CHAPTER FOUR

The Development of an Asymmetric Tsuji Allylation Reaction[†]

4.1 Introduction

The catalytic asymmetric synthesis of all-carbon quaternary stereocenters stands as a significant challenge in synthetic chemistry.[1] Despite the demanding sterics, a number of useful catalytic transformations, including Diels-Alder,[2] Heck,[3] cyclopropanation,[4] alkylation,[5] acylation,[6] and desymmetrization[7] reactions, have been demonstrated to form quaternary stereocenters with good levels of enantioinduction. Although palladium-catalyzed enantioselective allylation chemistry has long been an important asymmetric catalytic tool,[8] only recently has palladium (II) π-allyl chemistry been used for the formation of quaternary stereocenters. The vast majority of palladium (II) allylic alkylations studied by Trost, Helmchen, Pfaltz, and others form tertiary stereocenters by the attack of malonate anions on prochiral 1,3-disubstituted allyl fragments. Helmchen has shown that such reactions with palladium phosphinooxazoline (PHOX) complexes typically occur via an outer sphere malonate attack at the allyl termini.[9] The tendency of palladium to give the less branched products in allylic alkylations with differentially substituted allyl termini makes the formation of quaternary stereocenters on the allyl fragment problematic.[10]

An alternative, less common strategy in allylic alkylation is the use of prochiral nucleophiles. A quaternary stereocenter may formed on the prochiral nucleophile when it possesses three distinct carbon substituents. A priori, such reactions requiring the remote

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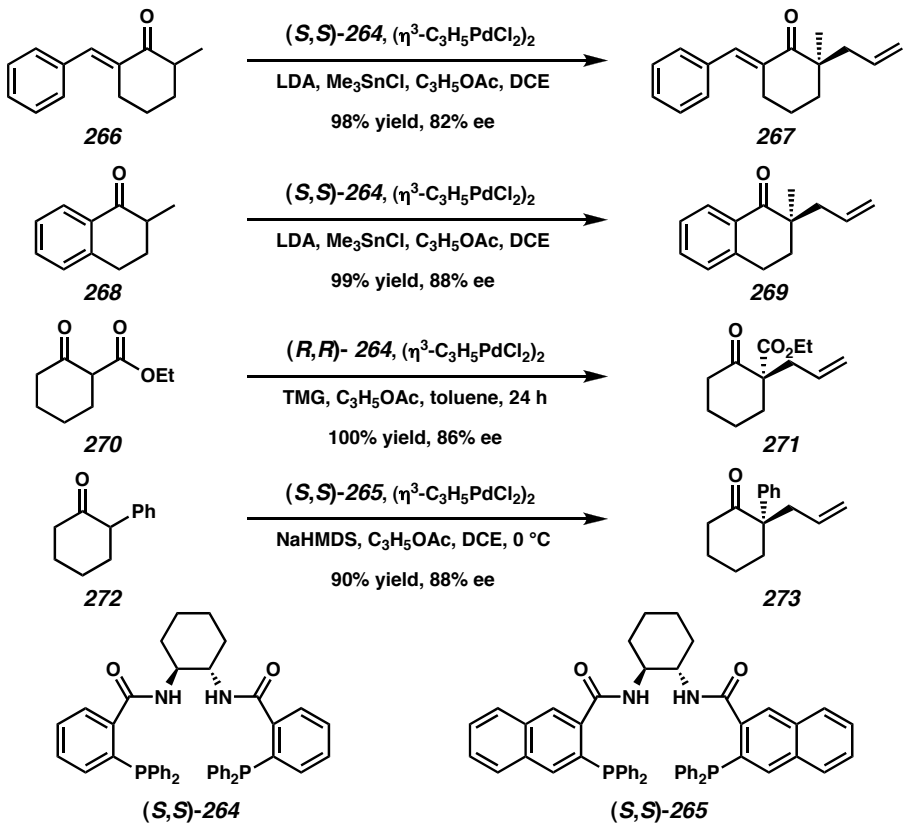
[†] This work was performed in collaboration with Justin Mohr, Dr. Andrew Harned, Dr. Kousuke Tani, Dr. Zoltán Novák, Sandy Ma, Nathaniel Sherden, Mike Krout, and Ryan McFadden.

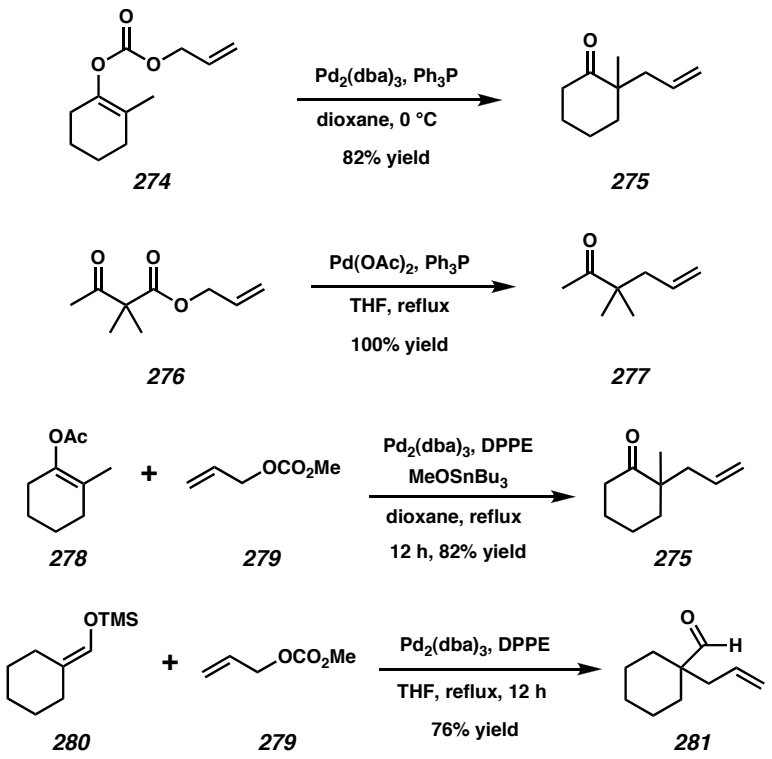
chiral ligand to discriminate between the prochiral faces of the incoming nucleophile seem improbable. However, Hayashi[11] and Ito[12] have demonstrated the asymmetric allylation of prochiral enolates derived from 1,3-dicarbonyl compounds. Trost and coworkers demonstrated that diamine-derived ligands **264** and **265**, which were designed to project bulk forward of the allyl fragment due to their large bite angle, are able to favor one face of the in situ generated ketone enolate (Scheme 4.1).[13] These reactions represent a significant advance in asymmetric allylation technology by forming quaternary stereocenters with excellent yield and good ee. However, the substrate scope of these reactions was limited by the restriction that the ketone contain either a single acidic site (e.g., ketone **266** and tetralone **268**) or two α sites that have a large difference in acidity (e.g., β-ketoester **270** and phenyl ketone **272**).[1a] These limitations prevented direct access to simple α-quaternary ketones, such as 2-methyl-2-allylcyclohexanone **275**. Indeed, this simple cyclohexanone derivative was not known as a single enantiomer prior to our work.

Scheme 4.1 Trost's Allylic Alkylations with Prochiral Nucleophiles



We were confronted by these limitations during studies toward the synthesis of several natural products. A survey of the literature revealed that the non-enantioselective allylation reactions developed by Tsuji in the early 1980s had the proper reactivity and selectivity to form quaternary stereocenters in the presence of similarly acidic and less substituted ketone α sites (Scheme 4.2). Allyl enol carbonate **274** and allyl β-ketoester **276** contain both the latent enolate and allyl fragment.[14] Alternatively, enol acetate **278** and silyl enol ether **280** may serve as enolate precursors in intermolecular reactions with allyl carbonates.[15] These allylations have the advantage that reaction occurs under nearly neutral conditions and at mild temperatures. Despite these advantages, these allylation reactions have been utilized rarely during the interceding twenty years.[16]

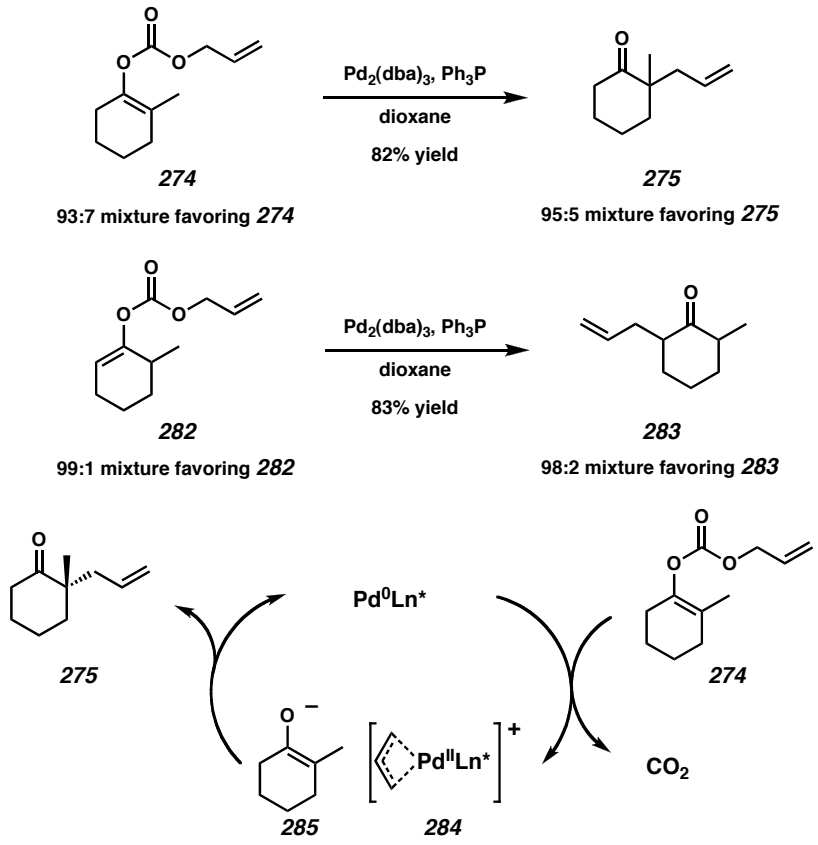
Scheme 4.2 Tsuji's Allylation Methods



Our analysis of Tsuji's allylation reaction showed it to be an ideal candidate for asymmetric catalysis. These high yielding allylation reactions are a clear case of ligand-accelerated catalysis, occurring only in the presence of phosphine ligands.[17] Of additional interest was the regiochemical fidelity observed in the allylation reactions (Scheme 4.3). Tsuji demonstrated that both the tetrasubstituted allyl enol carbonate isomer **274** and the trisubstituted allyl enol carbonate isomer **281** undergo reaction to give allylated ketones **275** and **283** in ratios essentially unchanged from that of the substrates.[14a] These reactions are believed to proceed via oxidative addition to the allyl fragment and loss of CO_2 to give Pd(II)(allyl) complex **284** and enolate **285**. However, the details involving the recombination of the ion pair to give cyclohexanone **275** and Pd(0) were unclear at the time of Tsuji's original reports. Coupled with the ability to

purify the stable enolate precursors, we believed that the regiochemical fidelity afforded in the palladium-catalyzed reaction would provide direct access to enantioenriched α-quaternary ketones if a suitable chiral ligand could be found.

Scheme 4.3 Regiochemical Fidelity in Tsuji's Palladium-Catalyzed Allylation



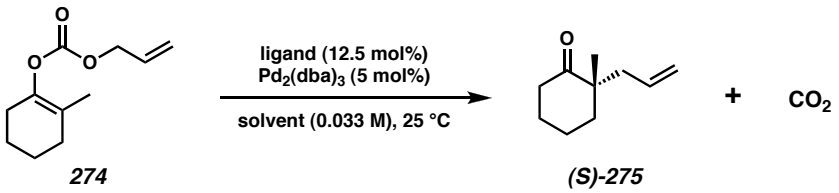
4.2 Results and Discussion

4.2.1 *Initial Screening of Chiral Ligands*

Our initial goal was to show that a chiral ligand could transmit useful levels of asymmetric induction in the reaction while maintaining the important property of enolate regiochemical fidelity found in the non-enantioselective system. We chose allyl enol carbonate **274** as a simple test substrate to evaluate the effect of various ligands (Table

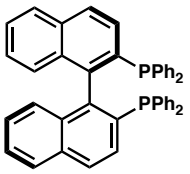
4.1). Although allyl enol carbonates are less common than the other enolate precursors explored by Tsuji, they allowed us to add a single reagent to our catalyst system without extraneous initiators or counter ions that might affect enantioselectivity. In accord with Tsuji's reports, we performed our initial trials in 1,4-dioxane solvent. Due to the prevalence of bisphosphine ligands in asymmetric catalysis, we began with several privileged bisphosphine ligands, but found that only Trost's ligand **264** gave significant ee. However, commercially available (*R*)-QUINAP (**290**), a chelating N/P-type ligand, gave more uniform ee. It is noteworthy that despite our change from monodentate ligands (i.e., PPh_3) to N/P chelates, high levels of conversion are still observed. Encouraged, we quickly found that the phosphinooxazoline (PHOX) class of N/P-type ligands also provides excellent reactivity and promising levels of enantioselectivity. The ready availability of numerous amino acid-derived PHOX ligands[18] allowed us to rapidly identify that bulkier aliphatic R groups provided higher levels of enantioinduction, with (*S*)-*t*-Bu-PHOX providing α-quaternary ketone **275** in 86% ee when 1,4-dioxane was used as solvent. Additionally, we found that the use of THF typically gave slightly higher ee in reactions with (*R*)-*i*-Pr-PHOX and (*S*)-*t*-Bu-PHOX.[19] Having attained satisfying levels of enantioselectivity and selectivity in forming ketone **275**, we began a more thorough investigation of reaction conditions.

Table 4.1 Initial Ligand Screen

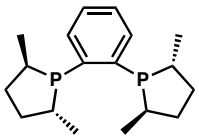


274 *(S)-275*

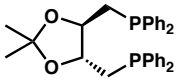
		1,4-dioxane			THF		
entry	ligand	time (h)	% yield[a]	% ee[b]	time (h)	% yield[a]	% ee[b]
1	*(R)-BINAP (286)*	5	92	5[c]	5	76	2[c]
2	*(R,R)-Me-DUPHOS (287)*	5	61	0	5	66	0
3	*(R,R)-DIOP (288)*	2	91	2[c]	2	59	2[c]
4	*(R)-MOP (289)*	3	93	18	3	47	13
5	*(R,R)-Trost ligand (264)*	2	97	46[c]	5	92	64[c]
6	*(R)-QUINAP (290)*	2	98	61	2	97	61
7	*(R)-Ph-PHOX (291)*	2	95	62[c]	2	95	65[c]
8	*(S)-Bn-PHOX (292)*	3	96	65	5	94	63
9	*(R)-i-Pr-PHOX (293)*	3	96	82[c]	2	95	83[c]
10	*(S)-t-Bu-PHOX (294)*	2	95	86	2	96	88



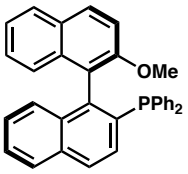
(R)-BINAP (286)



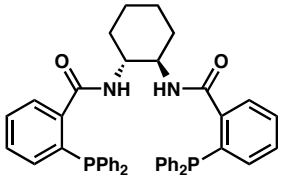
(R,R)-Me-DUPHOS (287)



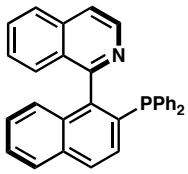
(R,R)-DIOP (288)



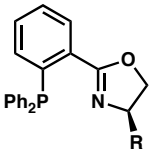
(R)-MOP (289)



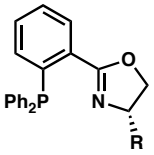
(R,R)-Trost ligand (264)



(R)-QUINAP (290)



R = Ph
(R)-Ph-PHOX (291)
R = i-Pr
(R)-i-Pr-PHOX (293)



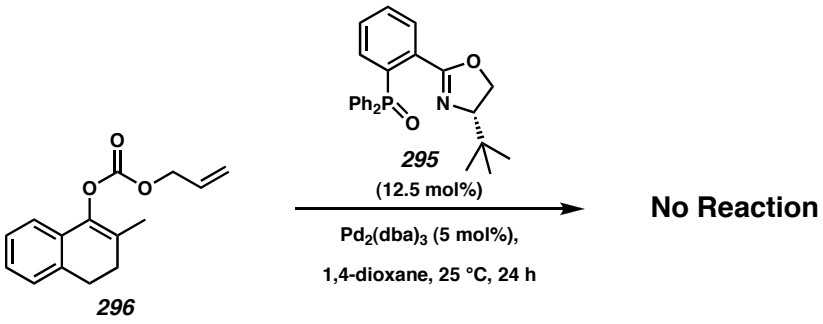
R = Bn
(S)-Bn-PHOX (292)
R = t-Bu
(S)-t-Bu-PHOX (294)

[a] GC yield relative to internal standard (tridecane). [b] Enantiomeric excess measured by chiral GC. [c] (*R*)-***275*** produced as the major product.

4.2.2 *Optimization of Reaction Parameters*

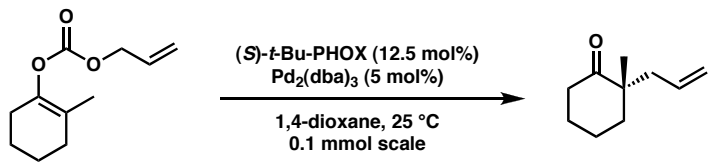
Tsuji's straightforward experimental procedure for allylation provided several opportunities to optimize the asymmetric reaction. One important experimental parameter is complexation time for the (*S*)-*t*-Bu-PHOX and $Pd_2(dba)_3$. Our optimal 30 minutes complexation time represents a balance between short complexation times (e.g., 5 minutes) in which lower yields but complete conversion were observed, and longer complexation times (e.g., 1-3 hours) in which poor conversion was observed. Long complexation times seem to be complicated by adventitious amounts of O_2 that readily oxidize the ligated PHOX molecule at phosphorus and prevent significant consumption of the starting material. We have independently synthesized (*S*)-*t*-Bu-PHOX oxide (**295**) and shown that it does not catalyze the allylation of tetralone-derived allyl enol carbonate **296** (Scheme 4.4).[20]

Scheme 4.4 Catalytic Inactivity of (*S*)-*t*-Bu-PHOX Oxide



In adapting Tsuji's non-enantioselective conditions, we also investigated the effect of concentration on the reaction (Table 4.2). At higher concentrations, significantly lower yields were observed, as well as slightly decreased ee. No further increase in enantioselectivity was observed below 0.03 M.

Table 4.2 Effect of Concentration on Asymmetric Allylation



274 *275*

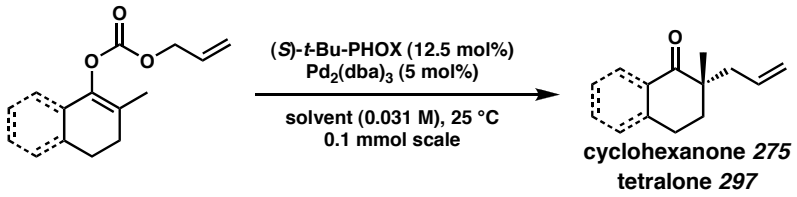
entry[a]	concentration (M)	time (h)	% yield[b]	% ee[c]
1	0.500	3	81	82
2	0.250	2	90	84
3	0.125	2	94	84
4[d]	0.063	2	99	85
5	0.031	2	95	86

[a] Data reported is the average of three trials. [b] GC yield relative to internal standard (tridecane). [c] Enantiomeric excess measured by chiral GC. [d] Data reported is the average of two trials.

Encouraged by our initial discovery that THF gave better levels of enantioinduction than 1,4-dioxane, we undertook a more thorough study of solvent effects on the reaction (Table 4.3). Many of the ethereal solvents investigated gave good results. Ethyl ether, *t*-butyl methyl ether (TBME), and diisopropyl ether all gave good yields and slightly higher ee than THF with allyl enol carbonate **274** (Entries 3 to 5). However, the methyl tetralone-derived allyl enol carbonate **296** gives substantially lower enantioselectivity in ethyl ether and TBME. The catalyst system's poor solubility in these solvents occasionally led to incomplete conversion, a disadvantage that outweighed the slight increase in ee. Interestingly, several non-ethereal solvents also perform well in the reaction. Benzene and toluene gave similar yields and enantioselectivity as THF (Entries 8 and 9). Carbonyl containing solvents are tolerated in the reaction (Entries 10 and 13). Ethyl acetate gives good yields and enantioselectivity in the asymmetric allylation, while acetone gives inferior yield and enantioinduction. Interestingly, triethyl amine produces a level of enantioselectivity equal to the best ethereal solvents, albeit

with lower yields. Halogenated solvents fair poorly in the reaction, producing small amounts of product (Entries 14 and 15). Overall, we were surprised that a variety of solvents with vastly different lone pair donating abilities and polarities perform equally well.

Table 4.3 Effect of Solvent on Asymmetric Allylation



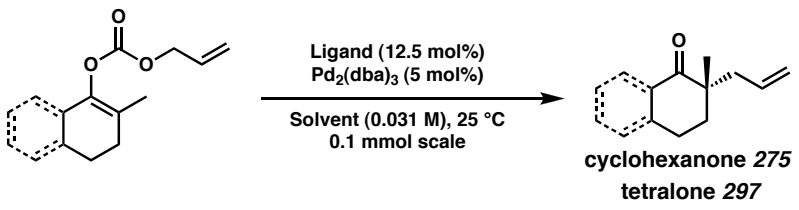
		275[a]			297[a,b]	
entry	solvent	time (h)	% yield[c]	% ee[d]	time (h)	% ee[e]
1	1,4-dioxane	2	95	86	1	87
2	tetrahydrofuran	2	96	88	1	88
3	ethyl ether	2	98	89	1	80
4	*t*-butyl methyl ether	2	98	89	1	78
5	diisopropyl ether	2	95	89		
6	anisole	3	82	81		
7	dimethoxy ethane	2	72	56		
8	benzene	2	99	88	1	89
9	toluene	2	99	88	1	87
10	ethyl acetate	2	97	86		
11	triethyl amine	2	72	89		
12	fluorobenzene	3	58	51		
13	acetone	3	26	60		
14	methylene chloride	3	42	13		
15	chloroform	6	0	NA		

[a] Data reported is the average of three trials. [b] All reactions went to complete conversion. [c] GC yield relative to internal standard (tridecane). [d] Enantiomeric excess measured by chiral GC. [e] Enantiomeric excess measured by chiral HPLC.

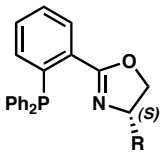
4.2.3 *Fine Tuning of Phosphinooxazoline Ligands*

A substantial effort was undertaken to improve the enantioselectivity of the reaction by modifying the PHOX ligand structure (Table 4.4).[21] Hoping to continue the trend of increasing enantioselectivity initially noted in moving from *i*-Pr to *t*-Bu-PHOX, we undertook the synthesis of numerous PHOX ligands with varied sterics and evaluated them in the reaction of allyl enol carbonates **274** and **296**. (Entries 1 to 9). In general, ligands bearing saturated substituents seem to perform better than those with aryl groups with respect to enantioselectivity. Moving the steric bulk away from the oxazoline framework by inserting a methylene group (i.e., ligand **299**) substantially lowers enantioselectivity. Of particular note are the L-serine-derived ligands **303** and **304**,[22] which allow access to the enantiomeric *R* product series with nearly the same level of enantioselectivity as *t*-Bu-PHOX, but without the need for prohibitively expensive (*R*)-*t*-Bu-glycine. The known 1-amino indanol-derived ligand **305** and bornyl-derived ligand **306**, both with uniquely shaped substituents, give slightly less enantioselectivity than *t*-Bu-PHOX.[23] It is noteworthy that regardless of the shape or type of the substituent on the PHOX ligand, they produced ketones with quaternary stereocenters with a consistent sense of configuration (e.g., (*S*)-PHOX ligands provide (*S*)-**275**). With *t*-Bu-PHOX established as the optimal steric frame work, we next considered the electronics of the ligand.

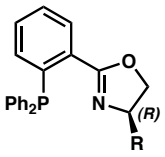
Table 4.4 Effect of Phosphinooxazoline Sterics on Asymmetric Allylation



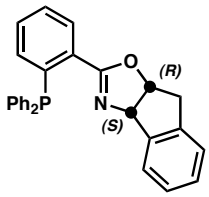
entry	ligand	product[a]	solvent	% ee[b]	major enantiomer
1	*294*	*275*	THF	88	*S*
2[c]	*298*	*297*	1,4-dioxane	78	*S*
3	*292*	*275*	THF	63	*S*
4	*299*	*297*	THF	59	*S*
5	*300*	*275*	THF	41	*S*
6	*293*	*275*	THF	83	*R*
7	*301*	*275*	THF	83	*R*
8	*291*	*275*	THF	85	*R*
9	*302*	*275*	THF	69	*R*
10	*303*	*297*	THF	85	*R*
11	*304*	*297*	THF	85	*R*
12	*305*	*297*	THF	79	*S*
13	*306*	*297*	THF	81	*S*



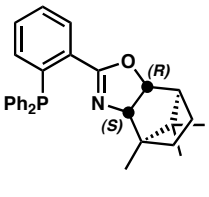
294, R = ***t*-Bu**
298, R = **1-Ad**
292, R = **Bn**
299, R = **CH_2-*t*-Bu**
300, R = **CH_2-1-Naphthyl**



293, R = ***i*-Pr**
301, R = **Cy**
291, R = **Ph**
302, R = **$CHPh_2$**
303, R = **$C(Me)_2OBn$**
304, R = **$C(Me)_2OTBS$**



305



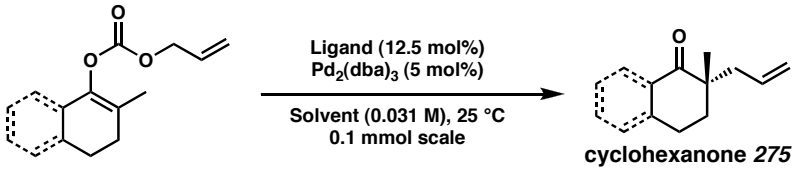
306

[a] All reactions went to complete conversion. [b] Enantiomeric excess measured by chiral HPLC or GC. [c] Reaction run at 0.2 M in 1,4-dioxane; result would likely be 3-5% ee higher under dilute concentrations in THF.

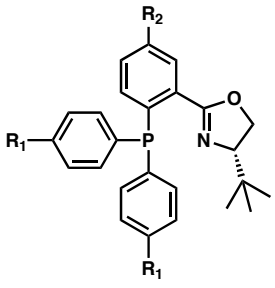
A number of *t*-Bu-PHOX derivatives were synthesized to probe the importance of phosphine electronics (Table 4.5). We investigated ligands ranging from electron rich to electron poor phosphines with allyl enol carbonates **296** and **274** (Entries 1 to 7 and 8 to

14, respectively). The electronic perturbation has no significant effect on reaction yield. However, electron releasing *para* substituents on the phenyl rings tend to lower the ee of the product relative to that observed with (*S*)-*t*-Bu-PHOX (Entries 1 and 8). When allyl enol carbonate **296** was used as the substrate, a slight increase in enantioselectivity is observed with electron withdrawing substitution at the *p*-phenyl positions (Entries 3 to 5). However, enantioselectivity decreases significantly with extremely electron poor PHOX ligands (Entries 6 and 7). This trend is not apparent in the enantioselectivities of cyclohexyl-derived allyl enol carbonate **274** (Entries 9 to 14).

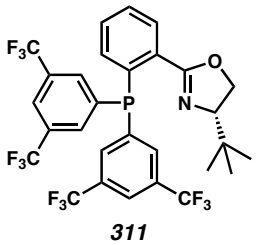
Table 4.5 Effect of Phosphine Electronics on Asymmetric Allylation



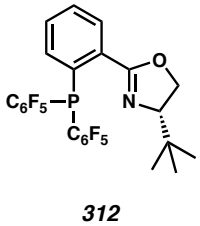
entry	ligand	product[a]	solvent	% ee[b]	entry	ligand	product	solvent	% yield[c]	% ee[d]
1	*307*	*297*	1,4-dioxane	81	8	*313*	*275*	THF	99	86
2	*294*	*297*	1,4-dioxane	87	9	*294*	*275*	THF	96	88
3	*308*	*297*	1,4-dioxane	88	10	*314*	*275*	THF	99	89
4	*309*	*297*	1,4-dioxane	89	11	*308*	*275*	THF	95	88
5	*310*	*297*	1,4-dioxane	90	12[e]	*309*	*275*	THF	97	87
6	*311*	*297*	1,4-dioxane	83	13[e]	*310*	*275*	THF	89	88
7	*312*	*297*	1,4-dioxane	81	14	*315*	*275*	THF	99	87



307, R_1 = Me, R_2 = H
294, R_1 = H, R_2 = H
308, R_1 = F, R_2 = H
309, R_1 = CF_3, R_2 = H
310, R_1 = H, R_2 = NO_2
313, R_1 = H, R_2 = OMe
314, R_1 = H, R_2 = CF_3
315, R_1 = CF_3, R_2 = CF_3



311

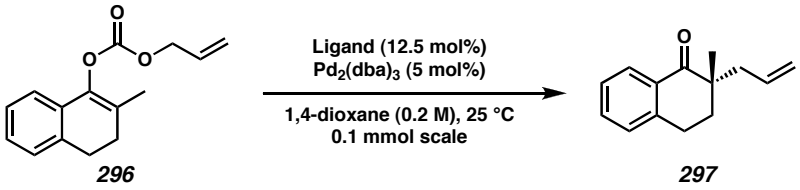


312

[a] All reactions went to complete conversion. [b] Enantiomeric excess measured by chiral HPLC. [c] GC yield relative to internal standard (tridecane). [d] Enantiomeric excess measured by chiral GC. [e] Data reported is the average of two trials.

As a final investigation into the PHOX ligand structure, we prepared a number of non-N/P mixed chelates based on the phenyl oxazoline skeleton of the PHOX ligands (Table 4.6). As mentioned above, the phosphine oxide of *t*-Bu-PHOX is inactive as a catalyst (Entry 2). Sulfur analogue **316** also fails to catalyze the reaction (Entry 3).[24] Moving down the periodic table from phosphorus, arsenic oxazoline analogue **317** has excellent activity as a catalyst, but gave tetralone **297** in only moderate ee (Entry 4). The nitrogen analogue **318** shows little activity as a catalyst, and the small amount of product produced is nearly racemic (Entry 5). As a final derivative that maintains the six-membered chelation, but changes the hybridization of the backbone atoms involved, known ligand **319** was found to give only moderate ee (Entry 6).[25]

Table 4.6 Effect of Varied Heteroatom Chelates on Asymmetric Allylation



296 ***297***

entry	ligand	% conversion[a]	% ee[b]
1	***294***, R = PPh_2	100	82
2	***295***, R = $P(O)Ph_2$	0	ND
3	***316***, R = SPh	0	ND
4	***317***, R = $AsPh_2$	100	52
5	***318***	<5	7
6[c]	***319***	87	56

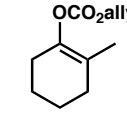
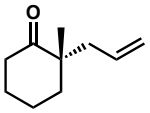
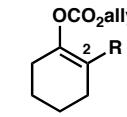
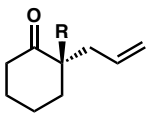
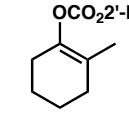
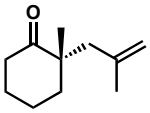
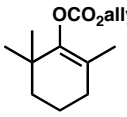
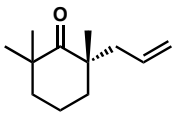
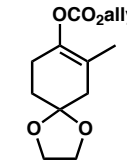
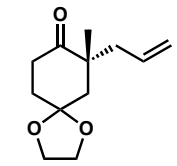
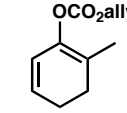
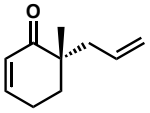
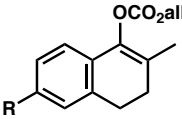
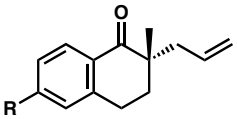
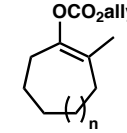
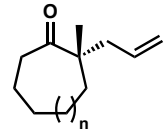
[a] Conversion based on TLC analysis. [b] Enantiomeric excess measured by chiral HPLC. [c] Trial performed with allyl enol carbonate ***274***. Conversion measured by GC relative to internal standard (tridecane). Enantiomeric excess measured by chiral GC.

Although some electron deficient derivatives of *t*-Bu-PHOX did provide slightly better enantioselectivities than those observed with *t*-Bu-PHOX on certain substrates, ultimately this slight improvement did not balance the added difficulty in synthesizing substituted PHOX ligands. Our studies clearly show that N/P chelates are particularly effective at inducing high levels of asymmetry in allylation. As a result, we retained the use of (*S*)-*t*-Bu-PHOX in our optimized conditions for exploring scope of the reaction.

4.2.4 *Asymmetric Allylation of Allyl Enol Carbonates*

A variety of allyl enol carbonates was demonstrated successfully in our asymmetric Tsuji allylation (Table 4.7).[26] Alkyl substitution at the 2-position of the allyl enol carbonates is well tolerated (Entries 4 to 7). *t*-Butyl substituted carbonate **322** is of note, as it forms a quaternary stereocenter vicinal to a quaternary carbon atom in the allylation. The allyl fragment may also be substituted at the internal position (Entry 8). Substitution at the 4 and 6 positions of the cyclohexyl ring do not greatly affect the rate or enantioselectivity of the process (Entries 9 and 10). Interestingly, unsaturation of the substrate still affords the desired α-quaternary ketone in excellent yield and good enantioselectivity (Entries 11 to 13). The isolation of enone **334** in excellent yield without the observation of any Michael products highlights the mild and nearly neutral reaction conditions. Performing the allylation reaction at 10-12 °C typically increases the enantioselectivity by 1-2%, but significantly lengthens the reaction time (Entries 3, 12, and 13). Reactions at 0 °C or lower appear to have difficulty undergoing oxidative addition and are only reliably performed with highly activated substrates.[27] In addition to six-membered ring substrates, seven- and eight-membered ring substrates also provide good yields.

Table 4.7 Substrate Scope for Asymmetric Allylation of Allyl Enol Carbonates

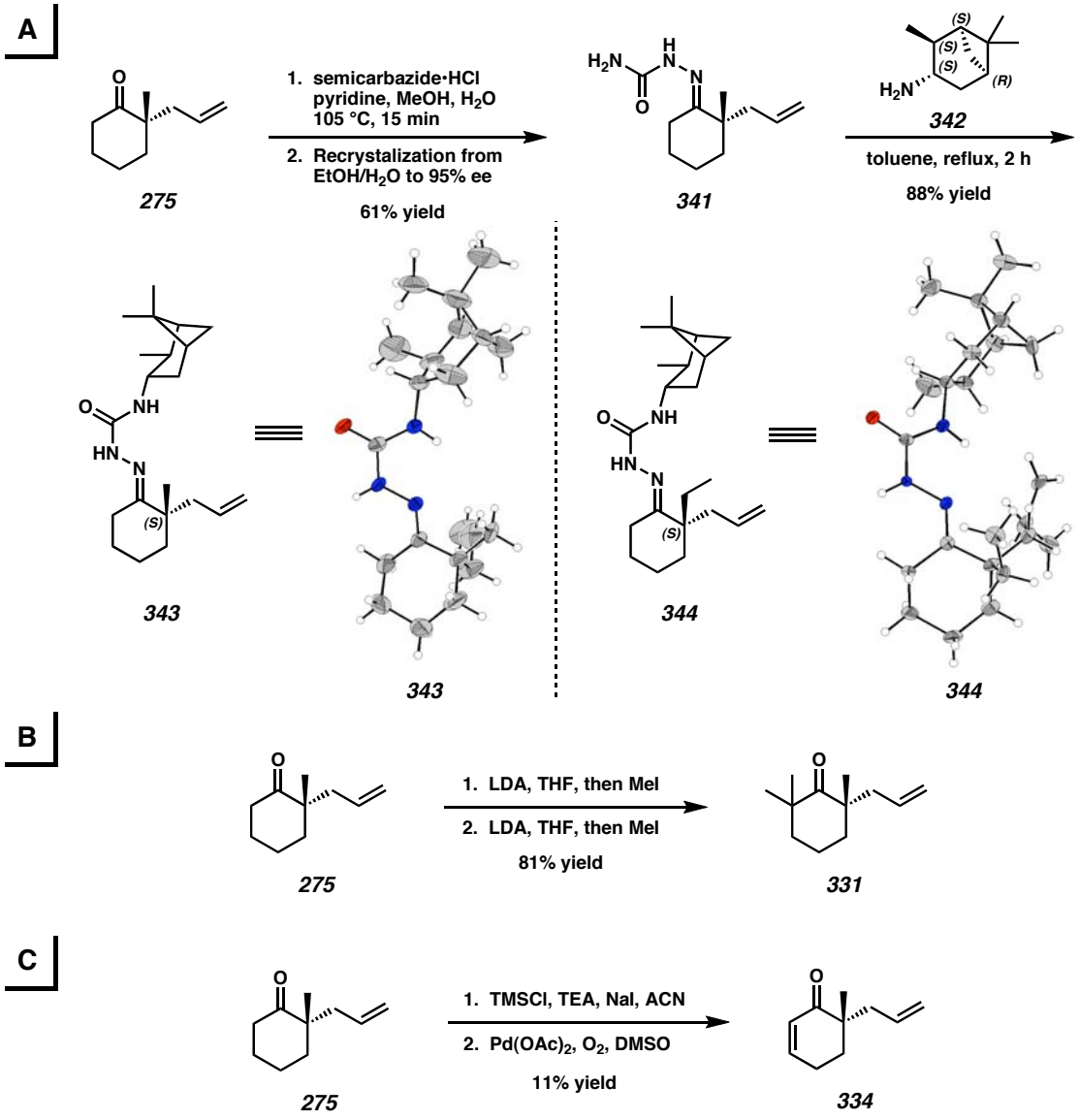
entry	substrate[a]	product	time (h)	% yield[b]	% ee[c]
1			2	85	87
2[d]	***274***	***275***	5	85	88 (96)[e]
3[f]			9	90	89
4	 ***320***, R = CH_2CH_3	 ***321***, R = CH_2CH_3	2	96	92
5[g]	***322***, R = *t*-Bu	***323***, R = *t*-Bu	10	55[h]	82
6	***324***, R = CH_2Ph	***325***, R = CH_2Ph	2	96	85
7	***326***, R = $(CH_2)_3OBn$	***327***, R = $(CH_2)_3OBn$	2	87	88
8[g]	 ***328***	 ***329***	8	89	91
9	 ***330***	 ***331***	1	94	92
10	 ***332***	 ***152***	1	87	86
11	 ***333***	 ***334***	1	91	89
12[i]	 ***296***, R = H	 ***297***, R = H	2	87	91
13[i]	***335***, R = OCH_3	***336***, R = OCH_3	8	94	91
14	 ***337***, n = 1	 ***338***, n = 1	6	81	87
15	***339***, n = 2	***340***, n = 2	2	90	79

[a] Reactions were performed using 1.0 mmol of substrate in THF (0.033 M in substrate) at 25 °C with $Pd_2(dba)_3$ (2.5 mol%), *(S)-t*-Bu-PHOX (6.25 mol%), unless stated otherwise. [b] Isolated yields. [c] Measured by chiral GC or HPLC. [d] Performed on 5.1 mmol scale. [e] In parentheses is the % ee after one recrystallization of the corresponding semicarbazone. [f] Reaction performed at 12 °C (GC yield). [g] Performed with 5 mol% $Pd_2(dba)_3$ and 12.5 mol% *(S)-t*-Bu-PHOX. [h] Isolated yield after conversion to the corresponding diketone via Wacker oxidation. [i] Performed at 10 °C.

At the time of our investigations, 2-methyl-2-allyl cyclohexanone was not known in enantioenriched form. Consequently, we wished to determine the absolute stereochemistry for several of our substrates (Scheme 4.5). To definitively assign the

absolute stereochemistry of the newly formed quaternary stereocenter, we derivatized ketone **275** as its semicarbazone **341**. Semicarbazone **341** is highly crystalline and recrystallization from EtOH/H_2O produced material of near enantiopurity (98% ee after two recrystallizations).[28] Treatment of the semicarbazone with amine **342** of known absolute stereochemistry in refluxing toluene gave the substituted semicarbazone **343**. Amino-substituted semicarbazone **343** also proved to be crystalline and amenable to X-ray structure determination when recrystallized from acetone. As the absolute stereochemistry of the isopinocampheylamine portion of semicarbazone **343** was known, the quaternary stereocenter set during the allylation could be assigned *S* configuration. This sequence was performed on ethyl quaternary ketone **321**, which confirmed that it too is of *S* configuration.[29] Additionally, quaternary ketone (*S*)-**275** could be transformed in a straightforward manner to trimethyl ketone **331** and enone **334** (Reactions B and C). These transformations confirmed that the allylation reaction forms ketone **331** and enone **334** with the same sense of absolute configuration. Finally, tetralone **297** was confirmed to be produced in our allylation with *S* stereochemistry by comparison with literature data.[13b]

Scheme 4.5 Determination of Absolute Stereochemistry



Our use of allyl enol carbonates enabled direct access to α-quaternary ketones with multiple acidic sites. However, allyl enol carbonates are rarely encountered in the literature, and the synthesis of isomerically pure enol carbonates often requires the synthesis of silyl enol ethers.[30] Since Tsuji had used silyl enol ethers in his racemic

allylation, we hoped to adapt our conditions such that silyl enol ethers could be employed as well.

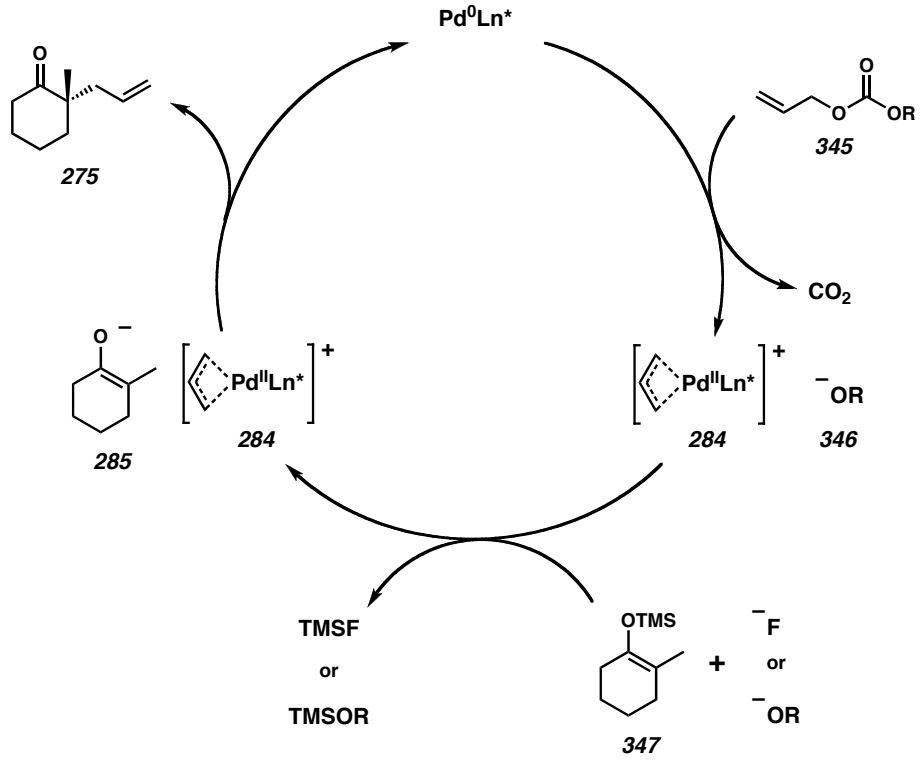
4.2.5 *Asymmetric Allylation of Silyl Enol Ethers*

The use of silyl enol ethers offered several advantages over allyl enol carbonates. Silyl enol ethers are commonly encountered enolate equivalents in organic chemistry. Unlike allyl enol carbonates, employing silyl enol ethers renders the reaction intermolecular, with the enolate precursor and allyl fragment introduced separately. We discovered in our initial studies that silyl enol ethers are not sufficiently nucleophilic to react with the Pd(II) allyl fragment under our reaction conditions at 25 °C. However, we found that the reaction could be initiated in the presence of $Bu_4NPh_3SiF_2$ (TBAT), a dry fluoride source.

The use of TBAT as an initiator complicates the proposed catalytic cycle (Scheme 4.6). In the case of allyl enol carbonates, the oxidative addition to allyl carbonate **274** leads immediately to the enolate and Pd(II) allyl ion pair, which can collapse directly to the product (Scheme 4.3). For the intermolecular reaction, we primarily use diallyl carbonates as an allyl precursor, but mixed carbonates are also effective. Oxidative addition of diallyl carbonate occurs readily at 25 °C to give Pd(II) allyl species **284** and alkoxide **346**. The addition of TBAT immediately generates the enolate. We hoped the enolate would react with the palladium complex **284** by the same enantioselective mechanism observed with the allyl enol carbonates. A substoichiometric amount of TBAT is sufficient, as the alkoxide generated in the reaction is also capable of generating the enolate in situ.[31] In principle, it should be possible for the small amount of allyl

alkoxide generated from oxidative addition to initiate the reaction. In practice, we found that 35 mol% TBAT was usually sufficient to ensure complete conversion of the silyl enol ether. Having developed an effective means of silyl enol ether activation, we attempted asymmetric allylation with a range of tetrasubstituted silyl enol ethers.

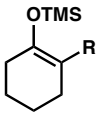
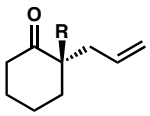
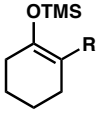
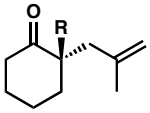
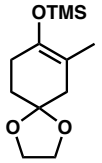
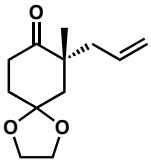
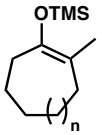
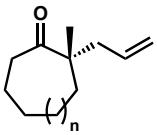
Scheme 4.6 General Mechanism for Silyl Enol Ether Allylation



Gratifyingly, allylation of the silyl enol ether substrates occurs with levels of enantioinduction similar to those observed for the allyl enol carbonate substrates and over a similar diversity of substrates (Table 4.8). Specifically, quaternary ketones **275** and **321** are produced with the same ee observed in the allyl enol carbonate reactions (Entries 1 and 2). α-Oxygenated silyl enol ether **349** undergoes allylation to give ketone **350** with a tertiary ether stereocenter, albeit with moderate enantioselectivity (Entry 3). In addition

to diallyl carbonate, dimethallyl carbonate serves as a suitable allyl fragment precursor (Entries 4 and 5). Impressively, allyl methallyl ketone **352**, bearing only a remote methyl group to engender chirality, is formed in 91% ee. As with the reactions of allyl enol carbonates, substitution about the ring and larger ring size are tolerated (Entries 6 to 8).

Table 4.8 Substrate Scope for Asymmetric Allylation of Silyl Enol Ethers

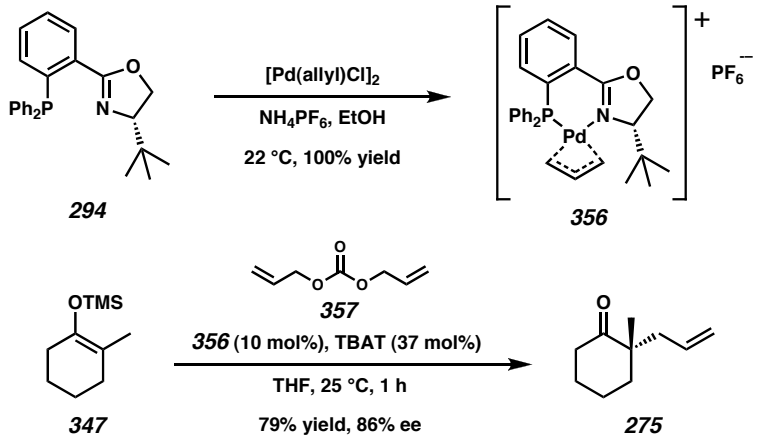
entry	substrate[a]		product		time (h)	% yield[b]	% ee[c]
1		***347*, R = CH_3**		***275*, R = CH_3**	2	95	87
2		***348*, R = CH_2CH_3**		***321*, R = CH_2CH_3**	3	96	92
3		***349*, R = OBn**		***350*, R = OBn**	3	83	59
4[d]		***347*, R = CH_3**		***329*, R = CH_3**	4	79	91
5[d]		**351, R = allyl**		**352, R = allyl**	5	82	91
6		***353***		***152***	2	99	81
7		***354*, n = 1**		***338*, n = 1**	2	94	86
8		***355*, n = 2**		***340*, n = 2**	3	96	79

[a] Reactions were performed using 1.0 mmol of substrate in THF (0.033 M in substrate) at 25 °C with $Pd_2(dba)_3$ (2.5 mol%), *(S)-t*-Bu-PHOX (6.25 mol%), diallyl carbonate (1.05 equiv), TBAT (35 mol%) unless stated otherwise. [b] Isolated yields. [c] Measured by chiral GC or HPLC. [d] Reaction performed with dimethallyl carbonate (1.05 equiv).

In addition to the flexibility afforded by the intermolecular reaction of silyl enol ethers and diallyl carbonates, the use of silyl enol ethers as a means to generate enolates independent of the allyl fragment allows the catalytic cycle to commence at the stage of a Pd(II) allyl salt **356** (Scheme 4.7). The Pd(II)(allyl)PHOX•PF_6 salt **356** readily precipitates upon mixing (*S*)-*t*-Bu-PHOX, $[Pd(allyl)Cl]_2$, and NH_4PF_6 in ethanol.[32] The

salt serves as an active catalyst in the asymmetric Tsuji allylation reaction, giving good yields and nearly identical enantioselectivity to the in situ generated catalyst. The Pd(II)PF_6 salt **356** has several practical advantages. It is a stable non-hygroscopic solid, which may be stored indefinitely. Moreover, using the preformed Pd(allyl)PHOX catalyst prevents the introduction of dba, which often complicates the purification of the α-quaternary ketone products.

Scheme 4.7 Allylation with Pd(II)•PF_6 Salt **356**

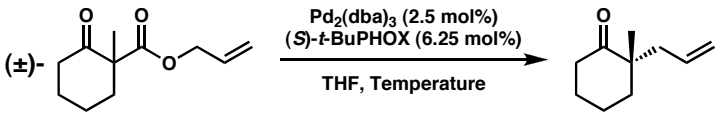


Our work with silyl enol ethers demonstrated that our enantioselective process is robust enough to overcome the intermolecular introduction of the enolate and allyl fragments and to tolerate the presence of other ions in solution. Silyl enol ethers are a more familiar substrate class and greatly increase the practicality of the reaction. However, we rely on thermodynamically driven silyl enol ether syntheses, which typically produce a 10:1 ratio of isomers that require tedious purification to obtain isomerically pure substrates.[33] A direct method for the synthesis of isomerically pure substrates would further increase the practicality of the catalyst system.

4.2.6 *Asymmetric Allylation with Racemic Allyl β-Ketoesters*

β-Ketoesters represent a classical solution to the problem of regioselective ketone alkylation. However, as stereogenic racemic substrates for a catalytic asymmetric reaction, the allyl β-ketoesters required could in principle undergo kinetic resolution or experience diastereomeric transition states. In the event, no significant kinetic resolution of the allyl β-ketoesters was observed.[34] The similar levels of enantioselectivity observed between the allyl β-ketoester substrates and the other classes of substrate suggest that the enantiodetermining transition state of the reaction remains unchanged. The only modification to our standard conditions required for the use of β-ketoester substrates is slight warming (Table 4.9). While the extent to which decarboxylation slowed at ambient temperature varied from substrate to substrate, β-ketoesters are uniformly more sluggish in decarboxylation than allyl enol carbonates.[35] However, this difficulty could typically be overcome by performing the reaction 5 °C warmer, which had a negligible effect on enantioselectivity.

Table 4.9 Temperature Effects on Decarboxylative Allylation of Allyl β-Ketoesters



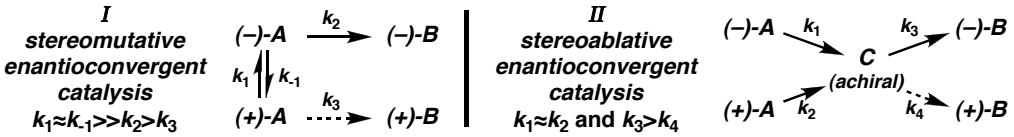
358 *275*

entry	temp (°C)	time (h)	% yield[a]	% ee[b]
1	18	48	0	ND
2	25	7.5	85	88
3	30	2.25	82	87
4	35	1.25	85	86
5	40	0.67	86	85
6	60	0.15	82	83

[a] Isolated yield from reaction of 1.0 mmol substrate at 0.033 M. [b] Determined by chiral GC.

The use of quaternary β-ketoesters renders this deracemization reaction unusual (Scheme 4.8). Typical deracemizations involve a pre-equilibrium epimerization of the starting material, A, followed by enantioselective conversion to product B (Pathway I).[36] However, quaternary stereocenters are not typically epimerizable, and we believe that both enantiomers of the starting material, A, are converted to a prochiral intermediate, C,[37] which preferentially forms one enantiomer of the product B under the influence of the chiral catalyst (Pathway II). We have termed such transformations stereoablative enantioconvergent catalysis.[38] As a result of this interesting mechanism and the facile synthesis of quaternary β-ketoesters, we have been able to expand our substrate scope greatly.

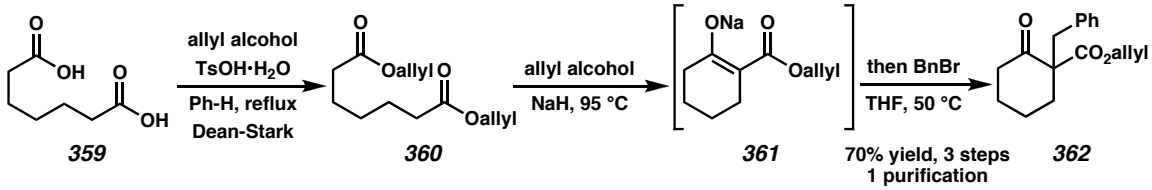
Scheme 4.8 Stereoablative Enantioconvergent Catalysis



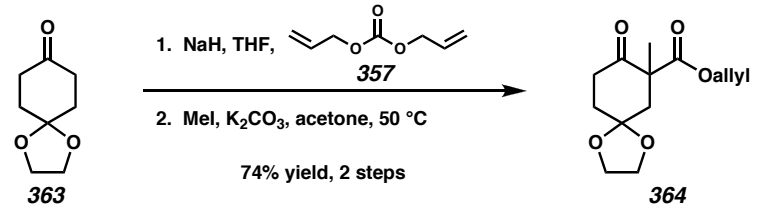
During the course of our studies, several practical methods for the synthesis of quaternary β-ketoesters have been frequently used (Scheme 4.9). The Dieckmann cyclization of pimelic acid diallyl ester (**360**) gives an intermediate cyclized sodium salt **361**, which can be alkylated to give quaternary β-ketoesters, such as benzylated compound **362**.[39] Alternatively, sodium salt **361** can be protonated to give the 2-carboxyallylcyclohexanone, and alkylated in a separate step. Cyclic ketones, such as 1,4-cyclohexandione *mono*-ethylene ketal (**363**), may be treated with base and diallyl carbonate to effect acylation. Mild alkylation conditions (MeI and K_2CO_3 in acetone) allow the C-methylated β-ketoester to be isolated in 74% yield over two steps with only one chromatographic purification. Both of these methods are inexpensive and can be readily carried out on large scale. In cases where O-acylation or multiple sites of C-acylation are problematic, such as enone **365**, treatment with LDA under kinetic conditions and then allyl Mander's reagent **366** frequently gives selective acylation.[40]

Scheme 4.9 Methods for the Synthesis of Racemic Quaternary β-Ketoesters

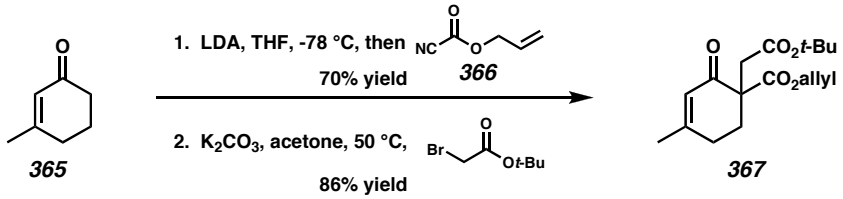
Dieckmann Cyclization Method



Diallyl Carbonate Method



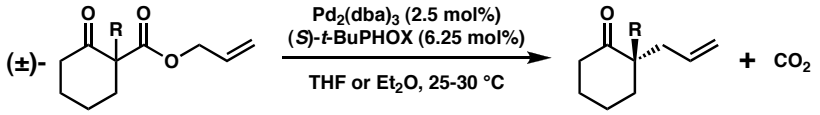
Mander's Reagent Method



A number of α-substituted 2-carboxyallylcyclohexanones are readily prepared by the above methods and were successfully subjected to enantioconvergent decarboxylative allylation (Table 4.10). Acrylonitrile and ethyl acrylate-derived substrates **370** and **372** undergo smooth reaction, to give the α-quaternary ketone products in excellent yield (Entries 4 and 5). Interestingly, these products are equivalent to the products of an asymmetric conjugate addition with the enolate of 2-allyl cyclohexanone. Silylated formaldehyde adduct **378** demonstrates the allylation of a substrate with a heteroatom positioned for β-elimination from the intermediate enolate (Entry 9).[41] Another noteworthy substrate is α-fluorinated β-ketoester **380**. Decarboxylative allylation of **380** afforded tertiary fluoride **381** in 80% yield and 91% ee.[42] Such α-fluorinated carbonyl

compounds with well defined absolute stereochemistry may find use as NMR probes in biological systems or as non-epimerizable isosteres for stereocenters α to carbonyls.[43]

Table 4.10 Enantioconvergent Decarboxylative Allylation of α-Substituted 2-Carboxyallylcyclohexanones



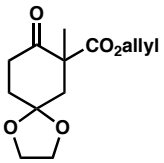
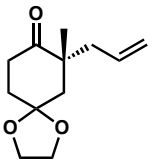
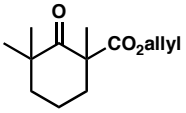
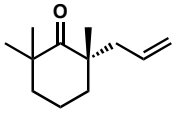
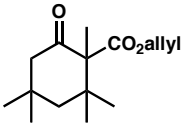
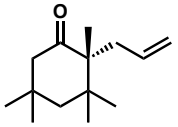
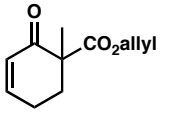
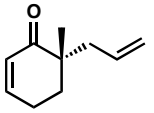
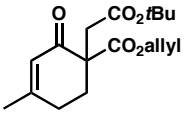
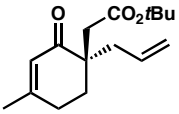
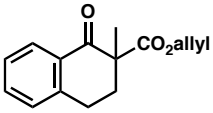
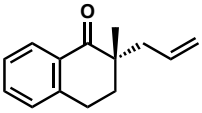
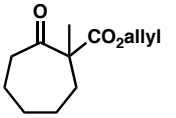
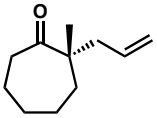
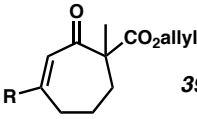
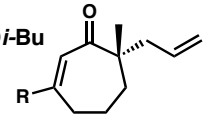
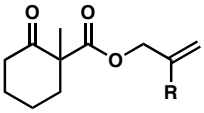
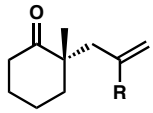
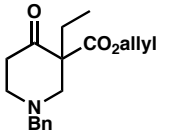
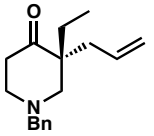
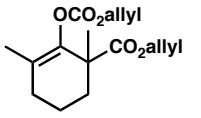
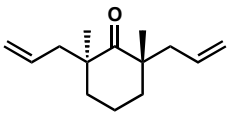
entry	R	substrate	product	solvent	temp (°C)	time (h)	% yield[a]	% ee[b]
1	CH_3	*358*	*275*	THF	25	7.5	85	88
2	CH_3	*358*	*275*	Et_2O	25	4.75	89	88
3	prenyl	*368*	*369*	Et_2O	30	6	97	91
4	CH_2CH_2CN	*370*	*371*	Et_2O	25	6.5	97	88
5[c]	$CH_2CH_2CO_2Et$	*372*	*373*	Et_2O	25	6	96	90
6	$CH_2C_6H_5$	*362*	*325*	THF	25	0.5	99	85
7	$CH_2(4\text{-}CH_3OC_6H_4)$	*374*	*375*	THF	25	10	80	86
8	$CH_2(4\text{-}CF_3C_6H_4)$	*376*	*377*	THF	25	0.5	99	82
9[c]	$CH_2OTBDPS$	*378*	*379*	THF	25	5	86	81
10	F	*380*	*381*	Et_2O	30	3.5	80	91

[a] Isolated yield from reaction of 1.0 mmol substrate at 0.033 M in solvent, unless otherwise noted. [b] Determined by chiral GC or HPLC. [c] 4 mol% $Pd_2(dba)_3$, 10 mol% (*S*)-*t*-Bu-PHOX, 0.021 M.

In addition to modifications at the α-position of the substrate, the decarboxylative asymmetric allylation tolerates a wide variety of modification to the carbocycle and allyl fragment of the substrate (Table 4.11). In particular, the reaction is exceptionally tolerant to the steric demands of substitution at the 3, 4, 5, and 6 positions of the cyclohexane ring. Each position can be fully substituted without significantly affecting yield or enantioselection (Entries 1 to 4). Unsaturated substrates (Entries 5 to 7) as well as seven-membered ring containing substrates (Entries 8 to 10) perform well in the reaction. Of note are vinylogous ester **388** and vinylogous thioester **390**. Interestingly, thioester

390 provides significantly higher enantioselectivity in the allylation than ester **388** (89 vs. 85% ee).[44] As with the previous substrate classes, substitution at the central position of the allyl fragment has a slightly beneficial effect on the enantioselectivity of the reaction (Entries 11 and 12). The incorporation of a chlorine atom on the allyl fragment provides another functional group handle for further manipulation and higher oxidation state. Piperidinone **395** demonstrates the use of a nitrogen heterocycle in the allylation (Entry 13). In an effort to construct more than one quaternary stereocenter in a single transformation, we prepared allyl enol carbonate **397**. This substrate contains a latent allyl β-ketoester moiety, which would be revealed by the reaction of the allyl enol carbonate portion of the molecule. To our delight, tandem allylation occurred to afford C_2 symmetric ketone **398** as the predominant product in 92% ee.

Table 4.11 Enantioconvergent Decarboxylative Allylation of β-Ketoesters with Substituted Carbocycles and Allyl Fragments

entry	substrate		product		temp (°C)	time (h)	% yield[a]	% ee[b]
1		*364*		*152*	25	1.5	94	85
2[c]		*364*		*152*	25	24	94	86
3		*382*		*331*	30	9	89	90
4		*383*		*256*	25	5	90	85
5[d,e]		*384*		*334*	30	4	77	90
6[d]		*367*		*385*	30	9	73	86
7[d]		*386*		*297*	25	10	97	92
8		*387*		*338*	25	9.5	83	87
9[d,e]		*388*, R = O*i*-Bu		*389*, R = O*i*-Bu	30	6	92	85
10[d,f]		*390*, R = SPh		*391*, R = SPh	30	5	86	89
11[d]		*392*, R = CH_3		*329*, R = CH_3	35	6.5	87	92
12[d,g]		*393*, R = Cl		*394*, R = Cl	35	2.5	87	91
13		*395*		*396*	25	2.5	91	92
14[h]		*397*		*398*	40	6	76[i]	92

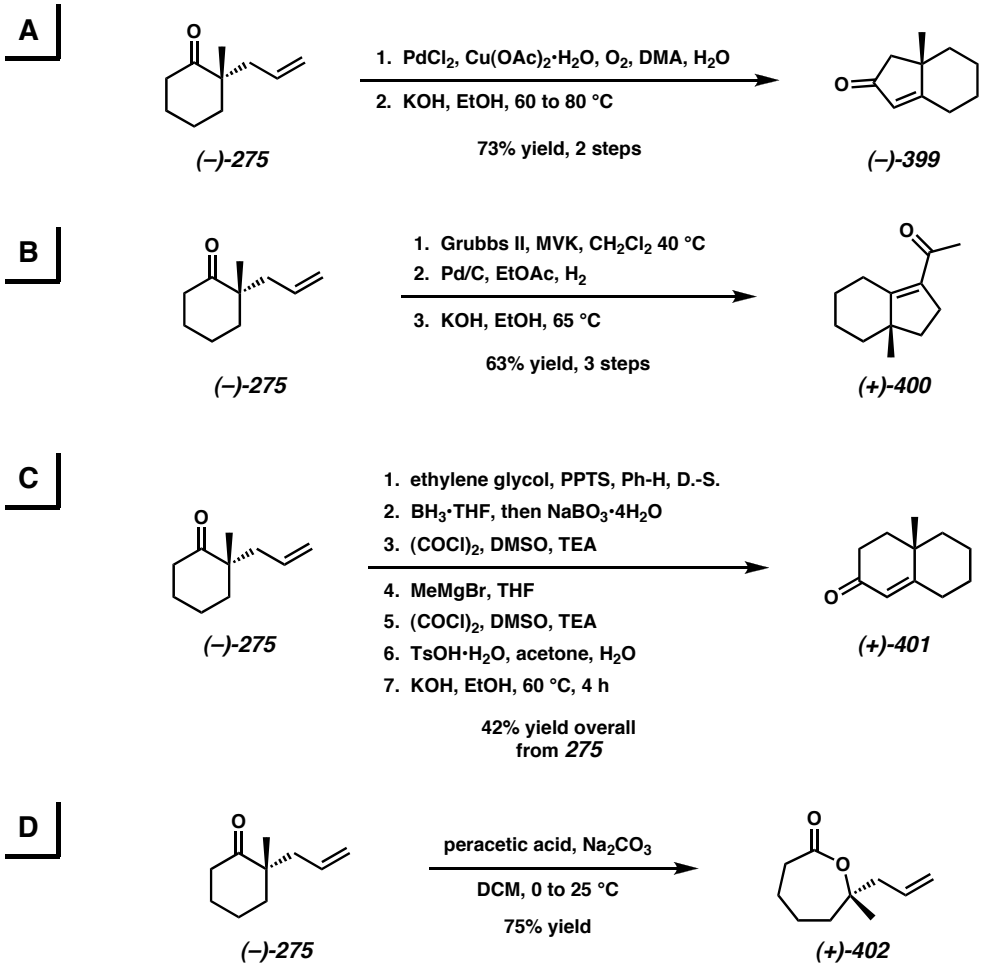
[a] Isolated yield from reaction of 1.0 mmol substrate, 2.5 mol% $Pd_2(dba)_3$ and 6.25 mol% (*S*)-*t*-Bu-PHOX at 0.033 M in THF, unless otherwise noted. [b] Determined by chiral GC or HPLC. [c] 25 mmol substrate, 1.5 mol% $Pd_2(dba)_3$, and 3.75 mol% (*S*)-*t*-Bu-PHOX. [d] Performed in Et_2O. [e] Reaction performed on 0.16 mmol scale, 5 mol% $Pd(dmdba)_2$, and 6.25 mol% (*S*)-*t*-Bu-PHOX at 0.100 M. [f] Reaction performed on 0.29 mmol scale, 5 mol% $Pd(dmdba)_2$, and 6.25 mol% (*S*)-*t*-Bu-PHOX at 0.100 M. [g] 4 mol% $Pd_2(dba)_3$, and 10 mol% (*S*)-*t*-Bu-PHOX at 0.021 M. [h] 4 mol% $Pd_2(dba)_3$ and 10 mol% (*S*)-*t*-Bu-PHOX. [i] 4:1 mixture of C_2:meso diastereomers.

4.3 Synthetic Applications

The α-quaternary allyl cycloalkanones produced in the asymmetric Tsuji allylation are highly useful chiral building blocks. Each substrate contains at least two functional groups, a ketone and an olefin, for further manipulation. Moreover, the preceding section has demonstrated these allylation reactions to be highly functional group tolerant. The application of this suite of allylation reactions to the catalytic asymmetric synthesis of natural products is an ongoing topic of research in our laboratories.[28b]

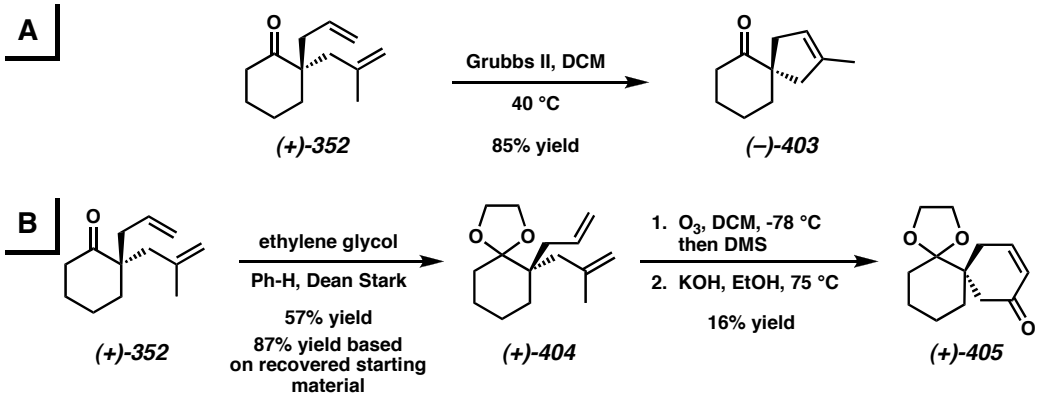
To demonstrate further the utility of these products, we transformed ketone (–)-(*S*)-**275** into several familiar cyclic frameworks (Scheme 4.10). Wacker oxidation of (–)-(*S*)-**275** followed by aldol condensation gave enone **399** in good yield (Reaction A). An alternative [6-5] skeleton was formed in a three-step sequence by olefin cross metathesis with methyl vinyl ketone, olefin hydrogenation, and aldol condensation under basic conditions to afford exocyclic enone **400** (Reaction B). Carbocyclic [6-6] ring systems are accessible as well. Multi-step elaboration of the allyl group afforded an intermediate diketone, which underwent aldol condensation to enone **401** in 43% overall yield (Reaction C). Enone **401**, which has been classically produced by Robinson annulation, has been extensively used in synthesis.[45] As a final transformation of (–)-(*S*)-**275**, we executed a Baeyer-Villiger oxidation with peracetic acid to give caprolactone **402**. This transformation demonstrates the conversion of our enantioenriched quaternary stereocenter into a latent tertiary alcohol with defined absolute stereochemistry (Reaction D).

Scheme 4.10 Useful Derivatives of *(–)-(S)-***275**



Spiro quaternary stereocenters represent a particularly challenging subclass of quaternary stereocenters. In addition to the fused cyclic skeletons above, allyl methallyl ketone **32** was used as an entry into the synthesis of ring systems containing spiro quaternary stereocenters (Scheme 4.11). Ketone **352** can be treated with Grubbs' second generation catalyst in methylene chloride to give a good yield of the spiro[4.5]ketone **403**. Spiro[5.5]enone **405** is produced in a modest yield by treatment of ketone **352** with standard ketal protection conditions, followed by ozonolysis, and base.

Scheme 4.11 Synthesis of Derivatives with Spiro Quaternary Stereocenters



4.4 Reaction Scope and Limitations

4.4.1 *Introductory Remarks*

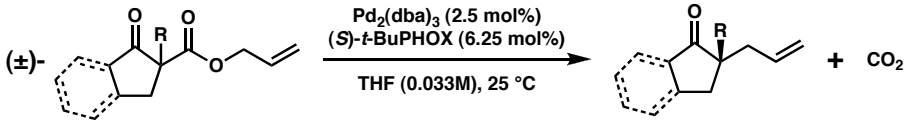
We have demonstrated that our allylation catalyst is capable of producing a great variety of highly enantioenriched quaternary stereocenters α to ketones, which were previously difficult to access, from several classes of pro-nucleophiles. However, in our studies we have encountered several substrate classes that provided substantially lower than expected levels of enantioselectivity. Interestingly, these substrates still give generally excellent chemical yield. We consider these substrates as an impetus for the development of more effective catalysts and as useful probes of the reaction's mechanism.

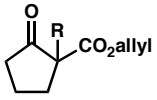
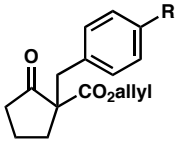
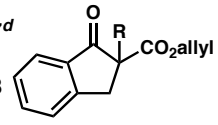
4.4.2 *Substrates Containing Five-Membered Rings*

While enolate precursors contained in six-membered rings comprise the bulk of our substrates, we have demonstrated that seven- and eight-membered rings are tolerated with only slight loss in enantioselectivity. Allyl β-ketoesters constructed on five-

membered rings also give useful levels of enantioselectivity (Table 4.12). These substrates generally give good yields of α-quaternary ketones with enantiomeric excesses about 10% lower than the cyclohexanone analogue. Ethyl substituted ketone **407** is formed in 86% ee, only 6% lower than the corresponding cyclohexanone (Entry 1). Benzyl appended cyclopentenone substrates give consistent yields, but electron deficient aromatic rings decrease enantioselectivity more significantly than in the reactions of six-membered β-ketoesters (Entries 4 to 6). Indanones are produced good yield and useful ee (Entries 7 and 8).

Table 4.12 Enantioconvergent Decarboxylative Allylation of β-Ketoesters Containing Five-Membered Rings.



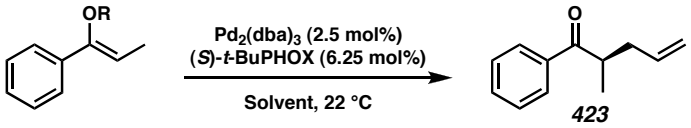
entry	substrate[a]	product	time (h)	% yield[b]	% ee[c]
1		***406***, R = CH_2CH_3	***407***, R = CH_2CH_3	3	82	86
2		***408***, R = $CH(CH_3)_2$	***409***, R = $CH(CH_3)_2$	3	77	84
3		***410***, R = CH_2NPhth	***411***, R = CH_2NPhth	2	67	48
4		***412***, R = OMe	***413***, R = OMe	2	84	73
5		414, R = Me	***415***, R = Me	2	84	73
6		***416***, R = CF_3	***417***, R = CF_3	2	83	60
7[d]		***418***, R = Me	***419***, R = Me	1	82	80
8		***420***, R = Bn	***421***, R = Bn	1	93	71

[a] Reactions were performed using 1.0 mmol of substrate in THF (0.033 M in substrate) with $Pd_2(dba)_3$ (2.5 mol%), *(S)-t*-Bu-PHOX (6.25 mol%) unless stated otherwise.
[b] Isolated yields. [c] Measured by chiral GC or HPLC. [d] Performed on 0.1 mmol scale with $Pd_2(dba)_3$ (5 mol%), *(S)-t*-Bu-PHOX (12.5 mol%).

4.4.3 *The Synthesis of Tertiary Stereocenters from Acyclic Enolate Precursors*

While we have principally employed our asymmetric allylation for the synthesis of quaternary stereocenters, the mild and nearly neutral conditions of the reaction are well suited for the synthesis of tertiary stereocenters α to carbonyls (Table 4.13).[46] Such stereocenters are prone to epimerization and over-alkylation under the strongly basic conditions traditionally used for enolate generation.[47] We found that allyl enol carbonate **422** underwent allylation to phenyl ketone **423** in 67% ee (Entry 1). In analogy to the results of Hou and coworkers, we found that the addition of silver (I) bromide gave a significant increase in the ee of the product (Entry 2).[48] Both TMS[49] and TBS[50] silyl enol ethers were competent enolate precursors when TBAT was used as an initiator (Entries 3 and 4). Unlike the tetrasubstituted silyl enol ethers, cesium fluoride proved to be the optimal fluoride source for the less substituted silyl enol ethers, engendering noticeably higher ee (Entry 5). Unfortunately, the use of silver(I) bromide in the presence of cesium fluoride greatly reduced reactivity and only slightly increased enantioselectivity (Entry 6). Similarly, the use of ethyl ether as a solvent increased enantioselectivity at the cost of lowered yield (Entry 7). Although our allylation methods have provided tertiary stereocenters in only moderate ee, we have recently disclosed a decarboxylative protonation of quaternary allyl β-ketoesters based on a similar catalyst system, which provides access to tertiary stereocenters α to ketones in excellent ee.[51]

Table 4.13 Asymmetric Allylation of Allyl Enol Carbonates and Silyl Enol Ethers Not Contained in Ring



423

entry	substrate[a]	solvent	additive	% yield[b]	% ee[c]
1	*422*, R = CO_2allyl	THF		79	67
2	*422*, R = CO_2allyl	THF	AgBr (40 mol%)	75	79
3[d]	*424*, R = TMS	THF	TBAT (35 mol%)	60	62
4[d]	*425*, R = TBS	THF	TBAT (35 mol%)	82	73
5[d]	424, R = TMS	THF	CsF (48 mol%)	79	77
6[d]	424, R = TMS	THF	CsF (48 mol%), AgBr (40 mol%)	20	79
7[d]	*424*, R = TMS	Ether	CsF (48 mol%)	38	82

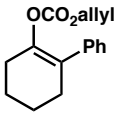
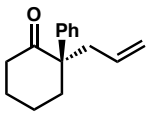
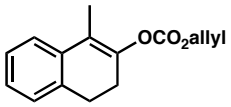
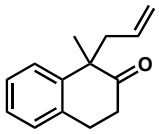
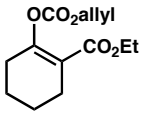
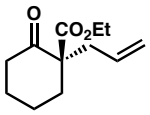
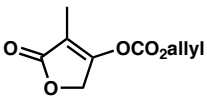
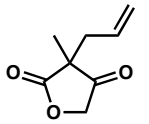
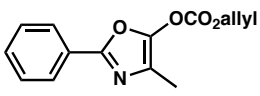
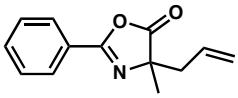
[a] Reactions were performed using 0.092 mmol of substrate (0.092 M in substrate). [b] Isolated yields. [c] Measured by chiral HPLC. [d] Reaction performed with diallyl carbonate (1.05 equiv).

4.4.4 *Substrates Proceeding via Weakly Basic Enolates*

The allylation of substrates derived from ketones of unusually low pK_a (i.e., stabilized enolates) as a group give by far the lowest levels of enantioselectivity we have observed with the PHOX catalyst system (Table 4.14). Despite this, these substrates give consistently excellent chemical yields of the allylated products. It is noteworthy that the phenyl ketone (Entries 1 and 2) and β-ketoester (Entries 3 and 4) derived enolates that gave excellent enantioselectivities in Trost's earlier asymmetric allylation reactions[13] fail to give useful levels of enantioselectivity under our conditions. Oxazole **431**, designed with the hope of executing an enantioselective synthesis of α,α-disubstituted amino acids, also underwent allylation with little enantioselectivity, presumably due to the stability of the intermediate aromatic enolate (Entry 5). The orthogonality of the

substrate scope, in terms of asymmetric induction, between our method and Trost's early reports may be indicative of fundamentally different mechanisms underlying the two allylation reactions.

Table 4.14 Asymmetric Allylation via Stabilized Allyl Enol Carbonates

entry	substrate[a]		product[b]		time (h)	% yield[c]	% ee[d]
1		*425*		*273*	2	99	11
2		*426*		*427*	2	93	0
3		*428*		*271*	2	89	24
4		*429*		*430*	2	87	2
5		*431*		*432*	2	89	2

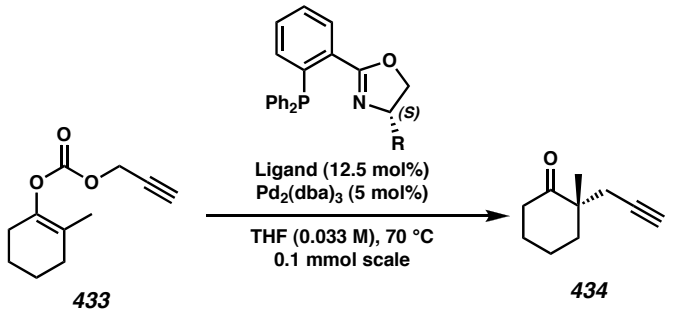
[a] Reactions were performed using 1.0 mmol of substrate in THF (0.033 M in substrate) at 25 °C with $Pd_2(dba)_3$ (2.5 mol%), *(S)-t*-Bu-PHOX (6.25 mol%). [b] Absolute stereochemistry of products assigned by analogy. [c] Isolated yields. [d] Measured by chiral GC or HPLC.

4.4.6 *Application of the Palladium PHOX Catalyst System to Propargylation*

In addition to allylation, we also explored propargylation of enol carbonates with the palladium/PHOX catalyst system (Table 4.15).[52] Our preliminary studies found that propargylation of ketone enolates required significantly higher temperatures than are required for allylation.[53] Additionally, the optimal structure of the PHOX ligand is significantly different for propargylation than for allylation. Moving the bulk of the *t*-Bu

group away from the oxazoline by insertion of a methylene group gave higher ee (Entry 2 vs. 1). Unlike allylation, PHOX ligands derived from amino acids containing aromatic side chains gave higher enantioselectivity than aliphatic side chains, with anthracenyl derivative **437** giving the highest level of enantioselectivity. While still preliminary, these studies suggest that the palladium/PHOX catalyst system may find use outside allylation reactions.[51]

Table 4.15 Asymmetric Propargylation



433 ***434***

entry	ligand	% yield[a]	% ee[b]	major enantiomer
1	***294,*** R = *t*-Bu	84	12	***S***
2	***299***, R = CH_2-*t*-Bu	83	32	***S***
3	***292***, R = CH_2Ph	54	26	***S***
4	***300***, R = CH_2-1-Naphthyl	57	37	***S***
5	***435***, R = CH_2-2-Naphthyl	71	26	***S***
6	***436***, R = CH_2-(3,5-di-*t*-Bu-Ph)	94	25	***S***
7	***437***, R = CH_2-9-Anthracenyl	80	44	***S***

[a] GC yield relative to internal standard (tridecane). [b] Enantiomeric excess measured by chiral GC.

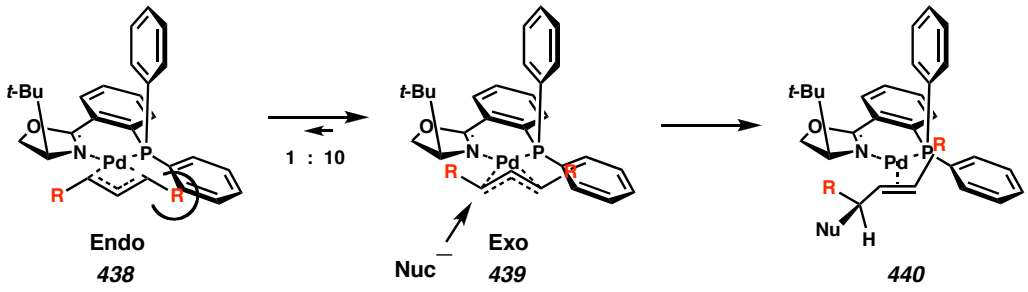
4.5 Mechanistic Insights

While it is premature at this time to make definitive statements about the fine mechanistic details of our palladium/PHOX-based allylation, an intriguing picture of the reaction's general mechanism has emerged from our experimental studies.[54] A number of

experimental observations suggest that our allylation of prochiral nucleophiles differs substantially in mechanism from palladium/PHOX-catalyzed malonate alkylation of prochiral allyl fragments, which has been studied in detail by Helmchen.[9]

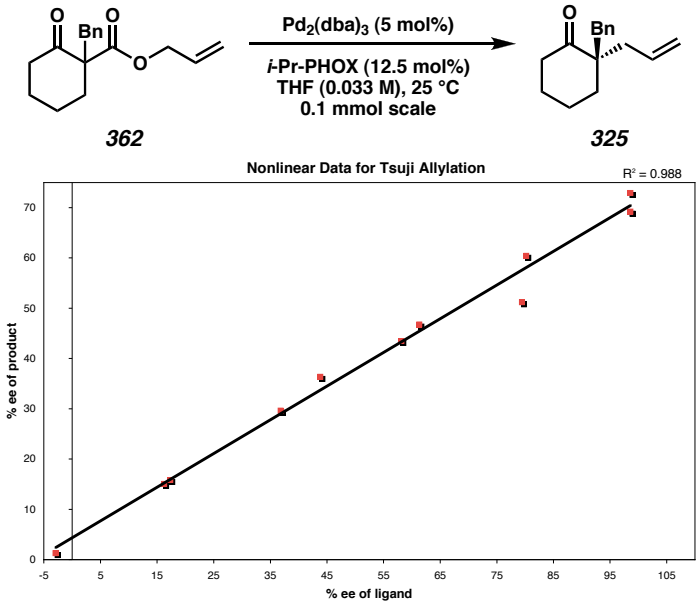
Helmchen's model for the asymmetric allylic alkylation of prochiral allyl electrophiles with palladium/PHOX catalysts involves attack at the allyl terminus by an outer sphere malonate anion (Scheme 4.12). The allyl group isomers **438** and **439** are in rapid equilibrium such that the nucleophile's preferred attack (**439**), from the open quadrant at the allyl terminus trans to phosphorus, is the nearly exclusive reaction pathway. The resulting palladium(0) olefin complex **440** has been observed at low temperature.[9] It is difficult to rationalize the high levels of stereoinduction observed in our allylation by this mechanism. In our case, the chiral palladium complex would be required to differentiate the prochiral faces of the unassociated enolate, when steric and electronic interactions should be minimal. Alternatively, an inner-sphere mechanism would allow for close contact of the enolate to the chiral environment and facilitate the discrimination between the prochiral enolates faces.[55]

Scheme 4.12 Helmchen's Mechanism for Asymmetric Allylation of Prochiral Allyl Electrophiles



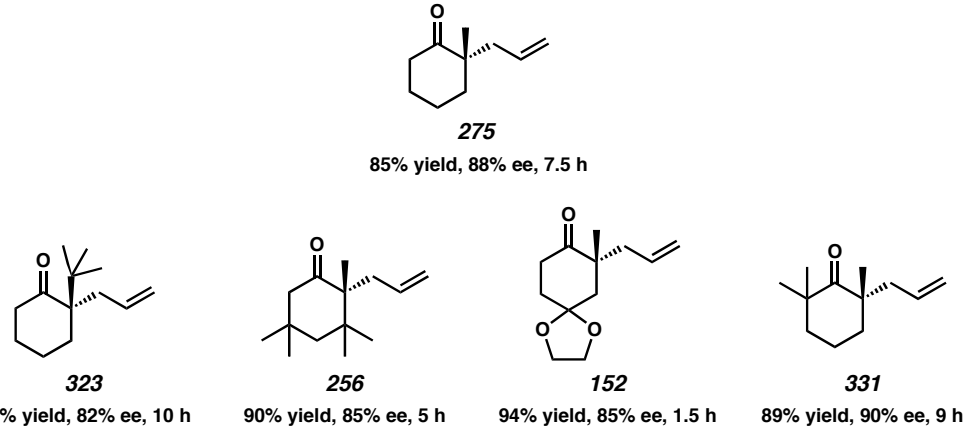
Allylation of a palladium bound enolate is consistent with many experimental trends we have observed, which do not correlate well to an outer-sphere enolate attack mechanism. The high enantioselectivity under our conditions appears to correspond with conditions that would keep ion pairs tightly associated. The range of effective solvents for our reaction demonstrates this trend. Ethereal solvents (e.g., THF), aromatic solvents (e.g., benzene), ethyl acetate, and triethylamine share few properties other than having low dielectric constants in the range of 2 to 8 (Table 4.3). In such low dielectric media, dissociative solvation of ion pairs is difficult. In conjunction with the lack of other counter ions in the reaction, the dielectric would tend to enforce an inner-sphere mechanism. While it is conceivable that multiple ion pairs could be involved in the transition state (e.g., an enolate bound to one Pd(allyl)PHOX fragment attacks the allyl fragment associated with another enolate), simple kinetics experiments[56] and the lack of a nonlinear effect suggest that a single Pd•PHOX is operative in the reaction mechanism (Figure 4.1). Furthermore, less basic enolates, whose charge is delocalized and should therefore tend to ion pair only weakly, give extremely low levels of enantioselectivity (Table 4.14).[57] This suggests that in such cases allylation proceeds via the more conventional outer-sphere attack.

Figure 4.1 Plot of *i*-Pr-PHOX ee vs. Product ee



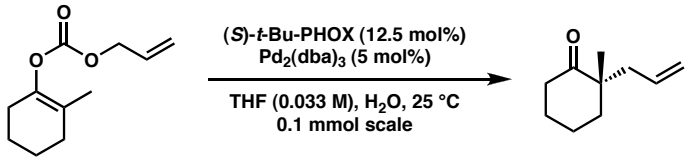
The reactivity of sterically demanding substrates is also inconsistent with an intermolecular nucleophilic enolate attack. In a nucleophilic bimolecular reaction, such as the Helmchen allylation mechanism, steric bulk near the site of bond formation typically impedes the rate of the reaction. However, there is very little difference in the reaction time, yield, or enantioselectivity when comparing the formation of ketone **275** with more sterically demanding ketones (Figure 4.2). This observation is more consistent with an intramolecular reaction mechanism.

Figure 4.2 Comparison of Sterically Varied Products Formed at 25 °C in THF



Another observation at odds with an external attack mechanism is the allylation's unusual tolerance of water (Table 4.16). Multiple equivalents of water introduced into the reaction have only a moderate effect on the yield of the reaction. This contrasts typical enolates, which are quickly quenched by water even at low temperatures, and suggests that the intermediate enolate formed in the reaction is tightly associated with its counterion for most of its lifetime.

Table 4.16 Effect of Water on Asymmetric Allylation



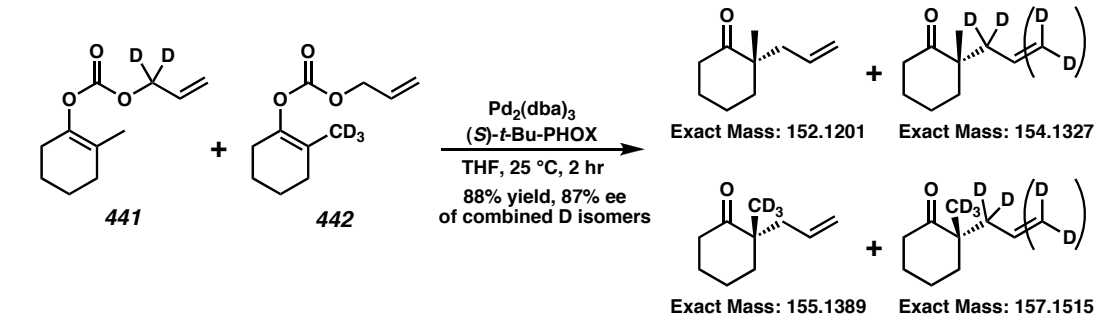
274 275

entry[a]	H_2O added (equiv)[b]	% yield[c]	% ee[d]
1	0	95	86
2	0.55	99	87
3	1.64	88	84
4	8.25	70	61
5	16.5	67	49
6	33.3	63	40

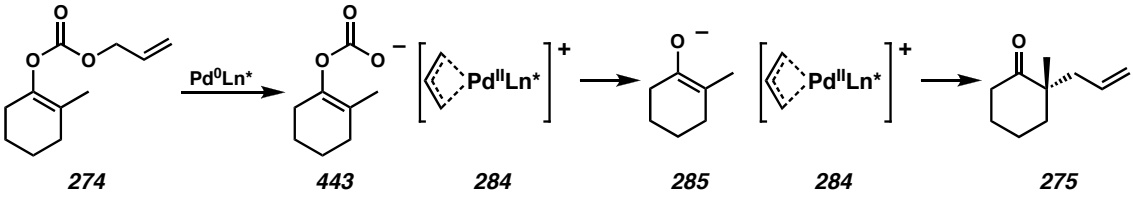
[a] Data reported is the average of three trials. [b] H_2O added after Pd/PHOX complexation, but before substrate. [c] GC yield relative to internal standard (tridecane). [d] Enantiomeric excess measured by chiral GC.

In an effort to trace the fate of the allyl and enolate fragments in the course of the reaction, we performed a crossover experiment with deuterated allyl enol carbonates **441** and **442** in THF, 1,4-dioxane, and benzene (Scheme 4.13).[58] Analysis of the products by high resolution mass spectrometry showed all four possible product masses in nearly equal amounts.[59] In conjunction with the water addition experiments, this observation suggests that a palladium enol carbonate species (**443**) may be a long-lived intermediate. Such an intermediate would not be readily protonated by water, and as a delocalized anion may facilitate crossover by dissociation from the metal center. In the case of β-ketoester substrates, a β-ketocarboxylate intermediate may play an analogous role.

Scheme 4.13 Crossover Experiments with Deuterated Allyl Enol Carbonates

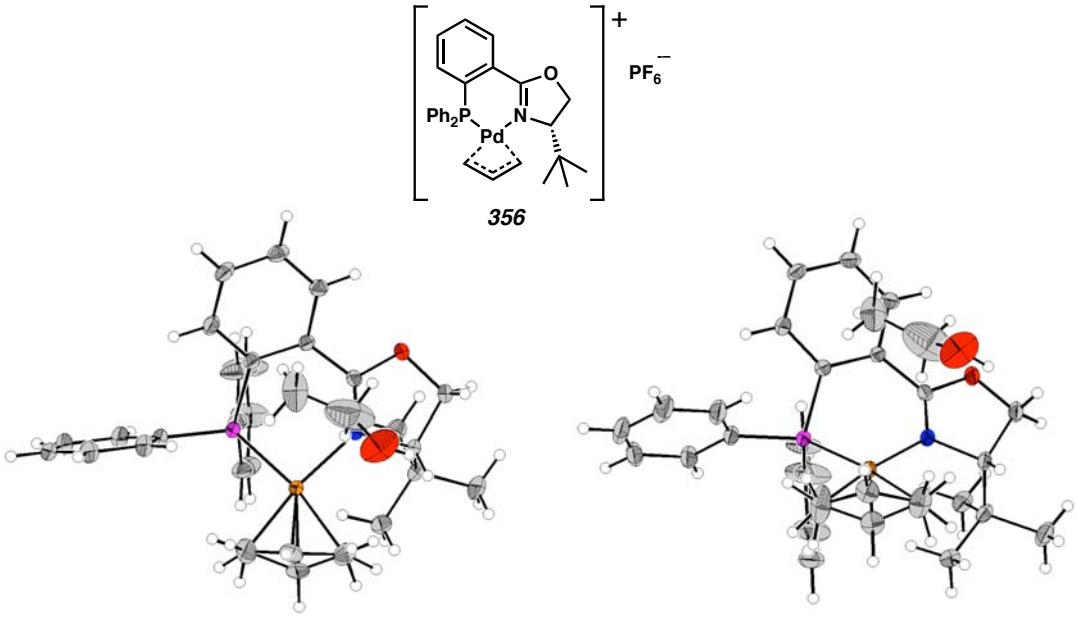


Mass	Integral	% Abundance
152	459336	21.23 %
154	478480	22.12 %
155	720536	33.31 %
157	504864	23.34 %
Total	2163216	100 %



Finally, the solid-state structure of Pd(II)(allyl)PHOX•PF_6 salt **356** lends credence to the possibility of a palladium bound enolate. As shown in Figure 4.3, the complex co-crystallizes with a molecule of ethanol in its unoccupied quadrant.[60] We envision this as the likely site of enolate coordination. Experiments and computational studies[54] to better characterize the reaction mechanism are under way with the hope of improving the enantioselectivity and scope of the asymmetric allylation.

Figure 4.3 Solid-State Structure of Pd(II)(allyl)PHOX•PF_6 Salt **356**



4.6 Concluding Remarks

Although palladium-catalyzed allylic alkylation is one of the most widely used asymmetric C-C bond forming reactions, at the outset of this work a significant limitation existed: the in situ generated enolate nucleophiles utilized were required to have a single acidic α-hydrogen or a large difference in acidity between sites to prevent multiple reactions. As a strategy to overcome this deficiency, we chose to adapt Tsuji's non-enantioselective allylation reactions. Critical to our success was the use of enolate precursors, which could be converted to enolates under mild conditions, and the use of a chiral catalyst that exhibited the enolate isomeric fidelity found in Tsuji's racemic system. We quickly discovered that N/P type ligands, and in particular *t*-Bu-PHOX, were capable of imparting enantioselectivity in the allylation of allyl enol carbonates, silyl enol ethers, and β-ketoesters. The reactivity and enantioselectivity of the allylation have

proven to be quite general with respect to substrate steric bulk, ring size, unsaturation, and diverse functional groups. The in situ enolate generation with TBAT enabled the use of silyl enol ethers, perhaps the most commonly used isolable enolate surrogate in organic chemistry, for intermolecular asymmetric allylation with varied allyl carbonates. The use of racemic allyl β-ketoesters was enabled by the enantioconvergent mechanism of the reaction, whereby both enantiomers of the starting material are converted to a common achiral intermediate and then proceed to an enantioenriched product. The utility of the reaction was greatly increased by the facile synthesis of a wide variety of α-alkylated allyl β-ketoesters. Additionally, we have demonstrated the relevance of the α-quaternary ketones produced in the reaction by their conversion to a number of carbocyclic chiral building blocks, including several spiro quaternary motifs.

A body of evidence has developed suggesting that our asymmetric Tsuji allylation proceeds by a mechanism distinct from that typically invoked in the asymmetric alkylation of prochiral allyl fragments with PHOX ligands. Indeed the coordination of the enolate to the palladium atom is likely essential to our use of prochiral enolates. Substrate classes with less than exemplary levels of enantioselectivity provide both insights about reaction mechanism and challenges for future catalyst development.

In summary, this work provides the first direct access to enantioenriched α-quaternary ketones with multiple similarly acidic α-hydrogens. This advance significantly increases the scope of one of more widely used catalytic asymmetric C-C bond forming reactions. Further development of the catalyst system to new applications is currently being pursued.[51] Our work highlights the broad applicability of this new allylation methodology. Indeed, studies directed toward the application of the

asymmetric Tsuji allylation as a key enantiodetermining step in natural products synthesis will be reported in due course.[28b]

4.7 Experimental Procedures

4.7.1 *Materials and Methods*

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Tetrabutylammonium triphenyldifluorosilicate (TBAT) was purchased from Sigma-Aldrich Chemical Company and azeotropically dried five times from acetonitrile prior to use. Bis(3,5,3',5'-dimethoxydibenzylideneacetone)-palladium(0) ($Pd(dmdba)_2$), alkyl halides, diallyl carbonate, Select-fluor, and pimelic acid were purchased from Sigma-Aldrich Chemical Company and used as received. 3-Methylcyclohex-2-en-1-one and cyclohex-2-en-1-one were purchased from Acros and used as received. Dimethyallyl carbonate was purchased from Alfa Aesar and used as received. Trimethylsilyl chloride (TMSCl) and triethyl amine (TEA) were distilled from sodium hydride immediately prior to use. Sodium iodide was dried by heating at 90 °C (2 torr) for 12 h. (*R,R*)-Trost Ligand, (*R*)-BINAP, (*R,R*)-Me-DUPHOS, (*R,R*)-DIOP, (*R*)-MOP, (*R*)-QUINAP, (*R*)-*i*-Pr-PHOX, and Tris(dibenzylideneacetone)-dipalladium(0) ($Pd_2(dba)_3$) were purchased from Strem and stored in a glovebox until immediately before use. (*R*)-Ph-PHOX and (*S*)-Bn-PHOX were prepared by the method of Helmchen.[18c] Allyl cyanoformate was prepared by known methods.[39b] Methallyl chloroformate was prepared by the method of Kirby.[2] Reaction temperatures were controlled by an IKAmag temperature modulator.

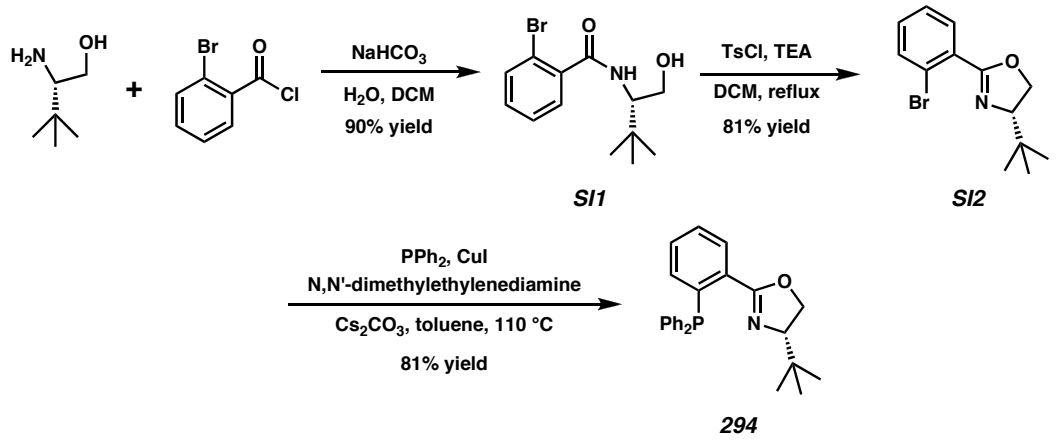
Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, or CAM staining. ICN Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing chiralcel AD, OD-H, or OJ columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd., with visualization at 254 nm. Analytical chiral GC was performed with an Agilent 6850 GC utilizing a G-TA (30 m x 0.25cm) column (1.0 mL/min carrier gas flow). Analytical achiral GC was performed with an Agilent 6850 GC utilizing a DB-WAX (30m x 0.25 mm) column (1.0 mL/min carrier gas flow). Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept. = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, bs = broad singlet. Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). ^{19}F NMR spectra were recorded on a Varian Mercury 300 spectrometer at 282 MHz, and are reported relative to the external standard F_3CCO_2H (δ -76.53 ppm) or $CFCl_3$ (δ 0.0 ppm). ^{31}P NMR spectra were recorded on a Varian Mercury 300 spectrometer at 121 MHz, and are reported relative to the external standard H_3PO_4 (δ 0.0 ppm). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the Caltech Mass

Spectral Facility. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number.

4.7.2 *Preparation of Compounds*

4.7.2.1 *Synthesis of PHOX ligands*

General Procedure 1: Synthesis of PHOX Ligands



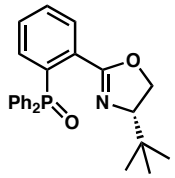
Amide SI1. To a solution of *(S)-t*-leucinol[61] (3.57 g, 30.5 mmol, 1.0 equiv) in DCM (100 mL) was added a solution of Na_2CO_3 (9.70 g, 91.5 mmol, 3.0 equiv) in water (75.0 mL). To the vigorously stirred biphasic mixture was added 2-bromobenzoyl chloride (4.58 mL, 35.1 mmol, 1.15 equiv) in a dropwise manner. After 12 h ambient temperature, the layers were separated, and aqueous layer extracted with DCM (2 x 50 mL). The combined organics were treated with KOH (15 mL of a 1 M methanolic solution) for 15 min, neutralized with 3 M HCl, and water (50 mL) was added. The layers were separated, and the aqueous layer extracted with DCM (2 x 50 mL). The combined organics were dried (Na_2SO_4), evaporated, and the residue chromatographed (25→35% Acetone in Hexanes on SiO_2) to give amide **SI1** (8.19 g, 89.5 % yield): m.p. 50.0-51.0 °C from acetone / hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, J = 7.8, 0.9 Hz, 1H), 7.54 (dd, J = 7.5, 1.8 Hz, 1H), 7.34 (app. dt, J = 7.4, 1.1 Hz, 1H), 7.26 (app. dt, J = 7.7, 1.8 Hz, 1H), 6.24 (bd, J = 8.1 Hz, 1H), 4.05 (m, 1H), 3.93 (dd, J = 11.4, 3.6 Hz, 1H), 3.66 (dd, J = 11.4, 7.5 Hz, 1H), 2.68 (bs, 1H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ 168.7, 137.9, 133.3, 131.2, 129.7, 127.6, 119.0, 62.9, 60.2, 33.8, 27.1; IR (Neat Film NaCl) 3245, 3070, 2963, 1640, 1557 cm^{-1}; HRMS *m/z* calc'd for $C_{13}H_{19}NO_2Br$ $[M+H]^+$: 300.0599, found 300.0590; $[\alpha]_D^{29}$ +20.19° (*c* = 2.38, methanol, 100% ee).

Phenyloxazoline SI2.[18c] A solution of amide **SI1** (8.10 g, 27.0 mmol, 1.0 equiv), tosyl chloride (6.69 g, 35.1 mmol, 1.3 equiv), triethylamine (18.7 mL, 135.0 mmol, 5.0 equiv) in DCM (200 mL) in a rb flask equipped with a reflux condenser was heated at 55 °C for 22 h. At which time, water (28 mL) was added and heating continued at 75 °C for 2 h. The reaction mixture was cooled, the layers separated, and the aqueous layer extracted with DCM (2 x 25 mL). The combined organics were dried (Na_2SO_4), evaporated, and the residue chromatographed (5% EtOAc in Hexanes on SiO_2) to give phenyloxazoline **SI2** (6.19 g, 81.2% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (app. dt, *J* = 8.7, 1.7 Hz, 2H), 7.33 (app. dt, *J* = 7.7, 1.5 Hz, 1H), 7.26 (m, 1H), 4.38 (dd, *J* = 10.5, 8.9 Hz, 1H), 4.25 (app. t, *J* = 8.3 Hz, 1H), 4.10 (dd, *J* = 10.2, 8.1 Hz, 1H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 133.6, 131.4, 131.2, 130.2, 127.0, 121.8, 76.6, 69.0, 34.0, 25.9; IR (Neat Film NaCl) 2956, 1661, 1478, 1354, 1099, 1022, 963 cm^{-1}; HRMS *m/z* calc'd for $C_{13}H_{17}NOBr$ $[M+H]^+$: 282.0493, found 282.0488; $[\alpha]_D^{29}$ -48.32° (*c* = 3.77, hexane, 100% ee).

***(S)-t*-Bu-PHOX (294).**[21] A mixture of copper(I) iodide (338.3 mg, 1.77 mmol, 0.125 equiv), diphenylphosphine (4.64 mL, 26.7 mmol, 1.88 equiv), N,N'-dimethylethylenediamine (1.32 mL, 12.4 mmol, 0.875 equiv) in toluene (60 mL) was stirred for 20 min at ambient temperature. At which point, phenyloxazoline **SI2** (4.00 g, 14.2 mmol, 1.0 equiv), cesium carbonate (17.4 g, 53.3 mmol, 3.75 equiv), and toluene

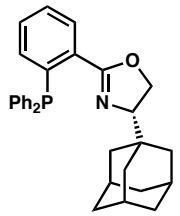
(60 mL) were added, the flask sealed and heated to 110 °C with stirring. The reaction mixture became deep red after ~15 min of heating. After 6 h, the reaction mixture was allowed to cool to ambient temperature, filtered, and washed with DCM (2 x 50 mL). Evaporation of the solvent and chromatography (3→7% EtO_2 in Hexanes on SiO_2) afforded the known[18c] *(S)-t*-Bu-PHOX (4.48 g, 81.4% yield).



295

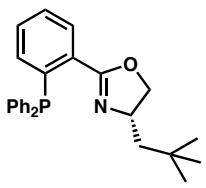
***(S)-t*-Bu-PHOX oxide (295).** To a solution of *(S)-t*-Bu-PHOX (150 mg, 0.387 mmol, 1.00 equiv) in THF (2.5 mL) was added a 5% aqueous H_2O_2 solution (1.94 mL). After 15 min the reaction mixture was diluted with EtOAc (5 mL) and brine (5 mL), washed with 10% aqueous Na_2CO_3 (5 mL) and brine (5 mL), dried ($MgSO_4$), and purified by flash chromatography on silica gel (5% MeOH in DCM) to give *(S)-t*-Bu-PHOX oxide **295** (149.3 mg, 96% yield) as a white foam: R_f 0.47 (10% MeOH in DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (ddd, J = 7.5, 3.9, 1.2 Hz, 1H), 7.81-7.33 (comp. m, 7H), 7.52-7.31 (comp. m, 7H), 3.84 (dd, J = 8.1, 8.1 Hz, 1H), 3.57 (dd, J = 9.9, 9.9 Hz, 1H), 3.41 (dd, J = 9.9, 8.4 Hz, 1H), 0.77 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 135.0 (d, J = 10.1 Hz), 133.7 (d, J = 107.1 Hz), 133.3 (d, J = 107.1 Hz), 132.6, 132.4-131.0 (7 lines), 130.8 (d, J = 8.6 Hz), 130.3 (d, J = 11.7 Hz), 138.2 (app. dd, J = 12.3, 1.4 Hz), 75.9, 68.8, 33.6, 25.8; ^{31}P NMR (121 MHz, $CDCl_3$) δ 30.3; IR (Neat Film NaCl) 3057, 2957, 2903, 2868, 2217, 1664, 1589, 1565, 1477, 1438, 1356, 1337, 1307, 1248, 1201, 1119, 1108,

1067, 1028, 963, 930, 905 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{27}O_2NP$ $[M]^+$: 404.1779, found 404.1799; $[\alpha]_D^{27.6}$ –69.3 (*c* 1.96, CH_2Cl_2).



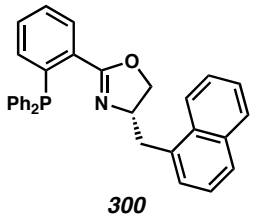
298

***(S)*-1-Ad-PHOX (298).** Prepared by general procedure 1 in 71% yield as a white solid; mp 163-164 ºC; R_f = 0.59 (Hexanes/AcOEt, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (m, 1H), 7.40-7.20 (m, 12H), 6.85 (m, 1H), 4.11 (t, *J* = 9.0 Hz, 1H), 4.03 (t, *J* = 9.0 Hz, 1H), 3.73 (t, *J* = 9.0 Hz, 1H), 1.85 (m, 3H), 1.68-1.46 (m, 6H), 1.44-1.34 (m, 3H), 1.24-1.14 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (d, J_{CP} = 3 Hz), 138.8-138.3 (6 lines), 134.4 (d, J_{CP} = 21 Hz), 134.1, 133.4 (d, J_{CP} = 20 Hz), 132.0 (d, J_{CP} = 20 Hz), 130.3, 129.7 (d, J_{CP} = 3 Hz), 128.5-128.0 (7 lines), 76.8, 66.8, 38.2, 37.0, 35.3, 28.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ -5.67; FTIR (Neat Film NaCl) 3053, 2902, 2848, 1651, 1586, 1477, 1434, 1346, 1248, 1089, 1044, 1026, 963, 744, 696 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{31}H_{33}NOP$ $[M+H]^+$: 466.2300, found 466.2309; $[\alpha]^{27}_D$ = -31.8 (*c* 0.48, $CHCl_3$).



299

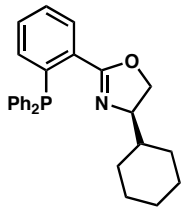
(*S*)-2-(2-(Diphenylphosphino)phenyl)-4-neopentyl-4,5-dihydrooxazole (299). Prepared by general procedure 1 in 73% yield as a white solid; mp 83-86 ºC; R_f = 0.52 (Hexanes/AcOEt, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (ddd, *J* = 7.8, 3.6, 1.5 Hz, 1H), 7.38-7.23 (m, 12H), 6.84 (ddd, *J* = 7.8, 4.5, 1.5 Hz, 1H), 4.25 (dd, *J* = 9.3, 8.1 Hz, 1H), 4.03 (m, 1H), 3.58 (t, *J* = 8.1 Hz, 1H), 1.52 (dd, *J* = 14.1, 4.5 Hz, 1H), 0.93 (dd, *J* = 14.1, 8.1 Hz, 1H), 0.84 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (d, J_{CP} = 3 Hz), 138.7 (d, J_{CP} = 25 Hz), 137.9 (d, J_{CP} = 12 Hz), 137.8 (d, J_{CP} = 10 Hz), 134.3 (d, J_{CP} = 21 Hz), 133.9 (d, J_{CP} = 21 Hz), 133.5 (d, J_{CP} = 2 Hz), 131.8 (d, J_{CP} = 18 Hz), 130.3, 129.8 (d, J_{CP} = 3 Hz), 128.6-128.3 (6 lines), 127.9, 73.9, 64.0, 49.7, 30.0, 29.8; ^{31}P NMR (121 MHz, $CDCl_3$) δ -3.95; FTIR (Neat Film NaCl) 3054, 2955, 1652, 1586, 1476, 1434, 1355, 1248, 1089, 1035, 968, 742, 697 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{26}H_{29}NOP$ $[M+H]^+$: 402.1987, found 402.2002; $[\alpha]^{26}_D$ = -6.9 (*c* 1.03, $CHCl_3$).



300

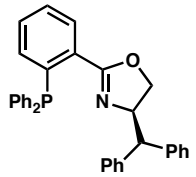
(*S*)-2-(2-(Diphenylphosphino)phenyl)-4-(naphthalen-1-ylmethyl)-4,5-dihydrooxazole (300). Prepared by general procedure 1 in 54% yield as a white amorphous solid; R_f = 0.29 (Hexanes/Et_2O, 3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 1H), 7.91 (m, 1H), 7.85 (m, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.56-7.45 (m, 2H), 7.42-7.28 (m, 13H), 7.16 (m, 1H), 6.87 (m, 1H), 4.55 (m, 1H), 3.97 (t, *J* = 8.4 Hz, 1H), 3.86 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.44 (dd, *J* = 14.4, 4.2 Hz, 1H), 2.39 (dd, *J* = 14.4, 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1 (d, J_{CP} = 3 Hz), 138.9 (d, J_{CP} = 25 Hz), 137.84 (d, J_{CP} =

10 Hz), 137.79 (d, J_{CP} = 12 Hz), 134.5 (d, J_{CP} = 21 Hz), 134.0, 133.82 (d, J_{CP} = 21 Hz), 133.80, 133.5 (d, J_{CP} = 3 Hz), 131.9, 131.3 (d, J_{CP} =17 Hz), 130.6, 130.0 (d, J_{CP} =3 Hz), 128.8-128.4 (6 lines), 127.9, 127.2, 126.6, 126.0, 125.6, 125.4, 123.8, 71.7, 66.7, 38.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ -3.59; FTIR (Neat Film NaCl) 3052, 2962, 1651, 1585, 1511, 1476, 1434, 1354, 1216, 1089, 1037, 963, 745, 697 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{32}H_{27}NOP$ $[M+H]^+$: 472.1830, found 472.1835; $[\alpha]^{24}_D$ = +29.7 (*c* 0.50, $CHCl_3$).



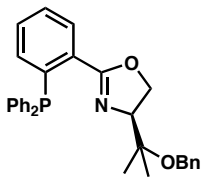
301

***(S)*-1-Cy-PHOX (301).** Prepared by general procedure 1 in 68% yield as a white solid; mp 122-124 ºC; R_f = 0.57 (Hexanes/AcOEt, 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (ddd, *J* = 7.7, 4.1, 1.7 Hz, 1H), 7.27 (m, 13H), 6.82 (ddd, *J* = 7.7, 4.1, 1.1 Hz, 1H), 4.12 (ddd, *J* = 14.6, 9.1, 1.4 Hz, 1H), 3.85 (t, *J* = 8.3 Hz, 1H), 3.81 (t, *J* = 8.5 Hz, 1H), 1.60 (m, 4H), 1.28 (d, *J* = 13.5 Hz, 1H), 1.05 (m, 4H), 0.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7 (d, J_{CP} = 3 Hz), 138.0-139.0 (6 lines), 134.5 (d, J_{CP} = 21 Hz), 133.8, 133.7 (d, J_{CP} = 20 Hz), 131.8 (d, J_{CP} = 19 Hz), 130.4, 129.8 (d, J_{CP} = 3 Hz), 128.6-128.0 (7 lines), 71.2, 70.1, 42.7, 29.4, 29.0, 26.4, 26.1, 26.0; ^{31}P NMR (121 MHz, $CDCl_3$) δ -4.21; FTIR (Neat Film NaCl) 3053, 2923, 2852, 1651, 1478, 1434, 1356, 1089, 1044, 964, 908 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{27}H_{28}NOP$ $[M^+]$: 413.1909, found 413.1923; $[\alpha]^{25}_D$ = +47.9 (*c* 0.175, $CHCl_3$).



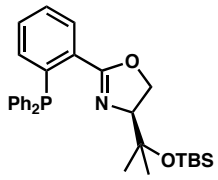
302

(*R*)-4-Benzhydryl-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole (302). Prepared by general procedure 1 in 89% yield as a white amorphous solid; R_f = 0.45 (Hexanes/AcOEt, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 1H), 7.38-7.13 (m, 22H), 6.88 (m, 1H), 4.92 (q, *J* = 9.0 Hz, 1H), 4.13 (dd, *J* = 9.3, 9.0 Hz, 1H), 3.79 (t, *J* = 9.0 Hz, 1H), 3.72 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 142.2, 142.1, 138.8 (d, J_{CP} = 25 Hz), 138.0-137.7 (3 lines), 134.1 (d, J_{CP} = 21 Hz), 133.9 (d, J_{CP} = 21 Hz), 133.7 (d, J_{CP} = 2 Hz), 131.7 (d, J_{CP} = 19 Hz), 130.5, 130.0 (d, J_{CP} = 3 Hz), 128.7-128.2 (9 lines), 128.0, 126.5, 126.2, 71.1, 70.1, 56.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ -5.22; FTIR (Neat Film NaCl) 3056, 3026, 2895, 1649, 1598, 1584, 1494, 1477, 1451, 1434, 1356, 1091, 1029, 909, 741 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{34}H_{29}NOP$ $[M+H]^+$: 498.1987, found 498.1963; $[\alpha]^{24}_D$ = +10.4 (*c* 1.00, $CHCl_3$).



303

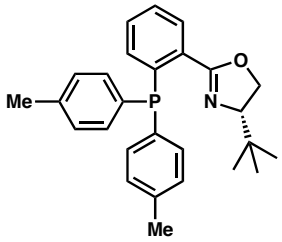
(*S*)-4-(2-(Benzyloxy)propan-2-yl)-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole (303). Prepared by general procedure 1 in 75% yield as a colorless viscous oil; R_f = 0.45 (Hexanes/AcOEt, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (ddd, *J* = 7.5, 3.6, 1.2 Hz, 1H), 7.41-7.19 (m, 17H), 6.88 (ddd, *J* = 7.5, 4.2, 0.9 Hz, 1H), 4.43-4.23 (m, 4H), 4.15 (dd, *J* = 9.6, 7.8 Hz, 1H), 1.21 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8 (d, J_{CP} = 3 Hz), 139.5, 139.1-138.3 (5 lines), 134.4 (d, J_{CP} = 21 Hz), 134.2, 133.5 (d, J_{CP} = 20 Hz), 131.6 (d, J_{CP} = 19 Hz), 130.5, 129.9 (d, J_{CP} = 3 Hz), 128.6-128.1 (6 lines), 127.14, 127.12, 76.9, 74.9, 68.5, 63.9, 23.9, 19.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ -5.51; FTIR (Neat Film NaCl) 3067, 2973, 2905, 1649, 1586, 1478, 1434, 1352, 1248, 1155, 1091, 1065, 1027, 964, 743, 697 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{31}H_{31}NO_2P$ $[M+H]_+$: 480.2092, found 480.2078; $[\alpha]^{26}_D$ = -2.0 (*c* 1.03, $CHCl_3$).



304

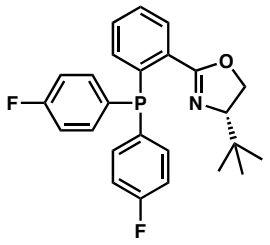
(*S*)-4-(2-(*tert*-Butyldimethylsilyloxy)propan-2-yl)-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole (304). Prepared by general procedure 1 in 84% yield as a white solid; mp 104-106 ºC; R_f = 0.62 (Hexanes/AcOEt, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (ddd, *J* = 7.5, 3.6, 1.2 Hz, 1H), 7.40-7.20 (m, 12H), 6.88 (ddd, *J* = 7.5, 3.9, 0.9 Hz, 1H), 4.32 (dd, *J* = 7.5, 6.6 Hz, 1H), 4.09 (dd, *J* = 10.2, 7.5 Hz, 1H), 4.02 (dd, *J* = 10.2, 6.6 Hz, 1H), 1.15 (s, 3H), 0.86 (s, 3H), 0.78 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 139.0-138.3 (6 lines), 134.3 (d, J_{CP} = 21 Hz), 134.2, 133.5 (d, J_{CP} = 20 Hz), 131.9 (d, J_{CP} = 19 Hz), 130.4, 129.8 (d, J_{CP} = 3 Hz),

128.5-128.0 (5 lines), 76.8, 74.9, 68.7, 28.7, 25.7, 23.9, 17.9, -2.2, -2.3; ^{31}P NMR (121 MHz, $CDCl_3$) δ -5.99; FTIR (Neat Film NaCl) 3054, 2955, 2929, 2856, 1652, 1586, 1472, 1434, 1353, 1251, 1162, 1091, 1058, 835, 774, 743, 696 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{30}H_{39}NO_2PSi$ $[M+H]^+$: 504.2488, found 504.2469; $[\alpha]^{26}_D$ = +19.8 (*c* 1.16, $CHCl_3$).



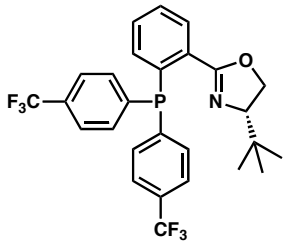
307

(*S*)-4-*tert*-Butyl-2-(2-(di-*p*-tolylphosphino)phenyl)-4,5-dihydrooxazole (307). Prepared by general procedure 1 using (*p*-Tol)$_2$PH in 73% yield as a colorless viscous oil; R_f = 0.39 (Hexanes/AcOEt, 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (ddd, *J* = 7.5, 3.6, 1.5 Hz, 1H), 7.33 (m, 1H), 7.26 (m, 1H), 7.23-7.05 (m, 8H), 6.89 (ddd, *J* = 7.5, 4.2, 1.5 Hz, 1H), 4.06 (dd, *J* = 10.2, 8.4 Hz, 1H), 3.98 (t, *J* = 8.3 Hz, 1H), 3.85 (dd, *J* = 10.2, 7.8 Hz, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 0.75 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (d, J_{CP} = 3 Hz), 139.3 (d, J_{CP} = 25 Hz), 138.4, 138.1, 135.0-134.7 (4 lines), 134.3 (d, J_{CP} = 21 Hz), 133.9, 133.6 (d, J_{CP} = 20 Hz), 131.9 (d, J_{CP} = 20 Hz), 130.2, 129.9 (d, J_{CP} = 3 Hz), 129.2 (d, J_{CP} = 7 Hz), 129.0 (d, J_{CP} = 7 Hz), 127.8, 76.5, 68.3, 33.6, 25.7, 21.3, 21.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ -6.98; FTIR (Neat Film NaCl) 2953, 1653, 1496, 1476, 1394, 1353, 1306, 1248, 1185, 1134, 1089, 1024, 967, 805, 743 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{27}H_{30}NOP$ $[M^+]$: 415.2065, found 415.2065; $[\alpha]^{25}_D$ = -58.8 (*c* 2.23, $CHCl_3$).



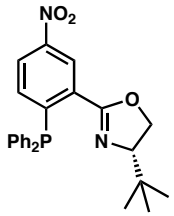
308

(*S*)-2-(2-(bis(4-fluorophenyl)phosphino)phenyl)-4-*tert*-butyl-4,5-dihydrooxazole (308). Prepared by Helmchen's Grignard method[18c] in 14% yield as a colorless oil; R_f = 0.50 (5% Et_2O in hexanes developed twice); ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (ddd, *J* = 7.0, 3.0, 1.0 Hz, 1H), 7.39 (ddd, *J* = 8.0, 8.0, 1.5 Hz, 1H), 7.31 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 7.26-7.14 (comp. m, 4H), 7.01 (app. dt, *J* = 13.0, 8.5 Hz, 4H), 6.83 (ddd, *J* = 7.5, 4.0, 1.0 Hz, 1H), 4.12 (dd, *J* = 10.0, 8.5 Hz, 1H), 4.03 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.90 (dd, *J* = 10.0, 8.0 Hz, 1H), 0.74 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3 (d, $J_{C\text{-}F}$ = 247.5 Hz), 163.1 (d, $J_{C\text{-}F}$ = 246.5 Hz), 162.3, 138.6 (d, $J_{C\text{-}P}$ = 25.3 Hz), 136.1 (dd, $J_{C\text{-}P}$ = 22.5 Hz, $J_{C\text{-}F}$ = 8.1 Hz), 135.3 (dd, $J_{C\text{-}P}$ = 21.9 Hz, $J_{C\text{-}F}$ = 8.1 Hz), 134.1 (dd, $J_{C\text{-}P}$ = 12.5, $J_{C\text{-}F}$ = 4.1 Hz), 134.0 (dd, $J_{C\text{-}P}$ = 10.4 Hz, $J_{C\text{-}F}$ = 4.0 Hz), 133.9, 131.7 (d, $J_{C\text{-}P}$ = 20.0 Hz), 130.5, 130.0 (d, $J_{C\text{-}P}$ = 2.9 Hz), 128.3, 115.6 (dd, $J_{C\text{-}F}$ = 18.6 Hz, $J_{C\text{-}P}$ = 7.6 Hz), 115.5 (dd, $J_{C\text{-}F}$ = 18.6 Hz, $J_{C\text{-}P}$ = 7.6 Hz) 76.8, 68.3, 33.6, 25.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ –8.2 (app. t, *J* = 3.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –113.6, –114.1; IR (Neat Film NaCl) 2955, 2904, 2868, 1653, 1587, 1494, 1392, 1354, 1336, 1225, 1159, 1091, 1039, 1025, 966, 827, 744 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{25}ONPF_2$ $[M + H]^+$: 424.1642, found 424.1622; $[\alpha]_D^{26.4}$ -17.7 (*c* 0.53, CH_2Cl_2).



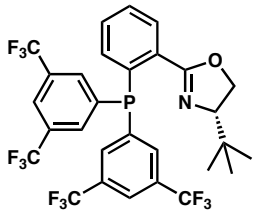
309

(*S*)-2-(2-(Bis(4-(trifluoromethyl)phenyl)phosphino)phenyl)-4-*tert*-butyl-4,5-dihydrooxazole (309). Prepared by general procedure 1 using (p-$CF_3Ph)_2PH$ in 75% yield as a white amorphous powder; R_f = 0.44 (Hexanes/AcOEt, 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (ddd, J = 7.5, 3.9, 1.2 Hz, 1H), 7.62-7.50 (m, 4H), 7.44 (m, 1H), 7.40-7.28 (m, 5H), 6.82 (ddd, J = 7.5, 3.9, 0.9 Hz, 1H), 4.20 (dd, J = 10.2, 8.4 Hz, 1H), 4.06 (t, J = 8.4 Hz, 1H), 3.93 (dd, J = 10.2, 8.4 Hz, 1H), 0.69 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (d, J_{CP} = 3 Hz), 143.4-143.2 (m), 136.7 (d, J_{CP} = 24 Hz), 134.4 (d, J_{CP} = 21 Hz), 134.2, 133.7 (d, J_{CP} = 20 Hz), 132.0 (d, J_{CP} = 20 Hz), 130.74, 130.65 (q, J_{CF} = 32 Hz), 130.5 (q, J_{CF} = 32 Hz), 129.9 (d, J_{CP} = 3 Hz), 128.9, 125.3-124.9 (m), 124.1 (q, J_{CF} = 271 Hz,), 77.0, 68.4, 33.6, 25.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ -7.29; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.23, -63.28; FTIR (Neat Film NaCl) 2958, 1653, 1606, 1480, 1396, 1324, 1166, 1128, 1106, 1061, 1017, 831, 700 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{27}H_{24}NOPF_6$ [M^+]: 523.1500, found 523.1494; $[\alpha]^{25}_D$ = -21.1 (*c* 2.26, $CHCl_3$).



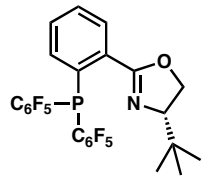
310

(*S*)-4-*tert*-Butyl-2-(2-(diphenylphosphino)-5-nitrophenyl)-4,5-dihydrooxazole (310). Prepared by a modification of Andreas' method[62] in 8% yield as a red oil; R_f = 0.57 (25% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 3.0, 3.0 Hz, 1H), 8.07 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.40-7.29 (comp. m, 6H), 7.29-7.18 (comp. m, 4H), 7.04 (dd, *J* = 8.5, 3.0 Hz, 1H), 4.15 (dd, *J* = 10.0, 8.5 Hz, 1H), 4.04 (dd, *J* = 9.0, 8.0 Hz, 1H), 3.90 (dd, *J* = 9.5, 8.0 Hz, 1H), 0.72 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7 (d, *J* = 3.8 Hz), 148.6 (d, *J* = 33.0 Hz), 147.4, 137.2 (d, *J* = 12.0 Hz), 136.9 (d, *J* = 8.5 Hz), 135.1 (d, *J* = 1.4 Hz), 134.3 (d, *J* = 21.5 Hz), 133.6 (d, *J* = 20.5 Hz), 132.7 (d, *J* = 18.6 Hz), 129.2-128.6 (6 lines), 124.4 (d, *J* = 1.9 Hz), 124.1, 77.2, 68.6, 33.6, 25.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ –3.4; IR (Neat Film NaCl) 3071, 2956, 2904, 2868, 1656, 1522, 1478, 1434, 1346, 1118, 1086, 1026, 970, 913, 742, 696 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{26}O_3N_2P$ $[M + H]^+$: 433.1681, found 433.1702; $[\alpha]_D^{26.4}$ -16.2 (*c* 0.87, $CHCl_3$).



311

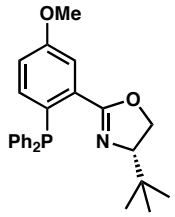
(*S*)-2-(2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)phenyl)-4-*tert*-butyl-4,5-dihydrooxazole (311). Prepared by Helmchen's Grignard method[18c] in 6% yield as a colorless oil; R_f = 0.29 (5% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (ddd, *J* = 7.5, 4.0, 1.5 Hz, 1H), 7.86 (app. d, *J* = 11.0 Hz, 2H), 7.64 (app. dd, *J* = 21.0, 6.0 Hz, 4H), 7.53 (ddd, *J* = 7.0, 7.0, 1.0, 1H), 7.42 (ddd, *J* = 7.5, 7.5 1.0 Hz, 1H), 6.77 (ddd, *J* = 7.5, 3.5, 1.0 Hz, 1H), 4.28 (dd, *J* = 10.0, 8.5 Hz, 1H), 4.12 (dd, *J* = 9.0, 9.0 Hz, 1H), 3.91 (dd, *J* = 10.5, 9.0 Hz, 1H), 0.68 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4 (d, *J* = 3.4 Hz), 141.9 (d, *J* = 13.9 Hz), 141.8 (d, *J* = 11.9 Hz), 134.8 (d, *J* = 23.9 Hz), 134.0, 133.7 (d, *J* = 19.1 Hz), 133.2 (d, *J* = 21.5 Hz), 131.8 (app. dq, *J* = 31.5, 4.8 Hz), 131.3, 130.0 (d, *J* = 2.9 Hz), 129.8, 123.1 (q, *J* = 271.8 Hz), 122.7 (app. d of septets, *J* = 25.3, 3.3 Hz), 77.1, 68.7, 33.4, 25.5;^{31}P NMR (121 MHz, $CDCl_3$) δ –6.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.9 (2 peaks); HRMS (FAB+) *m/z* calc'd for $C_{29}H_{23}ONPF_{12}$ $[M + H]^+$: 660.1325, found 660.1328; $[\alpha]_D^{26.2}$ -5.0 (*c* 0.35, $CHCl_3$).



312

(*S*)-4-*tert*-Butyl-2-(2-(diperfluorophenylphosphino)phenyl)-4,5-dihydrooxazole (312). Prepared by Helmchen's Grignard method[18c] in 13% yield as a

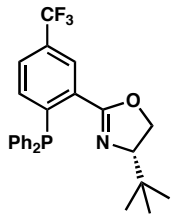
colorless oil; R_f = 0.39 (2.5% Et_2O in hexanes developed twice); ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (ddd, *J* = 7.4, 4.8, 1.3 Hz, 1H), 7.51 (app. tt, *J* = 7.5, 1.3 Hz, 1H), 7.41 (app. tt, *J* = 7.7, 1.3 Hz, 1H), 7.16 (dd, *J* = 7.7, 3.5 Hz, 1H), 4.35 (dd, *J* = 10.1, 8.8 Hz, 1H), 4.18 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.93 (dd, *J* = 10.1, 8.8 Hz, 1H), 0.75 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3 (d, *J* = 5.0 Hz), 132.5, 130.9, 129.7 (2 peaks), 129.6, 77.3, 69.1, 33.6, 25.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ -54.7 (app. quintet, *J* = 38.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -130.6 (app. t, *J* = 27.5 Hz), -131.1 (app. t, *J* = 27.5 Hz), -151.9 (app. t, *J* = 18.6 Hz), -152.4 (app. t, *J* = 21.2 Hz), –161.8 (app. t, *J* = 18.0 Hz), -162.0 (app. t, *J* = 15.0 Hz); IR (Neat Film NaCl) 2962, 2908, 2872, 1654, 1516, 1476, 1382, 1360, 1287, 1139, 1087, 1052, 978, 908, 834, 740 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{17}ONPF_{10}$ $[M + H]^+$: 568.0888, found 568.0868; $[\alpha]_D^{26.2}$ -6.3 (*c* 0.56, CH_2Cl_2).



313

(*S*)-4-*tert*-Butyl-2-(2-(diphenylphosphino)-5-methoxyphenyl)-4,5-dihydrooxazole (313). Prepared by general procedure 1 in 72% yield as a white amorphous powder; R_f = 0.61 (Hexanes/AcOEt, 3/1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (t, *J* = 2.9 Hz, 1H), 7.34-7.18 (m, 10H), 6.84 (ddd, *J* = 8.7, 2.4, 0.6 Hz, 1H), 6.78 (ddd, *J* = 8.7, 3.3, 0.6 Hz, 1H), 4.13 (dd, *J* = 10.2, 8.4 Hz, 1H), 4.03 (t, *J* = 8.1 Hz, 1H), 3.92 (dd, *J* = 10.2, 8.1 Hz, 1H), 3.82 (s, 3H), 0.73 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (d, J_{CP} = 3 Hz), 159.4, 139.0 (d, J_{CP} = 13 Hz), 138.7 (d, J_{CP} = 10 Hz), 135.8, 134.1 (d, J_{CP} =

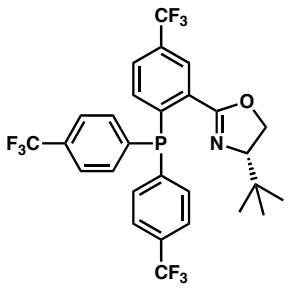
20 Hz), 133.41 (d, J_{CP} = 33 Hz), 133.36 (d, J_{CP} = 20 Hz), 129.3 (d, J_{CP} = 22 Hz), 128.3-128.0 (6 lines), 116.5, 114.9 (d, J_{CP} = 4 Hz), 76.7, 68.3, 55.3, 33.6, 25.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ -10.12; FTIR (Neat Film NaCl) 3069, 2956, 2903, 1654, 1594, 1561, 1479, 1434, 1354, 1336, 1297, 1224, 1181, 1093, 1050, 1022, 973, 744, 697 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{26}H_{28}NO_2P$ [M$^+$]: 417.1858, found 417.1844; $[\alpha]^{25}_D$ = -48.8 (*c* 2.11, $CHCl_3$).



314

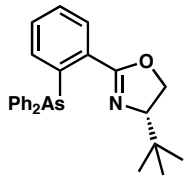
(*S*)-4-*tert*-Butyl-2-(2-(diphenylphosphino)-5-(trifluoromethyl)phenyl)-4,5-dihydrooxazole (314). Prepared by general procedure 1 in 77% yield as a white powder; mp 98-100 ºC; R_f = 0.45 (Hexanes/AcOEt, 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (m, 1H), 7.51 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.38-7.18 (m, 10H), 6.99 (dd, *J* = 8.1, 3.3 Hz, 1H), 4.12 (dd, *J* = 10.2, 8.4 Hz, 1H), 4.03 (t, *J* = 8.4 Hz, 1H), 3.90 (dd, *J* = 10.2, 8.4 Hz, 1H), 0.72 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4 (d, J_{CP} = 3 Hz), 144.2 (d, J_{CP} = 30 Hz), 137.7 (d, J_{CP} = 12 Hz), 137.3 (d, J_{CP} = 9 Hz), 134.6, 134.3 (d, J_{CP} = 21 Hz), 133.6 (d, J_{CP} = 20 Hz), 132.2 (d, J_{CP} = 19 Hz), 130.1 (q, J_{CF} = 33 Hz), 128.9-128.4 (6 lines), 126.6-126.3 (m), 123.7 (q, J_{CF} = 271 Hz), 77.0 (d, J_{CP} = 1 Hz), 68.4, 33.6, 25.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ -6.55 (J_{PF} = 2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.36; FTIR (Neat Film NaCl) 3071, 2957, 1655, 1478, 1434, 1407, 1357, 1343, 1326, 1302, 1262, 1244, 1174,

1131, 1080, 969, 744, 696 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{26}H_{25}NOPF_3$ [M^+]: 455.1626, found 455.1646; $[\alpha]^{25}_D$ = -36.3 (*c* 2.39, $CHCl_3$).



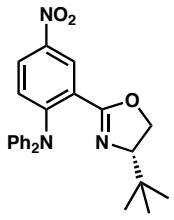
315

(*S*)-2-(2-(Bis(4-(trifluoromethyl)phenyl)phosphino)-5-(trifluoromethyl)phenyl)-4-*tert*-butyl-4,5-dihydrooxazole (315). Prepared by general procedure 1 using (*p*-$CF_3Ph)_2PH$ in 74% yield as a white amorphous powder; R_f = 0.63 (Hexanes/AcOEt, 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (m, 1H), 7.64-7.54 (m, 5H), 7.39-7.27 (m, 4H), 6.95 (dd, *J* = 7.8, 3.0 Hz, 1H), 4.25 (dd, *J* = 10.2, 8.7 Hz, 1H), 4.09 (t, *J* = 8.7 Hz, 1H), 3.95 (dd, *J* = 10.2, 8.7 Hz, 1H), 0.69 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7 (d, J_{CP} = 4 Hz), 142.6-141.7 (6 lines), 134.7-133.6 (5 lines), 132.4 (d, J_{CP} = 20 Hz), 131.1 (q, J_{CF} = 32 Hz), 130.9 (q, J_{CF} = 32 Hz), 127.0 (q, J_{CF} = 3 Hz), 126.7-126.4 (6 lines), 125.6-125.1 (8 lines), 123.9 (q, J_{CF} = 271 Hz), 123.5 (q, J_{CF} = 271 Hz), 77.3 (d, J_{CP} = 1 Hz), 68.6, 33.5, 25.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ -6.57; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.33, -63.39, -63.53; FTIR (Neat Film NaCl) 2960, 1657, 1606, 1479, 1397, 1324, 1169, 1129, 1107, 1082, 1061, 1017, 832, 700 cm^{-1}; HRMS (FAB, Pos) *m/z* calc'd for $C_{28}H_{24}F_9NOP$ $[M+H]^+$: 592.1452, found 592.1480; $[\alpha]^{24}_D$ = -16.0 (*c* 2.56, $CHCl_3$).



317

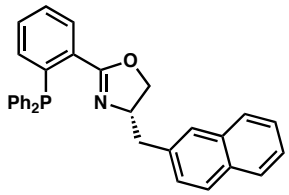
(*S*)-4-*tert*-Butyl-2-(2-(diphenylarsino)phenyl)-4,5-dihydrooxazole (317). Prepared by Helmchen's S_NAr method[18c] in 40% yield using lithium diphenylarsine generated by lithium reduction of triphenylarsine as a colorless oil; R_f = 0.42 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.37 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 7.34-7.23 (comp. m, 10H), 7.01 (dd, *J* = 8.0, 1.0, 1H), 4.15 (dd, *J* = 9.5, 8.0 Hz, 1H), 4.04 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.88 (dd, *J* = 10.5, 9.0 Hz, 1H), 0.75 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 141.9 (2 peaks), 141.5, 134.6, 134.0, 133.7, 131.8, 130.6, 129.5, 128.4 (2 peaks), 128.0, 127.9, 76.7, 68.3, 33.6, 25.7; IR (Neat Film NaCl) 3066, 3052, 2955, 2903, 2867, 1652, 1480, 1433, 1354, 1336, 1306, 1253, 1132, 1088, 1024, 967, 903, 736, 696 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{27}ONAs$ [M + H]$^+$: 432.1309, found 432.1290; $[\alpha]_D^{25.6}$ -33.8 (*c* 1.47, $CHCl_3$).



318

(*S*)-4-*tert*-Butyl-2-(2-(diphenylamino)-5-nitrophenyl)-4,5-dihydrooxazole (318). Prepared by a modification of Zhu's method[63] in 18% yield as a red oil; R_f = 0.45 (10% Et_2O in hexanes developed thrice); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, *J* = 3.0

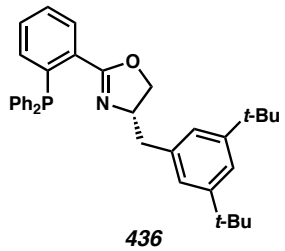
Hz, 1H), 8.13 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.28 (app. t, *J* = 7.5 Hz, 4H), 7.09 (app. t, *J* = 7.5, 2H), 7.09 (d, *J* = 9.0 Hz, 1H), 7.03 (app. d, *J* = 7.5 Hz, 4H), 3.77 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.59 (dd, *J* = 10.0, 8.5 Hz, 1H), 3.24 (dd, *J* = 10.0, 8.0 Hz, 1H), 0.80 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 151.8, 146.6, 141.8, 129.4, 128.6, 126.6, 126.5, 124.6, 124.3, 123.3, 75.0, 68.7, 33.6, 25.9; IR (Neat Film NaCl) 2958, 2904, 2868, 1647, 1588, 1574, 1518, 1490, 1333, 1299, 1278, 1116, 968, 912, 860, 751, 695 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{26}O_3N_3$ $[M + H]^+$: 416.1974, found 416.1969; $[\alpha]_D^{25.6}$ +203.9 (*c* 0.55, $CHCl_3$).



435

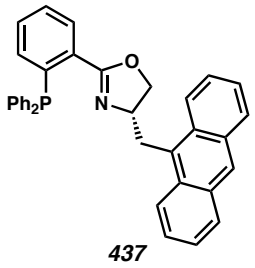
(*S*)-2-(2-(Diphenylphosphino)phenyl)-4-(naphthalen-2-ylmethyl)-4,5-dihydrooxazole (435). Prepared by general procedure 1 in 71% yield as a white amorphous solid; R_f = 0.24 (Hexanes/Et_2O, 3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (m, 1H), 7.82-7.72 (m, 3H), 7.53 (br s, 1H), 7.49-7.27 (m, 14H), 7.23 (m, 1H), 6.88 (m, 1H), 4.46 (m, 1H), 4.05 (dd, *J* = 9.0, 8.7 Hz, 1H), 3.83 (dd, *J* = 9.0, 7.5 Hz, 1H), 3.08 (dd, *J* = 14.1, 5.1 Hz, 1H), 2.30 (dd, *J* = 14.1, 9.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0 (d, J_{CP} = 3 Hz), 138.9 (d, J_{CP} = 25 Hz), 137.0-137.7 (3 lines), 135.6, 134.4 (d, J_{CP} = 21 Hz), 133.8 (d, J_{CP} = 21 Hz), 133.5 (d, J_{CP} = 2 Hz), 133.4, 132.1, 131.4 (d, J_{CP} = 18 Hz), 130.5, 129.9 (d, J_{CP} = 3 Hz), 128.7-127.4 (12 lines), 125.9, 125.4, 71.4, 67.7, 41.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ -4.05; FTIR (Neat Film NaCl) 3052, 1651, 1508, 1476, 1434,

1354, 1217, 1090, 1027, 964, 817, 743, 697 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{32}H_{27}NOP$ $[M+H]^+$: 472.1830, found 472.1845; $[\alpha]^{25}_D$ = +42.7 (*c* 0.50, $CHCl_3$).



436

(*R*)-4-(3,5-Di-*tert*-butylbenzyl)-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole (436). Prepared by general procedure 1 in 55% yield as a colorless viscous oil; R_f = 0.52 (Hexanes/EtOAc, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (m, 1H), 7.40-7.28 (m, 13H), 6.92 (d, *J* = 1.8 Hz, 2H), 6.86 (m, 1H), 4.33 (m, 1H), 4.00 (t, *J* = 8.7 Hz, 1H), 3.78 (dd, *J* = 8.7, 7.5 Hz, 1H), 2.95 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.01 (dd, *J* = 13.8, 10.2 Hz, 1H), 1.30 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9 (d, J_{CP} = 3 Hz), 150.8, 138.9 (d, J_{CP} = 25 Hz), 137.9 (d, J_{CP} = 12 Hz), 137.8 (d, J_{CP} = 10 Hz), 137.2, 134.4 (d, J_{CP} = 21 Hz), 134.0 (d, J_{CP} = 21 Hz), 133.4 (d, J_{CP} = 3 Hz), 131.5 (d, J_{CP} = 17 Hz), 130.5, 130.0 (d, J_{CP} = 3 Hz), 128.8-128.4 (6 lines), 127.9, 123.3, 120.3, 71.6, 68.1, 41.6, 34.7, 31.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ -3.60; FTIR (Neat Film NaCl) 2963, 1649, 1598, 1477, 1434, 1361, 1248, 1090, 1027, 965, 742, 696 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{36}H_{41}NOP$ $[M+H]^+$: 534.2926, found 534.2905; $[\alpha]^{25}_D$ = -49.3 (*c* 0.36, $CHCl_3$).



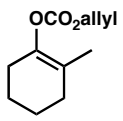
437

(*S*)-4-(Anthracen-9-ylmethyl)-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole (437). Prepared by general procedure 1 in 42% yield as a yellow powder; Mp 165-169 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.16 (m, 2H), 7.99 (m, 2H), 7.94 (m, 1H), 7.55-7.29 (m, 16H), 6.88 (m, 1H), 4.63 (m, 1H), 3.92 (dd, *J* = 9.0, 6.3 Hz, 1H), 3.77 (dd, *J* = 14.7, 4.5 Hz, 1H), 3.68 (t, *J* = 9.0 Hz, 1H), 3.17 (dd, *J* = 14.7, 10.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) d 164.3 (d, J_{CP} = 3 Hz, *C*=N), 138.9 (d, J_{CP} = 25 Hz), 138.1 (d, J_{CP} = 10 Hz), 137.8 (d, J_{CP} = 13 Hz), 134.6 (d, J_{CP} = 21 Hz), 133.8 (d, J_{CP} = 21 Hz), 133.5 (d, J_{CP} = 3 Hz), 131.5, 130.7, 130.2, 130.0, 129.2, 128.9-128.5 (6 lines), 128.0, 126.5, 125.8, 124.9, 124.5, 71.2 (CH*C*H_2O), 67.8 (CH_2*C*HN), 32.1 (Ar*C*H_2); ^{31}P NMR (120 MHz, $CDCl_3$) δ -3.57; IR (Neat Film NaCl) cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{36}H_{29}NOP$ [M^+]: 521.1909, found 521.1905; $[\alpha]^{26}_{D}$ = -5.1 (*c* 0.20, $CHCl_3$); TLC R_f = 0.38 (Hexanes/AcOEt, 5/1).

4.7.2.2 *Synthesis of Allyl Enol Carbonates*

General Procedures for the Synthesis of Allyl Enol Carbonates.

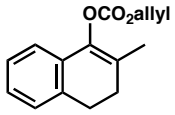
General Procedure 2:



274

Table 4.7 Entry 1. 274:[14a] To a solution of potassium *t*-butoxide (5.88 g, 52.5 mmol, 1.05 equiv) in DMF (100 mL) was added 2-methylcyclohexanone (6.13 mL, 50 mmol, 1.0 equiv). After 12 h, the reaction mixture was cooled in an ice bath and allyl chloroformate (6.4 mL, 60 mmol, 1.2 equiv) was added in a dropwise fashion. After an additional 30 min in the ice bath and 15 min at 25 °C, the reaction mixture was quenched into water (250 mL), extracted with DCM/hexanes 2/1 (4 x 125 mL), dried ($MgSO_4$), and evaporated. Chromatography (2.5 to 4 % Et_2O in Hexanes on SiO_2) afforded the allyl enol carbonate **274** (4.49 g, 46% yield) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (ddt, *J* = 17.4, 10.5, 5.6 Hz, 1H), 5.36 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.2, 1.2 Hz, 1H), 4.63 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.13 (m, 2H), 2.02 (m, 2H), 1.70 (m, 2H), 1.59 (m, 2H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 142.2, 131.5, 120.8, 118.8, 68.5, 30.0, 26.6, 23.1, 22.3, 15.7; IR (Neat Film NaCl) 3936, 1755, 1275, 1239, 1037 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{16}O_3$ $[M]^+$: 196.1100, found 196.1092.

General Procedure 3:

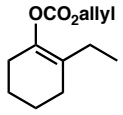


296

Table 4.7 Entry 12 (296).[64] To a cooled (0 °C) solution of LiHMDS (17.16 mmol, 1.1 equiv) in THF (37 mL) was added 2-methyl-1-tetralone (2.37 mL, 15.6 mmol, 1.0 equiv) in a dropwise manner over 15 min. After an additional 1.5 h at 0 °C, the enolate solution was added dropwise over 15 min to a -78 °C solution of allyl chloroformate (2.0 mL, 18.7 mmol, 1.2 equiv) in THF (80 mL). The reaction mixture

was allowed to warm to 25 °C in a Dewar vessel over 8 h. At which time, the reaction was quenched into DCM (100 mL) and half-saturated aqueous NH_4Cl (100 mL). The layers were separated and the aqueous layer extracted with DCM (2 x 50 mL). The organic fractions were washed with brine (100 mL), and dried (Na_2SO_4). Evaporation of the solvents under reduced pressure, and chromatography (2 to 5% Et_2O in Hexanes on SiO_2) afforded the allyl enol carbonate **296** (3.34 g, 88% yield) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.08 (m, 4H), 6.01 (ddt, *J* = 17.7, 10.4, 5.6 Hz 1H), 5.41 (dq, *J* = 17.3, 1.5 Hz, 1H), 5.32 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.72 (dt, *J* = 6.3, 1.4 Hz, 2H), 2.87 (t, *J* = 8.0 Hz, 2H), 2.40 (t, *J* = 8.0 Hz, 2H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 140.6, 135.2, 131.3, 130.8, 127.3, 127.0, 126.4, 124.4, 119.9, 119.1, 68.9, 28.8, 27.4, 16.5; IR (Neat Film NaCl) 2935, 2833, 1760, 1239 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{16}O_3$ $[M]^+$: 244.1100, found 244.1098.

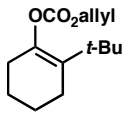
General Procedure 4:



320

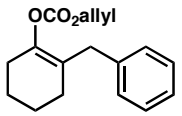
Table 4.7 Entry 4. (320):[65] To a solution of (2-ethylcyclohex-1-enyloxy)trimethylsilane (**348**) (1.50 g, 7.56 mmol, 1.0 equiv) in THF (14 mL) cooled to -78 °C was added a solution of potassium *t*-butoxide (0.933 g, 8.32 mmol, 1.1 equiv) in THF (8 mL) in a dropwise fashion over 2 min. The reaction mixture was maintained at -60 °C for 2.5 h, at which time allyl chloroformate (847 μL, 7.93 mmol, 1.05 equiv) in THF (3 mL) was added. After 1 h at -50 °C, the reaction mixture was poured into a

mixture of DCM (20 mL) and half-saturated aqueous NH_4Cl (20 mL). The layers were separated and the aqueous layer extracted with DCM (3 x 10 mL). The organic fractions were washed with water (50 mL), brine (50 mL), and dried (Na_2SO_4). Evaporation of the solvents under reduced pressure followed by chromatography on (2% Et_2O in Hexanes on SiO_2) and heating (rt to 105 °C) at 2 torr in a kugelrohr distillation apparatus afforded the allyl enol carbonate **320** (0.944 g, 59% yield) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.4, 10.5, 5.6 Hz, 1H), 5.37 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.64 (dt, *J* = 5.7, 1.5 Hz, 2H), 2.16 (m, 2H), 2.05 (m, 2H), 1.99 (q, *J* = 7.8, 2H), 1.70 (m, 2H), 1.61 (m, 2H), 0.4 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 141.7, 131.5, 126.3, 118.8, 68.5, 27.2, 26.6, 23.0, 22.9, 22.3, 11.9; IR (Neat Film NaCl) 2936, 1754, 1239 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1255.



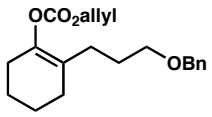
322

Table 4.7 Entry 5. (322): Prepared by general procedure 4 in 18% yield as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H), 5.38 (d, *J* = 17.4 Hz, 1H), 5.27 (d, *J* = 10.5 Hz, 1H), 5.65 (app. dt, *J* = 5.7, 1.2 Hz, 2H), 2.19 (m, 2H), 2.10 (m, 2H), 1.63 (m, 4H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 142.1, 131.6, 130.7, 118.9, 68.4, 34.8, 29.4, 28.1, 26.4, 23.1, 22.7; IR (Neat Film NaCl) 2926, 1754, 1241 cm^{-1}; HRMS *m/z* calc'd for $C_{14}H_{22}O_3$ $[M]^+$: 238.1569, found 238.1566.



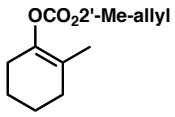
324

Table 4.7 Entry 6. (324): Prepared by general procedure 2 in 52% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.16 (m, 5H), 5.95 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H), 5.38 (dq, *J* = 17.3, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.2,1.2 Hz, 1H), 4.66 (app. dt, *J* = 5.7, 1.2 Hz, 2H), 3.35 (s, 2H), 2.27 (app. t, *J* = 6.3 Hz, 2H), 1.95 (m, 2H), 1.73 (m, 2H), 1.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 143.1, 139.3, 131.4, 128.8, 128.3, 126.0, 123.9, 119.0, 68.6, 36.0, 27.5, 26.7, 23.0, 22.2; IR (Neat Film NaCl) 2937, 1754, 1702, 1648, 1600, 1239 cm^{-1}; HRMS *m/z* calc'd for $C_{17}H_{20}O_3$ $[M]^+$: 272.1413, found 272.1416.



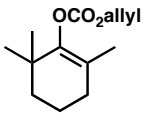
326

Table 4.7 Entry 7. (326): Prepared by general procedure 2 in 48% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H), 5.92 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.35 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.5, 1.1 Hz, 1H), 4.60 (app. dt, *J* = 5.7, 0.9 Hz, 2H), 4.49 (s, 2H), 3.44 (t, *J* = 6.6 Hz, 2H), 2.11 (m, 6H), 1.64 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 142.6, 138.7, 131.5, 128.3, 127.6, 127.4, 124.3, 118.8, 72.7, 70.0, 68.5, 27.7, 27.3, 26.6, 26.5, 23.0, 22.3; IR (Neat Film NaCl) 2924, 1754, 1240 cm^{-1}; HRMS *m/z* calc'd for $C_{20}H_{27}O_4$ $[M+H]^+$: 331.1909, found 331.1907.



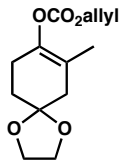
328

Table 4.7 Entry 8. (328): Prepared by general procedure 4 in 16% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (s, 1H), 4.96 (s, 1H), 4.57 (s, 2H), 2.16 (m, 2H), 2.034 (bs, 2H), 1.79 (s, 3H), 1.77-1.58 (m, 4H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 142.2, 139.4, 120.9, 113.4, 71.1, 30.1, 26.6, 23.1, 22.3, 19.3, 15.8; IR (Neat Film NaCl) 2926, 1755, 1236 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1259.



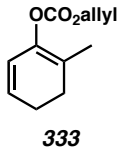
330

Table 4.7 Entry 9. (330): Prepared by general procedure 3 in 59% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (m, 1H), 5.38 (d, *J* = 17.4 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 4.65 (d, *J* = 6.9 Hz, 2H), 2.05 (t, *J* = 5.4 Hz, 2H), 1.56 (m, 4H), 1.49 (s, 3H), 1.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 147.9, 131.6, 120.7, 118.8, 68.5, 39.2, 34.9, 31.1, 26.7, 19.1, 16.5; IR (Neat Film NaCl) 2935, 1759, 1238 cm^{-1}; HRMS *m/z* calc'd for $C_{13}H_{20}O_3$ $[M]^+$: 224.1413, found 224.1418.



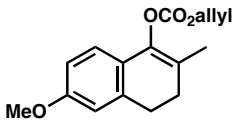
332

Table 4.7 Entry 10. (332): Prepared by general procedure 4 in 31% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.41 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.65 (app. dt, *J* = 5.7, 1.5 Hz, 2H), 3.97 (m, 4H), 2.37 (m, 2H), 2.30 (bs, 2H), 1.87 (app. t, *J* = 6.6 Hz, 2H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 141.3, 131.4, 119.0, 118.5, 107.3, 68.6, 64.5, 39.9, 31.3, 25.3, 15.8; IR (Neat Film NaCl) 2919, 1756, 1250 cm^{-1}; HRMS *m/z* calc'd for $C_{13}H_{19}O_5$ $[M+H]^+$: 255.1232, found 255.1227.



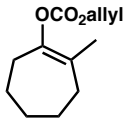
333

Table 4.7 Entry 11. (333): Prepared by general procedure 3 in 45% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.75 (m, 2H), 5.39 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.29 (d, *J* = 10.5, 1.2 Hz, 1H), 4.67 (app. dt, *J* = 5.7, 1.5 Hz, 2H), 2.42 (bs, 4H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 140.4, 131.3, 126.1, 122.7, 120.0, 119.1, 68.8, 28.2, 22.4, 15.7; IR (Neat Film NaCl) 2933, 1760, 1260 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943, found 194.0938.



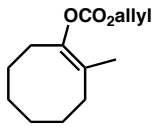
335

Table 4.7 Entry 13. (335): Prepared by general procedure 3 in 88% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (m, 1H), 6.70 (m, 2H), 5.98 (ddt, *J* = 17.1, 10.4, 5.7 Hz 1H), 5.42 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.32 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.71 (dt, *J* = 5.7, 1.2 Hz, 2H), 3.78 (s, 3H), 2.84 (t, *J* = 7.8 Hz, 2H), 2.38 (t, *J* = 8.1 Hz, 2H), 1.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 153.1, 140.4, 137.2, 131.3, 123.9, 121.4, 121.1, 119.1, 113.7, 110.9, 68.9, 55.2, 28.8, 27.8, 16.3; IR (Neat Film NaCl) 2933, 1758, 1237 cm^{-1}; HRMS *m/z* calc'd for $C_{16}H_{18}O_4$ $[M]^+$: 274.1205, found 274.1213.



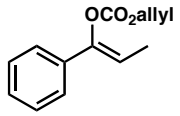
337

Table 4.7 Entry 14. (337): Prepared by general procedure 4 in 36% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.1, 10.5, 5.7 Hz 1H), 5.37 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.65 (app. dt, *J* = 6.0, 1.5 Hz, 2H), 2.33 (m, 2H), 2.10 (m, 2H), 1.70-1.54 (m, 6H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 146.2, 131.5, 125.5, 118.8, 68.5, 32.8, 32.5, 31.0, 25.7, 25.3, 18.3; IR (Neat Film NaCl) 2925, 1753, 1255, 1226 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1253.



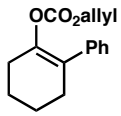
339

Table 4.7 Entry 15. (339): Prepared by general procedure 4 in 28% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (m, 1H), 5.39 (d, J = 16.5 Hz, 1H), 5.29 (d, J = 10.5 Hz, 1H), 4.66 (d, J = 5.4 Hz, 2H), 2.34 (app. t, J = 5.7 Hz, 2H), 2.15 (app. t, J = 5.4 Hz, 2H), 1.59 (s, 3H), 1.64-1.48 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 143.7, 131.5, 123.0, 118.8, 68.5, 31.4, 29.7, 28.7, 28.4, 26.6, 25.6, 15.5; IR (Neat Film NaCl) 2927, 1754, 1227 cm^{-1}; HRMS *m/z* calc'd for $C_{13}H_{20}O_3$ $[M]^+$: 224.1413, found 224.1419.



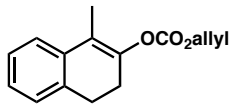
422

Table 4.13 Entry 1. (422): Prepared by general procedure 3 in 69% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46-7.43 (m, 2H), 7.37-7.26 (m, 3H), 6.04-5.85 (m, 2H), 5.44-5.28 (m, 2H), 4.71 (td, J_1 = 5.7 Hz, J_2 = 1.5 Hz, 2H), 1.80 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =152.6, 150.7, 147.2, 134.6, 131.1, 128.4, 128.1, 119.0, 68.9, 11.2; IR (Neat Film NaCl) 3061, 2920, 1760, 1673, 1496, 1446, 1366, 1227, 1186, 966, 765, 693 cm^{-1}; HRMS *m/z* calc'd for $C_{13}H_{14}O_3$ $[M]^+$: 218.0943, found 218.0938.



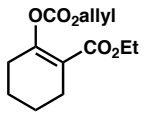
425

Table 4.14 Entry 1. (425): Prepared by general procedure 2 in 43% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.18 (comp. m, 5H), 5.80 (ddt, *J* = 17.4, 10.5, 5.4 Hz, 1H), 5.20 (ddt, *J* = 17.4, 1.8, 1.2 Hz, 1H), 5.18 (ddt, *J* = 10.5, 1.5, 1.2 Hz, 1H), 5.02 (ddd, *J* = 5.7, 1.5, 1.5 Hz, 2H), 2.46-2.38 (m, 2H), 2.37-2.30 (m, 2H), 1.90-1.72 (comp. m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 143.4, 138.8, 131.3, 128.1, 127.6, 126.8, 125.9, 118.4, 68.4, 30.1, 27.1, 22.8, 22.5; IR (Neat Film NaCl) 3081, 3057, 3024, 2938, 2862, 1753, 1687, 1601, 1492, 1444, 1367, 1238, 1178, 1091, 1036, 941, 784, 760, 700 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{18}O_3$ $[M]^+$: 258.1256, found 258.1256.



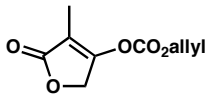
426

Table 4.14 Entry 2. (426): Prepared by general procedure 2 in 59% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.11 (comp. m, 4H), 6.00 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 5.43 (ddt, *J* = 17.1, 1.8, 1.2 Hz, 1H), 5.33 (ddt, *J* = 10.2, 1.5, 1.2 Hz, 1H), 4.72 (ddd, *J* = 6.0, 1.5, 1.2 Hz, 2H), 2.97 (t, *J* = 7.8 Hz, 2H), 2.55 (tq, *J* = 8.1, 1.5 Hz, 2H), 2.00 (t, *J* = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 145.9, 135.0, 134.1, 131.2, 127.1, 126.6, 126.5, 123.4, 119.7, 119.2, 68.9, 28.7, 26.0, 10.9; IR (Neat Film NaCl) 3021, 2993, 2944, 2891, 2836, 1757, 1674, 1488, 1451, 1365, 1304, 1279, 1246, 1217, 1181, 1157, 1031, 1018, 986, 943, 782, 760 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{16}O_3$ $[M]^+$: 244.1100, found 244.1095.



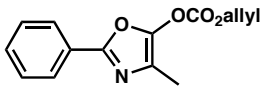
428

Table 4.14 Entry 3. (428): Prepared by general procedure 2 in 78% yield as a light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.39 (ddt, *J* = 17.1, 1.5, 1.5 Hz, 1H), 5.28 (ddt, *J* = 10.5, 1.5, 1.2 Hz, 1H), 4.67 (ddd, *J* = 5.7, 1.2, 1.2 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 2.44-2.34 (m, 2H), 2.32-2.24 (m, 2H), 1.80-1.58 (comp. m, 4H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 154.8, 152.2, 131.2, 119.2, 118.3, 69.0, 60.5, 28.6, 25.1, 21.9, 21.5, 14.0; IR (Neat Film NaCl) 3087, 1983, 2942, 2866, 1760, 1715, 1666, 1449, 1368, 1233, 1189, 1081, 1056, 1035, 994, 946, 767 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{18}O_5$ $[M]^+$: 254.1154, found 254.1153.



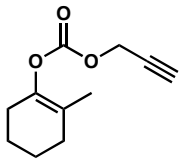
429

Table 4.14 Entry 4. (429): Prepared by a modification of general procedure 2 using TEA as the base and THF as solvent in 79% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 4.93 (ddt, *J* = 17.1, 2.7, 1.2 Hz, 1H), 5.37 (ddt, *J* = 10.2, 2.1, 0.9 Hz, 1H), 5.07 (q, *J* = 1.8 Hz, 2H), 4.74 (ddd, *J* = 6.0, 1.2, 0.9 Hz, 2H), 1.81 (t, *J* = 1.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 163.4, 150.2, 130.0, 120.8, 109.4, 70.3, 67.5, 6.9; IR (Neat Film NaCl) 3089, 2958, 2931, 1774, 1702, 1446, 1392, 1360, 1330, 1240, 1132, 1079, 1025, 945, 889, 775, 754 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_9H_{11}O_5$ $[M + H]^+$: 199.0606, found 199.0600.



431

Table 4.14 Entry 5. (431): Prepared by a modification of Leplawy's procedure[66] in 96% yield as a colorless oil that solidifies on standing; Mp 37.5-39 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97-7.90 (m, 2H), 7.45-7.38 (comp. m, 3H), 5.99 (ddt, *J* = 17.4, 10.5, 5.7 Hz, 1H), 5.45 (ddt, *J* = 17.4, 1.5, 1.2 Hz, 1H), 5.36 (ddt, *J* = 10.5, 1.2, 1.2 Hz, 1H), 4.78 (ddd, *J* = 6.0, 1.2, 1.2 Hz, 2H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 155.0, 151.6, 146.2, 130.5 (2C), 128.9, 127.3, 126.1, 120.6, 70.7, 10.5; IR (Neat Film NaCl) 3066, 2930, 1786, 1669, 1554, 1490, 1450, 1367, 1213, 1082, 1069, 1026, 992, 939, 774, 711, 692 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{13}O_4N$ $[M]^+$: 259.0845, found 259.0855.

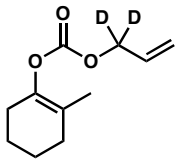


433

Propargyl enol carbonate 433: A 50 mL flask equipped with a septum was flame-dried under vacuum and cooled under dry nitrogen. To this was added methyllithium in ether (1.6 M, 7.5 mL, 12.0 mmol, 1.10 equiv) followed by dry ether (10 mL). To this solution was added ether (5 mL) solution of trimethyl(2-methylcyclohex-1-enyloxy)silane **(347)** (2.003 g, 10.9 mmol, 1.00 equiv) at 0 ºC and the resulting colorless solution was stirred for 1.5 h at ambient temperature to afford an ether solution of lithium enolate.

To a solution of propargyl chloroformate (1.18 mL, 12.0 mmol, 1.10 eq.) in ether (10 mL) was added the above lithium enolate solution at 0 ºC. The resulting mixture was

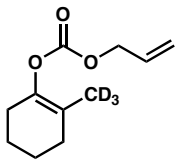
stirred and warmed to 10 ºC over 1 h. The resulting mixture was poured into saturated aqueous NH_4Cl and extracted with ether twice. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude oil. The crude residue was purified residue by SiO_2 chromatographed (2 to 10% Et_2O in hexanes) to give propargyl enol carbonate **443** (733 mg, 35% yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (d, J = 2.4 Hz, 2H), 2.53 (t, J = 2.4 Hz, 1H), 2.20-2.11 (m, 2H), 2.07-2.00 (m, 2H), 1.76-1.66 (m, 2H), 1.66-1.56 (m, 2H), 1.57 (m, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 142.3, 121.1, 76.9, 75.7, 55.4, 30.0, 26.5, 23.1, 22.3, 15.8; IR (Neat Film NaCl) 3295, 2937, 2862, 2130, 1756, 1709, 1439, 1376, 1275, 1250, 1220, 1045 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943, found 194.0939.



441

Dideuterio allyl enol carbonate 441. Prepared by general procedure 1 with dideuterioallyl chroroformate, which was synthesized from 1-dideuterioallyl alcohol[67] and 20% phosgene in toluene. Flash chromatography (SiO_2, 1 to 2.5% Et_2O in hexanes) gave dideuterio allyl enol carbonate **441** (6% yield) as a colorless oil; R_f = 0.82 (25% Et_2O in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (dd, *J* = 17.0, 10.4 Hz, 1H), 5.38 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 2.21-2.09 (comp. m, 2H), 2.08-1.98 (comp. m, 2H), 1.77-1.66 (comp. m, 2H), 1.65-1.53 (comp. m, 2H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 142.2, 131.4, 120.9, 119.0, 30.3, 26.6, 23.1, 22.3, 21.7,

15.8; IR (Neat Film NaCl) 2935, 2862, 1753, 1710, 1280, 1262, 1078 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{14}D_2O_3$ $[M]^+$: 198.1225, found 198.1217.



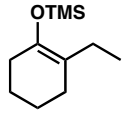
442

Trideuterio allyl enol carbonate 442. Prepared by general procedure 1 with 2-trideuteriomethylcyclohexanone.[68.] Flash chromatography (SiO_2, 2 to 2.5% Et_2O in hexanes) gave trideuterio allyl enol carbonate **442** (22% yield) as a colorless oil; $R_f = 0.82$ (25% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (ddt, *J* = 17.1, 10.8, 6.0 Hz, 1H), 5.38 (d, *J* = 17.3 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 4.65 (d, *J* = 5.7 Hz, 2H), 2.21-2.09 (comp. m, 2H), 2.08-1.98 (comp. m, 2H), 1.77-1.66 (comp. m, 2H), 1.66-1.53 (comp. m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 142.2, 131.5, 120.8, 118.8, 68.5, 30.0, 26.6, 23.1, 22.3; IR (Neat Film NaCl) 2936, 1755, 1705, 1367, 1276, 1247, 1216, 1034, 786 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{13}D_3O_3$ $[M]^+$: 199.1288, found 199.1280.

4.7.2.3 *Synthesis of Silyl Enol Ethers*

General Procedures for the Synthesis of Silyl Enol Ethers.

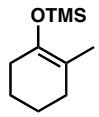
General Procedure 5:



348

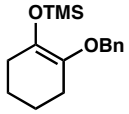
Table 4.8 Entry 2 (348).[69] To a solution of sodium iodide (15.0 g, 100 mmol, 1.25 equiv) in ACN (125 mL) were added 2-ethylcyclohexanone (10.1 g, 80 mmol, 1.0

equiv), TEA (14.0 mL, 100 mmol, 1.25 equiv), and finally TMSCl (11.6 mL, 91.2 mmol, 1.14 equiv) in a dropwise fashion. After 1 h, pentane (75 mL) was added, the biphasic mixture was stirred for 2 min, and the pentane decanted. After additional pentane extractions (5 x 75 mL), the combined pentane fractions were washed with water (2 x 50 mL) and brine (1 x 50 mL), and dried (Na_2SO_4). Evaporation under reduced pressure gave the crude silyl enol ether (12.0 g) as an 80:20 mixture (NMR) of isomers favoring the tetrasubstituted silyl enol ether. An oxygen balloon was affixed to a flask containing a solution of the crude silyl enol ether (6.0 g) and palladium (II) acetate (338.9 mg, 1.51 mmol) in DMSO (250 mL). The reaction mixture darkened and became heterogeneous. After 48 h, ^{1}H NMR analysis of an aliquot indicated less than 2% of the undesired isomer, and the reaction mixture was poured into a separatory funnel containing pentane (300 mL), water (300 mL), and ice (200 g). The layers were separated and the aqueous layer extracted with pentane (3 x 200 mL). The pentane fractions were washed with water (2 x 100 mL) and brine (100 mL), and dried (Na_2SO_4). Evaporation and chromatography (2% Et_2O in Hexanes on SiO_2) afforded the pure silyl enol ether **348** (3.21 g, 41% yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08-1.90 (m, 6H), 1.62 (m, 2H), 1.54 (m, 2H), 0.92 (t, J = 7.8 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 117.4, 30.4, 27.0, 23.7, 23.1, 22.9, 12.2, 0.7; IR (Neat Film NaCl) 2961, 2933, 1680, 1252, 922, 843 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{22}OSi$ $[M]^+$: 198.1440, found 198.1436.



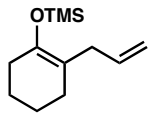
347

Table 4.8 Entry 1 (347). Prepared by general procedure 5, the initial 10:1 mixture favoring the tetrasubstituted isomer was purified by fractional distillation with a spinning band column[68] to give silyl enol ether **347** (84% yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (m, 2H), 1.94 (m, 2H), 1.64 (m, 2H), 1.58-1.49 (m, 5H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 111.8, 30.3, 30.1, 23.8, 23.0, 16.3, 0.7; IR (Neat Film NaCl) 2930, 1688, 1252, 1185, 843 cm^{-1}; HRMS *m/z* calc'd for $C_{10}H_{20}OSi$ $[M]^+$: 184.1284, found 184.1275.



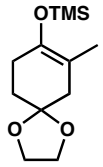
349

Table 4.8 Entry 3 (349). Prepared by general procedure 5 in 11% yield as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6) δ 7.40 (d, *J* = 7.2 Hz, 2H), 7.19 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 4.77 (s, 2H), 2.12-1.98 (comp. m, 4H), 1.39 (app. quintet, *J* = 3.3 Hz, 4H), 0.25 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 139.9, 136.9, 135.5, 128.8, 128.2, 128.0, 71.3, 30.8, 27.1, 23.9, 23.7, 1.2; IR (Neat Film NaCl) 3065, 3032, 2934, 2860, 2841, 1694, 1497, 1454, 1343, 1250, 1245, 1195, 1122, 1017, 930, 860, 844, 750, 698 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{24}O_2Si$ $[M]^+$: 276.1546, found 276.1545.



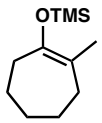
351

Table 4.8 Entry 5 (351). Prepared by general procedure 5 in 59% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (ddt, *J* = 16.8, 9.9, 6.9 Hz, 1H), 4.99 (ddt, *J* = 16.5, 2.1, 1.8 Hz, 1H), 4.95 (ddt, *J* = 9.6, 2.1, 1.5 Hz, 1H), 2.77 (app. d, *J* = 6.6 Hz, 2H), 2.14-1.88 (comp. m, 4H), 1.75-1.42 (comp. m, 4H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 136.9, 114.6, 113.5, 34.8, 30.4, 27.5, 23.7, 23.0, 0.7; IR (Neat Film NaCl) 3077, 2931, 2838, 1682, 1638, 1448, 1433, 1355, 1252, 1204, 1168, 948, 905, 888, 844, 753 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{22}OSi$ $[M]^+$: 210.1440, found 210.1449.



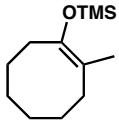
353

Table 4.8 Entry 6 (353). Prepared by general procedure 5 in 51% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (m, 4H), 2.21 (m, 4H), 1.79 (app. t, *J* = 6.9 Hz, 2H), 1.54 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 108.9, 108.0, 64.4, 39.9, 31.7, 28.7, 16.2, 0.69; IR (Neat Film NaCl) 2956, 1691, 1252 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{22}O_3Si$ $[M]^+$: 242.1338, found 242.1334.



354

Table 4.8 Entry 7 (354). Prepared by general procedure 5 in 39% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (app. t, J = 5.4 Hz, 2H), 2.01 (app. t, J = 5.1 Hz, 2H), 1.66 (m, 2H), 1.59 (s, 3H), 1.56-1.45 (m, 4H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 116.9, 35.1, 32.7, 31.6, 26.5, 25.5, 18.7, 0.6; IR (Neat Film NaCl) 2921, 1678, 1251, 1171, 892, 842 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{22}OSi$ [M]+: 198.1440, found 198.1439.



355

Table 4.8 Entry 8 (355). Prepared by general procedure 5 (pyridine substituted for TEA) in 29% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (m, 2H), 2.05 (m, 2H), 1.61-1.44 (m, 8H), 1.57 (s, 3H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 113.5, 31.7, 28.9, 28.8, 26.7, 26.3, 15.8, 0.8; IR (Neat Film NaCl) 2924, 1678, 1251 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{24}OSi$ [M]+: 212.1597, found 212.1590.

4.7.2.4 *Synthesis of Allyl β-Ketoesters*

General Procedures for the Synthesis of Allyl *b*-Ketoesters.

General Procedure 6: Dieckmann Cyclization Method

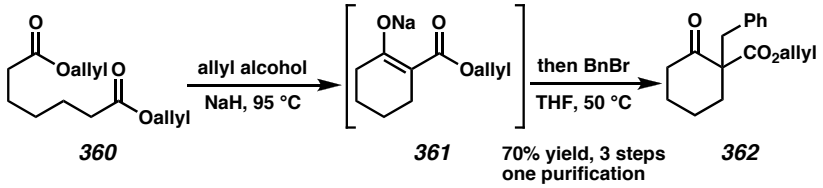


Table 4.10 Entry 6 (362). To a suspension of NaH (166.4 mg, 4.16 mmol, 1.0 equiv) in toluene (2 mL) was added allyl alcohol (79.2 μL, 1.17 mmol, 0.28 equiv). Once gas evolution ceased, pimelic acid diallyl ester (1.00 g, 4.16 mmol, 1.0 equiv) was added slowly and the resulting mixture heated to 95 °C for 1 h. Additional toluene (~2 mL) was added during this time to maintain a fluid reaction mixture. The reaction mixture was cooled to rt and the solvent removed by rotary evaporation *in vacuo*. The resulting solid salt was placed under dry N_2 and dissolved in THF (9 mL) at rt. Benzyl bromide (643.2 μL, 5.4 mmol, 1.3 equiv) was then added dropwise. The resulting mixture was warmed to 50 °C for 2.5 h, cooled to rt, quenched with saturated aqueous NH_4Cl solution (5 mL) followed by H_2O (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (1 x 10 mL), then dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5 x 18 cm SiO_2, 10% Et_2O in pentane) to afford the quaternary compound **362** as a colorless oil (781.4 mg, 70% yield). R_f = 0.30 (10% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.23 (comp. m, 3H), 7.20-7.13 (comp. m, 2H), 5.86 (dddd, J = 17.2, 10.3, 5.9, 5.9 Hz, 1H), 5.29 (m, 2H), 4.57 (m, 2H), 3.38 (d, 1H, J = 13.8 Hz), 2.94 (d, J = 13.8 Hz, 1H), 2.60-

2.39 (comp. m, 3H), 2.14-1.97 (m, 1H), 1.83-1.60 (comp. m, 3H), 1.59-1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 170.5, 136.3, 131.2, 130.2, 127.9, 126.5, 119.0, 65.6, 62.1, 41.1, 40.3, 35.7, 27.4, 22.3; IR (Neat Film NaCl) 3029, 2942, 1713, 1452, 1179, 1085 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{20}O_3$ $[M]^+$: 272.1412, found 272.1425.

General Procedure 7: Mander's Reagent Method

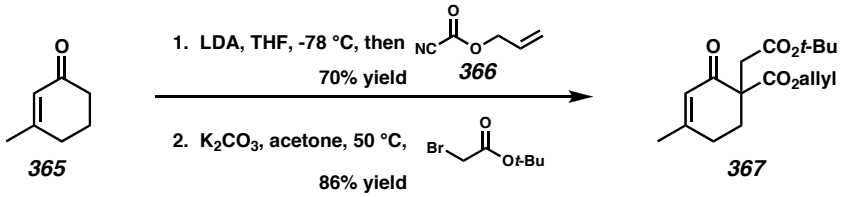
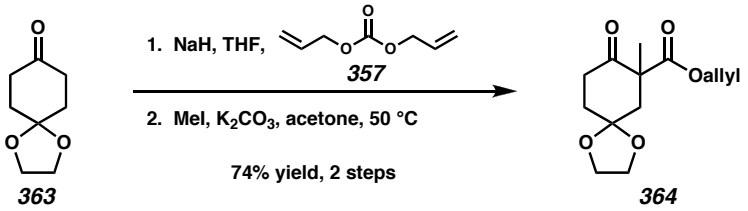


Table 4.11 Entry 6 (367). To a cooled (-78 °C) solution of LDA (18.70 mmol, 1.05 equiv) in THF (90 mL) was added 3-methylcyclohex-2-enone (2.02 mL, 17.81 mmol, 1.0 equiv) in a dropwise fashion. The resulting solution was stirred at -78 °C for 30 min and then allyl cyanoformate (2.00 g, 18.17 mmol, 1.02 equiv) was added dropwise. The dry ice bath was removed and the reaction mixture slowly warmed to rt and stirred for 8 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL) followed by H_2O (15 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (5 x 24 cm SiO_2, 50% EtOAc in hexanes) to afford the intermediate β-keto ester as a yellow oil (2.4152 g, 70% yield).

A portion of this β-keto ester (500.0 mg, 2.57 mmol, 1.0 equiv) was added to a suspension of anhydrous K_2CO_3 (711.8 mg, 5.15 mmol, 2.0 equiv) in acetone (2.5 mL). To the reaction mixture was added *t*-butyl bromoacetate (760.5 μL, 5.15 mmol, 2.0

equiv). The reaction mixture was then warmed to 50 °C and stirred for 48 h. The reaction mixture was then cooled, filtered, and the solids washed with acetone. The filtrate was concentrated and purified by flash chromatography (3 x 20 cm SiO_2, 10→30% EtOAc in hexanes) to afford the desired quaternary β-ketoester **367** as a colorless oil (684.7 mg, 86% yield; 60% overall yield for 2 steps). R_f = 0.28 (30% Et_2O in pentane). ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 (s, 1H), 5.87 (dddd, J = 17.3, 10.5, 5.4, 5.4 Hz, 1H), 5.23 (m, 2H), 4.61 (m, 2H), 2.83 (d, J = 16.4 Hz, 1H), 2.73 (d, J = 16.4 Hz, 1H), 2.58-2.36 (comp. m, 2H), 2.31-2.16 (comp. m, 2H), 1.94 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2, 169.8, 161.9, 131.7, 125.6, 118.2, 81.1, 65.8, 54.2, 39.8, 30.5, 28.7, 28.0, 24.2; IR (Neat Film NaCl) 2979, 1733, 1677, 1368, 1153 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{24}O_5$ $[M]^+$: 308.1624, found 308.1609.

General Procedure 8: Diallyl Carbonate Method



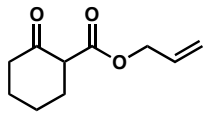
Part 1, Acylation:

To a cooled (0 °C) suspension of NaH (9.22 g, 240.1 mmol, 2.5 equiv) in THF (125 mL) was added a solution of 1,4-cyclohexanedione *mono*-ethylene ketal (15.0 g, 96 mmol, 1.0 equiv) in THF (30 mL) dropwise over 15 min. The reaction mixture was warmed to rt and diallyl carbonate (20.65 mL, 144.0 mmol, 1.5 equiv) was added and the reaction mixture stirred for 16 h. The reaction was quenched with saturated aqueous NH_4Cl and 1 N HCl until a pH of 4 was reached. The phases were separated and the

aqueous phase was extracted with EtOAc (7 x 150 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated, redissolved in DCM, dried ($MgSO_4$), filtered, and concentrated.

Part 2, Alkylation:

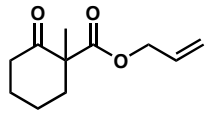
The resulting oil was added to a suspension of anhydrous K_2CO_3 (26.5 g, 192.0 mmol, 2.0 equiv) in acetone (128 mL). To the reaction mixture was added iodomethane (12.0 mL, 192.0 mmol, 2.0 equiv) and the reaction mixture was then heated to 50 °C for 14 h. The mixture was then cooled to rt, filtered, and the solids washed with acetone. The filtrate was concentrated and the resulting oil purified by flash chromatography (SiO_2, 5→40% Et_2O in hexanes) to afford the desired quaternary quaternary β-ketoester **364** as a colorless oil (18.0 g, 74% yield). R_f = 0.28 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (dddd, *J* = 17.4, 10.5, 5.7, 5.7 Hz, 1H), 5.26 (m, 2H), 4.60 (m, 2H), 3.97 (comp. m, 4H), 3.02 (dt, *J* = 14.8, 10.2 Hz, 1H), 2.68 (dt, *J* = 14.0, 2.0 Hz, 1H), 2.49 (dt, *J* = 14.8, 4.4 Hz, 1H), 2.00 (comp. m, 2H), 1.72 (d, *J* = 14.1 Hz, 1H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 172.9, 131.6, 118.5, 106.5, 65.9, 64.8, 64.3, 54.6, 43.6, 37.4, 35.2, 21.7; IR (Neat Film NaCl) 2939, 2891, 1733, 1717, 1304, 1141 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{18}O_5$ $[M]^+$: 254.1154, found 254.1153.



SI3

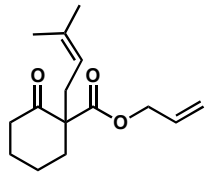
SI3: Prepared by method 1. The reaction was quenched with 10% HCl. The product was isolated by bulb-to-bulb distillation once at 150-155 °C (bath temp, 2 torr),

then at 136 °C (bath temp, 2 torr). 75% yield. R_f = 0.53 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of enol tautomers) δ 12.14 (s, 0.7H), 5.99 (dddd, *J* = 5.7, 5.7, 10.8, 17.1 Hz, 0.7H), 5.96 (dddd, *J* = 5.7, 5.7, 10.2, 17.1 Hz, 0.3H), 5.38 (dddd, *J* = 1.5, 1.5, 1.5, 17.1 Hz, 0.3H), 5.37 (dddd, *J* = 1.5, 1.5, 1.5, 17.1 Hz, 0.7H), 5.24 (dddd, *J* = 1.5, 1.5, 1.5, 10.5 Hz, 1H), 4.72-4.55 (m, 2H), 3.41 (ddd, *J* = 1.5, 6.6, 9.6 Hz, 0.3H), 2.52 (dddd, *J* = 1.5, 5.4, 5.4, 14.1 Hz, 0.3H), 2.37 (m, 0.3H), 2.26 (m, 2.7H), 2.22-2.10 (m, 0.6H), 2.04-1.78 (m, 0.9H), 1.75-1.55 (m, 3.3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 172.4, 172.2, 169.6, 132.3, 131.8, 118.4, 117.7, 97.5, 65.6, 64.6, 57.2, 41.5, 29.9, 29.1, 27.0, 23.3, 22.3, 22.3, 21.9; IR (Neat Film NaCl) 3086, 2941, 1746, 1716, 1659, 1617, 1299, 1259, 1217, 1176, 831 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{14}O_3$ $[M]^+$: 182.0943, found 182.0941.



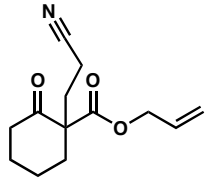
358

Table 4.10, Entry 1 (358). Prepared by general procedure 6. 62% yield. R_f = 0.38 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.1, 10.2, 5.9, 5.9 Hz, 1H), 5.24 (m, 2H), 4.59 (d, *J* = 5.7 Hz, 2H), 2.58-2.34 (comp. m, 3H), 2.08-1.88 (m, 1H), 1.80-1.54 (comp. m, 3H), 1.52-1.37 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 172.6, 131.4, 118.7, 65.6, 57.1, 40.5, 38.1, 27.4, 22.5, 21.1; IR (Neat Film NaCl) 3086, 2939, 2867, 1715, 1452, 1259, 1211, 1159, 1084, 976 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{16}O_3$ $[M]^+$: 196.1099, found 196.1096.



368

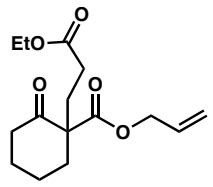
Table 4.10, Entry 3 (368). Prepared by general procedure 8 part B from **SI3** and prenyl bromide. Flash chromatography (SiO_2, 2→12% Et_2O in pentane). 20% yield. R_f = 0.24 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (dddd, J = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.31 (d, J = 17.1 Hz, 1H), 5.24 (d, J = 10.1 Hz, 1H), 5.06 (t, J = 7.7 Hz, 1H), 4.59 (d, J = 5.7 Hz, 2H), 2.65-2.27 (comp. m, 5H), 2.07-1.93 (m, 1H), 1.79-1.69 (m, 1H), 1.68 (s, 3H), 1.66-1.59 (m, 1H), 1.58 (s, 3H), 1.54-1.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 171.4, 134.8, 131.6, 118.8, 118.5, 65.7, 61.3, 41.2, 35.5, 33.2, 27.5, 26.0, 22.5, 17.8; IR (Neat Film NaCl) 2938, 2863, 1714, 1451, 1438, 1210, 1178, 989 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{22}O_3$ $[M]^+$: 250.1569, found 250.1574.



370

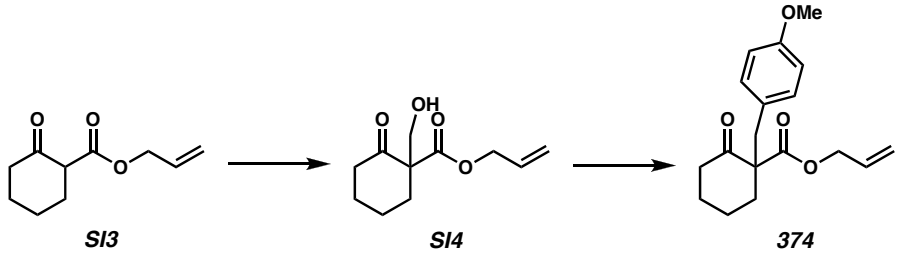
Table 4.10, Entry 4 (370). Prepared by general procedure 8 part B from **SI3** and acrylonitrile. Flash chromatography (SiO_2, 10% Et_2O in pentane). 55% yield. R_f = 0.27 (CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (dddd, J = 17.6, 10.2, 6.0, 6.0 Hz, 1H), 5.41-5.25 (m, 2H), 4.68 (d, J = 6.0 Hz, 2H), 2.64-2.38 (comp. m, 4H), 2.37-2.13 (comp. m, 2H), 2.13-1.86 (comp. m, 2H), 1.85-1.40 (comp. m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 170.6, 130.9, 120.0, 119.3, 66.4, 59.7, 40.9, 36.7, 30.8, 27.4, 22.4, 13.0; IR (Neat

Film NaCl) 2945, 2868, 2248, 1713, 1450, 1192, 1136, 941 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{17}NO_3$ $[M]^+$: 235.1208, found 235.1218.



372

Table 4.10, Entry 5 (372). Prepared by general procedure 8 part B from **SI3** and ethyl acrylate. Flash chromatography (SiO_2, 10% Et_2O in pentane). 81% yield. $R_f = 0.37$ (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (dddd, *J* = 17.3, 10.3, 5.9, 5.9 Hz, 1H), 5.33 (dd, *J* = 17.3, 1.1 Hz, 1H), 5.26 (dd, *J* = 10.4, 1.3 Hz, 1H), 4.63 (app. t, *J* = 14.9 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.51-2.31 (comp. m, 4H), 2.31-2.11 (comp. m, 2H), 2.08-1.85 (comp. m, 2H), 1.84-1.57 (comp. m, 3H), 1.55-1.40 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 173.0, 171.4, 131.3, 119.3, 65.9, 60.4, 60.1, 41.0, 36.2, 29.6, 29.5, 27.5, 22.5, 14.2; IR (Neat Film NaCl) 2943, 2868, 1734, 1715, 1456, 1181 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{22}O_5$ $[M]^+$: 282.1467, found 282.1474.

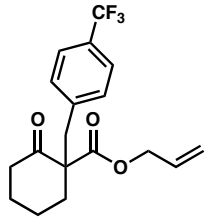


SI3 ***SI4*** ***374***

Table 4.10, Entry 7 (374). To a cooled (0 °C) solution of **SI3** (4.00 g, 22.0 mmol, 1.0 equiv) in THF (40 ml) was added 35% aqueous formaldehyde (11.3 mL) and

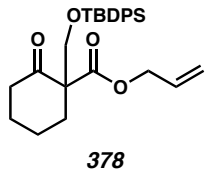
$KHCO_3$ (5.93 g, 65.9 mmol, 3.0 equiv). After 30 min at 0 °C the reaction mixture was allowed to warm to ambient temperature. After an additional 90 min, the reaction was quenched with water (100 mL) and DCM (100mL). After the layers were separated, the aqueous layer was extracted with DCM (4 x 50 mL), the combined organics dried (Na_2SO_4) and evaporated. The oil obtained was treated with THF (40 mL) and 3M HCl (4 drops) for 60 min, concentrated, and purified by flash chromatography (SiO_2, 10→45% EtOAc in hexanes) to give **SI4** (3.75g, 81% yield).

To a cooled (0 °C) suspension of 60% NaH (251 mg, 6.28 mmol, 1.1 equiv) in DMF (20 mL) was added **SI4** (1.20g, 5.71 mmol, 1.0 equiv) in a dropwise manner over 2 min. Once gas evolution had ceased (10 min), Bu_4NI (527 mg, 1.43 mmol. 0.25 equiv) and PMB-Cl (930 μL, 6.85 mmol, 1.2 equiv) were added, and the reaction mixture slowly allowed to warm to ambient temperature. After 12 h, the reaction mixture was quenched with water (50 mL) and 2/1 DCM/hexanes (50 mL), the aqueous layer extracted with 2/1 DCM/hexanes (3 x 50 mL), dried (Na_2SO_4), evaporated, and purified by flash chromatography (SiO_2, 10→20% Et_2O in hexanes) to give the desired compound **374** (485 mg, 28% yield). R_f = 0.30 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 5.89-5.76 (m, 1H) 5.31-5.21 (m, 2H), 4.59-4.47 (m, 2H), 3.76 (s, 3H), 3.25 (d, J = 14.1 Hz, 1H), 2.84 (d, J = 14.1 Hz, 1H), 2.51-2.35 (m, 3H), 2.04-1.96 (m, 1H), 1.76-1.54 (m, 3H), 1.50-1.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 170.8, 158.4, 131.4, 131.3, 128.4, 119.1, 113.4, 65.8, 62.3, 55.1, 41.3, 39.5, 35.8, 27.5, 22.5; IR (Neat Film NaCl) 2943, 1713, 1612, 1513, 1247, 1179 cm^{-1}; HRMS (EI) m/z calc'd for $C_{18}H_{22}O_4$ $[M]^+$: 302.1518, found 302.1514.



376

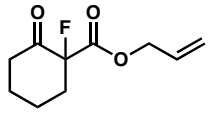
Table 4.10, Entry 8 (376). Prepared by general procedure 6 with 4-(trifluoroumethyl)benzyl bromide. Flash chromatography (SiO_2, 2→12% Et_2O in pentane). 56% yield. Mp 40-41 ºC; R_f = 0.63 (30% Et_2O in pentane); ^{1}H NMR (300 MHz, C_6D_6) δ 7.29 (d, J = 8.1 Hz, 2H), 7.02 (d, J = 8.1 Hz, 2H), 5.45 (dddd, J = 17.3, 10.4, 6.0, 6.0 Hz, 1H), 4.91 (m, 2H), 4.18 (m, 2H), 3.34 (d, J = 13.7 Hz, 1H), 2.78 (d, J = 13.7 Hz, 1H), 2.37-2.15 (comp. m, 3H), 1.57-1.38 (comp. m, 2H), 1.32-1.11 (comp. m, 2H), 1.09-0.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 170.4, 140.8 (q, J_{CF} = 1.2 Hz), 131.0, 130.7, 129.0 (q, J_{CF} = 32.3 Hz), 124.9 (q, J_{CF} = 3.9 Hz), 124.2 (q, J_{CF} = 271.7 Hz), 119.4, 65.9, 62.2, 41.2, 40.2, 36.2, 27.5, 22.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.0; IR (Neat Film NaCl) 2945, 1715, 1326, 1164, 1123, 1068 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{18}H_{19}F_3O_3$ $[M]^+$: 340.1286, found 340.1277.



378

Table 4.10, Entry 9 (378). To a solution of **SI4** (1.20 g, 5.71 mmol. 1.0 equiv), imidazole (583 mg, 8.57 mmol, 1.5 equiv), and DMAP (1.04 g, 8.57 mmol, 1.5 equiv) in DMF (20 mL) was added TBDPS-Cl (1.75 mL, 6.85 mmol, 1.2 equiv). After 24 h at ambient temperature, the reaction mixture was poured into water (75 mL) and 2/1

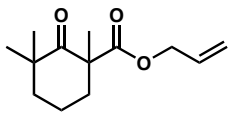
DCM/hexanes (150 mL), extracted with 2/1 DCM/hexanes (4 x 30 mL), dried (Na_2SO_4), and evaporated. Flash chromatography (SiO_2, 2.5→12% EtOAc in hexanes) gave the desired compound (1.85 g, 72% yield). Mp 59-60 °C; R_f = 0.24 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.72-7.68 (m, 4H), 7.48-7.37 (m, 6H), 6.00-5.86 (m, 1H), 5.38-5.31 (m, 1H), 5.28-5.23 (m, 1H), 4.74-4.59 (m, 2H), 4.24 (d, *J* = 9.9 Hz, 1H), 3.82 (d, *J* = 9.9 Hz, 1H), 2.78 (dq, *J* = 13.4, 3.3 Hz, 1H), 2.53-2.38 (m, 2H), 2.10-1.99 (m, 1H), 1.88-1.54 (m, 4H) 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4, 169.8, 135.6, 135.5, 133.1, 132.9, 131.5, 129.6, 127.6(2C), 118.8, 66.4, 65.8, 62.9, 41.2, 33.6, 27.3, 26.6, 22.1, 19.2; IR (Neat Film NaCl) 3072, 2933, 2858, 1715, 1428, 1200, 1112, 703 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{27}H_{33}O_4Si$ $[M-H]^+$: 449.2148, found 449.2165.



380

Table 4.10, Entry 10 (380). To a solution of **SI3** (946.4 mg, 5.19 mmol, 1 equiv) in 50 mL CH_3CN, was added $TiCl_4$ (50 mL, 0.456 mmol, 0.09 equiv). Select-fluor (2.2224 g, 6.27 mmol, 1.2 equiv) was added after 10 min and the mixture stirred at rt for 2 h and 40 min, over which time the orange color disappeared. The mixture was partitioned between H_2O (200 mL) and Et_2O (50 mL). The aqueous layer was separated and washed with Et_2O (30 mL). The combined organic layers were dried ($MgSO_4$), concentrated to about 30 mL, passed through a pad of silica that was washed with Et_2O (5 x 10 mL), and evaporated *in vacuo*. The residue was the bulb-to-bulb distilled at 180-190 °C (bath temp, 2 torr) to afford the title compound as a colorless oil (947.6 mg, 91% yield). R_f = 0.19 (10:1 Hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 (dddd, *J* =

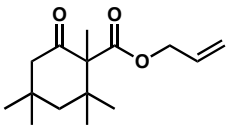
5.7, 5.7, 10.5, 17.1 Hz, 1H), 5.37 (dddd, J = 1.5, 1.5, 1.5, 17.4 Hz, 1H), 5.29 (dddd, J = 1.5, 1.5, 1.5, 10.5 Hz, 1H), 4.73 (bd, J = 5.7 Hz, 2H), 2.80-2.67 (m, 1H), 2.66-2.38 (m, 2H), 2.24-2.10 (m, 1H), 1.98-1.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5 (d, $J_{C\text{-}F}$ = 19.8 Hz), 166.4 (d, $J_{C\text{-}F}$ = 24.8 Hz), 130.8, 119.2, 96.2 (d, $J_{C\text{-}F}$ = 196.9 Hz), 66.5, 39.4, 35.8 (d, $J_{C\text{-}F}$ = 21.8 Hz), 26.4, 20.7 (d, $J_{C\text{-}F}$ = 6.0 Hz); IR (Neat Film NaCl) 3087, 2952, 1759, 1735, 1650, 1452, 1281, 1223, 1150, 1097, 990 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{13}O_3F$ $[M]^+$: 200.0849, found 200.0858.



382

Table 4.11, Entry 3 (382). To a cooled (-78 °C) solution of LDA (13.5 mmol, 1.12 equiv) in THF (30 mL) was added 2,2,6-trimethylcyclohexanone (1.6938 g, 12.08 mmol, 1.0 equiv) dropwise. The resulting solution was warmed to 0 °C for 1 hour, cooled to -78 °C and HMPA (2.2 mL, 12.6 mmol, 1.04 equiv) was added. After 5 min, allyl cyanoformate (1.5014g, 13.5 mmol, 1.12 equiv) was added dropwise. The reaction was warmed to rt and allowed to stir overnight. The reaction was then quenched with 50% saturated NH_4Cl (40 mL). The aqueous layer was separated and washed with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (SiO_2, 3% Et_2O in hexanes) to afford the β-keto ester as a colorless oil (585.6 mg, 22%), along with the known enol carbonate (R_f = 0.53, 10:1 Hexane:EtOAc) as a colorless oil (1.3117 g, 48%). R_f = 0.50 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dddd, J = 5.7, 5.7, 10.2, 16.8 Hz, 1H), 5.30 (dddd, J = 1.2, 1.2, 1.2, 17.1

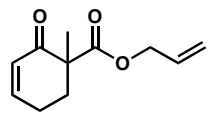
Hz, 1H), 5.22 (dddd, *J* = 0.9, 0.9, 0.9, 10.2 Hz, 1H), 4.62 (dddd, *J* = 1.2, 1.2, 5.7, 13.2 Hz, 1H), 4.51 (dddd, *J* = 1.2, 1.2, 5.7, 13.2 Hz, 1H), 2.54 (dddd, *J* = 2.4, 3.9, 3.9, 13.8 Hz, 1H), 1.98 (ddddd, *J* = 3, 4.2, 12, 14.1, 15.6 Hz, 1H), 1.77-1.68 (m, 1H), 1.66-1.52 (m, 2H), 1.42 (ddd, *J* = 4.2, 12.3, 13.8, 1H), 1.32 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.4, 172.4, 131.5, 118.8, 65.7, 55.1, 46.1, 40.6, 36.8, 26.8, 25.5, 23.6, 18.5; IR (Neat Film NaCl) 3089, 2938, 1736, 1707, 1649, 1456, 1377, 1243, 1209, 1174, 1150, 972 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{20}O_3$ $[M]^+$: 224.1413, found 224.1413.



383

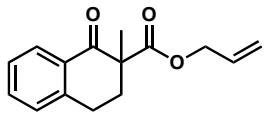
Table 4.11, Entry 4 (383). Prepared by a modification of general procedure 8. Part 1: Reaction of 3,3,5,5-tetramethylcyclohexanone in benzene (1 M) at 80 °C for 40 h using NaH (2 equiv) and diallylcarbonate (3 equiv) gave an ~1:1 mixture of mono and bisacylated material after flash chromatography (SiO_2, 1→8% Et_2O in hexanes). Part 2: Reaction in acetone (0.42 M) at 75 °C in a sealed flask for 24 h using Cs_2CO_3 (3 equiv) and MeI (4 equiv). Flash chromatography (SiO_2, 1→4% Et_2O in hexanes) gave the desired compound. 25% overall yield. R_f = 0.60 (25% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dddd, *J* = 17.4, 10.5, 6.0, 6.0 Hz, 1H), 5.29 (d, *J* = 17.1 Hz, 1H), 5.22 (d, *J* = 10.5 Hz, 1H), 4.55 (d, *J* = 6.0 Hz, 2H), 2.78 (d, *J* = 13.5 Hz, 1H), 2.23-2.12 (comp. m, 2H), 1.33 (d, *J* = 14.4 Hz, 1H), 1.26 (s, 3H), 1.11 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 171.5, 131.5, 118.8, 65.5, 62.6,

51.7, 49.4, 40.9, 34.8, 34.5, 29.6, 27.7, 26.9, 14.7; IR (Neat Film NaCl) 3087, 2959, 1715, 1456, 1371, 1216, 1101, 979 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{24}O_3$ $[M]^+$: 252.1725, found 252.1719.



384

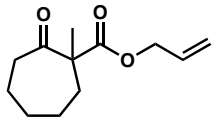
Table 4.11, Entry 5 (384). Prepared by general procedure 8 from cyclohex-2-en-1-one. Flash chromatography (SiO_2, CH_2Cl_2). 23% yield. R_f = 0.38 (30% Et_2O in pentane). ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (m, 1H), 6.06 (dt, *J* = 10.1, 2.1 Hz, 1H), 5.86 (dddd, *J* = 17.3, 10.4, 5.6, 5.6 Hz, 1H), 5.24 (m, 2H), 4.61 (m, 2H), 2.57-2.41 (m, 2H), 2.41-2.27 (m, 1H), 1.97-1.82 (m, 1H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 172.3, 149.4, 131.6, 128.9, 118.3, 65.7, 53.4, 33.3, 23.6, 20.3; IR (Neat Film NaCl) 2936, 1733, 1678, 1249, 1192, 1110 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943, found 194.0941.



386

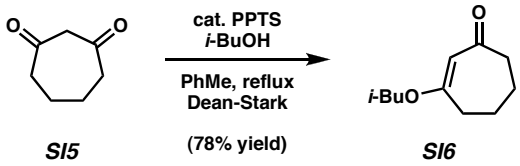
Table 4.11, Entry 7 (386). Prepared by general procedure 8 from 1-tetralone. Flash chromatography (SiO_2, 10% Et_2O in pentane). 60% yield. R_f = 0.61 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8 Hz, 1H), 7.47 (app. t, *J* = 7.5 Hz, 1H), 7.31 (app. t, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 5.79 (dddd, *J* = 17.1, 10.7, 5.4, 5.4 Hz, 1H), 5.19-5.09 (m, 2H), 4.58 (m, 2H), 3.12-2.87 (m, 2H), 2.68-2.57 (m,

1H), 2.13-2.01 (m, 1H), 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 172.5, 143.1, 133.4, 131.7, 131.5, 128.7, 128.0, 126.8, 118.0, 65.6, 53.9, 33.9, 26.0, 20.6; IR (Neat Film NaCl) 3071, 2982, 2938, 1736, 1690, 1602, 1456, 1377, 1308, 1228, 1189, 1112, 979, 743 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{16}O_3$ [M]$^+$: 244.1099, found 244.1094.



387

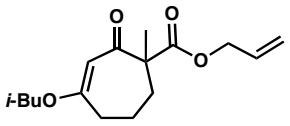
Table 4.11, Entry 8 (387). Prepared by general procedure 8 from cycloheptanone. Flash chromatography (SiO_2, 25→100% CH_2Cl_2 in pentane). 30% yield. R_f = 0.60 (30% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 17.3, 10.4, 5.6, 5.6 Hz, 1H), 5.26 (m, 2H), 4.61 (m, 2H), 2.81-2.67 (m, 1H), 2.57-2.45 (m, 1H), 2.25-2.11 (m, 1H), 1.91-1.70 (comp. m, 3H), 1.69-1.49 (comp. m, 4H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 131.6, 118.5, 65.6, 58.8, 42.0, 35.4, 30.1, 25.8, 24.7, 21.5; IR (Neat Film NaCl) 2936, 1740, 1710, 1229, 1151, 1105 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{18}O_3$ [M]$^+$: 210.1256, found 210.1249.



SI5 ***SI6***

SI6: To a flask containing a Dean-Stark trap, reflux condensor, and a solution of 1,3-cycloheptanedione (**SI5**) (5.2793 g, 41.85 mmol, 1.0 equiv) in toluene (42 mL, 1.0 M) was added *i*-butanol (30.9 mL, 335 mmol, 8.0 equiv) and PPTS (157.8 mg, 0.63 mmol, 0.015 equiv). The solution was immersed in an oil bath at 130 °C and monitored

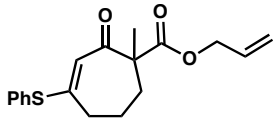
by TLC. When the starting material was consumed, the reaction was cooled to room temperature and concentrated under reduced pressure to a thick oil. The resulting oil was purified by short path distillation (1.0 torr, bp = 100-111 °C) to yield a light yellow oil (5.0073 g, 27.47 mmol). The residue remaining in the distillation pot was purified by flash chromatography (2.5 x 7 cm SiO_2, 2:1 Hex-EtOAc) to yield a maroon oil (0.9680 g, 5.31 mmol). The combined yield of vinylogous ester **SI6** was 5.9753 g (32.78 mmol, 78% yield); R_f = 0.22 (2:1 Hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (s, 1H), 3.49 (d, *J* = 6.6 Hz, 2H), 2.60-2.56 (comp. m, 4H), 2.00 (septuplet, *J* = 6.6 Hz, 1H), 1.88-1.77 (comp. m, 4H), 0.96 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 176.6, 106.0, 75.0, 41.9, 33.1, 27.9, 23.7, 21.5, 19.3; IR (Neat Film NaCl) 2958, 2872, 1646, 1607, 1469, 1237, 1190, 1174 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{18}O_2$ $[M]^{+\bullet}$: 182.1307; found 182.1310.



388

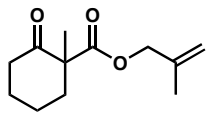
Table 4.11, Entry 9 (388). Prepared by general procedure 7 from **SI6** in 82% yield (1.220 g, 4.35 mmol) over two steps as a light yellow oil; purified by flash chromatography (2.5 x 22 cm SiO_2, 5:1 to 3:1 Hex-Et_2O); R_f = 0.43 (4:1 Hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dddd, *J* = 17.1, 10.7, 5.6, 5.6 Hz, 1H), 5.39 (s, 1H), 5.29 (ddd, *J* = 17.1, 2.9, 1.5 Hz, 1H), 5.20 (app d, *J* = 10.5 Hz, 1H), 4.59 (dddd, *J* = 19.0, 13.2, 5.6, 1.2 Hz, 2H), 3.50 (dd, *J* = 9.3, 6.8 Hz, 1H), 3.47 (dd, *J* = 9.3, 6.6 Hz, 1H), 2.59 (ddd, *J* = 17.8, 9.8, 3.9 Hz, 1H), 2.45-2.38 (comp. m, 2H), 2.02-1.94 (m, 1H),

1.84-1.75 (m, 1H), 1.70 (ddd, *J* = 14.4, 7.3, 4.4 Hz, 1H), 1.43 (s, 3H), 0.94 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 174.0, 173.5, 132.0, 118.4, 105.2, 74.8, 65.8, 59.1, 34.3, 33.9, 27.9, 24.2, 21.4, 19.3; IR (Neat Film NaCl) 2959, 2936, 2875, 1734, 1650, 1613, 1456, 1384, 1233, 1170, 1115, 994 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{24}O_4$ $[M]^{+\bullet}$: 280.1675; found 280.1686.



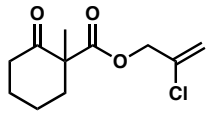
390

Table 4.11, Entry 10 (390). Prepared by general procedure 7 from the corresponding vinylogous thioester[44] in 33% yield (0.3426 g, 1.08 mmol) over two steps as a light yellow oil; purified by flash chromatography (2.5 x 15 cm SiO_2, 6:1 to 3:1 Hex-Et_2O); R_f = 0.25 (3:1 Hex:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.38 (comp. m, 5H), 5.86 (dddd, *J* = 10.5, 5.6, 5.6, 0.7 Hz, 1H), 5.56 (d, *J* = 1.5 Hz, 1H), 5.29 (dddd, *J* = 17.1, 1.5, 1.5, 1.5 Hz, 1H), 5.23 (dddd, *J* = 10.5, 1.2, 1.2, 1.2 Hz, 1H), 4.60 (dddd, *J* = 19.5, 5.9, 1.5, 1.5 Hz, 2H), 2.67 (dddd, *J* = 17.6, 10.3, 3.7, 1.7 Hz, 1H), 2.50-2.43 (comp. m, 2H), 2.08-1.98 (m, 1H), 1.86-1.77 (m, 1H), 1.68 (ddd, *J* = 14.2, 6.4, 5.4 Hz, 1H), 1.38 (s, 3H)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 173.6, 159.5, 135.6, 131.8, 130.1, 129.9, 123.8, 118.7, 66.0, 58.8, 34.2, 33.7, 23.9, 23.8; IR (Neat Film NaCl) 3060, 2982, 2935, 1735, 1650, 1593, 1440, 1230, 1178, 1113, 980, 750, 692 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{18}H_{20}O_3S$ $[M]^{+\bullet}$: 316.1133; found 316.1119.



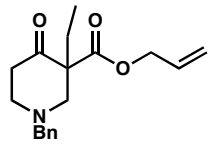
392

Table 4.11, Entry 11 (392). Prepared by general procedure 8 from cyclohexanone with dimethyallyl carbonate in part 1. Flash chromatography (SiO_2, 10% Et_2O in pentane). 46% yield. R_f = 0.24 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 4.94 (m, 2H), 4.54 (s, 2H), 2.58-2.42 (comp. m, 3H), 2.08-1.93 (m, 1H), 1.80-1.57 (comp. m, 6H), 1.55-1.40 (m, 1H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 172.8, 139.4, 113.5, 68.4, 57.2, 40.6, 38.2, 27.5, 22.6, 21.3, 19.5; IR (Neat Film NaCl) 2940, 2867, 1715, 1452, 1260, 1211, 1160, 1086, 907 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1256.



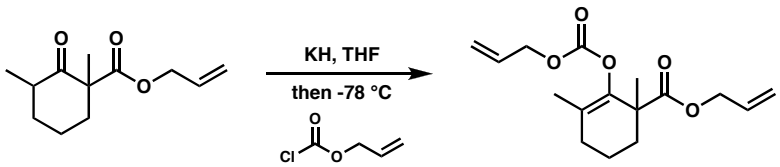
393

Table 4.11, Entry 12 (393). Prepared by method 3 from cyclohexanone with 1.25 equiv of 2-chloroallyl carbonate (*vide infra*) in part 1. Flash chromatography (SiO_2, 10% Et_2O in pentane). 62% yield. R_f = 0.20 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (m, 2H), 4.71 (m, 2H), 2.62-2.41 (comp. m, 3H), 2.10-1.93 (m, 1H), 1.81-1.62 (comp. m, 3H), 1.57-1.41 (m, 1H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 172.3, 135.4, 115.8, 66.5, 57.2, 40.6, 38.2, 27.4, 22.5, 21.2; IR (Neat Film NaCl) 2942, 2868, 1716, 1640, 1453, 1248, 1221, 1153, 1084, 903 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{15}O_3Cl$ $[M]^+$: 230.0710, found 230.0711.



395

Table 4.11, Entry 13 (395). Prepared by general procedure 8 from 1-benzylpiperidin-4-one (part 1) and iodoethane (part 2). Flash chromatography (SiO_2, 2.5→20% EtOAc in hexanes). 55% yield. R_f = 0.50 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.25 (m, 5H), 5.90 (dddd, *J* = 17.4, 10.7, 5.7, 5.7 Hz, 1H), 5.33 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.24 (dq, *J* = 10.4, 1.5 Hz, 1H), 4.70 (ddt, *J* = 13.0, 6.0, 1.4 Hz, 1H), 4.62 (ddt, *J* = 13.0, 6.0, 1.4 Hz, 1H), 3.62 (d, *J* = 13.2 Hz, 1H), 3.56 (d, *J* = 13.2 Hz, 1H), 3.42 (dd, *J* = 11.4, 2.7 Hz, 1H), 3.04-2.80 (m, 2H), 2.45-2.35 (m, 2H), 2.25 (d, *J* = 11.7 Hz, 1H), 1.94-1.82 (m, 1H), 1.65-1.53 (m, 1H), 0.87 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 171.3, 137.9, 131.7, 128.8, 128.2, 127.3, 118.7, 65.6, 61.8, 61.5, 61.0, 53.5, 40.6, 25.2, 9.1; IR (Neat Film NaCl) 2966, 2939, 1719, 1224, 1139, 699 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{18}H_{23}O_3$ $[M]^+$: 301.1678, found 301.1691.



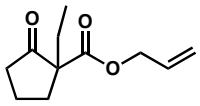
SI7 *397*

Allyl 2,6-dimethyl-2-cyclohexanonecarboxylate (SI7): To a cooled (-78 °C) solution of LDA (8.0 mmol, 1.09 equiv) in THF (24 mL) was added 2,6-dimethylcyclohexanone (1 mL, 7.33 mmol, 1.0 equiv) dropwise. The resulting solution was warmed to 0 °C for 1 hour, cooled to -78 °C and HMPA (1.3 mL, 7.47 mmol, 1.02 equiv) was added. After 15 min, allyl cyanoformate (845.3 mg, 7.61 mmol, 1.04 equiv)

was added dropwise. The reaction was warmed to ambient temperature for 30 min and then quenched with 50% saturated NH_4Cl. The aqueous layer was separated and washed with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (3 x 20 cm, SiO_2, 4% Et_2O in hexanes, then 8% Et_2O in hexanes) to afford β-ketoester **SI7** as a colorless oil (629.1 mg, 41%), along with the corresponding enol carbonate as a colorless oil (187.1 mg, 12%); R_f = 0.43 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (dddd, *J* = 6.0, 6.0, 10.5, 17.4 Hz, 1H), 5.28 (dddd, *J* = 1.5, 1.5, 1.5, 17.1 Hz, 1H), 5.22 (dddd, *J* = 1.2, 1.2, 1.2, 10.5 Hz, 1H), 4.63 (dddd, *J* = 1.2, 1.2, 5.4, 13.2 Hz, 1H), 4.56 (dddd, *J* = 1.5, 1.5, 5.7, 13.2 Hz, 1H), 2.61-2.46 (m, 2H), 2.01 (dddd, *J* = 3.2, 3.2, 6.3, 16.2 Hz, 1H), 1.85-1.63 (m, 2H), 1.45-1.31 (m, 2H), 1.28 (s, 3H), 1.03 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 172.9, 131.5, 118.7, 65.6, 57.1, 44.3, 38.9, 36.7, 22.8, 21.5, 14.7; IR (Neat Film NaCl) 3087, 2936, 1743, 1715, 1649, 1452, 1377, 1253, 1214, 1161, 976 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1249.

Table 4.11, Entry 13 (397). To a suspension of KH (155.9 mg, 3.89 mmol, 1.2 equiv, from a ~30% dispersion in mineral oil, oil removed by washing with hexane) in 10 mL THF was added **SI7** (680.9 mg, 3.24 mmol, 1 equiv) dropwise. The mixture was stirred at rt for 2.5 h, at which time it was cooled to -78 °C. Allyl chloroformate (420 μL, 3.95 mmol, 1.2 equiv) was added and the mixture stirred 30 min at -78 °C, then 30 min at rt. The reaction was quenched with 50% saturated NH_4Cl (10 mL). Et_2O (5 mL) was added and the organic layer separated. The aqueous layer was washed with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. Silica

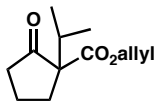
gel chromatography (2 x 16 cm, 20:1 hexane:EtOAc) afforded the title compound **397** as a colorless oil (883 mg, 93% yield). R_f = 0.29 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (dddd, *J* = 5.7, 5.7, 10.2, 17.1 Hz, 1H), 5.90 (dddd, *J* = 5.7, 5.7, 10.5, 17.1 Hz, 1H), 5.37 (dddd, *J* = 1.2, 1.2, 1.2, 17.1 Hz, 1H), 5.31 (dddd, *J* = 1.2, 1.2, 1.2, 17.1 Hz, 1H), 5.27 (dddd, *J* = 1.2, 1.2, 1.2, 10.2 Hz, 1H), 5.20 (dddd, *J* = 1.5, 1.5, 1.5, 10.5 Hz, 1H), 4.66-4.58 (m. 3H), 4.55 (dddd, *J* = 1.2, 1.2, 5.4, 13.5 Hz, 1H), 2.25-2.10 (m, 3H), 1.80-1.52 (m, 3H), 1.58 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 152.9, 142.0, 132.2, 131.5, 124.7, 118.9, 117.7, 68.7, 65.5, 46.7, 35.8, 30.6, 22.4, 19.2, 17.0; IR (Neat Film NaCl) 3087, 2942, 1760, 1732, 1649, 1452, 1366, 1235, 1168, 992 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{22}O_5$ $[M]^+$: 294.1467, found 294.1464.



406

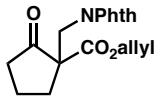
Table 4.12, Entry 1 (406). Prepared by general procedure 8 part B from allyl 2-cyclopentanonecarboxylate and using ethyl iodide as the electrophile. Flash chromatography (3 x 25 cm SiO_2, 10% Et_2O/hexane) afforded the title compound as a colorless oil (1.5335 g, 85% yield). R_F = 0.27 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 5.7, 5.7, 10.5, 17.4 Hz, 1H), 5.30 (dddd, *J* = 1.6, 1.6, 1.6, 17.1 Hz, 1H), 5.23 (dddd, *J* = 1.4, 1.4, 1.4, 10.5 Hz, 1H), 4.60 (dddd, *J* = 1.4, 1.4, 1.4, 5.7 Hz, 2H), 2.57-2.36 (m, 2H), 2.31-2.19 (m, 1H), 2.08-1.86 (m, 4H), 1.64 (dddd, *J* = 7.5, 7.5, 7.5, 21 Hz, 1H), 0.89 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.6, 170.6, 131.5, 118.1, 65.5, 60.7, 37.9, 32.0, 26.6, 19.4, 9.0; IR (Neat Film NaCl) 3085,

2971, 1752, 1726, 1225, 1142 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{16}O_3$ $[M]^+$: 196.1100, found 196.1099.



408

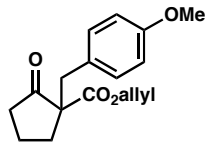
Table 4.12, Entry 2 (408). Prepared by general procedure 8 part B from allyl 2-cyclopentanonecarboxylate and using 2-iodopropane as the electrophile. Flash chromatography (3 x 25 cm SiO_2, 10% → 30% Et_2O/hexane) afforded the title compound as a colorless oil (1.5521 g, 82% yield). R_F = 0.32 (10:1 Hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 5.7, 5.7, 10.5, 17.1 Hz, 1H), 5.30 (dddd, *J* = 1.6, 1.6, 1.6, 17.4 Hz, 1H), 5.22 (dddd, *J* = 1.4, 1.4, 1.4, 10.5 Hz, 1H), 4.59 (dddd, *J* = 1.4, 1.4, 1.4, 5.7 Hz, 2H), 2.59 (qq, *J* = 6.9, 6.9 Hz, 1H), 2.51-2.34 (m, 2H), 2.19-2.06 (m, 1H), 1.99-1.83 (m, 3H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.4, 169.8, 131.5, 118.3, 65.6, 65.3, 38.9, 31.9, 27.2, 19.5, 18.3, 17.6; IR (Neat Film NaCl) 3085, 2967, 1752, 1723, 1228, 1130 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1255.



410

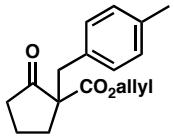
Table 4.12, Entry 3 (410). Prepared by general procedure 8 part B from allyl 2-cyclopentanonecarboxylate and using (*N*-chloromethyl)phthalimide as the electrophile. Purified by flash chromatography (SiO_2, 20 → 30% EtOAc in hexanes). 54% yield. Mp 56-57 °C. R_f = 0.27 (30% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, *J*

= 5.6, 3.2 Hz, 2H), 7.73 (dd, *J* = 5.6, 3.2 Hz, 2H), 5.92 (dddd, *J* = 17.0, 10.6, 5.9, 5.9 Hz, 1H), 5.32 (app. ddd, *J* = 17.0, 2.9, 1.6 Hz, 1H), 5.23 (app. ddd, *J* = 10.6, 2.7, 1.3 Hz, 1H), 4.65 (app. ddt, *J* = 5.9, 4.5, 1.3 Hz, 2H), 4.34 (d, *J* = 14.4 Hz, 1H), 3.99 (d, *J* = 14.4 Hz, 1H), 2.59-2.47 (m, 1H), 2.46-2.25 (comp. m, 2H), 2.11-1.84 (comp. m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 169.0, 168.3, 134.3, 131.9, 131.6, 123.7, 118.8, 66.8, 60.5, 41.0, 37.7, 32.1, 19.5; IR (Neat Film NaCl) 2953, 1774, 1752, 1718, 1467, 1457, 1428, 1395, 1359, 1256, 1231, 1170, 991, 722 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{17}O_5N$ $[M]^+$: 327.1107, found 327.1106.



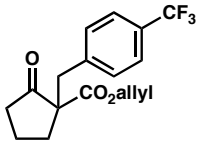
412

Table 4.12, Entry 4 (412). Prepared by general procedure 8 part B from allyl 2-cyclopentanonecarboxylate and using 4-methoxybenzyl chloride as the electrophile. Flash chromatography (3 x 25 cm SiO_2, 10:1 hexane/EtOAc) afforded the title compound as a colorless oil (2.5584 g, 95% yield). R_F = 0.17 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.87 (dddd, *J* = 5.7, 5.7, 10.8, 17.1 Hz, 1H), 5.31 (dddd, *J* = 1.5, 1.5, 1.5, 17.1 Hz, 1H), 5.24 (dddd, *J* = 1.2, 1.2, 1.2, 10.5 Hz, 1H), 4.61 (dddd, *J* = 1.4, 1.4, 1.4, 5.7 Hz, 2H), 3.77 (s, 3H), 3.15 (d, *J* = 13.8 Hz, 1H), 3.09 (d, *J* = 13.8 Hz, 1H), 2.45-2.31 (m, 2H), 2.08-1.81 (m, 3H), 1.67-1.53 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.7, 170.5, 158.3, 131.5, 131.0, 128.2, 118.3, 113.6, 65.8, 61.4, 55.0, 38.3, 38.0, 31.5, 19.3; IR (Neat Film NaCl) 2958, 1751, 1726, 1611, 1513, 1249 cm^{-1}; HRMS *m/z* calc'd for $C_{17}H_{20}O_4$ $[M]^+$: 288.1362, found 288.1369.



414

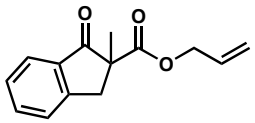
Table 4.12, Entry 5 (414). Prepared by general procedure 8 part B from allyl 2-cyclopentanonecarboxylate and using *p*-methyl benzyl bromide as the electrophile. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 89% yield. R_f = 0.20 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 5.89 (dddd, *J* = 17.3, 10.5, 5.5, 5.5 Hz, 1H), 5.31 (app. ddd, *J* = 17.3, 3.0, 1.7 Hz, 1H), 5.24 (app. ddd, *J* = 10.5, 2.4, 1.1 Hz, 1H), 4.61 (app. ddd, *J* = 6.9, 2.8, 1.4 Hz, 1H), 4.61 (app. ddd, *J* = 6.9, 2.8, 1.4 Hz, 1H), 3.17 (d, *J* = 13.8 Hz, 1H), 3.10 (d, *J* = 13.8 Hz, 1H), 2.52-2.32 (m, 2H), 2.30 (s, 3H), 2.12-1.81 (comp. m, 3H), 1.68-1.52 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.1, 170.9, 136.6, 133.5, 131.7, 130.2, 129.2, 118.7, 66.1, 61.6, 38.7, 38.6, 31.8, 21.2, 19.6; IR (Neat Film NaCl) 2963, 2925, 1752, 1724, 1652, 1515, 1456, 1404, 1264, 1220, 1184, 1158, 1141, 1116, 992, 924, 813 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{20}O_3$ $[M]^+$: 272.1412, found 272.1412.



416

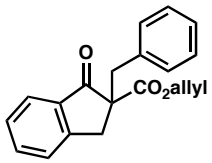
Table 4.12, Entry 6 (416). Prepared by general procedure 8 part B from allyl 2-cyclopentanonecarboxylate and using 4-(trifluoromethyl)benzyl bromide as the electrophile. ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 5.87 (dddd, *J* = 6.0, 6.0, 10.5, 17.4 Hz, 1H), 5.30 (dddd, *J* = 1.7, 1.7, 1.7, 17.4 Hz,

1H), 5.25 (dddd, J = 1.1, 1.1, 1.1, 10.5 Hz, 1H), 4.61 (bd, J = 6 Hz, 2H), 3.29 (d, J = 13.5 Hz, 1H), 3.15 (d, J = 13.5 Hz, 1H), 2.50-2.33 (m, 2H), 2.13-1.86 (m, 3H), 1.73-1.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 170.3, 140.7, 131.3, 130.6, 142.0, 133.1, 130.6, 129.2 (q, $J_{C\text{-}F}$ = 32.2 Hz), 125.3 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.1 (q, $J_{C\text{-}F}$ = 271.5 Hz), 118.8, 66.2, 61.3, 38.6, 38.1, 31,8, 19.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.54; IR (Neat Film NaCl) 3080, 2966, 1754, 1728, 1619, 1326, 1164, 1116, 1068 cm^{-1}; HRMS m/z calc'd for $C_{17}H_{17}O_3F_3$ $[M]^+$: 326.1130, found 326.1129.



418

Table 4.12, Entry 7 (418). Prepared by general procedure 8 from 1-indanone and using methyl iodide as the electrophile. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 30% yield. R_f = 0.55 (30% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 7.7 Hz, 1H), 7.63 (dd, J = 7.6, 7.3 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.41 (dd, J = 7.6, 7.3 Hz, 1H), 5.83 (dddd, J = 17.2, 10.6, 5.6, 5.6 Hz, 1H), 5.21 (dddd, J = 17.2, 2.7, 1.6, 1.1 Hz, 1H), 5.16 (dddd, J = 10.5, 2.4, 1.3, 1.3 Hz, 1H), 4.58 (ddd, J = 5.6, 2.7, 1.1 Hz, 1H), 4.58 (ddd, J = 5.6, 2.7, 1.1 Hz, 1H), 3.73 (d, J = 17.1 Hz, 1H), 3.01 (d, J = 17.1 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 171.8, 152.7, 135.5, 134.9, 131.7, 128.0, 126.6, 125.2, 118.3, 66.0, 56.2, 40.2, 21.2; IR (Neat Film NaCl) 3080, 2982, 2935, 1745, 1715, 1608, 1495, 1282, 1184, 967, 747 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{14}H_{14}O_3$ $[M]^+$: 230.0943, found 230.0936.



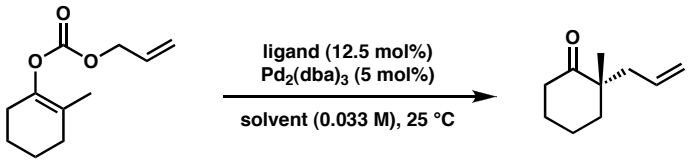
420

Table 4.12, Entry 8 (420). Prepared by general procedure 8 from 1-indanone and using benzyl bromide as the electrophile. Purified by flash chromatography (SiO_2, 20% Et_2O in pentane). 78% yield. Mp 49-50 °C. R_f = 0.18 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 1H), 7.53 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.33 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.23-7.06 (comp. m, 5H), 5.84 (dddd, *J* = 17.3, 10.4, 5.6, 5.3 Hz, 1H), 5.22 (app. ddd, *J* = 17.3,, 2.9, 1.6 Hz, 1H), 5.18 (dddd, *J* = 10.4, 2.4, 1.3, 1.1 Hz, 1H), 4.65-4.57 (m, 2H), 3.63 (d, *J* = 17.6 Hz, 1H), 3.50 (d, *J* = 13.8 Hz, 1H), 3.31 (d, *J* = 14.1 Hz, 1H), 3.18 (d, *J* = 17.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 170.6, 153.3, 136.4, 135.5, 135.3, 131.6, 130.2, 128.4, 127.8, 127.0, 126.4, 124.8, 118.5, 66.3, 61.9, 39.8, 35.5; IR (Neat Film NaCl) 3031, 2929, 1744, 1711, 1606, 1589, 1496, 1464, 1454, 1432, 1277, 1244, 1210, 1178, 1051, 1028, 930, 752, 703 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{20}H_{18}O_3$ $[M]^+$: 306.1256, found 306.1259.

4.7.2.5 *Asymmetric Allylation Methods*

General Procedures for Asymmetric Tsuji Allylation.

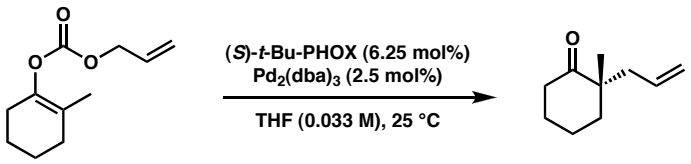
General Procedure 9: 0.1 mmol Optimization Reactions of Allyl Enol Carbonates



274 *(S)-275*

A 1 dram vial equipped with a magnetic stir bar was flame dried under vacuum. After cooling under dry argon, $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol, 0.05 equiv) and ligand (0.0125 mmol, 0.125 equiv) were added. After the flask was flushed with argon, THF (3.0 mL) was added, and the contents were stirred at 25 °C for 30 min, at which time tridecane (12.25 μL) and allyl enol carbonate **274** (19.6 mg, 0.1 mmol, 1.0 equiv) were added by syringe. When the reaction was complete by TLC, the reaction mixture was diluted with hexanes (5 mL), filtered through a small plug of silica gel and analyzed by GC. GC yield determined on DB-WAX column (70 °C initial temp, 5 °C/min ramp to 180 °C), tridecane ret. time = 7.000 min, ketone **275** Ret. Time = 12.309 min.

General Procedure 10: 1.0 mmol Preparative Reactions of Allyl Enol Carbonates

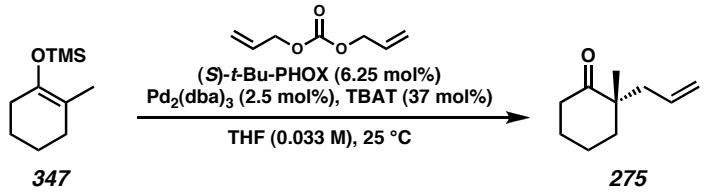


274 *(S)-275*

A 50 mL rb flask equipped with a magnetic stir bar was flame dried under vacuum. After cooling under dry argon, $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 0.025 equiv) and *(S)-t*-Bu-PHOX (24.2 mg, 0.0625 mmol, 0.0625 equiv) were added. After the flask

was flushed with argon, THF (30 mL) was added and the contents were stirred at 25 °C for 30 min, at which time allyl enol carbonate **274** (196.2 mg, 1.0 mmol, 1.0 equiv) was added by syringe in one portion. When the reaction was complete by TLC, the reaction mixture was evaporated under reduced pressure and the residue chromatographed (2 to 3 % Et_2O in pentane on SiO_2) to afford (*S*)-2-allyl-2-methylcyclohexanone (**275**) (129.6 mg, 85.1% yield) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75-5.61 (m, 1H), 5.05 (s, 1H), 5.01 (m, 1H), 2.40-2.31 (m, 3H), 2.21 (dd, *J* = 13.8, 7.5 Hz, 1H), 1.78 (m, 5H), 1.56 (m, 1H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 133.7, 117.9, 48.4, 41.9, 38.8, 38.5, 27.4, 22.6, 21.0; IR (Neat Film NaCl) 2934, 2865, 1707, 1451, 912 cm^{-1}; HRMS *m/z* calc'd for $C_{10}H_{16}O$ $[M]^+$: 152.1201, found 152.1204; $[\alpha]_D^{28}$ -22.90° (*c* 2.09, hexane, 98% ee).

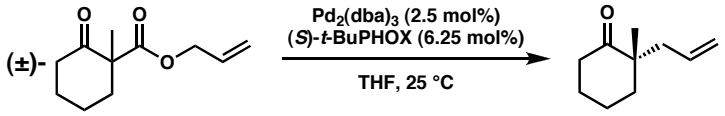
General Procedure 11: 1.0 mmol Preparative Reactions of Silyl Enol Ethers



A 50 mL rb flask equipped with a magnetic stir bar was flame dried under vacuum. After cooling under dry argon, $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 0.025 equiv), *(S)-t*-Bu-PHOX (24.2 mg, 0.0625 mmol, 0.0625 equiv), and TBAT (189 mg, 0.35 mmol, 0.35 equiv) were added. After the flask was flushed with argon, THF (30 mL) was added, and the contents were stirred at 25 °C for 30 min, at which time diallyl carbonate (150.6 μL, 1.05 mmol, 1.05 equiv) and then (2-methylcyclohex-1-enyloxy)trimethylsilane **347** (184.35 mg, 1.0 mmol, 1.0 equiv) were added by syringe in

one portion. When the reaction was complete by TLC, the reaction mixture was evaporated under reduced pressure and the residue chromatographed (2 to 3 % Et_2O in pentane on SiO_2) to afford ketone **275** (144.3 mg, 94.8% yield).

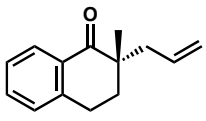
General Procedure 12: 1.0 mmol Preparative Reactions of Allyl β-Ketoesters



358 *275*

A 100 mL rb flask was equipped with a magnetic stir bar and flame dried under vacuum. After cooling under dry nitrogen, $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 0.025 equiv) and (*S*)-*t*-Bu-PHOX (24.2 mg, 0.0625 mmol, 0.0625 equiv) were added. The flask containing the solids was evacuated for 15 min and then refilled with dry nitrogen. Dry THF (30 mL) was then added and the resulting solution stirred at 25 ºC for 30 min. At this point, allyl 1-methyl-2-oxocyclohexanecarboxylate (**358**) was added via syringe in one portion. When the reaction was complete by TLC, the reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography (SiO_2, 1.5 to 2.5% Et_2O in pentane) to afford ketone **275** (129.6 mg, 85% yield, 88% ee).

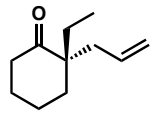
4.7.2.5 *Ketones Prepared by Asymmetric Tsuji Allylation*



297

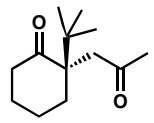
Ketone 297. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.45 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.29 (app. t, *J* = 7.2 Hz, 1H), 7.21 (app. d, *J* = 7.5 Hz, 1H),

5.85-5.71 (m, 1H), 5.10 (s, 1H), 5.05 (s, 1H), 2.97 (t, *J* = 6.3 Hz, 2H), 2.46 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.27 (ddt, *J* = 14.0, 7.5, 1.2 Hz, 1H), 2.07 (ddd, *J* = 13.4, 7.2, 6.0 Hz 1H), 1.89 (ddd, *J* = 14.0, 6.9, 5.7 1H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 143.2, 133.9, 133.0, 131.5, 128.6, 127.9, 126.5, 118.1, 44.5, 41.0, 33.2, 25.3, 21.8; IR (Neat Film NaCl) 3073, 2930, 1682, 1455, 1220, 916, 742 cm^{-1}; HRMS *m/z* calc'd for $C_{14}H_{16}O$ [M]$^+$: 200.1201, found 200.1194; $[\alpha]_D^{27}$ -18.59° (*c* 2.08, hexane, 88% ee).



321

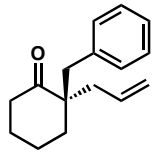
Ketone 321. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (m, 1H), 5.02 (m, 2H), 2.47-2.18 (m, 4H), 1.90-1.60 (m, 7H), 1.46 (ddd, *J* = 21.6, 15.0, 7.2 Hz, 1H), 0.75 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.0, 134.2, 117.6, 51.6, 39.2, 38.5, 36.0, 27.2, 27.1, 20.7, 7.8; IR (Neat Film NaCl) 2937, 1703 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{18}O$ [M]$^+$: 166.1358, found 166.1362; $[\alpha]_D^{28}$ +28.58° (*c* 1.51, hexane, 92% ee).



SI8

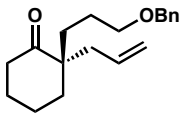
Diketone SI8. Prepared by Wacker odixation of ketone **322**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.29 (d, *J* = 18.0 Hz, 1H), 2.58 (app. dt, *J* = 16.2, 4.8 Hz, 1H), 2.34 (d, *J* = 17.7 Hz, 1H), 2.23 (dd, *J* = 11.1, 6.0 Hz, 1H), 2.18-2.00 (m, 2H), 2.07 (s, 3H), 1.92-1.60 (m, 4H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 207.6, 53.0, 51.3, 43.2, 36.6, 31.6, 30.5, 27.7, 24.0, 23.9; IR (Neat Film NaCl) 2955, 1716, 1692, 1372, 1171 cm$^-$

[1]; HRMS *m/z* calc'd for $C_{13}H_{22}O_2$ $[M]^+$: 210.1620, found 210.1615; $[\alpha]_D^{28}$ +132.01° (*c* 1.38, hexane, 81% ee).



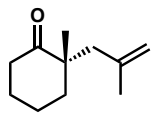
325

Ketone 325. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 3H), 7.12 (m, 2H), 5.74 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.12-5.03 (m, 2H), 2.91 (s, 2H), 2.46 (m, 2H), 2.28 (d, *J* = 7.2 Hz, 2H), 1.86-1.65 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 137.5, 133.7, 130.6, 127.9, 126.3, 118.2, 52.5, 40.8, 39.6, 39.2, 35.5, 26.8, 20.8; IR (Neat Film NaCl) 2937, 1704, 1638, 1602 cm^{-1}; HRMS *m/z* calc'd for $C_{16}H_{20}O$ $[M]^+$: 228.1514, found 228.1514; $[\alpha]_D^{28}$ -12.34° (*c* 2.07, hexane, 85% ee).



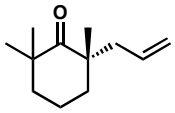
327

Ketone 327. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 5.68 (m, 1H), 5.06 (s, 1H), 5.01 (m, 1H), 4.84 (s, 2H), 3.44 (app. t, *J* = 6.3 Hz, 2H), 2.32 (m, 4H), 1.88-1.24 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 138.5, 133.9, 128.3, 127.5, 127.5, 117.8, 72.8, 70.5, 51.2, 39.2, 39.0, 36.4, 31.2, 27.1, 23.8, 20.7; IR (Neat Film NaCl) 2926, 1703, 1102 cm^{-1}; HRMS *m/z* calc'd for $C_{19}H_{27}O_2$ $[M+H]^+$: 287.2011, found 287.2001; $[\alpha]_D^{27}$ +24.19° (*c* 2.73, hexane, 88% ee).



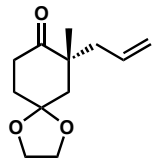
329

Ketone 329. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81 (s, 1H), 4.64 (s, 1H), 2.52 (m, 1H), 2.48 (d, *J* = 13.5 Hz, 1H), 2.36 (app. dt, *J* = 14.7, 6.0 Hz, 1H), 2.25 (d, *J* = 13.8 Hz, 1H), 1.94-1.53 (m, 6H), 1.65 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 142.2, 114.7, 48.7, 45.4, 40.0, 38.9, 27.6, 24.3, 23.3, 21.1; IR (neat) 2927, 1707 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{18}O$ $[M]^+$: 166.1358, found 166.1358; $[\alpha]_D^{27}$ -26.42° (*c* 1.85, hexane, 90% ee).



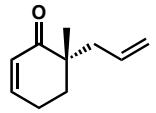
331

Ketone 331. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (m, 1H), 5.01 (m, 2H), 2.33 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.18 (dd, *J* = 13.8, 7.8 Hz, 1H), 1.82-1.53 (m, 6H), 1.11 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.8, 134.6, 117.9, 47.6, 44.4, 43.9, 39.7, 36.8, 27.8, 27.2, 25.5, 17.7; IR (Neat Film NaCl) 2933, 1697, 1463 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{20}O$ $[M]^+$: 180.1514, found 180.1521; $[\alpha]_D^{27}$ -35.69° (*c* 2.15, hexane, 92% ee).



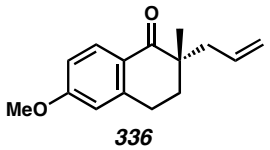
152

Ketone 152. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (ddt, *J* = 17.1, 10.5, 7.2 Hz, 1H), 5.07 (bs, 1H), 5.02 (app. d, *J* = 9.3 Hz, 1H), 3.99 (app. d, *J* = 1.5 Hz, 4H), 2.57 (app. t, *J* = 6.3 Hz, 1H), 2.42 (m, 2H), 2.00 (d, *J* = 13.8 Hz, 1H), 1.98 (app. t, *J* = 7.2 Hz, 1H), 1.75 (d, *J* = 14.1 Hz, 1H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.9, 133.7, 118.4, 107.6, 64.4, 64.3, 47.5, 44.3, 42.7, 35.7, 34.5, 23.9; IR (Neat Film NaCl) 2964, 1710, 1116 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1255; $[\alpha]_D^{29}$ -7.99° (*c* 2.41, hexane, 86% ee).



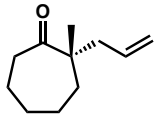
334

Ketone 334. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (app. dt, *J* = 10.2, 4.2 Hz, 1H), 5.91 (app. dt, *J* = 10.2, 2.1 Hz, 1H), 5.72 (m, 1H), 5.07 (m, 1H), 5.02 (d, *J* = 9.3 Hz, 1H), 2.35 (m, 3H), 2.16 (dd, *J* = 13.8, 7.5, Hz, 1H), 1.91 (dt, *J* = 13.8, 6.0 Hz, 1H), 1.74 (dt, *J* = 13.8, 6.0 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 148.8, 134.0, 128.4, 118.0, 44.4, 40.9, 32.9, 23.1, 21.6; IR (Neat Film NaCl) 2927, 1673 cm^{-1}; HRMS *m/z* calc'd for $C_{10}H_{14}O$ $[M]^+$: 150.1045, found 150.1039; $[\alpha]_D^{26}$ +14.62° (*c* 1.56, hexane, 89% ee).



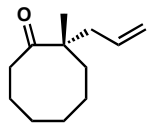
336

Ketone 336. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.7 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 5.78 (m, 1H), 5.09 (s, 1H), 5.04 (m, 1H), 3.84 (s, 3H), 3.93 (app. t, *J* = 6 Hz, 2H), 2.45 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.25 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.05 (m, 1H), 1.87 (m, 1H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 163.3, 145.7, 134.1, 130.4, 125.1, 118.0, 113.2, 112.2, 55.4, 44.3, 41.3, 33.4, 25.7, 22.0; IR (Neat Film NaCl) 2931, 1672, 1601, 1256 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{18}O_2$ $[M]^+$: 230.1307, found 230.1313; $[\alpha]_D^{26}$ -13.71° (*c* 1.5, hexane, 89% ee).



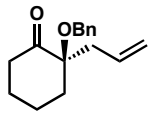
338

Ketone 338. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (ddt, *J* = 16.8, 10.2, 7.5, 1H), 5.02 (m, 2H), 2.59 (app. td, *J* = 11.1, 2.7 Hz, 1H), 2.42 (app. t, *J* = 9.0 Hz, 1H), 2.24 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.16 (dd, *J* = 13.8, 7.8 Hz, 1H), 1.78-1.30 (m, 8H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.4, 133.8, 117.9, 50.8, 43.6, 40.6, 36.6, 30.6, 26.4, 24.4, 22.3; IR (Neat Film NaCl) 2930, 1702, 1458 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{18}O$ $[M]^+$: 166.1358, found 166.1360; $[\alpha]_D^{28}$ -34.70° (*c* 1.52, hexane, 87% ee).



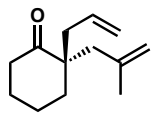
340

Ketone 340. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (m, 1H), 5.04 (app. d, *J* = 1.2 Hz, 1H), 5.00 (app. d, *J* = 8.1 Hz, 1H), 2.59 (m, 1H), 2.29 (m, 2H), 2.12 (dd, *J* = 14.1, 7.7 Hz, 1H), 2.01 (m, 1H), 1.83-1.70 (m, 3H), 1.61-1.32 (m, 5H), 1.18 (m, 1H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.3, 133.9, 117.8, 50.1, 42.0, 36.8, 33.5, 30.4, 25.9, 24.8, 24.3, 19.8; IR (Neat Film NaCl) 2929, 1699 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{20}O$ $[M]^+$: 180.1514, found 180.1508; $[\alpha]_D^{26}$ -21.22° (*c* 1.56, hexane, 79% ee).



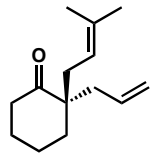
350

Ketone 350. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.25 (comp. m, 5H), 5.83 (dddd, *J* = 16.5, 10.8, 6.9, 6.9 Hz, 1H), 5.15 (app. ddd, *J* = 16.5, 3.0, 1.5 Hz, 1H), 5.13 (app. d, *J* = 10.8 Hz, 1H), 4.54 (d, *J* = 11.1 Hz, 1H), 4.16 (d, *J* = 11.1 Hz, 1H), 2.85-2.68 (m, 2H), 2.42-2.24 (comp. m, 3H), 2.13-1.95 (comp. m, 2H), 1.76-1.44 (comp. m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5, 138.2, 132.8, 128.4, 127.5, 127.3, 118.3, 82.1, 65.3, 39.5, 37.8, 36.0, 27.9, 20.6; IR (Neat Film NaCl) 3068, 3032, 2942, 2864, 1715, 1640, 1498, 1454, 1433, 1384, 1311, 1254, 1157, 1121, 1085, 1060, 1028, 997, 970, 915, 735, 696 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{20}O_2$ $[M]^+$: 244.1463, found 244.1455; $[\alpha]_D^{28.3}$ +47.3 (*c* 2.38, hexanes, 59% ee).



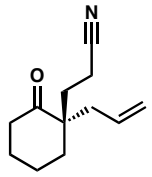
352

Ketone 352. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (dddd, *J* = 16.5, 10.8, 7.5, 7.2 Hz, 1H), 5.00 (dddd, *J* = 16.5, 2.1, 1.2, 1.2 Hz, 1H), 5.01 (dddd, *J* = 10.2, 2.1, 1.5, 1.5 Hz, 1H), 4.82 (app. ddd, *J* = 2.7, 1.2, 1.2 Hz, 1H), 4.66 (app. ddd, *J* = 3.0, 0.9, 0.9 Hz, 1H), 2.56-2.28 (comp. m, 6H), 1.91-1.66 (comp. m, 6H), 1.64 (app. ddd, *J* = 0.9, 0.9, 0.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 142.1, 134.1, 118.0, 115.0, 51.5, 43.0, 39.9, 39.5, 36.5, 27.1, 24.3, 20.9; IR (Neat Film NaCl) 3075, 2938, 2865, 1704, 1640, 1453, 1376, 1312, 1206, 1124, 1062, 997, 913, 894 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{20}O$ $[M]^+$: 192.1514, found 192.1514; $[\alpha]_D^{29.3}$ +3.9 (*c* 3.52, hexanes, 91% ee).



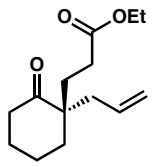
369

Ketone 369. Reaction performed in Et_2O at 30 ºC. Flash chromatography (SiO_2, 1.5→2.5% Et_2O in pentane). 97% yield. R_f = 0.38 (10% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (dddd, *J* = 16.5, 10.6, 7.2, 7.2 Hz, 1H), 5.07-4.93 (comp. m, 3H), 2.44-2.24 (comp. m, 5H), 2.16 (dd, *J* = 14.6, 7.2 Hz, 1H), 1.89-1.64 (comp. m, 9H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.7, 134.2, 134.1, 119.0, 117.7, 52.1, 39.4, 39.3, 35.9, 33.3, 27.1, 26.0, 20.9, 18.0; IR (Neat Film NaCl) 3075, 2934, 2863, 1706, 1446, 1124, 914 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{14}H_{23}O$ $[M+H]^+$: 207.1749, found 207.1744; $[\alpha]_D^{26.0}$ +1.95° (*c* 1.29, CH_2Cl_2, 91% ee).



371

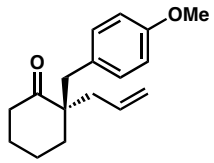
Ketone 371. Reaction performed in Et_2O. Flash chromatography (SiO_2, 25% Et_2O in pentane). 97% yield. R_f = 0.32 (CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (dddd, J = 16.7, 10.4, 7.4, 7.4 Hz, 1H), 5.17-5.07 (m, 2H), 2.53-2.16 (comp. m, 6H), 2.03-1.62 (comp. m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2, 131.9, 120.0, 119.3, 50.8, 39.0, 38.9, 35.4, 30.6, 26.9, 20.5, 12.1; IR (Neat Film NaCl) 3081, 2939, 2863, 2246, 1702, 1453, 1126, 921 cm^{-1}; HRMS (EI) m/z calc'd for $C_{12}H_{17}NO$ $[M]^+$: 191.1310, found 191.1307; $[\alpha]_D^{25.6}$ -27.00° (c 1.56, CH_2Cl_2, 88% ee).



373

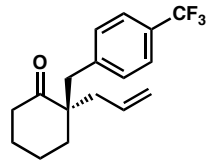
Ketone 373. Reaction performed in Et_2O. Flash chromatography (SiO_2, 5→14% Et_2O in pentane). 96% yield. R_f = 0.44 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (dddd, J = 16.2, 10.9, 7.7, 7.2 Hz, 1H), 5.11-5.07 (m, 1H), 5.07-5.02 (m, 1H), 4.11 (app. q, J = 7.1 Hz, 2H), 2.48-2.18 (comp. m, 5H), 2.16-1.94 (comp. m, 2H), 1.90-1.65 (comp. m, 7H), 1.24 (app. t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.2, 173.5, 133.3, 118.3, 60.4, 50.8, 39.1, 39.0, 36.2, 29.7, 28.8, 27.0, 20.7, 14.2; IR (Neat Film NaCl) 3076, 2937, 2866, 1735, 1704, 1454, 1377, 1309, 1181, 917 cm^{-1};

HRMS (EI) *m/z* calc'd for $C_{14}H_{22}O_3$ $[M]^+$: 238.1569, found 238.1574; $[\alpha]_D^{25.8}$ +9.60° (*c* 1.13, CH_2Cl_2, 90% ee).



375

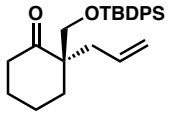
Ketone 375. Flash chromatography (SiO_2, 3% Et_2O in pentane). 80% yield. R_f = 0.54 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, *J* = 9.0 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 5.72 (dddd, *J* = 17.1, 9.8, 7.0, 7.0 Hz, 1H), 5.12-4.98 (m, 2H), 3.78 (s, 3H), 2.84 (s, 2H), 2.53-2.34 (m, 2H), 2.33-2.17 (m, 2H), 1.91-1.70 (comp. m, 4H), 1.70-1.61 (comp. m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.3, 158.1, 133.9, 131.5, 129.5, 118.1, 113.4, 55.2, 52.6, 40.1, 39.6, 39.3, 35.4, 26.8, 20.8; IR (Neat Film NaCl) 3076, 2935, 2863, 2361, 1702, 1611, 1513, 1456, 1249, 1179, 1036, 834 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{22}O_2$ $[M]^+$: 258.1620, found 258.1627; $[\alpha]_D^{25.9}$ +3.60° (*c* 1.05, CH_2Cl_2, 86% ee).



377

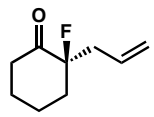
Ketone 377. Flash chromatography (SiO_2, 8→14% Et_2O in pentane). 99% yield. R_f = 0.85 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.71 (dddd, *J* = 17.0, 10.1, 7.4, 6.9 Hz, 1H), 5.17-5.04 (m, 2H), 3.01 (d, *J* = 13.8 Hz, 1H), 2.88 (d, *J* = 13.8 Hz, 1H), 2.50-2.31 (comp. m, 3H), 2.29-2.17

(m, 1H), 1.97-1.82 (m, 1H), 1.82-1.69 (comp. m, 3H), 1.70-1.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 142.0 (q, J_{CF} = 1.2 Hz), 133.0, 130.9, 128.4 (q, J_{CF} = 32.3 Hz), 124.7 (q, J_{CF} = 3.9 Hz), 124.2 (q, J_{CF} = 271.7 Hz), 118.5, 52.5, 40.4, 39.3, 39.3, 35.5, 26.6, 20.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.9; IR (Neat Film NaCl) 3076, 2940, 2867, 1705, 1618, 1418, 1326, 1164, 1123, 1068, 852 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{19}F_3O$ $[M]^+$: 296.1388, found 296.1402; $[\alpha]_D^{26.6}$ –16.31° (*c* 1.17, CH_2Cl_2, 82% ee).



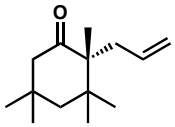
379

Ketone 379. Flash chromatography (SiO_2, 1→2.5% EtOAc in hexanes). 92% yield. R_f = 0.32 (5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H), 7.46-7.36 (m, 6H), 5.69-5.55 (m, 1H), 5.38-5.31 (m, 1H), 5.08-4.99 (m, 2H), 3.84 (d, *J* = 10.2 Hz, 1H), 3.66 (d, *J* = 10.2 Hz, 1H), 2.48 (d, *J* = 7.5 Hz, 2H), 2.40-2.20 (m, 2H), 1.90-1.60 (m, 6H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 135.7, 133.8, 133.3(2C), 129.7, 129.6, 127.6(2C), 117.9, 66.4, 53.8, 39.7, 37.3, 34.0, 26.9(2C), 21.0, 19.3; IR (Neat Film NaCl) 3072, 2933, 2858, 1708, 1428, 1113, 703 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{26}H_{35}O_2Si$ $[M+H]^+$: 407.2406, found 407.2398; $[\alpha]_D^{25}$ –3.96° (*c* 5.00, $CHCl_3$, 81% ee).



381

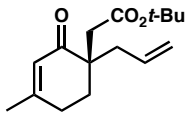
Ketone 381. Reaction performed in Et_2O at 30 ºC. Flash chromatography (SiO_2, 2% Et_2O/pentane). 80% yield. R_f = 0.36 (10:1 Hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.88-5.71 (m, 1H), 5.20-5.10 (m, 2H), 2.76-2.31 (m, 4H), 2.16-2.02 (m, 1H), 1.99-1.78 (m, 4H), 1.75-1.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2 (d, $J_{C\text{-}F}$ = 20.0 Hz), 130.7 (d, $J_{C\text{-}F}$ = 3.8 Hz), 119.2, 97.7 (d, $J_{C\text{-}F}$ = 184.3 Hz), 39.4, 38.7 (d, $J_{C\text{-}F}$ = 22.7 Hz), 37.3 (d, $J_{C\text{-}F}$ = 22.2 Hz), 27.2, 21.4 (d, $J_{C\text{-}F}$ = 6.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -158.15; IR (Neat Film NaCl) 3080, 2946, 1729, 1642, 1453, 1433, 1126, 923 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_9H_{13}OF$ $[M]^+$: 156.0950, found 156.0946; $[\alpha]_D^{24.4}$ -74.65° (*c* 1.05, CH_2Cl_2, 91% ee).



256

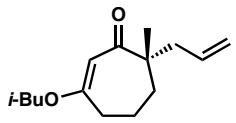
Ketone 256. Flash chromatography (SiO_2, 1→4% Et_2O in hexanes). 90% yield. R_f = 0.48 (10% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.63-5.46 (m, 1H), 5.10-4.94 (m, 2H), 2.61 (d, *J* = 13.5 Hz, 1H), 2.34 (d, *J* = 12.9 Hz, 1H), 2.11 (d, *J* = 12.9 Hz, 1H), 2.02 (d, *J* = 13.8 Hz, 1H), 1.83 (d, *J* = 14.6 Hz, 1H), 1.40 (d, *J* = 14.5 Hz, 1H), 1.02 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.5, 134.2, 117.9, 53.8, 51.0, 49.5, 40.5, 39.1, 35.7, 33.7, 29.8, 26.9, 26.3, 15.4; IR (Neat Film NaCl) 3077, 2957, 1708, 1639, 1460, 1392, 1370, 913 cm^{-1}; HRMS (EI) *m/z*

calc'd for $C_{14}H_{24}O$ $[M]^+$: 208.1827, found 208.1837; $[\alpha]_D^{22.5}$ -4.14° (*c* 2.705, hexane, 85% ee).



385

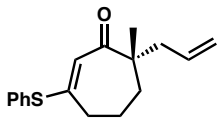
Ketone 385. Reaction performed in Et_2O at 30 ºC . Flash chromatography (SiO_2, 3% Et_2O in pentane). 73% yield. R_f = 0.45 (30% Et_2O in pentane). ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (s, 1H), 5.70 (dddd, *J* = 16.8, 10.2, 7.3, 7.3 Hz, 1H), 5.12-5.11 (m, 2H), 2.71 (d, *J* = 15.6 Hz, 1H), 2.48-2.13 (comp. m, 6H), 1.93 (s, 3H), 1.91-1.81 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 170.8, 160.3, 133.3, 125.4, 118.7, 80.5, 45.4, 40.5, 39.0, 29.8, 28.1, 27.8, 24.1; IR (Neat Film NaCl) 2978, 1728, 1670, 1367, 1213, 1152 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{25}O_3$ $[M+H]^+$: 265.1804, found 265.1803; $[\alpha]_D^{25.4}$ -39.22° (*c* 1.05, CH_2Cl_2, 86% ee).



389

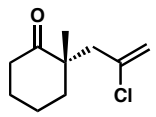
Ketone 389. Reaction run on 0.16 mmol at 30 °C in Et_2O (0.1 M) for 6 h using (*S*)-*t*-BuPHOX and $Pd(dmdba)_2$. The product was purified by flash chromatography (2 x 15 cm SiO_2, 12:1 → 9:1 Hex-Et_2O) and isolated in 91.7% yield (0.147 mmol) as a light yellow oil; R_f = 0.31 (3:1 Hexanes-Et_2O); ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (dddd, *J* = 16.6, 10.5, 7.3, 7.3 Hz, 1H), 5.31 (s, 1H), 5.05-5.00 (m, 2H), 3.50 (dd, *J* = 9.3, 6.6 Hz, 1H), 3.47 (dd, *J* = 9.3, 6.6 Hz, 1H), 2.53-2.42 (m, 2H), 2.38 (dd, *J* = 13.7, 7.1 Hz, 1H),

2.20 (dd, *J* = 13.7, 7.8 Hz, 1H), 1.98 (app septuplet, J = 6.6 Hz, 1H), 1.86-1.70 (comp. m, 3H), 1.62-1.56 (m, 1H), 1.14 (s, 3H), 0.95 (app d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 171.3, 134.6, 117.9, 105.0, 74.5, 51.5, 45.4, 36.1, 35.2, 28.0, 25.2, 19.9, 19.3, 19.3; IR (Neat Film NaCl) 2960, 2933, 2873, 1614, 1470, 1387, 1192, 1171, 998, 912 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{24}O_2$ $[M]^{+\bullet}$: 36.1776; found 36.1767; $[\alpha]_D^{25.5}$ – 50.84 ° (*c* 0.73, CH_2Cl_2, 85.0% ee).



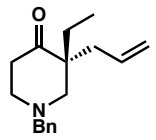
391

Ketone 391. Reaction run on 0.287 mmol at 30 °C in Et_2O (0.1 M) for 5 h using (*S*)-*t*-BuPHOX and $Pd(dmdba)_2$. The product was purified by flash chromatography (1.5 x 18 cm SiO_2, 15:1 → 9:1 Hex-Et_2O, PhMe load) and isolated in 86% yield (0.246 mmol) as a light yellow oil; R_f = 0.46 (3:1 Hex:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.46 (comp. m, 2H), 7.42-7.38 (comp. m, 3H), 5.66 (dddd, *J* = 16.8, 10.1, 7.3, 7.3 Hz, 1H), 5.54 (s, 1H), 5.04-4.98 (comp. m, 2H), 2.59-2.48 (m, 2H), 2.29 (dd, *J* = 13.7 7.3 Hz, 1H), 2.20 (dd, *J* = 13.7, 7.6 Hz, 1H), 1.93-1.77 (comp. m, 2H), 1.64-1.58 (m, 1H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 155.7, 135.5, 134.2, 130.4, 129.8, 129.8, 124.0, 118.1, 51.3, 44.6, 36.3, 35.2, 24.3, 22.5; IR (Neat Film NaCl) 3074, 2931, 2865, 1650, 1597, 1474, 1440, 1197, 916, 749, 691 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{20}SO$ $[M]^{+\bullet}$: 272.1235; found 272.1243; $[\alpha]_D^{24.8}$ –86.35 ° (*c* 0.905, CH_2Cl_2, 89.1% ee).



394

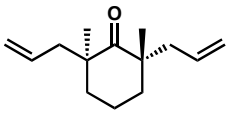
Ketone 394. Reaction performed in Et_2O at 35 ºC with 4 mol% $Pd_2(dba)_3$ (45.8 mg, 0.040 mmol), and 10 mol% (*S*)-*t*-BuPHOX (48.4 mg, 0.10 mmol). Flash chromatography (SiO_2, 1→2.5% Et_2O in pentane). 87% yield. R_f = 0.63 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.27 (app. d, *J* = 1.2 Hz, 1H), 5.15-5.09 (m, 1H), 2.80 (d, *J* = 14.4 Hz, 1H), 2.61 (d, *J* = 14.4 Hz, 1H), 2.56-2.37 (m, 2H), 1.94-1.61 (comp. m, 6H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.4, 138.7, 116.3, 48.4, 46.5, 39.2, 38.8, 27.4, 22.7, 21.1; IR (Neat Film NaCl) 2936, 2868, 1708, 1630, 1456, 1126, 887 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{16}ClO$ $[M+H]^+$: 187.0890, found 187.0884; $[\alpha]_D^{26.6}$ -5.40° (*c* 3.21, CH_2Cl_2, 91% ee).



396

Ketone 396. Flash chromatography (SiO_2, 5 → 7% Et_2O in pentane). 91% yield. R_f = 0.29 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.23 (comp. m, 5H), 5.62 (dddd, *J* = 12.3, 9.6, 7.2, 7.2 Hz, 1H), 5.03 (m, 1H), 4.99 (m, 1H), 3.56 (s, 2H), 2.83-2.69 (m, 1H), 2.65-2.33 (comp. m, 6H), 2.33-2.20 (m, 1H) 1.95 (dq, *J* = 15.3, 7.5 Hz, 1H), 1.51 (dq, *J* = 15.0, 7.5 Hz, 1H), 0.75 (dd, *J* = 7.5, 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.6, 138.6, 133.8, 128.7, 128.3, 127.2, 117.8, 62.2, 61.8, 53.4, 52.2, 39.3, 37.3, 26.7, 7.8; IR (Neat Film NaCl) 3065, 3028, 2965, 2801, 1709, 1454, 1352,

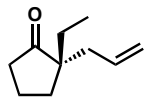
1200, 915, 699 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{23}NO$ $[M]^+$: 257.1780, found 257.1772; $[\alpha]_D^{26.6}$ +31.21° (*c* 1.51, CH_2Cl_2, 92% ee).



398

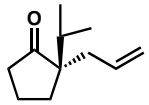
(2*S*,6*S*)-2,6-Diallyl-2,6-dimethylcyclohexanone (398). A 50 mL rb flask equipped with a magnetic stir bar was flame dried under vacuum. After cooling under nitrogen, $Pd_2(dba)_3$ (31.4 mg, 0.0343 mmol, 0.034 equiv) and *(S)-t*-Bu-PHOX (31.3 mg, 0.0808 mmol, 0.080 equiv) were added. After the flask was evacuated and filled with nitrogen three times, THF (32 mL) was added and the contents were stirred at 25 °C for 30 min, at which time allyl 2-(allyloxycarbonyloxy)-1,3-dimethylcycohex-2-enecarboxylate (298 mg, 1.012 mmol, 1.0 equiv) was added by syringe in one portion. The reaction was stirred at 40 °C for 6 hours at which time TLC indicated complete reaction. The reaction mixture was allowed to cool and then concentrated to ~1 mL under reduced pressure and the residue chromatographed (100 mL pentane, then 1 to 2% Et_2O in pentane on 2 x 14 cm SiO_2) to afford the title compound **398** and a colorless, volatile oil (157.9 mg, 76% yield). GC analysis indicated the isolated compound was an 80:20 mixture (R_f = 0.51, 10:1 Hexane:EtOAc) of C_2-symmetric:*meso* diastereomers. The C_2-symmetric isomer was isolated in pure form after ring closing metathesis of the *meso* isomer. C_2-symmetric ketone **398**: R_f = 0.17 (2% Et_2O in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.65 (m, 2H), 5.10-4.95 (m, 4H), 2.33 (dd, *J* = 6.9, 13.8 Hz, 2H), 2.18 (dd, *J* = 7.8, 13.8 Hz, 2H), 1.87-1.68 (m, 4H), 1.59-1.48 (m, 2H), 1.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.6, 134.4, 118.0, 47.6, 43.9, 36.4, 25.0, 17.3; IR (Neat Film NaCl)

3076, 2930, 1694, 1639, 1461, 1374, 992, 914 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{22}O$ $[M]^+$: 206.1671, found 206.1675; $[\alpha]_D^{23.6}$ -54.04° (*c* 0.95, hexane, 92% ee).



407

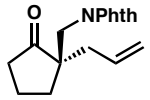
Ketone 407. Flash chromatography (2 x 12 cm SiO_2, 3% → 4% Et_2O/pentane) afforded the title compound as a colorless oil (125.9 mg, 82% yield). R_f = 0.44 (10:1 Hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (dddd, *J* = 7.2, 7.2, 9.3, 12.3 Hz, 1H), 5.09-5.00 (m, 2H), 2.24-2.14 (m, 4H), 1.90-1.80 (m, 4H), 1.46 (q, *J* = 7.2 Hz, 1H), 1.46 (q, *J* = 7.2 Hz, 1H), 0.83 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.4, 169.8, 131.5, 118.3, 65.6, 38.9, 31.9, 27.2, 19.5, 18.3, 17.6; IR (Neat Film NaCl) 3077, 2965, 1735, 1640, 1460, 1406, 1162, 915 cm^{-1}; HRMS *m/z* calc'd for $C_{10}H_{16}O$ $[M]^+$: 152.1201, found 152.1195; $[\alpha]_D^{25.2}$ -18.55 (*c* 1.050, CH_2Cl_2, 86% ee).



409

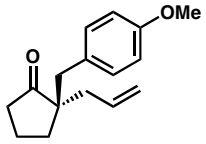
Ketone 409. Flash chromatography (2 x 13 cm SiO_2, 3% Et_2O/pentane) afforded the title compound as a colorless oil (130.4 mg, 77% yield). R_f = 0.44 (10:1 Hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (dddd, *J* = 7.5, 7.5, 9.3, 13.2 Hz, 1H), 5.07-5.00 (m, 2H), 2.30-2.07 (m, 4H), 2.01-1.69 (m, 5H), 0.87 (d, *J* = 7.2 Hz, 3H), 0.80 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 223.6, 134.2, 117.8, 55.1, 39.7, 39.6, 31.8, 29.0, 18.9, 18.2, 17.1; IR (Neat Film NaCl) 3077, 2963, 1734, 1640, 1471,

1406, 1388, 1370, 1190, 914 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{18}O$ $[M]^+$: 166.1358, found 166.1359; $[\alpha]_D^{24.9}$ +43.05 (*c* 1.085, CH_2Cl_2, 84% ee).



411

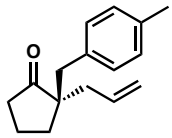
Ketone 411. Flash chromatography (SiO_2, 10 → 15% EtOAc in hexanes). 67% yield, 48% ee. R_f = 0.34 (30% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.9, 3.2 Hz, 2H), 7.72 (dd, *J* = 5.9, 3.2 Hz, 2H), 5.73 (dddd, *J* = 16.8, 9.8, 7.7, 6.4 Hz, 1H), 5.18-5.06 (m, 2H), 3.80 (d, *J* = 14.1 Hz, 1H), 3.74 (d, *J* = 14.1 Hz, 1H), 2.56-2.41 (m, 1H), 2.38-2.10 (comp. m, 3H), 2.10-1.86 (comp. m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.1, 168.8, 134.2, 133.3, 132.0, 123.6, 119.4, 53.0, 41.8, 38.7, 38.3, 31.9, 18.9; IR (Neat Film NaCl) 2966, 1773, 1734, 1713, 1429, 1395, 1354, 715, 666 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{17}O_3N$ $[M]^+$: 283.1208, found 283.1209; $[\alpha]_D^{26.5}$ 14.1 (*c* 1.49, CH_2Cl_2, 48% ee).



413

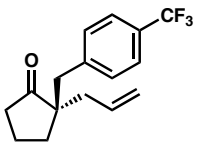
Ketone 413. Flash chromatography (2 x 14 cm SiO_2, 3% Et_2O/pentane) afforded the title compound as a colorless oil (207.6 mg, 84% yield). R_F = 0.32 (10:1 Hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.71 (dddd, *J* = 7.5, 7.5, 10.2, 14.7 Hz, 1H), 5.14-5.01 (m, 2H), 3.78 (s, 3H), 2.86 (d, *J* = 13.8 Hz, 1H), 2.53 (d, *J* = 13.8 Hz, 1H), 2.26 (dd, *J* = 7.2, 13.5 Hz, 1H),

2.20-2.09 (m, 2H), 1.99 (dd, *J* = 6.6, 8.7 Hz, 1H), 1.95-1.66 (m, 2H), 1.86 (app dd, *J* = 7.5, 7.5 Hz, 1H), 1.55-1.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 223.0, 158.2, 133.7, 131.1, 129.6, 118.5, 113.5, 55.1, 53.2, 40.8, 40.8, 38.9, 30.9, 18.6; IR (Neat Film NaCl) 3075, 2958, 1733, 1611, 1512, 1248, 1178, 1036 cm^{-1}; HRMS *m/z* calc'd for $C_{16}H_{20}O_2$ $[M]^+$: 244.1463, found 156244.1465; $[\alpha]_D^{25.1}$ +7.34 (*c* 1.065, CH_2Cl_2, 73% ee).



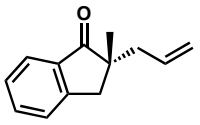
415

Ketone 415. Flash chromatography (SiO_2, 5% Et_2O in pentane). 84% yield, 73% ee. R_f = 0.39 (10% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, *J* = 7.7 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 5.72 (dddd, *J* = 17.0, 10.4, 8.0, 6.9 Hz, 1H), 5.10 (app. ddd, *J* = 10.1, 2.1, 1.1 Hz, 1H), 5.06 (app. ddd, *J* = 16.7, 2.1, 1.3 Hz, 1H), 2.87 (d, *J* = 13.3 Hz, 1H), 2.55 (d, *J* = 13.3 Hz, 1H), 2.31 (s, 3H), 2.29-2.22 (m, 1H), 2.21-2.07 (comp. m, 2H), 2.05-1.82 (comp. m, 3H), 1.82-1.65 (m, 1H), 1.56-1.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 223.2, 136.1, 134.7, 133.9, 130.3, 129.0, 118.8, 53.4, 41.4, 41.0, 39.1, 31.1, 21.2, 18.8; IR (Neat Film NaCl) 3080, 2961, 2915, 1737, 1515, 1441, 1157, 921, 810, 666 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{20}O$ $[M]^+$: 228.1514, found 228.1505; $[\alpha]_D^{26.2}$ +9.1 (*c* 2.68, CH_2Cl_2, 73% ee).



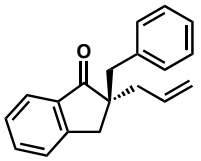
417

Ketone 417. Flash chromatography (2 x 14 cm SiO_2, 2% → 3% Et_2O/pentane) afforded the title compound as a colorless oil (239.3 mg, 83% yield). R_F = 0.39 (10:1 Hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 5.73 (dddd, *J* = 7.5, 7.5, 10.2, 17.4 Hz, 1H), 5.17-5.05 (m, 2H), 2.97 (d, *J* = 13.2 Hz, 1H), 2.66 (d, *J* = 13.2 Hz, 1H), 2.26 (dd, *J* = 7.2, 13.5 Hz, 1H), 2.24-2.19 (m, 1H), 2.16 (dd, *J* = 7.2, 13.5 Hz, 1H), 2.01-1.70 (m, 3H), 1.59-1.43 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 222.1, 142.0, 133.1, 130.6, 128.7 (q, $J_{C\text{-}F}$ = 32.2 Hz), 125.1 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.2 (q, $J_{C\text{-}F}$ = 269.2 Hz), 119.0, 53.1, 41.0, 40.7, 38.6, 31.0, 18.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.29; IR (Neat Film NaCl) 3078, 2964, 1736, 1618, 1326, 1163, 1123, 1068 cm^{-1}; HRMS *m/z* calc'd for $C_{16}H_{17}OF_3$ $[M]^+$: 282.1232, found 282.1237; $[\alpha]_D^{24.8}$ +5.65 (*c* 1.085, CH_2Cl_2, 60% ee).



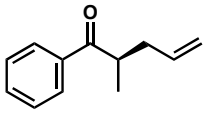
419

Ketone 419. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 82% yield, 80% ee. R_f = 0.37 (10% Et_2O in pentane); $[\alpha]_D^{26.4}$ -38.5 (*c* 0.47, CH_2Cl_2, 80% ee). Spectral data matched that reported in the literature.[26]



421

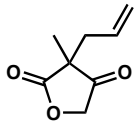
Ketone 421. Purified by flash chromatography (SiO_2, 2 → 4% Et_2O in pentane). 93% yield, 71% ee. R_f = 0.37 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.7 Hz, 1H), 7.63 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H), 7.49 (comp. m, 2H), 7.36-7.20 (comp. m, 5H), 5.74 (dddd, *J* = 16.7, 10.1, 8.0, 6.6 Hz, 1H), 5.21 (app. d, *J* = 16.8 Hz, 1H), 5.12 (app. d, *J* = 10.1 Hz, 1H), 3.26 (d, *J* = 17.3 Hz, 1H), 3.25 (d, *J* = 13.3 Hz, 1H), 3.10 (d, *J* = 17.3 Hz, 1H), 2.96 (d, *J* = 13.6 Hz, 1H), 2.70 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.46 (dd, *J* = 13.6, 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.3, 153.0, 137.3, 136.8, 134.8, 133.4, 130.2, 128.0, 127.2, 126.4, 126.3, 123.8, 118.7, 53.7, 42.7, 42.5, 35.3; IR (Neat Film NaCl) 3076, 3029, 2917, 1708, 1608, 1496, 1465, 1436, 1296, 1210, 1030, 995, 922, 756, 703 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{19}H_{18}O$ $[M]^+$: 262.1358, found 262.1365; $[\alpha]_D^{26.1}$ +28.4 (*c* 1.42, CH_2Cl_2, 71% ee).



423

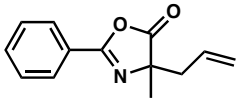
Ketone 423. Purified by preparative TLC. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 5.77 (m, 1H), 5.00 (m, 2H), 3.52 (sextet, *J* = 6.9 Hz, 1H), 2.54 (m, 1H), 2.19 (m, 1H), 1.21 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.6, 136.4, 135.9, 133.0, 128.5, 116.7, 40.5, 37.7, 17.1; IR (Neat Film NaCl) 3078, 2976, 2933, 1682, 1642, 1448, 1209, 976, 917,

704 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{14}O$ $[M]^+$: 174.1045, found 174.1048; $[\alpha]_D^{27.0}$ –38.1 (*c* 1.73, hexanes, 70% ee).



430

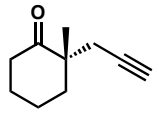
Ketone 430. Purified by flash chromatography (SiO_2, 2 →12% EtOAc in hexanes). 87% yield, 2% ee. R_f = 0.20 (10% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.62 (dddd, *J* = 17.7, 9.6, 7.5, 7.2 Hz, 1H), 5.13 (app. ddd, *J* = 9.6, 1.8, 0.9 Hz, 1H), 5.12 (app. ddd, *J* = 17.1, 1.5, 0.9 Hz, 1H), 4.59 (d, *J* = 17.1 Hz, 1H), 4.44 (d, *J* = 17.4 Hz, 1H), 2.53-2.37 (m, 2H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 176.6, 130.1, 121.1, 72.5, 45.6, 40.2, 19.0; IR (Neat Film NaCl) 3543, 3083, 2983, 2939, 2877, 1803, 1758, 1642, 1454, 1436, 1378, 1341, 1231, 1122, 1065, 1043, 998, 912, 664 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_8H_{10}O_3$ $[M]^+$: 154.0630, found 154.0626.



432

Ketone 432. Purified by flash chromatography (SiO_2, 4 →7% Et_2O in hexanes). 89% yield, 2% ee. R_f = 0.39 (25% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (ddd, *J* = 7.2, 1.5, 1.2 Hz, 2H), 7.57 (tt, *J* = 7.8, 1.2 Hz, 1H), 7.48 (ddd, *J* = 7.8, 6.9, 1.5 Hz, 2H), 5.67 (dddd, *J* = 17.1, 9.9, 7.5, 6.9 Hz, 1H), 5.18 (dddd, *J* = 17.1, 1.5, 1.5, 1.5 Hz, 1H), 5.11 (dddd, *J* = 10.2, 1.5, 0.9, 0.9 Hz, 1H), 2.64 (dddd, *J* = 13.8, 6.9, 0.9, 0.9 Hz, 1H), 2.57 (dddd, *J* = 13.8, 7.5, 1.2, 1.2 Hz, 1H), 1.53 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 180.2, 159.8, 132.7, 130.8, 128.7, 127.9, 125.9, 120.4, 69.7, 42.3, 23.2; IR (Neat Film NaCl) 3078, 2982, 2934, 1819, 1655, 1581, 1493, 1451, 1321, 1293, 1177, 1094, 1071, 1005, 930, 889, 780, 700 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{13}O_2N$ $[M]^+$: 215.0946, found 215.0938.



434

Propargyl ketone 434. A flame dried, 50 mL two-neck round-bottom flask containing a stirbar was equipped with a three-way stopcock, evacuated, and cooled under dry nitrogen. To this was added $Pd_2(dba)_3$ (11.4 mg, 0.0125 mmol, 0.05 equiv.) and (*S*)-*t*-Bu-PHOX (12.5 mg, 0.0313 equiv.). The flask was evacuated and backfilled with dry nitrogen twice. THF (15 mL) was then added and the mixture was stirred for 30 minutes at 25ºC. To the resulting yellow solution was added propargyl enol carbonate **433** (97.1 mg, 0.50 mmol) and then this mixture was stirred at 70 ºC. After the reaction was completed, the resulting mixture was concentrated in vacuo. The residue was purified by flash column chromatography to give propargyl ketone (*S*)-**434** (64.3 mg, 86% yield) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 2.55-2.29 (m, 4H), 1.99 (t, J = 2.7 Hz, 1H), 1.98-1.65 (m, 6H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.9, 81.1, 70.7, 47.8, 38.5, 37.8, 27.6, 27.3, 22.3, 21.1; IR (Neat Film NaCl) 3292, 2936, 2865, 2117, 1709, 1451, 1425, 1377, 1314, 1128, 1075 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{14}O$ $[M]^+$: 150.1045, found 150.1044; $[\alpha]^{25}_D$ = +0.74 (*c* 1.50, $CHCl_3$, 31% ee).

Table 4.17 Methods Utilized for the Determination of Enantiomeric Excess

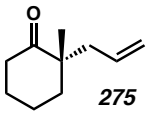
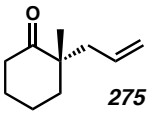
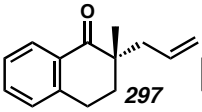
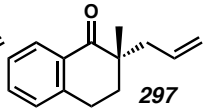
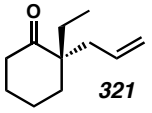
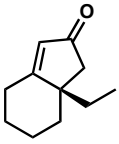
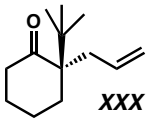
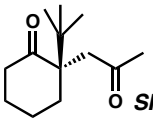
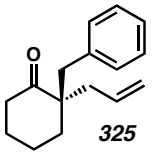
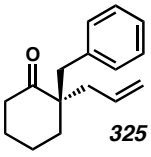
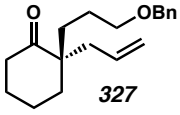
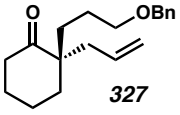
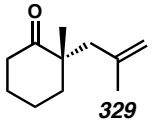
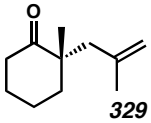
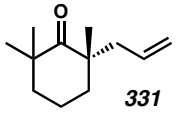
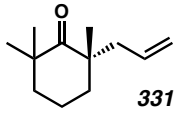
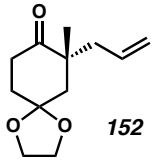
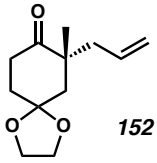
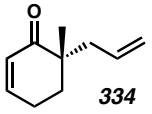
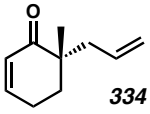
entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
1	 *275*	 *275*	GC, G-TA 100 °C isotherm	11.13	12.74	88
2	 *297*	 *297*	HPLC Chiracel OD-H 0.1% IPA in heptane isocratic, 0.7 mL/min	19.97	21.48	92
3	 *321*		GC, G-TA 100 °C isotherm	14.52	13.35	92
4	 *XXX*	 *SI8*	GC, G-TA 110 °C isotherm	63.65	62.01	82
5	 *325*	 *325*	HPLC Chiracel OJ 2% EtOH in hexane isocratic, 1.0 mL/min	19.81	13.82	85
6	 *327*	 *327*	HPLC Chiralpak AD 0.75% IPA in hexane isocratic, 1.0 mL/min	11.95	13.80	88
7	 *329*	 *329*	GC, G-TA 100 °C isotherm	15.76	17.65	92
8	 *331*	 *331*	GC, G-TA 80 °C isotherm	25.48	27.90	92
9	 *152*	 *152*	GC, G-TA 120 °C isotherm	26.90	28.64	86
10	 *334*	 *334*	GC, G-TA 100 °C isotherm	15.31	18.04	90

Table 4.17 (continued)

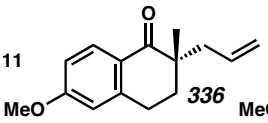
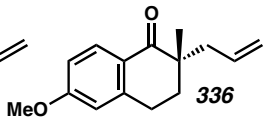
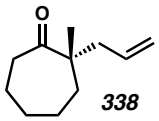
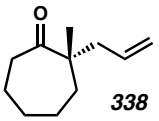
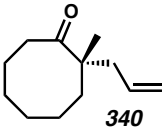
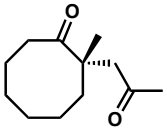
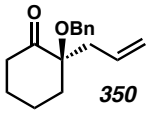
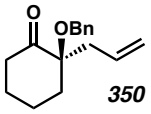
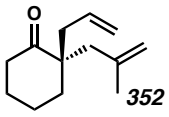
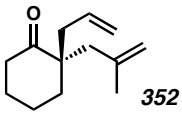
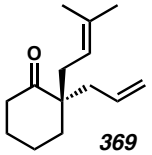
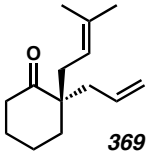
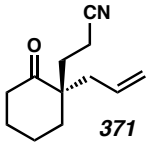
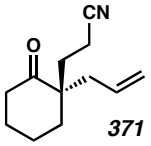
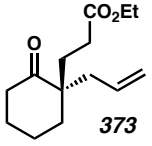
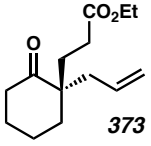
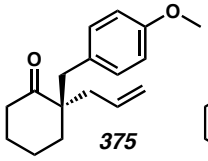
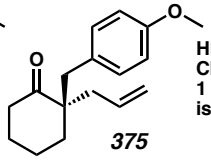
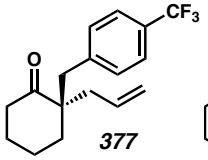
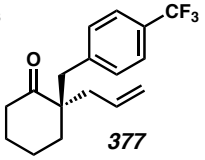
entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
11	 336	 336	HPLC Chiracel OJ 1% EtOH in hexane isocratic 1.0 mL/min	11.38	10.16	91
12	 338	 338	GC, G-TA 110 °C isotherm	9.88	10.68	87
13	 340		GC, G-TA 110 °C isotherm	63.25	61.94	79
14	 350	 350	HPLC Chiracel OB-H 0.2% EtOH in hexane isocratic, 1.0 mL/min	13.56	16.96	59
15	 352	 352	GC, G-TA 95 °C isotherm	49.77	47.98	91
16	 369	 369	GC, G-TA 100 °C isotherm	55.511	52.56	91
17	 371	 371	GC, G-TA 150 °C isotherm	18.75	21.06	88
18	 373	 373	GC, G-TA 120 °C isotherm	90.98	94.22	90
19	 375	 375	HPLC Chiracel AD 1 % EtOH in hexane isocratic, 1.0 mL/min	12.87	15.36	86
20	 377	 377	GC, G-TA 120 °C isotherm for 120 mins, then ramp 3 °C/min	127.74	126.43	82

Table 4.17 (continued)

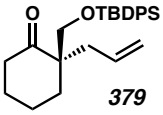
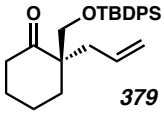
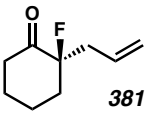
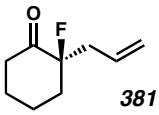
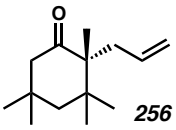
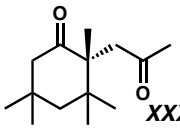
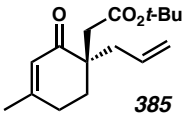
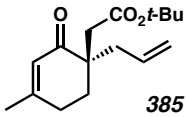
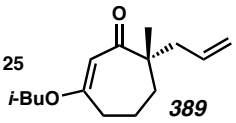
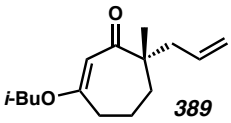
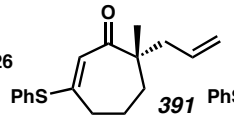
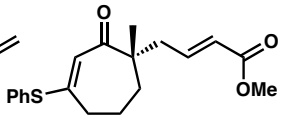
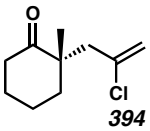
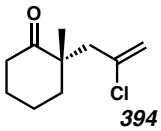
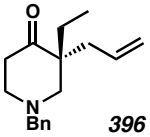
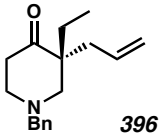
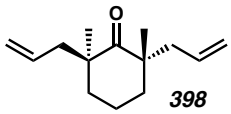
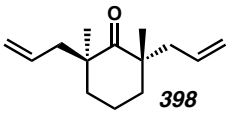
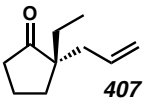
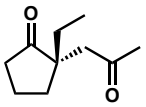
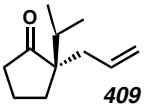
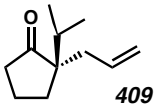
entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
21	 *379*	 *379*	HPLC Chiracel OD-H 100% hexane isocratic, 1.0 mL/min	16.75	23.91	81
22	 *381*	 *381*	GC, G-TA 110 °C isotherm	6.27	8.02	91
23	 *256*	 *XXX*	GC, G-TA 120 °C isotherm	49.12	50.57	85
24	 *385*	 *385*	GC, G-TA 130 °C isotherm	59.36	61.19	86
25	 *389*	 *389*	HPLC Chiracel OD-H 1% IPA in hexane isocratic, 1.0 mL/min	6.30	7.26	85
26	 *391*		HPLC Chiralpak AD 3% EtOH in hexane isocratic 1.0 mL/min	18.66	22.33	89
27	 *394*	 *394*	GC, G-TA 100 °C isotherm	44.91	50.06	91
28	 *396*	 *396*	HPLC Chiracel OJ 1 % EtOH in hexane isocratic, 1.0 mL/min	7.95	8.82	92
29	 *398*	 *398*	GC, G-TA 75 °C isotherm	118.51	127.37	92
30	 *407*		GC, G-TA 110 °C isotherm	45.22	38.91	86
31	 *409*	 *409*	GC, G-TA 80 °C isotherm	43.95	49.93	84

Table 4.17 (continued)

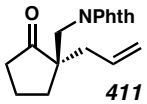
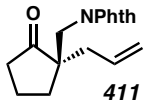
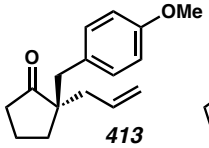
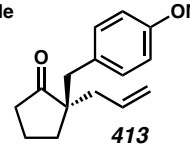
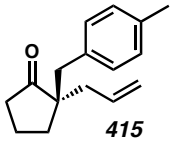
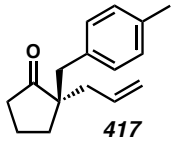
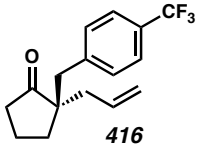
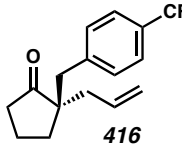
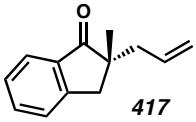
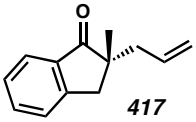
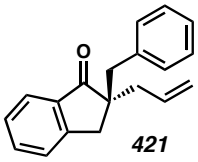
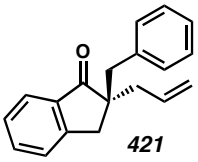
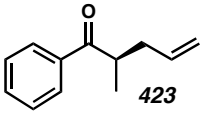
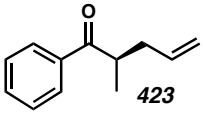
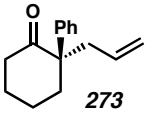
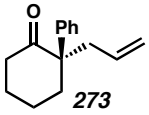
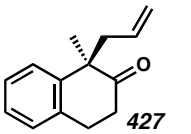
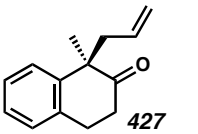
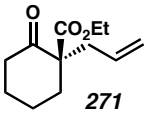
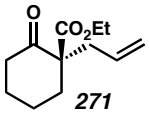
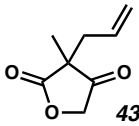
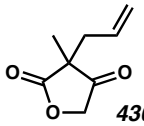
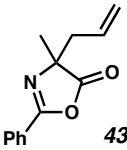
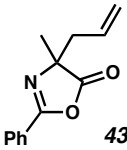
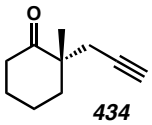
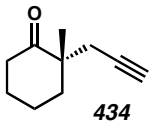
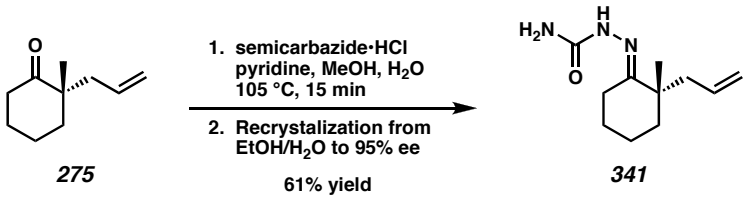
entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
32	 411	 411	HPLC Chiracel OD-H 4% IPA in hexane isocratic, 1.0 mL/min	24.13	18.26	48
33	 413	 413	HPLC Chiralpak AD 1% IPA in hexane isocratic, 1.0 mL/min	10.07	11.84	73
34	 415	 417	HPLC Chiracel OJ 0.3% EtOH in hexane isocratic, 1.0 mL/min	14.88	12.80	73
35	 416	 416	HPLC Chiralpak AD 1% EtOH in hexane isocratic, 1.0 mL/min	6.42	7.47	60
36	 417	 417	HPLC Chiracel OD-H 0.1% IPA in hexane isocratic, 0.7 mL/min	21.78	23.74	80
37	 421	 421	HPLC Chiracel OJ 1% EtOH in hexane isocratic, 1.0 mL/min	28.93	22.38	71
38	 423	 423	HPLC Chiracel OD-H 0.1% IPA in heptane isocratic, 0.7 mL/min	21.63	25.04	70
39	 273	 273	HPLC Chiracel OJ 0.1% IPA in hexane isocratic, 1.0 mL/min	7.76	8.59	11
40	 427	 427	HPLC Chiracel OJ 3% IPA in hexane isocratic, 1.0 mL/min	9.03	7.38	0
41	 271	 271	GC, G-TA 120 °C isotherm	15.55	16.66	24

Table 4.17 (continued)

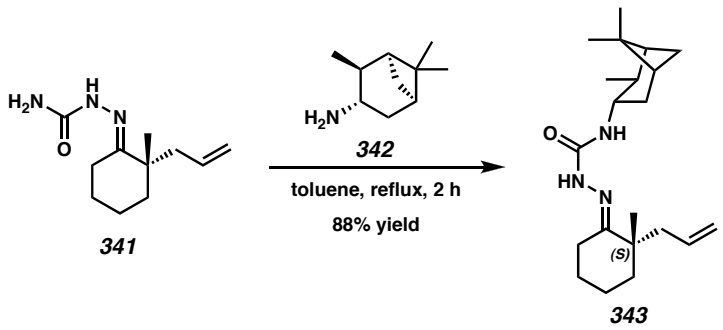
entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
42	 *430*	 *430*	GC, G-TA 100 °C isotherm	19.67	21.64	2
43	 *432*	 *432*	HPLC Chiracel OD-H 2% IPA in hexane isocratic, 1.0 mL/min	6.61	5.40	2
44	 *434*	 *434*	GC, B-DM 90 °C isotherm	21.8	23.0	31

4.7.2.6 *Preparation of α-Quaternary Ketone Derivatives*

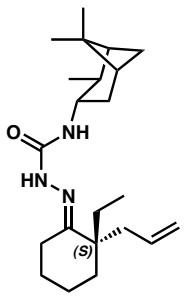


275 *341*

Semicarbazone 341. To a solution of ketone **275** (661.4 mg, 4.34 mmol, 1.0 equiv) of 88% ee in pyridine (1.22 mL), water (3.0 mL), and MeOH (8.0 mL) was added semicarbazide•HCl (848.1 mg, 7.60 mmol, 1.75 equiv). The reaction mixture was heated at 105 °C for 15 min, cooled, diluted with water (10 mL), filtered, and dried to give the semicarbazone (763 mg, 84% yield). The semicarbazone (3.10 g, 14.8 mmol, 87% ee) was suspended in EtOH/water (35/65 v/v 355 mL) and warmed to 90 °C. When all the material had dissolved, heating was discontinued, and the flask allowed to cool in the heating bath. After 8 h, crystals were filtered and dried giving the enantioenriched semicarbazone (1.894 g, 61% yield, 95% ee). Recrystalization of this material in EtOH/water (30/70 v/v 175 mL) by the same procedure gave semicarbazone (1.692 g, 89% yield, 98% ee) as white crystals; m.p. 188-189 °C (EtOH/water); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (bs, 1H), 5.73 (m, 1H), 5.05 (s, 1H), 5.00 (app. d, J = 3.3 Hz, 1H), 2.40-2.11 (m, 4H), 1.71-1.44 (m, 6H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 156.8, 134.6, 117.2, 42.9, 41.5, 38.6, 25.9, 24.5, 22.5, 21.0; IR (Neat Film NaCl) 3465, 3195, 1693, 1567, 1478 cm^{-1}; HRMS m/z calc'd for $C_{11}H_{20}N_3O$ $[M+H]^+$: 210.1606, found 210.1599; $[\alpha]_D^{28}$ -50.35° (c = 2.60, methanol).

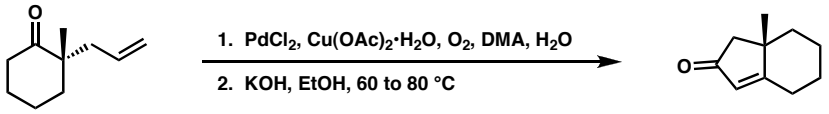


(isopinocampheylamine)-Semicarbazone (343): To a solution of the semicarbazone (100 mg, 0.43 mmol, 1.0 equiv) in xylenes (1.0 mL) was added (1*S*,2*S*,3*S*,5*R*)-(+)-isopinocampheylamine (76.2 μL, 0.45 mmol, 1.05 equiv). The reaction mixture was refluxed for 2 h, cooled, and concentrated. Chromatography (10→50 % EtOAc in Hexanes on SiO_2) afforded the (isopinocampheylamine)-semicarbazone **343** (130.5 mg, 87.8 % yield): m.p. 131-133° from acetone; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (bs, 1H), 6.08 (bd, *J* = 8.7 Hz, 1H), 5.77 (m, 1H), 5.06 (s, 1H), 5.01 (s, 1H), 4.18 (m, 1H), 2.63 (app. tdd, *J* = 9.9, 3.6, 2.4 Hz, 1H), 2.45-2.13 (m, 4H), 1.96 (m, 1H), 1.82 (m, 2H), 1.74-1.41 (m, 8H), 1.23 (s, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 0.89 (d, *J* = 9.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 155.5, 134.9, 117.0, 48.0, 47.8, 46.8, 43.0, 41.6, 41.5, 38.5, 38.3, 37.8, 35.3, 28.0, 25.9, 24.5, 23.4, 22.4, 21.0, 20.8; IR (Neat Film NaCl) 3400, 3189, 3074, 2929, 1672, 1526 cm^{-1}; HRMS *m/z* calc'd for $C_{21}H_{36}N_3O$ $[M+H]^+$: 346.2858, found 346.2874; $[\alpha]_D^{27}$ -18.92° (*c* = 0.53, hexane). The semicarbazone was recrystallized from EtOH/H_2O to provide suitable crystals for X-ray analysis.



344

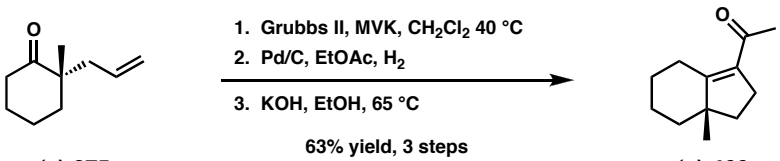
(isopinocampheylamine)-Semicarbazone (344). Prepared in an analogous manner to **343**: m.p. 145-146° from acetone; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 21.3 Hz, 1H), 6.07 (d, *J* = 4.4 Hz, 1H), 5.86-5.72 (m, 1H), 5.08-5.04 (m, 1H), 5.00 (s, 1H), 4.23-4.12 (m, 1H), 2.68-2.55 (m, 1H), 2.46-2.34 (m, 2H), 2.30 (d, *J* = 7.5 Hz, 2H), 2.12-2.00 (m, 1H), 1.98-1.90 (m, 1H), 1.88-1.40 (m, 11H), 1.22 (s, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.05 (s, 3H), 0.88 (d, *J* = 9.6 Hz, 1H), 0.77 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 154.4, 135.3, 116.7, 48.0, 47.9, 46.8, 44.2, 41.7, 39.9, 38.3, 37.9, 35.6, 35.3, 28.1, 28.0, 25.6, 23.4, 22.6, 20.8, 20.7, 7.8; IR (Neat Film NaCl) 3402, 3194, 3074, 2930, 1672, 1526 cm^{-1}; HRMS *m/z* calc'd for $C_{22}H_{37}N_3O$ $[M]^+$: 359.2937, found 359.2940; $[\alpha]_D^{29}$ -4.43° (*c* = 0.38, hexane). The semicarbazone was recrystallized from acetone to provide suitable crystals for X-ray analysis.



(–)-275 *(–)-399*

Enone 399.[70] To a solution of ketone **275** (304.4 mg, 2.0 mmol, 2.0 equiv) in dimethylacetamide (2.8 mL) and water (0.4 mL) was added palladium (II) chloride (53.1 mg, 1.2 mmol, 0.15 equiv), copper (II) acetate hydrate (217.9 mg, 1.20 mmol, 0.60

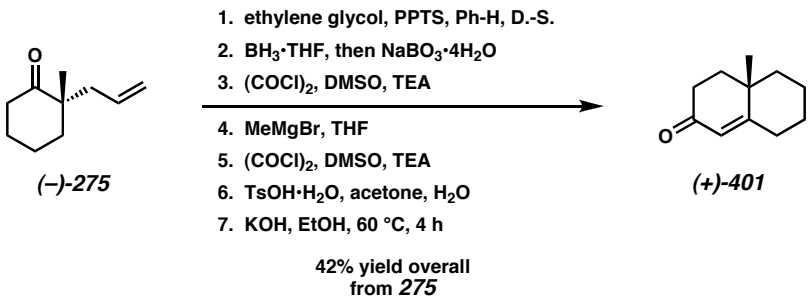
equiv), and an oxygen balloon. After 24 h of vigorous stirring at 25 °C the reaction mixture was chromatographed (5→25 % EtOAc in Hexanes on SiO_2). To a solution of the resulting diketone in EtOH (30 mL) was added KOH (3.4 mL of a 50 mg/mL ethanolic solution), and the reaction mixture was heated at 60 °C for 6 h. The temperature was increased to 80 °C and additional KOH (200 mg) was added. After 4 h the reaction was cooled and concentrated. The resulting residue was partitioned between EtOAc (30 mL) and water (20 mL) and acidified to pH = 2 with HCl (3 M). The layers were separated, and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. Chromatography (10→30% Et_2O in pentane on SiO_2) afforded enone **399** (219.1 mg, 72.9% overall yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (s, 1H), 2.62 (bd, *J* = 12.0 Hz, 1H), 2.35 (td, *J* = 13.5, 5.4 Hz, 1H), 2.27 (dd, *J* = 18.3, 0.9 Hz, 1H), 2.17 (d, *J* = 18.6 Hz, 1H), 2.26-1.88 (m, 2H), 1.64 (m, 2H), 1.36 (m, 2H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 188.6, 126.0, 52.1, 43.1, 40.6, 27.9, 27.8, 24.0, 21.8; IR (Neat Film NaCl) 2934, 1713, 1622, 1221 cm^{-1}; HRMS *m/z* calc'd for $C_{10}H_{14}O$ [M]$^+$: 150.1045, found 150.1041; $[\alpha]_D^{27}$ -44.86° (*c* = 3.55, hexane, 98 % ee).



(–)-275 *(+)-400*

Enone 400.[71] To a solution of ketone **275** (152.2 mg, 1.0 mmol, 1.0 equiv) and methyl vinyl ketone (208.1 μL, 2.5 mmol, 2.5 equiv) in DCM (5 mL) was added Grubbs' 2nd generation catalyst (42.4 mg, 0.05 mmol, 0.05 equiv). The reaction mixture was

heated at 40 °C for 18 h, cooled to 25 °C, and concentrated. Chromatography (20% EtOAc in hexanes on SiO_2) gave the enone (152.1 mg 78.3% yield), which was dissolved in EtOAc (12 mL) and treated with 10% Pd/C (30 mg) under an atmosphere of hydrogen gas for 12 h. The system was purged with argon, filtered through a small pad of silica gel, and concentrated. To a solution of the crude diketone in EtOH (12 mL) was added KOH (2.0 mL of a 50 mg/mL ethanolic solution). The reaction mixture was heated to 65 °C for 8 h, cooled to 25 °C, concentrated, and the residue partitioned between EtOAc (10 mL) and 1 M HCl (10 mL) The layers were separated, the aqueous layer extracted with Et_2O (3 x 25 mL), and the combined organics were washed with saturated $NaHCO_3$ (25 mL) then brine (25 mL), dried ($MgSO_4$) and concentrated. Chromatography (10→15 % Et_2O in hexanes on SiO_2) gave enone **400** (112.4 mg, 81% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32 (d, *J* = 14.7 Hz, 1H), 2.59 (m, 2H), 2.23 (s, 3H), 2.01 (app. t, *J* = 13.5 Hz, 1H), 1.82 (m, 3H), 1.59 (m, 3H), 1.43-1.23 (m, 2H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 162.2, 131.9, 48.6, 41.5, 39.0, 30.9, 30.5, 27.1, 25.2, 22.9, 22.0; IR (Neat Film NaCl) 2931, 1678, 1654, 1614, 1357 cm^{-1}; HRMS *m/z* calc'd for $C_{10}H_{18}O$ $[M]^+$: 178.1358, found 178.1355; $[\alpha]_D^{27}$ +82.91° (*c* = 3.26 , hexane, 98% ee).

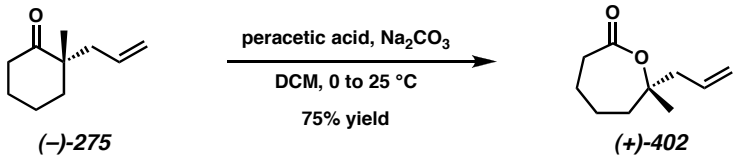


Enone 401. A solution of ketone **275** (1.23 g, 8.11 mmol, 1.0 equiv), ethylene glycol (1.8 mL), pyridinium tosylate (0.6 g),and benzene (45 mL) was refluxed for 22 h in a Dean-Stark apparatus. The reaction mixture was cooled, poured into saturated $NaHCO_3$ (50 mL), the aqueous layer extracted with hexanes/Et_2O (1/1) (2 x 20 mL), and washed with brine (2 x 15 mL). The combined organics were dried ($MgSO_4$), concentrated, and chromatographed to give the ketal (1.59 g). The ketal in THF (15 mL) was added dropwise to a cooled (-25 °C) solution of BH_3•THF (20.3 mmol, 2.5 equiv) in THF (100 mL), and after 4 h was allowed to warm to 25 °C overnight. The reaction mixture was then cooled to -10 °C, water (25 mL) was slowly added, followed by $NaBO_3$•$4H_2O$ (4.99 g, 32.4 mmol, 4.0 equiv), and the reaction mixture was allowed to warm to 25 °C. After 48 h, the reaction mixture was partitioned between water (100 mL) and EtOAc (100 mL), the layers separated, the aqueous layer extracted with EtOAc (5 x 75 mL), and the organic fractions were dried (Na_2SO_4). Evaporation of the solvents under reduced pressure, and chromatography (20→40% EtOAc in hexanes on SiO_2) gave the primary alcohol (1.50 g, 87% yield).

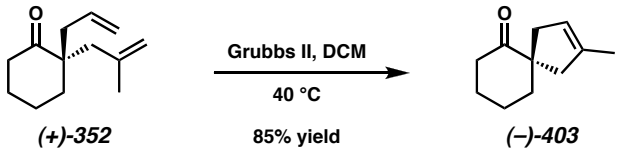
To a cooled (-78 °C) solution of DMSO (479.0 μL, 6.72 mmol, 1.6 equiv) in DCM (45 mL) was added oxalyl chloride (475.2 μL, 5.45mmol, 1.3 equiv). After 45 min, the primary alcohol (900 mg, 4.19 mmol, 1.0 equiv) in DCM (5 mL) was added in a dropwise manner. After an additional 30 min, TEA (2.32 mL, 16.8 mmol, 4.0 equiv) was

added, the reaction mixture warmed to 25 °C, and quenched with half-saturated aq. $NaHCO_3$. The aqueous layer was extracted with DCM (3 x 30 mL), the combined organics dried ($MgSO_4$), and solvents evaporated. This crude aldehyde in THF (45 mL) was cooled to -10 °C, treated with methyl magnesium bromide 3 M in Et_2O (8.40 mmol, 2.0 equiv), quenched with water (20 mL) and saturated aq. NH_4Cl (20 mL), extracted DCM (4 x 20 mL), dried ($MgSO_4$), and solvents evaporated. The resulting crude secondary alcohol was resubmitted to the Swern oxidation conditions described above to give a crude methyl ketone. A solution of the methyl ketone in acetone (45 mL) and water (0.7 mL) was treated with $TsOH•H_2O$ (60 mg), and heated at 50 °C for 4 h. The reaction mixture was then concentrated and chromatographed (7.5→20% EtOAc in hexanes on SiO_2) to give the diketone (515.8 mg, 68% yield for 4 steps).

To a solution of KOH (300mg 5.36 mmol, 1.91 equiv) in EtOH (40 mL) was added the diketone (510.0 mg, 2.80 mmol, 1.0 eq) dissolved in EtOH (15 mL), and the reaction mixture heated at 60 °C for 4 h. The reaction was quenched with acetic acid (306 μL, 5.36 mmol, 1.91 equiv), concentrated and chromatographed (5→20% Et_2O in hexanes on SiO_2) to give enone **401** (334.2 mg, 73% yield, 42% overall yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (s, 1H), 2.56-2.22 (m, 4H), 1.92-1.64 (m, 6H), 1.44-1.30 (m, 2H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 170.5, 124.1, 41.5, 38.0, 35.9, 34.0, 32.7, 27.1, 22.0, 21.7; IR (Neat Film NaCl) 2930, 1678 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{16}O$ $[M]^+$: 164.1201, found 164.1196; $[\alpha]_D^{28}$ +216.15° (*c* = 1.05, ethanol, 98% ee).

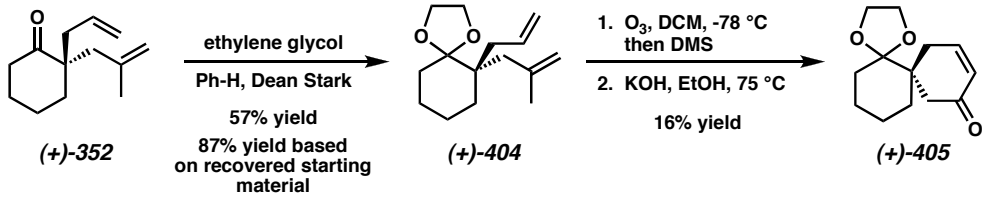


Lactone 402.[72] To a cooled (0 °C) solution of ketone **275** (152.2 mg, 1.0 mmol, 1.0 equiv) in DCM (20 mL) was added Na_2CO_3 (593.6 mg, 5.6 mmol, 5.6 equiv) and peracetic acid (800 μL of 32% solution in dilute acetic acid). The reaction mixture was maintained at 0 °C for 9 h, then allowed to warm to 25 °C for an additional 12 h, diluted with saturated $NaHCO_3$, and the organic layer dried (Na_2SO_4). Chromatography (5→20% EtOAc in hexanes on SiO_2) afforded lactone **402** (125.6 mg, 75% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.15 (m, 1H), 5.11 (app. d, J = 8.4 Hz, 1H), 2.78-2.61 (m, 2H), 2.51 (dd, J = 13.8, 7.2 Hz, 1H), 2.42 (dd, J = 14.1, 7.5 Hz, 1H), 1.86-1.62 (m, 6H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 132.8, 119.0, 82.7, 46.7, 38.4, 37.3, 24.8, 23.8, 23.3; IR (Neat Film NaCl) 2936, 1717, 1172 cm^{-1}; HRMS *m/z* calc'd for $C_{10}H_{16}O_2$ $[M]^+$: 168.1150, found 168.1154; $[\alpha]_D^{27}$ +20.58° (*c* = 3.46, hexane, 98% ee).



Spiro[4.5]ketone 403. To a sparged (Ar, 5 min) solution of ketone **352** (526 mg, 2.73 mmol, 1.00 equiv) in DCM (56 mL) was added the second generation Grubbs catalyst (69.6 mg, 0.082 mmol, 0.03 equiv) and the reaction was heated at 40 °C for 10 h. The reaction mixture was cooled to ambient temperature, concentrated, and the residue purified by flash chromatography (1→2% Et_2O in hexanes on SiO_2) to give

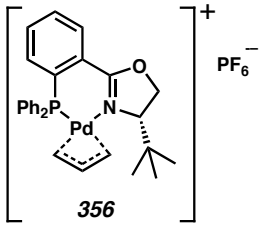
spiro[4.5]ketone **403** (381 mg, 85% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (m, 1H), 2.86-2.71 (m, 2H), 2.44-2.35 (m, 2H), 2.17 (dddd, *J* = 16.2, 5.4, 4.2, 2.1 Hz, 1H), 2.02 (ddd, *J* = 16.5, 3.0, 1.2 Hz, 1H), 1.88-1.68 (comp. m, 6H), 1.67-1.64 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 137.5, 121.1, 56.3, 45.7, 41.9, 40.3, 39.4, 27.2, 22.2, 16.4; IR (Neat Film NaCl) 3042, 2930, 2860, 1710, 1666, 1438, 1338, 1312, 1207, 1129, 1056, 1019, 899, 853, 838, 807 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{16}O$ $[M]^+$: 164.1201, found 164.1201; $[\alpha]_D^{27.1}$ –21.7 (*c* 2.65, CH_2Cl_2, 91% ee).



Ketal 404. A solution of ketone **352** (1.27 g, 6.60 mmol, 1.0 equiv), ethylene glycol (1.8 mL), pyridinium tosylate (0.600 g), and benzene (80 mL) was refluxed for 15 h in a Dean-Stark apparatus. The reaction mixture was cooled, poured into saturated $NaHCO_3$ (20 mL), and diluted with H_2O (30 mL) and DCM (30 mL). The aqueous layer extracted with DCM (3 x 30 mL). The combined organics were dried (Na_2SO_4), concentrated, and purified by flash chromatography (1→2% Et_2O in hexanes on SiO_2) to give ketal **404** (889 mg, 57% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (dddd, *J* = 16.2, 11.1, 7.2, 7.2 Hz, 1H), 4.95 (app. ddd, *J* = 15.9, 1.8, 1.8 Hz, 1H), 4.95 (app. ddd, *J* = 11.1, 1.2, 1.2 Hz, 1H), 4.85 (app. ddd, *J* = 4.2, 2.4, 1.5 Hz, 1H), 4.78-4.71 (m, 1H), 3.98-3.84 (comp. m, 4H), 2.43-2.17 (comp. m, 4H), 1.82 (s, 3H), 1.67-1.40 (comp. m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 136.9, 114.9, 114.8, 112.9, 64.4, 64.1, 45.0, 39.4, 38.1, 33.1, 30.5, 25.6, 23.4, 20.7; IR (Neat Film NaCl) 3073, 2936, 2882, 1638, 1452,

11374, 1275, 1215, 1173, 1089, 1060, 1026, 957, 892 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{24}O_2$ $[M]^+$: 236.1776, found 236.1779; $[\alpha]_D^{26.7}$ +5.0 (*c* 2.71, CH_2Cl_2, 91% ee).

Spiro[5.5]ketone 405. Through a cooled (-78 °C) solution of ketal **404** (441 mg, 1.86 mmol, 1.00 equiv) in CH_2Cl_2 (40 mL) was bubbled a stream of ozone until the reaction mixture turned blue. The reaction mixture was quenched with dimethyl sulfide (0.50 mL), allowed to warm to ambient temperature, and concentrated to an oil. This residue was dissolved in EtOH (35 mL), treated with an ethanolic KOH solution (3.0 mL of 50 mg/mL), and heated to 75 °C for 3 h. The reaction mixture was cooled to ambient temperature, neutralized with acetic acid, concentrated, and purified by flash chromatography (5→25% EtOAc in hexanes on SiO_2) to give spiro[5.5]ketone **305** (65.7 mg, 16% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (ddd, *J* = 10.2, 5.7, 2.7 Hz, 1H), 5.98 (app. dd, *J* = 9.9, 3.0 Hz, 1H), 4.02-3.87 (comp. m, 4H), 2.66 (ddd, *J* = 19.2, 2.7, 2.7 Hz, 1H), 2.64 (d, *J* = 16.2 Hz, 1H), 2.46 (d, *J* = 15.9 Hz, 1H), 2.33 (ddd, 19.2, 6.0, 1.5 Hz, 1H) 1.68-1.50 (comp. m, 6H), 1.48-1.34 (comp. m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 148.1, 128.5, 111.1, 65.0 (2C), 44.7, 43.3, 31.5, 31.1, 30.1, 23.1, 20.4; IR (Neat Film NaCl) 2935, 2865, 1677, 1448, 1389, 1346, 1253, 1179, 1142, 1101, 1063, 1022, 961, 909, 885, 736 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{13}H_{17}O_3$ $[(M + H) - H_2]^+$: 221.1178, found 221.1185; $[\alpha]_D^{28.1}$ +27.9 (*c* 1.13, CH_2Cl_2, 91% ee).



356

Pd(II)(allyl)PHOX•PF_6 salt 356. Prepared using Zehnder's method[32] with (*S*)-*t*-Bu-PHOX, as a mixture of *endo* and *exo* isomers (ca. 60:40 ratio) quantitative yield as a light yellow powder; Mp (EtOH) 152-154 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (app. ddd, *J* = 7.7, 4.1, 1.1 Hz, 0.6H), 8.24 (app. ddd, *J* = 7.7, 4.4, 1.1 Hz, 0.4H), 7.74-7.42 (comp. m, 8H), 7.39-7.11 (comp. m, 4H), 7.04-6.87 (comp m, 1H), 5.96-5.82 (m, 0.4H), 5.82-5.67 (m, 0.6H), 4.96-4.86 (comp. m, 1H), 4.68 (app. q, *J* = 9.9 Hz, 1H), 4.49 (app. dt, *J* = 11.3, 3.9 Hz, 1H), 4.19 (app. dt, *J* = 10.2, 4.4 Hz, 1H), 4.03 (app. dd, *J* = 14.3, 9.4 Hz, 0.6H), 3.63-3.48 (comp. m, 1H), 3.32 (app. d, *J* = 6.6 Hz, 0.4H), 3.16 (app. d, *J* = 12.7 Hz, 0.4H), 2.77 (app. d, *J* = 12.1 Hz, 0.6H), 0.64 (s, 3.5H), 0.56 (s, 5.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9-164.8 (3 peaks), 134.9, 134.8, 134.0-133.3 (7 peaks), 132.9-132.6 (4 peaks), 132.2-132.1 (3 peaks), 131.8 (app. d, *J* = 2.3 Hz), 130.2-128.8 (13 peaks), 128.5-127.8 (5 peaks), 127.3, 122.4 (app. d, *J* = 6.0 Hz), 122.4, 83.3-79.4 (6 peaks), 69.8, 69.7, 58.6, 54.1, 54.0, 34.3, 25.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ 22.7 (d, *J* = 118.1 Hz), -143.8 (septet, 711.0 Hz); IR (Neat Film from $CDCl_3$, NaCl) 3062, 2964, 2872, 2271, 1971, 1899, 1826, 1621, 1584, 1568, 1482, 1437, 1372, 1315, 1249, 1211, 1145, 1121, 1100, 1060, 1028, 958, 913, 836, 778, 732, 697, 678 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{28}H_{31}ONPPd$ $[M]^+$: 534.1178, found 534.1182; $[\alpha]_D^{27.1}$ +256.6 (*c* 3.72, CH_2Cl_2).

4.8 Notes and Citations

(1) For excellent general reviews on the catalytic enantioselective generation of quaternary stereocenters, see: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363-5367. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591-4597. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388-401.

(2) For examples, see: (a) Maruoka, K. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 467-491. (b) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650-1667. (c) Hayashi, U. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S.; Jorgensen, K. A., Eds.; Wiley-VCH: New York, 2002; pp 5-56. (d) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 3, pp 1177-1235. (e) Ryu, D. U.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388-6390. (f) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10162-10163.

(3) For examples, see: (a) Donde, Y.; Overman, L. E. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 675-697. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945-2963. (c) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738-4739. (d) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5845-5848.

(4) For examples, see: (a) Pfaltz, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp 513-538. (b) Lydon, K. M.; McKervey, M. A. In *Comprehensive Asymmetric*

Catalysis; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp 539-580. (c) Charette, A. B.; Lebel, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp 581-603. (d) Doyle, M. P. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 191-228. (e) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 584-594.

(5) For examples, see: (a) Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62-63. (b) Bhattacharya, A.; Dolling, U.-H.; Grabowski, E. J. J.; Karady, S.; Ryan, K. M.; Weinstock, L. *Angew. Chem., Int. Ed.* **1986**, *25*, 476-477. (c) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187-2209.

(6) For examples, see: (a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985-3012. (b) Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 4050-4051. (c) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921-3924. (d) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368-13369. (e) Buono, G.; Chiodi, O.; Wills, M. *Synlett* **1999**, 377-388.

(7) For examples, see: (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861-2903. (b) Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2012-2014. (c) Watanabe, N.; Ogawa, T.; Ohtake, Y.; Ikegami, S.; Hashimoto, S. *Synlett* **1996**, 85-86. (d) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615-1621.

(8) (a) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; 593-649. (b) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H.,

Eds.; Springer: New York, 1999; Vol. 2, 833-884. (c) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203-214. (d) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1-14. (e) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422. (f) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355-364. (g) Trost, B. M. *J. Org Chem.* **2004**, *69*, 5813-5837.

(9) (a) Steinhagen, H.; Regglin, M.; Helmchen, G. *Angew. Chem., Int. Ed.* **1997**, *36*, 2108-2110. (b) Helmchen, G.; Steinhagen, H.; Reggelin, M.; Kudis, S. In *Selective Reactions of Metal-Activated Molecules*; Werner, H., Schreier, P., Eds.; Vieweg Verlag: Wiesbaden, 1998; 205-215.

(10) While palladium often produces the linear product, other transition metals tend to produce the more branched products in allylic allylation, see: (a) Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 17192-17193. (b) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104-1105. (c) Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141-144. (d) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581-5582. (e) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1995**, *34*, 462-464.

(11) Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113-120.

(12) (a) Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586-2592. (b) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236-3237. (c) Kuwano, R.; Uchida, K.; Ito, Y. *Org. Lett.* **2003**, *5*, 2177-2179.

(13) (a) Trost, B. M.; Schroeder, G .M.; Kristensen, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3492-3495. (b) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*,

6759-6760. (c) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879-7880.

(14) (a) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793-1796. (b) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199-3202.

(15) (a) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 4713-4714. (b) Tsuji, J.; Minami, I.; Shimizu, I. *Chem. Lett.* **1983**, 1325-1326.

(16) For examples of Tsuji enol-carbonate allylations in synthesis, see: (a) Ohmori, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 755-767. (b) Nicolaou, K. C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2482-2486. (c) Herrinton, P. M.; Klotz, K. L.; Hartley, W. M. *J. Org. Chem.* **1993**, *58*, 678-682.

(17) Treatment of allyl enol carbonate **274** with $Pd_2(dba)_3$ in 1,4-dioxane gave no reaction after 24 h.

(18) (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000,** *33*, 336-345. (b) Williams, J. M. J. *Synlett* **1996**, 705-710, and references therein. (c) Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiesse, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547-7583.

(19) THF also offered practical advantages of being easier to obtain pure and dry than 1,4-dioxane. THF also simplified the isolation of volatile ketones like **275**.

(20) ^{31}P NMR of (*S*)-*t*-Bu-PHOX oxide **295** shows a peak at 27.2 ppm in THF very similar to the peak seen at 27.7 ppm in THF for reactions when air has been introduced. Non-ligated (*S*)-*t*-Bu-PHOX has a ^{31}P resonance at -5.8 ppm in THF

while what we believe to be the active Pd complex is observed at 31.1 ppm during the reaction.

(21) As a result of our desire to generate a large variety of PHOX ligands, we adapted a procedure for C-P bond formation disclosed by Buchwald and coworkers for the synthesis of PHOX ligands. See experimental section for details. Gelman, D.; Jiang, L.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2315-2318.

(22) Synthesized in analogy to PHOX ligands prepared by Helmchen, see reference 18c.

(23) Wiese, B.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 5727-5730.

(24) Dawson, G.J.; Frost, C. G.; Martin C. J.; Williams, J. M.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 7793-7796.

(25) Smidt, S. P.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, *6*, 2023-2026.

(26) Subsequent to our report on the use of allyl enol carbonates in asymmetric allylation, a similar report appeared using a different catalyst system, see: Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846-2847.

(27) Goodwin, N. T. Application of iminium activation technologies to natural product synthesis: Total syntheses of the spiculisporic acids, progress towards the total synthesis of cylindrocyclophane F, and a formal synthesis of cylindrocyclophane A. Ph.D., California Institute of Technology, Pasadena, CA, July 2006.

(28) (a) The recrystallization of semicarbazone derivatives as a means to increase the ee of our products has proved to be of general use with the α-quaternary ketones and their derivatives. For an example, see: (b) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738-7739.

(29) Allyl fragment is disordered over two conformations in the solid state structure.

(30) While isomerically pure enol carbonates and silyl enol ethers were desired for substrate characterization and to maximize the yield of α-quaternary ketone, it should be noted that this is not required for the allylation reaction. The less substituted enolate precursors are cleanly transformed to 2,6-substituted ketones, which are typically readily removed by chromatography, and has no effect on the ee of the desired product.

(31) Sodium and potassium methoxide (1 equiv) could be used directly as silyl enol ether activators. However, lower yields (14% and 36%, respectively) and slightly lower ee (81% and 80%, respectively) were observed.

(32) For procedure, see: Liu, S.; Müller, J. F. K.; Neuburger, M.; Schaffner, S.; Zehnder, M. *J. Organomet. Chem.* **1997**, *549*, 283-293.

(33) Isomerically pure substrates are required only to achieve the highest yield possible of the desired α-quaternary compounds. The presence of the trisubstituted silyl enol ethers or allyl enol carbonates does not effect the ee of the α-quaternary product. The 2,6-substituted ketones generated from the trisubstituted impurity are typically easily removed by chromatography.

(34) Aliquots taken during the reaction of β-ketoester **358** at 30 °C in THF show the starting material reaches a maximum of 5% ee at 83% conversion for a K_{rel} of 1.1.

(35) Presumably this is the result of the cleavage of a C-C bond during decarboxylation, rather than C-O bond found in carbonates.

(36) For reviews, see: (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36-56. (b) Stecher, H.; Faber, K. *Synthesis* **1997**, 1-16. (c) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321-331. (d)

Pellissier, H. *Tetrahedron* **2003**, *59*, 8291-8327. For representative stereomutative examples, see: (d) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp. 833-884. (e) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968-5976.

(37) This hypothesis has been experimentally supported for non-enantioselective systems, see: (a) Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988-2995. (b) Detalle, J.-F.; Riahi, A.; Steinmetz, V.; Hénin, F.; Muzart, J. *J. Org. Chem.* **2004**, *69*, 6528-6532.

(38) For representative stereoablative examples, see: (a) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261-1268. (b) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420-2423. (c) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594-4595.

(39) This is an adaptation of a procedure by Tsuji and coworkers, see: (a) Tsuji, J.; Nisar, M.; Shimizu, I,; Minami, I. *Synthesis* **1984**, *12*, 1009. (b) Donnelly, D. M. X.; Finet, J.-P.; Rattigan, B. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1729-1735.

(40) This procedure is a modification of the acylation procedure reported in: Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425-5428.

(41) While only trace β-elimination was observed with this substrate, substrates with better leaving groups (e.g., OAc) predominantly underwent β-elimination to the α,β unsaturated compounds.

(42) Subsequent to our studies, others have used our method for the synthesis of other fluorinated substrates in related allylation reactions, see: (a) Nakamura, M.; Hajra,

A.; Endo, K.; Nakamura, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 7248-7251. (b) Burger, E. C.; Barron, B. R.; Tunge, J. A. *Synlett* **2006**, 2824-2826.

(43) Fluorinated compounds have gained frequent use in medicinal chemistry, see: (a) Zoute, L.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Org. Biomol. Chem.* **2003**, *1*, 1833-1834. (b) Nagai, K.; Davies, T. A.; Dewasse, B. E.; Jacobs, M. R.; Appelbaum, P. C. *J. Antimicrob. Chemother.* **2001**, *48*, 365-374.

(44) Recently thioesters substrates have been demonstrated in similar allylation reactions, see: Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109-3112.

(45) Boger, D. L. Key Ring Forming Reactions. *Modern Organic Synthesis: Lecture Notes*, TSRI Press: La Jolla, CA, 1999; pp 273-281.

(46) Recently a report of allylic alkylation for the synthesis of acyclic tertiary stereocenters using a different catalyst system has appeared, see: Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180-17181.

(47) Under our conditions we found that negligible racemization of phenyl ketone **423** was observed when allowed to remain under the reaction conditions for an additional 12 h.

(48) Yan, X.-X.; Liang, C.-G.; Zhang, Y.; Hong, W.; Cao, B.-X.; Dai, L.-X.; Hou, X.-L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6544-6546.

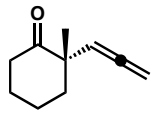
(49) Munoz-Muniz, O.; Quintanar-Audelo, M.; Juaristi, E. *J. Org. Chem.* **2003**, *68*, 1622-1625.

(50) Trimitsis, G.; Beers, S.; Ridella, J.; Carlon, M.; Cullin, D.; High, J.; Brutts, D. J. *Chem. Soc., Chem. Commun.* **1984**, 1088-1089.

(51) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348-11349.

(52) For examples of propargylation of similar enolates, see: (a) Matsuda, I.; Komori, K.; Itoh, K. *J. Am. Chem. Soc.* **2002**, *124*, 9072-9073. (b) Bienaymé, H. *Tetrahedron Lett.* **1994**, *35*, 7383-7386. (c) Bienaymé, H. *Tetrahedron Lett.* **1994**, *35*, 7387-7390.

(53) In addition to α-propargylated ketone **434**, small amounts of (*S*)-allene **xxxiii** are produced in 56% ee.



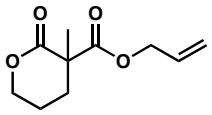
xxxiii

(54) The fine details of the reaction mechanism involving the origin of enantioselectivity are being studied computationally in collaboration with John Keith of the Goddard research group and will be reported in due course.

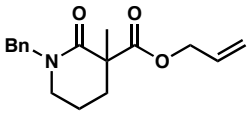
(55) Unusual patterns in enantioselectivity in a different asymmetric allylation system have led other researchers to consider enolate associated allylation mechanisms as well, see: (a) Reference 25. (b) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590-4591.

(56) Varying the concentration of Pd•PHOX gives a proportional decrease in reaction rate, suggesting the reaction is 1st order in Pd•PHOX. This supports the hypothesis that a single metal center is involved in the mechanism.

(57) Substrates which would possess highly basic enolate intermediates, such as lactone **xxxiv** and lactam **xxxv**, have been problematic as decarboxylation has proved difficult.

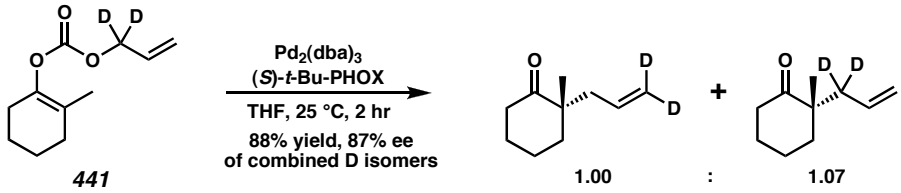


xxxiv



xxxv

(58) A separate reaction with dideuterio allyl enol carbonate **441** confirms that the allyl termini are scrambled during the course of the reaction.



441

(59) While the total ion counts are not rigorously quantitative, they clearly suggest that all four masses are present in nearly equal proportions. The slight excess of the 155 m/z ion is likely due to the natural abundance of ^{13}C present in the dideuterio product.

(60) PF_6^- counterions removed for clarity. Two out of four of the crystallographically unique Pd(allyl)PHOX complexes in the unit cell crystallized with a molecule of ethanol. The endo and exo allyl isomers were present in equal electron density and are modeled as a superposition of the two isomers.

(61) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. . *J. Org. Chem.* **1993**, *58*, 3568-3571.

(62) Laue, S.; Greiner, L.; Woelfinger, J.; Andreas, L. *Adv. Syn. Catal.* **2001**, *343*, 711-720.

(63) Neuville, L.; Chastanet, J.; Zhu, J. *Tetrahedron Lett.* **1999**, *40*, 7087-7090.

(64) Aboulhoda, S. J.; Henin, F.; Muzart, J.; Thorey, C. *Tetrahedron Lett.* **1995**, *36*, 4795-4796.

(65) (a) Yu, W.; Jin, Z. *Tetrahedron Lett.* **2001**, *42*, 369-372. (b) Duhamel, P.; Cahard, D.; Quesnel, Y.; Poirier, J.-M. *J. Org. Chem.* **1996**, *61*, 2232-2235. (c) Duhamel, P.; Cahard, D.; Poirier, J.-M. *Chem. Soc., Perkin Trans. 1* **1993**, 2509-2511.

(66) Slomczynska, U.; Kaminski, Z. J.; Leplawy, M. T. *Bull. Pol. Acad. Sci. Chem.* **1991**, *39*, 85-88.

(67) Dua, S.; Taylor, M. S.; Buntine, M. A.; Bowie, J. H.; *J. Chem. Soc. Perkin Trans. 2* **1997**, 1991-1997.

(68) House, H. O.; Roelofs, W. L.; Trost, B. M. *J. Org. Chem.* **1966**, *31*, 646-655.

(69) (a) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dungogues, J. *Tetrahedron* **1987**, *43*, 2075-2088. (b) Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, *36*, 2423-2426.

(70) Smith, A. B.; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765-8768.

(71) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783-3784.

(72) Buono, F.; Tenaglia, A. *J. Org. Chem.* **2000**, *65*, 3869-3874.