a nickel-mediated cross coupling in high yields and good regioselectivities in favor of carboxylation at the terminal alkene position.[10] Although based upon Saito and Yamamoto's observations for the formation of metallacycle **15**, Mori's studies introduced organozinc reagents to intercept the initial metallacycle and form an additional C-C bond.

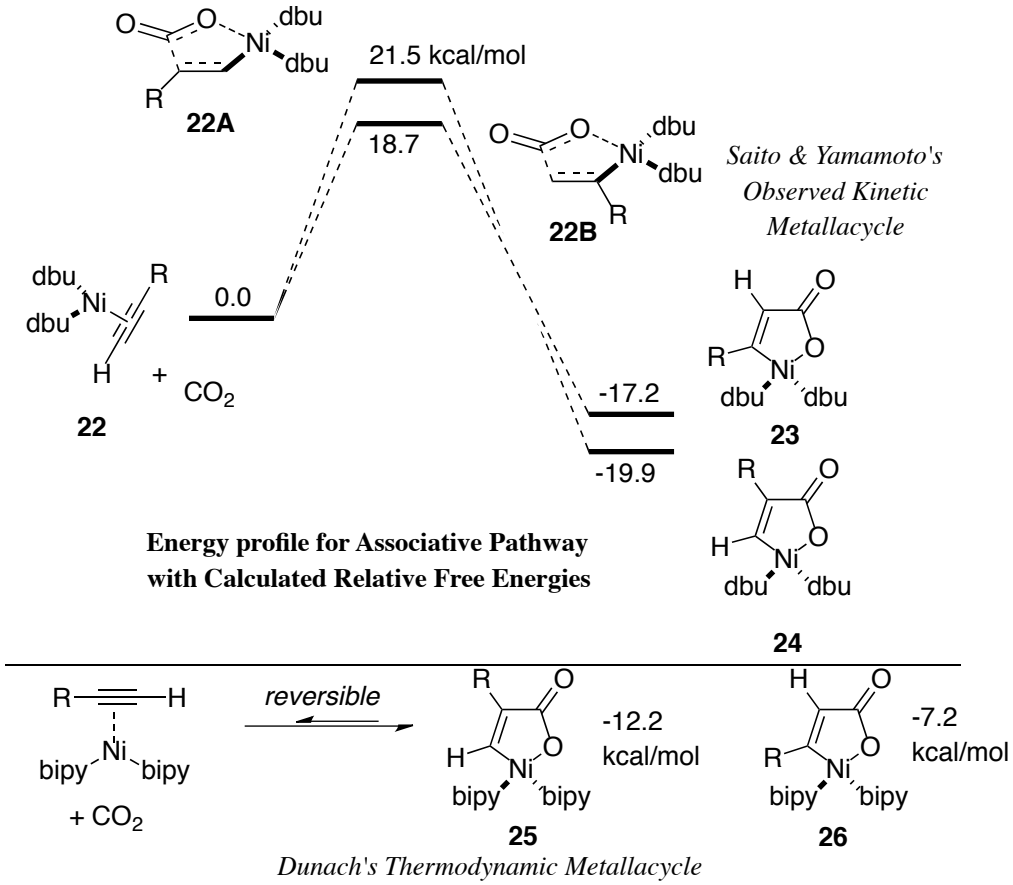
Although these stoichiometric approaches described production of the linear regioisomer, one of the few examples that favors the formation of the branched regioisomer was developed by Duñach and coworkers.[11] This report uses electrochemical potential to 'fix' carbon dioxide with terminal alkynes (Scheme 5). Although this study has generated little synthetic interest, the differing product regioselectivity is relevant to the discussion of metallacycle formation.

Scheme 5.



To rationalize the observed regioselectivity in the nickel-mediated cross-coupling of alkynes with carbon dioxide, computational studies were performed by Jia and Lin.[12] In the dissociative mechanism, the Ni(DBU)$_2$(alkyne) complex coordinates to CO_2 promoting loss of one DBU ligand, which triggers the oxidative addition. In contrast, in the associative mechanism, CO_2 directly attacks the nickel-coordinated alkyne. These studies revealed the overall free energy (ΔG) barriers are lower in an associative-type mechanism (Figure 1). Additionally, the energy of activation of TS **22A** vs **22B** is 21.5 and 18.7 kcal/mol, respectively. Thus, the observed metallacycle regioisomer (**23**) in Saito and Yamamoto's studies is the kinetically preferred species.[10]

Figure 1.



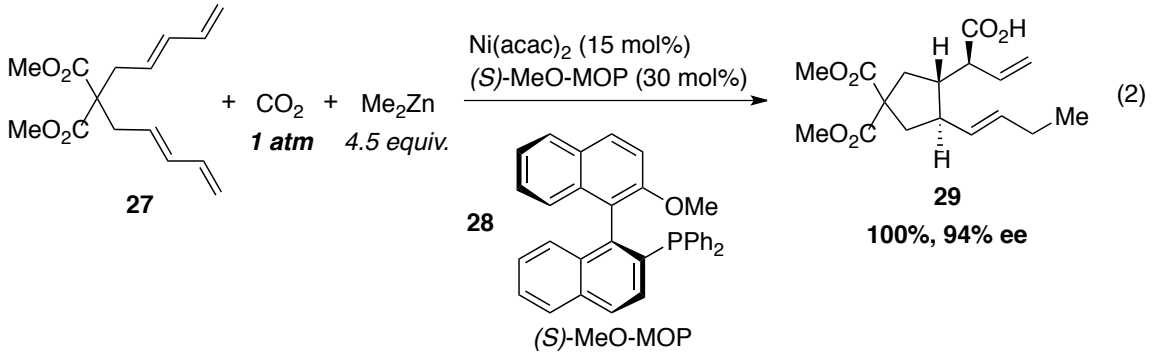
In contrast, Duñach metallacycle with bipy ligated nickel favors the formation of the thermodynamic metallacycle **25** (ΔG=-12.2 and -7.2 kcal/mol), with the R group located proximal to the carbonyl of carbon dioxide. The mechanism of this transformation is unknown and anticipated to be different from Saito and Yamamoto's work as the overall free energy barrier for an associative mechanism was calculated to be high in energy (30.4 and 28.2 kcal/mol).

1.1.2 Catalytic approaches for the fixation of CO_2.

All of these early examples describe the use of stoichiometric nickel and ligand reagents. Although these conditions are sufficient to examine reactivity, stoichiometric nickel reagent is cost-prohibitive for use in most industrial reaction processes. Catalytic carbon dioxide fixation has been known for thirty years. However, the majority of examples of these reactions are limited to the formation of carbonates and polycarbonates from epoxides.[13] Although this methodology is very efficient, the products which are obtained are relevant to areas of materials chemistry and generally not applicable to complex molecule synthesis.[14] More relevant for synthesis are examples resulting in C-C bond formation between activated, unsaturated alkene and alkyne substrates and carbon dioxide.

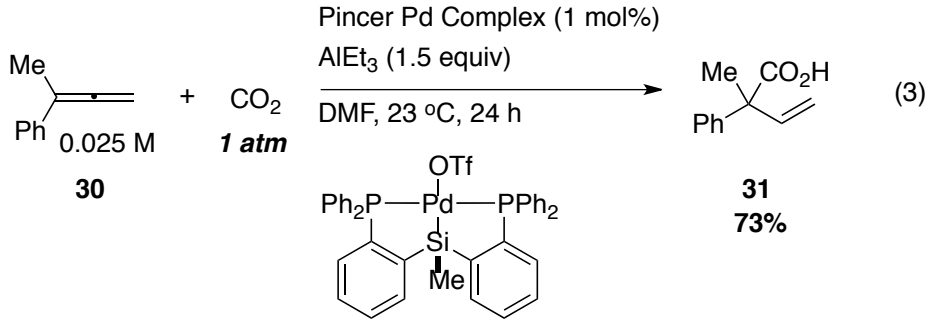
One type of reactivity utilizing π-systems to facilitate C-C bond formation was first developed by Miwako Mori. Her seminal publication concerning the carboxylation of bis-1,3-dienes established an important precedent for catalytic approaches to carbon dioxide fixation (eq. 2).[15] This reaction is promoted by the use of inexpensive, bench-stable precatalyst $Ni(acac)_2$, which is reduced to an active $Ni(0)L_n$ catalyst *in situ* with Me_2Zn in the presence of chiral ligand. As the

first example in this area of an enantioselective cyclization, this work is a groundbreaking report which introduces a binol-derived monodentate phosphine ligand (**28**) as a controller.



The incorporation of carbon dioxide and concomitant C-C bond formation was efficiently accomplished with only catalytic amounts of $Ni(acac)_2$. A limitation of this methodology is its specificity for bis-1,3-dienes which dictates its utility in synthesis. In addition, the substrates may require multiple steps for their preparation.

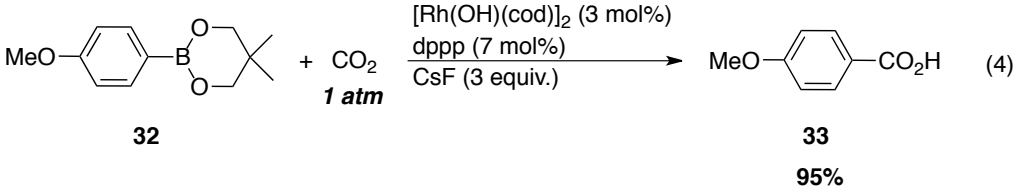
In 2008, Iwasawa described the coupling of allenes with silyl pincer-type palladium complexes (eq. 3). This reaction proceeds through generation of a silyl pincer-type palladium(II) hydride complex via reactions with $AlEt_3$. The reactive complex promotes hydrometalation of the allene which is followed by nucleophilic addition of CO_2 to form the α-quaternary β,γ-unsaturated carboxylic acid **31**.



Pincer Complex

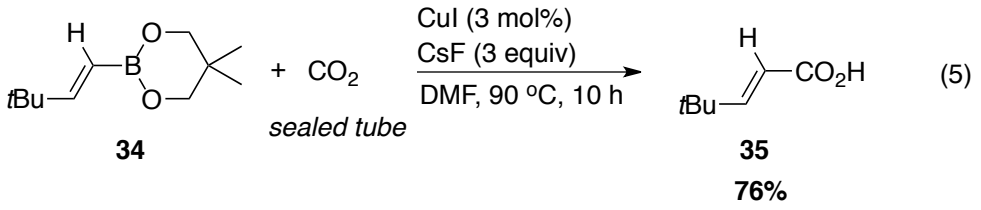
This is an important contribution to the field as it is a highly efficient and fairly tolerant of a variety of functionalities. Although the use of pincer complexes in organic synthesis has become more popular in recent years,[16] their tedious preparation is seen as a drawback for further development.

An interesting class of transition-metal catalyzed carboxylation reactions utilizes boronic esters instead of π-systems as cross-coupling partners. At the forefront of this methodology are the reports of Iwasawa and coworkers who have demonstrated the reactivity of various aryl- boronic esters with carbon dioxide using rhodium(I) catalysis (eq. 4).[17]



This chemistry is compatible with a wide variety of electron-deficient and electron-rich aryl-boronic esters and provides moderate to good yields of the corresponding aryl carboxylic acids (**33**). In 2008, Iwasawa and coworkers generalized their initial discoveries by adopting a copper(I)-catalyst system which

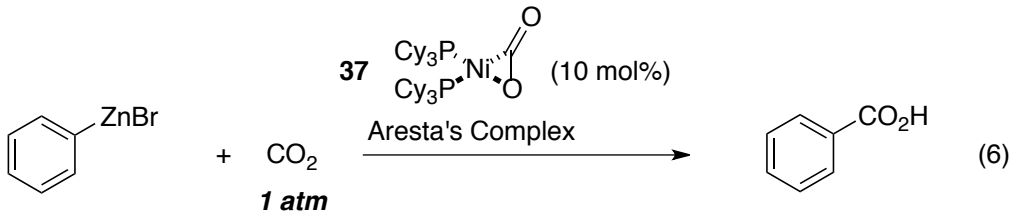
effectively expands the substrate scope to include alkenyl-boronic esters (eq. 5).[18]



34 **35** **76%** (5)

Concurrently, Hou and coworkers reported an *N*-heterocyclic carbene copper(I)-catalyzed system which increased functional group tolerance of the aryl- and alkenyl-boronic esters.[19] These approaches are useful for the carboxylation of a range of boronic esters.

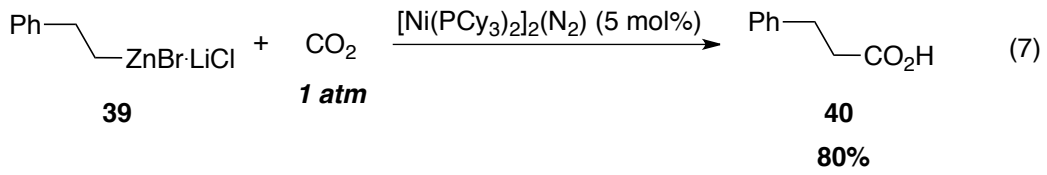
Another class of transition metal catalyzed carbon dioxide fixation reactions is an extension of the Negishi coupling with CO_2 as the electrophile. This cross-coupling strategy was first developed by Vy Dong and coworkers.[20] Initially inspired by Aresta's complex (**37**),[21] their study couples aryl- and alkylzinc species with carbon dioxide (eq. 6) to form aryl- and alkyl- carboxylic acids (**38**). This reactivity also proceeds with palladium and electron-rich phosphine ligands.



36 **38** **95%** (6)

The zinc reagents are typically prepared from the corresponding aryl- and alkyl-halides. Although aryl zinc halides are sufficiently reactive nucleophiles in this

approach, more reactive alkyl-zinc lithium chloride species (developed by Knochel[22]) were required to extend this reactivity to sp^3 systems (eq. 7).



(7)

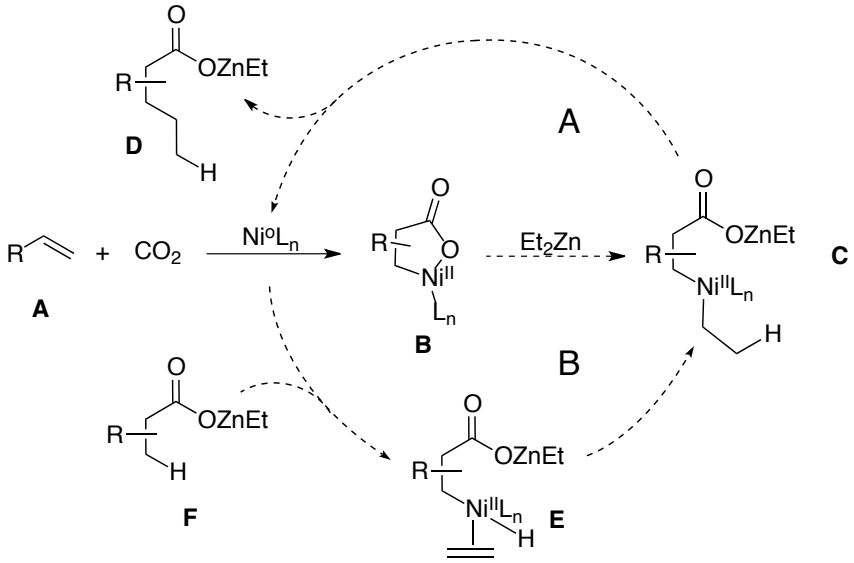
Concurrently, Oshima and coworkers extended this reactivity to secondary alkylzinc-lithium chloride species using $Ni(acac)_2$ and PCy_3.[23,24] The Negishi-type cross coupling of activated zinc reagents with carbon dioxide is an important development for transition-metal catalyzed reactions allowing for the formation of C-C bonds with CO_2.

1.1.3 The origin of catalytic carbon dioxide fixation in the Rovis laboratory.

Although the catalytic approaches for carbon dioxide fixation described herein effectively form C-C bonds with carbon dioxide, these methods often require fairly complex substrates derived synthetically using multiple functional group transformations. Our interest in the area of carbon dioxide fixation has focused on the development of methods which exploit readily available, feedstock materials and thereby offer an important contribution which has not been addressed by previous developments.[25] The basis of our hypothesis was inspired by considerations of the metallacycles presented in Hoberg's early stoichiometric studies in this area.[26] By introducing organozinc reagents in the same pot as the nickel(II) reagent and ligand we could effect a catalyst turnover and render a catalytic cycle.

The mechanism we envisioned originated with oxidative addition of an unactivated alkene (**A**), CO_2, and nickel(0) to form metallacycle **B**. Interception with an organozinc nucleophile, as shown for Et_2Zn, could follow one of two reaction pathways: reductive elimination to provide the alkylative carboxylation product **D** (Scheme 6, Path A) or alternatively β-hydride elimination followed by reductive elimination to provide the reductive carboxylation product **F** (Scheme 6, Path B).

Scheme 6.

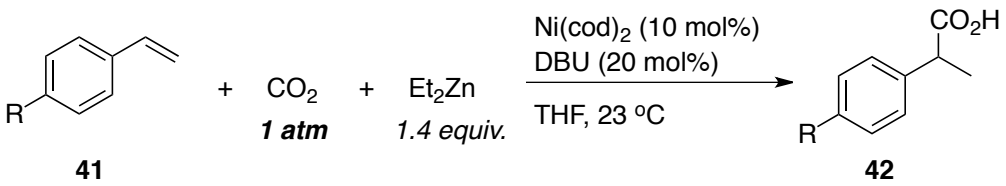


Both pathways described above would allow for catalyst turnover. If realized, our studies hold promise as a scaleable, economically effective route for a general production of functionalized carbonyl compounds from feedstock olefins and CO_2. Furthermore, the use of appropriately substituted alkenes and chiral ligands may allow for the development of asymmetric induction.

The metal and ligand chosen for initial screening was $Ni(cod)_2$ and DBU. Surprisingly, Et_2Zn, an organozinc reagent capable of divergent reaction

pathways, provided complete conversion to the reductive carboxylation product. A screen of styrene electron-deficient derivatives provided high yields of the carboxylation product **42** (Table 1).[27]

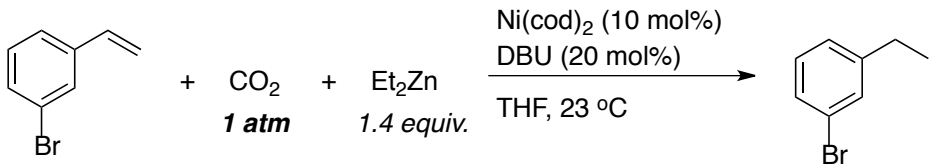
Table 1.



41 **42**

Entry	Substituent (R)	Yield
1	R=CF_3	**85%**
2	R=CO_2Bn	**85%**
3	R=CN	**85%**
4	R=COPh	**81%**

Additionally it was gratifying that the product obtained was the α-substituted or branched carboxylic acid. This impressive regioselectivity is counter to the early findings of Hoberg and others. Our observations suggest reactivity that is compatible with a range of functionalities, including esters, ketones, and nitriles. With ortho- and meta- substituted styrene derivatives and less electron-deficient alkene systems, reactivity favors reduction of the alkene (eq. 8).



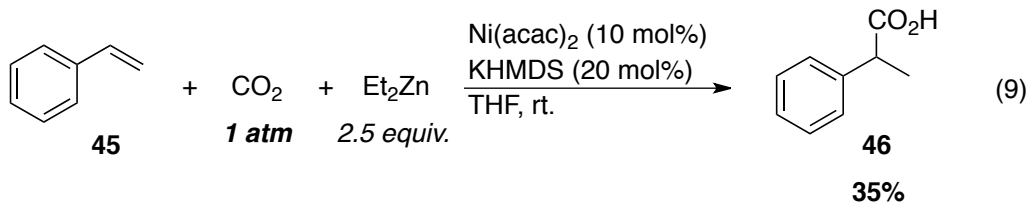
43 **44**

70%

(8)

Expanding the tolerance of this reaction manifold to allow for the use of halo-, ortho-, meta-, and para-substituated styrenes featuring a broader range of electron density in the starting material would make this method more synthetically attractive. To this end, a variety of ligands were screened.

Surprisingly, sub-stoichiometric quantities of KHMDS, which presumably acts as a ligand for nickel(II)[28], provided moderate success in reactions of styrene (**45**) itself with a yield of 35% (eq. 9).



(9)

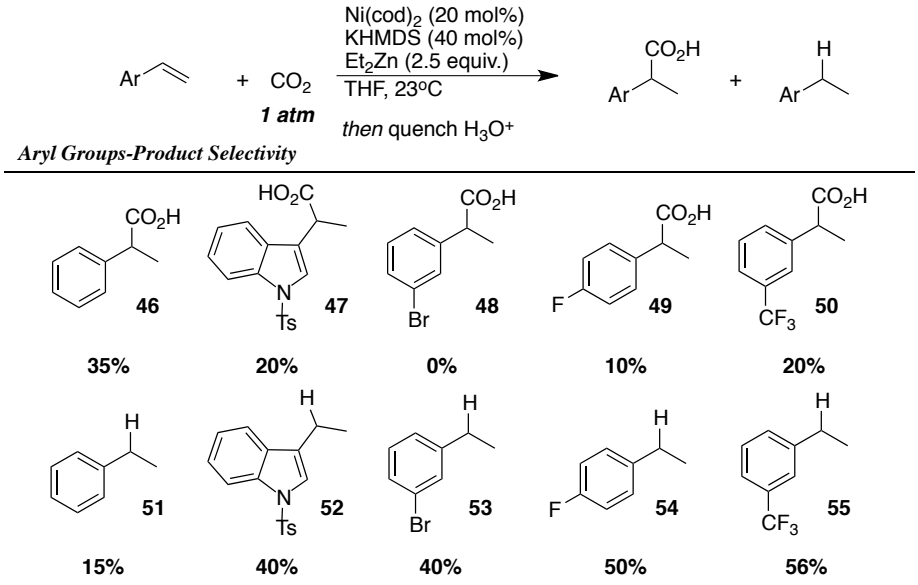
1.2 Further development of the hydrocarboxylation of styrenes.

Our observations of catalytic carbon dioxide fixation provided the foundation for a new investigation. The goals of this project were to address a number of questions that arose during the course of the initial studies including the compatibility of basic additives such as DBU and KHMDS in this reaction manifold, as well as factors which contribute to the general reactivity of the catalyst toward alkene substrates. We hoped to extend the reaction to unreactive and unactivated substrates while maintaining high reactivity and efficiency. Additionally, we sought to understand the unusual preference for the branched isomer as opposed to the linear isomer observed in the stoichiometric work of Hoberb, Saito and Yamamoto, and Mori. Where feasible, relevant mechanistic studies could be undertaken to aid our efforts. Furthermore, we also sought to find an alternative, user-friendly reducing agent as compared to Et_2Zn, which requires careful handling.

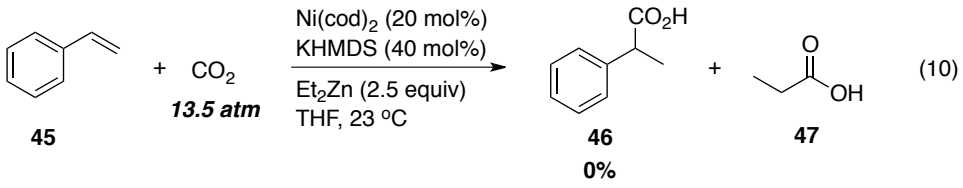
To undertake this effort, a multi-pronged approach was devised. First, we sought to probe the extent of reactivity with KHMDS by screening substrates, solvent, temperature, and CO_2 pressure. A screen focused on the reactivity of

previously unreactive styrene derivatives showed little enhanced reactivity (Scheme 7, 49-50). However, significant amounts of the reduced alkene side products were obtained (51-55). No enhancements of desired product yields were observed with electron poor as well as electron 'neutral' substrates (**46**).

Scheme 7.



Initially, we considered the presence of the reduced product to be an indicator of sluggish reactivity. Thus studies were undertaken to increase the pressure of carbon dioxide in the reaction vessel, by running it in a Parr Bomb. Unfortunately, when the pressure of CO_2 was increased, no boost in yield was observed (eq. 10).

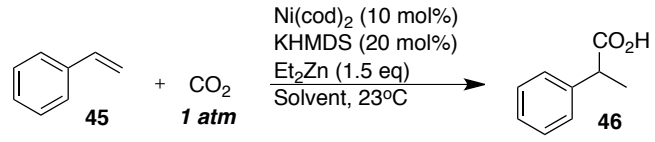


(10)

A screen of solvents of differing polarity showed slight improvements of yield with EtOAc (Table 2). Somewhat surprising was the moderate reactivity

observed with the use of toluene and benzene as well as the complete lack of reactivity with DMF or 1,4-dioxane (Table 2, Entries 2, 3, 7-9).

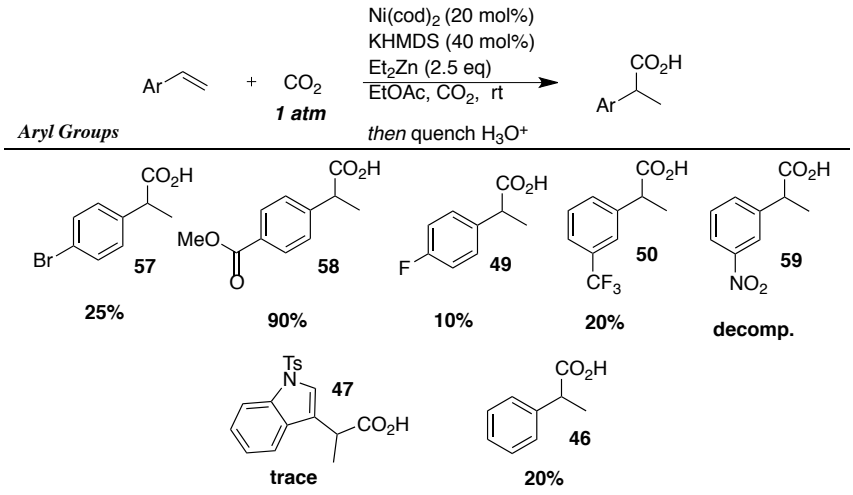
Table 2.



Entry	*Solvent*	*Product Yield*
1	DMSO	NR
2	DMF	NR
3	1,4-Dioxane	NR
4	DCM	NR
5	EtOAc	40%
6	THF	35%
7	PhH	10%
8	Toluene	10%
9	$PhCF_3$	15%

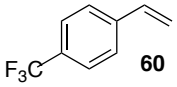
Unfortunately, the use of EtOAc as a solvent failed to provide a boost in yields for a variety of functionalized systems (Scheme 8). Thus, the use of KHMDS as an additive, while sufficient to promote reactivity of styrene to 40% yield, failed to improve the reaction for additional substrates.

Scheme 8.

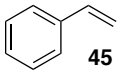


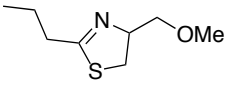
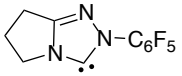
The use of KHMDS as an additive proved insufficient. Additional phosphorus and nitrogen ligands were also investigated, but no improvements were observed (Table 3). The lack of success with traditional nitrogen and phosphorus ligands was particularly discouraging since the use of chiral nitrogen and phosphine ligands provides a common rationale for introducing asymmetric induction.

Table 3.

Substrate  **60**

Entry	Additive[a]	Yield
1	none	0%
2	bipy	NR
3	PPh_3	NR
4	MONOPHOS	NR
5	(-)-sparteine	10%
6	DBU	88%
7	Pyridine	90%

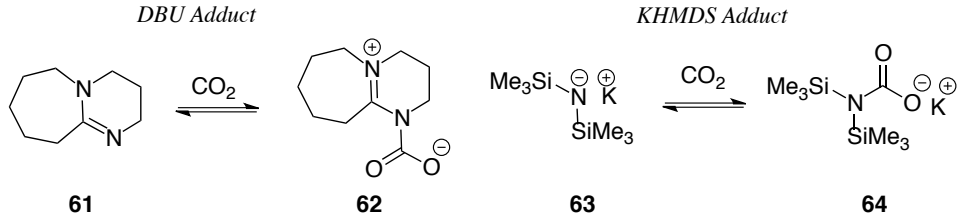
Substrate  **45**

Entry	Additive[a]	Yield
8	DBU	NR
9	Pyridine	NR
10	Taddol-$PNMe_2$	NR
11	PCy_3	NR
12		NR
13		NR
14	KHMDS	35%

[a]Standard conditions: $Ni(cod)_2$ 10 mol%, additive 20 mol%, Et_2Zn 150 mol%, CO_2 1 atm, THF, 23°C

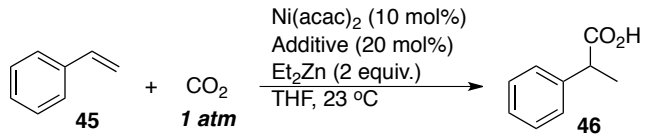
The poor reactivity of this system led us to reconsider and re-evaluate the mechanistic hypothesis. Instead of the usual pre-coordination of nickel(II) to ligand, perhaps substrate reactivity can be explained by the ligand binding to carbon dioxide prior to involvement in the catalytic cycle. Indeed, DBU has been shown to attack carbon dioxide and form stable zwitterionic adduct **62** (Scheme 9). This reactivity was recognized almost 30 years ago.[29] Invoking a similar reaction between KHMDS (**63**) and carbon dioxide is plausible, and could explain the value of both DBU and KHMDS as additives for our reaction.

Scheme 9.



Although the role of such adducts in our reaction is unclear, it suggested that trial reactions using carbonates, acetates, and other related inorganic bases as additives might be explored. It is plausible such additives could bind to nickel directly and promote the desired reactivity. The results of a screen of inorganic bases with several cations are presented in Table 4. In general, atomic radii of the alkali metal cation seemed to vary directly with yield; that is, bases with larger counterions provide product more efficiently. It is likely that this observed trend reflects differences in solubility of the organic bases. For example, cesium carbonate is significantly more soluble in THF at room temperature as compared to lithium carbonate which is insoluble.

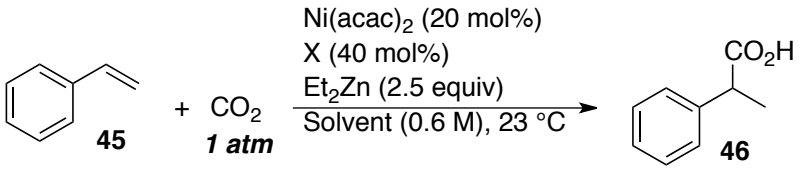
Table 4.



Entry	*Cation Atomic Radius*	*Additive*	*Yield*
1		LiH	trace
2		LiHMDS	10%
3		LDA	15%
4		NaHMDS	<10%
5		NaH	10%
6		KH	40%
7		KDA	10%
8		KHMDS	35%
9		K_2CO_3	NR
10		Cs_2CO_4	30%
11		Cs_2CO_3	56%

The hypothesis that base solubility correlates with product yield is supported by experiment. Carbonate sources with different counterions were examined (Table 5). Very poor reactivity was observed with Li^+, Na^+, and K^+ counterions (Entries 3,4, and 5), which is consistent with poor solubility in THF. To enhance the solubility of K_2CO_3 in THF, crown ethers were examined. Crown ethers coordinate the metal cation, by sometimes increasing the organic solubility of the salt. Unfortunately, when 18-Crown-6 was added to the reactions in THF, substantial amounts of insoluble material were observed. To address this problem, the reaction was performed in toluene. Although toluene had initially provided a lower yield in our solvent screens (Table 5, Entry 2), an improvement in yield was observed in this trial reaction performed with K_2CO_3 and 18-Crown-6 (Table 5, Entry 32).

Table 5.



Entry	Carbonate Source (X)	Crown Ether	Solvent	Yield %
1	Cs_2CO_3	None	THF	56
2	Cs_2CO_3	None	PhMe	15
3	Li_2CO_3	None	THF	trace
4	Na_2CO_3	None	THF	trace
5	K_2CO_3	None	THF	0
6	K_2CO_3	18-Crown-6	THF	0
7	K_2CO_3	18-Crown-6	Toluene	32

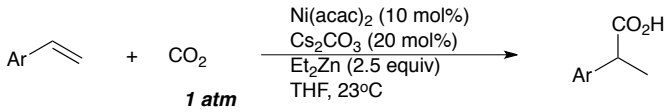
The enhanced reactivity in the latter system suggested that carbonate sources may be important for reactivity.

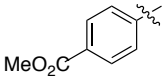
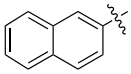
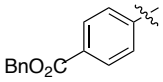
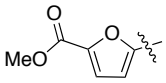
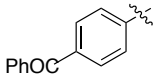
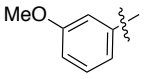
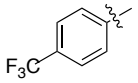
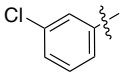
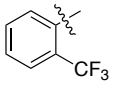
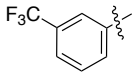
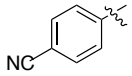
1.3 Reaction efficiency and scope

In an effort to optimize the transformation, solvents, concentration, and reagent stoichiometries were screened using cesium carbonate. Notably, the most reliable yield was observed when excess (2.5 equiv.) Et_2Zn (neat) was introduced. A substantial loss of reactivity was observed when commercially available solutions of Et_2Zn in heptanes, hexanes, or toluene were used.

A variety of styrene derivatives ranging from electron-neutral to strongly electron-deficient systems undergo reductive carboxylation in moderate to excellent yields using cesium carbonate as a soluble, basic additive (Table 6).[30] In addition, product yields appear to be independent of substitution pattern on the arene, and similar yields for *ortho*-, *meta*-, and *para*- substituted derivatives were now observed (Table 6, Entries 11,12,7). Furthermore, these reaction conditions are tolerant of a broader range of reactive functionalities such as chlorides, esters, ketones, and nitriles.

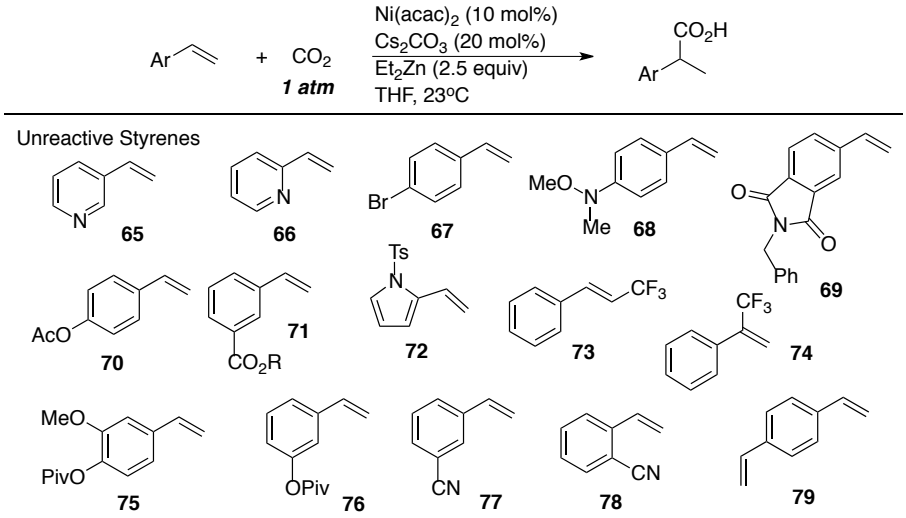
Table 6.



Entry	Aryl Group (Ar)	$\sigma_{m/p}/\sigma_+$	yield(%)	Entry	Aryl Group (Ar)	$\sigma_{m/p}/\sigma_+$	yield(%)
1		0	56	8		0.45/0.48	84
2		-	60	9		0.45/0.48	81
3		-	66	10		0.50/0.51	72
4		0.12	92	11		0.54/0.61	92
5		0.37	68	12		-	87
6		-	65				
7		0.43	79	13		0.66/0.66	61

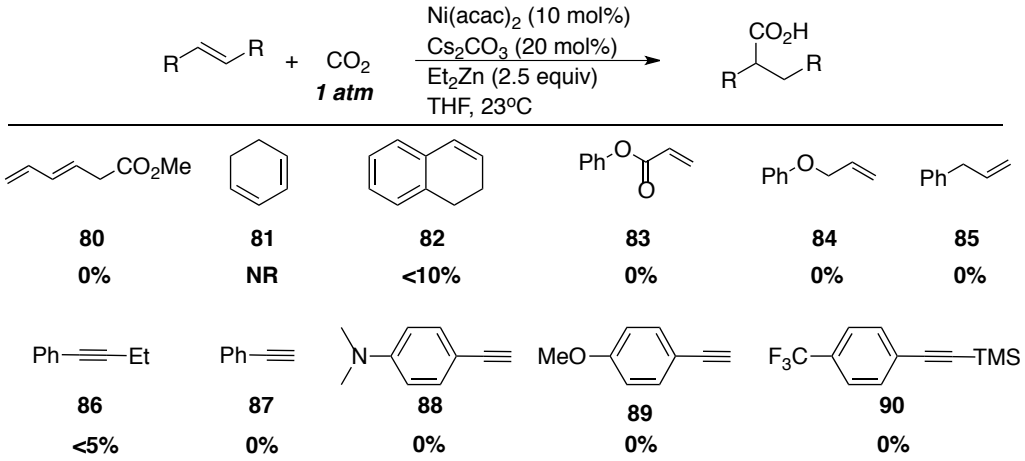
To analyze the observed reactivity of different styrenes, Hammett $\sigma_{m/p}$ and σ_p^+ values were examined.[31] With few exceptions, electron deficient styrenes with positive σ values undergo reductive carboxylation efficiently regardless of the aryl substitution pattern, while those with negative σ values fail to produce the desired carboxylic acid. In general, electron-rich styrenes were observed to undergo polymerization under our conditions. The addition of reagents known to suppress polymerization, such as *tert*-butylcatechol, hydrazine, $ZnCl_2$, $AlCl_3$, and CuBr resulted in suppressed polymerization as well as carboxylation. Additional reactivity limitations were imposed by steric effects and in these cases, reactivity of electron-deficient examples containing ortho-substituents and/or additional substitution on the olefin suppressed the reaction (Scheme 10, examples **72**, **74**, and **78**).

Scheme 10.

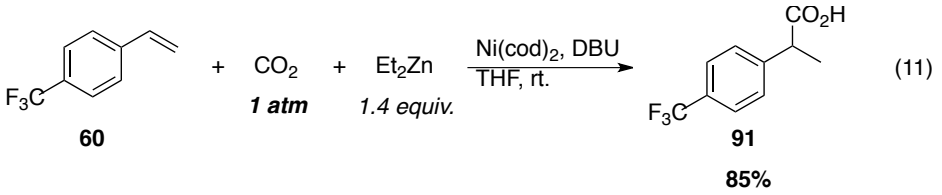


A number of studies to extend the scope of the reductive carboxylation to other π-systems proved problematic under our optimized conditions. Specifically, terminal and internal alkynes were unreactive, regardless of substitution pattern, as were unconjugated olefins and dienes (Scheme 11). The failure of these systems is surprising due to the successes of Saito and Yamamoto as well as Mori's stoichiometric study.[8,9]

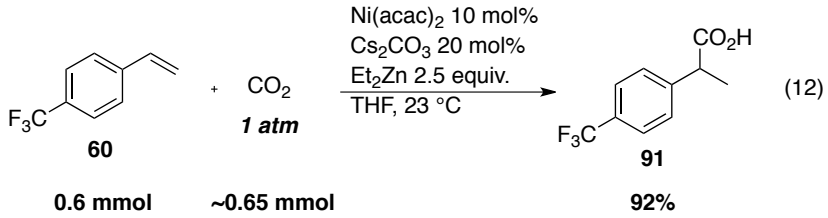
Scheme 11.



Reaction efficiency in terms of catalyst loading and carbon dioxide uptake could be an important advantage of any approach towards carbon dioxide fixation. Towards this end, experiments with lower catalyst loadings were undertaken. To our gratification, the catalyst loading in our reaction conditions can be reduced to 1 mol% without detriment (eq. 11).



Typically carbon dioxide is supplied to the reaction by a balloon at ambient pressure inserted into the headspace of a reaction vessel via needle. To test the uptake efficiency of this reaction, the headspace of the reaction flask was filled with CO_2 by a balloon, which was subsequently removed. Although the solubility of carbon dioxide was not accounted for in these calculations, it was reported to be 0.4 mmol in 2 mL of THF.[32] The molar equivalents of carbon dioxide in the system was estimated from the volume of gas in the headspace of the flask, and calculated to be approximately one equivalent. Gratifyingly, this technique was sufficient for complete conversion to the reductive carboxylation product (eq. 12).



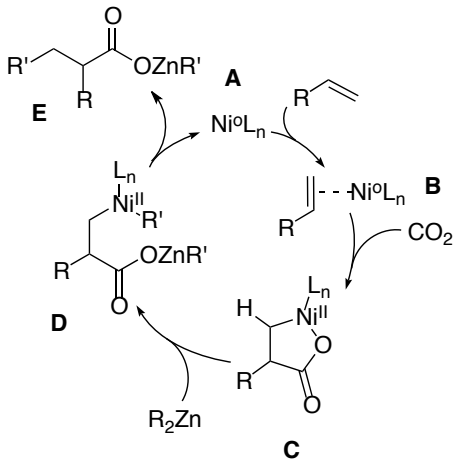
The success of this reaction system is interesting for a number of reasons. Specifically, the success of cesium carbonate as an additive raises some important questions about the mechanism of the reaction. Additionally, the

observed regiochemistry is opposite to previous observations. We sought to elucidate these questions by designing a number of experiments to probe these issues.

1.4 Investigations of the mechanism

The observed regiochemistry of our reaction as well as the success of the cesium carbonate additive was puzzling in the context of the metallacycle mechanism we envisioned at the start of this work (Scheme 12), in which metallacycle **C** is formed via oxidative addition, opened by transmetallation with Et_2Zn, followed by reductive elimination to provide **E** and regenerate nickel(0).

Scheme 12.

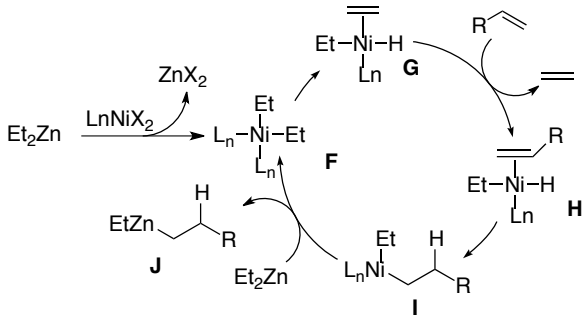


However, the definitive role of cesium carbonate in a metallacycle mechanism remains unclear, as very little is known about its ability to bind to late-transition metals. Alternatively, its presence in solution could induce an alkali environment and increase the effective concentration of carbon dioxide in solution.

An initial hydrozincation event could explain the formation of ethylbenzene as a side product when styrene is used as a substrate. Hydrozincation chemistry

has been described by Knochel,[33] and a catalytic cycle illustrating this theme is shown in Scheme 13.

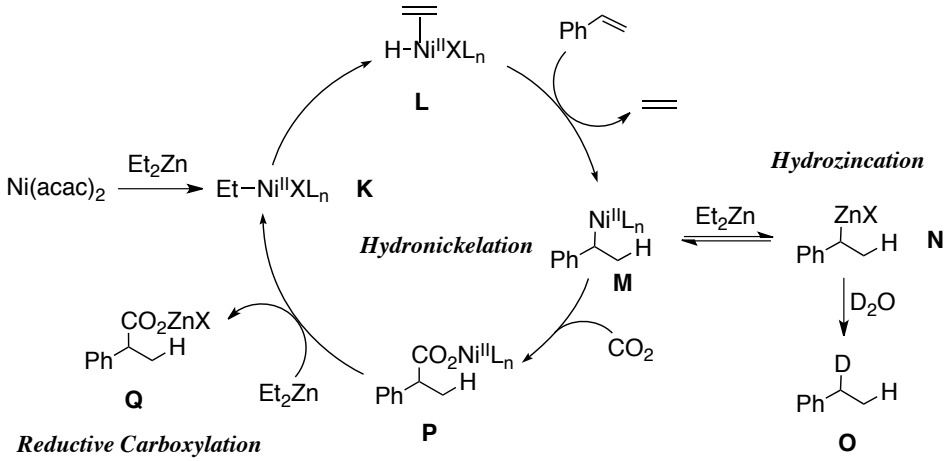
Scheme 13.



The key features of Knochel's chemistry are the formation of a Ni-H active catalyst **G** formed by β-hydride elimination, followed by exchange of ethylene by an alkene (**H**), migratory insertion to form the alkyl nickel species **I**, followed by a rapid transmetallation event to access the zinc species **J** and regenerate the active catalyst.

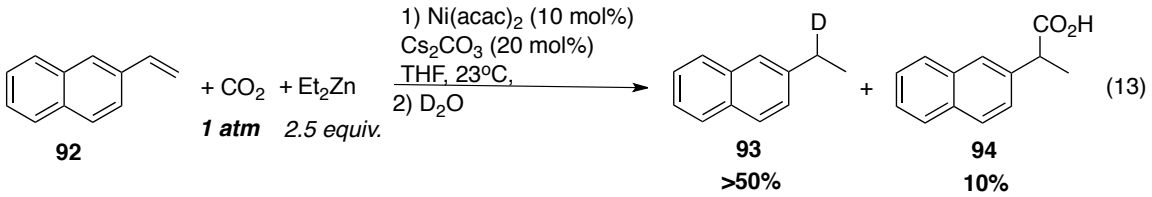
A catalytic cycle combining the salient features of Knochel's hydrozincation chemistry with a carbon dioxide insertion event could explain the observed reactivity (Scheme 14).

Scheme 14.



The proposed cycle begins with ligand exchange of Et_2Zn with $Ni(acac)_2$ to form ethyl nickel complex **K**, followed by β-hydride elimination to form the active nickel-hydride catalyst **L**. An exchange of ethylene and styrene followed by migratory insertion of styrene into the nickel-hydride bond provides benzyl nickel complex **M**. This "hydronickelation" intermediate can then undergo one of two pathways: the productive route proceeding through insertion of carbon dioxide into the C-Ni bond to obtain **P**, followed by transmetallation with another equivalent of Et_2Zn to form zinc carboxylate species **Q**, or the unproductive pathway proceeding through a reversible transmetallation event with Et_2Zn to generate benzyl zinc species **N**. This unproductive pathway would be responsible for generation of the ethyl benzene side product.

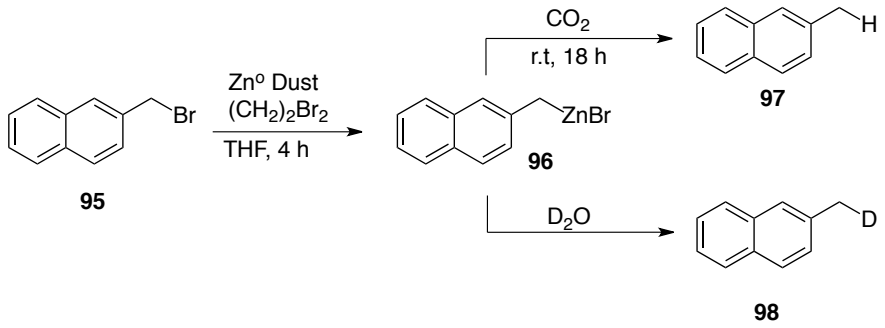
A deuterium quench experiment to track the progress of the reaction after one hour revealed greater then 50% deuteroethylbenzene **93**. Presumably, this material is derived from intermediate **N** (of Scheme 14), which upon exposure to D_2O, provides deuterium incorporation in the benzylic position (**O**) (eq. 13). We have noted that intermediate **M** could also provide **93** upon deuterium quench. A maximum of 10% incorporation would have been obtained due to the small quantity of nickel(II) catalyst present in the reaction.



Although the reactivity of the benzyl zinc intermediate **N** towards carbon dioxide has not been established, we believed that the nickel complex is required to trap

CO_2. Importantly, dialkylzinc reagents are not observed to add directly to CO_2. within the time frame of our reactions. Nevertheless, benzyl zinc reagents may be more reactive. To confirm that the zinc intermediate **N** does not trap CO_2 in the absence of nickel(II) complex, napthyl methylzinc reagent was prepared and was placed under atmospheric CO_2 pressure for 18 hours (Scheme 15).

Scheme 15.



In this experiment, no carboxylic acid was produced under an atmosphere of carbon dioxide. In addition, quenching with D_2O provided deuterium incorporation at the benzylic position, confirming the reactivity proposed in our mechanistic hypothesis.

Although the hydrozincation/carboxylation mechanism is most probable, heterogeneous catalysis has also been considered. The prevalence of reactions proceeding through surface reactions on insoluble metal clusters is under-appreciated by synthetic chemists as many reactions are commonly mistaken for homogeneous catalysis.[34] These reactions are prevalent in the following scenarios: 1) when easily reducible transition-metal complexes are employed 2) when forcing reaction conditions including reducing agents are used, and 3) when stabilizers are present, such as halides, carboxylates, and polar solvents.[35]

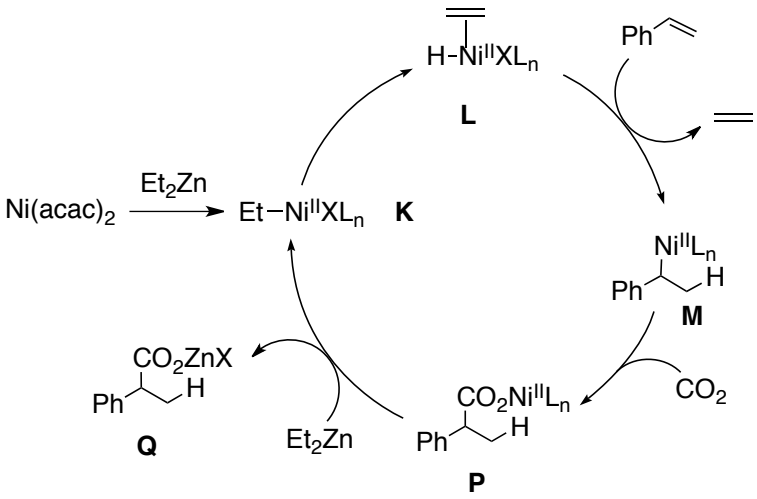
In general, these reactions are dark in color with metallic precipitates. The reactions commonly display induction periods and sigmoidal kinetics. Perhaps the success of cesium carbonate can be rationalized by a role as a nanocluster stabilizer. The concept of heterogeneous catalysis is also consistent with the use of nickel and excess of the very strong reducing agent, Et_2Zn. The reaction developed herein is commonly very dark in color with some precipitates, a general description fitting nano-catalysis. There are a number of strategies employed to distinguish homogeneous catalysis from heterogeneous catalysis, one of which is mercury poisoning. If the reaction is poisoned by Hg^o this represents a positive indication of a heterogenous system. To probe the validity of a heterogeneous system in this reaction manifold, Hg^o was added to the reaction at ~20% conversion.[36] In this case, the addition of mercury had no effect on the yield. Although more then one experiment is required to confirm the validity of a colloidal catalyst, further mechanistic studies along these lines were abandoned.

1.5 An examination of alternate reducing agents

Although the described method is attractive for its efficient reactivity, Et_2Zn is a strong reducing agent requiring anhydrous, oxygen-free techniques. Thus, a more user-friendly and readily available alternative to Et_2Zn is of interest. This presents a significant challenge, due to the multitude of roles Et_2Zn may play in this reaction (Scheme 16). If the hydrozincation/carboxylation mechanism is accurate, Et_2Zn is responsible for generating the active Ni-H catalyst (**R**) as well

as effecting catalyst turnover by transmetallation with the carboxylate nickel complex (Scheme 16). For this reason, Me_2Zn would be ineffective.

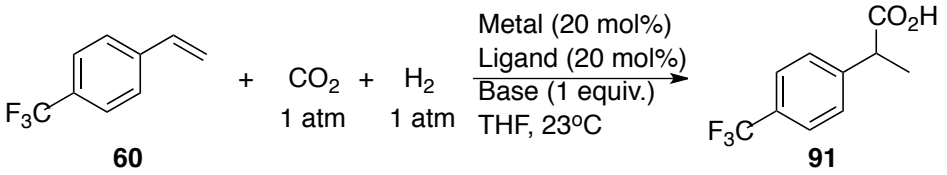
Scheme 16.



Et_3Al is a potent organometallic reagent with similar reactivity compared to Et_2Zn[37], however this reagent proved ineffective for our system. Silyl hydrides were also investigated as hydride sources and reducing agents; however, no reactivity was observed with a variety of organosilanes. Inspired by Krische's report of reductive couplings utilizing isopropanol,[38] attempts modeled after his study failed to display any reactivity.

A reaction system employing H_2 as the hydride source represents the most mild, inexpensive, atom efficient reductive carboxylation. Towards this end, a number of studies introducing hydrogen gas were directed at forming a reactive M-H complex to no avail (Table 7).

Table 7.



Entry	Metal	Ligand	Base	Yield
1*	$Ni(cod)_2$	none	Pyridine	NR
2	$Ni(cod)_2$	none	Cs_2CO_3	NR
3	$Ni(cod)_2$	bipy	Cs_2CO_3	NR
4	$Ni(cod)_2$	PCy_3	Cs_2CO_3	NR
5	$Ni(cod)_2$	$ZnCl_2$	none	NR
6	$Pd(PPh_3)_4$	none	none	reduced productc
7	$RhCl(PPh_3)_4$	none	none	reduced product
8	Cp_2ZrCl_2H	none	none	NR
9	$HRh(CO)(PPh_3)_3$	none	none	SM, reduced product
10	$HRh(CO)(PPh_3)_3$	none	Pyridine	SM, reduced product
11	$HRh(CO)(PPh_3)_3$	iPrPHOX	none	SM, reduced product
12	$HRh(CO)(PPh_3)_3$	pyphos	none	SM, reduced product
13	$HRh(CO)(PPh_3)_3$	bipy	none	SM, reduced product
14	Raney Nib	none	KOH (solution)	NR
15	Raney Nib	none	K_2CO_3	NR

*Jeff Johnson had reported a 15% yield of desired product X in these conditions
[b]Raney Nickel was used in a mixture of $EtOH/H_2O$
[c]Reduced product is derived from reduction of the vinyl group

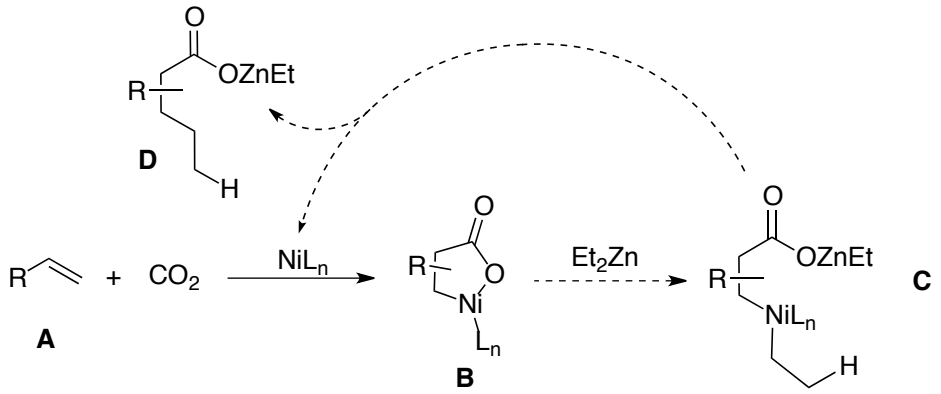
Even at 50 psi of CO_2 and H_2, we failed to observe any reaction.[39] In summary, a number of hydride sources and reducing agents were attempted to improve upon our reaction conditions without success.

1.6 Investigations of alkylative carboxylation

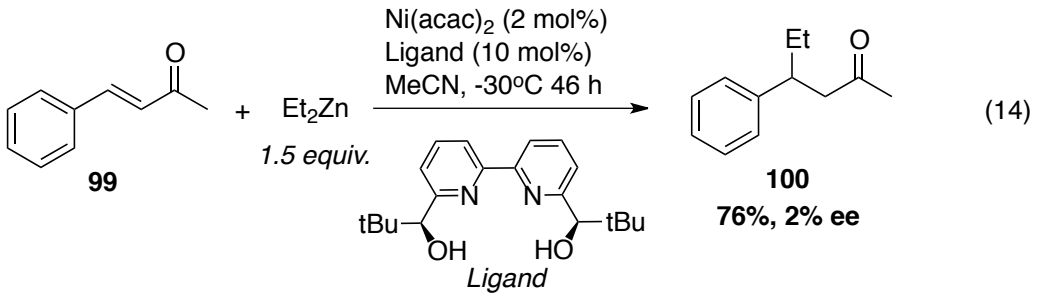
At this time, our focus shifted towards the development of a system for catalytic alkylative carboxylation (Scheme 17). As opposed to the hydrocarboxylation product resulting from β-hydride elimination of intermediate **C**, immediate reductive elimination to regenerate the active catalyst would allow

for the formation of alkylative carboxylation product **D**. If realized, this approach would rapidly assemble molecular complexity by combining two C-C bond forming events in one sequence.

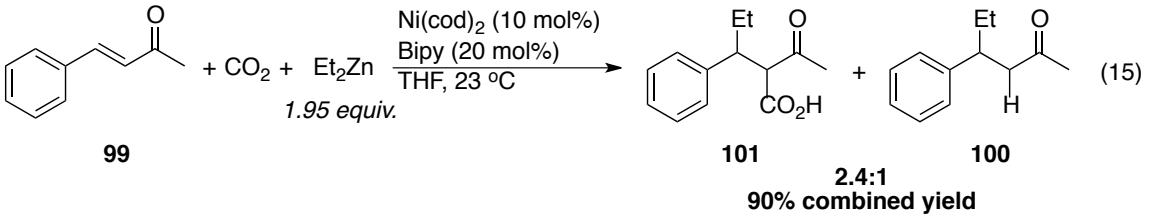
Scheme 17.



Towards this goal, enones were investigated as reactive π-systems. The soft nucleophilicity of zinc reagents and known affinity with Michael acceptors should favor the desired reaction with enones.[40] In fact, this reactivity pathway has been explored by Bolm and coworkers (eq 14).

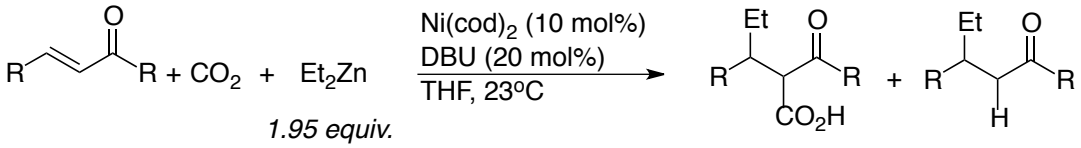


Trapping of the resulting enolates with carbon dioxide was initially investigated by Jeffrey B. Johnson in the Rovis laboratories. He found success with chalcone substrates catalyzed by $Ni(cod)_2$ and bipy (eq. 15).[41]

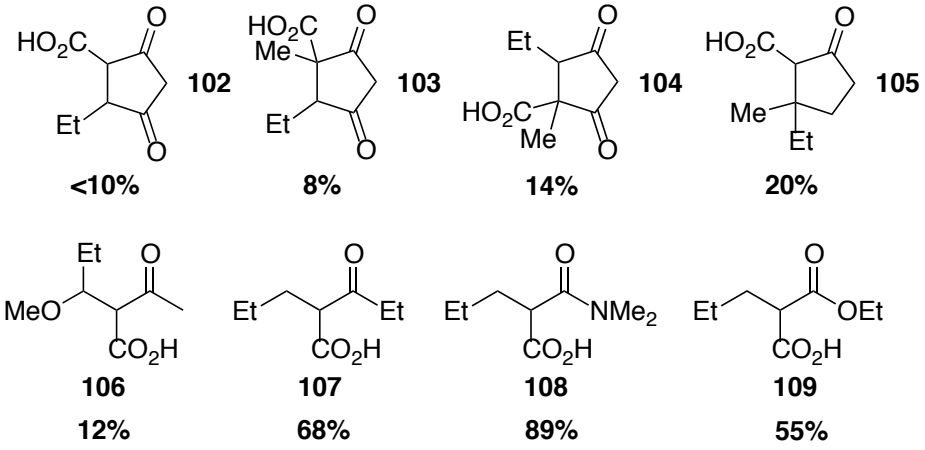


Although the documented yield was low, the problem was thought to be the sluggish nature of carbon dioxide trapping, evidenced by the prevalence of an alkylative-protonation side product. The compatibility of these conditions with a variety of α,β-unsaturated ketones, amides, and esters was most promising (Scheme 18). Although higher reactivity was observed in non-cyclic systems, alkylation occurred readily in all examples and the CO_2 fixation event was viewed as a fixable problem.

Scheme 18.

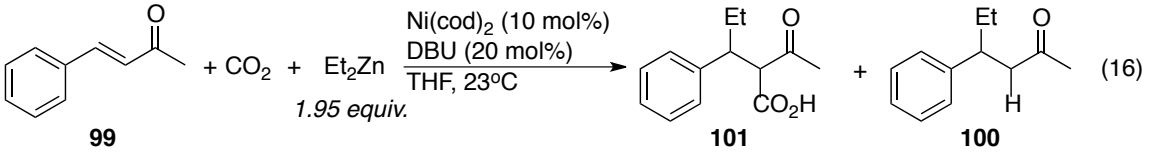


Compatible substrates



The initial goals for this project were to examine different reaction conditions to favor carboxylation. The variables that were examined included:

base/additive, solvent, and metal. A screen of ligands/additives provided disappointing results as no reaction trend could be ascertained. A number of ligands induced polymerization of the starting materials as opposed to alkylation. This side reaction rapidly degraded the enone and shut down the desired reaction. DBU provided some advantage, yielding a ratio of 2.5:1 in favor of alkylative-carboxylation product (eq. 16).



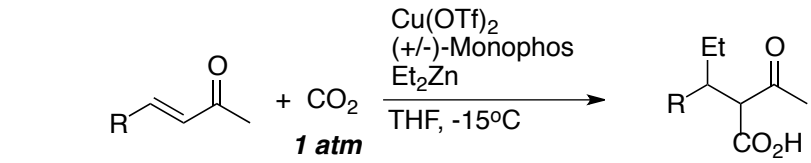
99 **101** **100** (16)

2.7:1
90% combined yield

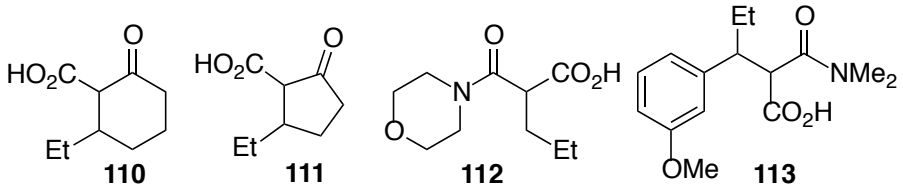
During the course of these studies, new control experiments determined that nickel reagents and ligand were unnecessary for the transformation; without these additives a ratio of 1:4 in favor of alkylative-protonation was observed. However, the use of nickel in these systems was not abandoned since an improved product ratio is observed in the presence of Ni complex and ligand. Our studies suggest increased reactivity of the metal enolate towards CO_2 trapping.

As product selectivity and starting material decomposition as well as product decomposition were a problem in this reaction manifold, copper(II) was sought as a replacement for zinc. Copper was thought to behave similarly without the propensity towards polymerization and decomposition pathways. Gratifyingly, copper(II) was successful in this reaction, providing modest yields of the desired products (Scheme 19).

Scheme 19.



Compatible Substrates

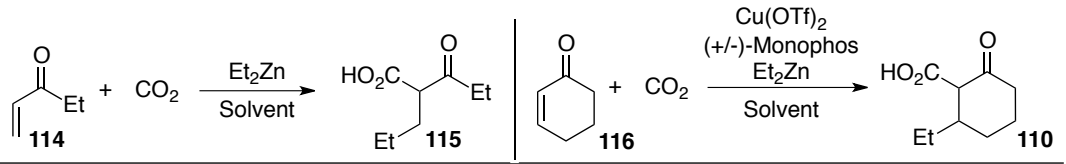


110 **111** **112** **113**

62% **67%** **5%** **<5%**

Solvent selection exerts some control over product selectivity. Table 8 compares the reactivity of an uncatalyzed zinc system to a copper(II) catalyzed system in various solvents. In general, without the presence of nickel catalyst, reactivity was enhanced by the use of polar solvents.[42] In contrast, the copper(II) catalyzed system shows the best results using THF.

Table 8.

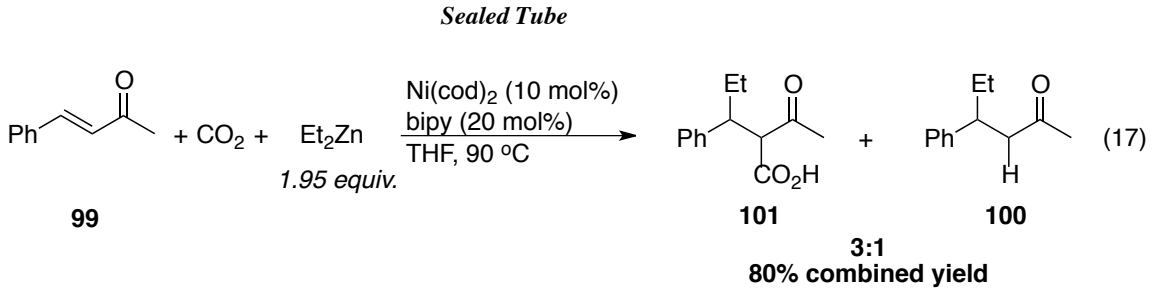


Entry[a]	Solvent	Yield (%)[c]	Entry[b]	Solvent	Yield (%)[c]
1	PhMe	8	1	PhMe	40
2	THF	46	2	THF	67
3	DMF	43	3	Et_2O	47
4	DMSO	58	4	DMF	10

*a*Jeff Johnson's results: Standard conditions: 1 equiv. enone, 1.4 equiv Et_2Zn, 1 atm CO_2, 2 mL of solvent at 23°C
*b*Conditions: 10 mol% $Cu(OTf)_2$, 10 mol% (+/-)-Monophos, 2 equiv Et_2Zn, 1 atm CO_2, 2 mL of solvent at 23°C
*c*Yield based upon enone

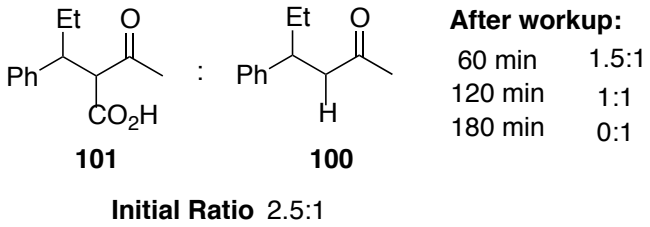
No substantial advantage or trend was unearthed by changing any of the variables initially investigated; thus, we reexamined the origin of the alkylative-protonation product. Initially, we believed it arose from incomplete or inefficient

trapping of carbon dioxide by the enolate. Unfortunately, experiments designed to accelerate this trapping by increasing CO_2 pressure were ineffective (eq. 17).



In fact, during the course of these analyses it became clear that the time between work-up and characterization also changed the product ratio in favor of alkylative-protonation via β-ketoacid decarboxylation. During the course of these studies, time (minutes) following work-up was seen as the most important variable, demonstrating a clear trend towards decarboxylation with increasing time. It was concluded decarboxylation occurs as early as the reaction quench, and rapidly continues at room temperature until complete decarboxylation in 2-3 hours (Figure 2).

Figure 2.

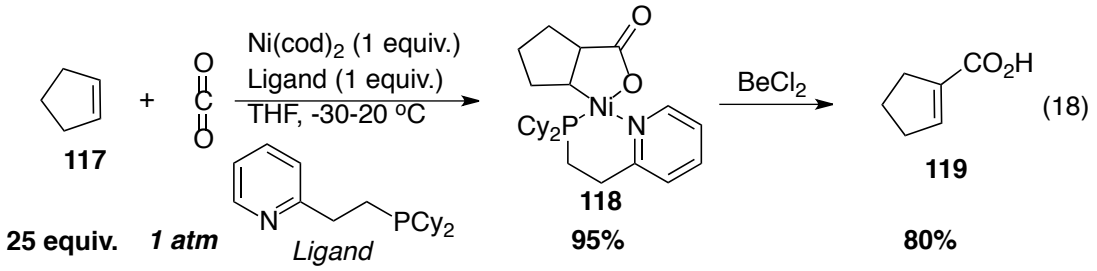


A number of alternate workups were attempted to combat this problem, including immediate esterification with diazomethane as well as amidation with DCC and dibenzylamine or EDC following acid or base work up; however, decomposition

persisted and only trace amounts of derivatized acids could be isolated. In conclusion, the same reactivity that drew us to enones as substrates was responsible for this project's ultimate downfall. The equilibrium of enolate carboxylation and decarboxylation inherently favors decarboxylation.

1.7 Reactivity of alternative π-systems

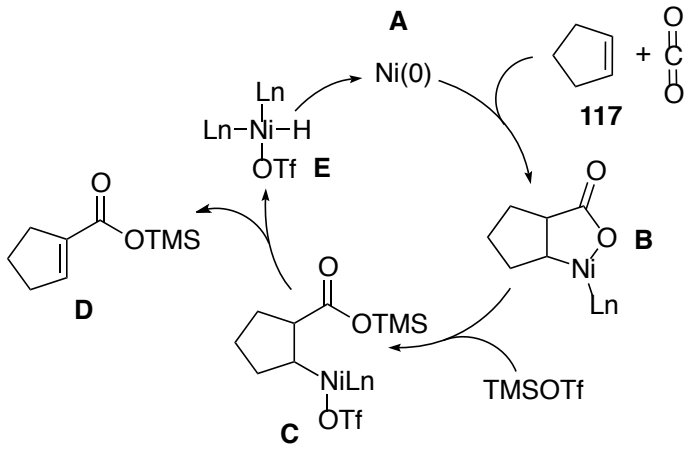
At this point, the carboxylation of electron-deficient styrenes and α,β-unsaturated systems has been investigated. Our laboratory sought reactivity with unactivated alkenes, and a re-evaluation of Hoberg's investigations led us to consider the reactivity of metallacycles with Lewis acids. Hoberg had reported that metallacycles react with Lewis acids to provide ene-type products **119** (eq. 18).[43]



(18)

This proposed reaction is far from ideal since it requires stoichiometric nickel(II) and ligand and excessive amounts of alkene. However, the reactivity of these metallacycles with Lewis acid could provide insights for a novel pathway for catalytic carboxylation. The proposed catalytic cycle of this transformation is shown below (Scheme 20).

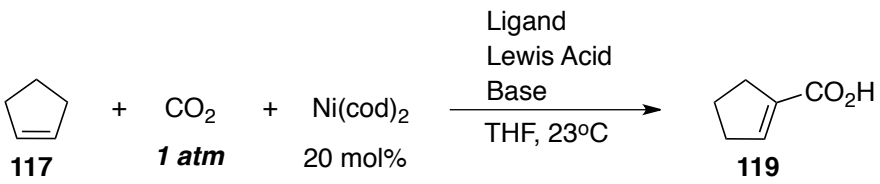
Scheme 20.



Hoberg's early precedent supports rapid oxidative cyclization to **B**. The resulting metallacycle should open upon exposure to Lewis acid (**C**). The key to our strategy is the β-hydride elimination, promoted by base (**D**). Turnover of the nickel(0) active catalyst can occur following reductive elimination of **E**. An ideal reagent for this transformation is TMSOTf, which is capable of not only facilitating metallacycle opening, but also promoting the β-hydride elimination.

Initial studies began with cyclopentene and different Lewis acid/base additives (Table 9). Particular attention was paid to $Be(acac)_2$ as it was a common Lewis acid that Hoberg employed in his studies (entries 1-7).

Table 9.



117 119

Entry	Ligand	Lewis Acid	Base	Yield[a]
1	PCy_3	$Be(acac)_2$	None	SM + Cb
2	PCy_3	$Be(acac)_2$	Cs_2CHO_3	NR
3	PCy_3	$Be(acac)_2$	DTBPy	SM + Cb
4	PCy_3	$Be(acac)_2$	KHMDS	NR
5	Pyphos	$Be(acac)_2$	Cs_2CHO_3	NR
6	DBHU	$Be(acac)_2$	None	NR
7	Bipy	$Be(acac)_2$	Cs_2CHO_3	NR
8	Pyphos	TMSOTfc	None	Decomp.
9	Pyphos	TMSCl	None	NR
10	Pyphos	$BF_3.OEt_3$	None	NR

aStandard conditions: 40 mol% Ligand, 1 equiv. Lewis Acid, 1 equiv. Base
bCarboxylation product observed derived from acid quench of the metalacycle
cDioxane was used as a solvent to avoid THF polymerization

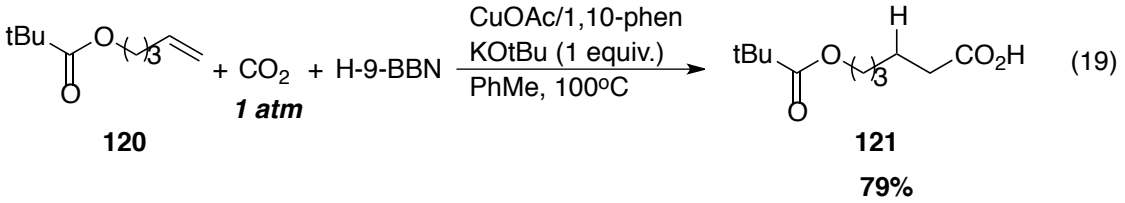
Although this proposed chemistry appeared promising, no reactivity was observed. Efforts with TMSOTf resulted in polymerization or decomposition of starting material. Our experiments indicated metallacycle formation did not occur in the presence of Lewis acids. Additionally, if Lewis acid was added in a second operation, the reaction failed to proceed to the desired product **119**. This set back is a significant problem for the envisioned reaction pathway, as Lewis acid is essential for opening the metallacycle and for allowing for catalyst turnover. As a result, this avenue of experimentation was abandoned.

1.8 Summary and Outlook

Our method for the hydrocarboxylation of electron-deficient styrenes represents an important advancement in the field of carbon dioxide fixation which had important ramifications for future studies in the area. Specifically, our

method remains the only reliable synthetic route towards branched carboxylic acids. It is applicable for even unactivated systems, such as styrene. Additionally, this reactivity is tolerant of a variety of electron deficient *ortho-, meta-,* and *para*-styrene analogues containing reactive functionalities. Unlike most of the reactions in the area, our chemistry is catalyzed by the inexpensive, bench-stable $Ni(acac)_2$ precatalyst and the readily available additive, Cs_2CO_3. The success of Cs_2CO_3 and other inorganic bases in our reaction had important reactivity ramifications for other work in the area. Additionally, the efficiency of the catalytic cycle and the uptake of CO_2 under one atmosphere at room temperature is an attractive feature of this work.

After our work in this area was published, further advances on the reductive carboxylation of alkenes were reported in the laboratories of Ohmiya and Sawamura. Their report reveals a copper-catalyzed reductive carboxylation of terminal alkenes mediated by alkylboranes (eq. 19).[44]

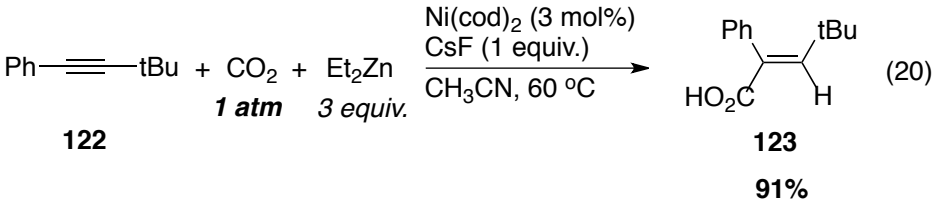


120 **121** **79%** (19)

The work of Ohmiya and Sawamura represents an important extension in methodology for the fixation of CO_2 with π-systems, which allows for the use of alkyl alkenes as substrates. Their chemistry most likely proceeds via an alternate mechanism to our own, as it provides the linear regioisomer (**121**).

Most recently, Ma and coworkers developed a reductive carboxylation reaction compatible with internal alkynes.[45] This chemistry is an important

extension of our work, which allows for the use of electron-rich internal alkynes to provide unsaturated carboxylic acids in moderate to excellent yields and excellent regioselectivities (eq. 20).



122 **123** **91%** (20)

Our discovery of inorganic additives had important ramifications for this work, where large differences in reactivity were observed with different inorganic additives. In this system, excellent reactivity was observed with LiCl, KF, and CsF. The authors invoke a very similar mechanism to our own proposed hydrozincation/carboxylation mechanism. However, the role of the additive in this chemistry is not as a ligand; rather, CsF is proposed to increase the rate of hydrozincation of the alkyne and activate CO_2 by forming FCO_2^-.

Although current methods in the area of carbon dioxide fixation with π-systems have greatly evolved since Hoberg's pioneering work on metallacycles, further studies in this area are warranted to advance our understanding of this chemistry. Specifically, further mechanistic investigations on the origin of the favorability of the branched regioisomer obtained in our work would clarify this pathway. Additionally, studies to probe the role of inorganic additives in recent approaches could have important ramifications for gaining substrate generality and mechanistic understanding.

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CHAPTER 2

CHEMICAL FIXATION AND PROGRAMMED RELEASE OF CO_2 FOR SEQUESTRATION

IN COLLABORATION WITH BRIAN COCHRAN

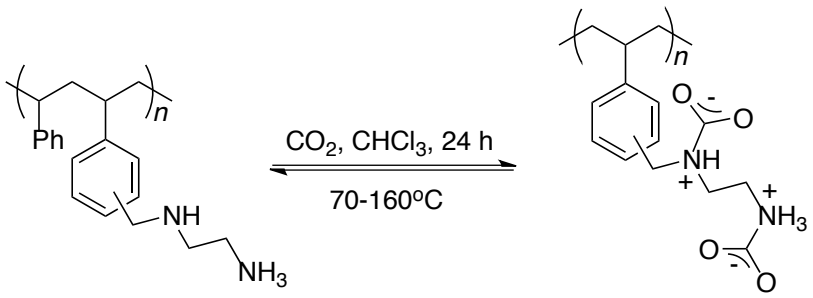
2.1 Introduction

Carbon dioxide is a ubiquitous small molecule, billions of tons of which are absorbed and emitted naturally each year. Since the beginning of the industrial period, the atmospheric concentration of CO_2 has increased globally by 36%.[1] Between 1990 and 2006, atmospheric concentrations have been rising at a rate of 1.1% annually. Today, more than 94% of CO_2 emissions in the United States result from the burning of fossil fuels. In 2005, twenty-eight billion metric tons of CO_2 were added to the atmosphere.[1] Thus, carbon dioxide is an abundant resource, which is capable of functioning as a reactant for biological systems as well as a synthon for the construction of complex molecules.[2]

Rising concentrations of atmospheric carbon dioxide and concerns linked to the enhanced Greenhouse Effect[3] have provided a significant incentive for the development of methods to activate and fix CO_2. Although a variety of synthetic methods have been developed in recent years, these approaches are not practical for large scale carbon dioxide fixation.[4] In contrast, a macromolecule, such as organic polymers, based on developed carbon dioxide fixation

methodology, could provide an inexpensive and highly efficient solution to carbon dioxide storage which would allow for planned release and recycling of the polymer. Such a system could transport carbon dioxide in a safe and thermally stable package for later use in the production of environmentally friendly fuel precursors[5] or for permanent storage.

The idea of macromolecules for carbon dioxide storage and planned release is not a new one. In general, these approaches take advantage of the basicity of amines and their demonstrated reactivity with carbon dioxide.[6] An early example, reported by the laboratory of Beckman and coworkers, reports reversible CO_2 trapping and release of styrene based amine copolymers.[7] Ethylenediamine (EDA)-functionalized polymers provide the greatest efficiency, demonstrating 13% bound CO_2 by weight when the polymer is in $CHCl_3$ (eq. 1).[8] Desorption of this material occurs as low as 70 ^oC. This system is reactive enough to sequester carbon dioxide directly from the air, albeit sacrificing efficiency.



(1)

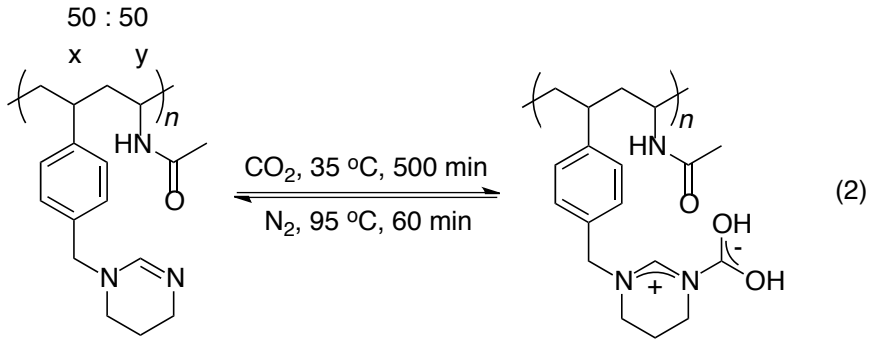
1 **2**

13% CO_2 fixation by weight

An additional example developed by Tsuda and coworkers was also based on the reactivity of carbon dioxide with amines. In this process, amino-

functionalized silica gels were suspended in polar solvents, such as DMF and H_2O, to provide up to 1.1 mmol CO_2/g gel absorption of CO_2 at 30 °C.[9] The uptake and release of CO_2 was efficiently monitored by GC. The drawback of the described method is the preparation of properly functionalized silica gels.[10]

The most recent developments in this area are based on the reactivity of amidines with carbon dioxide.[11] The synthesis of appropriately functionalized polymers proves cumbersome.[12] Additionally, copolymers of the styrene derived amidine functionality and *N*-vinylacetamide were required to maintain catalyst elasticity, which is required for CO_2 permeability. Functionalized amidine copolymers are capable of fixating carbon dioxide with up to 34% efficiency and subsequent release at 100 °C provides reusable polymer (eq. 2).[13] Furthermore, these polymers can fixate CO_2 as a thin-film or solution in DMF.



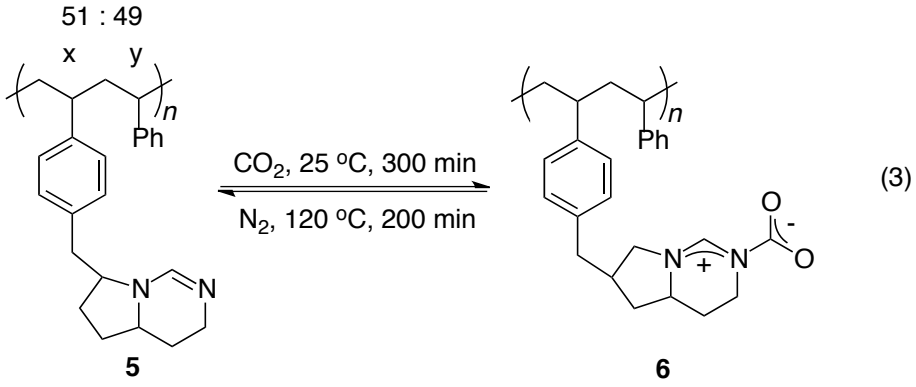
(2)

3 **4**

34% CO_2 fixation by weight

An alternative approach, avoiding some of the difficulty of amidine copolymer polymerization, was devised using DBU and DBN functionalized polymers. These polymers still require copolymer to maintain elasticity, and display more sluggish reactivity (eq. 3).[14] The authors suggest DBN

functionalized polymers provide the added benefit of increased CO_2 retention; unfortunately, this comes at the cost of additional energy required to release carbon dioxide and recycle the polymer.



(3)

17% CO_2 fixation by weight

2.2 Development of carbon dioxide fixation and planned release.

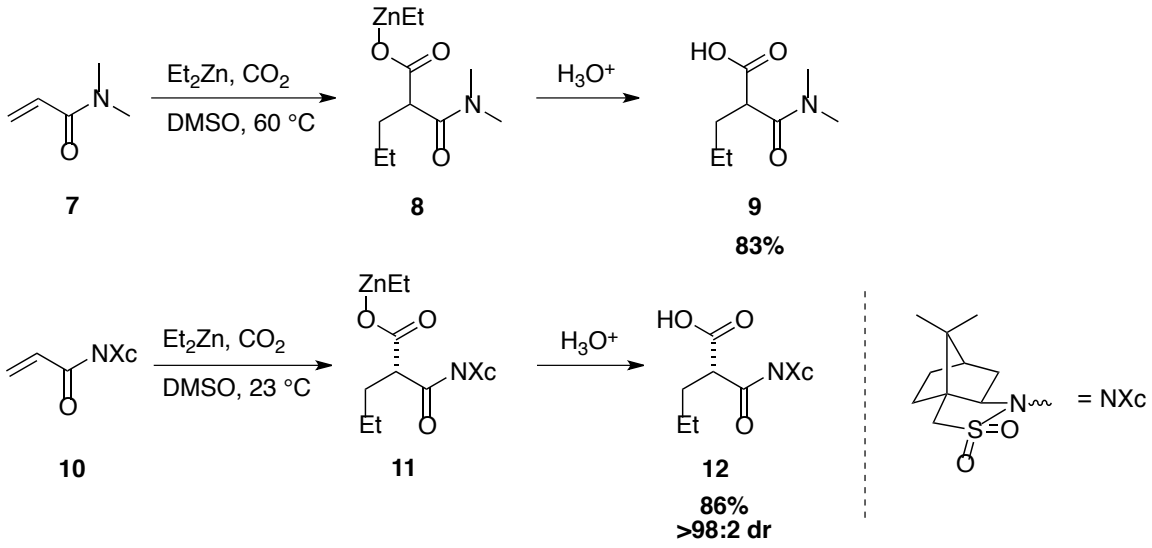
The Rovis laboratory sought to approach this problem with a more synthetic perspective. Specifically, we sought to avoid polymers with cumbersome, inefficient, and costly syntheses. Additionally, we recognized the importance of developing a reaction system sufficient for industrial scale and more efficient then previously developed strategies. Restated, the goals of this project were:

1. To develop a reversible storage/release system allowing the safe and efficient transfer of CO_2 from areas where it is generated to areas where it may be stored or further utilized.
2. Allow for sufficient scale up to establish economic viability.

The basis of our envisioned reactivity was the observed activity of α,β-unsaturated carbonyl compounds with zinc reagents and carbon dioxide.[15] We

have found that acrylates undergo thermal carboxylation reactions when treated with alkylzinc reagents under an atmosphere of CO_2 (Scheme 1). The reaction occurs across a range of temperatures and may be rendered diastereoselective through the use of an appropriate chiral auxiliary. Importantly, the reaction affords a zinc carboxylate *in situ* which forms the carboxylic acid upon acidic aqueous workup.

Scheme 1.

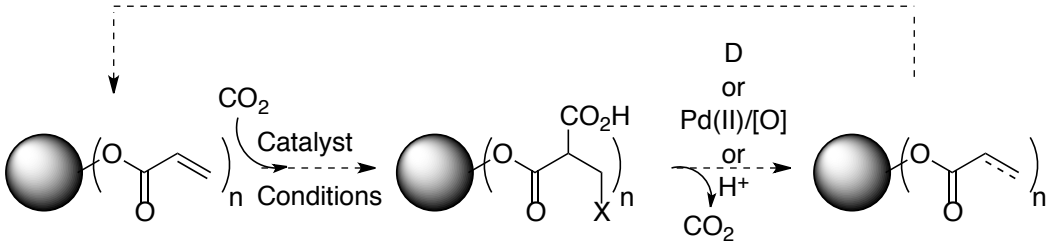


The mechanism of the transformation described above involves the conjugate addition of a nucleophile and generation of a metal-enolate *in situ*. The enolate thus generated traps CO_2 to form the carboxylated product. It should be possible to use any of a range of nucleophiles to induce this transformation.

Although this method provides a reasonable synthetic approach towards diastereoselective acid formation, it fails to provide a practical approach towards carbon dioxide fixation on a large scale. In contrast, a polymeric substance with many acrylate functional groups under appropriate conditions may react with CO_2

to form a covalent, irreversible bond. This material would not leak CO_2, would not require special handling and it would be inexpensive to prepare. These features will allow preparation on scale, reaction under conditions that are compatible with the wide diversity of significant CO_2 generators, and transport to locales which will allow CO_2 release. The release will be triggered by thermal, photochemical or chemical means (Scheme 2).

Scheme 2.



13 **14** **15**

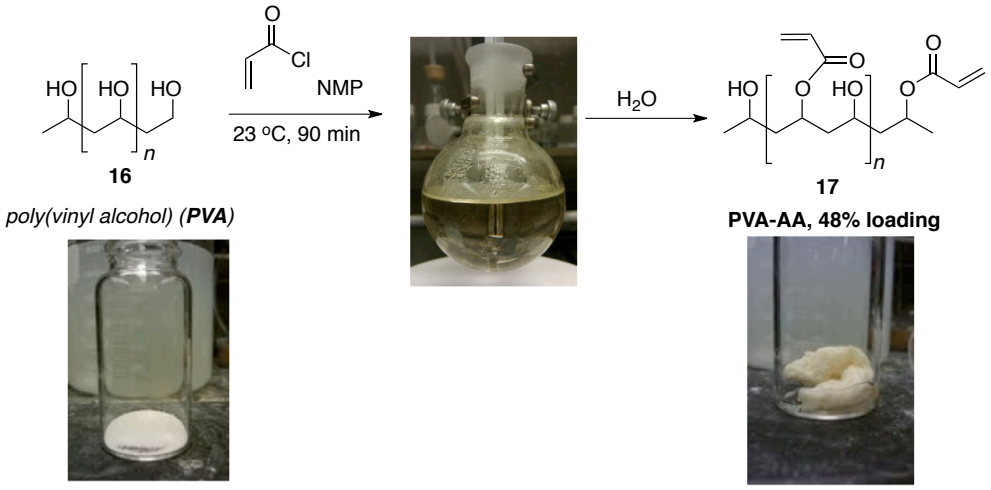
2.3 Polymer Preparation

In order for this strategy to be marketable, the polymeric substrate must be readily available and inexpensive. Ideally, this substrate would be a common byproduct of industrial processes. Unfortunately, no commercial polymer has the right mix of solubility properties, functional group loading, and cost to be used in our planned research. However, there are several commercially available polymers that may be derivatized trivially to provide these features, and a suitable de novo polymer could potentially be assembled in a cost efficient manor.

To successfully develop and test the proposed of CO_2 capture and storage device, the synthesis of an adequate support must be investigated. Ideally, this

support must contain many unsaturated acryloyl units to successfully capture carbon dioxide. The synthesis of acylated poly(vinyl alcohol), PVA, has been previously reported by Wang *et al.*[16,17,18] Treatment of PVA with acryloyl chloride in hot *N*-methyl-2-pyrrolidone yields the target polymer PVA-AA as a fiber-like material upon precipitation with cold water (Scheme 3). This reaction was successfully employed on a multi-gram scale, providing between 36 and 48% esterification.

Scheme 3.



Following reaction with excess CO_2, this material has the capacity (assuming 36% loading) to capture 220 mg of carbon dioxide per gram of polymeric material (22% storage capability by weight). Extrapolating these numbers, 175 lbs of this material should fix ~10,000 liters of CO_2 (about 400 moles) per use. In addition, variable lengths of polymer can be made by using different molecular weights of PVA. In this study, units of 9,000-10,000, 13,000-23,000, and 89,000-98,000 monomers were investigated.

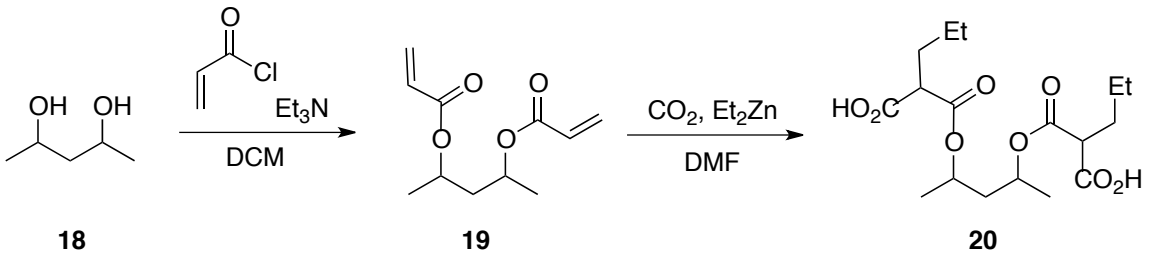
2.4 Polymer Loading and Release

Following its preparation, the PVA-AA polymer can be dried or used slightly wet. Although the use of wet material provided challenges for characterization, it was easier to manipulate and it swelled in polar organic solvents, allowing for greater surface area exposure to carbon dioxide. The best solvents for this purpose included MeOH, DMSO, NMP, and DMF. Although we envisioned different molecular weight polymers having a different solubility profile, we found identical solubility characteristics for all polymers tested. In addition, ionic liquids were initially envisioned to be excellent candidates for solvents in this chemistry due to their low volatility and solubility profile; however, heating the polymer in various ionic liquids decomposed the polymer.

Exposure of the polymer to various Cu(I) and Cu(II) nucleophiles elicited no observable reaction. Only Et_2Zn under an atmosphere of carbon dioxide was visually promising, providing vigorous bubbling and swelling of polymer. Following the reaction, the polymer was completely insoluble in all solvents, making characterization impossible. Exposure to acid as well as base accompanied by aggressive heating of the polymer failed to decarboxylate the polymer using our detection methods.[19] In addition, derivation of the polymer with various reagents failed to produce a reaction demonstrating successful carboxylation.

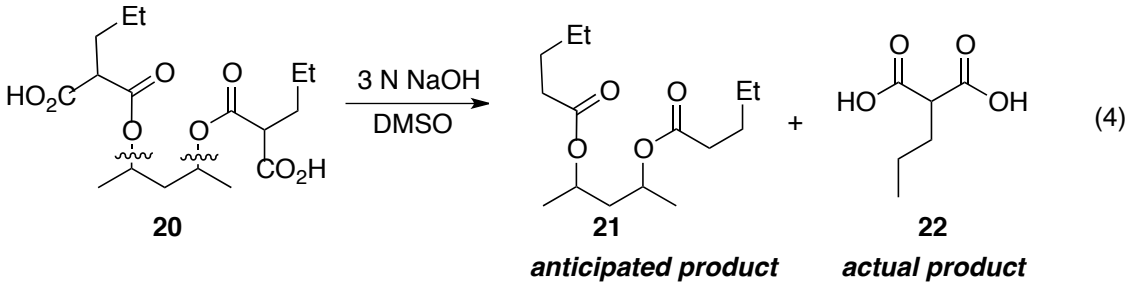
To address the issue of solubility, we made a dimer and subjected it to similar esterification and carboxylation reactions (Scheme 4).

Scheme 4.



18 **19** **20**

The dimer was successfully esterified with acryloyl chloride and characterized. Reaction with Et_2Zn in the presence of excess CO_2 provided the carboxylation product. Unfortunately, the material proved capricious, readily decomposing in some conditions used to promote decarboxylation, such as acid and LiCl. Basic conditions (3 N NaOH/DMSO) provided the product of saponification rather then decarboxylation (eq. 4).



(4)

20 **21** **22**

anticipated product ***actual product***

Although this cleavage demonstrates successful sequestration and release, it is not reversible and currently cannot be applied to larger scale systems.

2.5 Conclusions and Outlook

Currently, the inherent poor solubility of the materials chosen limits the success of our current approach. For this goal to be realized significant alteration in the structure of the polymer is required to increase its solubility and carbon dioxide permeability. In previous literature examples this was achieved by copolymerizing with other materials. This process would require significant

substrate development that might quickly surpass the original goals of this project, which were to develop an inexpensive, efficient substrate. In addition, the requirement of organozinc reagents to promote soft enolization provides an impractical system for industrial scale carbon dioxide fixation. In summary, although the development of a reversible storage system remains feasible, advances in our current equipment and expertise are required before this goal can be realized in our laboratories.

2.6 References

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[3] Environmental Protection Agency: Greenhouse Gas Emissions. (accessed April 25, 2008). http://www.epa.gov/climatechange/emissions/index.html#ggo

[4] In these synthetic examples a maximum of 1 equivalent of carbon dioxide is fixated relative to substrate. Even if the reaction can be scaled up, the benefit from the amount of CO_2 sequestered would be far outweighed by the amount of materials required and waste generated.

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[17] Gung, Y. W.; Kuo, S. M.; Wang, Y. J. *Biomaterials* **1997**, *18*, 367-371

[18] Kuo, S. M.; Chang, S. J.; Wang, Y. J. *J. Appl. Polym. Research* **1999**, *6*, 191.

[19] Detection methods included checking for release of carbon dioxide, monitoring the weight of the polymer by balance, as well as analytical methods such as 1H-NMR and FTIR.

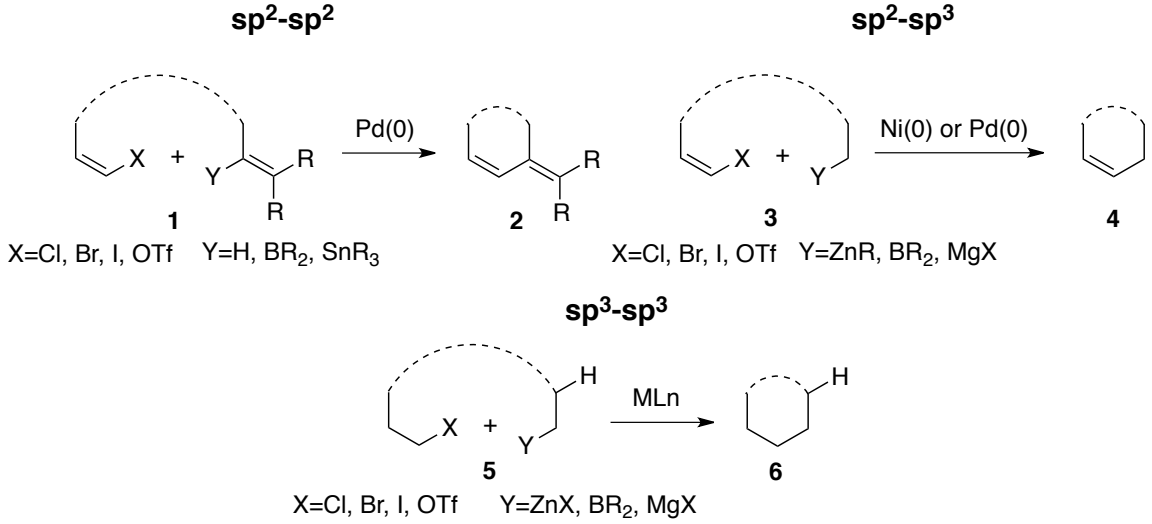
CHAPTER 3

APPLICATION OF RHODIUM-CATALYZED ANHYDRIDE DESYMMETRIZATION TO THE SYNTHESIS OF ABYSSOMICIN C

3.1 Introduction: Anhydride Desymmetrization

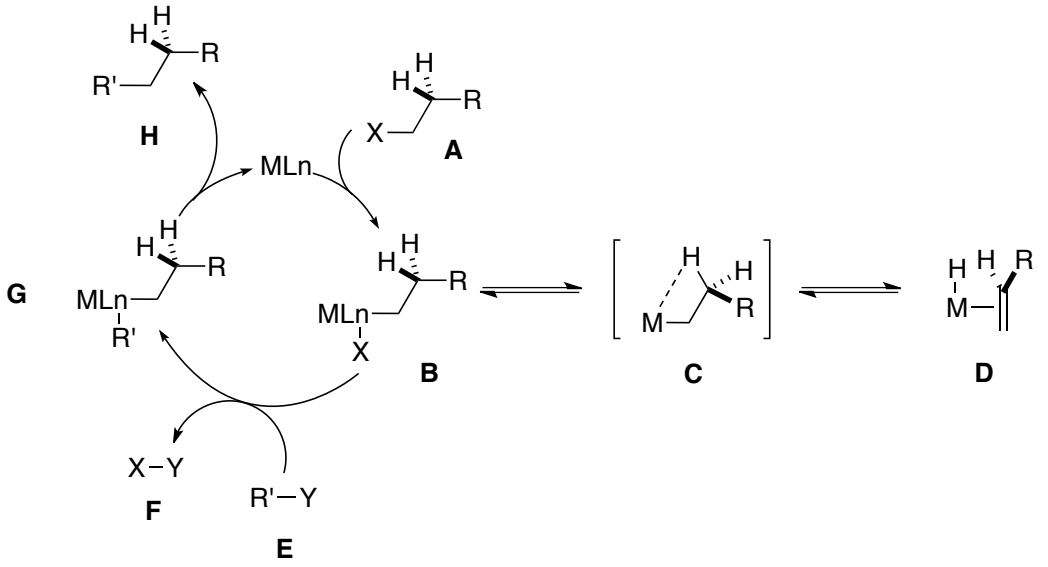
Chemical reactions that form carbon-carbon bonds are among the most important transformations in organic chemistry and are of paramount importance to synthetic chemists.[1] Due to the demand for selective transformations featuring excellent stereocontrol, transition-metal catalyzed cross-coupling reactions have increased in importance.[2] Some of these C-C bond forming reactions use a variety of organometallic reagents, and have become well known in the field. Examples include the Kumada-Corriu coupling using magnesium, the Suzuki-Miyaura coupling using boron, the Stille-Migita coupling using tin, the Negishi coupling using zinc, and the Hiyama coupling using silicon. The Sonogashira (copper), and Mizoroki-Heck (palladium) reactions use terminal alkynes and alkenes as coupling partners.[3] Many of these cross-coupling approaches display excellent reactivity for coupling sp or sp^2 carbon centers with sp^2 or sp^3 centers, but show reduced reactivity with sp^3-sp^3 systems (Scheme 1).[4]

Scheme 1.



Difficulties associated with these couplings are depicted in Scheme 2. Oxidative addition of the metal into a C-X bond (**A** to **B**) is thought to be prohibitively slow for alkyl halides. In addition, β-hydride elimination of **C** to **D** may proceed far more rapidly then the transmetallation event (**E** to **F**).

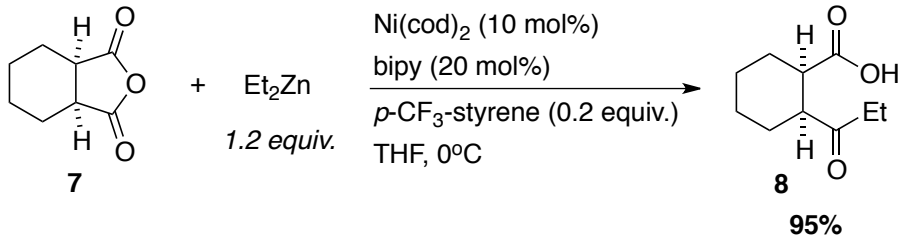
Scheme 2.



Although these difficulties were once thought to be insurmountable, a variety of methods have been developed to challenge these perceptions. Most of these reports provide a means to execute sp^3-sp^3 Kumada, Negishi, and Suzuki

couplings[5,6] by relying on ligands or additives to accelerate the transmetallation step versus the competing undesired β-hydride elimination. For example, Knochel's chemistry uses π-acceptor ligands associated with the nickel catalyst to accelerate the rate of transmetallation.[5]

A different approach to the problem of β-hydride elimination uses substrates less prone to undergo this unwanted reaction. Specifically, anhydrides are suitable reaction partners possessing reactive C-O bonds which favor oxidative addition by a transition metal to provide metalalactones.[7] These acyl intermediates cannot conform to the requisite synclinal conformation for β-hydride elimination and are stable at room temperature.[8] The use of *meso*-anhydrides with chiral centers in the backbone allow for rapid assembly of stereodefined keto acids in one step. Rovis and Bercot have made an important advancement in this area by demonstrating high reactivity in the desymmetrization of *meso*-succinic anhydrides to keto acids (eq 1).

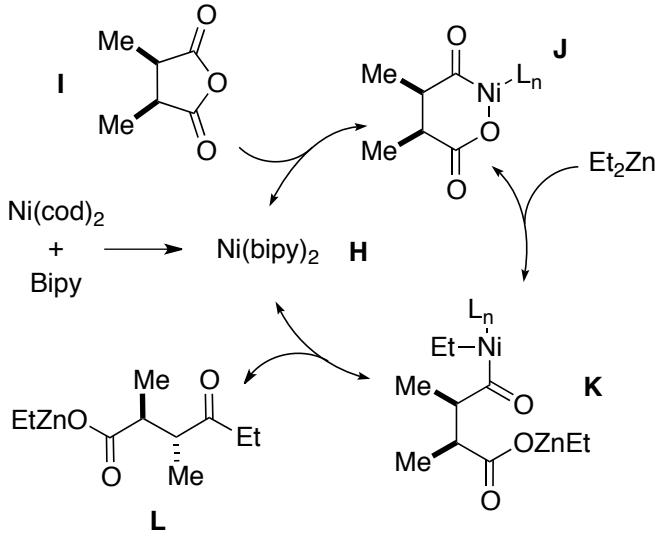


(1)

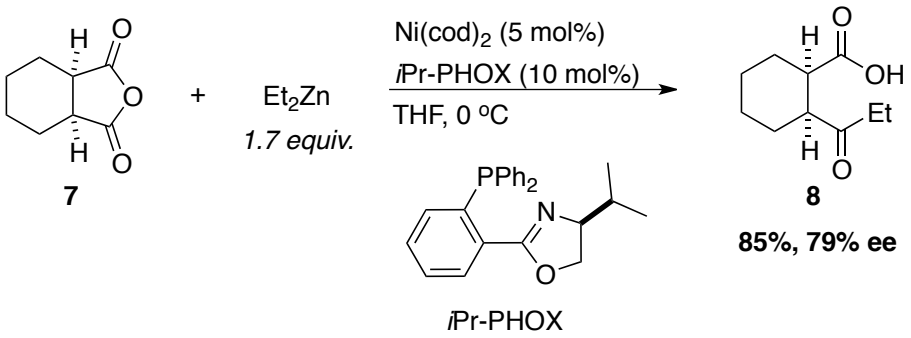
Diorganozinc reagents were essential for the transformation and mediated the transmetallation of metallacycle **J** with concomitant R-group transfer to the nickel center (Scheme 3).[9] Reductive elimination from intermediate **K** results in C-C bond formation and regeneration of the active catalyst. Styrene additives were

found to greatly accelerate the reaction, possibly by increasing the rate of the reductive elimination.[10]

Scheme 3.



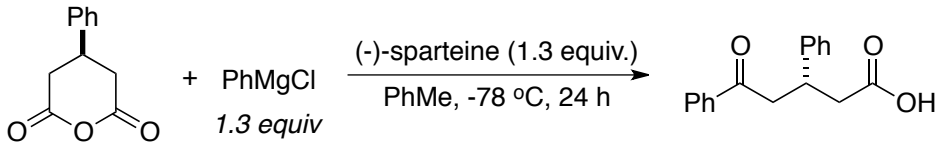
The use of the transition-metal and its associated ligands in this chemistry allows for the introduction of chirality derived from suitable nonracemic ligands. A proof-of-principle reaction of anhydride **7** with Et_2Zn and *i*Pr-PHOX provides the ketone **8** in 79% ee (eq. 2).



(2)

After this initial report, Fu and coworkers described the asymmetric desymmetrization of *meso*-glutaric anhydrides using Grignard reagents. Enantioselectivity is imparted by stoichiometric (-)-sparteine. Although

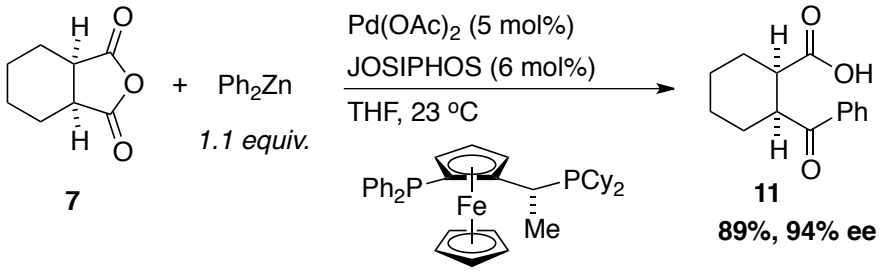
anhydrides with a variety of R-groups in the 4-position are reactive, groups other then phenyl afford modest enantioselectivities (eq 3).[11]



9 **10**

91%, 92% ee (3)

The transition-metal catalyzed approach for the desymmetrization of *meso*-cyclic anhydrides promised greater efficiency with greater substrate compatibility. By changing the original system from nickel(0) to palladium(II), increased reactivity was observed and excellent stereoselectivity was achieved using the JOSIPHOS ligand (eq 4).[12] This reactivity was compatible with a variety of five-membered cyclic anhydrides. Unfortunately, only commercially available organozinc reagents such as Ph_2Zn or Me_2Zn were compatible using these conditions.



7 **11**

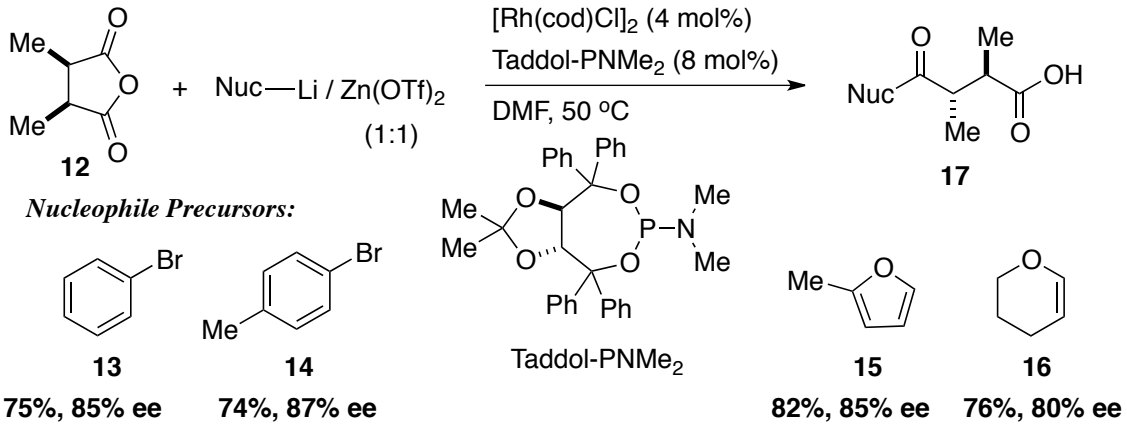
89%, 94% ee (4)

(R,S)-JOSIPHOS

Our ultimate goal was to develop a system with greater substrate tolerance in regards to these nucleophilic and electrophilic partners. Towards this end, Rovis and coworkers in 2006 developed a reaction system utilizing a rhodium(I) catalyst. This catalyst permitted the incorporation of *in situ* generated zinc reagents and *meso*-succinic anhydrides (Scheme 4).[13] Although the highest

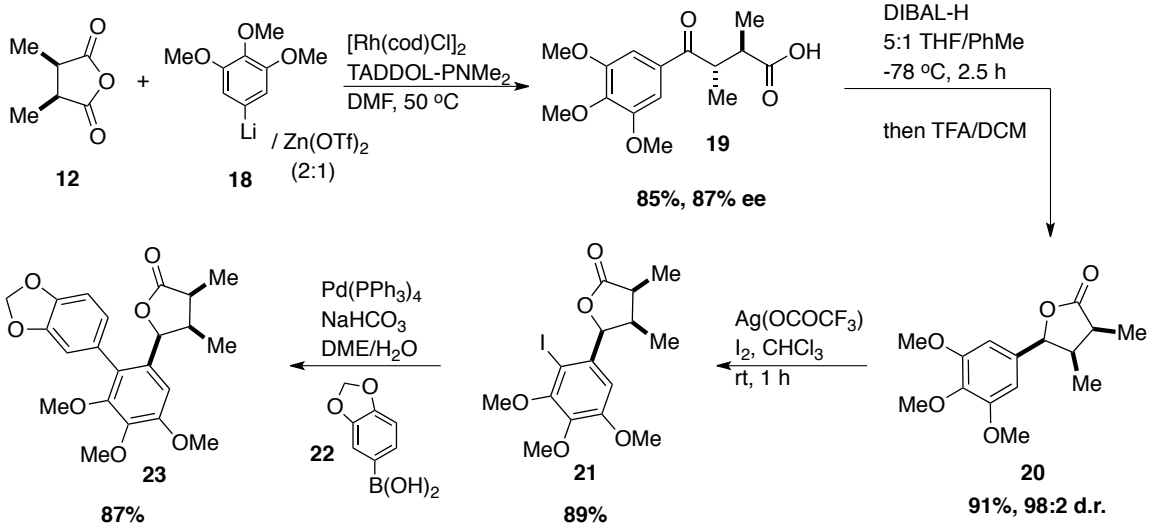
yielding zinc reagents are primarily aryl- and heteroaryl-zinc triflates, the observed reactivity provided for more useful applications to organic synthesis.

Scheme 4.



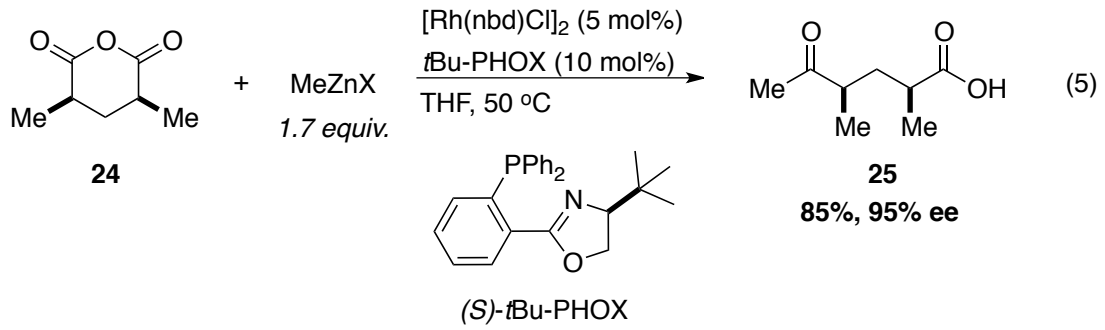
The plant derived eupomatilone family of lignan natural products possess a unique structural framework composed of a substituted γ-lactone ring system.[14] Multiple synthetic approaches to members of this family have appeared in the literature; the majority of these approaches produce racemic material and require greater then ten synthetic steps.[15] The rhodium-catalyzed anhydride desymmetrization process has allowed for an improved synthesis of compounds of this class. As exemplified using Scheme 5, eupomatilones 4, 6, and 7 were constructed using this approach, as demonstrated by the synthesis of the structure assigned for eupomatilone-6.

Scheme 5.



In this example, anhydride desymmetrization provided the stereodefined backbone of **19** in 85% yield and 87% ee. Subsequent steps to reduce the ketone, dehydrate to form the lactone, and halogenate were followed by Suzuki cross-coupling with boronic acid **22**, to give in high yields *epi*-eupomatilone 6 in four total steps and 40% overall yield. This is a substantial improvement over Gurjar's reported ten step synthesis.[16]

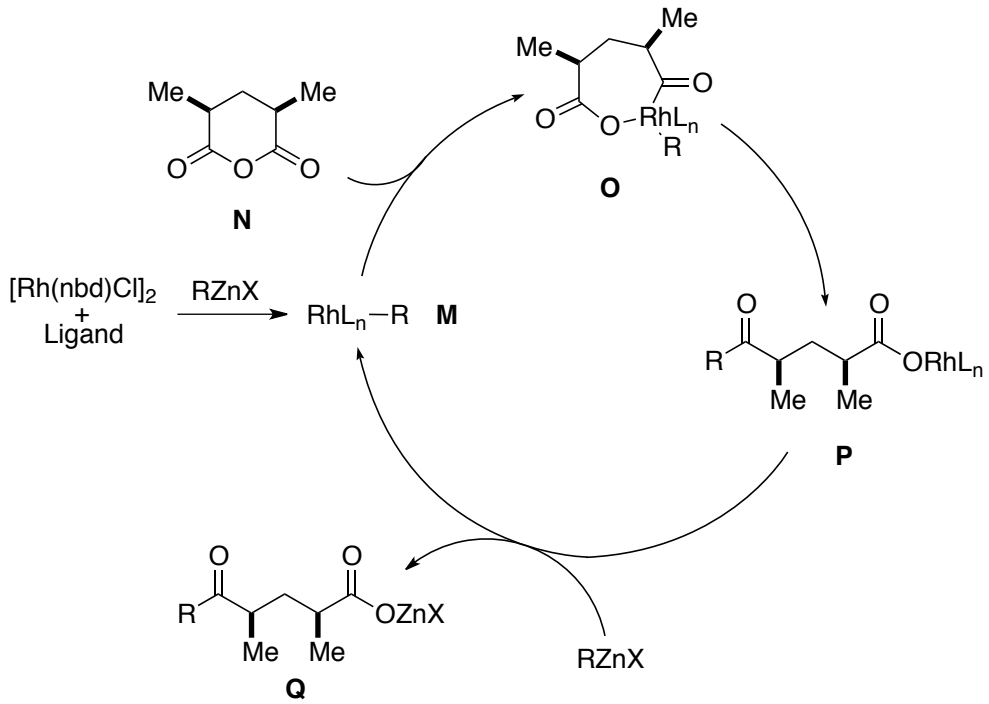
Although glutaric anhydrides were found to be unreactive in the phosphoramidite/DMF reaction conditions, chiral phosphinooxazoline (PHOX) ligands proved effective in THF for a variety of alkyl zinc nucleophiles (eq. 5).[17] Interestingly, the nature of the neutral ligand bound to the rhodium precatalyst also has a pronounced effect on reactivity. The rhodium-cyclooctadiene precatalyst provided just 40% yield and 80% ee as compared to 87% yield and 86% ee with the rhodium-norbornadiene reagent at room temperature.[18]



(5)

The mechanism of this transformation is believed to proceed through an initial transmetallation of the rhodium precatalyst and the organozinc reagent to provide active catalyst **M** (Scheme 6). Oxidative addition into the C-O bond of the anhydride provides metallacycle **O**. Ligand exchange followed by reductive elimination regenerates the active rhodium catalyst and produces zinc carboxylate **Q**.

Scheme 6.

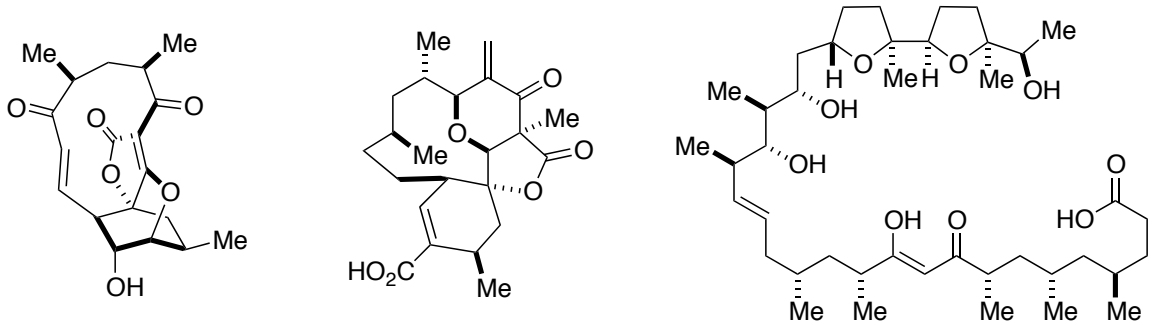


When this reaction was extended to aryl zinc halides or trisubstituted glutaric anhydride frameworks, little reactivity was observed. Despite these limitations, this conversion accomplishes a rapid assembly of *syn*-deoxypolypropionate fragments in a single transformation.

3.2 Application towards deoxypolypropionate natural products

The desymmetrization of *meso*-3,5-dimethylglutaric anhydrides is a powerful strategy for the synthesis of deoxypolypropionate natural products. A variety of important synthetic targets possessing these subunits are shown in Figure 1.

Figure 1.



26
abyssomicin C

27
(+)-okilactomycin

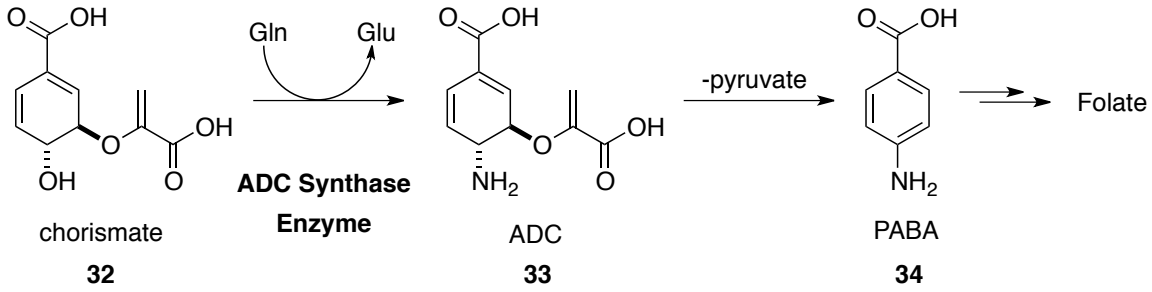
28
ionomycin

The Rovis group was interested in developing synthetic approaches to these targets utilizing anhydride desymmetrization chemistry. If realized, these approaches would not only access complicated targets rapidly, but would showcase the efficiency and application of this methodology in natural product synthesis.

3.3 Introduction to Abyssomicin C

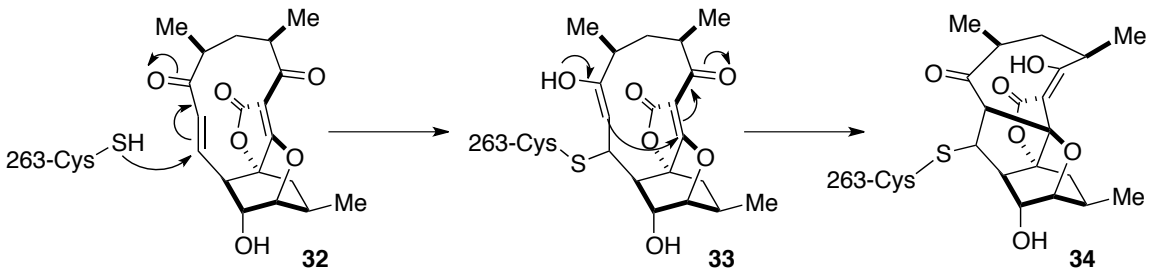
Abyssomicin C (**26**) is a complex natural product isolated from a *Verrucosispora* bacterial broth which was found in a sediment sample in the Sea of Japan in 2004.[19] Importantly, this metabolite was identified to be the first natural product inhibitor of *p*ABA (*para*-aminobenzoate) biosynthesis (Scheme 7).[20] This biosynthetic pathway is a critical pathway for the synthesis of tetrahydrofolate in microorganisms.[21]

Scheme 7.



The conversion of chorismate to ADC is mediated by the ADC synthase enzyme. Abyssomicin C is proposed to interfere with this enzyme by presenting a reactive electrophile for the sidechain of Cys_{263} which is located in the binding pocket of the ADC synthase enzyme (Scheme 8).[22] By alkylation and alterations in the conformation of the binding pocket, the action of the enzyme is prohibited.

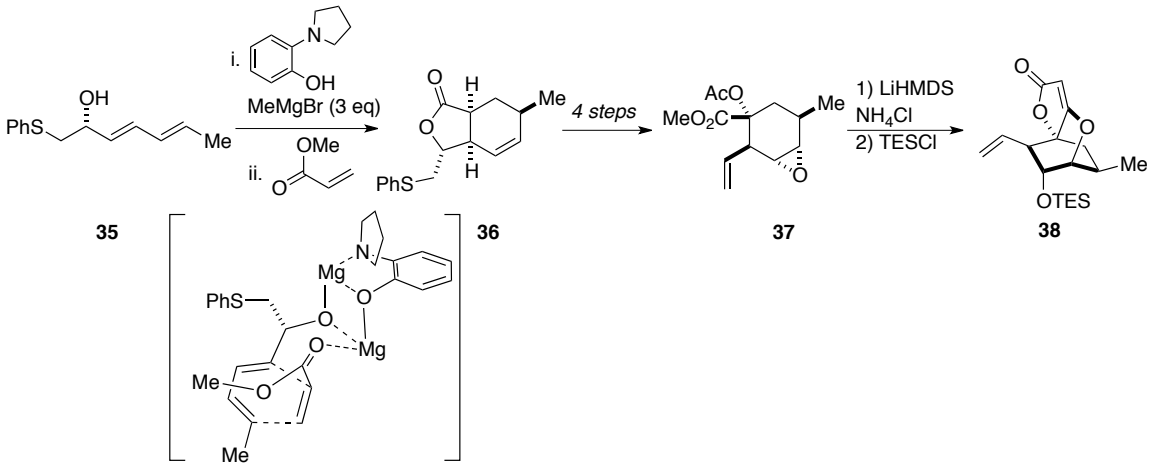
Scheme 8.



In this fashion, abyssomicin C acts as a suicide inhibitor. Unfortunately, in complex media broth, abyssomicin C loses its specificity for the ADC synthase enzyme. In spite of its reactivity profile, abyssomicin C is an interesting target for synthetic chemists because it possesses a unique structure and a variety of novel functionalities. These characteristics include: an eleven-membered macrocycle containing a deoxypolypropionate subunit, an α,β-unsaturated ketone, seven stereogenic centers, and an unusual oxabicyclo[2.2.2]octane core.[23]

Inspired by this interesting architecture, Nicolaou and Harrison explored and completed the synthesis of abyssomicin C in 2006.[24] Their synthesis focused on the initial construction of the oxabicyclic[2.2.2]octane core **38** via a route featuring a templated Diels-Alder reaction as the key step followed by intramolecular trapping of the epoxide **37** (Scheme 9).

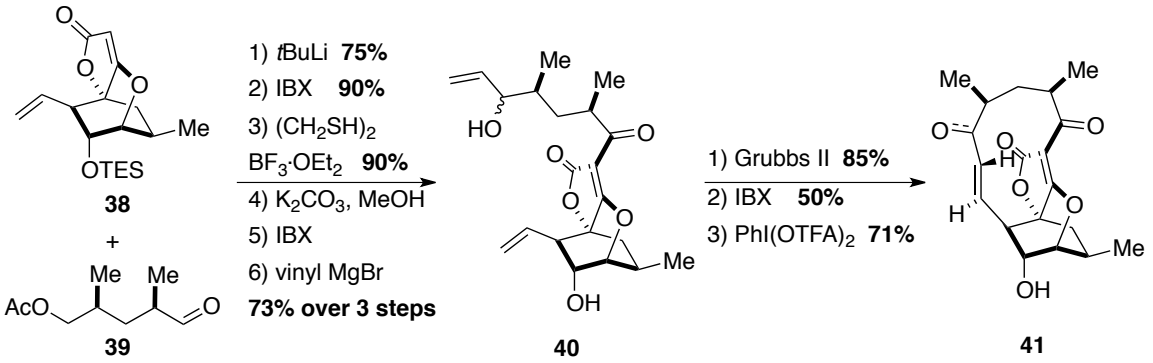
Scheme 9.



The deoxypolypropionate scaffold was installed using the novel α-lithio carbanion derived from **35** for addition into aldehyde **39**, which was derived from enzymatic

desymmetrization of *meso*-3,5-dimethylglutaric anhydride. The eleven-membered macrocycle was closed via ring closing metathesis (RCM) of **40.** Two additional functional group manipulations completed the synthesis (Scheme 10).[25] This synthesis was concluded in 16 linear steps. However, in an unexpected turn of events, the spectroscopic data of the synthetic material was nearly identical but failed to match the natural product.

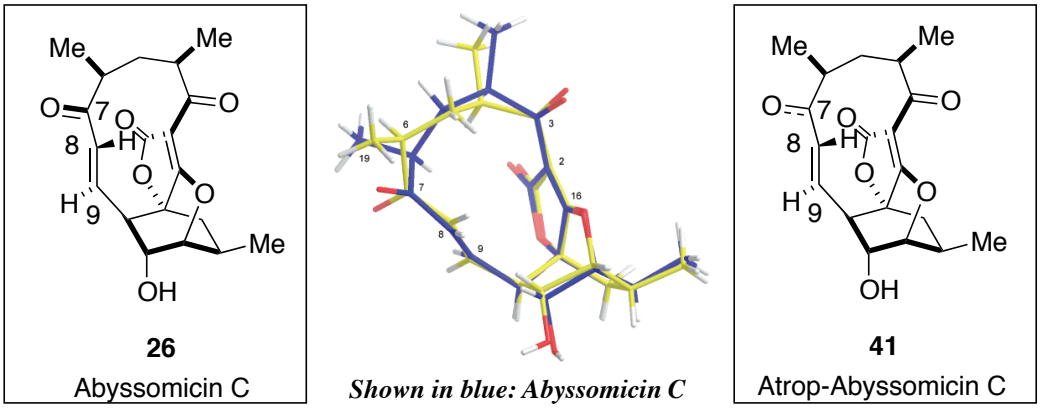
Scheme 10.



The synthetic material was determined by X-ray crystallography to be the atropisomer of abyssomicin C. The difference in the two compounds was the conformational geometry of the carbonyl in the α,β-unsaturated carbonyl system. The bond angle measured from $O=C_7-C_8=C_9$ is 144.8° in abyssomicin C itself as compared to 26.9° in *atrop*-abyssomicin C. Thus, the Michael acceptor of abyssomicin C contains a *transoid* conformation relative to the *cisoid* conformation of *atrop*-abyssomicin C (Figure 2). The *cisoid* conformation of *atrop*-abyssomicin C allows for improved conjugation due to better orbital overlap, resulting in heightened reactivity for conjugate additions. The ramifications of this heightened reactivity are reflected in more potent biological

activity for the synthetic atropisomer against methicillin-resistant *Staphylococcus aureus* (3.5 µg/mL) compared to the natural product (5.2 µg/mL).

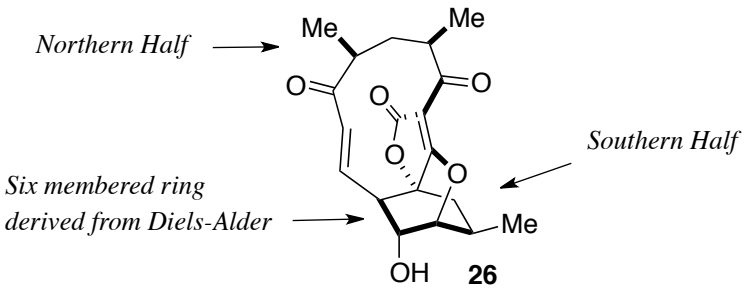
Figure 2.



As a consequence of these studies, *atrop*-abyssomicin C was determined to be the major biological metabolite.[26] Nicolaou and coworkers discovered exposure to mildly acidic conditions promotes the isomerization to abyssomicin C. This isomerization occurs slowly in unstabilized $CDCl_3$.

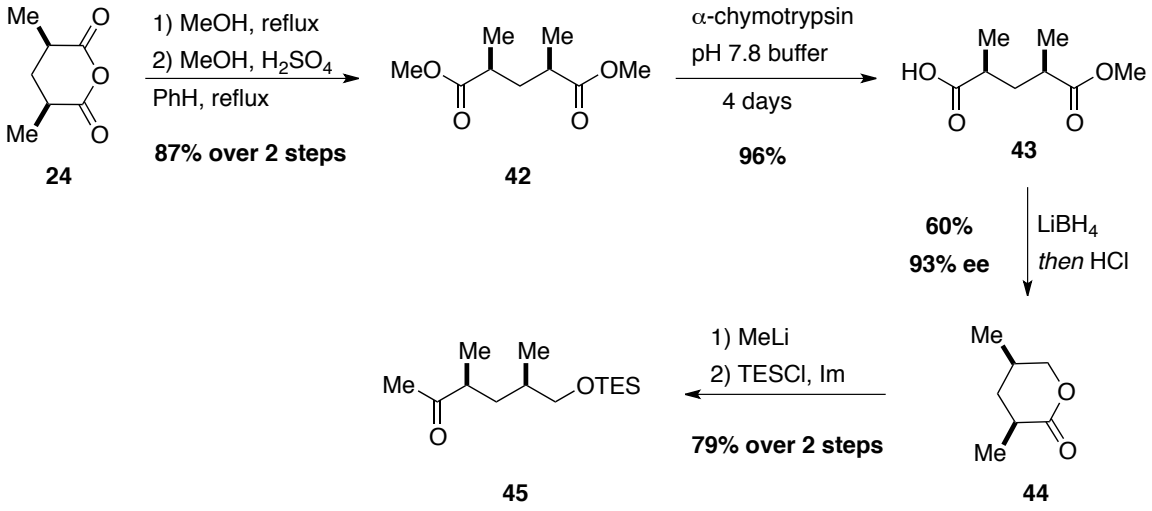
Another important synthesis of abyssomicin C was completed in the laboratories of Erik Sorensen.[27] This synthesis divided the molecule into a northern and a southern half. The northern half contains the macrocycle with the deoxypolypropionate subunit. The southern portion contains the oxabicyclo [2.2.2]octane core. A Diels-Alder reaction constructs the six-membered ring of the bicycle (Figure 3).

Figure 3.



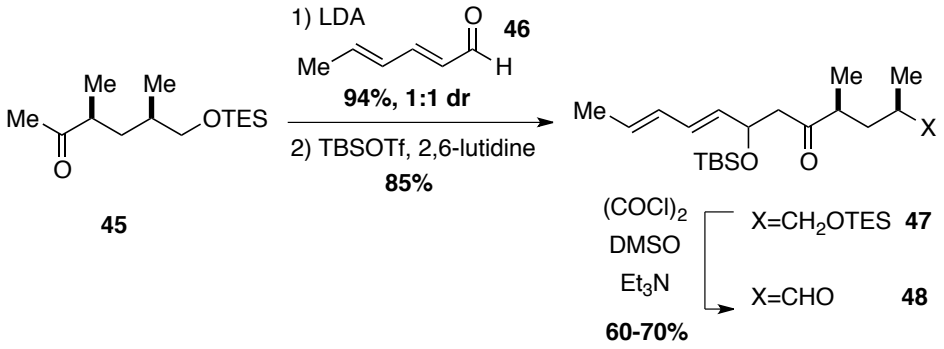
Elaboration of *meso*-3,5-dimethylglutaric anhydride provides the deoxypolypropionate subunit of the northern portion. The anhydride was opened to the diacid and protected as the dimethylester. A four day enzymatic desymmetrization to the mono-carboxylic acid followed by lithium borohydride reduction of the ester and acid-catalyzed cyclization provided the lactone **44** in 93% optical purity (Scheme 11). Nucleophilic attack of MeLi provided a lactol which afforded methyl ketone **45** following protection of the alcohol in six total steps.

Scheme 11.

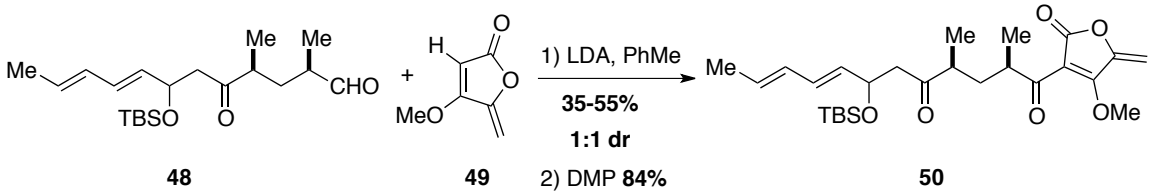


An aldol reaction of the methyl ketone **45** with aldehyde **46** prepared Sorensen's northern fragment **48** (Scheme 12).

Scheme 12.

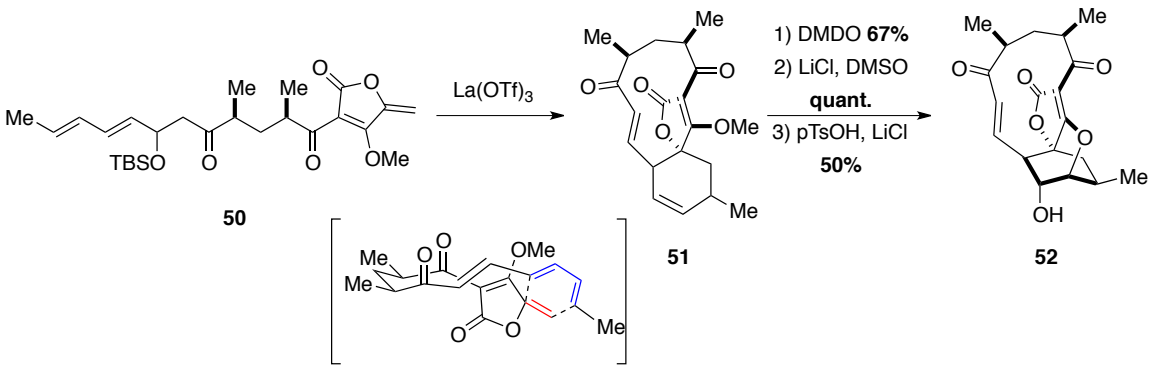


Lithiation of tetranate **49** with LDA prior to addition to aldehyde **46** gave an intermediate alcohol which was subsequently oxidized with DMP to yield ketone **50**. This synthetic intermediate contains most of the molecular architecture of the northern fragment and is the precursor to the Diels-Alder reaction (eq. 6).



A one step β-elimination/Diels-Alder reaction sequence promoted by $La(OTf)_3$ provided the cyclized product **51**. This material could be smoothly converted to the natural product in three steps by epoxidation, deprotection of the methoxy group, and cyclization of the epoxide to form abyssomicin C (Scheme 13).

Scheme 13.



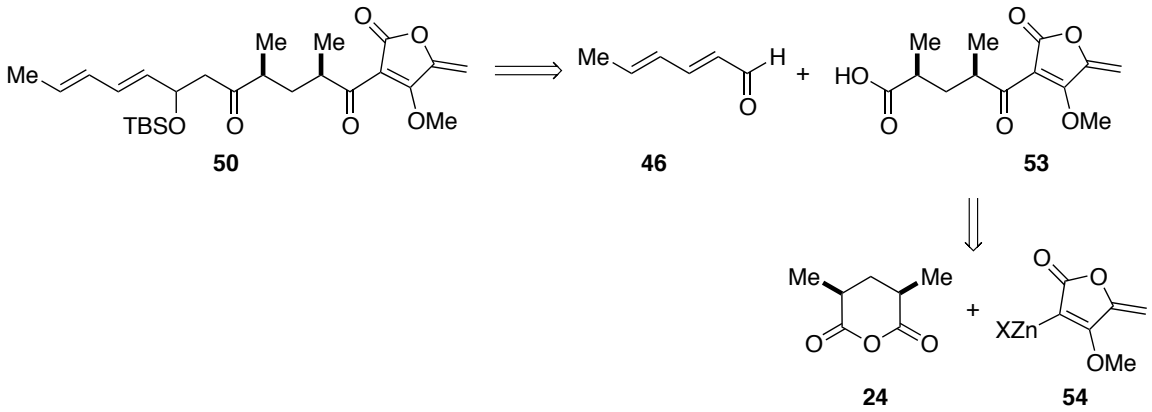
In summation, Sorensen's synthesis features an elegant Diels-Alder reaction and rapid end-game. However, the preparation of the advanced intermediate **50** requires several inefficient transformations over the course of multiple days. Ultimately, a method utilizing the desymmetrization of *meso*-glutaric anhydrides developed in the Rovis group could provide rapid access to Sorensen's Diels-Alder precursor with efficient transformations.

3.4 Synthetic Approaches to Abyssomicin C utilizing enantioselective anhydride desymmeterization.

3.4.1. First Generation

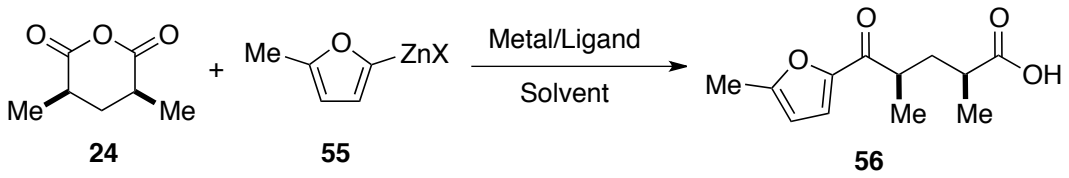
We sought to apply the desymmetrization of *meso*-3,5-dimethylglutaric anhydride with zinc reagents as developed by Cook and Rovis[17] for the synthesis of abyssomicin C. Our retrosynthesis began with the desymmeterization of the *meso*-3,5-dimethylglutaric anhydride with the tetranate zinc moiety **54** (Scheme 14). An aldol reaction using *trans*-2,4-hexadienal **46** would lead to an intermediate in Sorensen's scheme, thus completing a formal synthesis of abyssomicin C in seven total steps.

Scheme 14.



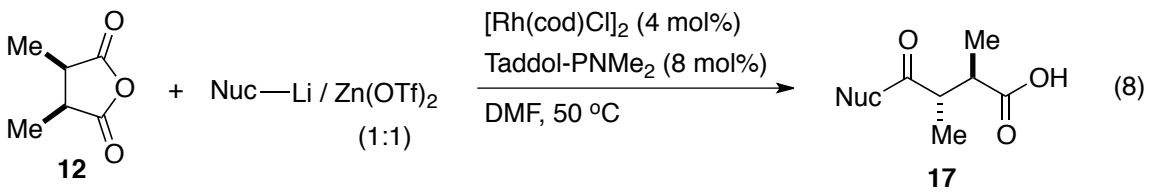
One drawback to this approach is the lack of precedence for heteroaryl zinc nucleophiles with glutaric anhydride. Our current method for the desymmetrization of glutaric anhydride is applicable to alkyl zinc nucleophiles. Thus, we believed that changes to the reaction conditions would allow for the development of a successful reaction protocol to overcome this deficiency.

Since the tetranate species requires four synthetic steps to produce, our initial studies began with commercially available 2-methylfuran. Developing a protocol which would be compatible with the model heteroaryl-system (eq 7) would offer immediate success and provide a direction for future efforts.



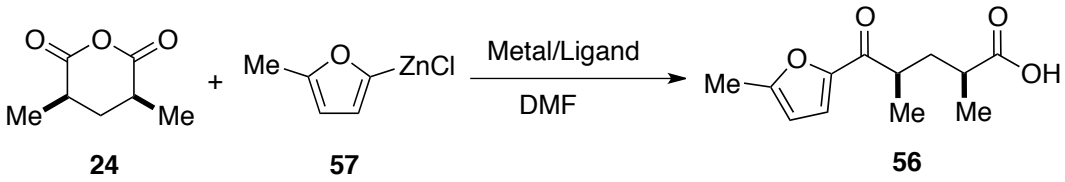
(7)

Towards this end, we first reexamined the conditions developed by Rovis and coworkers for the desymmetrization of *meso*-succinic anhydrides by aryl zinc nucleophiles (eq. 8).[13] In these cases, rhodium(I) with phosphoramidite ligands in DMF was found to provide the most reactive catalyst system.



In these studies, the organozinc reagent was prepared in THF by lithiation of the aryl nucleophile followed by transmetallation with $ZnOTf_2$. The solvent was changed to DMF after removal of the THF under vacuum. Gratifyingly, extending this method to the desymmetrization of *meso*-3,5-dimethylglutaric anhydride (**24**) with the 2-methylfuranyl zinc chloride, provided modest reactivity with promising enantioselectivity as shown in Table 1 (Entry 1). PHOX ligands were also examined in this study, providing similar reactivity with significantly reduced enantioselectivities (Entries 2, 3).

Table 1.

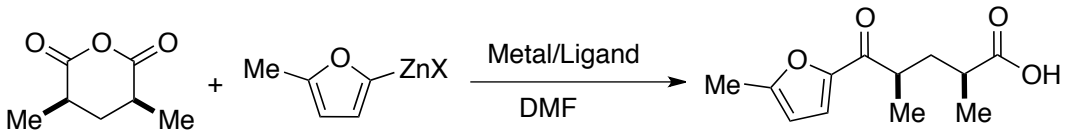


Entry	Metal/Ligand	Yield[a]
1	$[Rh(COD)Cl]_2$/TADDOL-$PNMe_2$	30%, 83% ee
2	$[Rh(COD)Cl]_2$/iPrPHOX	29%, 39% ee
3	$Ni(COD)_2$/IndanePHOX	N.D., 48% ee

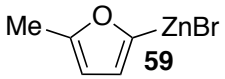
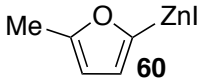
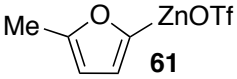
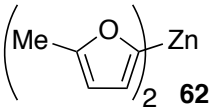
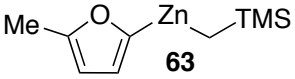
[a]Standard conditions: 10 mol% Metal, 20 mol% ligand, 1.6 equiv RZnX, 0.06 M DMF

Previous research in our laboratory had indicated an enhancement in reactivity could be obtained by changing the nontransferable group of the zinc nucleophile. Thus we sought to vary the halide moiety. Indeed, greater reactivity was observed when the halide was replaced by bromide (RZnBr), however a loss of reactivity was observed with non-halide ions (Table 2).

Table 2.



24 **58** **56**

Entry	Nucleophile	Metal/Ligand	Yield[a]
1	 **59**	$[Rh(cod)Cl]_2$/TADDOL-$PNMe_2$	70%, 74% ee
2		$[Rh(cod)Cl]_2$/iPrPHOX	63%, 80% ee
3	 **60**	$[Rh(cod)Cl]_2$/TADDOL-$PNMe_2$	24%, 83% ee
4	 **61**	$[Rh(cod)Cl]_2$/*t*BuPHOX	NR
5	 **62**	$[Rh(cod)Cl]_2$/TADDOL-$PNMe_2$	NR
6	 **63**	$[Rh(cod)Cl]_2$/TADDOL-$PNMe_2$	7%, 37% ee

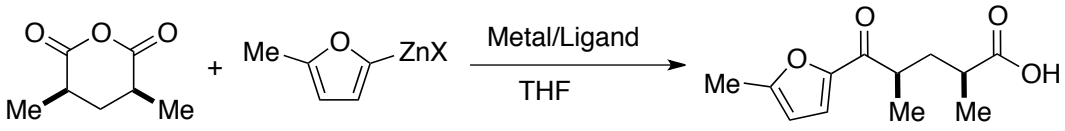
[a]Standard conditions: 10 mol% Metal, 20 mol% ligand, 1.6 equiv RZnX, 0.06 M DMF

The reactivity with RZnBr (Entry 1) provided the best results at 70% yield; however, higher enantioselectivities were obtained with RZnI (Entry 3). During the course of reaction optimization, these results proved challenging to reproduce. We believe that discrepancies originate with the quality of the RZnX reagents; thus, we sought to address potential pitfalls in their preparation. As zinc halides are notoriously hydroscopic, careful drying of the ZnX_2 reagents prior to transmetallation with lithiated 2-methylfuran was attempted. This precaution also failed to provide reproducible yields. Additionally, the solvent change from THF to DMF was examined. This process is problematic as it introduces the possibility of contamination or unintended removal or decomposition of the zinc reagent. To address this, DMF was added prior to removal of the THF under vacuum to avoid some of the concerns. This troubleshooting failed to provide

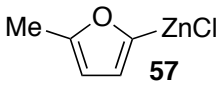
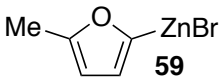
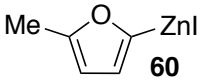
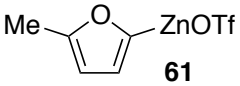
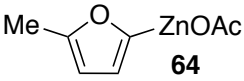
reproducible yields. Thus, we sought a reaction system where solvent changes could be avoided.

Initially we explored the reactivity in THF in some detail. To our gratification, success was found with the use of the PHOX family of ligands previously employed by our studies (Table 3). These ligands were synthesized following the reports of Stoltz and coworkers.[28]

Table 3.



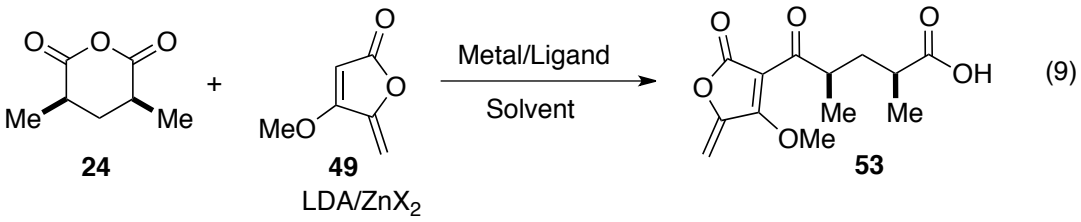
24 **58** **56**

Entry	Nucleophile	Metal/Ligand	Yield[a]
1	 **57**	$[Rh(cod)Cl]_2$/*i*PrPHOX	29%, 39% ee
2		$[Rh(cod)Cl]_2$/TADDOL-$PNMe_2$	20%, 65% ee
3	 **59**	$[Rh(cod)Cl]_2$/*i*PrPHOX	33%, 39% ee
4		$[Rh(cod)Cl]_2$/*t*BuPHOX	59%, 46% ee
5	 **60**	$[Rh(cod)Cl]_2$/*i*PrPHOX	46%, 68% ee
6		$[Rh(cod)Cl]_2$/(+/-)PhPHOX	78%, NA
7	 **61**	$[Rh(cod)Cl]_2$/*i*PrPHOX	NR
8	 **64**	$Ni(cod)_2$/*i*PrPHOX	NR
9		$[Rh(cod)Cl]_2$/*i*PrPHOX	<5%

[a]Standard conditions: 10 mol% Metal, 20 mol% ligand, 1.6 equiv RZnX, 0.06 M THF

In general, zinc bromides and iodides provided increasing yields and enantioselectivities (Table 3, Entry 3-6). As observed in our previous reactions using DMF, a loss of reactivity was observed with zinc triflates and acetates (Entries 7, 8, 9). The best outcome of enantioselectivity and yield was obtained with RZnI and iPrPHOX (Entry 5).

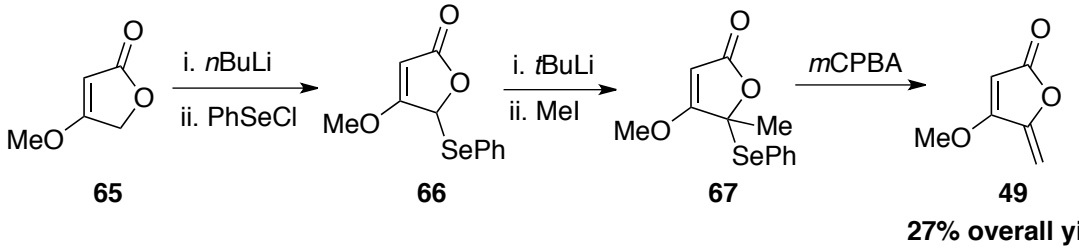
Although initial conditions demonstrated promising reactivity with the 2-methylfuranyl zinc reagents, this model system is distinctly less complex compared to the actual system proposed for our synthetic route toward abyssomicin C (eq. 9).



(9)

In order to examine the potential reactivity of this species, the tetranate **49** was prepared in four known reaction steps using a selenoxide elimination to provide the exocyclic unsaturation beginning with lactone **65** (Scheme 15).[29] Although the yield for this series of transformations is fairly low (27% overall yield), the reactions could be carried out on multi-gram scale without difficulties.

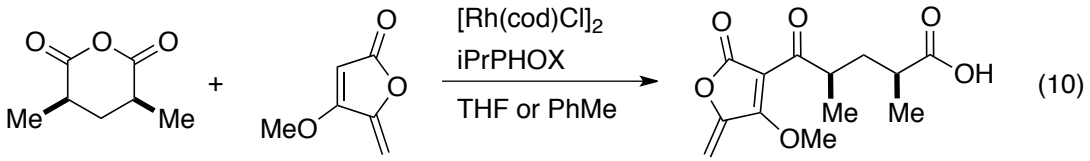
Scheme 15.



27% overall yield

To prepare the desired zinc reagent from the tetranate moiety **49**, α-lithiation was followed by transmetallation with anhydrous ZnX_2. When prepared in THF, an immediate color change to deep red/purple was observed. As observed by quenching experiments and ^{1}H-NMR data, this color change was consistent with decomposition of the tetranate moiety. Specifically, the disappearance of the exocyclic olefin hydrogen signals was observed in the ^{1}H-NMR data of recovered

material. This did not occur when deprotonation and transmetallation of the tetranate was conducted in toluene. However no yield of the desired product **53** was obtained when this procedure was applied to the desymmetrization of *meso*-3,5-dimethylglutaric anhydride (eq. 10). In addition, it appeared that the zinc reagent had decomposed during the reaction as indicated by examination of ^{1}H-NMR spectra of crude product.



24 **49** **53**

LDA/ZnX_2 in PhMe

0%, Decomposition

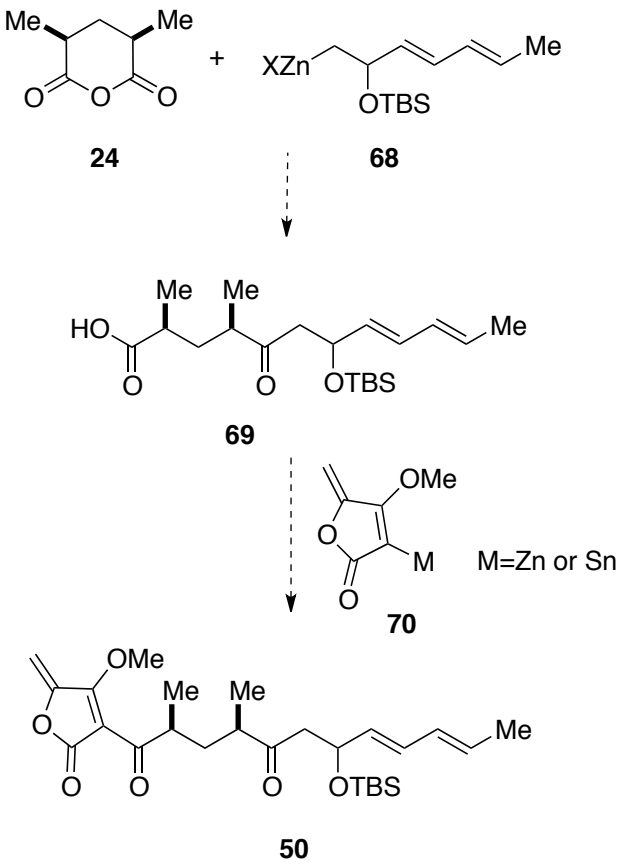
(10)

The observed decomposition was believed to result from the use of the reactive zinc reagent in the presence of the rhodium catalyst leading to the recovery of unreacted anhydride **24**.

3.4.2. Second Generation

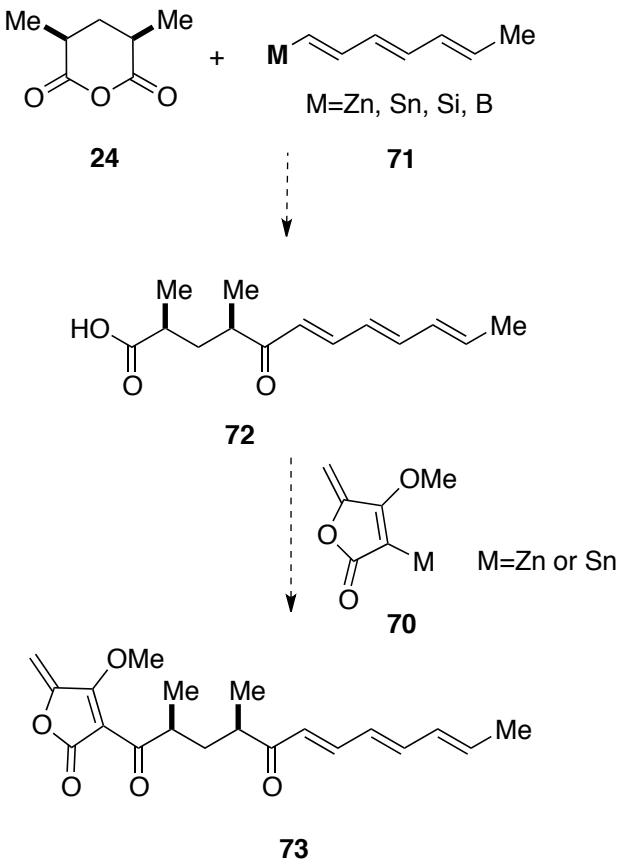
The use of a organometallic tetranate species as a nucleophile was abandoned in favor of a more promising synthetic route. Originally, we envisioned the synthesis of the same Diels-Alder precursor by installation of the triene prior to the attachment of the tetranate moiety (Scheme 16). In this alternative route, organometallic species **68** would be the nucleophile for the desymmetrization of *meso*-3,5-dimethylglutaric anhydride. This species could be unstable and favor immediate elimination.

Scheme 16.



Alternatively, the triene organometallic reagent **71** (Scheme 17) could be used as a coupling partner in the key anhydride desymmetrization step to provide triene intermediate **73.** Although alkenylzinc reagents such as **70** have not been investigated, their reactivity is anticipated to be analogous to that of known vinylzinc reagents. These species are not appropriate for our anhydride desymmetrization chemistry as they were too reactive, adding uncatalyzed to the anhydride without selectivity.[30]

Scheme 17.



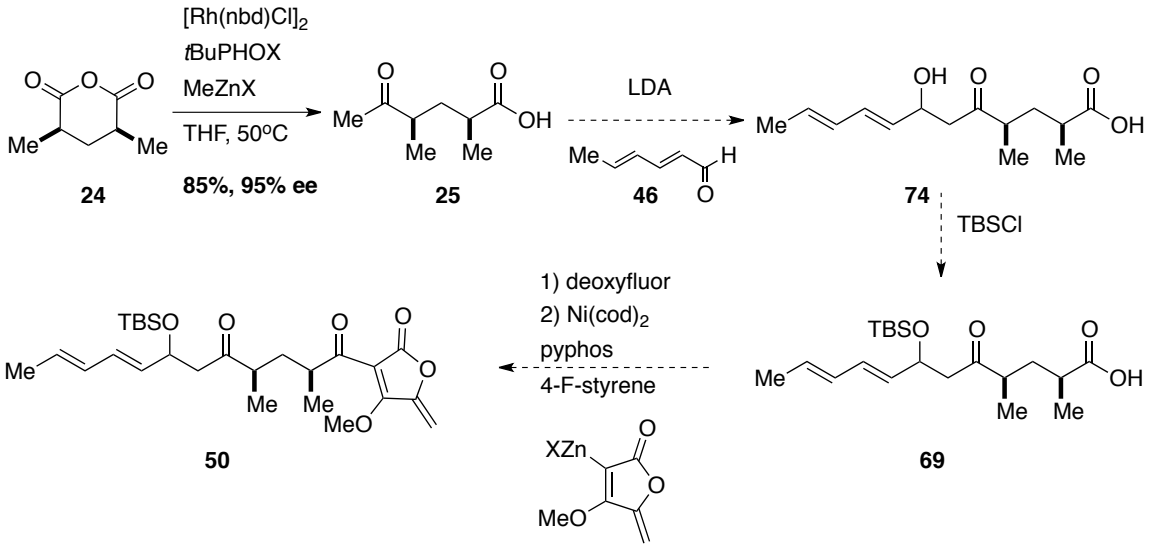
In contrast, a softer nucleophile such as an organostannane or boronic ester, acid or trifluoroborate moiety could be envisioned to avoid these pitfalls. However, there is little precedent for the use of these organometallic species in anhydride desymmetrizations. Although a few attempts were probed for reactivity, no products were observed, and this route was abandoned due to the anticipated instability of the triene product **73**.

3.4.3. Third Generation

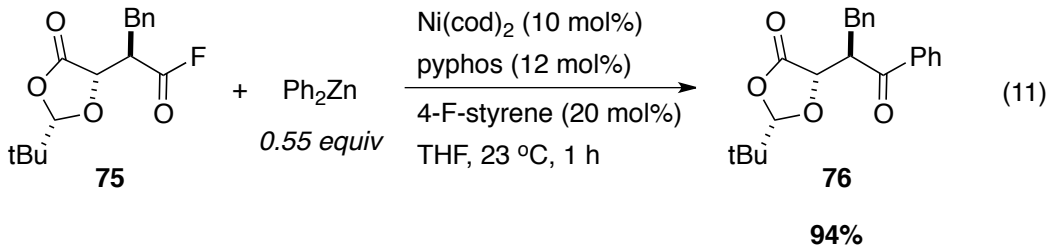
Poor characteristics of stability and reactivity of our zinc reagents in previously proposed approaches guided us to the simple and well precedented use of methyl zinc halides for the desymmetrization of *meso*-3,5-dimethylglutaric

anhydride (24). A route proceeding through the resulting methyl ketone **25** closely resembles Sorensen's route; however, it allows for a much more rapid synthesis of late stage intermediates. This method could construct the natural product, abyssomicin C, in as few as 8 steps. The highlights of the newly envisioned route are the anhydride desymmetrization of *meso*-3,5-dimethylglutaric anhydride **24** with a MeZnX reagent via a precedented step that proceeds in up to 85% yield and 95% ee (Scheme 18).

Scheme 18.

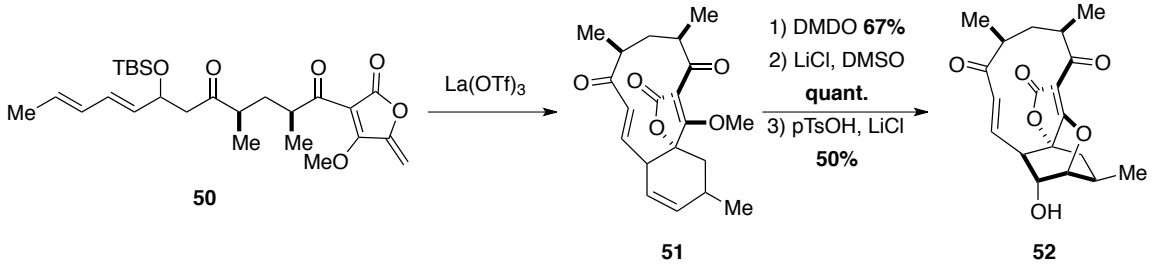


An aldol reaction of the resulting ketoacid enolate with *trans*-2,4-hexadienal could provide **74** under appropriate conditions, and TBS protection of the resulting hydroxyl group with subsequent conversion to the acid fluoride under nucleophilic fluorination conditions (deoxyfluor or DAST) provides the cross-coupling precursor **69**. Finally, a cross-coupling reaction intercepts Sorensen's route prior to the Diels-Alder reaction by using a method pioneered by Zhang and Rovis for the nickel-catalyzed cross-coupling of acid fluorides with zinc reagents (eq. 11).[31]



This methodology is compatible with labile acid fluorides containing epimerizable stereocenters, and this catalyst system boasts rapid reaction times with aryl- or alkylzinc reagents. This procedure has not been extended to more complicated heteroaryl zinc reagents, which poses an unresolved question for our system. If this technique fails, a Stille cross-coupling should provide the desired product (50). Our advanced intermediate can be brought through this sequence to the natural product in four transformations previously described by Sorensen (Scheme 19).

Scheme 19.

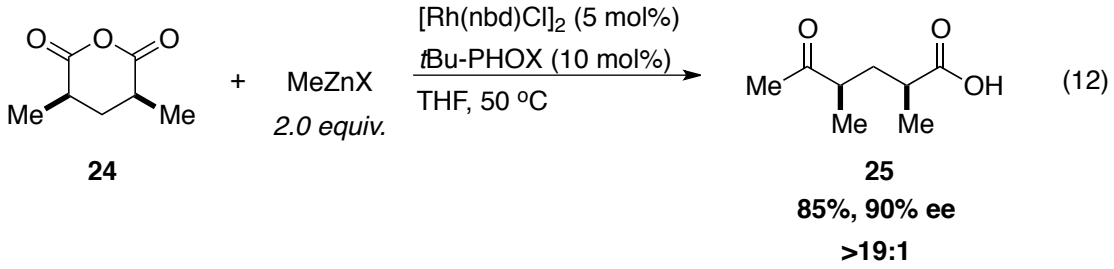


In summary, if our synthetic hypothesis is realized, it would enable a rapid synthesis of abyssomicin C and atrop-abyssomicin C in a total of 8 or 9 steps overall.

3.5 Completion of the Formal Synthesis of Abyssomicin C.

The first operation of our proposed route to abyssomicin C began with the anhydride desymmetrization chemistry previously described. This chemistry

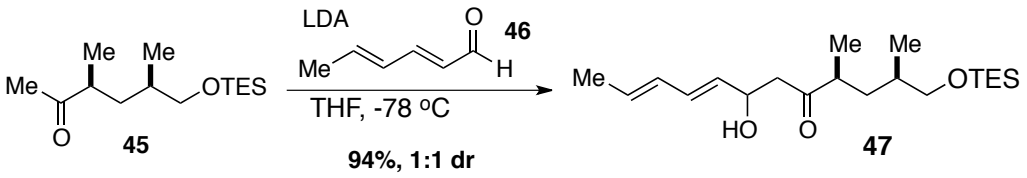
proceeded in high yield and with excellent enantioselectivity even on gram scale (eq. 12).



(12)

Although commercially available Me_2Zn is also compatible in this reaction, a slight loss in yield and enantioselectivity is observed with these conditions. This reaction provides an ideal first step in a total synthesis because it scales readily and reliably, and our catalyst loading can be reduced to as low as 1 mol% without loss in reactivity.

The second step in our route is the aldol reaction of the ketoacid **25**. Our initial results began with Sorensen's aldol conditions (eq. 13). In this report, the reaction is complete in under 4 hours.

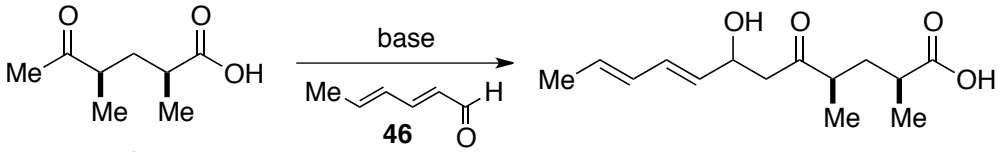


(13)

When Sorensen's conditions were attempted with keto acid **25**, none of the desired product **74** was obtained even after longer reaction times (Table 4, Entry 1). If the temperature of the reaction was warmed to 0 °C, modest results (46% yield) were observed (Entry 2). The product **74** was characterized and the remaining mass balance proved to be aldehyde and methyl ketone. Additional warming of the reaction to 50 °C provided none of the desired product (Entry 3).

Although the reactivity differences at different temperatures were puzzling, we believed that these issues could be addressed by deprotonating the carboxylic acid moiety prior to enolate formation. Towards this end, NaH in dispersion was used prior to kinetic deprotonation with LDA (Entry 5). This procedure initially promoted the desired results with increased yields of 60%.

Table 4.



25 **46** **74**

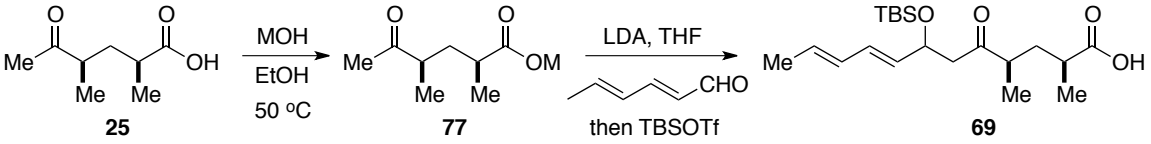
Entry	**Base**	**Temp** (°C)	**Yield (%)**
1	LDA (2 equiv)	-78	NR
2	LDA (2 equiv)	0	46
3	LDA (2 equiv)	50	NR
4	LiHMDS (2 equiv)	-78-0	6
5	NaH (60% disp.) + LDA	0 to -78 to -10	60

When these reactions were repeated, they often provided inconsistent results. To resolve this problem, we explored the potential pitfalls in the reaction. Initially, base seemed an obvious source of potential variability. Although the use of NaH (60% in dispersion) is convenient, it can be unreliable on small scale and significant quantities of mineral oil could provide additional problems for the reaction. To address these issues, NaH in dispersion was rinsed with hexanes in a Schlenk vessel to remove the mineral oil. Reactions utilizing this NaH gave no improvement.

To avoid the addition of external base, efforts were undertaken to isolate the carboxylate salt. This was accomplished by stirring the keto acid in EtOH in the presence of one equivalent of LiOH or NaOH at slightly elevated

temperature. A white solid crashed out of solution and the Li- or Na- carboxylate could be isolated by filtration. This solid was dried *in vacuo,* and proved to be moderately soluble in dry THF. This carboxylate was cooled to -78°C and subjected to the aldol conditions with aldehyde **46**. The reduced yield with K and Cs (Table 5, Entries 3, 4) seem to be a reflection of poor solubility of **77** in THF.

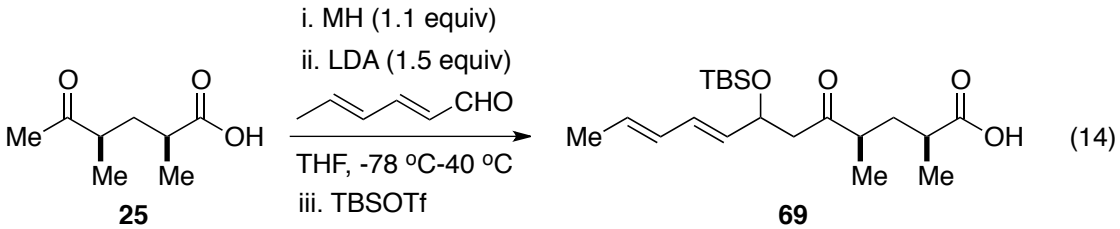
Table 5.



25 **77** **69**

Entry	Metal	Yield
1	Li	89%
2	Na	63%
3	K	40%
4	Cs	0%

Although a substantial increase in yield was observed in the first example, this reaction was difficult to reproduce on a larger scale. On large scale, more reliable results were obtained with anhydrous bases which were stored in the glovebox. In these studies, anhydrous LiH and KH, were used in place of NaH. The highest yield was obtained with KH (eq. 14).



25 **69**

(14)

6.0 mmol	**Metal**	**Yield**
	LiH	15%
	KH	25%

As the aldol reaction is an important step in our synthesis of abyssomicin C, additional studies were undertaken to probe the source of variability in our results. Important variables considered related to the aldehyde and the enolate. Specifically, the aldehyde could be unreactive, or it could be destroyed by undesired side reactions. Decomposition seemed unlikely as starting aldehyde could be reisolated at the conclusion of the reaction.[32] Although we believed reactivity was not a serious issue, several Lewis acids capable of activating the aldehyde were tested as additives including $TiCl_4$, $ZnCl_2$, $Mg(OTf)_2$ and $MgCl_2$. In these cases, no product was observed.

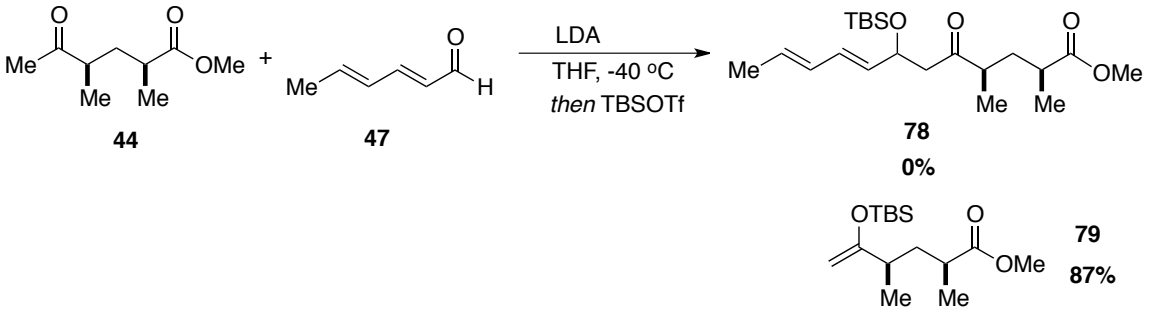
Inconsistent results could also stem from the use of impure keto acid, incomplete enolate formation, and poor enolate solubility. The solubility seemed a potential problem, as cloudy solutions were frequently observed. Although this could result from the use of 60% NaH dispersions, cloudy solutions might indicate the formation of insoluble carboxylate salts or insoluble enolate. A number of additives commonly used to break up lithium aggregates were examined, including anhydrous HMPA, TMEDA, HMPT, and DMPU, all without success. These studies are inconclusive, as these additives may not enhance the solubility of the enolate in solution.

As the quality of the keto acid directly relates to the quality of the zinc reagent employed in its preparation, variability could also be derived from the keto acid. The use of commercially available Me_2Zn resulted in lower yields and often produced impurities that were difficult to remove by acid/base extraction. By preparing MeZnBr *in situ* prior to every reaction, these issues could be

avoided. Incomplete enolate formation was examined by quenching experiments with D_2O. As observed by our ^{1}H-NMR data and confirmed by GC/MS, approximately 60% of the enolate was formed. This development suggested a problem with the quality of the LDA used for deprotonation. As it is made *in situ* prior to every reaction attempt, this could be a source of variability. By carefully titrating the *n*BuLi prior to use, freshly distilling the *i*Pr_2NH, and using anhydrous THF from the solvent system desired product could be obtained in every experiment, but variability in yields particularly with large scale reactions were still problematic.

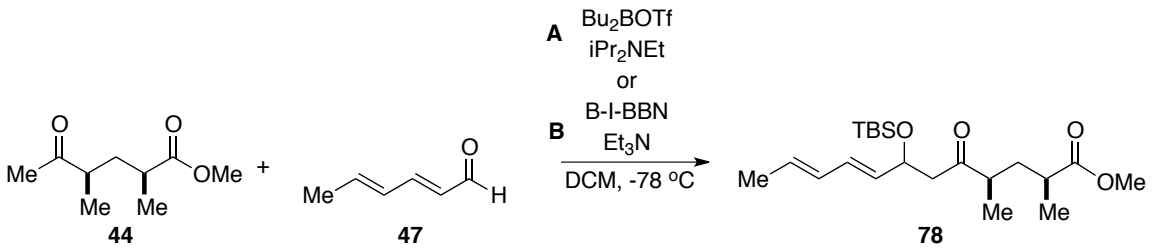
Although the source of our inconsistent results remained a mystery, we surmised that this problem could be bypassed by derivatizing the carboxylic acid to provide its the methyl ester. Shockingly, the methyl ketone ester provided no product in our aldol conditions with LDA (Scheme 20). Instead of the desired product **78**, the silyl enol ether **79** and aldehyde were isolated following a quench with TBSOTf.

Scheme 20.



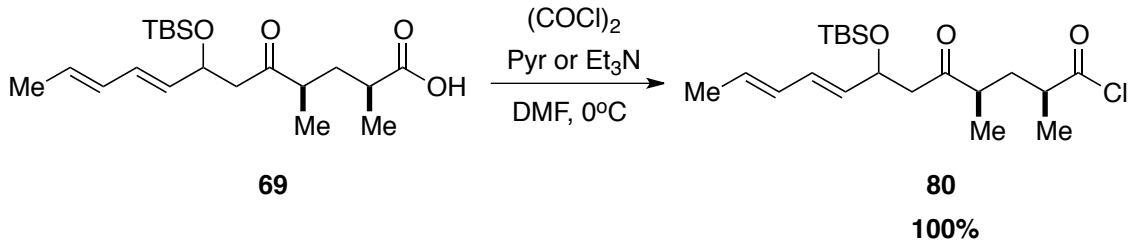
Soft enolization using two different sets of conditions; **A** using Bu_2BOTf/iPr_2NEt, and **B** using B-I-9-BBN/Et_3N, provided small quantities of desired product (Scheme 21).

Scheme 21.



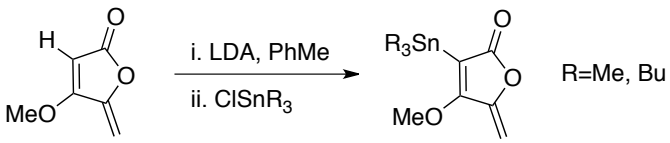
Although the inconsistent aldol reaction is a significant problem in our synthesis, small amounts of aldol product accumulated, and were subjected to the cross-coupling conditions. Our initial experiments using *in situ* generated zinc reagent for the acid fluoride/zinc cross-coupling methodology provided no evidence of product formation. Thus, this cross-coupling application was abandoned in favor of a Stille coupling procedure. Conversion of **69** to the acid chloride proceeded smoothly in the presence of weak base. Et_3N or pyridine was sufficient to remove HCl formed as a byproduct in the oxalyl chloride/DMF exchange without removal of the TBS protecting group (Scheme 22).

Scheme 22.



The organostannane **81** was readily prepared from the tetranate moiety as shown in Scheme 23. Both the Bu_3Sn-R and the Me_3Sn-R derivatives were prepared using this technique.

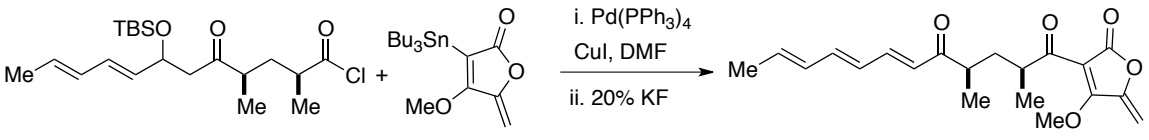
Scheme 23.



50 **81** **100%**

Explorations with Stille cross-coupling reactions began with $Pd(PPh_3)_4$, and initially none of the desired reactivity was observed. However, the addition of CuI promoted the transmetallation step, and a modest amount of the coupling product was obtained (Scheme 24). Although the use of the tri-*n*-butylstannane was successful, the workup was troublesome, producing a thick emulsion. Extractions with a 20% aqueous solution of KF solved this problem but resulted in facile elimination of the OTBS β-silyloxy ether.

Scheme 24.



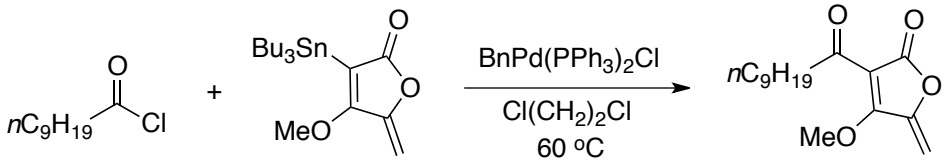
80 **82** **84** **~30%**

The resulting triene **84** was heated in toluene in an effort to promote the intramolecular Diels-Alder cycloaddition, decomposition of the triene occurred rapidly. Triene **84** is also an advanced intermediate in Sorensen's synthesis of

abyssomicin C; however, this is an unsatisfying completion to our proposed study as the material decomposed before it could be completely characterized.

Alternate conditions for the Stille reaction were sought to further promote the desired transformation and avoid a problematic workup requiring unsuitable conditions for an acid labile protecting group. The use of trimethylstannanes are unprecedented functionalities on the tetranate moiety in cross-coupling reactions; however, conditions for the tributylstannane **82** have been reported by Ley and coworkers.[33] These conditions use $BnPd(PPh_3)_2Cl$ in $Cl(CH_2)_2Cl$ to provide the desired coupling product in good yields (Scheme 25).

Scheme 25.



85 **82** **86**

49%

We believed the use of the α-trimethylstannyl tetranate with this palladium catalyst might provide the desired product in a cleaner reaction. Initial investigations with this catalyst system are underway.

3.6 Summary and Future Studies

Our approach for the synthesis of abyssomicin C, represents an important alternate strategy for the preparation of deoxypolypropionate natural products. Our strategy highlights the utility of anhydride desymmetrization methodology in synthesis. In one highly efficient step, our reaction provides a key intermediate which is appropriately functionalized for bi-directional synthesis. Additionally, the

aldol reaction investigated in this study is unprecedented. Although significant results were achieved in small scale reactions, the process proved to be highly variable. Stille cross-coupling reactions of the acid chloride **80** and stannane **82** have led to the highly functionalized triene **84** for further studies.

3.6 References

[1] Five nobel prizes to date have been awarded to chemists developing strategies to form carbon-carbon bonds: Grignard reaction (1912), Diels-Alder reaction (1950), Wittig Reaction (1979), Olefin-metathesis (2005), Pd catalyzed cross-coupling (2010). See Backvall, J.-E. “Palladium-Catalyzed Cross Couplings in Organic Synthesis” Scientific Background on the Nobel Prize in Chemistry 2010,

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CHAPTER 1 SUPPORTING INFORMATION

THE DEVELOPMENT OF CARBON DIOXIDE FIXATION METHODOLOGY

General Methods.

All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Tetrahydrofuran (THF) was purged with argon and passed through two columns of neutral alumina. Column chromatography was performed using EM Science silica gel 60 (230-400 mesh.) Thin layer chromatography was performed using EM Science 0.25 mm silca gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, aqueous ceric ammonium molybdate or bromocresol green dips followed by heating. Unless otherwise noted, starting materials are commercially available from Sigma Aldrich and Alfa Aesar and were utilized without further purification. ^{1}H and ^{13}C NMR spectra were obtained on a Varian 300 MHz spectrometer at ambient temperature unless otherwise noted. GC/MS data was obtained on a Agilent 6890 GC System with Agilent 5973 Mass Selective Detector and Agilent 7683 Series injector equipped with a SUPELCO SPB-1 non-polar capillary column.

General Hydrocarboxylation Procedure.

The general hydrocarboxylation procedure will be illustrated with a specific example. $Ni(acac)_2$ (10.0 mg, 0.04 mmol) and Cs_2CO_3 (26 mg, 0.08 mmol) were weighed into an oven-dried 10 mL round bottom flask which was sealed with a

septum, evacuated and refilled with argon two times. The solid was dissolved in THF (1 mL) and 4-CF_3-styrene (60 µl, 0.4 mmol) was added via syringe. The flask was spurged with CO_2 from a balloon three times. Finally, Et_2Zn (100 µL, 0.97 mmol) was added via syringe. The reaction was allowed to stir at room temperature. After 10 hours, the reaction was diluted with EtOAc (5 mL) and quenched with 1 M HCl (5 mL). After separation, the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under low pressure to yield the crude product. The crude material was dissolved in acetone, adsorbed onto silica gel, and purified by column chromatography using the method described by W.C. Still (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.)

Quenching Experiment Procedure.

Three reactions were set up at the same time with the procedure that follows. Ni $(acac)_2$ (2.5 mg, 0.01 mmol), Cs_2CO_3 (6.3 mg, 0.02 mmol), and 2-vinylnapthalene (**92**) (15 mg, 0.1 mmol) were weighed into an oven dried vial which was sealed with a septum, evacuated and refilled with argon two times. The solid was dissolved in THF (0.25 mL). The vial was spurged with CO_2 from a balloon three times. Finally, Et_2Zn (25 µL, 0.24 mmol) was added via syringe. The reactions were allowed to stir at room temperature. The reactions were quenched with d1-acetic acid/D_2O after 1 hour, 3 hours, and 9 hours by removing the septum and immediately adding d^1 acetic acid/D_2O by pipet. After bubbling subsided, 1 mL of EtOAc was added and organic layer was separated and combined after extracting twice with 1 mL of EtOAc. A 1 mL sample of the organic layer was

subjected to analysis by GC/MS. A constant flow rate of 1.0 L/min and an initial temperature of 50 ^{o}C ramped to 150 ^{o}C over 5 min at a rate of 30.0 ^{o}C/min, followed by temperature ramping of 5.00 ^{o}C/min to a final temperature of 260 ^{o}C. Total run time: 31.33 min.

General method for preparation of 5-Vinyl-furan-2-carboxylic acid methyl ester.

5-Vinyl-furan-2-carboxylic acid methyl ester. Following the procedure of Molander 5-Bromo-furan-2-carboxylic acid methyl ester (410 mg, 2.0 mmol) was combined with potassium vinyl trifluoroborate (268 mg, 2.0 mmol), $PdCl_2$ (7.0 mg, 0.02 mmol), PPh_3 (32 mg, 0.06 mmol) and Cs_2CO_3 (6.0 mmol) in a sealed tube under argon and suspended in 9:1 THF:H_2O (5 mL). Heating at 85 °C for 24 h and purification by silica gel column chromatography (19:1 hexanes:Et_2O) provided the desired alkene (190 mg, 62% yield). R_f = 0.24 (19:1 Hex:Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$): 7.14 (d, 1H, *J* = 3.6 Hz), 6.54 (dd, 1H, *J* = 11.4, 18.0 Hz), 6.38 (d, 1H, *J* = 3.6 Hz), 5.93 (d, 1H, *J* = 18 Hz), 5.37 (d, 1H, *J* = 11.4 Hz), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 159.4, 156.7, 143.5, 124.6, 119.8, 117.1, 109.5, 52.1. IR (NaCl, $CDCl_3$) 1727, 1506, 1436, 1302, 1223, 1207, 1141 cm^{-1}. HRMS (FAB+) calcd for $C_8H_9O_3^{+}$, 153.0552. Found 153.0547.

Procedure and Characterization of propionic acids.

α-(2-Naphthyl)propionic acid (2a). According to the general procedure for the general hydrocarboxylation procedure, THF (1 mL) was added to a flask containing 2-vinylnapthalene (**92**) (62 mg, 0.4 mmol), $Ni(acac)_2$ (10 mg, 0.04 mmol), and Cs_2CO_3 (26 mg, 0.08 mmol). After switching to a CO_2 atmosphere and addition of Et_2Zn (100 µL, 0.97 mmol), the reaction was allowed to stir at 23 °C for 12 h. The reaction mixture was diluted with EtOAc (5 mL) and quenched with 1 M HCl (5 mL). After separation, the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under low pressure to provide the crude product. The acid was purified by silica gel column chromatography (19:1:1 Hexanes:EtOAc:AcOH) to provide a yellow oil (48 mg, 0.24 mmol, 60%). Spectral data matched the literature description (see Clericuzio, M.; Degani, I.; Dughera, S.; Fochi, R. *Synthesis*. **2002**, *7*, 921.

2-(3-methoxyphenyl)propionic acid (4a). According to the general procedure for the general hydrocarboxylation procedure, 3-vinylanisole (55 µL, 0.4 mmol) was added to a THF solution (1 mL) containing $Ni(acac)_2$ (10 mg, 0.04 mmol) and Cs_2CO_3 (26 mg, 0.08 mmol). After switching to a CO_2 atmosphere and addition of Et_2Zn (100 µL, 0.97 mmol), the reaction was stirred at 23 °C for 12 h. The reaction mixture was diluted with EtOAc (5 mL) and quenched with 1 M HCl (5 mL). After separation, the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under low pressure to provide the crude product. The acid was purified by silica gel column chromatography (19:1:1 Hexanes:EtOAc:AcOH) to provide a pale yellow

oil (66 mg, 0.36 mmol, 92%). Spectral data matched literature description (see Kübler, W.; Petrov, O.; Winterfeldt, E.; Ernst, L.; Schomburg, D. *Tetrahedron*, **1988**, *44*, 4371).

2-phenylpropionic acid (1a). According to the general procedure for the general hydrocarboxylation procedure, styrene (50 µL, 0.4 mmol) purified by washing twice with NaOH followed by water, drying over $MgSO_4$ for three hours, and distilled under reduced pressure at ambient temperature in the presence of 0.005% *p-tert*-butylcatechol (see Armarego, W.L.F; Perrin, D.D. *Purification of Laboratory Chemicals*. 3rd ed. Butterworth-Heinemann: Woburn, MA, 1996), was added to a THF solution (1 mL) containing $Ni(acac)_2$ (20 mg, 0.08 mmol) and Cs_2CO_3 (52 mg, 0.16 mmol). After switching to a CO_2 atmosphere and addition of Et_2Zn (100 µL, 0.97 mmol), the reaction was stirred at 23 °C for 12 h. The reaction mixture was diluted with EtOAc (5 mL) and quenched with 1 M HCl (5 mL). After separation, the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under low pressure to provide the crude product. The acid was purified by silica gel column chromatography (19:1:1 Hexanes:EtOAc:AcOH) to provide a clear oil (33 mg, 0.22 mmol, 56%). Spectral data matched literature description (see Li, P.; Alper, H. *JOC,* **1986,** *51,* 4354).

2-(3-chlorophenyl)propionic acid (5a). According to the general procedure for the general hydrocarboxylation procedure, 3-chlorostyrene (51 µL, 0.4 mmol) was added to a THF solution (1 mL) containing $Ni(acac)_2$ (10 mg, 0.04 mmol) and

Cs_2CO_3 (26 mg, 0.08 mmol). After switching to a CO_2 atmosphere and addition of Et_2Zn (100 µL, 0.97 mmol), the reaction was stirred at 23 °C for 12 h. The reaction mixture was diluted with EtOAc (5 mL) and quenched with 1 M HCl (5 mL). After separation, the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under low pressure to provide the crude product. The acid was purified by silica gel column chromatography (19:1:1 Hexanes:EtOAc:AcOH) to provide a clear oil (50 mg, 0.27 mmol, 68%). Spectral data matched literature description (Page, P.; McKenzie, M.; Allin, M.; Klair, S. *Tetrahedron,* ***1997,*** *53,* 13149.)

2-(3-trifluoromethylphenyl)propionic acid methyl ester (7a). According to the general procedure for the general hydrocarboxylation procedure, 3-chlorostyrene (51 µL, 0.4 mmol) was added to a THF solution (1 mL) containing $Ni(acac)_2$ (10 mg, 0.04 mmol) and Cs_2CO_3 (26 mg, 0.08 mmol). After switching to a CO_2 atmosphere and addition of Et_2Zn (100 µL, 0.97 mmol), the reaction was stirred at 23 °C for 12 h. The reaction mixture was diluted with EtOAc (5 mL) and quenched with 1 M HCl (5 mL). After separation, the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under low pressure to provide the crude product. The acid was converted to the corresponding ester by refluxing in methanol with catalytic sulfuric acid. The ester was purified by silica gel column chromatography (95:5 hexanes:EtOAc) to provide the desired ester as a clear oil (73 mg, 0.32 mmol, 79%). Spectral data matched literature description (see Durandetti, M; Gosmini, C.; Périchon, J. *Tetrahedron,* ***2007,*** *63,* 1146.)

2-(4-Trifluoromethyl-phenyl)-propionic acid methyl ester (11a). According to the general procedure for the general hydrocarboxylation procedure, 4-trifluoromethylstyrene (60 μL, 0.4 mmol) was added to a THF solution (1 mL) containing $Ni(acac)_2$ (10 mg, 0.04 mmol) and Cs_2CO_3 (26 mg, 0.08 mmol). After switching to a CO_2 atmosphere and addition of Et_2Zn (100 μL, 0.97 mmol), the reaction was stirred at 23 °C for 12 h. The reaction mixture was diluted with EtOAc (5 mL) and quenched with 1 M HCl (5 mL). After separation, the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under low pressure to provide the crude product. The acid was converted to the corresponding ester by dissolving the oil in 1:1 MeOH:benzene and treating the solution with $TMSCHN_2$. The ester was purified by silica gel column chromatography (95:5 hexanes:EtOAc) to provide the desired ester as a clear oil (85 mg, 0.37 mmol, 92% yield). R_f = 0.38 (9:1 hexanes:EtOAc). ^1H NMR (300 MHz, $CDCl_3$): δ 7.58 (2H, d, *J* = 7.5 Hz), 7.42 (2H, d, *J* = 7.5 Hz), 3.79 (1H, q, *J* = 7.5 Hz), 3.67 (3H, s), 1.52 (3H, d, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): 174.4, 144.6, 129.6 (q, J_{C-F} = 41.5 Hz), 128.1, 125.7 (q, J_{C-F} = 4 Hz), 125.6 52.4, 45.5, 18.7. IR (NaCl) 1740, 1327, 1166, 1124 cm^{-1}. HRMS (FAB+) calcd for $C_{11}H_{12}F_3O_2$, 233.0789. Found 233.0785.

2-(2-Chlorophenyl)-propionic acid (6a). According to the general procedure for the general hydrocarboxylation procedure, 2-Cl-styrene (51 μL, 0.4 mmol) was added to a THF solution (1 mL) containing $Ni(acac)_2$ (10 mg, 0.04 mmol) and

Cs_2CO_3 (26 mg, 0.08 mmol). After switching to a CO_2 atmosphere and addition of Et_2Zn (100 µL, 0.97 mmol), the reaction was allowed to stir at 23 °C for 12 h. The reaction mixture was diluted with EtOAc (5 mL) and quenched with 1 M HCl (5 mL). After separation, the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under low pressure to provide the crude product. The desired acid was purified by silica gel column chromatography (19:1:1 hexanes:EtOAc:AcOH) to provide the desired ester as a white solid (48 mg, 0.26 mmol, 65% yield). R_f=0.53 (9:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (m, 4H), 4.23 (q, 1H, *J* = 7.0 Hz), 1.49 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.5, 137.9, 134.0, 129.8, 128.7, 77.2, 42.3, 17.5. IR (NaCl, $CDCl_3$) 2983, 2229, 1707, 1476, 1234, 1035 cm^{-1}.

2-(2-trifluoromethylphenyl)-propionic acid (12a). According to the general procedure for the general hydrocarboxylation procedure, 2-CF_3-styrene (59 µL, 0.4 mmol) was added to a THF solution (1 mL) containing $Ni(acac)_2$ (10 mg, 0.04 mmol) and Cs_2CO_3 (26 mg, 0.08 mmol). After switching to a CO_2 atmosphere and addition of Et_2Zn (100 µL, 0.97 mmol), the reaction was allowed to stir at 23 °C for 12 h. The reaction mixture was diluted with EtOAc (5 mL) and quenched with 1 M HCl (5 mL). After separation, the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under low pressure to provide the crude product. The desired acid was purified by silica gel column chromatography (19:1:1 hexanes:EtOAc:AcOH) to provide the desired ester as a clear oil (75 mg, 0.35 mmol, 87% yield). Rf=0.56

(9:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, 1H, *J* = 7.9 Hz), 7.5 (m, 2H), 7.3 (m, 1H), 4.17 (q, 1H, *J* = 7.0 Hz), 1.50 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1, 139.0, 132.4, 128.4, 126.1, 125.8, 123.1, 77.2, 40.8, 19.3. IR (NaCl, $CDCl_3$) 2997, 1711, 1314, 1244, 1158, 1037 cm^{-1}.

4-(1-Methoxycarbonyl-ethyl)-benzoic acid methyl ester (8a). According to the general hydrocarboxylation procedure, 4-CO_2Me-styrene (65 mg, 0.4 mmol) was added to a THF solution (1 mL) containing $Ni(acac)_2$ (10 mg, 0.04 mmol) and Cs_2CO_3 (26 mg, 0.08 mmol). After switching to a CO_2 atmosphere and addition of Et_2Zn (100 µL, 0.97 mmol), the reaction was stirred at 23 °C for 12 h. The reaction mixture was diluted with EtOAc (5 mL) and quenched with 1 M HCl (5 mL). After separation, the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under low pressure to provide the crude product. The acid was converted to the corresponding ester by dissolving the oil in 1:1 MeOH:benzene and treating the solution with $TMSCHN_2$. The ester was purified by silica gel column chromatography (95:5 hexanes:EtOAc) to provide the desired ester as a clear oil (99 mg, 0.33 mmol, 84% yield). R_f = 0.25 (9:1 hexanes:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (2H, d, *J* = 6.6 Hz), 7.35 (2H, d, *J* = 6.6 Hz), 3.89 (3H, s), 3.77 (1H, q, *J* = 7.2 Hz), 3.65 (3H, s), 1.50 (3H, d, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 167.0, 145.8, 130.2, 129.3, 127.8, 52.4, 52.3, 45.6, 18.6. IR (NaCl, $CDCl_3$) 1736, 1720, 1610, 1455, 1273 cm^{-1}. HRMS (FAB+) calcd for $C_{12}H_{15}O_4^+$, 223.0965. Found 223.0972.

4-(1-Methoxycarbonyl-ethyl)-benzoic acid benzyl ester (9a). According to the general procedure for the general hydrocarboxylation procedure, 4-CO_2Bn-styrene (79 mg, 0.4 mmol) was added to a THF solution (1 mL) containing Ni $(acac)_2$ (10 mg, 0.04 mmol) and Cs_2CO_3 (26 mg, 0.08 mmol). After switching to a CO_2 atmosphere and addition of Et_2Zn (100 µL, 0.97 mmol), the reaction was stirred at 23 °C for 16 h. The reaction mixture was diluted with EtOAc (5 mL) and quenched with 1 M HCl (5 mL). After separation, the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under low pressure to provide the crude product. The acid was converted to the corresponding ester by dissolving the oil in 1:1 MeOH:benzene and treating the solution with $TMSCHN_2$. The ester was purified by silica gel column chromatography (95:5 hexanes:EtOAc) to provide the desired ester as a clear oil (120 mg, 0.32 mmol, 81% yield). R_f = 0.24 (9:1 hexanes:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): 8.04 (d, 2H, *J* = 8.1 Hz), 7.47-7.30 (m, 7H), 5.36 (s, 2H), 3.78 (q, 1H, *J* = 7.2 Hz), 3.66 (s, 3H), 1.52 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 174.3, 166.1, 145.7, 136.0, 130.1, 129.0, 128.5, 128.2, 128.1, 127.6, 66.6, 52.2, 45.4, 18.4. IR (NaCl, $CDCl_3$) 1721, 1608, 1436, 1315, 1280 cm^{-1}. HRMS (FAB+) calcd for $C_{18}H_{19}O_4^+$, 299.1278. Found 299.1277.

2-(4-Cyano-phenyl)-propionic acid methyl ester (13a). According to the general procedure for the general hydrocarboxylation procedure, 4-CN-styrene

(71 mg, 0.4 mmol) was added to a THF solution (1 mL) containing $Ni(acac)_2$ (10 mg, 0.04 mmol) and Cs_2CO_3 (15 µL, 0.10 mmol). After switching to a CO_2 atmosphere and addition of Et_2Zn (100 µL, 0.97 mmol) the reaction was stirred at 23 °C for 16 h. The reaction mixture was diluted with EtOAc (5 mL) and quenched with 1 M HCl (5 mL). After separation, the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under low pressure to provide the crude product. The acid was converted to the corresponding ester by dissolving the oil in 1:1 MeOH:benzene and treating the solution with $TMSCHN_2$. The ester was purified by silica gel column chromatography (95:5 hexanes:EtOAc) to provide the desired ester as a clear oil (46 mg, 0.24 mmol, 61% yield). R_f = 0.28 (9:1 hexanes:EtOAc). ^1H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, 2H, *J* = 8.4 Hz), 7.42 (d, 2H, *J* = 8.4 Hz), 3.79 (q, 1H, *J* = 7.5 Hz), 3.69 (s, 3H), 1.52 (d, 3H, *J* = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 145.6, 132.4, 128.4, 118.7, 111.1, 52.3, 45.5, 18.3. IR (NaCl, $CDCl_3$) 3425, 2229, 1737, 1608, 1210, 1168 cm^{-1}. HRMS (FAB+) calcd for $C_{11}H_{12}NO_2^+$, 190.0868. Found 190.0872.

5-(1-Methoxycarbonyl-ethyl)-furan-2-carboxylic acid methyl ester (3a). According to the general procedure for the general hydrocarboxylation procedure, 5-Vinyl-furan-2-carboxylic acid methyl ester (61 mg, 0.4 mmol) was added to a THF solution (1 mL) containing $Ni(acac)_2$ (10 mg, 0.04 mmol) and Cs_2CO_3 (26 mg, 0.08 mmol). After switching to a CO_2 atmosphere and addition of Et_2Zn (100 µL, 0.97 mmol) the reaction was stirred at 23 °C for 16 h. The

reaction mixture was diluted with EtOAc (5 mL) and quenched with 1 M HCl (5 mL). After separation, the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under low pressure to provide the crude product. The acid was converted to the corresponding ester by dissolving the oil in 1:1 MeOH:benzene and treating the solution with $TMSCHN_2$. The ester was purified by silica gel column chromatography (9:1 hexanes:EtOAc) to provide the desired ester as a clear oil (56 mg, 0.26 mmol, 66% yield). R_f = 0.37 (9:1 hexanes:EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, 1H, *J* = 3.2 Hz), 6.32 (d, 1H, *J* = 3.2 Hz), 3.90 (q, 1H, *J* = 7.2 Hz), 3.87 (s, 3H), 3.72 (s, 3H), 1.56 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 159.0, 157.7, 143.6, 119.0, 108.5, 52.5, 51.8, 39.5, 15.9. IR (NaCl, $CDCl_3$) 2954, 1739, 1521, 1437, 1376, 1308, 1207 cm^{-1}. HRMS (FAB +) calcd for $C_{10}H_{13}O_5^+$, 213.0758. Found 213.0758.

2-(4-Benzoyl-phenyl)-propionic acid methyl ester (10a). According to the general procedure for the general hydrocarboxylation procedure, phenyl-(4-vinyl-phenyl)-methanone (47 mg, 0.4 mmol) was added to a THF solution (1 mL) containing $Ni(acac)_2$ (10 mg, 0.04 mmol) and Cs_2CO_3 (26 µL, 0.08 mmol). After switching to a CO_2 atmosphere and addition of Et_2Zn (100 µL, 0.97 mmol) the reaction was stirred at 23 °C for 16 h. The reaction mixture was diluted with EtOAc (5 mL) and quenched with 1 M HCl (5 mL). After separation, the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under low pressure to provide the crude product. The acid was converted to the corresponding ester by dissolving the oil

in 1:1 MeOH:benzene and treating the solution with $TMSCHN_2$. The ester was purified by silica gel column chromatography (9:1 hexanes:EtOAc) to provide the desired ester as a clear oil (77 mg, 0.29 mmol, 72% yield). R_f = 0.31 (9:1 hexanes:EtOAc). ^1H NMR (300 MHz, $CDCl_3$): 7.83-7.75 (m, 4H), 7.63-7.55 (m, 1H), 7.52-7.45 (m, 2H), 7.44-7.39 (m, 2H), 3.82 (qrt, 1H, *J* = 6.9 Hz), 3.69 (s, 3H), 1.54 (d, 2H, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 196.4, 174.5, 145.3, 132.6, 130.7, 130.2, 128.5, 127.7, 52.4, 45.6, 18.6. IR (NaCl, $CDCl_3$) 2927, 2254, 1732, 1659, 1607, 1456, 1280, 1211 cm^{-1}. HRMS (FAB+) calcd for $C_{17}H_{17}O_3^+$, 269.1172. Found 269.1162.

CHAPTER 2 SUPPORTING INFORMATION

CHEMICAL FIXATION AND PROGRAMMED RELEASE OF CO_2 FOR SEQUESTRATION

Polymer Synthesis.

Poly(vinyl alcohol) (PVA) was used as obtained from Sigma Aldrich. Unless otherwise mentioned, the PVA used was 99+% hydrolyzed with a typical molecular weight of 89,000-98,000 g/mol. The lower molecular weight PVA was 98% hydrolyzed with a molecular weight of 13,000-23,000 g/mol and 80% hydrolyzed with a MW of 9,000-10,000 g/mol. Acryloyl chloride and N-methyl-2-pyrrolidone (NMP) were used as obtained from Sigma Aldrich.

Based on the preparation by Wang et al (*J. Appl. Polym. Sci.* **1992**, *46*, 1967), PVA (1 g) was dissolved in NMP (33 mL) at 50 ^{o}C. This solution was allowed to cool to room temperature prior to addition of acryloyl chloride (6 mL). This solution was allowed to stir for 90 minutes. Next, this solution was added to 2 times its volume of cold tap water. A fibrous white to off-white material immediately precipitated. This material was filtered out of the water. Further purification was achieved by dissolving in a minimum amount of MeOH before addition to two times its volume of water to precipitate the polymer. This process was repeated twice to obtain slightly wet PVA-AA. By changing the amount of acryloyl chloride added from 6 mL to 2 mL, the percentage of alcohols capped varied between 32 and 69%. Less then 2 mL of acryloyl chloride failed to provide

a polymer insoluble in water. The esterification content was estimated using Wang's method: calculated from the ratio of peak heights at 5.8-6.4 and 5.1-5.2 ppm in the 1H-NMR. The polymer was partially characterized by ^{1}H and ^{13}C NMR on a Varian 300 MHz spectrometer at ambient temperature.

General methods for reactions with PVA-AA and Et_2Zn.

PVA-AA was either used slightly wet, as obtained from the process described above, or dried by gentle heating (50 ^{o}C) under vacuum. If used dry, the polymer was a darker yellow in color and brittle, making it significantly harder to manipulate as it failed to swell in polar solvents.

If used wet, the polymer was elastic and swelled in appropriate solvent (either MeOH, DMSO, NMP, or DMF). DMSO and DMF were dried by purging with argon and passing through neutral alumina. Prior to exposure with various nucleophiles, the atmosphere of the reaction flask containing polymer and solvent was purged and flushed with carbon dioxide 2-3 times. Neat Et_2Zn (used as obtained from Sigma Aldrich), was added to the reaction flask via syringe. Immediate and vigorous bubbling on the surface of the polymer was observed, frequently accompanied by a color change to brown. The reaction was allowed to sit for an hour. Finally, water was added to the reaction mixture to quench any remaining Et_2Zn. The polymer was filtered off as a hard, brown, solid. This material was completely insoluble in all substances, preventing characterization.

General Methods for Release.

To determine if the resulting polymeric material could release carbon dioxide, solid polymer and either concentrated solutions of acid (12 N HCl or glacial acetic

acid) or base (3 N NaOH) were placed in an oven dried round bottom flask sealed with a septum. A balloon was inserted by a needle through the septum. The solution was heated to approximately 150 ^{o}C in an oil bath. No bubbling or release of carbon dioxide was detected visually. At the conclusion of these studies the polymer could be re-isolated and no change in weight was observed. In addition, the material was still insoluble in a wide variety of solvents.

Methods for Derivatization.

Derivatization studies of to confirm the uptake of carbon dioxide within the polymer were attempted using diazomethane. In this study, the dry solid polymer obtained following reaction with Et_2Zn and CO_2, was placed in a solution of MeOH and approximately 5 mL of diazomethane were added. Little bubbling was observed, and the resulting polymer was insoluble in all solvents.

Preparation and studies with the dimer.

Pentane-2,4-diol (**18**) (3.3 mmol), used as obtained from Sigma-Aldrich, was dissolved in dichloromethane. Et_3N (1.1 equiv) was added and the reaction was allowed to stir for approximately one hour. Next, acryloyl chloride (2.1 equiv) was added and the reaction was allowed to stir at room temperature for approximately two hours. The resulting reaction solution was concentrated by vacuum and ~90% of the desired acrylate dimer (**19**) was obtained by column chromotography.

This material (3.0 mmol) was dissolved in dry DMF or DMSO in an oven dried round bottom flask under argon. The atmosphere was flushed with carbon

dioxide, and 2.5 equivalents of neat diethyl zinc was added by syringe. After two to three hours water was added to quench the excess diethyl zinc.

Exposure of the resulting acid (**20**) with 3 N NaOH in DMSO resulted in quantitative conversion to the saponification product (**22**) as opposed to the decarboxylation product (**21**).

Characterization of Relevant Materials

Poly(vinyl alcohol)-Acrylic Acid (17).

Matches material characterized by Wang et al (*J. Polym. Res*. **1999**, *6*, 191.) ^{1}H NMR (300 MHz, $CDCl_3$): 6.3-6.4 (broad s), 6.0-6.2 (broad s), 5.8-5.9 (broad s), 5.1-5.2 (broad s), 4.6 (broad s), 4.8 (broad s), 2.35 (broad s), 2.32 (broad s), 2.0 (broad s), 1.6-1.8 (broad s). IR (NaCl, $CDCl_3$) 3400, 2900, 1725, 1640, 1400, 1300, 1200 cm^{-1}

2,2'-((pentane-2,4-diylbis(oxy))bis(carbonyl))dipentanoic acid (20).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.35 (3H, m, *J*=1.5 Hz), 6.09 (3H, m, *J*=5.7 Hz), 5.81 (3H, m, *J*=1.2 Hz), 5.06 (2H, m, *J*=6.3 Hz), 2.09 (1H, m, *J*=6.9 Hz), 1.86 (1H, t, *J*=6.6), 1.76 (1H, m, *J*=5.7 Hz), 1.28 (12H, d, *J*=4.5). ^{13}C NMR (100 MHz, CDCl3): δ 165.6, 130.5, 128.7, 68.2, 67.6, 42.8, 41.7, 20.4.

CHAPTER 3 SUPPORTING INFORMATION

APPLICATION OF RHODIUM-CATALYZED ANHYDRIDE DESYMMETRIZATION TO THE SYNTHESIS OF ABYSSOMICIN C

General Methods.

All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Tetrahydrofuran (THF), Et_2O, DMF, and PhMe were purged with argon and passed through two columns of neutral alumina. Column chromatography was performed using EM Science silica gel 60 (230-400 mesh.) Thin layer chromatography was performed using EM Science 0.25 mm silca gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, aqueous ceric ammonium molybdate, iodine, or bromocresol green dips followed by heating. Unless specifically mentioned, reagents were used as obtained from Sigma Aldrich. $[Rh(nbd)Cl]_2$, $Ni(cod)_2$, $[Rh(cod)Cl]_2$ were used as obtained from Strem. Aldehyde **46**, *trans*-2,4-hexadienal, was vacuum distilled and stored in the freezer under argon prior to use. The *meso*-3,5-dimethylglutaric anhydride was prepared following Paquette's method (Synthesis, 2002, 888). A solution of LDA was prepared fresh prior to each reaction. ^{1}H and ^{13}C NMR spectra were obtained on a Varian 300 MHz spectrometer at ambient temperature unless otherwise noted. Analytic high performance liquid chromatography (HPLC) was performed on an Agilent 1100 series HPLC using Chiracel chiral columns.

General Methods for Preparing Zinc Nucleophiles.

Preparation for Drying Zinc Halides.

This preparation will be illustrated with a specific example. An 50 mL Schlenk flask was flame dried under vacuum with a stirbar. Following drying, the flask was filled with Argon and allowed to cool to room temperature. Flask was charged with $ZnBr_2$ (4.0 g, 17.7 mmol) and placed under vacuum. Flame from a bunsen burner was applied to the bottom of the flask. After a couple minutes of heating, $ZnBr_2$ was observed to melt and begin to sublime on the sides of the reaction vessel. At the point when the majority of $ZnBr_2$ had melted, the flame was removed and the vessel was purged with argon and allowed to cool to room temperature.

Preparation of *in situ* Generated Furyl Zinc Reagents in DMF. This preperation will be illustrated with a specific example. An oven-dried round bottom flask was charged with 2-methylfuran (0.225 mL, 2.5 mmol) and purged with Ar. The oil was subsequently dissolved in THF and cooled to -78 °C in a dry ice/ acetone bath. To this solution, *t*BuLi (1.6 M in hexanes, 1.56 mL, 2.5 mmol) was slowly added and the mixture was allowed to stir for 60 min. Meanwhile, an oven-dried Schlenk flask with freshly dried $ZnBr_2$ (0.56 g, 2.5 mmol) was purged with Argon. This solid was suspended in 5 mL of THF. The aryl lithium formed in the initial step was then added via syringe to the suspension of $Zn(OTf)_2$ over blowing Ar. The mixture was stirred at ambient temperature for 2 h, at which time the THF

was evaporated under reduced pressure. Addition of 5 mL DMF over blowing Ar to the resulting residue provided a solution (0.5 M) of the desired organozinc halide.

Preparation of *in situ* Generated Alkyl Zinc Reagent in THF.

This preparation will be illustrated with a specific example. Following the general procedure for drying zinc halides, the resulting solid was suspended in 45 mL of dry THF. Solution was cooled to 0 ^{o}C in an ice bath. A 3.0 M solution of MeMgBr (17.7 mmol) was added by syringe. The reaction solution was stirred for one hour at 0 ^{o}C prior to warming to room temperature and stirring for 40 additional minutes. At this point, stirring was ceased and the metal salts were allowed to settle to the bottom of the schlenk flask. The supernatent contains the desired solution of Alkyl-ZnX in THF.

General Methods for the Enantioselective Desymmetrization of Dimethyl Glutaric Anhydride Using *in situ* Prepared Nucleophiles.

General Method for Rhodium-catalyzed Desymmetrization on Small Scale.

To a flame dried 10 mL round bottom flask was added $[Rh(cod)Cl]_2$ (4 mg, 0.0088 mmol) and tBuPHOX (6.5 mg, 0.0176 mmol) in a glovebox. The flask was sealed with a septum, removed from the glovebox and purged with argon for 15 minutes. Anhydrous THF (2 mL) was added and then the nucleophile solution (0.3 mmol) was added via syringe. The solution was heated to 50 ^{o}C and dimethyl glutaric anhydride (25 mg, 0.176 mmol) in THF (1 mL) was added. The reaction was stirred at 50 ^{o}C overnight then subjected to an acid base workup. Specifically, the reaction mixture was partitioned between Et_2O (5 mL) and HCl (1 M, 5 mL)

and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic washings were extracted with $NaHCO_3$ (saturated, 3 x 5 mL) and the combined aqueous phases were acidified to pH 1 with concentrated HCl, and extracted with Et_2O (3 x 10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo to afford the free acid.

Method for (-)-(2R, 4S)-2,4-Dimethyl-5-oxo-hexanoic acid (24) on Gram Scale.

The title compound was prepared according to the general procedure for generating alkyl zinc reagents in THF. An oven dried round bottom flask was brought into the glovebox and charged with $[Rh(nbd)Cl]_2$ (0.031 g, 1 mol%) and *t*-BuPHOX (0.050 g, 2 mol%). The flask was sealed with a septum and removed from the glove box. The nitrogen atmosphere of the flask was flushed with argon. The metal and ligand were dissolved in 10 mL of dry THF. A solution of the zinc reagent in THF (0.5 M, 13.5 mmol) were added to the flask by syringe. A color change to dark red was observed. Reaction solution was stirred at room temperature for 30 minutes. The anhydride (1.0 g, 6.75 mmol) was added quickly by removing the septa and replacing it following addition. The atmosphere of the flask was flushed with positive pressure of argon. Reaction solution was allowed to stir for 16 hours at room temperature. After the reaction, an acid base extraction (see general work up procedure) provided pure acid as a light yellow oil.

General Methods for Preparation of Tetranate 49.

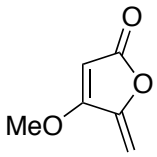
Preparation of 66

Into an oven dried 25 mL flask add lactone (0.500 g, 4.4 mmol). Pump/purge with argon. Add 3 mL of THF and cool to -78 ^{o}C in a dry ice/acetone bath. Add nBuLi (1.6 M in hexanes, 4.8 mmol). Let stir for 45 minutes. Add PhSeCl as a solution in THF (5 mL) dropwise over 20 minutes. Color changed from dark red to an orange red. The reaction was quenched with water, partitioned between water and EtOAc. Combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo to provide a red oil. Rf=0.5 in 1:1 Hexanes:EtOAc. This material was purified by silica gel column chromotography (2:1 hexanes/EtOAc).

Preparation of 67

In an oven dried scintillation vial, add stirbar and lactone oil (0.327 g, 1.2 mmol). Dissolve in anhydrous THF (5 mL) and cool the reaction to -78 ^{o}C in a dry ice/ acetone bath. Add tBuLi (1.7 M in pentanes, 0.895 mL, 1.5 mmol) and let stir at this temperature for one hour. At this point, MeI (stabilized by copper) was added by syringe (0.083 mL, 1.34 mmol) and the solution was stirred while gradually warming to room temperature. The reaction turned bright red at room temperature. The desired material was obtained following an aqueous extraction partitioned between water and EtOAc (30 total mLs). A yellow oil was obtained (94% yield).

Preparation of 49.



The lactone (0.269 g, 1.1 mmol) obtained from the previous step was charged to an oven dried scintillation vial. The atmosphere of the vial was pump/purged with argon, and 7.5 mL of DCM was added by syringe. The reaction vessel was cooled to 0 ^{o}C before adding mCPBA (0.214 g, 1.2 mmol) by quickly removing and replacing the septum. The reaction was flushed with positive pressure of argon for 2 minutes before allowing to stir for 3 hours. The reaction was quenched by adding water and stirring for an additional one hour. Finally the desired product was extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to provide the desired material as a colorless oil. The oil was purified by column chromotography eluted with 80:20 Hexanes:EtOAc and purity was checked by ^{1}H-NMR.

General Methods for the Aldol Reaction.

General Procedure for Isolating Metal Carboxylates

An oven dried 10 mL round bottom flask was charged with keto acid (0.115 g, 0.73 mmol) obtained from the general procedure for rhodium-catalyzed anhydride desymmetrization. This oil was dissolved in 2 mL of absolute EtOH. Next, LiOH (0.017 g, 0.730 mmol) was added to the solution followed by 3 mL of absolute EtOH and the reaction was allowed to stir while warming to 50 ^{o}C for 3 hours. Initially during this period LiOH was only partially soluble, as the solution

was heated it fully dissolved. By the conclusion of the three hours, another solid was observed to crash out. At this time the reaction was allowed to cool to room temperature before removing solvent in vacuo. Alternatively the solid can be filtered and dried in vacuo to provide pure carboxylate salt **77**.

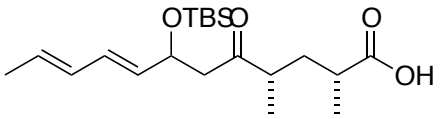
General Procedure for Aldol Reactions with Metal Carboxylates.

A 50 mL oven dried flask was charged with metal carboxylate solid as obtained from the general procedure for isolating metal carboxylates, and a stirbar. The flask was purged with argon and anhydrous THF (20 mL) was added by syringe. The solid was allowed to stir in THF for 30 minutes with agitation to facilitate uptake of the solid into solution. At this time the solution was cooled to -78 ^{o}C and a 2.0 M solution of LDA was added. The reaction was allowed to stir at this temperature for 2-3 hours. At this point, the reaction was slowly warmed to -40 ^{o}C before quenching with 10 mL of water. The organic phase was extracted with 3 x 10 mL of EtOAc. The combined organic phases were dried with Mg_2SO_4, filtered and dried *in vacuo* to provide the product as a crude yellow oil which was purified by column chromotography.

Procedure for Aldol Reactions on Gram Scale

A 100 mL oven dried round bottom flask was charged with NaH as a 30% dispersion in THF (0.504 g, 6.3 mmol, 1.1 equiv.). The flask was purged with argon and 20 mL of anhydrous THF was added by syringe. The reaction solution was cooled to -10 ^{o}C, and a solution of (-)-(2R, 4S)-2,4-Dimethyl-5-oxo-hexanoic acid (25) in 5 mL of THF, as prepared according to the general procedure for

rhodium-catalyzed desymmetrizations, was added slowly by syringe (0.9062 g, 5.7 mmol). Reaction was allowed to stir for 60 minutes. At the conclusion of this time, the reaction was cooled to -78 ^{o}C in a dry ice/acetone bath. A 2.0 M solution of freshly prepared LDA in THF (7.98 mmol) was added by syringe. The reaction was allowed to stir at -78 ^{o}C for 2 hours. At this time, freshly distilled aldehyde **46** (0.632 mL, 5.7 mmol, 1 equiv) was added. Reaction was allowed to stir for 6 hours, with slow warming to -40 ^{o}C. At this time, TBSOTf was added by syringe (0.028 mmol). The reaction was allowed to warm to room temperature before adding water. The organic layer was extracted 3 x 25 mL with EtOAc. Combined organic layers were dried over Mg_2SO_4, filtered and concentrated in vacuo to provide a brown oil. The resulting oil was purified by column chromotography (gradient 90:10 to 60:40) to provide the pure aldol product as a light yellow oil.



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The product was obtained as a light yellow oil (0.4135 g, 25%). This material was found to have an Rf of 0.25 in 4:1 Hexanes, EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$): 5.9-6.15 (m, 2H), 5.5-5.7 (m, 1H), 5.4-5.5 (dd, 1H, *J*=6.6), 4.6-4.7 (m, 1H), 2.7-2.9 (m, 1H), 2.35-2.55 (m, 4H), 1.7-1.8 (d, 3H, *J*=11.4), 1.5-1.65 (m, 1H), 1.1-1.2 (d, 3 H, J=6.9), 1.0-1.1 (m, 3H), 0.8 (s, 9H), 0.0 (s, 6H) ^{13}C NMR (75 MHz, $CDCl_3$): 181.3, 180.6, 142.5, 141.4, 134.6, 130.3, 127.0, 125.8, 97.4, 52.

7, 41.2 40.9, 37.2, 36.4, 36.0, 35.4, 28.2, 17.5, 16.8, 15.6. IR (NaCl, $CDCl_3$) 3500, 2959, 2857, 1712, 1580, 1462, 1361, 1252, 1071 cm^{-1}.

General Procedure for Conversion to Acid Chloride 80.

To a 100 mL oven dried round bottom flask, aldol product **69** (0.200 g, 0.54 mmol)was added. Flask was purged with argon and DMF (10 mL, 5 equiv) was added. The reaction was cooled to -10 ^oC. Et_3N (0.376 mL, 2.7 mmol, 5 equiv) was added by syringe. Oxalyl chloride (0.343 mL, 2.7 mmol) was added dropwise by syringe. Reaction was allowed to stir 30 min before concentrating in vacuo. This material was typically used without further purification.

General Procedure for Preparing 5-Methylene-4-methoxy-3-(tri-n-butylstannyl)-furan-2(5H)-one 81.

An oven dried round bottom flask was charged with tetranate **50** (0.102 g, 0.81 mmol) and the flask was purged with argon. Anhydrous toluene was added by syringe (3 mL) and the resulting solution was cooled to -78 ^oC. A 2.0 M solution of LDA (0.81 mmol) in toluene was added by syringe. The resulting solution was allowed to stir at this temperature for 1 hour. Finally, a solution of $ClSnBu_3$ (0.95 mmol) was added by syringe. The reaction was allowed to stir for an additional hour. Finally the reaction was warmed to room temperature and concentrated in vacuo to provide an oil. The resultant oil can be purified by column chromatography (3% ether/petroleum ether) to afford the pure material as a colorless oil. Matches reported by Ley and coworkers (Tetrahedron 1991, 47,

8285). 1H NMR (300 MHz, $CDCl_3$) 0.93 (9H, t, J = 7.3 Hz), 1.11 -1.55 (18H), 3.91 (3H, s), 4.88 (lH, d, J = 2.4 Hz), 4.91 (1H. d, J = 2.4 Hz).

General Procedure for Stille Cross-Couplings of 80.

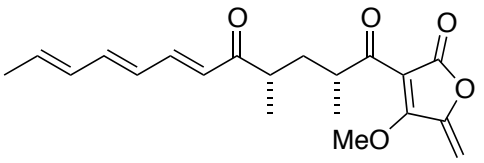
General Procedure for Stille Coupling with $Pd(PPh_3)_4$.

An oven dried 25 mL flask was charged with Pd(PPh3)4 (0.025 g, 0.0219 mmol) and CuI (0.042 g, 0.219 mmol) in the glove box. The flask was sealed with a septum and removed from the glove box. The atmosphere of the flask was flushed with argon for 2 minutes prior to the addition of 10 mL of DMF. The solution was stirred for several minutes at room temperature. A solution of acid chloride **80** (0.060 g, 0.219 mmol) in 5 mL of DMF was added by syringe. The reaction was stirred overnight prior to warming to 50 ^oC and stirring for an additional 10 hours. The reaction solution as cooled to room temperature, and partitioned with water and ether. A emulsion formed and a 20% solution of KF was added. The resulting layers were extracted with ether, combined, and dried over Mg_2SO_4. The ether layers were then filtered off and solvent was removed in vacuo to provide a crude oil.

General Procedure for Stille Cross-Coupling with $BnClPd(PPh_3)_2$

An oven dried 50 mL flask was charged with $BnClPd(PPh_3)_2$ (41 mg, 0.054 mmol), acid chloride **80** (0.54 mmol) as a solution in DCE (4 mL), and stannane **81** (0.81 mmol) as a solution in DCE (10 mL). The atmosphere of the flask was flushed with positive pressure of argon for 2 minutes before sealing with a septum. Anhydrous DCE (6 mL) was added by syringe, and the resulting

solution was heated to 60 °C for 16 hours. After this period, 10 mL of water was added and the organic layer was extracted with 3 x 15 mL ether. The combined organic layers were dried over Mg_2SO_4, filtered, and concentrated in vacuo to provide a red oil. The resulting oil was purified by running through a plug of silica gel eluted with 1:4 EtOAc, Hexanes. The combined fractions were concentrated in vacuo to provide a orange oil. Further purification was achieved with column chromotography eluted with 9:1 Hexanes, EtOAc to provide the product as a yellow oil (Rf=0.46 with 4:1 Hexanes/EtOAc).



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The product was obtained as a light yellow oil (16 mg, 20%). Preliminary data matches Sorensen's report (ACIE 2005, 117, 6691). Rf = 0.18 (4:1 Hexanes: EtOAc). 1H NMR ($CDCl_3$, 300 MHz, δ): 7.24 (dd, 1H), 6.57 (dd, 1H), 6.11–6.25 (m, 3H), 5.89–6.01 (m, 1H), 5.25 (d, 1H), 5.19 (d, 1H), 4.10 (s, 3H), 3.58–3.67 (m, 1H), 2.75–2.84 (m, 1H), 1.81 (dd, 3H), 1.25–1.33 (m, 1H), 1.13 (d, 3H), 1.11 (d, 3H). After a few hours of sitting at room temperature, the material was dissolved in toluene and heated to 100 °C overnight to provide complete decomposition.