Chapter 1

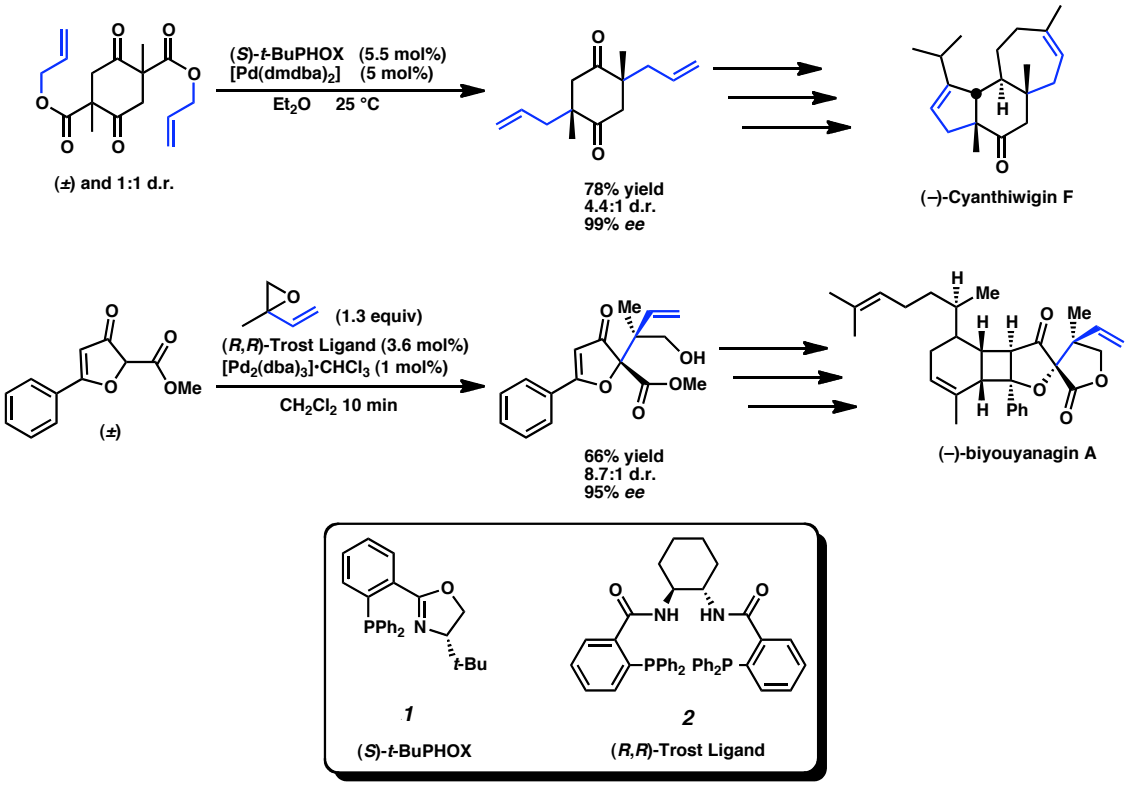
The History and Previous Investigations of Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of Ketone Enolates Using the PHOX Ligand Architecture

1.1 Introduction and Background

1.1.1 General Background

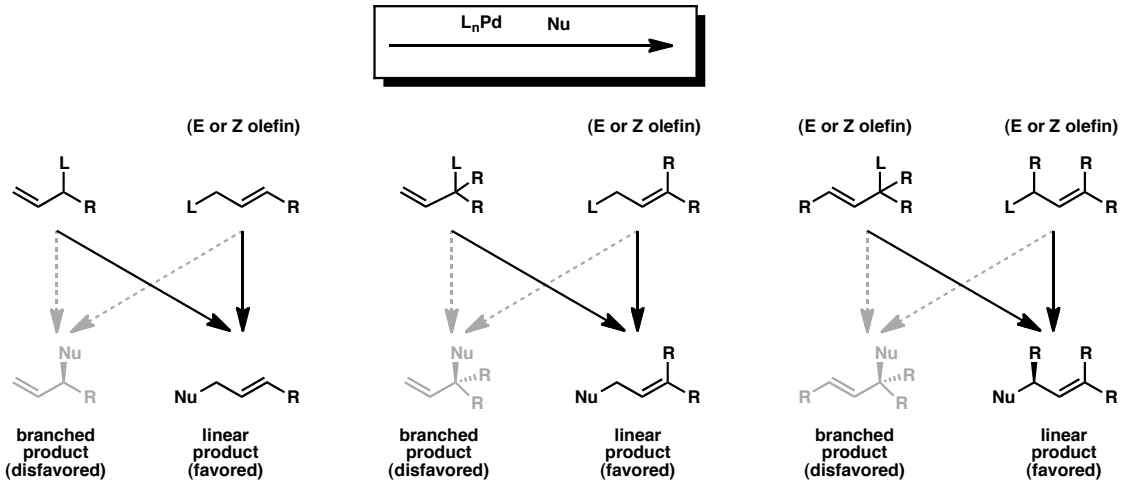
The asymmetric catalytic synthesis of all-carbon quaternary stereocenters remains an important challenge in chemical synthesis.[1] Continuous advancement in palladium-catalyzed asymmetric allylic alkylation chemistry has caused it to emerge as a particularly versatile solution among the few general classes of methodologies capable of rising to this challenge (Scheme 1.1 on page 2).[2] Initially, however, stereocontrol over carbon-carbon bond formation at highly substituted carbon centers in palladium-catalyzed asymmetric allylic alkylation was limited to the allyl fragment, and achiral nucleophiles were necessary in most implementations.[3,4]

Scheme 1.1. Asymmetric Allylic Alkylation Used for the Synthesis of Chiral Quaternary Carbons[5]

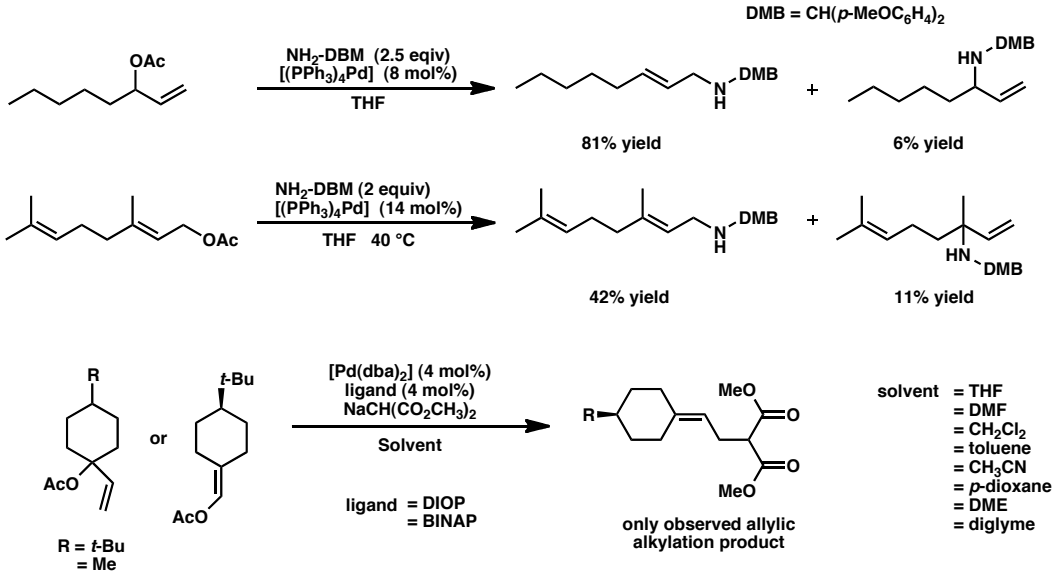


These early methodologies were generally limited to the formation of tertiary carbon stereocenters.[6] This is because palladium-catalyzed allylic alkylation has a strong preference for alkylating with the least-hindered terminus of a differentially substituted allyl electrophile (Scheme 1.2 on page 3 and Scheme 1.3 on page 3).[6] The preference of palladium for generating these linear instead of branched allylic alkylation products means that the formation of allylic quaternary centers is inherently disfavored whenever there is a less-substituted allyl terminus where alkylation can occur (Scheme 1.2, middle and right situations).

Scheme 1.2. Branched Versus Linear Allylic Alkylation Products Are Favored By Palladium Impeding the Generation of Allylic Quaternary Carbon Stereocenters.



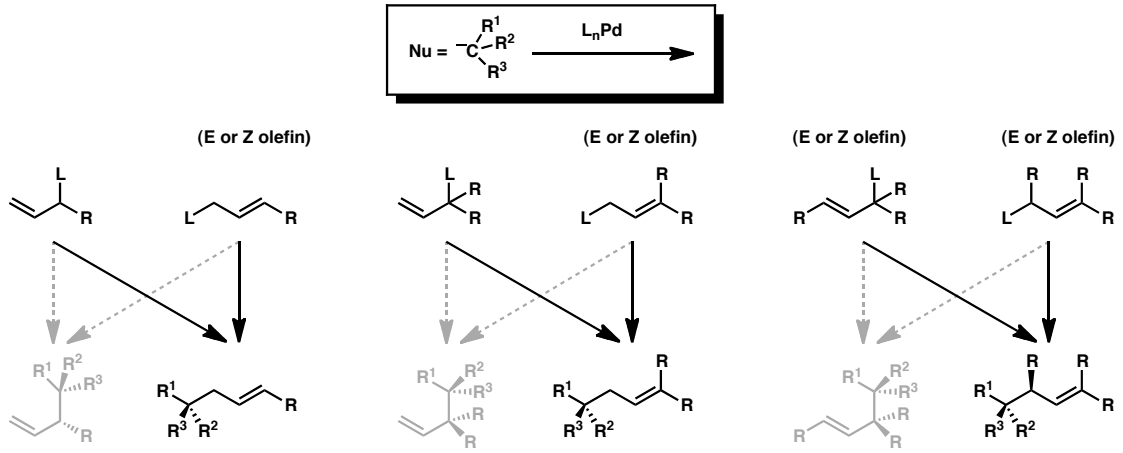
Scheme 1.3. Select Examples of Palladium Catalyzed Allylic Alkylation Product Distributions[7]



Subsequent developments in palladium-catalyzed asymmetric allylic alkylation by a number of groups allowed for the stereoselective generation of all-carbon quaternary stereocenters on the nucleophile for prochiral nucleophiles.[8,9] These systems benefit from the fact that the linear over branched alkylation product preference of palladium, does not effect or limit the formation of quaternary stereocenters on prochiral nucleophiles (Scheme 1.4 on page 4). Thus by using nucleophiles that possess only a single reactive

site, the formation of chiral all-carbon quaternary stereocenters can reliably be made by these methodologies.

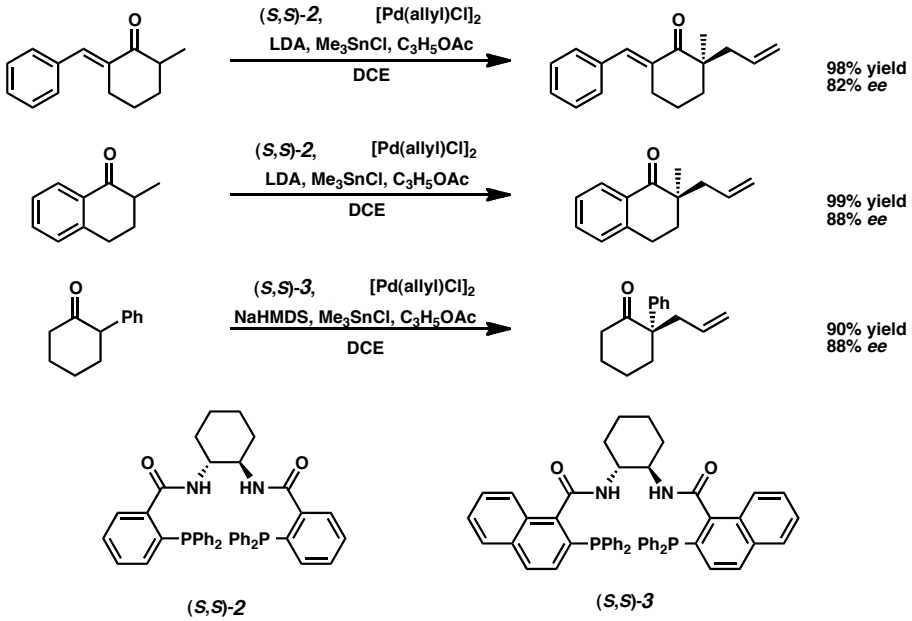
Scheme 1.4. The Linear Product Preference Found for Palladium-Catalyzed Asymmetric Allylic Alkylation Does Not Limit the Formation of Chiral Quaternary Carbon Stereocenters from Prochiral Nucleophiles.



While this development represents a key advancement in the synthesis of chiral all-carbon quaternary stereocenters, its early incarnations have some limitations. Most of these methodologies generate their carbon nucleophiles via stoichiometric deprotonation.[8,9] For many carbon nucleophiles, such as ketone enolates, this requires the stoichiometric addition of strong base, such as LDA, to the reaction (Scheme 1.5 on page 5).[9] Such harsh conditions can limit the functional group tolerance of these reactions. Successful substrates tend to be absent of functional groups that are sensitive to base, strong nucleophiles, or modest electrophiles. Also, because allylic alkylation occurs at any sufficiently nucleophilic site, it becomes necessary under such conditions to find means to prevent both ambiguous and multiple deprotonation events, as this would form alternate carbon nucleophiles prone to alkylation.[1b] As a result, the scope of the nucleophiles used in these earlier methodologies is generally limited by the need for the

intended site of allylic alkylation to be the most acidic by a number of pK_a units (Scheme 1.5).[1b]

Scheme 1.5. Trost's Initial Allylic Alkylation Methodologies for Prochiral Ketone Nucleophiles[9]

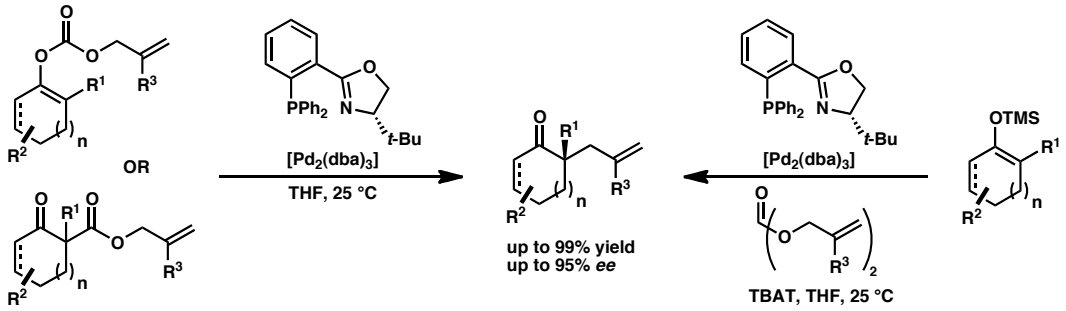


1.1.2 Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation

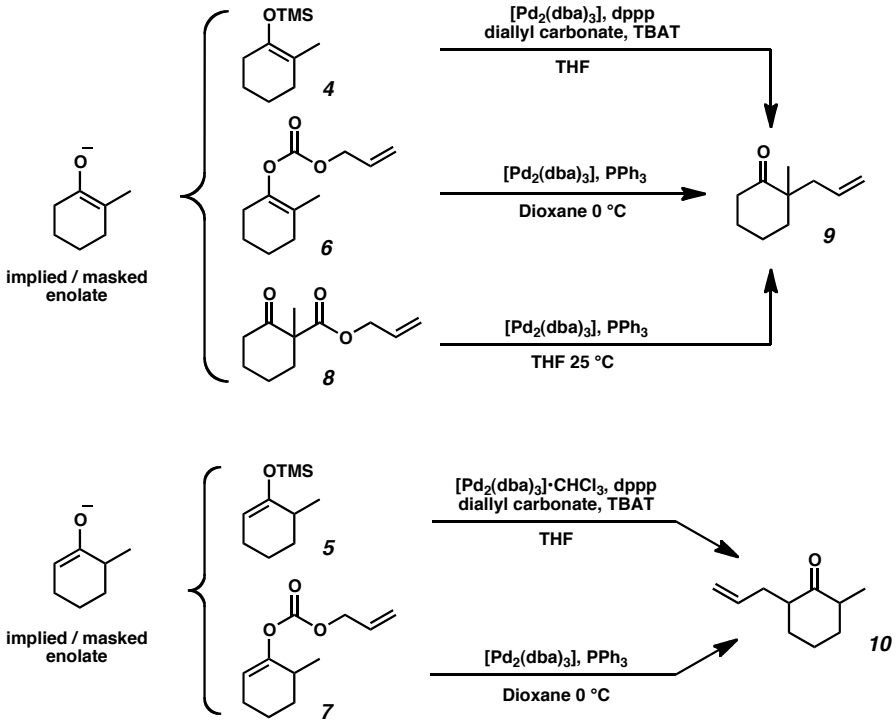
More recently, our group,[10] and independently others,[11] reported a series of mild base-free palladium-catalyzed decarboxylative allylic alkylation conditions for ketone enolate nucleophiles (Scheme 1.6 on page 6). These methodologies are effective for generating chiral tetrasubstituted carbons, including all-carbon quaternary stereocenters, in high yield and good *ee*. The decarboxylative conditions employed by these methodologies are regiospecific even for substrates possessing multiple sites of similar acidity to the one intended for alkylation. The success of these procedures relies on a few key enolate precursors as substrates: silyl enol ethers (**4** and **5**), allyl enol carbonates (**6** and **7**), and allyl β-ketoesters (**8**), which all function as masked ketone enolates and yield

the same allylic alkylation products (**9** and **10**) (Scheme 1.7 on page 6).[10,11,12] The use of these masked enolate substrates in palladium catalyzed allylic alkylation was pioneered by Tsuji *et al.*, who demonstrated the strict regioselectivity for alkylation at the enolate geometry implied in the corresponding masked enolate.[12]

Scheme 1.6. Base-Free Palladium-Catalyzed Decarboxylative Allylic Alkylation of Ketone Enolates



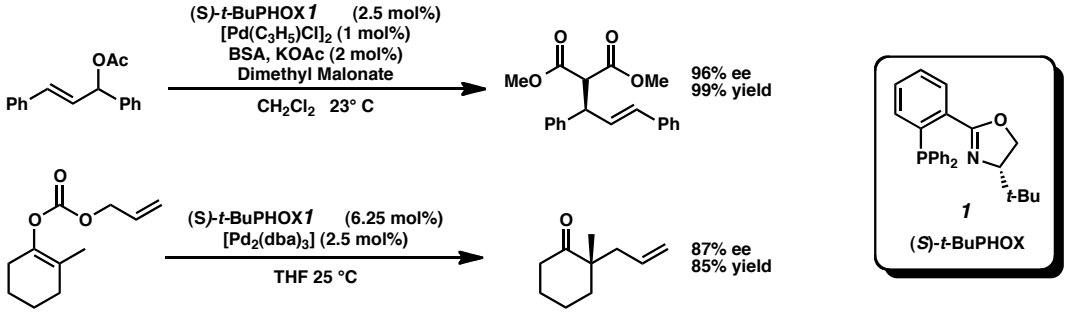
Scheme 1.7. Regioselective Preference in Tsuji's Allylic Alkylation Substrate Classes



Since its initial synthesis, the phophinooxazoline (PHOX) ligand architecture has proven highly effective for various palladium-catalyzed asymmetric allylic alkylation methodologies involving soft nucleophiles (Scheme 1.8, top reaction, on page 7).[13] Our

initial system optimizations revealed that (*S*)-*t*-BuPHOX **1** was also an optimal ligand for effecting an asymmetric variant of the Tsuji alkylation while maintaining the mild conditions and regiospecificity found in Tsuji's original methodologies (Scheme 1.8, bottom reaction).[10b] Subsequent to our initial reports, (*S*)-*t*-BuPHOX **1** has also found use in a few highly related decarboxylative asymmetric allylic alkylation systems.[11a,f,14]

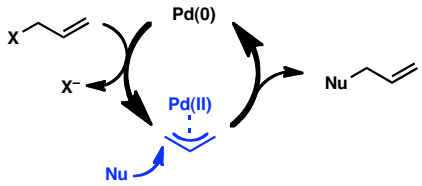
Scheme 1.8. Palladium-Catalyzed Allylic Alkylation and the PHOX Ligand Architecture



1.2 A Question of Mechanism

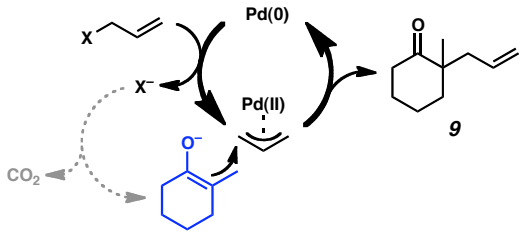
The mechanism of palladium-catalyzed asymmetric allylic alkylation of soft nucleophiles, defined as nucleophiles with a $pK_a < 20$,[4,15] has been the subject of significant investigation, and is now well understood.[4,15,16] The consensus of these studies is that bond forming occurs when soft nucleophiles attack directly at a π-allyl ligand of a palladium complex (Scheme 1.9 on page 8). This S_N2-like reaction is generally referred to as an outer-sphere allylic alkylation mechanism. Helmchen conducted some of the most pivotal of these seminal mechanistic studies on the PHOX ligand framework. It is thus accepted that outer-sphere allylic alkylation with soft nucleophiles is the standard allylic alkylation mechanism found for PHOX-ligand-based palladium catalysts.[17]

Scheme 1.9. General Outer-Sphere Mechanism for Palladium-Catalyzed Allylic Alkylation of Soft Nucleophiles



For the allylic alkylation of unstabilized ketone enolates, an outer-sphere mechanism would imply the formation of a free enolate species at least transiently during the course of the reaction (Scheme 1.10 on page 8). Mindful of the literature precedent concluding that palladium-catalyzed allylic alkylation functions by an outer-sphere mechanism, both in general and on the PHOX ligand framework, the initial supposition was that a free enolate was active in our allylic alkylation system. Subsequent to our initial publication, however, an increasingly large range of reaction conditions and substrate functional group diversity was explored.[10a,18,19] In doing so it has become apparent that our methodology is surprisingly robust in light of a putative free enolate intermediate.

Scheme 1.10. An Outer-Sphere Allylic Alkylation of Ketone Enolates Implies a Free Enolate.



Substrates have been synthesized that present functionality with additional acidic sites or that serve as electrophiles potentially sensitive to free unstabilized ketone enolates, including: enones (**11** and **12**), nitriles (**13**), esters (**11** and **14**), and even unprotected aldehydes (**15**) (Scheme 1.11 on page 9).[10b,19] Notably, all these substrates readily undergo palladium-catalyzed decarboxylative asymmetric allylic alkylation with

no more then the occasional trace of side products under our conditions. Even the addition of up to 33.3 equivalents of water to the reaction failed to quench the putative enolate intermediate and only modestly reduced the yield of allylic alkylation product (Table 1.1 on page 9).[18] While some of the more challenging asymmetric allylic alkylation substrates we attempted produced alkylation products in modest or low *ee*, extremely few substrates were found to produce any side products or to significantly perturb allylic alkylation. Together these results raised serious questions about the possibility of a free enolate intermediate and thus the nature of the mechanism itself.

Scheme 1.11. The Success of Potentially Enolate Sensitive Substrates[10b,19]

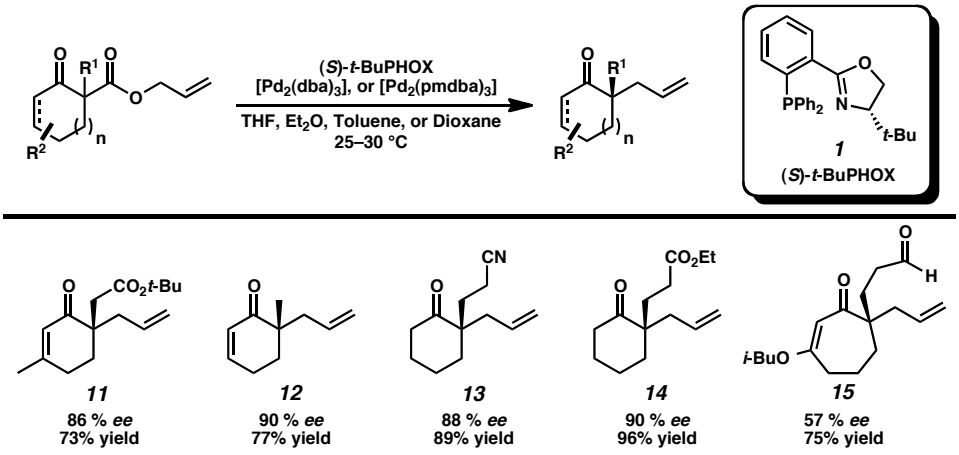
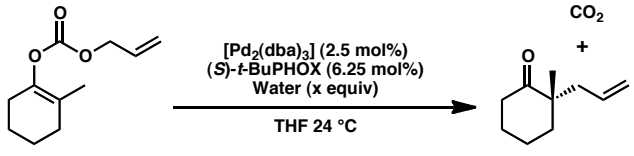


Table 1.1. The Effects of Water on Decarboxylative Asymmetric Allylic Alkylation



Water (equiv)	Yield[a]	ee[b]
0	99.9%	88.5%
0.55	99.6%	86.7%
1.6	88.1%	83.8%
8.3	70.3%	60.9%
17	66.8%	48.8%
33	67.9%	40.5%

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

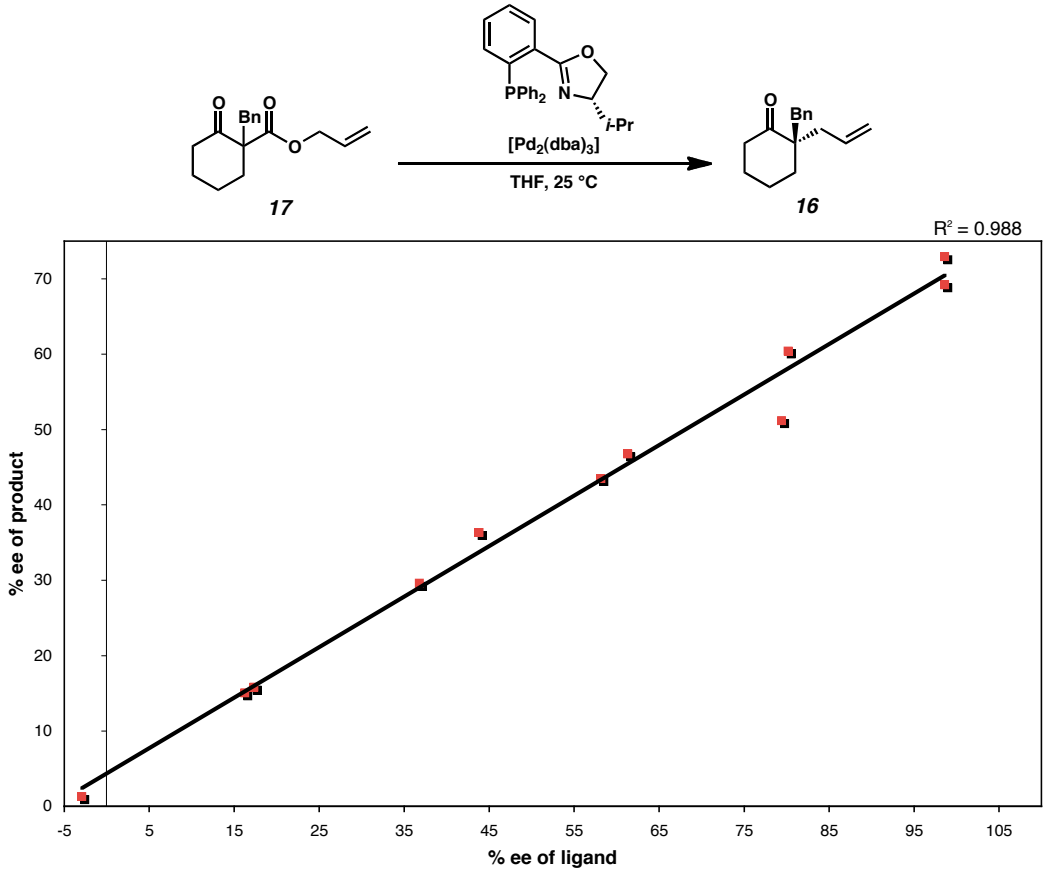
1.3 Initial Mechanistic Investigation

We began our mechanistic investigation by determining the molecularity of the active catalyst in the reaction as starting point from which to direct the design of subsequent experiments. The enantioinduction imparted by our catalyst system was high enough to make it a good candidate for performing a nonlinear effect study to determine active catalyst molecularity as pioneered by Kagan.[20] By plotting the *ee* of the alkylation product formed versus the *ee* of the source of enantioinduction used in the reaction, the linearity of the dependence between the two can be determined. A positive or negative nonlinear dependency requires that the source of enantioinduction must aggregate under reaction conditions while a linear correlation implies a reaction mechanism that is likely devoid of such aggregation.

To this end, the dependency of the *ee* of ketone **16**, produced via the palladium-catalyzed decarboxylative allylic alkylation of racemic allyl β-ketoester **17**, was plotted against the *ee* of isopropyl PHOX ligand used in the reaction (Figure 1.1 on page 11).[21] The resulting linear dependency is strongly suggestive of no PHOX ligand aggregation under reaction conditions. This implies the exclusion of a number of mechanistic possibilities. First, it is likely that only one PHOX ligand binds to palladium under the reaction conditions as opposed to bis-PHOX-ligated palladium species, which have been reported.[22] Second, the linear dependence suggests that there are no PHOX ligated palladium-catalyst aggregates in solution either as catalytically active species or as unproductive catalyst resting states. Third, the linear dependence suggests that the step

or steps related to enantioinduction and bond forming in the mechanism involve only a single palladium species.

Figure 1.1. Nonlinear Effect Study of Palladium-Catalyzed Decarboxylative Allylic Alkylation

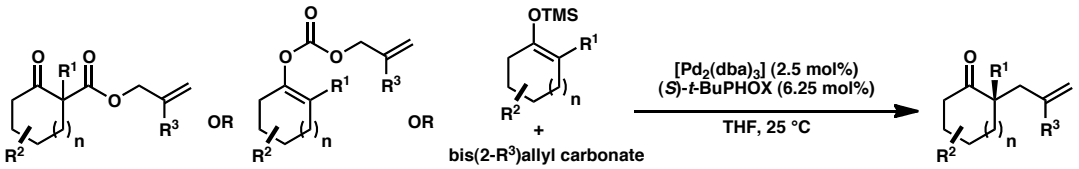


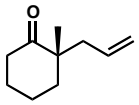
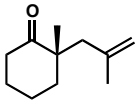
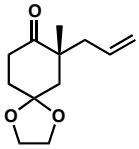
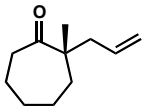
The *ee* of the *i*-PrPHOX ligand (X-axis) was varied by mixing freshly prepared stock solutions of enantiopure (*S*) and (*R*) *i*-PrPHOX ligand prior to each experiment and the mixture ratio confirmed by chiral HPLC. The product of each reaction was isolated and purified before obtaining *ee* (Y-axis) via HPLC.

The nonlinear effects studies were supported with traditional reaction kinetics studies. Kinetics studies of the decarboxylative allylic alkylation of allyl enol carbonate **XX** and allyl β-ketoester **XX** to form tetralone **23** determined that both the allyl enol carbonate and β-ketoester reactions were first order in catalyst and zero order in substrate (Figure 1.2 on page 13).[23] Notably all three substrate classes give allylic alkylation products in similar yields and practically identical *ee* (Table 1.2 on page 12).[10] This is

strongly suggestive of a single underlying mechanism that must converge at or before the formation of the ketone enolate intermediate (Scheme 1.12 on page 14). Together these results favor a universal mechanism involving a single monomeric PHOX palladium species for each step of both the productive catalytic cycle as well as any unproductive catalyst resting states that might exist.

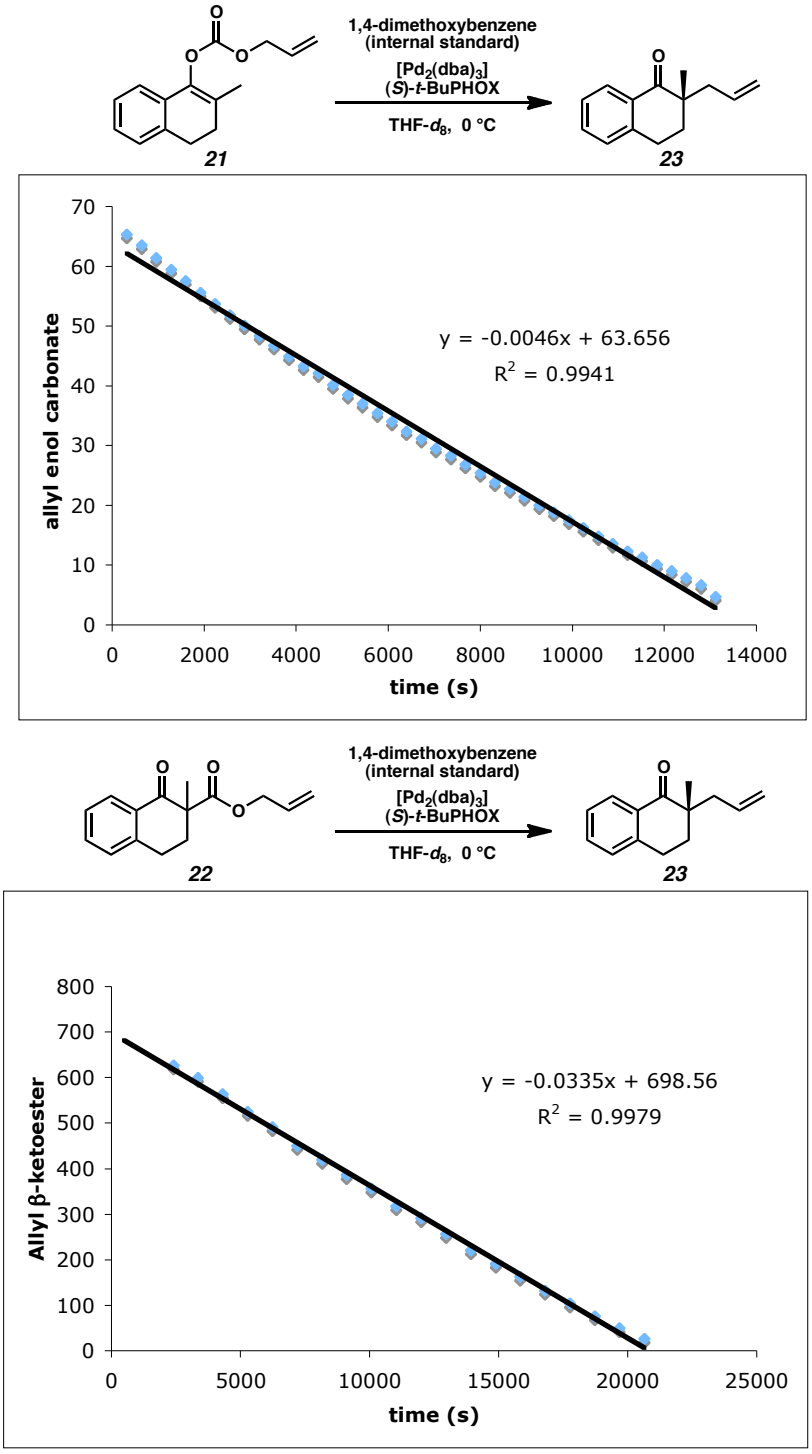
Table 1.2. Consistent Results Across All Three Substrate Classes[10]



		allyl β-ketoester		*allyl enol carbonate*		*silyl enol ether*	
Product		**yield[a]**	**ee[b]**	**yield[a]**	**ee[b]**	**yield[a]**	**ee[b]**
	***9***	85	88	85	87	95	87
	***18***	87	92	89	92	79	91
	***19***	94	85	87	86	99	81
	***20***	83	87	81	87	94	86

[a] Isolated yield (%) from reactions with 1 mmol of substrate. [b] Measured by chiral GC or HPLC

Figure 1.2. Kinetics Studies Show Zero-Order Dependence on Substrate



Reactions were performed in an NMR tube on an 0.05 mm scale and monitored by ^{1}H NMR. Substrate concentration (Y-axis) is in arbitrary integration units relative to an internal standard consisting of 0.0175 mmol (35 mol%) 1,4-dimethoxybenzene.

With this knowledge in hand we turned to DFT to simulate the reaction of free enolate **24** with a single PHOX palladium π-allyl species **25**.[23,24] Via DFT a traditional outer-sphere allylic alkylation path was identified favoring nucleophilic attack at the π-allyl terminus *trans* to phosphorous. This is in perfect accordance with previous mechanistic studies for palladium-catalyzed asymmetric allylic alkylation using the PHOX ligand architecture (Figure 1.3 on page 15).[17] However, DFT simulation also predicted that this outer-sphere attack has practically no energy difference between the two facial approaches of the enolate nucleophile. If so, such an outer-sphere mechanism should result in near racemic allylic alkylation product.[24] The inconsistency of this simulated mechanism versus the experimentally observed results was highly unsatisfactory.

Scheme 1.12. Consistent Product Yield and Enantioinduction Implies a Common Mechanism.

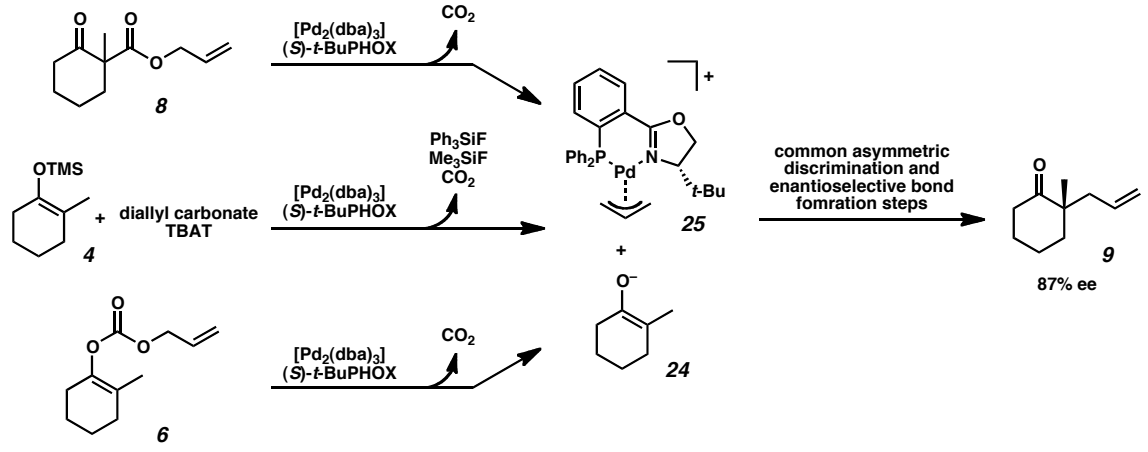
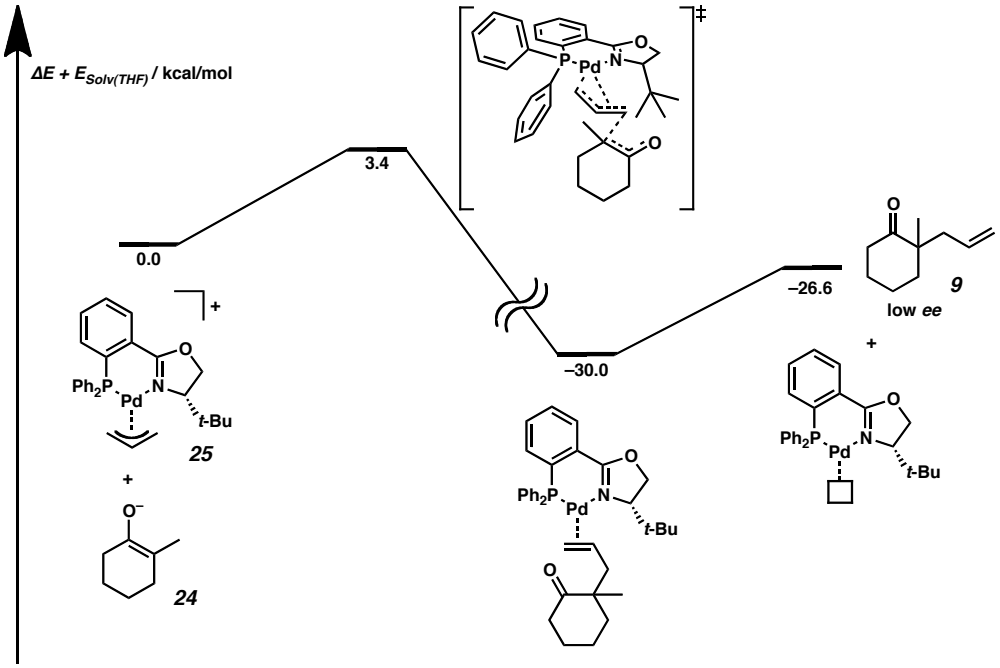


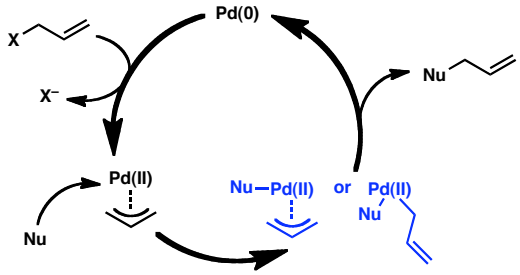
*Figure 1.3. Results of DFT Simulation for Outer-Sphere Allylic Alkylation Starting with **24** and **25***



Literature precedent for the palladium-catalyzed allylic alkylation of hard nucleophiles suggests that they can proceed via an inner-sphere mechanism, whereby nucleophilic attack occurs at the metal center and subsequent bond forming occurs by a reductive elimination process (Scheme 1.13 on page 16).[4,15] Noting this, we sought to use DFT to investigate an alternate inner-sphere alkylation pathway. DFT placed the energy of the ion-paired free enolate **24** and palladium π-allyl cation **25** as roughly isoenergetic to palladium π-allyl complex **26** with the enolate apically bound (Figure 1.4 on page 17). From complex **26** It was determined that an internal rearrangement involving the isomerization of the allyl ligand from an η-3 to an η-1 binding mode in conjunction with the collapse of the apical enolate ligand into the square plane could form palladium allyl enolate **27**. This internal rearrangement was computed to have a kinetic barrier 1.9 kcal/mole smaller then the outer-sphere allylic alkylation process

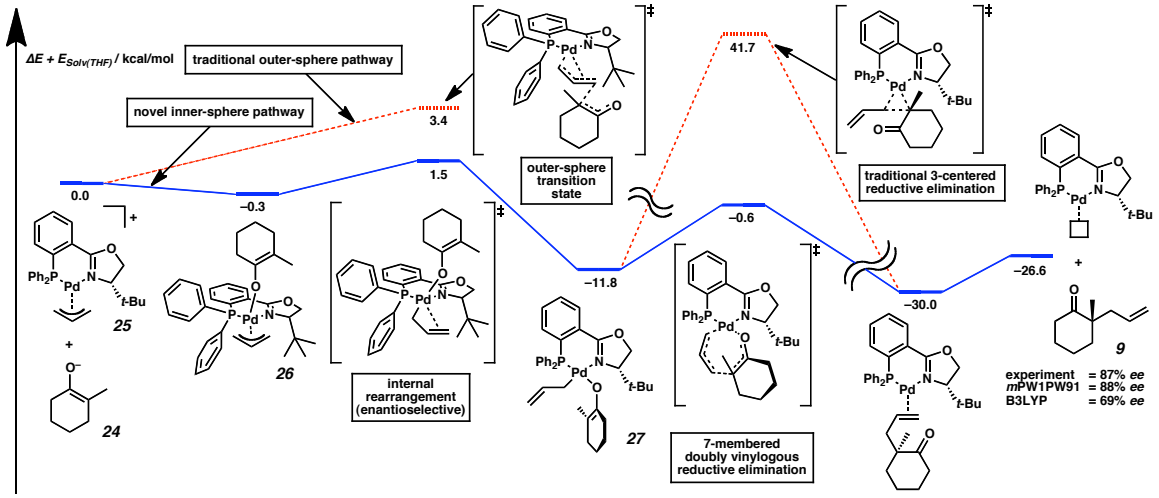
making the internal rearrangement the more kinetically favorable of the two processes.[24,25]

Scheme 1.13. Generalized Inner-Sphere Mechanism for Palladium-Catalyzed Allylic Alkylation



O- to C-bond rearrangement of the enolate ligand from palladium allyl enolate **27** followed by a traditional 3-centered reductive elimination was calculated to have a prohibitively high kinetic barrier.[23,24,26] However, a 7-centered doubly vinylogous reductive elimination directly from palladium allyl enolate **27** was determined to have a small kinetic barrier and thus be a viable mechanism for the production of ketone **9**. Previous calculation work[27] and subsequent experimentation[28] by others has demonstrated the feasibility and facile nature of highly related all-carbon 7-centered doubly vinylogous reductive eliminations from palladium to form carbon-carbon bonds. One particularly relevant example, the palladium-catalyzed allyl-allyl coupling of allylic carbonates and allylic boronic esters, has been achieved asymmetrically yielding products in high *ee*.[28a] Subsequent calculations of orbital contribution and symmetry with all-carbon doubly vinylogous reductive eliminations from palladium have concluded that these are true pericyclic concerted reactions remarkably similar to the homo-Cope rearrangement but with a significantly smaller kinetic barrier.[29]

*Figure 1.4 Results of DFT Simulation for Inner-Sphere Allylic Alkylation Starting with **24** and **25***

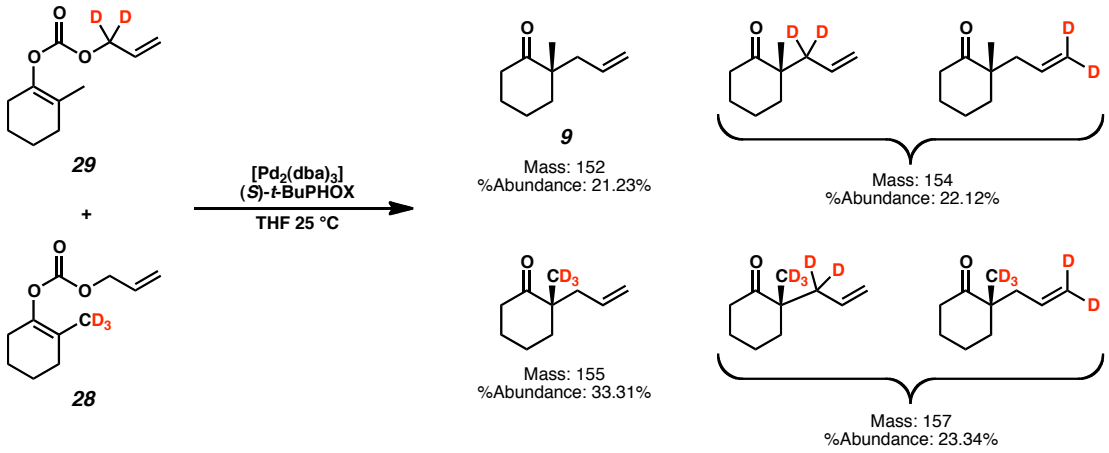


Notably DFT simulations found that the internal rearrangement from π-allyl palladium complex **26** to palladium allyl enolate **27** is enantioselective. The pro-*S* rearrangement that eventually gives rise to the experimentally observed enantiomer of product was calculated to be lower in energy then the pro-R rearrangement by 1.0 kcal/mol using the B3LYP basis set.[24] It was determined that most of the energy difference between the pro-*S* and pro-*R* rearrangements is due to the effects of chiral steric clashes manifested via intermolecular van der Waals interactions. To this effect, calculations on these internal rearrangements were also performed with the *m*PW1PW91 functional, a hybrid DFT method considered better suited for accurately computing van der Waals interactions. The energy difference between the kinetic barriers for the pro-*S* and pro-*R* internal rearrangements arrived at by *m*PW1PW91 was 1.6 kcal/mol, predicting product formation in roughly 88% *ee* at room temperature in excellent agreement with the experimentally observed results.

In search of experimental confirmation for an inner-sphere allylic alkylation mechanism we looked to a series of crossover experiments. Two different deuterium-

labeled forms of allyl enol carbonate **6** were synthesized, one with deuteration on the latent enolate fragment (**28**) and the other with deuteration on the allyl portion of the molecule (**29**) (Scheme 1.14 on page 18).[10a] Performing a series of reactions with a one-to-one mixture of allyl enol carbonates **28** and **29** produced a statistical mixture of all six possible products, including those formed from allyl termini scrambling.[10a] These results are a clear indication of complete crossover, seemingly indicating an outer-sphere mechanism.

Scheme 1.14. Original Crossover Experiment



Together these early mechanistic investigations painted a perplexing picture. The crossover experiments and literature precedence suggested an outer-sphere mechanism. However, DFT simulation, and the remarkable water and functional group tolerance of the reaction suggested an inner-sphere mechanism. A thorough follow-up study became necessary to reconcile these seemingly contradictory findings and to construct a complete and unifying mechanistic theory.

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(1) For reviews on the asymmetric catalytic synthesis of all-carbon quaternary stereocenters, see: (a) Trost, B. M.; Jiang, C.; *Synthesis* **2006**, *3*, 369–396. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363–5367. (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*,

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