Synthesis and Decarboxylative Coupling of Sulfonyl Acetic Esters

By

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Submitted to the Department of Chemistry and the Faculty of the Graduate School of the University of Kansas in partial fulfillment of the requirements of the degree of Doctor of Philosophy

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April 20, 2010

Date Defended

The Dissertation Committee for Jimmie D. Weaver certifies that this is the approved version of the following dissertation:

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Abstract

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The synthesis and palladium-catalyzed decarboxylative allylation (DCA) of α-sulfonyl allyl esters is the central focus of this dissertation. Specifically we describe the development of the racemic reaction in which the scope and mechanism are investigated. In addition, we demonstrate the superiority of Pd-catalyzed DCA to current methodology for the formation of tertiary sulfones. Furthermore, we demonstrate how the chemistry of the sulfone and the DCA, we developed, can be used in concert to obtain products that are not easily accessible. We next developed an asymmetric variant of the reaction in which the asymmetry comes from the substrate itself and not an outside source. Specifically, we observed high levels of conservation of enantioenrichment when the reaction proceeded in the presence of an achiral or racemic catalyst. We investigated this unusual behavior and propose a mechanism to explain the observation. Again, we compare the DCA to existing methodologies and demonstrate that it compares very favorably synthetically and in part answers unsolved challenges in asymmetric organic chemistry. In the course of this work it became apparent that the synthesis of our starting materials would also be a significant contribution to the field of organic chemistry. We have detailed the syntheses of both asymmetric and racemic sulfonyl acetic esters.

Finally, we detail experiments that have been performed to probe related and unrelated questions that have arisen throughout the course of this work.

For my family

When I stop to think about how I came to be in this position (writing an acknowledgement to this dissertation) I am overwhelmed with a since of gratitude for the many people in my life who have helped to guide me to this point. First, to my mother, Brenda Weaver, who devoted her life to rearing her children-I am so thankful. In addition to a healthy since of worth that you imparted, I also have taken from you an almost compulsive need to understand and get things "just" right. This can be both valuable and crippling and I have spent much of my graduate school career trying to harness this part of my personality that is so attributable to you. To my father, Jim Weaver, you told me and always demonstrated to your children that hard work was vital to success. I have taken these words to heart and they have served me well. To Robert and Donna, I am very blessed to have such wonderful people as in-laws. To my sisters Gina and Jana, I am very proud of both of you and currently seem to be able to remember only fond memories. Jana, for the record there were sheep in the field that day, maybe now you can let it go. To my wife, Rachel, I am so fortunate that you said yes and chose to come with me. I hope that you have enjoyed the last five years as much as I have. I look forward to and excited about sharing the rest of our life together. To our daughter, Ella, I maybe the luckiest dad around. I think you are beautiful and you make my heart warm every time I think about you.

Former lab mates, Erin, Shelli and Chao you guys set the standard high and I hope that I have met your expectations of a Tunge group member. Shelli, I am forever indebted to you for teaching a young headstrong graduate student and I will always cherish our friendship. I hope life allows our paths to cross frequently. To my current lab mates, Robert your diligence is amazing I hope life treats you well. Alex and Tony, it

has been fun to watch you guys "grow up" in a graduate student since. I am sure the Tunge group will be in good hands when you guys are on the elder students. I have enjoyed all conversations which sharpened all of our chemical intuition and often started as soon as two of us showed up in the morning and would last as long as two of us were at work. James, Yamuna, David, and Lucas I have enjoyed getting to know you and feel confident that you will all do well.

Committee members, Tim I have enjoyed our conversations, KU is lucky to have you here. Tom I have enjoyed getting to know you over the last two years. You have always been more than willing to share your insight on everything from Endnote to organic chemistry as well as chemical biology. Your insight into the importance and background of many of the molecules we have studied in problem sets and Molecule of the Semester has been invaluable as well as the insight of a seasoned organic chemist that you bring to the conversations. Helena, I have really enjoyed learning synthesis from you and to watch you teach about a subject that you are passionate-is inspiring. I have also enjoyed our conversations concerning chemistry and life in which you always shared thoughtful insight. Paul, your commitment to education is contagious. It is clear that problem set is a priority to you. You foster education. This is something that has been influential and I hope to take with me. Furthermore, your perpetual ability to see the silver lining in results and in people is admirable and is a testament to the ability to make good from bad.

Finally to my mentor Jon. I consider myself lucky to have been able to work with you over the last five years. You have created an atmosphere where students are allowed to be creative and to grow at their own pace. You share insight on every level, from the

best way to work up reactions to big picture things such as the things that make problems worth pursuing. You are slow to anger and quick to listen and this is a trait that can be ucommon. I consider myself very fortunate to have enjoyed my graduate career as much as I have, it is rare. However, this degree of contentment has come to be the norm in your group and this is a testament to your character and ability to help us see the importance of the work.

To all those who have helped me get here I am incredibly thankful.

Synthesis and Decarboxylative Coupling of Sulfonyl Acetic Esters

Abbreviations

Ac	acetyl
Ar	aryl
ADH	asymmetric dihydroxylation
Bn	benzyl
Bu	butyl
cat.	catalytic
COSY	correlation spectroscopy
Cp	cyclopentadienyl
dba	dibenzylidene acetone
DCA	decarboxylative allylation
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DIEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMF	*N*, *N*-dimethylformamide
DMSO	dimethylsulfoxide
dppb	diphenylphosphinobutane
dppe	diphenylphosphinoethane
dppp	diphenylphosphinopropane
dr	diastereomeric ratio
ee	enantiomeric excess
ent	enantiomer
Et	ethyl
EWG	electron-withdrawing group
GC	gas chromatography
Het	heteroaryl
HPLC	high pressure liquid chromatography

HRMS	high resolution mass spectrometry
IR	infrared radiation
L_L	large ligand
L_n	ligand
L_S	small ligand
Me	methyl
NBS	*N*-bromosuccinimide
n-BuLi	*n*-butyl lithium
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
Np	naphthyl
Nuc	nucleophile
Pd	palladium
Ph	phenyl
ppm	part per million
Succ	succinimide
TBAB	tetrabutylammonim bromide
TBAF	tetrabutylammonium fluoride
$_t$Bu	*tert*-butyl
Tf	triflate
TMEDA	tetramethylethylene diamine
TMG	tetramethylguanidine
TMSCl	trimethylsilyl chloride
tol	toluene
Ts	tosyl
μW	microwave

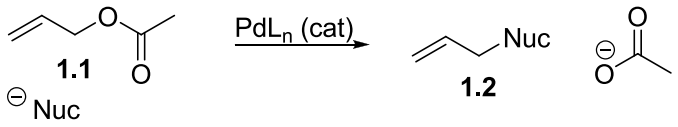
Chapter 1

Palladium-Catalyzed Decarboxylative Allylation:

1.1 Introduction to Tsuji-Trost Allylation

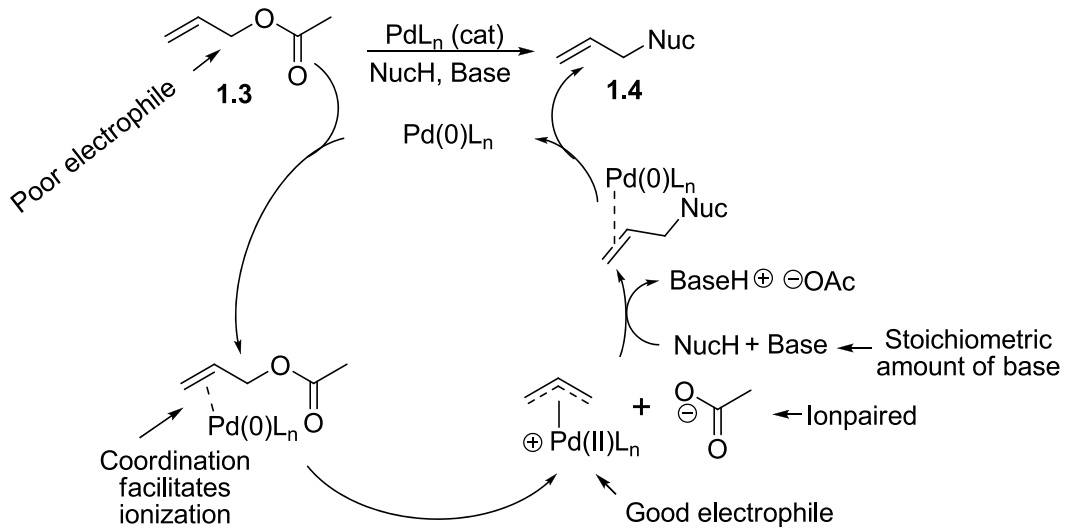
Historical Background for Pd-Catalyzed C-C Bond Forming Reactions

Carbon—carbon bond formation is the heart of organic chemistry. Naturally, reactions that generate new carbon—carbon bonds in a tolerant and selective manner are valuable. In 1965, Tsuji disclosed an allylation of stabilized nucleophiles via reaction with a palladium-π-allyl complex.[1] In the 1970's this reaction was rendered catalytic in palladium (Scheme 1.1).[2] In general, the Tsuji-Trost reaction refers to this catalytic nucleophilic substitution of an allyl acetate.



Scheme 1.1

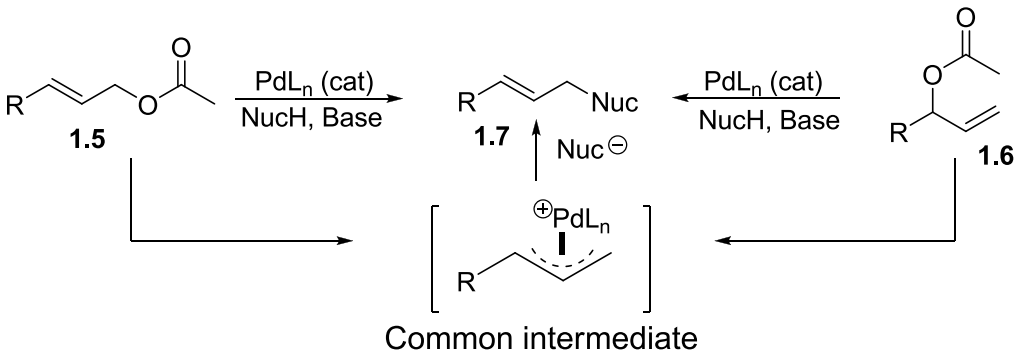
In general, the mechanism of the Tsuji-Trost reaction is as follows (Scheme 1.2); an electron-rich palladium(0) complex coordinates the olefin of the allyl acetate followed by nucleophilic displacement of the acetate by the palladium, generating a palladium-π-allyl complex that is ion-paired with the displaced acetate. The ability to access the ion-paired cationic palladium π-allyl complex is a crucial aspect which allows the complex to react as an electrophile. Meanwhile, the pronucleophile is deprotonated by the stoichiometric amount of base and undergoes a substitution to produce the product and regenerate the catalyst.



Scheme 1.2

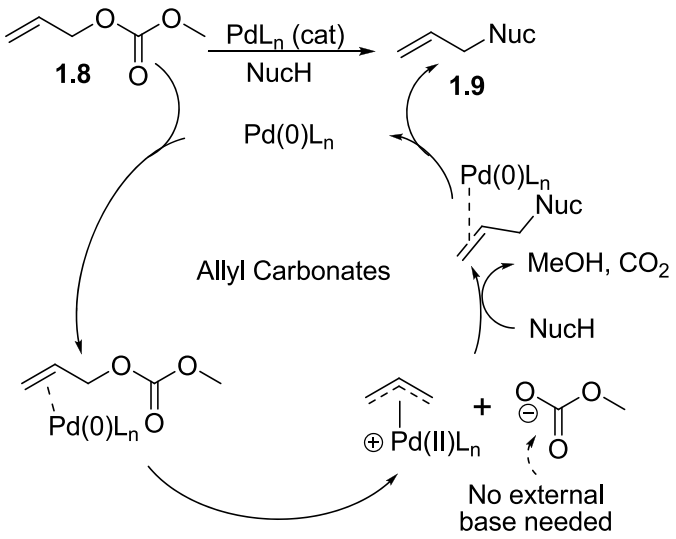
Regio- and Stereoselectivity of the Tsuji-Trost Reaction

Much of the mechanistic understanding of the Tsuji-Trost reaction comes from work done by Trost and coworkers.[3] When an unsymmetrical allyl acetate is used as a substrate, the nucleophile typically attacks at the less substituted carbon of the palladium-π-allyl intermediate affording the linear product (Scheme 1.3).[3a] Thus, regardless of the initial regiochemistry of the allyl acetate, the Pd-catalyzed Tsuji-Trost reaction provides the linear product selectively. This linear selectivity is typical of palladium. It is not typical of several other metals known to facilitate allylic substitutions similar to Pd. Specifically, Ni,[4] Mo,[5] Rh,[6] and Ru[7] have been similarly utilized in the Tsuji-Trost and selectively provide the complementary branched products.



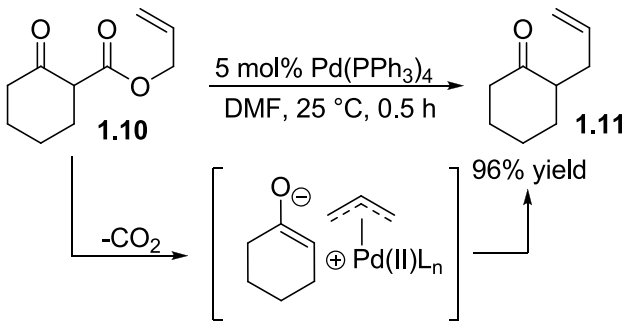
Scheme 1.3

As stated, the substitution of allyl acetates requires a full equivalent of base. In 1982,[6] Tsuji demonstrated that the palladium-catalyzed substitution of allyl carbonates could take place under neutral conditions (Scheme 1.4). The use of allyl carbonates effectively utilizes decarboxylation to reveal a latent base. The active base in most situations is the initial carbonate anion generated after ionization but ultimately loss of CO_2 provides the corresponding alcohol.[7] The use of allyl carbonates represents a significant advancement, not only allowing reaction with more base-sensitive substrates, but also reducing the number of necessary reagents needed to carry out the substitution. When the allyl carbonates are used, the catalyst generates the electrophile and reveals the latent base and after deprotonation of the pronucleophile generates the reactive nucleophile. One practical aspect of this is a reduction of over allylation of the nucleophile that is often problematic when there are stoichiometric amounts of nucleophile present.



Scheme 1.4

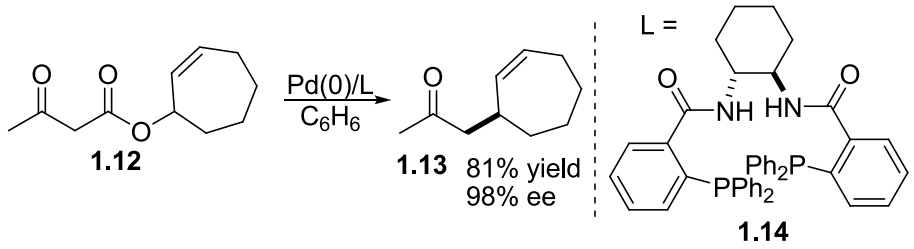
In 1980,[8] Saegusa and Tsuji demonstrated the palladium-catalyzed decarboxylative allylation of allyl β-ketoesters (Scheme 1.5). Upon decarboxylation, rather than generation of a base which could deprotonate a pronucleophile, a mono-stabilized nucleophile was generated. The nucleophile, a ketone enolate then underwent attack of the palladium-π-allyl complex to provide the homoallylic ketones and regenerate the catalyst. Though mechanistically distinct, the decarboxylative allylation of β-ketoesters affords the same products as that of the Carroll-rearrangement which typically requires high temperatures, ~240 ^{o}C.[9]



Scheme 1.5

The ability to generate and control highly reactive intermediates via decarboxylation has profound implication in the realm of bond making. It (1) removes the need for a base, as loss of carbon dioxide is responsible for the generation of the anion, (2) keeps reactive intermediates to a catalytic amount-allowing the reaction to be more functional group tolerant, and (3) replaces stoichiometric amounts of by-product salts with CO_2-making it a green alternative. Despite the potential of this methodology, surprisingly, very little[10] was done over the next two decades since Saegusa and Tsuji provided proof of concept.[8]

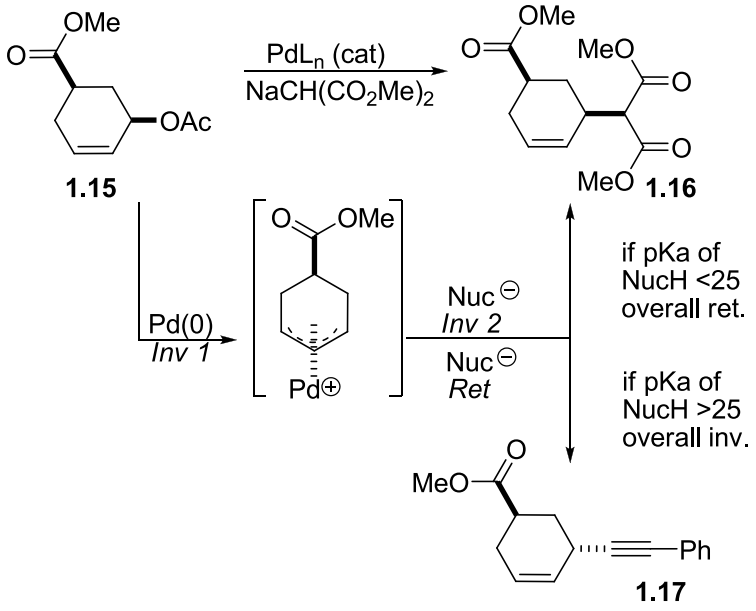
In 2004,[11] Erin Burger, a fellow Tunge group member, published the first example of an asymmetric decarboxylative allylation (Scheme 1.6). The homoallylic ketone product (**1.13**) is the apparent product of an asymmetric Carroll rearrangement.[9]



Scheme 1.6

Before the preceding reaction can be fully appreciated, a discussion concerning the stereochemistry of the Tsuji-Trost reaction is appropriate. Generally, the Tsuji-Trost reaction is a stereospecific process. By using both the *cis* and *trans* 3-acetoxy-5-carbomethoxycyclohexene, Trost[3c] showed unambiguously that the substitution with sodiodimethyl malonate, went with overall retention of stereochemistry (Scheme 1.7). This is general for "soft" nucleophiles ($pK_a < 25$). The overall retention can be envisioned as occurring via an inversion when the palladium displaces the leaving group followed by a

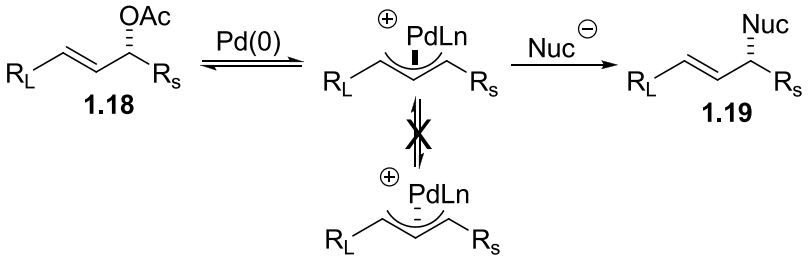
second inversion process when the nucleophile displaces the palladium. However, the mechanism and stereochemistry changes if the nucleophile is "hard" (pK_a > 25). Rather, than attacking the allyl ligand directly the "hard" nucleophile attacks the metal which then undergoes a reductive coupling from the same face as palladium. Thus, for hard nucleophiles the process involves inversion followed by retention to give an overall product of inversion.[12] In either case the initial stereochemistry is transferred to the product, thus the process is stereospecific.



Scheme 1.7

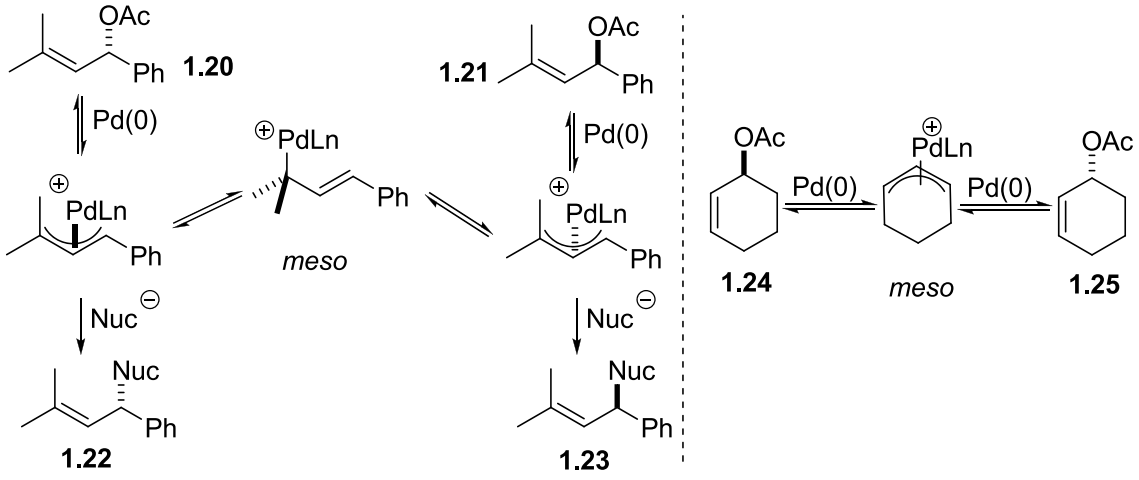
The palladium-catalyzed Tsuji-Trost reaction is stereospecific. One corollary is that the stereochemistry of the substitution is not always influenced by catalysts bearing chiral ligands (Scheme 1.8). In order for the palladium to be able to distinguish which face of the allyl is attacked it would need a manifold for isomerization between the two faces of the allyl ligand. A ligand, chiral or not, generally will not promote isomerization of the Pd-π-allyl

complex. However, in some cases when monodentate phosphine catalysts at high loadings were used with less reactive allyl substrates, it has been shown that a second Pd(0) molecule can displace the first thus providing a mode of isomerization.[13] This manifold is not significant at low catalyst concentrations since the stereochemical isomerization is bimolecular in palladium.



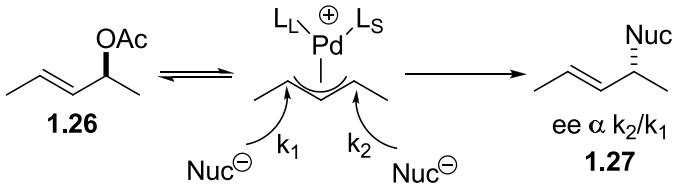
Scheme 1.8

A second corollary is that racemic allyl acetate leads to a racemic product, unless the substrate is part of a subclass of allyl acetates in which ionization is a stereoconvergent process (Scheme 1.9). In the first example, initial ionization leads to a chiral, non-racemic Pd-π-allyl complex, however, rapid slippage to the η^1-allyl leads to the achiral meso complex, from which the initial chiral information is lost. Likewise in the second example, upon ionization, the initial η^3-allyl complex is also meso and the chiral information of the acetate is lost. Within this subclass, enantioselective substitution is possible.



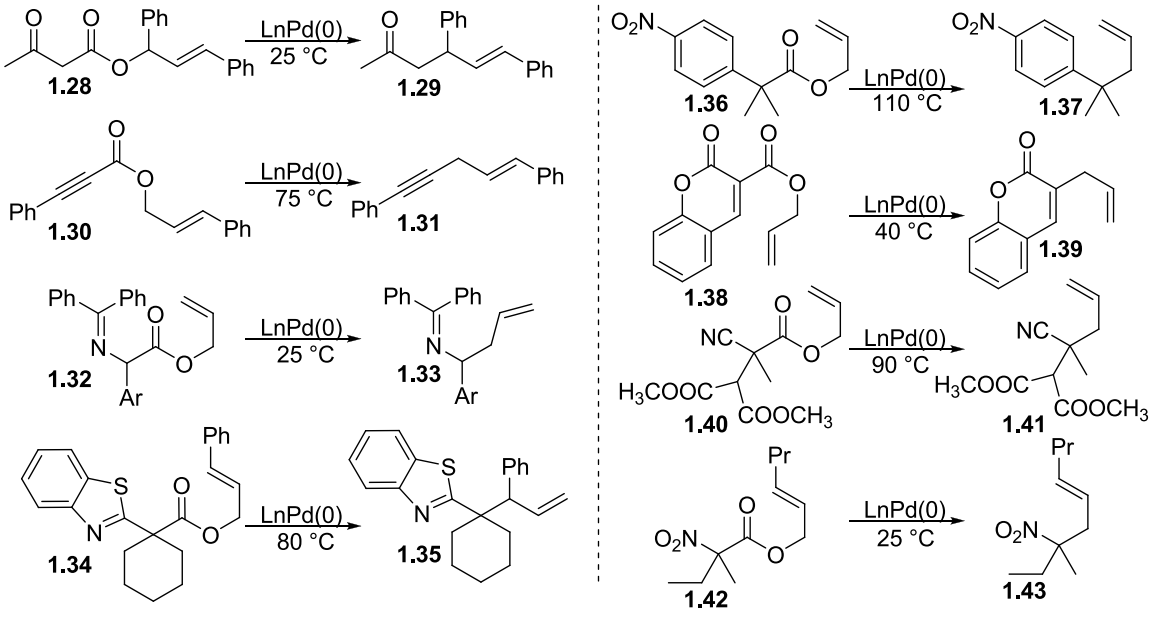
Scheme 1.9

Within the subclass of allyl acetates that undergo stereoconvergent ionization, asymmetric allylic alkylation is possible. A significant volume of work has been done utilizing these allyl acetates and much progress has been made in the field of asymmetric synthesis.[14] Once the palladium has erased the stereochemical history of the allyl acetate, asymmetry can be achieved if the ligand can create a rate difference between the attacks of the nucleophile to the enantiotopic termini (Scheme 1.10). Use of a chiral, non-racemic ligand on palladium has been used to achieve the necessary rate difference. The ligand differentially blocks one enantiotopic terminus more than the other, thus resulting in two possible diastereomeric transition states with unequal $\Delta G^{\ddagger}$, ultimately affecting the product distribution and the enantiomeric excess.



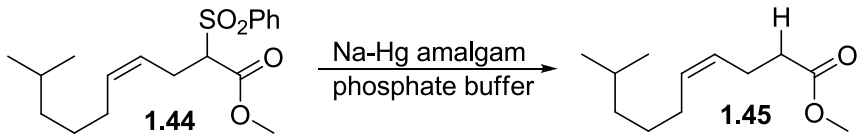
Scheme 1.10

After developing the decarboxylation of β-keto esters, the Tunge group has focused much of its efforts developing similar methods for a variety of functional groups that can stabilize the incipient anion generated via decarboxylation. As mentioned, Burger developed the decarboxylative allylation (DCA) of the β-keto esters[11,15] (Scheme 1.11). Rayabarapu showed that phenyl propiolate esters could also undergo DCA reactions.[12b] Additionally Burger developed the DCA of α-imino esters.[16] While Waetzig demonstrated that heteroaromatic esters[17] as well as nitroaromatic substrates[18] smoothly underwent decarboxylative coupling. More recently, Jana demonstrated that the coumarin derivatives also underwent DCA,[19] likewise Recio has shown that the α-cyano esters[20] are competent substrates for DCA and finally, Grenning has shown that the α -nitroester[21] undergoes rapid DCA.



Scheme 1.11

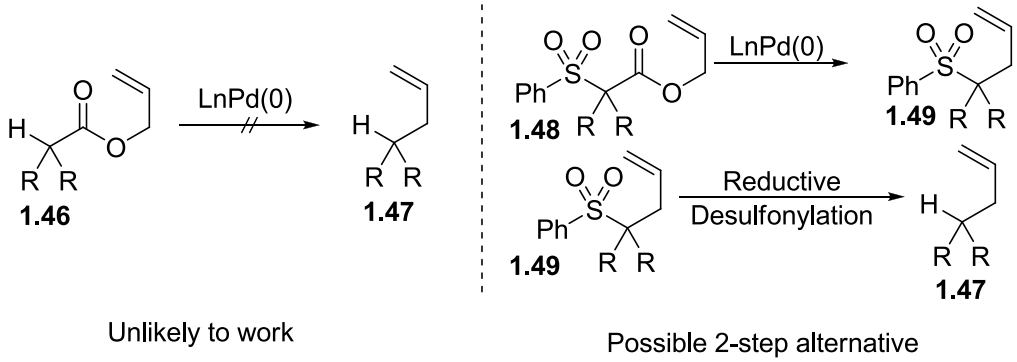
It should be noted that, with the exception of the coumarin substrates, the anion is stabilized and that the pK_a's are generally 32 or lower for the corresponding conjugate acid.[22] This seems to be the upper limit of where the barrier for decarboxylation becomes insurmountable and the rate of DCA becomes too slow for productive reaction. Within this limitation a wealth of chemistry has been developed, however, we felt it would be desirable to expand the limits of DCA. While it is unlikely that decarboxylative allylation involving unstabilized alkyl anions will ever come to fruition, we sought to develop an alternative that might provide the apparent products of a hydrocarbon DCA. Towards this end, the sulfone has a distinct advantage. Like other stabilizing functional groups such as the ketone, cyano, esters, etc. the pK_a of the alpha C-H's to a sulfone (ca. 23-31 in DMSO) is significantly lower than the corresponding hydrocarbon.[22] Unlike the other stabilizing functional groups, the sulfone is easily removed as demonstrated in this example by Trost and coworkers (Scheme 1.12).[3d]



Scheme 1.12

While the decarboxylative coupling of alkanes shown in Scheme 1.13 is unlikely to work due to the high reaction barriers associated with the intermediate anion formed, the DCA of the α-sulfonyl ester, (**1.48**), is more likely to work in analogy with the other DCA's that have been demonstrated.[11,12b,15-18,20-21] Merging the two preceding concepts suggest that the sulfones might be able to act as a surrogate for hydrocarbon decarboxylation. First, the

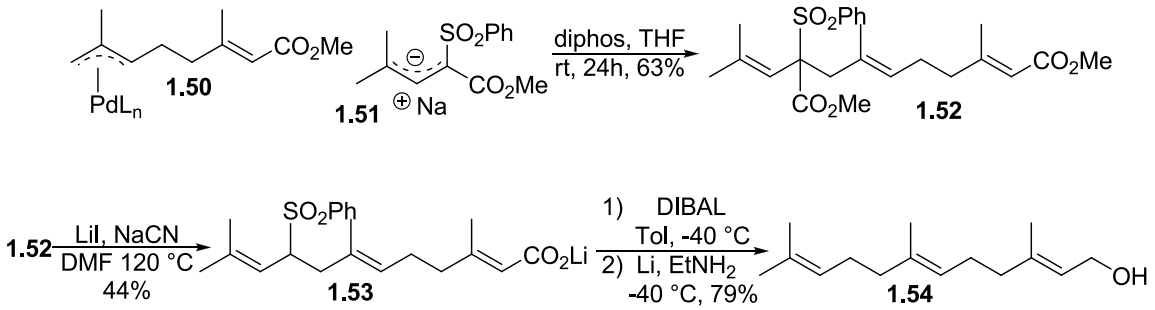
sulfone would facilitate the decarboxylative allylation afterwards the sulfone could be reductively cleaved to give the apparent product of hydrocarbon decarboxylative allylation (Scheme 1.13).



Scheme 1.13

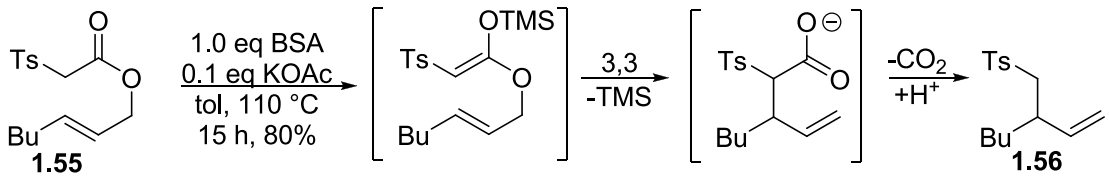
Synthesis of homoallylic sulfones

There are several general classes of reactions that allow for the synthesis of homoallylic sulfones. The sulfonyl-ester is a soft nucleophile that is ubiquitous in Tsuji-Trost chemistry and is often used for its ability to undergo catalyzed substitutions of allyl acetates. The ester can then be saponified and decarboxylated providing a homoallylic sulfone. Trost and coworkers elegantly utilized the sulfone in the first natural product synthesis[23] involving a palladium-π-allyl species (Scheme 1.14). A palladium-π-allyl complex, formed from methyl geraniate, (**1.50**) was subjected to the sulfonyl anion **1.51** and provided the homoallylic sulfone **1.52** in a 63% yield. In the next step, **1.52** was decarbomethoxylated to give the sulfone in 44% yield. Reduction of the carboxylate to the alcohol and reduction of the sulfone provided farnesol, **1.54**, over two steps 79%.



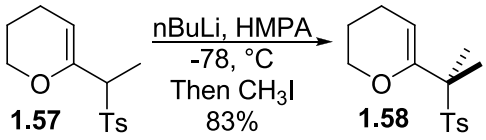
Scheme 1.14

While the Trost prenylation is a powerful method for sequential extension of acyclic terpenes, a functional group manipulation step is required in which a sensitive and poor yielding decarboxylation step removes the ester. More recently, Donald Craig and coworkers have developed a method that allows access to homoallylic sulfones from the α-sulfonyl allyl esters via a decarboxylative sigmatropic rearrangement (Scheme 1.15).[26] Treatment of the tosyl ester with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) traps the substrate as the silyl enol ether. The ether undergoes a 3,3-sigmatropic rearrangement and after desilylation reveals the carboxylate which decarboxylates generating a sulfonyl anion that protonates, providing a homoallylic sulfone. It is worth noting that this methodology can provide the complimentary branched regioisomer that would be difficult to obtain utilizing the palladium-catalyzed Tsuji-Trost reaction. However, the method requires that the ester have an enolizable proton, thus limiting it to secondary sulfones.



Scheme 1.15

If a tertiary sulfone is desired, the available methods for preparing such a compound are less attractive. Generally these sulfones are accessed by deprotonation and alkylation of a secondary sulfone. Deprotonation of the sulfone typically require strong bases (alkyl lithiums) as well as superstoichiometric amounts of highly toxic HMPA. Furthermore, reactions are usually carried out at cryogenic temperatures and utilize high energy and reactive alkyl halides. A typical procedure is shown in Scheme 1.16, in which Edwards was able to alkylate the sulfone (Scheme 1.16).[24]



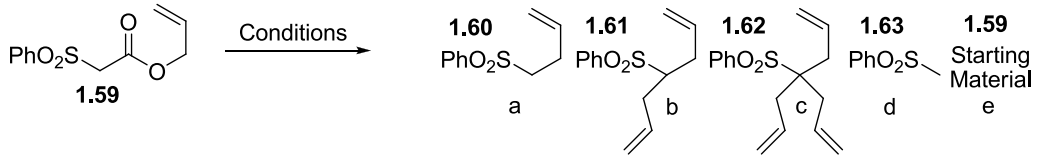
Scheme 1.16

The sulfone has been frequently employed in synthesis due in part to the versatile nature of this functional group which undergoes a wealth of chemistry.[25] Given the broad utility of sulfones and the less than ideal conditions for accessing tertiary sulfones, we believed a method that provides tertiary sulfones without the need for an external base or other additives would be a valuable addition to the field of organic chemistry. More specifically, we hoped that a palladium-catalyzed decarboxylative allylation of α-sulfonyl allyl esters analogous to other methods previously reported by our group[13,14b,18-20] might be developed. Furthermore, we believed that, if realized, this would be a valuable methodology that would allow access to tertiary sulfones that thus far had only been accessible via use of extremely basic, toxic, and high energy reagents.

1.2—**Development of methods for the DCA of sulfones**

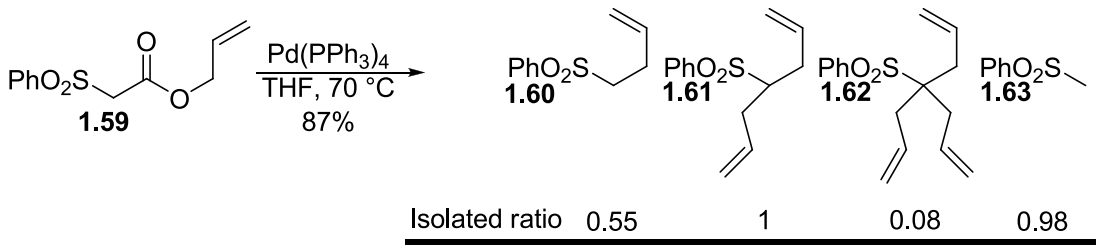
At the outset, we began our investigation of the decarboxylative allylation (DCA) of sulfones by looking at the simple unsubstituted allyl ester of α-sulfonyl acetic acid, synthesized via a DCC/DMAP coupling, in the presence of a Pd catalyst.[29] First we screened solvents (Table 1.1) and observed, in every solvent tried, complete consumption of the starting material. However, all of the reactions produced a mixture of products based on the crude ^{1}H NMR spectra after removal of the solvent. The one exception to this was the reaction run in DCM which provided only the product of protonation. While it was clear that the solvent played some role in product distribution, no choice of solvent allowed for the selective monoallylation in satisfactory quantity. The best result used 1,4-dioxane in which we observed ~1:1 ratio of monoallylation to protonation.

Table 1.1 Solvent Screening of Pd-DCA of Unsubstituted α-Sulfonyl Allyl Ester



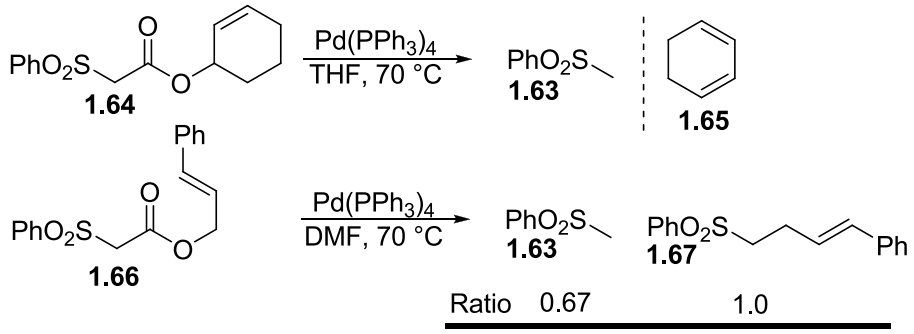
					Product Ratio				
Entry	Experiment	Solvent	Temp °C	Catalyst	a	b	c	d	e
1	JW2080	THF	70	$Pd(PPh_3)_4$	0.71	0.14	0	1	0
2	JW2083	MeCN	40	$Pd(PPh_3)_4$	1	0	0	1	0
3	JW2084	DCM	40	$Pd(PPh_3)_4$	0	0	0	1	0
4	JW2085	1,2-dichloroethane	40	$Pd(PPh_3)_4$	0.82	0.70	0	1	0
5	JW2086	Et_2O	40	$Pd(PPh_3)_4$	0.49	0.10	0	1	0
6	JW2087	1,4-dioxane	40	$Pd(PPh_3)_4$	1	0	0	0.96	0
7	JW2088	DMF	40	$Pd(PPh_3)_4$	0.36	0	0	1	0
8	JW2090	THF	70	$Pd(PPh_3)_4$	0.55	1	0.08	0.98	0

We scaled up the reaction in THF and isolated all of the products which aided in the analysis of the complex mixtures (Scheme 1.17). Overall the reaction gave an 87% yield based on the sum of all the products. Interestingly the amount of diallylation was far more prevalent than in the corresponding reaction in the solvent screening. This might have been due to differences in concentration which we later learned plays an important role.



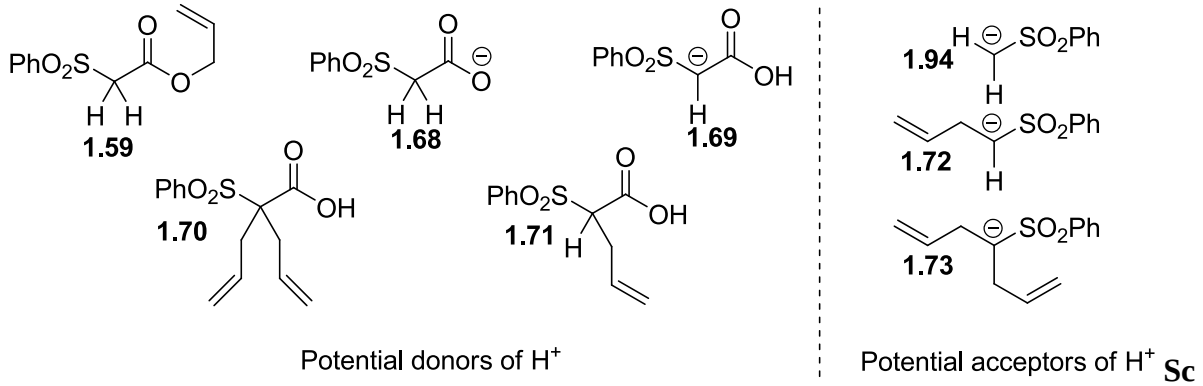
Scheme 1.17

In addition to the allyl ester, we attempted the DCA of two other esters (Scheme 1.18). One ester was derived from cyclohexenyl alcohol and the other cinnamyl alcohol. The cyclohexenyl ester gave all protonation product and presumably cyclohexadiene. This result is not surprising considering the problematic protonation that we had already observed in the case where no β-hydrogen was available (Scheme 1.16). Slightly better product distribution were observed when the cinnamyl ester was decarboxylated in DMF using $Pd(PPh_3)_4$ as the catalyst.



Scheme 1.18

One possible explanation for the protonation and over allylation products is a series of proton transfer from several potential intermediates (Scheme 1.19). There is evidence that some DCA's occur by initial transfer of an α-proton to the exposed carboxylate[26] which in DMSO is considerably more basic.[22] If the rate of this type of reaction is on par with decarboxylation it is likely that several products will arise. Thus we believed that more substitution in the alpha position might allow for a more selective reaction.

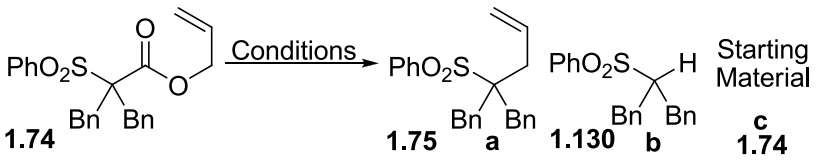


Sc heme 1.19

In an attempt to circumvent the over allylation products we observed, we synthesized and subjected an α,α-dibenzyl sulfonyl acetic ester to Pd-catalyzed DCA (Table 1.2). It was found that when DMF was used as a solvent at various temperatures and with various ligands, the protonation product was formed almost exclusively. The solvent was altered and $Pd(PPh_3)_4$ was used; better results were obtained using CH_3CN and THF, while 1,4-dioxane gave an inextractable mixture that did not resemble any known product. In addition, we ran the reaction in toluene-d_8 and using $Pd(PPh_3)_4$ as the catalyst and found this gave our best

results, a 1:1 mixture of the desired monoallylation to the protonation product. In each of the reactions the starting material was completely consumed.

Table 1.2 Initial Screening of Pd-DCA of α,α-Dibenzyl α-Sulfonyl Allyl Ester



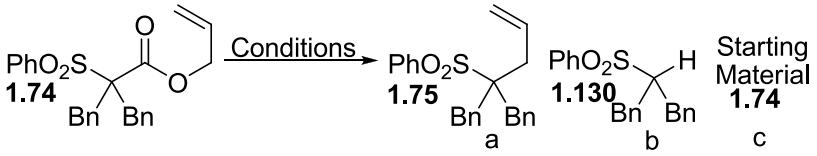
Entry	Experiment	Solvent	Temp °C	Catalyst	Product Ratio a	b	c
1	JW2102	DMF	50	$Pd(PPh_3)_4$	0.1	1	0
2	JW2101	DMF	70	$Pd(PPh_3)_4$	0	1	0
3	JW2103	DMF	90	$Pd(PPh_3)_4$	0.1	1	0
4	JW2104	DMF	70	dppf	0	1	0
5	JW2105	DMF	70	dppp	0.1	1	0
6	JW2100	THF	70	$Pd(PPh_3)_4$	0.63	1	0
7	JW2106	1,4-dioxane	70	$Pd(PPh_3)_4$	NA*	NA*	NA*
8	JW2107	CH_3CN	70	$Pd(PPh_3)_4$	0.33	1	0
9	JW2109	d-Tol	70	$Pd(PPh_3)_4$	1	1	0

* indiscernible mixture.

Utilizing α,α-dibenzyl α-sulfonyl acetic allyl ester, we found that the temperature did have some effect on the product distribution (Table 1.3). At 50 ^{o}C protonation was the major product but heating to 70 ^{o}C or 95 ^{o}C seemed to mitigate the amount of protonation. Next, we looked at the effect of the ligand. The use of bidentate ligands had a dramatic effect on the product ratio; dppf, dppe, dppp, dppb all gave roughly 3:1 mixture of the desired product to protonated product. Josiphos gave a slightly improved product ratio of ~4.5. To our

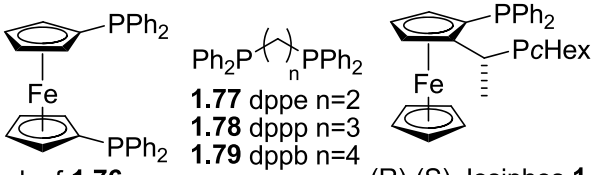
delight, we found that racemic-BINAP gave ~12:1 ratio, while racemic amino BINAP essentially shutdown the reaction and the starting material remained.

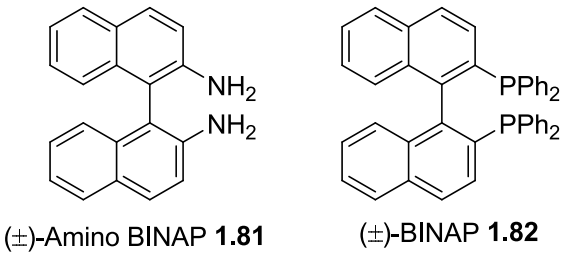
Table 1.3 Ligand Screening of Pd-DCA of α,α-Dibenzyl α-Sulfonyl Allyl Ester



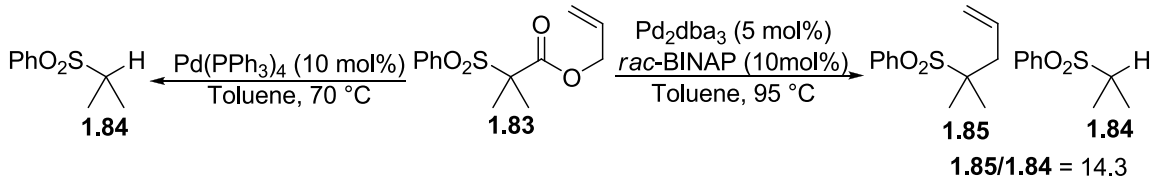
Entry	Experiment	Solvent	Temp °C	Catalyst	Product Ratio a	b	c
1	JW2110	d-Tol	50	$Pd(PPh_3)_4$	0.48	1	0
2	JW2109	d-Tol	70	$Pd(PPh_3)_4$	1	1	0
3	JW2111	d-Tol	95	$Pd(PPh_3)_4$	1	0.95	0
4	JW2112	d-Tol	70	dppf*	1	0.32	0
5	JW2113	d-Tol	70	dppp*	1	0.72	0
6	JW2116	Tol	95	dppe*	1	0.38	0
7	JW2117	Tol	95	dppp*	1	0.29	0
8	JW2118	Tol	95	dppb*	1	0.38	0
9	JW2119	Tol	95	dppf*	1	0.32	0
10	JW2120	Tol	95	Josiphos*	1	0.22	0
11	JW2121	Tol	95	*rac*-BINAP*	1	0.09	0
12	JW2122	Tol	95	*rac*-Amino BINAP*	0.1	0	1

*Pd_2dba_3 (0.05 eq) and Ligand (0.01 eq)





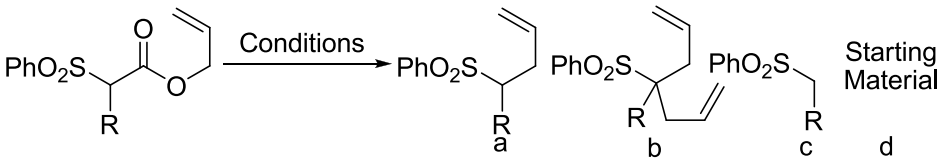
It is not clear how it is that the BINAP ligand is so effective in shutting down the protonation or alternatively accelerating the allylation pathway but further evidence is provided in Scheme 1.20. The same substrate was subjected to two sets of similar conditions with the major exception of catalyst choice. Use of $Pd(PPh_3)_4$ led solely to protonation while use of the bidentate ligand BINAP provided the homoallylic sulfone with high selectivity.



Scheme 1.20

We briefly looked at substrates that had only one acidic proton (Table 1.4). In short, under none of the conditions could we obtain the desired product in a satisfactory manner. Again the amino BINAP shut the reaction down, DMF generally promoted diallylation and protonation, and BINAP promoted monoallylation, however, not sufficiently. The best result gave a ratio of 1: 0.4: 0.4 of monoallylated; to diallylated; to protonated products. It is quite possible that further optimization would allow for more selective product formation. For instance, another condition that might be important but which we did not optimize is the substrate concentration. It is possible a proton transfer between two substrates is necessary in order to achieve the diallylation product and thus might be sensitive to concentration. We were curious whether the conditions that gave good results for the dibenzylated substrates would also improve selectivity in unsubstituted substrates.

Table 1.4 Initial Screening of Pd-DCA of α-Benzyl α-Sulfonyl Allyl Ester

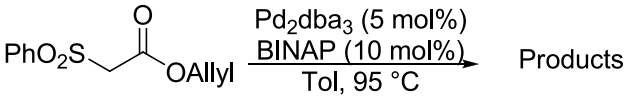


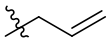
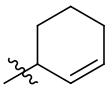
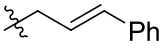
Entry	Experiment	Solvent	Temp °C	R	Catalyst	Product Ratio a	b	c	d
1	JW2126	d-Tol	110	Bn	*rac*-Amino BINAP*	0	0	0	1
2	JW2128	DMF	90	Bn	$Pd(PPh_3)_4$	0.59	0.05	1	0
3	JW2129	d-DCM	45	Bn	$Pd(PPh_3)_4$	0	0	0	0
4	JW2130	Tol	90	Bn	$Pd(PPh_3)_4$	1	0.19	0.9	0
5	JW2132	THF	70	Bn	$Pd(PPh_3)_4$	1	0.32	0.54	0
6	JW2158	Tol	95	Me	*rac*-BINAP*	1	0.62	0.28	0
7	JW2159	Tol	95	Bn	*rac*-BINAP*	1	0.4	0.4	0
8	JW2160	THF	70	Me	*rac*-BINAP*	1	0.42	0.53	0
9	JW2161	THF	70	Bn	*rac*-BINAP*	1	0.66	0.66	0
10	JW2164	DMF	95	Me	*rac*-BINAP*	1	0.75	0.75	0
11	JW2165	DMF	95	Me	Josiphos*	0.1	1	1	0
12	JW2166	DMF	95	Me	P(*o*-Tol)$_3$*	0	1	1	0
13	JW2167	DMF	60	Me	$Pd(PPh_3)_4$	0	1	1	0

*Pd_2dba_3 (0.05 eq) and Ligand (0.01 eq)

Thinking that conditions that were optimal for the α,α-dialkyl sulfones might also improve selectivity for the unsubstituted sulfones we subjected three unsubstituted sulfones to 10 mol% Pd/BINAP, unfortunately the reactions were not very selective for our desired product (Table 1.5).

Table 1.5 Attempts to Improve Selectivity Using Optimal Conditions

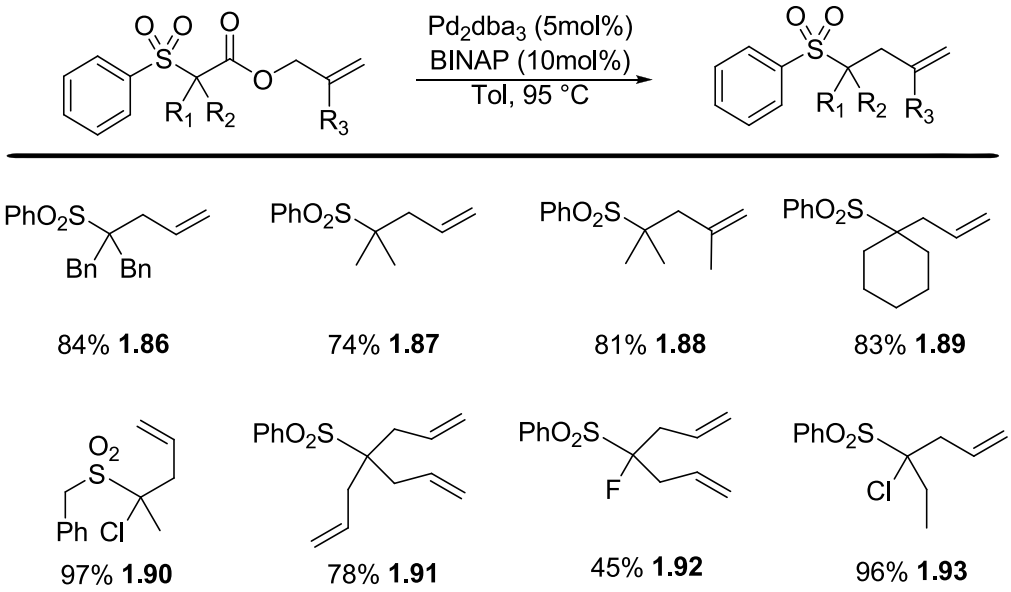


Allyl	PhO_2S	PhO_2S Allyl	PhO_2S (Allyl)$_2$	PhO_2S (Allyl)$_3$
	1	0.95	0.41	0.24
	1	0	0	0
	1	1	0.3	0

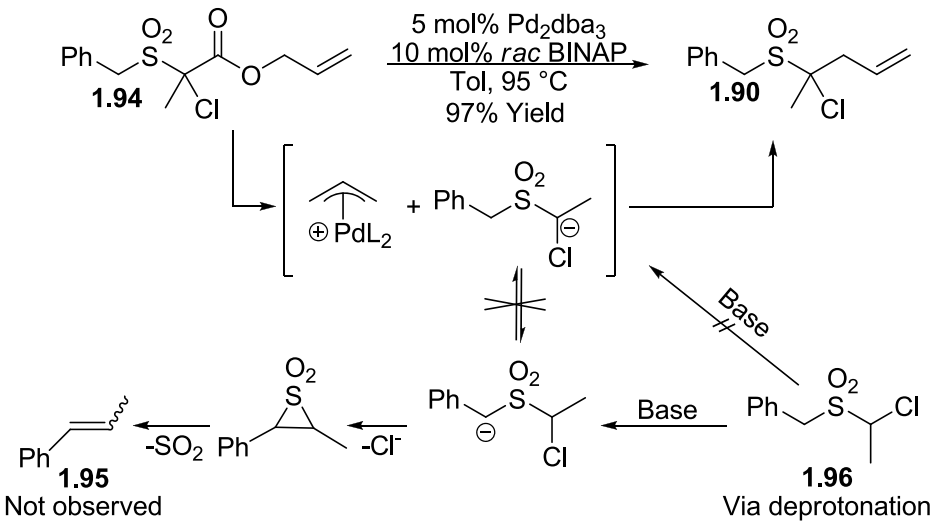
We next synthesized and subjected a range of dialkyl allyl sulfones to the optimized conditions for DCA.[29] The Pd-catalyzed DCA typically gives yields between 74-84% of most dialkyl sulfones (Table 1.6). The inclusion of either a fluoro or chloro substituent has a significant effect. The fluoro group seems to slow the reaction compared to a dialkyl substrate and gives reduced yield (45%), though this yield was somewhat reduced because of isolation issues. A chloro substituent, on the other hand, dramatically accelerates the reaction and provides the product in a higher yield. For example the benzyl sulfone with α-chloro and α-methyl substituents undergoes DCA to provide the product in 97% yield. The phenyl sulfone with α-chloro and α-ethyl substituents also undergoes DCA to provide the product in 96%. Typically the α-chloro substrates reached completion within a couple of hours. It was later learned that a slight increase in yield could be achieved by increasing the concentration; most of these reactions were run with an initial ester concentration of ~0.1 M. Increasing the reaction concentration to 0.2 M, with respect to substrate, typically results in

~10% higher yields compared to those shown Table 1.5 of the dialkyl substrates, however, the catalyst seems to be at the limits of its solubility.

Table 1.6 Isolated Yields of Pd-Cat DCA Dialkyl Sulfonyl Esters



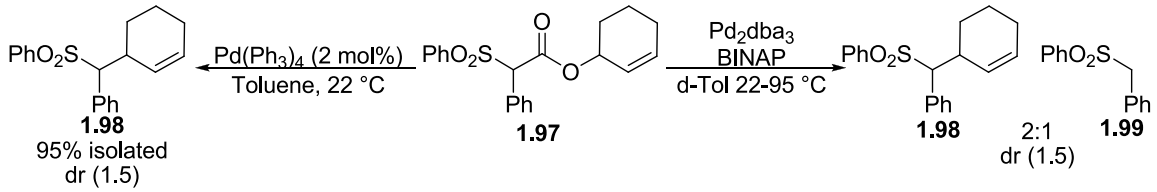
While most substrates were phenyl sulfonyl esters, a benzyl sulfonyl ester provided a high yield of DCA product as well. The benzyl sulfonyl ester is worth noting for two reasons (Scheme 1.21). First, it demonstrates that the phenyl sulfur substituent is not required for the reaction to work. Secondly, it illustrates the regiospecific nature of the anion formed from decarboxylation, no allylation of the benzylic position or olefin from a Ramberg-Bäcklund[27] reaction were observed. The anion that is generated via decarboxylation is approximately 3 pK_a units more basic than a benzylic sulfone. The anion that could be formed via deprotonation would likely be limited to the benzylic position as it is also the kinetic product of deprotonation.[28] Thus DCA of **1.94** gives access to an anion that is not accessible via traditional methods.



Scheme 1.21

Benzylic α-sulfonyl anions ($PhSO_2CH_2Ph$, pK_a = 23) are significantly more stable than the corresponding hydrocarbon anion ($PhSO_2CH_2Me$, pK_a = 31).[22] Consequently, it is not uncommon to see significant differences in mechanism and substrate scope when the allyl ester has an α-aryl group and this has been observed in several of the DCA methods developed by our group to date.[12b,16,20] Hoping that the addition of a phenyl group in the alpha position would make the reaction more tolerant of both α-H's and β-H's on the allyl component, cyclohex-2-enyl 2-phenyl-2-(phenylsulfonyl)acetate was synthesized. The substrate was first subjected to the standard conditions which required some heating but gave more allylation product than any other substrate with β-H's (2:1 allylation to protonation). Additionally, the reaction was not very diastereoselective giving a dr of 1.5:1.0 (Scheme 1.22). Because of this result, we were optimistic that we might find conditions that would allow us to expand the scope to include α-aryl species. Believing that the Pd/BINAP

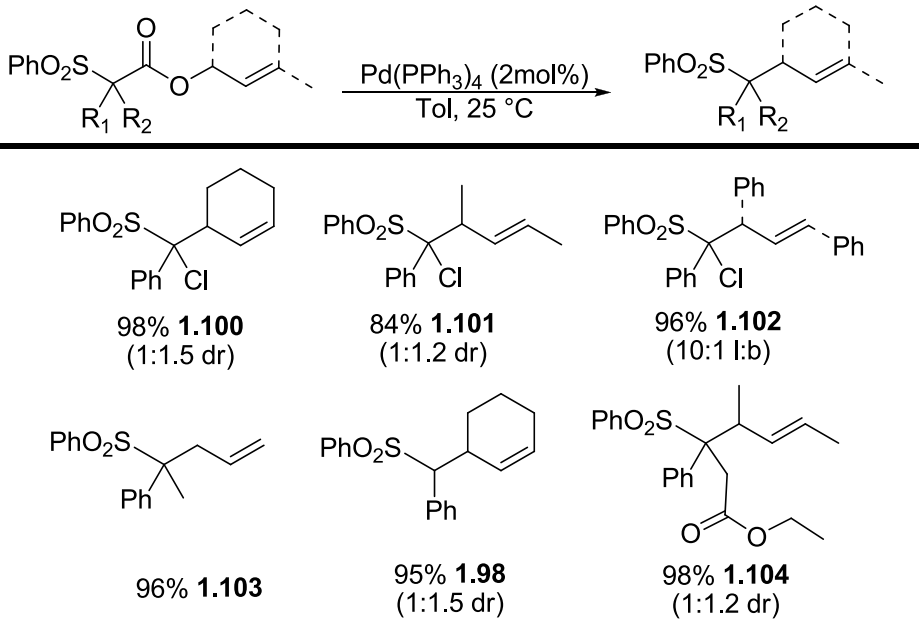
catalyst, formed *in situ*, struggles to ionize terminally substituted allyl acetates we thought that changing to a more labile monodentate phosphine ligand would allow more facile ionization. Furthermore, we expected that the added benzylic stabilization of the incipient anion would help to circumvent some of the problems previously mentioned including elimination. Changing the catalyst to $Pd(PPh_3)_4$ had several remarkable effects. First, the desired allylation product was formed in much greater quantity-giving an isolated yield of 95%. Second, the temperature could be reduced to room temperature. Third, the catalyst loading was reduced from 10 mol% Pd to 2 mol%. Last, the reaction time was considerably shorter ~2 half-lives in 2.5 h at 22 °C compared to no observable reaction using the Pd/BINAP catalyst.



Scheme 1.22

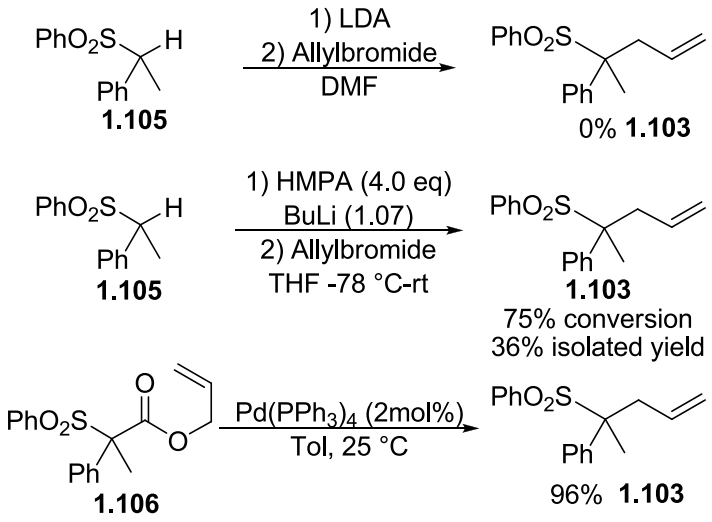
Next, a range of α-phenyl substituted sulfonyl esters were synthesized and subjected to DCA (Table 1.7). It is noteworthy that in general yields were excellent. Furthermore, the reaction was regioselective, giving the expected linear selectivity (**1.102**, 10:1 l:b). The reaction was also highly chemoselective as the chloro substituent remained unchanged during the reaction.[29] Formation of quaternary centers next to tertiary centers is a challenging problem and the DCA of these sulfonyl esters allows smooth carbon-carbon formation between two hindered centers. Unfortunately, the reaction is not highly diastereoselective.

Table 1.7 Isolated Yields of Pd-Cat DCA of α-Phenyl Sulfonyl Esters



One of the primary goals of this project was to develop a superior method that gave access to tertiary homoallylic sulfones. To demonstrate the advantage of our DCA method we attempted to synthesize the same homoallylic sulfone under several traditional conditions (Scheme 1.23). The sulfone, **1.105**, was subjected to LDA and then allyl bromide was added. However, none of the desired product could be detected by ^{1}H NMR spectroscopy after a standard workup. It is likely that the hindered base struggled to remove the hindered proton. With the use of 4.0 equivalents of toxic HMPA and a slight excess of BuLi at -78 ^{o}C, then addition of allyl bromide gave 75% conversion by ^{1}H NMR spectroscopy but only a 36% yield of the desired product. Using the conditions that we had found gave a 96% isolated yield under essentially neutral conditions at ambient temperature. Thus, based on the ability to avoid toxic and high energy reagents, improved yields, and more simplistic

reaction procedures we believe that the Pd-catalyzed DCA is superior to traditional methodology.

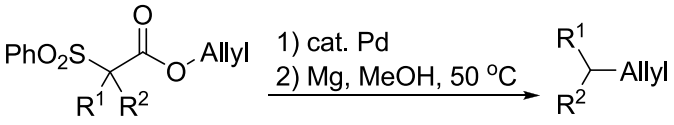


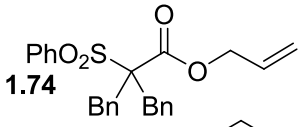
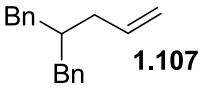
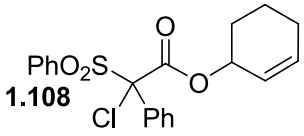
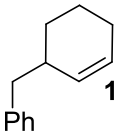
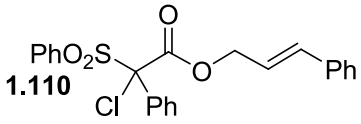
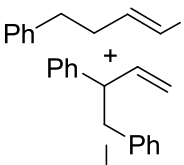
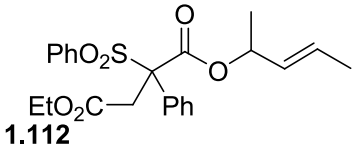
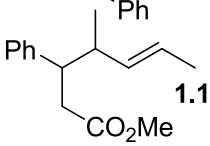
Scheme 1.23

Having established DCA of sulfonyl esters as a green alternative for the synthesis of homoallylic sulfones we turned our attention to our second goal demonstrating the ability of the sulfone to act as a "traceless" activator for hydrocarbon DCA. As discussed previously, the sulfone has been used synthetically for its ability to stabilize negative charge and then be reductively removed, i.e. "traceless" activation.[25] Usually this is accomplished by a dissolving metal reduction that utilizes mercury amalgams in a protic solvent. Traditional sulfone reductions do have the drawback that they produce superstoichiometric amounts of toxic metal salts. Furthermore, these reductions are not terribly chemoselective and thus limit the number of substrates that can survive the conditions. In 1985, Brown and Carpino[30] reported the use of magnesium in methanol as an alternative to the traditional mercury-

amalgam. To our delight, utilizing reagent grade magnesium and methanol afforded the corresponding reduced hydrocarbons in good yields (Table 1.8). The reactions typically required 2-3 h and were easily monitored by TLC. As the reaction progressed, it was often necessary to add more magnesium as it was consumed independent of the substrate reduction. Thus we demonstrated the two-step yields of DCA and reduction for several substrates (Table 1.8). Entry one demonstrates that the dialkyl sulfone can undergo reduction while entries 2 and 3 show that chloride is also reduced. Entry 3 gives some branched product which is a result of the DCA linear to branch selectivity. Entry 4 shows that reduction must take place faster than elimination. In this case, transesterification to the methyl ester also occurred, but at a slower rate than reduction. Thus, extended reaction times were necessary to allow the reaction to go to completion. Unfortunately, the diastereomeric ratio of the decarboxylative coupling product did not significantly change upon reduction.

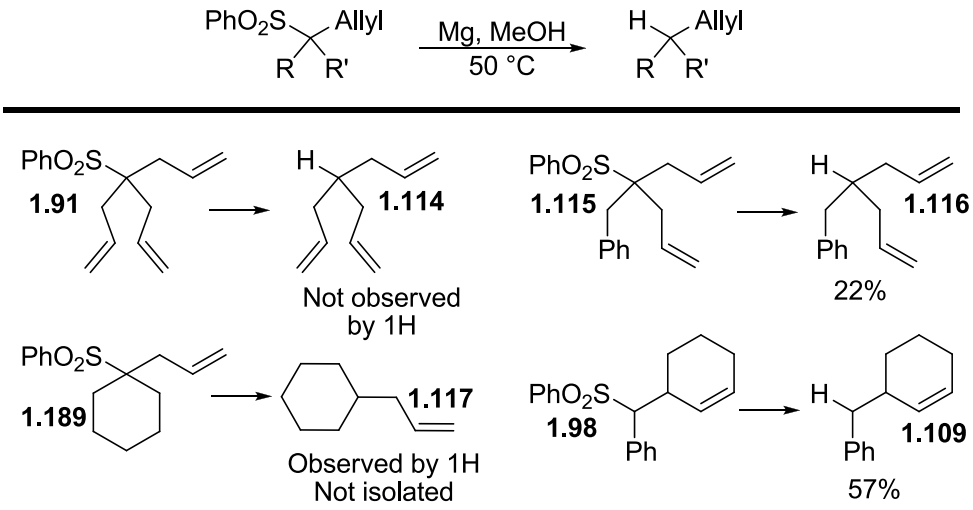
Table 1.8 Two Step Yields: Pd-Cat DCA and Desulfonylation



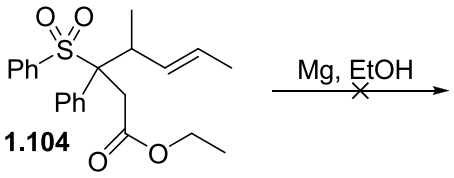
Entry	Substrate	Product	Yield (%)
1	 **1.74**	 **1.107**	74
2	 **1.108**	 **1.109**	83
3	 **1.110**	 **1.111**	69 (10:1 l:b)
4	 **1.112**	 **1.113**	79 (1:1 dr)

We subjected several other sulfones to the magnesium-methanol procedure (Table 1.9) and in every reaction the sulfone was consumed. It is likely that diallyl substrates, rather than the reduction, undergo other chemistry, as none of the expected product was observed in the ^{1}H NMR spectrum after filtering and removing the methanol. However, it is also possible that this substrate was too volatile to observe after removal of the phenyl sulfonyl group. The cyclohexyl substrate, on the other hand, was observed by ^{1}H NMR spectroscopy, but could not be isolated by column chromatography. The diallyl substrate also has a benzyl substituent and is less volatile, however, it still gave a reduced yield, hinting that multiple olefins in homoallylic position are potentially detrimental to the reduction.

Table 1.9 Magnesium-Methanol Desulfonylation



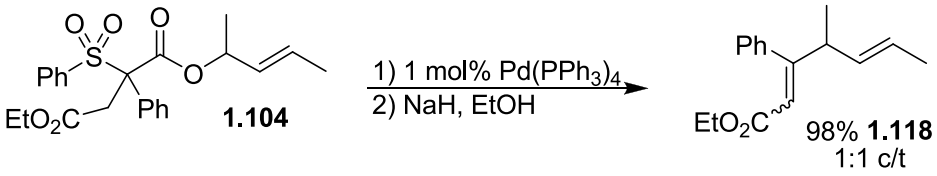
As previously discussed, we observed eventual transesterification from the ethyl ester to the methyl ester in substrates possessing an ester functional group. In an attempt to avoid this we tried the reduction in EtOH rather than MeOH (Scheme 1.24). Interestingly, the reaction does not work; this selectivity was also observed by group member Chao Wang when he attempted to desulfonylate a sulfonamide.[31]



Scheme 1.24

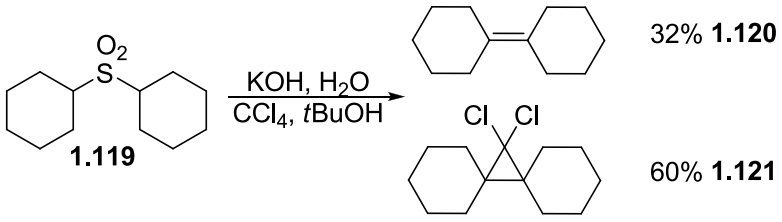
Like other electron withdrawing groups, the ability for the sulfone to stabilize the incipient anion allows for the decarboxylative allylation to occur. Unlike other functional groups that facilitate DCA, the sulfone can also act as a leaving group. Consequently, substrates with a relatively acidic hydrogen β to the sulfone should be able to undergo

elimination. To demonstrate this we subjected **1.104** (Scheme 1.25) to K_2CO_3 as well as triethylamine in H_2O, acetone-d_6, CH_3CN-d_3, and toluene-d_8 but none of these conditions led to any elimination product. Use of an alkoxide base, however, smoothly eliminated the sulfinate salt affording a skipped diene ester. Such an elimination allows a facile two step procedure, Pd-cat DCA then elimination, to afford a 98% yield of a 1:1 *cis:trans* mixture of the skipped diene ester.



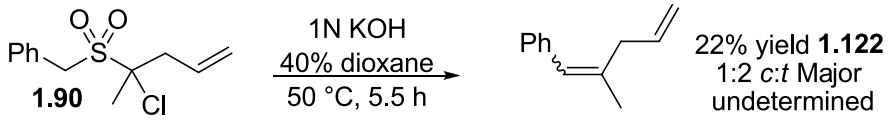
Scheme 1.25

We demonstrated that α-chloro sulfonyl esters undergo facile DCA (Tables 1.6 and 1.7). This suggests that DCA reactions might provide a facile route to substrates for Ramberg-Bäcklund reactions. The Meyers modification of the Ramberg-Bäcklund reaction nicely allows for the *in situ* formation of the α-chloro sulfone but often suffers from dichlorocarbene addition to the newly formed olefin (Scheme 1.26).[32] Several solutions have been put forth including carbene scavengers such as phenols or addition of sacrificial olefins as well as the use of CBr_2F_2 which produces the less reactive difluorocarbene.



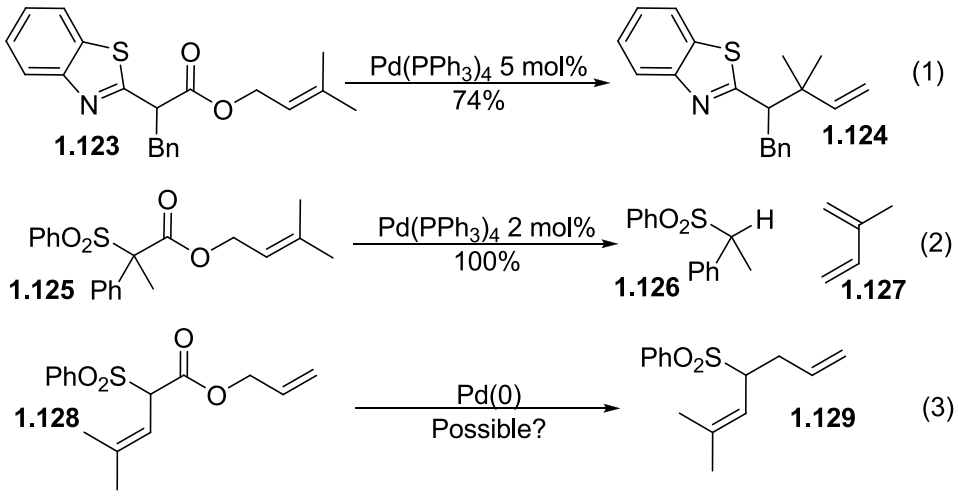
Scheme 1.26

We subjected one of our homoallylic sulfones to standard conditions[33] for Ramberg-Bäcklund reactions and were able to isolate a meager 22% yield of the product as a 1:2 mixture of the *cis* and *trans* isomers, though we did not determine the major isomer (Scheme 1.27). Based on TLC and the ^{1}H NMR spectrum, the starting material was completely consumed. However, it is suspected that polymerization of the product (**1.122**) was also occurring since there was a spot that did not move at all on the TLC but stained when exposed to permanganate stain, indicating that olefins were likely present. Since the results were disappointing, we did not try to optimize this but rather turned our attention to other questions.



Scheme 1.27

Prenylation is an outstanding challenge since prenyl groups are important building blocks that frequently occur in the form of the terpene natural products. We believe that DCA can play an important role in prenylation methodology. For example, Shelli Waetzig, a former Tunge group member, published a Pd-DCA method that allows prenylation of heterocyclic aromatic esters (eq.. 1, Scheme 1.28).[17] This strategy forms a Pd-π-allyl complex from the prenol ester, and is rather sensitive to basic functional groups-as can be seen when decarboxylation generates the sulfonyl anion this leads completely to protonation and isoprene (eq. 2). Alternatively if the prenyl group resides on the nucleophilic portion of the ester, then the basicity issues might be avoided (eq. 3).

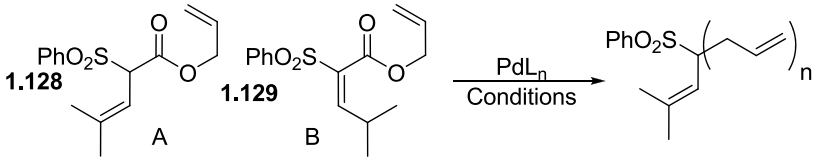


Scheme 1.28

We began by synthesizing the sulfonyl ester **1.128** via condensation with isobutyraldehyde (Table 1.10). The major regioisomer, as discussed in chapter 3, is the deconjugated isomer; however, some product was isolated as a mixture regioisomeric mixture of A (**1.128**) and B (**1.129**) while some was isolated as the pure allylic isomer (A, **1.128**). Initially both isomers were used for screening purposes (Table 1.10). In all cases in which BINAP was used as the ligand (entries 1, 4-17) the major product was the desired monoallylated sulfone. This is most likely Pd-mediated as the reaction did not proceed in the absence of the metal (entry 2). Cesium carbonate, appeared to give some isomerization (~10%) (entry 3), though it is unknown what the thermodynamic mixture is. Hoping that the addition of a weak base would facilitate isomerization of B to the reactive A (**1.128**), under the reaction conditions, Cs_2CO_3 was added. As hoped some of B (**1.129**) was consumed, unfortunately more protonation and diallylation also occurred (entry 4). NaOAc also did not seem to change the product distribution but did seem to lead to a slight consumption of B (entry 5). DMAP led to significant increases of the undesired products, however, it did

effect complete consumption of the starting material (entry 6). Use of K_2CO_3 led to similar results to NaOAc (entry 7). Use of a stoichiometric amount of *t*BuOK led to complete consumption of B and no diallylation product was detected but slightly increased amounts of protonation product (entry 8). A catalytic amount of *t*BuOK led to significant increases of undesired products, but complete consumption of both A (**1.128**) and B (**1.129**) (entry 9). When the starting material was first treated in the glovebox with the *t*BuOK and then catalyst, which ensured that the *t*BuOH formed from deprotonation was not removed, some protonation was observed but not diallylation and B was consumed (entries 12 and 13). When the previous method was repeated using DCM the reaction was much less clean (entry 14). When isomerically pure sulfone, A (**1.128**), was reacted under the standard conditions (entry 15) only trace amounts of the undesired products were observed. Addition of bases, to force allylation prior to decarboxylation, did not improve the product ratios (entries 16 and 17) and again led a slurry that upon acidic quench became soluble. However, when the quench was carried out with DOAc, no deuterium was seen in the products (entry 16). Finally, when $Pd(PPh_3)_4$ was used as the catalyst instead of Pd(BINAP), the reaction led to many products and several new olefinic signals not previously seen.

Table 1.10 Pd-Catalyzed Prenylation



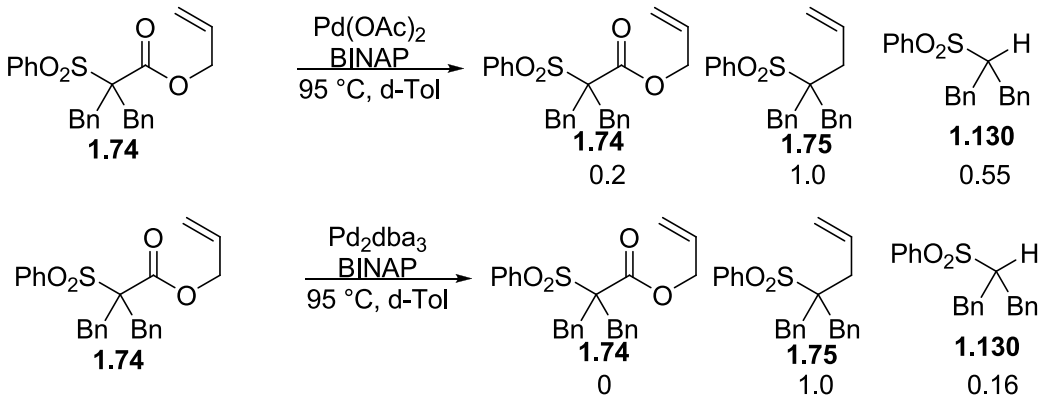
							n=				
Entry	Temp °C	Solv.	Ligand	Additive	A:B	Conv.	0	1	2	B	Comments
(1)	95	d-Tol	BINAP	–	5:1	100	0.17	1	0.16	0.21	
(2)	95	d-Tol	--	–	5:1	0	--	--	--	--	No-Pd
(3)	95	d-Tol	--	$Cs_2(CO)_3$	5:1	0	--	--	--	--	No-Pd. A:B 9:1
(4)	95	d-Tol	BINAP	$Cs_2(CO)_3$	5:1	100	0.21	1	0.31	0.07	
(5)	95	d-Tol	BINAP	NaOAc	5:1	100	0.17	1	0.17	0.13	
(6)	95	d-Tol	BINAP	DMAP	5:1	100	0.54	1	0.5	0	
(7)	95	d-Tol	BINAP	K_2CO_3	5:1	100	0.18	1	0.2	0.09	
(8)	23	d-Tol	BINAP	*t*BuOK	5:1	100	0.23	1	--	0	No diallylation detected
(9)	23	d-Tol	BINAP	*t*BuOK	5:1	100	0.45	1	0.85	0	Catalytic *t*BuOK
(10)	23	d-Tol	BINAP	*t*BuOK	5:1	100	P	P	0	0	2.0 eq *t*BuOK. P = present, 1H difficult to interpret.
(11)	23	d-Tol	BINAP	NaH	5:1	100	0.11	1	0.34	0	
(12)	95	Tol	BINAP	*t*BuOK*	5:1	100	0.20	1	0	0	Base at rt then Pd[a]
(13)	67	THF	BINAP	*t*BuOK*	5:1	100	0.20	1	0.10	0	Base at rt then Pd[a]
(14)	40	DCM	BINAP	*t*BuOK*	5:1	100	0.30	1	0.35	0.1	Base at rt then Pd
(15)	95	d-Tol	BINAP	--	1:0	100	0.03	1	0.03	--	Very Clean
(16)	95	d-Tol	BINAP	*t*BuOK	1:0	100	0.25	1	0.25	--	Base at rt then Pd[a,b]
(17)	95	d-Tol	BINAP	DBU	1:0	100	0.75	1	0	--	Base at rt then Pd
(18)	23	d-Tol	$P(Ph)_3$	--	1:0	100	--	--	--	--	Very messy, new olefins

[a] Reaction became a thick slurry until the addition of HOAc to quench the reaction. [b] Rather than HOAc, DOAc was used to quench, interestingly no D-incorporation into the sulfone was seen.

1.3—**Mechanistic considerations**

One drawback to the chemistry we have developed is that it requires an air free atmosphere to facilitate catalyst turnover. Furthermore, we begin with a Pd(0) precatalyst, Pd_2dba_3, which is also air sensitive. There are numerous examples of Pd(0)-mediated processes that use air-stable Pd(II) precatalyst which are reduced *in situ* to their active state. With this in mind, we tried to catalyze our reaction using $Pd(OAc)_2$ rather than standard

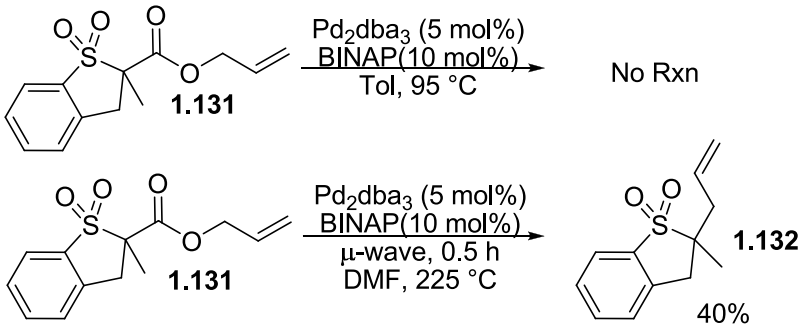
Pd_2dba_3 (Scheme 1.29). While the reaction worked, it did not reach completion and there was starting material present indicating the catalyst had likely crashed out of solution. In addition to not reaching completion the amount of protonation product increased significantly. The incomplete reaction might be explained if the phosphine ligand is the reductant. If the BINAP ligand is oxidized, it would likely not ligate comparably with the unoxidized BINAP and would likely lead to a catalyst that was more prone to form Pd-black. It is possible that the addition of some external reductant might facilitate the process but we did not try any experiments to demonstrate this.



Scheme 1.29

In the course of our studies we synthesized the cyclic sulfonyl ester derived from benzothiopene (**1.131** Scheme 1.30) and subjected it to our decarboxylation conditions. To our surprise, the substrate was unchanged. Changing the solvent to DMF allowed the reaction to reach higher temperature in the microwave reactor and completely consumed the starting material, but provided a 1:1 mixture of allylated:protonated product (**1.132**), from which the desired product was isolated in 40%. While the yield of this reaction is not

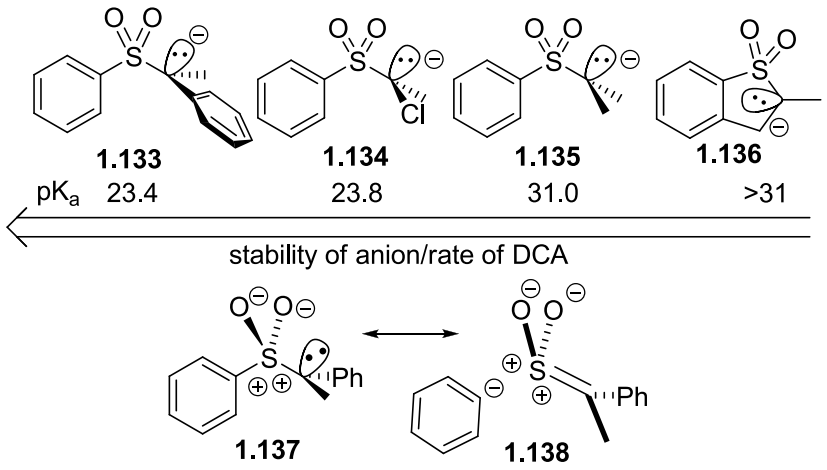
impressive, the difficulty associated with the DCA of this substrate was important in furthering our mechanistic understanding of the DCA of sulfones.



Scheme 1.30

In general, we observed that the rates of the DCA of the sulfones loosely correlates with the ability to stabilize the incipient anion formed after decarboxylation (Scheme 1.31). The most stable conformer of the anion places the lone pair *anti*-periplanar to the other sulfur substituent, as evidenced by the following results. The cyclic sulfone is "locked" into a conformer that is unable to achieve the favored *anti*-periplanar conformation resulting in a much higher barrier to decarboxylation. In the acyclic dialkyl sulfones the most stable conformer of the α-sulfonyl anion can be achieved, accelerating the reactions. The difference in reactivity of the cyclic vs. acyclic substrates suggests that the conformation is vital to the stabilization and cannot be easily explained by inductive stabilization which would be less dependent on orientation. Substrates that contained an α-chloro substituent were further accelerated. This is likely due to the electron withdrawing nature of the chlorine. Finally, substrates that are substituted with an α-phenyl substituent were further stabilized by the benzylic nature of the incipient anion.

The most stable conformer is the one that that puts the major lobe of the anion orbital *anti*-periplanar to the sulfur substituent.[34] Sulfur has empty 3d orbitals, and often delocalization into these orbitals is incorrectly invoked as the source of stabilization of α-anions. Numerous studies have concluded that the LUMO is actually the σ* of the sulfur substituent.[35] Thus, maximum overlap is achieved when the anion is anti-periplanar to an S-X bond. This can simply be thought of as a no-bond resonance structure.

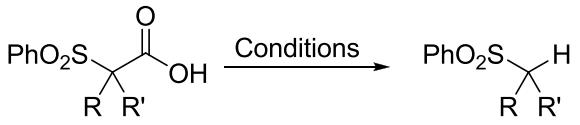


Scheme 1.31

The fact that the rate of the reaction depends on the stability of the anion implies that the decarboxylation is the rate-limiting step in our decarboxylative coupling. A large body of work has shown that the α-sulfonyl carboxylate will undergo loss of CO_2 regardless of the counterion.[39] While a number of α-sulfonyl acetates undergo thermal decarboxylation, we specifically wanted to test for the possibility of a Pd(II)-allyl-catalyzed decarboxylation as this might have implications in the formation of a discrete organometallic vs. an ion-pair. In order to test for Pd catalysis, several controls involving Pd(II) salts were run (Table 1.10). In the first set of reactions, (entries 1 and 2), the acid was subjected to Cs_2CO_3 with or without

10 mol% $Pd(OAc)_2$. A known amount of MTBE was added so that the amount of product formation could be monitored. It should be disclosed that the acid is only poorly soluble in toluene and presumably the carboxylate is even less soluble. The two reactions progressed at essentially the same rate. In the second set of reactions (entries 3 and 4), α-methyl α-benzyl phenyl sulfonyl acetic acid was subjected to Et_3N and the temperature was raised to 95 °C and 1,4-dioxane was used as a standard. To one reaction $Pd(OAc)_2$ was added (entry 4) and within statistical error the two reactions proceeded at identical rates. Additionally, we ran a set of reactions (entries 5 and 6) similar to the previous reactions, using Cs_2CO_3 the reaction was considerably slower than the corresponding reaction with Et_3N-presumably because of decreased solubility. In this set the Pd control went slightly faster though the palladium reaction had an additional equivalent of Cs_2CO_3 which potentially made a difference. If this increased rate is due to the catalytic amount of Pd(II) then it is only a small increase and insignificant. In the final set of controls, we attempted to see just the effect of the counterion. Thus, in one reaction (entry 7) we placed a catalytic amount of KOAc (20 mol%) and the other $Pd(OAc)_2$ (10 mol%) (entry 8), such that each reaction had the same amount of base-20 mol% acetate. This way the Pd-carboxylate does not have to out-compete an excessive amount cesium or ammonium carboxylate to be noticed. After 1 h, the reaction with KOAc had progressed 24% while the reaction with $Pd(OAc)_2$ had progressed 34%. The slight differences are likely explained by differences in solubility of the two different acetate salts. Thus, we feel confident that the reaction is not significantly catalyzed by a Pd(II) intermediate but rather is a result of a thermal instability of the sulfonyl carboxylate under the reaction conditions.

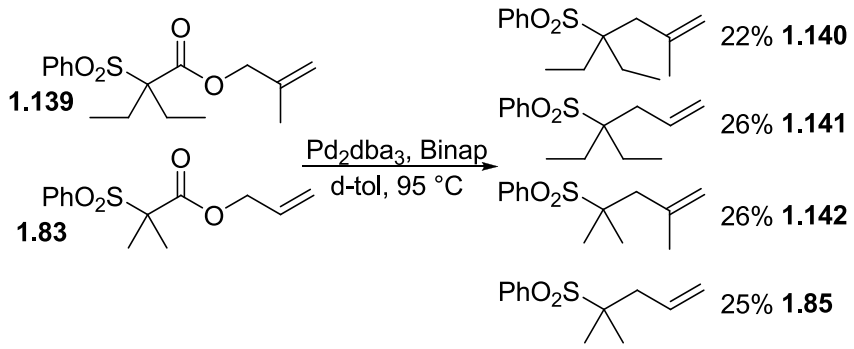
Table 1.11 Control Studies



Entry	R	R'	Conditions	Time	Conversion
1	Me	H	$CsCO_3$ (2.5 eq) d-Tol (.2 M), 23 °C MTBE (4 μL)	36 h	59%
2	Me	H	$CsCO_3$ (2.5 eq) $Pd(OAc)_2$ (0.1 eq) d-Tol (.2 M), 23 °C MTBE (4 μL)	36 h	59%
3	Me	Bn	Et_3N (1.2 eq) d-Tol, 95 °C 1,4-dioxane (26.0 μL)	0.75 h	25%
4	Me	Bn	Et_3N (1.2 eq) $Pd(OAc)_2$ (0.1 eq) d-Tol, 95 °C 1,4-dioxane (26.0 μL)	0.75 h	27%
5	Me	Bn	$CsCO_3$ (1.5 eq)) d-Tol, 95 °C 1,4-dioxane (18.5 μL)	13 h	59%
6	Me	Bn	$CsCO_3$ (2.5 eq) $Pd(OAc)_2$ (0.1 eq) d-Tol, 95 °C 1,4-dioxane (18.5 μL)	13 h	77%
7	H	H	KOAc (0.2 eq) d-Tol, 95 °C 1,4-dioxane (26.0 μL)	1 h	24%
8	H	H	$Pd(OAc)_2$ (0.1 eq) d-Tol, 95 °C 1,4-dioxane (26.0 μL)	1 h	34%

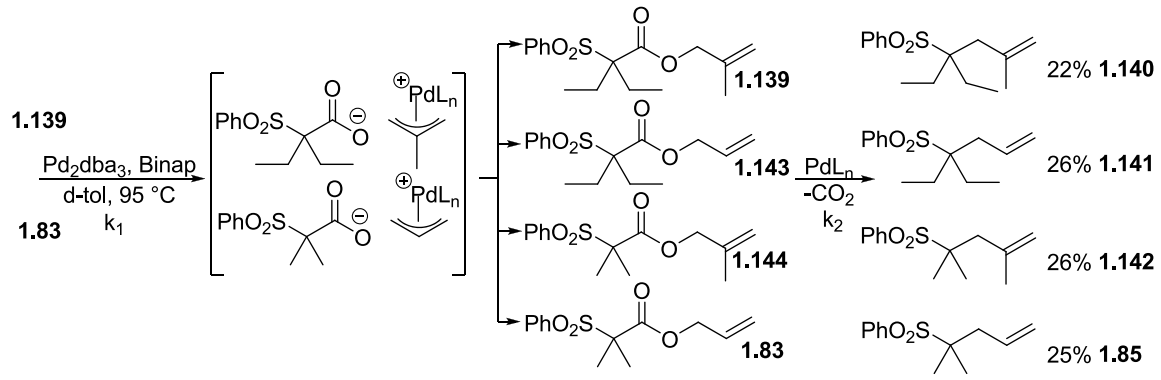
Another mechanistic experiment that we have run is a cross-over reaction. Unfortunately, this experiment is only potentially relevant in a few cases. The first case is when the rate-determining-step is ionization. The second is if there is actually no crossover. Thus far, no one from our group has observed a crossover free reaction. In a crossover

experiment two sulfones are placed together and subjected to the reaction conditions. The sulfones need to be distinguishable on both the allyl and the carboxylate. Thus, if crossover occurs four products will arise. When we subjected these two sulfones to a crossover experiment all four possible products were observed by ^{1}H NMR spectroscopy in nearly equal concentrations (Scheme 1.32).



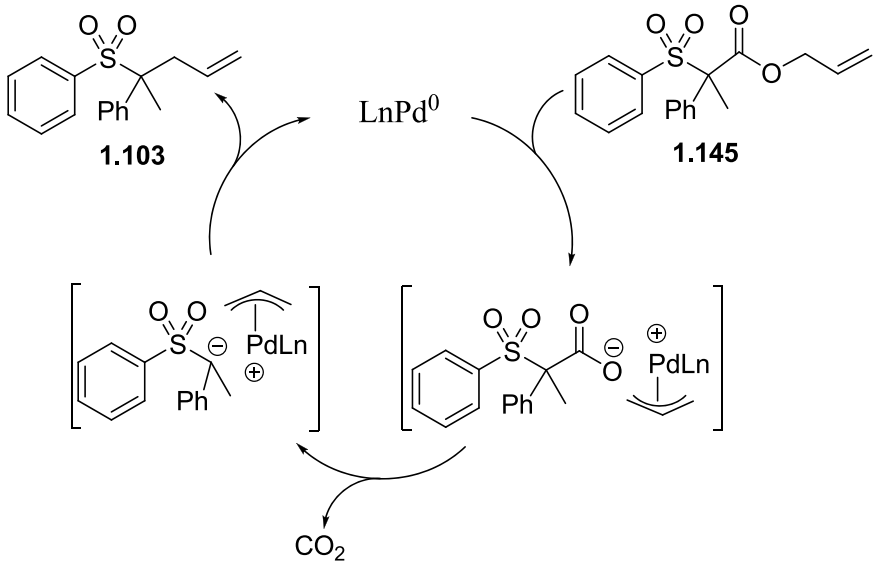
Scheme 1.32

The crossover experiment is often inconclusive because a slow decarboxylation allows for transesterification faster than decarboxylation ($k_1>k_2$) (Scheme 1.33) thus rendering the fate of the reaction after decarboxylation unclear since the substrates have already undergone crossover. In fact, the only definitive result one can hope to gain from this type of experiment would be no crossover, which would imply that $k_2>k_1$ and that indeed no crossover of the intermediates were occurring.



Scheme 1.33

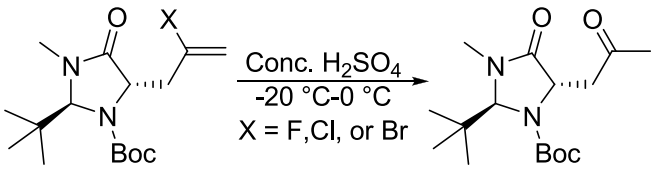
Thus our current understanding of the catalytic cycle is as follows (Scheme 1.34). An electron rich Pd(0) coordinates the olefin of the allyl ester followed by ionization to generate a Pd-allyl carboxylate which is likely ion-paired in toluene, but can undergo transesterification. Eventually, the carboxylate will lose CO_2 generating a sulfonyl anion and Pd-allyl ion which are likely ion-paired in a nonpolar solvent such as toluene. Next, recombination of the ions occurs. The sulfonyl anion attacks the allyl ligand to afford the product and regenerate the catalyst.



Scheme 1.34

Other Noteworthy Observations:

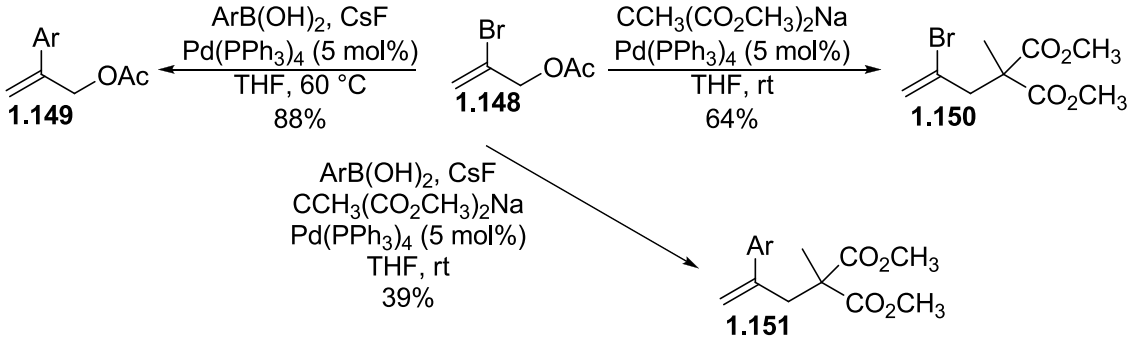
The use of 2-halo substituted allyl acetates is a potentially attractive idea. One use of olefins of this type is as a synthetic equivalent of acetyl group as revealed by hydrolysis (Scheme 1.35).[40]



1.146 **1.147**

Scheme 1.35

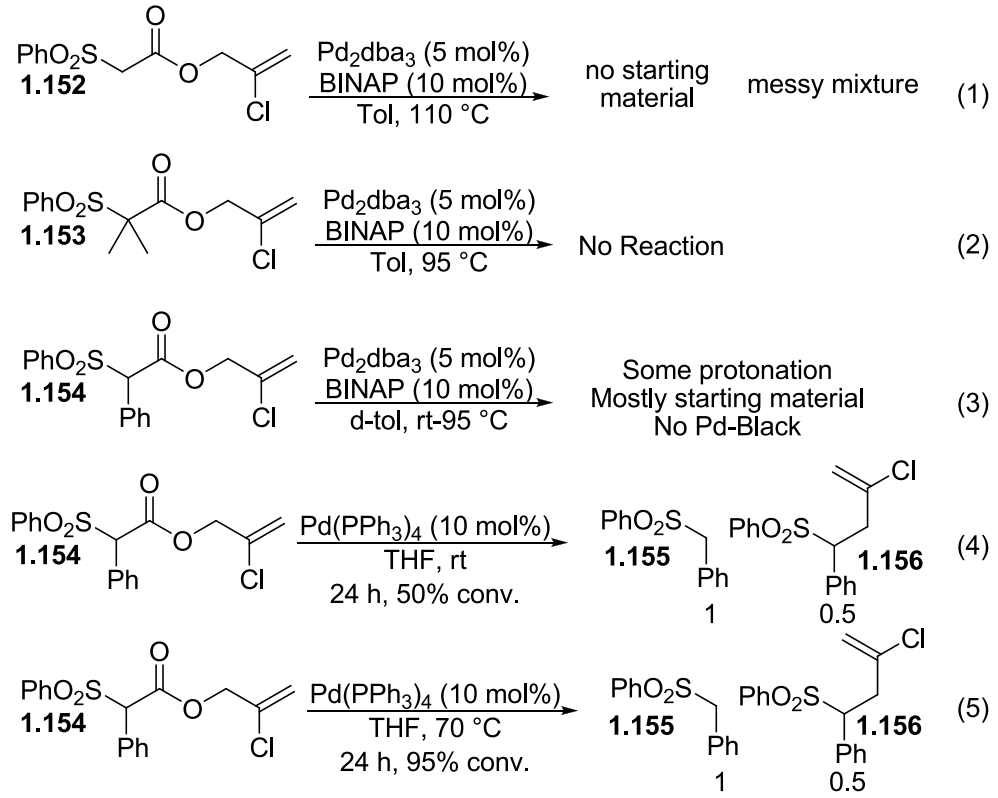
A second potentially useful quality of the 2-halo allyl acetates is the potentially orthogonal ionization which can allow multiple reactions to occur in the same pot in a controlled fashion. Michael Organ published a detailed report demonstrating the ability to selectively perform either a Tsuji-Trost or a Suzuki coupling or both in a single reaction (Scheme 1.36).[36] Thus, we reasoned that the ability to utilize the 2-halo allyl sulfonyl esters would increase the utility of the DCA.



1.149 **1.148** **1.150** **1.151**

Scheme 1.36

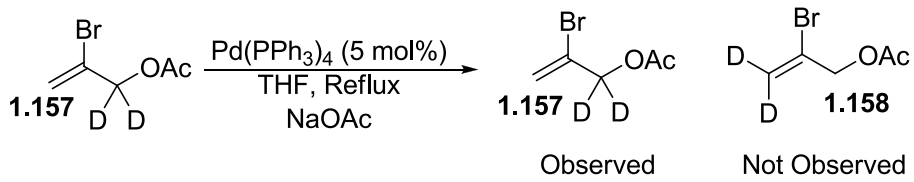
Given the demonstrated utility of the 2-halo allyl acetates we wanted to see if the 2-halo allyl esters could be incorporated into our chemistry. We first looked at the DCA of 2-chloroallyl 2-(phenylsulfonyl)acetate. Subjecting the substrate to the reaction conditions overnight led to complete consumption of the starting material but resulted in a mixture of products (Scheme 1.37). This was not surprising considering the typical mixture of products that would be expected from a substrate having an unsubstituted alpha position. We next looked at a substrate that was geminally substituted. Surprisingly, no reaction occurred overnight. The lack of reaction probably occurs because no ionization occurs. We subjected an α-phenyl substituted ester to the reaction conditions and monitored the reaction progress at increasing temperatures. Interestingly, some protonation occurred but then the reaction seemed to stop-despite the fact that the catalyst remained in solution. This is somewhat unusual because typically a reaction stops because the catalyst has crashed out of solution. In this case, some stable, soluble form of the catalyst must have been formed. It might be possible that the palladium inserted into the vinyl chloride forming a stable PdRClLn intermediate. Changing to $Pd(PPh_3)_4$ catalyst and THF as the solvent led to slow consumption of the starting material and gave protonation as the major product in a 2:1 ratio. The reaction was run again at reflux and after 24 h approximately 95% of the starting material had been consumed, however, the product ratio did not change. Unfortunately, we never found satisfactory conditions for the desired DCA but this is not incredibly surprising when compared to Organ's report.



Scheme 1.37

Organ observed[36] similar results; in THF in the absence of a good nucleophile the allyl acetate (**1.157**) with $Pd(PPh_3)_4$ catalyst resulted in no deuterium scrambling (Scheme 1.38). Organ suspects this is likely because the substrate did not ionize, however, he cannot rule out the "memory" effect. We can conclude, with confidence, that lack of reaction is a result of not ionizing because if ionization occurred we would expect to see decarboxylation. While Organ does see ionization of the 2-chloro allyl acetates, they do not look at sterically encumbered substrates, which likely accentuate the deactivating effect of the chloro-substituent. While we never found conditions that allowed for the selective allylic ionization we never attempted to do chemistry at the vinyl halogen first. This possibly would have

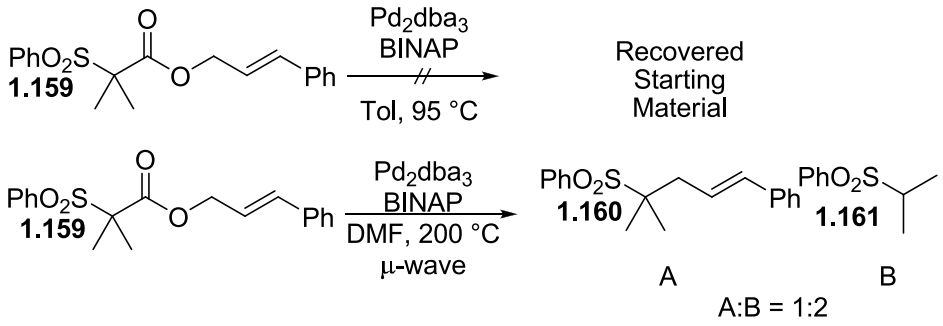
allowed for multiple reactions in one pot. This probably would be easier if **1.157** were changed to the more reactive bromide or iodide.



Scheme 1.38

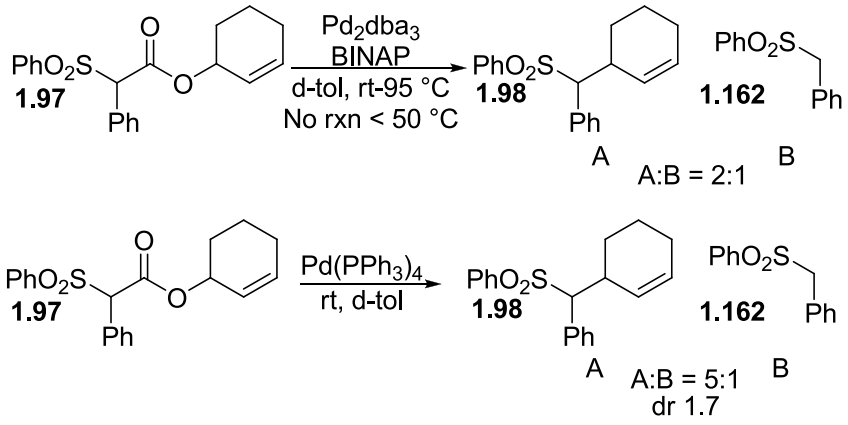
Substrate compatibility with BINAP ligand

Unexpectedly, when substrates with substitution at the terminal end of the allyl were subjected to standard conditions, no reaction occurred and the starting material was recovered (Scheme 1.39). The lack of reaction is probably a result of difficult ionization. It is not clear why Pd/BINAP catalyst is sensitive to the steric nature of the allyl ligand. When the reaction was heated in microwave reactor at 200 °C the starting material was completely consumed but gave a 1:2 mixture of the desired allylated product to the protonated. It is not clear whether the solvent, DMF, or the catalyst had the greater influence on the low selectivity, but unfortunately, it is difficult to achieve such elevated temperature in the microwave with toluene.



Scheme 1.39

Reaction of **1.97** is another example of the Pd/BINAP catalyst struggling to ionize the sulfones with terminal allylic substitution (Scheme 1.40). The reaction with the Pd/BINAP catalyst does not occur at less than 50 °C but goes through 3 half-lives within 2.5 h at 95 °C, and leads to a poor mixture of products. Interestingly, the reaction takes place smoothly at room temperature when $Pd(PPh_3)_4$ is employed as the catalyst and provides the desired allylated sulfone as the major product with a dr of 1.7. Our current understanding of the subtleties concerning the steric demands of the catalyst and substrate is limited.

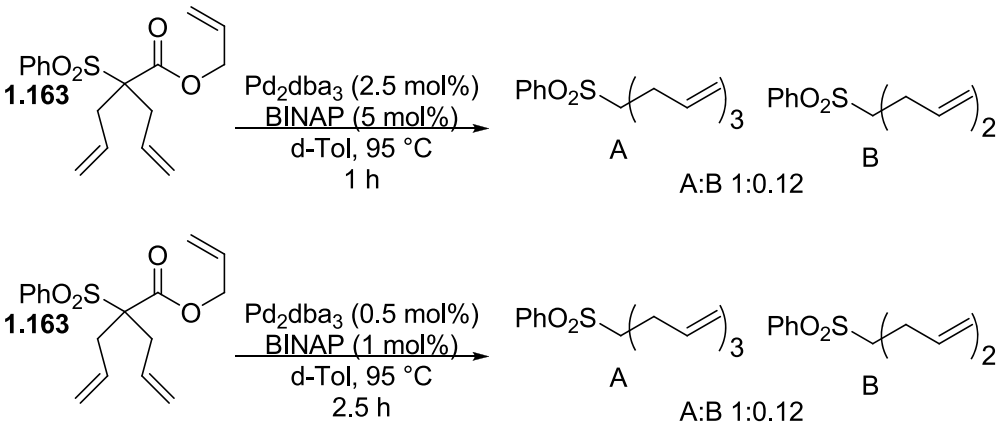


Scheme 1.40

Catalyst loading-anomaly

Typically, esters that were α,α-dialkyl substituted were decarboxylated using 10 mol% catalyst. We believe that some substrates were slower to decarboxylate which allowed time for the catalyst to undergo non-productive reactions which ultimately led to catalyst decomposition. Consequently, higher catalyst loadings were used to accommodate for the catalyst decomposition. 10 mol% seemed to be an amount of catalyst with which all α,α-dialkyl esters would reach completion. One exceptionally fast reacting dialkyl substrate is α,α-diallyl ester, **1.163** (Scheme 1.41). As can be seen using only 5 mol% Pd/BINAP

catalyst the reaction is over in less than 1 h and gives the allylated product in a 8.3 fold excess to the protonated. Further reduction of the catalyst loading to 1 mol% led to the same product distribution but required ~2.5 h to reach completion. Clearly, this substrate undergoes DCA significantly faster than many other dialkyl substrates. One potential explanation is the added olefins somehow facilitate coordination of the catalyst and the allyl ester and could facilitate ionization. However, it is suspected that decarboxylation is rate determining and thus more rapid ionization does not really explain anything. If we assume that decarboxylation is rate determining then the allyl substituents must raise the ground state energy of the intermediate carboxylate or somehow lower the transition state energy to decarboxylation. Currently, it is not clear how this might be happening.

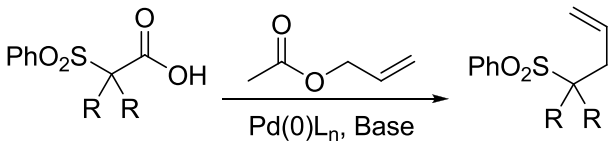


Scheme 1.41

Intermolecular Pd-DCA

One potentially valuable improvement to the sulfonyl ester Pd-catalyzed DCA would be an intermolecular variant. While esters are simple, low energy compounds, coupling of an acid and alcohol is not always straightforward and might require saponification of an

existing ester. Thus if an acid and allyl acetate could directly undergo DCA this would be an important improvement (Scheme 1.42).

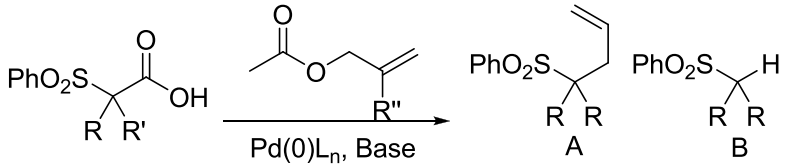


Scheme 1.42

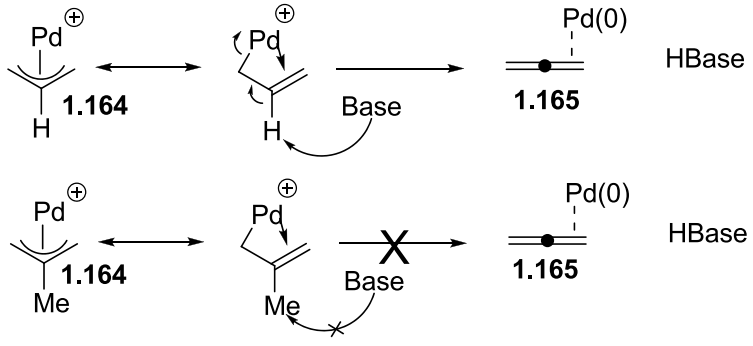
We began our investigation using the gem-dimethyl sulfonyl acetic acid and allyl acetate (entry 1, Table 1.11). The major side product was that of protonation (allylation to protonation 1.37:1) of the anion formed from decarboxylation. Disappointingly, this was the best result we obtained even after systematically varying many conditions. Entries 1-4 look at the effect of the base. The bases, Cs_2CO_3 and NaH, seem to give similar results while *t*BuOK stopped the reaction and caused a degradation of the starting material. DBU (entry 4) on the other hand gave more protonation (A:B = 0.2) likely a result of relatively acidic ammonium ion in toluene that out competes the Pd-allyl as the electrophile and hence leads to an increased amount of protonation. Next, we looked at α-phenyl substituted sulfonyl acetic acids (entries 5-13). Initially, the standard conditions for α-phenyl substituted esters along with the addition of Cs_2CO_3 to deprotonate the acid were used (entry 5), but only 12% of the desired product was isolated. The reaction was run in the absence of a base and gave an A:B ratio of 0.19 (entry 6), though the catalyst eventually crashed out of solution as Pd-black. Additionally, the allyl source was changed to the methyl carbonate which could also service as the base, similar results were obtained. Use of NaH in THF (entry 8) led to protonation only, while in DCM (entry 9) gave the best result in this series (A:B = 0.48).

Changing to DMF (entry 10) led exclusively to protonation. Use of BINAP as the ligand in DCM (entry 11), did not outperform PPh_3 (entry 9) even though excessive amounts of the acid were used. It is not atypical to see less protonation when the 2-position of the allyl is substituted.[19d,20] It suspected, that one degradation path of the Pd-π-allyl is β-hydride elimination to form an allene; substitution of this position prevents this from occurring (Scheme 1.43). Thus, we used the meth allyl acetate in place of allyl acetate. However, it made no beneficial difference in the product distribution (entry 12 vs. 9). Use of excess base might have made a slight increase in yield (entry 13 vs. 12). Consequently, our best results were not particularly noteworthy nor synthetically useful. These results are not surprising considering the number of variables associated with the desired mechanism, for instance the presence of two acidic hydrogens (entries 5-13) and the thermal instability of the monoanion (rapid decarboxylation of the α-phenyl substituted carboxylate at room temperature), as well as heterogeneous reactions as the acids were only poorly soluble in toluene.

Table 1.12 Attempted Intermolecular Pd-DCA



Entry	R	R'	R"	L_n	Base	Temp °C	Solvent	A:B	Notes
1	Me	Me	H	BINAP	Cs_2CO_3	95	Toluene	1.37	
2	Me	Me	H	BINAP	NaH	95	Toluene	1	
3	Me	Me	H	BINAP	*t*BuOK	95	Toluene	-	No rxn. degradation of SM
4	Me	Me	H	BINAP	DBU	95	Toluene	0.20	
5	Ph	H	H	PPh_3	Cs_2CO_3	23	Toluene	12%	Isolated
6	Ph	H	H	PPh_3	--	50	Toluene	0.19	Pd-black formation
7	Ph	H	-	PPh_3	--	95	Toluene	0.22	Allyl methyl carbonate
8	Ph	H	H	PPh_3	NaH	70	THF	B only	
9	Ph	H	H	PPh_3	NaH	40	d-DCM	0.48	
10	Ph	H	H	PPh_3	NaH	95	DMF	B only	
11	Ph	H	H	BINAP	NaH	40	d-DCM	0.38	excess acid
12	Ph	H	Me	PPh_3	NaH	40	d-DCM	0.31	
13	Ph	H	Me	PPh_3	NaH	40	d-DCM	0.37	3.0 equiv. NaH



Scheme 1.43

To summarize we have developed conditions for the Pd-catalyzed DCA of α-sulfonyl acetic allyl esters. The reaction is quite general for α-disubstituted α-sulfonyl acetic allyl

esters. However, β-hydrogens on the allyl portion are not well tolerated unless an additional electron withdrawing substituent is present, such as phenyl. There are some limitations concerning sterics and the ability of the catalyst to ionize such substrates. In general, the methodology is superior to existing technology for the synthesis of tertiary sulfones. We favor a mechanism in which decarboxylation is slow and a tight ion pair result from the decarboxylation. We speculate that attack of the Pd-π-allyl occurs from outside the coordination sphere, which would lead to a product of overall retention of configuration. Experiments are underway to confirm this hypothesis. Finally, we highlight some other observations about the reaction as well as some failed attempts to expand the utility or scope of the reaction.

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Appendix A: General Methods and Compound Characterization

Materials. All moisture sensitive reactions were run in flame-dried glassware under an Ar atmosphere using standard Schlenk techniques. Methylene chloride, toluene, THF, Et_2O wer dried over activated alumina and toluene and THF were then distilled over sodium. Acetone was distilled from magnesium sulfate and stored over activated mol sieves. Commercially available reagents were used without additional purification unless otherwise stated. Tris(dibenzylideneacetone) dipalladium (0), $Pd(PPh_3)_4$, and rac-BINAP were purchased from Strem and stored in a glovebox under an Ar atmosphere. Compound purification was effected by flash chromatography using 230x400 mesh, 60 Å porosity, silica obtained from Sorbent Technologies. Thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5715-7, EMD chemicals). Visualization of the plateswas accomplished with a UV lamp (254 nm) or $KMnO_4$ stain. ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance 400 or a Bruker Avance 500 DRX, or a Bruker AVIII 500 spectrometer and referenced to residual protio solvent signals (some spectra were taken using a broadband observe probe and a dual 13C/1H Cryoprobe). Structural assignments are based on ^1H, ^{13}C, DEPT-135, COSY, HSQC and IR spectroscopies. FTIR spectra were recorded using either a ATI Mattson Genesis Series FTIR or Shimadzu 8400-S FTIR spectrometers. High Resolution Mass Spectrometry (HRMS) were performed using EI, ESI, and FAB techniques. EI MS spectra were obtained on an AUTOSPEC-Q tandem hybrid mass spectrometer (VG Analytical Ltd, Manchester, UK). ESI MS spectra were acquired either on a LCT Premier (Waters Corp., Milfpord, MA) or Q-Tof-2 (Microsmass Ltd, Manchester UK) spectrometers.

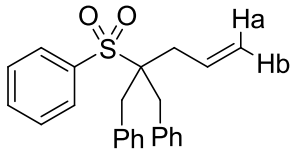
FAB MS spectra were obtained on a ZAB HS mass spectrometer (VG Analytical Ltd, Manchester UK). Elemental Analyses were performed by Desert Analytics Laboratory (Tuscon, AZ). Chiral high pressure liquid chromatography was performed on a Shimadzu SCL-10AVP instrument using Daicel Chiralpak AD, AS and OD-H columns.

General procedure A screening of the Pd-catalyzed DCA (Table 1.2, 3, 4 and 5): To an NMR tube was added substrate **1.74** (0.0238 mmol) and then taken into the glovebox where $Pd(PPh_3)_4$ (0.00238 mmol)or Pd_2dba_3 (0.00119 mmol) and Ligand (0.00238 mmol-bidentate) or (0.00476 mmol monodentate) was added then 500μL of DMF (or indicated solvent) was added. The NMR tube was capped with a rubber septum and taken out of the glovebox. The septum was secured with parafilm and the tube was heated in an oil bath for 18h at the indicated temperature. After 18h the reaction was concentrated *in vacuo* or washed away (dmf). The crude residue was brought up in chloroform-d_3 and ^1H NMR spectra were collected.

General procedure B the optimized Pd-catalyzed DCA of α-dialkyl sulfonyl esters (Table 1.6): To a flame-dried Schlenk tube was added sulfonyl ester, **1.74**, (0.334 mmol) and stirbar. The tube was taken into the glovebox where it was charged with Pd_2dba_3(0.0167 mmol) and (±)-BINAP (0.0334 mmol) and toluene (3.5 mL) then capped with a septum which was secured with parafilm. The tube was then placed in an oil bath at 95 °C and magnetically stirred for 16 h until it was concentrated *in vacuo* and purified by column chromatography. It should be noted that slight adaptations to this procedure can result in

slightly better yields. These adaptations can be found in the corresponding general procedure for the stereospecific substrates (Appendix B).

General procedure for the palladium catalyzed decarboxylation of α-phenyl substituted acetic esters: To a flame dried Schlenk tube was added allyl 2-phenyl-2-(phenylsulfonyl)propanoate (88mg, .267mmol), toluene (2ml), $Pd(PPh_3)_4$ (3.1mg, .00267mmol) under an atmosphere of Argon. The reaction was allowed to react 10min at room temperature. The reaction was quenched and purified by flash column chromatography using 90:10 hexanes: ethyl acetate, yielding the product (2-phenylpent-4-en-2-ylsulfonyl)benzene in 85%.



(2-allyl-2-(phenylsulfonyl)propane-1,3-diyl)dibenzene

(**1.86**)(JW2162)

White Solid

Yield: 84%

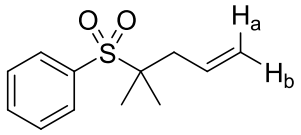
Purification: flash chromatography(98:2 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.50 (1 H, t, *J*=1.58 Hz, diastereotopic C*H*HCHCH$_2$), 2.52 (1 H, t, *J*=1.58 Hz, diastereotopic CH*H*CHCH$_2$), 3.15 (2 H, d, *J*=14.50 Hz, diastereotopic (quat)CC*H*HPh), 3.31 (2 H, d, *J*=14.19 Hz, diastereotopic (quat)CC*H*HPh), 5.14 (1 H, dq, *J*=16.87, 1.73 Hz, H_a), 5.18 (1 H, dq, *J*=10.29, 1.62 Hz, H_b), 6.02 (1 H, dddd, *J*=16.91, 10.21, 6.62 Hz, $CH_2CHCH_aH_b$), 7.11 - 7.18 (5 H, m, $ArCH_2$), 7.21 - 7.26 (5 H, m, $ArCH_2$), 7.41 - 7.48 (2 H, m, *m*-SO_2ArCH's), 7.59 (1 H, tt, *J*=7.53, 1.14 Hz, ρ-SO_2ArCH), 7.72 - 7.79 (2 H, m, *o*-SO_2ArCH's).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 37.5 (1 C, s, (quat)C$CH_2CHCH_aH_b$), 38.8 (2 C, s, (quat)CCHHPh), 70.5 (1 C, s, (quat)*C*), 119.4 (1 C, s, $CH_2CHCH_aH_b$), 127.0 (4 C, s, ArCH'sCH2), 128.1 (2 C, s, *m*-SO_2ArCH's), 128.4 (1 C, s, (quat)Ar*C*CH2), 130.8 (1 C, s, (quat)Ar*C*CH2), 131.3 (2 C, s, *o*-SO_2ArCH's), 132.8 (6 C, s, ArCH'sCH2), 133.3 (1 C, s, (quat)Ar*C*SO_2R), 135.3 (1 C, s, $CH_2CHCH_aH_b$), 137.4 (1 C, s, ρ-SO_2ArCH).

FTIR (CH_2Cl_2) υ_{max}: 3069, 3031, 2925, 2852, 1635, 1601, 1583, 1495, 1455, 1444, 1299, 1139, 1076.

Anal. Calcd for C24H24O2S: C, 76.56; H, 6.42. Found: C, 75.43; H, 6.74.



(2-methylpent-4-en-2-ylsulfonyl)benzene

(**1.87**)(JW2163)

Yellow oil

Yield: 74%

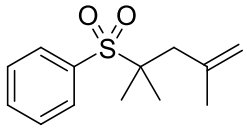
Purification: flash chromatography(97:3 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.28 (6 H, s: C*H*$_3$'s), 2.45 (2 H, d, *J*=7.57 Hz: C*H*$_2$), 5.10 (1 H, d, *J*=17.02 Hz: CH=C*H*$_a$H$_b$), 5.16 (1 H, d, *J*=10.09 Hz: CH=CH$_a$*H*$_b$), 5.68 - 5.80 (1 H, app. m: C*H*= CH$_a$H$_b$), 7.56 (2 H, app. t, *J*=7.72 Hz: *m*-SO_2ArC*H*'s), 7.66 (1 H, t, *J*=7.41 Hz: ρ-SO_2ArC*H*), 7.88 (2 H, d, *J*=7.57 Hz: *o*-SO_2ArC*H*'s).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 20.42 (2 *C*H$_3$'s), 39.24 (*C*H$_2$), 62.54 (quat. *C*), 120.01 (CH=*C*H$_a$H$_b$), 128.71 (2 Ar CH's), 130.50 (2 Ar CH's, s), 131.51 (*C*H=CH$_a$H$_b$), 133.58 (Ar *C*H), 135.23 (quat Ar *C*).

FTIR (CH_2Cl_2) υ_{max}: 3065, 2979, 2934, 1637,1582, 1469, 1446, 1300, 1158, 1126, 1079.

Anal. Calcd for C12H16O2S: C, 64.25; H, 7.19. Found: C, 64.88; H, 7.38.



(2,4-dimmethylpent-4-en-2-ylsulfonyl)benzene

(**1.88**)(JW2197)

Colorless oil

Yield: 81%

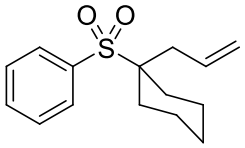
Purification: flash chromatography(97:3 then 96:4 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.31 (6 H, s: 2 C*H*$_3$'s), 1.76 (3 H, s: C*H*$_3$CR=CH$_2$), 2.45 (2 H, s: C*H*$_2$), 4.71 (1 H, s: CMeR=C*H*H), 4.96 (1 H, s: CMeR=CH*H*), 7.56 (2 H, app. t, *J*=7.57 Hz: *m*-SO_2ArC*H*'s), 7.65 (1 H, t, *J*=7.41 Hz: ρ-SO_2ArC*H*), 7.87 (2 H, d, *J*=7.57 Hz: *o*-SO_2ArC*H*'s).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 20.70 (2 *C*H_3's), 25.08 (1 *C*H_3CR=CH_2), 41.46 (1 *C*H_2), 63.32 (1 quat. *C*R_2Me_2), 117.23 (1 CH_3CR=*C*H_2), 128.67 (2 Ar *C*H's), 130.56 (2 Ar*C*H), 133.54 (1 CH_3*C*R=CH_2), 135.16 (1 Ar*C*H), 139.58 (1 quat. Ar*C*).

FTIR (CH_2Cl_2) υ_{max}: 3062, 2982, 2941, 1643, 1468, 1447, 1298, 1273, 1159, 1124, 1076.

Anal. Calcd for C13H18O2S: C, 65.51; H, 7.61. Found: C, 65.49; H, 7.67.



(1-allylcyclohexylsulfonyl)benzene

(**1.89**)(JW3147)

White solid

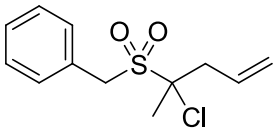
Yield: 83%

Purification: flash chromatography(99:1 hexanes:ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.05 - 1.21 (1 H, m, diastereotopic C*H*H), 1.31 - 1.46 (2 H, m, , diastereotopic C*H*'s), 1.57 - 1.75 (3 H, m, diastereotopic C*H*'s), 1.79 (4 H, m, diastereotopic C*H*'s), 2.50 (2 H, d, *J*=7.07 Hz, CH_2CHCH_2), 5.05 - 5.17 (2 H, appar. dd, *J*=5.56, 8.59 Hz, CH_2CHCH_2R), 5.97 - 6.12 (1 H, appar. M, CH_2C*H*CH_2R), 7.55 (2 H, t, *J*=7.58 Hz, *m*ArC*H*'s), 7.65 (1 H, t, *J*=7.33 Hz *p*ArC*H*), 7.87 (2 H, d, *J*=7.83 Hz, *o*ArC*H*'s).

^{13}C NMR (126 MHz, CDCl3) δ ppm 20.98 (1 C, s, *C*H), 24.53 (2 C, s, *C*H_2), 28.33 (2 C, s, *C*H_2), 34.42 (1 C, s, R*C*H_2CHCH_2), 65.74 (1 C, s, (quat) *C*), 118.26 (1 C, s, R*C*H_2), 128.64 (2 C, s, Ar*C*H's), 130.53 (2 C, s, Ar*C*H's), 132.87 (1 C, s (quat)Ar*C*), 133.47 (1 C, s, Ar*C*H), 135.56 (1 C, s, R*C*HCH_2).

FTIR (CH_2Cl_2) υ_{max}: 3054, 2940, 2865, 1637, 1461, 1445, 1303, 1283, 1136.



((2-chloropent-4-en-2-ylsulfonyl)methyl)benzene

(**1.90**)(JW3261)

White crystals

Yield: 97%

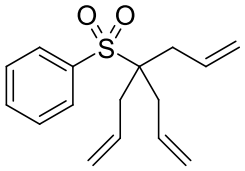
Purification: flash chromatography(97:3 hexanes:ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.84 (3 H, s, C*H*$_3$R), 2.87 - 2.93 (2 H, m, C*H*$_2$(R)CHCH2), 4.54 (2 H, s, C*H*$_2$Ph S(O)$_2$R), 5.24 - 5.37 (2 H, m, C*H*$_2$CHR), 5.79 - 5.99 (1 H, m, CH$_2$C*H*R), 7.38 - 7.51 (5 H, m, ArC*H*'s).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 23.44 (1 C, s, *C*H$_3$), 41.22 (1 C, s, *C*H$_2$CHCH2), 53.20 (1 C, s, *C*H2S(O)$_2$R,Ph), 84.39 (1 C, s, quat *C*CH$_3$Cl), 121.72 (1 C, s, *C*H$_2$CHR), 128.85 (1 C, s, Ar*C*H), 128.95 (1 C, s, quat Ar*C*), 129.13 (1 C, s, Ar*C*H), 129.75 (1 C, s, Ar*C*H), 131.47 (1 C, s, CH$_2$*C*HR).

FTIR (CH_2Cl_2) υ_{max}: 3053, 2986, 2253, 1797, 1471, 1382, 1094, 908.

HRMS calcd for [M+Na] 281.0379 found 281.0379.



(4-allylhepta-1,6-dien-4-ylsulfonyl)benzene

(**1.91**)(JW3051)

Yellow oil

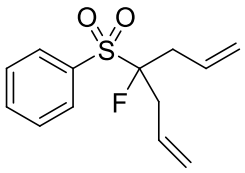
Yield: 78%

Purification: flash chromatography(10:1 hexanes: ether)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.50 (6 H, dt, *J*=7.07, 1.26 Hz, quat. $CCH_2CH{=}CH_2$), 5.06 - 5.19 (6 H, m, $CH{=}CH_2$), 5.87 - 6.04 (3 H, m, *J*=17.02, 10.07, 7.17, 7.17 Hz, $CH{=}CH_2$), 7.57 (2 H, app. t, *J*=6.82 Hz, *m*-SO_2ArCH's), 7.68 (1 H, t, *J*=7.45 Hz, ρ-SO_2ArCH), 7.91 (2 H, dd, *J*=8.34, 1.26 Hz, *o*-SO_2ArCH's).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 37.2 (3 $CH_2CH{=}CH_2$), 67.7 (1 quat. C), 119.4 (3 $CH{=}CH_2$), 128.8 (2 ArCH's), 130.4 (2 ArCH's), 132.1 (3 $CH{=}CH_2$), 133.8 (1 ArCH), 136.2 (1 quat. ArC).

Matches previously characterized *J. Org. Chem.* **1990**, *55*, 2237(6d).



(4-fluorohepta-1,6-dien-4-ylsulfonyl)benzene

(**1.92**)(JW3115)

Colorless oil

Yield: 45%

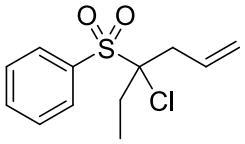
Purification: flash chromatography(95:5 hexanes: ether –partial separation)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.69 - 2.89 (4 H, m, diastereotopic C*H*$_2$'s), 5.14 - 5.30 (4 H, m, CH_2CHCH_2's), 5.73 - 5.89 (2 H, m, *J*=17.22, 10.13, 7.13, 7.13 Hz, C*H*CH_2), 7.60 (2 H, t, *J*=7.72 Hz, *m*-SO_2ArC*H*'s), 7.72 (1 H, t, *J*=7.5 Hz, *p*-SO_2ArC*H*'s), 7.88 - 8.01 (2 H, m, *o*-SO_2ArC*H*'s).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 35.80 (2 C, d, *J*=20.16Hz, (quat)CF(*C*H_2's)), 108.42 (1 C, d, *J*=220.5Hz, (quat)*C*F(CH_2's)), 121.00 (2 C, s CH_2CHCH_2), 128.92 (2 C, d, *J*=7.56 Hz, (quat)CF(CH_2CHCH_2)$_2$), 129.11 (2 C, s, *m*-SO_2Ar*C*H's), 130.51 (1 C, s, *p*-SO_2Ar*C*H's),), 134.30 (1 C, s, (quat)Ar*C*-SO_2R),), 134.52 (2 C, s, *o*-SO_2Ar*C*H's).

FTIR (CH_2Cl_2) υ_{max}: 3089, 2922, 1640, 1583, 1448, 1435, 1324,1308, 1160, 1081.

Anal. Calcd for C13H15FO2S: C, 61.39; H, 5.94. Found: C, 61.65; H, 6.34.



(3-chlorohex-5-en-3-ylsulfonyl)benzene

(**1.93**)(JW3141)

Yellow oil

Yield: 96%

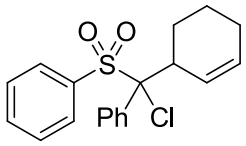
Purification: flash chromatography(95:5 hexanes: ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.16 (3 H, t, *J*=7.41 Hz), 2.04 - 2.14 (1 H, m), 2.24 - 2.33 (1 H, m), 2.78 (1 H, dd, *J*=15.13, 6.94 Hz), 3.01 (1 H, dd, *J*=14.98, 7.09 Hz), 5.20 - 5.27 (2 H, m), 5.93 (1 H, dd, *J*=16.87, 10.25 Hz), 7.59 (2 H, t, *J*=7.88 Hz), 7.71 (1 H, t, *J*=7.57 Hz), 8.00 (2 H, d, *J*=8.51 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 8.85 (1 C, s, *C*H_3CH2), 28.83 (1 C, s, *C*H_2CH_3), 39.86 (1 C, s, *C*H_2CHCH_2), 88.48 (1 C, s, (quat)*C*(CH_2CH_3)($PhSO_2$)), 120.30 (1 C, s, CH*C*H_2), 128.68 (2 C, s, *m*-SO_2Ar*C*H's), 130.77 (1 C, s, *C*HCH_2), 131.37 (2 C, s, *o*-SO_2Ar*C*H's), 134.32 (2 C, s, *p*-SO_2Ar*C*H and (quat)*C* -SO_2Ar*C*H).

FTIR (CH_2Cl_2) υ_{max}: 3053, 2945, 1642, 1588,1444, 1415, 1323, 1307, 1155.

Anal. Calcd for C12H15ClO2S: C, 55.70; H, 5.84. Found: C, 56.17; H, 6.08.



(chloro(cyclohex-2-enyl)(phenyl)methylsulfonyl)benzene

(**1.100**)(JW3125)

White solid

Yield: 98% (1:1.5 dr)

Purification: flash chromatography(97:3 hexanes: ethyl acetate)

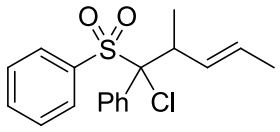
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.23 - 1.34 (1 H, m, diasterotopic C*H*HRR'), 1.36 - 1.43 (1 H, m, diasterotopic CH*H*RR'), 1.54 - 1.79 (2 H, m, diasterotopic RC*H*HCHCHR', diasterotopic CH*H*RR'), 1.95 - 2.13 (6 H, m, diasterotopic C*H*'s), 2.71 (1 H, br. s., diasterotopic RCH*H*CHCHR'), 4.14 (2 H, dt, *J*=5.24, 2.56 Hz, diasteromeric $RCH_2CHCHCHR'$), 4.95 (1 H, d, *J*=10.11 Hz, $RCH_2CHCHCHRR$), 5.81 (1 H, d, *J*=4.29 Hz, $RCH_2CHCHCHRR$), 6.01 (1 H, d, *J*=10.61 Hz, $RCH_2CHCHCHRR$), 6.63 (1 H, dt, *J*=10.29, 1.80 Hz, $RCH_2CHCHCHRR$), 7.15 - 7.37 (11 H, m, ArC*H*'s), 7.31-7.35 (5 H, m, ArC*H*'s), 7.39 - 7.57 (7 H, m, ArC*H*'s).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 14.16 (1 C, s, RR'CH_2), 21.02 (1 C, s, RR'CH_2), 21.61 (1 C, s, RR'CH_2), 22.00 (1 C, s, RR'CH_2), 24.55 (1 C, s, RR'CH_2), 24.74 (1 C, s, RR'CH_2), 25.41 (1 C, s, RR'CH_2), 25.48 (1 C, s, RR'CH_2), 42.33 (1 C, s, RR'R''*C*H), 43.49 (1 C, s, RR'R''*C*H), 95.21 (1 C, s, (quat) *C*), 95.26 (1 C, s, , (quat) *C*), 124.91 (1 C, s, Ar*C*H),

126.24 (1 C, s, olefinic *C*H), 127.80 (1 C, s, Ar*C*H), 127.82 (1 C, s, Ar*C*H), 127.91 (1 C, s, olefinic *C*H), 128.02 (1 C, s, Ar*C*H), 128.71 (1 C, s, Ar*C*H), 128.98 (1 C, s, Ar*C*H), 129.17 (1 C, s, Ar*C*H), 130.35 (1 C, s, Ar*C*H), 130.72 (1 C, s, Ar*C*H), 132.03 (1 C, s, olefinic *C*H), 133.44 (1 C, s, olefinic *C*H), 133.90 (1 C, s, (quat)Ar*C*), 134.24 (1 C, s, (quat)Ar*C*), 135.15 (1 C, s, (quat)Ar*C*), 135.27 (1 C, s, (quat)Ar*C*).

FTIR (CH_2Cl_2) υ_{max}: 3052, 2982, 2934, 2934, 1684, 1606, 1446, 1422, 1320, 1309, 1146.

Anal. Calcd for C19H19ClO2S: C, 65.79; H, 5.52. Found: C, 65.85; H, 5.79.



(E)-(1-chloro-2-methyl-1-(phenylsulfonyl)pent-3-enyl)benzene

(**1.101**)(JW3140)

Colorless oil

Yield: 84% (1:1.2 dr)

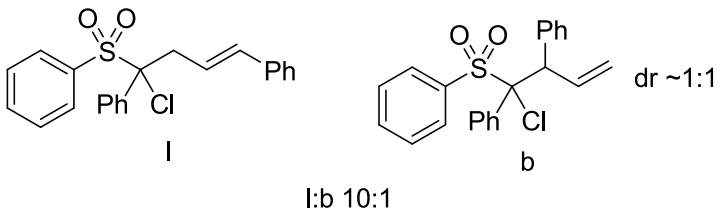
Purification: flash chromatography(95:5 hexanes: ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.84 (3 H, d, *J*=6.94 Hz, C*H*$_3$CHRR), 1.36 (3 H, d, *J*=6.31 Hz, C*H*$_3$CHCHR), 1.59 (3 H, d, *J*=6.31 Hz, C*H*$_3$CHRR), 1.72 (3 H, d, *J*=5.04 Hz, C*H*$_3$CHCHR), 3.95 (2 H, ddd, *J*=21.75, 6.94, 6.62 Hz, CH$_3$C*H*RR), 5.03 (1 H, dd, *J*=15.29, 7.72 Hz, CH$_3$C*H*CHR), 5.34 (1 H, dd, *J*=14.82, 7.25 Hz, CH$_3$CHC*H*R), 5.70 - 5.86 (2 H, m, CH$_3$C*H*C*H*R), 7.06 (3 H, t, *J*=7.57 Hz, ArC*H*'s), 7.12 (8 H, q, *J*=7.46 Hz, ArC*H*'s), 7.16 - 7.21 (2 H, m, ArC*H*'s), 7.26 (4 H, dd, *J*=17.97, 7.57 Hz, ArC*H*'s), 7.36 (3 H, t, *J*=8.83 Hz, ArC*H*'s), 7.33 (1 H, br. s. , ArC*H*'s), 7.44 (2 H, d, *J*=7.88 Hz, ArC*H*'s).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 17.28 (1 C, s, *C*H$_3$CHRR), 17.81 (1 C, s, *C*H$_3$CHRR), 17.93 (1 C, s, *C*H$_3$CHCHR), 18.15 (1 C, s, *C*H$_3$CHCHR), 42.92 (1 C, s, *C*HCH$_3$RR'), 43.15 (1 C, s, *C*HCH$_3$RR'), 95.45 (1 C, s, (quat)*C*PhClRR'), 96.08 (1 C, s, (quat)*C*PhClRR'), 127.66 (1 C, s, Ar*C*H), 127.74 (1 C, s, Ar*C*H), 127.81 (1 C, s, Ar*C*H), 127.96 (1 C, s, Ar*C*H), 128.01 (1 C, s, Ar*C*H), 128.40 (1 C, s, olefinic *C*H), 128.62 (1 C, s, olefinic *C*H), 128.86 (1 C, s, olefinic *C*H), 129.05 (1 C, s, olefinic *C*H), 129.10 (1 C, s, Ar*C*H), 129.78 (1 C, s, Ar*C*H), 130.13 (1 C, s), 130.31 (1 C, s, Ar*C*H), 130.52 (1 C, s, Ar*C*H), 133.30 (1 C, s, Ar*C*H), 133.37 (1 C, s, Ar*C*H), 134.34 (1 C, s, (quat)*C*Ar), 134.62 (1 C, s, (quat)*C*Ar), 135.38 (1 C, s, (quat)*C*Ar), 135.59 (1 C, s, (quat)*C*Ar).

FTIR (CH_2Cl_2) υ_{max}: 3053, 2983, 1445, 1424, 1320, 1310, 1154.

Anal. Calcd for C18H19ClO2S: C, 64.56; H, 5.72. Found: C, 64.74; H, 6.01.



(E)-(4-chloro-4-(phenylsulfonyl)but-1-ene-1,4-diyl)dibenzene

(**1.102**)(JW3128)

White Solid

Yield: 96%

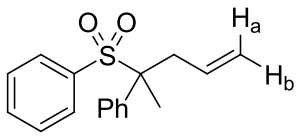
Purification: flash chromatography(95:5 hexanes: ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.46 (1 H, ddd, *J*=14.91, 7.58, 1.26 Hz, diastereotopic C*H*HCHCHPh), 3.94 (1 H, ddd, *J*=14.97, 6.38, 1.39 Hz, CH*H*CHCHPh), 5.88 - 5.96 (1 H, m CH_2C*H*CHPh), 6.59 (1 H, appt. dt, *J*=15.92, 1.26Hz CH_2CHC*H*Ph), 7.22 - 7.25 (3 H, m ArC*H*'s), 7.30 - 7.34 (1 H, m ArC*H*'s), 7.35 - 7.42 (3 H, m ArC*H*'s), 7.51 (3 H, dd, *J*=7.83, 2.02 Hz, ArC*H*'s), 7.58 - 7.63 (1 H, m ArC*H*'s).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 38.73 (1 C, s, *C*H_2RR'), 90.33 (1 C, s, (quat) *C*ClPhRR'), 121.03 (1 C, s, Olefinic *C*H), 126.26 (1 C, s, Ar*C*), 127.63 (1 C, s, Ar*C*), 127.93 (1 C, s, Ar*C*), 127.99 (1 C, s, Ar*C*), 128.17 (1 C, s, Olefinic *C*H), 128.43 (1 C, s, Ar*C*), 129.59 (1 C, s, Ar*C*), 131.33 (1 C, s, Ar*C*), 131.97 (1 C, s, Ar*C*), 133.14 (1 C, s, Ar*C*), 134.21 (1 C, s, Ar*C*), 135.86 (1 C, s, Ar*C*), 136.57 (1 C, s, Ar*C*).

FTIR (CH_2Cl_2) υ_{max}: 3052, 2985, 1734, 1448, 1422, 1320, 1310, 1151.

Anal. Calcd for C22H19ClO2S: C, 69.01; H, 5.00. Found: C, 68.55; H, 5.65.



(2-phenylpent-4-en-2-ylsulfonyl)benzene

(**1.103**, **2.31**)(JW3078)

Yellow oil

Yield: 96%

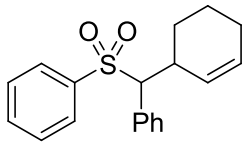
Purification: flash chromatography(95:5 hexanes: ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.66 (3 H, s: C*H*$_3$), 2.83 (1 H, dd, *J*=14.02, 8.46 Hz: diastereotopic C*H*HRCH=CH_2), 3.37 (1 H, dd, *J*=13.89, 5.56 Hz: diastereotopic CH*H*RCH=CH_2), 5.00 (1 H, app. d, *J*=10.11 Hz: H_b), 5.12 (1 H, dd, *J*=17.05, 1.14 Hz: H_a), 5.37 (1 H, dddd, *J*=16.99, 10.04, 8.59, 5.56 Hz: C*H*=CH_2), 7.16 - 7.34 (9 H, m: Ar CH's), 7.43 - 7.51 (1 H, m: Ar CH's).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 19.2 (*C*H_3), 37.8 (*C*H_2), 68.5 (Quat *C*), 119.9 (CH=*C*H_2), 128.0 (2 Ar *C*H), 128.1 (2 Ar *C*H), 128.4 (ρ-CR_3Ar *C*H), 129.1 (2 Ar *C*H), 130.3 (2 Ar *C*H), 131.4 (*C*H=CH_2), 133.3 (ρ-SO_2Ar *C*H), 134.7 (quat Ar *C*), 134.9 (quat Ar *C*).

FTIR (CH_2Cl_2) υ_{max}: 3055, 2985, 1447, 1300, 1264, 1148, 742.

Anal. Calcd for C17H18O2S: C, 71.30; H, 6.34. Found: C, 71.48; H, 6.71.



(cyclohex-2-enyl(phenyl)methylsulfonyl)benzene

(**1.98**)(JW3078)

White solid

Yield: 95% (1:1.5 dr)

Purification: flash chromatography(95:5 hexanes: ethyl acetate)

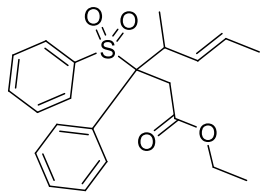
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.14 - 1.33 (3 H, m, RC*H*$_2$R), 1.46 - 1.79 (9 H, m, RC*H*$_2$R), 1.95 (4 H, m, RC*H*$_2$R), 2.19 (1 H, m, RC*H*$_2$R), 3.40 (1 H, bm, RC*H*RR), 3.43 - 3.53 (2 H, m, *J*=7.99, 5.34, 2.68, 2.68 Hz, RC*H*RR), 3.97 (1 H, d, *J*=7.83 Hz,

C*H*(Ph)(SO2Ph)), 4.08 (1 H, d, *J*=9.60 Hz, C*H*(Ph)(SO2Ph)), 5.65 (2 H, d, *J*=10.61 Hz, Olefinic C*H*), 5.76 (1 H, td, *J*=6.76, 3.16 Hz, Olefinic C*H*), 5.87 (1 H, dd, *J*=10.23, 1.89 Hz, Olefinic C*H*), 6.37 (1 H, dd, *J*=10.23, 2.65 Hz, Olefinic C*H*), 7.04 - 7.23 (17 H, m, ArC*H*), 7.29 (6 H, dt, *J*=9.54, 7.86 Hz, ArC*H*), 7.39 - 7.53 (10 H, m, ArC*H*).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 20.63 (1 C, R*C*H_2R), 21.29 (1 C, R*C*H_2R), 24.83 (1 C, R*C*H_2R), 24.98 (1 C, R*C*H_2R), 27.10 (1 C, R*C*H_2R), 28.33 (1 C, R*C*H_2R), 35.32 (1 C, R*C*HRR), 36.09 (1 C, R*C*HRR), 75.65 (1 C, *C*H(Ph)(SO2Ph)), 76.43 (1 C, *C*H(Ph)(SO2Ph)), 127.05 (1 C, Ar *C*H), 128.30 (1 C, Ar *C*H), 128.36 (1 C, Olefinic *C*), 128.39 (1 C, Olefinic *C*), 128.42 (1 C, Olefinic *C*), 128.46 (1 C, Olefinic *C*), 128.55 (1 C, Ar *C*H), 128.74 (1 C, Ar *C*H), 129.15 (1 C, Ar *C*H), 130.13 (1 C, Ar *C*H), 130.27 (1 C, Ar *C*H), 130.56 (1 C, Ar *C*H), 132.58 (1 C, quat Ar *C*), 132.98 (1 C, Ar *C*H), 133.01 (1 C, quat Ar *C*), 133.05 (1 C, Ar *C*H), 138.91 (1 C, quat Ar *C*).

FTIR (CH_2Cl_2) υ_{max}: 3065, 3030, 2929, 2864, 2839, 1648, 1586, 1494, 1447, 1308, 1143, 1082.

Anal. Calcd for C19H20O2S: C, 73.04; H, 6.45. Found: C, 73.00; H, 6.91.



(E)-ethyl 4-methyl-3-phenyl-3-(phenylsulfonyl)hept-5-enoate

(**1.104**)(JW3048)

White solid

Yield: 98% (1:1.2 dr)

Purification: flash chromatography(91:9 hexanes: ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.01 (3 H, d, *J*=7.07 Hz, C*H*$_3$CHRR), 1.21 (7 H, m, OCH_2CH_3), 1.50 (3.7 H, dt, *J*=6.32, 1.39 Hz, C*H*$_3$CHRR), 1.68 (3.8 H, d, *J*=6.82 Hz, C*H*$_3$CHCHR), 1.82 (3 H, dd, *J*=6.57, 1.52 Hz, C*H*$_3$CHCHR), 3.20 (2.3 H, dd, *J*=15.28, 6.69 Hz, diastereotopic RC*H*HCO), 3.62 (2.3 H, dd, *J*=15.28, 3.16 Hz, RCH*H*CO), 3.92 - 4.13 (6.6 H, m, OCH_2CH_3, and RC*H*CH_3CHCHCH_3), 5.25 (1.3 H, ddd, *J*=15.16, 6.19, 1.64 Hz, RCHC*H*CH_3), 5.50 (1.3 H, dq, *J*=16.86, 6.51 Hz, RC*H*CHCH_3), 5.74 - 5.85 (1 H, m, RCHC*H*CH_3), 5.98 (1 H, dq, *J*=8.02, 1.54 Hz, RC*H*CHCH_3), 7.10-7.26 (15.5 H, m), 7.36 (4.4 H, t, *J*=7.20 Hz), 7.40 - 7.46 (2.4 H, m).

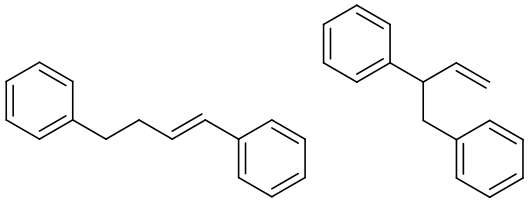
^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 13.83 (1 C, s, OCH_2CH_3), 13.90 (1 C, s, OCH_2CH_3), 16.34 (1 C, s, *C*H_3CHCHR), 17.94 (1 C, s, *C*H_3CHRCHCHR), 18.10 (1 C, s, *C*H_3CHRCHCHR), 18.29 (1 C, s, *C*H_3CHCHR), 32.65 (1 C, s, R*C*H2CO), 33.19 (1 C, s,

R*C*H2CO), 37.86 (1 C, s, CH3*C*HCHRCPh), 38.30 (1 C, s, CH3*C*HCHRCPh), 60.79 (1 C, s, O*C*H_2CH_3), 60.90 (1 C, s, O*C*H_2CH_3), 75.85 (1 C, s (quat) *C*), 77.20 (1 C, s, (quat) *C*), 126.64 (1 C, s, Ar*C*H), 127.24 (1 C, s, Ar*C*H), 127.41 (1 C, s, RCH*C*HCHCH$_3$), 128.02 (1 C, s, Ar*C*H), 128.07 (1 C, s, Ar*C*H), 128.09 (1 C, s, RCHCH*C*HCH$_3$), 128.26 (1 C, s, Ar*C*H), 128.31 (1 C, s, Ar*C*H), 129.73 (1 C, s, Ar*C*H), 129.81 (1 C, s, Ar*C*H), 130.27 (1 C, s, Ar*C*H), 130.68 (1 C, s, Ar*C*H), 130.81 (1 C, s, Ar*C*H), 131.96 (1 C, s, RCH*C*HCHCH$_3$), 132.97 (1 C, s, Ar*C*H), 133.05 (1 C, s RCHCH*C*HCH$_3$), 133.30 (1 C, s, (quat) *C*), 133.41 (1 C, s, (quat) *C*), 136.21 (1 C, s, (quat) *C*), 136.42 (1 C, s, (quat) *C*), 169.11 (1 C, s, (quat) *C*), 169.50 (1 C, s, (quat) *C*).

FTIR (CH_2Cl_2) υ_{max}: 3057, 2988, 1734, 1424, 1299, 1143, 1078.

General procedure for the reduction of the homoallylic sulfones: The sulfone, [(E)-ethyl 4-methyl-3-phenyl-3-(phenylsulfonyl)hept-5-enoate)] (45mg, .117mmol) was dissolved in MeOH (2.5ml) and magnesium turnings were added 1-2 pieces (~.5g) at a time as consumed and heated at 50°C for 3h until the reaction was complete by TLC (usually 2-3h). The reactions were concentrated to dryness in vacuo, and then extracted with Et_2O (50ml) and then the mixture was carefully washed with 3M HCl until any remaining magnesium metal or salts were dissolved and the solution cleared, and then washed with water (1X25ml). The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo* and purified by flash

column chromatography using 97:3 hexanes:EtOAc, yielding (E)-methyl 4-methyl-3-phenylhept-5-enoate in 67%.



(E)-but-1-ene-1,4-diyldibenzene

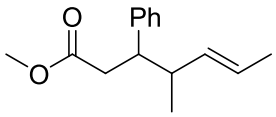
(**1.111**)(JW3158)

White crystals

Yield: 72% (10:1 L:B)

Purification: flash chromatography(90:10 hexanes: DCM)

Matches previously characterized compounds *J. Org. Chem*. **1983**,*48*, 4022-4025. Minor isomer matches: *J. Am. Chem. Soc.* **2003**, *125*, 7158-7159.



(E)-methyl 4-methyl-3-phenylhept-5-enoate

(**1.113**)(JW3149)

Yellow oil

Yield: 81%

Purification: flash chromatography(97:3—95:5 hexanes: ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.77 (3 H, d, *J*=6.62 Hz, C*H*$_3$CHRR), 0.92 (3 H, d, *J*=6.94 Hz, C*H*$_3$CHRR), 1.63 (3 H, d, *J*=6.31 Hz, C*H*$_3$CHCHR), 1.68 (3.4 H, dd, *J*=6.62, 1.58 Hz, C*H*$_3$CHCHR), 2.28 (1.4 H, dddd, *J*=15.88, 9.18, 6.62, 6.46 Hz, C*H*(CH_3)(CHCHCH$_3$)(CHPh)), 2.40 (1 H, dd, *J*=13.08, 7.09 Hz, C*H*(CH_3)(CHCHCH$_3$)(CHPh)), 2.48 (1.2 H, dd, *J*=15.29, 9.62 Hz, C*H*Ph), 2.61 - 2.77 (2.2 H, ddd, C*H*PhCH$_2$RCH), 2.77 - 2.84 (1.2 H, m, CH*H*CO), 2.88 (1 H, m, C*H*HCO), 3.14 (1H, m, CH*H*CO), 3.51 (3.3 H, s, OC*H*$_3$), 3.57 (3 H, s, OC*H*$_3$), 5.16 - 5.23 (1 H, m, RC*H*CHCH$_3$), 5.26-5.32 (1.2 H, dddd, *J*=14.31, 10.13, 2.36, 2.21 Hz, RC*H*CHCH$_3$), 5.34-5.42 (1.2 H, m, RCHC*H*CH$_3$), 5.45-5.54 (1.2 H, dd, *J*=15.29, 7.09 Hz, RCHC*H*CH$_3$), 7.11-7.22 (5.6 H, m, ArC*H*'s), 7.25 - 7.31 (5 H, m ArC*H*'s).

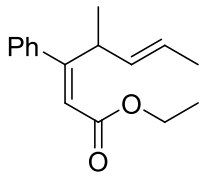
^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 14.07 (1 C, s, *C*H$_3$), 17.91 (1 C, s, *C*H$_3$), 18.01 (1 C, s, *C*H$_3$), 19.46 (1 C, s, *C*H$_3$), 37.44 (1 C, s, RCO*C*H2CHPhR), 39.90 (1 C, s,

RCO*C*H2CHPhR), 41.26 (1 C, s, *C*H), 43.22 (1 C, s, *C*H), 46.95 (1 C, s, *C*H), 47.83 (1 C, s, *C*H), 51.34 (1 C, s, O*C*H_3), 51.47 (1 C, s, O*C*H_3), 125.46 (1 C, s, Olefinic RCH*C*HCH$_3$), 125.59 (1 C, s, Olefinic RCH*C*HCH$_3$), 126.29 (1 C, s, Ar*C*H), 126.35 (1 C, s, Ar*C*H), 127.83 (1 C, s, Ar*C*H), 128.01 (1 C, s, Ar*C*H), 128.22 (1 C, s, Ar*C*H), 128.59 (1 C, s, Ar*C*H), 133.42 (1 C, s, Olefinic R*C*HCHCH$_3$), 135.33 (1 C, s, Olefinic R*C*HCHCH$_3$), 141.46 (1 C, s, (quat) Ar*C*), 143.08 (1 C, s, (quat) Ar*C*), 173.24 (1 C, s, R*C*OOR), 173.26 (1 C, s, R*C*OOR).

FTIR (CH_2Cl_2) υ_{max}: 3053, 2964, 1733, 1455, 1272, 1256.

HRMS calcd for [M+Na] 255.1361 found 255.1349.

Procedure for the elimination of the sulfinate (Scheme 1.25): To 1.5 mL of ethanol was added sodium hydride (17 mg, 0.454 mmol) after the evolution of hydrogen gas the resulting solution of EtOH/NaOEt was added to [(E)-ethyl 4-methyl-3-phenyl-3-(phenylsulfonyl)hept-5-enoate)] (35 mg, 0.0907mmol). After 15 min. at room temperature H_2O (20 mL) was added. The reaction was extracted with CH_2Cl_2 (2 x 100 mL), and dried with ($MgSO_4$) the solution was concentrated *in vacuo*. The crude reaction mixture was absorbed onto silica gel and purified by flash column chromatography using 99:1 hexanes:EtOAc to give 5-ethyl,4-methyl-3-phenylhepta-2,5-dienoate in >99% yield.



(2E,5E)-ethyl 4-methyl-3-phenylhepta-2,5-dienoate

(**1.118**)(JW3154Frc 5-12)

Yellow oil

Yield: >49%

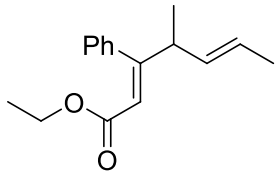
Purification: flash chromatography(99:1 hexanes: ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.11 (3 H, d, *J*=6.94 Hz, C*H*$_3$CH), 1.32 (3 H, t, *J*=7.25 Hz, C*H*$_3$CH$_2$OC(O)), 1.70 (3 H, dt, *J*=3.15, 1.58 Hz, C*H*$_3$CHCH), 4.22 (2 H, q, *J*=7.04 Hz, CH$_3$C*H*$_2$OC(O)), 4.70 - 4.89 (2 H, m, RC*H*(CH$_3$)CHCH(CH$_3$)), 5.52 - 5.67 (2 H, m, CH$_3$C*HCH*CH(CH$_3$)R), 5.80 (1 H, s, C*H*(C(O) OR)C((Ph)CHR)), 7.26 - 7.45 (5 H, m, ArC*H*'s).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 14.28 (1 C, s, *C*H$_3$CH$_2$), 18.03 (1 C, s, *C*H$_3$CHCH), 18.53 (1 C, s, *C*H$_3$CH$_2$OC(O)), 37.03 (1 C, s, *C*H(CH$_3$)CHCHCH$_3$), 59.91 (1 C, s, CH$_3$*C*H$_2$OC(O)), 118.45 (1 C, s, *C*H(C(O) OR)C(Ph)CHR), 124.97 (1 C, s, R*C*H*C*HCH$_3$), 127.73 (1 C, s, Ar*C*H), 127.77 (1 C, s, Ar*C*H), 127.82 (1 C, s, Ar*C*H), 133.58 (1 C, s, R*C*H*C*HCH$_3$) 140.64 (1 C, s, (quat) Ar*C*), 164.21 (1 C, s, quat *C*), 166.26 (1 C, s, (quat) *C*).

FTIR (CH_2Cl_2) υ_{max}: 3054, 2969, 2936, 1711, 1624, 1456, 1175.

HRMS calcd for [M+H] 245.1542 found 245.1542.



(2Z,5E)-ethyl 4-methyl-3-phenylhepta-2,5-dienoate

(**1.118**)(JW3154Frc 5-12)

Yellow oil

Yield: >49%

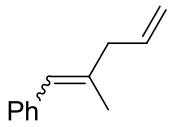
Purification: flash chromatography(99:1 hexanes: ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.05 (3 H, td, *J*=7.09, 1.89 Hz, C*H*$_3$CH$_2$OC(O)), 1.12 (3 H, dd, *J*=6.94, 1.89 Hz, C*H*$_3$CHR), 1.69 (3 H, d, *J*=5.04 Hz, C*H*$_3$CHCHR), 3.15 (1 H, m, *J*=6.31 Hz, RC*H*(CH$_3$)CHCHCH$_3$), 3.96 (2 H, app. dq, *J*=7.04, 2.21 Hz, CH$_3$C*H*$_2$OC(O)), 5.42 - 5.49 (2 H, m, CH$_3$C*H*C*H*CH(CH$_3$)R), 5.87 (1 H, s, C*H*(C(O) OR)C((Ph)CHR)), 7.11 (2 H, dd, *J*=6.46, 1.73 Hz, m-ArC*H*'s), 7.24 - 7.40 (3 H, m, *o,p*-ArCH's).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 13.90 (1 C, s, *C*$H_3CH_2OC(O)$), 17.96 (1 C, s, *C*H_3CHCHR), 18.90 (1 C, s, C*H*$_3$CHR), 45.57 (1 C, s, R*C*H$(CH_3)CHCHCH_3$), 59.75 (1 C, s, CH_3*C*$H_2OC(O)$), 116.92 (1 C, s, C*H*(C(O) OR)C((Ph)CHR)), 125.94 (1 C, s, *RC*$HCHCH_3$, or RCH*C*HCH_3), 127.23 (1 C, s, *p*-Ar*C*H), 127.34 (2 C, s, ArCH's), 127.57 (2 C, s, ArCH's), 132.70 (1 C, s, *RC*$HCHCH_3$, or RCH*C*HCH_3), 140.01 (1 C, s, (quat)ArC), 163.22 (1 C, s, (quat) *C* , 166.41 (1 C, s, (quat)*C*).

FTIR (CH_2Cl_2) υ_{max}: 3053, 2977, 2935, 1720, 1634, 1442, 1369, 1218, 1165.

HRMS calcd for [M+H] 245.1542 found 245.1543.



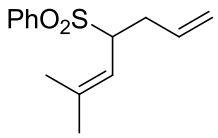
(2-methylpenta-1,4-dienyl)benzene

(**1.122**)(JW3259)

Yield: 22% Crude

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.13 (m ArC*H*'s), 6.37 (s, PhC*H*R^{a}), 6.28 (s, PhC*H*R^{b}), 5.98 – 5.77 (m, $RCH_2CHCH_2^{ab}$), 5.13-5.07 (m, $RCH_2CHCH_2^{ab}$), 2.95 (d, *J* = 6.3 Hz, $RCH_2CHCH_2^{a}$), 2.89 (d, *J* = 6.8 Hz, $RCH_2CHCH_2^{b}$), 1.87 (s, RCH_3^{a}), 1.84 (s, RCH_3^{b}). (^{a} represents one isomer; ^{b} represents the other isomer)

General procedure for Pd-catalyzed prenylation screening (Table 1.10): To a flame dried NMR tube was added sulfonyl ester (**1.128**)(JW6129) (0.1 mmol) and taken into the glovebox. Then the appropriate additive (Table 1.10) was added and then solvent (from table 1.10) (0.5 mL). Then Pd_2dba_3 (0.001 mmol) and (±)-BINAP (0.002 mmol). The tube was capped with a rubber septum and removed from the glovebox and heated to the indicated temperature. The reactions were usually monitored by and conclusions were based on ^1H NMR spectroscopy but for some (entries 12-14, Table 1.10) the solvent was first removed and the crude reaction mixture taken up in $CHCl_3$-d.



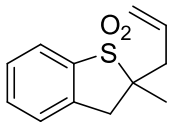
(6-methylhepta-1,5-dien-4-ylsulfonyl)benzene

(**1.129**)(JW6132)

Yield: 93%

^{1}H NMR (500 MHz, Tol) δ 7.75 – 7.67 (m, 2H, *o*-ArC*H*'s), 7.04 – 6.88 (m, 3H, ArC*H*'s), 5.54 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H, RC*H*CH_2), 5.01 – 4.84 (m, 3H, RC*H*$C(CH_3)_2$ and RCHC*H*$_2$), 3.64 (td, *J* = 10.5, 3.5 Hz, 1H, $PHSO_2C$*H*RR'), 2.98 (ddd, *J* = 14.0, 7.0, 3.5 Hz, 1H, diasterotopic RC*H*HCHCH_2), 2.47 – 2.36 (m, 1H, diasterotopic RCH*H*CHCH_2), 1.48 – 1.32 (m, 3H, RC*H*$_3$), 0.92 (d, *J* = 1.3 Hz, 3H, RC*H*$_3$).

Synthesis and decarboxylation of sulfonyl ester (1.131): The corresponding acid, purchased from Sigma-Aldrich, was placed in a flask equipped with a stirbar (0.407 mmol) and allyl alcohol was added (5 mL) then 3 drops of conc. H_2SO_4 the reaction was fitted with a reflux condenser and heated to reflux for 12 h. The reaction was extracted with ethyl acetate and washed with $NaHCO_3$ (aq) and the organic layer was dried with magnesium sulfate, then concentrated and purified by flash chromatography. The sulfonyl ester (**1.131**, JW2192) (0.259 mmol) was placed in a flame dried microwave vessel equipped with stirbar and then taken into the glovebox where it was charged with Pd_2dba_3 (0.013 mmol) and (±)-BINAP (0.026 mmol) and DMF (1.5 mL). It was capped with a microwave vessel cap and then placed into a microwave reactor where it was heated to 200 °C for 0.5 h. It was purified by flash chromatography.



2-methyl-2-propenyl-3-hydro-1-benzothiophene

(**1.132**)(JW2198)

Yield: 40%

Purification: flash chromatography(98:2 hexanes: ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.44 (3 H, s, C*H*$_3$), 2.53 (1 H, dd, *J*=14.19, 7.88 Hz, diastereotopic C*H*HCH=CH_2), 2.68 (1 H, dd, *J*=13.87, 6.94 Hz, CH*H*CH=CH_2), 2.99 (1 H, d, *J*=16.08 Hz, diastereotopic C*H*HC(quat)ArCH), 3.24 (1 H, d, *J*=15.76 Hz, diastereotopic CH*H*C(quat)ArCH), 5.14 - 5.25 (2 H, app. m, CH=C*H*$_2$), 5.86 (1 H, ddd, *J*=16.63, 6.86, 2.36 Hz, C*H*=CH_2), 7.31 (1 H, d, *J*=7.57 Hz, ArC*H*), 7.46 (1 H, app. t, *J*=7.57 Hz, ArC*H*), 7.55 (1 H, app. td, *J*=7.57, 1.26 Hz), 7.76 (1 H, d, *J*=7.88 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 19.40 (1 *C*H_3), 38.49 (1 *C*H_2CH=CH_2), 39.05 (1 Ar*C*H_2, s), 63.44 (1 quat. *C*CH_2CH_2), 120.23 (1 CH=*C*H_2), 122.44 (1 Ar*C*H), 127.18 (1 Ar*C*H), 128.68 (1 Ar*C*H), 131.72 (1 *C*H=CH_2), 133.30 (1 Ar*C*H), 135.96 (1 quat. Ar*C*), 137.65 (1 quat. Ar*C*).

FTIR (CH_2Cl_2) υ_{max}: 3060, 2973, 2933, 1642, 1601, 1472, 1456, 1434, 1297, 1273, 1149, 1125.

Anal. Calcd for C12H14O2S: C, 64.83; H, 6.35. Found: C, 64.06; H, 6.64.

General procedure for control studies (Table 1.11): The indicated acid (0.1 mmol), additives (amounts indicated), and solvent (amounts indicated) were placed in an NMR tube. The tube was capped and heated to the indicated temperature and the appearance of the

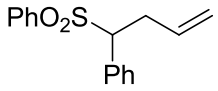
decarboxylated/protonated sulfone was monitored by ^{1}H NMR spectroscopy and concentrations were calculated based on the internal standard that was added.

Crossover experiment (Scheme 1.32): To a flame dried NMR tube was added sulfonyl esters (**1.139** and **1.83**) (0.05 mmol each). The tube was taken into the glovebox where Pd_2dba_3 (0.005 mmol) and (±)-BINAP (0.01 mmol) and toluene-d_8 (0.5 mL) were added. The tube was capped with a rubber septum, which was secured with parafilm. The reaction was heated in an oil bath at 95 °C for 14 h. The relative amounts were determined by the ^{1}H NMR spectrum.

Reduced catalyst loading experiments Scheme 1.41: Decarboxylation of sulfonyl ester (**1.163**) was performed using the same procedure as Table 1.6 but with reduced catalyst and ligand.

General procedure for intermolecular Pd-DCA (Table 1.12): To an NMR tube was added the indicated acid (Table 1.12) (1.25 equivalents) and taken into glovebox where base (1.25 equivalents), solvent (0.5 mL), and catalyst (0.1 equivalents) were added. The NMR tube was capped and allyl acetate (1.0 equivalent) was injected. The product ratio was determined either directly from ^{1}H NMR spectrum (if deuterated solvent was used) or the solvent was first evaporated and the crude reaction mixture extracted with CHCl3-d and then determined by ^{1}H NMR spectroscopy.

Scaled procedure for intermolecular Pd-DCA (Table 1.12): To a flame dried Schlenk tube equipped with stirbar was added (2-phenyl-2-(phenylsulfonyl)acetic acid) (0.156 mmol), and $CsCO_3$ and taken into the glovebox where $Pd(PPh_3)_4$ (0.125 mmol) and toluene (1.5 mL) were added. The tube was capped with a rubber septum and removed from glovebox. Allyl acetate (0.125 mmol) was injected and the reaction was stirred for 24 h.



(1-phenylbut-3-enylsulfonyl)benzene

(Entry 5 from Table 1.12)(JW3152)

Yield: 12%

Purification: flash chromatography(93:7 and then 90:10 hexanes: ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 13.3, 7.2 Hz, 3H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.29 – 7.16 (m, 3H), 7.07 (d, *J* = 7.6 Hz, 2H), 5.59 – 5.44 (m, 1H), 5.15 – 5.00 (m, 1H), 4.95 (d, *J* = 10.1 Hz, 1H), 4.08 (dd, *J* = 11.5, 3.9 Hz, 1H), 3.17 (s, 1H), 2.91 (dd, *J* = 18.7, 13.9 Hz, 1H).

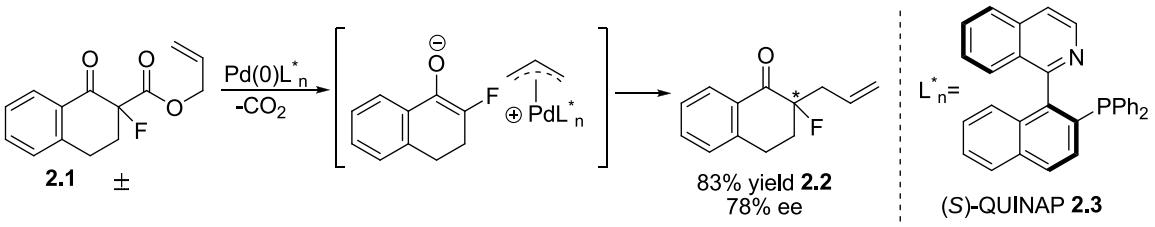
Chapter 2

Asymmetric Palladium-Catalyzed Decarboxylative Allylation

2.1—**Background: Control of the α-Position**

Stereoconvergence

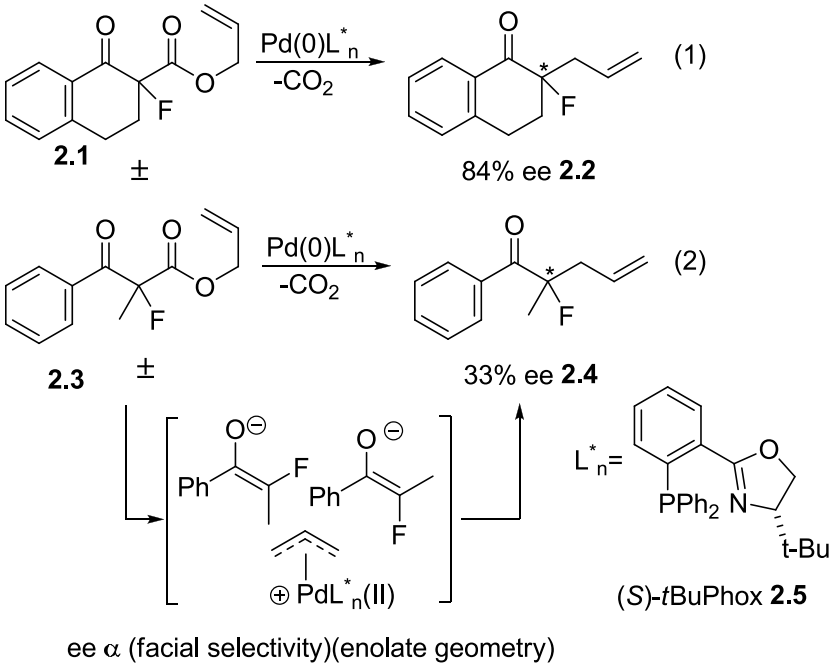
As previously discussed (Scheme 1.10), Burger and Tunge reported the asymmetric allylic alkylation of the ketone enolates formed by decarboxylation.[1] This is a valuable process in which chiral, but racemic, material undergoes a stereoconvergent process from which it can form enantioenriched product of higher value. Stereoconvergence is a general concept and not limited to palladium-π-allyl chemistry. In fact, the DCA of β-keto esters also proceeds through a stereoconvergent process with respect to the position alpha to the ketone. In Scheme 2.1 the chiral, racemic allyl ester (**2.1**) undergoes decarboxylation to generate an enolate which is achiral. A chiral, non-racemic ligand on the metal bound to the ligand can now influence which face of the enolate attacks the allyl ligand and thus can lead to enantioenriched product proportional to the facial selectivity.[2] Stereoconvergence is common among processes that generate anions that are resonance stabilized and consequently planar.



Scheme 2.1

In the case of acyclic β-keto esters, the ability to control the stereochemistry is undermined by the inability to control the geometry of the incipient enolate. Previously the β-keto esters (Scheme 2.1) that underwent enantioselective DCA reactions were all cyclic—effectively forcing a single enolate geometry and simplifying the problem. In the more

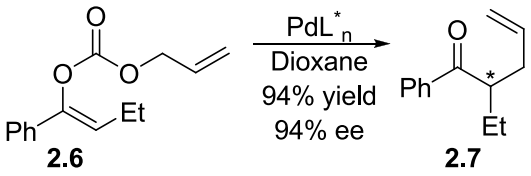
general case of acyclic esters, the lack of enolate control (Scheme 2.2) is detrimental to the enantioenrichment of the product. For example, a cyclic β-keto ester (**2.1**) undergoes DCA with good levels of enantioselectivity (eq. 1, Scheme 2.2), while the acyclic analog (**2.3**) gives only 33% ee (eq. 2, Scheme 2.2).[1]



Scheme 2.2

Another less direct but more successful approach is to set the enolate geometry prior to the reaction. Recently, Trost has shown[2] that use of the preformed allyl enol carbonate (**2.6**, Scheme 2.3) is a viable path to asymmetric homoallylic ketones, even though the substrate is acyclic. However, this method has two primary drawbacks, the synthesis and the scope. First, substrates are made by deprotonation of the corresponding ketone and trapping with allyl chloroformate. O/E or O/Z enol carbonates can be achieved to varying degrees depending on substrate and conditions used. The need to preform the enolate with a strong base under highly optimized conditions detracts from the elegance of the DCA. The second

drawback is the need to have an α-hydrogen as a substituent. To date there are no reports of the ability to control the stereochemistry in which the alpha position a) was not cyclic or b) did not possess an α-hydrogen. The reason for this might be the inability to control the geometry of the enol carbonate and thus has not been attempted. Alternatively it might be that there is little energy difference in the two possible transition states when the substituents on the α-carbon are not of significantly different sizes, i.e. H vs. C.



2.6 **2.7**

Scheme 2.3

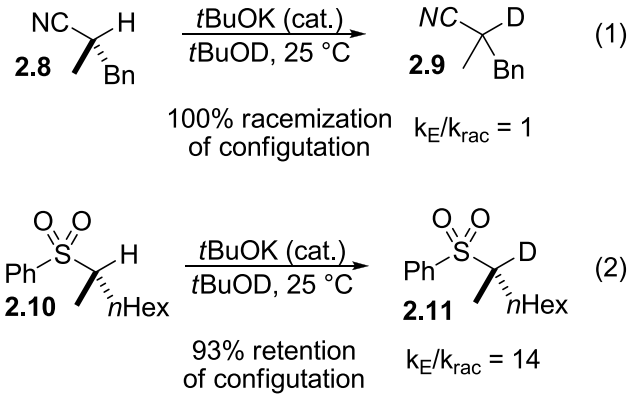
Acyclic Stereocontrol

The difficulty associated with distinguishing between enantiotopic faces of substrates that are substituted with sterically similar substituents such as Me vs Et is an outstanding challenge. One possible solution is to rely on methods that are not stereoconvergent. A process in which the stereochemistry of the product is determined by the starting material stereochemistry is defined as stereospecific.[3] Comparatively, there are far fewer examples of stereospecific carbon—carbon bond forming reactions than stereoselective reactions.

Stereospecificity

In 1960 Donald Cram explored the effect of the nature of the stabilizing group on the configurational stability of carbanions undergoing hydrogen/deuterium exchange.[4] In these

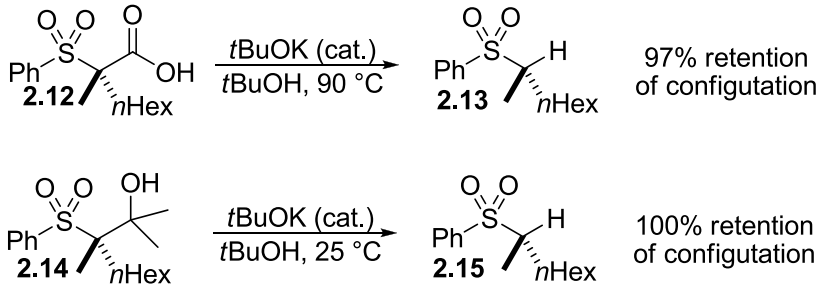
experiments enantioenriched substrates were subjected to a catalytic amount of base, the rate of racemization and hydrogen/deuterium exchange were monitored. A comparison of these two rates gives valuable information about the nature of the prerequisite anion for exchange, specifically the configurational stability of the anion that is formed. Not surprisingly when substrates such as the nitrile (**2.8**, Scheme 2.4) were exposed to the conditions complete racemization was observed (eq. 1). Racemization occurs because the anion is stabilized by delocalization into the nitrile π-bond and is consequently achiral. Protonation then occurs equally from either face, leading to racemization. This is a well known phenomenon and in fact was reported in 1938 as way to monitor the rate of enolization of chiral ketones.[5] Quite remarkable, was the high degree of enantioretention observed by the anion stabilized by the sulfone. The chiral, non-racemic sulfone (**2.10**) underwent base catalyzed deuterium exchange with only a slight amount of racemization (eq 2).



Scheme 2.4

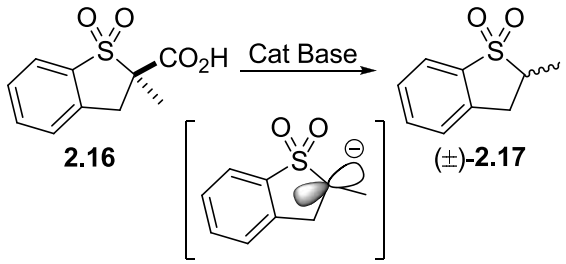
The unusual behavior of the sulfonyl anion peaked the curiosity of others, including E.J. Corey and over the next few years much attention was devoted to understanding the reasons for the high configurational stability. In 1959, Taylor and Verhoek[6] reported that the

ammonium salts of *l*-α-sulfonyl α-methyl butryric acid underwent thermal decarboxylation to afford the protonated *d*-sulfones that were nonracemic. This report was primarily empirical and did not quantify the purity of either the acid or the product sulfone thus limiting the conclusions that can be drawn. However, the fact that that the product was optically active implies that the sulfonyl anion generated from decarboxylation must also be chiral, non-racemic like that later observed by Cram (Scheme 2.4, 2.5).[4]



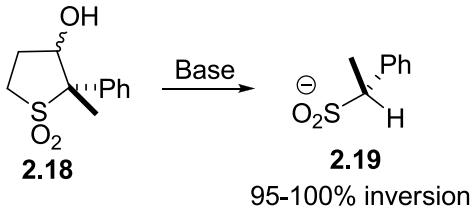
Scheme 2.5

A significant amount of work which attempted to elucidate the mechanism responsible for stereoretention was performed and several hypotheses were put forth that, in hindsight, turned out to be not quite correct.[5,8] Several key experiments helped to elucidate the mechanism that follows. One postulate for the observed asymmetry was that the anion formed was tetrahedral and had a high barrier to inversion.[7] In the reaction in Scheme 2.6[8] the optically active thiophene derived sulfonyl acid (**2.16**) was decarboxylated to afford optically inactive sulfone (**2.17**). This result is best explained by the formation of an achiral intermediate in which the hybridization is sp^2 and not tetrahedral. If formation of a tetrahedral α-sulfonyl carbanion were sufficient to maintain the chirality then, as posited by Cram, this substrate would be expected to maintain its enantioenrichment.



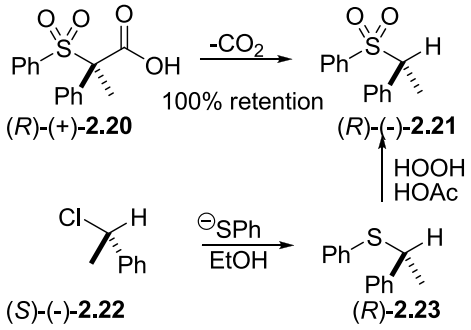
Scheme 2.6

Another key experiment was the generation of an α-sulfonyl anion via a retro-aldol reaction (Scheme 2.7).[9] In this experiment a chiral, non-racemic cyclic-β-hydroxy sulfone (**2.18**) is exposed to base which undergoes a retro-aldol to generate the sulfonyl anion which protonates from the *opposite face* of the carbon leaving group and subsequently undergoes a retro-Michael to form the chiral, non-racemic sulfinate salt (**2.19**). This is important as it rules out a high barrier to anion inversion and hints at a preference for protonation antiperiplanar to the sulfone substituent. If a high barrier to inversion is ruled out, then the asymmetry must be due to a high barrier to rotation about the αC-S bond.



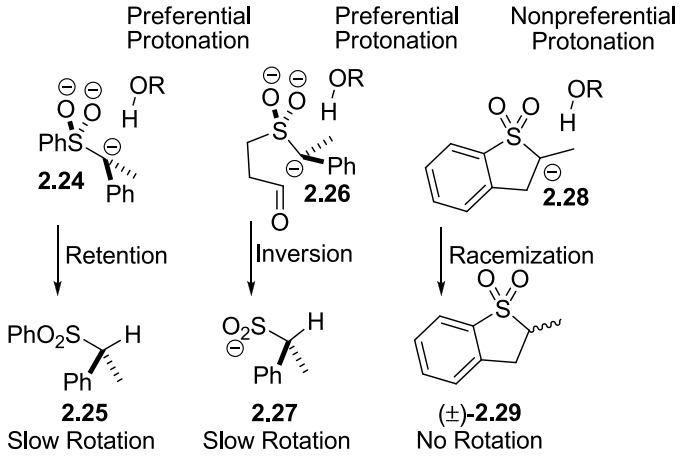
Scheme 2.7

In addition to this experiment Corey demonstrated that the acyclic sulfonyl acid (**2.20**, Scheme 2.8) undergoes decarboxylative protonation with retention of stereochemistry via an independent synthesis of the product sulfone (**2.21**), in which the stereochemistry was known.[9]



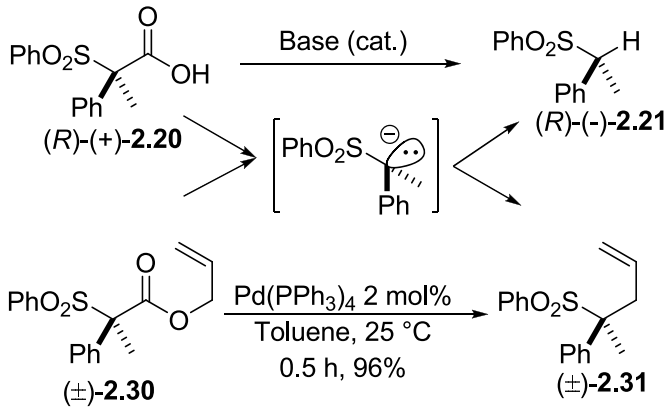
Scheme 2.8

To summarize this research, sulfonyl anions exhibit axial chirality and are sufficiently configurationally stable to undergo protonation in protic solvent significantly faster than racemization. Furthermore, the sulfonyl anion demonstrates a strong preference for protonation *syn* to the sulfone oxygen atoms regardless of the initial anion conformation that is formed (Scheme 2.9). Consequently, the sulfonyl anion must have a small barrier to anion inversion since inversion happens faster than protonation. In addition, there must be a sufficiently large barrier to rotation about the αC-S bond such that protonation of the anion occurs faster than rotation, less the preferential protonation would cause racemization; thus the sulfonyl anion must exhibit axial chirality.



Scheme 2.9

Work from Corey and Cram[7-10] with the base-catalyzed decarboxylative-protonation of substituted sulfonyl acetic acids is of particular interest to our work. While the reaction provides a different product, we believe that a common sulfonyl anion intermediate is formed in both the protonation and the Pd-DCA (Scheme 2.10).[10] If true, racemic product would be expected as we were beginning with racemic ester. The implications, if this were true, warranted investigation. To date, the use of the sulfonyl acetic acid as a source of chiral sulfonyl anion seems limited to protonation reactions. While it is remarkable that racemization of the anion generated from decarboxylation does not occur, it is synthetically flawed because the product is simpler than the starting material. We speculated that if the decarboxylation could be harnessed to generate a carbon-carbon bond in a nonracemic fashion the product would be more complex than the starting material and thus, synthetically, a valuable process.

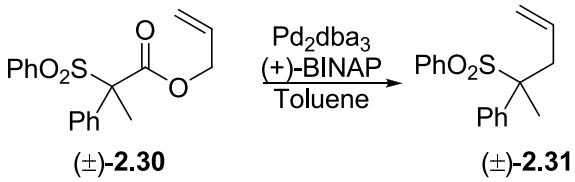


Scheme 2.10

2.2—Development of the Stereospecific Pd-DCA

Investigation of the Stereospecificity of the Pd-DCA of Sulfonyl Esters

We began our investigation of the asymmetric reaction by subjecting racemic sulfonyl ester **2.30** (Scheme 2.11) to Pd-catalyzed DCA in which chiral, non-racemic (+)-BINAP was used as the ligand. Based on chiral stationary phase HPLC analysis the product (**2.31**) was completely racemic. Apparently, the ligand imposes little influence over the stereochemistry of the attacking nucleophile. While it is quite likely that ee's of a potential *enantioselective* reaction would be small, it would be a nonzero number.

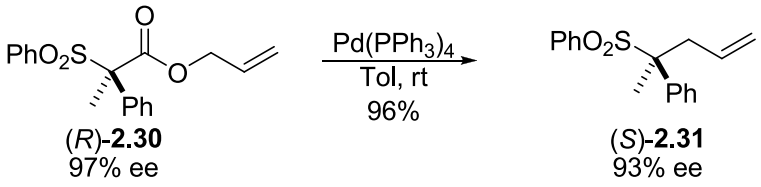


(±)-**2.30** (±)-**2.31**

Scheme 2.11

The previous result is consistent with, but not definitive of, a reaction that is stereospecific; starting with racemic ester would lead to racemic product unless racemization of the incipient anion could occur faster than carbon-carbon bond formation. To further investigate whether or not the reaction was stereospecific we synthesized chiral, non-racemic sulfonyl ester (**2.30**, Scheme 2.12) and subjected it to a catalytic amount of $Pd(PPh_3)_4$ in toluene at room temperature. If the reaction was truly stereospecific then the chirality of the product would reflect the stereochemistry of the starting material; in other words one enantiomer of the starting material would lead to one enantiomer of the product.[3] Pd-DCA of **2.30** (97% ee) gave the homoallylic sulfone (**2.31**) in 96% yield and 93% ee. The important number in a test of stereospecificity is the cee, which is the conservation of ee or simply the (product ee%)/(starting material ee%)x100. Therefore, a reaction that gave total

stereotransfer without racemization, would give a cee of 100%. We were delighted to see such a high cee. Further evidence that the decarboxylation is a stereospecific process is the use of an achiral catalyst $Pd(PPh_3)_4$ which cannot impart stereochemistry to the product. With this result in hand we attempted to demonstrate the scope of the reaction as well as determine a plausible mechanism and to perform a stereospecific reduction.



(*R*)-**2.30**
97% ee

(*S*)-**2.31**
93% ee

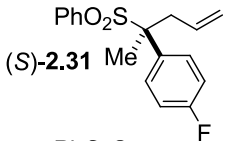
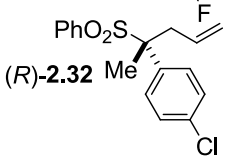
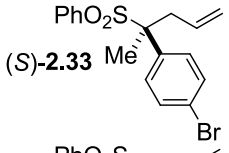
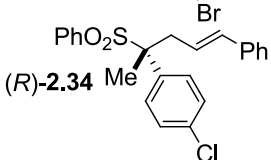
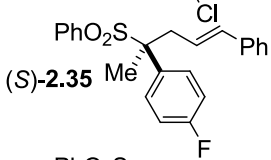
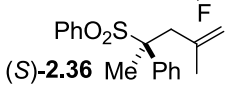
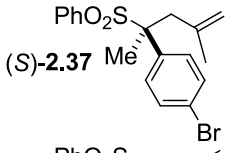
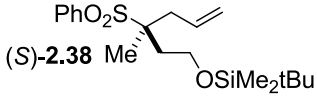
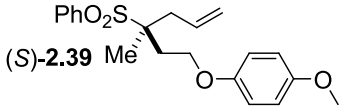
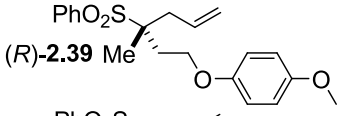
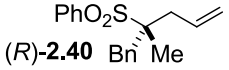
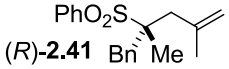
% cee = [(Product ee%) / (Starting Material ee%)]100 = 96% cee

Scheme 2.12

Uniformly, entries 1-12 (Table 2.1), the reactions proceeded with high levels of cee (>92% cee). We used two sets of conditions depending on the nature of the parent ester. Substrates with an α-aryl substituent (entries 1-7) were subjected to DCA using 2 mol% $Pd(PPh_3)_4$ and underwent smooth decarboxylation in near quantitative yields. The reactions were very clean and were essentially "spot-to-spot" reactions. Entries 4 and 5 in which a cinnamyl ester was used gave ~8:1 linear to branched ratio which were inseparable by flash column chromatography. This linear to branched ratio is typical of a palladium catalyst, in DCA chemistry. Also noteworthy and valuable, is the chemoselectivity that is possible because of the mild conditions used. $Pd(PPh_3)_4$ can oxidatively insert into Ar-X, where X is a halogen (rate Br>Cl>>F) but the reaction proceeds cleanly leaving the Ar-Br (entry 3 and 7) unchanged. Conditions B were used for substrates that were α,α-dialkyl and used 5 mol% Pd_2dba_3 and 10 mol% (±)-BINAP in toluene (0.2 M in substrate) at 95 °C for 11-15 h. We

found that increasing the concentration from 0.1 M used previously[10] to 0.2 M led to slight increases in both the rate and the yield of the reaction. For the dialkyl substrates (entries 6-12) very nice yields (82-97%) were obtained. The TBDMS protecting group (entry 8) is well tolerated under the reaction conditions as well as PMP group (entries 9 and 10). As expected both enantiomers are obtainable if the corresponding ester is used (entries 9 and 10). Also noteworthy is the slight improvement in yield as the reaction was scaled up (870 mg, 2.14 mmol entry 10 vs. 9). A 2-methyl group is well tolerated on the allyl portion of the ester (entries 7,12). The absence of anything other than an α-methyl group might lead to concern that the reaction only works or is only stereospecific in the case of an α-methyl substituent, we do not believe this to be the case. Racemic substrates that are more elaborately functionalized in the alpha position are known to react under the same reaction conditions[10] therefore it is unlikely that the stereospecific-DCA is limited only to substrates that posses an α-methyl substituent. Rather, the frequent reoccurrence of the alpha-methyl substituent is due to limitations in the synthesis of the parent ester (see chapter 3).

Table 2.1 Results of Stereospecific Decarboxylative Allylation

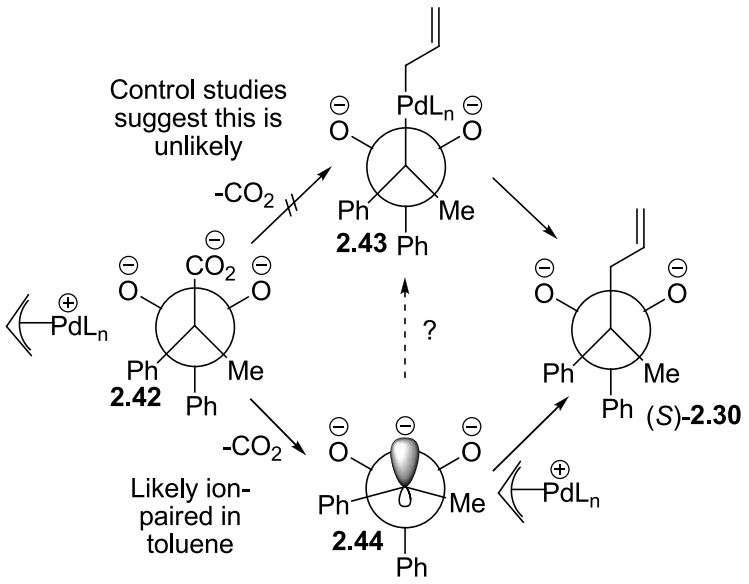
entry	product	procedure[a]	yield (%)[b]	SM ee (%)[c]	Pdt ee (%)[c]	cee (%)[c]
1	 (*S*)-**2.31**	A	96	46	43	92
2	 (*R*)-**2.32**	A	99	88	87	98
3	 (*S*)-**2.33**	A	99	97	96	99
4	 (*R*)-**2.34**	A	99	64	64	99[d]
5	 (*S*)-**2.35**	A	99	73	69	96[d]
6	 (*S*)-**2.36**	A	99	97	93	96
7	 (*S*)-**2.37**	A	99	80	80	99
8	 (*S*)-**2.38**	B	82	94	92	99
9	 (*S*)-**2.39**	B	95	94	92	98
10	 (*R*)-**2.39**	B	97	>99	>99	98
11	 (*R*)-**2.40**	B	85	98	95	97
12	 (*R*)-**2.41**	B	93	98	>95	97

a) Conditions A: 2 mol % $Pd(PPh_3)_4$, 0.2 M toluene, 23 °C, 0.25-2 h. Conditions B: 5 mol % Pd_2dba_3, 10 mol % (±)-BINAP, 0.2 M toluene, 95 °C, 11-15 h. b) isolated yields. c) determined via chiral stationary phase HPLC analysis d) 8:1 linear:branched

Mechanism

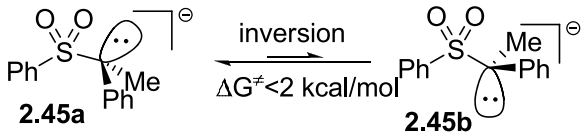
Thus far we had assumed that the Pd-DCA proceeded with retention in analogy to the decarboxylative protonation. However, due to serendipitous crystallization of a derivative of *R*-**2.39** (Table 2.1) we have unambiguously established that the Pd-DCA occurs with retention of configuration as determined by an X-ray analysis of a crystal structure of the derivative. The origin and configuration of the stereochemistry can be traced back to the dihydroxylation of the 1,1-disubstituted olefin.[11]

As previously described in Table 1.11 control studies suggest that the Pd(II) intermediate does not facilitate decarboxylation, thus, it is unlikely that the substrate undergoes decarboxylation to directly generate a Pd-C organometallic species (**2.43**, Scheme 2.13). Rather an ion-pair is likely formed in toluene (**2.44**) which we believe leads to product (**2.30**).



Scheme 2.13

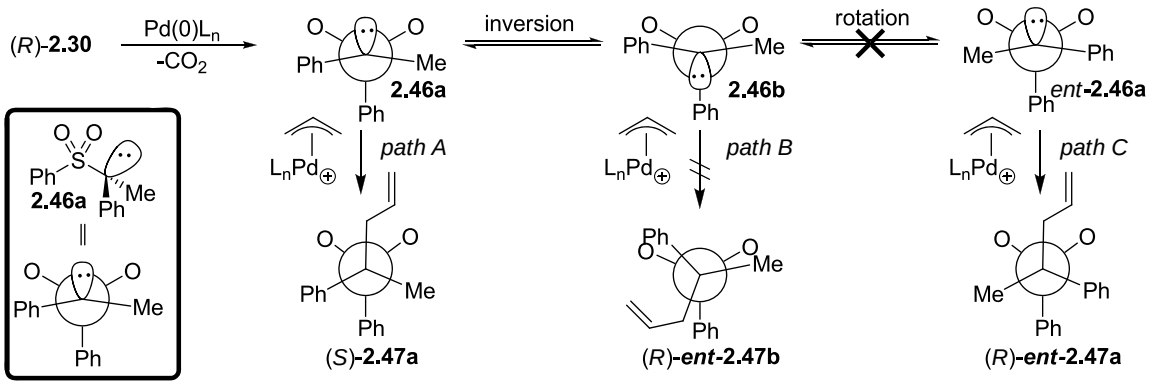
It is very peculiar that a free sulfonyl carbanion is formed and yet does not racemize, especially since Gais reports rapid racemization at -80 °C.[12] One potential way to maintain stereochemistry of the carbanion is to for the anion to have a high barrier to inversion, as proposed by Cram[7] and refuted by Corey.[9] We collaborated with Ward Thompson and Being Ka, who performed high level DFT calculations to determine the energy barrier to inversion. All attempts to minimize structure **2.45b** (Scheme 2.14) gave structure **2.45a**, which is slightly pyramidalized with the major lobe of the anion anti-periplanar to the Ph-S bond, making it impossible to get a definitive number for a barrier for inversion, this is consistent with other studies involving sulfonyl carbanions.[12-13] However, the fact that it is too small to find-suggest an upper limit of ~2 kcal/mol. Thus the sulfonyl anion cannot be chiral because of the inability to invert, consistent with decarboxylative protonation, and must be configurationally stable for other reasons.



Scheme 2.14

We believe that the reaction progresses as follows (Scheme 1.15); ionization and thermal decarboxylation of (*R*)-**2.30** leads to anion-**2.46a**. Sulfonyl anion **2.46a** then attacks the allyl ligand or Pd followed by reductive elimination to generate sulfone (*S*)-**2.47a** (path A). It is reasonable for attack from this face of the anion to be more rapid as it attacks from the more populated conformer and presumably occurs through the lower energy staggered transition state. Enantioenrichment may be eroded by the following reaction pathways. As

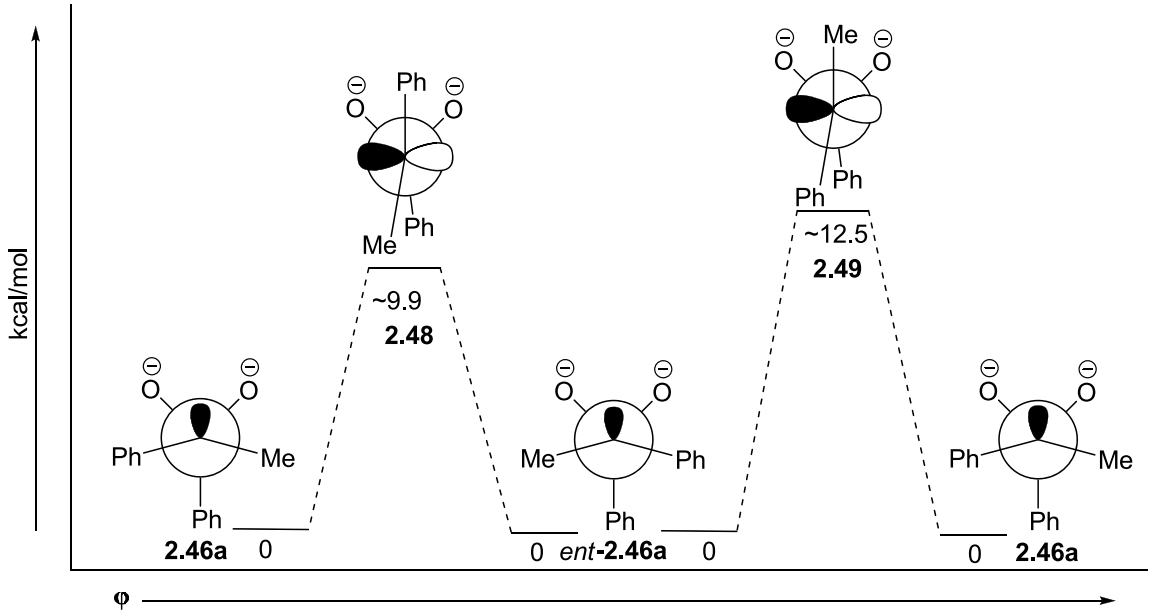
previously discussed there is only a small barrier to anion inversion, as a consequence it is conceivable that reaction of the π-allyl ligand and the inverted anion (**2.46b**) could lead to *ent*-**2.47b** and a decrease in ee, path B. However, attack of the π-allyl ligand from anion **2.46b** requires attack from the less populated conformer and furthermore proceeds through a higher energy-fully eclipsed transition state. The high cee's dictate that only one reaction manifold is dominant. The crystal structure also strongly implies that it is anion **2.46a** that reacts to give product **2.47a**. Alternatively, rotation about the αC-S could lead to *ent*-**2.46a** (path C). *Ent*-**2.46a** would be expected to allylate with the same facial preference as **2.46a** and would lead to a lower ee. Since the reaction is highly stereospecific we believe that path C must not be operative. Thus the high levels of enantiospecificity we observed are due to 1) facile allylation of **2.46a** and 2) slow rotation about the αC-S bond. DFT calculations were used to calculate the energy for rotation about the αC-S bond.



Scheme 2.15

Barrier to Rotation

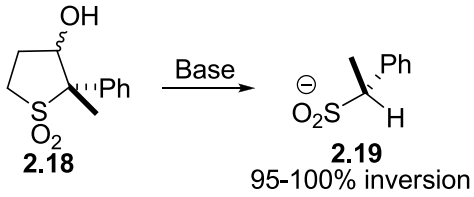
The energy of the anion, determined by DFT calculations, is plotted as a function of rotation about the αC-S bond. DFT calculations found that in the lowest transition state the α-methyl substituent was fully eclipsed with the sulfur substituent and had an energy of 9.9 kcal/mol (**2.48**, Scheme 2.16). Thus the upper limit to the barrier to allylation must be smaller than 9.9 kcal/mol, less deterioration of the ee due to rotation would be observed. Recall, in Corey's experiment with the cyclic sulfone (Scheme 2.6), the enatioenriched acid gave racemic product. Racemization would be expected since anion genesis is at the conformation of the transition state for rotation, a prerequisite of the small cycle. At the transition state the anion (**2.48**, Scheme 2.16) is achiral and consequently is equally likely to relax to **2.46a** or *ent*-**2.46a**.



Scheme 2.16

Sulfonyl Anion-Slow Rotation

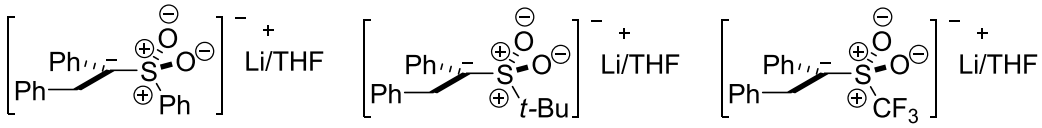
DFT calculations found a barrier to rotation of 9.9 kcal/mol; it is not immediately obvious what interactions lead to the slow rotation. Work by a great host of chemists have concluded that the sulfonyl anion is stabilized primarily by the electrostatic interaction between the electron-poor sulfur and electron-rich carbon and-to a lesser extent-negative hyperconjugation into the σ* of the S-phenyl substituent.[13b,c,14] Delocalization into empty d orbitals or resonance into S-O bonds has little effect. We have demonstrated that the key to the racemization barrier, in the DCA, is most likely due to a barrier to rotation about the αC-S bond rather than inversion of the anion. This finding is consistent with Corey's experiment in which the sulfonyl anion underwent inversion prior to protonation (Scheme 2.7).[9]



Scheme 2.7

Gais has found that the sulfur substituent makes a dramatic difference in the stereostability of the sulfonyl anion (Scheme 2.17).[12,15] The following barriers to racemization were determined from dynamic ^{1}H NMR spectroscopy. Barriers of 9.6, 13.5, and 16.0 kcal/mole were found for the S-Ph (**2.50**), S-(*t*-Bu) (**2.51**), and the S-(CF_3) (**2.52**) α-sulfonyl anions respectively, at the indicated temperatures. Comparison of the phenyl α-sulfonyl anion (**2.50**) to the *tert*-butyl α-sulfonyl anion (**2.51**) highlights the importance of the sterics of the sulfur substituent. It is easy to see that in a transition state such as **2.48**

(Scheme 2.17) the barrier to rotation will be highly dependent on the steric nature of the S-X substituent. Comparison of the *tert*-butyl α-sulfonyl anion (**2.51**) and the trifluoro methane α-sulfonyl anion (**2.52**) exemplify the role of the electronic nature of the sulfur substituent. While the triflone provides less steric inhibition than the *tert*-butyl sulfone donation into the σ* orbital provides a greater amount of stabilization to the anion and thus provides a higher energy barrier to racemization. The half-lives corresponded to the stability such that even at -80 °C the phenyl α-sulfonyl anion (**2.50**) rapidly racemized, whereas the *tert*-butyl α-sulfonyl anion (**2.51**) and the trifluoro methane α-sulfonyl anion (**2.52**) had synthetically viable half-lives. Given the rapid racemization of the phenyl α-sulfonyl anion (**2.50**), it is quite remarkable that we were able to allylate the phenyl α-sulfonyl anions faster than racemization.



2.50 $\Delta G^{\neq}_{-58\,°C}$=9.6±0.2 kcal/mol, $t_{1/2}$ (-80 °C) = rapid

2.51 $\Delta G^{\neq}_{10\,°C}$=13.5±0.2 kcal/mol, $t_{1/2}$ (-105 °C) ≈ 3 h

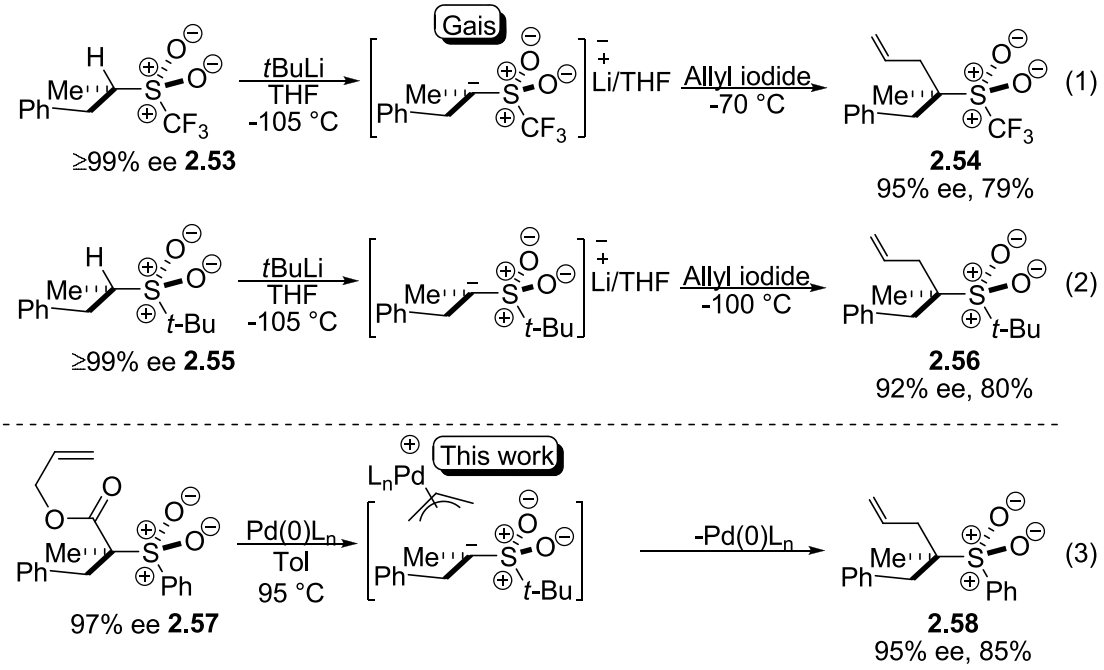
2.52 $\Delta G^{\neq}_{60\,°C}$=16.0±0.2 kcal/mol

Scheme 2.17

Synthetic application

Gais has also demonstrated the ability to generate and allylate the sulfonyl anions stereospecifically with excellent cee's (Scheme 2.18).[12,15] The process we have developed compares favorably with this method. While feasible, Gais' method requires highly pyrophoric tert-butyl lithium, in addition to extremely low temperatures, and finally requires use of energy rich allyl iodide. Comparatively, our Pd-catalyzed DCA method has no

additives, is run at ambient or elevated temperatures, and uses low energy allyl acetates. Furthermore, due to rapid racemization of phenyl sulfones Gais is forced to use other sulfone substituents in order to obtain good results, reducing the generality of the method. Deprotonation and allylation of the triflone (**2.53**, eq. 1) gave **2.54** in 95% cee, while deprotonation and allylation of *tert* butyl sulfone (**2.55**) gave **2.56** in 92% cee and 80% yield (eq. 2). Using the phenyl sulfone (**2.57**), we obtained **2.58**, in a 97% cee and 85% yield (eq. 3). Thus, the Pd-catalyzed DCA expands the scope of the sulfone to the phenyl analogs and provides a higher yield and cee's without the drawbacks, previously discussed.

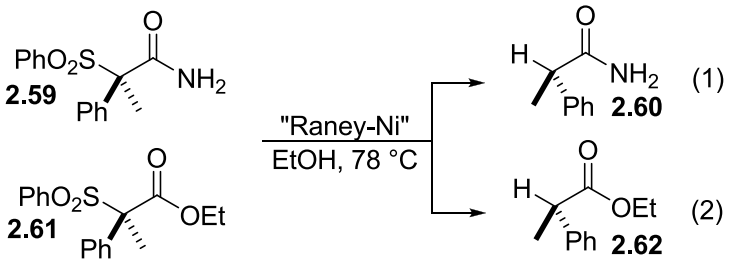


Scheme 2.18

2.3—Attempted Stereospecific Reduction of Sulfones

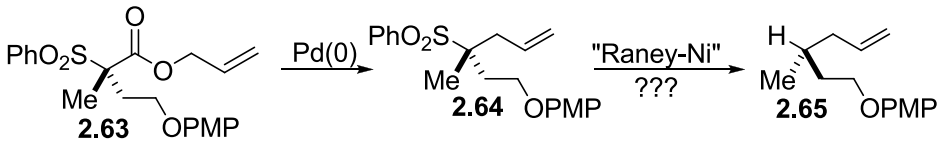
Finally, we attempted to stereospecifically reduce the product sulfones. Bonner[16] reported that sulfonyl amide (**2.59**, Scheme 2.19) and ester (**2.61**) when exposed to "Raney-

Ni" in refluxing ethanol undergo stereospecific hydrogenation of the C-S bond and that this takes place with inversion of the stereocenter to afford the reduced products (**2.60** and **2.62**).



Scheme 2.19

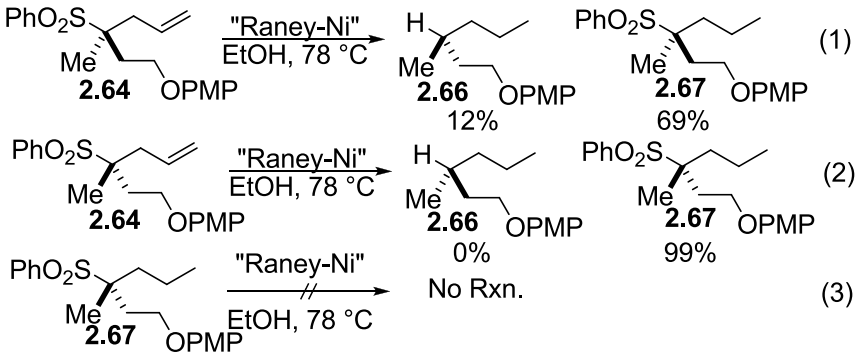
We believed that this methodology coupled with our stereospecific DCA might allow the formation of highly enantioenriched hydrocarbon stereocenters. This two step procedure (Scheme 2.20) would allow the stereochemistry of a chiral center, conspicuously absent of any functional group handle, to be controlled. This would be quite remarkable and a valuable synthetic method, thus we explored reductions of the sulfone.



Scheme 2.20

We began our investigation using Bonner's method.[16] One of the product sulfones (**2.64**) from the Pd-DCA was subjected to "Raney-Ni" hydrogenation on a small scale (eq. 1, Scheme 2.21) and afforded 12% of the desired product (**2.66**), though the stereochemistry, as shown, is based on Bonner's report. The majority of the mass balance was made up by clean hydrogenation of the double bond in which the sulfone had not been cleaved (69%, **2.67**).

Despite the dismal yield of the desired product (12%, **2.66**), we scaled up the reaction but only the undesired saturated product was obtained (eq. 2). Furthermore, resubjection of this product (**2.67**, eq. 3) to the reaction conditions did not lead to further reaction, suggesting that there is a competition between desulfurization and hydrogenation of the olefin, and that if hydrogenation occurs first the desulfurization would not occur. One difference in Bonner's work and ours is that he used benzylic sulfones which may have been crucial to the desulfurization.

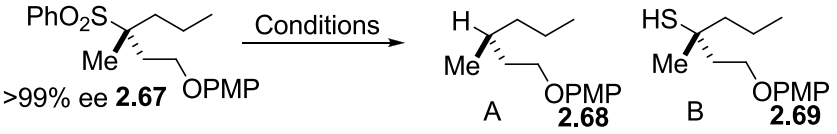


Scheme 2.21

We screened several more reduction methods in hopes that we might find one that allowed for the ee to be maintained in a reduction product (Table 2.2). We were able to partially resolve the enantiomers of **A** by chiral stationary phase HPLC such that we could determine if **A** were racemic but our uncertainty increased proportionally to the ee% **A**. Magnesium in warm MeOH had been used previously to cleave the C-S bond, but appears to lead to racemic **A** (entry 1). There is a report that these conditions at room temperature lead to S-deoxygenation on related sulfones.[17] However, in our hands this led to **A** (entry 2). We hoped zinc might insert into the C-S and proceed to protonate (entries 3 and 4),

unfortunately, this did not occur and only starting material was observed. Excess LAH, on the other hand, did react and the product distribution was dependent on the reaction temperature (entries 5-8). At lower temperatures the Ph-S bond was cleaved and the free thiol **B** was obtained (entries 6 and 8). However, at elevated temperatures (entry 7) racemic **A** was obtained as the sole product. At 0 °C most of the stating material was recovered after 8h (entry 5). Cl_3SiH had also been used as a reductant of S-O species, however this led to no reaction (entry 9). One alternative hope was that we might access **B** selectively which could then be converted to a sulfoxide which could undergo a stereospecific lithiation,[18] which could be a versatile anion that could be used in many ways. To date, we have not found any method that gives the reduced hydrocarbon without significant, if not complete, racemization. We did, however, develop a workable method for screening reduction methods which is noteworthy.

Table 2.2 Outcome of various reductants on tertiary sulfone.



Entry	Reductant	Sol.	Temp °C	Conv.	A:B	ee%	Comments
(1)	Mg(0)	MeOH	50	100	1:0	<22	
(2)	$Mg(0)/I_2$	MeOH	23	100	1:0	nd	Attempted S-deoxygenation
(3)	$Zn(0)/NH_4Cl$	H_2O/THF	50	0	--	--	No Rxn.
(4)	Zn(0)	HOAc	110	0	--	--	No Rxn.
(5)	LAH	THF	0	<10	nd	--	8 h
(6)	LAH	THF	23-35	100	0:1	0	
(7)	LAH	THF	67	100	1:0	0	
(8)	LAH	THF	30	100	1:3.5	0	57% B isolated, 17% A isolated
(9)	Cl_3SiH/Et_3N	d-Tol	110	0	--	--	No reaction

To summarize we successfully developed the stereospecific Pd-catalyzed DCA. The reaction demonstrates high levels of enantiospecificity, even in substrates that only have slight steric differences of the substituents, in contrast to most enantioselective methods where the size difference is crucial to the enantioselectivity. Furthermore, we determined that the enantiospecificity is observed because of a barrier to rotation about the αC-S bond. In addition we found a barrier to this rotation, via DFT calculations, to be 9.9 kCal/mol. Finally, we attempted, without success, to reduce the product sulfone to the hydrocarbon without racemization but did find conditions to make the chiral, non-racemic thiol.

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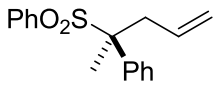
Appendix B: General Methods and Compound Characterization

Materials. All moisture sensitive reactions were run in flame-dried glassware under an Ar atmosphere using standard Schlenk techniques. Methylene chloride, toluene, THF, Et_2O wer dried over activated alumina and toluene and THF were then distilled over sodium. Acetone was distilled from magnesium sulfate and stored over activated mol sieves. Commercially available reagents were used without additional purification unless otherwise stated. Tris(dibenzylideneacetone) dipalladium (0), $Pd(PPh_3)_4$, and rac-BINAP were purchased from Strem and stored in a glovebox under an Ar atmosphere. Compound purification was effected by flash chromatography using 230x400 mesh, 60 Å porosity, silica obtained from Sorbent Technologies. Thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5715-7, EMD chemicals). Visualization of the plateswas accomplished with a UV lamp (254 nm) or $KMnO_4$ stain. ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance 400 or a Bruker Avance 500 DRX, or a Bruker AVIII 500 spectrometer and referenced to residual protio solvent signals (some spectra were taken using a broadband observe probe and a dual 13C/1H Cryoprobe). Structural assignments are based on ^1H, ^{13}C, DEPT-135, COSY, HSQC and IR spectroscopies. FTIR spectra were recorded using either a ATI Mattson Genesis Series FTIR or Shimadzu 8400-S FTIR spectrometers. High Resolution Mass Spectrometry (HRMS) were performed using EI, ESI, and FAB techniques. EI MS spectra were obtained on an AUTOSPEC-Q tandem hybrid mass spectrometer (VG Analytical Ltd, Manchester, UK). ESI MS spectra were acquired either on a LCT Premier (Waters Corp., Milfpord, MA) or Q-Tof-2 (Microsmass Ltd, Manchester UK) spectrometers.

FAB MS spectra were obtained on a ZAB HS mass spectrometer (VG Analytical Ltd, Manchester UK). Elemental Analyses were performed by Desert Analytics Laboratory (Tuscon, AZ). Chiral high pressure liquid chromatography was performed on a Shimadzu SCL-10AVP instrument using Daicel Chiralpak AD, AS and OD-H columns.

General procedure B the optimized Pd-catalyzed DCA of α-dialkyl sulfonyl esters (Table 2.1): To a flame-dried Schlenk tube equipped with stir bar was added (R)-allyl 4-(4-methoxyphenoxy)-2-methyl-2-(phenylsulfonyl)butanoate (0.160 mmol). The tube was taken into the glovebox where it was charged with Pd_2dba_3(0.0080 mmol) and (±)-BINAP (0.0160 mmol) and toluene (0.8 mL) then capped with a septum which was secured with parafilm. The tube was then placed in an oil bath at 95 °C and magnetically stirred for 11 h at which point it was purified by column chromatography (loaded directly).

General procedure A the optimized Pd-catalyzed DCA of α-phenyl sulfonyl esters (Table 2.1): To a flame dried Schlenk tube equipped with stir bar was added (R)-allyl 2-(4-fluorophenyl)-2-(phenylsulfonyl)propanoate (29 mg, 0.0833 mmol), toluene (0.42 ml), $Pd(PPh_3)_4$ (1.9 mg, 0.00167 mmol) under an atmosphere of Argon. The reaction was stirred at room temperature until TLC indicated all the starting material had been consumed, (<2 h). The reaction was quenched and purified by flash column chromatography using 90:10 hexanes: ethyl acetate, yielding the product (S)-1-fluoro-4-(2-(phenylsulfonyl)pent-4-en-2-yl)benzene in 96%.



(S)-(2-phenylpent-4-en-2-ylsulfonyl)benzene

(**2.31**)(JW4124)

Colorless amorphous solid

Yield: 96%, 93% ee

Purification: flash chromatography (95:5 hexanes:ethyl acetate)

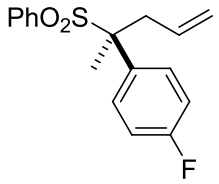
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.66 (3 H, s: C*H*$_3$), 2.83 (1 H, dd, *J*=14.02, 8.46 Hz: diastereotopic C*H*HRCH=CH_2), 3.37 (1 H, dd, *J*=13.89, 5.56 Hz: diastereotopic CH*H*RCH=CH_2), 5.00 (1 H, app. d, *J*=10.11 Hz: H_b), 5.12 (1 H, dd, *J*=17.05, 1.14 Hz: H_a), 5.37 (1 H, dddd, *J*=16.99, 10.04, 8.59, 5.56 Hz: C*H*=CH_2), 7.16 - 7.34 (9 H, m: Ar CH's), 7.43 - 7.51 (1 H, m: Ar CH's).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 19.2 (*C*H_3), 37.8 (*C*H_2), 68.5 (Quat *C*), 119.9 (CH=*C*H_2), 128.0 (2 Ar *C*H), 128.1 (2 Ar *C*H), 128.4 (ρ-CR_3Ar *C*H), 129.1 (2 Ar *C*H), 130.3 (2 Ar *C*H), 131.4 (*C*H=CH_2), 133.3 (ρ-SO_2Ar *C*H), 134.7 (quat Ar *C*), 134.9 (quat Ar *C*).

FTIR (CH_2Cl_2) υ_{max}: 3055, 2985, 1447, 1300, 1264, 1148, 742.

Chiral HPLC Column: Chiracel Chiralpak-AD column. **Eluent:** 99:1 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** major R_t = 18.0 minutes, minor R_t = 21.7 minutes.

Optical rotation: $[\alpha]_D^{25}$ = -46.7 (*c* .00075, DCM).



(S)-1-fluoro-4-(2-(phenylsulfonyl)pent-4-en-2-yl)benzene

(**2.70**)(JW6073)

Colorless amorphous solid

Yield: 96%, 42% ee

Purification: flash chromatography (90:10 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 1H, ArC*H*), 7.25 (s, 2H, ArC*H*), 7.24 (d, *J* = 0.5 Hz, 1H, ArC*H*), 7.13 (s, 2H, ArC*H*), 7.12 (s, 3H, ArC*H*), 5.25 (dddd, *J* = 17.0, 10.0, 8.4, 5.8 Hz, 1H, RC*H*CHH), 5.03 (dd, *J* = 17.0, 1.1 Hz, 1H, RCHCH*H*), 4.93 (d, *J* = 10.0 Hz, 1H,

RCHC*H*H), 3.22 (dd, *J* = 14.1, 5.6 Hz, 1H, RCH*H*CHCH2), 2.82 – 2.60 (m, 1H, RC*H*HCHCH2), 1.44 (s, 3H, RC*H*3).

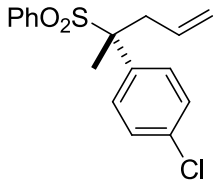
^{13}C NMR (126 MHz, $CDCl_3$) δ 134.7 (s, (qaut)Ar*C*), 134.7 (s, (qaut)Ar*C*), 133.6 (s, Ar*C*H), 133.5 (s, (qaut)Ar*C*), 131.0 (s, Ar*C*H), 130.6 (s, R*C*HCH2), 130.4 (s, Ar*C*H), 128.4 (s, Ar*C*H), 128.2 (s, Ar*C*H), 120.3 (s, RCH*C*H2), 68.2 (s, RRRR*C*), 37.9 (s, R*C*H2CHCH2), 19.3 (s, R*C*H3).

FTIR (CH_2Cl_2) υ_{max}: 1300, 1147.

HRMS calcd for [M+NH4] 322.1277 found 322.1276.

Chiral HPLC Column: Chiracel Chiralpak-AD column. **Eluent:** 99:1 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** major R_t = 19.2 minutes, minor R_t = 24.1 minutes.

Optical rotation: $[\alpha]_D^{25}$ = -12.5 (*c* .00325, DCM).



(R)-1-chloro-4-(2-(phenylsulfonyl)pent-4-en-2-yl)benzene

(**2.32**)(JW6072)

Colorless amorphous solid

Yield: 96%, 87% ee

Purification: flash chromatography (90:10 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 1H, ArC*H*), 7.25 (s, 2H, ArC*H*), 7.24 (d, *J* = 0.5 Hz, 1H, ArC*H*), 7.13 (s, 2H, ArC*H*), 7.12 (s, 3H, ArC*H*), 5.25 (dddd, *J* = 17.0, 10.0, 8.4, 5.8 Hz, 1H, RC*H*CHH), 5.03 (dd, *J* = 17.0, 1.1 Hz, 1H, RCHCH*H*), 4.93 (d, *J* = 10.0 Hz, 1H, RCHC*H*H), 3.22 (dd, *J* = 14.1, 5.6 Hz, 1H, RCH*H*CHCH2), 2.82 – 2.60 (m, 1H, RC*H*HCHCH2), 1.44 (s, 3H, RC*H*3).

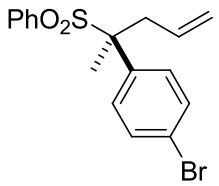
^{13}C NMR (126 MHz, $CDCl_3$) δ 134.7 (s, (qaut)Ar*C*), 134.7 (s, (qaut)Ar*C*), 133.6 (s, Ar*C*H), 133.5 (s, (qaut)Ar*C*), 131.0 (s, Ar*C*H), 130.6 (s, R*C*HCH2), 130.4 (s, Ar*C*H), 128.4 (s, Ar*C*H), 128.2 (s, Ar*C*H), 120.3 (s, RCH*C*H2), 68.2 (s, RRRR*C*), 37.9 (s, R*C*H2CHCH2), 19.3 (s, R*C*H3).

FTIR (CH_2Cl_2) υ_{max}: 1303, 1143.

HRMS calcd for [M+Na] 343.0536 found 343.0547.

Chiral HPLC Column: Chiracel Chiralpak-AD column. **Eluent:** 99:1 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** minor R_t = 21.9 minutes, major R_t = 27.1 minutes.

Optical rotation: $[\alpha]_D^{25}$ = +42.8 (*c* .00375, DCM).



(S)-1-bromo-4-(2-(phenylsulfonyl)pent-4-en-2-yl)benzene

(**2.33**)(JW6071)

Colorless amorphous solid

Yield: 99%, 96% ee

Purification: flash chromatography (90:10 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.50 (m, 1H, ArC*H*), 7.37 (dd, *J* = 12.7, 6.7 Hz, 6H, ArC*H*), 7.15 (d, *J* = 8.8 Hz, 2H, ArC*H*), 5.35 (dddd, *J* = 16.9, 10.0, 8.4, 5.8 Hz, 1H, RC*H*CH2), 5.13 (ddd, *J* = 17.0, 2.7, 1.5 Hz, 1H, RCHC*H*H), 5.04 (d, *J* = 10.0 Hz, 1H,

RCHCH*H*), 3.33 (dd, *J* = 14.1, 5.7 Hz, 1H, RC*H*HCHCH2), 2.83 (dd, *J* = 14.1, 8.4 Hz, 1H, RCH*H*CHCH2), 1.66 (s, 3H, RC*H*3).

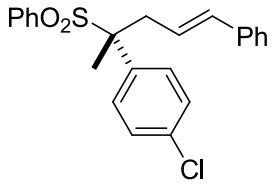
^{13}C NMR (126 MHz, $CDCl_3$) δ 134.9 (s, (q)Ar*C*), 134.2 (s, (q)Ar*C*), 133.9 (Ar*C*H), 131.4 (Ar*C*H), 131.2 (Ar*C*H), 131.1 (Ar*C*H), 130.6 (Ar*C*H), 128.6 (vinyl *C*H), 123.2 ((q)Ar*C*-Br), 120.6 (RCH*C*H2), 68.5 (RRRRC), 38.1 (R*C*H2CHCH2), 19.4 (R*C*H3).

FTIR (CH_2Cl_2) υ_{max}: 1302, 1146.

HRMS calcd for [M+NH4] 382.0476 found 382.0500.

Chiral HPLC Column: Chiracel Chiralpak-AD column. **Eluent:** 99:1 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** major R_t = 20.1 minutes, minor R_t = 25.9 minutes.

Optical rotation: $[\alpha]_D^{25}$ = -42.2 (*c* .00325, DCM).



(R,E)-1-chloro-4-(5-phenyl-2-(phenylsulfonyl)pent-4-en-2-yl)benzene

(**2.34**)(JW6065)

White amorphous solid

Yield: 99%, 63% ee

8.3:1 l:b (dr 1:1)

Purification: flash chromatography (90:10 hexanes:ethyl acetate)

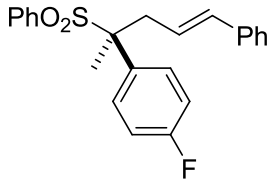
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (t, *J* = 6.8 Hz, 1H, ArC*H*'s), 7.48 – 7.38 (m, 4H, ArC*H*'s), 7.35 – 7.17 (m, 9H, ArC*H*'s), 6.53 (d, *J* = 15.7 Hz, 1H, RCHC*H*Ph), 5.87 – 5.70 (m, 1H, RC*H*CHPh), 3.54 (dd, *J* = 14.1, 5.6 Hz, 1H, RC*H*HCHCHPh), 3.07 (dd, *J* = 14.2, 8.8 Hz, 1H, RCH*H*CHCHPh), 1.76 (s, 3H, RC*H*3).

^{13}C NMR (126 MHz, $CDCl_3$) ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.8 ((q)Ar*C*), 135.3 ((q)Ar*C*), 135.0 ((q)Ar*C*), 133.9 (Ar*C*H), 133.8 ((q)Ar*C*), 130.7 (Ar*C*H), 130.6 (Ar*C*H), 128.7 (RCH*C*HPh), 128.6 (Ar*C*H), 128.5 (Ar*C*H), 128.3 (Ar*C*H), 127.8 (Ar*C*H), 126.4 (Ar*C*H), 122.6 (R*C*HCHPh), 68.7 (RRRR*C*), 37.4 (R*C*H2CHCHPh), 19.6 (R*C*H3).

FTIR (CH_2Cl_2) υ_{max}: 1302, 1147.

HRMS calcd for [M+Na] 419.0849 found 419.0834.

Chiral HPLC Column: Chiracel Chiralpak-AD column. **Eluent:** 99.4:0.6 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** minor R_t = 49.4 minutes, major R_t = 55.5 minutes.



(S,E)-1-fluoro-4-(5-phenyl-2-(phenylsulfonyl)pent-4-en-2-yl)benzene

(**2.35**)(DM1064)

Slighty yellow amorphous solid

Yield: 99%, 69% ee

8:1 l:b (dr 1:1)

Purification: flash chromatography (90:10 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (td, *J* = 6.1, 3.3 Hz, 1H, ArC*H*SO2R), 7.38 – 7.33 (m, 4H, ArC*H*'s), 7.31 (dd, *J* = 8.9, 5.3 Hz, 2H, ArC*H*'s), 7.23 – 7.13 (m, 5H, ArC*H*'s), 6.96 (t, *J* = 8.7 Hz, 2H, ArC*H*'s), 6.49 (d, *J* = 15.7 Hz, 1H, RCHC*H*Ph), 5.75 (ddd, *J* = 14.7, 8.8, 5.9

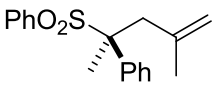
Hz, 1H, RC*H*CHPh), 3.50 (dd, *J* = 14.1, 5.8 Hz, 1H, RC*H*HR), 3.03 (dd, *J* = 14.1, 8.8 Hz, 1H, Diastereotopic RC*H*HR), 1.72 (s, 3H, RC*H*3).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0 (d, *J* = 249.2 Hz, Ar*C*F), 136.9 ((q)ArC), 135.2 (RCH*C*HPh), 135.0 ((q)ArC), 133.8 (s, 1H), 131.3 (d, *J* = 8.2 Hz, 1H, RArCAr*C*H'sACH'sArCF), 130.6 (Ar*C*H), 128.7 (Ar*C*H), 128.6 (Ar*C*H), 128.3 (Ar*C*H), 127.8 (Ar*C*H), 126.4 (Ar*C*H), 122.7 (R*C*HCHPh), 115.3 (d, *J* = 21.3 Hz, RAr*C*H'sArCF), 68.6 (RRRR*C*), 37.5 (R*C*H2CHCHPh), 19.8 (R*C*H3).

FTIR (CH_2Cl_2) υ_{max}: 1301, 1146.

HRMS calcd for [M+Na] 403.1144 found 403.1148.

Chiral HPLC Column: Chiracel Chiralpak-AS column. **Eluent:** 99:1 Hexanes:isopropanol. **Flow rate:** 0.95 mL/min. **Wavelength:** 210 nm. **Retention times:** minor R_t = 42.7 minutes, major R_t = 47.2 minutes.



(S)-(4-methyl-2-(phenylsulfonyl)pent-4-en-2-yl)benzene

(**2.36**)(JW4118)

White amorphous solid

Yield: 99%, 93% ee

Purification: flash chromatography (95:5 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (ddd, *J* = 8.6, 5.9, 2.6 Hz, 1H, ArC*H*SO2R), 7.37 (d, *J* = 7.5 Hz, 2H, ArC*H'*sSO2R), 7.30 – 7.25 (m, 5H, ArC*H*), 7.21 (d, *J* = 6.8 Hz, 2H, ArC*H*), 4.77 (s, 1H, vinyl C*H*), 4.63 (s, 1H, vinyl C*H*), 3.38 (d, *J* = 14.0 Hz, 1H, diastereotopic C*H*2), 2.99 (d, *J* = 14.0 Hz, 1H, diastereotopic C*H*2), 1.67 (s, 3H, vinylC*H*3), 1.28 (s, 3H, quatCC*H*3).

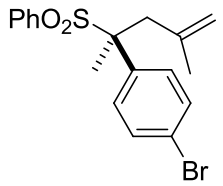
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0 (Ar*C*H), 135.7 (RC(Me)CH2), 135.2 (Ar*C*), 133.5 (Ar*C*H), 130.6 (Ar*C*H), 129.3 (Ar*C*H), 128.7 (Ar*C*H), 128.3 (Ar*C*H), 128.1 (Ar*C*H), 116.8 (RCH(Me)*C*H2), 69.1 (RRRR-*C*), 40.6 (R*C*H2R), 24.5 (*C*H3vinyl), 19.4 ((q)C*C*H3).

FTIR (CH_2Cl_2) υ_{max}: 1302, 1145.

HRMS calcd for [M+NH4] 318.1528 found 318.1519.

Chiral HPLC Column: Chiracel Chiralpak-AD column. **Eluent:** 99:1 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** major R_t = 17.2 minutes, minor R_t = 25.3 minutes.

Optical rotation: $[\alpha]_D^{25}$ = -55.9 (*c* .0055, DCM).



(S)-1-bromo-4-(4-methyl-2-(phenylsulfonyl)pent-4-en-2-yl)benzene

(**2.37**)(DM1068)

Off white amorphous solid

Yield: 99%, 80% ee

Purification: flash chromatography (90:10 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dt, *J* = 8.7, 4.2 Hz, 1H, ArC*H*), 7.37 (d, *J* = 8.9 Hz, 2H, ArC*H*'s), 7.33 (d, *J* = 4.5 Hz, 4H, ArC*H*'s), 7.24 (d, *J* = 8.6 Hz, 2H, ArCC*H*'sCH'sCBr), 4.78 (s, 1H, RC(CH3)C*H*H), 4.61 (s, 1H, RC(CH3)CH*H*), 3.30 (d, *J* = 14.1 Hz, 1H, RC*H*HC(CH3)CH2), 2.95 (d, *J* = 14.1 Hz, 1H, RCH*H*C(CH3)CH2), 1.64 (s, 3H, RC(C*H*3)CH2), 1.29 (s, 3H, (q)CC*H*3).

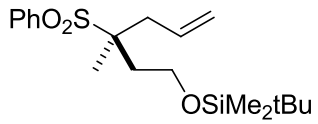
^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6 ((q)Ar*C*), 135.0 (R*C*(CH3)CH2), 134.9 ((q)Ar*C*), 133.8 (ArCH), 131.3 (ArCH's), 131.0 (ArCH's), 130.6 (ArCH's), 128.5 (ArCH's), 123.1 (Ar*C*Br), 117.1 (RC(Me)*C*H2), 68.7 (RRRR*C*), 40.6 (R*C*H2R), 24.5 (RC(*C*H3)CH2), 19.3 ((q)*C*H3).

FTIR (CH_2Cl_2) υ_{max}: 1301, 1145.

HRMS calcd for [M+H] 379.0367 found 379.0347.

Chiral HPLC Column: Chiracel Chiralpak-AD column. **Eluent:** 99:1 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** major R_t = 17.4 minutes, minor R_t = 25.5 minutes.

Optical rotation: $[\alpha]_D^{25}$ = -55.7 (*c* .0215, DCM).



(S)-tert-butyldimethyl(3-methyl-3-(phenylsulfonyl)hex-5-enyloxy)silane

(**2.38**)(JW6062)

Colorless amorphous solid

Yield: 82%, 92% ee

Purification: flash chromatography (90:10 hexanes:ethyl acetate then 1:1 hexanes:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 2H, *o*ArC*H*'s), 7.64 (t, *J* = 7.5 Hz, 1H, *p*ArC*H*), 7.54 (t, *J* = 7.7 Hz, 2H, *m*ArC*H*'s), 5.85 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H, RCH2C*H*CH2), 5.18 – 5.01 (m, 2H, RCH2CHC*H2*), 3.83 (t, *J* = 7.2 Hz, 2H, RCH2C*H*2OSiR), 2.58 (dd, *J* = 14.4, 7.2 Hz, 1H, RC*H*HCHCH2), 2.36 (dd, *J* = 14.4, 7.3 Hz, 1H, RCH*H*CHCH2), 1.93 (ddt, *J* = 22.2, 14.5, 7.3 Hz, 2H, RC*H*2CH2OSiR), 1.27 (s, 3H, quatC*Me*), 0.85 (s, 9H, RSiMe2*tBu*), 0.02 (s, 6H, RSi*Me*2tBu).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.0 (quat Ar*C*), 133.9 (vinyl-*C*H), 132.4 (ArCH), 130.7 (ArCH), 129.4 – 128.8 (ArCH), 119.7 (vinyl *C*H2), 65.2 (CCC-*C*), 59.2 (R*C*H2OR), 38.8 (quatC*C*H2vinyl), 36.3 (R*C*H2CH2OR), 26.1 (RSiMe2C(*C*H3)3), 20.1 (quatC*C*H3), 18.4 (RSiMe2*C*Me3), -5.1 (RSi(*C*H3)2tBu).

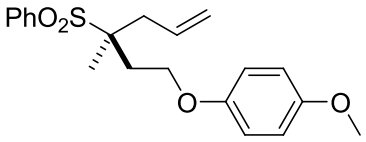
FTIR (CH_2Cl_2) υ_{max}: 1302, 1146, 1077.

HRMS calcd for [M+H] 369.1920found 369.1917.

Chiral HPLC Column: Chiracel Chiralpak-AD column. **Eluent:** 90:10 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** minor

R_t = 19.1 minutes, major R_t = 21.7 minutes. The enantioenrichment was determined using the free alcohol. Conversion to the corresponding alcohol was accomplished by stirring overnight in a 4:1:1 solution of AcOH:H_2O:THF the alcohol was then separated.

Optical rotation: $[\alpha]_D^{25}$ = +5.0 (*c* .002, DCM).



(S)-1-methoxy-4-(3-methyl-3-(phenylsulfonyl)hex-5-enyloxy)benzene

(**2.39**)(JW6052)

Colorless amorphous solid

Yield: 95%, 92% ee

Purification: flash chromatography (90:10 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.1 Hz, 2H, *o*ArCH'sSO2R), 7.65 (t, *J* = 7.5 Hz, 1H, *p*ArCHSO2R), 7.55 (t, *J* = 7.8 Hz, 2H, *m*ArCH'sSO2R), 6.81 (s, 4H, RO*Ar*OMe), 5.90 – 5.75 (m, 1H, RC*H*CH2), 5.13 (dd, *J* = 24.2, 13.5 Hz, 2H, RCHC*H*2), 4.19 (t, *J* = 7.2 Hz, 2H, RC*H*2OAr), 3.75 (s, 3H, ArOC*H*3), 2.62 (dd, *J* = 14.1, 7.3 Hz, 1H, (q)CCH*H*vinyl), 2.39

(dd, *J* = 14.1, 7.3 Hz, 1H, (q)CC*H*Hvinyl), 2.27 – 2.08 (m, 2H, (q)CC*H*2CH2OAr), 1.32 (s, 3H, (q)CC*H*3).

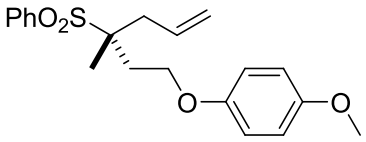
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2 (RO-(q)ArC), 152.8 (RO-(q)ArC), 135.7 (R*C*HCH2), 134.0 (Ar*C*SO2R), 131.8 (Ar*C*HSO2R), 130.7 (Ar*C*HSO2R), 129.1 (Ar*C*HSO2R), 120.3 (RCH*C*H2), 115.7 (ROAr*C*H's), 114.9 (ROAr*C*H's), 64.9 ((q)*C*), 64.6 (R*C*H2OAr), 55.9 (ArO*C*H3), 38.8 ((q)C*C*H2vinyl), 33.1 ((q)C*C*H2CH2R), 20.2 (R*C*H3).

FTIR (CH_2Cl_2) υ_{max}: 1510, 1300, 1231, 1145, 1075, 1037.

HRMS calcd for [M+NH4] 378.1739found 378.1717.

Chiral HPLC Column: Chiracel Chiralpak-AD column. **Eluent:** 90:10 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** minor R_t = 19.1 minutes, major R_t = 21.7 minutes. The enantioenrichment was determined using the free alcohol. Conversion to the corresponding alcohol was accomplished by a CAN oxidative removal of *p*-methoxy phenol in a 1:1 solution of MeCN/H_2O at 0°C for 10min. The alcohol was then separated.

Optical rotation: $[\alpha]_D^{25}$ = +3.8 (*c* .00725, DCM).



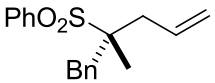
(R)-1-methoxy-4-(3-methyl-3-(phenylsulfonyl)hex-5-enyloxy)benzene

(**2.39**)(JW6242)

Colorless amorphous solid

Yield: 97%, >99% ee

Chiral HPLC Column: Chiracel Chiralpak-AD column. **Eluent:** 90:10 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** major R_t = 19.1 minutes, minor expected at R_t = 21.7 minutes. The enantioenrichment was determined using the free alcohol. Conversion to the corresponding alcohol was accomplished by a CAN oxidative removal of *p*-methoxy phenol in a 1:1 solution of MeCN/H_2O at 0°C for 10min. The alcohol was then separated.



(R)-(2-methyl-1-phenylpent-4-en-2-ylsulfonyl)benzene

(**2.40**)(JW5256)

Yellow amorphous solid

Yield: 85%, 93% ee

Purification: flash chromatography (95:5 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.2 Hz, 2H, *o*ArCH'sSO2R), 7.66 (t, *J* = 7.5 Hz, 1H, *p*ArCHSO2R), 7.56 (t, *J* = 7.7 Hz, 2H, *m*ArCH'sSO2R), 7.31 – 7.20 (m, 3H, ArC*H*'sCH2R), 7.11 (dd, *J* = 7.7, 1.7 Hz, 2H, ArC*H*'sCH2R), 5.92 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H, RC*H*CH2), 5.08 (dd, *J* = 10.2, 1.9 Hz, 1H, RCHCH*H*), 4.99 (dd, *J* = 17.0, 1.8 Hz, 1H, RCHC*H*H), 3.07 (dd, *J* = 46.3, 13.3 Hz, 2H, RC*H*2Ph), 2.38 (ddd, *J* = 52.4, 15.3, 7.0 Hz, 2H, RC*H*2vinyl), 1.21 (s, 3H, RC*H*3).

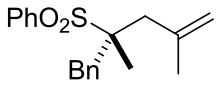
^{13}C NMR (126 MHz, $CDCl_3$) δ 136.1 (Ar*C*), 135.3 (Ar*C*), 133.9 (Ar*C*H), 133.0 (R*C*HCH2), 131.3 (Ar*C*H), 130.8 (Ar*C*H), 129.1 (Ar*C*H), 128.4 (Ar*C*H), 127.3 (Ar*C*H), 119.0 (RCH*C*H2), 66.5 ((q)*C*), 39.5 (R*C*H2Ph), 38.4 (R*C*H2vinyl), 19.4 (R*C*H3)

FTIR (CH_2Cl_2) υ_{max}: 1301, 1144.

HRMS calcd for [M+Na] 323.1082found 323.1093.

Chiral HPLC Column: Chiracel Chiralpak-OD-H column. **Eluent:** 98:2 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** major R_t = 16.8 minutes, minor R_t = 18.1 minutes.

Optical rotation: $[\alpha]_D^{25}$ = +14.2 (*c* .00425, DCM).



(R)-(2,4-dimethyl-1-phenylpent-4-en-2-ylsulfonyl)benzene

(**2.41**)(JW5255)

Off white amorphous solid

Yield: 93%, >95% ee

Purification: flash chromatography (95:5 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.81 (m, 2H, oArCH'sSO2R), 7.64 (t, *J* = 7.5 Hz, 1H, *p*ArCHSO2R), 7.54 (t, *J* = 7.7 Hz, 2H, *m*ArCH'sSO2R), 7.33 – 7.19 (m, 3H, RCH2ArCH's), 7.15 (d, *J* = 8.0 Hz, 2H, RCH2ArCH's), 4.91 (s, 1H, RCMeC*H*H), 4.66 (s, 1H, RCMeCH*H*), 3.13 – 2.94 (m, 2H, RC*H*2Ph), 2.48 (dd, *J* = 37.7, 13.9 Hz, 2H, RC*H*2CMeCH2), 1.69 (s, 3H, RC(C*H*3)CH2), 1.33 (s, 3H, (q)CC*H*3).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7 (R*C*(Me)CH2), 136.4 (Ar*C*), 135.6 (Ar*C*), 133.8 (Ar*C*HSO2R), 131.5 (Ar*C*H'S), 130.9 (Ar*C*H'S), 129.0 (Ar*C*H'S), 128.3 (Ar*C*H'S), 127.2 (Ar*C*H), 117.6 (RC(Me)*C*H2), 67.1 (RRRR*C*), 41.8 (R*C*H2C(Me)CH2), 40.9 (R*C*H2Ph), 25.0 (RC(*C*H3)CH2), 19.6 ((q)*C*H3).

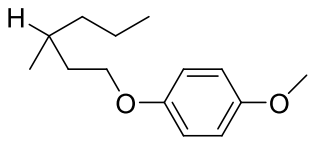
FTIR (CH_2Cl_2) υ_{max}: 1300, 1143.

HRMS calcd for [M+Na] 337.1238 found 337.1236.

Chiral HPLC Column: Chiracel Chiralpak-AD column. **Eluent:** 98:2 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** major R_t = 18.6 minutes, minor R_t = 20.0 minutes.

Optical rotation: $[\alpha]_D^{25}$ = +9.2 (*c* .003, DCM).

Procedure for the attempted "Raney-Ni" desulfurization (Scheme 2.21): (S)-1-methoxy-4-(3-methyl-3-(phenylsulfonyl)hex-5-enyloxy)benzene (**2.64**) was added a Schlenk tube equipped with stirbar. "Raney-Ni" (~0.5 g), stored under H_2O, was repeatedly decanted and rinsed with absolute EtOH (4X) and transferred to the schlenk tube and 3 mL of EtOH was added. The tube was connected to a bubler and heated. Rapid stirring was nessecary as the "Raney-Ni" was paramagnetic. After 4 h the reaction was filtered over Celite and the ethanol removes *in vacuo.* The reaction was purified via flash chromatography.



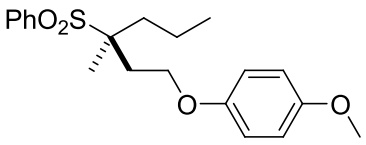
1-methoxy-4-(3-methylhexyloxy)benzene

(**2.66**, **2.68**)(JW6208)

Yield: 12% (contains DCM and ethyl acetate)

Purification: flash chromatography (95:5 hexanes:ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 4H, ArC*H*'s), 3.98 – 3.85 (m, 2H, RCH_2OAr), 3.75 (s, 3H, CH_3OAr), 1.76 (dd, *J* = 10.7, 7.0 Hz, 1H), 1.65 (s, 1H), 0.94 (d, *J* = 6.6 Hz, 1H), 0.90 (d, *J* = 6.6 Hz, 3H, CH_3CHRR), 0.87 (d, *J* = 4.3 Hz, 6H).



(S)-1-methoxy-4-(3-methyl-3-(phenylsulfonyl)hexyloxy)benzene

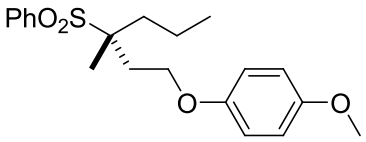
(**2.67**)(JW6208)

Yield: 69%

Purification: flash chromatography (95:5 then 1:1 hexanes:ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 2H, ArC*H*'sSO_2R), 7.64 (t, *J* = 7.4 Hz, 1H, ArC*H*SO_2R), 7.53 (t, *J* = 7.6 Hz, 2H, ArC*H*'sSO_2R), 6.81 (s, 4H, MeOArC*H*'s), 4.24 – 4.05 (m, 2H, ArOCH_2R), 3.73 (d, *J* = 9.5 Hz, 3H, CH_3OAr), 2.33 – 2.18 (m, 1H), 2.18 – 2.04 (m,

1H), 1.89 – 1.74 (m, 1H), 1.59 (td, *J* = 12.9, 4.4 Hz, 1H), 1.54 – 1.33 (m, 2H), 1.30 (s, 3H, C*H*$_3$(q)C), 0.90 (t, *J* = 7.2 Hz, 3H).



(R)-1-methoxy-4-(3-methyl-3-(phenylsulfonyl)hexyloxy)benzene

(**2.67**)(JW6246, JW7046)

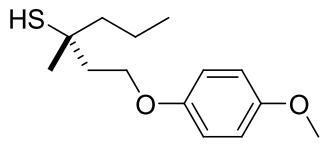
Yield: 99%

Purification: Filtered over Celite and silica plug.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.4 Hz, 2H, *o*ArCH'sSO2R), 7.64 (t, *J* = 7.4 Hz, 1H, *p*ArCHSO2R), 7.54 (t, *J* = 7.7 Hz, 2H, *m*ArCH'sSO2R), 6.81 (s, 4H, RO*Ar*OMe), 4.26 – 4.03 (m, 2H, RC*H*2OAr), 3.74 (s, 1H, ArOC*H*3), 2.25 (ddd, *J* = 14.5, 8.1, 6.1 Hz, 1H, RC*H*HCH2OAr), 2.11 (ddd, *J* = 14.6, 8.2, 6.0 Hz, 1H, RCH*H*CH2OAr), 1.81 (td, *J* = 13.2, 4.2 Hz, 1H, (q)CC*H*HEt), 1.71 – 1.55 (m, 1H, (q)CCH*H*Et), 1.55 – 1.45 (m, 1H, (q)CCH2C*H*HMe), 1.45 – 1.34 (m, 1H, (q)CCH2C*H*HMe), 1.30 (s, 3H, (q)CC*H*3), 0.90 (t, *J* = 7.2 Hz, 3H, RCH2C*H*3).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1 (MeO(q)Ar*C*RR), 152.9 (Ar(q)*C*OR), 136.0 (Ar(q)*C*SO2R), 133.9 (Ar-ρ*C*HSO2R), 130.6 (Ar-*mC*HSO2R), 129.1 (Ar-*oC*HSO2R), 115.7 (Ar-*oC*H's), 114.9 (Ar-*mC*H's), 65.4 ((q)*C*RRR), 64.7 (ArO*C*H2R), 56.0 (*C*H3OAr), 36.1 ((q)C*C*H2Et), 33.0 ((q)C*C*H2CH2OAr), 20.7 (*C*H3(q)C), 17.4 ((q)CH2*C*H2CH3), 14.8 ((q)CH2CH2*C*H3).

Procedure for LAH reduction of tertiary sulfone. To a flame dried Schlenk tube was added (R)-1-methoxy-4-(3-methyl-3-(phenylsulfonyl)hexyloxy)benzene (**2.67**)(JW6246, JW7046) (0.206 mmol). The atmosphere was replaced with Ar (2X). THF (2.1 mL) was added via syringe. Finally, LAH (2.06 mmol) was added with a positive flow of Ar coming out of the tube. The reaction was stirred at 35 °C for 9.5 h and then cooled and quenched (Caution!). The reaction was extracted with ethyl acetate (2X) and the combined organic layer was washed with brine and dried with magnesium sulfate and concentrated *in vacuo*.



(R)-1-(4-methoxyphenoxy)-3-methylhexane-3-thiol

(**2.69**)(JW6288)

Yield: 57%

Purification: flash chromatography (95:5 then 85:15 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 – 6.77 (m, 4H, ArC*H*'s), 4.10 (t, *J* = 6.3 Hz, 2H, RCH_2OAr), 3.74 (s, 3H, CH_3OAr), 2.32 (s, 1H, RS*H*), 2.02 – 1.85 (m, 2H, ArOCH$_2$CH_2(q)C), 1.55 – 1.44 (m, 2H, (q)CCH_2CH$_2$CH$_3$), 1.44 – 1.32 (m, 2H, (q)CCH$_2$CH_2CH$_3$), 1.22 (s, 3H, CH_3(q)C), 0.92 (t, *J* = 7.2 Hz, 3H, (q)CCH$_2$CH$_2$CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.23 (s, Ar*C*), 152.91 (s, Ar*C*), 115.68 (s, Ar*C*'s), 114.88 (s, Ar*C*'s), 72.47 (s), 65.90 (s), 55.92 (s), 45.14 (s), 40.10 (s), 27.08 (s), 17.48 (s,), 14.87 (s).

Computational Methods.

All calculations were performed with Gaussian 03[1] program. The 6-31+G* basis set was chosen for both density functional theory (DFT) and second-order Møller-Plesset[2] (MP2) calculations. The B3LYP[3] functional was used for all DFT computations. All geometry optimizations and transition state searches were conducted using B3LYP/6-31+G*; these were followed by single point MP2 energy calculations for these critical point structures. The transition state structures and corresponding energies were obtained using the QST2 algorithm.[4] The DFT and MP2 critical point energies are shown in Figure S1.

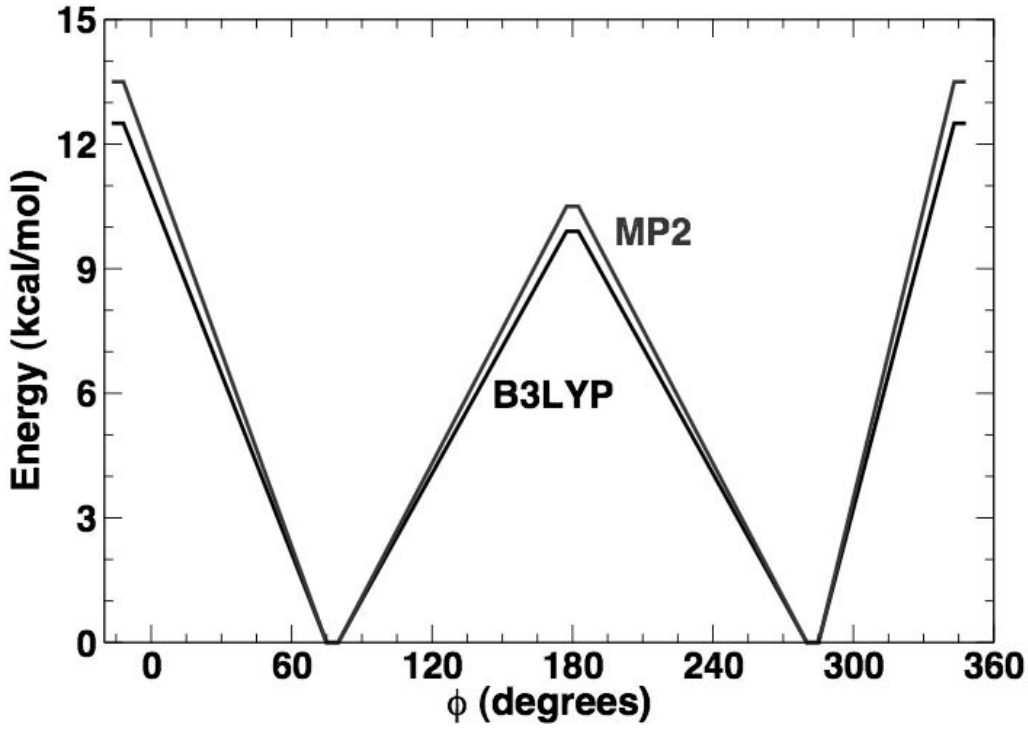
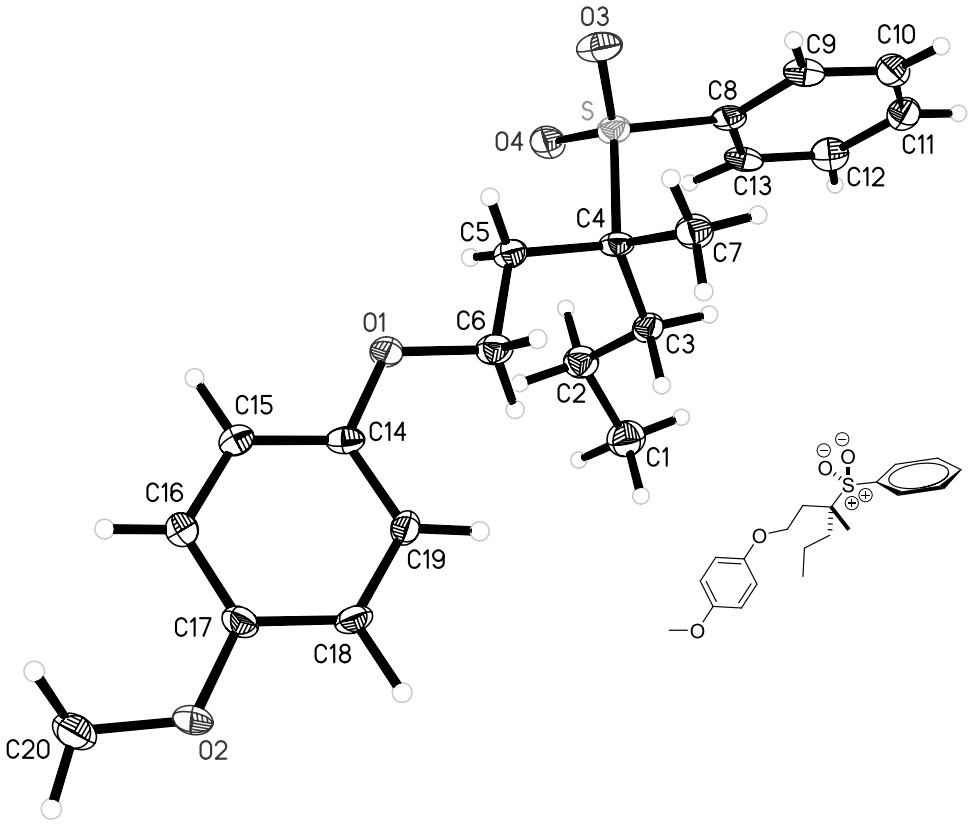


Figure S1. DFT (B3LYP/6-31+G*) and MP2 (MP2/6-31+G*//B3LYP/6-31+G*) energies at global minima and rotational barriers.

Procedure for growing an X-ray quality crystal. ~2 mg of (R)-1-methoxy-4-(3-methyl-3-(phenylsulfonyl)hexyloxy)benzene (JW6246) were placed in a 1 dram scintillation vial and dissolved in 70 μL of hot EtOH. The cap was loosely placed on the vial and it was placed on the shelf at room temperature and within 3 h crystals had formed. These crystals were used X-ray analysis. Inferior crystals were grown in this manner using Et_2O. Use of MeOH, and isopropanol never resulted in crystallization.



Needle-shaped crystals of $C_{20}H_{26}O_4S$ are, at 100(2) K, orthorhombic, space group $P2_12_12_1$- D_2^4 (No. 19)[1] with **a** = 6.7287(2) Å, **b** = 11.7484(3) Å, **c** = 23.4172(5) Å, V = 1851.16(8) $Å^3$ and Z = 4 molecules {d_{calcd} = 1.301 g/cm^3; μ_a(CuKα) = 1.729 mm^{-1}}. A full hemisphere of diffracted intensities (6993 3-second frames with a ω scan width of 0.50°) was measured[2] for a single-domain specimen using monochromated CuKα radiation (λ= 1.54178 Å) on a Bruker X8 Prospector Single Crystal Diffraction System equipped with Qazar MX optics, an APEXII CCD detector and an IμS microfocus x-ray source operating at

45kV and 0.65mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 9813 reflections. A total of 24091 integrated reflection intensities having $2\theta(CuK\alpha) < 132.25°$ were produced using the Bruker program SAINT[3]; 3081 of these were unique and gave $R_{int} = 0.032$ with a coverage which was 98.4% complete. The data were corrected empirically for variable absorption effects using equivalent reflections; the relative transmission factors ranged from 0.835 to 1.000. The Bruker software package SHELXTL was used to solve the structure using "direct methods" techniques. All stages of weighted full-matrix least-squares refinement were conducted using F_o^2 data with the SHELXTL Version 6.10 software package[4].

The final structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. All hydrogen atoms were located in a difference Fourier and included in the structural model as independent isotropic atoms whose parameters were allowed to vary in least-squares refinement cycles. A total of 330 parameters were refined using no restraints, 3081 data and weights of $w = 1/ [\sigma^2(F^2) + (0.0319\ P)^2 + (0.2974\ P)]$, where $P = [F_o^2 + 2F_c^2] / 3$. Final agreement factors at convergence are: R_1(unweighted, based on F) = 0.021 for 3046 independent absorption-corrected "observed" reflections having $2\theta(CuK\alpha) < 132.25°$ and $I > 2\sigma(I)$; R_1(unweighted, based on F) = 0.022 and wR_2(weighted, based on F^2) = 0.057 for all 3081 independent absorption-corrected reflections having $2\theta(CuK\alpha) < 132.25°$. The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference map had maxima and minima of 0.22 and -0.23 $e^-/Å^3$, respectively. The absolute configuration was determined

experimentally using anomalous dispersion of the x-rays; the Flack "absolute structure" parameter refined to a final value of 0.02(1).

Table 1. Crystal data and structure refinement for $C_{20}H_{26}O_4S$.

Empirical formula	$C_{20}H_{26}O_4S$	
Formula weight	362.47	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$- D_2^4 (No. 19)	
Unit cell dimensions	**a** = 6.7287(2) Å	**α** = 90.000°
	b = 11.7484(3) Å	**β** = 90.000°
	c = 23.4172(5) Å	**γ** = 90.000°
Volume	1851.16(8) Å3	
Z	4	
Density (calculated)	1.301 g/cm^3	
Absorption coefficient	1.729 mm^{-1}	
F(000)	776	
Crystal size	0.19 x 0.10 x 0.05 mm^3	
Theta range for data collection	3.78° to 66.13°	
Index ranges	$-4 \le h \le 7$, $-13 \le k \le 13$, $-27 \le l \le 26$	
Reflections collected	24091	
Independent reflections	3081 [R_{int} = 0.032]	
Completeness to theta = 66.13°	98.4 %	
Absorption correction	Multi-scan	
Max. and min. transmission	1.000 and 0.835	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3081 / 0 / 330	
Goodness-of-fit on F^2	1.085	
Final R indices [I>2sigma(I)]	R_1 = 0.021, wR_2 = 0.057	
R indices (all data)	R_1 = 0.022, wR_2 = 0.057	
Absolute structure parameter	0.02(1)	
Largest diff. peak and hole	0.22 and -0.23 e$^-$/Å^3	

$R_1 = \Sigma \, ||F_o| - |F_c|| \, / \, \Sigma \, |F_o|$

$wR_2 = \{ \, \Sigma \, [w(F_o^2 - F_c^2)^2] \, / \, \Sigma \, [w(F_o^2)^2] \, \}^{1/2}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for $C_{20}H_{26}O_4S$. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
S	8771(1)	616(1)	4264(1)	21(1)
O(1)	4444(1)	3816(1)	3613(1)	25(1)
O(2)	-1984(2)	6428(1)	2942(1)	28(1)
O(3)	9732(2)	1365(1)	4665(1)	29(1)
O(4)	9577(2)	556(1)	3693(1)	27(1)
C(1)	3871(3)	-847(1)	2984(1)	31(1)
C(2)	5226(2)	66(1)	3228(1)	24(1)
C(3)	4942(2)	147(1)	3874(1)	20(1)
C(4)	6144(2)	1028(1)	4220(1)	20(1)
C(5)	6197(2)	2221(1)	3948(1)	21(1)
C(6)	4151(2)	2751(1)	3897(1)	20(1)
C(7)	5328(2)	1078(1)	4830(1)	22(1)
C(8)	8781(2)	-771(1)	4559(1)	22(1)
C(9)	8768(2)	-895(1)	5152(1)	25(1)
C(10)	8612(2)	-1982(1)	5380(1)	29(1)
C(11)	8491(2)	-2919(1)	5025(1)	29(1)
C(12)	8564(3)	-2788(1)	4436(1)	28(1)
C(13)	8693(2)	-1711(1)	4201(1)	24(1)
C(14)	2781(2)	4441(1)	3468(1)	20(1)
C(15)	3160(2)	5453(1)	3178(1)	21(1)
C(16)	1597(2)	6127(1)	2993(1)	22(1)
C(17)	-338(2)	5803(1)	3102(1)	20(1)
C(18)	-714(2)	4803(1)	3401(1)	22(1)
C(19)	841(2)	4123(1)	3586(1)	20(1)
C(20)	-1650(2)	7326(1)	2541(1)	28(1)

Table 3. Bond lengths [Å] for $C_{20}H_{26}O_4S$.

S-O(3)	1.442(1)	C(7)-H(7B)	0.99(2)
S-O(4)	1.443(1)	C(7)-H(7C)	0.95(2)
S-C(8)	1.770(1)	C(8)-C(13)	1.388(2)
S-C(4)	1.836(1)	C(8)-C(9)	1.394(2)
O(1)-C(14)	1.381(2)	C(9)-C(10)	1.388(2)
O(1)-C(6)	1.431(2)	C(9)-H(9)	0.99(2)
O(2)-C(17)	1.381(2)	C(10)-C(11)	1.382(2)
O(2)-C(20)	1.430(2)	C(10)-H(10)	0.95(2)
C(1)-C(2)	1.520(2)	C(11)-C(12)	1.388(2)
C(1)-H(1A)	0.98(2)	C(11)-H(11)	0.96(2)
C(1)-H(1B)	0.95(2)	C(12)-C(13)	1.382(2)
C(1)-H(1C)	0.97(2)	C(12)-H(12)	0.94(2)
C(2)-C(3)	1.527(2)	C(13)-H(13)	0.93(2)
C(2)-H(2A)	1.01(2)	C(14)-C(19)	1.386(2)
C(2)-H(2B)	1.01(2)	C(14)-C(15)	1.392(2)
C(3)-C(4)	1.543(2)	C(15)-C(16)	1.386(2)
C(3)-H(3A)	0.98(2)	C(15)-H(15)	0.91(2)
C(3)-H(3B)	1.04(2)	C(16)-C(17)	1.381(2)
C(4)-C(7)	1.532(2)	C(16)-H(16)	0.91(2)
C(4)-C(5)	1.540(2)	C(17)-C(18)	1.391(2)
C(5)-C(6)	1.515(2)	C(18)-C(19)	1.386(2)
C(5)-H(5A)	0.92(2)	C(18)-H(18)	0.97(2)
C(5)-H(5B)	0.97(2)	C(19)-H(19)	0.96(2)
C(6)-H(6A)	0.97(2)	C(20)-H(20A)	0.96(2)
C(6)-H(6B)	0.97(2)	C(20)-H(20B)	0.98(2)
C(7)-H(7A)	1.00(2)	C(20)-H(20C)	1.01(2)

Table 4. Bond angles [°] for $C_{20}H_{26}O_4S$.

O(3)-S-O(4)	117.71(7)	C(6)-C(5)-C(4)	112.6(1)
O(3)-S-C(8)	107.76(6)	C(6)-C(5)-H(5A)	109(1)
O(4)-S-C(8)	108.41(6)	C(4)-C(5)-H(5A)	108(1)
O(3)-S-C(4)	107.89(6)	C(6)-C(5)-H(5B)	109(1)
O(4)-S-C(4)	108.84(6)	C(4)-C(5)-H(5B)	111(1)
C(8)-S-C(4)	105.57(6)	H(5A)-C(5)-H(5B)	108(2)
C(14)-O(1)-C(6)	117.9(1)	O(1)-C(6)-C(5)	105.7(1)
C(17)-O(2)-C(20)	116.4(1)	O(1)-C(6)-H(6A)	110(1)
C(2)-C(1)-H(1A)	111(1)	C(5)-C(6)-H(6A)	111(1)
C(2)-C(1)-H(1B)	110(1)	O(1)-C(6)-H(6B)	109(1)
H(1A)-C(1)-H(1B)	107(2)	C(5)-C(6)-H(6B)	111(1)
C(2)-C(1)-H(1C)	108(1)	H(6A)-C(6)-H(6B)	110(1)
H(1A)-C(1)-H(1C)	110(2)	C(4)-C(7)-H(7A)	109(1)
H(1B)-C(1)-H(1C)	111(2)	C(4)-C(7)-H(7B)	111(1)
C(1)-C(2)-C(3)	110(1)	H(7A)-C(7)-H(7B)	110(1)
C(1)-C(2)-H(2A)	108(1)	C(4)-C(7)-H(7C)	112(1)
C(3)-C(2)-H(2A)	110(1)	H(7A)-C(7)-H(7C)	107(1)
C(1)-C(2)-H(2B)	113(1)	H(7B)-C(7)-H(7C)	109(1)
C(3)-C(2)-H(2B)	111(1)	C(13)-C(8)-C(9)	121.1(1)
H(2A)-C(2)-H(2B)	106(1)	C(13)-C(8)-S	119.7(1)
C(2)-C(3)-C(4)	119.7(1)	C(9)-C(8)-S	119.1(1)
C(2)-C(3)-H(3A)	108(1)	C(10)-C(9)-C(8)	118.7(1)
C(4)-C(3)-H(3A)	109(1)	C(10)-C(9)-H(9)	121(1)
C(2)-C(3)-H(3B)	106(1)	C(8)-C(9)-H(9)	121(1)
C(4)-C(3)-H(3B)	105(1)	C(11)-C(10)-C(9)	120.3(1)
H(3A)-C(3)-H(3B)	109(1)	C(11)-C(10)-H(10)	122(1)
C(7)-C(4)-C(5)	111.0(1)	C(9)-C(10)-H(10)	117(1)
C(7)-C(4)-C(3)	109.1(1)	C(10)-C(11)-C(12)	120.5(1)
C(5)-C(4)-C(3)	114.0(1)	C(10)-C(11)-H(11)	123(1)
C(7)-C(4)-S	107.6(1)	C(12)-C(11)-H(11)	116(1)
C(5)-C(4)-S	104.0(1)		
C(3)-C(4)-S	110.9(1)		

Table 4. Bond angles [°] for $C_{20}H_{26}O_4S$. (continued)

C(13)-C(12)-C(11)	119.9(1)	O(2)-C(17)-C(16)	124.0(1)
C(13)-C(12)-H(12)	119(1)	O(2)-C(17)-C(18)	116.1(1)
C(11)-C(12)-H(12)	121(1)	C(16)-C(17)-C(18)	119.9(1)
C(12)-C(13)-C(8)	119.4(1)	C(19)-C(18)-C(17)	120.4(1)
C(12)-C(13)-H(13)	120(1)	C(19)-C(18)-H(18)	121(1)
C(8)-C(13)-H(13)	120(1)	C(17)-C(18)-H(18)	119(1)
O(1)-C(14)-C(19)	124.9(1)	C(14)-C(19)-C(18)	119.7(1)
O(1)-C(14)-C(15)	115.2(1)	C(14)-C(19)-H(19)	121(1)
C(19)-C(14)-C(15)	119.9(1)	C(18)-C(19)-H(19)	119(1)
C(16)-C(15)-C(14)	120.2(1)	O(2)-C(20)-H(20A)	111(1)
C(16)-C(15)-H(15)	122(1)	O(2)-C(20)-H(20B)	105(1)
C(14)-C(15)-H(15)	118(1)	H(20A)-C(20)-H(20B)	110(2)
C(17)-C(16)-C(15)	119.9(1)	O(2)-C(20)-H(20C)	110(1)
C(17)-C(16)-H(16)	121(1)	H(20A)-C(20)-H(20C)	113(2)
C(15)-C(16)-H(16)	119(1)	H(20B)-C(20)-H(20C)	107(2)

Table 5. Anisotropic displacement parameters ($Å^2 \times 10^3$) for $C_{20}H_{26}O_4S$. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [$h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}$]

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S	17(1)	20(1)	25(1)	1(1)	-1(1)	1(1)
O(1)	19(1)	21(1)	34(1)	9(1)	0(1)	2(1)
O(2)	20(1)	28(1)	34(1)	11(1)	-1(1)	4(1)
O(3)	23(1)	25(1)	41(1)	-3(1)	-9(1)	0(1)
O(4)	22(1)	30(1)	30(1)	6(1)	5(1)	4(1)
C(1)	32(1)	34(1)	26(1)	-5(1)	-1(1)	-4(1)
C(2)	27(1)	24(1)	23(1)	0(1)	0(1)	-1(1)
C(3)	20(1)	20(1)	21(1)	2(1)	-1(1)	1(1)
C(4)	18(1)	19(1)	22(1)	2(1)	0(1)	2(1)
C(5)	21(1)	18(1)	23(1)	1(1)	-1(1)	-1(1)
C(6)	22(1)	17(1)	21(1)	3(1)	1(1)	-1(1)
C(7)	23(1)	21(1)	21(1)	0(1)	0(1)	2(1)
C(8)	18(1)	23(1)	25(1)	1(1)	-1(1)	3(1)
C(9)	23(1)	27(1)	24(1)	-3(1)	-4(1)	6(1)
C(10)	26(1)	36(1)	24(1)	7(1)	0(1)	7(1)
C(11)	23(1)	26(1)	37(1)	7(1)	-2(1)	3(1)
C(12)	26(1)	22(1)	34(1)	-3(1)	-1(1)	5(1)
C(13)	22(1)	26(1)	24(1)	-1(1)	-1(1)	4(1)
C(14)	19(1)	21(1)	19(1)	-2(1)	-2(1)	3(1)
C(15)	18(1)	23(1)	23(1)	1(1)	0(1)	-2(1)
C(16)	26(1)	19(1)	21(1)	4(1)	1(1)	-1(1)
C(17)	20(1)	21(1)	20(1)	0(1)	-1(1)	3(1)
C(18)	18(1)	24(1)	23(1)	1(1)	1(1)	-2(1)
C(19)	22(1)	19(1)	18(1)	1(1)	1(1)	-1(1)
C(20)	28(1)	27(1)	28(1)	8(1)	-1(1)	4(1)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for $C_{20}H_{26}O_4S$.

	x	y	z	U(eq)
H(1A)	4030(30)	-898(14)	2569(8)	34(4)
H(1B)	2520(30)	-667(17)	3060(7)	37(5)
H(1C)	4230(30)	-1567(16)	3159(7)	32(4)
H(2A)	4860(30)	812(15)	3045(7)	31(4)
H(2B)	6670(30)	-63(14)	3129(7)	26(4)
H(3A)	5190(20)	-612(14)	4035(6)	18(3)
H(3B)	3460(20)	359(12)	3939(6)	14(3)
H(5A)	6980(30)	2674(15)	4173(7)	28(4)
H(5B)	6790(30)	2193(14)	3572(7)	26(4)
H(6A)	3280(20)	2271(12)	3670(6)	11(3)
H(6B)	3570(30)	2887(13)	4271(7)	21(4)
H(7A)	3880(30)	1259(14)	4813(6)	24(4)
H(7B)	6030(20)	1666(14)	5054(6)	22(4)
H(7C)	5460(20)	367(14)	5018(6)	22(4)
H(9)	8900(30)	-229(14)	5403(7)	29(4)
H(10)	8640(30)	-2048(15)	5786(8)	36(5)
H(11)	8370(30)	-3683(15)	5164(7)	25(4)
H(12)	8480(30)	-3421(19)	4192(8)	49(5)
H(13)	8780(30)	-1620(14)	3810(7)	28(4)
H(15)	4450(30)	5622(14)	3096(6)	22(4)
H(16)	1870(20)	6770(15)	2793(7)	25(4)
H(18)	-2090(20)	4608(13)	3489(6)	18(4)
H(19)	560(20)	3446(15)	3800(7)	25(4)
H(20A)	-1010(30)	7040(14)	2204(8)	32(4)
H(20B)	-2970(30)	7618(15)	2448(8)	36(5)
H(20C)	-890(30)	7970(15)	2729(7)	35(5)

Table 7. Torsion angles [°] for $C_{20}H_{26}O_4S$.

C(1)-C(2)-C(3)-C(4)	-179.3(1)	C(4)-S-C(8)-C(9)	-86.4(1)
C(2)-C(3)-C(4)-C(7)	170.2(1)	C(13)-C(8)-C(9)-C(10)	-1.7(2)
C(2)-C(3)-C(4)-C(5)	45.4(2)	S-C(8)-C(9)-C(10)	174.8(1)
C(2)-C(3)-C(4)-S	-71.5(1)	C(8)-C(9)-C(10)-C(11)	0.6(2)
O(3)-S-C(4)-C(7)	-51.5(1)	C(9)-C(10)-C(11)-C(12)	1.3(3)
O(4)-S-C(4)-C(7)	179.7(1)	C(10)-C(11)-C(12)-C(13)	-2.1(3)
C(8)-S-C(4)-C(7)	63.5(1)	C(11)-C(12)-C(13)-C(8)	1.1(2)
O(3)-S-C(4)-C(5)	66.3(1)	C(9)-C(8)-C(13)-C(12)	0.8(2)
O(4)-S-C(4)-C(5)	-62.5(1)	S-C(8)-C(13)-C(12)	-175.6(1)
C(8)-S-C(4)-C(5)	-178.7(1)	C(6)-O(1)-C(14)-C(19)	1.2(2)
O(3)-S-C(4)-C(3)	-170.8(1)	C(6)-O(1)-C(14)-C(15)	-178.2(1)
O(4)-S-C(4)-C(3)	60.4(1)	O(1)-C(14)-C(15)-C(16)	177.6(1)
C(8)-S-C(4)-C(3)	-55.8(1)	C(19)-C(14)-C(15)-C(16)	-1.9(2)
C(7)-C(4)-C(5)-C(6)	-61.8(2)	C(14)-C(15)-C(16)-C(17)	1.0(2)
C(3)-C(4)-C(5)-C(6)	61.9(2)	C(20)-O(2)-C(17)-C(16)	13.4(2)
S-C(4)-C(5)-C(6)	-177.3(1)	C(20)-O(2)-C(17)-C(18)	-167.9(1)
C(14)-O(1)-C(6)-C(5)	174.7(1)	C(15)-C(16)-C(17)-O(2)	178.9(1)
C(4)-C(5)-C(6)-O(1)	-177.1(1)	C(15)-C(16)-C(17)-C(18)	0.3(2)
O(3)-S-C(8)-C(13)	-154.8(1)	O(2)-C(17)-C(18)-C(19)	-179.3(1)
O(4)-S-C(8)-C(13)	-26.4(1)	C(16)-C(17)-C(18)-C(19)	-0.6(2)
C(4)-S-C(8)-C(13)	90.1(1)	O(1)-C(14)-C(19)-C(18)	-177.8(1)
O(3)-S-C(8)-C(9)	28.7(1)	C(15)-C(14)-C(19)-C(18)	1.6(2)
O(4)-S-C(8)-C(9)	157.1(1)	C(17)-C(18)-C(19)-C(14)	-0.4(2)

References

(1) International Tables for Crystallography, Vol A, 4th ed., Kluwer: Boston (1996).

(2) Data Collection: SMART Software Reference Manual (1998). Bruker-AXS, 5465 E. Cheryl Parkway, Madison, WI 53711-5373 USA.

(3) Data Reduction: SAINT Software Reference Manual (1998). Bruker-AXS, 6300 Enterprise Dr., Madison, WI 53719-1173, USA.

(4) G. M. Sheldrick (2000). SHELXTL Version 6.10 Reference Manual. Bruker-AXS, 5465 E. Cheryl Parkway, Madison, WI 53711-5373 USA.

Chapter 3

Synthesis of Sulfonyl Esters:

3.1—Importance of Sulfonyl Esters

The hope and intention of this chapter is to chronicle the best ways to synthesize various sulfonyl esters. Our primary interest in sulfonyl ester syntheses has been as a source of starting materials for the Pd-catalyzed DCA reactions.

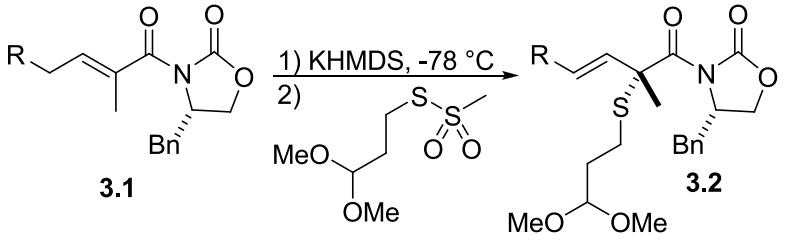
Stability

Sulfonyl esters are, in general, thermally robust and will survive a number of other conditions. However, some of the corresponding sulfonyl acetic acids are only meta-stable and are even less stable under basic conditions and thus limit the ways in which they can be synthesized.

3.2—Asymmetric Synthesis of Sulfonyl Esters

Due to our interest in the stereospecific DCA (chapter 2) we needed to obtain enantioenriched α-sulfonyl allyl esters. A survey of the literature revealed no general and enantioselective method for the synthesis of tertiary α-sulfonyl esters. More often when a search for enantioenriched sulfones was performed the sulfone had been obtained via preparatory chiral HPLC.[1] However, expanding the search to tertiary α-sulfidyl esters (related compound at a lower *S*-oxidation state) did reveal a moderately successful asymmetric α-sulfenylation in which the alpha center was quaternarized. In this reaction an oxazoladinone auxiliary is used to direct the facial selectivity. This reaction was, at best, moderately successful; the average yield for 6 substrates was 51% and required reactions to be run at low temperature and used strong base (Scheme 3.1). The use of the auxiliary to provide the enantioselectivity is less than ideal as it requires two additional

steps in the synthesis of starting materials additionally it uses a stoichiometric amount of costly chiral, non-racemic auxiliary.



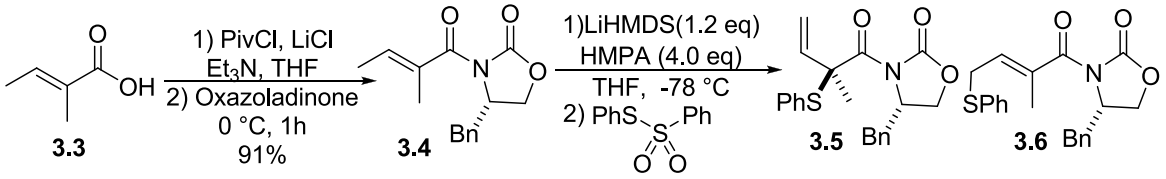
R =	H	Me	Et	*n*Pr	*n*Bu	*n*Hex
Yield	18	56	60	50	*80*	*59*
ee%[a]	>90	>99*	>90	>95	>90*	>94*

a) ee% were determined by the de% via ^{1}H unless * in which Chiral HPLC was used after auxillary was removed.

Scheme 3.1

Nonetheless this strategy was attempted. Tiglic acid and (*S*)-4-benzyloxazolidin-2-one were cleanly coupled utilizing the modified acylation technique (Scheme 3.2).[2] Ohata was interested in making an asymmetric thiol and thus used the masked thiol which is revealed after hydrolysis of the acetal and a retro-Michael.[3] We desired to install a phenyl sulfide and thus we changed the source of the electrophilic sulfur to S-phenyl benzenethiosulfonate. Subjecting the acylated oxazolidinone to LHMDS with excess HMPA gave γ-deprotonation to generate the allyl enolate. There are two potential sites from which the anion can attack the electrophile, α and γ. Ohata does not report the isomeric ratio and given the low yields it is quite possible that a significant amount of γ-sulfenylation occurred. The first attempt (entry 1, Scheme 3.2) led to the best α:γ ratio, 2.7. Hoping to improve the conversion, the reaction was given longer time to deprotonate before the electrophile was added, thinking that perhaps the substrate was not

fully deprotonated (entry 2). While this led to a slight increase in conversion, γ-sulfenylation became the major product. Interestingly, when the equivalents of electrophilic sulfur were increased, the product ratio was better. This reaction likely could have been further optimized but it is unlikely that we would have found conditions that would allow for the formation of a single product in satisfactory yields. While, it had only been demonstrated with conjugated systems and thus did not qualify as general we were curious if the reaction might work better if the question of α vs. γ selectivity were removed.

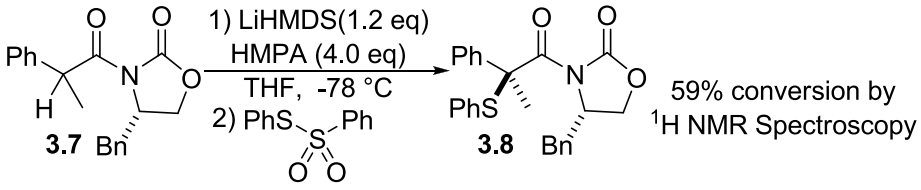


Entry	Time Step 1	Electrophile equivalents	Time step 2	Conversion	α:γ	dr of α
1	0.25h	1.0	2h	54%	2.7	>20:1
2	2.5h	1.0	2h	66%	0.07	>20:1
3	2.5h	3.0	15h	60%	0.91	>20:1

Scheme 3.2

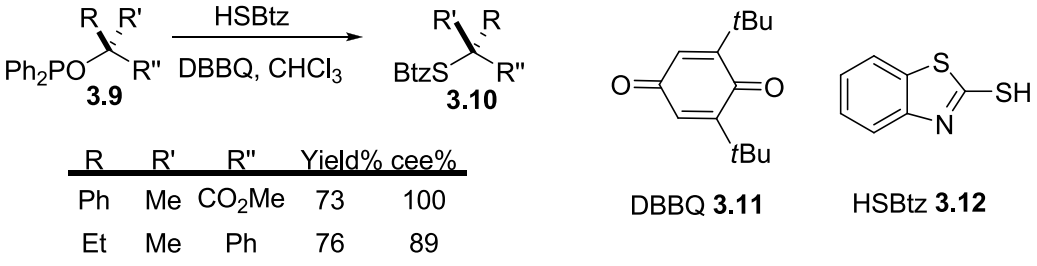
Wanting to avoid the α vs. γ selectivity issue we tried the asymmetric sulfenylation using chiral oxazolidinone chemistry with the substrates that were only nucleophilic at the alpha position (Scheme 3.3). The single result was rather promising giving 59% conversion and what appears to be a single product by the ^{1}H NMR spectrum after working the reaction up. However, it is worth pointing out that 1) the prior step had an isolated yield of 16%, 2) the *syn*- and anti-**3.7** diastereomers were not separable via

column chromatography and 3) the sulfenylation was performed using both diastereomers.



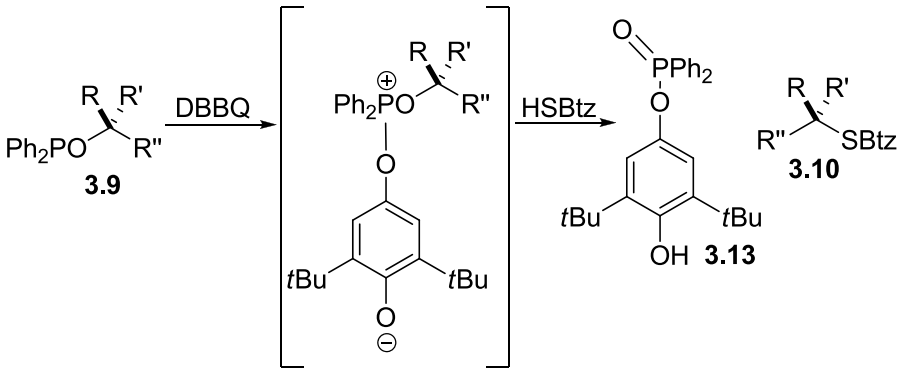
Scheme 3.3

Another strategy that has been employed for accessing asymmetric α-sulfonyl esters relies on activation of chiral, non-racemic tertiary hydroxy groups for displacement with nucleophile. Methodologies of this type can be classified as S_N2 displacements to afford the asymmetric tertiary sulfide, which is readily oxidized to the sulfone. This type of methodology has been somewhat overlooked by organic chemists potentially because of the general rule that S_N2 displacements will not work when the leaving group is at a tertiary carbon, though a handful of examples do exist.[4] In the first method tertiary hydroxy groups are subjected to modified Mitsunobu conditions, which the authors claim leads to cleanly substituted products (Scheme 3.4).[4] Two representative examples show the type of yield and conservation of enantioenrichment that are reported.



Scheme 3.4

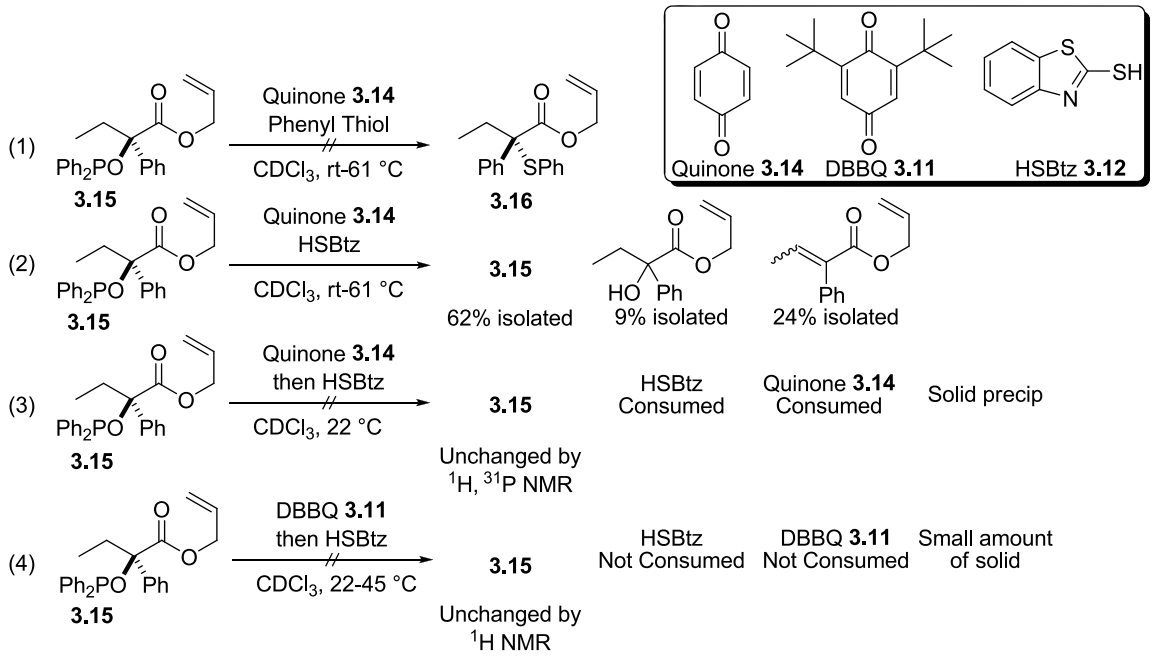
In this reaction the quinone oxidizes the preformed phosphinite ester (Scheme 3.5) and in turn the newly generated phenolate deprotonates the HSBtz, the sulfur nucleophile then displaces the activated leaving group. Mukaiyama reports that this reaction is quite general and clean.[5a]



Scheme 3.5

Given the reported success and generality and the accessibility of α-hydroxy acids[4] it made sense to try Mukaiyama's procedure. We began by using the allyl phosphinite ester synthesized from the commercially available (*R*)-2-hydroxy-2-phenylbutanoic acid hydroxy ester.[4a] The methodology was first tried using PhSH, a different thiol than reported in the literature (Scheme 3.6). Even at reflux no change was observed. While there is a real difference in pK_a between PhSH (10.3 in DMSO) and HSBtz (<10.3 in DMSO) this does not explain the lack of oxidation of the phosphinite that should have occurred (eq. 1) Scheme 3.6). This is quite perplexing since Mukaiyama reports that 1,4-quinone is not ideal, not because it will not oxidize the phosphinite, but rather because it leads to a phenolate anion capable of facilitating an elimination.[5] Perhaps, for reasons unknown, the HSBtz is absolutely necessary and thus switching to this pronucleophile should allow the smooth transformation, but alas this was not the

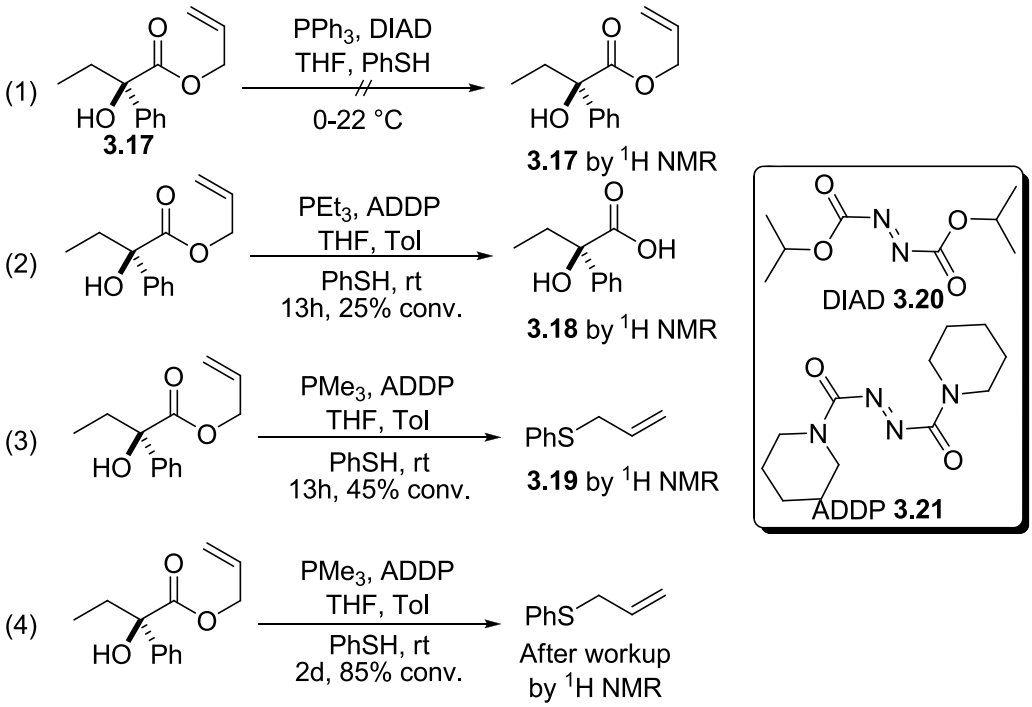
case. Rather upon heating to reflux overnight with the same thiol (HSBtz), most (62%) of the starting material was recovered as well as 9% of the hydroxy ester and 24% of the eliminated product (eq. 2). However, when the reaction was run at room temperature (eq. 3), like that reported by Mukaiyama[5] no oxidation of the phosphinite was observed by ^{1}H or ^{31}P NMR spectroscopy but the quinone and the thiol were consumed; a likely reaction involving these two reagents is a thio-Michael-addition. Additionally, a solid precipitate was formed, potentially a polymeric substance. Finally, when the optimal quinone B was used (eq. 4) essentially no reaction occurred and neither the quinone nor the HSBtz were consumed, implying that the increased steric bulk shut down the reaction pathway that consumed the quinone A and HSBtz (eq. 3). Even upon heating, no change to the phosphinite ester was observed (eq. 4). One potential rational is the slight increase in steric demand of the phosphinite ester in Scheme 3.6 and that of Scheme 3.4 but this seems very subtle and it is expected that if the methodology was severely limited in this fashion the authors would acknowledge it. Another possibility is that there was some contaminant in all of Mukaiyama's work that facilitated the process. Given the lack of oxidation that we saw using quinones as the oxidant we thought we would try more conventional Mitsunobu conditions.



Scheme 3.6

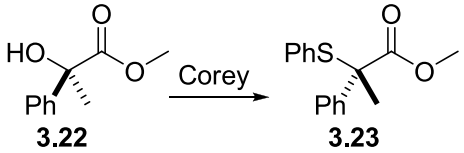
Having established that quinones, under the preceding conditions, are not capable oxidants for the phosphinite allyl ester (Scheme 3.6), more traditional Mitsunobu conditions were tried (Scheme 3.7). Using triphenyl phosphine and DIAD and benzene thiol resulted in no change to the starting hydroxy ester, **3.17** (eq. 1, Scheme 3.7). Use of PEt_3, with a greater reduction potential than PPh_3, and ADDP, azodicarboxyilic acid dipiperidine, gave ~25% conversion to what is likely the free acid (eq. 2). Consistent with this, the hydroxy ester provided phenyl allyl thiol almost completely when PMe_3 and ADDP were given sufficient time (eq. 3 and 4). A likely explanation for this product is a slow transesterification to the thioester which allows the primary alcohol to undergo Mitsunobu reaction and apparently this was happening faster than activation of the tertiary alcohol. Convinced that the direct Mitsunobu substitution reaction could not be

accomplished for this substrate we next looked at the less direct-2 step activation and then substitution of the hydroxy ester.



Scheme 3.7

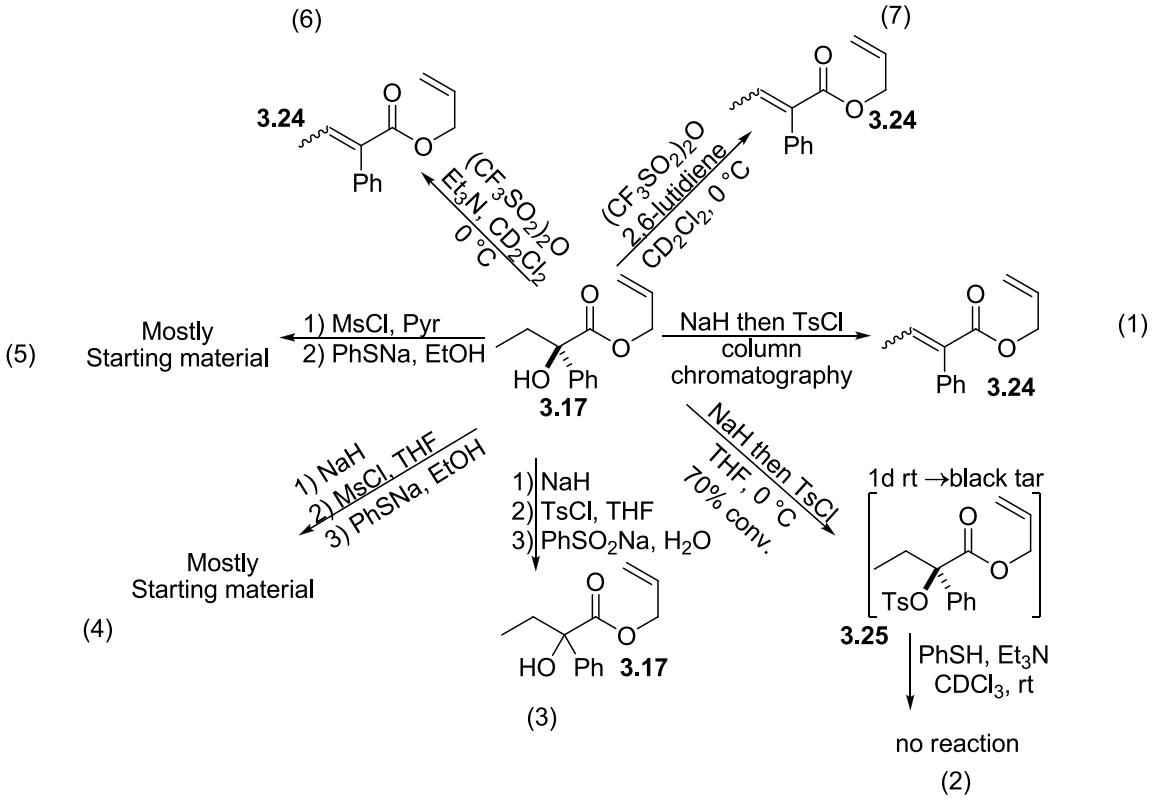
Corey, like us, needed chiral, non-racemic α-sulfonyl acids. He tersely describes the synthesis of this single example in which an atrolactic acid derivative (**3.22**, Scheme 3.8) is converted to the α-thio methyl ester (**3.23**) which is then converted to the α-sulfonyl acid. Corey gives no yields, ee's, experimental details, or scope.[5] Nonetheless, it was sufficient evidence that the reaction must be possible-to some extent.



Scheme 3.8

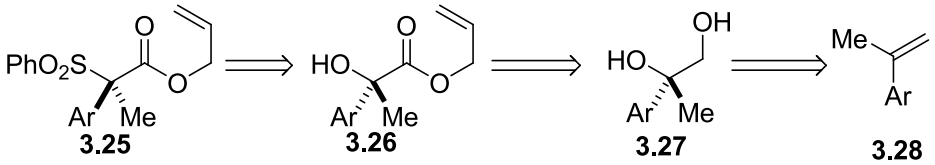
We began our investigation into the two step activation/substitution procedure using hydroxy ester **3.17** (Scheme 3.9). First, we looked at the ability to generate the tosylate leaving group via deprotonation with NaH and trapping with TsCl (eq. 1). Attempted purification of the product led to the α,β-unsaturated ester which suggest that the tosylate was indeed formed but not stable to chromatography. Running the reaction in THF-d_8 allowed us to observe the intermediates, interestingly, even with purified TsCl only a 70% conversion was observed; one potential explanation for this is the formation of a sulfene formed by deprotonation of the ρ-methyl of the TsCl. However, the substrate did not react after exchanging the solvent and exposure to the ammonium thiolate (eq. 2). When the tosylate was exposed to the sulfinate salt the only product observed was the original alcohol (eq. 3). Assuming the tosylation worked, this product is likely a result of S_N1 by the H_2O added for solubility purposes. Attempts to make the sterically less demanding mesylate led to mostly regeneration of the starting material (eq. 4). This is most likely explained by more facile sulfene formation. Thus it was concluded that the alkoxide was more likely to act as a base than a nucleophile. One potential way around this was to mesylate the hydroxy group using MsCl and pyridine (eq. 5). Disappointingly mostly starting material was observed, suggesting that Corey's conditions (Scheme 3.8) would not work when the methyl substituent was changed to an ethyl. One final attempt was to use a more reactive sulfonylating reagent, triflic anhydride. Unfortunately, even at 0 °C rapid elimination occurred (eq. 6). Thinking that perhaps the triethyl amine was facilitating the elimination; less basic 2,6-lutidiene was used but again elimination was prevalent (eq. 7). Thus we concluded that α-phenyl butanoates were unlikely to work for several reasons. First, mesylate formation is very

slow and secondly if a sulfonate ester is formed substitution is slower than side reactions. We thought that perhaps the slight steric difference in methyl vs. ethyl did, in fact, limit Corey's conditions to the α-phenyl propanoates. Consequently, we began to test this by first synthesizing several α-hydroxy α-phenyl propanoic esters.



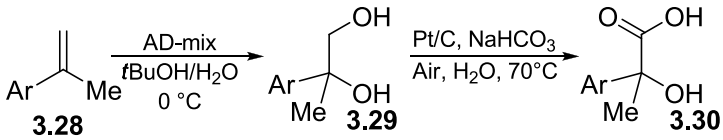
Scheme 3.9

We envisioned that we might obtain enantioenriched sulfones (Scheme 3.10) from the enantioenriched hydroxy esters which could be obtained from the enantioenriched 1,2-diols which can be formed with good enantioselectivity from ADH of the corresponding α-methyl styrene derivatives.



Scheme 3.10

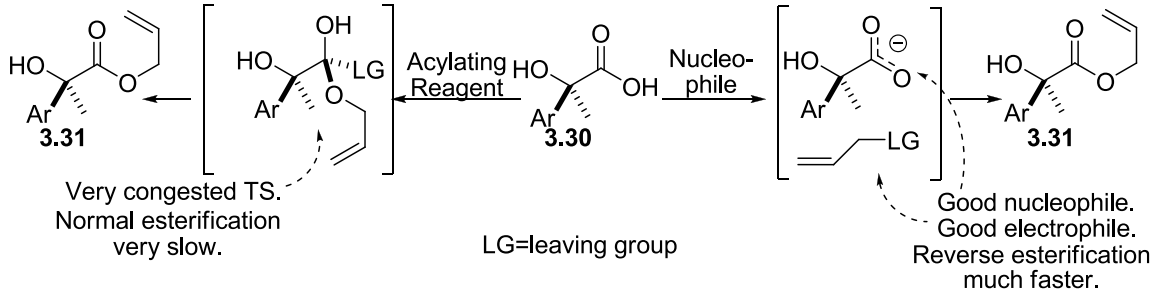
To begin, several α-methyl styrene derivatives were subjected to Sharpless-ADH conditions to afford enantioenriched 1,2-diols (**3.29a-e**, Scheme 3.11) in excellent to good yields with known configuration.[6] We next subjected **3.29a-e** to aerobic oxidation with Pt/C to cleanly afford the corresponding acids **3.30a-e**, in acceptable yields with the only exception being **3.30a**. The low yield is likely to due to hydrolysis of the ester functional group under the reaction conditions.



Ar	AD-mix	product	**3.29** yield (%)	product	**3.30** yield (%)
p-$CO_2MeC_6H_4$	α	(*S*)-**3.29a**	79	(*S*)-**3.30a**	<10
p-BrC_6H_4	β	(*R*)-**3.29b**	78	(*R*)-**3.30b**	81
p-ClC_6H_4	α	(*S*)-**3.29c**	99	(*S*)-**3.30c**	85
p-MeC_6H_4	α	(*S*)-**3.29d**	99	(*S*)-**3.30d**	64
p-FC_6H_4	β	(*R*)-**3.29e**	98	(*R*)-**3.30e**	82

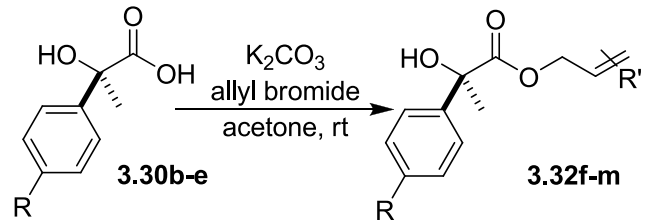
Scheme 3.11

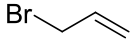
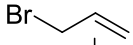
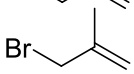
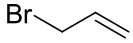
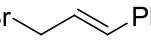
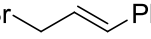
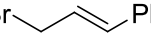
With α-hydroxy acids in hand we next attempted to esterify the acids. Typical esterification methods did not work well primarily due to the slowness of the esterification (Scheme 3.12), which requires formation of two adjacent quaternary carbons. However, a less common approach of esterification where the alcohol is converted to the leaving group and the carboxylate is used as the nucleophile works well.



Scheme 3.12

In this manner, several allyl bromides were subjected to the potassium carboxylate, in acetone to afford the allyl esters (**3.32f-m**) in high yields (Scheme 3.13).

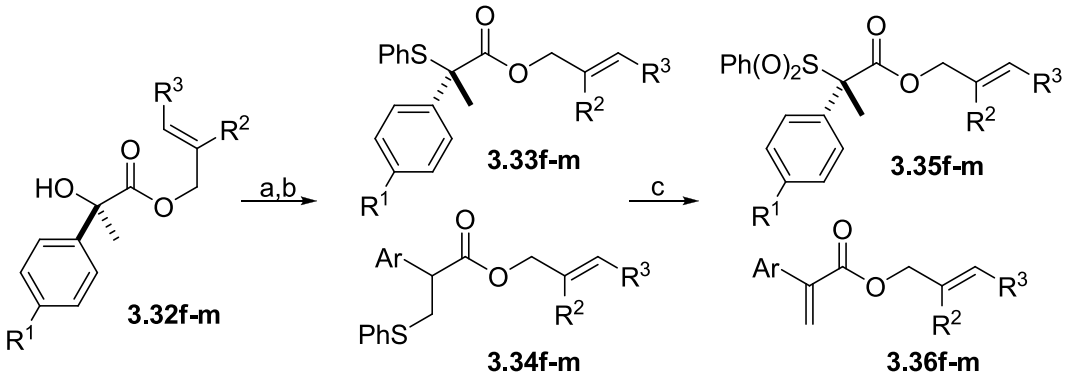


Entry	3.30	R	Allyl bromide	Yield	3.32
1	**e**	F		93%	**f**
2	**d**	Me		92%	**g**
3	**b**	Br		90%	**h**
4	**b**	Br		97%	**i**
5	**c**	Cl		99%	**j**
6	**e**	F		99%	**k**
7	**c**	Cl		99%	**l**
8	**d**	Me		97%	**m**

Scheme 3.13

With a series of α-hydroxy α-aryl propanoic allyl esters in hand (**3.32f-m**) we began to test the scope of the two step mesylation/substitution protocol (Scheme 3.14).[7] Subjecting these hydroxy esters to the mesylation conditions followed by careful workup and immediately subjecting them to the thiolate led to poor to modest yields (10-50%) of

the desired sulfide esters, **3.33f-m**. Unfortunately, these were contaminated with the regioisomeric β-sulfide ester (**3.34f-m)**, which most likely arose via elimination followed by a conjugate addition of the thiolate. A few trends can be attributed to the substitution of the aryl ring. Electron donors are most likely detrimental (**3.32g**, **m**) as even the weakly donating methyl substituent led to significantly reduced yields and 1:1 mixture of the regioisomeric sulfides **5:6**. Preservation of the ee% followed the trend Br>Cl>F. All of the initial esters likely began at 95 ee%, based on literature precedence as well as a recrystalization step, but the exact number was not determined at this point.[9] Upon oxidation, the regioisomeric β-sulfone was easily removed as it was unstable and eliminated sulfinic acid to afford the acrylate derivates, **8f-m**, and the desired sulfones, **7f-m**. Having demonstrated it was feasible to generate some chiral, non-racemic sulfonyl esters via the activation/substitution protocol; albeit in modest yields and cee's%. We began to wonder whether this methodology might be better suited for α,α-dialkyl substrates.



Reagents and Conditions: a) MsCl, DMAP, Pyridine, -5 °C to 0 °C. b) NaSPh, EtOH, 0 °C. c) *m*CPBA, CH_2Cl_2, 23 °C

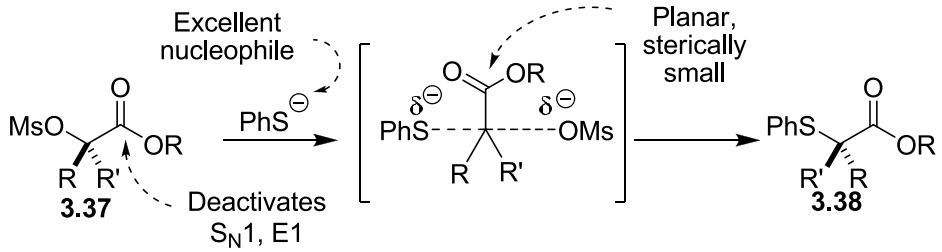
3.32	R^1	R^2	R^3	**3.33** Yield (%)	Ratio **3.33**/**3.34**[a]	**3.35** Yield (%)	**3.35** ee (%)[b]	Configuration **3.35**
(f)	F	H	H	29	2.5	77	46	(*S*)
(g)	Me	H	H	10	1	-	-	-
(h)	Br	H	H	41	19	38	97	(*S*)
(i)	Br	Me	H	39[c]	19	48	80[c]	(*S*)
(j)	Cl	H	H	23	nd[d]	38	89	(*R*)
(k)	F	H	Ph	38	8	59	73	(*S*)
(l)	Cl	H	Ph	50	5	72	61	(*R*)
(m)	Me	H	Ph	15	1	-	-	-

[a] determined by ^{1}H NMR. [b] Determined by chiral HPLC. [c] Mesylation inadvertantly performed at room temperature. [d] Ratio not determined before oxidation.

Scheme 3.14

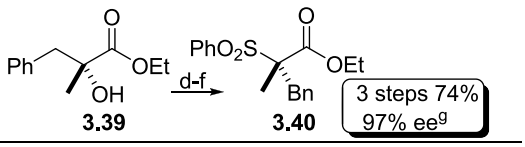
The fact that S_N2 substitution by a thiolate for a mesylate at a tertiary center can occur at all is quite remarkable; several factors make this possible. First, the ester carbonyl is an electron-withdrawing functional group that disfavors carbocation formation and thus deactivates S_N1 and E1 mechanisms that generate a carbocation (Scheme 3.15). Next, the thiolate is an excellent nucleophile capable of making bonds from long distances which is important in a crowded transition state. Finally, the

carbonyl is sp^2 hybridized and planar making it a somewhat smaller substituent, which also helps in the crowded transition state. Given the competing elimination we thought that competing ionization might be problematic. Replacing an aryl group with an alkyl substituent might disfavor the competing ionization mechanism the incipient carbocation would no longer be benzylic and thus make ionization more difficult.

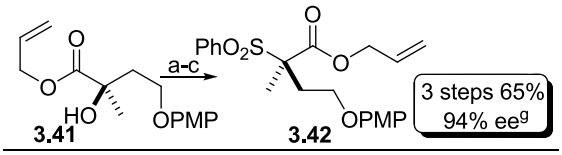


Scheme 3.15

Indeed, when chiral, non-racemic α-hydroxy esters that were substituted with two alkyl groups were used the substitution proceeded cleanly with excellent stereofidelity (**3.39** and **3.41**, Scheme 3.16). In fact, both the mesylates generated from **3.39** and **3.41** were isolable (78% and 81% yields respectively) and were stable for months at room temperature. The substitution with the NaSPh proceeded smoothly and with out racemization or elimination. This was followed by oxidation with *m*CPBA to yield the desired sulfones, **3.40** and **3.42**, in excellent yields and ee's.



d) MsCl, DMAP, pyr, rt, 78%; e) NaSPh, EtOH, 96%; f) *m*CPBA, DCM, rt, 99%; [g] ee determined by chiral HPLC

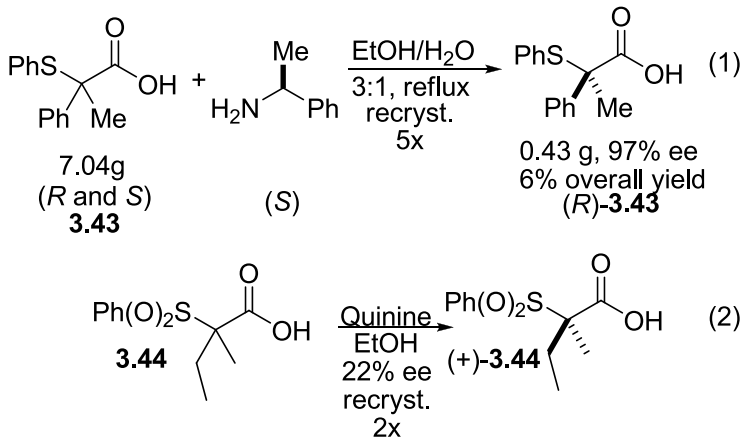


a) MsCl, DMAP, pyr rt, 81%; b) NaSPh, EtOH, 96%;c) *m*CPBA, DCM rt, 84%, 94% ee; [g] ee determined by chiral HPLC. PMP = *p*-methoxyphenyl.

Scheme 3.16

Resolution

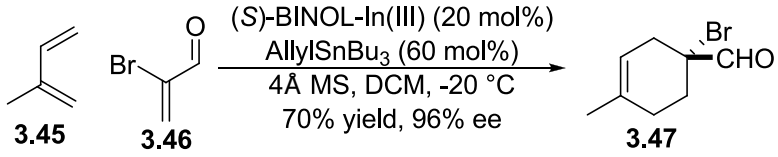
We also accessed chiral α-sulfonyl esters via chiral resolution. The classical method for accessing many types of chiral, non-racemic substrates, especially acids, is a resolution of the acid with a chiral amine base (Scheme 3.17). In this type of chiral resolution, the two enantiomers to be resolved lead to diastereomeric salts with different solubility's. In the first the resolution, 7.04 g of the α-sulfidyl acid is subjected to (*S*)-α-methyl benzyl amine which results in crystallization. Subsequent decantation of the supernatant liquid removes the more soluble diastereomer (and enantiomer after liberation) disproportionately. Repeating this process five times gave the acid in high purity, 97% ee%, and an overall recovery of 6%. Likewise, the α-phenyl sulfonyl-α-methyl butanoic acid, which is stable at room temperature, can be resolved using quinine (eq. 2).[8] After 2 recrystallizations this ee% was determined to be 22% but it was determined that insufficient quantities of substrate remained such that there would be enough when it was highly enriched and was thus abandoned. These two examples illustrate some of the difficulties associated with chiral resolutions. First, each substrate to be resolved requires a stoichiometric amount of chiral, non-racemic compound making it less than ideal. Secondly, the resolving amine is usually different for every substrate and consequently requires an independent search for each substrate-making it not a general method. Finally, recoveries are typically dismal as enrichment comes at the expense of yield.



Scheme 3.17

Attempted asymmetric sulfonyl synthesis

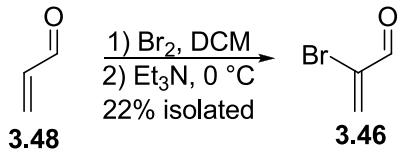
In 2005, Loh[10] reported an asymmetric Diels-Alder reaction in which bromo acrolein underwent smooth enantioselective cycloaddition to afford the Diels-Alder adducts that contained an α-bromo aldehyde (**3.47**, Scheme 3.18). If the bromide could be substituted and the aldehyde oxidized then these would serve as a rapid and general method for accessing asymmetric sulfonyl esters.



Scheme 3.18

We believed that if we could reproduce Loh's results we might have facile access to the coveted sulfonyl esters. First, the bromo acrolein (**3.46**) had to be synthesized. This was readily accomplished in a two step procedure in which acrolein is first dibrominated followed by elimination of HBr by Et_3N (Scheme 3.19). The yield is very

dependent on the workup and storage technique. Care should be taken to remove excess Br_2 as well as any excess base. In addition, the product should be stored cold as it is prone to polymerization.



Scheme 3.19

With the bromoacrolein (**3.46**) in hand, we next attempted to repeat Loh's results (Scheme 3.18). Unfortunately, in our hands this reaction was not repeatable and in fact led to a mixture of products from which none of the product signals could be detected by ^{1}H NMR spectroscopy of the mixture after workup. Nonetheless, an attempt to isolate something from the reaction mixture led to the isolation of two products that contained allyl fragments suggesting that the allyl is transferred to the acrolein derivative. We did not pursue this avenue any further.

3.3—Racemic sulfonyl ester syntheses

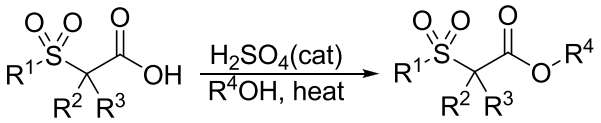
Esterifications

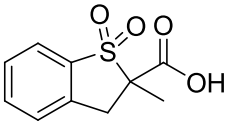
While there are only a few methods for accessing chiral, non-racemic sulfonyl esters, in the course of our studies, we have developed many methods for the synthesis of racemic sulfonyl esters. Often there are subtle differences in the desired sulfone that make one synthesis preferable over another. The aim of this section is to aid in the selection of the best method. The first method is simply esterification of sulfonyl acetic

acids. Esterification is usually straightforward; however, there are some substrates for which it is not a trivial step. One complicating issue is the thermal instability of the carboxylate form of the acid when it posses an α-phenyl substituent. This is due to the added stability of the benzylic anion and is expected to be general for any substitution which stabilizes the sulfonyl anion and will thus facilitate decarboxylation. Simple Fischer esterification works well for many substrates (Table 3.1). Phenyl sulfonyl acetic acid is commercially available, as well as the methyl ester, and is a convenient stating material that allows the syntheses of many more complex sulfonyl esters. Fischer esterification to make the methyl ester of the phenyl sulfonyl acetic works well, giving yields > 91% (entry 1). When allyl alcohol is used at reflux, the yields are reduced and side products are formed (entry 2). However, if the temperature is reduced, the reaction proceeds smoothly and cleanly (entry 3). This esterification also works well for monosubstituted acids (entry 4 and 5) but when the fully substituted sulfonyl acid was used the reaction afforded an undesirable mixture of unknown products (entry 6). When the α-phenyl-sulfonyl acetic acid was used, the methyl ester was cleanly formed (entry 7) the yield for this reaction is uncertain as it was part of a three step sequence and, based on the final product yield, the lower limit is 50%. In general, esterification under acidic conditions might be the best strategy for sulfonyl acids, whose carboxylates are prone to decarboxylate, though it was not frequently employed. When the isoprenyl alcohol was used in a variant of the Fischer conditions in which water is azeotropically removed (entry 8) the reaction was a complete failure primarily because the alcohol is not stable to the acidic conditions which catalyze the elimination of H_2O from the alcohol faster than esterification. When the benzothiophene derived sulfonyl acid was used esterification

occurred in good yield, though the reaction was somewhat messy and required column chromatography to isolate it.

Table 3.1 Fischer esterifications of α-sulfonyl acetic acid derivatives

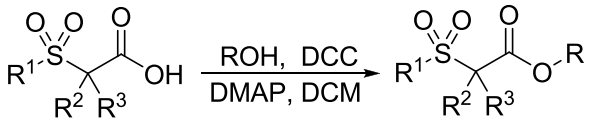


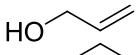
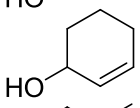
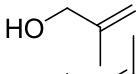
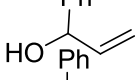
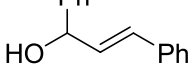
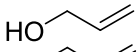
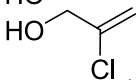
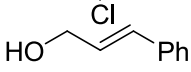
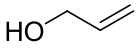
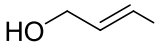
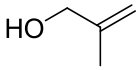
Entry	R^1	R^2	R^3	R^4	temp °C	Yield	Comments
(1)	Ph	H	H	Me	65	91, 96, 100%	
(2)	Ph	H	H	Allyl	97	38%	Side reactions occur
(3)	Ph	H	H	Allyl	50	94%	
(4)	Ph	Me	H	Me	65	65%	
(5)	Ph	Me	H	Et	78	79%	
(6)	Ph	Me	Et	Me	65	--	Messy rection
(7)	Ph	Ph	H	Me	45	50-100%	
(8)	Ph	H	H	isoprenyl	80	0	TsOH, C_6H_6, Dean-Stark rapidly eliminates H_2O
(9)				Allyl	97	91%	

Another frequently employed esterification method utilized DCC/DMAP in which the acid is converted to an acylating reagent which then allows the alcohol to be acylated. One benefit to this reaction is the ambient temperatures at which they take place. Another benefit is that the reactions usually need only one equivalent of both the acid and the alcohol. One drawback is the formation of a stoichiometric amount of the corresponding urea, which must be separated from the product. The majority of the urea is quickly removed by passing the reaction mixture directly through a silica plug, which is only sparingly soluble in the CH_2Cl_2, the DMAP is also removed. Table 3.2 shows typical results for esterifications that are facilitated by carbodiimides. The coupling of sulfonyl acetic acid and most allyl alcohols is rapid and clean (entries 1-4, 7-8, Table 3.2)

with only a few exceptions (entries 5, 6 and 9). Even prenol underwent smooth coupling (entry 4) which did not work well under Fischer conditions (entry 8, Table 3.1). Allyl alcohols that are substituted at the carbinol are sluggish often resulting in reduced yields. 1,3-diphenyl allyl alcohol (entry 6) is somewhat slower to couple. Interestingly, the alcohol is not stable under the conditions and gives a significant amount of side product. I suspect that it might be oxidizing under the reaction conditions. Interestingly, when the alpha position is fully substituted (entries 10-12) the acid and alcohol can still be coupled albeit in reduced yields and with the formation of what appears to be, by ^{1}H NMR spectroscopy, acylated urea which coeluted with the product. Fortunately we found it could be removed by changing the mobile phase to a toluene/CH_2Cl_2 mixture. In some cases DIC was used but very little difference was noticed and given the price difference in the two reagents, DCC was typically used.

Table 3.2 DCC/DMAP esterifications of α-sulfonyl acetic acid derivatives

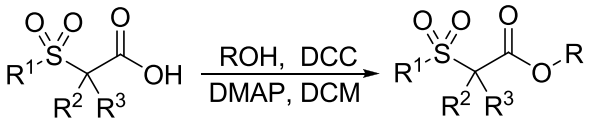


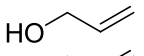
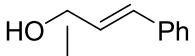
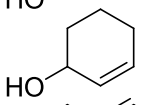
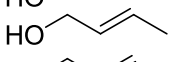
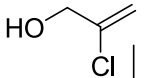
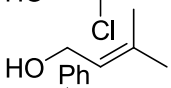
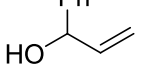
Entry	R^1	R^2	R^3	ROH	Yield(s)	Comments
(1)	Ph	H	H		89, 97, 90, 100, 100%	
(2)	Ph	H	H		89%	
(3)	Ph	H	H		100%	
(4)	Ph	H	H		97%	
(5)	Ph	H	H		63, 85%	
(6)	Ph	H	H		70%	Alcohol oxidation occurs
(7)	Bn	H	H		84, 85%	
(8)	Ph	H	H		90%	DIC
(9)	Ph	H	H		63%	DIC
(10)	Ph	Bn	Me		58, 65%	Slow, acylated urea
(11)	Ph	Bn	Me		74, 29%	Slow, acylated urea
(12)	Ph	Bn	Me		50, 33%	Slow, acylated urea

A number of alpha phenyl substituted sulfonyl acetic acids were also synthesized via DCC/DMAP couplings. The coupling occurs smoothly but accurate yields are difficult to obtain since often the acid is contaminated with the decarboxylated material. It is also likely that some of the acid decarboxylates in the reaction prior to esterification but this doesn't happen too fast as synthetically viable amounts of the esters are obtained. Some of the yields in Table 3.3 are lower estimates in which the esterification was part of a sequence of reactions. The yield is based only on the cumulative yield and designated by a ">" before the yield. Very good yields are obtainable (entry 1) but more common are yields in the range of 42-75% (entries 2-6, 8). DIC gives comparable results (entry 6).

Given the propensity for α-phenyl sulfonyl acetates to decarboxylate, there are likely better synthetic routes. However, if the acetate is not "valuable" then it can serve as a rapid way to get to α-phenyl sulfonyl esters. Unlike enolates which suffer from O vs. C selectivity issues, lithiated sulfones undergo only C-carboxylation.

Table 3.3 DCC/DMAP esterifications of α-sulfonyl α-phenyl acetic acid



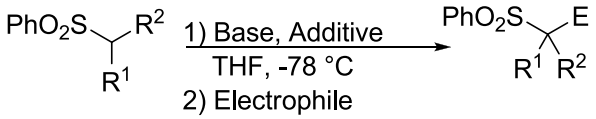
Entry	R^1	R^2	R^3	ROH	Yield(s)	Comments
(1)	Ph	Ph	H		>50, 88%	
(2)	Ph	Ph	H		47%	
(3)	Ph	Ph	H		42, 58, 60, 42%	
(4)	Ph	Ph	H		65, 74, 75%	
(5)	Ph	Ph	H		69%	
(6)	Ph	Ph	H		65%	DIC
(7)	Ph	Ph	H		>15%	
(8)	Ph	Ph	H		68%	

Carboxylation of sulfones

We briefly investigated and have employed the use of metalated sulfones as a way to get to the desired sulfonyl esters. At the outset, it is worth noting this strategy is not ideal because it generally requires alkyl lithiate bases and stoichiometric amounts of additives to break up the metal aggregates as well as high energy electrophiles. However, for the rapid synthesis of sulfonyl esters on a small scale we were not concerned with these "big picture" issues. The results of our findings are shown in Table 3.4. In general, all attempts to make the ester directly via the use of an allyl chloroformate resulted in

poor yields, 20% at best (entries 1-5, Table 3.4) and required 2-4 equivalents of HMPA. When NaH was used as the base no product formation was observed. In moving to the methallyl chlorofomate no product formation was observed. However, carboxylation of the lithiated sulfones was moderately-to reasonably successful (entries 6-9). We found that the use 1 equivalent of nBuLi and then adding solid dry ice (CO_2) at -78 °C (primarily to prevent violent effervescence) gave reasonable yields of the lithium carboxylates. Over the course of the several repeated reactions it was found that the key to a good yield was in the workup. The best workup is one in which the lithium carboxylate is extracted with 0 °C H_2O and then the aqueous layer acidified with 0 °C HCl and the product acid extracted with ethyl acetate several times. The key is to keep the aqueous *carboxylate as cold as possible* during workup. The carboxylation of alkyl sulfones appears to be general (entries 6,8 and 9). While the reaction requires the use of alkyl lithiates (entry 7 vs. 8) which is a harsh base and not ideal it does not require HMPA. The fact that we could avoid the use of HMPA and still get access sulfonyl esters, via esterification of the acids, in two steps from commercially available phenyl alkyl sulfone was enticing. Consequently, this procedure was frequently used when the synthesis of the compound was pressing but the yield was not critically important.

Table 3.4 Carboxylations of sulfones



Entry	R^1	R^2	Base	Additive	Electrophile	Yield(s)	Comments
(1)	Ph	H	nBuLi	HMPA	Allyl chloro formate	20%	
(2)	Ph	Me	NaH	--	Allyl chloro formate	<5%	No conv. in dmf
(3)	Ph	Me	nBuLi	HMPA	Allyl chloro formate	8,6% isolated	
(4)	Ph	Me	nBuLi	HMPA	Methallyl chloro formate	<5%	
(5)	$CHCH_2$	H	nBuLi	--	Allyl chloro formate	<5%	
(6)	$CHCH_2$	H	nBuLi	--	CO_2(s)	50% by mass	
(7)	Ph	H	NaH	--	CO_2(s)	<5%	
(8)	Ph	H	nBuLi	--	CO_2(s)	32,43,46,45,28,34,80,54 59,51,40,49,55,33,51, 72%	
(9)	Me	H	nBuLi	--	CO_2(s)	59%	

Alkylations of sulfonyl esters

A methylene group between a sulfone and a carbonyl are said to be "activated". This is because the two neighboring electron withdrawing groups make the anion generated via deprotonation rather stable and thus easily accessible. The anion, though stabilized, is a potent nucleophile capable of reacting with a range of electrophiles. We have utilized its ability to undergo alkylations, halogenations, and Knoevenagel condensations.

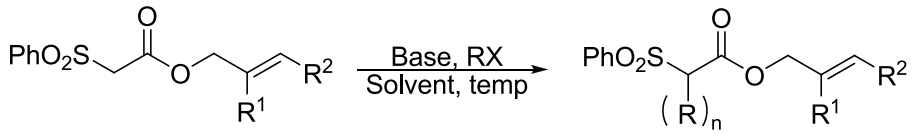
Monoalkylations

In the course of our work, we desired α-sulfonyl esters in which the alpha position was fully substituted. One straightforward approach that takes advantage of the activated methylene is to subject sulfonyl acetic ester derivatives to alkylative conditions. One subtlety concerning sulfonyl esters that was not apparent at the outset is the tendency

to over alkylate. Alkylation of sulfonyl esters, at least with some electrophiles, seems to follow Curtin-Hammett kinetics[9] and are alkylated to afford a mix of un-, mono-, and disubstituted esters. Standard alkylation with *t*BuOK in THF at 70 °C (entry 1, Table 3.5) led to significant amounts of the dibenzylated substrate and yet did not fully consume the starting material. The monoalkylations were carried out in DMF as the solvent in hopes that less aggregation of the anion might lead to cleaner alkylation (entry 2-11). Methylations were particularly difficult to control the degree of alkylation (entries 2-6). This is a problem that has been observed before[10] and several variations were attempted to see if the a single product could be obtained. It was thought that perhaps a small scale reaction could be leading to significant error in the masses of reagents, but despite the scale, 0.417 mmol vs. 1.67 mmol (entry 2 and 3) we observed only slight differences in the product ratio. Increasing the amount of base used from 1 equivalent to 2 (entry 4 vs. 2) provides more dimethylated and unsubstituted substrate. Use of the cyclohexenyl ester provided slightly better results than the allyl ester (entry 5 vs. 2). When sulfones have two acidic positions (entry 6) the diactivated position is selectively alkylated but with the typical product distribution. Using a larger electrophiles seems to shut down the over alkylation (entries 7-9 vs. 2) but the reactions still struggled to reach full conversion. Again when 2 equivalents of NaH were used (entry 10) the diallylation product was the major. Strong bases are not necessary and the alkylation can be performed using K_2CO_3 and, in fact, gave the best result. In this reaction a slight excess of the electrophile was unintentionally used. It is possible that had no excess been used very little over alkylation would have been seen. Besides a reduced yield of the desired product, the primary problem is that the mix of un-, mono-, and disubstituted sulfonyl

esters are only slightly different polarities and consequently are very difficult to separate from one another. One solution is to use substrates that already contain one α-substituent and thus avoiding over alkylation problem all together.

Table 3.5 Monoalkylation of Sulfonyl esters



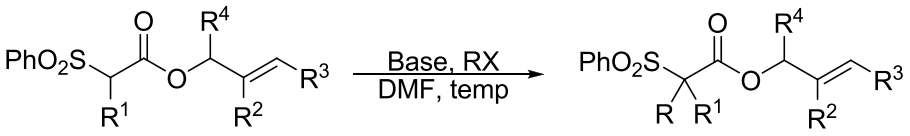
Entry	R^1	R^2	Base	RX	Solvent	Temp °C	n=0	1	2	Comments
(1)	H	H	*t*BuOK	BnBr	THF	70	0.07	1	0.36	
(2)	H	H	NaH	MeI	DMF	22	0.15	1	0.10	
(3)	H	H	NaH	MeI	DMF	22	0.18	1	0.16	Scaled up
(4)	H	H	NaH	MeI	DMF	22	0.25	1	0.38	2X base
(5)	--	--	NaH	MeI	DMF	22	0	1	0.13	Cyclohexenyl ester
(6)	H	H	NaH	MeI	DMF	22	0.09	1	0.19	Benzyl sulfone. 3.0 eq. MeI
(7)	H	H	NaH	EtI	DMF	22	0.54	1	0	repeated results
(8)	Me	H	NaH	EtI	DMF	22	0.58	1	0	
(9)	H	H	NaH	AllylBr	DMF	22	0.78	1	0	
(10)	H	H	NaH	AllylBr	DMF	22	0.31	0.68	1	2X base
(11)	H	H	K_2CO_3	AllylBr	DMF	22	0	1	0.25	1.14eq AllylBr

Monoalkylations of monosubstituted α-sulfonyl esters

Performing a second alkylation is also possible and generally experimentally simple. If the starting material is clean and simple alkyl halides are used, typically excellent yields (entries 5,8,11-13, Table 3.6) are obtained. For the second alkylation, our preferred conditions use K_2CO_3 and alkyl halide in DMF at room temperature (entries 5-8, 10-13). The reaction is simple and consistently gives high yields. Excess base and alkyl halides can be used since the over alkylation is a non issue. It is important that the *K_2CO_3 and DMF are dry*; the presence of H_2O leads to a decreased yield possibly via eventual hydrolysis of the ester. Alkyl halides that provide an acidic β-hydrogen can be

somewhat problematic, most likely because of the propensity to undergo elimination of the sulfinate to provide an α,β unsaturated ester (entries 2-4, 6,9,10). While substrates that formed a γ-ketone were evidently formed, I was never able to isolate the desired products (entries 2-4, 10). The fact that the alkylations that generate products with an acidic β-hydrogen were best carried out using NaH as the base suggests that the products are sensitive to carbonate bases (entries 3 vs. 4). However, the γ-ester was isolable (entries 6,7, and 9), though it too required a specialized workup to avoid elimination (entry 9 vs. 6, and 7). In the case of entries 6 and 7 the substrate was heated while removing the solvent. The best way to work these reactions up was to extract with copious organic solvent and wash away the DMF before running a column. In general the second alkylation works very well, provided a stable product is made-otherwise special conditions maybe needed to avoid side reactions. These conditions also work for symmetrically substituted sulfonyl esters that have undergone exhaustive alkylations.

Table 3.6 Second alkylation of sulfonyl esters

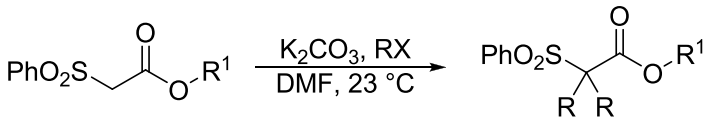


Entry	R^1	R^2	R^3	R^4	Base	RX	temp °C	Yield %	Comments
(1)	Me	H	H	H	NaH	MeI	22	74	
(2)	Et	Me	H	H	NaH	$PhCOCH_2Br$	22	–	At least 5 pdts.
(3)	Et	Me	H	H	K_2CO_3	$PhCOCH_2Br$	0	–	Messy rxn
(4)	Et	Me	H	H	NaH	$PhCOCH_2Br$	0	60*	*Conversion
(5)	Allyl	H	H	H	K_2CO_3	BnBr	22	99	
(6)	Ph	H	Me	Me	K_2CO_3	$BrCH_2CO_2Et$	22	17	1:2 pdt:elimination-heated
(7)	CH_2CO_2Et	H	H	H	K_2CO_3	EtI	22	71*	* = elimination pdt-heated
(8)	Ph	H	H	H	K_2CO_3	MeI	22	82	
(9)	Ph	H	Me	Me	NaH	$BrCH_2CO_2Et$	0	50	
(10)	Me	--	--	–	K_2CO_3	$ArCOCH_2Br$	22	–	Messy rxn. Ar=ρ-$MeOC_6H_4$
(11)	Allyl	H	H	H	K_2CO_3	AllylBr	22	97	1.14eq AllylBr
(12)	Ph	H	H	H	K_2CO_3	EtI	22	>95	
(13)	Me	--	--	–	K_2CO_3	BnBr	22	93	Ethyl ester

The same conditions used for the second alkylation can also be used for exhaustive alkylation, in which two substitutions occur in the same reaction. In every comparable example, exhaustive alkylations give far superior yields than the corresponding two step alkylations (entry 1, Table 3.6 vs. entry 4, Table 3.7). The ideal base is thoroughly dried K_2CO_3, though NaH works too (entries 1,2 vs. 3-7, Table 3.7). One added benefit of the mild base is that slight impurities don't seem to effect the reaction much. The yields given for entries 5-7 are based on the acid that was esterified via DCC/DMAP coupling in which the urea was removed with a simple silica plug and then alkylated, without any further purification. The ability to rapidly generate fully substituted sulfonyl esters has been very helpful in our chemistry. In addition to

alkylations, the activated methylene of sulfonyl acetic esters readily undergoes halogenation and condensation reactions.

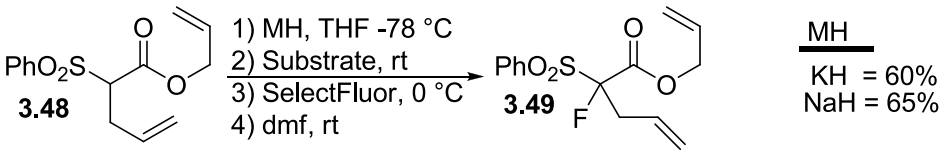
Table 3.7 Exhaustive alkylation of sulfonyl esters



Entry	R^1	RX	Yield %	Comments
(1)	CH_2CHCH_2	BnBr	57	*t*BuOK, THF
(2)	CH_2CHCH_2	$ICH_2(CH_2)_3$	83	NaH
(3)	CH_2CHCH_2	AllylBr	68	wet DMF
(4)	Me	MeI	99	
(5)	$CH_2CHC(CH_3)_2$	MeI	>93	Yield from acid
(6)	CH_2CHCH_2	MeI	>92	Yield from acid
(7)	$CH_2C(CH_3)CH_2$	EtI	>87	Yield from acid

Halogenation of α-sulfonyl esters

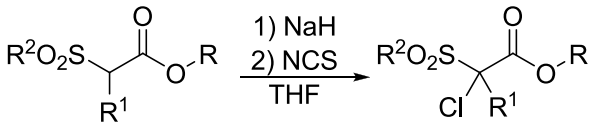
Fluorinated molecules are prevalent in medicinal compounds. They are often used because of their ability to make the parent drug molecule more potent for various reasons.[11] As a consequence there is interest in reactions that allow for the formation of carbon fluorine bonds. Incorporation of the fluorine into the activated sulfonyl allyl ester, prior to decarboxylation, is readily accomplished and then can undergo the Pd-catalyzed DCA to provide a much less accessible fluorinated compound. We were able to successfully synthesize a fluorinated sulfonyl ester by deprotonation with KH as well as NaH, then subjecting the carbanion to selectfluor-an electrophilic source of fluorine (Scheme 3.20).[12]

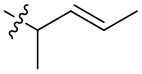
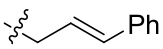
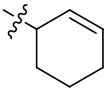
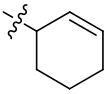
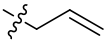
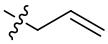
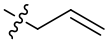


Scheme 3.20

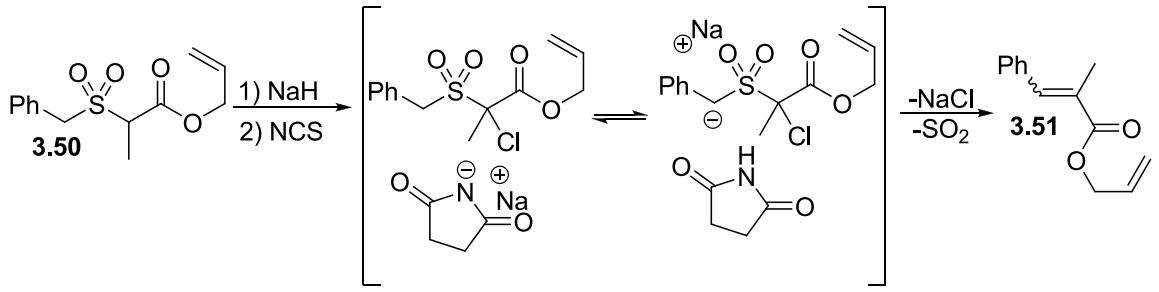
In addition to fluorination we found that sulfonyl esters were readily chlorinated. Subjecting monosubstituted sulfonyl esters to NaH and then *N*-chloro succinimide in THF led to the desired product in acceptable-to-excellent yields (Table 3.8).[13] In general, the chlorinations worked well (entries 1-5) but could be sporadic (entry 1). The desired product was obtained in reduced yields when a (benzyl)-sulfonyl ester with an additional acidic site was used (entry 6). Switching to K_2CO_3 as the base (entry 7) allowed a much more selective reaction although the yield is not reflective of this (there were some problems in the workup).

Table 3.8 Chlorination of sulfonyl esters



Entry	R^1	R	R^2	Yield %	Comments
(1)	Ph		Ph	45, 99	
(2)	Ph		Ph	62, 57	
(3)	Ph		Ph	87	
(4)	Me		Ph	99	
(5)	Et		Ph	70	
(6)	Me		Bn	53, 30	Side product formed
(7)	Me		Bn	65	K_2CO_3

When the (benzyl)-sulfonyl ester with the additionally activated site was used, yields were reduced and there was a side product that was formed (based on ^{1}H NMR spectrum of the reaction mixture after workup) it also contained an allyl ester. It is possible that the side product is the α,β-unsaturated ester formed by the product undergoing a Ramberg-Bäcklund reaction (Scheme 3.21).[14] It is possible that the amide generated from the NCS facilitates the extrusion of SO_2 to form the observed α,β-unsaturated ester.

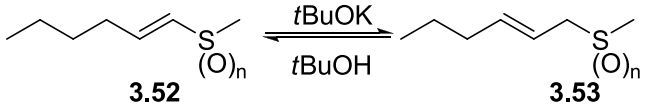


Scheme 3.21

Condensation reactions

A normal mode of reactivity of diactivated methylene is condensation reactions with aldehydes to form α,β-unsaturated compounds, this is commonly known as Knoevenagel condensation. Like many diactivated methylene units, the α-sulfonyl esters also undergo condensation reactions, however, unlike other groups in which the conjugated product is formed the isomeric deconjugated product is the major product when sulfones are used. While this is not as well known among organic chemists, it is certainly documented (Scheme 3.22).[15] This is best understood by considering that an sp^2-hybridized carbon is more electron withdrawing than a corresponding sp^3 carbon and the sulfur is slightly more electronegative than carbon and thus based solely on electronegativity sulfur would prefer to be adjacent to the sp^3 carbon. However, in lower oxidation state (n = 0 or 1) this affect is offset to varying degrees by conjugation of the lonepair of electrons on the sulfur and the π-bond and/or lower group electronegativity of the S. At higher oxidation states (n = 2) the sulfur becomes more electron withdrawing and no longer has any conjugative ability. Consequently, the only detectable isomer is **B** which separates the sp^2 carbon and the sulfone group with an sp^3 carbon. We thought we

might be able to take advantage of the tendency to isomerize to synthesize sulfonyl esters capable of undergoing DCA.

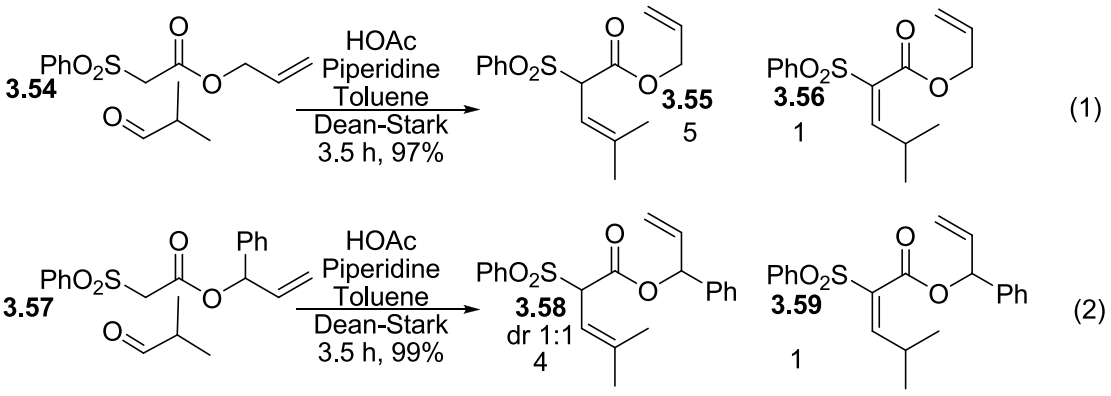


n	3.52	3.53
0	67	33
1	4	96
2	<1	>99

Scheme 3.22

We subjected unsubstituted sulfonyl esters (**3.54** and **3.57**, Scheme 3.23) to mixture of acetic acid and piperidine in toluene along with excess isobutyraldehyde. Heating for 3.5 h with azeotropic removal of H_2O led to nearly quantitative yields of the condensation products and in all cases the desired deconjugated product was the primary product (4-5:1 allyl vs. vinyl sulfone). While the scope of this reaction is far from tested, it appears to be a nice way to get to the sulfonyl esters with an α-vinyl substituent. Our isomeric ratio is significantly different from that observed by O'Connor and Lyness[15] but this is attributed to the presence of the ester functional group which makes the vinyl sulfone more stable. Fortunately, the isomers were separable by column chromatography allowing access to either isomer. The choice of isobutyraldehyde was not accidental; it was suspected that this would increase the amount of the desired isomer (**3.55** and **3.58**) as the added substitution would further increase the stability of the allyl sulfone. Substrates of this nature have many uses; in essence it is a prenyl anion equivalent. After decarboxylation it would have the ability to undergo a Cope rearrangement,[16] in addition allyl sulfones can be substituted with other nucleophiles under palladium catalysis. Furthermore, there are many possibilities in the realm of terpene syntheses-since (**3.55**

and **3.58**) contain an isoprene unit. In addition this is a simple way to synthesize monosubstituted sulfonyl esters which is difficult via alkylation chemistry (Table 3.5). Entry 2 (Scheme 3.23) was also synthesized using an enantiopure sulfonyl ester to afford enantiopure diastereomers (**3.58,** dr 1:1).



Scheme 3.23

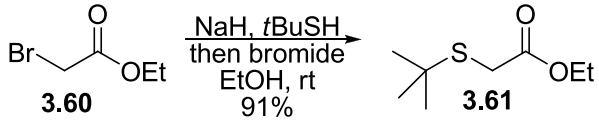
Substitutions

Another method of accessing sulfonyl esters is by substitution of esters that contain an alpha leaving group with some form of sulfur nucleophile. We have successfully employed substitutions of α-bromo and α-sulfonate esters. We have employed sulfur nucleophiles at several oxidation states with several substitution patterns on the bromide. Interestingly, the best conditions for substitutions are rarely the same if either of the oxidation state of the nucleophile or the substitution pattern of the bromide is different.

Primary Bromides

Ethyl bromo acetate is a common reagent that can be used to rapidly build interesting sulfonyl esters. We desired to have an α-sulfoxide ester with a bulky sulfur

substituent. We envisioned this could come from mono-oxidation of the corresponding sulfide which could come from reaction of the corresponding bromide and a nucleophilic thiolate. So we subjected α -bromo ethyl acetate and sodium *t*-butyl thiolate in ethanol at room temperature which rapidly underwent substitution to cleanly afford the desired product (**3.61**, Scheme 3.24).



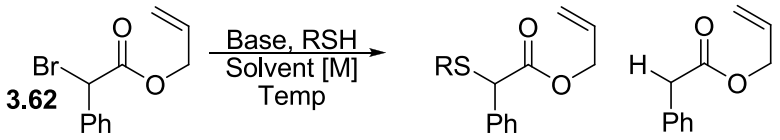
Scheme 3.24

Secondary bromides

The synthesis of sulfonyl esters is greatly aided by the ability to deliver the sulfur as a nucleophile. Previously, monosubstituted sulfonyl esters were synthesized via alkylation of the sulfonyl ester. The monoalkylations had a persistent problem of over alkylation. One solution we implemented was carboxylation of the corresponding sulfone (Table 3.4). However, this method necessitates the use of high energy alkyl lithiates and is a process that we try to avoid. We thought an alternative solution might be the displacement of secondary α-bromo esters with a sulfur nucleophile which would avoid the problems of alkylation. We started with the conditions which had been used to successfully substitute α-bromo ethyl acetate (entry 1, Table 3.9). We were surprised to find that none of the desired product was formed but rather only product that had undergone transesterification. We tried DMF as a solvent, hoping to maintain the allyl ester, and used K_2CO_3 as a base which worked and provided the desired product in a low yield (entry 2). When we used NaH as a base, only traces of the desired product were

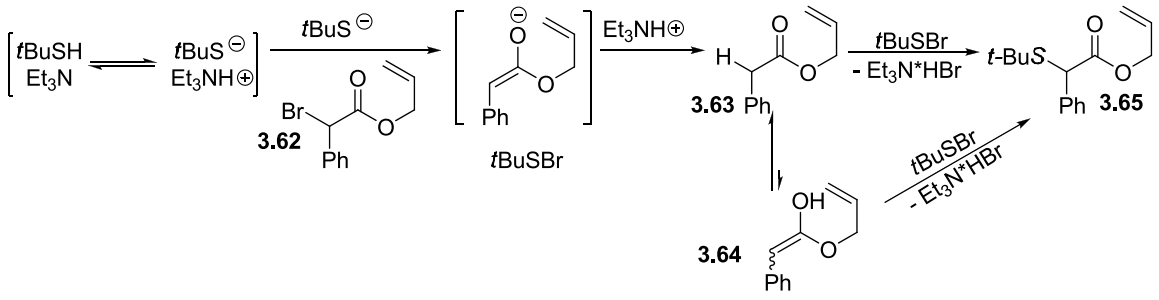
observed (entry 3). When BnSH was used under the same conditions the reaction was quite messy and provided many products (entry 4). Interestingly when conditions of entry 2 were used with BnSH as the nucleophile at 50 °C, the reaction cleanly provided the corresponding debrominated-reduced product. This result made us begin to question how exactly this reaction was working. Clearly, this is not a simple S_N2 displacement of the bromide-as this does not explain the reduced product. When we used Et_3N and $CHCl_3$ we observed very clean sulfide formation (entry 6).[17] Again when *t*BuSH was used in protic solvent, we only observed transesterification product. Using Et_3N and $CHCl_3$ also worked for *tert*-butyl thiol (entry 8) interestingly this reaction needed to run overnight for high yields but by TLC the starting material was consumed much faster. Assuming the reaction was complete when the starting material was consumed, we stopped the reaction after 4h (entry 9) compared to (entry 8) which had been run overnight. Interestingly, we isolated the reduced product in 48%. These results imply that the reduced product is actually an intermediate in product formation. Nonetheless, we were happy to find conditions that allowed access to α-phenyl α-sulfide esters.

Table 3.9 Sulfenylations of α-bromo α-phenyl allyl acetate



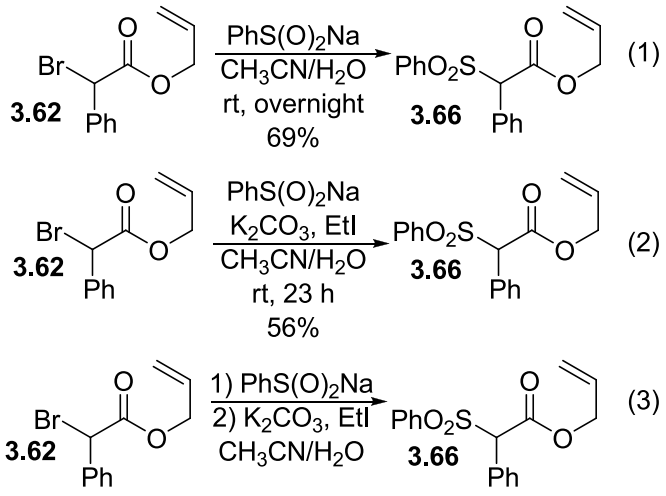
Entry	Base	Solvent	Conc. [M]	R	Temp °C	Yield %	Comments
(1)	MeONa	MeOH	0.1	Et	22	0	Transesterification
(2)	K_2CO_3	DMF	0.7	Et	22	39	
(3)	NaH	DMF	0.5	Et	50	0	Trace
(4)	NaH	DMF	0.5	Bn	50	0	Messy
(5)	K_2CO_3	DMF	0.2	Bn	50	94*	* Reduced product isolated
(6)	Et_3N	$CHCl_3$	0.2	Bn	22	99	Very clean
(7)	NaH	EtOH	0.4	*t*Bu	22	0	Transesterification
(8)	Et_3N	$CHCl_3$	4.0	*t*Bu	22	95	
(9)	Et_3N	$CHCl_3$	4.0	*t*Bu	22	48*	* Reduced product isolated Rxn stopped after 4h vs 15h

The apparent reduction that seems to be taking place under several sets of reaction conditions suggests that a simple S_N2 displacement of the secondary bromide is not the operative mechanism. One potential explanation (Scheme 3.25) would begin by *in situ* reduction of the bromide (**3.62**) by the thiolate attack on the bromine atom followed by protonation of the enolate by the ammonium to afford **3.63** and *t*BuSBr. Homolytic cleavage of the S—Br could initiate a radical process which ultimately places the sulfur on the carbon and the HBr would be sequestered by the Et_3N. Alternatively, the minor enol tautamer (**3.64**) of the reduced product might be responsible for the formation of the sulfide. These findings definitely warrant more investigation into this process. If the reduced product (**3.63**) is a viable intermediate this might allow a bromination step to be avoided and could result a shortened and greener synthesis.



Scheme 3.25

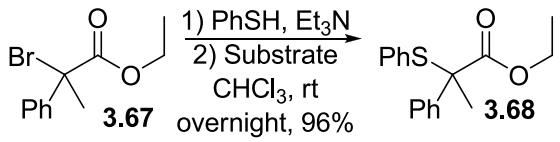
We also briefly looked at the substitution of secondary bromide esters with sulfinate nucleophiles (Scheme 3.26). Water was used as a co-solvent with acetonitrile because of the poor solubility of the sulfinate salt. The reaction was not optimized and probably suffered from competing hydrolysis and decarboxylation. The ability to go directly from the bromide to the sulfone without an oxidation step made us believe that we might be able to accomplish a one-pot substitution and alkylation which would provide fully substituted sulfonyl esters from the bromide. However, attempts to accomplish this in one pot were unsuccessful. In the first attempt at the one-pot reaction (eq. 2) $PhSO_2Na$, EtI and K_2CO_3 were naively added simultaneously to the bromide. Not surprisingly, none of the desired quaternerized sulfonyl ester was observed; it is likely that the sulfinate underwent nucleophilic displacement of the iodide of the EtI. Next, the sulfinate was added first and allowed to displace the bromide (entry 3), then EtI and and K_2CO_3 were added but none of the alkylated product was observed while some of the sulfone was observed. It is a likely possibility that under the wet conditions the EtI was consumed by oxygen nucleophiles, in addition, hydrolysis is likely problematic. This is consistent with our other attempts to alkylate in which wet DMF led to lower yields (entry 3, Table 3.7).



Scheme 3.26

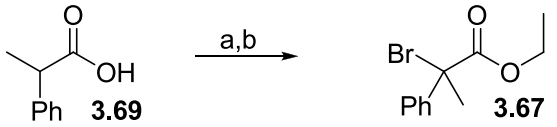
Tertiary bromides

We also hoped to be able to substitute tertiary bromides with sulfur nucleophiles. We began by applying conditions which had led to clean substitution of secondary benzylic bromides with thiols (entry 8, Table 3.9). To our delight, the same conditions were ideal for the substitution of α-bromo α-phenyl ethyl propanoate (Scheme 3.27). The reaction went to completion overnight and cleanly afforded the corresponding sulfide in excellent yield; furthermore this was successful on a 10 g scale of the starting bromide. The bromide was made in two steps from commercially available α-phenyl propanoic acid by esterification and bromination.



Scheme 3.27

The bromo ester could be made on a large scale in two steps from the inexpensive acid (Scheme 3.28). One non-intuitive fact is that a catalytic amount of bromine is required for the bromination to take place. This was discovered when, prior to scale up, the NBS was recrystallized and consequently the bromination failed. Suspecting that the original NBS had been contaminated with Br_2 and that the Br_2 was not innocent, a small amount of Br_2 was added and the reactivity of the NBS was restored.

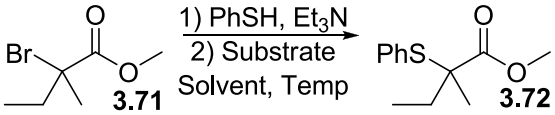


a) H_2SO_4 (cat), EtOH 99%. b) NBS, Br_2 (cat) CCl_4 95%

Scheme 3.28

We subjected a simple alkyl bromide to the preceding conditions, however, under these conditions the bromides were unreactive (entry 1, Table 3.10). Use of toluene and higher temperatures made little difference (entry 2) however, use of DMF at 110 °C cleanly afforded the substituted product in 88% (entry 3). This bromide was also made from the acid which was converted to the α-bromo acid[18] and then esterified via the standard DCC/DMAP procedure.

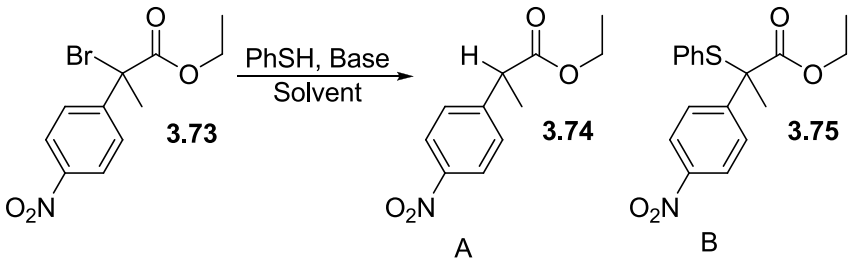
Table 3.10 Substitutions of α-bromo α-dialkyl methyl acetate



Entry	Solvent	Temp °C	Yield %	Comments
(1)	$CHCl_3$	50	NR	
(2)	$C_6H_5CH_3$	110	NR	
(3)	DMF	110	88	1g

Hoping to synthesize several sulfonyl ester analogs, we subjected ethyl 2-bromo-2-(4-nitrophenyl)propanoate (**3.73**, Table 3.11). Unfortunately every attempt to substitute it simply led to the reduced product (**3.74**, Table 3.11). Standard conditions cleanly afforded the undesired reduced product **3.74** (entry 1). Use of either acetone or DMF (entries 2 and 3) appeared to provide the reduced product which had a characteristic pink color. A reaction set up in the glovebox suggests that oxygen is not needed since the same reduced product was formed (entry 4). The reaction proceeded smoothly in pentane which might help to destabilize any ionic intermediates, nonetheless, only **3.74** was observed (entry 5). Finally, the nature of the thiolate does not appear crucial as both the ethyl and benzyl thiolate also provide **3.74** exclusively (entries 6 and 7). Without any success we abandoned the idea of sulfonyl esters based on this bromide. The reduction of bromides that have distabilized methylene units is not unprecedented, and while the nitro group is remote, its effects are felt through the aromatic ring.

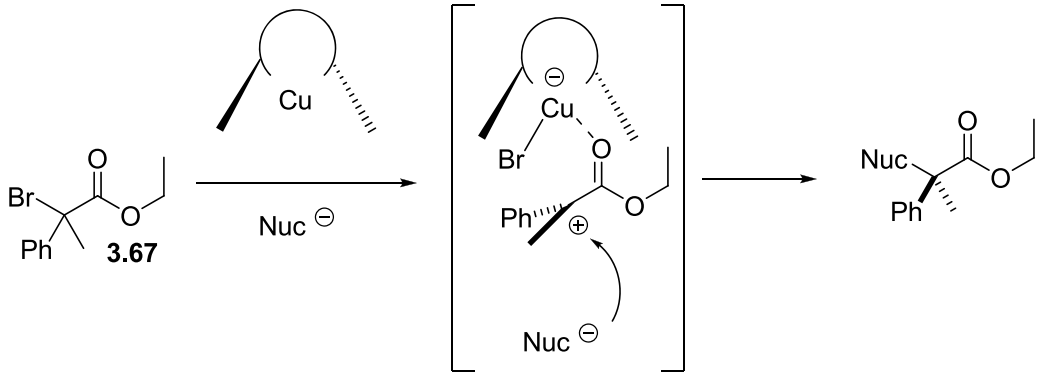
Table 3.11 Attempted substitution of α-bromo α-(*p*-nitrophenyl) ethyl acetate



Entry	Solvent	Base	Conv.	A:B	Comments
(1)	$CHCl_3$	Et_3N	100	1:0	
(2)	Acetone	K_2CO_3	<100	1:0	
(3)	DMF	K_2CO_3	–	1:0	
(4)	$CHCl_3$	Et_3N	100	1:0	Rigourous exclusion of O_2
(5)	Pentane	Et_3N	100	1:0	
(6)	$CHCl_3$	Et_3N	100	1:0	EtSH
(7)	$CHCl_3$	Et_3N	100	1:0	BnSH

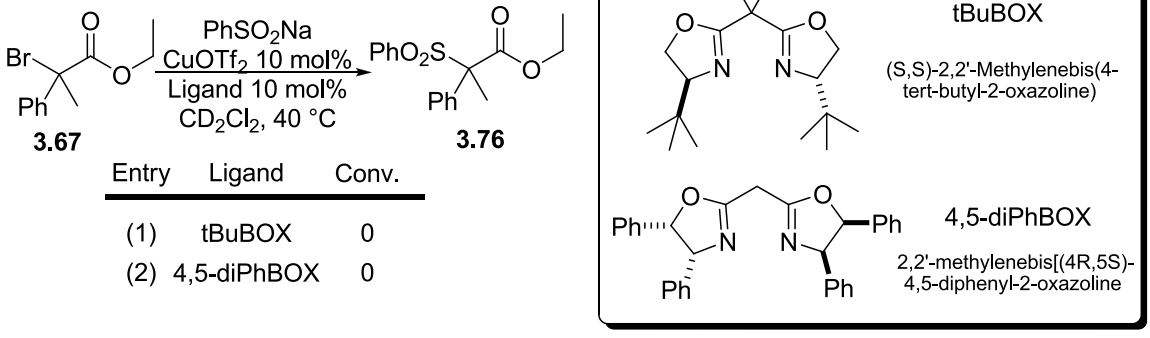
Tertiary bromides with sulfinates

We had a need for chiral, non-racemic sulfonyl esters; the absence in the literature of any general syntheses made us believe that methodology that would allow synthesis of such substrates from the corresponding racemic bromide would be valuable. We thought it might be possible to transform racemic bromide into nonracemic sulfone. One potential strategy was to heighten the electrophilicity of the bromide by use of a chiral Lewis-acid which could potential ionize the bromide to give a chiral, ion-pair that could be selectively attacked on one face by a nucleophile, leading to enantioenriched product (Scheme 3.29). There are several significant challenges to this strategy. The nucleophile is a Lewis base and would likely out-compete the only poorly Lewis-basic bromide for a position on the Lewis-acid. In addition, if the bromide is ionized, elimination would likely be problematic.



Scheme 3.29

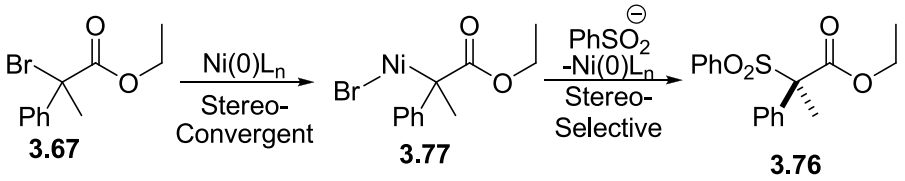
Nonetheless we gave this somewhat improbable scenario a chance. Use of $Cu(OTf)_2$ ligated with two different BOX ligands gave no conversion in CD_2Cl_2 at 40 °C overnight (Scheme 3.30). One potential reason the reaction did not work is that the sulfinate coordinated the metal and thus it never had opportunity to facilitate the ionization of the bromide.



Scheme 3.30

Recently, work[19] from Greg Fu's group has shown that α-bromo esters, amides, and ketones are competent partners for carbon bond formation via nickel catalysis. This

made us believe that it might be possible for an electron rich Ni(0) to oxidatively insert into the C—Br bond (Scheme 3.31). This process would be stereoconvergent since the O-bound enolate is achiral and would allow access to either face. Thus, with the appropriate ligand it might be possible to discriminate between the enantiotopic faces of the enolate. Coordination of a sulfinate anion to the metal could result in reductive elimination alternatively, sulfinate could attack the backside of the C—Ni to turnover the catalyst.



Scheme 3.31

Our first attempts using $Ni(COD)_2$ in DMSO-d_6 resulted in complete conversion to product, however, the control which did not contain the metal or ligand also gave rapid and clean substitution (entries 1-3, Table 3.12). In our attempts to design a catalytic method to obtain enantioenriched substrates we did find nice conditions for the uncatalyzed substitution as DMSO appeared to be superior at promoting the substitution. We began our search for a competent catalyst with $Ni(COD)_2$, a good source of Ni(0), but unfortunately it rapidly turned to Ni-black thus we limited our search to Ni(II) catalyst that might be reduced *in situ* to the active catalyst. No substitution was observed when the reaction was run in CD_2Cl_2 and THF-d_8 (entry 4 and 5). Believing that the Ni(II) was not being reduced we attempted to add a catalytic amount of Et_2Zn to aid in the reduction of the Ni(II) (entry 6) but still no conversion was observed. Use of glyme, a common

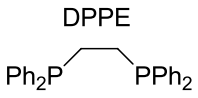
solvent used in Fu's Ni—catalyzed substitution of α-bromo substrates, with $NaBH_4$ as a reductant gave 33% conversion to the sulfone (entry 7) while the control showed no reaction (entry 8). Using Et_2Zn as the reductant also gave 33% conversion (entry 9) and also gave a small amount of conversion when run at room temperature (entry 10) using Et_3NHSO_2Ph to rule out low solubility as a cause for low conversion. However, increasing the catalyst loading to 50% (entry 11) seemed to have a detrimental effect and caused significant amount of precipitation to occur. Finally, thinking that the amine was causing problems with the catalyst, K_2CO_3 was used along with the sulfinic acid but again this gave no conversion (entry 12). It seems, in a few cases, that some reaction occurs but we did not investigate this enough to gain any insight as to what is actually happening. The low conversion suggests that the catalyst is taking part in a reaction but is not being turned over, however, without more evidence this is just speculation.

Table 3.12 Attempted Ni—catalyzed sulfinate substitution

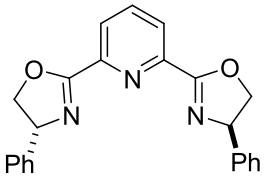
3.67 **3.76**

Entry	Solvent	Metal	Ligand	Temp °C	Conv.	Additive	Comments
(1)	d-DMSO	$Ni(COD)_2$	--	rt	100		JW4152
(2)	d-DMSO	$NiCl_2$	DPPE	rt	100		JW4153
(3)	d-DMSO	--	--	rt	100		40% conv 5min JW4154
(4)	CD_2Cl_2	$NiCl_2$	DPPE	40	0		JW4159
(5)	d-THF	$NiCl_2$	DPPE	67	0		JW4160
(6)	d-THF	$NiCl_2$	DPPE	67	0	Et_2Zn	Attempt to reduce Ni(II)
(7)	GLYME	$NiCl_2$	(R)-PhPyBox	85	33	$NaBH_4$	JW4168
(8)	GLYME	--	--	85	0		Control. no rxn. JW4175
(9)	GLYME	$NiCl_2$	(R)-PhPyBox	85	33	Et_2Zn	JW4169
(10)	GLYME	$NiCl_2$	(R)-PhPyBox	rt	25	Et_2Zn	JW4172. (.2) Ni Used Et_3NHSO_2Ph
(11)	GLYME	$NiCl_2$	(R)-PhPyBox	rt	0	Et_2Zn	JW4181. (.5) Ni Used Et_3NHSO_2Ph
(12)	GLYME	$NiCl_2$	(R)-PhPyBox	rt	0	Et_2Zn, K_2CO_3	JW4182. used sulfinic acid

DPPE

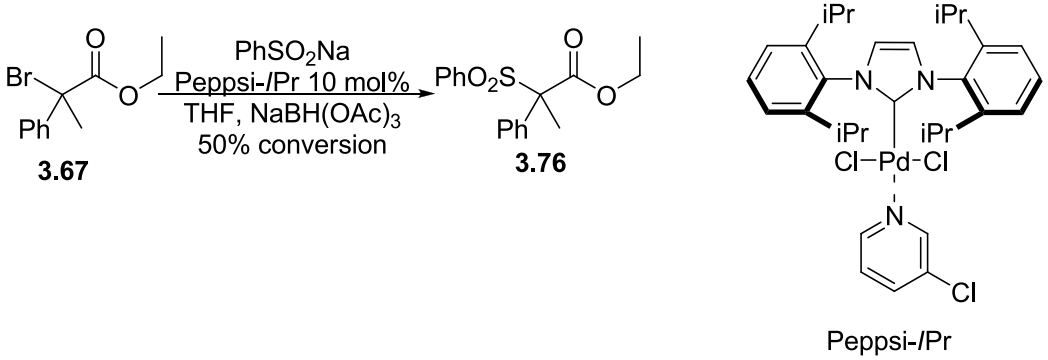


(R)-PhPyBOX



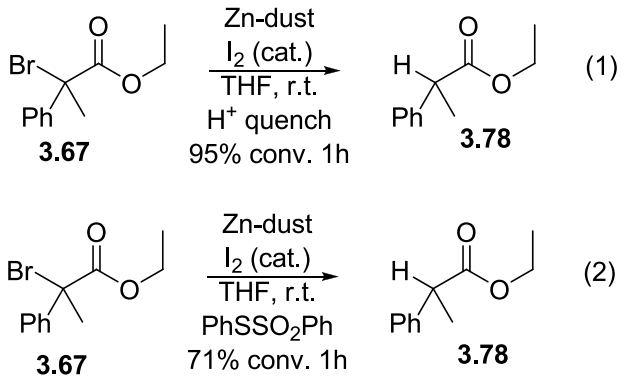
Finally, simultaneous with the investigation into the nickel catalyzed reaction a palladium catalyst, Peppsi-*i*Pr, was used (Scheme 3.32). It seemed a little unusual that palladium could undergo oxidative addition into this hindered sp^3 bond but the control was negative, thus a rather extensive screening and optimization was undertaken. Unfortunately, under what seemed to be ideal conditions the reaction was scaled up but an additional control revealed that the background reaction was significant. Most of the screening had taken place in NMR tubes in which the heterogeneity (the sulfinate is only sparingly soluble in most organic solvents) of reaction apparently made results irreproducible. When the control reaction was run in a Schlenk tube with a stir bar

rapidly mixing the contents it became apparent that we could not trust any of the findings we had learned and we abandoned this idea.



Scheme 3.32

We also briefly looked at the formation of a Reformatsky reagent from the bromide (Scheme 3.33). From a simple reduction experiment in which Zn-dust and a catalytic amount of I_2 were added to the substrate in THF showed that after 1 h more than 95% of the starting bromide had been consumed giving primarily the reduced product (**3.78**, eq.1). Excited about this result an electrophilic source of sulfur was added as the quench (eq.2) but the reduced product, **3.78**, was still the major product. This might be explained by wet solvent or reagent. However, with out any easy way to make this reaction asymmetric, if we could get it to work, the idea was abandoned.



Scheme 3.33

One potential flaw in many of the strategies aimed at asymmetric synthesis is that the asymmetry is proportional to a related enolate geometry equilibrium which is rarely selective enough to be synthetically useful in acyclic systems. Thus the strategies would likely not give high ee's even if we were successful in catalyzing the reaction unless we limited ourselves to cyclic substrates.

In conclusion, we demonstrated strategies to synthesize α-sulfonyl esters including; esterifications, carboxylations, alkylations, halogenations, and condensations. In addition we have shown that sulfonyl esters can be synthesized via substitutions of α-bromo esters. Finally, we have developed a couple asymmetric strategies that rely on an S_N2 displacement of tertiary mesylate as a key step. Furthermore, we provided significant discussion concerning the success of several other potential asymmetric routes to sulfonyl esters.

References—Chapter 3

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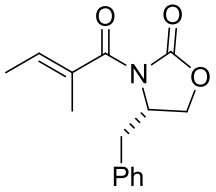
Asymmetric Cross-Couplings of Racemic alpha-Bromoketones with Arylzinc Reagents *Angew. Chem., Int. Ed.* **2009**, *48*, 154-156.

Appendix C: General Methods and Compound Characterization

Materials. All moisture sensitive reactions were run in flame-dried glassware under an Ar atmosphere using standard Schlenk techniques. Methylene chloride, toluene, THF, Et_2O wer dried over activated alumina and toluene and THF were then distilled over sodium. Acetone was distilled from magnesium sulfate and stored over activated mol sieves. Commercially available reagents were used without additional purification unless otherwise stated. Tris(dibenzylideneacetone) dipalladium (0), $Pd(PPh_3)_4$, and rac-BINAP were purchased from Strem and stored in a glovebox under an Ar atmosphere. Compound purification was effected by flash chromatography using 230x400 mesh, 60 Å porosity, silica obtained from Sorbent Technologies. Thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5715-7, EMD chemicals). Visualization of the plateswas accomplished with a UV lamp (254 nm) or $KMnO_4$ stain. ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance 400 or a Bruker Avance 500 DRX, or a Bruker AVIII 500 spectrometer and referenced to residual protio solvent signals (some spectra were taken using a broadband observe probe and a dual 13C/1H Cryoprobe). Structural assignments are based on ^1H, ^{13}C, DEPT-135, COSY, HSQC and IR spectroscopies. FTIR spectra were recorded using either a ATI Mattson Genesis Series FTIR or Shimadzu 8400-S FTIR spectrometers. High Resolution Mass Spectrometry (HRMS) were performed using EI, ESI, and FAB techniques. EI MS spectra were obtained on an AUTOSPEC-Q tandem hybrid mass spectrometer (VG Analytical Ltd, Manchester, UK). ESI MS spectra were acquired either on a LCT Premier (Waters Corp., Milfpord, MA) or Q-Tof-2 (Microsmass Ltd, Manchester UK) spectrometers. FAB MS

spectra were obtained on a ZAB HS mass spectrometer (VG Analytical Ltd, Manchester UK). Elemental Analyses were performed by Desert Analytics Laboratory (Tuscon, AZ). Chiral high pressure liquid chromatography was performed on a Shimadzu SCL-10AVP instrument using Daicel Chiralpak AD, AS and OD-H columns.

Procedure for the coupling of tiglic acid and the oxizolidinone (Scheme 3.2): To a flame-dried Schlenk tube equipped with stir bar was added LiCl (6.00 mmol), Et_3N (12.00 mmol), THF (30 mL) and Pivaloyl chloride (4.8 mmol). The slurry was cooled to 0 °C. Then tiglic acid (4.00 mmol) dissolved in THF (6 mL) was added dropwise over 20 minutes. The reaction was allowed to stir for an additional hour at 0 °C. Then (*S*)-(-)-4 benzyl-2-oxazolidinone (4.00 mmol) was added and the reaction was allowed to warm and stir overnight.[1] The reaction was concentrated *in vacuo* and the residue extracted with ethyl acetate and washed with 0.2N HCl, brine, saturated bicarbonate solution. The organic layer was dried with magnesium sulfate and concentrated. The residue was triturated with hot hexanes and decanted.[2] The crystals were rinsed with a small amount of cold hexanes.



(S,E)-4-benzyl-3-(2-methylbut-2-enoyl)oxazolidin-2-one

(**3.4**)(JW4023)

Crystaline solid

Yield: 91%, >99% ee

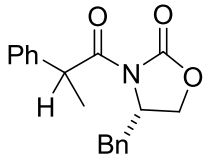
Purification: Tituration with hexanes

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 3H, ArC*H*'s), 7.21 (d, *J* = 7.7 Hz, 2H, ArC*H*'s), 6.22 (q, *J* = 6.9 Hz, 1H, CH3C*H*CRR), 4.72 (dq, *J* = 11.8, 4.0 Hz, 1H, RRNC*H*RR), 4.29 – 4.19 (m, 1H, OC*H*HCHRR), 4.15 (dd, *J* = 8.4, 5.1 Hz, 1H, OCH*H*CHRR), 3.36 (dd, *J* = 13.5, 3.2 Hz, 1H, PhC*H*HCHRR), 2.84 (dd, *J* = 13.2, 9.5 Hz, 1H, PhCH*H*CHRR), 1.92 (d, *J* = 0.9 Hz, 3H, C*H*$_3$CRR), 1.82 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CHR).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.81 (s, R*C*ONRR), 153.20 (s, RRN*C*OOR), 135.19 (s, Ar*C*), 134.82 (s, CH_3*C*HR), 131.67 (s, CH_3*C*RR), 129.46 (s, Ar*C*H's), 128.90 (s, Ar*C*H's), 127.32 (s, Ar*C*H), 66.41 (s, RO*C*H2R), 55.48 (s, RRN*C*HRR), 37.53 (s, Ph*C*H_2R), 14.12 (s, *C*H_3CHR), 13.29 (s, *C*H_3CRR).

Procedure for the sulfenylation of (S,E)-4-benzyl-3-(2-methylbut-2-enoyl)oxazolidin-2-one (3.4): To **3.4** (0.359 mmol) was added THF (4 mL) and LiHMDS (0.431 mmol) and HMPA (1.436 mmol) and the mixture was stirred for 15 minutes and then cooled to -78 °C and S-phenyl benzenesulfonothioate (0.359 mmol) was added and the solution warmed to 0 °C and stirred for 2 h. The reaction was quenched NH_4Cl (Aq) and extracted with ethyl acetate and washed with H_2O, brine, and dried with magnesium sulfate and concentrated to afford a mix of starting material and isomeric products.

Synthesis of (4S)-4-benzyl-3-(2-phenylpropanoyl)oxazolidin-2-one (3.7): In a flame dried Schlenk flask with stir bar was added 2-phenylpropanoic acid (2.00 mmol), oxalyl chloride (2.1 mmol), and THF (10 mL) and 2 drops of DMF and stirred for 1 h at room temperature. At which point the acid chloride was concentrated *in vacuo*. Meanwhile, (S)-4-benzyloxazolidin-2-one (2.0 mmol) was lithiated with *n*BuLi (2.1 mmol) in THF (10 mL) and cooled to -78 °C. The lithiate was cannula transferred to the acid chloride also at -78 °C and the reaction was allowed to warm to room temperature and stirred for 30 minutes. The reaction was concentrated and purified by flash chromatography to afford two diastereomers in 1:1 dr in 16% yield.



(4S)-4-benzyl-3-(2-phenylpropanoyl)oxazolidin-2-one

(**3.7**)(JW4023)

Yield: 16%, >99% ee, dr 1:1

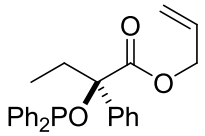
Purification: flash chromatography (99:1—1:1 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.2 Hz, 2H), 7.36 – 7.29 (m, 5H), 7.27 (t, *J* = 7.4 Hz, 2H), 7.22 – 7.08 (m, 3H), 6.95 (d, *J* = 3.6 Hz, 2H), 5.10 (q, *J* = 7.0 Hz, 1H), 4.73 (t, *J* = 8.5 Hz, 1H), 4.17 (t, *J* = 8.6 Hz, 1H), 4.06 (dd, *J* = 9.1, 3.2 Hz, 1H), 3.73 (q, *J* = 7.2 Hz, 1H), 3.08 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.57 (dd, *J* = 13.5, 8.9 Hz, 1H), 1.51 (dd, *J* = 7.1, 4.5 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.01 (s), 179.82 (s), 174.71 (s), 153.30 – 153.06 (m), 140.35 (s), 140.01 (s), 135.24 – 135.08 (m), 129.61 (s), 129.05 (s), 128.91 (s), 128.50 (s), 127.80 (s), 127.60 (s), 127.49 (s), 127.43 (s), 66.01 (s, RO*C*H_2R), 55.14 (s, RO*C*H_2R), 45.42 (s, RRN*C*HRR), 43.43 (s, RRN*C*HRR), 37.60 (s, Ph*C*H_2R's), 19.36 (s, *C*H_3), 18.35 (s, *C*H_3).

Synthesis of 3.15: (R)-2-hydroxy-2-phenylbutanoic acid (5.3 mmol), K_2CO_3 (15.9 mmol) and acetone (13 mL) were stirred and allyl bromide (5.83 mmol) was added and

the mixture was vigorously stirred. 5h later a second addition of allyl bromide was added (5.83 mmol) and stirring was continued for 11 h more at which point the reaction was concentrated *in vacuo* and extracted with ethyl acetate, washed with H_2O, dried with magnesium sulfate and concentrated *in vacuo.* The oil was purified by flash chromatography (Toluene:DCM 9:1). NOTE-it was later learned that rigorously dried K_2CO_3 and acetone led to increased yields and decreased the amount of necessary bromide and decreased side reactions-of which competing hydrolysis is the major. Following a literature prep[3] the hydroxy ester (1.00 mmol), DMAP (0.30 mmol) and THF (2.0 mL) were placed in a flame dried Schlenk tube with stir bar then Et_3N (1.30 mmol) and then $ClPPh_2$ (1.15 mmol) were added and the reaction was stirred at room temperature 3.25 h.



(R)-allyl 2-(diphenylphosphinooxy)-2-phenylbutanoate

(**3.15**)(JW5196)

Clear colorless oil

Yield: 93%, >99% ee

Contaminated with alcohol 15%

Purification: Pass through an alumina plug as 9:1 hexanes:ethyl acetate solution

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (ddd, *J* = 43.9, 12.5, 7.1 Hz, 5H), 7.51 – 7.17 (m, 14H), 5.70 – 5.53 (m, 1H), 5.03 (t, *J* = 12.8 Hz, 2H), 4.54 (d, *J* = 5.9 Hz, 1H), 4.49 – 4.38 (m, 1H), 4.10 (d, *J* = 7.1 Hz, 0H), 2.62 (dt, *J* = 18.7, 7.3 Hz, 2H), 2.02 (s, 0H), 1.24 (d, *J* = 7.1 Hz, 1H), 0.56 (t, *J* = 7.3 Hz, 3H).

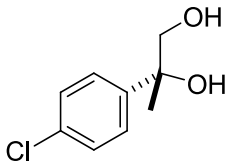
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.21 (d, *J* = 4.1 Hz, 1H), 138.51 (d, *J* = 7.1 Hz, 1H), 134.42 (d, *J* = 14.5 Hz, 1H), 133.05 (d, *J* = 8.8 Hz, 1H), 131.88 (t, *J* = 2.7 Hz, 1H), 131.61 (d, *J* = 1.9 Hz, 1H), 131.50 (d, *J* = 2.7 Hz, 1H), 128.50 (s, 1H), 128.38 (s, 1H), 128.32 (s, 1H), 125.70 (s, 1H), 118.58 (s, 1H), 88.03 (d, *J* = 6.9 Hz, 1H), 66.48 (s, 1H), 31.45 (s, 1H), 7.89 (s, 1H).

^{31}P NMR (162 MHz, $CDCl_3$) δ 31.27 (s).

General procedure for the synthesis of chiral non racemic hydroxy acids 3(a-e).[4] In a 250 mL Erlynmeyer flask placed on a cooling plate and *t*BuOH (12 mL) and H_2O (12 mL) and 7.0g of AD-mix-β and methyl sulfonamide (5.00 mmol) were added and the heterogeneous mixture was rapidly stirred. Then 4-chloro-α-methyl styrene (5.00 mmol) was injected and the reaction was rapidly stirred and the temperature was maintained 0-5 °C for ~24h a significant color change occurs (from orange to yellow) seems to be indicative of reaction completion. The reaction was quenched with Na_2SO_3 (3.5 g). The reaction was extracted with a copious amount of ethyl acetate and washed with water,

dried with magnesium sulfate, and concentrated. The residue was purified via flash chromatography (90:10 hexanes:ethyl acetate to afford[5] (*R*)-2-(4-chlorophenyl)propane-1,2-diol (**3.29c**) in 99% yield.

General procedure for the synthesis of chiral racemic hydroxy acids 3(a-e). Upjohn conditions were used to obtain the racemic diols.[6] To a flask was added 4-chloro-α-methyl styrene (1.00 mmol), NMO (1.5 mmol), and an OsO_4 solution (0.013 mmol), *t*BuOH (1 mL), H_2O (1 mL) and acetone (5 mL). The reaction was stirred for 23 h at room temperature. The reaction was partially concentrated (CAUTION! Remove the acetone and not the H_2O which contains the OsO_4). The remaining mixture was extracted with ethyl acetate and washed with H_2O, brine and dried with magnesium sulfate, and concentrated. The residue was purified via flash chromatography (90:10 hexanes:ethyl acetate to afford (±)-2-(4-chlorophenyl)propane-1,2-diol in 75% yield.



(*R*)-2-(4-chlorophenyl)propane-1,2-diol

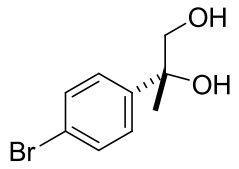
((*R*)-**3.29c**)(JW5273)

99%, >90% ee[7]

Purification: Flash chromatography (9:1 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 24.0, 8.5 Hz, 4H, ArC*H*'s), 3.67 (d, *J* = 10.7 Hz, RC*H*HOH), 3.55 (d, *J* = 6.2 Hz, 1H, RCH*H*OH), 3.02 (s, 1H, RO*H*), 2.50 (s, 1H, RO*H*), 1.45 (s, 3H, CH_3CRRR).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.74 (s, Ar*C*), 133.20 (s, Ar*C*), 128.65 (s, Ar*C*'s), 126.84 (s, Ar*C*'s), 74.77 (s, *C*RRROH), 70.95 (s, HO*C*H_2R), 26.17 (s, *C*H_3R).



(R)-2-p-tolylpropane-1,2-diol

((*R*)-**3.29b**)(DM1015)

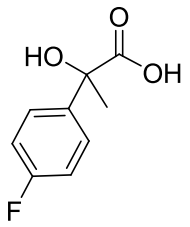
Clear colorless oil

78%, >90% ee[7]

Purification: Flash chromatography (9:1 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 8.6, 2.1 Hz, 2H), 7.35 – 7.29 (m, 2H), 3.75 (dd, *J* = 11.1, 4.9 Hz, 1H), 3.61 (dd, *J* = 11.0, 7.7 Hz, 1H), 2.50 (s, *J* = 1.7 Hz, 1H), 1.69 (d, *J* = 7.6, 5.0 Hz, 1H), 1.50 (s, *J* = 2.1 Hz, 3H).

General procedure for the oxidation of the 1,2-diol. To a 500 mL round bottom flask with stir bar were added (*R*)-2-(4-chlorophenyl)propane-1,2-diol (**3.29c**) (4.66 mmol), NaHCO3 (10.25 mmol), JM Type B103018-5 Pt/C (0.233 mmol) and H_2O (80 mL). The flask was fitted with a rubber septum and a needle blowing air was inserted such that air was bubling through the solvent a vent needle was also put in place. With stirring the flask was heated overnight at 75 °C. The disappearance of the diol could be monitored by TLC. After 19 h the reaction was filtered over celite and the basic aqueous solution was extracted 3X with ethyl acetate (recover any diol or aldehyde) then the aqueous layer was acidified with H_2SO_4 and extracted 3X with ethyl acetate. The combined organic layers were dried and concentrated to afford (R)-2-(4-chlorophenyl)-2-hydroxypropanoic acid (Scheme 3.11) in 85% yield. The acid was recrystallized in $CHCl_3$.



2-(4-fluorophenyl)-2-hydroxypropanoic acid

(**3.29e**)(JW5282)

Colorless crystals

38%

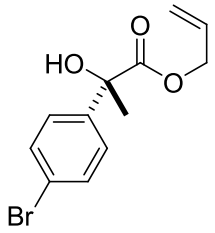
Purification: Crystallization in boiling $CHCl_3$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.9, 5.2 Hz, 2H), 7.02 (t, *J* = 8.7 Hz, 2H), 5.91 (s, 2H), 1.79 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.16 (s, 1H), 161.54 (s, 1H), 156.72 (s, 1H), 127.42 (d, *J* = 8.3 Hz, 1H), 115.49 (d, *J* = 21.5 Hz, 1H), 75.45 (s, 1H), 27.12 (s, 1H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -114.33 (dt, *J* = 13.7, 4.3 Hz, 1H).

Synthesis of hydroxy ester, 4h. Hydroxy acid **3b** was synthesized via an adaptation of a known method.[4] **3b** (200mg, 0.82 mmol) and dry K_2CO_3 (566 mg, 4.1 mmol) were added to a flamed-dried flask followed by the addition of allylbromide (296 mg, 2.4 mmol). Next, acetone (2 mL, distilled from $MgSO_4$) was added and the mixture stirred vigorously for 5 h. The mixture was then extracted with ethyl acetate (20 mL), washed with water (2 × 5 mL), dried over $MgSO_4$ and concentrated *in vacuo* Azeotropic removal of excess allyl bromide and allyl alcohol provided pure **4h** (210 mg, 0.74 mmol).[8]



(S)-allyl 2-(4-bromophenyl)-2-hydroxypropanoate

(**3.32h**)(DM1042)

90%

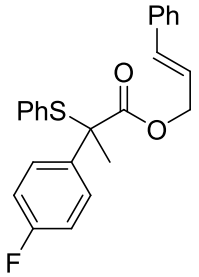
Purification: Azeotropic removal of allyl bromide and alcohol with toluene.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 4H, ArC*H*'s), 5.90 – 5.78 (m, *J* = 16.4, 11.3, 5.7 Hz, 1H, CH_2CHCH_2), 5.24 (dd, *J* = 7.5, 1.3 Hz, 1H, CH_2CHCHH), 5.21 (t, *J* = 1.3 Hz, 1H, , CH_2CHCHH), 4.70 – 4.57 (m, *J* = 13.2, 11.8, 5.7 Hz, 2H, $ROCH_2R$), 3.76 (s, 1H, RO*H*), 1.75 (s, 3H, quatCCH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.13 (RCO_2R), 141.92 (qAr*C*), 131.61 (Ar*C*'s), 131.24 ($RCHCH_2$), 127.40 (Ar*C*'s), 122.21 (qAr*C*), 119.34 ($RCHCH_2$), 75.62 (q*C*), 67.12 ($ROCH_2R$), 27.02 (RCH_3).

Conversion of α-hydroxy esters (3.32f-m) to α-sulfide esters 3.33f-m. To a flask, cooled to 0 °C, was added cinnamyl 2-hydroxy-2-p-tolylpropanoate ((±)-**3.32k**) (1.39 mmol), MsCl (6.47 mmol), DMAP (0.208 mmol) and pyridine (1.4 mL). The temperature was maintained between -5 and 0 °C for 25 h. After 18 h, an additional aliquot of MsCl (1.04 mmol) was added. After 25 h, the reaction was poured into a mix

of ice and 1N HCl and extracted with ethyl acetate (2X) and then dried and concentrated with **no heating**. No further purification was attempted. Reaction progress could be monitored by chiral stationary phase HPLC analysis (**Chiral HPLC Column:** Chiracel Chiralpak-AD column. **Eluent:** 90:10 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. The mesylate from ((±)-**3.32k**) was then immediately placed into a flask with a stir bar and cooled to 0 °C and a chilled solution of PhSNa (10.9 mL of 0.1 M) in EtOH was added the temperature was maintained 7 h. After 7 h, the EtOH was aspirated off and the remaining slurry was extracted with ethyl acetate and washed with a saturated K_2CO_3 solution The oil was purified by flash chromatography (95:5—3:1 hexanes:DCM) to afford the product in a 38% yield as 8:1 mix of the desired α-sulfide (**3.33k**) to the undesired β-sulfide ester (**3.34k**).



cinnamyl 2-(4-fluorophenyl)-2-(phenylthio)propanoate

((±)-**3.33k**)(JW6005)

38% (8:1 mix α:β sulfide)

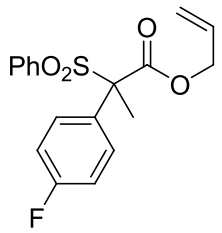
Purification: Flash chromatography (95:5—3:1 hexanes:DCM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.42 (m, 2H), 7.39 – 7.14 (m, 14H), 7.08 – 6.94 (m, 3H), 6.55 (t, *J* = 15.9 Hz, 1H), 6.19 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.76 (dd, *J* = 6.4, 1.3 Hz, 2H), 3.80 (s, 0H), 3.63 – 3.53 (m, 0H), 3.22 (dd, *J* = 13.4, 6.3 Hz, 0H), 1.81 (s, 3H), 1.57 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.37 (s), 160.83 (s), 136.81 (s), 136.54 (s), 136.07 (s), 134.67 (s), 131.17 (s), 130.47 (s), 129.40 (s), 129.09 (d, *J* = 8.1 Hz), 128.65 (s), 128.21 (s), 126.66 (s), 122.44 (s), 115.17 (s), 114.96 (s), 77.38 (s), 77.06 (s), 76.74 (s), 66.34 (s), 59.06 (s), 25.48 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -114.29 (dd, *J* = 9.5, 4.3 Hz, β-sulfide), -114.58 (ddd, *J* = 10.4, 8.4, 5.2 Hz, α-sulfide).

Oxidation of sulfide 3.33f-m to sulfone 7f-m. The mix of isomeric sulfides **3.33f** and **3.34f** (0.278 mmol) were dissolved in DCM (1.4 mL). *m*CPBA (0.613 mmol) is added and the mixture is stirred for 5 minutes and then Na_2SO_3 (0.5g) and H_2O were added the mixture was extracted with ethyl acetate (2X). To the combined organic layer was added NaOH solution until basic by pH indicator then it was washed with brine and dried with magnesium sulfate and filtered over a silica plug. The oil was purified by flash chromatography.



allyl 2-(4-fluorophenyl)-2-(phenylsulfonyl)propanoate

((±)-**3.35f**, Scheme 3.14)(JW6038)

79% yield

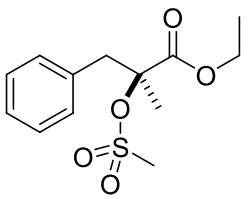
Purification: Flash chromatography (90:10 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (t, *J* = 7.4 Hz, 1H), 7.48 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.34 (ddd, *J* = 9.9, 6.3, 3.3 Hz, 4H), 6.97 (t, *J* = 8.6 Hz, 2H), 5.84 (ddd, *J* = 16.3, 11.0, 5.8 Hz, 1H), 5.26 (ddd, *J* = 13.8, 11.6, 1.3 Hz, 2H), 4.68 (dd, *J* = 5.6, 4.1 Hz, 2H), 2.11 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.44 (s, 1H), 162.45 (s, 1H), 136.19 (s, 3H), 134.00 (s, 5H), 131.34 (s, 9H), 131.15 – 130.83 (m, 13H), 128.99 (s, 3H), 128.24 (s, 9H), 119.76 (s, 5H), 115.57 (s, 6H), 115.40 (s, 5H), 75.80 (s, 4H), 67.06 (s, 4H), 18.84 (s, 6H).

Synthesis of sulfone 3.40 (Scheme 3.16). (E)-ethyl 2-methyl-3-phenylacrylate is subjected to ADH under the same conditions outlined for the synthesis of chiral non racemic 1,2-diols from α-methyl styrenes. The diol, (2R,3S)-ethyl 2,3-dihydroxy-2-

methyl-3-phenylpropanoate (1.87 mmol) was placed in a flame dried round bottom flask and TFA anhydride was added (4.0 mL). The diol slowly went into solution as it reacted. After 25 minutes the TFAA is removed *in vacuo* (CAUTION! TFAA is rather volatile and nasty and will build up a significant amount of pressure-furthermore the pump used to pull off the TFAA should be cleaned afterwards to prevent damage to the pump) and the residue is azeotroped (2X) with DCM. The residue was then dissolved in EtOH (28 mL) and 1% Pd/C (418 mg) was added. The flask was fitted with a septum and hydrogen balloon was added. The reaction was stirred overnight. The reaction was filtered over celite and rinsed with ethyl acetate concentrated. The residue was purified via flash chromatoghraphy (90:10 hexanes:ethyl acetate). The ee% could be determined by chiral stationary phase HPLC analysis (**Chiral HPLC Column:** Chiracel Chiralpak-AD column. **Eluent:** 99.4:0.6 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. The α-hydroxy ester was mesylated in the same manner described for the conversion of α-hydroxy esters to α-sulfide esters previously described but with three major exceptions 1) the mesylation was run at room temperature 2) the mesylate could be purified by flash chromatography and 3) the substitution was performed at room temperature. Oxidation to the sulfone was also carried out as previously described.



(S)-ethyl 2-methyl-2-(methylsulfonyloxy)-3-phenylpropanoate

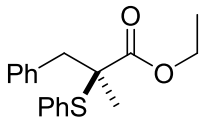
(**3.39 intA**)(JW5113)

73% Yield (Contains 5% MsCl)

Purification: Flash chromatography (90:10—80:20 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (q, *J* = 6.6 Hz, 3H, ArC*H*'s), 7.20 – 7.14 (m, 2H, ArC*H*'s), 4.18 (q, *J* = 7.2 Hz, 2H, ROCH_2CH$_3$), 3.65 (s, 0H, MsCl), 3.20 – 3.11 (m, 2H, PhCH_2(q)C), 3.09 (s, 3H, CH_3SO$_2$R), 1.75 (s, 3H, CH_3(q)C), 1.21 (t, *J* = 7.1 Hz, 3H, ROCH$_2$CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.80 (s), 134.05 (s), 130.63 (s), 128.47 (s), 127.66 (s), 89.14 (s), 62.22 (s), 52.73 (s, MsCl), 46.06 (s), 40.77 (s), 23.17 (s), 14.10 (s).



(S)-ethyl 2-methyl-3-phenyl-2-(phenylthio)propanoate

(**3.39 int B**)(JW5122)

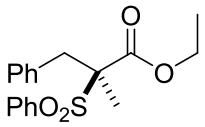
96% Yield, >99% ee

Purification: Flash chromatography (80:20 hexanes:DCM then 90:10 hexanes:ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 6.9 Hz, 2H), 7.39 (dt, *J* = 14.4, 5.9 Hz, 3H), 7.34 – 7.15 (m, 5H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.49 (d, *J* = 13.4 Hz, 1H), 2.95 (d, *J* = 13.4 Hz, 1H), 1.37 (s, 3H), 1.21 (t, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.90 (s, 1H), 137.25 (s, 5H), 136.74 (s, 1H), 131.21 (s, 1H), 130.63 (s, 5H), 129.67 (s, 3H), 128.87 (s, 6H), 128.35 (s, 5H), 127.06 (s, 3H), 61.33 (s, 2H), 55.59 (s, 2H), 44.58 (s, 3H), 22.45 (s, 3H), 14.21 (s, 3H).

Chiral HPLC Column: Chiracel Chiralpak-AD column. **Eluent:** 99:1 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** major R_t = 7.9 minutes, minor R_t = 8.3 minutes.



(S)-ethyl 2-methyl-3-phenyl-2-(phenylsulfonyl)propanoate

(**3.40**)(JW5131)

99% Yield, >97% ee

Purification: Flash chromatography (90:10—80:20 hexanes:ethyl acetate)

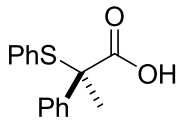
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.4 Hz, 2H, *o*-ArC*H*'sSO_2R), 7.68 (t, *J* = 7.5 Hz, 1H, *p*-ArC*H*SO_2R), 7.56 (t, *J* = 7.7 Hz, 2H, *m*-ArC*H*'sSO_2R), 7.24 – 7.18 (m, *J* = 7.1 Hz, 3H, ArC*H*'sCH_2R), 7.07 (d, *J* = 7.6 Hz, 2H, ArC*H*'sCH_2R), 4.09 (q, *J* = 7.1 Hz, 2H, ROCH_2R), 3.63 (d, *J* = 12.9 Hz, 1H, diastereotopic RC*H*HR), 3.05 (d, *J* = 13.0 Hz, 1H, RCH*H*R), 1.47 (s, 3H, qCCH_3), 1.15 (t, *J* = 7.1 Hz, 3H, RCH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.93 (R*C*O_2R), 136.00 (Ar*C*), 134.48 (Ar*C*), 134.42 (Ar*C*), 130.83 (Ar*C*'s), 130.53 (Ar*C*'s), 128.96 (Ar*C*'s), 128.70 (Ar*C*'s), 127.59 (Ar*C*), 73.97 (qC), 62.55 (RO*C*H_2R), 38.82 (Ph*C*H_2R), 16.29 (qC*C*H_3), 14.02 (RCH_2*C*H_3).

Chiral HPLC Column: Chiracel Chiralpak-OD-H column. **Eluent:** 90:10 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** minor R_t = 8.2 minutes, major R_t = 15.2 minutes.

Chiral resolution of 2-phenyl-2-(phenylthio)propanoic acid (3.43).[9] In a medium porosity fritted filter equipped with a screw valve and a 24/40 adapter was added a solution of the acid (27.3 mmol) in EtOH (9.1 mL), a solution of (*S*)-α-methyl benzyl amine (27.3 mmol) in EtOH (9.1 mL) and H_2O (18.2 mL). The contents were heated with a heat gun until everything went into solution. The whole apparatus was then cooled to 0 °C. After precipitation had ceased, the filter was fitted to a flask with a side arm and

the supernatant was filtered (the mother liquor was kept). The crystals were dried by aspiration and the mass of the crystals were obtained without removing from the filter (the tare weight had been recorded). Recrystallization was accomplished using 4.2 mL/g crystals (3:1 EtOH:H_2O). The solvent was added to the crystals directly on the filter and heated to reflux and then allowed to sit overnight and again dried by vacumm aspiration. The recrystallization procedure was repeated 5X and then the acid was reconstituted by extracting with ethyl acetate and washing with 3N HCl. The ee% was determined after esterification to the allyl ester and oxidation to the sulfone (**2.30**). **Chiral HPLC Column:** Chiracel Chiralpak-OD-H column. **Eluent:** 99:1 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** minor R_t = 24.4 minutes, major R_t = 27.5 minutes. This procedure afforded (*R*)-2-phenyl-2-(phenylthio)propanoic acid, in 97% ee and 6% yield.



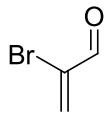
(R)-2-phenyl-2-(phenylthio)propanoic acid

(**3.43**)(JW4077)

6% yield, 97% ee

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.50 (m, 2H, ArC*H*'s), 7.43 – 7.30 (m, 5H, ArC*H*'s), 7.27 (dd, *J* = 12.2, 4.4 Hz, 3H, ArC*H*'s), 1.85 (s, 3H, CH_3(q)C).

Synthesis of α-bromo acrolein. To a stirring solution of acrolein (74.9 mmol) in DCM (100 mL) at °C was added Br_2 (84.9 mmol). The reaction was stirred for 15 minutes and then Et_3N (127 mmol) was added. The reaction was quenched by a saturated solution $NaHSO_3$, then ice was added and 3N HCl was added until acidic. The organic layer was dried with magnesium sulfate and passed through a silica plug. The solvent was removed *in vacuo*. The product is rather volatile and consequently difficult to remove all the solvent.



2-bromoacrylaldehyde

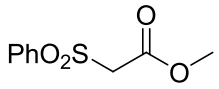
(**3.46**)(JW5232)

22% yield (contains some DCM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H, RC*H*O), 6.87 (d, *J* = 0.9 Hz, 2H, RCH_2), 5.26 (s, 0H, DCM).

^{13}C NMR (101 MHz, $CDCl_3$) δ 185.92 (s, R*C*HO), 136.99 (s, R*C*H_2), 132.65 (s, CH_2*C*BrCHO).

General procedure for Fischer esterification. To a solution of phenyl sulfonyl acetic acid (1.01 mmol) in MeOH (15 mL) was added H_2SO_4 (100 μL). The flask was fitted with a reflux condenser and the solution heated at reflux for 5 h. The reaction was concentrated and extracted with ethyl acetate and washed with H_2O, brine and dried with magnesium sulfate and concentrated no further purification was necessary.



methyl 2-(phenylsulfonyl)acetate

(Entry 1 from Table 3.1)(JW3024)

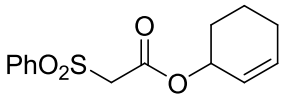
91% Yield

Purification: None.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.88 (m, 2H, ArC*H*'s), 7.68 (t, *J* = 7.4 Hz, 1H, ArC*H*), 7.57 (t, *J* = 7.7 Hz, 2H, ArC*H*'s), 4.11 (s, 2H, $PhSO_2CH_2CO_2CH_3$), 3.69 (s, 3H, RCO_2CH_3).

General procedure for DCC/DMAP esterification of sulfonyl esters. To a test tube equipped with a stir bar was added phenyl sulfonyl acetic acid (1.00 mmol) and cyclohex-2-enol (1.10 mmol) and DCM (2 mL) and in another tube DCC (1.00 mmol)

and DMAP (0.1 mmol) were added and dissolved in DCM (3 mL). The DCC/DMAP solution was pipetted into the acid/alcohol mix (typically the acid is not very soluble). Depending on the substitution pattern-more substitution of the alpha position of the acid leads to slower precipitation-precipitation occurs within a few minutes and stirring is continued overnight. However, the reaction can be accelerated by increasing the concentration (CAUTION! At higher concentrations such as 0.4M the reaction tends to exotherm but can be controlled by slow addition of the DCC/DMAP or cooling the reaction to 0 °C for the addition of DCC/DMAP and then warming to room temperature). The reaction mixture is filtered over a silica-plug and the filtrand is washed with copious amounts of DCM. Often no further purification was necessary but if traces of DCU are problematic it is easily removed via flash chromatography.



cyclohex-2-enyl 2-(phenylsulfonyl)acetate

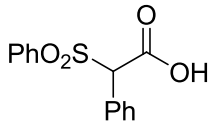
(Entry 2 from Table 3.2)(JW3127)

89% Yield

Purification: Flash chromatography (90:10—85:15 hexanes:ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 5.93 (d, *J* = 10.1 Hz, 1H), 5.57 (d, *J* = 10.0 Hz, 1H), 5.20 (s, 1H), 4.10 (s, *J* = 5.1 Hz, 2H), 2.10 – 1.83 (m, 2H), 1.81 – 1.68 (m, 1H), 1.67 – 1.49 (m, 3H).

General procedure for the carboxylation of phenyl benzyl sulfone (Table 3.4). To a flame dried Schlenk flask equipped with stir bar is added phenyl benzyl sulfone (4.31 mmol) and fitted with a septum and the atmosphere is exchanged for Ar (2X) and then THF (22 mL) is added. *n*BuLi (4.10 mmol) is added via syringe over 3 minutes. The reaction is then cooled to -78 °C and several pieces of dry ice (CO_2) (s) (~5g) were added all at once. The reaction was stirred for an additional hour. The reaction was extracted with cold H_2O and the aqueous layer was washed with Et_2O, acidified with 3N HCl and extracted with ethyl acetate. The acid was concentrated *in vacuo* and azeotroped with hexanes to afford the product 72%. No further purification was performed on this acid. This acid should be stored dry and in the freezer (no apparent breakdown after 6 months). However, slow ($t_{1/2}$=~1 month) decomposition on the bench was observed and the acid will rapidly undergo decarboxylation under basic conditions.



2-phenyl-2-(phenylsulfonyl)acetic acid

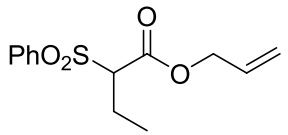
(Entry 8 from Table 3.4)(JW6165)

72% Yield

Purification: None.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 2H, ArC*H*'s), 7.42 (s, 1H, ArC*H*), 7.29 (s, 2H, ArC*H*'s), 5.12 (s, 1H, C*H*RRR), 1.54 (s, 1H, COO*H*).

General procedure for the mono alkylation of α-sulfonyl esters (Table 3.5). To a flame dried round bottom flask with stir bar was added allyl 2-(phenylsulfonyl)acetate (2.083 mmol) and dissolved in DMF (25 mL). The solution was cooled to 0 °C and NaH (2.292) was added and the reaction was stirred for 15 minutes. Then EtI (2.083 mmol) was added and the reaction was allowed to slowly warm to room temperature. The reaction was extracted with a copious volume of ethyl acetate and washed with water (4X) the organic layer was dried with magnesium sulfate and concentrated *in vacuo* and purified via flash chromatography to afford the mono alkylated product in 62% yield. The mass balance in this reaction was unreacted starting material. It is typically difficult to prevent some overalkylation from occurring and difficult to separate the compounds.



allyl 2-(phenylsulfonyl)butanoates

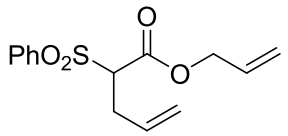
(Entry 7 from Table 3.5)(JW2300)

62% Yield

Purification: Flash chromatography (90:10—80:20 hexanes:ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.71 – 7.61 (m, 1H), 7.53 (dd, *J* = 10.6, 4.8 Hz, 2H), 5.75 (ddt, *J* = 16.3, 10.4, 5.9 Hz, 1H), 5.31 – 5.15 (m, 2H), 4.63 – 4.46 (m, 2H), 3.87 (dd, *J* = 11.2, 3.9 Hz, 1H), 2.14 – 2.03 (m, 1H), 2.01 – 1.87 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H).

Adaptation to the general procedure for the mono alkylation of α-sulfonyl esters. K_2CO_3 is a competent base and if the base and solvent were thoroughly dried this woul likely be the best way to mono alkylate. To a flame dried round bottom flask with stir bar was added allyl 2-(phenylsulfonyl)acetate (0.379 mmol) and dissolved in DMF (3.8 mL). To the solution at room temperature was K_2CO_3 (2.275) and then allyl bromide (0.432 mmol) and the reaction was stirred overnight. The reaction was extracted with a copious volume of ethyl acetate and washed with water (4X) the organic layer was dried with magnesium sulfate and concentrated *in vacuo* and purified via flash chromatography to afford the mono alkylated product in 84% yield.



allyl 2-(phenylsulfonyl)pent-4-enoate

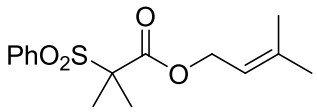
(Entry 11 from Table 3.5)(JW3064)

84% Yield (Contains ~25% diallylated)

Purification: Flash chromatography (50:50 hexanes:DCM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.78 (m, 2H), 7.73 – 7.61 (m, 1H), 7.53 (dt, *J* = 13.2, 7.7 Hz, 2H), 5.92 – 5.57 (m, 2H), 5.32 – 5.02 (m, 5H), 4.60 – 4.43 (m, 2H), 4.01 (dd, *J* = 11.4, 3.9 Hz, 1H), 3.00 – 2.56 (m, 3H).

General procedure for exhaustive alkylation of α-mono or unsubstituted α-sulfonyl esters. To a flame dried tube with stir bar was added 3-methylbut-2-enyl 2-(phenylsulfonyl)acetate (5.0 mmol), thoroughly dried K_2CO_3 (25 mmol), **dry** DMF (17 mL) and iodomethane (30 mL). The hetrogenous mixure was stirred rapidly overnight. The reaction was extracted with ethyl acetate (70 mL) and washed with H_2O (4X), and brine then it was dried with magnesium sulfate and concentrated *in vacuo*. The oil was purified by flash chromatography to afford the dimethylated sulfonyl ester in at least 93% yield (isolated yield for the esterification was not obtained).



3-methylbut-2-enyl 2-methyl-2-(phenylsulfonyl)propanoate

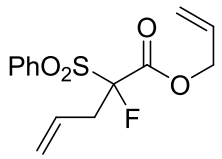
(Entry 5 from Table 3.7)(JW6259)

>93% Yield

Purification: Flash chromatography (80:20 hexanes:ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.69 (m, 2H, ArC*H*'s), 7.61 – 7.51 (m, 1H, ArC*H*), 7.48 – 7.37 (m, 2H, ArC*H*'s), 5.10 (tdd, *J* = 5.9, 2.8, 1.4 Hz, 1H, $ROCH_2CHR$), 4.44 (d, *J* = 7.3 Hz, 2H, $ROCH_2CHR$), 1.65 (d, *J* = 10.7 Hz, 3H, $RC(CH_3)_2$), 1.56 (s, 3H, $RC(CH_3)_2$).

General procedure for the fluorination of α-sulfonyl esters. This prep was adapted from a known fluorination method.[10] To a solution of allyl 2-(phenylsulfonyl)pent-4-enoate (0.729 mmol) in THF (7.3 mL) at -78 °C was added NaH (0.911 mmol). The reaction was warmed to room temperature and then cooled to 0 °C and selectfluor (1.094 mmol) and DMF (4.4 mL) were added. After 2 h the reaction was quenched with NH_4Cl (aq) and the reaction was extracted with ethyl acetate and washed with brine and dried with magnesium sulfate and concentrated *in vacuo*. The resulting residue was purified by flash chromatography.



Allyl 2-fluoro-2-(phenylsulfonyl)pent-4-enoate

(**3.49**) (JW3050)

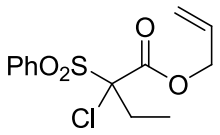
42% Yield

Purification: Flash chromatoghaphy (90:10 hexanes:Et_2O)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 2H), 5.83 – 5.70 (m, 1H), 5.70 – 5.60 (m, 1H), 5.37 – 5.18 (m, 4H), 4.59 (dd, *J* = 7.2, 5.9 Hz, 2H), 3.23 (dd, *J* = 36.8, 8.0 Hz, 1H), 2.94 (s, 1H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -157.94 (dd, *J* = 36.7, 10.6 Hz, 1H).

General procedure for the chlorination of α-sulfonyl acetic esters. In a Schlenk tube allyl 2-(phenylsulfonyl)butanoates (0.190 mmol) is dissolved in THF (2 mL) and cooled to 0 °C. NaH (0.190 mmol) was added and the reaction was allowed to stir for 15 minutes then NCS (0.190 mmol) was added and the reaction was allowed to slowly warm up overnight. The reaction was concentrated and directly purified by flash chromatography to afford the desired product in 70% yield. Alternatively, K_2CO_3 can be used rather than NaH and seem to give superior yields.



allyl 2-chloro-2-(phenylsulfonyl)butanoate

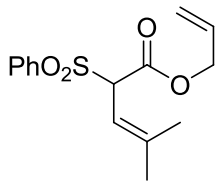
(Entry 5 from Table 3.8)(JW3144)

70% Yield

Purification: Flash chromatoghaphy (85:15 hexanes:ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.87 (m, 2H, ArC*H*'s), 7.69 (t, *J* = 7.5 Hz, 1H, ArC*H*), 7.54 (t, *J* = 7.9 Hz, 2H, ArC*H*'s), 5.82 (ddd, *J* = 16.3, 11.0, 5.8 Hz, 1H, $ROCH_2CHCH_2$), 5.40 – 5.21 (m, 2H, $ROCH_2CHCH_2$), 4.71 – 4.56 (m, 2H, $ROCH_2CHCH_2$), 2.77 (dq, *J* = 14.2, 7.2 Hz, 1H, CH_3CHH(q)C), 2.19 (ddd, *J* = 19.4, 13.3, 6.1 Hz, 1H, CH_3CHH(q)C), 1.07 (t, *J* = 7.2 Hz, 3H, CH_3CHH(q)C).

General procedure for the Knoevenagel condensation of α-sulfonyl acetic esters.[11]
In a 100 mL roundbottom flask equipped with stir bar was placed allyl 2-(phenylsulfonyl)acetate (2.083 mol) and isobutyraldehyde (3.125 mmol) and toluene (40 mL) the flask was fitted with a Dean-Stark trap and the condenser and the reaction was refluxed for 5 h. After 5 h the reaction was cooled and without any workup the reaction was loaded onto the column and purified via flash chromatography to afford a mix of regioisomeric products in a 97% yield.



allyl 4-methyl-2-(phenylsulfonyl)pent-3-enoate

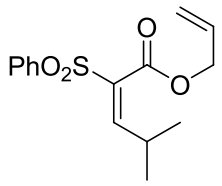
(**3.55**)(JW6129)

97% Yield(5:1 **allyl**:vinyl)

Purification: Flash chromatoghaphy (90:10—80:10 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.8 Hz, 2H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 5.80 (ddd, *J* = 22.8, 11.0, 5.8 Hz, 1H), 5.34 – 5.17 (m, 3H), 4.77 (d, *J* = 10.4 Hz, 1H), 4.57 (d, *J* = 5.8 Hz, 2H), 1.73 (s, 3H), 1.48 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.94 (s, 1H), 144.56 (s, 1H), 137.39 (s, 1H), 134.26 (s, 1H), 131.14 (s, 1H), 129.69 (s, 1H), 129.00 (s, 1H), 119.38 (s, 1H), 112.02 (s, 1H), 70.55 (s, 1H), 66.89 (s, 1H), 26.15 (s, 1H), 18.58 (s, 1H).



(E)-allyl 4-methyl-2-(phenylsulfonyl)pent-2-enoate

(**3.56**) (JW6129)

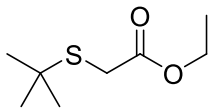
97% Yield(5:1 allyl:**vinyl**)

>20:1 E/Z E suspected major

Purification: Flash chromatoghaphy (90:10—80:10 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 10.4 Hz, 1H), 5.75 (ddd, *J* = 16.3, 11.1, 5.9 Hz, 1H), 5.27 – 5.15 (m, 2H), 4.57 (dd, *J* = 5.9, 1.2 Hz, 2H), 3.16 (qd, *J* = 13.2, 6.6 Hz, 1H), 1.18 – 1.05 (m, 6H).

Procedure for the substitution of ethyl bromo acetate with *t*BuSH. To a flame dried Schlenk tube with stir bar was added ethyl bromo acetate (1.0 mmol). The *t*BuSNa salt was made in a separate tube by dissolving *t*BuSH (1.1 mmol) in EtOH and slowly (CAUTION! This is rather dangerous and should not be performed on a large scale due to the risks associated with the procedure) NaH (1.0 mmol) was added. Once evolution of H_2 had ceased the solution was transferred to the flask containing the bromide. Reaction was complete within 5 h and was extracted with ethyl acetate and washed with H_2O, dried with magnesium sulfate and concentrated *in vacuo*. No further purification was necessary.



Ethyl 2-(tert-butylthio)acetate

(**3.61**) (JW5185)

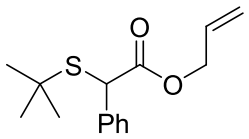
95% Yield

Purification: None.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 – 3.98 (m, 2H, ROCH_2CH$_3$), 3.22 (dd, *J* = 10.4, 5.6 Hz, 2H, RSCH_2CO$_2$R), 1.36 – 1.17 (m, 12H, (CH_3)$_3$CSR and ROCH$_2$CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.35 (s, R*C*O$_2$R), 61.48 (s, RO*C*H$_2$CH$_3$), 43.17 (s, RS*C*H$_2$CO$_2$R), 31.58 (s, (q)*C*SR), 30.80 (s, (*C*H$_3$)$_3$CSR), 14.25 (s, ROCH$_2$*C*H$_3$).

Synthesis of allyl 2-(tert-butylthio)-2-phenylacetate (From Table 3.9). In a Schlenk tube under an atmosphere of Ar allyl 2-bromo-2-phenylacetate (2.0 mmol) and *t*BuSH, and Et_3N (0.5 mL) and $CHCl_3$ (0.5 mL) were mixed at room temperature overnight. The resulting gelatinous mixture was extracted with ethyl acetate and washed with HCl (2X), brine, and dried with magnesium sulfate and concentrated *in vacuo*. No further purification was needed.



allyl 2-(tert-butylthio)-2-phenylacetate

(Entry 8 from Table 3.9)(JW5202)

95% Yield (unknown contaminant)

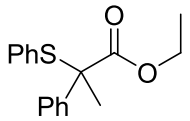
Purification: None.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.0 Hz, 0H), 7.37 – 7.18 (m, 5H), 5.96 – 5.80 (m, 1H), 5.32 – 5.14 (m, 2H), 4.59 (t, *J* = 7.4 Hz, 2H), 3.64 (s, 2H), 1.31 (d, *J* = 9.8 Hz, 16H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.42 (s, 1H), 134.11 (s, 1H), 132.20 (s, 1H), 129.47 (s, 1H), 128.81 (d, *J* = 7.9 Hz, 1H), 128.55 (s, 1H), 128.09 (s, 1H), 127.31 (s, 1H), 118.43 (s, 1H), 66.29 (s, 1H), 65.65 (s, 1H), 50.22 (s, 1H), 46.35 (s, 1H), 45.01 (s, 1H), 41.51 (s, 1H), 31.13 (s, 1H), 30.76 (s, 1H).

Synthesis of ethyl 2-phenyl-2-(phenylthio)propanoate. To a flame dried flask equipped with stir bar was added phenyl thiol (50.0 mmol) and Et_3N (17.9 mL) and $CHCl_3$ (90 mL) and *then* ethyl 2-bromo-2-phenylpropanoate (39.1 mmol). The reaction was stoppered and stirred overnight at room temperature. The reaction was extracted with ethyl acetate and washed with 3N HCl (2X), bicarb, brine, and dried with

magnesium sulfate, and concentrated *in vacuo*. The remaining oil was azeotroped several times with $CHCl_3$ to remove traces of PhSH to afford the sulfide ester in 96% yield.



ethyl 2-phenyl-2-(phenylthio)propanoate

(**3.68**)(JW4039)

Yield 99%

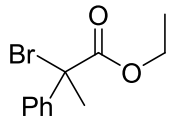
Purification: Flash chromatography (95:5 hexanes:isopropanol)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 2H), 7.50 – 7.32 (m, 8H), 4.33 (tdd, *J* = 10.7, 7.1, 3.6 Hz, 2H), 1.95 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.96 (s, 1H), 141.13 (s, 1H), 136.86 (s, 1H), 131.79 (s, 1H), 129.32 (s, 1H), 128.68 (s, 1H), 128.37 (s, 1H), 127.73 (s, 1H), 127.27 (s, 1H), 62.02 (s, 1H), 59.90 (s, 1H), 25.64 (s, 1H), 14.18 (s, 1H).

General procedure for the bromination of α-aryl propanoate esters. To a flask equipped with stir bar ethyl 2-phenylpropanoate (73.9 mmol), NBS (125.7 mmol) amd

CCl_4 (74 mL) and Br_2 (0.15 mL). The reaction had reached completion within 4h. The reaction was concentrated *in vacuo* (CAUTION! Reaction produces bromine gas and vapor must be safely vented). The residue was extracted with Et_2O and washed with H_2O, dried and concentrated to afford the bromide in 95% yield with a trace contaminant of succinimide and NBS (~2% and 1%).



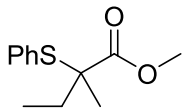
Ethyl 2-bromo-2-phenylpropanoate

(**3.67**)(JW4069)

95% Yield (~2% cont. Succinimide and NBS)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.35 (dt, *J* = 14.4, 8.4 Hz, 3H), 4.29 (td, *J* = 7.1, 4.6 Hz, 2H), 2.98 (s, 0H), 2.79 (s, 0H), 2.32 (d, *J* = 1.2 Hz, 3H), 1.30 (td, *J* = 7.1, 1.2 Hz, 3H).

General procedure for the substitution of α-dialkyl α-bromo acetic esters. In a Schlenk with stir bar was added PhSH (5.56 mmol), Et_3N (2.5 mL) and DMF (25 mL) *then* methyl 2-bromo-2-methylbutanoate (5.052 mmol). The reaction was heated at 110 °C for 3 h. The reaction was extracted with copious amounts of ethyl acetate and washed with H_2O, HCl, brine, dried and concentrated to afford the α-thio ester in an 88% yield.



Methyl 2-methyl-2-(phenylthio)butanoates

(**3.72**)(JW4117)

Yield 88%

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 26.8, 7.2 Hz, 2H), 7.42 – 7.30 (m, 3H), 3.69 (s, 3H), 1.99 (dd, *J* = 13.9, 7.3 Hz, 1H), 1.74 (dd, *J* = 14.0, 7.2 Hz, 1H), 1.43 (s, 3H), 0.98 (t, *J* = 7.4 Hz, 3H).

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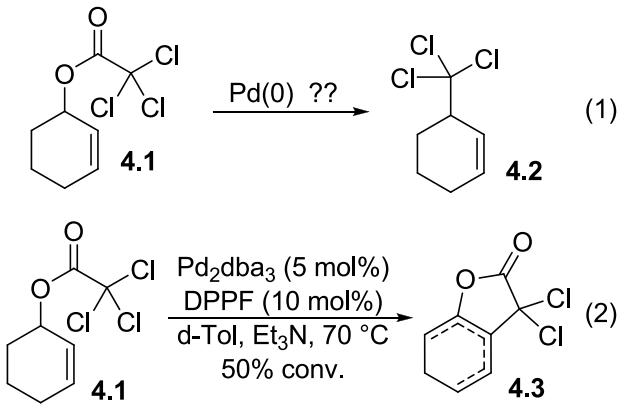
Chapter 4

Odds and Ends

And things you should've learned in school had you been paying attention

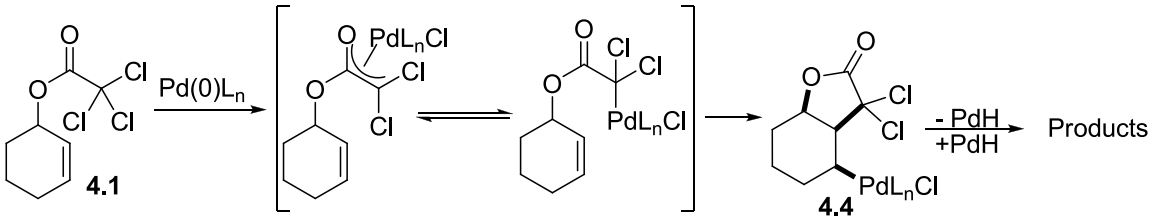
Attempted DCA of trichloromethyl allyl acetates

The trichloromethyl group is a useful functional group as it can readily be hydrolyzed to a carboxylic acid. We thought that we might be able to generate the trichloro methyl anion via decarboxylation of the corresponding allyl acetates which then would subsequently undergo attack of the Pd-allyl complex to generate trichloromethyl alkanes. We believed that this could be a convenient method for accessing such substrates (eq. 1, Scheme 4.1). Interestingly when cyclohexenyl trichloro acetate was subjected to Pd(0) sources we did not see typical products of decarboxylation but rather, new olefinic signals in the crude ^{1}H NMR spectra suggested products of a Heck reaction. We thought this was an interesting product and tried with a few catalyst and solvents the best result (eq. 2) gave only 50% conversion to a mix of regioisomeric products as determined by crude ^{1}H NMR spectra (the products were not stable to chromatography). In addition, the catalyst was very prone to crash out of solution under our reaction conditions.



Scheme 4.1

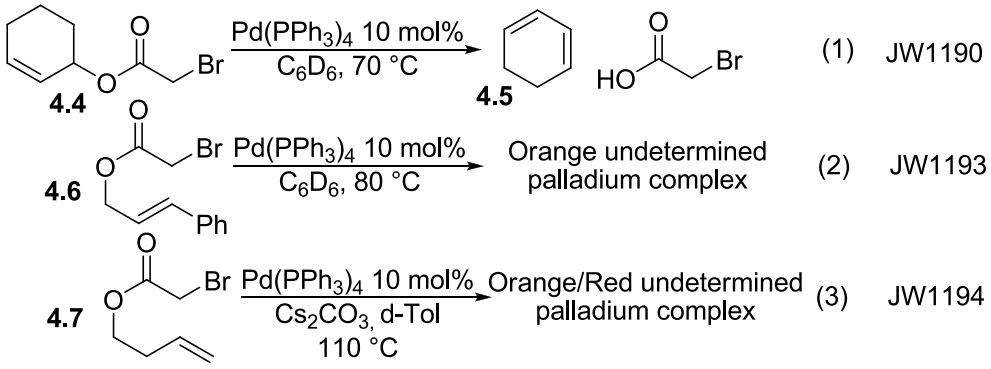
One potential mechanism that might explain the products is shown in Scheme 4.2. Rather than ionization of the allyl acetate, as hoped, the electron rich Pd(0) undergoes oxidative insertion to form the Pd-enolate. The C-bound Pd-enolate could then undergo *syn*-migratory insertion into the olefin generating a new C-bound Pd species (**4.4**). This intermediate would undergo a series of βHE's and reinsertion of the Pd-H's to form the mix of observed products.



Scheme 4.2

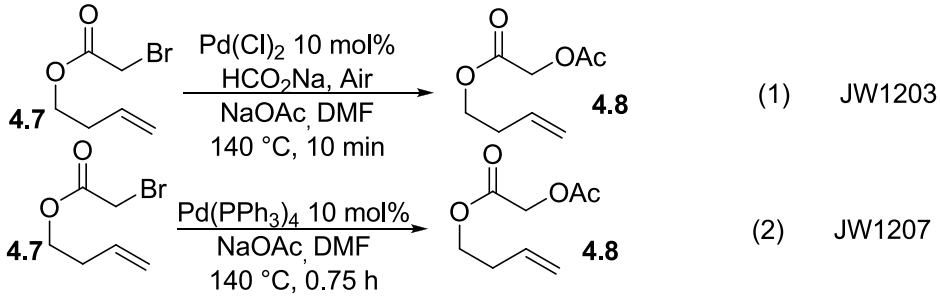
Curious whether any Pd-enolate would undergo a Heck reaction to an olefin that was favorably tethered we changed to a substrate that could be handled easier. Ester, **4.4**, (Scheme 4.3) was synthesized from cyclohexenyl alcohol and α-bromo acetic acid and was subjected to the reaction conditions. The only product we observed by monitoring the reaction by ^{1}H NMR spectroscopy was the formation of cyclohexadiene (**4.5**, eq. 1). We next simplified the problem by changing to a substrate that did not contain β-hydrogens, **4.6**, and subjecting it to Pd(0) (eq. 2). Interestingly, the catalyst formed an orange complex, presumably with the substrate; unfortunately, no characterization of the complex was obtained. We further reduced the complexity of the reaction by removing the ability to ionize the ester (eq. 3). Again a colored, insoluble complex formed. We felt it was probable that oxidative insertion into the C-Br bond was occurring but the

Heck reaction did not seem facile so we began to look at other potential reactions of Pd-enolates.



Scheme 4.3

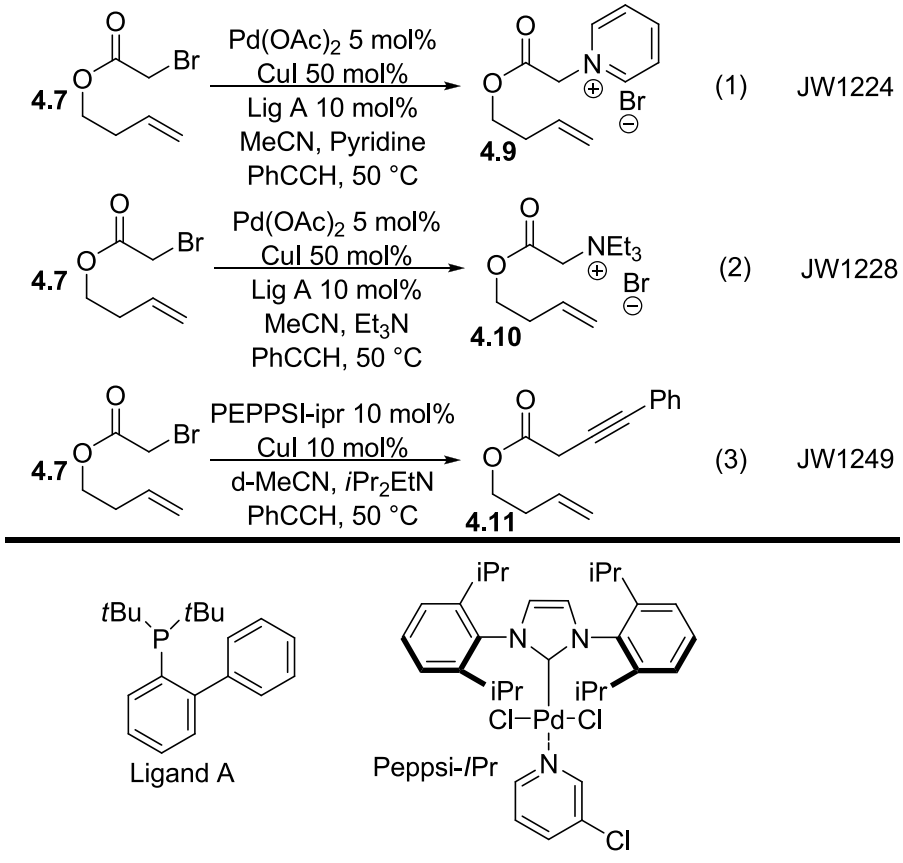
A search of the literature revealed ligand free-Heck conditions.[1] We applied this to our substrate (Scheme 4.4); the substrate (**4.7**) at these temperatures undergoes substitution to provide the α-acetoxy esters despite the presence of the formate salt. We did not do the control reaction to be able to say definitively but the substitution is likely uncatalyzed.



Scheme 4.4

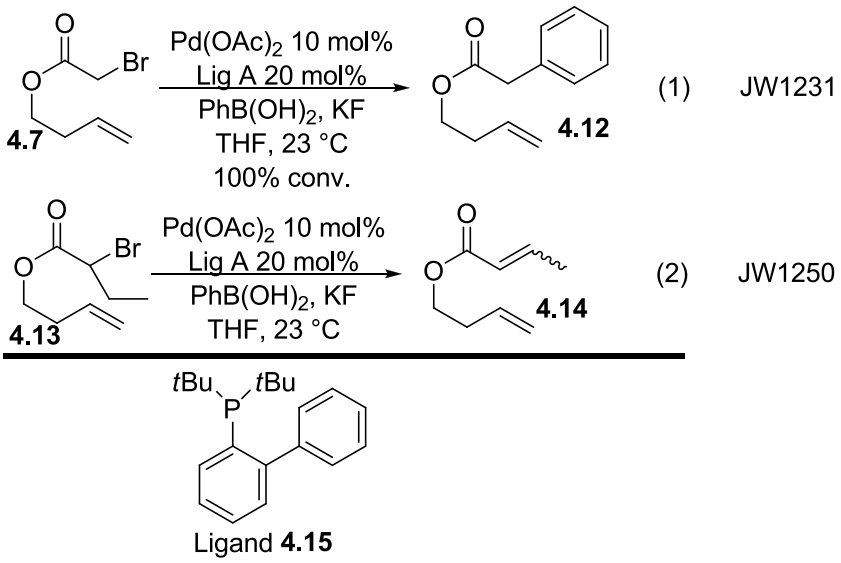
We next looked at the possibility to perform a Sonagoshira reaction on the α-bromo esters. Using typical Sonagashira conditions we found that when pyridine was

used as the base the α-pyridinium salt (**4.9**) was formed (eq. 1, Scheme 4.5). Switching to a more hindered base, Et_3N (eq. 2), also gave the corresponding ammonium salt (**4.10**)(even iPr_2EtN underwent substitution-not shown). However, when the catalyst was changed to the PEPPSI-ipr (eq. 3) the disappearance of the starting material to form a new ester in the ^1H NMR spectrum of the crude reaction mixture is suggestive of a coupled product. However, this reaction was never scaled up or isolated but certainly warrants more experimentation. A search of the literature has not revealed any reports of this type of transformation.



Scheme 4.5

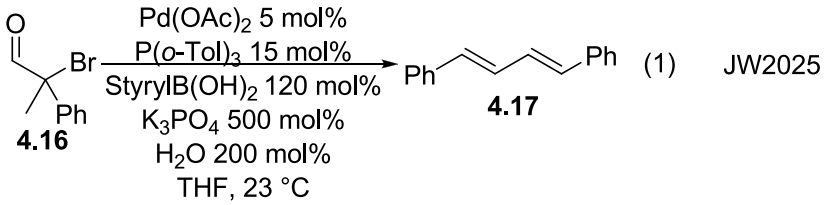
We also investigated Suzuki couplings of the α-bromo ester (Scheme 4.6). We were successful and had spent a significant amount effort optimizing conditions and had begun to test the reaction scope before we found a report by Lucas Goossen[2] in which very similar conditions had already been reported for the transformation. As a side note this paper is difficult to find because it is incorrectly listed in SciFinder. In the report, substrates were limited to α-bromo acetates. We attempted the chemistry on a secondary bromide (**4.13**) some elimination (**4.14**) was observed but no cross-coupled product was observed.



Scheme 4.6

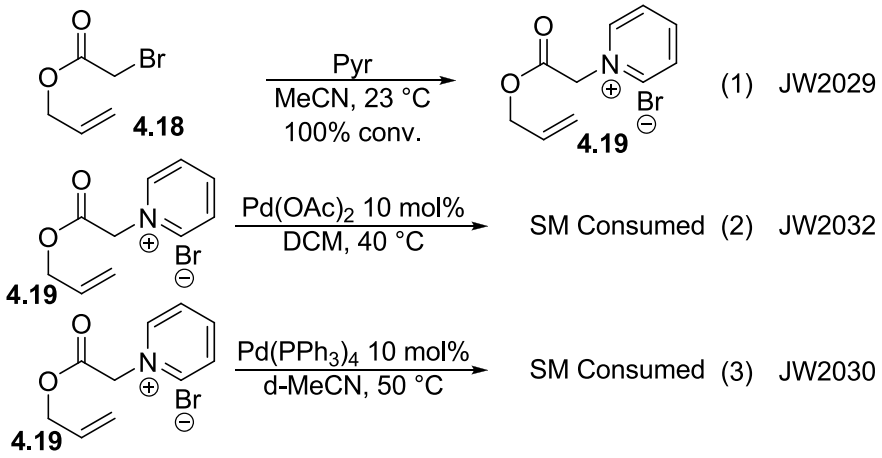
To date, there have been no reports demonstrating the analogous Suzuki type of coupling for α-bromo aldehydes. Aldehyde enolates are notoriously difficult to handle in part because their inherent electrophilicity makes homo-coupling problematic. We thought it would be valuable if this type of Suzuki coupling were to work for aldehydes circumventing the problems associated with enolate chemistry. The simplest aldehyde

analog is not widely available and thus α-phenyl α-bromo propanaldehyde (**4.16**) was used (Scheme 4.7). While this took care of some of the handling issues it also significantly changed the nature of the substrate, so it is not surprising that the only product isolated was a dimerization product (**4.17**) of the boronic acid.[3]



Scheme 4.7

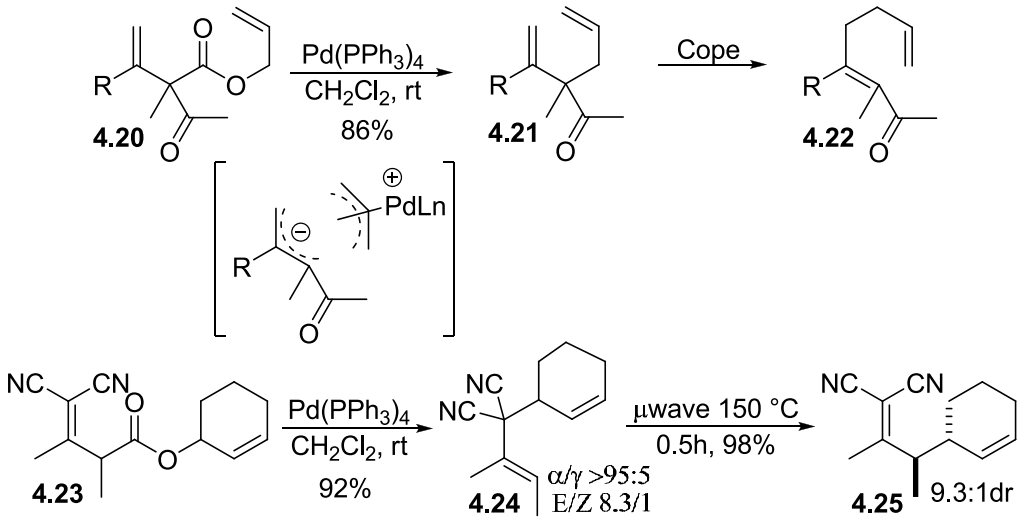
In the course of our investigations into α-functionalization we became curious how α-pyridinium allyl esters would behave (Scheme 4.8). We suspected that pyridinium formation that we had seen previously (Scheme 4.5) was not Pd-catalyzed. Indeed, we found that the pyridinium salt (**4.19**) could be cleanly and simply formed in CH_3CN (eq. 1, Scheme 4.8). After removal of the solvent we subjected the salt to two different Pd-catalysts (eq 2 and 3) and in both cases the starting material was consumed. Unfortunately, no more speculation can really be made as to the outcome of these reactions as no clean products were isolated from these reactions. It is quite possible that new salts were formed and potentially a functionalized carboxylic acid. However, this is a peculiar system and it is not clear how it will react and thus warrants more investigation.



Scheme 4.8

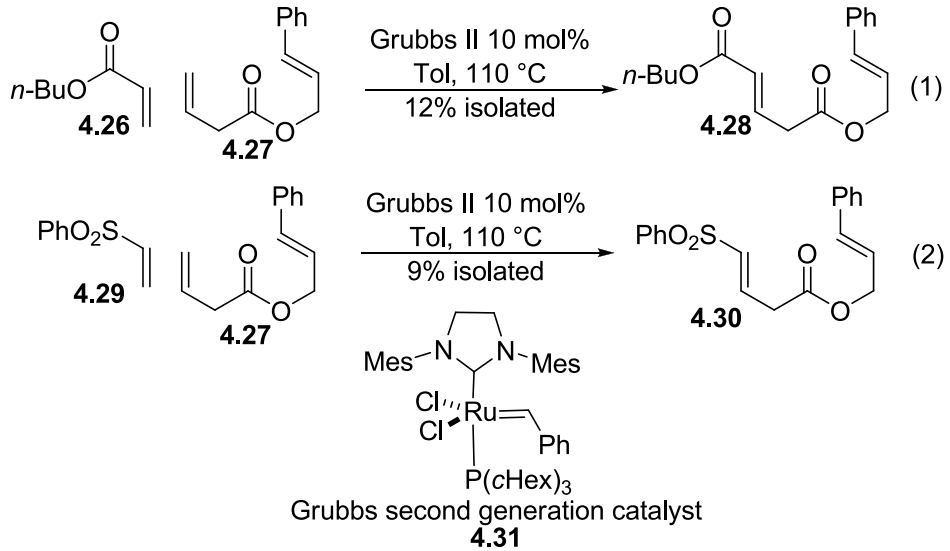
Allylic Stabilization

In 2006, Tunge and Waetzig[4] demonstrated the electron withdrawing group need not be α-to the ester, but could also be γ-to the ester if the two groups were vinylogously connected (Scheme 4.9). Furthermore, in this work they demonstrate that α-allylation is the kinetic product (**4.21** and **4.24**). This is particularly useful as it allows for the selective synthesis of both regioisomers; the thermodynamic isomers (**4.22** and **4.25**) can be accessed via a Cope rearrangement. The malononitriles were a convenient choice since they were readily synthesized from the corresponding β-keto ester. We believed this vinylogous-DCA might be extended to other substrates with only one stabilizing group if we could make the starting materials.



Scheme 4.9

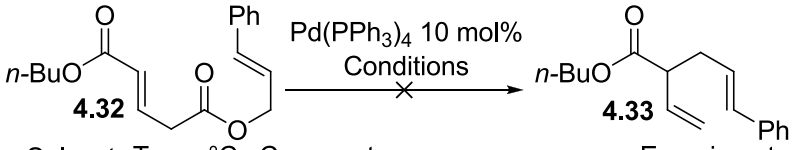
To begin our investigation into the mono-stabilized vinylogous DCA we first synthesized a couple of substrates (Scheme 4.10). We thought cross-metathesis might be a facile method for the synthesis but this proved rather difficult. Nonetheless, a small amount of substrate was made, the vinylogous ester (**4.28**, eq. 1) and the vinylogous sulfone (**4.30**, eq. 2). With these substrates we probed mono-stabilized vinylogous DCA.



Scheme 4.10

To begin, we subjected the vinylogous ester **4.28** to a catalytic amount of palladium in several solvents (Table 4.1). Use of DCM seemed to generate new vinyl signals in the ^{1}H NMR spectrum of the reaction mixture, after solvent exchange, however, it appeared that some allyl ester still existed so it is likely that decarboxylation was not occurring. However, when THF was used as the solvent then the allyl ester, the OC*H*$_2$R of **4.28** was absent, suggesting that decarboxylation was occurring, but it resulted in a complex mixture of products. In Et_2O no reaction occurred based on the ^{1}H NMR spectrum of the crude reaction mixture.

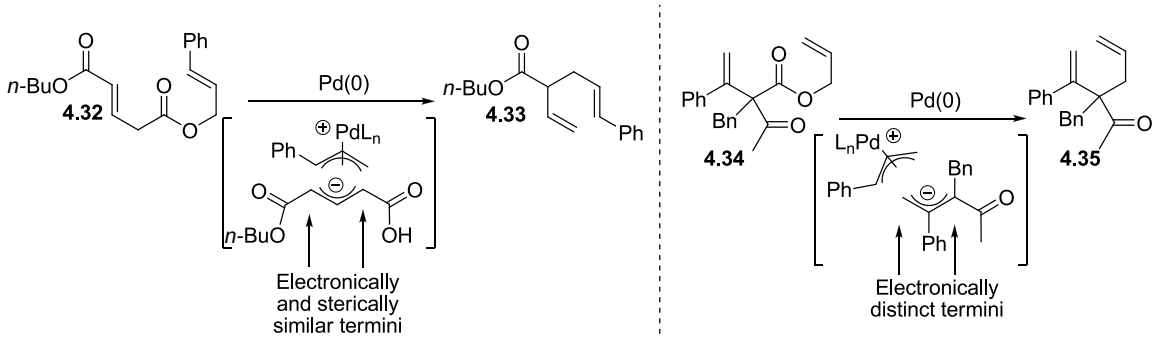
Table 4.1 Attempted Vinylogous-DCA of Diester



Entry	Solvent	Temp °C	Comments	Experiment
(1)	DCM	23	Possible isomerization	JW2058
(2)	THF	23	Complete consumption, messy	JW2059
(3)	Et_2O	23	No reaction	JW2060

When the diester substrate did react (Table 4.1) it provided a mixture of products. This is could be understood if the reaction is taking place through an intermediate in which proton transfer to the carboxylate occurs prior to decarboxylation (Scheme 4.11). Proton transfer would generate a nucleophile that is distabilized, with the stabilizing groups at both termini leading to a nucleophile that is not selective. A careful examination of the substrates in the hexadiene synthesis[4] (Scheme 4.9) reveals that it is required to undergo decarboxylation prior to allylation and the termini of the intermediate anion formed, in going from **4.34** to **4.35**, are electronically distinct. There is certainly

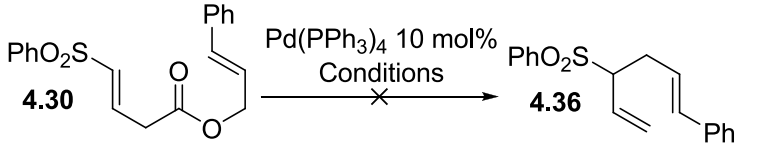
promise in this reaction and a more refined choice of substrate-in which intermediates were more prone to react via a single path, would likely lead to synthetically useful reaction.



Scheme 4.11

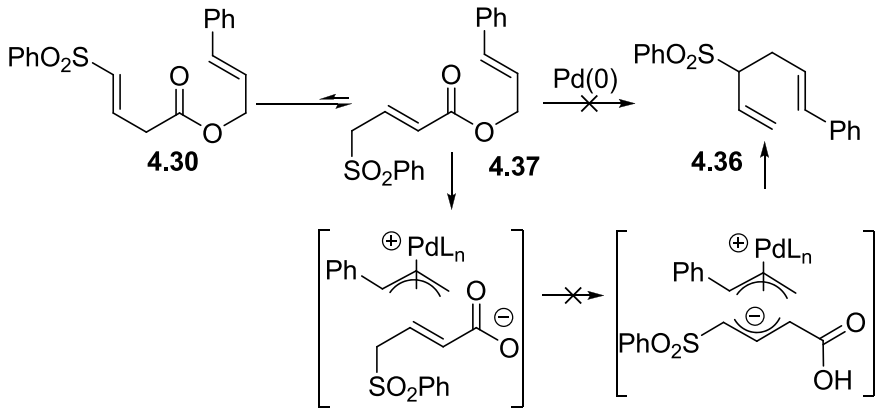
We also looked the Pd-cat. vinylogous sulfonyl ester (**4.30**, Table 4.2) but even at elevated temperatures (entry 1) in several different solvents this substrate seemed unreactive (entries 1-3). Looking back, this seems rather odd given all that we have learned concerning the decarboxylation of sulfonyl esters.

Table 4.2 Attempted Vinylogous-DCA of Sulfonyl Ester



Entry	Solvent	Temp °C	Comments	Experiment
(1)	d-Tol	23-110	No reaction, no isomerization	JW2068
(2)	DCM	23	No reaction, no isomerization	JW2069
(3)	THF	23-40	Mostly starting material, no desired product	JW2070

One hypothesis that might explain the observed lack of reaction assumes that the starting material was misassigned. Given the propensity of the sulfone to isomerize out of conjugation and the tendency of the ester to isomerize into conjugation, it seems quite possible that the isolated product from the cross-metathesis was actually the isomerized product and was in fact the actual starting material subjected to Pd-catalysis. There is some evidence from our own work that the carboxylate is not a sufficient base to facilitate the proton exchange from the γ-position of an α,β-unsaturated sulfonyl ester.

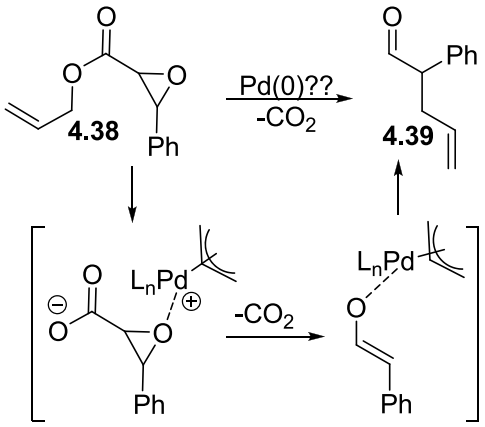


Scheme 4.12

α-Allylated Aldehydes

The synthesis of α-allylated aldehydes via deprotonation of an aldehyde and attack of an allyl electrophile doesn't work well and there are no reports of DCA of β-aldehydic esters. Both of these methods are difficult because the inherent electrophilicity of the aldehyde creates several compatibility issues. However, the products of α-allylated aldehydes have been made via enamine allylation and hydrolysis of the iminium to reveal the aldehyde product.[5] We became curious if α-allylated products could be accessible via a decarboxylative epoxide opening and tandem allylation (Scheme 4.13).

We believed that this experiment was worth investigating since it would 1) provide access to the homoallylic aldehydes via a new route and 2) could open a new type of decarboxylative reactivity (ring opening vs. anion formation).

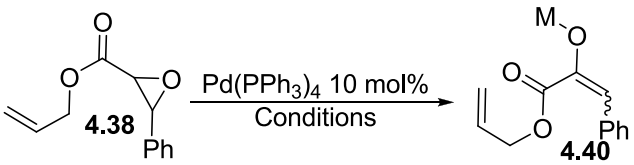


Scheme 4.13

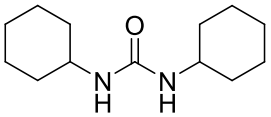
Initially, we subjected the epoxy ester (**4.38**) to a catalytic amount of $Pd(PPh_3)_4$ but this resulted in no change of the starting material, even at elevated temperature (entries 1 and 2, Table 4.3). However, when reaction was performed on substrate that was contaminated with dicyclohexyl urea from the coupling, the starting material was consumed, although the desired product could not be detected (entries 3,4). Believing that perhaps the consumption of the ester was catalyzed by hydrogen-bonding with the DCU we tried the reaction with simple urea (entries 5 and 6). The reaction was much slower (entry 5) but did seem to consume the ester (entry 6). Perhaps the reduction in rate was due to the decreased solubility of urea, compared to DCU. Regardless, the desired product was never detected. This made us think that the opening of the ring might be facilitated by the use of a Lewis-acid, thus we began screening using 1.1 equivalents of various Lewis-acids. $Ti(iOPr)_4$ led to clean transesterification of the ester

to the isopropyl ester (entry 7). While the use of $SnCl_4$ cleanly led to what is most likely the tin enolate of a single geometry (entry 8). While it was not our desire to form the tin enolate, the ability to form a trisubstituted metal enolate as a single isomer could be very useful methodology. The fact that it did not go on to react with the Pd-allyl suggest that there was no Pd-allyl present. It is possible that the $SnCl_4$ had a detrimental effect on the stability of the Pd(0) catalyst. However, when we attempted to scale this reaction and isolate something definitive several products were formed and none that resembled what was seen on the NMR-scale. This is not surprising that a reactive enolate might be difficult to isolate. When we used $TiCl_4$, only consumption of the starting material was observed the ^1H NMR spectrum after solvent exchange was conspicuously absent of anything containing an allyl fragment (entry 9). However, use Y_2O_3 seemed to give a small but clean conversion to a C-allylated product (entry 10). Use of $ZrCl_4$ gave complete consumption of the starting material but gave multiple signals consistent with O-allyl -potentially E/Z isomers of the zirconium enolate (entry 11). Interestingly, when the more soluble zirconium (IV) was used no reaction took place (entry 12). Use of scandium (III) hexafluoroacenato led to an indiscernible mess (entry 13). Use of BF_3*Et_2O led to complete consumption of the starting material and provided both O-allyl and some type of ill-defined C-allyl products (entry 14). Use of CuOAc (entry 15) simply led to transesterification to give allyl acetate. Use of TMSOTf led to the silyl enol ether in a 1:1 *cis/trans* mix of isomers. While we were able to open the ring it appears this usually occurred with loss of the α-proton and not decarboxylation from the Pd-carboxylate.

Table 4.3 Attempted Decarboxylative Ring Opening/Allylation



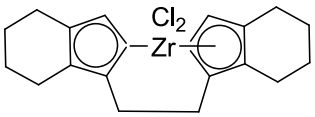
Entry	Solvent	Temp °C	Additive	Conv.	Comments	Experiment
(1)	d-Tol	23-110	–	0	No reaction	JW3192
(2)	DCM	40	–	0	No reaction	JW3200
(3)	d-Tol	23	DCU	100	Starting material consumed, unknown pdt	JW3189
(4)	d-DCM	40	DCU	100	Starting material consumed, unknown pdt	JW3190
(5)	d-DCM	40	urea	<10	Mostly unreacted	JW3206
(6)	d-Tol	110	urea	100	Only aromatic signals	JW3207
(7)	DCM	40	$Ti(OiPr)_4$	100	Transesterified starting material	JW3210
(8)	DCM	40	$SnCl_4$	100	Clean tin enolate	JW3211
(9)	DCM	40	$TiCl_4$	100	Complete consumption of starting material, unclear	JW3212
(10)	DCM	40	Y_2O_3	15	C-allyl	JW3213
(11)	DCM	40	$ZrCl_4$	100	Multiple O-allyl	JW3214
(12)	DCM	40	$ZrCl_2L$	0	No reaction	JW3217
(13)	DCM	40	ScX_3	--	undiscernable	JW3215
(14)	DCM	40	BF_3*Et_2O	100	O-allyl, C-allyl	JW3218
(15)	DCM	40	CuOAc	60	Allyl acetate	JW3219
(16)	DCM	40	TMSOTf	100	O-allyl *c/t* 1.1	JW3220



DCU **4.41**

$Sc(C_5HF_6O_2)_3$

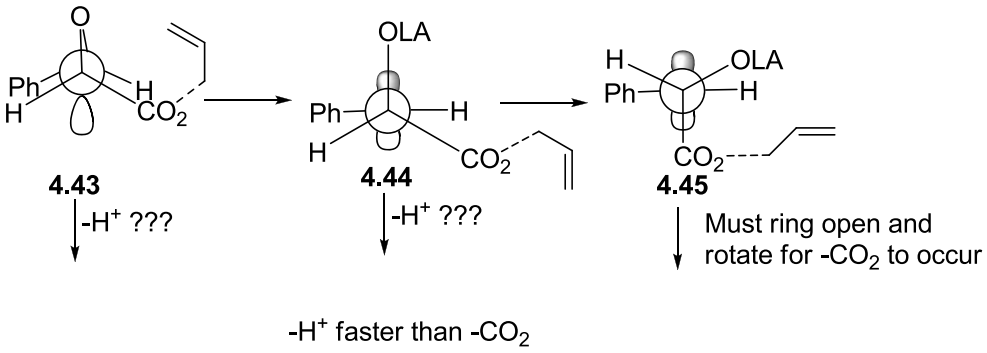
ScX_3



$ZrCl_2L$ **4.42**

The inability of the Pd-carboxylate to undergo decarboxylate ring opening likely arises from the poor overlap of the σ* orbital of the epoxide and the σ orbital of the CO_2 group (Scheme 4.14). However, it appears that in most cases the loss of a proton-to open the epoxide out-competes decarboxylation. The fact that α-H elimination occurs faster is also not surprising considering the stoichiometric amount of Lewis acid present-which would facilitate the ring opening on all the substrate while at best only a catalytic amount could undergo decarboxylative elimination. The simplest solution would be to substitute

the α-H for a substituent such as an alkyl group. This would remove this mode of activity and potentially allow for the acyclic system to undergo loss of CO_2. However, the resulting product would be the apparent product of DCA of a β-keto allyl ester. Consequently, the reaction looses some of its appeal because it moves in the wrong synthetic direction-from complex to simple.



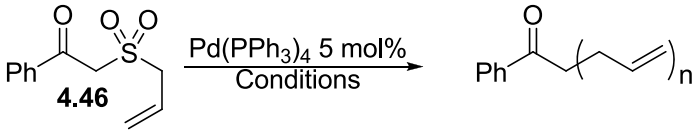
Scheme 4.14

Palladium Catalyzed Wittig Rearrangement

The focus of our group has impenitently been to take full advantage the loss of CO_2 to generate reactive intermediates that are not readily accessible or controllable-when generated prior to consumption, and use them in a constructive manner. The loss of a small molecule as an entropic driving force is not unique to CO_2. We became curious if other gases could be expelled from organic molecules and used as a driving force for bond formation. We sought to design a system that would resemble the allyl esters and we started by synthesizing an allyl, acetophenone sulfone (**4.46**, Table 4.4). Subjecting the sulfone to 5 mol% $Pd(PPh_3)_4$ in DCM-d_2 led to the slow conversion of the starting material (entry 1). Heating this reaction led to full conversion and gave a mixture of monoallyl, diallyl, and protonated product. When the solvent was changed to toluene-

d_8 and the reaction was run at room temperature (entry 3) no product was formed. Serendipitously, when heated to 110°C, the reaction cleanly proceeded to the desired product (entry 4). A control reaction was run in which no Pd was added and since no product or decomposition was observed (entry 5) it is likely that the reaction is indeed Pd-catalyzed. This is a really nice result and should be followed up on. This reaction has the potential to be useful but we have not yet optimized the conditions of the reaction or tested the scope.

Table 4.4 Conditions for Desulfitative Allylation

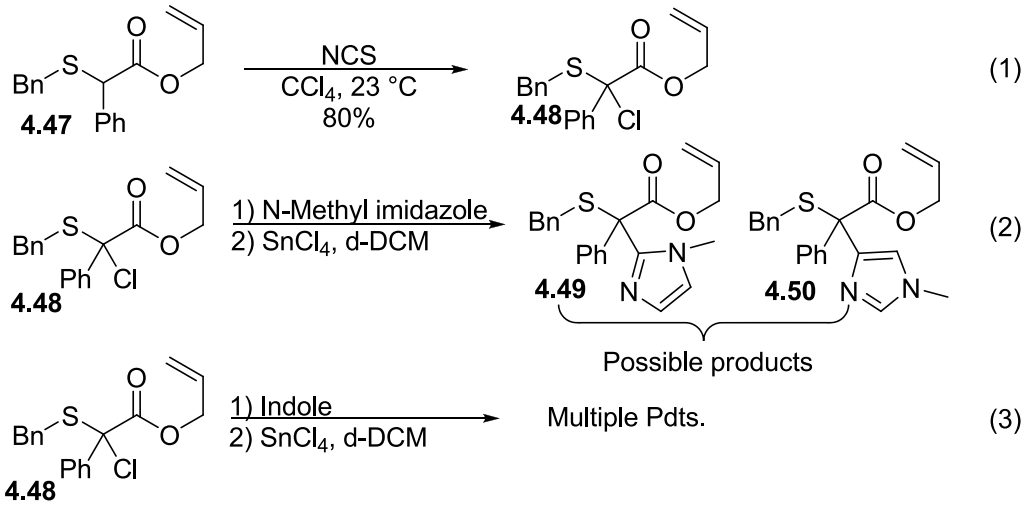


Entry	Solvent	Temp °C	Conv.	n = 1:2:0	Comments	Experiment
(1)	d-DCM	23	25%	--	Slow conv.	JW3225
(2)	d-DCM	40	100%	1:0.34:0.66	Much faster than rt	JW3225
(3)	d-Tol	23	0%	--	No pdt.	JW3226
(4)	d-Tol	110	100%	1:0:0	Very clean	JW3226
(5)	d-Tol	95	0%	--	No-Pd no decomp.	JW3235

Electrophilic Substitution of α-Chloro α-sulfide esters

In the course of our research we became interested in the synthesis of sulfones. While several routes including enantioselective routes to sulfonyl substrates were developed, we believed that the α-chloro sulfide might be a nice entry point to substrates with more elaborate aromatic substituents than phenyl. There is literature precedence[5] that the sulfides with an α-chloro group can act as an electrophilic center under the right conditions, which allows for electrophilic aromatic substitution with nucleophilic arenes to occur. Thus, we began by synthesizing an α-chloro sulfide ester (**4.48**), via NCS

chlorination in CCl_4, at room temperature (eq. 1, Scheme 4.15). We found that this compound was not stable on silica, but that the succinimide byproduct could be removed by selectively extracting the product with Et_2O. $SnCl_4$ was used as halophilic Lewis-acid that could help abstract the choride and form the electrophilic species. We first subjected the substrate to substitution with N-Methyl imidazole (eq. 2) the reaction worked very quickly and consumed the starting material but at least two products were formed. Using indole, we hoped would lead to fewer regioisomeric products-given its tendency to react at the 3 position, but unfortunately also gave several products. It does seem that this could be a viable way to get to interesting substrates but we did not run enough reactions to determine best type of conditions for the reaction and the workup.

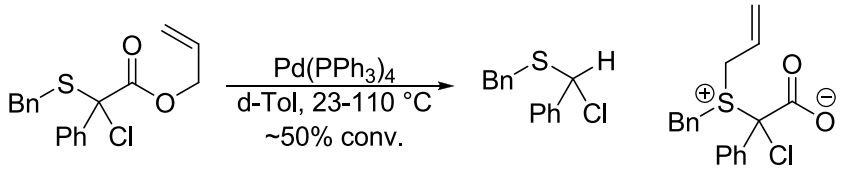


Scheme 4.15

Pd-Catalyzed DCA of α-Sulfide Allyl Ester

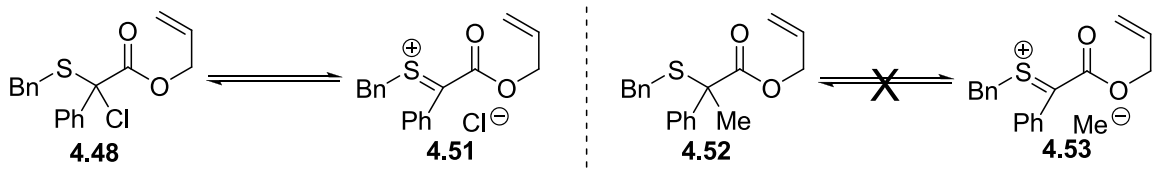
As a group we are rather opportunistic in looking for substrates that might undergo DCA. En route to the synthesis of a sulfonyl ester, a sulfide was made. We believed it had a reasonable chance to undergo DCA. When we subjected the substrate to

$Pd(PPh_3)_4$ at room temperature very little happened (Scheme 4.16). However, when it was heated to reflux slow consumption of the starting material occurred. One product looks like protonation where the other product looks like it could be the carboxylate-zwitterion as new signals in the ^1H NMR spectrum of the reaction were all shifted downfield.



Scheme 4.16

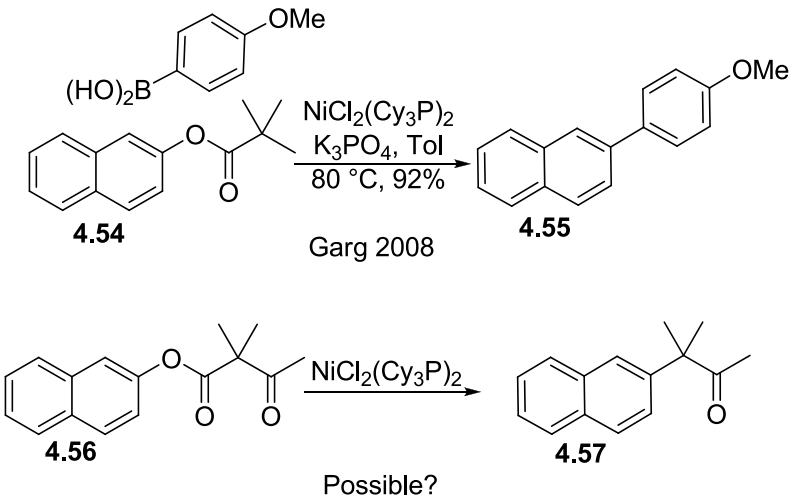
Initially we believed that the chloro group might help facilitate the reaction as it did in the DCA of the sulfone.[5] However, it is possible that it actually slows the reaction (Scheme 4.17). If decarboxylation occurs from the zwitterionic species then substituents that remove electron density from the S should make it less nucleophilic furthermore oxidative addition into the C-Cl bond might also be occurring which could prevent productive reaction from happening. A better substrate might be one in which the chloro group has been replaced with an alkyl substituent such as **4.52** in which the sulfur is more sp^3 like than **4.48** which has greater sp^2 and as a consequence **4.52** might be more prone to undergo S-allylation.



Scheme 4.17

Attempted Decarboxylative Arylation

In 2008 Niel Garg published a method demonstrating the ability to cross couple aryl pivalates and boronic acids[6] and later expanded on the aryl leaving group via nickel catalysis.[7] This methodology is synthetically useful as it allows *Ar*C-O bonds to be easily activated towards oxidative addition, which usually required formation of the aryl triflate. The triflation is usually carried out with expensive and highly reactive triflic anhydride making it unattractive on a large scale. We became curious if we could build off of Garg's work and rather than using the oxidative addition intermediate for transmetallation we hoped to couple it with another reactive intermediate generated from the oxidative addition process (Scheme 4.18). If this worked, it would generate a whole new class of substrates that could be coupled by decarboxylation.

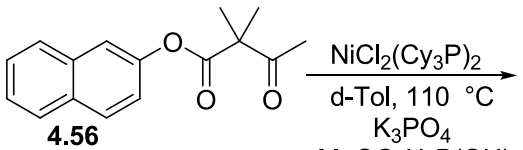


Scheme 4.18

To start our investigation into this question we synthesized the napthol β-keto ester (**4.56**) that was geminally methylated as well as the nickel catalyst. Subtle but significant challenges became apparent from the outset and ultimately prevented this

project from getting off the ground. One significant difference in Garg's method and the one we hoped to develop was the ability to form the catalyst *in situ*. Garg starts from a Ni(II) precatalyst that presumably uses some of the boronic acid in order to reduce the catalyst, it is common among transition metal-catalyzed transmetallations to use a catalytic amount of sacrificial reductant to generate the active catalyst. In our system there is no external reductant, so we must either start with a much less stable Ni(0) source or find some way to reduce initially *in situ*. We attempted to reduce the Ni(II) precatalyst with diethyl zinc and a color change occurred, causing us to believe the catalyst was reduced, but the starting material was unchanged after 24 h (entry 1, Table 4.5). We attempted to use a Ni(0) precatalyst, but this led to rapid formation of Ni-black and no reaction. We next added the boronic acid and other reagents reported by Garg (entry 3) we saw formation of the Suzuki product as well as corresponding protonated ketone. This reaction confirmed that when the boronic acid was present we were getting insertion into the ArC-O bond as well as decarboxylation. Unfortunately, coupling of the two components did not occur.

Table 4.4 Attempted Ni-Catalyzed Decarboxylative Arylation

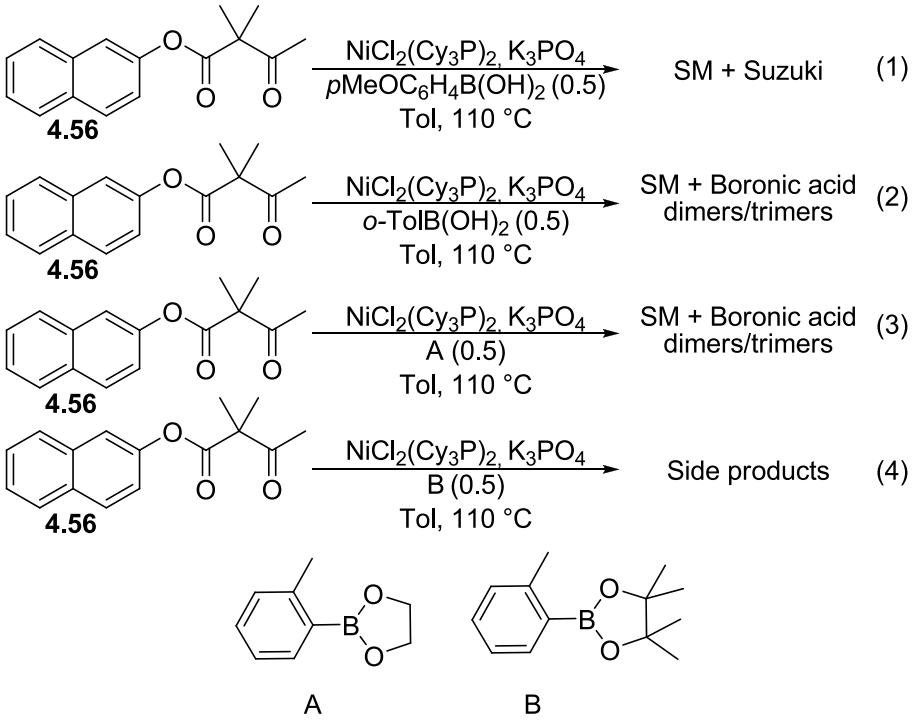


4.56

Entry	Differences	Comments
(1)	None	Suzuki pdt. and protonated ketone
(2)	Et_2Zn	Reduction occurred rapidly but no reaction
(3)	$Ni(COD)_2/Cy_3P$	Ni-Black <1h, No reaction

We attempted to reduce the Ni(II) with several reductants other than the boronic acids; including MeMgBr, Et_2Zn, $NaBH(OAc)_3$, $Bu_3SnCHCH_2$, and $NaBH_4$. Most of these reductants seemed to reduce the Ni(II) but based on the similarity of the colors of the active catalyst and that observed when the metal was reduced we chose to try using $NaBH_4$ as an external reductant. Interestingly, when the Ni(II) was reduced with $NaBH_4$ and then filtered, in the glovebox under an atmosphere of argon, and subjected to the substrate only alkyl signals were seen after working the reaction up. It would be somewhat remarkable if true but it seems like the aromatic napthyl system was hydrogenated. Alternatively, it could be that the substrate was trapped on the silica plug and the phosphine ligand passed through and these are the signals from the tricyclohexyl phosphine, the ^1H NMR spectra from these two compounds would be similar. Furthermore, when the precatalyst was treated with $Bu_3SnCHCH_2$ as the reductant, in the same manner, the starting material was unchanged. Given the potential of such a mild reductant, a second experiment would be worthwhile. We next looked at use of a substoichiometric amount of the boronic acid (Scheme 4.19). The hope was that the small amount of boronic acid would allow the reduction of the precatalyst and then would be consumed and then the catalyst would carry on and the decarboxylative coupling would take place. When the *para*-methoxy phenyl boronic acid was used the product of Suzuki coupling was observed as well as starting material (entry 1). We next changed to a boronic acid which Garg reported as poor, in hopes that it would slow the Suzuki reaction and allow the desired reaction to occur (entry 2). In the ^1H NMR spectra we frequently saw small but significant methyl signals we eventually discovered that these signals were coming from dimers and trimers of the boronic acid that were being formed

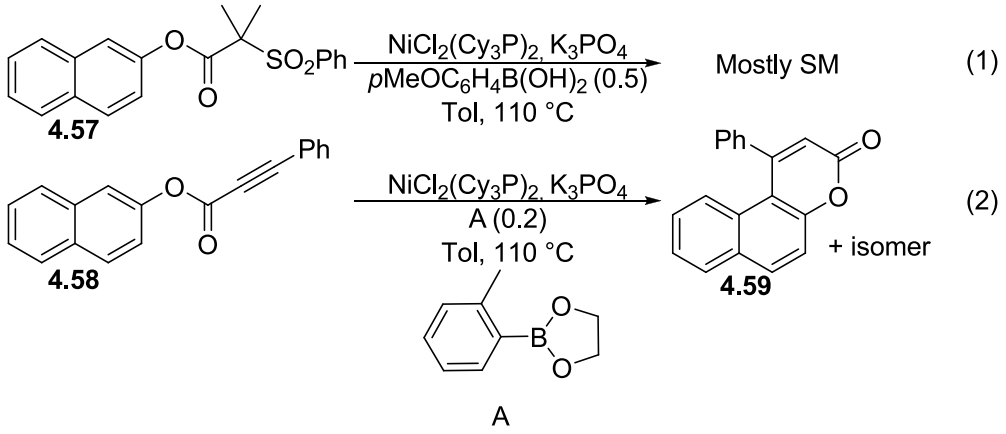
in situ. Additionally, we thought that if we were truly forming an enolate that the water from the dimers and trimers would lead to protonation. So we synthesized two boronate esters. However, we found no evidence for the desired product (entry 3) but interestingly when the solvent in the reaction escaped and the reaction was run neat, the starting material was completely consumed (entry 4).



Scheme 4.19

Frustrated with our lack of success we thought maybe we would have better luck with a substrate that contained a different pronucleophile i.e. a sulfonyl ester or a propiolic ester (Scheme 4.20). When the naphthol sulfonyl ester was subjected to the Garg's conditions, no Suzuki product was observed and most of the starting material was unchanged (entry 1). However, when the phenyl propiolic ester was subjected to the modified Garg conditions the starting material was consumed and provided what appears

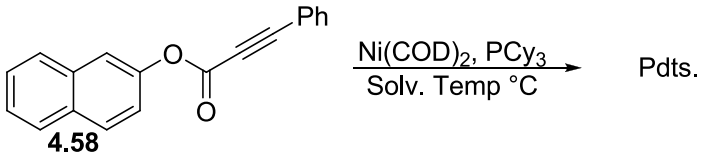
consistent with the regioisomeric products of an intramolecular-hydroarylation of the alkyne in a 1:0.9 ratio (major undetermined) (entry 2). While the hydroarylation was interesting, it was not surprising and we thought we could perhaps avoid it by starting with a Ni(0) source. Indeed, when the Ni(II) was allowed to stir with a boronic acid for 2.5 h the hydroarylation product was not observed.



Scheme 4.20

Given the difference seen when the metal was first allowed to reduce we thought it prudent to limit the rest of the investigation of the propiolic esters to Ni(0) catalyst. However, as can be seen in table 4.5 that despite the use of $Ni(COD)_2$, a Ni(0) source, no conditions provided any of the decarboxylated product. We synthesized the desired product via a Stille coupling and developed conditions on GCMS that would separate the molecule to aid in this investigation.

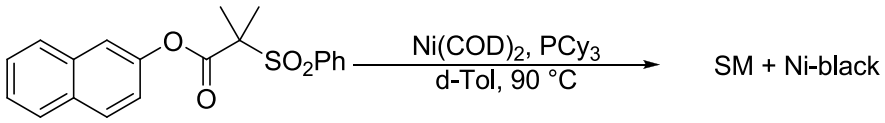
Table 4.5 Attempted Ni-Cat. Decarboxylative Arylation of Napthyl Propiolates



4.58

Entry	Solvent	Temp °C	Additive	Comments
(1)	Tol	100	--	SM consumed but no pdt by GCMS, some Ni-black
(2)	THF	66	--	Same as entry 1
(3)	DMA	100	--	SM
(4)	DMF	100	--	SM, Ni-black
(5)	THF/DMA	100	$ZnCl_2$	SM, no pdt, side pdt

Interestingly, the same conditions previously employed (entry 1, table 4.5) led to the rapid formation of Ni-black when used for the sulfone substrate (Scheme 4.21).

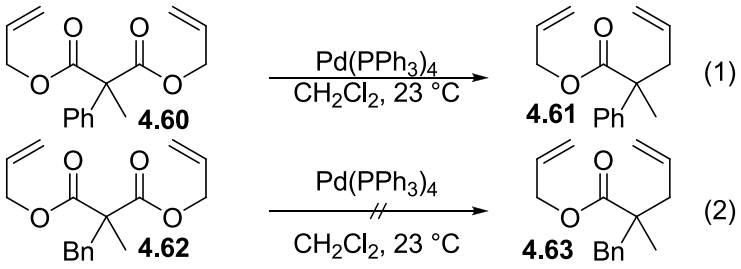


Scheme 4.21

We were forced to concede that we did not understand how the reaction was working. We were able to demonstrate the ability to perform the Suzuki coupling on β-keto naphthyl esters and have evidence that they decarboxylate but unfortunately were never able to get this to happen in the absence of the boronic acid. Additionally, we showed evidence that naphthyl propiolates, under these conditions, give hydroarylation products.

Decarboxylative Allylation of Malonic Ester Derivatives

Malonic ester synthesis is a classic method for the formation of substituted acetic acids. Recently, Ohata[8] reported that the α-phenyl malonic allyl esters underwent smooth DCA at room temperature (**4.60** eq. 1, Scheme 4.22) but that substrates that were α-dialkyl (**4.62)** did not decarboxylate under these conditions (eq. 2). We believed that the addition of a Lewis-acid cocatalyst could help stabilize the incipient anion and might thus reduce the transition state energy for decarboxylation and consequently allow the decarboxylation to occur under more mild conditions (for dialkyl substrates).

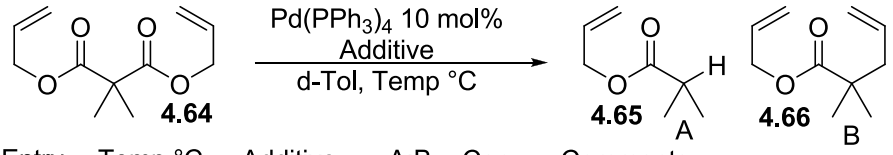


Scheme 4.22

To answer the question, we first synthesized diallyl α-dimethyl malonate and subjected it to 10 mol% $Pd(PPh_3)_4$ in toluene-d_8 and monitored the reaction by ^1H NMR spectroscopy; watching for the formation of the protonation and C-allylated product (Table 4.6). The reaction with no cocatalyst (entry 1) underwent decarboxylation to afford only protonation. When $MgCl_2$ was added the same product ratio (all protonation) was seen but the conversion to product had been substantially reduced, less than 10% (entry 2). Interestingly, when $Rh(PPh_3)_4Cl$ was used conversion was high and the amount of allylation product increased (entry 3). Use of TMSTFA (entry 3) led to only protonation product but again halted the reaction. Interestingly, use of $Zn(OAc)_2$ (entry

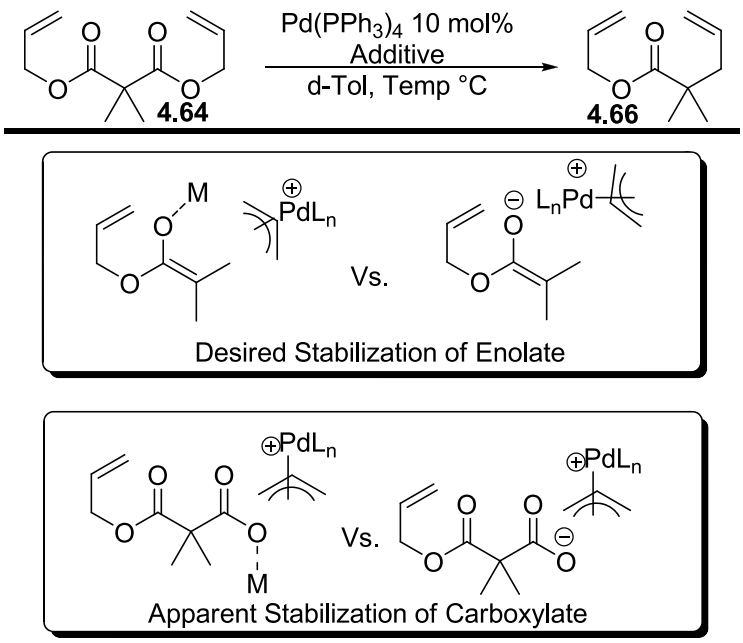
6), Cu(OAc) (entry 7), and $Cu(OAc)_2$ (entry 8) all led to slower reaction (compare with entry 5). In general use of Lewis-acids did not catalyze the decarboxylation, rather most seemed to have a detrimental effect on the rate, with the exception of the Rh cocatalyst (entry 3).

Table 4.6 Effects of Lewis-Acid Cocatalyst on DCA of Diallyl Malonate



Entry	Temp °C	Additive	A:B	Conv.	Comments
(1)	90	–	20	85	Major product protonation
(2)	90	$MgCl_2$	20	<10	Primarily SM
(3)	90	$Rh(PPh_3)_3Cl$	5.7	85	Give some C-Allyl pdt
(4)	90	TMSTFA	20	<10	Primarily SM
(5)	75	–	20	30	11h
(6)	75	$Zn(OAc)_2$	20	21	11h
(7)	75	Cu(OAc)	20	5	11h
(8)	75	$Cu(OAc)_2$	20	16	11h, $Cu(OAc)_2$ very insoluble

A likely explanation for the observation that the Lewis-acid seem to inhibit decarboxylation can be interpreted as a stabilization of the ground state energy (carboxylate stabilization) rather than the desired transition state energy (enolate stabilization) (Scheme 4.23).



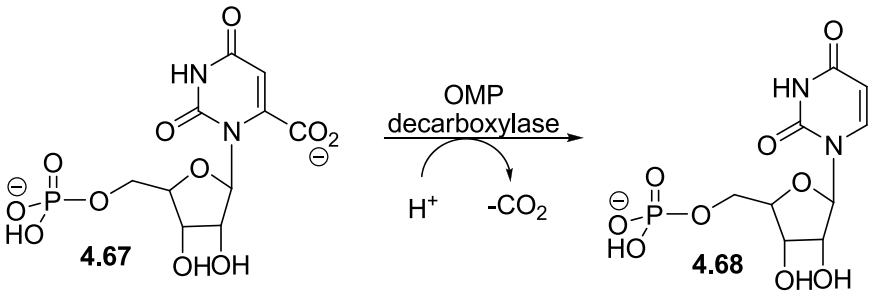
Scheme 4.23

In addition, one more way in which the Lewis-acid inhibited the reaction was by complexing the catalyst and causing it to precipitate out of solution. When $Sc(OTf)_3$ was used with $Pd(PPh_3)_4$ the metals immediately precipitated from solution.

Orotic Acid Decarboxylation

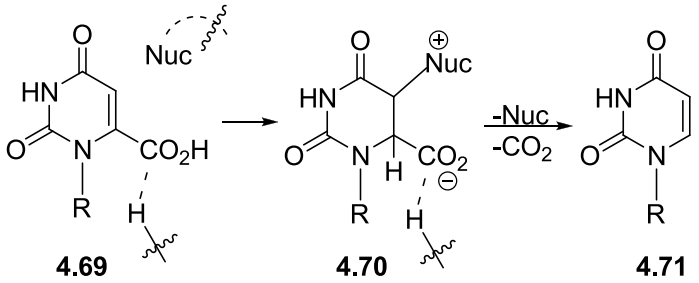
OMP decarboxylase or ODCase (orotidine 5'-decarboxylase) is a pure protein enzyme (no metals or cofactors) and generates one of the largest rate accelerations among enzymatic processes $k_{cat}/K_m/k_{non}$ of 2.0×10^{23} M^{-1}.[9] It is a key enzyme in biosynthesis of nucleic acids[10] and has generated a significant amount of interest in its mechanism (Scheme 4.24).[10-12] A commonly postulated mechanism is one that invokes ground state destabilization such that barrier to decarboxylation (to form a vinyl anion) is significantly lowered.[10] This field of chemistry is conspicuously devoid of the possibility of

"transformative catalysis" in which the substrate undergoes a reaction that creates an intermediate that is more prone to undergo the decarboxylation reaction that restores the substrate hiding the evidence of the transformation.



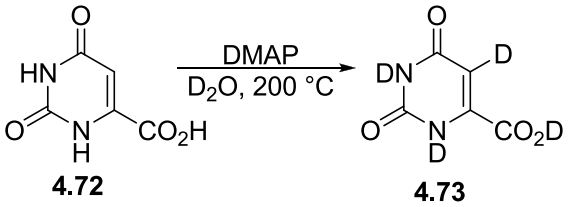
Scheme 4.24

We were curious whether it might be possible that catalysis might be occurring via a Micheal-addition of a strategically located nucleophile in the enzymatic pocket (Scheme 4.25). Supporting this idea is the fact that of the eight conserved amino acid residues in this family seven come in direct contact and are necessary for protein activity also important is the location of Lys-93 at or near the CO_2 group. We have no evidence that the role of the lysine is to undergo a Michael-addition but it seems more probable than decarboxylation to form a vinyl anion. We thought it might be possible to see decarboxylation if a nucleophilic catalyst such as DMAP were used, albeit we expected it to be much more difficult than the enzymatic decarboxylation which is likely additionally activated by hydrogen bonding.



Scheme 4.25

When orotic acid was heated with DMAP in D_2O deuteration of every possible position was observed but no decarboxylation (Scheme 4.26). Deuterium exchange for the N-H bonds is not surprising but somewhat surprising is the exchange of the vinyl position. It is not known whether the DMAP is facilitating this exchange or if this is uncatalyzed exchange. It is clear that a nucleophilic catalyst, on its own, does not appear to facilitate decarboxylation. We have not proceeded with this question any further.

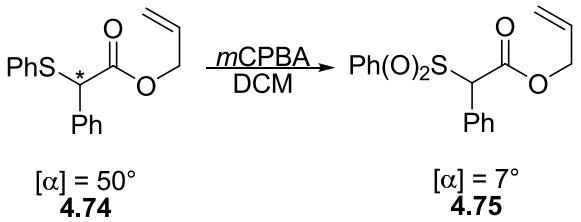


Scheme 4.26

Attempted Enantioselective 3,3-Rearrangement of Chiral non Racemic Sulfonyl Esters

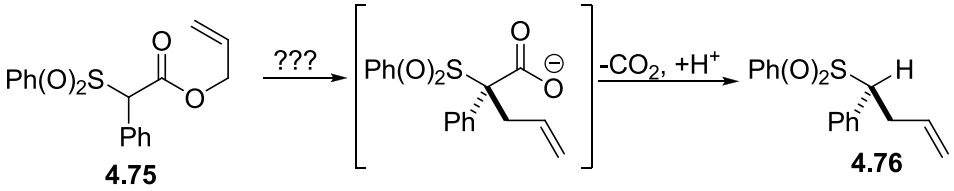
Having demonstrated that the Pd-catalyzed DCA was stereospecific we became curious if we might expand the scope to make chiral nonracemic secondary sulfones. Unfortunately, this is not possible if the starting material rapidly racemizes as it does with α-sulfonyl esters (Scheme 4.27). The sulfidyl ester, which had been partially resolved with a chiral amine as the acid before esterification, had a specific rotation 50 ° in the

positive direction but upon oxidation (**4.75**) the specific rotation 7 ° in the positive direction. It is possible that the sulfone just has a small specific rotation but a more likely scenario is the racemization under the reaction or workup conditions. We concluded that it would be highly improbable to generate the prerequisite enantioenriched starting materials such that we could even attempt the Pd-catalyzed the stereospecific DCA.



Scheme 4.27

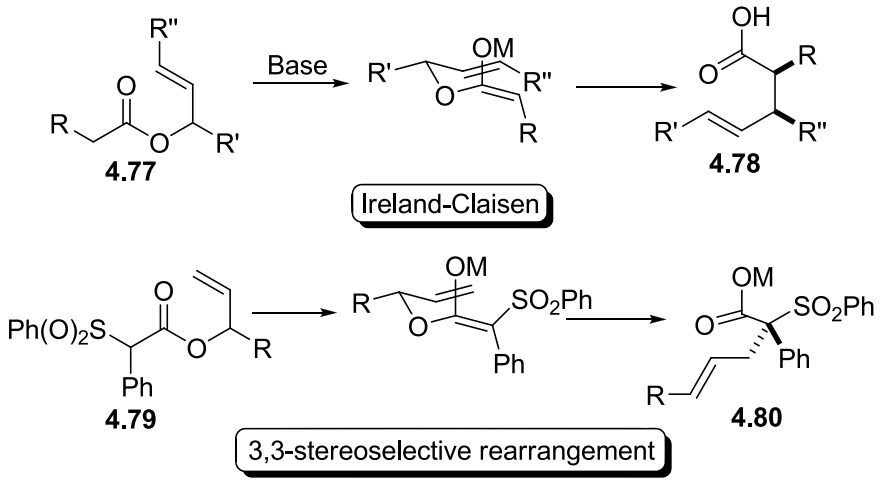
However, we wondered if the merging of Craig's 3,3-sigmatropic rearrangement[11] and Cram's[12] and Corey's[13] decarboxylative protonation could lead to nonracemic secondary sulfones. The problem then becomes finding conditions that allow a stereoselective 3,3-rearrangement because the following decarboxylation, under the appropriate conditions, should be stereospecific (Scheme 4.28).



Scheme 4.28

We thought it might be possible to use a chiral non racemic allylic alcohol to make an ester that would undergo rearrangement with a high degree of stereo transfer,

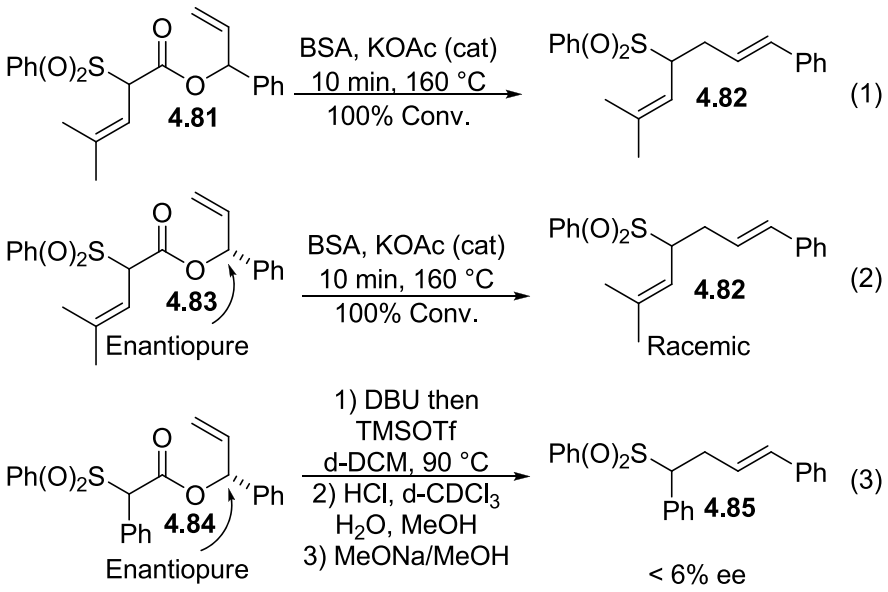
much like that of an Ireland-Claisen rearrangement (Scheme 4.29). The expectation was that the R group would dictate which conformer would be reactive. It was also believed that the $-SO_2Ph$ group would want to be in the pseudo-equatorial position.



Scheme 4.29

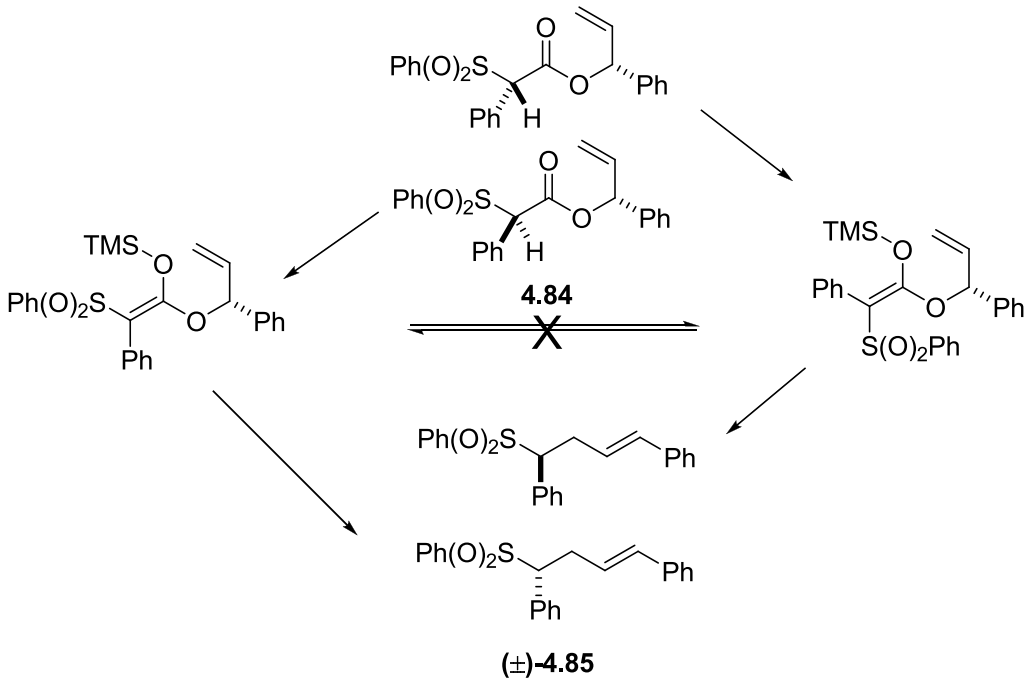
After some work we found that we could effect a sigmatropic rearrangement like that reported by Craig and coworkers (eq 1, Scheme 4.30).[11] When the ester was made with enantiopure allylic alcohol (see chapter 3 for the synthesis) and subjected to reaction conditions the product was racemic as determined by separation of the enantiomers using chiral-HPLC (eq 2). One potential explanation for this was that racemization of the chiral non racemic sulfonyl anion (presumably formed) was faster than protonation under these conditions another explanation was that the rearrangement was stereospecific with respect to the α-position. We were able to rule out the first hypothesis. We found that the rearrangement occurred in the absence of KOAc but was essential in order to get decarboxylation to occur-as it probably facilitated desilylation which allowed decarboxylation to occur. Removing the acetate (eq. 3) we were able to get spectral

information for the intermediate silyl ester then desilylate it followed by decarboxylative protonation under conditions known to be stereospecific. Effectively, this allowed us to separate the problem and let us determine whether we were forming an enantioenriched intermediate that underwent racemization or whether the intermediate was formed as a racemic mixture. Unfortunately, the experiment (eq. 3) suggested that the rearrangement occurred with little stereotransfer.



Scheme 4.30

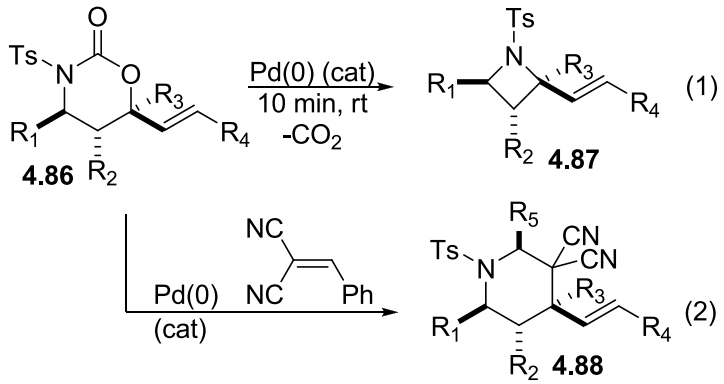
This lack of stereotransfer is likely caused by a kinetic trapping of the silyl enol ether that cannot equilibrate (Scheme 4.31). The ability of the enol ethers to equilibrate between geometries is necessary because a mix of silyl enol ethers is expected to lead to deterioration of stereochemical transfer from the allyl portion. The concept still has a possibility to work if a system was designed that gave only a single enolate geometry. A chelate between a metal, sulfur and the enolate oxygen might be possible at lower oxidation states.



Scheme 4.31

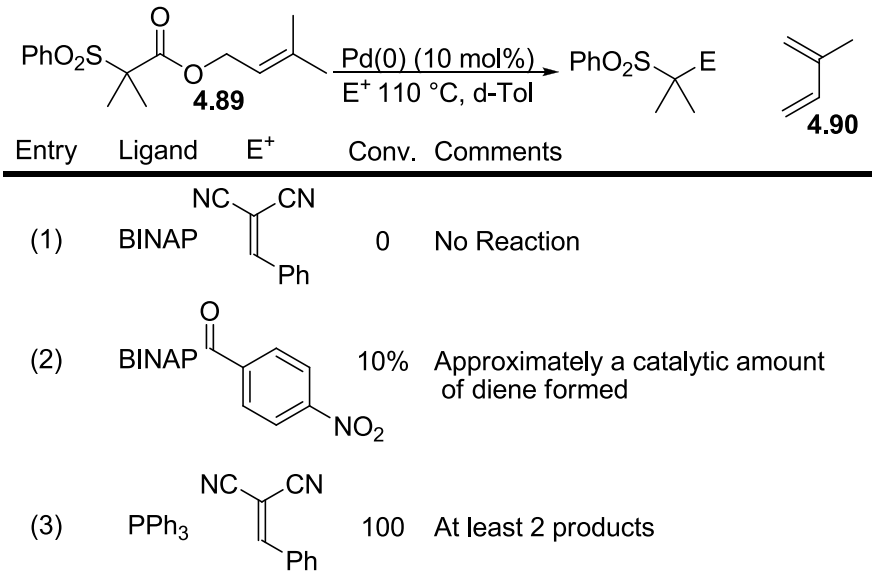
Attempted Nucleophilic Interceptive DCA

Decarboxylative allylation can be a very useful bond making reaction (Chapters 1 and 2). The reaction has even more potential utility if the intermediates can be "intercepted" with other reaction partners in a controlled fashion (Scheme 4.32).[14] Most DCA-interceptions, to date, have worked by either 1) intercepting the nucleophile before it can attack the Pd-π-allyl or 2) formation of a kinetic product that can undergo a reversible reaction. However, the resting state of the catalytic cycle is the metal-allyl complex.[15] This implies that there is a build up of an electrophilic species in the reaction which should be capable of undergoing substitution with an external nucleophile. The nucleophile itself should become an electrophile after attack of the allyl.



Scheme 4.32

Initially, we actually tried to take advantage of the rapid elimination from prenol esters to facilitate a Michael addition (eq 1 and 3, Scheme 4.33) and an aldol reaction (eq. 2) under neutral conditions. These types of products can be difficult to access via traditional methods. Interestingly, when the bidentate ligand, BINAP, is used benzylidene malononitrile completely shuts down the reaction (eq 1) and the highly electron deficient ρ-nitro benzaldehyde seems to allow 1 turnover (eq 2). The highly electron deficient π-bonds most likely coordinate to the open coordination sites on the metal center and reduce the nucleophilicity of the Pd below what is necessary to undergo oxidative addition of the allyl ester..

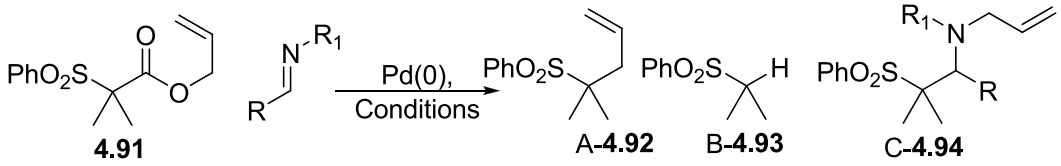


Scheme 4.33

We next looked at the ability of electronically rich, neutral, and poor imines to take part in an interceptive DCA (desired C-**4.94**, Table 4.7) with two catalyst ($Pd(PPh_3)_4$ or Pd_2dba_3/BINAP) under several conditions (Table 4.7). Typically the reactions produced the products A-**4.92** or B-**4.93**, though some side product(s) were seen frequently in many of the reactions. Use of electron neutral benzyl imine led primarily to B-**4.93** when PPh_3 was the ligand (entry 1) and when the ligand was BINAP the normal C-allylated, A-**4.92**, was the major. These two results are fairly typical of the standard reaction and make me believe that the benzyl imine had little impact on the reaction. Reactions with BINAP in CH_2Cl_2-d_2 or THF-d_8 were unremarkable (entries 3 and 4). Use of electron rich imine (entries 5-10), derived from anisaldehyde, were expected to lead to the most N-allylation product-since the imine should be the most nucleophilic in the series. However, this was not the case when BINAP was used as the ligand (entries 5 and 6) which gave almost exclusively product A-**4.92**. Cs_2CO_3 made little difference

(entry 6). Results were varied when PPh_3 was the ligand (entries 7-10). When the reaction was run in either toluene-d_8 or THF-d_8 (entries 7 and 9) the major product was B-**4.93** but when the reaction was run in DCM-d_2 or MeCN-d_3 (entries 8 and 10) the major product was A-**4.92**. When an electron deficient nosyl imine was used (entries 11, 12) the main result was that the reaction was very sluggish and the small amount of starting material that was consumed led primarily to products that had not been seen and could not be identified. In conclusion none of the imines examined seemed capable of interceptive DCA.

Table 4.7 Attempted Interceptive DCA with Imines.

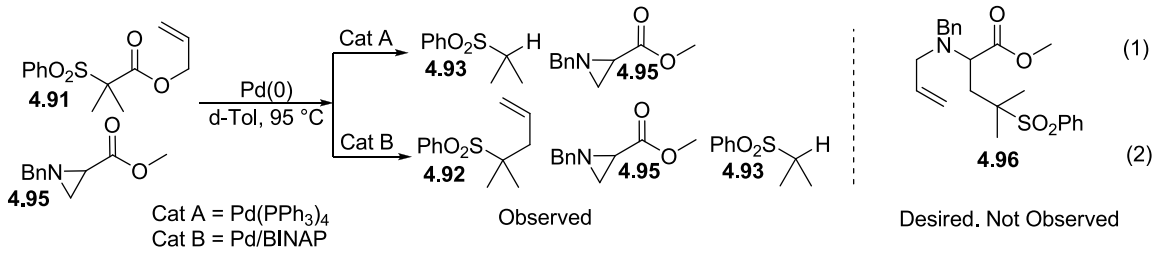


Entry	Ligand	R	R_1	Solv.	Temp °C	Conv.	Ratio (A:B)	Comments
(1)	PPh_3	Ph	Bn	d-Tol	110	100	0:0.80	
(2)	BINAP	Ph	Bn	d-Tol	110	100	1:0.20	
(3)	BINAP	Ph	Bn	d-DCM	40	5[a]	1:0	
(4)	BINAP	Ph	Bn	d-THF	67	75[a]	1:0.13	
(5)	BINAP	Ar	Bn	d-Tol	95	94[a]	1:0.05	
(6)	BINAP	Ar	Bn	d-Tol	95	100	1:0.06	Cs_2CO_3 additive
(7)	PPh_3	Ar	Bn	d-Tol	80	100	0:1	
(8)	PPh_3	Ar	Bn	d-DCM	40	40	1:0	
(9)	PPh_3	Ar	Bn	d-THF	67	100	0:1	
(10)	PPh_3	Ar	Bn	d-MeCN	80	100	1:0.5	
(11)	BINAP	Ph	Ns	d-Tol	95	15	0:0.25	
(12)	PPh_3	Ph	Ns	d-Tol	95	15	0:1	

[a] Stopped after 6h. Ar = ρ-$MeOC_6H_4$ Ns = SO_2C6H_4-ρ-NO_2

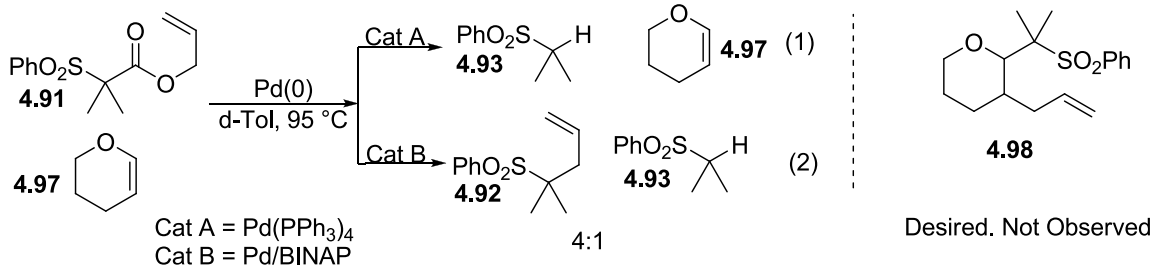
We next looked at the ability of the aziridine (**4.95**) to undergo an interceptive DCA (**4.96**, Scheme 4.34). Unfortunately, the aziridine showed little promise. The most intriguing observation of this reaction was the absence of any type of vinyl signal when

PPh_3 was the ligand (eq. 1). Potentially allene is formed which is volatile enough to escape, but why this should happen under these conditions is not clear.



Scheme 4.34

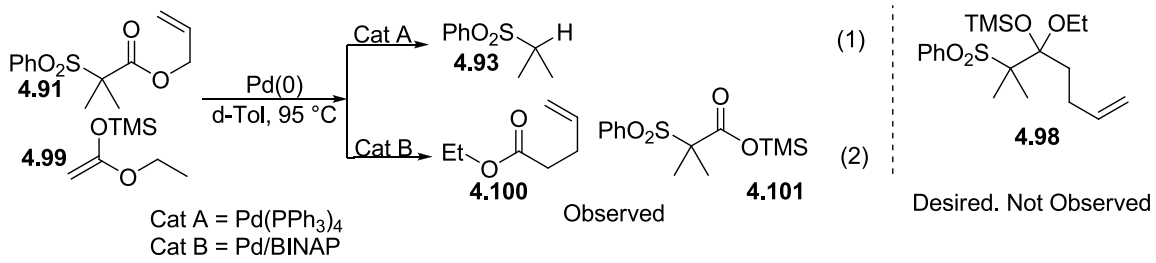
We next looked at the ability of vinyl ethers to undergo interceptive DCA (**4.98,** Scheme 4.35). The dihydropyran was added to the sulfonyl ester but seemed to have very little impact on the outcome of the reactions (entries 1 and 2) as they are nearly identical to the product ratios previously observed without the ether (**4.97**) present.



Scheme 4.35

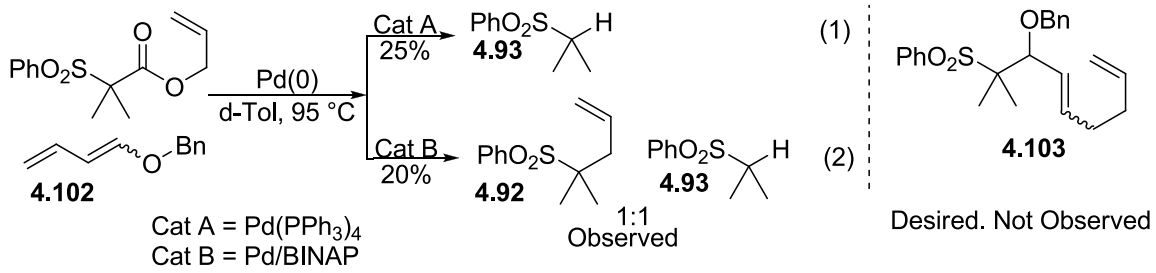
We next looked at even more nucleophilic silyl ketene acetals (**4.99**, Scheme 4.36). Again, when $Pd(PPh_3)_4$ (eq 1, Scheme 4.36) was used as a catalyst, protonation was the only discernable product. However use of Pd/BINAP (eq. 2) led to the allylated ethyl acetate (**4.100**) and the silyl carboxylate (**4.101**). This was both exciting and frustrating as it was the first nucleophile that had intercepted the π-allyl but resulted in

silyl transfer which quenched the reaction rather than undergoing a second carbon-carbon forming reaction to give the desired (**4.98**). Consequently, we stayed away from nucleophiles that could transfer a silyl group in this manner.



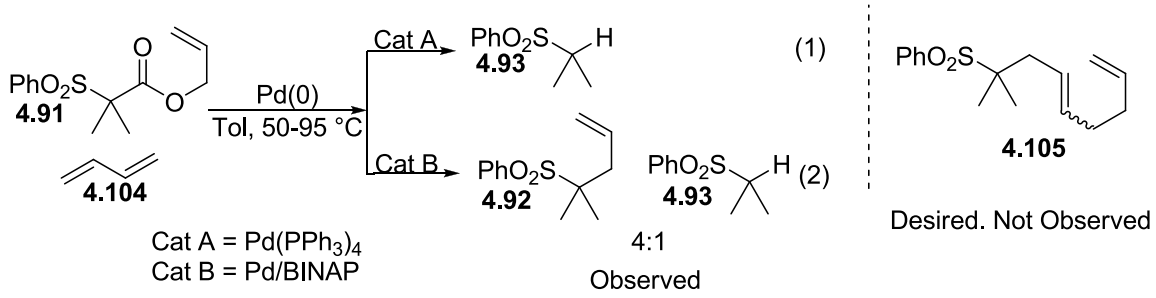
Scheme 4.36

We next looked at electron rich dienes that might typically be used for Diels-Alder reactions (**4.102,** Scheme 4.37) and hoped to form **4.103**. Unexpectedly, the reaction with $Pd(PPh_3)_4$ (entry 1) was very sluggish and only resulted in about 25% conversion to protonation product. When Pd/BINAP (entry 2) was used with this diene rapid precipitation of the metal was observed, the ligand was allowed to ligate the metal prior to the addition of the diene. This is likely caused by a kinetic coordination of the diene(s) to the metal center but that ultimately allow it to precipitate. Thus we thought that if we used a more electron neutral diene we might strike an important balance between nucleophilicity and coordination ability.



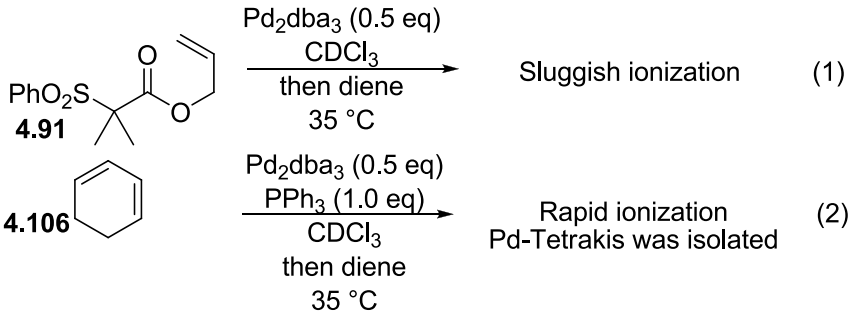
Scheme 4.37

We next looked at unactivated conjugated dienes (**4.104**, Scheme 4.38). Again we were unsuccessful, however, we did turn over some old literature of a Pd-catalyzed process in which butadienes were dimerized when allowed to react with Pd-allyl complexes.[15] This strategy seems promising but so far we have not been able to make any headway.



Scheme 4.38

Related to the previous reaction we ran a reaction that was stoichiometric in palladium. It is difficult to interpret the ^{1}H NMR spectra from this reaction and it is not clear what occurs but a few things can be gleamed from these experiments. The ionization in the absence of phosphine ligands (eq. 1, Scheme 4.39) is slow. The addition of phosphine in a 1:1 ratio with the metal allows for rapid ionization. Several interesting peaks grew in over course of 2 days but it was not clear to what they corresponded. After filtering over silica and addition of toluene, $Pd(PPh_3)_n$ crystallized out of solution.

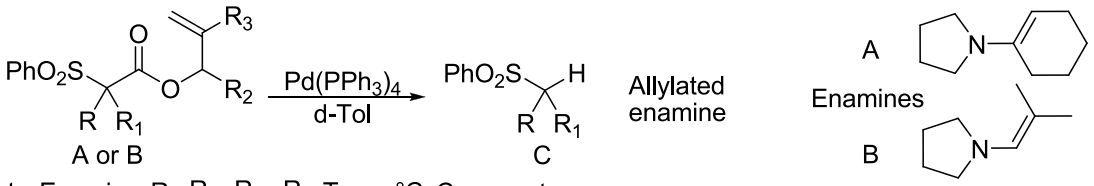


Scheme 4.39

We also looked at the ability of enamines to undergo the interceptive DCA. The hope was that the enamine would rapidly allylate and to generate an iminium that would be attacked by the sulfonyl anion-generated upon decarboxylation (Table 4.8). We were successful in allylating the enamine (entries 1-3) but were never successful in getting the sulfonyl anion to attack the iminium carbon. Enamine A undergoes rapid allylation (entry 1), ~15 min at rt which then formed an insoluble oil in the NMR tube; presumably this was an ionic liquid comprised of the carboxylate and the iminium. However, upon heating decarboxylation occurred rapidly but the only sulfone observed was the protonated form, C, as well as a mix of enamines that had been allylated. We suspected that the sulfonyl anion or the carboxylate were deprotonating the intermediate iminium thus we attempted to circumvent this problem by using the enamine B which does not have an α-H (entries 2 and 3). Enamine B allylates considerably slower than A and when the reaction was performed at rt for 1 h followed by heatingto 110 °C (entry 2). This protocol led to a mixture of products, though the only detectable sulfone was the protonated sulfone, C. However, when enamine B was allowed to react for 1 h at 70 °C followed by heating at 95 °C sulfone C was cleanly formed. The fact that protonation was still seen is a bit surprising perhaps the iminium undergoes isomerization into the

ring to form a new enamine and generate a proton. Finally, in trying to circumvent this we tried using a sulfonyl ester that had an α-H, which might allow for a different mechanism to take place. Interestingly, the sulfonyl ester allylated faster than enamine A, and led to a mixture of protonation, mono-allylation and diallylation with only a small amount of enamine allylation, 1:1:0.5:0.1 respectively. While we were successful in intercepting the allyl we were never able to make the coveted second C-C bond. It would be worth trying the reaction using BINAP, given its propensity to shut down the protonation manifold in the normal DCA.[5,16] Given the potential of interception we were not ready to abandon this idea but thought we might have better chance with other nucleophiles generated via decarboxylation.

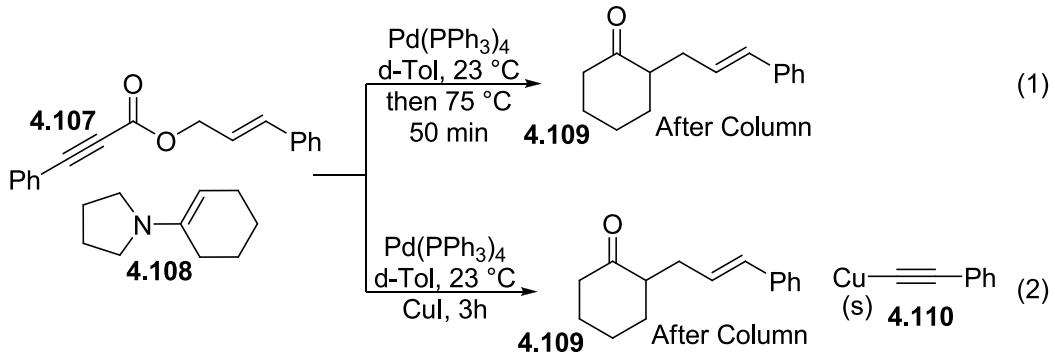
Table 4.8 Attempted Interceptive DCA with Enamines.



Entry	Enamine	R	R_1	R_2	R_3	Temp °C	Comments
(1)	A	Me	Me	H	H	23, 95	Rapid allylation at rt, but the only sulfone formed was C
(2)	B	Me	Me	H	H	23, 110	Allylation slower at rt, but the only sulfone formed was C
(3)	B	Et	Et	H	Me	70, 95	only sulfone formed, was C
(4)	A	Ph	H	Ph	H	23	Protonation,MonoC-allyl,DiC-allyl, enamine-allyl 1:1:0.5:0.1

We next looked briefly at the ability of phenyl propiolate allyl ester to undergo interceptive-DCA. We hoped that the reduced steric size of the nucleophile might help facilitate attack of the iminium. Again, allylation of the enamine rapidly occurred to give a presumed ionic liquid in toluene. However, upon decarboxylation only protonation of the acetylene was observed (entry 1, Scheme 4.40). There are two nonobvious observations that might have significant implications; 1) the Pd-catalyzed step is fast and

therefore the catalyst loading can potentially be reduced from what it typically is in the noninterceptive reaction and 2) the resting state of the catalyst is most likely not a Pd(II)-allyl species. This could have implications, especially in reactions in which Pd(II) species were implicated to facilitate decarboxylation. For instance, the Pd-acetylide is likely less basic than the iminium acetylide. We believe that most of the Pd is a Pd(0) species and not a Pd(II)-acetylide-the implication is that a much more basic acetylide was forming. We thought perhaps the addition of a Cu(I) salt might lead to a more stabilized Cu-acetylide that would be less basic and more likely to undergo C-C bond formation. However, the CuI salt was not soluble and formed a red brick like precipitate but still seemed to catalyze the decarboxylation as the reaction had reached completion within 3h at room temperature.



Scheme 4.40

Given the potential implications of a resting state that is an electrophilic species (Pd-π-allyl) that might be intercepted to make multiple C-C bonds in a single reaction and the absence of this in the literature we will likely continue our investigation in this area.

To summarize, we have attempted to develop an interceptive DCA in which a nucleophile attacks the Pd-π-allyl first before undergoing a second carbon-carbon bond forming reaction. We have found several systems in which one of the desire bonds are made but none in which the second bond is made. We also investigated the 3,3-sigmatropic rearrangement and decarboxylation of α-sulfonyl allyl acetates and have found it most likely to be stereospecific with respect to the racemic α-position. We briefly looked at orotic acid decarboxylation. Interestingly, we were able to deuterate every position of the orotic acid. This suggest that the conjugate addition is occurring but from the wrong direction. We briefly looked at the ability to facilitate Pd-DCA of malonic esters via use of a Lewis acid cocatalyst. We found that the cocatalyst almost always retarded the decarboxylation event. It was rationalized by a stabilization of the carboxylate rather than the incipient enolate. We also looked at extending decarboxylative coupling to aryl esters via nickel catalysis. Unfortunately we were unsuccessful but learned a few things and saw some potential in a couple of side reactions. We also briefly looked at the Pd-DCA of an α-sulfide allyl ester, which appeared to slowly decarboxylate though the reaction was not clean. In addition we briefly looked at the ability of α-chloro α-sulfide esters to undergo electrophilic aromatic substitution. We successfully found conditions to facilitate a desulfitative allylation. We also investigated the ability to use decarboxylation to ring open an adjacent epoxide but found that in this system other chemistry occurred much more rapidly. We also investigated the vinylogous DCA for a sulfonyl ester and a diester which had some promising results. We also made and briefly investigated the reactivity of an α-

pyridinium salt of an allyl ester in the presence of palladium. We also developed conditions for a Suzuki cross coupling of unsubstituted α-halo esters.

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Appendix D: General Methods and Compound Characterization

Materials. All moisture sensitive reactions were run in flame-dried glassware under an Ar atmosphere using standard Schlenk techniques. Methylene chloride, toluene, THF, Et_2O wer dried over activated alumina and toluene and THF were then distilled over sodium. Acetone was distilled from magnesium sulfate and stored over activated mol sieves. Commercially available reagents were used without additional purification unless otherwise stated. Tris(dibenzylideneacetone) dipalladium (0), $Pd(PPh_3)_4$, and rac-BINAP were purchased from Strem and stored in a glovebox under an Ar atmosphere. Compound purification was effected by flash chromatography using 230x400 mesh, 60 Å porosity, silica obtained from Sorbent Technologies. Thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5715-7, EMD chemicals). Visualization of the plateswas accomplished with a UV lamp (254 nm) or $KMnO_4$ stain. ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance 400 or a Bruker Avance 500 DRX, or a Bruker AVIII 500 spectrometer and referenced to residual protio solvent signals (some spectra were taken using a broadband observe probe and a dual 13C/1H Cryoprobe). Structural assignments are based on ^1H, ^{13}C, DEPT-135, COSY, HSQC and IR spectroscopies. FTIR spectra were recorded using either a ATI Mattson Genesis Series FTIR or Shimadzu 8400-S FTIR spectrometers. High Resolution Mass Spectrometry (HRMS) were performed using EI, ESI, and FAB techniques. EI MS spectra were obtained on an AUTOSPEC-Q tandem hybrid mass spectrometer (VG Analytical Ltd, Manchester, UK). ESI MS spectra were acquired either on a LCT Premier (Waters Corp., Milfpord, MA) or Q-Tof-2 (Microsmass Ltd, Manchester UK) spectrometers. FAB MS

spectra were obtained on a ZAB HS mass spectrometer (VG Analytical Ltd, Manchester UK). Elemental Analyses were performed by Desert Analytics Laboratory (Tuscon, AZ). Chiral high pressure liquid chromatography was performed on a Shimadzu SCL-10AVP instrument using Daicel Chiralpak AD, AS and OD-H columns.

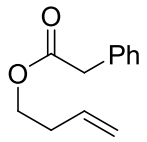
Procedure for Scheme 4.1. To an NMR tube was added cyclohex-2-enyl 2,2,2-trichloroacetate (0.0394 mmol). The tube was taken into the glovebox where $Pd(PPh_3)_4$ (0.00394 mmol), and d_6-benzene (0.5 mL) were added. The NMR tube was fitted with a rubber septum and taken out. The reaction was heated at 80 °C and the reaction monitored by ^1H NMR spectroscopy.

Procedure for Scheme 4.3. To an NMR tube was added cinnamyl 2-bromoacetate (0.0413 mmol). The tube was taken into the glovebox where Pd_2dba_3 (0.00216 mmol), DPPF (0.00432) and d_8-toluene (0.5 mL) were added. The NMR tube was fitted with a rubber septum and taken out. Et_3N (0.0455 mmol) was injected and the reaction was heated at 70 °C and the reaction monitored by ^1H NMR spectroscopy.

Procedure for Scheme 4.4.[1] To a Schlenk flask equipped with stir bar was added but-3-enyl 2-bromoacetate (0.513 mmol), $PdCl_2$ (0.0256 mmol), sodium formate (0.103 mmol), NaOAc (0.564 mmol). The atmosphere of the flask was exchanged for Ar and DMF (0.5 mL) was added and the reaction was heated to 140 °C. The reaction was extracted with 9:1 hexanes:Et_2O, washed with H_2O (4X), dried and concentrated.

Procedure for Scheme 4.5. To an NMR tube were added but-3-enyl 2-bromoacetate (0.104 mmol), $Pd(OAc)_2$ (0.00518 mmol), CuI (0.00518 mmol). The tube was taken into the glovebox where P*t*Bu_2(*o*-biphenyl) (0.0104) and d_3-MeCN (0.5 mL) were added. The NMR tube was fitted with a rubber septum and taken out. Et_3N (0.311 mmol) and phenyl acetylene (0.155 mmol) were injected and the reaction was heated at 50 °C and the reaction monitored by ^1H NMR spectroscopy.

General procedure for Suzuki coupling; procedure for Scheme 4.6. To a Schlenk flask equipped with stir bar was added but-3-enyl 2-bromoacetate (0.777 mmol), $Pd(OAc)_2$ (0.0777 mmol), $PhB(OH)_2$ (1.166 mmol), KF (2.332 mmol). The flask was taken into the glovebox where P*t*Bu_2(*o*-biphenyl) (0.155) and THF (3 mL) were added. The reaction was stirred at 23 °C overnight. The reaction was concentrated and purified by flash chromatography.



but-3-enyl 2-phenylacetate

(**4.12**)(JW1231)

99% Yield

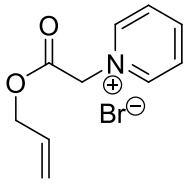
Purificiation: Flash chromatography (95:5 hexane Et_2O)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.12 (m, 5H, ArC*H*'s), 5.85 – 5.52 (m, 1H, RC*H*CH_2), 5.02 (ddd, *J* = 8.7, 5.1, 1.4 Hz, 2H, RCHC*H*$_2$), 4.10 (td, *J* = 6.7, 1.3 Hz, 2H, ROC*H*$_2$R), 3.58 (d, *J* = 12.8 Hz, 2H, PhC*H*$_2$$CO_2$R), 2.39 – 2.26 (m, 2H, $ROCH_2CH_2CHCH_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.75 (s, R*C*O_2R), 134.24 (s, R*C*HCH_2), 134.06 (s, Ar*C*), 129.46 (s, Ar*C*'s), 128.72 (s, Ar*C*'s), 127.25 (s, Ar*C*), 117.48 (s, RCH*C*H_2), 64.07 (s, RO*C*H_2R), 41.59 (s, Ph*C*$H_2$$CO_2$R), 33.23 (s, $ROCH_2CH_2CHCH_2$).

Procedure for Scheme 4.7.[2] To a Schlenk flask equipped with stir bar, 2-bromo-2-phenylpropanal (0.255 mmol), $Pd(OAc)_2$ (0.0127 mmol), *trans*-syrylB$(OH)_2$ (0.306mmol), K_3PO_4 (1.275 mmol), P(*o*-Tol)$_3$ (0.0383), H_2O (0.510 mmol) and THF (3 mL) were added. The reaction was stirred at 23 °C for 17 h. The reaction was concentrated and purified by flash chromatography to afford the diene.

Synthesis of α-pyridinium bromide; Scheme 4.8. To a flame dried Shlenk tube, equipped with stir bar was added allyl 2-bromoacetate (1.12 mmol) and the atmosphere was exchanged for Ar. Then pyridine (1.24 mmol) and MeCN (5 mL) were added and stirred overnight at 23 °C. The reaction was concentrated and azeotroped. No further purification was needed.



1-(2-(allyloxy)-2-oxoethyl)pyridinium bromide

(**4.19**) (JW2029)

99% Yield

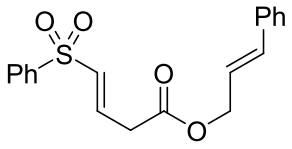
Purification: Azeotropic removal of trace pyridine

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, *J* = 5.6 Hz, 2H, ArC*H*'s), 8.51 (t, *J* = 7.8 Hz, 1H, ArC*H*), 8.17 – 8.01 (m, 2H, ArC*H*'s), 6.43 (s, 2H, ArCH_2CO_2R), 5.88 (ddt, *J* = 16.3, 10.4, 6.0 Hz, 1H, $ROCH_2CHCH_2$), 5.30 (ddd, *J* = 13.8, 11.5, 1.2 Hz, 2H, $ROCH_2CHCH_2$), 4.69 (dd, *J* = 5.9, 1.2 Hz, 2H, $ROCH_2CHCH_2$), 2.01 (s, *J* = 19.7 Hz, 3H, CH_3CN).

Procedure for Scheme 4.8. To an NMR tube were added 1-(2-(allyloxy)-2-oxoethyl)pyridinium bromide (0.0778 mmol). The tube was taken into the glovebox where , $Pd(PPh_3)_4$ (0.00389 mmol) and d_3-MeCN. The NMR tube was fitted with a rubber septum and taken out. The reaction was heated at 50 °C and the reaction monitored by ^{1}H NMR spectroscopy.

Procedure for Scheme 4.10. To a Schlenk flask equipped with stir bar, butyl acrylate (5.20 mmol), cinnamyl but-3-enoate (1.73 mmol), Grubb's 2nd generation catalyst (0.173 mmol) and toluene (8 mL) were added. The reaction was stirred at 110 °C for 18 h with

a constant flow of Ar. The reaction was concentrated and purified by flash chromatography to afford the product in 12%.



(E)-cinnamyl 4-(phenylsulfonyl)but-3-enoate

(**4.30**) (JW2066)

9% Yield

Purification: flash chromatography (90:10 hexanes:ethyl acetate)

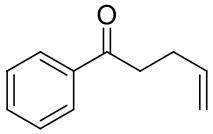
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.17 (m, 10H), 6.66 (d, *J* = 15.9 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.38 – 6.23 (m, 2H), 4.77 (dd, *J* = 6.5, 1.2 Hz, 2H), 3.29 (dd, *J* = 7.1, 1.3 Hz, 2H).

Procedure for Table 4.1. To an NMR tube was added (E)-1-butyl 5-cinnamyl pent-2-enedioate (5 mg). The tube was taken into the glovebox where , $Pd(PPh_3)_4$ (1 mg) and $MeCl_2$ (0.5 mL) were added. The NMR tube was fitted with a rubber septum and taken out. The reaction was heated at 40 °C after 18 h the reaction was concentrated and taken up in $CDCl_3$ and checked by ^{1}H NMR spectroscopy.

Procedure for Table 4.2. Same as the procedure for table 4.1 exception one sample run with deuterated solvent and was monitored by ^{1}H NMR spectroscopy.

Procedure for Table 4.3. To an NMR tube was added allyl 3-phenyloxirane-2-carboxylate (0.0294 mmol). The tube was taken into the glovebox where , $Pd(PPh_3)_4$ (0.00147 mmol) and CH_2Cl_2 (0.5 mL) were added, and then TMSOTf (0.0323 mmol) was added. The NMR tube was fitted with a rubber septum and taken out. The reaction was heated at 40 °C after 13 h the reaction was concentrated and taken up in $CDCl_3$ and checked by ^{1}H NMR spectroscopy.

Procedure for Table 4.4. To an NMR tube was added 2-(allylsulfonyl)-1-phenylethanone (0.0223 mmol). The tube was taken into the glovebox where $Pd(PPh_3)_4$ (0.00112 mmol) and d_8-toluene (0.5 mL) were added. The NMR tube was fitted with a rubber septum and taken out. The reaction was heated at 100 °C and within 13 h the starting material was consumed to afford, what appears to be, a single product by ^{1}H NMR spectroscopy.



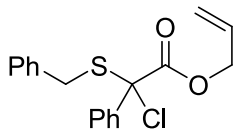
1-phenylpent-4-en-1-one

(Entry 4 from Table 4.4)(JW3226)

100% Yield by ^{1}H NMR spectroscopy

^{1}H NMR (400 MHz, Tol) δ 7.82 (s, 0H), 7.78 – 7.63 (m, 4H), 7.08 (ddd, *J* = 27.0, 18.0, 11.7 Hz, 11H, ArC*H*'s and PPh_3), 5.78 (dt, *J* = 16.8, 8.4 Hz, 1H, $CH_2CHCH_2CH_2COPh$), 5.04 – 4.93 (m, 2H, $CH_2CHCH_2CH_2COPh$), 2.56 (t, *J* = 7.2 Hz, 2H, $CH_2CHCH_2CH_2COPh$), 2.40 (t, *J* = 7.0 Hz, 2H, $CH_2CHCH_2CH_2COPh$).

Procedure a for Scheme 4.15. To a Schlenk flask equipped with stir bar, allyl 2-(benzylthio)-2-phenylacetate (0.134 mmol), NCS (0.134 mmol) and CCl_4 (1.3 mL) were added. The reaction was stirred at 23 °C for 13 h. The reaction was extracted with Et_2O and washed with bicarb (2X) and dried with magnesium sulfate and concentrated. No further purification was needed and the compound was found to be unstable on silica.



allyl 2-(benzylthio)-2-chloro-2-phenylacetate

(**4.48**)(JW4008)

100% Yield by ^{1}H NMR spectroscopy

Purification: None. (No Silica)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.68 (m, 2H, ArC*H*'s), 7.44 – 7.19 (m, 8H, ArC*H*'s), 5.84 (ddd, *J* = 22.7, 10.9, 5.6 Hz, 1H, RC*H*CH_2), 5.24 (ddd, *J* = 13.8, 11.5, 1.2 Hz, 2H, RCHC*H*$_2$), 4.68 – 4.55 (m, 2H, ROC*H*$_2$R), 3.99 (d, *J* = 11.8 Hz, 1H, PhC*H*HSR), 3.84 (d, *J* = 11.8 Hz, 1H, PhCH*H*SR).

Procedure a for Scheme 4.15. To an NMR tube were added allyl 2-(benzylthio)-2-chloro-2-phenylacetate (0.0150 mmol), indole (0.300 mmol) and d_2-CH_2Cl_2 (0.5 mL). Then $SnCl_4$ (0.0150 mmol) was added. After 5 minutes the reaction was extracted with CH_2Cl_2 and washed with 3N HCl, H_2O, dried and concentrated. Flash chromatography was performed (80:20 hexanes:ethyl acetate). However, new signals were formed during workup or purification; the stability of the compounds formed are uncertain.

Procedure for Scheme 4.16. To an NMR tube was added allyl 2-(benzylthio)-2-chloro-2-phenylacetate (0.0150 mmol). The tube was taken into the glovebox where $Pd(PPh_3)_4$ (0.00151 mmol) and d_8-toluene (0.5 mL) were added. The NMR tube was fitted with a

rubber septum and taken out. The reaction was run at several temperatures up to 100 °C and monitored by ^{1}H NMR spectroscopy.

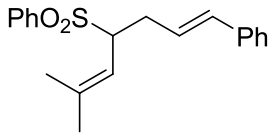
Procedure for Table 4.4. To an NMR tube were added naphthalen-2-yl 2,2-dimethyl-3-oxobutanoate (0.0195 mmol), $NiCl_2(PCy_3)_2$ (0.00195 mmol), ρ-$MeOC_6H_4B(OH)_2$ (0.0488 mmol), K_3PO_4 (0.0878) and the atmosphere was exchanged for Ar. Then d_8-toluene (0.5 mL) was added. The reaction was heated at 110 °C unfortunately the reaction is difficult to monitor by ^{1}H NMR spectroscopy due in part to the heterogeneity and perhaps the metal. After 20 h the reaction was stopped and the mixture passed over a mini-column to afford a compound that matches the Suzuki product.

Procedure for Table 4.6. To an NMR tube was added diallyl 2,2-dimethylmalonate (0.0283 mmol) and taken into the glovebox. $Pd(PPh_3)_4$ (0.00283 mmol), [(0.3 eq) additive] and d_8-toluene (0.5 mL) were added. The reaction was heated at the indicated temperature and reaction progress was monitored by ^{1}H NMR spectroscopy.

Procedure for Scheme 4.26. To a microwave vial with stir bar were added orotic acid (0.1 mmol), DMAP (0.12 mmol) and D_2O (0.5 mL). The vial capped and the vessel heated in the μwave reactor at 200 °C for 2 h. By ^{1}H NMR spectroscopy the orotic acid had been completely consumed and no new product could be found.

Procedure for Scheme 4.30 (eq 1). To a dried microwave vial with stir bar were added 1-phenylallyl 4-methyl-2-(phenylsulfonyl)pent-3-enoate (0.135 mmol), BSA (0.135

mmol), *dry* KOAc (0.0135 mmol) and toluene (0.5 mL). The vial capped and the vessel heated in the μwave reactor at 160 °C for 10 minutes. The product was recrystallized from hot solution of 95:5 hexanes:ethyl acetate. The starting material was contaminated with vinyl sulfone which is unreactive under these conditions.



(E)-(6-methyl-1-phenylhepta-1,5-dien-4-ylsulfonyl)benzene

(**4.82**)(JW6135)

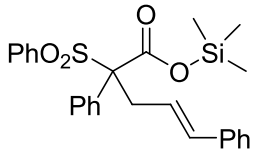
100% Yield by ^{1}H NMR spectroscopy (contaminated with starting material isomer)

Purification: Crystallization (95:5 hexanes:ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.61 – 7.51 (m, 1H), 7.38 – 7.16 (m, 7H), 6.47 (d, *J* = 15.7 Hz, 1H), 6.11 – 6.01 (m, 1H), 5.27 – 5.19 (m, 0H), 5.06 (d, *J* = 10.3 Hz, 1H), 3.87 (td, *J* = 10.4, 3.6 Hz, 1H), 3.12 – 3.02 (m, 1H), 2.65 – 2.56 (m, 1H), 1.70 (d, *J* = 1.2 Hz, 3H), 1.19 (d, *J* = 1.2 Hz, 3H), 1.13 (dt, *J* = 10.6, 5.3 Hz, 0H).

Chiral HPLC Column: Chiracel Chiralpak-OD-H column. **Eluent:** 95:5 Hexanes:isopropanol. **Flow rate:** 1 mL/min. **Wavelength:** 210 nm. **Retention times:** R_t = 12 minutes, R_t = 21 minutes.

Procedure for Scheme 4.30 (eq 2). To a dried microwave vial with stir bar was added 1-phenylallyl 2-phenyl-2-(phenylsulfonyl)acetate (0.0545 mmol) and the vial was sealed under an atmosphere of Ar, **then** DCM (0.27 mL) and DBU (0.0572 mmol) finally TMSOTf (0.0572 mmol) were injected. The vial was heated in the μwave reactor at 90 °C for 15 minutes. The product was subjected to 3N HCl (1 mL) and $CHCl_3$, CD_2Cl_2 and MeOH were present as cosolvents and stirred for 5 h at 50 °C. Then the solution was made basic by the addition of 30% MeONa/MeOH solution (0.05 mL) and stirring was continued for 8 h. The reaction was extracted with Et_2O and washed with H_2O. Separation on chiral staitionary phase HPLC revealed that the product was not more than 6% ee.



(E)-trimethylsilyl 2,5-diphenyl-2-(phenylsulfonyl)pent-4-enoate

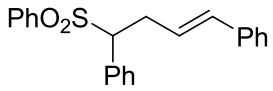
(**4.85**int. from Scheme 4.30)(JW6234)

90-95% conversion by ^{1}H NMR spectroscopy

Purification: NA

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (t, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 7.3 Hz, 2H), 7.40 – 7.17 (m, 14H), 6.52 (d, *J* = 15.7 Hz, 1H), 6.32 – 6.22 (m, 1H), 3.72 (dd, *J* = 14.8, 6.7 Hz,

0H), 3.57 – 3.46 (m, 0H), 3.45 – 3.35 (m, 0H), 2.74 (d, *J* = 6.1 Hz, 0H), 2.09 – 1.99 (m, 0H), 1.73 (d, *J* = 34.2 Hz, 0H), 0.26 (s, 9H).



(E)-(4-(phenylsulfonyl)but-1-ene-1,4-diyl)dibenzene

(**4.85**)(JW6235)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 0H), 7.57 (d, *J* = 7.9 Hz, 3H), 7.47 (s, 0H), 7.47 – 7.12 (m, 14H), 6.45 (d, *J* = 15.8 Hz, 1H), 6.00 – 5.88 (m, 1H), 4.19 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.38 (s, 1H), 3.12 (d, *J* = 18.0 Hz, 1H).

Chiral HPLC Column: Chiracel Chiralpak-AS-H column. **Eluent:** 95:5 Hexanes:isopropanol. **Flow rate:** 0.9 mL/min. **Wavelength:** 210 nm. **Retention times:** R_t = 42 minutes, R_t = 45 minutes.

Procedure for Scheme 4.33, 34, 35, 36, 37, 38, 40 and table 4.7, 8. To a flame dried NMR tube were added 3-methylbut-2-enyl 2-methyl-2-(phenylsulfonyl)propanoate or appropriate substrate (0.100 mmol) and benzylidene malononitrile or appropriate interceptive partner (0.100 mmol) and taken into the glovebox. The catalyst $Pd(PPh_3)_4$ (0.01 mmol) or Pd_2dba_3 (0.005 mmol) / (±)-BINAP (0.010 mmol) and d_8-toluene or indicated solvent (0.5 mL). The tube was capped and removed from the glovebox and

the reaction was heated at 110 °C or indicated temperature. The reaction progress was monitored by ^{1}H NMR spectroscopy. This is the typical procedure for interceptive screening. One exception, if the intercepting molecule was too volatile to be taken into the glovebox it was simply added after the NMR tube was removed from the glovebox but prior to heating.

Procedure for stoichiometric Pd-reactions, Scheme 4.39. To an NMR tube was added substrate, allyl 2-methyl-2-(phenylsulfonyl)propanoate (0.32 mmol) and taken into glovebox where Pd_2dba_3 (0.16 mmol), or (and 1.0 eq of PPh_3) and *d*-$CHCl_3$ were added. The NMR tube was fitted with a rubber septum and taken out of the glovebox. Cyclohexadiene (0.32 mmol) was injected and the reaction warmed to room temperature.