

Transition Metal-Catalyzed Decarboxylative Allylation and Benzylation Reactions

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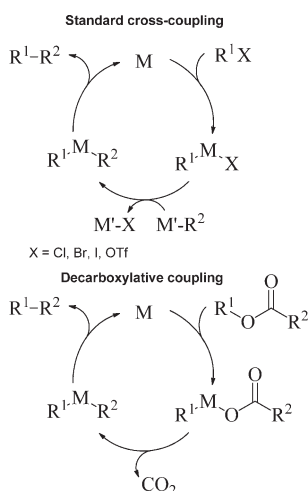
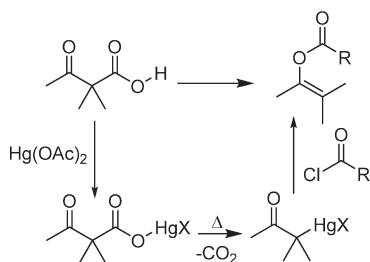
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1. INTRODUCTION TO DECARBOXYLATIVE COUPLING

Catalytic cross-coupling reactions have had a profound impact on the synthesis of pharmaceuticals, biologically active natural products, and materials.¹ Such reactions typically involve the oxidative addition of an aryl or alkyl halide to a low-valent metal, followed by transmetalation and reductive elimination of the desired product (Scheme 1).² The transmetalation steps in cross-coupling reactions often use relatively expensive, toxic, or highly basic reagents that must be prepared from other functional precursors. In addition, the reagents required for transmetalation necessarily produce stoichiometric quantities of hazardous by-products that can complicate product purification. With this in mind, it has been recognized that it is highly desirable to develop new strategies for the generation of organometallic intermediates that utilize inexpensive substrates, proceed under mild conditions, and are environmentally benign. One such strategy is decarboxylative coupling. Decarboxylative coupling reactions utilize decarboxylative metalation to generate organometallic intermediates that are coupled via reductive elimination (Scheme 1). As compared to traditional cross-coupling methods, decarboxylative coupling has several potential advantages: (i) carboxylic acid derivatives are ubiquitous and inexpensive reactants; (ii) decarboxylation can drive the formation of reactive intermediates under neutral conditions; and (iii) the only

Scheme 1. Standard Cross-Coupling Versus Decarboxylative Coupling**Scheme 2. Formation of Mercury Enolate via Decarboxylation**

stoichiometric byproduct is CO_2 , which is nonflammable, non-toxic, and easily removed from the reaction medium. Moreover, decarboxylation allows the site-specific generation and coupling of reactive intermediates, in contrast to reactions that generate reactive intermediates by C–H activation, where regioselective formation of specific intermediates can be difficult.³

In this review, we will focus on discussion of homogeneous catalysis of decarboxylative allylation and benzylation reactions, a subject that highlights the breadth of nucleophilic species that can be generated by decarboxylation. In addition, studies of decarboxylative allylations have shown that there are several mechanisms for decarboxylative coupling that do not necessarily follow the simplified rubric shown in Scheme 1. While several accounts have been published on this topic in the last several years,⁴ none has done so in the comprehensive manner of this review, which covers relevant publications through August 2010.

2. DECARBOXYLATIVE ALLYLATION OF ENOLATES

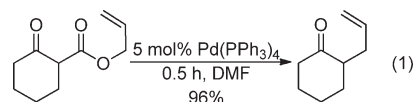
2.1. Introduction to Decarboxylative Allylation

The Tsuji–Trost reaction is a reaction that has garnered much attention because of its ability to couple allyl electrophiles with nucleophiles in a chemo-, regio-, and stereoselective fashion.^{5,6} In a typical Tsuji–Trost reaction, an allyl acetate or carbonate

reacts with a palladium catalyst by displacement of the leaving group to give a π -allyl palladium intermediate that can undergo substitution by a nucleophile. Frequently, the nucleophiles have been limited to “soft” nucleophiles, like malonates, whose corresponding $\text{p}K_{\text{a}}$'s are <20 . However, successful allylation of monostabilized enolates has been achieved using preformed tin,⁷ boron,⁸ magnesium,⁹ and lithium enolates,¹⁰ as well as silyl enol ethers.¹¹ While these methods have demonstrated the ability to form a new carbon–carbon bond selectively, they all suffer from the need to make a preformed organometallic, which typically requires subjecting the substrate to highly basic conditions and results in a stoichiometric amount of metal salt waste. An ideal alternative synthesis would be one in which the same reaction can be accomplished yet produces only easily removed waste and does not require preformed nucleophiles, thus allowing a greater synthetic efficiency. Such a strategy requires an alternative method for the in situ generation of enolates. This review will focus on synthetic strategies that involve the direct generation of enolates and other nucleophiles via decarboxylation. Indeed, the in situ generation of nucleophiles via decarboxylation distinguishes decarboxylative allylation (DcA) reactions as an important subset of Tsuji–Trost reactions.

In 1950, Nesmeyanov et al. showed that metal enolates can be readily accessed under neutral conditions and without additives by the decarboxylation of metal β -ketocarboxylates (Scheme 2).¹² Although Nesmeyanov utilized this decarboxylative metalation in stoichiometric transformations, he set the stage for later catalytic transformations. In the early 1960s, divalent metals like Ni(II) and Mn(II) were shown to decarboxylate malonic acids and were proposed to form intermediate metal enolates.¹³ Although the knowledge of these transformations was applied to understanding enzymatic decarboxylations, the synthetic potential of the intermediates was not realized.

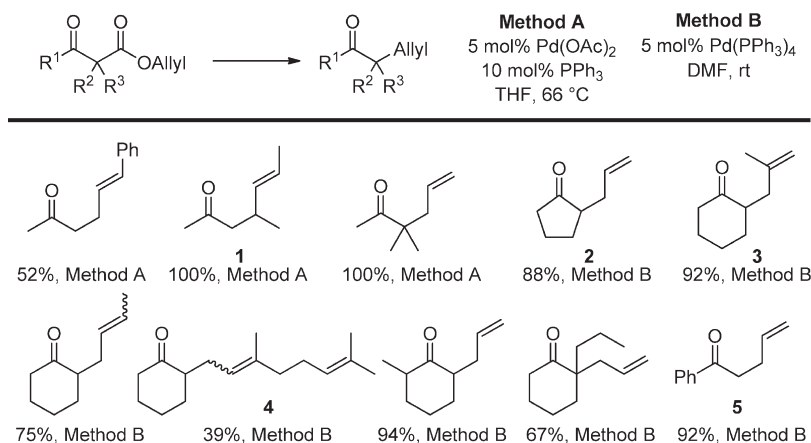
Then in 1980, Tsuji and co-workers¹⁴ and Saegusa and co-workers¹⁵ almost simultaneously reported the decarboxylative allylation of β -keto allyl esters (eq 1). In this method, the loss of CO_2 replaces the need to selectively prepare preformed enolate equivalents. A further potential benefit of the decarboxylative allylation (DcA) is the ability to generate both nucleophile and electrophile in situ. Thus, greater functional group compatibility can be expected since the high-energy intermediates are formed in catalytic concentration and the pH is formally neutral. Consequently, decarboxylative allylation is a valuable addition to the toolbox of the organic chemist. In the following section of the review, we cover the developments for which chemical lineage can be traced back to these seminal works.



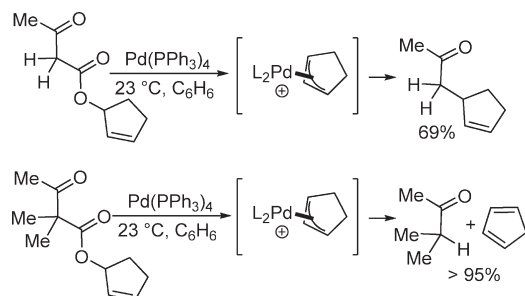
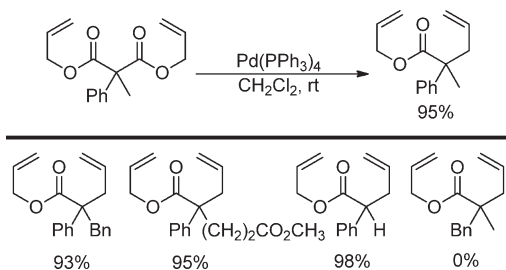
2.1.1. Decarboxylative Allylation: Scope and Chemoselectivity.

In the first disclosure of a decarboxylative allylation (DcA) reaction by Tsuji and co-workers,¹⁴ allyl esters of acetoacetic acid were subjected to a catalytic amount of $\text{Pd}(\text{OAc})_2$ and PPh_3 (method A, Chart 1), providing γ,δ -unsaturated methyl ketones in high yield. Alternatively, Saegusa and co-workers demonstrated that a variety of acyclic and cyclic ketoenolates would undergo decarboxylative coupling using 5 mol % $\text{Pd}(\text{PPh}_3)_4$ as the catalyst (method B, Chart 1).¹⁵ While these

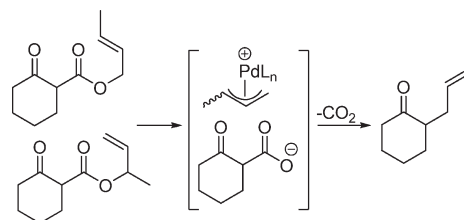
Chart 1. Tsuji–Saegusa Decarboxylative Allylation



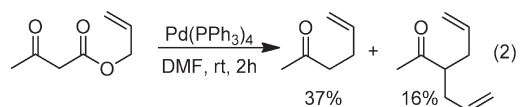
Scheme 3. Effect of Substitution on Allylation Versus Elimination

Chart 2. DcA of α -Phenyl Diallyl Malonates

reports did not detail the functional group compatibility of decarboxylative allylation (DcA) reactions, they did demonstrate that the reaction could tolerate β -hydrogens on the allyl fragment; however, the yield is significantly reduced when the product is derived from the geranyl ester (4, Chart 1). This illustrates a common challenge in decarboxylative allylation: *substitution and elimination are often competitive*. A recent report illustrates that substitution is favored when the α -position of the β -ketoester is unsubstituted while elimination is favored when the α -position is substituted (Scheme 3).¹⁶ This may reflect different mechanisms of allylation for the two substrates as discussed *vide infra*.

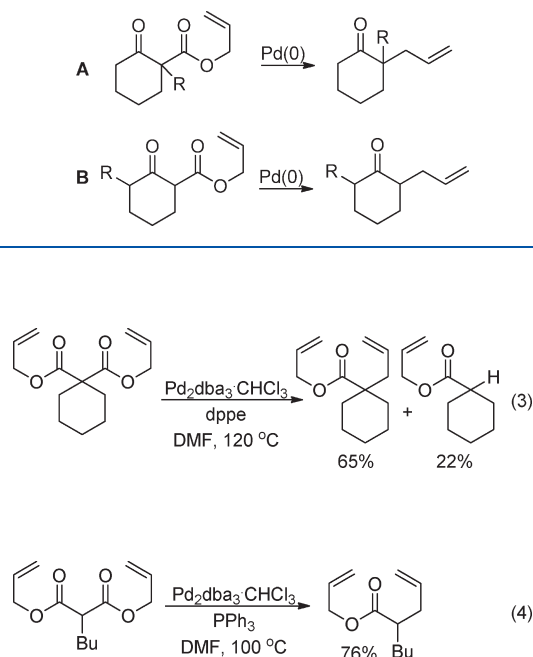
Scheme 4. Regioconvergent DcA: Evidence for Pd- π -Allyl Intermediates

While β -ketoester substrates that contain an α -hydrogen are less prone to competing elimination, they do suffer from competing diallylation. For example, allyl acetoacetate undergoes decarboxylative coupling to give a poor yield of the desired monoallylation product due to competing diallylation (eq 2). The diallylation can be thought to result from a combination of Tsuji–Trost allylation of the ketoester followed by decarboxylative allylation. The problematic diallylation is reduced when the substrate is an aryl or cyclic ketone (2, 3, 5, Chart 1). Alternatively, diallylation can also be mitigated by additional substitution on the allyl electrophile (1, Chart 1).



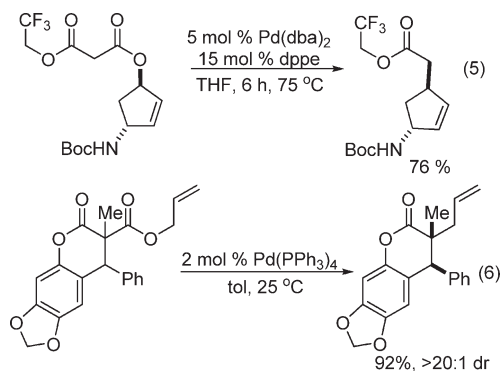
2.1.2. Ester Enolates. Tsuji and co-workers showed that it was also possible to perform the decarboxylative allylation of malonate derivatives (eq 3);¹⁷ however, the reactions were much slower than their ketone counterparts and required heating at or above 100 °C. In doing so, Tsuji and co-workers also reported the concomitant formation of a byproduct resulting from protonation of the ester enolate; such protonation products are commonly observed byproducts of DcA reactions. Finally, the researchers found that the DcA of α -monoalkylated substrates worked similarly to that of the α,α -dialkyl derivative; however, it took place at slightly lower temperature (eq 4).

Scheme 5. Regiospecific DcA



More recently, Ohta and co-workers investigated the DcA reactions of α -aryl malonic acid derivatives (Chart 2).¹⁸ Unlike in Tsuji's report,¹⁷ the DcA of α -phenyl substituted malonic ester derivatives took place readily at room temperature. This highlights the dependence of the rate of DcA reactions on the stability of the incipient enolate; making the enolate benzylic lowers its pK_a by ca. 6–7 pK_a units, allowing facile decarboxylation. Such observations also suggest that decarboxylation is the rate-limiting step in the DcA of allyl malonic esters. The authors further reported that both monodentate and bidentate phosphine ligands worked well for catalysis; however, no reaction was observed with more electron-deficient phosphite ligands.

In their synthesis of precursors to carbocyclic nucleoside analogues, Miller showed that allyl trifluoroethyl malonic esters undergo facile decarboxylative allylation even when the α -carbon is not benzylic (eq 5).¹⁹ Similarly, Tunge and co-workers showed that aryl esters undergo decarboxylative allylation under mild conditions (eq 6).¹⁶ Once again, the favorable reaction of these substrates can be attributed to the more facile formation of the enolates of these esters, which are less basic than those of alkyl malonates.



2.1.3. Regioselectivity of Addition to the Allyl Electrophile. Like other related palladium-catalyzed Tsuji–Trost

Chart 3. Hexadiene Synthesis via DcA

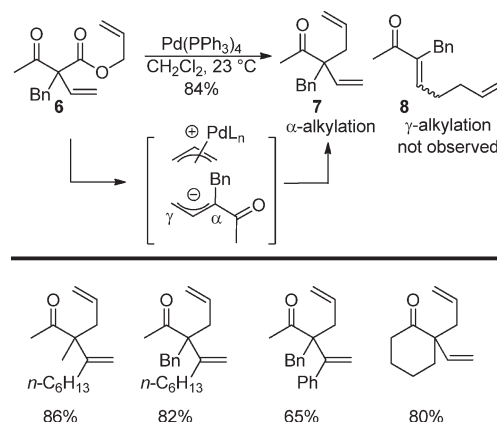
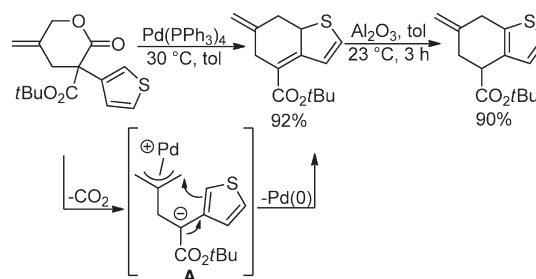
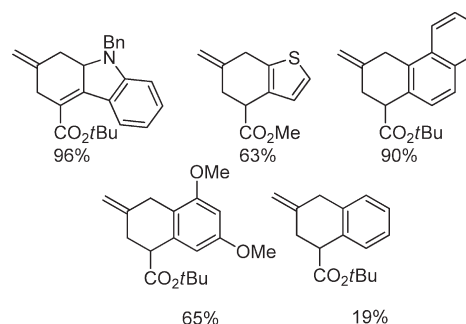
Scheme 6. Kinetic γ -Allylation of Valerolactones

Chart 4. Decarboxylative Cyclization of Valerolactones

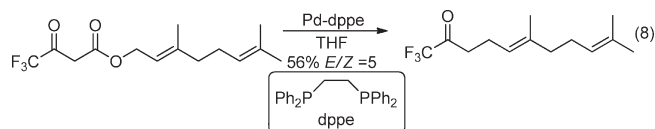
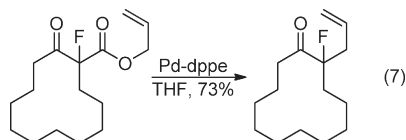


reactions, decarboxylative allylation (DcA) is regioselective, typically affording the linear product as the major regioisomer regardless of the regiochemistry of the reactant (Chart 1). This is easily understood if the reaction proceeds through a common Pd- π -allyl intermediate that reacts selectively with nucleophiles at the less-hindered allyl terminus (Scheme 4).

A significant advantage of a decarboxylative method over more traditional deprotonation and electrophilic trapping of ketone enolates is the ability to regioselectively generate enolates. Decarboxylation allows the site-specific generation of an enolate at the α -position that bears the CO_2 (Scheme 5). Importantly, the nucleophile that is kinetically formed by decarboxylation does not isomerize to the more thermodynamically stable

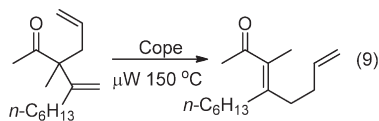
enolate; rather, it is rapidly trapped by the allyl electrophile. Thus, the regiospecific generation of enolates via decarboxylation provides a method to access enolates that are difficult to access using acid–base chemistry. In cases such as **A** (Scheme 5), this regiospecificity is likely the result of the short lifetime of the enolates such that isomerization is not kinetically competitive with allylation of the enolate. In cases such as **B**, the regiospecificity may reflect the selective allylation of the stabilized β -ketoester enolate prior to decarboxylation (see section 4.2.2).

Shimizu and Ishii utilized the regiospecificity of decarboxylative coupling to allylate an α -fluoro ketone that proceeds via a fluorinated enolate (eq 7);²⁰ such fluorinated enolates are difficult to generate and alkylate using standard methods.²¹ Shimizu et al. likewise demonstrated that trifluoromethyl β -ketoesters could undergo DcA to give trifluoromethyl ketones (eq 8).²² The tolerance of β -hydrogens on the allyl fragment is noteworthy and may reflect the reduced basicity of the nucleophile that bears the electron-withdrawing CF_3 group.



2.1.4. Regioselectivity in Allylation of Dienolates. Allyl–allyl cross-coupling has historically been accomplished via transmetalation of allyl magnesiates or stannanes with Pd- π -allyl complexes formed by oxidative addition of allyl acetates.²³ This type of coupling suffers from low yields and stoichiometric metal salt waste. Tunge and co-workers recognized that decarboxylation might replace the transmetalation step to allow a new type of catalytic allyl–allyl coupling.²⁴ The decarboxylation of vinyl-substituted β -ketoesters generates the dienolate, which can undergo allylation at either the α - or the γ -carbon to afford regioisomeric products (Chart 3). Indeed, when β -ketoester **6** was subjected to a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$, the authors observed only the formation of the α -allylated product (**7**) and none of the regioisomeric γ -allylated product **8**. The reaction establishes that the kinetic product is the α -allylation product, and this regioselectivity appears to be quite general (Chart 3). Regiocontrol of the allylation event appears to be dictated primarily by electronics because the bond formation occurs exclusively at the more-hindered α -position rather than the less-hindered γ -position.

Importantly, the γ -allylation isomers can be readily accessed by Cope rearrangement of the kinetic products to the conjugated thermodynamic products (eq 9). Thus, controlled access to either the α - or γ -allylated regioisomers is possible.



In an intramolecular decarboxylative allylation, Hayashi and co-workers took advantage of the slow cyclization of the

Table 1. DcA of β -Keto Acids

entry	β -keto acid	allyl acetate	product ^a	yield
1				93%
2	9			71%
3	9			78%
4	9			64%
5	9			83%
6				89%

^a $\text{Pd}(\text{PPh}_3)_4$, 23 °C, THF or C_6H_6 , 0.5–20 h

zwitterionic intermediate (**A**, Scheme 6) to promote a γ -selective allylation.²⁵ The allylation also results in dearomatization of the thiophene; however, the products could be rearomatized by simply stirring them with alumina. Although the reaction did not extend to simple α -phenyl lactones, it did work well for electron-rich aromatics (Chart 4). The ease of reaction apparently correlates with the ability to dearomatize the nucleophilic arene.

2.2. Intermolecular Coupling of β -Keto Acids

2.2.1. Coupling with Allyl Acetates. One drawback to the aforementioned decarboxylative coupling methodologies can be the need to preform the ester from the corresponding acid and allyl alcohol. However, Saegusa and co-workers have shown that the acylation step is not necessary when β -keto acids are utilized as reactants.²⁶ Specifically, they demonstrated the intermolecular coupling of allyl acetates and β -keto acids or β -keto carboxylates (Table 1). The largest limitation to this reaction appears to be the requirement of a substrate β -keto acid that bears an α -proton; we will return to this subject in the discussion of the mechanisms of decarboxylative allylation. One remarkable difference between what Saegusa observed and the corresponding Tsuji–Trost reaction,²⁷ in which the geometry of the trisubstituted olefin is preserved, is high selectivity for the *E*-olefin (entries 3–5). Substitution at the 2-position of the allyl (entry 2) and β -hydrogens (entries 3–5) were tolerated while maintaining selective mono-allylation (entry 6).

2.2.2. Coupling with Vinyl Epoxides. In 1986, Saegusa and co-workers similarly demonstrated the ability to utilize vinyl epoxides and β -keto acids to facilitate DcA.²⁸ Once again, the substrate scope suggests the requirement of a β -keto acid that bears an α -hydrogen for successful coupling. As will be discussed later (section 4.2), this has important mechanistic implications. The reaction is remarkable but, in general, gives modest yields, and some epoxides seem prone to elimination rather than C–C bond formation (entry 5, Table 2).

2.3. Decarboxylative Allylation via Enol Carbonates

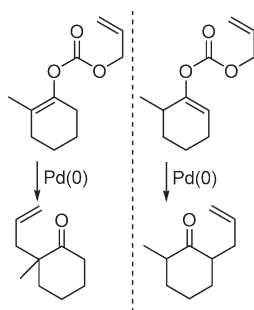
A few years after his initial report on decarboxylative coupling of β -ketoesters, Tsuji demonstrated the ability of allyl vinyl carbonates to undergo a decarboxylative allylation to afford identical products to those observed from the DcA of the β -ketoesters.²⁹ Some key results are shown in Chart 5. Once again,

Table 2. Intermolecular DcA of β -Keto Acids and Vinyl Epoxides

entry	β -keto acid	vinyl epoxide	product ^a	yield
1				86% E/Z = 4.5
2				59%
3				54%
4				67%
5				27%

^a Pd(PPh₃)₄, 23 °C, THF or C₆H₆, 0.5–20 h

Scheme 7. Regiospecificity in the DcA of Allyl Enol Carbonates



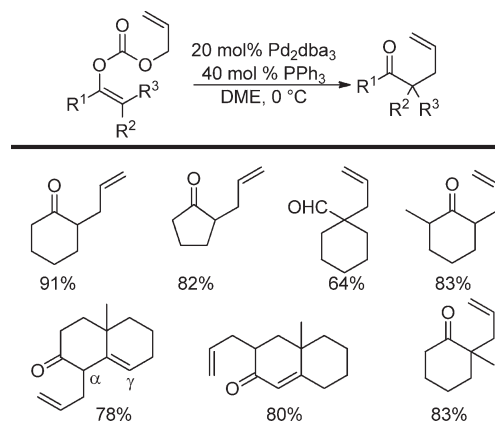
the reaction is regiospecific, so either regioisomer of the product can be obtained exclusively by use of the appropriate enol carbonate (Scheme 7). However, the regiospecific DcA of enol carbonates requires that one is able to regioselectively generate the enol carbonate precursor via a classic base-induced enolization. Thus, while enol carbonates and β -ketoesters both allow regiospecific allylation, there is some synthetic advantage to the use of β -ketoesters.

Enol carbonate precursors do have some advantages as well. For example, the use of enol carbonates allows the formation of homoallylic aldehydes (Chart 5); aldehyde products have not been prepared from the corresponding β -oxo esters, presumably due to the instability of the reactants. Furthermore, Tsuji showed that α -allylation of the dienolate occurs preferentially over γ -allylation. Thus, dienolates generated from either β -ketoesters or enol carbonates undergo kinetic α -allylation rather than γ -allylation, and the mild conditions prevent isomerization of the double bond to give the α,β -unsaturated enone.

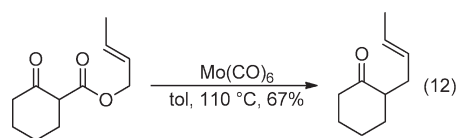
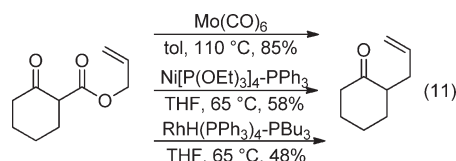
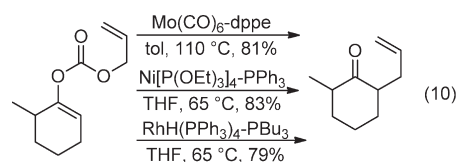
2.4. Catalysis with Molybdenum, Nickel, and Rhodium

Although palladium-based catalysts have been utilized for DcA reactions more widely than any other transition metal catalyst,

Chart 5. DcA of Allyl Enol Carbonates



several other metals have proven to be active catalysts for the decarboxylative allylation of enolates. For example, Tsuji et al. demonstrated that Mo, Ni, and Rh catalysts were capable of facilitating DcA reactions using enol carbonates or β -ketoesters (eqs 10–12).³⁰ To date, the scope of these transformations has not been adequately examined. Nonetheless, these few examples do provide proof that DcA is not uniquely catalyzed by Pd. The regioselectivities of the reactions with Mo, Ni, and Rh are not well-documented; however the limited information suggests that, in the case of the enol carbonates (eq 10), the intermediate enolate does not isomerize to the more stable enolate under the reaction conditions. Because only unsubstituted allyl esters were allowed to react with Ni and Rh, the regioselectivity about the allyl electrophile cannot be determined. Interestingly, when a crotyl ester was used with the Mo(CO)₆ catalyst, the linear product was the major product (eq 12); this result lies in contrast to some Mo-catalyzed allylations of stabilized malonate enolates, which favor production of the branched product.³¹

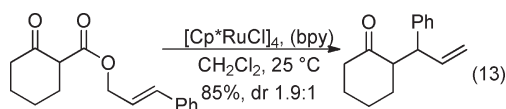


2.5. Catalysis with Ruthenium

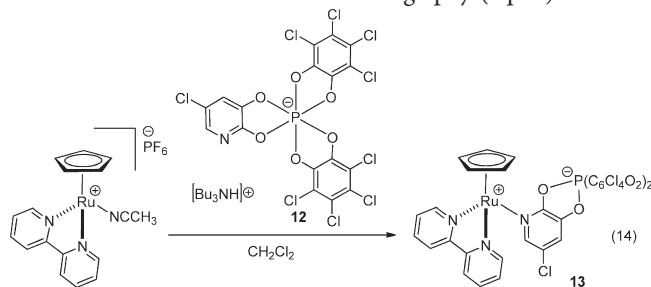
2.5.1. Regioselectivity. Recently, ruthenium catalysts have also been found to be active catalysts for the DcA of allyl

β -ketoesters.^{4a,32} Specifically, it was found that $[\text{Cp}^*\text{RuCl}]_4$ and bipyridine formed an effective catalyst for decarboxylative allylation (Scheme 8). The bipyridine (bpy) was found to be an essential ligand as it helped form the active monomeric catalyst from the tetrameric precatalyst. On the basis of NMR spectra of a 1:1 complex of bpy/Ru and the known coordination of ruthenium,³³ the active catalyst was proposed to be a 16-electron $\text{Cp}^*\text{Ru}(\text{bpy})^+$ complex. The reaction is regioselective for reaction of the enolate at the more substituted allyl terminus, as both the linear ester and the branched ester lead to the branched product (Scheme 8). This is easily explained by the existence of a Ru- π -allyl species that preferentially undergoes carbon-carbon bond formation at the more-hindered position. This electronically driven regioselectivity is typical for a reaction between Ru- π -allyl complexes and stabilized nucleophiles.³⁴ Although it was initially thought that decarboxylation preceded carbon-carbon bond formation, it is more likely that carbon-carbon bond formation precedes decarboxylation (see section 4.2).

2.5.2. Scope of the Ru-Catalyzed DcA. The ruthenium-catalyzed DcA is sensitive to the electronics of the aryl substituent R^1 , such that electron-rich allyl esters undergo DcA faster than electron-poor substrates (Table 3). In addition, the rate of reaction is sensitive to the sterics of the allyl substitution (entries 1 vs 2). Furthermore, the reaction of 1,3-disubstituted substrates occurs but results in lower yield (entry 7). Although the majority of substrates that were utilized did not contain α -substitution, the coupling does tolerate substitution at the α -position; however, the resulting product was formed with a low dr (eq 13).



2.5.3. Recyclable Ruthenium Catalyst. Lacour and co-workers have made some significant strides in the area of developing recyclable catalysts for DcA reactions.³⁵ One problem with the active ruthenium catalysts that are typically used for DcA reactions is their sensitivity to air and moisture. Lacour and co-workers found that exchanging the PF_6^- counterion with the TRISPHAT-N anion **12** gave catalyst **13**, which was air-stable and even isolable via column chromatography (eq 14).



The catalytic competency of the zwitterionic Ru species was tested by subjecting an allyl β -ketoester to DcA reaction conditions (eq 15); at the completion of the reaction, the catalyst was recovered and reused. After each run, 84–90% of the catalyst was recovered. Importantly, the recovered catalyst gave identical results to the freshly prepared catalyst in subsequent DcA reactions. Although catalyst **13** was somewhat less active than the precursor PF_6^- complex (eq 14), it was found to be superior at higher temperatures. This observation can be attributed to the increased stability of the TRISPHAT-N catalyst complex and its decreased propensity to undergo decomposition.

Scheme 8. Regioselectivity of the Ru-Catalyzed DcA of β -Ketoesters

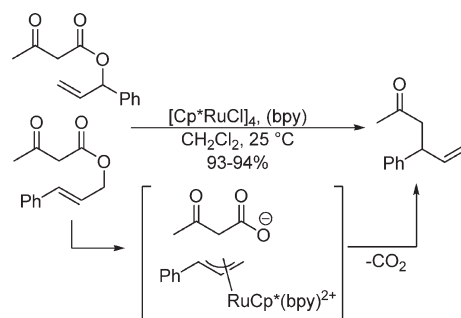
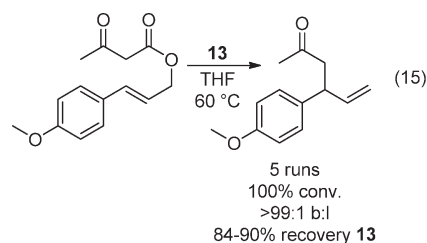


Table 3. Ru-Catalyzed DcA of β -Keto Esters

entry	R^1	R^2	time (h)	yield (%)
1	<i>p</i> -tolyl	H	2	96
2	<i>o</i> -tolyl	H	120	81
3	<i>p</i> - $\text{C}_6\text{H}_4\text{OMe}$	H	0.25	93
4	<i>o</i> - $\text{C}_6\text{H}_4\text{OMe}$	H	0.25	91
5	<i>p</i> - $\text{C}_6\text{H}_4\text{Cl}$	H	4	96
6	<i>p</i> - $\text{C}_6\text{H}_4\text{CF}_3$	H	40	90
7	Ph	Ph	1	67

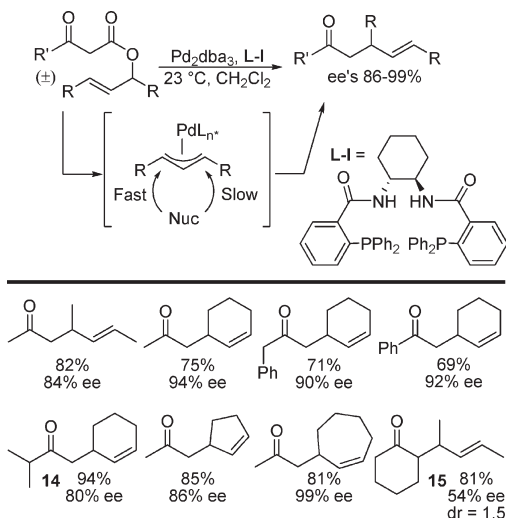


3. ASYMMETRIC DCA OF ENOLATES

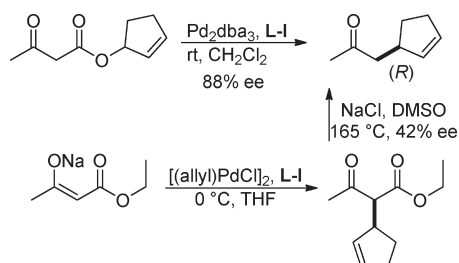
3.1. Control of Stereochemistry at the β -Carbon

3.1.1. Enantioselective DcA of β -Ketoesters. Although the first disclosures of the formation of homoallylic ketones via Pd-catalyzed DcA appeared in 1980,^{14,15} the first enantioselective variants did not appear until 2004 when Burger and Tunge were able to use the Trost ligand **L-1** to effect the enantioselective DcAs of allyl β -ketoesters (Chart 6). In doing so, the authors were able to efficiently control the stereochemistry at the β -position of the homoallylic ketone product.³⁶ As with similar asymmetric allylic alkylations,^{1d,2i,2k} the racemic starting ester affords a *meso*-Pd-allyl complex upon ionization. The Trost ligand introduces a chiral environment and ultimately favors attack of the nucleophile at one of the prochiral allyl termini. Ultimately, the yields of the asymmetric DcA ranged from 69 to 94%, and enantiomeric excesses (ee's) ranged from 80–99%,

Chart 6. First Enantioselective DcA of Ketones



Scheme 9. Comparison of DcA and Traditional Two-Step Method



with ee's increasing with ring size $7 > 6 > 5$. The enantioselectivity was slightly influenced by the substitution pattern at the remote α -position (14) and was quite sensitive to substitution at the reacting α -position (15, Chart 6). Unfortunately, the reaction proceeded with very little diastereoselectivity (15, dr = 1.5:1).

In addition, by comparison with the same product derived from the Tsuji–Trost reaction with the same ligand, the authors determined the absolute configuration of the DcA product to be *R* when the Trost ligand **L-I** was used (Scheme 9). Notably, the enantioselectivity of the DcA is higher than that for the two-step Tsuji–Trost/decarboxylation path. The authors attributed this increase in enantioselectivity to the intermediacy of an enolate with a soft metal counterion.³⁷

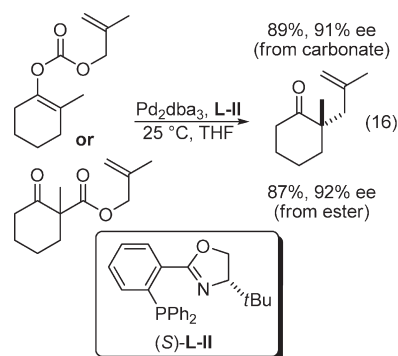
3.1.2. Stereospecific DcA of β -Ketoesters. More recently, Yan and Spilling hoped to take advantage of the double-inversion mechanism for decarboxylative allylation to develop an enantiospecific DcA that would provide access to chiral non-racemic vinyl phosphonates (Table 4).³⁸ As anticipated, the reaction was highly stereospecific, with perfect transfer of the reactant stereochemistry to the product. Unfortunately, competing elimination was problematic for allyl substrates that contained β -hydrogens. While Tsuji has shown that the addition of a base can help to alleviate problematic elimination,¹⁸ the authors were able to avoid elimination using a more classical intermolecular Tsuji–Trost allylation of a stabilized enolate.

3.2. Control of α -Stereochemistry

3.2.1. Enantioselective DcA of Allyl Vinyl Carbonates.

While Tunge and Burger demonstrated the ability to control the stereochemistry at the β -position of the ketone, Behenna and Stoltz,³⁹ and later Trost and co-workers,⁴⁰ demonstrated the ability to control the stereochemistry at the α -carbon via enantioselective decarboxylative allylation of enol carbonates (Chart 7). In these reactions, the disadvantage associated with the preparation of the precursor enol carbonates is mitigated by the ability to form highly enantioenriched alkylated ketones. Both investigators demonstrated the ability to achieve carbon–carbon bond formation in high yield and in good to excellent enantioselectivity. Stoltz's method (conditions A) was used to quaternarize the α -position, whereas Trost (conditions B) described formation of both quaternary and tertiary α -stereocenters with no apparent racemization of the tertiary products (17 and 18, Chart 7). Interestingly, Trost notes that, when 16 is formed from the lithium enolate, using the same ligand, the opposite stereoisomer is formed. Remarkably, Trost's method tolerates terminal substitution on the allyl as well as β -hydrogens (19 and 20); as mentioned above, such substrates are often prone to undergoing competing elimination. In addition, it appears that the carbon–carbon bond-forming step is slower than π – σ – π allyl isomerization; product 19 is obtained regardless of whether the reactant is the *cis*- or *trans*-crotyl ester.

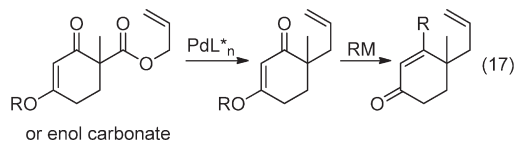
3.2.2. Enantioselective DcA of β -Ketoesters. The year following that of their initial publication, Stoltz and co-workers demonstrated that the DcA of the isomeric β -ketoesters is also highly enantioselective (eq 16).⁴¹ Furthermore, the consistent results, whether starting from enol carbonate or isomeric β -ketoester, lend credence to the proposal of a common intermediate.



While the Trost ligands and *tert*-butyl PHOX ligands are the most generally applicable ligands for the decarboxylative coupling of enol carbonates, ligand modifications can have a significant influence on the enantioselectivity of DcA reactions. For example, Stoltz and co-workers recently reported the superiority of an electron-deficient *tert*-butyl PHOX derivative, (S)-**L-IV**, for the asymmetric synthesis of a protected diketone (Scheme 10).^{42a} while the Trost ligand (**L-I**) provided the product with very low ee. The authors further demonstrated that superior enantioselectivities are obtained when using hexane/toluene solvent mixtures. The authors suggest that both the low polarity solvent and the ligand serve to increase the affinity between the metal center and the enolate, and as a consequence, the ee is improved.

3.2.3. DcA of Vinylogous Ester Derivatives. Trost and co-workers recognized that an asymmetric DcA of cyclic

vinyllogous esters followed by a Stork–Danheiser addition of an organometallic reagent would give access to α,β -unsaturated enones with a γ -stereocenter, an important motif in the synthesis of a variety of terpenes and alkaloids (eq 17).⁴³



Treatment of the β -ketoester reactant **21** with palladium catalyst and the anthracenyl Trost ligand, (*R,R*)-**L-III**, provided

Table 4. Stereospecific DcA

entry	R	yield A	yield B
1	<i>n</i> -C ₄ H ₈	61	27
2	H	71	2
3	CH(CH ₃) ₂	35	31

the product in high ee; however the reaction was slow and formed product in low yield (Scheme 11). Although the carbon backbone of the nucleophilic enolate generated from **21** is similar to cyclic β -ketoesters that readily react, the electronics of the enolate are more akin to the corresponding malonates, which typically are sluggish reactants for DcA reactions (vida supra).

With the goal of developing an asymmetric DcA of cyclic vinyllogous esters, allyl enol carbonate **22** was synthesized and subjected to Pd and (*R,R*)-**L-III** in toluene and afforded the desired ketone in 87% yield and 85% ee (Scheme 11). The reaction was more facile than that of the β -ketoester, presumably

Scheme 10. Superior ee's with an Electron-Deficient PHOX Ligand

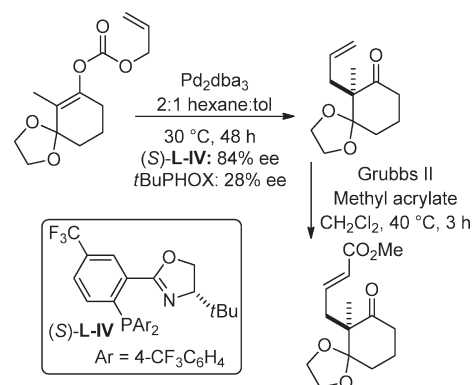
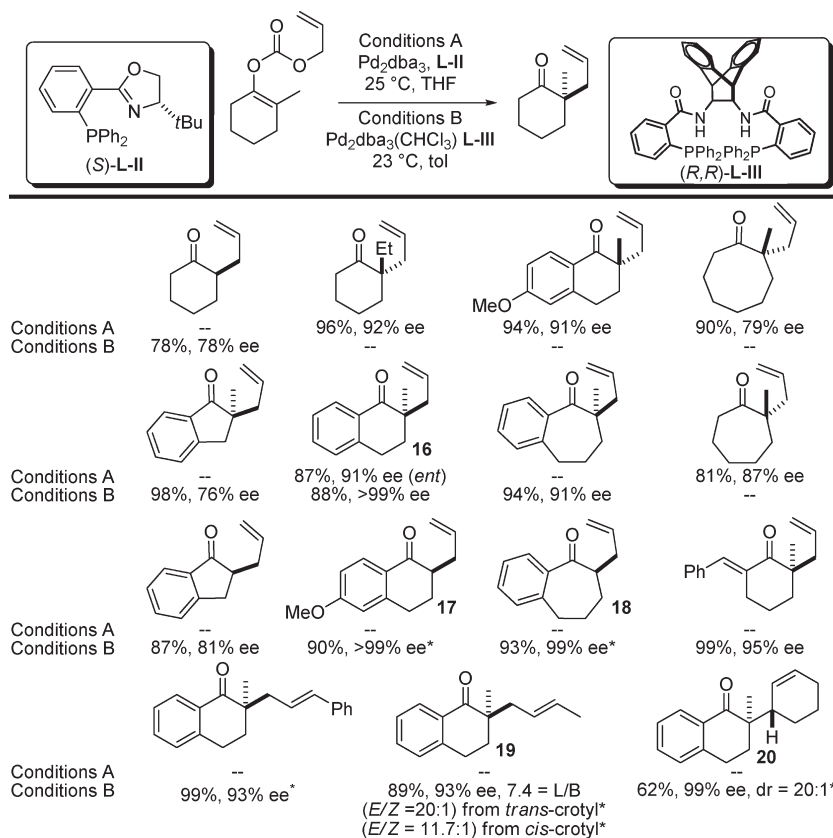


Chart 7. Enantioselective DcA of Allyl Vinyl Carbonates



Scheme 11. DcA of Vinylogous Ester Enolates

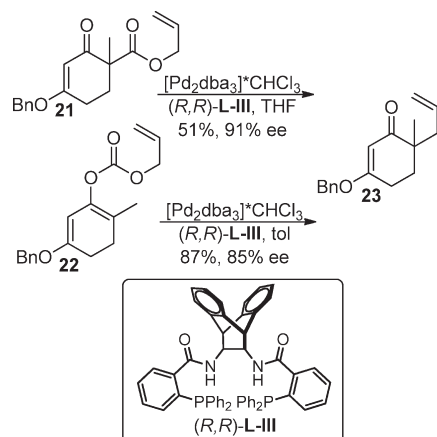
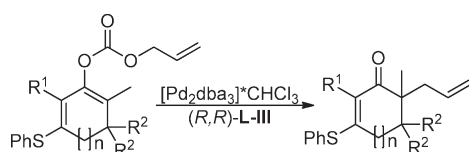


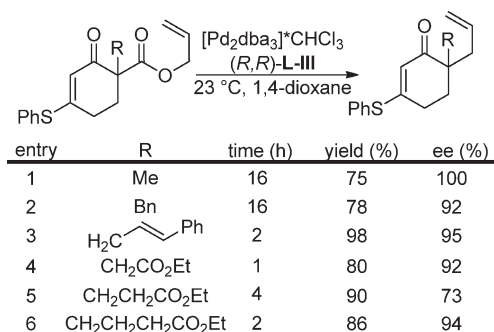
Table 5. Asymmetric DcA of Allyl Vinyl Carbonates Generated from Vinylogous Thioesters



entry	<i>n</i>	R ¹	R ²	solvent	temp (°C)	yield (%)	ee (%)
1	1	H	H	THF	−20	100	98
2	2	H	H	THF	0–4	100	94
3	1	Me	H	THF	0–4	100	99
4	0	Me	H	THF	0–4	96	80
5	1	Ph	H	dioxane	23	100	97
6	1	H	Me	THF	0–4	91	79

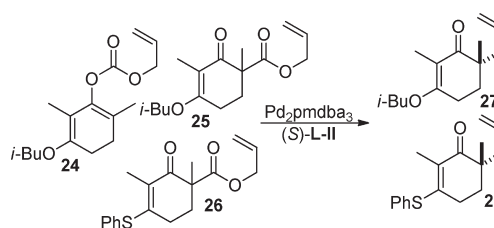
due to the faster decarboxylation of enol carbonates as compared to malonates. Unfortunately, while the DcA reaction worked well, the synthesis of the requisite enol carbonate (**22**) was challenging, giving primarily *C*-carboxylation instead of *O*-carboxylation.

Trost et al. envisioned that replacing the vinyl ether of the vinylogous ester with a thioether would lead to a β -ketoester that would undergo more facile decarboxylation. Serendipitously, when the oxygen was replaced with a sulfur atom, trapping the enolate gave clean *O*-carboxylation. Fortunately, these carbonates readily underwent asymmetric DcA (Table 5). Six-membered cyclic enolates gave the highest levels of enantioenrichment, although five- and seven-membered cyclic enolates also worked well (entries 1 vs 2 and 3 vs 4). Interestingly, the allylation was facile and highly selective even when there was a quaternary carbon adjacent to the site of allylation (entry 6). Finally, the Pd-catalyzed asymmetric DcA of vinylogous thioesters also worked for the corresponding isomeric β -ketoester reactants (Table 6), in contrast to the low reactivity of the related oxygen analogues (**21**, Scheme 11).

Table 6. Asymmetric DcA of β -Ketoesters Generated from Vinylogous Thioesters

entry	R	time (h)	yield (%)	ee (%)
1	Me	16	75	100
2	Bn	16	78	92
3	H ₂ C=CH-Ph	2	98	95
4	CH ₂ CO ₂ Et	1	80	92
5	CH ₂ CH ₂ CO ₂ Et	4	90	73
6	CH ₂ CH ₂ CH ₂ CO ₂ Et	2	86	94

Table 7. Asymmetric DcA of Vinylogous Ester Derivatives with PHOX-Ligand



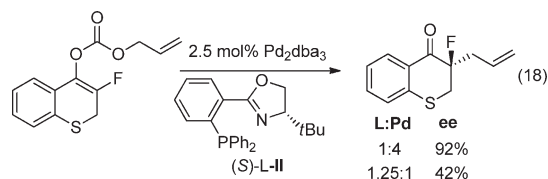
entry	substrate	solvent	<i>T</i> (°C)	product	yield (%)	ee (%)
1	24	tol	25	27	22–61	84–88
2	25	tol	50	27	19	79
3	25	tol	80	27	86	75
4	26	tol	50	28	86	92
5	26	PhH	50	28	61	92
6	26	THF	50	28	88	92
7	26	dioxane	50	28	90	91

In their effort toward the synthesis of (+)-cassiol, the Stoltz group compared three related vinylogous ester reactants for their ability to form the desired enantioenriched vinylogous esters using the *tert*-butyl PHOX ligand (**L-II**) (Table 7).^{43,44} While the ee of **27** was good when it was derived from the enol carbonate (**24**), the substrate was found to be unstable in air, complicating its use. When the β -ketoester analogue (**25**) was used, the reaction was sluggish at 50 °C and required elevated temperatures to achieve high conversions (entry 2). Unfortunately, the temperatures needed for high conversion led to lower enantioselectivity (entry 3). Finally, the vinylogous thioester (**26**, entries 4–7) allowed the reaction to occur at milder temperatures with high enantioselectivity. The authors further reported that the enantioselectivity obtained was rather insensitive to the solvents used (aromatic and ethereal), although the yield of product **28** dropped substantially when benzene was used as the solvent (entry 5).

3.2.4. AREA Reaction. Schulz and Blechert developed a DcA reaction that they called an AREA reaction (asymmetric ring-expanding allylation).^{42b} In this reaction, allyl carbonates derived from 1,3-hydroxy fused bicyclic systems such as **29** undergo enantioselective Pd-catalyzed ring-opening, ring-expanding allylation to form tertiary and quaternary stereocenters resulting in selectively allylated cyclic 1,4-diketones (**30**, Chart 8). The reaction is presumed to take place via ionization and decarboxylation to generate the expected alkoxide ion. The intermediate alkoxide undergoes a retro-aldol reaction to form an enolate (**A**), which undergoes allylation. Importantly, the requisite substrates are readily made from the cyclic β -diketone via a photo-induced $[2 + 2]$ -reaction. In general, the AREA reaction works quite well for making quaternary stereocenters, but the enantioselectivity of the reaction is slightly lower when tertiary stereocenters are formed. Furthermore, substrates that are substituted in the 2-position of the allyl electrophile also provide products with diminished ee's. Ultimately, this methodology is unique in its use of a fragmentation to generate the reactive nucleophile. Such a strategy allows access to enantioenriched medium-ring ketones that are not easily accessed by other methods.

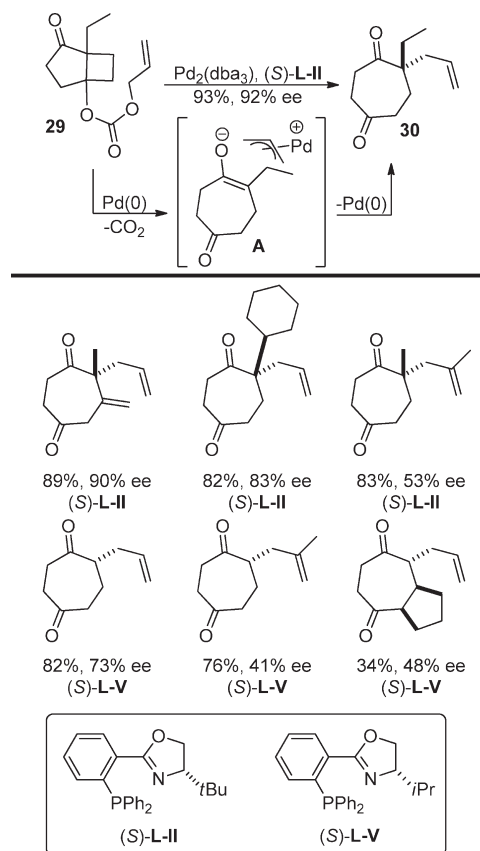
3.2.5. Asymmetric DcA of α -Fluoro- β -Ketoesters. Having been inspired by the seminal work of Shimizu and Ishii,²⁰ the research groups of Nakamura,⁴⁵ Tunge,⁴⁶ and Stoltz⁴¹ recognized the potential to control the stereochemistry of α -fluoroketones using DcA reactions. Controlling the α -stereochemistry through a carbon–carbon bond-forming reaction could accomplish the equivalent of an asymmetric fluorination of a ketone,⁴⁷ a challenging transformation. Nakamura detailed the use of the *tert*-butyl PHOX ligand (**L-II**), while Tunge compared the PHOX ligand with another P,N-ligand, (*S*)-QUINAP (**L-VI**, Chart 9). (*S*)-QUINAP (conditions B) provided excellent yields of the allylated fluoroketones; however, the *tert*-butyl PHOX ligand produced higher enantioselectivities in most cases. It is also noteworthy that the two ligands provided access to products of the opposite absolute configuration, with (*S*)-QUINAP giving rise to the (*S*)-ketone and (*S*)-*tert*-butyl PHOX giving rise to the (*R*)-ketone.

Paquin and co-workers have investigated the asymmetric decarboxylative allylation of the related fluorinated enol carbonates.^{48a} Interestingly, the authors reported that the ee's of the product fluoroketones were highly dependent on the Pd/L ratio. For example, a "traditional" use of a 1.25:1 ligand/Pd ratio provided the product in low ee (eq 18). Alternatively, use of substoichiometric amounts of ligand (L/Pd = 1:4) produced the product with high enantioselectivity. This same effect was not observed in the decarboxylative coupling of fluorinated β -ketoesters, nor was it observed in the allylations of a fluorinated silyl enol ether or an *alkyl*-substituted enol carbonate. Thus, the unusual ligand effect is unique to fluorinated enol carbonates. While it is difficult to explain this behavior, these results do show that the reactions of enol carbonates and β -ketoesters do not always exhibit the same selectivities.



With regard to the decarboxylative allylation of fluorinated β -ketoesters (Chart 9), it is noteworthy that acyclic products are

Chart 8. Select Examples of the AREA Reaction

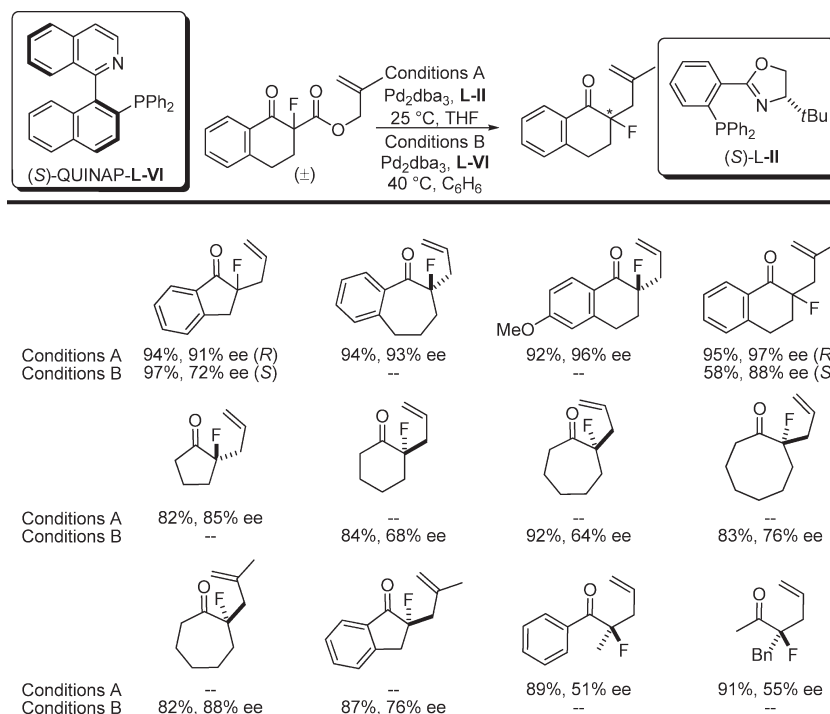


significantly less enantioenriched than their cyclic counterparts. This limitation is common among decarboxylative methods that generate enolates from acyclic ketones. The ee is proportional to both the facial selectivity as well as the *E/Z* ratio of enolates formed; the lower enantioenrichments observed for acyclic ketones may be attributed to the formation of an imperfect mixture of enolate geometries from such substrates.

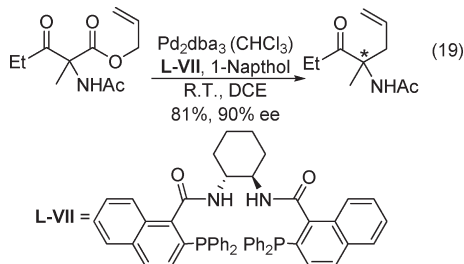
3.3. Acyclic Stereocontrol

The low enantioselectivity of DcA reactions of *acyclic* β -ketoesters is a general problem and is not limited to α -fluoro substrates. The apparent mixture of enolate geometries generated via decarboxylation is a general problem for DcA reactions; however, a few creative solutions to this problem have emerged. Among the simplest solutions is the appropriate placement of functional groups in the ester to favor a single enolate geometry. Another, perhaps more general solution is the use of allyl enol carbonate reactants with predefined enolate geometry.

3.3.1. α -Acetamido- β -Ketoesters. Kuwano, Naoki, and Murakami have demonstrated that acyclic α -acetamido- β -ketoesters can lead to enantioenriched γ,δ -unsaturated ketones (eq 19).^{48b} The authors did not investigate the scope of the DcA, nor did they explicitly comment on why the enantioselectivity is higher for α -acetamido β -ketoesters than for α -alkyl and α -fluoro ketoesters. That said, it is possible that the amido group in combination with the naphthol additive helps to favor a single enolate geometry via hydrogen bonding; the

Chart 9. Enantioselective DcA of α -Fluoro- β -Ketoesters

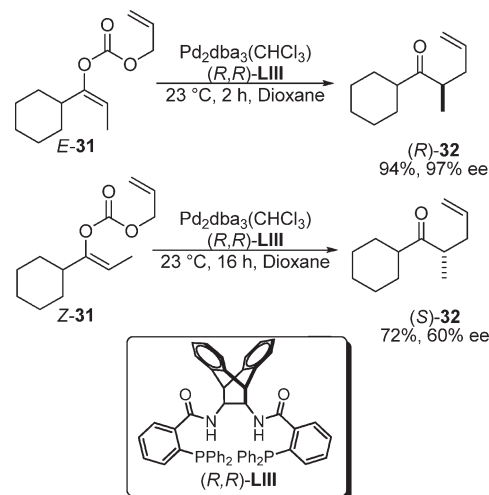
enantioselectivity was much lower (51% ee) without the naphthol additive.



3.3.2. Acyclic Allyl Enol Carbonates. Trost et al. have offered a more general solution to the problem of acyclic control of α -stereochemistry.^{40b} Use of preformed enol carbonates gives a handle on the geometry of the enolate that is not present when starting from the acyclic β -ketoesters. Indeed, an *E*-enol carbonate (*E*-31) smoothly underwent DcA to afford the homoallylic ketone in high yield and excellent enantioenrichment (Scheme 12). When the isomeric *Z*-enol carbonate was allowed to react under the same conditions, the opposite enantiomer of the product (32) was obtained. However, the reaction of the *Z*-enol carbonate proceeds more slowly and with lower enantioselectivity than the analogous reaction with the *E*-enol carbonate. This indicates that the *E*-isomer is matched with the catalyst while the *Z*-isomer is mismatched. This is not general for all acyclic carbonates but seems to be the case with carbonates derived from dialkyl ketones.

While the *Z*-enol carbonates of alkyl ketones provide relatively low enantioselectivities, *Z*-enol carbonates that are derived from a phenyl ketone are excellent substrates for asymmetric DcA reactions (Table 8). The reaction is general for a variety of α -alkyl substituents (entries 2–4), but the enantioselectivity is

Scheme 12. Matched/Mismatched Asymmetric DcA

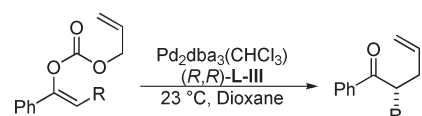


somewhat sensitive to the steric nature of the α -substituent; when an isopropyl group was used, the reaction became very sluggish and the selectivity dropped dramatically (entry 5, Table 8).

Interestingly, the reaction with the *Z*-enol carbonates was quite tolerant of substitution of the phenyl ring (Chart 10). The major exception was the mesityl-derived substrate, which was unreactive (34). The chemoselectivity was also noteworthy, allowing the DcA to take place while a pendant aryl bromide was unscathed (33).

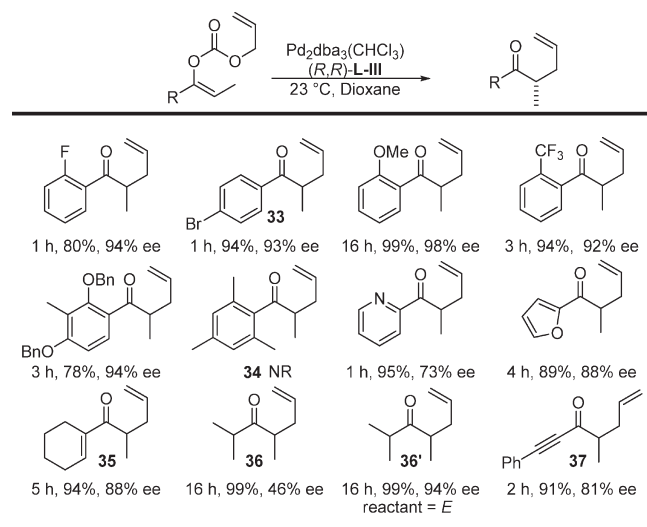
Finally, variation of the hybridization of the enol carbonate substituent revealed substantial differences in reactivity and

Table 8. Enantioselective DcA of Z-Enol Carbonates



entry	R	time (h)	yield (%)	ee (%)
1	Me	3	96	94
2	Et	2	94	94
3	<i>n</i> -Pent	16	93	92
4	Bn	1	75	88
5	<i>i</i> -Pr	24	30	32

Chart 10. Enantioselective DcA of Z-Enol Carbonates

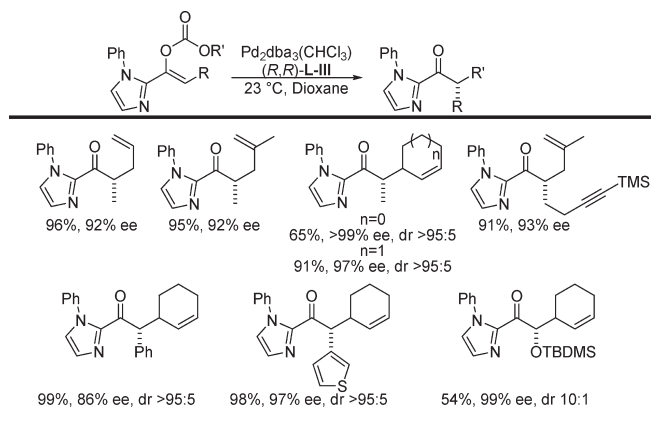


selectivity. Specifically, the Z-enol carbonates underwent efficient asymmetric DcA reactions for sp^2 -hybridized ketone substituents (**35**, Chart 10) but led to poor ee's if the substituent was sp^3 -hybridized (**36**); however, the DcA is well-suited for the analogous *E*-enol carbonate (**36'**). An ynone provided product in good yield and moderate enantiomeric excess (**37**).

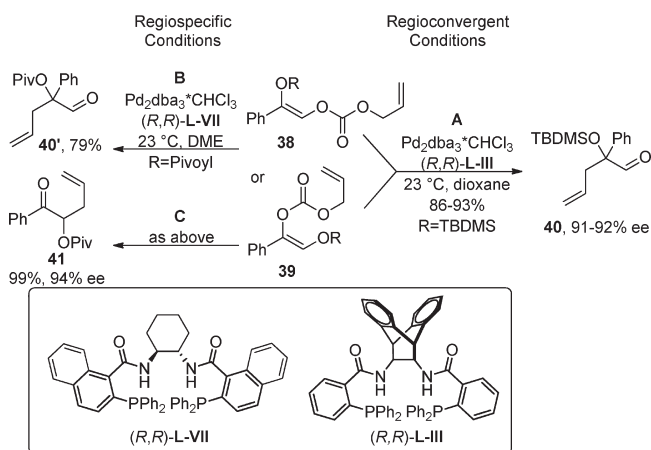
3.3.3. DcA of 2-Acyl Imidazole Derivatives. More recently, Trost et al. have circumvented the sluggish transformations of ester enolate derivatives by utilizing 2-acyl imidazoles as surrogates for ester enolates.⁴⁹ The increased electrophilicity of the 2-acyl ketone, compared to the carbonyl of the ester, makes the DcA of the corresponding enol carbonates more facile. Indeed, such reactions took place at ambient temperatures, affording products in high yields and ee's (Chart 11). Notably, the DcA with cyclic allyl esters allowed the formation of adjacent carbon stereocenters with high enantio- and diastereoselectivity.

Having established that the 2-acyl imidazole derivatives undergo highly enantioselective DcA, the authors next demonstrated that they could easily access acids, esters, amides, and ketones in high ee's from the acyl imidazole products. Using methyl triflate to activate the imidazole toward nucleophilic acyl substitution, the allylated ketone was converted into cetiedil, a compound that

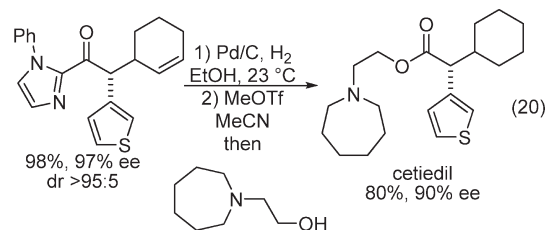
Chart 11. Enantioselective DcA of 2-Acyl Imidazoles



Scheme 13. Diverse Reactivity of Protected Hydroxy Ketones



is used clinically for the treatment of vascular disease in its racemic form (eq 20).



3.3.4. Protected α -Hydroxy Allyl Vinyl Carbonates. In 2007, Trost and co-workers published an interesting twist on DcA reactions that involved regioconvergent, enantioselective generation of α -tertiary hydroxy aldehydes from protected α -hydroxy enol carbonates (path A, Scheme 13).⁵⁰ This report was shortly followed by a related demonstration of the dramatic ability of the ligand to alter the outcome of the DcA, such that the reaction was regiospecific rather than regioconvergent (paths B and C, Scheme 13).⁵¹ Specifically, use of the naphthyl-Trost ligand (R,R) -L-VII and a pivoyl protecting group led to a regiospecific DcA. Thus, either α -hydroxy aldehydes (**40**) or

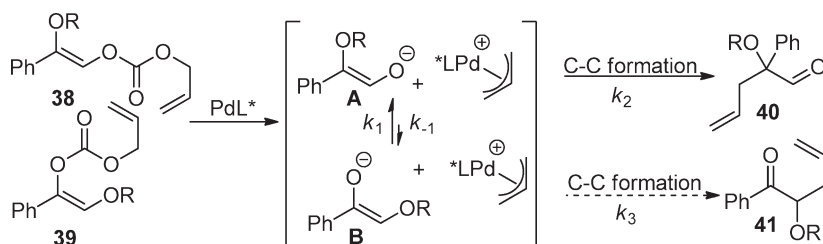
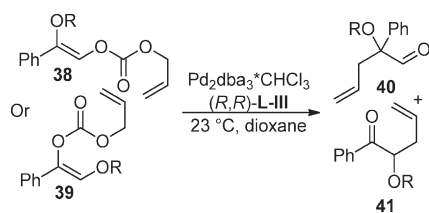
Scheme 14. Regioconvergent, Enantioselective DcA of α -Hydroxy Aldehydes

Table 9. Influence of the Ligand on the Regioselectivity



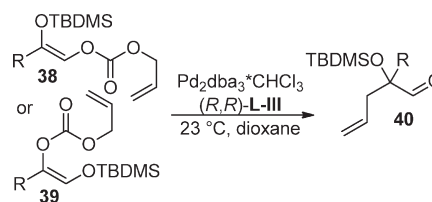
entry	SM	R	yield 40	yield 41
1	38	TBDMS	93	0
2	39	TBDMS	86	0
3	38	benzoyl	93	0
4	39	benzoyl	11	75 (dppe)
5	38	acetyl	40	60

protected α -hydroxy ketones (**41**) were accessible in high yield and enantiomeric excess via regiocontrolled synthesis of enol carbonates **38** and **39**.

In the initial report on regioconvergent DcA reactions, Trost et al. disclosed conditions for the formation of protected α -hydroxy homoallylic aldehydes from either of the two isomeric protected α -hydroxy enol carbonates (**38** and **39**, path A, Scheme 13).⁵⁰ The fact that two regioisomeric reactants led to a single product (**40**) implied that the reaction was a convergent process where equilibration of the intermediate enolates **A** and **B** occurred more rapidly than C–C bond formation ($k_1 + k_{-1} > k_2, k_3$; Scheme 14). Furthermore, the formation of **40** from either **A** or **B** indicates that allylation preferably occurs through intermediate **A** (Scheme 14).

Studying the effect of the hydroxy protecting group on the regioconvergent DcA showed that silyl groups tend to allow more isomerization, while carbonyl-based protecting groups slow the transfer process (Table 9). The effect of the ligand was perhaps more surprising. When bisdiphenylphosphinoethane (dppe) was used as opposed to the Trost ligand [(*R,R*)-**L-III**], the ketone **41** was the major product, regardless of which starting isomer was used (Table 9). These results suggest that the ligand plays an intimate role in controlling the relative rates of allylation (k_2, k_3 , Scheme 14) and/or the favored enolate isomer (**A** or **B**, Scheme 14).

Using the TBDMS protecting group to facilitate enolate isomerization, the scope of the regioconvergent DcA was investigated (Table 10). As expected, use of either isomeric starting materials **38** or **39** led to the aldehydes **40** in similar yields

Table 10. Scope of Protected α -Hydroxy Aldehydes

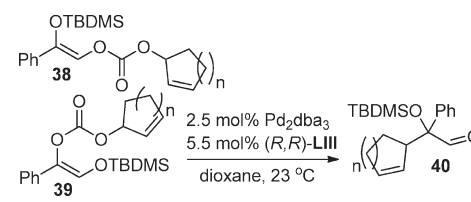
entry	SM	R	yield (%)	ee (%)
1	38	Ph	93	92
2	39	Ph	89	91
3	38	<i>p</i> -MeOC ₆ H ₄	94	92
4	39	<i>p</i> -MeOC ₆ H ₄	86	92
5	38	<i>o</i> -NO ₂ C ₆ H ₄	69	79
6	39	<i>o</i> -NO ₂ C ₆ H ₄	69	72
7	38	2-furyl	81	93
8	38	1-cyclohexenyl	93	98
9	38	PhCC	76	89

and ee's. The asymmetric allylation worked well with substrates derived from aromatic ketones (entries 1–7, Table 10) as well as enones and ynones (entries 8, 9).

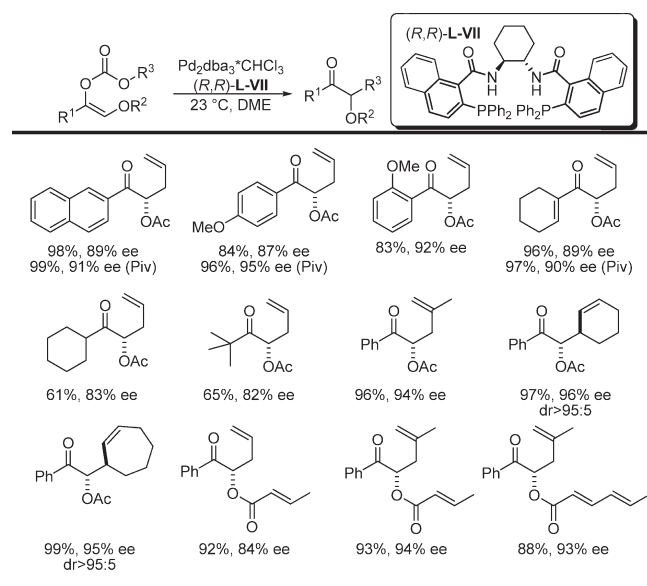
As expected for a reaction involving intramolecular transfer of the protecting group, the geometry of the enol carbonate is important (eq 21). For example, when the protected α -hydroxy substituent is *trans* to the enolate oxygen, allylation is faster than silyl transfer and the allylated ketone is the only product formed.



In addition to allylations with simple allyl electrophiles, a number of cyclic allyl carbonates were also tested for their ability to undergo asymmetric regioconvergent DcA reactions (Table 11). The reaction appears to be remarkably tolerant of allyls that can undergo elimination. The products were all formed with high enantioselectivity; however, the cyclopentenyl allyl electrophile provided the product with poor dr (2.5:1). In contrast, the cyclohexenyl and cycloheptenyl carbonates formed product with good dr (entries 2–5). While both isomeric carbonates (**38** and **39**) underwent the DcA reaction, the authors

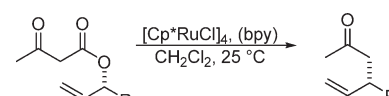
Table 11. DcA of Protected α -Hydroxy Allyl Vinyl Carbonates


entry	SM	<i>n</i>	yield (%)	dr	ee (major)
1	39	1	quant.	2.5:1	92%
2	38	2	quant.	11:1	>99%
3	39	2	quant.	11:1	>99%
4	38	3	quant.	50:1	>99%
5	39	3	30%	50:1	>99%

Chart 12. Scope of DcA of α -Protected Hydroxy Allyl Vinyl Carbonates

did note that the reactions that utilized the internal carbonate (39) were sluggish.

Given the ability of the dppe ligand to alter the regiochemical outcome of the reaction of protected α -hydroxy enol carbonates, it is not surprising that Trost and co-workers followed up their initial report with a study that detailed conditions that prevented enolate isomerization and allowed synthesis of the isomeric ketone products (Chart 12).⁵¹ Screening of reaction conditions showed that (i) (R,R) -L-III and the *i*-Pr-PHOX ligand (L-V) tended to favor the formation of aldehyde via isomerization and (ii) use of esters as protecting groups tended to slow transfer of the protecting group relative to silyl groups. Thus, optimal conditions for regiospecificity and enantioselectivity utilized acetyl or pivoyl protecting groups, naphthyl Trost ligand [(R,R)-L-VII], and 1,2-dimethoxyethane (DME) as the solvent.

Table 12. Ru-Catalyzed Stereospecific DcA of β -Ketoesters


entry	R	time (h)	cee %	yield (%)
1	Ph	1.5	83	86
2	<i>p</i> -tolyl	2	87	81
3	<i>p</i> -C ₆ H ₄ OMe	0.25	93	83
4	<i>p</i> -C ₆ H ₄ Cl	0.5	94	56
5	<i>p</i> -C ₆ H ₄ Cl	4	86	70
6	<i>p</i> -C ₆ H ₄ NO ₂	3	98	49

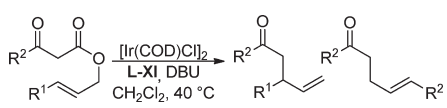
In general, the DcA of the protected α -hydroxyl allyl vinyl carbonates proceeded with good to excellent yields and ee's (Chart 12). However, substrates with an sp^3 -hybridized carbon in the R¹ position provide lower yields and ee's. Aryl ketones are particularly well suited for the DcA reaction, regardless of whether an acetyl or pivoyl protecting group was used. Cyclic allyl electrophiles are also well suited for the allylation of aryl ketones and provided products with high enantio- and diastereoselectivity. Furthermore, acrylate protecting groups could be used without significantly affecting the yield or ee.

3.4. Asymmetric DcA Using Metals other than Palladium

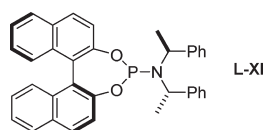
3.4.1. Ru-Catalyzed Stereospecific DcA. After establishing that Ru could facilitate the DcA of allyl β -ketoesters,³² Burger and Tunge turned their attention to the development of an asymmetric synthesis of branched γ,δ -unsaturated ketones.⁵² Believing that it might be possible to take advantage of a slow π – σ – π epimerization of the Ru-allyl intermediate,⁵³ chiral non-racemic β -ketoesters were subjected to the reaction conditions for decarboxylative allylation. Indeed, good levels of stereochemical fidelity (conservation of enantioenrichment = cee = 100 \times ee product/ee reactant) were observed, giving access to enantioenriched homoallylic ketones that contain a β -stereocenter (Table 12). The reaction does, however, proceed with some racemization. The authors noted that the use of N,N,N',N' -tetramethylethylenediamine (TMEDA) as a ligand, as opposed to bipyridine, led to increased amounts of racemization.

Importantly, it was recognized that the cee was dependent on the conversion to product for slow-reacting substrates (entries 4 vs 5). Closer investigation showed that, after 3 h reaction time, the *p*-nitrophenyl derivative (entry 6) had reached complete conversion, forming the desired product 44 in high ee as well as the linear ester 43. Prolonged reaction resulted in the DcA of achiral ester 43, which necessarily produced racemic product (Scheme 15). Thus, higher conversion to product resulted in lower enantiospecificity. Ultimately, the imperfect stereofidelity of the reaction was attributed to formation and DcA of the achiral linear isomer 43 and not π – σ – π isomerization.

3.4.2. Ru-Catalyzed Enantioselective DcA. A few years later Lacour and co-workers developed an enantioselective ruthenium-catalyzed DcA that allowed the more accessible linear esters to undergo an asymmetric conversion to the branched homoallylic ketones (Table 13).⁵⁴ Although the DcAs of only three linear esters were investigated, the enantioselectivity appears to be dependent on the substitution of the aryl ring. The

Table 15. Ir-Catalyzed Enantioselective DcA of β -Ketoesters


entry	R ¹	R ²	ee %	time (h)	yield (%)	b:l
1	4-MeOC ₆ H ₄	Ph	95	12	70	>99:1
2	Ph	Ph	95	16	83	99:1
3	4-CF ₃ C ₆ H ₄	Ph	91	17	71	>99:1
4	2-furyl	Ph	94	3	73	98:2
5	Ph	2-naphthyl	93	16	71	98:2
6	Ph	4-MeOC ₆ H ₄	95	4	67	99:1
7	Me	Ph	90	21	61	94:6
8	<i>n</i> -C ₅ H ₁₁	Ph	89	22	52	80:20



reduced. The role of the base was not completely understood, but the authors noted that similar results could be achieved by the use of several weak bases other than DBU. As shown by Hartwig, one role of the base is to facilitate formation of an active metallacyclic iridium complex from phosphoramidite ligand L-XI.⁵⁶ Another possible role of the base is to deprotonate the ketoester, forming a stabilized enolate that can undergo iridium-catalyzed Tsuji–Trost-type allylation prior to decarboxylation.⁵⁶ The next section of this review will address the likelihood of such alternate reaction mechanisms for DcA.

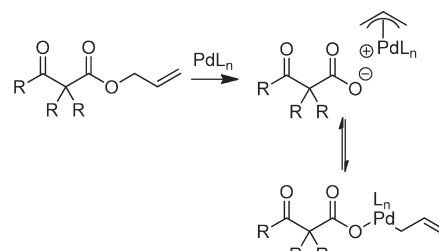
4. MECHANISTIC ASPECTS OF THE DCA OF ENOLATES

As alluded to several times throughout this review, there are several feasible mechanisms that have been proposed for decarboxylative allylation reactions. In this section, it is our goal to summarize the known mechanistic information and to provide general conclusions. However, it is apparent that the mechanism of decarboxylation can change based on substrate, and it is also expected that simple changes to the reaction conditions or ligands may also result in changes in mechanism. For those reasons, the mechanistic features that are characteristic of PPh₃-ligated palladium may not be identical to those of palladium ligated by the Trost ligand, PHOX ligand, or any other ligand. Similar caution must be used in applying the mechanistic knowledge of palladium-catalyzed DcA reactions to the less-studied molybdenum-, nickel-, ruthenium-, and rhodium-catalyzed DcA reactions.

4.1. Ionization/Oxidative Addition

Although there are several different mechanisms that are possible for palladium-catalyzed DcA reactions, all proposals begin with palladium-induced ionization of the allyl carboxylate or carbonate, similar to that proposed for allyl acetates in Tsuji–

Scheme 16. Ionization of Allyl Carboxylates



Trost chemistry.^{1d,2i,2k} The ionization likely produces a π -allyl palladium carboxylate ion pair that is in equilibrium with the neutral σ -allyl complex (Scheme 16). When L_n is a bidentate ligand, as is the case with most asymmetric allylation catalysts, the binding of the carboxylate requires the slippage of the π -allyl ligand to a σ -allyl binding mode to preserve the preferred 16 e[−], square-planar geometry about palladium. The Stoltz group has characterized such a (σ -allyl)palladium- β -ketocarboxylate intermediate and identified it as the resting state for the catalytic cycle mediated by a Pd(PHOX) complex.⁵⁷

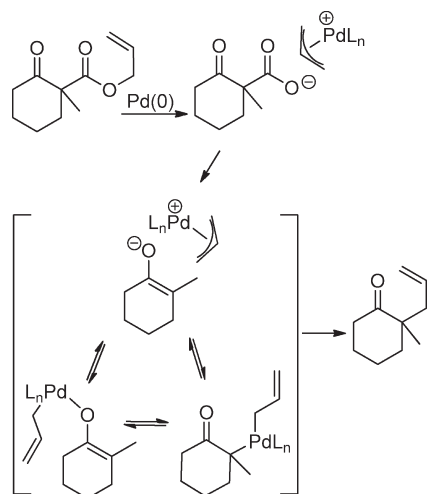
Although the (allyl)palladium carboxylate intermediates have several potential binding modes, the main mechanistic classes for decarboxylative allylation are really defined by the answers to two fundamental questions: (1) Does decarboxylation precede allylation, or does allylation precede decarboxylation? and (2) Does allylation occur through an inner-sphere mechanism where the enolate is bound to palladium prior to reductive elimination or via an outer-sphere mechanism where the enolate directly attacks the allyl ligand?

4.2. Which Comes First, Allylation or Decarboxylation?

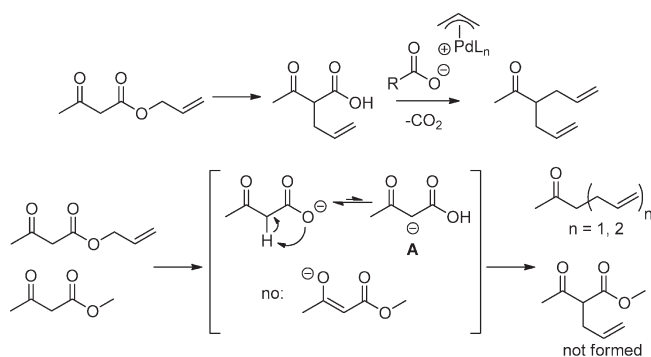
4.2.1. Case of α,α -Disubstituted Esters. The former question can be answered definitively in several specific classes of β -oxoesters. Specifically, α,α -disubstituted- β -oxoesters *must* undergo decarboxylation prior to allylation (Scheme 17). In this class of compounds, decarboxylation is necessary to form a reactive site for allylation. Decarboxylation of the intermediate palladium allyl carboxylate leads to a palladium enolate species. Like the carboxylates, the palladium enolate can potentially exist as an ion pair or a neutral O- or C-bound enolate. Allylation of this enolate produces the product.

4.2.2. Case of Substrates that Possess an α -Hydrogen. In the case of β -oxoesters that bear α -hydrogens, a new mechanistic possibility arises. In these cases, the intermediate carboxylate can undergo proton transfer to form the stabilized enolate (A, Scheme 18). This enolate can undergo Tsuji–Trost allylation followed by decarboxylation of the β -oxo acid to form product. Evidence that this path is occurring is provided by stereochemical studies by Tunge and co-workers that suggest that the α -stereochemistry of the allylation is determined by decarboxylative protonation of the β -oxo acid intermediate,¹⁶ the observation of β -oxo acid intermediates in the decarboxylative couplings of dihydrocoumarins (Scheme 19),¹⁶ and the formation of diallylated byproducts in decarboxylative allylations (Scheme 18).¹⁴ Interestingly, Tsuji and co-workers showed that, when decarboxylative allylation was performed in the presence of methyl acetoacetate, the external acetoacetate was not allylated (Scheme 18).¹⁴ This suggests that the intramolecular proton transfer from the α -position ($pK_a \approx 14$ in DMSO) to the

Scheme 17. Decarboxylation Prior to Allylation



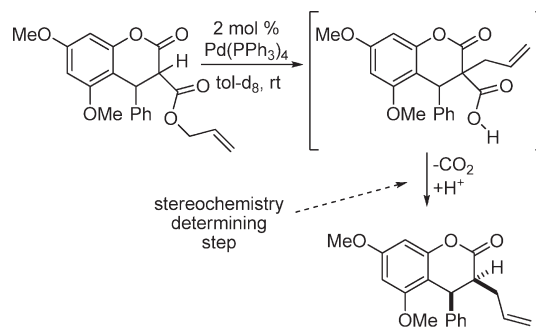
Scheme 18. Allylation Before Decarboxylation



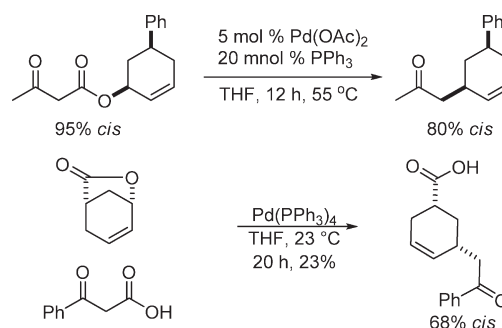
carboxylate ($pK_a \approx 13$ in DMSO) is faster than intermolecular proton transfer. Although less is known about the mechanisms of catalysis with metals other than palladium, Burger and Tunge observed a similar result with a ruthenium catalyst, suggesting a similar mechanism.³²

Ultimately, although it is possible for β -oxoesters that have α -hydrogens to react via a mechanism where decarboxylation precedes allylation, the preponderance of the evidence at this point suggests that decarboxylation of such substrates primarily occurs after allylation. This proposal also readily explains why substrates that contain α -hydrogens are much less likely to undergo competing elimination reactions (see Table 1); such substrates react via less basic, stabilized enolates that are less prone to promote elimination. In addition, the proposal fits with the results of the groups of Fiaud,^{58a} Bäckvall,^{58b} Saegusa,²⁶ Spilling,³⁸ and Tunge,³⁶ which show that such substrates undergo decarboxylative allylation through a double-inversion mechanism with outer-sphere attack of the stabilized nucleophile on the allyl ligand (Scheme 20). The somewhat lower stereospecificities reported in the examples in Scheme 20 could be attributed to competing inner-sphere reductive elimination; however, epimerization of the reactant has been implicated in similar reactions.⁵⁸

Scheme 19. Evidence for Allylation Prior to Decarboxylation



Scheme 20. Evidence for an Outer-Sphere Allylation

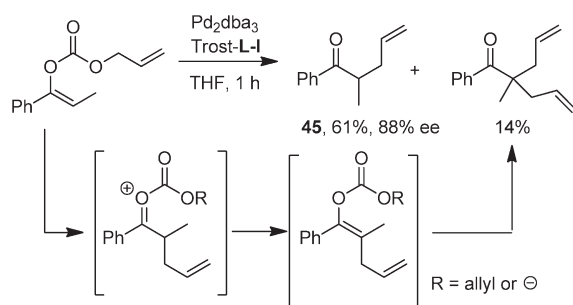


4.2.3. Case of Allyl Vinyl Carbonates. Whether enol carbonates undergo decarboxylation prior to or after allylation remains an unanswered question. Since enol carbonates are expected to decarboxylate more readily than their β -ketocarboxylate counterparts, most researchers have assumed that decarboxylation precedes allylation. With respect to the Trost ligand-supported palladium catalyst, it has been suggested that the decarboxylation is probably rate-limiting and must occur with assistance from Pd; however, the authors offer no support for the latter conclusion and, to our knowledge, definitive experiments have not been conducted.^{40b} One result that suggests that allylation before decarboxylation may be possible is the observation of diallylated products from the DcA of enol carbonates (Scheme 21); the observation of similar products in the DcA of β -ketoesters has been used as evidence for allylation prior to decarboxylation. Diallylated products could also arise from deprotonation and allylation of the product monoallylated ketone; however, such intermolecular proton transfers have not been previously observed, and the allyl ketone product (45) was not significantly racemized as would be expected if it were possible to deprotonate it under the reaction conditions.

4.3. Decarboxylation: Birth of a Nucleophile

Decarboxylation is the key step in decarboxylative coupling and is believed to be the rate-limiting step in the decarboxylative allylation of β -oxo esters as well as enol carbonates (with Trost ligand/Pd). Unfortunately, little is known with regard to this all-important elementary step. Saegusa and co-workers showed that palladium was necessary to catalyze decarboxylation of a sodium β -ketocarboxylate,¹⁵ so palladium plays a critical role in the

Scheme 21. Hypothetical Allylation Prior to Decarboxylation



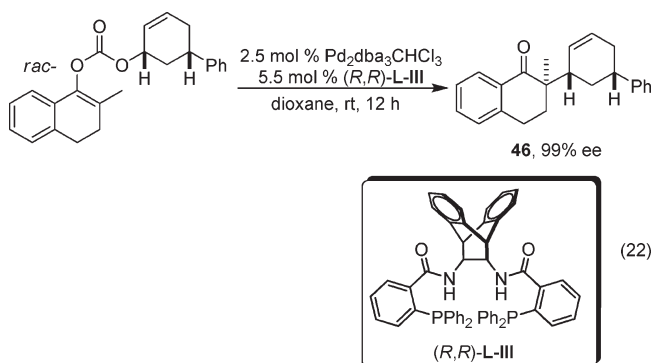
decarboxylation. It has been suggested that the “softness” of palladium, which leads to facile ionization of Pd–carboxylate complexes, is important in facilitating decarboxylation.¹⁸ Although the intimate details of decarboxylation have not been studied using Pd, we can infer possible mechanisms based on other known mechanisms for decarboxylation. For example, one is tempted to suggest decarboxylation via mechanism A (Scheme 22) that is akin to the decarboxylation of β -keto acids.⁵⁹ Such a suggestion is fitting with the relative insensitivity of DcA reactions to different solvents. However, Darensbourg et al. have investigated the catalytic decarboxylation of malonic acids with metals including Cu(I) and Zn(II) and shown that ionization of the metal carboxylate bond facilitates decarboxylation.⁶⁰ Their conclusion that softer metals promote faster decarboxylation is in line with Tsuji’s hypothesis. This would indicate decarboxylation by mechanism C, which closely resembles the mechanism of decarboxylation of other β -ketocarboxylates.⁶¹ Moreover, Darensbourg et al. suggest that coordination of the ketone oxygen may facilitate decarboxylation by allowing the formation of M-bound enolate as opposed to a “free” enolate (D).^{13,60} Applying these observations to palladium-catalyzed decarboxylation of β -oxo esters suggests that an ionic mechanism for decarboxylation is favored over the cyclic transition state favored for decarboxylation of β -keto acids. While ionic mechanisms may not seem favorable for decarboxylations in nonpolar solvents, it is known that nonpolar solvents increase the rates of related decarboxylations.^{59,62} Moreover, it is well-known that palladium allyl carboxylates can exist as ion pairs even in nonpolar solvents.^{1d,2i,2k}

As mentioned, the decarboxylation of enol carbonates has not been the subject of direct experimentation. However, the related decarboxylation of simple alkyl carbonates is known to occur spontaneously as well as by acid catalysis.⁶³ That said, most mechanistic investigations of carbonate decarboxylation reactions were conducted in water, where solvation is substantially different than in the organic solvents used in DcA reactions. A strong correlation of decarboxylation rates with pK_a of the alkoxide ($\beta = 1.4$) does suggest a facile spontaneous decarboxylation of enol carbonates (G);^{63b} the decarboxylation of phenyl carbonate is predicted to occur with a rapid rate of $2 \times 10^3 \text{ s}^{-1}$ in water at 25 °C. Alternatively, a Lewis acid could facilitate the decarboxylation via mechanism H, which is similar to the mechanism for Brønsted acid-catalyzed decarboxylation. The assessment of the true pathway for decarboxylation will require more detailed experimentation, perhaps in combination with computation.

4.4. Reductive Elimination: Inner-Sphere Versus Outer-Sphere

4.4.1. Calculated Transition States. We have already detailed that substrates that allylate prior to decarboxylation do so via an outer-sphere mechanism where the nucleophile directly attacks the allyl ligand of a π -allyl palladium complex. However, there remains a debate over whether nonstabilized palladium enolates react via an inner-sphere or outer-sphere mechanism; it is likely that both are possible. Stoltz has proposed that PHOX-ligated palladium allyl enolates react via an inner-sphere mechanism on the basis of density functional theory (DFT) calculations (Chart 13).⁷¹ That said, the difference in transition state energies for the inner-sphere (B) and outer-sphere processes (A) is a mere 1.6 kcal/mol, and the calculations are reported to have a root-mean-squared (rms) deviation of 1.2 kcal/mol. Nonetheless, the calculated mechanism for the inner-sphere process provides useful insight and suggests an interesting elimination via a seven-membered transition state (B) akin to that proposed by Echavarren and co-workers.⁶⁴ Notably, this seven-membered transition state (B) is 41 kcal/mol lower in energy than the “traditional” 3-center reductive elimination (C). The proposal of a seven-membered transition state for reductive elimination via a σ -allyl palladium complex suggests that the regioselectivity of allylation (linear vs branched) may be different for decarboxylative allylations via Pd(PHOX) complexes and may favor the branched product rather than the typical linear product. To date, the regiochemical outcomes of Pd(PHOX)-catalyzed DcA reactions have not been reported.

4.4.2. Stereochemical Probes. Trost et al. were able to experimentally verify that the decarboxylative allylation, as catalyzed by Trost ligand complexes of palladium, occurs with retention of stereochemistry via a typical double-inversion mechanism.^{40b} This indicates that the DcA occurs via an outer-sphere process similar to that observed for the allylation of lithium enolates (eq 22). Interestingly, however, the analogous synthesis of product 46 from the lithium enolate produced the opposite enantiomer. Thus, the nature of the attacking nucleophile in this DcA is substantially different from a typical enolate.



4.4.3. Crossover Reactions. Another potential way to probe whether “free” enolates or Pd-bound enolates are being formed is through a crossover experiment. In fact, the groups of Saegusa,¹⁵ Tunge,³⁶ Trost,^{40b} Stoltz,⁴¹ and Danishefsky⁶⁵ have all performed crossover experiments aimed at determining whether the intermediate palladium enolates exchange between different palladium complexes (Scheme 23). Unfortunately, the initial ionization of the allyl carboxylate or carbonate likely creates ion pairs that are capable of complete crossover *prior to decarboxylation*. Thus, the observation of crossover can have ambiguous interpretations.

Scheme 22. Potential Mechanisms for Decarboxylation

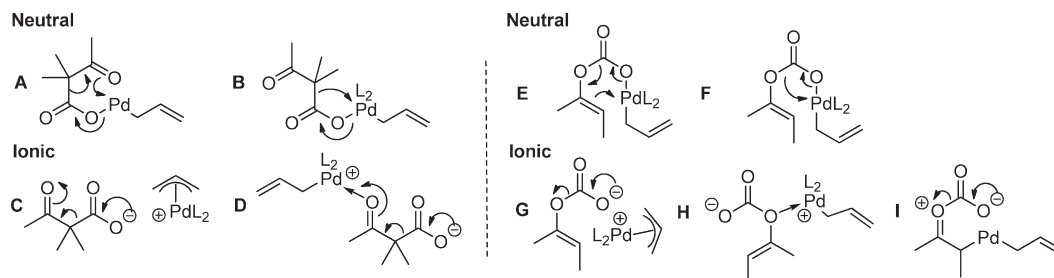
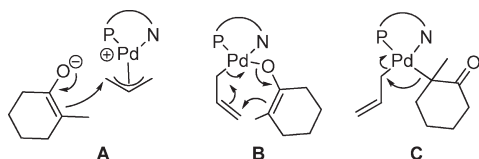


Chart 13. Representations of Calculated Transition States



Trost et al. have argued that crossover in DcA of enol carbonates occurs via ion pairs and not charge-separated enolates based on the fact that acidic additives [e.g., $\text{CH}_2(\text{CO}_2\text{Me})_2$] are not extensively deprotonated under the standard conditions for DcA in dioxane (Scheme 24).^{40b} Whereas a charge-separated, unstabilized enolate would be expected to deprotonate such an acidic additive on thermochemical grounds, these experiments are complicated by the notoriously slow kinetics for deprotonation of carbon acids. Nevertheless, the small amount of proton transfer in dioxane coupled with the observation of more protonation in a more ionizing solvent (THF), suggests that palladium enolates exist as tightly associated species in dioxane. Trost et al. further suggest that protonation and crossover are more likely to occur from π -allylpalladium carbonates because the more stable carbonate anion should be more charge-separated than the analogous palladium enolate.

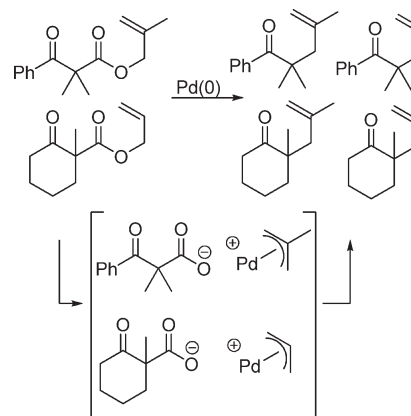
4.5. Kinetics

Little experimentation on the kinetics of decarboxylative allylation has been published. Stoltz has reported that the decarboxylative allylation of enol carbonates is first-order in $\text{Pd}(\text{PHOX})$ catalyst and zero-order in substrate.⁷¹ The zero-order dependence on substrate is most easily attributed to the rapid formation of the resting state (allyl) $\text{Pd}(\text{carboxylate})$ complex under conditions of catalysis, consistent with a mechanism involving rate-limiting decarboxylation.

4.6. Mechanistic Conclusions

Ultimately, decarboxylative allylation is a field that would benefit from more in-depth mechanistic knowledge. That said, some important mechanistic features can be inferred from the vast knowledge of Tsuji–Trost allylation reactions. In addition, stereochemical studies have provided significant insight into the process. The current state of understanding of the mechanisms is summarized below (Scheme 25). Allyl β -oxo esters that contain an α -hydrogen undergo DcA reactions primarily via an allylation–decarboxylation mechanism involving outer-sphere attack of a stabilized enolate on a π -allyl palladium complex (top mechanism, Scheme 25), while allyl β -oxo esters that do not

Scheme 23. Ambiguous Results of a Typical Crossover Experiment



contain α -hydrogens undergo DcA reactions through a decarboxylation–allylation mechanism (middle mechanism, Scheme 25). It is reasonable to propose that allyl enol carbonates undergo DcA by decarboxylative formation of enolates followed by allylation. However, definitive rate data are needed to eliminate alternative mechanisms. The C–C bond-forming allylation can occur either by outer-sphere attack of the enolate or via a 7-membered cyclic transition state for reductive elimination; outer-sphere attack is favored by the Trost ligand, whereas the inner-sphere process may be favored by PHOX ligands, although both pathways are feasible.

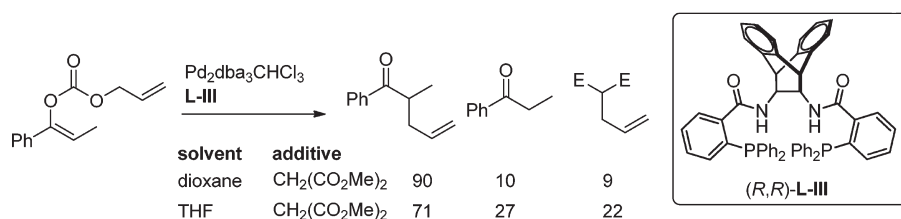
5. APPLICATIONS OF THE DCA OF ENOLATES

Given the ability to allylate enolates under formally neutral conditions, it is not surprising that DcA reactions have found utility in the synthesis of numerous biologically active natural products. Rather than providing an in-depth review of these syntheses, this section aims to concisely communicate how DcA reactions have facilitated some of these syntheses.

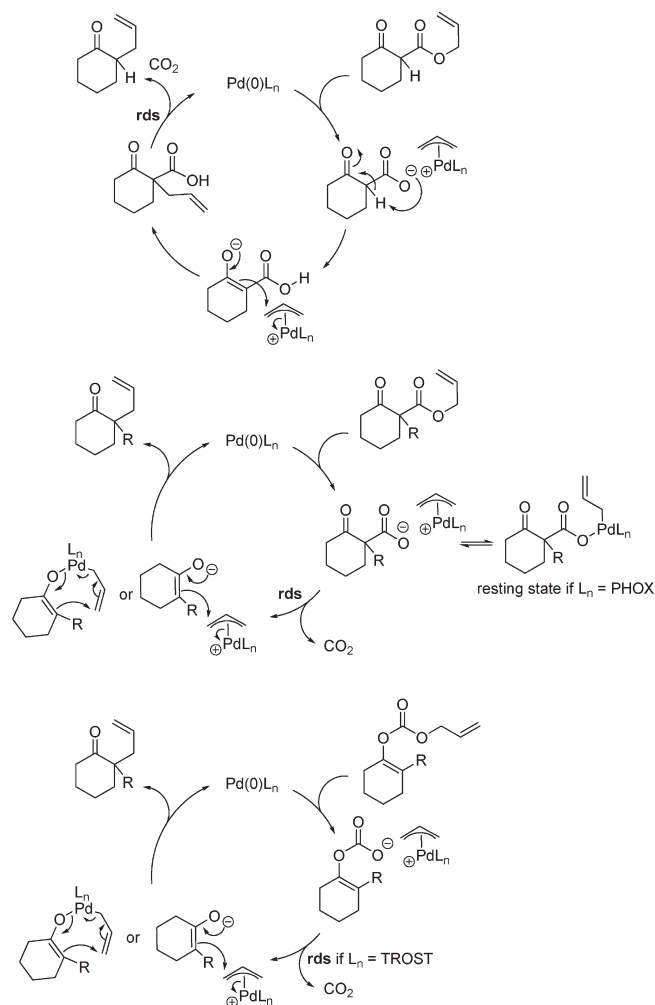
5.1. Dienolate DcA

The Upjohn company utilized DcA of a dienol carbonate in their synthesis of trospoctomycin sulfate, an aminocyclitol antibiotic **48** (Scheme 26).⁶⁶ In the DcA, the γ -position is selectively allylated in preference to the α -position to afford product **47** in modest yield. Whereas simple dienolates derived from β -ketoesters give rise to selective α -allylation,²⁴

Scheme 24. Acidic Additives in DcA of an Enol Carbonate



Scheme 25. Current Mechanistic Understanding

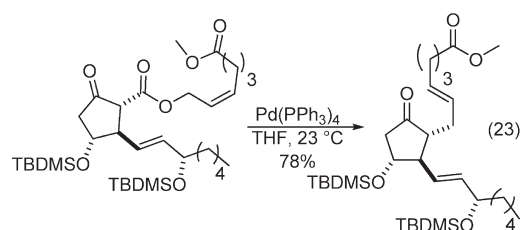


the incorporation of the diene within a pyran moiety may alter the electronics such that γ -allylation is preferred.

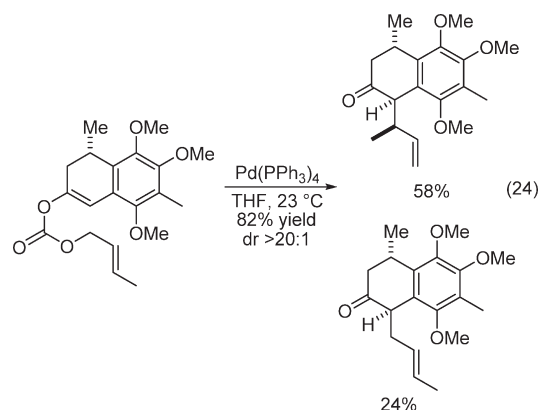
5.2. Diastereoselective DcA

Tanaka and co-workers utilized Pd-catalyzed DcA to provide access to the prostaglandin analogue (*5E*)-PGE₂ (eq 23).⁶⁷ Rather than production of the naturally occurring *Z* configuration of PGE₂, isomerization of the *Z*-olefin under the reaction conditions provided the *E*-olefin product. The *trans*-olefin product forms because C–C bond formation is slower than π – σ –

π isomerization to the thermodynamically more stable *syn*-Pd- π -allyl complex, which gives the *trans*-olefin.

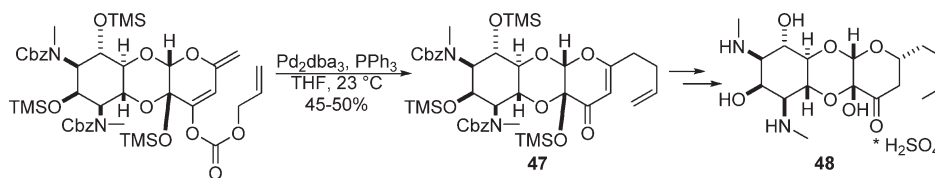


Nicolaou and co-workers performed a diastereoselective DcA of an enol carbonate in the total synthesis of colombiasin A (eq 24).⁶⁸ Interestingly, this DcA favored a single diastereomer of the branched allylation product over the corresponding linear product. This observation of branched selectivity is somewhat unexpected;⁶⁹ however, crotylations are known to give rise to increased branched products in some Tsuji–Trost allylations.⁷⁰ A more intriguing possibility is that the branched selectivity results from an inner-sphere attack of the enolate as proposed by Soltz and co-workers (B, Chart 13).⁷¹

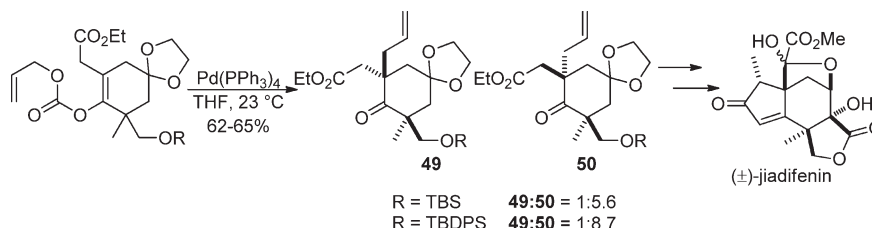


Danishefsky and co-workers have performed a diastereoselective DcA of an allyl enol carbonate as a key step in the synthesis of (\pm)-jiadifenin (Scheme 27).⁶⁵ Importantly, Danishefsky and co-workers reported that attempts to synthesize the required allylated ketone (**50**) by conventional enolate chemistry produced mixtures of allylated products. Believing that allylation α to the ester was a complicating side reaction, they turned to the regioselective DcA reaction. The DcA allowed the synthesis of the requisite allylated ketone in 62–65% yield with acceptable diastereocontrol. The observed relative stereochemistry, along with its dependence on the size of the silyl protecting group, suggests that the distal α -position exhibits moderate diastereocontrol in the allylation of an intermediate enolate.

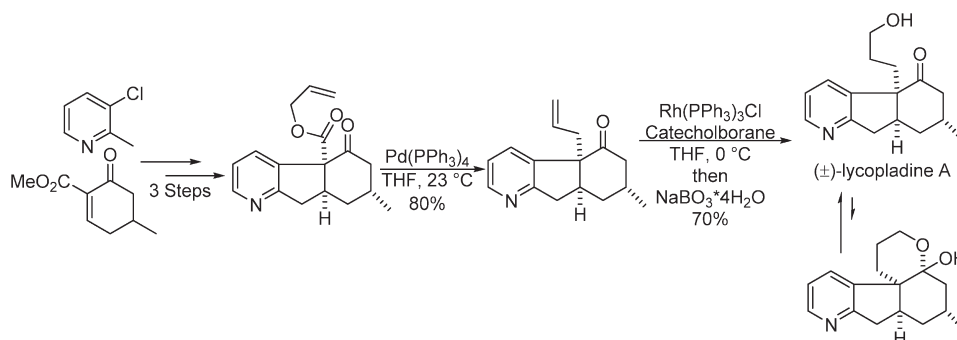
Scheme 26. Synthesis of Trospectomycin Sulfate



Scheme 27. Synthesis of (±)-Jiadifenin



Scheme 28. Synthesis of (±)-Lycopladiene A



Martin and co-workers utilized DcA of a tricyclic β -ketoester as a key step in the total synthesis of (±)-lycopladiene A (Scheme 28).⁷² Here, the authors demonstrated the use of a DcA reaction following a facile cycloaddition to an alkylidene ketoester. This highlights a particular advantage of DcA reactions of β -ketoesters; the ketoester fragment that is required for DcA often facilitates the synthesis of the requisite reactant in addition to the desired product. Decarboxylation and allylation led to the *cis*-ring fused allyl ketone in 80% yield. A catalytic hydroboration/oxidation sequence completed the total synthesis.

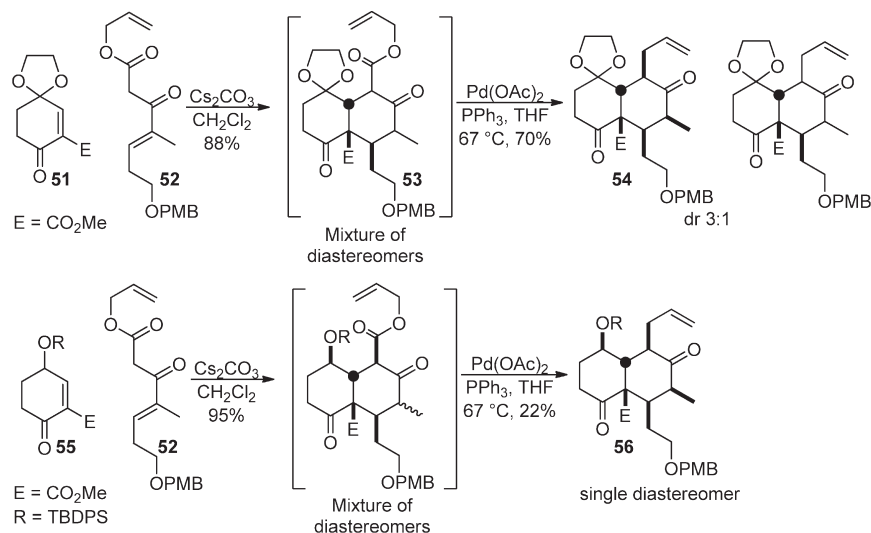
Building off of work by Lavallée and Deslongchamps,⁷³ in which the allyl ester **52** undergoes an annulation followed by decarboxylative protonation, Tricotet and Brückner investigated the ability to perform a DcA to form a new carbon–carbon bond rather than the traditional decarboxylative protonation (Scheme 29).^{74a} When the ketal **51** reacted with **52**, a mixture of diastereomeric allyl ketoesters was formed (**53**). When the mixture of diastereomers was subjected to the DcA conditions described by Tsuji and co-workers,¹⁴ two diastereomeric products were formed in a 3:1 ratio (Scheme 29). Interestingly, when the silyl-protected alcohol (**55**) was used, the DcA formed only a single diastereomer, albeit in modest yield. Nonetheless, the ability to control 5-contiguous stereocenters from one center is remarkable.

Similarly to the lycopladiene synthesis above, this annulation–allylation strategy illustrates the ability of the ketoester to facilitate a cyclization prior to DcA. Thus, the allyl ester activates the reactant (**52**) and delivers an olefin functional group via DcA.

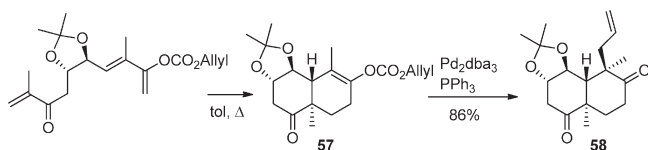
Burns and Forsyth utilized a clever Diels–Alder/DcA reaction to set the stereochemistry of the *trans*-decalin required for the synthesis of salvinorin A (Scheme 30).^{74b} Although the Diels–Alder reaction led to a 1:1 mixture of the *trans*-decalin along with the undesired *cis*-decalin, it did regioselectively produce the enol carbonate **57** that would be difficult to form by other means. DcA of **57** proceeded smoothly and diastereoselectively to form **58** with the two key quaternary stereocenters in place.

Trost and co-workers utilized the DcA of a highly stabilized allyl anion in a recent synthesis of spirotryprostatin B. Trost and Stiles took particular advantage of the destabilized allyl nucleophile, which is less prone to promote elimination, in developing a decarboxylative prenylation (Scheme 31).⁷⁵ The requisite substrate for the prenylation had significant complexity but was made as a mixture of diastereomers in just four steps. Reaction with an achiral catalyst provided the desired product in low dr, implying only a small degree of substrate control. Consequently, catalyst control of the stereochemistry was achieved by utilizing

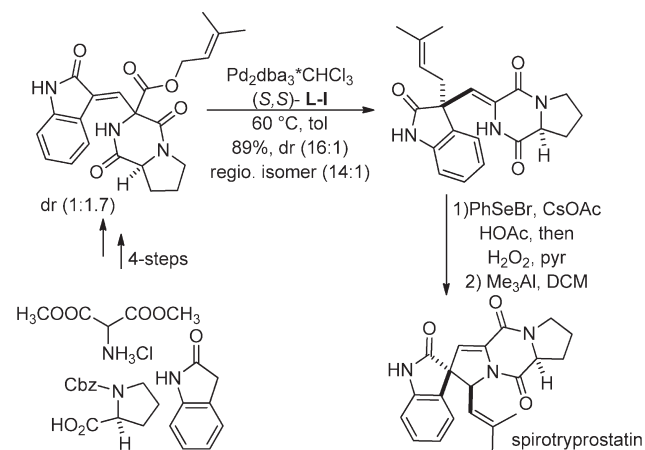
Scheme 29. Outcome of Annulation/DcA



Scheme 30. Diels–Alder/DcA



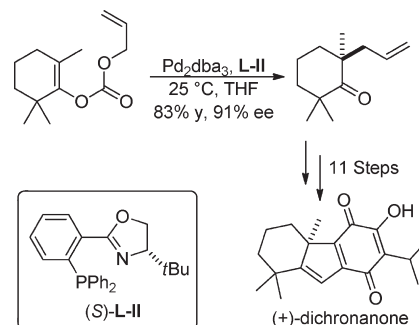
Scheme 31. Synthesis of Spirotryprostatin B



the Trost ligand to effect the formation of the desired isomer with excellent dr. It is noteworthy that decarboxylation produces a nucleophile that could undergo allylation at either of the two nucleophilic sites; however, prenylation occurs preferably at the oxindole terminus with good regioselectivity (14:1).

5.3. Total Syntheses via Enantioselective DcA

Using the asymmetric DcA reaction developed in their lab, McFadden and Stoltz⁷⁶ completed the total synthesis of the (+)-*R*-dichronanone (Scheme 32). This synthesis, and many others

Scheme 32. Synthesis of (+)-*R*-Dichronanone

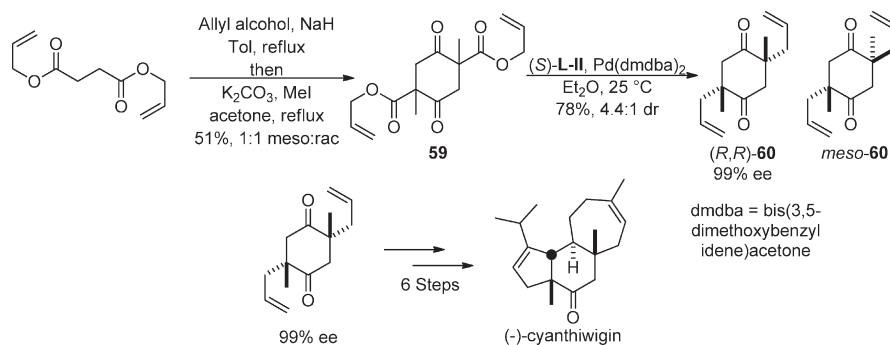
that use DcA reactions, take advantage of the ability to set quaternary carbon stereocenters that are difficult to control using other methods. Thus, the α -stereocenter formed from the DcA of the allyl enol carbonate was carried through to establish the stereochemistry of the relatively congested carbocyclic core of dichronanone.

Enquist Jr. and Stoltz⁷⁷ published a concise synthesis of (–)-cyanthiwigin in which a key step was the asymmetric double decarboxylative allylation (Scheme 33). This synthesis takes full advantage of the stereoconvergent nature of the DcA and allows a 1:1 mix of diastereomeric diesters (**59**), prepared on a large scale through classical chemistry, to be transformed to the desired diastereomer of the enantioenriched ketone **60** (dr = 4.4:1). Furthermore, the clever use of two sequential DcA reactions allowed for statistical asymmetric amplification,⁷⁸ affording a highly enantioenriched product ((*R,R*)-**60**) from a moderately enantioselective allylation. In six more steps, the product was transformed to the natural product, (–)-cyanthiwigin, with the two quaternary carbon centers in place.

5.4. Synthesis via Enantioselective DcA of Vinylogous Ester Derivatives

Stoltz and co-workers have also utilized the decarboxylative allylation of vinylogous esters and thioesters in the synthesis of a

Scheme 33. Synthesis of (–)-Cyanthiwigin



number of natural products. For example, the asymmetric DcA of vinylogous thioester **61** using *t*-Bu-Phox ligand allowed access to the key quaternary carbon stereocenter for the synthesis of (+)-cassiol, a compound with potent antiulcerogenic activity in rats (Scheme 34).⁷⁹ Optimal conditions involved the use of the *p*-methoxy dibenzylidene acetone (pmdba) ligated palladium precatalyst. This more electron-rich dba analogue binds more weakly to the palladium and provides a more active catalyst. A key feature of this synthesis was the use of Stork–Danheiser addition/hydrolysis to introduce the olefinic side chain and translate the α -quaternary center to the γ -quaternary center necessary for cassiol. From the same intermediate allylated ketone, Stoltz and co-workers completed the total synthesis of (+)-carrisone.⁴⁴ Again, the remaining carbons were installed via a Stork–Danheiser addition/hydrolysis protocol.

Stoltz and co-workers also successfully employed an asymmetric DcA of an allyl enol carbonate that was derived from a cyclic vinylogous ester in the total synthesis of elatol, a member of the chamigrene subclass of sesquiterpenes (Scheme 35).⁸⁰ The authors found that reaction of **62** using the standard (*S*)-*tert*-butyl PHOX ligand proceeded sluggishly, and they reasoned that this was due to slow alkylation. This conclusion was based on their ability to get **62** to undergo decarboxylative protonation under alternative conditions as well as on the ability for the nonchlorinated analogue to undergo DcA. In support of their theory, inclusion of CF_3 substituents into the ligand led to more rapid allylation and smoother DcA. This synthesis also highlights the ability to use DcA in combination with ring-closing metathesis (RCM) to control the stereochemistry of spirocyclic carbocycles. A more detailed report has recently been published.⁸¹

6. CARBON NUCLEOPHILES OTHER THAN ENOLATES

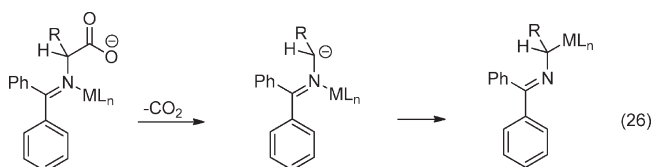
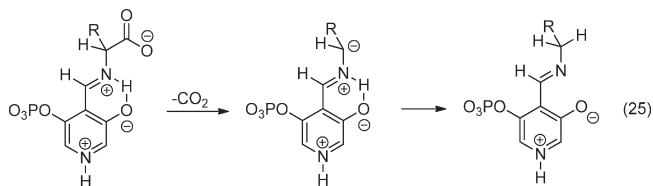
Although the majority of synthetic efforts have focused on the decarboxylative allylation of enolates, DcA has proven to be a rather general method for in situ formation of a number of carbon nucleophiles including acetylides,¹⁵ α -cyano anions,¹⁵ acrylonitriles,¹⁵ coumarins,⁸² nitronates,¹⁸ heteroaromatic alkanes,⁸³ nitrotolyl anions,⁸⁴ α -ketimine anions,⁸⁵ and α -sulfonyl anions.⁸⁶ In addition to the carbon nucleophiles generated via decarboxylation, heteroatom nucleophiles have also been shown to participate in DcA reactions and will be discussed in a later section. These decarboxylative coupling methods have often proven complementary or superior to more classical methods for generating reactive carbon nucleophiles because DcA reactions occur under mild, formally neutral conditions. Moreover, catalytic

decarboxylative couplings ensure that reactive nucleophiles are generated in low concentration and in close proximity to electrophilic reaction partners. As a consequence, the coupling is often faster than many other competing processes, such as proton transfer from more acidic functional groups.

6.1. 2-Azallyl Anions

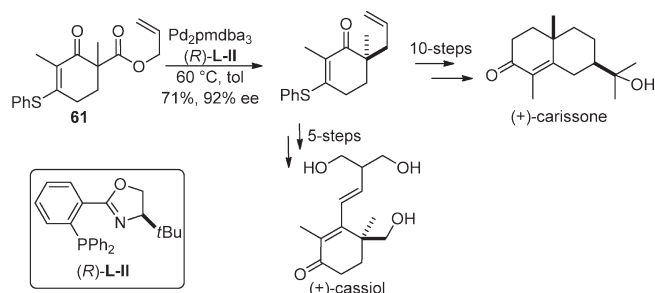
Homoallylic amines are an important building block for a variety of nitrogen-containing natural products. Much of the synthetic methodology for accessing homoallylic amines has focused on the addition of stoichiometric organometallic allyl nucleophiles to imines.⁸⁷ Burger and Tunge sought to design a complementary route in which an allyl electrophile is coupled to a nucleophilic α -imino anion that is derived from an α -amino acid.⁸⁵

Taking note of how nature achieves the decarboxylative protonation of amino acids, pyridoxal-5'-phosphate (PLP)-dependent decarboxylases facilitate condensation of PLP and the amino acid to generate an iminium carboxylate (eq 25). The iminium carboxylate decarboxylates to generate an α -imino anion, which ultimately protonates.⁸⁸ Burger and Tunge postulated that coordination to a metal, rather than a proton, might also facilitate the decarboxylation and give rise to an anion that could be used for C–C bond formation (eq 26).

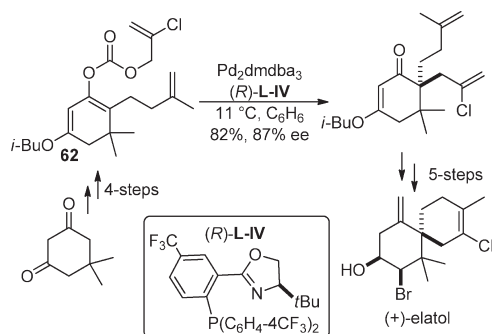


To begin their investigation, Burger and Tunge synthesized several ketimine-protected α -amino allyl esters and subjected them to a variety of $Pd(0)$ catalyst sources. The DcA reaction took place smoothly at 25–40 °C and gave rise to isomeric products **63** and **64** (Scheme 36). Additionally, in some cases protonation of the α -imino anion was problematic, but

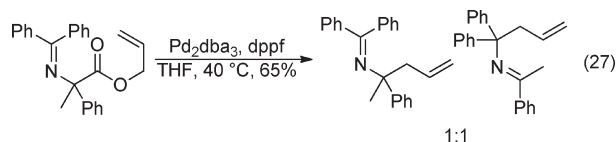
Scheme 34. Syntheses of (+)-Cassioid and (+)-Carrisone



Scheme 35. Synthesis of (+)-Elatol

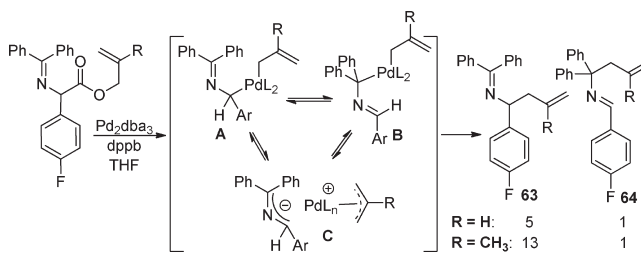


protonation could be mitigated by using *dppb* as the ligand. The formation of **64** was suggested to arise from an intermediate 2-azaallyl anion (**C**) or equilibrating palladium σ -azaallyl complexes (**A** and **B**). The ratio of **63**/**64** was somewhat dependent on solvent, with THF providing the highest ratios of **63**/**64**. In addition, the effect of substitution on the 2-position of the allyl was notable. Although the reaction was more sluggish when the 2-position was substituted, the ratio of **63**/**64** was substantially improved ($R = \text{H}$ vs Me , Scheme 36). Thus, a substituent in the 2-position led to significantly more of the desired product. One potential explanation is that C–C bond formation is primarily determined by sterics, and an increase in the steric size of the electrophilic $\text{Pd}-\pi$ -allyl increases the regioselectivity. In partial support of this hypothesis, reaction of a sterically more encumbered α,α -disubstituted amino acid gave poor regioselectivity (eq 27). Although not synthetically valuable, the ability of disubstituted amino acid derivatives to undergo DcA has an important implication; it suggests that decarboxylation of the amino acid precedes allylation.

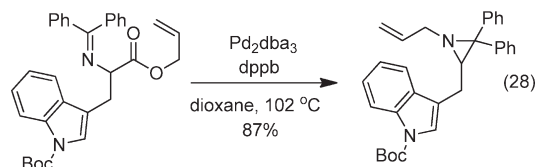


A series of α -ketimine-protected amino allyl esters were subjected to the DcA reaction conditions, and modest to excellent yields of the product homoallylic amines were achieved (entries 1–10, Table 16). Whereas the reactions of a variety of aryl amino acids proceeded under mild conditions (entries 2, 5, and 6), DcA of alkyl-substituted amino acid derivatives required

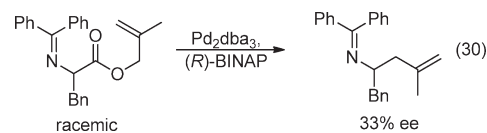
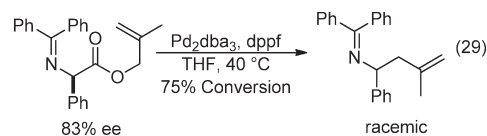
Scheme 36. DcA of Amino Acid Derivatives



substantially higher temperatures to achieve reaction. This likely reflects the more difficult decarboxylation of α -alkyl imino acids and implicates decarboxylation as the rate-limiting step of the reaction. In addition to their requisite reaction conditions, some α -alkyl amino acids undergo a different DcA reaction when coupled with unsubstituted allyl esters. For example, the attempted DcA of a protected tryptophan derivative gave the *N*-allyl aziridine rather than the expected C-allylation product (eq 28).



Like the observation of allyl aziridine side products, the stereochemistry of amino acid DcA has important mechanistic implications. Specifically, when a nonracemic ester was allowed to undergo DcA, it produced racemic product (eq 29). Importantly, the reactant was not racemized under the reaction conditions. Not only does this show that racemization occurs via an intermediate formed in the reaction, it also supports a mechanism involving decarboxylation prior to allylation. Since the loss of stereochemistry in the DcA of an enantioenriched substrate is indicative of an achiral or rapidly racemizing intermediate, the C–C bond formation is likely to be the stereo-determining step, which should allow for enantioselective DcA. Indeed, when a racemic substrate was subjected to DcA using $(R)\text{-BINAP}$ as a ligand, a modestly enantioenriched homoallylic amine was produced (eq 30).



The authors proposed the following mechanism (Scheme 37). Ionization of the reactant ester leads to $\text{Pd}-\pi$ -allyl carboxylate **A**. This intermediate may undergo spontaneous decarboxylation to form an azaallyl anion. Alternatively, decarboxylation may be facilitated through an intermediate like **B**, in analogy to related

Table 16. DcA of α -Ketimine-Protected Amino Acid Allyl Esters

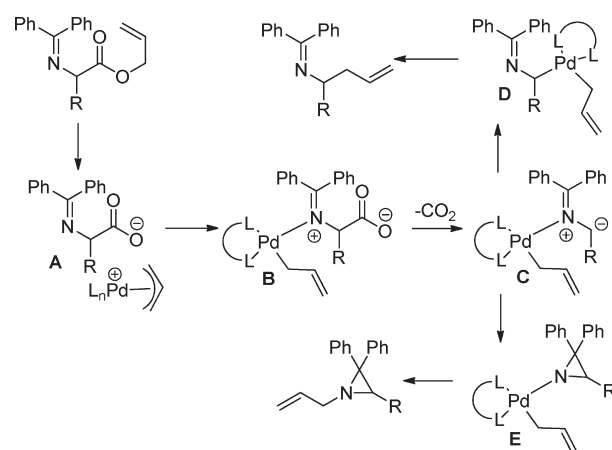
entry	R ¹	R ²	solvent	temp (°C)	ligand	yield (%)
1	Ph	H	THF	25	dppf	67
2	Ph	Me	THF	40	dppf	81
3	Ph	Ph	THF	40	dppf	75
4	4-F-C ₆ H ₄	H	THF	25	dppb	66
5	4-F-C ₆ H ₄	Me	THF	40	dppb	93
6	4-MeO-C ₆ H ₄	Me	THF	40	dppb	85
7	CH ₂ Ph	Me	Toluene	110	dppf	63
8	CH ₂ Ph	Ph	Toluene	110	dppf	46
9		H	Dioxane	102	dppb	67
10		Me	Toluene	110	dppf	26

acid-catalyzed decarboxylations.^{88b} Intermediate C can react via two pathways; a 1,2-Pd-shift leads to D and ultimately the observed homoallylic amine product. Alternatively, electrocyclization leads to the Pd-aziridine E, ultimately forming the *N*-allyl aziridine. The observed *N*-allyl aziridines could likewise be formed by *N*-allylation followed by electrocyclization.

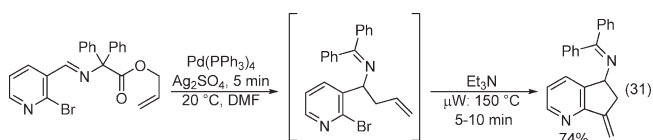
Soon after Burger and Tunge⁸⁵ published their findings, Yeagley and Chruma⁸⁹ published a complementary method that generates the same intermediates through diphenylglycinate imines (Scheme 38). By utilizing diphenylglycine as the amino acid, the authors showed that the coupling partner could be readily varied by condensation with a variety of aromatic aldehydes. This provides isomeric starting materials to those utilized by Tunge. Ultimately, by deriving the precursor from condensation with aldehydes, the Chruma method allows for more straightforward access to products that are derived from non-natural amino acids.

The dependence of the regiochemical outcome of the allylation on the electronics of the R substituent as observed by Chruma are consistent with observations made by Tunge, suggesting the formation of a common intermediate from either isomeric allyl amino acid (Scheme 38, Table 17). In addition, an increase in the steric size of the R² substituent also makes the reaction more selective for allylation of the less-crowded terminus of the 2-azaallyl anion (Table 17, entries 1 and 2). Entries 6–8 demonstrate the advantage of Chruma's DcA strategy; synthesis of these products using Tunge's strategy would require the arduous synthesis of unusual, unnatural amino acids.

Chruma and co-workers have gone on to disclose slightly different conditions that utilize Pd(PPh₃)₄ as a catalyst to facilitate a tandem DcA–Heck cyclization (eq 31).⁹⁰ Although the reaction can be conducted in one step, the one-pot, two-step reaction provides higher yields. This chemistry highlights a common theme in decarboxylative couplings: decarboxylative allylation is facile and tolerant of aryl halide substituents. Thus,

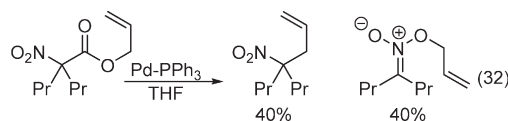
Scheme 37. Proposed Mechanism for the DcA of α -Imino Esters

tandem decarboxylative allylation/cross-coupling reactions can allow multiple bond formations in single-pot reactions.

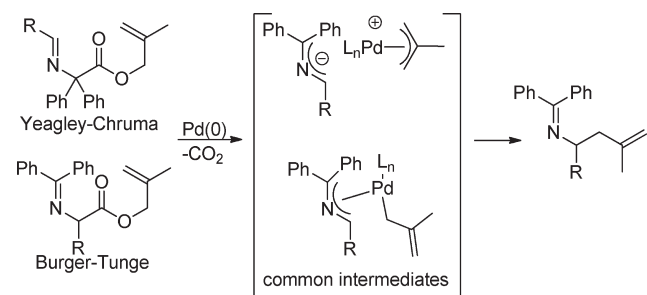


6.2. Nitronates

Although DcA reactions of amino acid derivatives provide access to protected homoallylic amines, the formation of tertiary homoallylic amines from amino acids is plagued by poor regiochemistry (eq 27). Similar homoallylic amine derivatives can potentially be accessed via the DcA of nitroacetic esters followed by reduction of the nitrogen, a reaction first demonstrated by Tsuji.¹⁸ Specifically, Tsuji reported the successful DcA of a single substrate, in which equal amounts of the isomeric C- and O-allylation products are formed (eq 32). Grenning and Tunge recognized that, if competing O-allylation could be avoided, the DcA of α -nitroacetic allyl esters might allow facile access to tertiary homoallylic amines that cannot be accessed via the DcA of amino acid esters.⁹¹



Tunge found that the DcA of allyl nitroacetic esters took place smoothly and rapidly in CH₂Cl₂ in the presence of 5 mol % Pd(PPh₃)₄ to afford the desired C-allylated product in high yield (Chart 14). The reaction works well for a range of α , α -dialkyl substrates as well as an α -phenyl α -fluoro ester. In addition, because the intermediate nitronates are relatively nonbasic, the reaction tolerates some β -hydrogens on the allyl electrophile. Similar to the DcA of enolates, the reaction of α -nitro acetates is stereoconvergent with the α -stereoselectivity of the reaction being determined by the allylation. Furthermore, the *anti*- or *exo*-diastereoselectivity that is observed suggests that the allylation occurs via steric control (Chart 14).

Scheme 38. Regioconvergent DcA of α -Imino Allyl EstersTable 17. DcA of α -Imino Allyl Esters

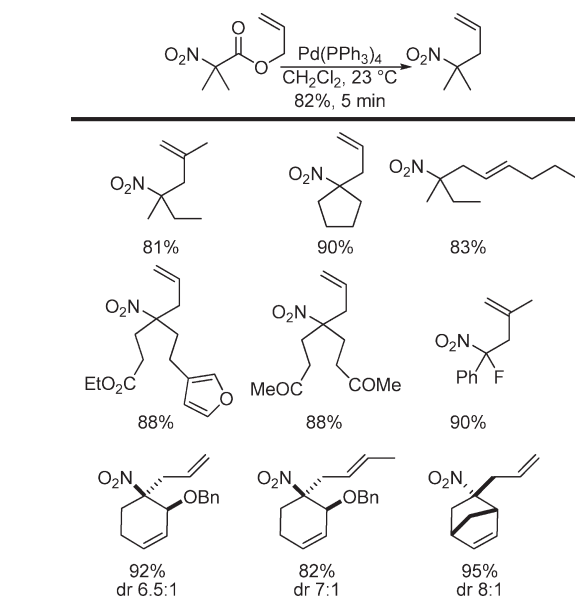
entry	R ¹	R ²	time (h)	yield %	63:64
1		H	0.5	96	6.1:1
2		Me	2	82	>20:1
3		H	1	97	5.5:1
4		H	1	91	20:1
5		H	7	52	2.2:1
6		H	2.5	47	>20:1
7		H	2	75	4.1:1
8		H	1.5	91	>20:1

Although no *O*-allylation product was observed by Grenning and Tunge,⁹¹ they did observe competing formation of α,β -unsaturated aldehyde, which they propose came from the break-down of the *O*-allylated product (**B**, Scheme 39). Consistent with a reversible *O*-allylation, they found that increasing the concentration of catalyst or reaction favored the C-allylated product. This higher catalyst concentration favors bimolecular reformation of the π -allyl palladium complex (**A**) from the *O*-allyl nitronate (**B**), allowing formation of C-allylated product **65** to occur more rapidly than unimolecular decomposition of **B** (Scheme 39).

6.3. Nitroaromatic Alkanes

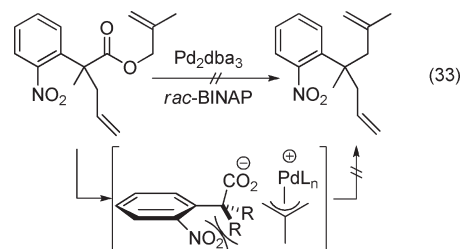
Waetzig and Tunge showed that anilines, a common motif in the pharmaceutical industry, could be accessed via DcA of nitroarene acetic esters.⁸⁴ Optimizations revealed that little reaction of an allyl *ortho*-nitrobenzene acetic ester took place at ambient temperature (entry 1, Table 18), but proceeded

Chart 14. DcA of Allyl Nitroacetic Esters



smoothly at 110 °C to give a mixture of the desired product (**66**) and undesired allylated aromatics, **67** (entry 2). Changing to the bidentate *rac*-BINAP ligand (entry 3) led exclusively to the desired product. The product ratio decreased when changing to the *para*-nitro analog, but allylated alkane **66** was still the dominant product (entry 4).

With optimal conditions in hand, Waetzig and Tunge set about studying the scope of the reaction. Pendant electron-withdrawing functional groups are well-tolerated, and the reaction works well even with electron-donating substituents on the nitroaromatic ring (Chart 15). While the *para*-nitro derivatives allowed use of α,α -disubstituted substrates (**68**), the α -position cannot be fully substituted if the substrate is an *ortho*-nitro arene. This is likely due to the inability to achieve the requisite conformer for decarboxylation because of developing *A*-strain with the *ortho*-nitro substituent (eq 33).



In addition to α,α -disubstituted *o*-nitrobenzene acetates that were unreactive, allyl ester **69** (eq 34) was unreactive under standard conditions. However, when the catalyst was switched to $\text{Pd}(\text{PPh}_3)_4$, the substrate underwent elimination to afford the diene, showing that β -hydrogens on the allyl fragment are not tolerated (eq 34). However, if a second nitro group was included on the substrate (eq 35), several effects were noted: (1) the reaction took place smoothly at room temperature; (2) $\text{Pd}(\text{PPh}_3)_4$ was a competent catalyst; and (3) the additional stabilization of the anion made the reaction more tolerant toward allyls that possessed β -hydrogens; however, prenylation was still not possible.

Scheme 39. C- Versus O-Allylation

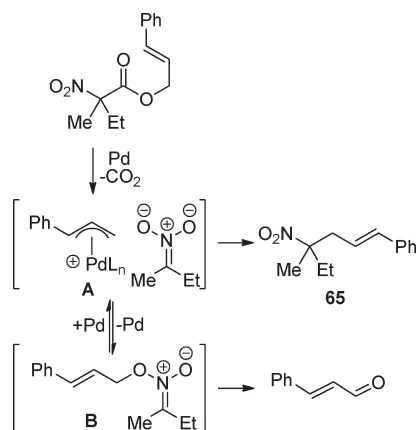
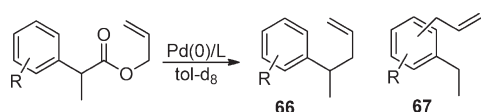
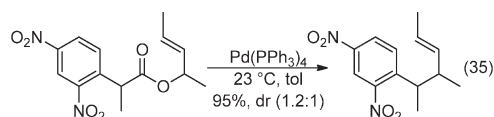
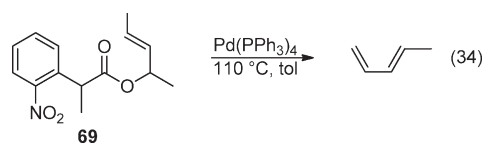


Table 18. Optimization of the DcA of Nitroarene Acetic Esters



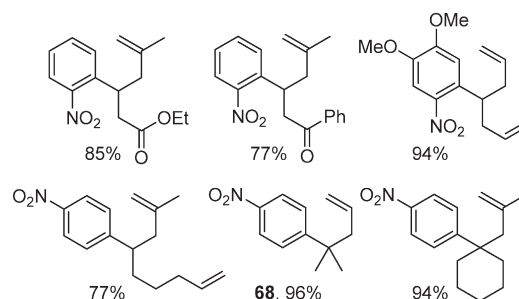
entry	R	catalyst/Ln	temp (°C)	66/67
1	<i>o</i> -NO ₂	Pd(PPh ₃) ₄	25	NR
2	<i>o</i> -NO ₂	Pd(PPh ₃) ₄	110	1.8:1
3	<i>o</i> -NO ₂	Pd ₂ dba ₃ /rac-BINAP	110	>20:1
4	<i>p</i> -NO ₂	Pd ₂ dba ₃ /rac-BINAP	110	4.9:1
5	<i>p</i> -NO ₂	Pd ₂ dba ₃ /dppe	110	2:1
6	<i>p</i> -NO ₂	Pd ₂ dba ₃ /dppf	110	1.6:1



6.4. Heteroaromatic Alkanes

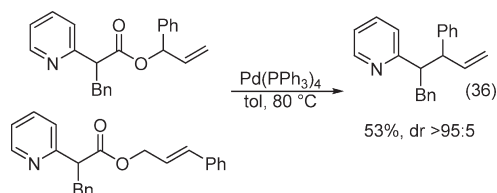
In looking at DcA reactions of other electron-deficient aryl acetic esters, Waetzig and Tunge demonstrated the ability for the allyl esters of α -heteroaromatic acetic acids to undergo DcA (Chart 16).⁸³ Several things were unusual about this coupling: (1) the reaction was highly selective for the branched product; (2) the resulting dr was unusually high for an allylation of an acyclic substrate; and (3) prenyl groups were reasonably well-

Chart 15. DcA of Nitroarene Allyl Acetic Esters

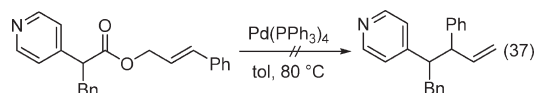


tolerated. The ability of aromatic substrates with an *N*-atom at the 2-position to undergo DcA was fairly general (Chart 16). Moreover, the reaction was unusually tolerant of β -hydrogens on the allyl portion such that even reverse prenylation to form adjacent quaternary centers was accomplished, albeit in modest yields (70). Reverse prenylation of substrates possessing only one α -substituent provided better yields of allylated products (69). Crotylation took place more readily than prenylation (71 and 72) but occurred with variable diastereoselectivity.

The ability to accomplish the decarboxylative reverse prenylation suggested that a benzylic anion is not formed; such a basic reactant would be expected to cause extensive elimination. Furthermore, a Lewis acid-mediated Carroll-like rearrangement was ruled out based on the fact that the branched ester leads to the branched product (eq 36). The same product is formed from linear ester, suggesting a common Pd- π -allyl intermediate is formed in the reaction (eq 36).



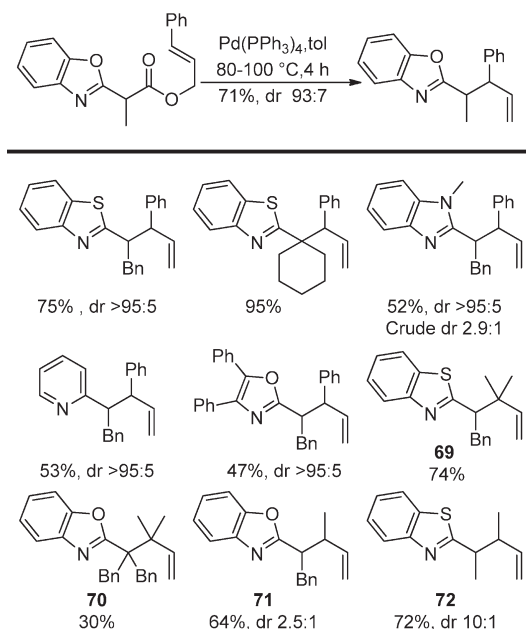
Furthermore, when a 4-pyridyl analogue was subjected to the catalytic conditions, it did not lead to formation of any desired product (eq 37). Thus, a nitrogen must be in the 2-position for successful reaction.



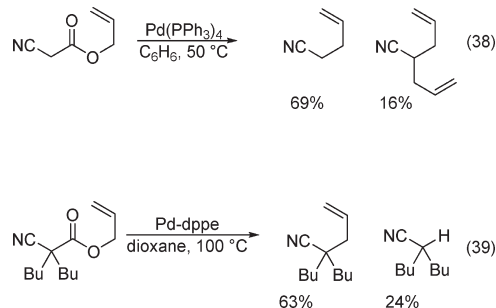
On the basis of these results, the authors proposed the following mechanism. Ionization leads to Pd- π -allyl carboxylate A (Scheme 40). *N*-allylation of the heteroaromatic leads to pyridinium B. This pyridinium is activated to undergo charge-neutralizing decarboxylative dearomatization to generate C, which undergoes facile aza-Cope rearrangement via a boat conformation to lead to the observed allylated alkyl pyridine.

6.5. α -Cyano Anions

In his seminal paper on the decarboxylative coupling of β -ketoesters,¹⁵ Saegusa attempted the DcA of an allyl cyanoacetic ester. In one example, the substrate decarboxylated to provide the product in 69% yield accompanied by 16% of the diallylated product (eq 38). Tsuji later reported two examples of a similar

Chart 16. DcA of α -Heteroaromatic Acetic Allyl Esters

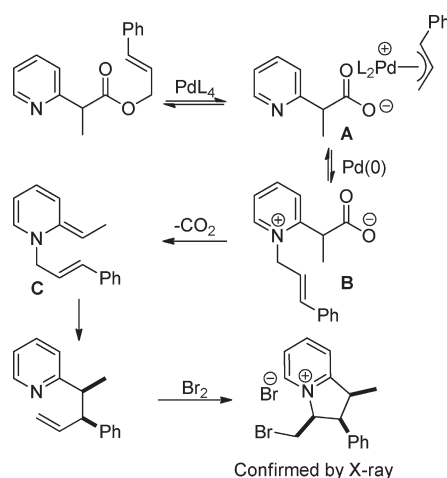
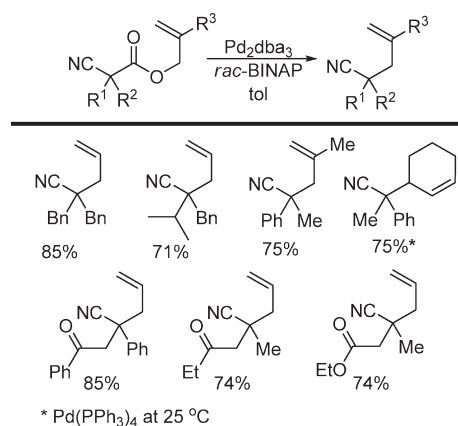
reaction and showed that it was possible for an α -quaternary cyanoacetic acid derivative to undergo DcA, but the formation of protonation byproduct was problematic (eq 39).



In 2009, Recio and Tunge published an improved synthetic protocol for decarboxylative allylations of α -cyanoacetic esters and included a study of the scope.⁹² Ligand screening revealed that *rac*-BINAP could almost completely suppress the protonation product observed with many other ligands (Chart 17). The reaction appears to tolerate terminal substitution of the allyl electrophile with α -aryl nitriles, but α,α -dialkyl substrates promoted extensive β -hydride elimination in such cases. As with other DcA reactions, the α -phenyl substituent also has a pronounced effect on the rate of the reaction; α -aryl nitriles undergo DcA at room temperature, whereas α,α -dialkyl nitriles only react at elevated temperature (100 °C).

Like the preceding reaction involving heteroaromatic alkanes, this reaction differs from most other DcA in its preferences for formation of the branched product when α,α -dialkyl-substituted cyanoacetates are utilized (Table 19). The preference for the branched product is not uniform but rather appears to be substrate-dependent (entries 1 and 2 vs 3). If the ester possesses an α -phenyl substituent, then the ratio changes in favor of the linear product (entry 3).

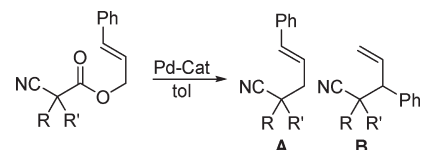
Scheme 40. Proposed Mechanism for the DcA of Heteroaromatic Allyl Acetic Esters

Chart 17. DcA of α -Cyano Allyl Acetic Esters

The authors explain this observation via competing kinetic *N*- and *C*-allylation of a common intermediate (Scheme 41). When the nucleophile is unstabilized and sterically large at the α -position, *N*-allylation is preferred (entries 1 and 2, Table 19), and when the nucleophile is stabilized by an α -phenyl group, the major kinetic product is *C*-allylation. In this case, the low regioselectivity suggests there is only a small energy difference between the competing pathways. After kinetic *N*-allylation, [3,3]-sigmatropic rearrangement is expected to occur to afford the branched product; related rearrangements are known to take place rapidly at room temperature.⁹³ Such regioselectivity could also be explained via competing inner-sphere and outer-sphere allylation mechanisms as discussed for enolate intermediates (section 4.4.1). With this mechanism in mind, the less-stabilized α,α -dialkyl anions would be prone to react via an inner-sphere mechanism giving the branched product, while the benzylically stabilized anion could prefer to react via an outer-sphere mechanism.

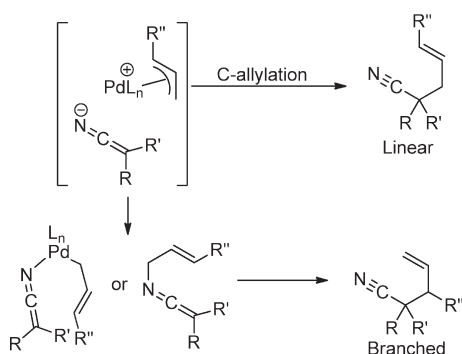
Lastly, the decarboxylative generation of nitrile-stabilized anions is regioselective, allowing the site-specific generation and reaction of a nucleophile at the position that bears CO₂. In this

Table 19. DcA of α -Cyano Allyl Acetic Esters—Regioselectivity



entry	R, R'	yield %, A/B
1	allyl, allyl	73%, 1:>9
2	Bn, Bn	62%, 1:5
3	Ph, Me	65%, 1.5:1

Scheme 41. Rationale for Linear and Branched Products



way, decarboxylation is capable of circumventing pK_a issues that hinder formation of anions derived from less-acidic positions using traditional acid–base chemistry. For example, the DcA of **73** is regiospecific (Scheme 42), with no isomerization of the intermediate nucleophile to the more stable anion, even though the malonate hydrogen is $\sim 10^{15}$ more acidic than a tertiary nitrile (H_a vs H_b , **74**). In this way, decarboxylative metalation could be a useful synthetic tool for kinetic formation of anions that are not accessible by standard acid–base chemistry.

6.6. Vinylogous Malononitriles

Tunge and co-workers have also demonstrated that the DcA of vinylogous malononitriles is facile and kinetically favors α -allylation (Chart 18).²⁴ Allylation occurred preferentially α to the nitriles, suggesting that the regiochemistry is electronically controlled. The yields were generally good to excellent, and the regioselectivities were high; however, allylation with a 2-substituted allyl electrophile provided the product with low regioselectivity (**75**). Finally, the fact that product **76** could be obtained in high yield suggested that decarboxylation must precede C–C bond formation (Chart 18).

The authors also found that the α -allylated kinetic product could undergo a net Pd(0)-mediated Cope rearrangement (Scheme 43).⁹⁴ This presumably occurs by Pd(0) reionizing the kinetic product (**77**) to form the sufficiently stable anion, which ultimately gives rise to the conjugated product (**78**) via attack of the Pd- π -allyl from the γ -terminus.⁹⁵ Notably, the Cope rearrangement of **77** to product **78** did not occur at 70 °C

Scheme 42. Access to Thermodynamically Unfavorable Nucleophiles

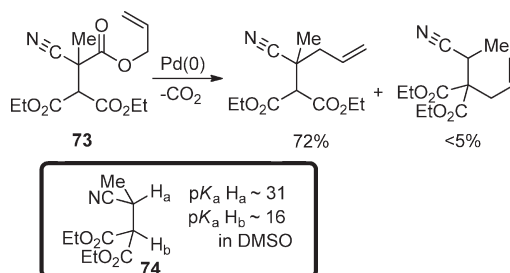
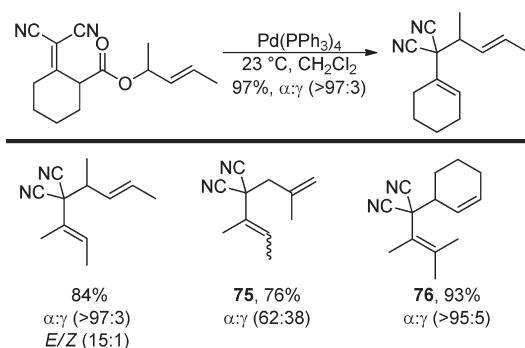


Chart 18. DcA of Vinylogous Malononitriles



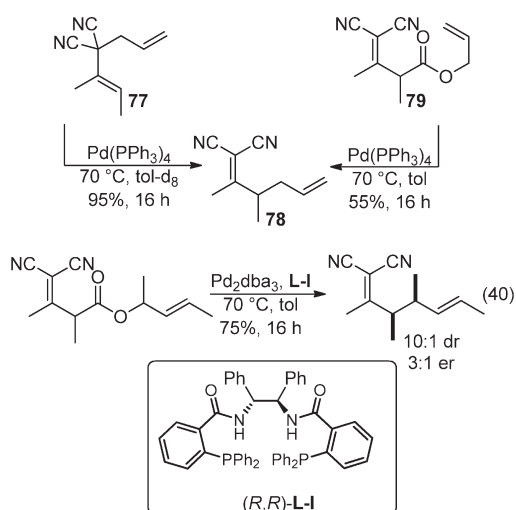
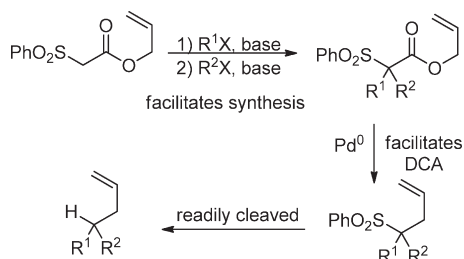
without the Pd(0) catalyst. The same product could be obtained starting directly from the ester (**79**) by heating the reactant at 70 °C in the presence of catalyst. Thus, the authors could access either the α - or γ -allylated products depending on the temperature of the reaction mixture. In addition they showed that the reaction could be made modestly enantioselective if the Trost ligand **L-I** was used (eq 40).

6.7. α -Sulfonyl Anions

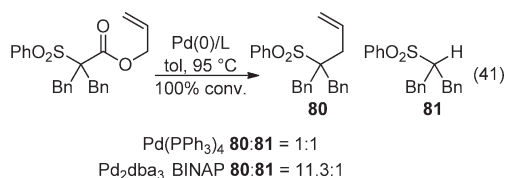
6.7.1. Racemic Decarboxylative Allylation. In all the DcA's developed, successful reaction is reliant on substrate stabilization of the anion that is formed upon decarboxylation. However, a methodology that would allow the DcA of unstabilized hydrocarbon nucleophiles would be valuable. Weaver and Tunge posited that sulfones might allow such a transformation in a two-step process (Scheme 44).⁸⁶ Given the electron-withdrawing nature of the sulfone, it was envisioned that the α -sulfonyl carboxylate should be activated toward decarboxylation, generating an α -sulfonyl anion that could undergo C–C bond formation to give homoallylic sulfones. Reductive removal of sulfones is a well-established process, thus allowing the formal allylation of an unactivated hydrocarbon.⁹⁶ Furthermore, the α -sulfonyl ester reactant is activated for derivatization, which facilitates synthesis of more complex sulfones.

The most common method for alkylation of a secondary sulfone requires cryogenic temperatures and alkyl lithium base and frequently utilizes stoichiometric, toxic hexamethylphosphoramide (HMPA).⁹⁷ Thus, Weaver, Tunge, and co-workers believed that a DcA methodology that occurred under neutral conditions and produced only CO_2 as the byproduct might be

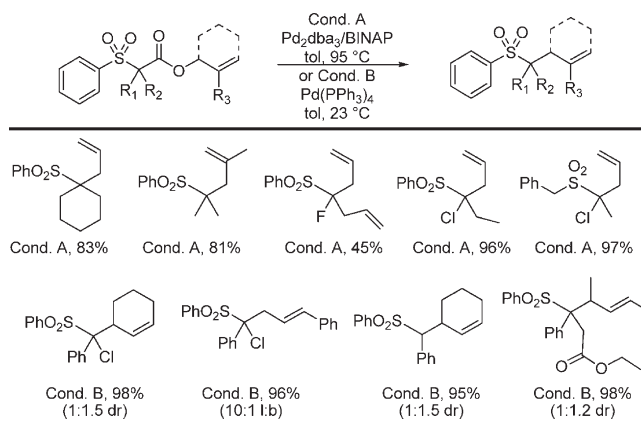
Scheme 43. Pd(0)-Catalyzed Allylation/Cope Rearrangement

Scheme 44. α -Sulfonyl Esters: Surrogates of Hydrocarbon DcA

superior to existing methodology for the synthesis of tertiary sulfones. Toward this end, a fully substituted α -sulfonyl ester was synthesized and exposed to $\text{Pd}(\text{PPh}_3)_4$ under a variety of reaction conditions (eq 41). Temperatures that were $<95^\circ\text{C}$ led to sluggish reaction, and other solvents led to increased amounts of protonated product (**81**) rather than the desired allylated product (**80**). A screening of ligands revealed that bidentate ligands were superior to $\text{Pd}(\text{PPh}_3)_4$, and the reaction using *rac*-BINAP as the ligand suppressed the formation of **81**, giving the highest yields of homoallylic sulfone **80**.



Investigation of the reaction scope showed that α,α -dialkyl-substituted substrates worked well at 95°C , using *rac*-BINAP as the ligand (Chart 19). Substitution was tolerated in the 2-position of the allyl fragment and often led to slightly increased yields. Allyls with β -hydrogens were compatible reaction partners with α -aryl sulfones but primarily underwent elimination with α,α -dialkyl sulfones. Whereas an α -fluoro substituent slowed the

Chart 19. DcA of α -Sulfonyl Allyl Esters

DcA, an α -chloro substrate accelerated the reaction and led to increased yields. An α -phenyl substituent had a more dramatic accelerating effect, allowing use of the simpler $\text{Pd}(\text{PPh}_3)_4$ catalyst at reduced loadings of 1–2 mol %. In addition, the reaction temperature could be reduced to room temperature and the reaction time was significantly shortened (cond. B, Chart 19). Lastly, it is noteworthy that an alkyl sulfone (specifically a benzyl sulfone) provided similar yields to the phenyl sulfones.

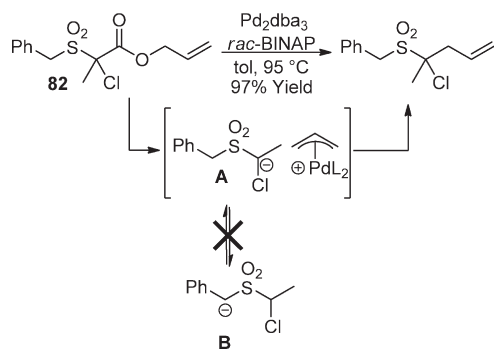
As with other DcA reactions, the DcA of sulfones is highly regioselective. For example, upon decarboxylation the benzyl sulfonylester **82** led to the homoallylic sulfone that arises from coupling at the carbon that bore CO_2 (Scheme 45). No product arose from isomerization to the more thermodynamically stable benzylic α -sulfonyl anion (**B**). Again, this highlights the ability to generate anions via decarboxylation that are not readily accessible via deprotonation.

Weaver, Tunge, and co-workers further showed that the DcA of sulfones occurs via an outer-sphere mechanism with attack of a sulfonyl anion on the π -allyl ligand (Scheme 46).⁹⁸ Moreover, they showed that, in contrast to most other decarboxylations, palladium does not catalyze the decarboxylation. Fittingly, the qualitative rates of DcA of sulfones correlated with the expected stability of the intermediate α -sulfonyl anion (Scheme 47). This suggested that decarboxylation is rate-limiting. Thus, substrates that formed α -sulfonyl anions that were benzylically stabilized (**D**) reacted rapidly, whereas an anion (**A**) that could not achieve the ideal conformation of the α -sulfonyl anion required heating at 200°C in a microwave reactor to convert the reactant to product in just 40% yield.⁸⁶

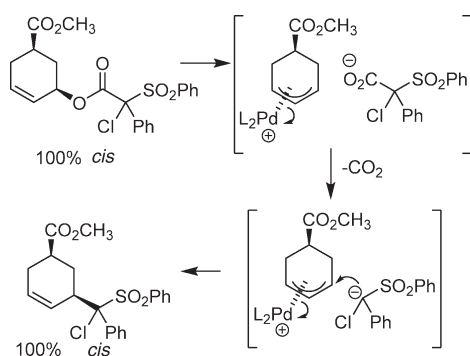
Finally, having established that the sulfone moiety could competently activate the substrate for DcA, the reductive removal of the sulfone was performed. The sulfones were readily cleaved by exposing the substrates to Mg^0 turnings in warm methanol (Table 20). As might be expected, α -chlorine atoms were also removed under these conditions, allowing access to either tertiary or secondary coupling products.

6.7.2. Enantiospecific Decarboxylative Allylation. Having established the racemic reaction, Tunge and co-workers developed an asymmetric DcA of sulfonyl anions.⁹⁸ Early work by the groups of Corey¹⁰⁰ and Cram¹⁰¹ showed that chiral nonracemic α -sulfonyl acetic acid derivatives underwent base-catalyzed stereospecific decarboxylative protonation. Indeed, chiral nonracemic α -phenyl propanoic allyl esters underwent

Scheme 45. Regiospecificity of the Anion



Scheme 46. Outer-Sphere DcA



DcA to form the corresponding highly enantioenriched homoallylic sulfones (Chart 20). The conservation of enantioenrichment [$\text{cee} = (100 \times \% \text{ ee of product}) / (\% \text{ ee of starting material})$] was uniformly high, and allylation occurred with retention of stereochemistry. An examination of the substrate scope shows that the yields of the DcA are high and the cee's are excellent regardless of the substrate. It is noteworthy that an increase in the concentration led to higher yields than those obtained in their first publication (cond. B, Chart 20).⁸⁶

Because the DcA of sulfones has been shown to proceed via α -sulfonyl anions (Scheme 46), the ability to achieve stereospecificity at 100 °C is remarkable. Gais and co-workers reported that a lithio *phenyl* sulfonyl anion racemized rapidly even at -100 °C.¹⁰² However, to achieve highly stereospecific DcA, the C–C bond formation must occur faster than racemization. This is possible due to the formation of electrophile and nucleophile in situ in close proximity, where the lifetime of the α -sulfonyl anion is not long enough to allow significant racemization. Tunge and co-workers performed DFT calculations to gain insight into the energies associated with the possible modes of racemization of the anion. Specifically, the DFT calculations showed that the barrier to inversion of the α -sulfonyl anion is <2 kcal/mol (Scheme 48). Thus, the observed stereofidelity is *not* a result of slow inversion of the anion. Rather, the stereospecificity was attributed to allylation of the most stable conformation of the α -sulfonyl anion (A) via path A and slow rotation about the S–C bond of the α -sulfonyl anion (9.9 kcal/mol barrier, Scheme 48).^{100,101}

Scheme 47. Qualitative Correlation between Stability and Rate

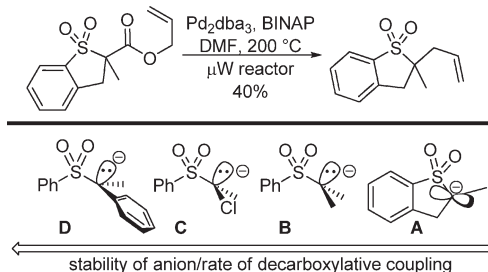


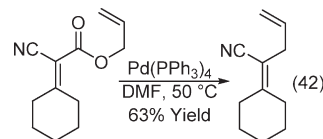
Table 20. Two-Step DcA/Reduction

$\text{PhO}_2\text{S}-\text{C}(\text{R}^1)(\text{R}^2)-\text{CO}_2\text{Allyl} \xrightarrow[50^\circ\text{C}]{1) \text{ cat. Pd}, 2) \text{ Mg, MeOH}} \text{R}^1-\text{C}(\text{R}^2)-\text{Allyl}$			
entry	substrate	product	yield (%)
1			74
2			83
3			69 (10:1 l:b)
4			79 (1:1 dr)

7. SP²-HYBRIDIZED CARBON NUCLEOPHILES

7.1. α -Allylation of Acrylonitriles

In Saegusa's seminal paper describing DcA reactions of β -ketoesters, he also disclosed the DcA of an α,β -unsaturated α -cyanoester (eq 42).¹⁵ Although metal-catalyzed decarboxylations of vinyl carboxylates typically require high temperatures,¹⁰³ the DcA of the α,β -unsaturated α -cyano allyl ester occurred at just 50 °C. Decarboxylations of α -cyano acrylic acids do, however, occur under mild conditions under nucleophilic catalysis via conjugate addition intermediates.¹⁰⁴ Thus, triphenylphosphine may play a role in this reaction.



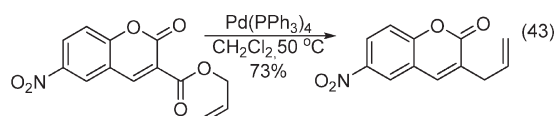
7.2. Silyl Enol Ethers

Tsuji et al. reported that silyl enol ethers derived from allyl β -ketoesters would undergo DcA to form allylated silyl enol ethers.¹⁰⁵ The reaction likely proceeds via allylation of the silyl

enol ether to form **A**, followed by reformation of the silyl enol ether by decarboxylation (Scheme 49). Snider and Buckman used this strategy in a 1992 synthesis of velloziolone (Scheme 49).¹⁰⁶ In the synthesis, Snider and Buckman took full advantage of Tsuji's allylation, which preserves the silyl enol ether nucleophile, by using it in a one-pot transformation to the desired α -iodo ketone.

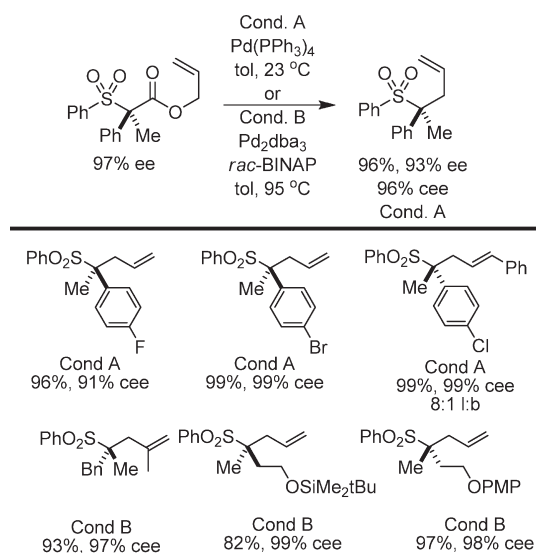
7.3. α -Allylation of Coumarins

In search of applications of DcA reactions to biologically relevant substrates, Jana, Trivedi, and Tunge found that allyl esters of 3-carboxycoumarins readily underwent DcA at 25–50 °C in the presence of $\text{Pd}(\text{PPh}_3)_4$ (eq 43).⁸² Approximately 10% of 6-nitrocoumarin was also formed via the apparent protonation of a vinyl anion equivalent.

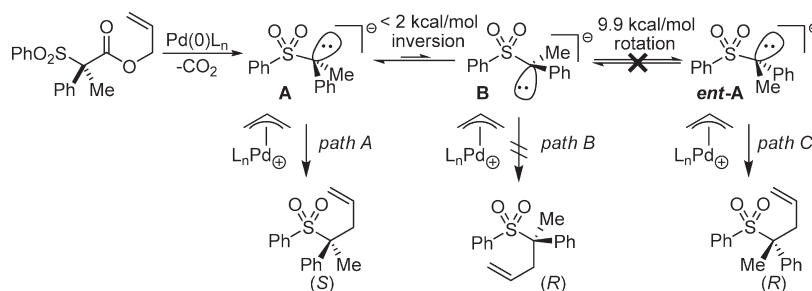


The mild conditions for this DcA are quite remarkable and puzzling considering that copper-catalyzed decarboxylative metalation of 3-carboxy coumarins takes place at 248 °C in refluxing quinoline.¹⁰⁷ Investigation of the substrate scope showed that coumarins with electron-withdrawing and -donating groups generally worked well (Chart 21), although an amine substituent led to reduced yields (**84**). Interestingly, a methyl

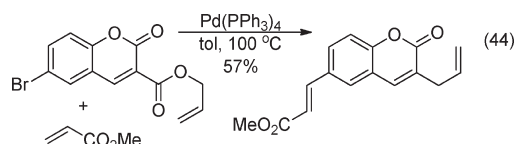
Chart 20. Stereospecific DcA α -Sulfonyl Esters



Scheme 48. Origin of Enantiospecificity



substituent on the 2-position of the allyl led to a substantial increase in the desired product (**85** vs **83**) and substitution at a terminus showed that the reaction takes place with the normal linear selectivity (**86**, **87**). Coupling of an allyl group that has β -hydrogens was also successful (**86**); however, the yield was somewhat reduced due to competing elimination. As expected, the DcA took place preferentially over oxidative addition into aryl bromide bonds, allowing tandem decarboxylative coupling/cross-coupling reactions, albeit in modest yield (eq 44).

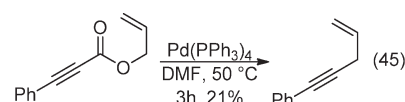


A variety of substrates related to coumarins also underwent DcA reactions. The ability to form allylated pyrone in 62% yield showed that the benzenoid motif is not necessary. Good yields of DcAs of thiocoumarin and chromones were also realized, suggesting that other heteroaromatic substrates may also be competent partners (Chart 22). It is noteworthy that an open-chain analogue of coumarin gave no conversion to product **88**. This indicates either that having a phenolic ester is important or that resonance with the phenolic oxygen of the coumarin is important; the methoxy substituent in **88** is expected to have less resonance contribution because the acrylate is likely rotated out of conjugation.

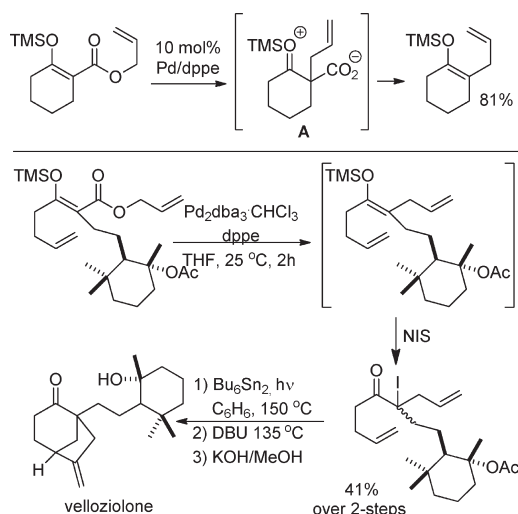
8. SP-HYBRIDIZED CARBON NUCLEOPHILES

8.1. DcA of Acetylides

In 1980, Saegusa and co-workers included a single example of DcA of a propiolic allyl ester in their seminal publication that demonstrated the ability to generate homoallylic ketones via decarboxylative allylation.¹⁵ Saegusa and co-workers reported a 21% GC yield and suggested that the reaction does not work well because the substrate possessed only a poor electron-withdrawing group (eq 45).

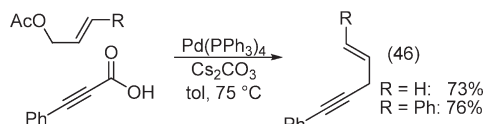


Skipped enyne products are typically prepared via Stille cross-couplings of alkynyl stannanes. Rayabarapu and Tunge recognized that development of a useful decarboxylative coupling of allyl propiolates would obviate the need for the preparation and use of toxic tin reagents, effectively replacing transmetalation with decarboxylative metalation.^{108a} Thus, they initiated their

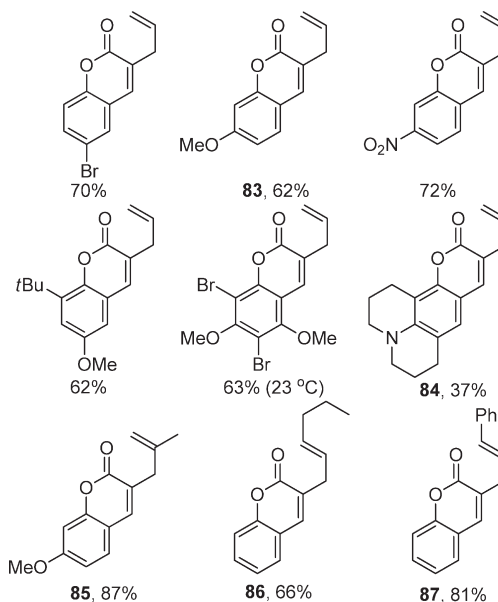
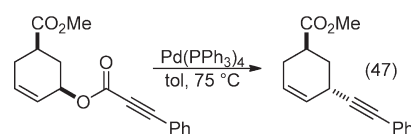
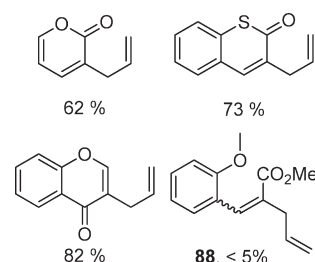
Scheme 49. DcA of Silyl Enol Ethers: Synthesis of Vellozolone

study with the phenyl cinnamyl propiolate and found that a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ would facilitate the decarboxylative allylation in good yield in 2 h (Chart 23). These conditions proved to be quite general (Chart 23). The reaction was somewhat tolerant of β -hydrogens; cyclohexenyl and 1,3-dimethyl allyl esters provided products in moderate to good yield. The electronics of the aryl ring do not appear to play a significant role in the outcome of the reaction as oxygen and halogen substituents were both compatible with the DcA. Concerning the acetylide, the reaction was not limited to phenyl propiolates, as the TMS-, cyclohexenyl-, and alkyl-substituted acetylide nucleophiles all underwent coupling in good yield. However, no reaction was observed for terminal alkynes. Moreover, the authors showed that, when the alkyne substituent was small (i.e., CH_3), a bis-allylated alkyne byproduct was formed (**89**).

Tunge also demonstrated that the intermolecular reaction between the propiolic acid and an allyl acetate could be achieved in similar yields, obviating the need for the two components to be coupled prior to DcA. However, it did require a stoichiometric amount of base to prevent the Pd-catalyzed decarboxylative protonation of the propiolic acid (eq 46).



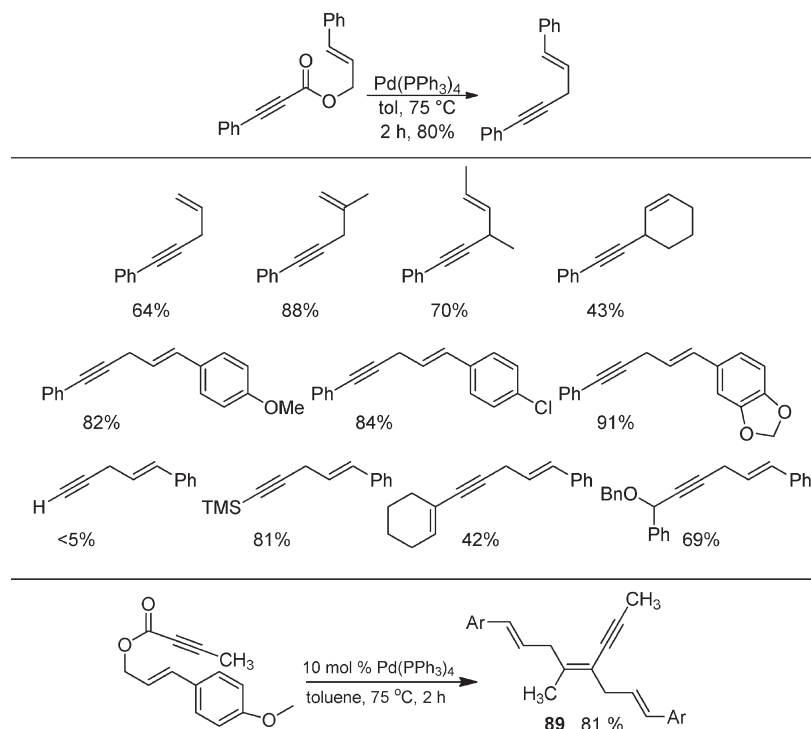
The rates of the DcA of propiolates were dependent on the allyl substitution and followed the order of monosubstituted aromatic > disubstituted > terminally unsubstituted. This unusual rate dependence suggested that $\text{Pd}-\pi$ -allyl formation was not rate-determining, but it did loosely correlate with the expected rate of σ -allyl formation. Additionally, Rayabarapu and Tunge demonstrated that the carbon–carbon bond formation took place via an inner-sphere process, such that the overall reaction led to inversion of an allyl stereocenter (eq 47). Additional control studies demonstrated that a $\text{Pd}(\text{II})$ species is intimately involved in the decarboxylation step. Taken together, the mechanism for decarboxylative allylation of alkynes was proposed to involve decarboxylative metalation of the alkyne and reductive elimination of a σ -allyl palladium acetylide (Scheme 50).

Chart 21. DcA of 3-Carboxylcoumarins**Chart 22. DcA of Heteroaromatics**

8.2. Decarboxylative Coupling of Allenes with Acetylides

In 2008, Chung and co-workers developed the DcA of allenyl propiolates in which the carbon–carbon bond formation took place exclusively at the internal position of the allene to produce useful conjugated dienynes (Table 21).¹⁰⁹ After some screening, very similar conditions to those reported by Rayabarapu and Tunge^{108a} were found to be useful in effecting the transformation. The reaction was quite general and tolerated rather large allenyl substituents (entry 1). The *E/Z* selectivity appears to be sterically controlled such that there is little distinction between Me and Et (entry 3), but good selectivities are observed when the substituents are sterically different (Ph vs Me, entry 4). In addition to aryl propiolates, the DcA worked well for silyl and alkenyl propiolates (entries 5 and 7). Several other substrates were tested and found to be unfit for Pd-catalyzed DcA (Chart 24).

Chart 23. DcA of Allyl Propiolic Esters

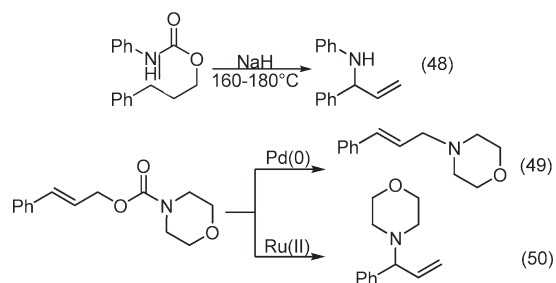


9. DCA OF HETEROATOMS

The application of transition metal-catalyzed decarboxylative coupling of allyl alcohol derivatives and heteroatoms has resulted in the development of several new reactions that are complementary to existing methods, often offering enantioselective variants, altered regioselectivity, or greener alternatives to conventional methods. Specifically, methods to form C–N, C–Se, and C–O bonds via decarboxylation have been developed. The methods are versatile and allow facile access to allylic amines,¹¹⁰ vinyl azetidines,¹¹¹ vinyl piperidines,¹¹¹ and vinyl hydroquinolines,¹¹² as well as enantioenriched allylic selenides¹¹³ and selenocarbonates.¹¹³

9.1. Allylic Amination

9.1.1. Reaction Development. It is known that allyl carbamates undergo regio- and stereospecific thermal rearrangements under extreme conditions (eq 48). It was envisioned that a nucleophilic metal might facilitate these reactions under mild conditions in a manner similar to that reported for β -ketoesters.¹¹⁰ Indeed, palladium(0) and ruthenium(II) catalysts were found to efficiently catalyze the decarboxylative allylic amination of allyl carbamates (eqs 49 and 50).



Initial catalyst screening revealed that $[\text{Cp}^*\text{RuCl}]_4$ was an effective catalyst, facilitating the decarboxylative allylic amination, albeit

with low regioselectivity. Addition of N,N,N',N' -tetramethylethylenediamine (TMEDA) as a ligand was found to improve the regioselectivity, but this catalyst mixture promoted equilibration of the branched allylic amine to the more thermodynamically stable linear allylic amine.

Although the equilibration of the branched and linear products is interesting and allows access to both products, more expedient access to the linear products was sought. Given that $\text{Pd}(0)$ catalysts typically favor formation of the linear allylated products,⁶ it was expected that a $\text{Pd}(0)$ catalyst might selectively yield the linear allylic amine. Indeed it was found that $\text{Pd}(\text{PPh}_3)_4$ gave the greatest conversion and highest regioselectivity in CH_2Cl_2 at 40 °C.

An exploration of the scope of the decarboxylative amination showed that the reaction tolerated substitution at the allyl ester fragment (Chart 25), including allyl electrophiles with β -hydrogens that are capable of undergoing elimination—except in the case of aniline-derived carbamates, which underwent elimination exclusively. The reaction appeared to be sensitive to the $\text{p}K_a$ of the corresponding nucleophilic nitrogenous species. Carbamates derived from dialkyl amines worked well in all cases, whereas those derived from aniline and pyrrole resulted in decreased yields or no product formation at all. Heteroaromatic amines such as pyrazoles, imidazoles, and triazoles were all compatible partners for DcA; however, attempts to form cyclohexenyl pyrrole resulted in elimination (Chart 26).

The authors performed an experiment with an imidazole with a regiochemical indicator (eq 51). They reported that the DcA of carbamate **90** produced two isomeric products **91** and **92** in a 1:1.1 ratio. This experiment suggested that, in the case of heteroaromatic imidazoles, decarboxylation was occurring prior to allylation.

Scheme 50. DcA of Allyl Propiolates

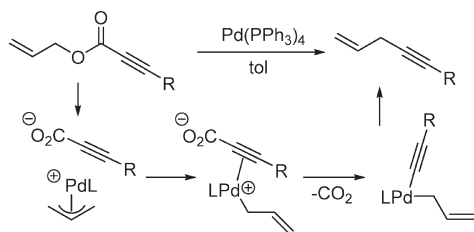
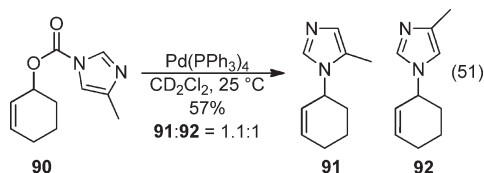
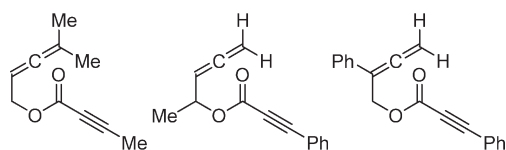


Chart 24. Substrates Unfit for DcA



To explain the observation of elimination with anilines and pyrroles, but not with more basic amines like piperidine, the authors proposed two competing mechanisms. In the first pathway, mechanism A, *N,N*-dialkyl carbamates undergo allylation of the *N*-atom *prior* to decarboxylation, generating a zwitterionic species, which facilitates decarboxylation, affording the neutral allylic amine product (Scheme 51). Alternatively, mechanism B involves decarboxylation *prior* to allylation, generating an anionic nitrogen that can then undergo allylation. Thus, the authors argued that the reaction mechanism is controlled by the pK_a of the corresponding amine. In the case of dialkyl amines, decarboxylation is unlikely to take place to generate an extremely basic amide. However, decarboxylation of less basic aniline carbamates could take place to generate the corresponding amides. Thus, more basic amides are formed from aniline-derived carbamates, which explained the preference for elimination with those substrates.

To summarize, the difference in reactivity is best explained by pK_a . Carbamates derived from amines with pK_a roughly between 21 and 32 were shown to favor elimination. In contrast, the reduced basicity of pyrazole, imidazole, and triazole anions allowed the reactions to proceed smoothly (Scheme 52).

9.1.2. Synthetic Applications. The DcA of amines has proven to be useful in a number of synthetic efforts. For example, Bates and Dewey have applied the DcA of allyl carbamates in the formal synthesis of swainsonine.¹¹⁴ The paper highlighted the superiority of the DcA over the more traditional base-mediated allylation with allyl bromide (Scheme 53).

Table 21. DcA of Allenyl Alkynoates

entry	product	temp. (°C)	time (h)	yield (%)	E:Z
1		100	1	38	--
		70	3	68	--
2		100	4	97	--
3		100	1	77	1.2:1
4		70	3	62	19:1
5		100	0.5	80	--
6		100	0.5	87	--
7		100	0.25	86	--

Hoveyda et al. opted to utilize a DcA protocol to achieve a more efficient synthesis of quebrachamine (eq 53) than would be possible using a standard Calverley protocol (eq 52). In essence, DcA allowed the authors to avoid a two-step deprotection–allylation sequence and form the desired allylic amine in high yield. In doing so, the authors beautifully illustrated that carbamates not only can be used as activating or protecting groups but also can deliver useful functionality. In this case, the olefin of the allylic amine was utilized in an enantioselective RCM to establish the absolute stereochemistry of quebrachamine.

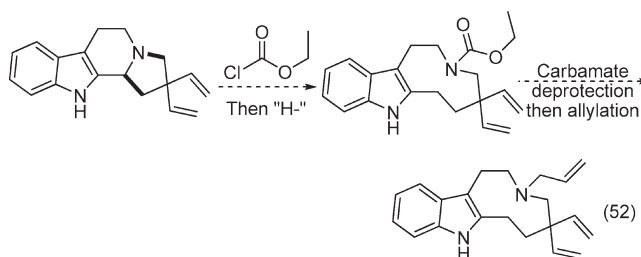
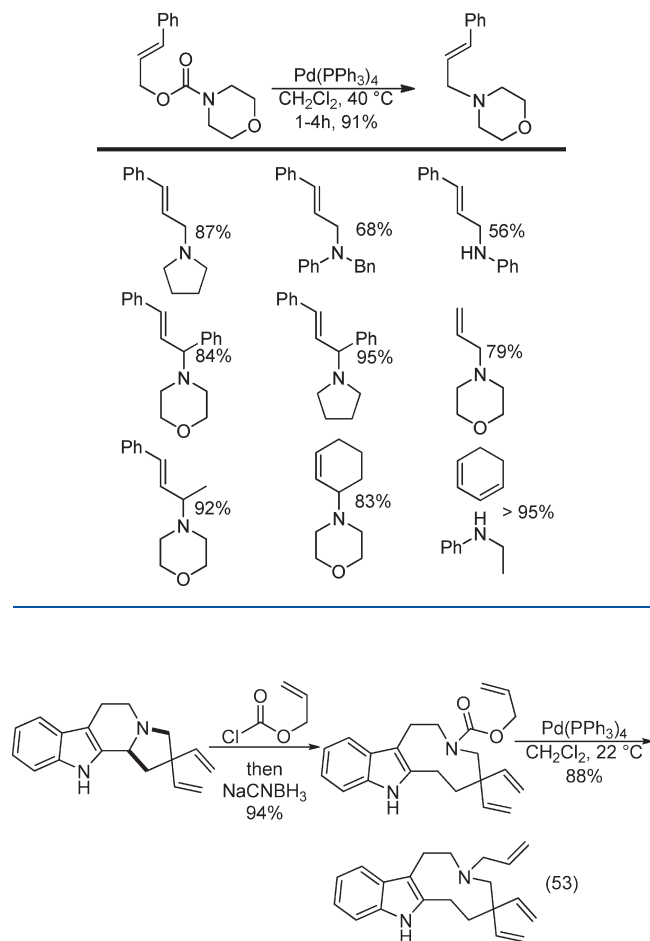


Chart 25. Decarboxylative Allylic Amination



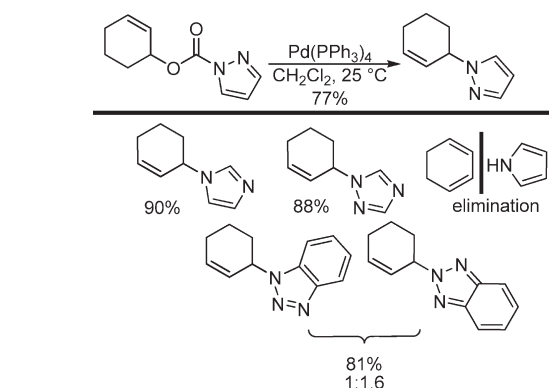
9.1.3. Intramolecular Decarboxylative Cyclization.

Having successfully demonstrated the decarboxylative allylation of acyclic allylic carbamates,¹¹⁰ Tunge and co-workers investigated the use of cyclic carbamates as precursors to nitrogen-containing heterocycles. More specifically, they showed that 1,3-amino alcohols could be activated such that they gave rise to vinyl azetidines and piperidines via intramolecular attack of amide anions on the palladium π -allyl ligands. For example, the *trans*-vinyl azetidine was formed rapidly from the *trans*-carbamate in a 16:1 dr (Scheme 54). Interestingly, decarboxylative ring contraction of the *cis*-carbamate also afforded the *trans*-azetidine with the same diastereoselectivity. This result indicated that π -allyl palladium isomerization, via π - σ - π epimerization, occurred faster than C–N bond formation.

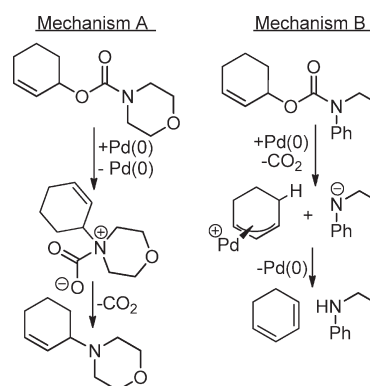
Investigation of the scope of the azetidine synthesis showed that the reaction is highly diastereoselective (Chart 27). Terminal substitution was tolerated, whereas the electronics of the R² substituent seem relatively unimportant.

Wang and Tunge also investigated the mechanism of the decarboxylative ring contraction. Use of terminally substituted substrate **93**, which cannot epimerize via π - σ - π allyl isomerization, allowed the authors to determine that the C–N bond formation took place via outer-sphere attack on the π -allyl ligand to give product with overall retention of stereochemistry, via a double-inversion mechanism (Scheme 55). That determination suggested the intermediacy of zwitterionic π -allyl palladium sulfonamides like **B**.

Chart 26. DcA of Heteroaromatic Amines

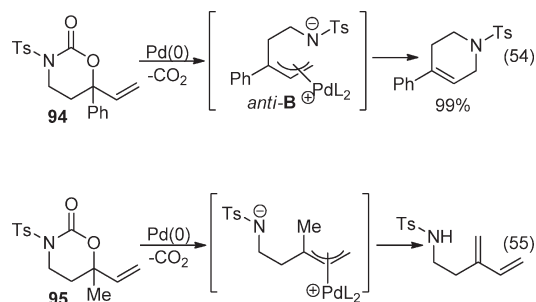


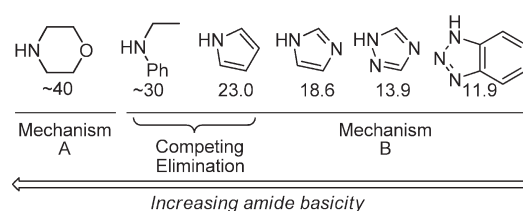
Scheme 51. Two Potential Mechanisms



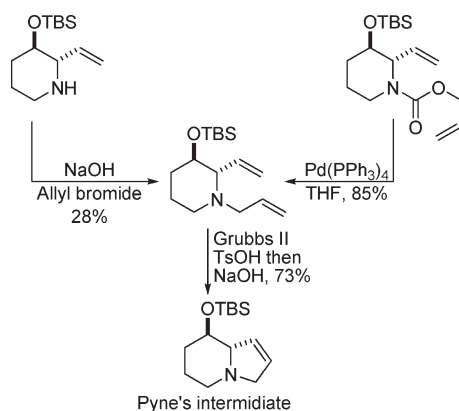
The results also suggested that the preferential formation of the four-membered azetidine over the six-membered tetrahydropyridine could be explained by reaction through the thermodynamically favorable *syn*-Pd- π -allyl intermediate (Scheme 56). Allylic strain in the *anti*-**B** conformer led to slower production of the tetrahydropyridine product.

To test this hypothesis, a substrate, **94**, which would cause the nucleophilic substituent to adopt the *anti*-conformer, was subjected to the reaction conditions (eq 54) and did indeed afford the tetrahydropyridine as the kinetic product in high yield. Presumably, this occurs because the Pd- π -allyl (**B**) adopts a conformer that places the larger phenyl substituent in the *syn*-position to reduce allylic strain. When a substrate with a smaller methyl substituent (**95**) was used, the diene was the primary product (eq 55). As a consequence, tertiary C–N bonds cannot be formed via this methodology.

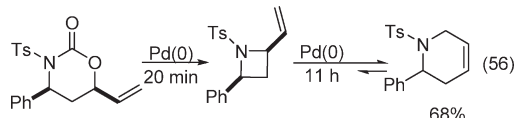


Scheme 52. Correlation of Mechanism to pK_a of Corresponding Amine

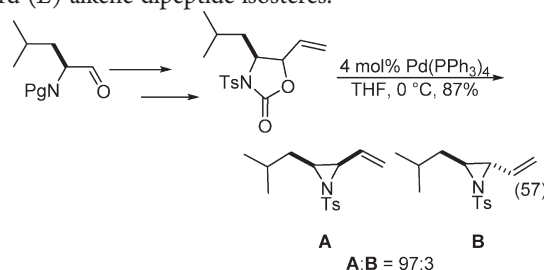
Scheme 53. DcA En Route to Swainsonine



In addition, it was found that, when vinyl azetidines are formed kinetically, they undergo palladium-catalyzed isomerization to the tetrahydropyridine if given sufficient time (eq 56). Thus, one can access either the vinyl azetidine or tetrahydropyridine products by simply adjusting the duration of the reaction.

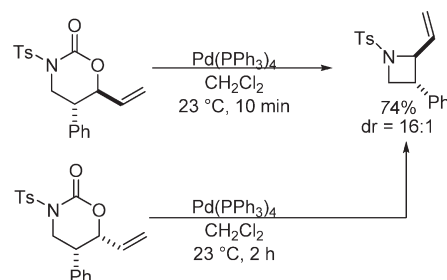


9.1.4. Enantiospecific Vinyl Aziridine Formation. Yamamoto and co-workers demonstrated that vinyl oxazolidinones also undergo decarboxylative ring contraction to form vinyl aziridines (eq 57).¹¹⁵ The activated vinyl aziridines are epimerizable in the presence of Pd(0), and Yamamoto and co-workers took advantage of this to convert mixtures of 1,2-amino alcohol diastereomers to highly diastereomerically enriched, enantiopure aziridines (eq 57). Here the stereochemistry of amino acids can be used to control the stereochemistry in the thermodynamically preferred *cis*-vinyl aziridines. The enantioenriched vinyl aziridines produced by this method were further functionalized to afford (*E*)-alkene dipeptide isosteres.



9.1.5. Enantioselective Allylic Amidation. In 2007, Singh and Han reported an asymmetric Ir(I)-catalyzed decarboxylative

Scheme 54. Decarboxylative Ring Contraction



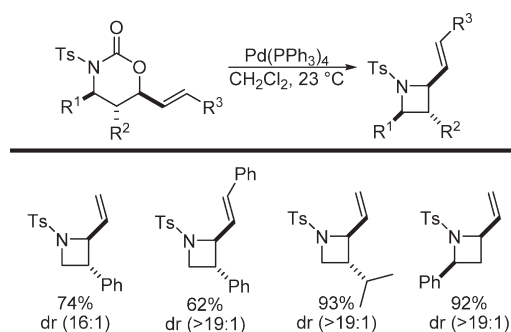
amidation of Cbz-protected allylic carbamates (Chart 28).¹¹⁶ The DcA provides access to highly enantioenriched allylic carbamates that can be readily deprotected to form allylic amines. Notably, the reaction is quite tolerant of allyl electrophiles that possess β -hydrogens. Furthermore, a reaction between two different allylic imide reactants resulted in complete crossover, suggesting that the reaction proceeded via π -allyl iridium intermediates rather than through a [3,3]-rearrangement. In this report, the authors generally utilized an equivalent of DBU as well as proton sponge to promote the reaction. Given the need for the base and the tolerance of β -hydrogens on the allyl moiety, it is probable that C–N bond formation occurs prior to decarboxylation. In support of this assertion, the authors reported that the lithium amide of benzyl carbamate did not undergo successful reaction with an Ir- π -cinnamyl complex; a mechanism that involved decarboxylation prior to allylation would need to proceed via similar intermediates. Thus, the data support a mechanism involving enantioselective allylation followed by decarboxylation, where reaction of the catalyst with one of the enantiotopic faces of the olefin is probably the enantio-discriminating step.

9.1.6. Enantiospecific Allylic Amidation. Soon after their first report, Singh and Han reported a complementary enantiospecific decarboxylative amidation.¹¹⁷ In this report, optically enriched branched Cbz-protected carbamates were converted with high enantiospecificity to their corresponding allylic carbamates. The enantiospecific methodology allowed Singh and Han to address a shortcoming in their enantioselective decarboxylative amidation, which was limited to substrates with sterically small allyl substituents. The authors reported that the reaction of terminally unsubstituted allyl carbamates reacted more smoothly, with the stereochemistry of the carbinol carbon being effectively transferred to the product (Chart 29). Thus, epimerization via π - σ - π isomerization was slow on the reaction time scale. Interestingly, the authors used a chiral ligand for the reaction; however, the absolute stereochemistry of the ligand had no effect on the reaction. Thus, there was no evidence for a matched/mismatched catalyst–substrate pair. Ultimately, the chiral phosphoramidite ligand was utilized primarily because catalysts generated from standard achiral ligands, like $P(OPh)_3$, were ineffective.

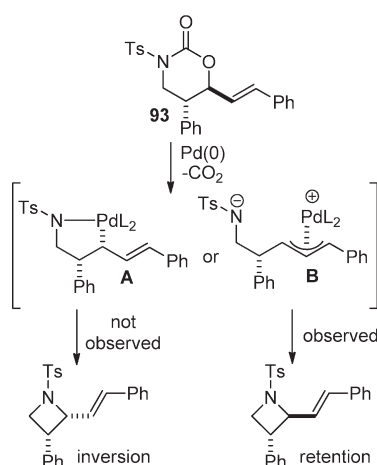
9.2. Allylic Etherification

9.2.1. Alkyl Allyl Ethers. Similar to the formation of allylic amines (*vide supra*), allylic ethers have been generated by DcA of allyl carbonates. Most of these reactions have focused on allyl aryl carbonates, but a few examples of DcAs of allyl alkyl carbonates have been reported. Specifically, in 1981, Guibe and M'Leux

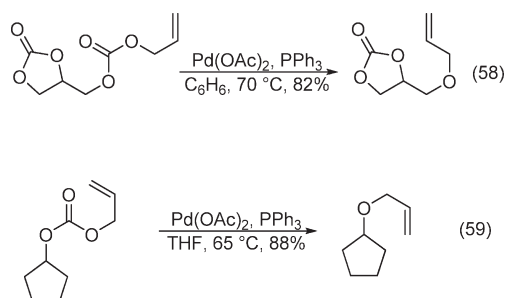
Chart 27. Scope of the Azetidine Formation



Scheme 55. DcA: An Outer-Sphere Process

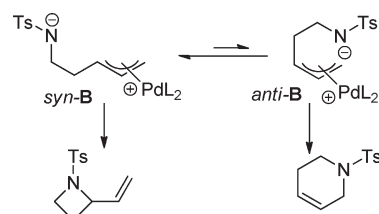


reported a single example of DcA of a primary alcohol generated from the carbonate generated from glycerol (eq 58).¹¹⁸ Similarly, Tsuji and co-workers reported an 88% yield of the *O*-allylation product when screening for production of another desired product (eq 59).¹¹⁹ One potential reason for relatively sparse examples of DcA to generate alkyl allyl ethers is because the methods have not yet been shown to afford advantages compared to more straightforward, traditional allylations.

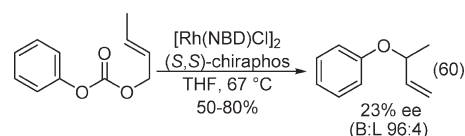


9.2.2. Allyl Aryl Ethers. DcA has been used more widely to make aryl allyl ethers. In an early report, Rama and co-workers screened Ni, Pd, and Rh catalysts for their ability to facilitate the

Scheme 56. Preferential Formation of Four-Membered Ring



asymmetric DcA of crotyl phenyl carbonates. Interestingly, each of these metals produced the branched product as the major product. In addition to the catalyst screening, the authors also reported the first enantioselective decarboxylative etherification; however the ee's were poor at best (23% ee, eq 60).¹²⁰

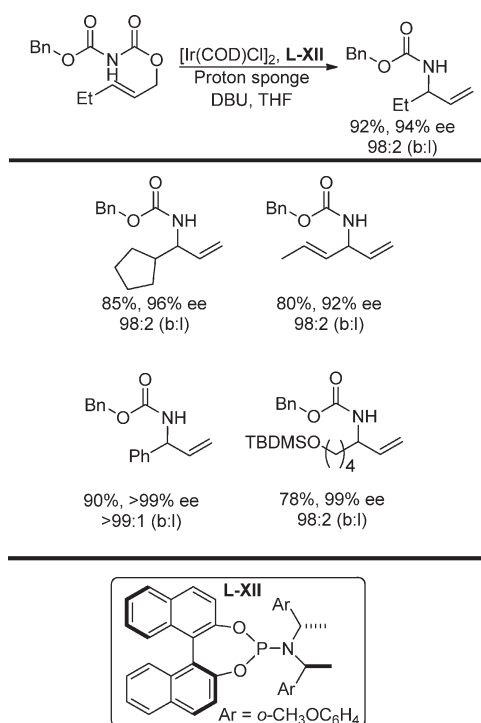


A few years later, Larock and Lee made significant strides in the development of the DcA of allyl aryl carbonates.¹²¹ Their DcA of allyl aryl carbonates has several noteworthy aspects: first, the reaction is typically moderately regioselective for the branched product, unless a conjugated linear product (**91**) is possible (Chart 30). Typically when olefin geometry is an issue, the *E*-olefin was formed preferentially. It is noteworthy that bulky ortho-substituents on the phenol were also well-tolerated. Finally, the reaction occurs with overall retention of configuration, presumably via a double-inversion mechanism.⁵⁸

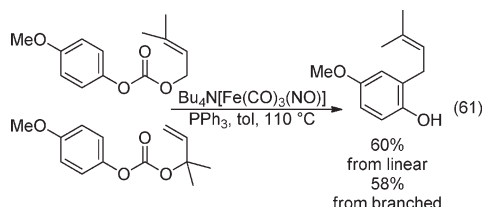
In 2008, Lacour and co-workers applied their ruthenium catalyst system to the asymmetric DcA of aryl allyl carbonates (Chart 31).¹²² In general, good ee's and conversions were observed unless the aryl component had a nitro group. Interestingly, the authors showed that the ee deteriorates after the reaction has reached completion, concomitant with an increase in the amount of the thermodynamic linear product. A similar result was seen by Mellegaard-Waetzig, Rayabarapu, and Tunge in their allylic amination.¹¹⁰ Furthermore, subjecting two *pro*-ducts to a crossover experiment led to complete crossover, providing evidence for reversibility of the C–O bond formation. Thus, the branched ethers are the kinetic products, and achieving their synthesis with high enantioselectivity requires that the reaction be stopped before competing reionization/racemization become problematic.

More recently, Trivedi and Tunge demonstrated that an anionic iron catalyst is competent at facilitating the DcA of allyl aryl carbonates and that the reaction takes place in high yields (Chart 32).¹²³ They demonstrated that the reaction is regioselective, giving the same regioisomeric product regardless of whether the linear or branched carbonate reactant was used. This selectivity lies in contrast to related iron-catalyzed allylations that proceed with regiospecificity.¹²⁴ Instead, the selectivities are similar to those reported by Larock and Lee using a Pd catalyst, though the yields are somewhat higher with the iron catalyst.¹²¹ That said, the major advantage of this methodology is the use of the iron catalyst compared to the more commonly utilized precious metal catalysts, which are far more scarce and costly. Lastly, although the *O*-allylation products were typically

Chart 28. Enantioselective Decarboxylative Allylic Amidation



formed, the authors demonstrated the synthesis of C-allylated phenols via a tandem DcA/Claisen rearrangement (eq 61).



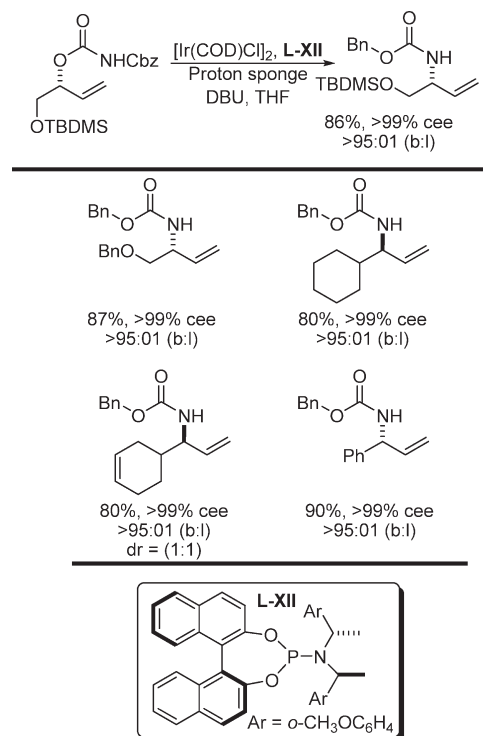
9.3. Allylic Selenation

Waetzig and Tunge showed that allyl selenides are available via decarboxylative coupling of allyl selenocarbonates.¹¹³ They reasoned that the ability of the allylic selenide derivatives to readily undergo stereospecific [2,3]-sigmatropic rearrangements to afford allylic amines, chlorides, and alcohols would make the selenide a versatile synthon (Scheme 57).

9.3.1. Racemic Reaction. Traditional methods of generating nucleophilic selenium include superstoichiometric amounts of SmI_2 or selenium–tin reagents.¹²⁵ In hopes of developing a decarboxylative alternative, Waetzig and Tunge demonstrated that palladium can facilitate decarboxylative coupling of easily accessible allylic selenocarbonates.¹¹³ The racemic reaction was facilitated by $\text{Pd}(\text{PPh}_3)_4$ catalyst, affording allylic selenides in moderate to excellent yields (Chart 33). Once again, the stereochemistry of the reaction suggests that the decarboxylative allylation occurs via an outer-sphere mechanism, giving products with retention of stereochemistry.

9.3.2. Kinetic Resolution. After establishing the racemic reaction, a screening of chiral nonracemic ligands was performed; however, the results were initially puzzling. The reaction proceeded to ~50% conversion in 2 h and then ~55–80% in 24 h.

Chart 29. Enantiospecific Decarboxylative Allylic Amidation



Moreover, efforts to increase the conversion by heating or extending the reaction time had a negative effect on the enantioselectivity of the product. One explanation of such observations could be a kinetic resolution of the starting selenocarbonate. Indeed, when palladium ligated by the naphthyl Trost ligand **L-VII** was utilized, the conversion stopped at 53%. Highly enantioenriched starting material, as well as enantioenriched allylic selenide, were recovered from the resulting mixture (eqs 62 and 63).

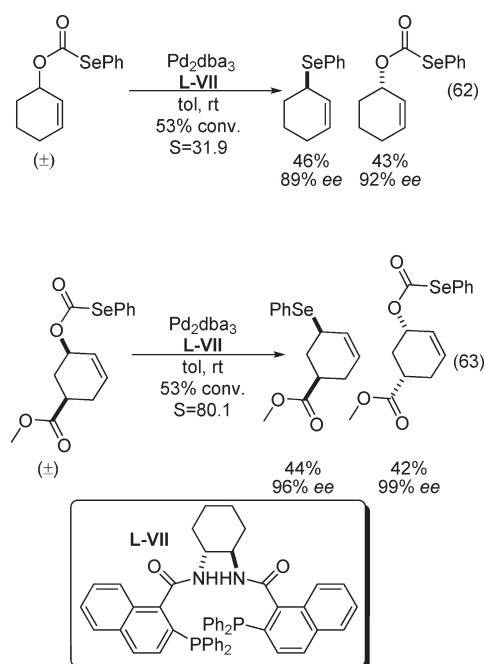
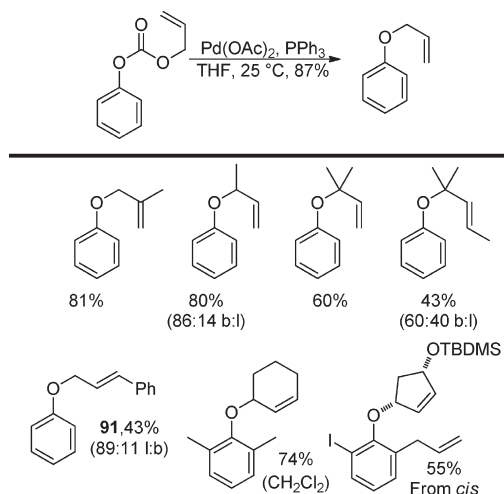
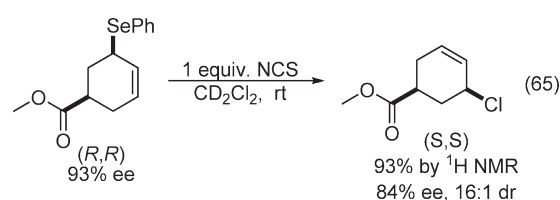
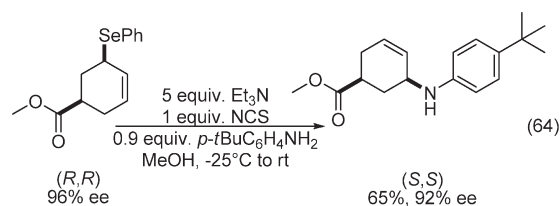


Chart 30. Pd-Catalyzed DcA of Aryl Allyl Carbonates



Cyclohexenyl selenocarbonate proved to be a good substrate for kinetic resolution with a selectivity factor of 31.9 (eq 62), and addition of the ester further increased the selectivity factor to 80.1 (eq 63). The observed kinetic resolution is likely a consequence of rate-determining ionization, which allows the chiral ligand to distinguish between the enantiomers of the substrate. Ionization was proposed to be followed by fast decarboxylation and fast bond formation.

Given the high selectivity factor, enantioenriched allylic selenides were isolated in good yields, allowing access to enantioenriched allylic amines, chlorides, and alcohols. To demonstrate this transfer of stereochemistry, the selenide was converted to an allylic aniline and allyl chloride with a high degree of stereo-transfer (eqs 64 and 65).

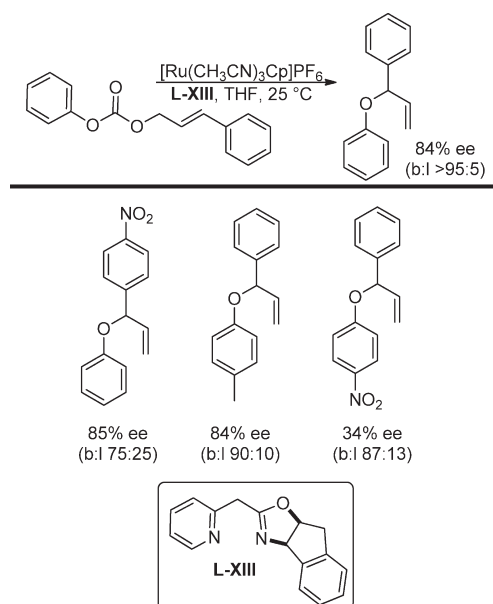


10. INTERCEPTIVE DECARBOXYLATIVE ALLYLATIONS (IDcA)

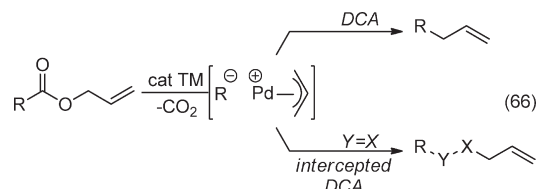
10.1. IDcA of Cyclic and Acyclic β -Ketoesters

As noted above, allyl esters can be thought of as masked nucleophiles and electrophiles, which are both contained in a single moiety. Treatment of these compounds with an appropriate transition metal catalyst effectively reveals both reactive intermediates.¹²⁶ If DcA reactions are performed in the presence

Chart 31. Ru-Catalyzed Asymmetric DcA of Allyl Aryl Carbonates



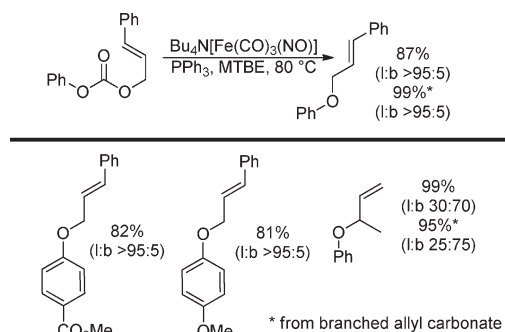
of a sufficiently reactive electrophile, these intermediates can be intercepted before their combination to form DcA products (eq 66). In this section of the review, we aim to detail the scope of interceptive DcA (IDcA) reactions that have been developed over the past two decades.



10.1.1. Intramolecular IDcA. In 1989, Tsuji and co-workers reported that an enolate intermediate, formed by decarboxylation, could be intercepted by a tethered Michael acceptor (Scheme 58).¹²⁷ A brief investigation of potential reaction conditions found that the monodentate phosphine ligand PPh_3 was more effective than a bidentate phosphine ligand dppe [1,2-bis(diphenylphosphino)ethane] at promoting the IDcA reaction. In addition to ligand choice, the source of the palladium catalyst was also important; reactions performed with $\text{Pd}(\text{PPh}_3)_4$ rather than $\text{Pd}(\text{OAc})_2/(\text{PPh}_3)_2$ facilitated product formation much more efficiently. The reaction was suggested to proceed via π -allyl palladium enolate (**A**) formation followed by Michael addition to generate a new π -allyl palladium enolate intermediate (**B**). The newly formed palladium enolate can then react with the electrophilic Pd π -allyl complex to generate the observed allylated ketone product (Scheme 58). As illustrated in Scheme 58, this methodology provides a potentially useful route for the generation of quaternary spirocyclic carbon centers.

10.1.2. Intermolecular IDcA. Nearly a decade after Tsuji's seminal report, Yamamoto and co-workers reported the intermolecular β -acetonation- α -allylation of activated olefins with allyl acetoacetate.¹²⁸ Like the previous intramolecular reaction of

Chart 32. Fe-Catalyzed DcA of Allyl Aryl Carbonates



Scheme 57. Enantioenriched Allyl Selenides Are Useful Intermediates

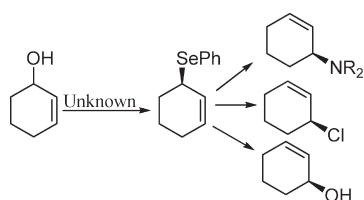
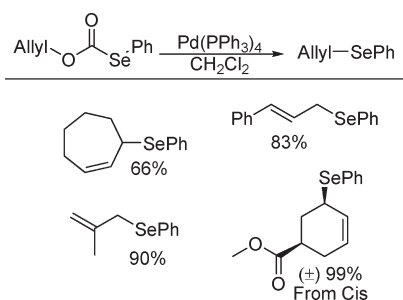
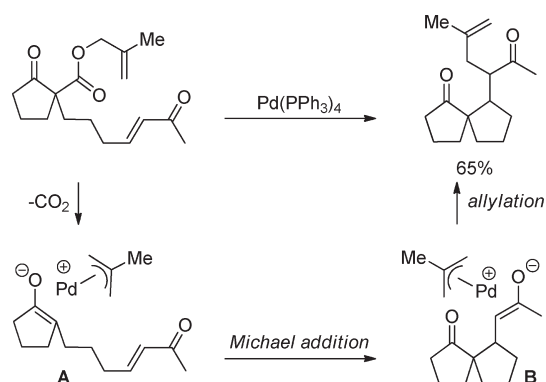
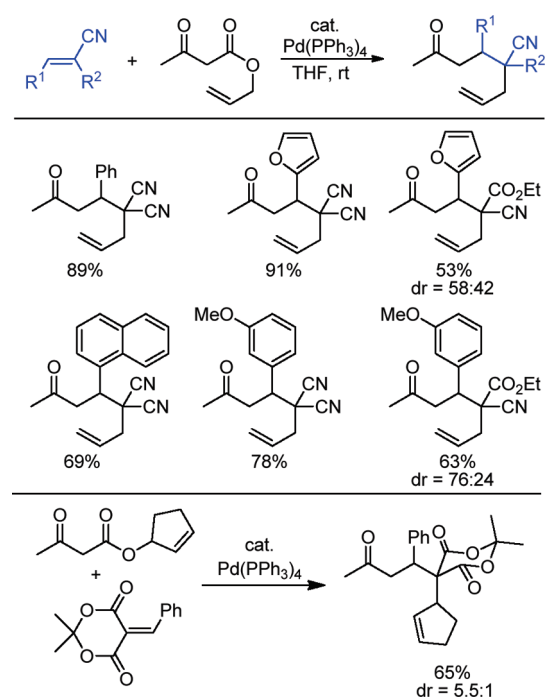


Chart 33. Decarboxylative Allylic Selenation



Tsuji, the intermolecular IDcA proceeded in the presence of a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ in THF (Chart 34). As depicted in Chart 34, Yamamoto and co-workers reported that the reaction allowed additions to both arylidene malononitriles and arylidene- α -cyano esters. Products derived from the latter acceptors contain two adjacent stereocenters, which were formed with minimal diastereoselectivity. In addition to the acrylonitrile derivatives utilized by Yamamoto and co-workers, Wang and Tunge later showed that Meldrum's acid adducts of aldehydes were sufficiently electrophilic to undergo palladium-catalyzed IDcA, and further demonstrated the compatibility of these reactions with substituted allyl groups.¹²⁹ Thus, Meldrum's acid adducts of aldehydes are competent electrophiles for IDcA, whereas simple benzylidene malonates $[\text{RCH}=\text{C}(\text{CO}_2\text{Et})_2]$ are not.¹²⁸ Yamamoto and co-workers attributed the lack of reactivity of $\text{RCH}=\text{C}(\text{CO}_2\text{Et})_2$ to "steric inhibition of resonance", where imperfect coplanarity of the two ester groups reduces the electrophilicity of the alkene. Indeed, the more planar benzylidene malononitriles and Meldrum's acid adducts

Scheme 58. Decarboxylative Michael Addition and Allylation

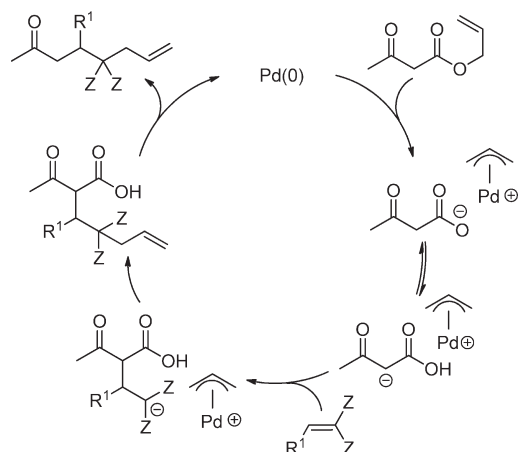
Chart 34. Decarboxylative β -Acetonation- α -Allylation

are many orders of magnitude more electrophilic than benzylidene malonates.¹³⁰

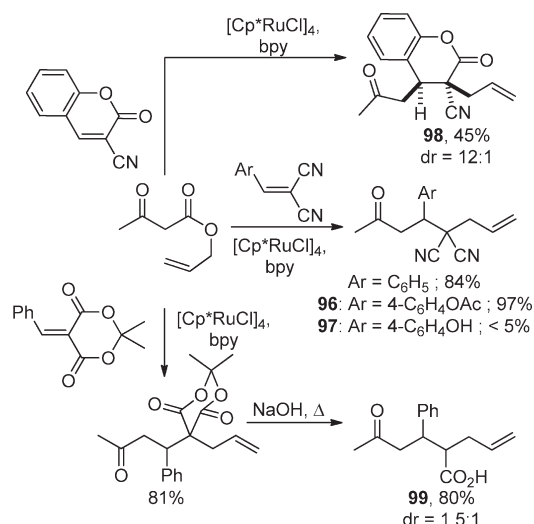
Yamamoto and co-workers proposed a mechanism for the IDcA in which decarboxylation precedes Michael addition and allylation. Although this proposed mechanism is reasonable, the mechanistic discussion in section 4.2 of this review suggests an alternative mechanism in which formation of a stabilized enolate, Michael addition, and allylation occur prior to decarboxylation (Scheme 59).¹¹¹ Decarboxylation of the β -ketoacid would then lead to the observed products.

10.1.3. Ruthenium-Catalyzed IDcA. In 2005, Wang and Tunge reported the ruthenium-catalyzed decarboxylative insertion of electrophiles into allyl β -ketoesters.¹²⁹ Exposure of allyl β -ketoesters to 2.5 mol % $[\text{Cp}^*\text{RuCl}]_4$ and 10 mol % bipyridine (bpy) in the presence of sufficiently electrophilic Michael

Scheme 59. Proposed Mechanism for IDcA



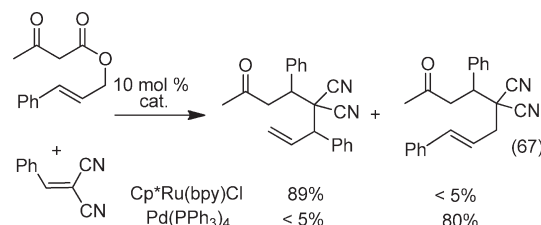
Scheme 60. Ruthenium-Catalyzed Decarboxylative Insertion of Electrophiles



acceptors led to good yields of IDcA products (Scheme 60). Although a benzylidene malononitrile with a *p*-acetyl substituent underwent smooth IDcA (**96**), the reaction was not successful with a more electron-rich *p*-hydroxy-substituted Michael acceptor (**97**); instead, only the standard DcA product was formed. This lack of reactivity highlights the fact that, for successful IDcA, the intercepting electrophile must be more electrophilic than the ruthenium- π -allyl complex (estimated $E \approx -10$).¹³⁰ An α -cyanocoumarin was also sufficiently electrophilic to intercept the DcA reaction to produce **98**, although that reaction proceeded in lower yield compared to other olefinic coupling partners (Scheme 60). Addition to the cyclic olefin did, however, proceed with good diastereoselectivity. Another interesting olefinic coupling partner used was the benzylidene Meldrum's acid adduct. Tunge and co-workers reported that decarboxylative addition of allyl β -ketoesters to such alkenes produced products that could be hydrolyzed to form γ,δ -unsaturated acids like **99**. This is significant because these

products are not directly obtainable from additions to mono-activated olefins like cinnamic acid.

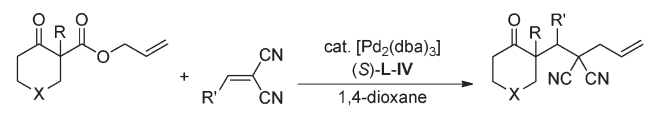
10.1.4. Regioselective IDcA. Tunge and Wang also demonstrated the first regioselective IDcA of benzylidene malononitriles to give the branched allylation product (eq 67). A large breadth of work investigating metal-catalyzed allylic alkylations suggested that the regioselectivity of allylation could be controlled by appropriate selection of transition metal catalyst.^{32,36,131} This was confirmed by treatment of a β -ketoester with benzylidene malononitrile and either $[\text{Cp}^*\text{RuCl}]_4/\text{bpy}$ or $\text{Pd}(\text{PPh}_3)_4$. Although the ruthenium catalyst delivered only the branched Michael addition-allylation product,^{131b} a palladium catalyst selectively formed the linear allylation product (eq 67).



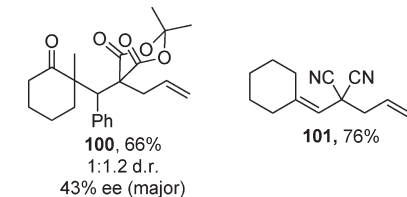
10.1.5. Asymmetric IDcA. In 2010, Stoltz and co-workers reported the asymmetric decarboxylative addition of cyclic β -ketoesters to activated olefins (Scheme 61).¹³² Building on the earlier observations of the groups of Yamamoto^{128b} and Tunge,¹²⁹ Stoltz and co-workers developed an asymmetric IDcA reaction that proceeded well in the presence of electron-deficient arylidene malononitriles (Table 22, entries 1–4) and benzylidene Meldrum's acid derivatives (Table 22, **100**). Cyclic β -ketoesters and arylidene malononitriles smoothly underwent the IDcA in the presence of the PHOX-ligated palladium catalyst, allowing generation of adjacent quaternary and tertiary carbon stereocenters with high enantioselectivity and diastereoselectivity. Similar to their proposed mechanism for DcA of β -ketoesters, Stoltz and co-workers propose that an η^1 -allyl, *O*-bound palladium enolate intermediate **I** is intercepted in an enantioselective fashion with prochiral electrophiles (Scheme 61, path B).¹³²

Table 22 highlights a number of substrates and olefin coupling partners for which both excellent diastereoselectivity and enantioselectivity were reported. The asymmetric transformation is tolerant of small alkyl groups in the α -position as well as tertiary amines in the backbone of the cyclic β -ketoesters; however, the yield is diminished with electron-donor substituents on the arylidene malononitrile (entry 3). This reduced yield may reflect less effective trapping of the enolate with the less electrophilic Michael acceptor. The benzylidene Meldrum's acid adduct was also a suitable reaction partner (**100**); however, the reaction suffers from low diastereo- and enantioselectivity. Lastly, use of alkylidene malononitriles resulted in deprotonation of the malononitrile followed by allylation to provide **101** (Table 22).¹³³

The proposed catalytic cycle for asymmetric IDcA involves ionization of the allyl β -ketoester with the $\text{Pd}(\text{PHOX})$ catalyst followed by loss of CO_2 (Scheme 62). This process generates the η^1 -allyl palladium enolate intermediate **A**, a proposed key intermediate in the normal DcA reaction. Conjugate addition delivers intermediate **B**. The ensuing stabilized malononitrile anion attacks the π -allyl palladium complex delivering product and regenerates the $\text{Pd}(0)$ catalyst. Interestingly, compared to the products of normal DcA reactions, the IDcA products have the opposite absolute configuration at the α -carbon (Scheme 61). However, the stereochemistry of addition of the electrophile is

Table 22. Asymmetric Interceptive DcA of Cyclic β -Ketoesters


entry	R	R'	yield	dr (A:B)	A	B
1	Me		97%	1:>20	—	 89% ee
2	Et		99%	1:>20	 71% ee	 97% ee
3	Me		54%	1:>20	—	 97% ee
4	Et		92%	1:2.3	 89% ee	 96% ee



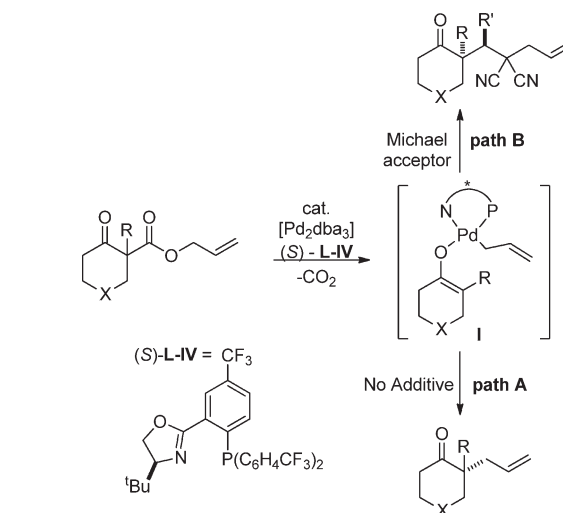
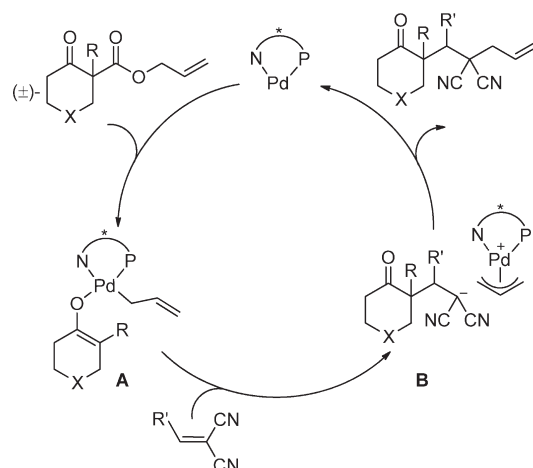
100, 66%, 1:1.2 d.r., 43% ee (major)

101, 76%

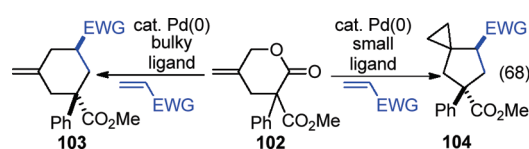
the same as that observed for protonation of the enolate intermediates.⁷¹ Thus, it appears that the intermediate palladium enolates react with external electrophiles and palladium allyl electrophiles with the opposite sense of stereoselection.

10.2. IDcA of γ -Methylidene- δ -Valerolactones

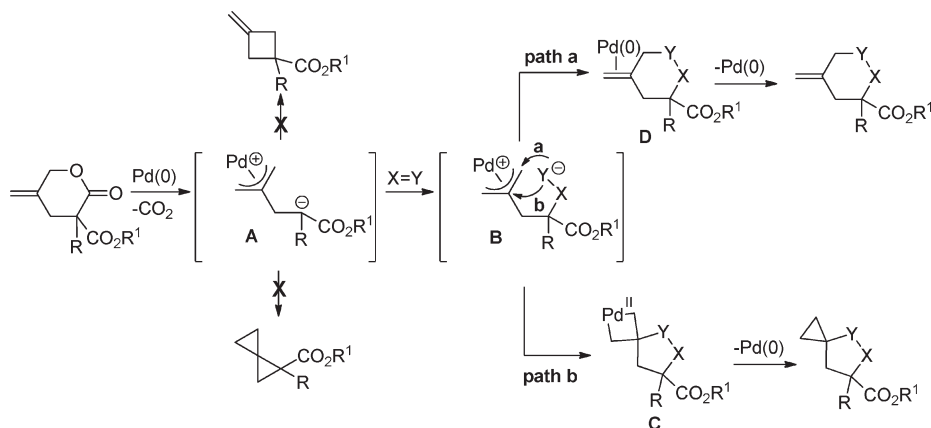
Recently, Shintani, Hayashi, and co-workers have extended the palladium-catalyzed decarboxylation of allyl ester moieties to malonate-derived valerolactones. In doing so, they developed an elegant method for the palladium-catalyzed decarboxylative formation of 1,4-dipoles **A** from γ -methylidene- δ -valerolactones (Scheme 63).¹³⁴ Subjecting the γ -methylidene- δ -valerolactones to a catalytic amount of palladium resulted in the ionization of the allyl moiety followed by loss of CO₂ to form the zwitterionic species **A**. Because the intramolecular attack of the enolate on the π -allyl ligand of **A** to form a four-membered ring is disfavored, Hayashi and co-workers proposed that one could intercept such intermediates even with relatively weak electrophiles to form **B**.^{134b,d,g,h} At this point, regioselective attack on the π -allyl palladium moiety generates two potential products. Attack at the terminal carbon of the palladium π -allyl leads to an *exo*-methylene cyclohexane product (path a, Scheme 63). On the other hand, attack at the central carbon of the π -allyl palladium results in a spiro-[2.4]heptane product (path b, Scheme 63).¹³⁵

Scheme 61. Asymmetric IDcA of Cyclic β -Ketoesters**Scheme 62. Proposed Cycle for Asymmetric IDcA**

10.2.1. [4 + 2]-Cycloadditions with α,β -Unsaturated Electrophiles. Taking full advantage of these mechanistic manifolds, Shintani, Park, and Hayashi developed the palladium-catalyzed decarboxylative [4 + 2]-cycloaddition of γ -methylidene- δ -valerolactones **102** with electron-deficient α,β -unsaturated ketones, esters, and nitriles (eq 68).^{134b} Cycloadducts **103** were obtained when valerolactones were treated with Michael acceptors in the presence of 5 mol % CpPd(η^3 -C₃H₅) and bulky phosphine ligands [(*t*-Bu)₂P(*o*-PhC₆H₄), P(*o*-Tol)₃]. Interestingly, when smaller monodentate and bidentate phosphines (PPh₃, BINAP, dppf) or phosphite ligands [P(OMe)₃, P(OiPr)₃] were employed, the reaction did not result in *exo*-methylene cyclohexanes, **103**. Instead, the major products obtained were the spiro[2.4]heptanes **104** (eq 68).



Scheme 63. Proposed Mechanism for Decarboxylative [4 + 2]-Cycloadditions



On the basis of the observed selectivity, Hayashi investigated the scope of substituents that are tolerated on the γ -methylidene- δ -valerolactones and activated olefin coupling partners (Chart 35). The spiro[2.4]heptane formation with methyl acrylate is tolerant of a variety of α -aromatic substituted valerolactones, and the respective products were obtained in good yield and moderate diastereoselectivities. Employment of *tert*-butyl acrylate as the acceptor led to substantially higher diastereoselectivities as compared to methyl and ethyl acrylates. In addition, α,β -unsaturated cyclic ketones and esters were both competent olefins for cycloaddition, providing the tricyclic products **105** and **106** in good yield, albeit with minimal diastereoselectivities (Chart 35).

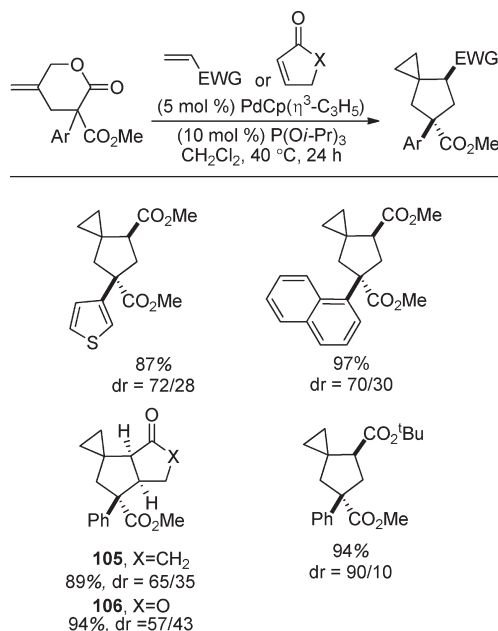
10.2.2. [4 + 2]-Cycloadditions with Isocyanates. Shin-tani, Hayashi, and co-workers extended their IDcA method to the palladium-catalyzed asymmetric decarboxylative [4 + 2]-lactamization of γ -methylidene- δ -valerolactones with isocyanates.¹³⁴

^d The reaction is proposed to proceed through a similar 1,4-zwitterionic intermediate (A, Scheme 63), which is efficiently trapped with aryl isocyanates to afford enantioenriched lactams (Scheme 64). Once again, ligand effects could be utilized to access either the spiro lactam **107** or the six-membered lactam **108**.

Hayashi reported that treatment of racemic lactone reactant with a palladium catalyst in the presence of alkyl isocyanates and chiral phosphoramidite ligand **L-XI** at 40 °C delivered the spiro- γ -lactam **109** in good yield, although with relatively low enantioselectivity (55% ee, Scheme 64). Interestingly, the seemingly minor modification of adding *o*-methoxy groups to the ligand (phosphoramidite **L-XI** \rightarrow **L-XII**, Scheme 64) combined with changing from an alkyl isocyanate to an aryl isocyanate resulted in the formation of the highly enantioenriched δ -lactam **110** (93% ee).

The interesting reversal of the regiochemistry, and its dependence on subtle changes to the ligand, was further probed via an investigation of the effect of the electronic nature of the ligand on the regioselectivity of product formation (Table 23).¹³⁶ The regioselectivity of the lactamization is not affected by the aryl α -substituent of the lactone. Instead, the observed regioselectivity is dependent on the electronic effects imparted by the ligand on the metal center. Employment of electron-rich aryl-substituted phosphines favors nucleophilic attack at the terminal carbon of the π -allyl palladium complex, affording the six-membered

Chart 35. Regioselective Decarboxylative Formation of Spiro[2.4]heptanes



lactams exclusively (Table 23). On the contrary, reactions using electron-deficient aryl-substituted phosphines favored nucleophilic attack at the central carbon of the π -allyl palladium complex, which resulted in formation of the spiro[2.4]lactams (Table 23). These results suggest that minor alteration of ligand electronics greatly influences the electrophilicity of the central and terminal carbons of the π -allyl metal complex, which in turn has a significant influence on the regiochemistry of nucleophilic substitution. To explain this, the authors proposed that the reactive orbitals on the allyl moiety (n and π^* orbitals) are energetically similar and easily attenuated via the choice of phosphine ligand.¹³⁷ In addition, stronger nucleophiles, like those derived from alkyl isocyanates, were suggested to have better orbital overlap with the central carbon, leading to spiro[2.4]lactams (Scheme 63).^{137b}

Scheme 64. Decarboxylative Cycloadditions with Isocyanates

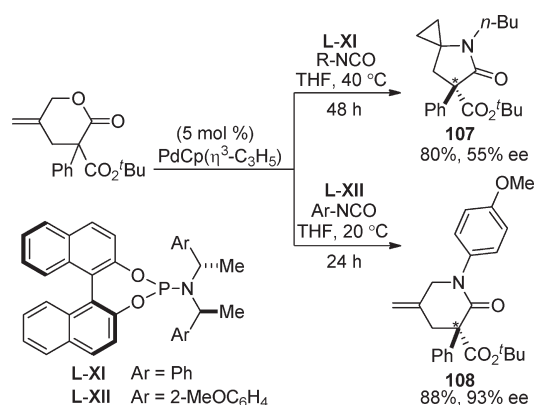


Table 23. Regioselectivity of Decarboxylative Lactamizations

R = 4-MeOC₆H₄

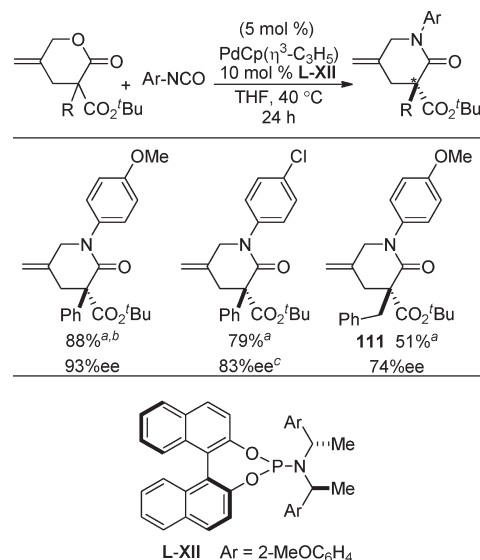
entry	Ar	ligand	110 : 109	% yield ^a
1	4-MeOC ₆ H ₄	P(4-MeOC ₆ H ₄) ₃	>99 : 1	80
2	4-MeOC ₆ H ₄	P(4-CF ₃ C ₆ H ₄) ₃	4 : 96	64
3	4-MeC ₆ H ₄	P(4-MeOC ₆ H ₄) ₃	>99 : 1	86
4	4-MeC ₆ H ₄	P(4-CF ₃ C ₆ H ₄) ₃	5 : 95	73
5	3-MeC ₆ H ₄	P(4-MeOC ₆ H ₄) ₃	>99 : 1	85
6	3-MeC ₆ H ₄	P(4-CF ₃ C ₆ H ₄) ₃	5 : 95	62
7	ferrocenyl	P(4-MeOC ₆ H ₄) ₃	97 : 3	76
8	ferrocenyl	P(4-CF ₃ C ₆ H ₄) ₃	6 : 94	71

^a Isolated yield.

On the basis of the discovery that electron-rich ligands could give rise to δ -lactams with enantioselectivity (Scheme 64), Hayashi, Shintani, and co-workers investigated the electronic effects of the aryl isocyanates on the outcomes of their IDCA. These studies revealed that electron-rich aryl-substituted isocyanates were smoothly incorporated into the decarboxylated lactones in good yield and with high enantioselectivity (Chart 36), whereas an electron-poor aromatic isocyanate resulted in reduced yields and lower enantioselectivity. A screen of the α -substituents on the lactone revealed that electron-rich and electron-poor aromatic groups as well as heteroaromatic substituents are tolerated well under the reaction conditions. Interestingly, α -alkyl substituents were tolerated as well; however, these substrates provided products in slightly lower yields and diminished enantioselectivities (e.g., **111**, Chart 36). Nonetheless, the decarboxylative functionalization of α -alkyl malonates usually requires more forcing conditions to effect decarboxylation (see section 2.1.2).¹⁸ Thus, the observed decarboxylation of an α -alkyl malonate at 30 °C may provide insight regarding ways to lower the barriers for decarboxylation.¹³⁶

To further investigate the reactivity of lactones with α -alkyl substituents, Hayashi, Shintani, and co-workers performed a series of experiments with deuterium-labeled lactones (Scheme 65). When deuterium-labeled α -benzyl lactone **112-**

Chart 36. Asymmetric Generation of Lactams



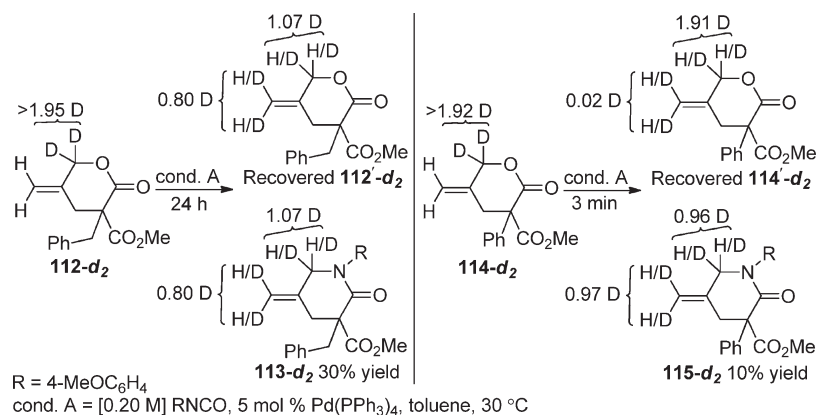
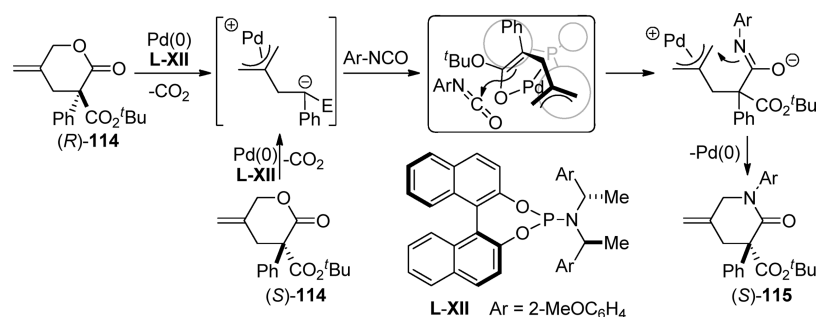
^a Isolated yield. ^b Reaction at 20 °C. ^c Determined to be (S) by X-ray crystallographic analysis.

d₂ was subjected to 5 mol % Pd(PPh₃)₄ in toluene at 30 °C, 30% of the deuterated lactam **113-d₂** was obtained. The observation of nearly equal deuterium incorporation in the ring and *exo*-methylene positions of **113** is consistent with the formation of a symmetrical π -allyl intermediate. Importantly, analysis of recovered lactone **112-d₂** also showed 40% deuterium incorporation into the *exo*-methylene carbon. The deuterium incorporation into the *exo*-methylene carbon of the lactone suggests that ionization of the allyl carboxylate is a more facile process than decarboxylation to reveal the 1,4-zwitterionic intermediate (Scheme 63). This could be attributed to the difficulty of decarboxylation of the α -alkyl malonate derivative. To test this hypothesis, deuterium-labeled α -phenyl lactone **114-d₂** was subjected to the identical reaction conditions. After 3 min, analysis of the product lactam **115-d₂** revealed equal amounts of deuterium incorporation in the *exo*-methylene as well as into the δ -position. However, analysis of recovered lactone **114-d₂** revealed that there was only trace amounts of deuterium incorporation into the *exo*-methylene. This observation suggests that palladium-catalyzed ionization of the α -aryl- δ -valerolactones is succeeded by rapid decarboxylation.

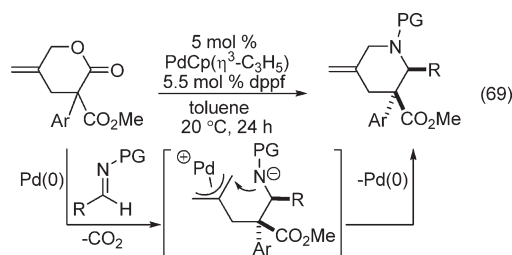
To further investigate the mechanism of the decarboxylative isocyanate insertion, Hayashi, Shintani, and co-workers reported that subjecting enantioenriched (+)- or (−)-**114** (Scheme 66) to the palladium catalyst resulted in the identical enantiomeric lactam (S)-**115**. Additionally, when racemic lactone (±)-**114** is used, the ee of the lactone **114** remains at <15% throughout the reaction. The combination of these two observations suggests that the lactone substrate is not kinetically resolved under the reaction conditions.

As detailed in Scheme 66, reaction of the proposed zwitterionic intermediate with aryl isocyanate is the stereochemistry-determining step. As Hayashi explains, ligand coordination to the metal center blocks the *si* face of the enolate, which facilitates C–C bond formation with the aryl isocyanate from the *re* face, generating an intermediate that is poised to form the product via intramolecular nucleophilic attack.

Scheme 65. Isotopic Labeling Experiments

Scheme 66. Origin of Enantioselectivity: Formation of δ -Lactams

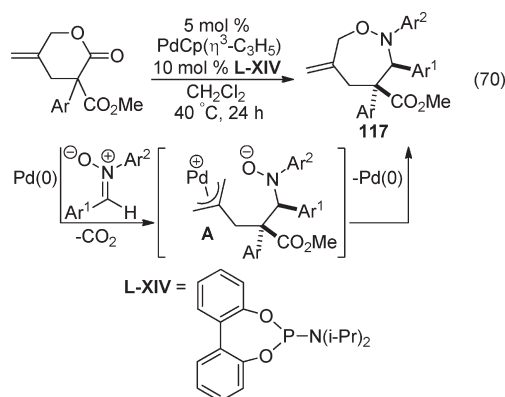
10.2.3. [4 + 2]-Cycloadditions with Phosphinate-Protected Imines. In a similar manner to the palladium-catalyzed decarboxylative formation of δ -lactams from δ -lactones, Hayashi, Shintani, and co-workers reported accessing piperidine-3-carboxylic acids diastereoselectively via [4 + 2]-decarboxylative cycloaddition of γ -methylidene- δ -valerolactones with phosphinate ester-protected imines (eq 69).^{134g} Use of the diphenylphosphinoferrocene (dppf) in toluene provided the highest yields with optimal diastereoselectivity. The reaction is proposed to proceed similarly to the reaction with isocyanates. However, in contrast to the reaction with isocyanates, the reaction with imines results in the formation of vicinal stereocenters.



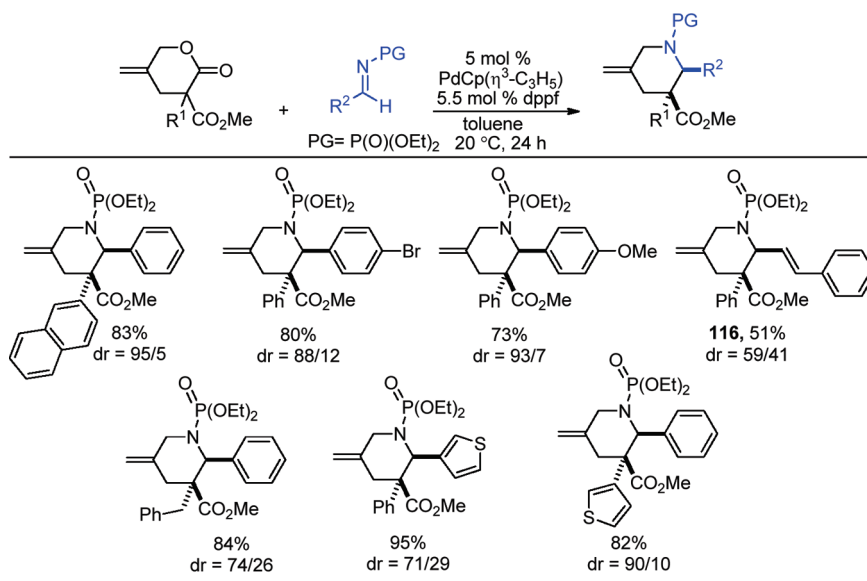
The overall yield of the reaction was not substantially influenced by the α -aryl substituent of the lactone; electron-rich, electron-poor, and heteroaromatic substituents and alkyl substituents were all tolerated under the reaction conditions. Likewise, electronically differing aromatic imine substituents were also well-suited for the cycloaddition reaction (Chart 37). However, a conjugated styryl-substituted imine was not an ideal coupling partner, resulting in a

significantly lower yield and low diastereoselectivity (**116**, Chart 37). This result is fitting with a sterically driven diastereoselection where the size of the imine substituent has an important influence on the diastereoselectivity.

10.2.4. [4 + 3]-Cycloadditions with Nitrones. Utilizing the same pro-zwitterionic γ -methylidene- δ -valerolactones, Hayashi, Shintani, and co-workers developed a method for the stereoselective synthesis of 1,2-oxazepines via a palladium-catalyzed [4 + 3]-cycloaddition with nitrones (eq 70).^{134a,c} Exposure of a lactone to a catalytic amount of palladium and aryl-substituted nitrone delivered the highly functionalized oxazepines **117**. The reaction was suggested to proceed in a stepwise fashion through intermediate **A** (eq 70).

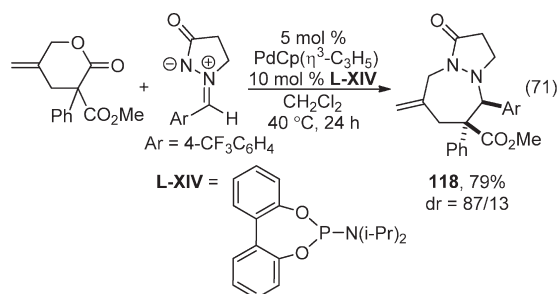


An investigation of the scope of the diastereoselective [4 + 3]-cycloaddition revealed that electron-deficient, heteroaromatic,

Chart 37. Piperidine-3-Carboxylic Acids via Decarboxylation of γ -Methylidene- δ -Valerolactones

and α -naphthyl valerolactones were all tolerated well (Chart 38). Similarly, various aryl-substituted nitrones provided the product oxazepines in good to excellent yield with moderate to good diastereoselectivity. Similar to their previous results, the authors reported an enantioselective variant of the [4 + 3]-cycloadditions utilizing chiral phosphoramidite ligand **L-XI** (Chart 38).

10.2.5. [4 + 3]-Cycloadditions with Azomethine Imines. In addition to nitrones, Hayashi and co-workers were able to extend their palladium-catalyzed decarboxylative [4 + 3]-cycloadditions to azomethine imine coupling partners (eq 71). These reactions provided the *exo*-methylene bicyclic heterocycles **118** in good yield with moderate diastereoselectivity.



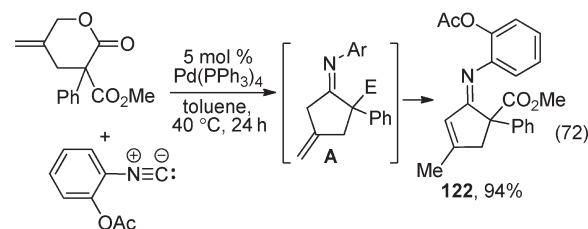
10.2.6. Heptanyl Carbocycles and Heterocycles via IDcA.

In keeping with the strategy of synthesizing seven-membered rings by IDcA reactions with 1,3-dipoles, Shintani, Hayashi, and co-workers reported the synthesis of heptanyl carbocycles and heterocycles from the palladium-catalyzed cycloaddition of γ -methylidene- δ -valerolactones with 1,1-dicyanocyclopropane and *N*-tosyl aziridines (Scheme 67).¹³⁸

As depicted in Scheme 67, exposure of γ -methylidene- δ -valerolactones to palladium catalyst and 1,1-dicyanocyclopropane resulted in the heptanyl carbocycle (\pm)-**119** as long as the ester contained an α -aryl substituent; similar treatment with *N*-tosyl aziridines provided the analogous seven-membered cyclic amines (\pm)-**120**. However, as discussed above, α -alkyl-substituted lactones do not readily decarboxylate, which resulted in the

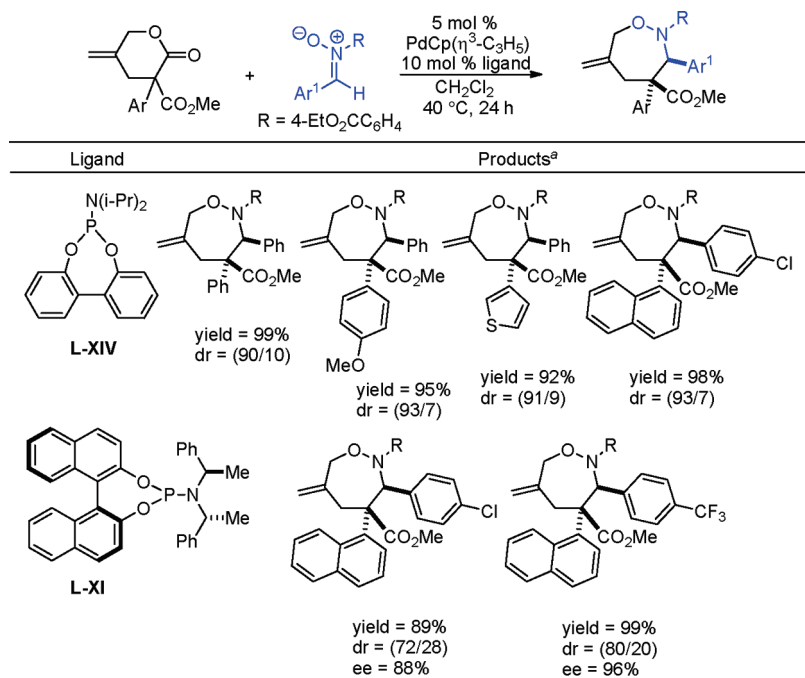
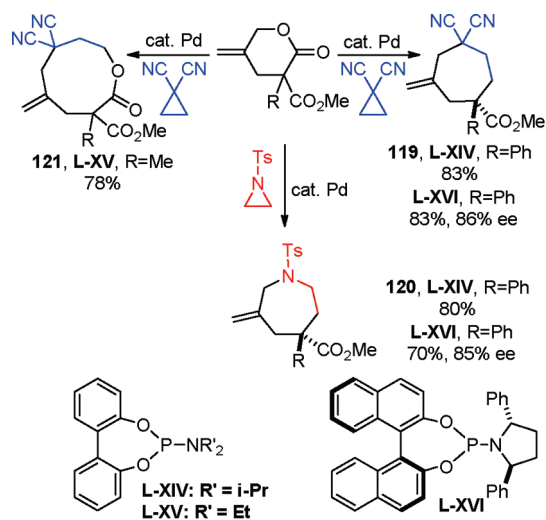
formation of nine-membered lactones like **121** (Scheme 67). As before, an asymmetric variant of the reaction using a chiral phosphoramidite ligand **L-XVI** provided enantioenriched carbo- and heterocyclic esters **119** and **120** in good yield and enantioenrichment. A proposed catalytic cycle and mechanistic rationale for the products obtained is detailed in Scheme 68.

10.2.7. [4 + 1]-Cycloadditions with Isocyanides. As detailed above, Hayashi has developed a variety of palladium-catalyzed decarboxylative [4 + 2]- and [4 + 3]-cycloadditions. A more recent report involved the palladium-catalyzed [4 + 1]-cycloaddition between isocyanides and decarboxylated γ -methylidene- δ -valerolactones to deliver cyclopentenyl imines (eq 72).^{134e} Treatment of lactone with a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ facilitated ionization and decarboxylation followed by insertion of the isocyanide to deliver **A**. Under the reaction conditions, **A** undergoes olefin isomerization to form the observed cyclopentenyl imine **122**.

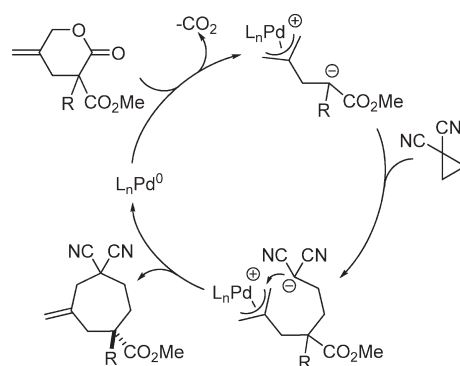


The results of an investigation of the electronic effects of the aryl substituents on both the valerolactones and the isocyanide reagents are highlighted in Chart 39. The data suggest that, of the various *N*-substituted isocyanides that were tested, both aryl- and alkyl-substituted isocyanides gave products in moderate to good yield. However, electron-rich, *p*-substituted aryl isocyanides ($\text{R} = p\text{-MeOC}_6\text{H}_4$) required a change in catalyst from $\text{Pd}(\text{PPh}_3)_4$ to the more active $\text{CpPd}(\eta^3\text{-C}_3\text{H}_5)/\text{dppf}$ catalyst. The authors also developed an asymmetric palladium-catalyzed decarboxylative [4 + 1]-cycloaddition using $\text{CpPd}(\eta^3\text{-C}_3\text{H}_5)$ and (*R*)-DTMB-Segphos ligand (**123**, Chart 39) but have not elaborated on the scope of this transformation.

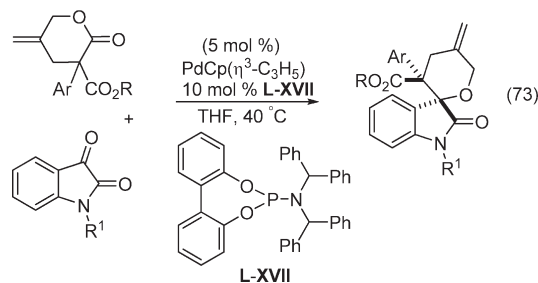
Chart 38. Decarboxylative Synthesis of Functionalized 1,2-Oxazepines

^aIsolated yield of combined diastereomers.Scheme 67. Decarboxylative Cycloaddition with Dicyanocyclopropane and *N*-Tosyl Aziridines

Scheme 68. Proposed Catalytic Cycle for Cycloheptane Formation

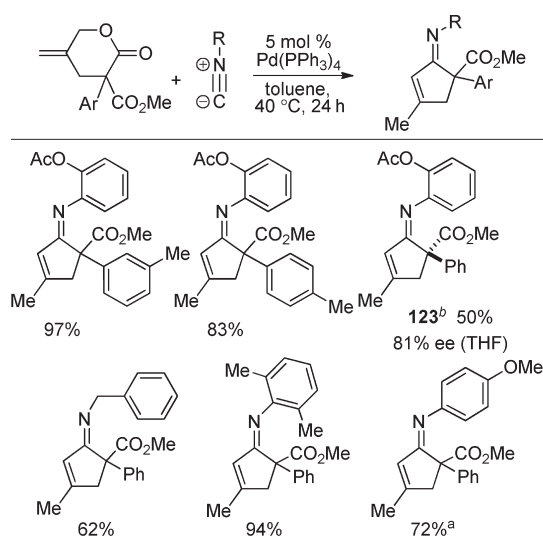


phosphoramidite ligand L-XVII and various isatins produced spirooxindole products in excellent yields and diastereoselectivities (eq 73).



10.2.8. [4 + 2]-Cycloadditions with Isatins and Other Activated Ketones. Another interesting application of the γ -methylidene- δ -valerolactones was the synthesis of spirooxindole derivatives via decarboxylative [4 + 2]-cycloaddition with isatins and other activated ketones (eq 73).^{134f} This report represents an interesting transformation, because ketones are normally not competent partners for Pd-catalyzed IDcA reactions. Hayashi and co-workers reported that treatment of γ -methylidene- δ -valerolactones with palladium catalyst in the presence of

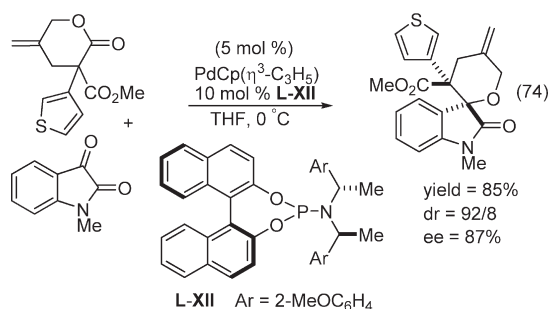
Investigating the scope of the decarboxylative cycloaddition revealed that simple benzyl-protected isatins are converted to the

Chart 39. Cyclopentenimines via Decarboxylation of γ -Methylidene- δ -valerolactones

^a 5 mol % $\text{PdCp}(\eta^3\text{-C}_3\text{H}_5)/\text{dppf}$. ^b 5 mol % $\text{PdCp}(\eta^3\text{-C}_3\text{H}_5)/(\text{R})\text{-DTMB-Segphos}$.

spirooxindole product in high yield and excellent diastereoselectivity (entry 1, Table 24). Moreover, the reaction also proceeded smoothly with both electron-rich and electron-deficient isatins (entries 2–4). Last, Hayashi reported successful decarboxylative [4 + 2]-cycloadditions in the presence of other activated ketones (entries 5 and 6).

Hayashi was also able to develop an asymmetric variant of the decarboxylative [4 + 2]-cycloaddition with isatins utilizing the chiral phosphoramidite ligand **L-XII**, allowing for the formation of adjacent quaternary and tertiary stereocenters (eq 74). Treatment of α -3-thienyl γ -methylidene- δ -valerolactones with 5 mol % of palladium catalyst and 10 mol % **L-XII** in the presence of isatin at 0 °C in THF delivered the enantioenriched spirooxindole in good enantiomeric excess.



10.3. Diphenylglycinate Esters

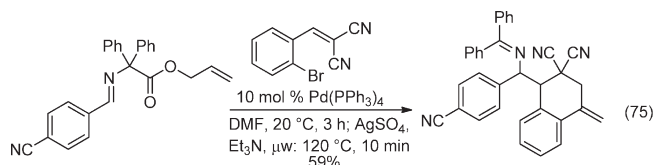
10.3.1. IDcA of Amino Acid Derivatives. In 2009, Chruma and co-workers reported that treatment of amino acid-derived allyl diphenylglycinate imines **124** with catalytic palladium and benzylidenemalononitrile led to successful IDcA (Scheme 69).¹²⁶ It was proposed that transition metal-catalyzed ionization of the allyl ester **124** and loss of CO₂ generates the 2-azaallyl anion **A**, which is intercepted by the benzylidene malononitrile to form **B**. The resultant anion then reacts with the π -allyl palladium intermediate, delivering allylated imine **125** as a (1:1) mixture of diastereomers. Interestingly, an

investigation of the solvent effects on the diastereoselectivity of the IDcA with diphenylglycinate imines revealed that the reactions proceeded smoothly even in mixtures of toluene/H₂O and MeCN/H₂O. This observation is quite interesting in light of the fact that related DcA reactions are often quite sensitive to protic conditions.^{76,86,92}

Chruma and co-workers also investigated the scope of each component of the IDcA reaction of allyl diphenylglycinate esters (Chart 40). Notably, arylidene malononitriles bearing electron-rich or electron-poor aromatics and heteroaromatics are smoothly converted to products under the above conditions with yields ranging from 77 to 99% (Chart 40). Aliphatic isobutylidene malononitriles proved to be competent olefins for interception of the DcA (**126**). However, neopentylidene malononitriles were not favorable coupling partners (**127**); instead, the normal DcA product **127'** resulted. A brief investigation of the effect of the substituent on the diphenylglycinate moiety (R¹) showed that, with electron-deficient aromatics and esters, the reaction proceeded smoothly; however, an electron-rich (**128**) aromatic substituent led to competing formation of the regioisomeric allylation product **128'**. As previously noted,¹²⁹ benzylidene Meldrum's acid adducts are sufficiently reactive to engage in many IDcA reactions. Thus, Chruma and co-workers investigated the scope of additions to aldehyde adducts of Meldrum's acid. Indeed, both electron-rich and electron-deficient aromatic β -substituted arylidene Meldrum's olefins were competent for IDcA reactions (i.e., **129**); however, the reactions occurred with lower yields than with their arylidene malononitrile counterparts. Remarkably, Chruma and co-workers also reported the IDcA using an electron-deficient aldehyde to produce **130** as a mixture of diastereomers. To our knowledge, this is the only successful intermolecular IDcA reaction with an aldehyde electrophile.⁸⁹

Chruma and co-workers proposed that the intercepted DcA reaction was initiated by oxidative addition of the allyl carboxylate leading to **A**. Loss of CO₂ from this intermediate generates the *N*-bound Pd(II) intermediate **B**. At this point, the reaction can proceed in one of three potential directions: protonation, allylation, or addition to the Michael acceptor. On the basis of the lack of protonated product for reactions performed in the presence of H₂O, Chruma and co-workers speculated that the α -amino anion equivalent remains tightly coordinated to the metal center and that introduction of the activated arylidene moiety produces intermediate **C** (Scheme 70). Reductive elimination, or Tsuji–Trost allylation, completes the construction of the IDcA product.

10.3.2. Tandem IDcA–Heck Coupling. In addition to extending the scope of IDcA reactions to allyl diphenylglycinate esters, Chruma and co-workers were able to demonstrate the synthetic utility of the products by extending the method to a stepwise, one-pot IDcA–Heck cyclization (eq 75).



10.4. Allylic Alkynoate Esters

In 2005, Rayabarapu and Tunge reported that the palladium-catalyzed DcA of allylic alkynoates proceeded through palladium allyl acetylide complexes **A** (Scheme 71).^{108a} Byproduct **130**, observed when R' = Me, suggested that intermediates **A** could be

Table 24. Decarboxylative Cycloadditions with Activated Ketones

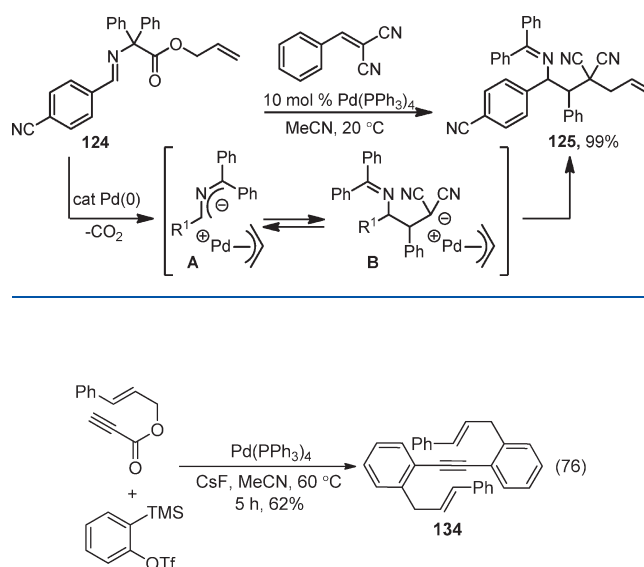
entry	ketone	product	% yield(dr)	entry	ketone	product	% yield(dr)
1			93 (95/5)	4			94 (95/5)
2			93 (98/2)	5			94 (98/2)
3			92 (95/5)	6			98 -

intercepted by alkynes. Li, Liang, and co-workers recognized that use of more reactive alkynes, specifically benzyne derived from *ortho*-silyl triflates, would lead to a more general interceptive DcA to give products **131**.^{108b}

10.4.1. IDcA with Benzyne. En route to determining the optimal reaction conditions, Li, Liang, and co-workers performed catalyst, fluoride source, solvent, and temperature screens and found that Pd(PPh₃)₄, CsF, and MeCN at 60 °C provided optimal conversion to product.^{108b} The scope of the IDcA of allylic alkynoates is detailed in Chart 41. Investigation of the alkynyl substituents of the propiolate esters revealed that both heteroaryl and electron-rich aryl propiolates provided excellent yields. Alkyl propiolates also proved to be competent substrates under the reaction conditions; however, products were formed in lower yields (Chart 41). A reaction with an electron-deficient aryl propiolate (R = 4-FC₆H₄) also formed product in low yield. A crotyl ester (R¹ = CH₃) was also smoothly converted to product, albeit with relatively low linear to branched selectivity (l/b = 3:1). Longer-chain aliphatic substituents were also tolerated, and only the linear products were observed (**132**, Chart 41). Li, Liang, and co-workers also investigated the scope of the substituents on the aryne moiety, showing that alkyl-substituted benzyne and naphthyne compounds effectively intercepted the DcA; however, electron-deficient aryne moieties greatly reduced the product yield (**133**, Chart 41).

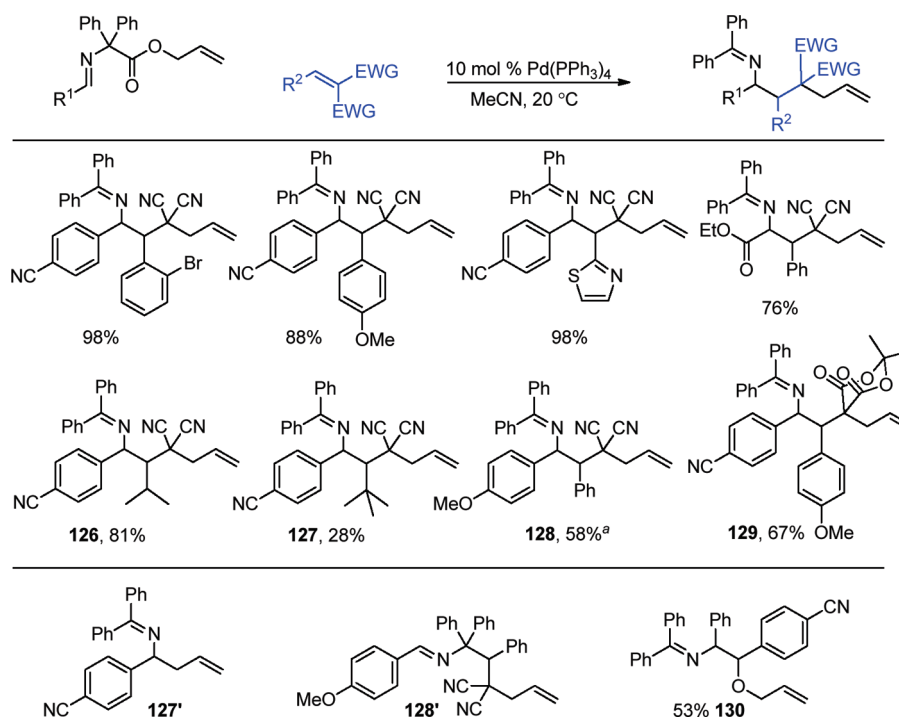
Terminal cinnamyl propiolic esters were also investigated as reactive partners for the IDcA under the above reaction conditions. It was reported that a terminal propiolate and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate underwent decarboxylative coupling; however, the reactants formed an unexpected product **134** (eq 76). Compound **134** could potentially be rationalized by a Sonogashira-like coupling from an intermediate IDcA product.

Scheme 69. IDcA of Amino Acid Esters



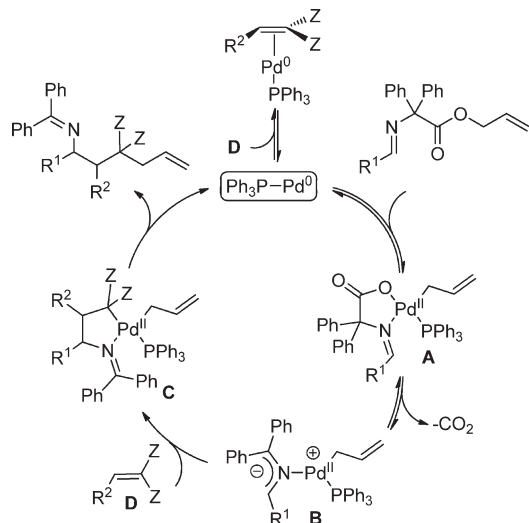
Several mechanisms were proposed to rationalize the formation of IDcA products (Scheme 70). For simplicity, the substituents on both allyl and aryne moieties have been ignored. Beginning with allylic alkynoate, exposure to the Pd(0) catalyst could generate π -allyl palladium propiolate **II**, or rapid decarboxylation could deliver π -allyl palladium alkynyl intermediate **I**. This palladium allyl acetylide complex can react via two related paths. Path A involves migratory insertion of the Pd-acetylide onto the aryne functionality, which results in aryl palladium- π -allyl intermediate **III**; subsequent reductive elimination results in a new sp²–sp³ C–C bond. Path B involves migratory insertion of the π -allyl palladium moiety onto the aryne functionality, resulting in aryne–palladium–alkyne intermediate **IV**. The ensuing reductive coupling generates a new sp–sp² C–C bond.

Chart 40. IDcA of Allyl Diphenylglycinates



^aMass balance is the regioisomeric diphenylglycinate product **128'**.

Scheme 70. Proposed Catalytic Cycle for IDcA

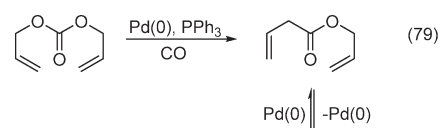
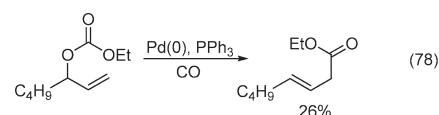
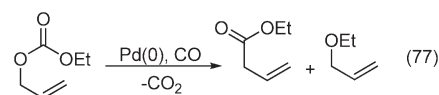


A plausible alternative reactive manifold is path C, which entails migratory insertion of aryne into the π -allyl palladium bond, resulting in aryl–palladium–propionate intermediate V. Loss of CO_2 would lead to intermediate IV, which proceeds to product through reductive elimination (Scheme 72).

10.5. Allyl Carbonate Esters

10.5.1. Decarboxylative Carbonylation of Acyclic Carbonates. It is well-known that allylic carbonates are efficient allylating reagents vis-à-vis the Tsuji–Trost reaction.¹³⁹ In the same vein, Tsuji reported another mode of interceptive DcA involving the decarboxylative carbonylation of acyclic allyl carbonates with carbon

monoxide to form β,γ -unsaturated esters.¹⁴⁰ Specifically, allyl ethyl carbonate was converted to a mixture of the β,γ -unsaturated ester and ethyl allyl ether in the presence of a catalytic $\text{Pd}(0)$ source under an atmosphere of carbon monoxide (eq 77). The regiochemistry of the reaction was investigated with the branched isomeric 3-hept-1-enyl carbonate, which formed the linear substituted β,γ -unsaturated ester, albeit in low yield (eq 78). Similarly, a diallyl carbonate was allowed to react with the palladium catalyst and CO. Although decarboxylative carbonylation to form β,γ -unsaturated allyl esters was facile (eq 79), even prolonged exposure to the reaction condition did not result in further IDcA of the allyl acetate derivative to form the anhydride product.



Optimized reaction conditions for the decarboxylative carbonylation were established after a solvent, temperature, CO

Scheme 71. Interception of Palladium Acetylides

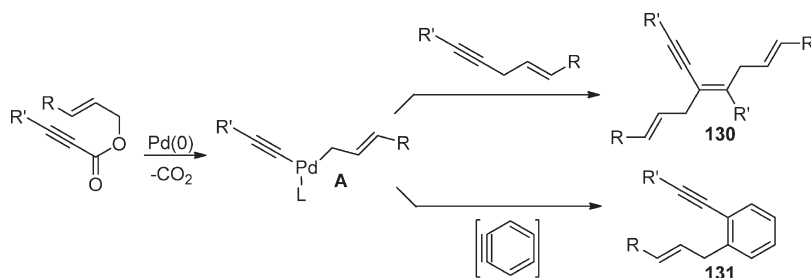
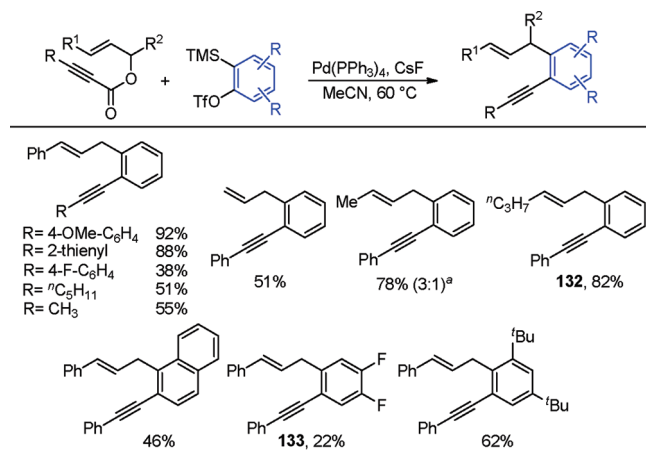
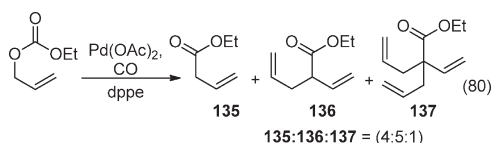


Chart 41. IDcA of Allylic Alkynoates with Benzyne



^aLinear/branched ratios.

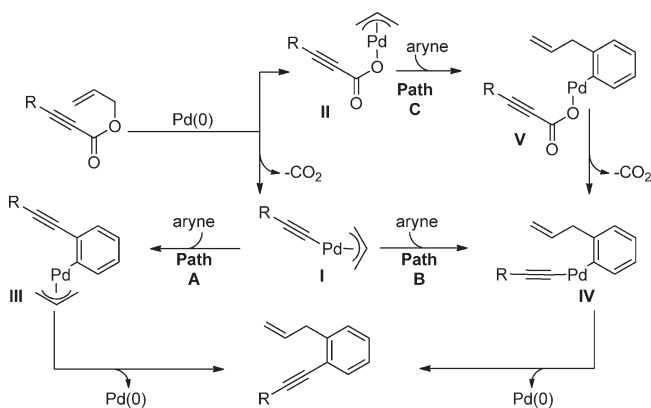
pressure, and ligand screen. Traditional solvents such as toluene, benzene, THF, and acetonitrile were not ideal for the decarboxylative carbonylation reaction. For this reason, the reactions were performed neat. The ideal reaction temperature was found to be 50 °C, and 5–10 atm was the most effective CO pressure. Although the entirety of reactions with allyl carbonates detailed in the schemes above were performed with monodentate phosphine ligands, Pd(OAc)₂ and bidentate bisdiphenylphosphinoethane (dppe) also formed an active catalyst for the decarboxylative carbonylation of ethyl allyl carbonate (eq 80). In addition to obtaining the target β,γ-unsaturated ethyl ester 135, Tsuji also reported generating the mono- and diallylated β,γ-unsaturated ethyl esters 136 and 137.



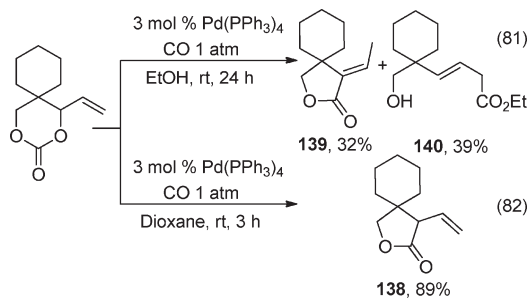
The mechanism proposed by Tsuji for the decarboxylative carbonylation of ethyl allyl carbonates is detailed in Scheme 73. Ionization of allyl ethyl carbonate with a catalytic amount of Pd(0) generates π-allyl-palladium-carbonate A, which decarboxylates to form the π-allyl-palladium-alkoxide B. Migratory insertion of CO generates C, and subsequent reductive elimination, or acyl substitution,¹⁴¹ affords the γ,δ-unsaturated ester product and regenerates the palladium catalyst.

10.5.2. Decarboxylative Carbonylation of Cyclic Carbonates. In 1987, Tamaru, Bando, and co-workers reported the

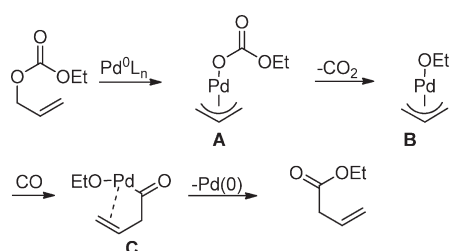
Scheme 72. Proposed Catalytic Cycles for IDcA of Allylic Alkynoates



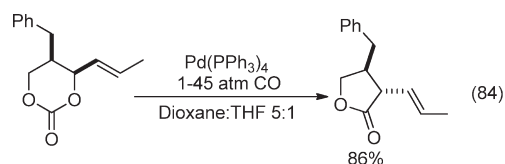
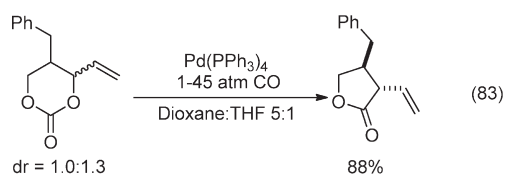
extension of carbonylative DcA reactions to a cyclic carbonate leading to 2-vinyl-γ-butyrolactones 138 (eq 82).^{141b} As the reaction conditions were optimized, Tamaru et al. found that the product selectivity was solvent-dependent. A mixture of dioxane/THF proved to be the ideal solvent system, achieving product yields up to 89%. The authors further noted that reactions in polar protic solvents did not result in the formation of the butyrolactone 138; rather, a mixture of isomerized butyrolactone 139 and a β,γ-unsaturated ester 140 was obtained (eq 81). An investigation of the scope of the reaction revealed that nonsubstituted vinyl carbonates (R¹ = R² = R³ = H) were converted to product, albeit with reduced yield (141, Chart 42). A carbonate with a *tert*-butyl substituent (R¹ = ^tBu) was subjected to the above reaction conditions and converted to the disubstituted γ-butyrolactone (142); however, the reaction proceeded with no diastereoselectivity. Lastly, it is notable that 3-methyl vinyl carbonate was converted to the α-quaternary butyrolactone 143 in relatively good yield (Chart 42); typically carbonylation of sterically hindered carbon centers is difficult.



Scheme 73. Proposed Mechanism for Decarboxylative Carbonylation

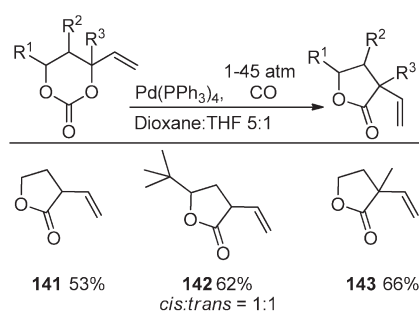


The stereoselectivity of the decarboxylative carbonylation reaction was revealed via a series of reactions with diastereomerically enriched substrates. For example, a nearly 1:1 mixture of *cis*/*trans*-carbonate was stereoselectively converted to the α -vinyl- β -benzyl- γ -butyrolactone as a single diastereomer (eq 83). The stereoconvergence can be attributed to the facile π - σ - π interconversion of the intermediate π -allyl complex.^{1d} On the other hand, a *cis*-carbonate, which cannot epimerize through π - σ - π interconversion, underwent stereospecific conversion to the *trans*- γ -butyrolactone (eq 84). Under the same conditions, the *trans*-carbonate **144** yielded nearly equal amounts of both the *cis*- and *trans*- γ -butyrolactones **145** and **146** (Scheme 74). Interestingly, **146** was obtained with a *cis*-configuration about the olefin. To explain the observed diastereoselectivities, Tamaru, Bando, and co-workers proposed that the palladium-catalyzed ionization of the allylic carbonate proceeded with inversion of stereochemistry (**A**, Scheme 74).¹⁴² Subsequent CO₂ loss and CO insertion is achieved with retention of stereochemistry, thus rationalizing the stereospecific formation of the *cis*-**145**. However, the high energy *cis*-intermediate **A** can isomerize to the *trans*-palladacycle **C** via the intermediacy of an η^1 -allyl palladium complex. As such, rotation about the Pd-C bond in **B**, followed by CO insertion, explains the observed formation of the *cis*-olefinic product **146** (Scheme 74).



In a similar manifold, Tamaru, Bando, and co-workers employed cyclic vinyl carbonates along with isocyanates to access cyclic vinyl carbamates **147** (Scheme 75).^{141a,143} In this case, the intermediate π -allyl-palladium alkoxide **A** is intercepted with isocyanates (instead of CO) to form amides **B**; subsequent attack of the carbamate on the π -allyl-palladium moiety results in cyclic carbamate **147**.

A probe into the scope of the reaction showed that both electron-rich and electron-poor aryl isocyanates underwent

Chart 42. γ -Butyrolactones Via Decarboxylative Carbonylation

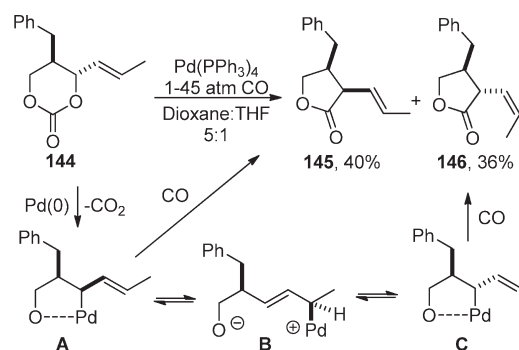
carbamate formation smoothly, and the carbonate-carbamate transformation tolerated substitution at all carbons with the exception of C-3 (Chart 43). Investigating the scope of isocyanates further revealed that reactions with the *N*-alkyl isocyanate, benzyl isocyanate, did not result in carbamate formation. Fitting with the proposed formation of an intermediate carbamate anion, the highest yields were obtained with *N*-substituents that could stabilize the intermediate carbamate anion. Thus, tosyl isocyanate was chosen as the isocyanate of choice for investigating the diastereoselectivity of the reaction (Chart 43).^{141a,143}

Investigating the effect of the carbonate substituent at R² revealed that methyl and phenyl groups were compatible; however, the diastereoselectivity for formation of the *trans* product was much better for the phenyl substituent (**148** and **149**, Chart 43). Carbonates with both aromatic as well as bulky alkyl groups at R¹ provided products in high yield (**150** and **151**). For these cases, it is noteworthy that the reaction conditions determined the major diastereomer that was obtained. At lower temperature and reduced reaction times, the *cis*-diastereomers were favored; however, at a higher temperature and longer reaction time, the *trans*-diastereomers were favored. These results suggest a kinetic preference for formation of the *cis*-product, which can isomerize to the more stable *trans*-isomer via ionization and π - σ - π equilibration upon prolonged reaction. As expected, reactions beginning with diastereomerically enriched carbonates that cannot undergo epimerization via π - σ - π equilibration stereospecifically form either *cis*- or *trans*-**152** from the *cis*- and *trans*-carbonates, respectively (Chart 43).

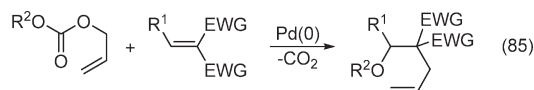
The rationale of Bando, Tamaru, and co-workers for the observed diastereoselectivity for products **148** and **149** is depicted in Scheme 76. Palladium-catalyzed ionization of either *cis*- or *trans*-carbonate proceeds with inversion at C-3; subsequent decarboxylation and addition to the isocyanate results in intermediates **A** and **D**. Equilibration of **A** and **D** via η^1 -allyl palladium intermediates is much faster than cyclization to form the carbamates. Thus, the diastereoselectivity is controlled by the rates of ring closure. The transition state to form the *cis*-product is destabilized by a developing 1,3-diaxial interaction, which favors the formation of the *trans*-product.

10.5.3. Decarboxylative Michael Addition/Allylation.

Yamamoto and co-workers further expanded the concept of inserting activated olefins into the intermediates of palladium-catalyzed decarboxylation of allyl carbonates.^{128a,133} Specifically, treatment of acyclic allylic ethyl carbonates with a palladium catalyst in the presence of electron-deficient olefins delivered alkoxyallylation products (eq 85). Similar to their IDCA reactions

Scheme 74. Rationale for Observed Stereochemistry for the Decarboxylative Carbonylation

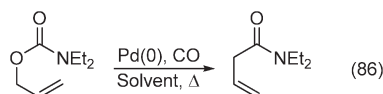
using β -ketoesters,^{128b} Yamamoto and co-workers investigated how the electrophilicity of benzylidene and alkylidene malononitriles affected the palladium-catalyzed decarboxylative alkoxyallylation of electron-deficient olefins. Arylidene malononitriles with electron-donating and electron-withdrawing substituents underwent IDCa with allyl ethyl carbonates in high yield (entries 3 and 4, Table 25). A bulky alkylidene malononitrile that does not have acidic hydrogens was also sufficiently reactive to undergo IDCa in high yield (entry 6). Allylic carbonates with substituents on the allyl moiety were also subjected to the reaction conditions in the presence of benzylidene malononitriles and provided the linear allylation product selectively (entry 7, Table 25).



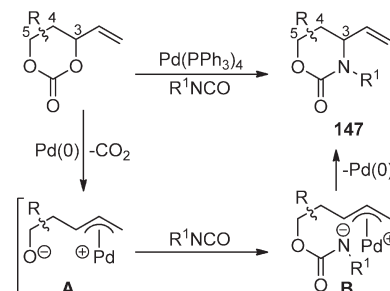
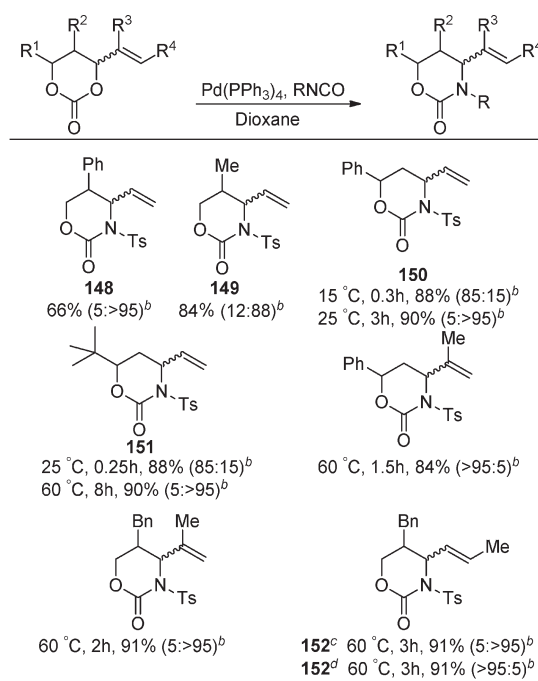
The proposed catalytic cycle for the decarboxylative alkoxyallylation reaction begins with ionization of the allyl ester moiety and loss of CO_2 (Scheme 77). The resulting ethoxide then reacts with the electrophilic arylidene malononitrile, forming a new C—O bond to deliver ion-pair intermediate B. Subsequent regioselective attack of the stabilized nucleophile on the cationic π -allyl palladium moiety generates alkoxyallylated product and regenerates the Pd(0) catalyst.

10.6. Allyl Carbamate Esters

10.6.1. Decarboxylative Carbonylation Acyclic Carbamates. In 1984, Tsuji et al. reported the decarboxylative carbonylation of allylic carbonates to form β,γ -unsaturated esters.^{140b} In an analogous fashion, Miyazawa, Yamamoto, and co-workers reported the decarboxylative carbonylation of acyclic allylic carbamates (eq 86).¹⁴⁴



The reaction entailed treatment of allyl diethyl amido carbamates with a catalytic source of Pd(0) under an atmosphere of CO to afford β,γ -unsaturated diethylamides (eq 86). The specific reaction conditions used to convert the carbamates into amides were 5 mol % $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$, 20 mol % PPh_3 , under 80 atm of CO, at 100 °C. As before, the reactions were performed under solvent-free conditions. Under these conditions, methallyl

Scheme 75. Decarboxylative Isocyanation**Chart 43. Palladium-Catalyzed Decarboxylative Carbamate Formations**

^aStarting material carbonate: *cis/trans* = 1:1. ^b*cis/trans*. ^cFrom *trans*-carbonate. ^dFrom *cis*-carbonate.

and cinnamyl carbamates were converted to β,γ -unsaturated diethylamides **153** and **154** in moderate to good yields (Chart 44). Likewise, aliphatic allyl carbamates were converted to the corresponding amides in moderate yields; however, the control of the olefin geometry was not high (**155** and **156**). An acryloyl carbamate was likewise converted to the substituted β,γ -unsaturated amide **157** with high regio- and diastereoselectivity; however, the reaction suffered from a low yield due to significant competing elimination.

10.6.2. Decarboxylative Carbonylation of Cyclic Carbamates. Similar to the aforementioned decarboxylative carbonylation of allylic carbonates, Tamaru and co-workers reported the decarboxylative carbonylation of allylic carbamates in 1992 (Scheme 78).¹⁴⁵ The reaction involved smooth conversion of cyclic allyl carbamates to γ -lactams **158** in the presence of catalytic palladium under an atmosphere of CO in dioxane solvent. The authors further showed that ionization of a 1:1

Scheme 76. Rationale for Observed Diastereoselectivities

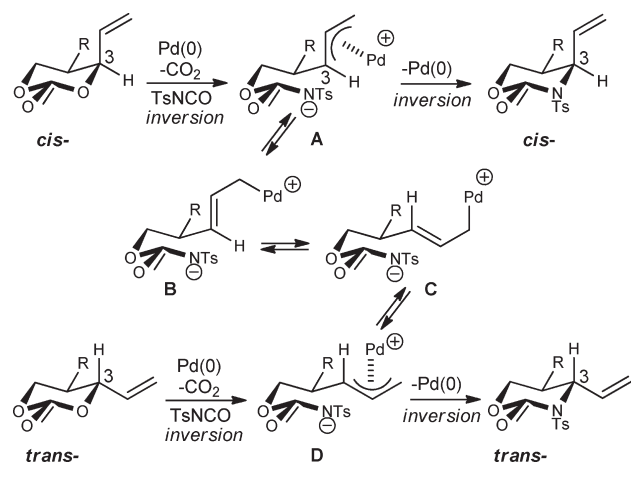


Table 25. Palladium-Catalyzed Alkoxyallylation of Alkylidene Malononitriles

entry	R ¹	R ²	R ³	yield % ^a (l/b)
1	Ph	H	H	92
2	4-MeC ₆ H ₄	H	H	81
3	4-MeOC ₆ H ₄	H	H	92
4	4-MeO ₂ CC ₆ H ₄	H	H	85
5	1-naphthyl	H	H	90
6	^t Bu	H	H	99
7	Ph	Me	H	92 (78:22)

^a Isolated via column chromatography.

mixture of diastereomeric carbamates generated the product as a single diastereomer via facile epimerization of intermediate A.

Tamaru and co-workers further investigated the effect of substituents on the tertiary amide of the cyclic carbamates on the IDcA reaction. As detailed in Scheme 79, when the substituent on the tertiary amide is benzyl, the reaction was not successful (**159c** → **162**). The lack of reactivity was attributed to the inability of allyl carbamates with electron-donor substituents on nitrogen to decarboxylate.¹⁴⁶ Moreover, when reactions were performed in ethanol with electron-withdrawing Ts or CPh N-substituents, cyclic lactams were not observed (e.g., **159a** and **159b**). Instead, Tamaru and co-workers suggested that intermediate A (R = Ts, CPh) is protonated in the polar protic solvent, allowing for the formation of the acyclic amino ester products **160** and **161** (Scheme 79).

10.6.3. Decarboxylative Carbonylation of Oxazolidinones. In 2000, Knight et al. extended the decarboxylative carbonylation method to the asymmetric synthesis of 3,6-dihydro-1H-pyridin-2-ones **163** from nonracemic 5-vinylloxazolidin-2-ones (eq 87).¹⁴⁷ Similar to the report by Tamaru, if the nitrogen of the oxazolidinone was Boc-protected (R = Boc), the authors obtained the acyclic β,γ-unsaturated amino ester **164** (eq 88). However, when the amide nitrogen was not protected (R = H), the reaction resulted in formation of dihydropyridinone **163** (eq 87). Optimization of the lactam formation showed that decarboxylative carbonylation proceeded in good yield with 5 mol % Pd(OAc)₂(PPh₃)₂ under 65 atm of CO pressure, in EtOH at 70 °C, although extended reaction times (120 h) were

Scheme 77. Proposed Mechanism for Decarboxylative Alkoxyallylation

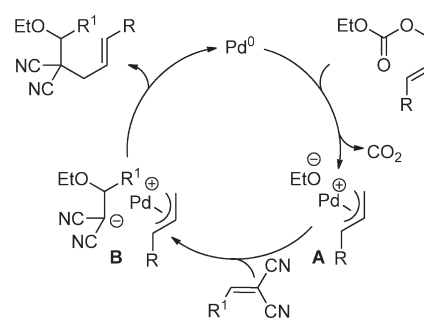
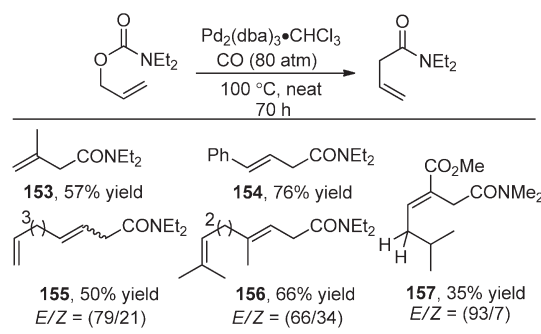
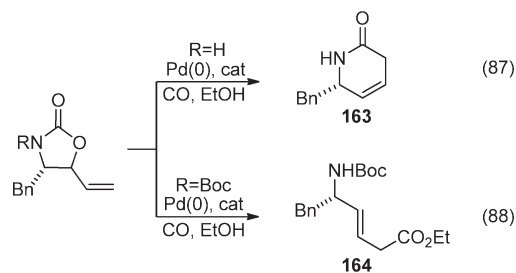


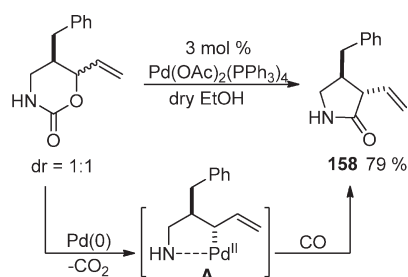
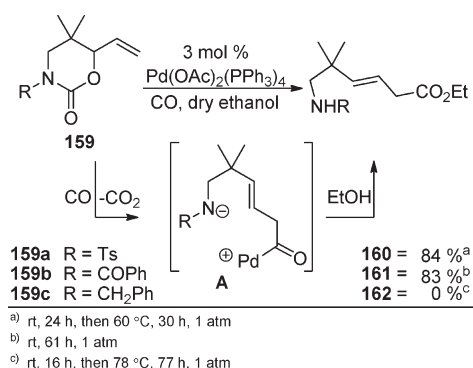
Chart 44. Decarboxylative Carbonylation of Allyl Carbamates



required. With these reaction conditions in hand, Knight et al. investigated the scope of the reaction and showed that substrates with aliphatic substituents at R¹ were converted in good yield to the respective dihydropyridinones (Chart 45). In contrast, a substrate with substitution at R³ (R³ = Me) did not afford any product and only the starting material was recovered from the reaction solution. This lack of reactivity could be attributed to the difficulty of carbonylation of a sterically hindered tertiary carbon center.



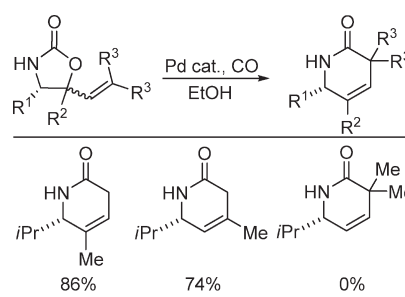
A mechanistic rationale for the formation of the dihydropyridinones involves initial ionization of the ester moiety to generate a syn-π-allyl palladium carbamate intermediate A (Scheme 80). To investigate the π-allyl palladium formation, Knight et al. found that treatment of a mixture of vinyl oxazolidinone diastereomers (R¹ = *i*-Pr, R² = R³ = H) with Pd(PPh₃)₄ resulted in recovery of only the *trans*-vinyl oxazolidinone. On the basis of this observation, Knight et al. postulated that ring-opening of the vinyl carbamates is reversible. This result also suggested that decarboxylation to form primary amine intermediate B is not facile. A

Scheme 78. Decarboxylative Carbonylation of Cyclic Vinyl Carbamates**Scheme 79. Decarboxylative Carbonylation of Cyclic Vinyl Carbamates**

sluggish decarboxylation allows for the π -allyl palladium intermediate to isomerize to the *anti*-A configuration, which is more favorable for formation of the cyclic lactam.¹⁴⁸ Subsequent decarboxylation and carbonylation followed by cyclization delivered dihydropyridinone. It should be noted that the maintenance of the enantioenriched center indicates that reversible β -hydride elimination from any π -allyl intermediates is likely not occurring. Knight et al. also extended the palladium-catalyzed decarboxylative carbonylation method to the diastereospecific,¹⁴⁸ diastereoselective,¹⁴⁹ and enantiospecific¹⁵⁰ synthesis of 3,6-dihydro-1H-pyridin-2-ones.

10.6.4. Cycloadditions of Divinyl Oxazolidinones. In addition to their cycloadditions with CO, Knight et al. showed that vinyl oxazolidinones undergo a palladium-catalyzed [3 + 2]-cycloaddition with activated olefins to afford highly substituted pyrrolidines (Chart 46).¹⁵¹ The decarboxylative cycloaddition occurs with benzylidene malononitriles (165), benzylidene Meldrum's acid adducts (166), and a cyano chromone (167) to provide substituted pyrrolidines in good yield.¹⁵¹

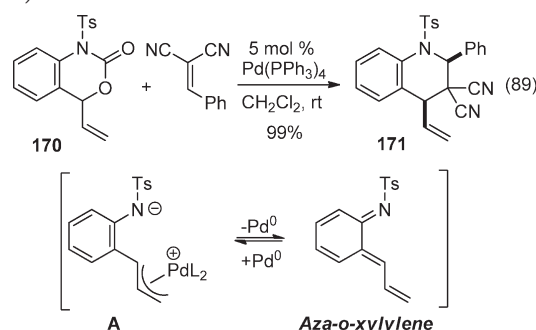
10.6.5. Diastereoselective Cycloadditions of Vinyl Oxazinones. Building on investigations of palladium-catalyzed reactions of allylic carbamates by the groups of Tsuji,¹⁴⁶ Tamaru,¹⁴⁵ Cook,¹⁵² and Tunge,^{110,111} Tunge and Wang developed a similar palladium-catalyzed IDcA of vinyl oxazinones with Michael acceptors to form highly substituted 4-vinylpiperidines (Scheme 81). Specifically, treatment of *rac*-168 with 1 equiv of benzylidene malononitrile and 5 mol % $\text{Pd}(\text{PPh}_3)_4$ in CH_2Cl_2 produced vinyl piperidine 169 as a single diastereomer (Scheme 79). The reaction was believed to proceed via the ionized and decarboxylated intermediate tosyl amide A. This

Chart 45. Dihydropyridinones Via Decarboxylation of Vinyloxazolidinones

ambiphilic intermediate can undergo addition to benzylidene malononitrile, reversibly generating the zwitterionic intermediate B. Both *cis*- and *trans*-168 were converted to the same product, showing that epimerization through π - σ - π allyl interconversion is more rapid than cyclization.¹⁵³

An investigation of the scope of the IDcA demonstrated that the reaction tolerated substitution at the carbinol carbon ($\text{R}^2 = \text{Me}$), providing products in high yield (entries 5–7, Table 26). Substitution at the 5-position of the carbonate (R^1) and at the vinyl carbon (R^3) generated lower yields; however, the products were generated with good diastereoselectivity (entries 1 and 2). Carbamates lacking any substitution underwent cycloaddition with low diastereoselectivity, favoring the *trans*-diastereomer (entries 3 and 4, Table 26). Likewise, for substrates in which $\text{R}^2 = \text{methyl}$, the reactions proceeded in excellent yield but exhibited minimal *trans*-diastereoselectivity (entries 5 and 6). This *trans*-selectivity was amplified when a larger Ph substituent was used in the R^2 position (entry 7, Table 26). To explain the observed selectivities, the authors speculated that reversible addition of the tosyl amide to the benzylidene malononitrile would allow the cyclization to take place through the lowest energy conformer. The observed diastereoselectivities were then rationalized using a model that placed the large substituents in the equatorial positions about a six-membered cyclization transition state (A or B, Chart 47). Thus, if either R^1 or R^2 was large, high diastereoselectivities resulted.

10.6.6. Asymmetric Cycloaddition of Benzoxazinone. In 2008, Wang and Tunge reported a similar palladium-catalyzed decarboxylation of benzoxazinone 170 followed by cycloaddition with arylidene malononitriles to generate highly substituted dihydroquinolines 171 (eq 89).¹¹² In analogy to the intermediates derived from simple vinyl oxazinones, vinyl benzoxazinones are proposed to form zwitterionic intermediates A. These intermediates are equivalent to *aza-ortho*-xylenes that are coordinated to, and polarized by, palladium (eq 89).



Scheme 80. Proposed Catalytic Cycle for Decarboxylative Carbonylation

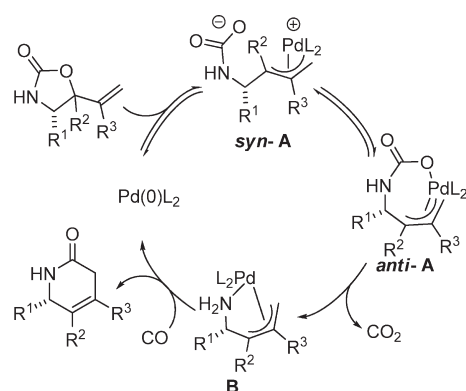
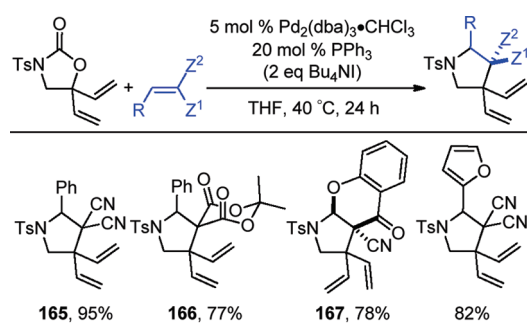


Chart 46. Decarboxylative [3 + 2]-Cycloaddition with Activated Olefins



Ligand studies directed at developing an asymmetric cycloaddition revealed that the anthracenyl Trost ligand (**L-III**) provided both high enantioselectivity and diastereoselectivity (Chart 48). The reaction conditions chosen to probe the scope of the decarboxylative aza-*o*-xylylene formation and subsequent cycloaddition with arylidene malononitriles entailed 5 mol % $\text{Pd}_2(\text{dba})_3$ and 10 mol % **L-III** in CH_2Cl_2 at room temperature for 4–6 h. Electron-rich and electron-poor vinyl benzoxazinones were screened for cycloaddition, enantioselection, and diastereoselection as well as compatibility with various arylidene malononitriles. In general, the cycloadditions proceeded smoothly under the reaction conditions, delivering products with good yield, high enantioselectivities, and diastereoselectivities (Chart 48). As detailed above, more electron-rich benzylidene malononitriles are not as well-suited for the cycloaddition; thus, electron-deficient arylidene malononitriles proved to be ideal reactive partners for cycloaddition. In addition, vinyl benzoxazinones that lacked a substituent para to the nitrogen provided products in substantially lower yield.

Wang and Tunge proposed a stepwise cycloaddition mechanism that is based on their previous determination that such reactions proceed through zwitterionic intermediates like **A** (Scheme 82).¹¹¹ Treatment of **170** with the active catalyst generates a palladium-polarized aza-*o*-xylylene intermediate **A** (Scheme 82). Subsequent conjugate addition to the benzylidene malononitrile resulted in two potential equilibrating intermediates **B** or **C**. The stereochemical influence of the chiral ligand

Scheme 81. Diastereoselective Cycloadditions of Vinyl Oxazinones

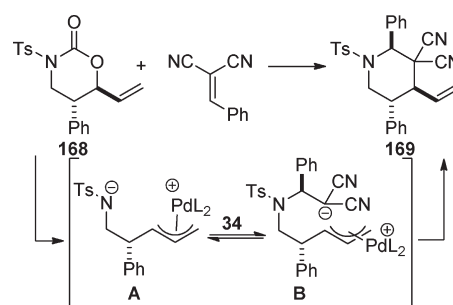


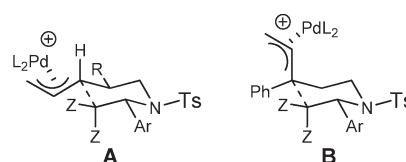
Table 26. Yields and Diastereoselectivities of IDcA

entry	R ¹	R ²	R ³	R ⁴	yield (dr) ^{a,b}
1	Ph	H	Ph	<i>p</i> -AcOC ₆ H ₄	53 (>19:1)
2	Ph	H	Ph	Ph	54 (10:1)
3	H	H	H	<i>p</i> -AcOC ₆ H ₄	99 (1:2.8)
4	H	H	H	Ph	85 (1:3)
5	H	CH ₃	H	<i>p</i> -AcOC ₆ H ₄	92 (1:2)
6	H	CH ₃	H	Ph	99 (1:2)
7	H	Ph	H	Ph	87 (1:>19)

entry	R ¹	R ²	R ³	R ⁴	yield (dr) ^{a,b}
1	Ph	H	Ph	<i>p</i> -AcOC ₆ H ₄	53 (>19:1)
2	Ph	H	Ph	Ph	54 (10:1)
3	H	H	H	<i>p</i> -AcOC ₆ H ₄	99 (1:2.8)
4	H	H	H	Ph	85 (1:3)
5	H	CH ₃	H	<i>p</i> -AcOC ₆ H ₄	92 (1:2)
6	H	CH ₃	H	Ph	99 (1:2)
7	H	Ph	H	Ph	87 (1:>19)

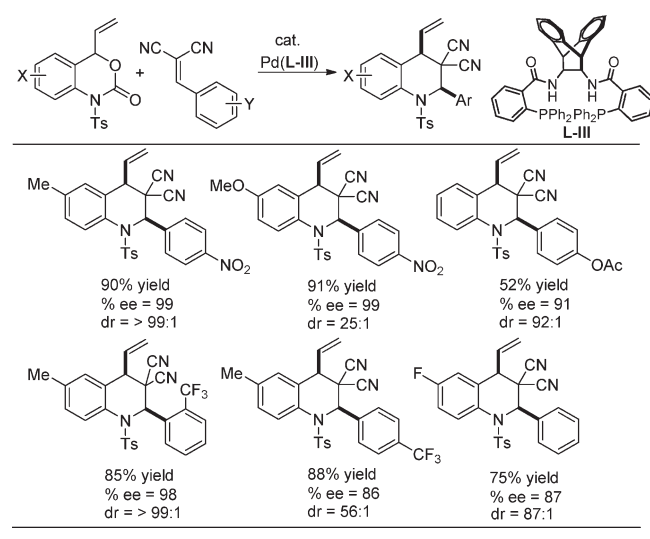
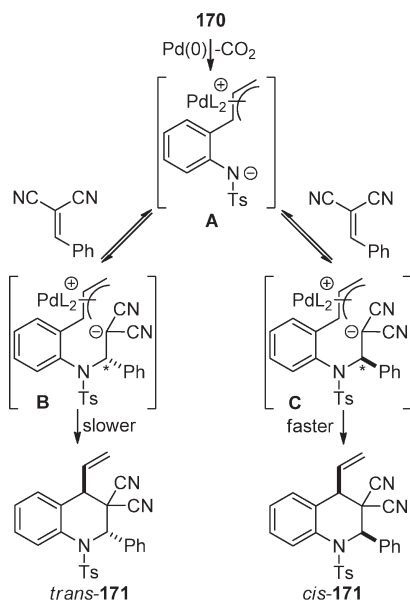
^a Yield and syn/anti ratio of isolated product. ^b >19:1 indicates that the minor diastereomer was not detected by ¹H NMR spectroscopy.

Chart 47. Rationale for Observed Diastereoselectivity

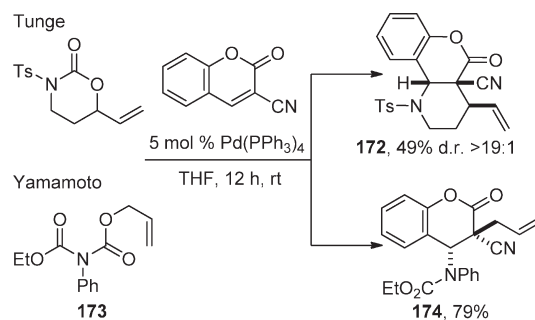
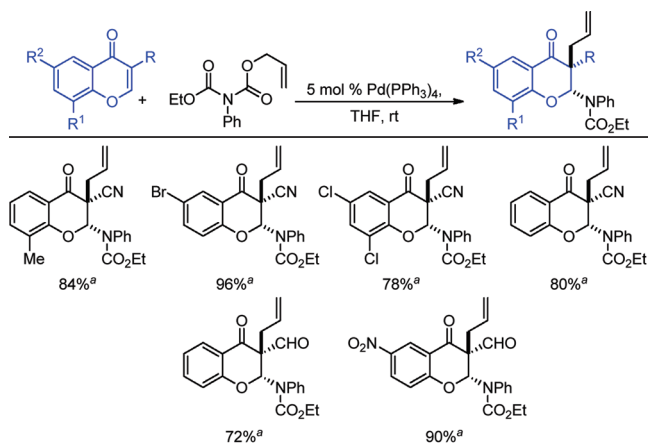


suggests that the cyclization of one of these intermediates is favored. Thus, Tunge speculated that the reaction proceeded via an initial reversible conjugate addition followed by a stereochemical defining cyclization.

10.6.7. IDcA of Acyclic Carbamates. Previously, Wang and Tunge reported that cyanocoumarins were competent

Chart 48. Diastereo- and Enantioselective Decarboxylative Cycloaddition**Scheme 82. Stereochemical Rationale**

partners for the ruthenium-catalyzed decarboxylative insertion of electrophiles into β -ketoesters.¹²⁹ Further investigation proved that the 3-cyanocoumarins were indeed sufficiently reactive toward the palladium-catalyzed IDcA with a cyclic allyl carbamate to generate the tricyclic product **172** (Scheme 83). Moreover, *syn*-addition to the 3-cyanocoumarin set three contiguous stereocenters with high diastereoselectivity. Similar studies were published in the same year by Yamamoto and co-workers, in which acyclic *N*-phenyl carbamates **173** underwent interceptive decarboxylative allylation with 3-cyanocoumarins in the presence of catalytic palladium to generate α -allyl- β -amino dihydrocoumarins **174** (Scheme 83).¹⁵⁴ Yamamoto and co-workers also extended the scope of the reaction to 3-substituted

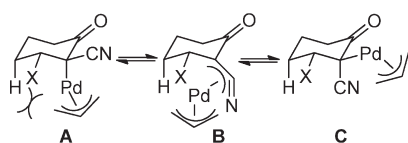
Scheme 83. Interception with 3-Cyanocoumarin**Chart 49. α -Allyl- β -amino Chromones**

^aIsolated yield. Single diastereomer.

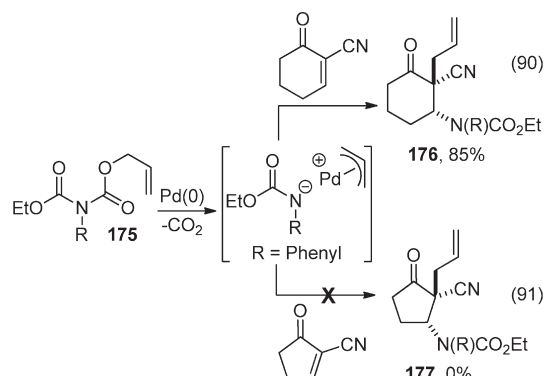
cyano- and formylchromones (Chart 49). The reactions of 3-cyanochromenones with *N*-phenyl carbamates were tolerant of methyl-, bromo-, and chloro-substituents on the phenyl ring, providing products in good to excellent yields. Moreover, the products were formed as single diastereomers resulting from *trans*-addition to the olefin. Examples utilizing the 3-formylchromones suggested that conversion to product was more favorable with electron-withdrawing substituents on the phenyl ring.

Another competently reactive olefin for interceptive DcA was 2-cyanocyclohexenone (eq 90). Interestingly, 2-cyanocyclopentenone was not converted to product **177** under the above reaction conditions (eq 91). Other unreactive olefins include simple acrylonitriles (e.g., PhHC=CHCN) as well as other activated olefins [PhHC=C(CN)CO₂H, PhHC=C(CN)SO₂Ph, and H₂C=C(CN)₂]. Further investigation of the scope of carbamates that add to cyanocyclohexenone showed that electron-rich aryl, or alkyl, *N*-substituents provided the best results (eq 90, R = *p*-MeC₆H₄, *p*-OMeC₆H₄, C₆H₁₁, CH₃). Notably, the *trans*-stereoselectivity for addition to 2-cyanocyclohexenone is the same as that observed for additions to the chromones. Yamamoto and co-workers suggested that the observed stereoselectivity is explained by the disfavored 1,3-diaxial interactions of the large π -allylpalladium (Chart 50). It was further suggested that equilibration via hetero bis- π -allylpalladium complex **B** facilitates the formation of the more energetically favorable equatorial π -allylpalladium species (**C**), leading to the observed

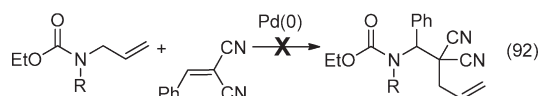
Chart 50. Yamamoto and Co-workers' Proposed Stereochemical Rationale



anti-stereoselectivities.¹⁵⁵ That model of stereoselection assumes an inner-sphere allylation mechanism;¹⁵⁵ however, related stabilized nucleophiles typically react via an outer-sphere mechanism.^{1d} In such a case, the stereochemistry can be attributed to allylation anti to the bulky carbamate.

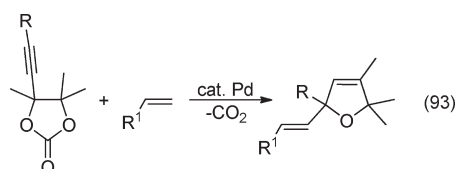


Lastly, Yamamoto and co-workers showed that treatment of simple allyl amides with Pd(0) in the presence of benzylidene-malononitrile does not result in intercepted DcA product (eq 92). This result highlights the importance of generating the carbamate nucleophile via decarboxylation.



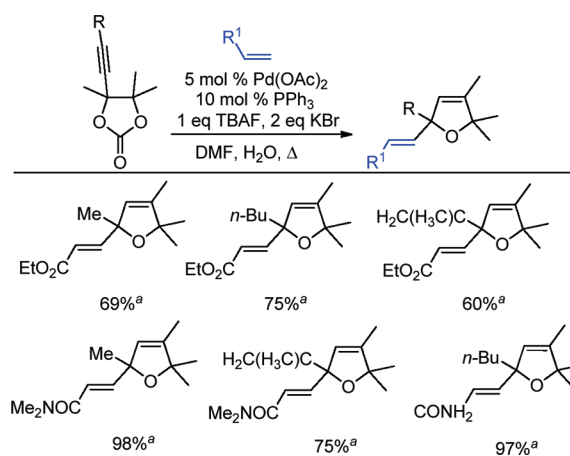
10.7. IDcA of Propargyl Carbonates

In 1996 Bruneau, Dixneuf, and co-workers reported a palladium-catalyzed decarboxylative dihydrofuran synthesis that represents an interesting type of IDcA reaction (eq 93).¹⁵⁶ Specifically, treatment of cyclic propargyl carbonates with acrylates and a catalytic amount of palladium generated allenyl-2,5-dihydrofuran upon loss of CO₂ (eq 93). An investigation into the scope of the reaction revealed that aliphatic alkynyl substituents are reactive coupling partners with ethyl acrylate to produce dihydrofurans (Chart 51). The same was observed for reactions using acrylamides.



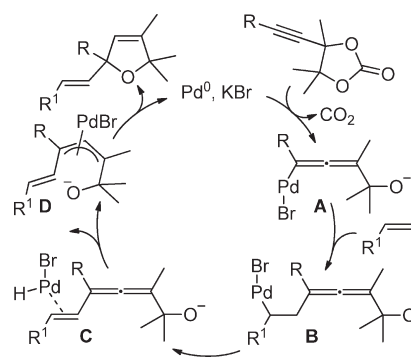
Bruneau, Dixneuf, and co-workers proposed the following mechanism to explain this interesting transformation (Scheme 84). Exposure of the cyclic propargyl carbonate to potassium bromide and the palladium catalyst results in nucleophilic ring-opening and decarboxylation to provide decarboxylated

Chart 51. Palladium-Catalyzed Decarboxylative Synthesis of Dihydrofurans



^aIsolated via column chromatography.

Scheme 84. Catalytic Cycle for IDcA of Propargyl Carbonates



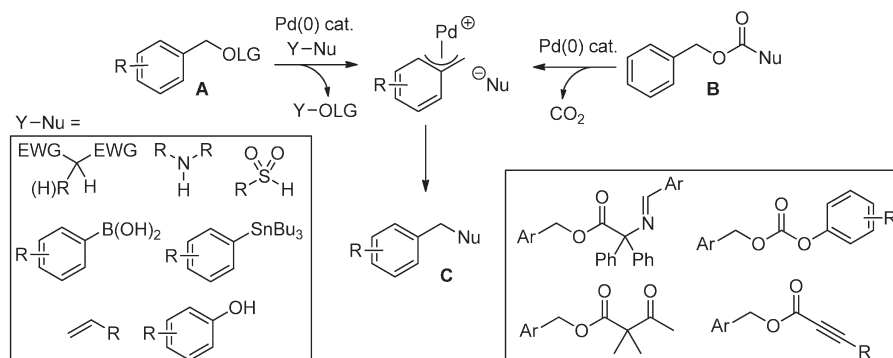
allenylpalladium intermediate **A** (Scheme 84). Heck-type coupling of intermediate **A** with the activated olefin forms intermediate **C** and a palladium hydride. Subsequent hydrideopalladation of the allenyl moiety results in π -allyl palladium intermediate **D**, which can undergo nucleophilic attack from the alkoxide moiety to afford the observed dihydrofuran product (Scheme 84).

11. DECARBOXYLATIVE BENZYLATION

11.1. Introduction to Decarboxylative Benzylations

Much of the chemistry discussed thus far has relied on the ability of metals to undergo oxidative addition with allyl acetate derivatives to form π -allyl metal complexes and then form a nucleophile via decarboxylation (vide supra). Analogous decarboxylative benzylation reactions have recently started to appear in the literature. To close this review, we will discuss these advancements.

As decarboxylative allylation had its beginnings with the Tsuji–Trost reaction of malonates, decarboxylative benzylation emanated from related reactions with stabilized nucleophiles (Scheme 85). Starting in the early 1990s, various benzyl acetates and carbonates were shown to couple with nucleophiles in the

Scheme 85. Comparison of π -Benzyl Substitution Reactions

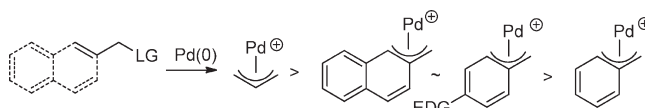
presence of palladium catalysts (Scheme 85, A–C). Since that time, the breadth of nucleophilic coupling partners has steadily increased, and this work has been recently reviewed.¹⁵⁷ For example, malonate-type nucleophiles,¹⁵⁸ boronic acids,¹⁵⁹ and more recently, direct arylation methods,¹⁶⁰ have been utilized to make new benzyl C–C bonds through palladium–benzyl intermediates. With respect to heteroatomic nucleophiles, catalytic benzylations of phenols,¹⁶¹ amines,^{158d} and sulfonyl nucleophiles¹⁶² have all been disclosed. Although this review focuses on the decarboxylative benzylation of relatively unstabilized nucleophiles (Scheme 85, B and C), some relevant information can be gained by briefly discussing aspects of the previous catalytic benzylations of stabilized nucleophiles.

The earliest examples of palladium-catalyzed benzylation reactions were limited to naphthyl or quinolyl acetates, because simple benzyl acetates provided poor conversion.^{158b} The decreased rate of π -benzyl formation from benzyl acetates compared to aromatics with extended π -systems has been ascribed to the disruption of aromaticity upon π -benzyl formation.^{158b} In the case of naphthyl, or other benzyl derivatives where aromaticity is not completely disrupted, the rate of π -benzyl formation is greater than that observed for simple benzyl derivatives (Scheme 86). Nonetheless, certain palladium catalysts have been shown to promote π -benzyl formation of even simple benzyl esters.^{158d} It should also be noted that, while it is often assumed that palladium π -benzyl intermediates are involved in these reactions, π -benzyl complexes may prefer to form the corresponding σ -benzyl isomers, and the σ -benzyl isomers may be the actual reactive intermediates.¹⁶³

As stated, benzyl substitution reactions where a pro-nucleophile and a benzyl acetate or carbonate are coupled using a palladium catalyst has been reviewed in detail.^{157b} Conversely, decarboxylative benzylations are still in their infancy; decarboxylative benzylations of phenols,¹⁶¹ diphenylglycinate imines,¹⁶⁴ acetylides,¹⁶⁵ and ketones¹⁶⁵ have only recently been reported.

11.2. Decarboxylative Benzylation of Various Nucleophiles

11.2.1. Decarboxylative Benzyl Ether Synthesis. The first general method for decarboxylative benzylation was reported by Kuwano and Kusano, who showed that aryl benzyl carbonates would undergo decarboxylative coupling to form benzyl phenyl ethers (Chart 52).¹⁶¹ Importantly, such benzyl ethers are frequently used as protecting groups in organic synthesis. In contrast to common methods for benzyl ether synthesis that require basic or acidic conditions and often utilize stoichiometric coupling reagents,¹⁶⁶ Kuwano and co-workers'

Scheme 86. Relative Rates of Palladium π -Allyl/Benzyl Formation

palladium-catalyzed decarboxylative benzylation of alcohols allows benzyl ethers to be synthesized under neutral conditions with no stoichiometric additives.

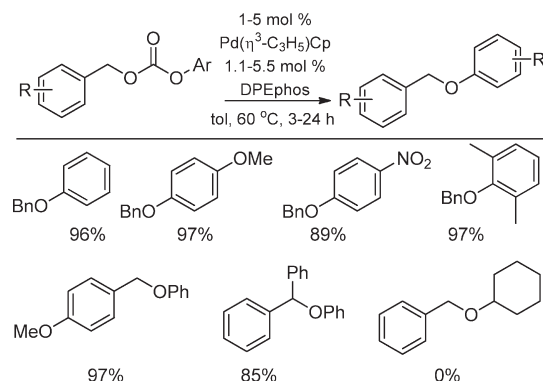
Kuwano and co-workers investigated a number of palladium catalysts and reaction conditions for decarboxylative benzylation, eventually achieving quantitative formation of benzyl phenyl ether utilizing 1 mol % of CpPd(allyl) precatalyst with DPEphos as a ligand at 60 °C. Although alkyl benzyl carbonates could not be coupled, various benzyl phenyl carbonate derivatives provided high yields of product under the optimal reaction conditions (Chart 52).

With regard to the phenolic coupling component, electron-rich, electron-poor, and sterically encumbered substrates all provided high yields (Chart 52); however, in order to achieve a high yield for benzylation of a nitrophenol, longer reaction times (22 h) and a high catalyst loading (5 mol % Pd) were required. Presumably, this was due to the decreased nucleophilicity of the in situ generated 4-nitrophenoxide. This decarboxylative strategy was also applicable for benzylation with diaryl-methanes as well as *p*-methoxybenzyl groups, both of which are important alcohol protecting groups in organic synthesis.

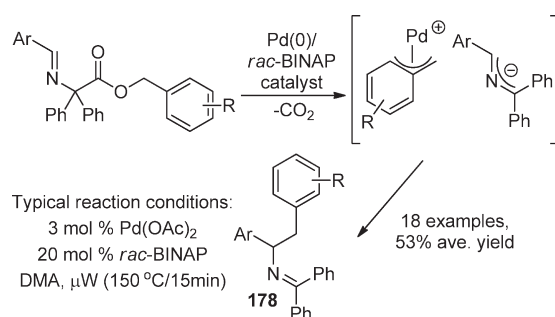
11.2.2. Decarboxylative Benzylation of Diphenylglycinate Imines. Building off their previous work on the decarboxylative allylation of allyl diphenylglycinate imines,⁸⁹ Fields and Chruma reported the palladium-catalyzed decarboxylative benzylation of diphenylglycinate imines in early 2010 (Scheme 87).¹⁶⁷ In this approach, the palladium catalyst promotes the formation of the π -benzyl complex and, upon decarboxylation, generates the 2-azaallyl anion coupling partner. As observed in the related allylation, the α -imino anion undergoes benzylation at the least-hindered carbon to generate the desired benzylated adduct 178.

Under the optimal reaction conditions, yields varied from good to poor with some degree of predictability. Electron-donating substituents that stabilize the π -benzyl complex allowed for favorable ionization and provided higher yields of

Chart 52. Decarboxylative Benzylation of Phenols



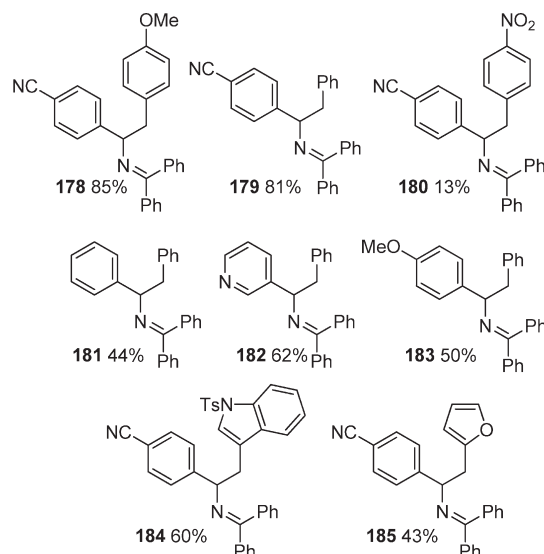
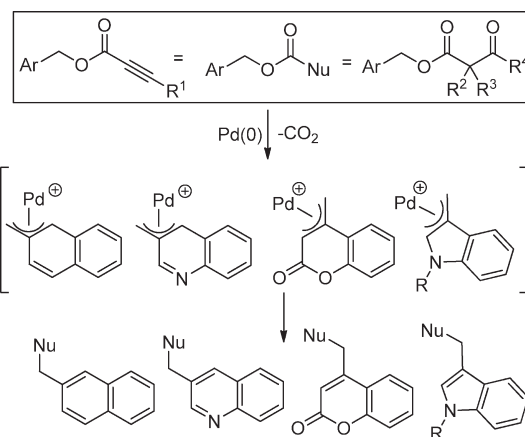
Scheme 87. Decarboxylative Benzylation of Azaallyl Anions



product (**178**, Chart 53). Conversely, when the benzyl substituent was substituted with a *para*-nitro substituent, the yield was drastically lowered (**180**). In addition, electron-withdrawing groups on the imine component, which are expected to accelerate decarboxylation, also facilitate the reaction. The importance of a stabilized azaallyl anion can be seen in the comparison of **179** and **181**, as the benzylation of the *p*-cyano-substituted anion led to 81% yield of the desired product while the analogous unsubstituted product was formed in a modest yield of 44%. Ultimately, the combination of electron-rich benzyl electrophiles with electron-deficient amino acid derivatives provided the highest yields of products (**178**, Chart 53). In general, deviation from the optimal electronics of the coupling partners led to less-favorable π -benzyl formation or decarboxylation and decreased the yields of the desired products. That said, many examples, including couplings of heteroarenes (**184** and **185**), were shown to lead to desired product formation with an average yield of 53%. In addition to the desired benzylation products, the mass balance was stated to emanate from decarboxylative protonation of the azaallyl anion and acetoxylation of the π -benzyl intermediate (from the Pd(OAc)₂ precatalyst).

11.2.3. Decarboxylative Benzylation of Acetylides. As stated earlier, π -benzyl formation occurs more readily with extended aromatic systems than with simple benzyl esters. Tunge and co-workers have demonstrated that various polyaromatic benzyl propiolates and benzyl β -ketoesters undergo high yielding decarboxylative coupling in the presence of a palladium catalyst (Chart 54).¹⁶⁵

Specifically, the decarboxylative benzylation of propiolic esters was shown to be catalyzed by Pd(PPh₃)₄ at 110 °C in toluene

Chart 53. Select Examples of Benzylation of α -Imino AnionsChart 54. Decarboxylative Coupling of Benzyl Propiolate and β -Ketoesters

(Chart 55); the related allylation chemistry takes place at 75 °C.¹⁰⁸ The higher temperature required for benzylation likely reflects a change in the rate-limiting step from decarboxylation (DcA) to ionization (for benzylation). With regard to the benzyl component, various isomers of naphthalene, quinoline, and indole were all viable coupling partners. Phenyl and alkyl propiolates likewise led to high yielding decarboxylative coupling with the aforementioned benzyl derivatives. Although the terminal propiolate yielded no decarboxylative benzylation, TMS-protected alkynes provided high yields of the protected benzyl acetylenes (Chart 55). Importantly, the neutral conditions of the reaction allow the synthesis of base-sensitive benzylic alkynes that are prone to isomerize to allenes when synthesized by typical methods that utilize base or stoichiometric organometallic reagents.¹⁶⁵

While Tunge's method provides access to a variety of benzylation of alkynes under neutral conditions, the reaction is still limited to couplings of benzyl groups with extended conjugation. Li and

Chart 55. Decarboxylative Coupling of Benzyl Propiolates

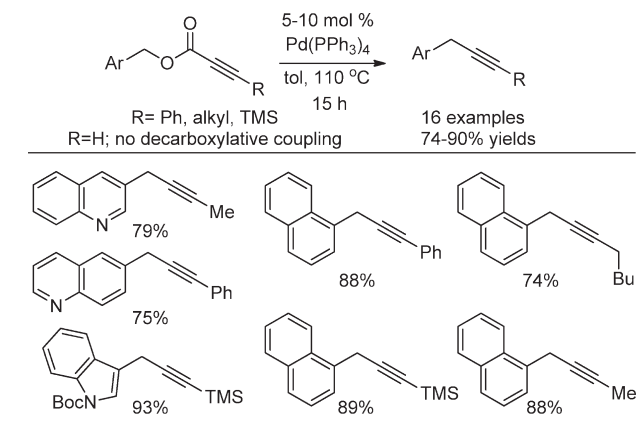
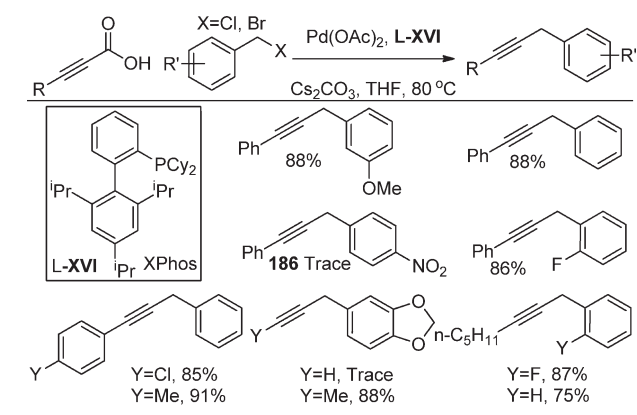


Chart 56. Palladium-Catalyzed Benzylation of Propiolic Acids



co-workers reported an intermolecular palladium-catalyzed decarboxylative coupling of propiolic acids with benzyl halides, which circumvents this problem (Chart 56).¹⁶⁸ Because benzyl halides undergo more facile ionization than benzyl acetates, Li and co-workers were able to couple electron-deficient benzyl moieties that were not viable partners for Tunge's decarboxylative benzylation. In Li's approach, the active palladium/XPhos (L-XVI) catalyst facilitates the oxidative addition into the benzyl halide (Scheme 88). This palladium(II) species then facilitates decarboxylation followed by reductive elimination to generate the desired product.

With regard to the propiolic acid derivative, the reaction was accepting of various aryl and alkyl substituents, while an unsubstituted propiolic acid failed to give the desired product (Chart 56). Many benzyl bromides and chlorides were viable coupling partners as long as the benzyl halide was not too electron-deficient (186, Chart 56).

11.2.4. Decarboxylative Benzylation of Enolates. In analogy to the seminal decarboxylative allylations described by the groups of Tsuji and Saegusa in 1980,^{14,15} decarboxylative benzylations of β -ketoesters were recently reported by the Tunge group (Chart 57).¹⁶⁵ Utilizing $\text{Pd(PPh}_3)_4$ as a catalyst, many α -benzyl ketones could be accessed in good yield. However, a Pd/PBu_3 catalyst system generally provided superior results for

Scheme 88. Palladium-Catalyzed Benzylation of Propiolic Acids

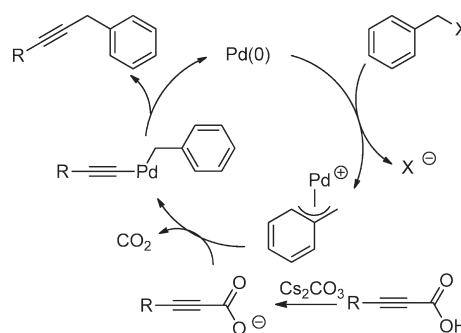
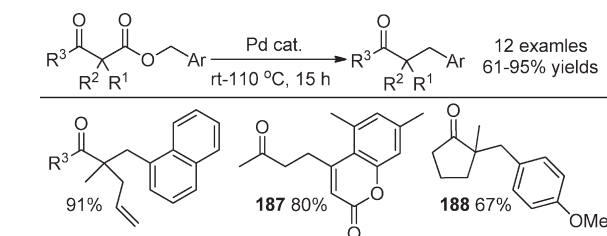
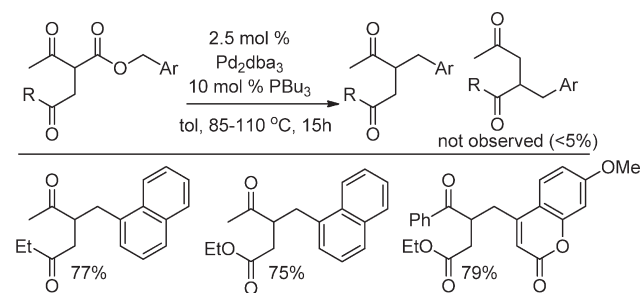
Chart 57. Decarboxylative Coupling of Benzyl β -Ketoesters

Chart 58. Regiospecific Decarboxylative Benzylation



coupling of α,α -disubstituted esters. Under the appropriate reaction conditions, benzyl ketones with quaternary, tertiary, and secondary α -carbon centers could be synthesized in good to high yields (Chart 57). Interestingly decarboxylative benzylation leading to **187** took place at room temperature. Whereas a variety of benzyl derivatives with extended conjugation underwent decarboxylative benzylation, a simple benzyl electrophile required an electron-donating substituent to couple in moderate yield (**188**).

Notably, the benzylation was regiospecific for C–C bond formation at the site of decarboxylation (Chart 58). For example, decarboxylative benzylation of substrates with other acidic sites lead to site-specific benzylation at the position that bore CO_2 . Thus, unsymmetrical 1,4-diketones could be readily synthesized by benzylation. Once again, this demonstrates how the regiospecificity of decarboxylative coupling can be taken advantage of

to synthesize materials that would be difficult to access using standard base-mediated enolate chemistry.

In conclusion, metal-catalyzed decarboxylative benzylation is a viable approach to electrophilic benzylation reactions that are difficult to accomplish otherwise. Nucleophilic coupling partners disclosed thus far include phenols,¹⁶¹ diphenylglycinate imines,¹⁶⁴ acetylides,¹⁶⁵ and ketones.¹⁶⁵ With these strong initial publications, it can be expected that this field of chemistry will flourish over the upcoming years.

12. CONCLUSIONS

Decarboxylative allylations have received significant attention by many research groups. Although decarboxylative coupling reactions offer a “greener” alternative to standard allylation and benzylation reactions, significant progress still has to be made to realize this promise. A major limitation of current methods is that anion-stabilizing groups are often required to achieve decarboxylative metalation. The development of decarboxylative allylations of simple alkyl or alkenyl nucleophiles would significantly expand the scope of products that can be accessed via DcA. In addition, the development of asymmetric allylations has been mostly limited to enolate allylation and cycloadditions. Thus, the discovery of methods for asymmetric decarboxylative allylation of a wide variety of nucleophiles is critical for continued advancement of this field. Moreover, developing interceptive decarboxylations of less activated pronucleophiles would allow the synthesis of many relevant chemical building blocks. Nonetheless, if researchers can continue to advance the state of the art of decarboxylative couplings, as has been seen in the last 6–7 years, DcA reactions are likely to become widely used by synthetic chemists. Ultimately, continued innovation will likely require a better mechanistic understanding of the diverse decarboxylative couplings presented herein.

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BIOGRAPHIES



Jimmie Weaver was born in 1981 in Oklahoma (U.S.A.). He studied at Southern Nazarene University, where he obtained his degree in chemistry in 2004. After spending the next year working

under William Hildebrand (OUHSC) in an immunology lab, he began his graduate studies at the University of Kansas under the supervision of Jon Tunge. The primary focus of his graduate work was the synthesis and decarboxylative coupling of α -sulfonyl acetic esters. He completed his Ph.D. in the spring of 2010 and began postdoctoral research under the direction of Jon Ellman at Yale, where he is currently working on organocatalysis and drug delivery projects.



Antonio Recio III is a native of south Texas and received his B.Sc. in Chemistry in 2005 from the University of Texas at San Antonio, where he performed undergraduate research for Professor George Negrete. After briefly working for Genzyme, Inc., under Dr. William Bauta, Antonio joined the research group of Professor Jon Tunge in 2007 in the Department of Chemistry at the University of Kansas, where he is currently working toward obtaining a Ph.D. His current research involves the development of new methods for decarboxylative carbon–carbon bond formation.



Alexander Grenning is a fourth year graduate student. He received his B.A. from Lake Forest College and did thesis work under the guidance of William Martin. Currently, his research in the Tunge laboratory has focused on the development of new allylation techniques, including catalytic deacylative allylation, a complementary process to decarboxylative allylation.



Jon A. Tunge received a B.S. in Chemistry from the University of Idaho, where he worked with Prof. Ray von Wandruszka on the development of fluorescent probes for high explosives. From 1995 to 2000, he worked on developing asymmetric transformations of organozirconocenes under the direction of Prof. Jack R. Norton. After receiving his Ph.D. from Columbia University in 2000, he moved to the University of Wisconsin—Madison to study the mechanism of catalytic olefin polymerization under the guidance of Prof. Charles P. Casey. In the fall of 2002, Dr. Tunge joined the faculty at the University of Kansas, where he has established a research program combining the topics of catalytic reaction development, parallel synthesis, and green synthetic chemistry.

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