

Transition Metal Catalyzed Decarboxylative Additions of Enolates

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Dedicated to Jack R. Norton on the occasion of his 60th birthday

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Transition metal catalyzed decarboxylation of β -keto acids and esters provides a convenient route for the regiospecific generation of enolates under neutral conditions. Enolates generated by decarboxylation have been utilized in aldol and Michael additions as well as allylic alkylations. The

scope and mechanisms of these transformations are discussed.

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Introduction

The advent of acetoacetic and malonic ester syntheses brought to light the utility of decarboxylations in organic synthesis. Acetoacetic ester synthesis demonstrated a vision wherein β -keto esters are synthetic equivalents of ketones; yet, in contrast to simple ketones, β -keto esters can be alkylated in a completely regioselective manner. Thus, the carboxyl group is a “traceless” directing group that dictates

the regiochemistry of enolization.^[1] The elimination of CO_2 is also important as a driving force for the formation of reactive intermediates. In the early 80's, Barton recognized that elimination of CO_2 could be used to drive selective formation of radicals and in doing so ushered in the era of synthetically useful radical reactions.^[2]

Likewise, many biosynthetic pathways rely on decarboxylation as a driving force. In an early study of a metal-dependent decarboxylase, Colman recognized that the function of Mn^{II} in isocitrate dehydrogenase is to provide “an electrophilic sink to stabilize an enolate intermediate” of α -ketoglutarate (Scheme 1).^[3] Thus, β -keto acids are masked enolates that can be readily released under the influence of an appropriate decarboxylation catalyst. The focus of this review is the synthetic application of such transition metal catalyzed decarboxylative enolate formation.

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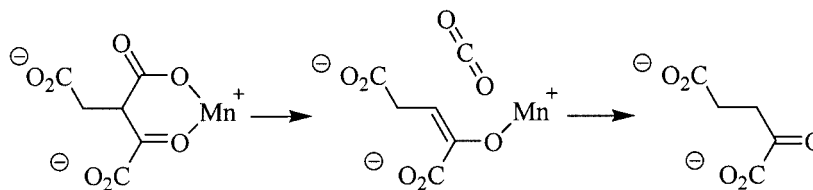


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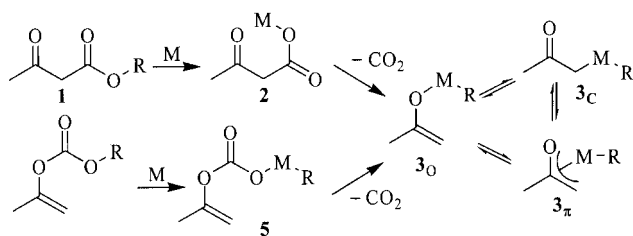


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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

Scheme 1. Decarboxylation by Mn^{II} -dependent isocitrate dehydrogenase.

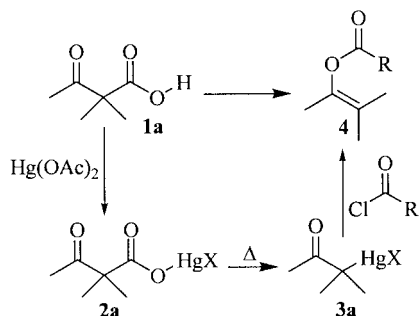
Two main routes for the decarboxylative generation of enolates can be envisioned (Scheme 2). First, β -keto carboxylates (**1**) containing an O–R bond that undergoes facile oxidative addition will produce metal β -keto carboxylates which can decarboxylate by a mechanism similar to that for β -keto acids.^[4] Secondly, vinyl carbonates **4** which undergo oxidative addition to produce metal carbonates will form metal enolates **3** upon decarboxylation. While both of these processes have been used to produce metal-bound enolates, the nature of such transition metal enolates is not always well-defined. In fact, palladium enolates have been shown to adopt *O*-bound (**3_O**),^[5] *C*-bound (**3_C**),^[6] oxa- π -allyl (**3 _{π}**),^[7] or dimeric structures^[6] and the factors that determine the preferred structure are only beginning to be elucidated.^[5,8]



Scheme 2. Decarboxylative generation of transition metal enolates.

Acylation of Enolates Generated by Decarboxylation

The strategy of utilizing decarboxylation to generate enolates for use in synthesis was first demonstrated by Nesmeyanov who used decarboxylation as a route to form mercury enolates (Scheme 3).^[9] Mercury β -keto carboxylates were synthesized by pseudo-degenerate exchange of $\text{Hg}(\text{OAc})_2$ with α,α -disubstituted β -keto acids. Thermolysis of the resulting mercury β -keto acetate produced the α -mercurated

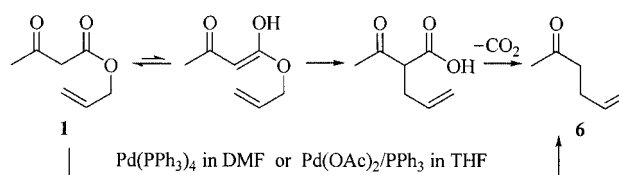


Scheme 3.

ketones **3a**, alternatively described as a *C*-bound mercury enolate. Heating the mercury enolate **3a** with acetyl chloride produced a 60% yield of vinyl acetate ($\text{R} = \text{Me}$). Several mercury enolates were similarly formed and treated with acetyl or benzoyl chloride resulting in *O*-acylation in similar yields.

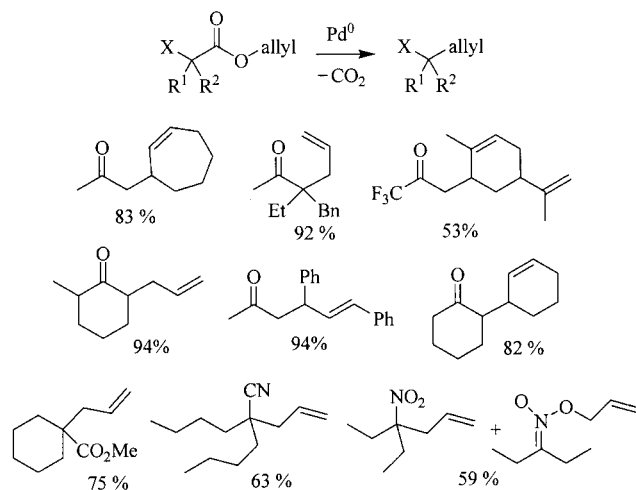
Catalytic Carroll Rearrangements/Decarboxylative Allylation

The thermal rearrangement of allyl β -keto esters **1** to provide γ,δ -unsaturated ketones **6** occurs at temperatures above 170 °C and is termed the Carroll rearrangement (Scheme 4).^[10] The net transformation is the decarboxylative α -allylation of ketones and numerous transition-metal complexes have been found to facilitate this rearrangement.



Scheme 4. Thermal Carroll rearrangement.

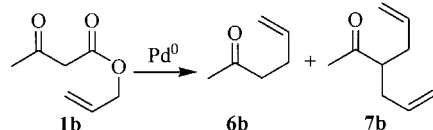
Having studied the formation of palladium enolates from silyl enol ethers,^[7b] Saegusa recognized that oxidative addition of allyl β -keto esters **1** to palladium would result in the formation of palladium enolates, provided that decarboxylation of the palladium β -keto carboxylate is fast.^[11] Thus, addition of 5 mol% $[\text{Pd}(\text{PPh}_3)_4]$ allowed the room temperature decarboxylative rearrangement of **1** to **6**. That same year, in attempting intramolecular allylic alkylation, Tsuji discovered the ability of palladium to induce decarboxylative allylation.^[12] While Tsuji investigated the decarboxylative allylation of methyl ketones using a $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ catalyst system in refluxing THF, Saegusa demonstrated that decarboxylative allylation also proceeds well with cyclic ketones. Since these initial reports, the substrate scope has been shown to encompass β -nitro, cyano, and trifluoromethyl keto acetates (Scheme 5).^[13,14] Interestingly, the allyl nitroacetic acid rearrangement was particularly facile (–50 °C in THF), however both *C*- and *O*-allylation were observed, limiting the yields.



Scheme 5.

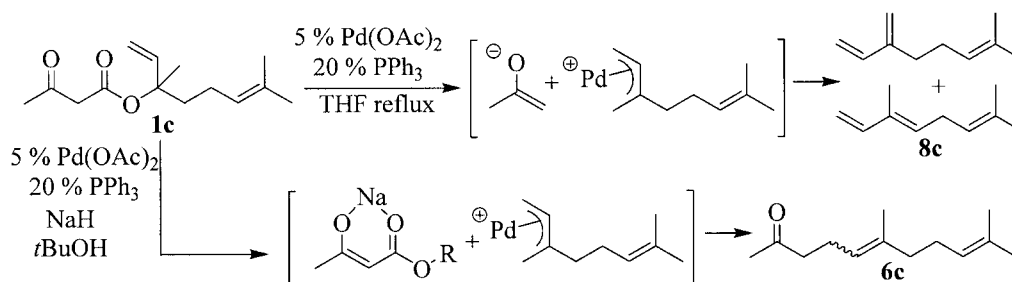
Competing Reactions

Diallylation: While α -substituted allyl keto esters provide good yields of allylation products in DMF,^[11] allyl acetoacetate (**1b**) provides allyl acetone (**6b**) in only 37% yield coupled with significant formation of diallyl acetone (**7b**); the same products were noted in refluxing THF,^[12] but diallyl acetone (**7b**) was the major product (Scheme 6). The observation of diallylation products when unsubstituted β -keto esters are utilized is general, and is particularly prevalent with unsubstituted allyl fragments. In fact, we have not observed diallylation products when 1,3-disubstituted allyl acetoacetates are used as substrates.



Scheme 6.

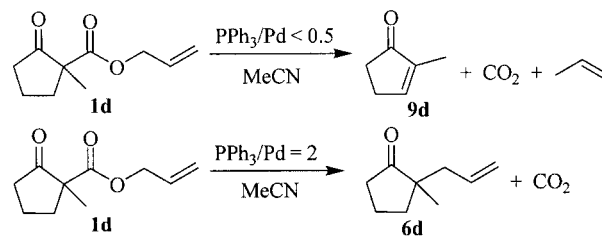
Elimination to Form Dienes: Attempting the decarboxylative rearrangement using the tertiary-allyl acetoacetate **1c** under standard conditions led instead to 1,2-elimination (Scheme 7).^[12] Dienes are a common byproduct observed with particularly difficult substrates. In fact, $\text{Pd}(\text{OAc})_2$ -catalyzed formation of dienes from the analogous allyl acetates has evolved into a useful synthetic method.^[15] In the case



Scheme 7.

of **1c**, elimination was precluded by performing the reaction in *t*BuOH with NaH, allowing isolation of allylation product **6c** in 56% yield. Under these basic conditions, the reaction probably proceeds through addition of a *stabilized* enolate to a π -allylpalladium complex in a manner similar to Tsuji–Trost allylation. Perhaps by avoiding formation of the more basic nonstabilized enolate, this pathway disfavors elimination.

Elimination to Form Enones: 2,2-Disubstituted allyl β -keto esters such as **1d** are incapable of enolization, and thus are not viable substrates for the thermal Carroll rearrangement. Palladium-catalyzed decarboxylative allylation does not require enolization of the substrate, thus there is no such limitation on substrates. However, the palladium-catalyzed reaction of these sterically hindered substrates requires higher temperatures and enone formation can be competitive with allylation.^[16] Enones presumably arise through β -hydride elimination from a *C*-bound palladium enolate. Using 1-methyl-2-oxocyclopentanecarboxylate (**1d**) as a standard Tsuji investigated the effect of the $\text{Pd}:\text{PPh}_3$ ratio on the allylation:elimination ratio (**6d**:**9d**, Scheme 8). At low ligand loadings ($\text{Pd}:\text{PPh}_3 > 0.5$) elimination accounts for 99% of the products while a 1:2 $\text{Pd}:\text{PPh}_3$ ratio provided allylation product in 98% yield. Consistent with this observation, chelating ligands such as diphenylphosphanylene (dppe) promote allylation over elimination.

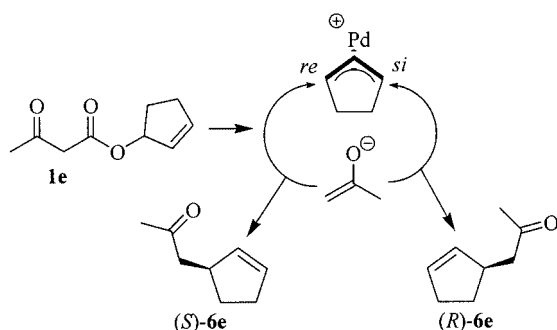


Scheme 8.

Asymmetric Decarboxylative Allylation.

Given the intermediacy of π -allylpalladium complexes in decarboxylative allylation, we chose to investigate ligand control of the stereochemistry, a strategy which has been proven in Tsuji–Trost allylation.^[17] Starting with 1,3-disubstituted allylic β -keto esters that would be expected to form symmetric π -allylpalladium complexes, the asymmetry of

the reaction can be controlled by ligand influence on the site of nucleophilic attack (Scheme 9).

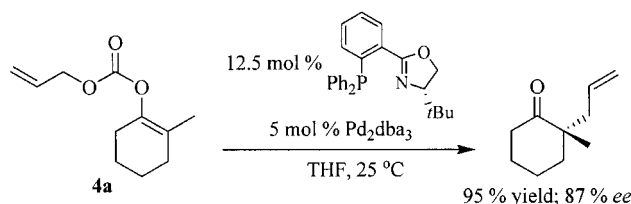


Scheme 9.

Having established that this substrate class was compatible with decarboxylative allylation, we turned to the asymmetric reaction.^[22] Recognizing the similarities of decarboxylative allylation and Tsuji–Trost allylation, we chose Trost's ligand **10** for initial study. The 1:1 combination of Pd/ligand in C₆H₆ provided the optimal system for rearrangement, providing good yields of allylation products. The enantioselectivities of the rearrangement utilizing α-unsubstituted β-keto esters and a small variety of cyclic and acyclic allyl partners ranged from > 98–54% *ee* (Figure 1). Using acetoacetate as a standard and varying the ring size of the allyl fragment showed that the *ee*'s increased with ring size: Five-membered (86%), six-membered (94%), and seven-membered (98%). Similar variation of enolate structure while keeping the allyl fragment constant (cyclohexenyl) shows that a variety of enolates add with selectivities that are relatively independent of steric size. While most substrates were rearranged in the presence of 5 mol% Pd₂dba₃ and 10 mol% **10** at room temperature, the *ee*'s were not significantly affected by running reactions at 75 °C. This allowed either accelerated reaction times or the lowering of catalyst loading or both. For instance cyclopent-2-enyl acetoacetate (**1m**) was rearranged with 0.2 mol% Pd₂dba₃/0.4 mol% **10** in nearly identical time, yield, and enantioselectivity compared with the reaction under “standard” conditions. Interestingly the enantioselectivity (86%

ee) for this reaction is much higher than that for the Tsuji–Trost allylation involving the addition of sodium dimethylmalonate to cyclopentenyl acetate (38% *ee*). Trost has reported that tetrahexylammonium enolates significantly increase *ee*'s relative to the use of sodium enolates, highlighting the importance of the nature of the enolate on enantioselectivity.^[18]

In a similar vein, Stoltz has recently shown that decarboxylation of allyl enol carbonates (**4a**) allows asymmetric formation of quaternary stereocenters α to ketones (Scheme 10).^[19] A brief ligand screen revealed that the *tert*-butyl PHOX ligand enforces superior asymmetry in the reaction. A variety of cyclohexanone-derived allyl carbonates react to provide products in high yield (55–96%; Ave. 87%) and good enantiomeric excess (79–92%; Ave. 88%). This accomplishment is particularly noteworthy since the products can not be synthesized by traditional Tsuji–Trost allylation of stabilized nucleophiles.



Scheme 10.

Mechanism of the Decarboxylative Rearrangement of Allyl β-Keto Esters

Palladium π-Allyl Intermediates: Based on the observation that isomeric allyl β-keto esters like **1f** and **1g** provide the same product (Scheme 11),^[11] π-allylpalladium complexes were suggested as intermediates. Therefore, the regiochemistry of alkylation of the allyl group follows the same trend as observed for palladium-catalyzed allylic substitution of allylic acetates, with the alkylation occurring predominantly at the least hindered allyl terminus.^[20] Thus, despite having been referred to as catalytic Carroll rearrange-

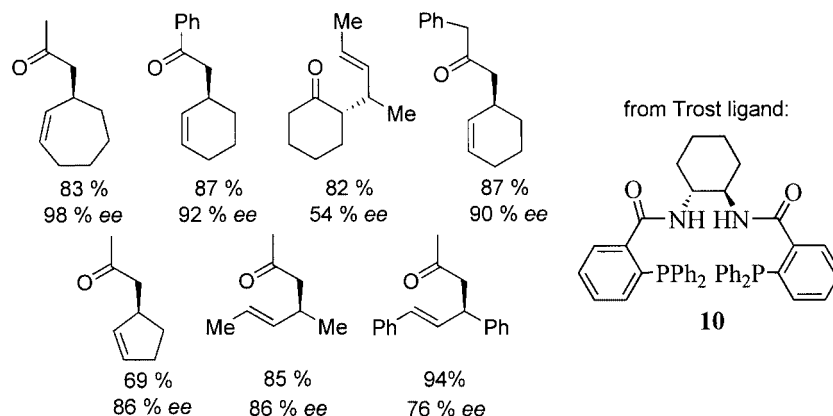
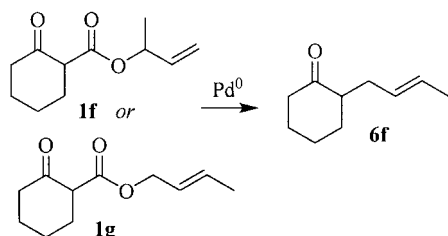


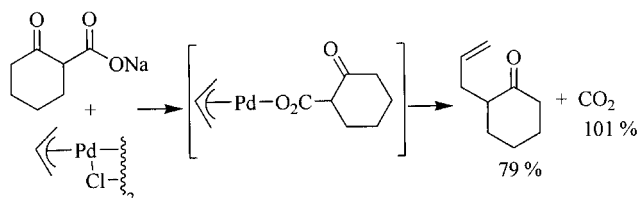
Figure 1. Representative products prepared by decarboxylative allylation.

ments in the literature, the metal-catalyzed variant is regioselective rather than regiospecific with respect to the allyl fragment.



Scheme 11.

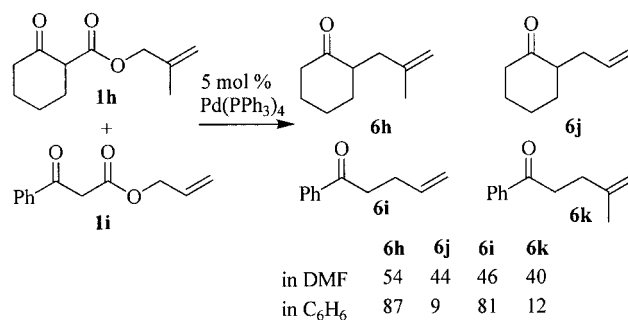
Consistent with the proposal of π -allylpalladium intermediates, allylpalladium chloride dimer has been shown to allylate β -keto carboxylates (Scheme 12).^[11] As a mechanistic probe, sodium 2-oxocyclohexanecarboxylate was treated with a stoichiometric amount of allylpalladium chloride dimer in DMF. Quantitative evolution of CO_2 was observed with concomitant formation of allylation product. Importantly, sodium cyclohexanone-2-carboxylate does not spontaneously decarboxylate in DMF in the absence of catalyst.



Scheme 12.

The formation of π -allylpalladium complexes from the analogous allylic acetates has been shown to proceed predominantly by an $\text{S}_{\text{N}}2$ -like displacement.^[21] As expected for an $\text{S}_{\text{N}}2$ -like displacement of a carboxylate from the allyl β -keto carboxylate, complete crossover is observed when **1h** and **1i** are allowed to react in DMF (Scheme 13). However, only ca. 10% crossover was observed for the same reaction in C_6H_6 . In contrast, we have observed complete crossover when two allyl β -keto esters that react at similar rates are treated with $[\text{Pd}(\text{PPh}_3)_4]$ in C_6H_6 .^[22] Since crossover is more consistent with the known stepwise mechanism for oxidative addition of allyl acetates to palladium,^[23] we attribute

the low crossover observed with **1h** and **1i** in benzene to differential reaction rates.

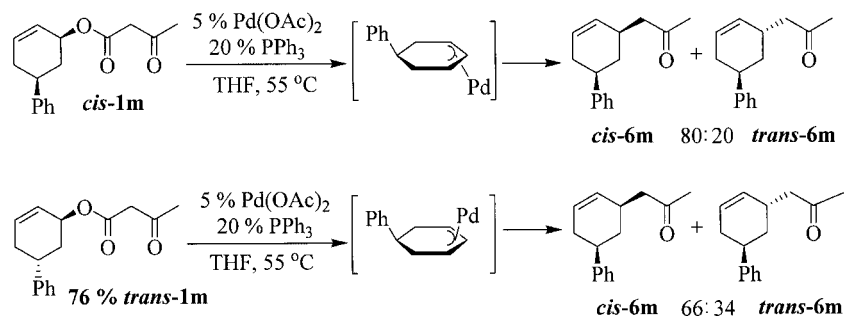


Scheme 13.

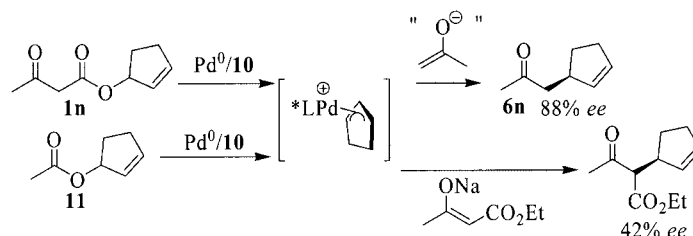
Stereochemistry

Stereochemistry of Enolate Addition: It had been known that π -allylpalladium complexes react with soft malonate carbanions with inversion of configuration (attack *anti* to Pd).^[20] On the other hand, hard nucleophiles were believed to attack first at palladium,^[24] resulting in retention of configuration after reductive elimination. Early attempts were made to examine the stereochemistry of the addition of nonstabilized enolates using the rearrangement of cyclohexenyl acetoacetates that contain a stereochemical marker (Scheme 14). In order to ascertain the stereochemistry of addition of the nucleophile, the authors assumed that displacement of the carboxylate occurs strictly with inversion of stereochemistry. While the major product of the rearrangement of *cis*-**1m** was that of stereochemical retention (double inversion), the rearrangement was not stereospecific. Thus, treatment of *trans*-**1m** under identical conditions provided the product of stereochemical inversion as the major compound. The interpretation of these results is hampered by the assumption of carboxylate displacement with strict inversion of stereochemistry, which although common is not entirely correct.^[25] Furthermore, the possibility of palladium-catalyzed epimerization of **1m**, creates further ambiguity.^[25]

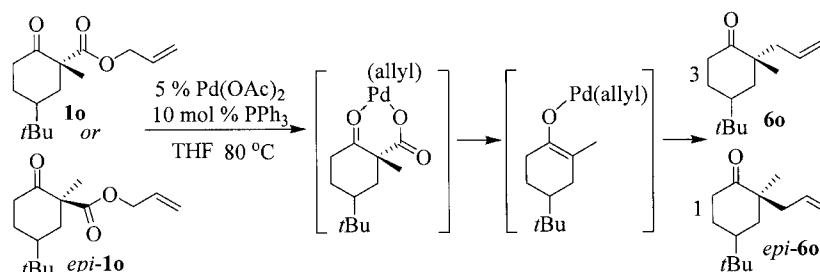
We have addressed this problem by eliminating the stereochemical ambiguity involved with the formation of π -allylpalladium complex.^[22] To do so, we have compared the



Scheme 14.



Scheme 15.



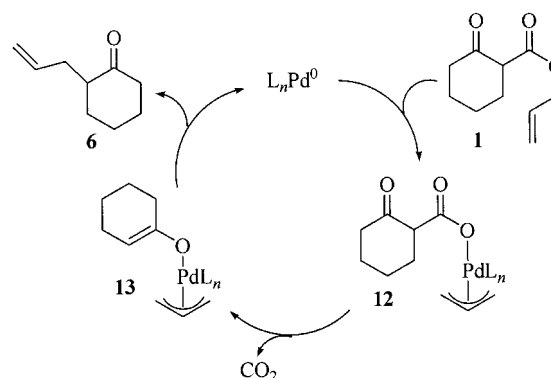
Scheme 16.

enantioselectivity of the rearrangement of **1n** with that of a standard asymmetric allylic alkylation using the palladium complex of Trost's ligand **10** in both cases (Scheme 15). Since the allyl fragment is symmetrical, the same π -allyl complex is expected to form from either substrate. Stabilized nucleophiles like dimethyl malonate are known to attack the allyl fragment *anti* to palladium, and the absolute configuration of this addition using the Trost ligand is known.^[26] Thus, comparing absolute stereochemistry allows one to discern which allyl π -face is attacked in the rearrangement of allyl β -keto carboxylates. Since both processes give rise to the same stereochemistry of the major enantiomer, we conclude that in this case the product of decarboxylative allylation is the result of nucleophilic attack *anti* to palladium and not by reductive elimination from a π -allylpalladium enolate complex.

Stereochemistry of the Enolate: The stereochemical lability of the putative palladium enolate was investigated by treating epimeric allyl β -keto carboxylates **1o** and *epi-1o* with $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ in THF (Scheme 16).^[13] Either diastereomer of the starting allyl keto ester gave rise to the same mixture of products, indicating that the stereochemistry at the α -carbon is labile. Since recent evidence suggests that chiral *C*-bound palladium enolates exhibit high stereochemical fidelity,^[27] this result may be more consistent with a decarboxylation mechanism that initially forms the *O*-bound palladium enolate as opposed to a *C*-bound enolate.

Catalytic Cycle: The experiments detailed *vide supra* led to the suggestion of the following mechanism for decarboxylative rearrangement of allylic β -keto carboxylates (mechanism A, Scheme 17). The catalytic cycle begins with formal oxidative addition of the allylic carboxylate to palladium resulting in palladium β -keto carboxylate **12**. Decarboxylation from this intermediate produces a palladium enolate (**13**). The enolate must then attack the allyl group from the external π -face, but the elementary steps leading to nucleophilic

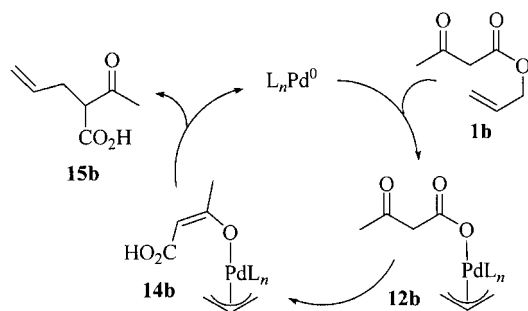
attack of the enolate on the palladium- π -allyl are not known. Suggestions include ionization of the enolate prior to reaction or alternatively a bimolecular mechanism wherein **13** delivers the enolate to a π -allylpalladium compound (**12** or **13**).^[28] While ionization is conceivable in DMF, the rearrangement is equally facile in C_6H_6 . Clearly, a more detailed investigation of this step is required for full understanding of the mechanism.



Scheme 17. Mechanism A for decarboxylative allylation.

While mechanism A (Scheme 17) accommodates the observation of elimination byproducts (enones and dienes), it does not readily account for the occurrence of diallylation products. An alternative mechanism that explains competitive diallylation involves formation of the allyl β -keto carboxylate palladium complex **12b** as the first step (mechanism B, Scheme 18). However, rather than decarboxylating a proton shift forms the stabilized palladium enolate **13b**. This stabilized enolate attacks a π -allyl ligand giving allylated β -keto acid **15b**. The allyl keto acid can re-enter the cycle by ligand exchange with the carboxylate of **12b**, eventually resulting in diallylation. While this mechanism explains the formation of diallylated products, it does not

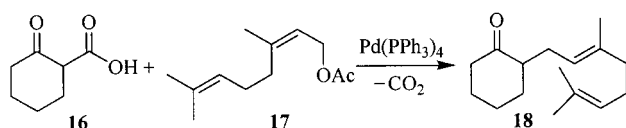
account for competitive enone formation, which seemingly requires a palladium-bound ketone enolate. Furthermore, the fact that α,α -disubstituted allyl β -keto esters (which cannot react through mechanism B) undergo facile rearrangement suggests that mechanism A is viable. The proposal that α -unsubstituted allyl keto esters access mechanism B more readily than α -monosubstituted allyl β -keto esters is fitting with the observed substituent effects on enolization of β -keto esters.^[29]



Scheme 18. Mechanism B for decarboxylative allylation.

Allylation of β -Keto Acids

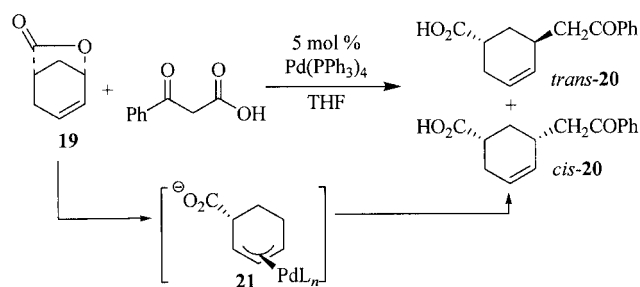
The proposal that keto acid **15b** can re-enter the catalytic cycle for further allylation led Tsuda and Saegusa to study the allylation of β -keto acids with allylic acetates.^[30] The decarboxylative substitution is facile, occurring at room temperature in either benzene or THF. A variety of allylic acetates are alkylated with regioselectivities that resemble those for addition of stabilized nucleophiles to π -allylpalladium complexes. However, alkylation of neryl acetate with 2-oxocyclohexanecarboxylic acid proceeds with isomerization of the olefin geometry, in contrast to the reaction with stabilized nucleophiles (Scheme 19). This implies that the olefin isomerization is more rapid than either enolate formation or addition.



Scheme 19.

The stereochemistry of decarboxylative allylation was addressed using allyl carboxylate **19** (Scheme 20). Given that substitution of acetate by palladium occurs with inversion of configuration, addition of $[\text{Pd}(\text{PPh}_3)_4]$ to **19** is expected to provide π -allyl-palladium complex **21**. The resulting 68:32 ratio of *cis*:*trans*-**20** in THF (79:21 in DMF) suggests competing attack of the enolate *anti* to palladium as well as from a palladium-bound enolate (*syn*). Only the *cis* configuration is observed in the palladium-catalyzed addition of stabilized enolates to **19**.^[25] The major product in all cases results from attack of the “free” enolate *anti* to palladium, however in decarboxylative allylation the reaction occurs in the presence of a molar equivalent of carbox-

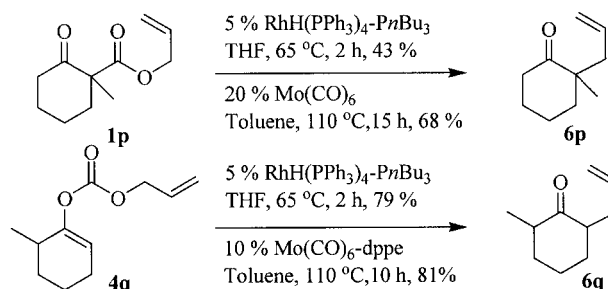
ylic acid. This indicates that the enolate reacts much faster with the π -allyl complex than acid, which is difficult to rationalize.



Scheme 20.

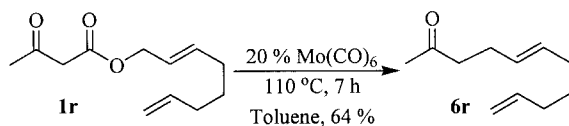
Catalysts other than Palladium

Tsuiji extended decarboxylative allylations of β -keto carboxylates toward catalysis by metals other than palladium.^[31] $\text{Ni}[\text{POEt}_3]_4\text{-PPh}_3$, $\text{RhH}(\text{PPh}_3)_4\text{-PnBu}_3$, and $[\text{Mo}(\text{CO})_6]$ all proved to be active catalysts for the rearrangement but the substrate scope was narrow (Scheme 21). The use of $[\text{Mo}(\text{CO})_6]$ required high loading (20 mol%) and temperature (110 °C) to provide moderate yields of allylation products in 7–15 h. Nickel and rhodium catalyzed the rearrangements under milder conditions (65 °C) and lower catalyst loading (5 mol%) in 1–3 h, however diallylation was problematic.



Scheme 21.

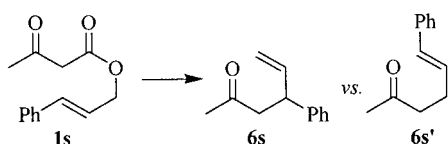
The problems of low turnover and competitive diallylation were largely overcome by using isomeric allyl enol carbonate substrates **4**. Using these more reactive substrates, the loading of $[\text{Mo}(\text{CO})_6]$ could be lowered to 10 mol% without affecting the yield. The yields with Ni and Rh catalysts increased as expected if diallylation was avoided. While the use of **4** as starting material offers the advantage of higher yields and lower catalyst loadings, the synthesis of substrates relies on base-induced formation of ketone enolates. In contrast, the synthesis of β -keto ester substrates does not rely on such regioselective enolization. Regardless, the catalytic release of enolate from substrates **1** or **4** is regiospecific with respect to enolate. It is also noteworthy that substrate **1r** provided allylation product **6r** in 64% yield, whereas under the conditions of palladium catalysis, diallylated products predominate (Scheme 22).^[13]



Scheme 22.

In the quest for more effective decarboxylative allylation catalysts, which would provide regioselectivities that are complementary to palladium, we have turned to the investigation of ruthenium catalysts.^[32,33]

Using cinnamyl acetoacetate (**1s**) as a standard substrate, a variety of ruthenium catalysts were screened (Scheme 23). While $(\text{CH}_2\text{CMeCH}_2)_2\text{Ru}(\text{COD})$ catalyzed the rearrangement with high conversion, the undesired linear product **6s'** was formed in 2:1 selectivity. $[\text{Cp}^*\text{RuCl}]_4$ catalyzed the reaction with better selectivity for the branched product (**6:1**), however in this case the reaction was sluggish. A screen of ligands showed that the addition of bipyridine to $[\text{Cp}^*\text{RuCl}]_4$ was advantageous, providing branched product with none of the linear product visible by ^1H NMR spectroscopy. Not only did the bipyridine additive increase the regioselectivity, but it also decreased the reaction time by approximately 10-fold. The dramatic acceleration by added ligand can be explained by the need to form monomeric catalyst $[\text{Cp}^*\text{Ru}(\text{bpy})\text{Cl}]$ from the tetrameric precursor.^[34] Regioselectivities for a variety of substituted cinnamyl esters were all excellent ($> 19:1$), however the rates were much slower for electron poor aryls ($p\text{-C}_6\text{H}_4\text{CF}_3$, 40 h) than for electron-rich aryls ($p\text{-C}_6\text{H}_4\text{OMe}$, 15 min).



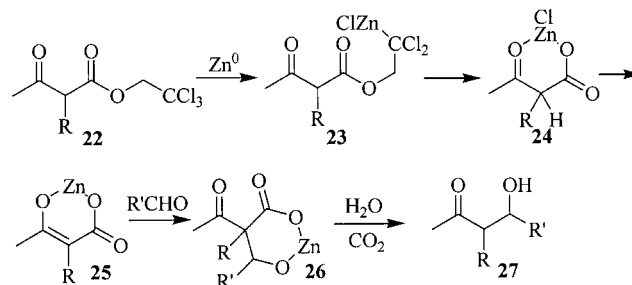
Scheme 23.

Mechanistically, the reaction resembles the palladium-catalyzed variant. Thus, regioisomeric allyl β -keto carboxylates provide the same product (Scheme 24), implying the intermediacy of π -allyl ruthenium complexes. Furthermore, complete scrambling is observed in a crossover experiment showing that the “rearrangement” is not intramolecular.

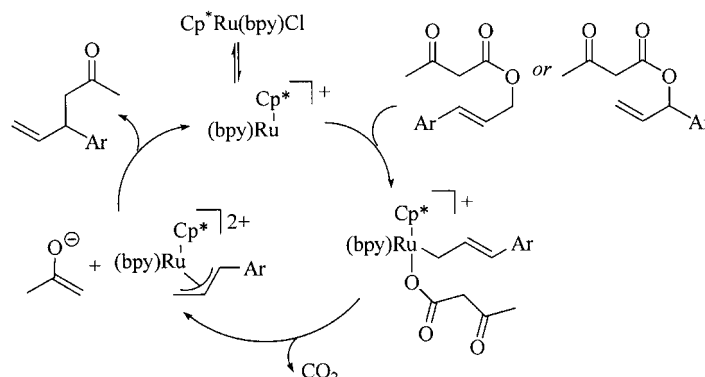
Unlike the palladium catalysts previously utilized, $[\text{Cp}^*\text{Ru}(\text{bpy})\text{Cl}]$ is an 18-electron complex. Therefore, the active catalyst is likely formed after dissociation of chloride. The resulting complex, $[\text{Cp}^*\text{Ru}(\text{bpy})]^+$, oxidatively adds substrate to form a π -allyl ruthenium complex. The formation of the enolate and its addition to the π -allyl ruthenium complex is less well-defined and more mechanistic studies are clearly required.

Decarboxylative Aldol Additions

Mukaiyama was the first to realize the potential of decarboxylation as a technique for the regiospecific generation of enolates in aldol addition chemistry.^[35] 2,2,2-Trichloroethyl β -keto esters were prepared by the thermal reaction of diketene with 2,2,2-trichloroethanol, then alkylated. In the presence of stoichiometric Zn, 2,2,2-trichloroethyl β -keto esters coupled with aldehydes in good yield to provide aldol products (Scheme 25). A survey of conditions found trichloro esters to be superior to bromo or iodo analogs and DMSO was the best of the polar solvents investigated. A variety of aldehyde partners, including aliphatic, aromatic, and α,β -unsaturated aldehydes provided good yields of aldol products. The ability to do crossed aldol reactions with enolizable aliphatic aldehydes such as acetaldehyde and 3-phenyl propionaldehyde under mild conditions is particularly noteworthy. While the yields were good, diastereoselectivities ranged from 0.74–3.0 *threolerythro*. Based on the observation that the α -proton of **22** disappears upon addition of Zn and that “most” of the CO_2 is evolved upon



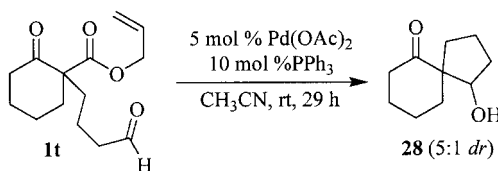
Scheme 25.



Scheme 24.

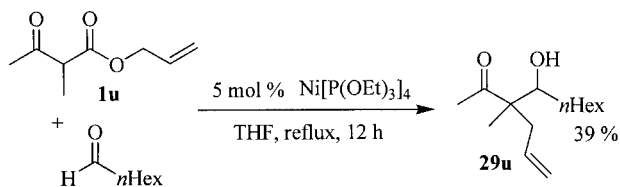
water workup, the following mechanism was suggested. Insertion of Zn into a C–Cl bond would provide **23**, which eliminates dichloroethylene followed by HCl to form **25**. Addition to the aldehyde would provide chelate **26**. Finally decarboxylation upon water workup provided the aldol adducts **27**.

Over a decade after Mukaiyama's initial communication, the potential to use a transition metal in a catalytic decarboxylative-directed aldol addition was realized. The reaction was based on the facile addition and decarboxylation of allyl β -keto carboxylates to Pd^0 resulting in palladium allyl enolates (vide supra). In an attempt to trap the transient enolate, an aldehyde was tethered to the allyl β -keto ester (Scheme 26).^[36] Unexpectedly, treatment with $\text{Pd}(\text{OAc})_2/2 \text{ PPh}_3$ in acetonitrile resulted in the formation of aldol adduct rather than the diketone. The combination of $(\text{PPh}_3)_2\text{NiCl}_2/\text{Zn}$ also proved effective for the intramolecular aldol, however near-stoichiometric quantities were required (50 mol%, 74% yield of **28**).^[37] Unlike the zinc-mediated aldol addition, decarboxylation necessarily occurs prior to nucleophilic attack on the aldehyde, so nonstabilized palladium enolates are likely intermediates. Similar to the Zn-promoted directed aldol, the diastereoselectivities were low (*threolerythro* ratio: 1–5). Initial attempts to extend the reaction to intermolecular aldol additions were not successful and a mixture of allylation and aldol products was produced even in the presence of excess hexanal.



Scheme 26.

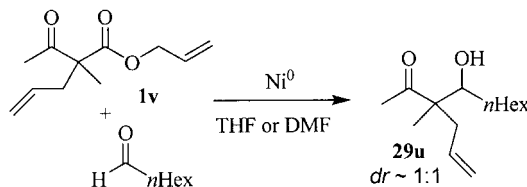
Nickel catalysts proved to be advantageous for the intermolecular directed aldol additions of allyl β -keto esters to aldehydes. Initially, it was observed that reaction of **1u** with hexanal in the presence of 5 mol% $[\text{Ni}\{\text{P}(\text{OEt})_3\}_4]$ resulted in a low yield of product **29u** (Scheme 27). This product presumably arose from a combined nickel-catalyzed allylation-aldehyde addition.



Scheme 27.

Subsequently, α,α -dialkyl-disubstituted allyl β -keto esters like **1v** were employed as reaction partners in order to avoid multiple additions to the α -carbon atom (Scheme 28). While $[\text{Ni}\{\text{P}(\text{OEt})_3\}_4]$ led to full conversion in THF, the catalyst loading was high (20 mol%) and the yields of aldol product **29u** were low 33–50%. Nonetheless, turnover was demonstrated. Switching to DMF solvent led to a slightly in-

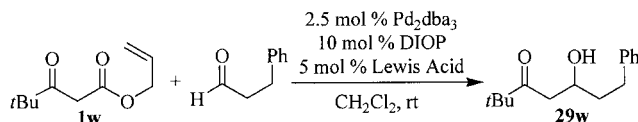
creased yield of aldol product (60%). Finally, when $[(\text{PPh}_3)_2\text{NiCl}_2]$ (50 mol%) was reduced in situ with Zn, a 99% yield of aldol product was obtained; without PPh_3 the reaction only proceeded to 14% conversion in 30 h. The turnover limitations were apparent at a catalyst load of 25 mol% $[(\text{PPh}_3)_2\text{NiCl}_2]$, which resulted in a 78% yield of aldol product ($\approx 3 \text{ TO's}$).



Scheme 28.

Using $[(\text{PPh}_3)_2\text{NiCl}_2]$ and Zn (50 mol%) in DMF at 20–40 °C as a standard catalyst mixture, it was demonstrated that aliphatic, α,β -unsaturated, and aromatic aldehydes react with a variety of nickel-enolates to give aldol adducts in 52–94% yield (71% ave.). Once again diastereoselectivities were all low ($\approx 1:1$). Nevertheless, this was the first report of a catalytic, regiospecific, aldol reaction utilizing decarboxylation as a means of enolate formation. Moreover, the reaction occurs under mild conditions. The role of the ZnCl_2 formed in the reduction of $[\text{L}_2\text{NiCl}_2]$ is an interesting question given the precedent of zinc-mediated directed aldol additions;^[35] it might be expected to activate the aldehyde or β -keto carboxylate. However, these issues were not addressed.

More recently, a catalytic aldol reaction has been developed that takes advantage of the higher catalytic activity of palladium as compared to nickel. Schaus et al. have shown that the intermolecular aldol addition can be favored over enolate allylation if an appropriate Lewis acid is used to activate the aldehyde, form a more reactive enolate, or both (Scheme 29).^[38]



Scheme 29.

A screen of Lewis acids revealed that YbCl_3 was the most effective additive (93%, **29w**); however, it is worth mentioning that ZnCl_2 was also active (68%, **29w**). Similar to the examples that were previously discussed, the chemistry takes advantage of the facile addition of allyl β -keto carboxylates **1** to palladium. Aliphatic and aromatic aldehyde partners that contain TBS protected alcohols, olefins, pyran, and α -amino groups all provided aldol adducts in good to high yields (Figure 2; 24 examples, 81% ave. yield).^[39]

The diastereoselectivity for addition of allyl acetoacetate to 2-phenylpropanal was low (1.5) consistent with previous observations. Interestingly, *N*-Boc-valinal reacted with allyl acetoacetate to provide the *syn* aldol adduct as the major product in a 6:1 ratio. Although the selectivity is not high,

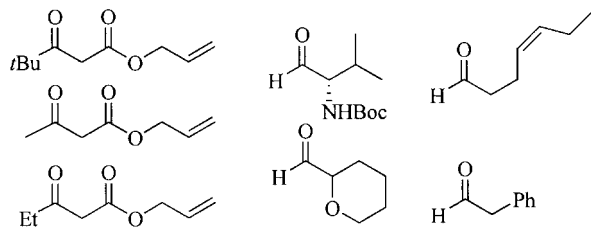
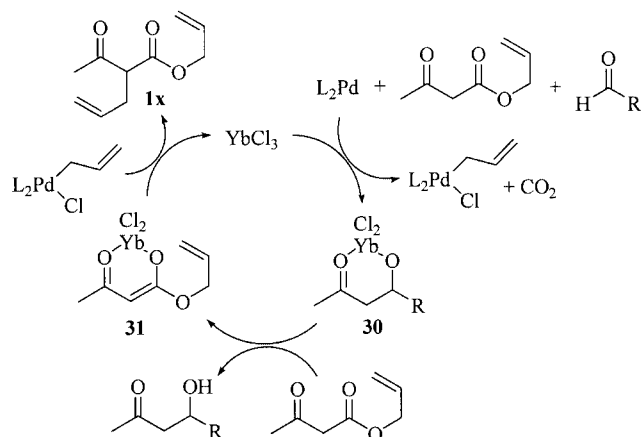


Figure 2. Representative substrates.

it represents the highest diastereoselectivity observed in a palladium-catalyzed decarboxylative aldol reaction.

A noteworthy feature of the chemistry is that it uses > 2 molecules of allyl keto ester per aldol product formed. The mass balance is used to form allylation byproduct **1x** (Scheme 30). To account for this, the authors proposed the following mechanism. First, the allyl keto ester oxidatively adds to palladium to form the π -allyl complex. Decarboxylation followed by transmetalation of the enolate to Yb provides **30**. Yb then mediates the aldol reaction. The fact that the use of optically active DIOP ligand produced racemic aldol product supports the idea that Yb mediates the aldol reaction.



Scheme 30.

Lastly, Shair recognized the widespread use of decarboxylation in biosynthesis (particularly for polyketide synthesis) as related to decarboxylative thioester aldol chemistry

(Scheme 31).^[40] An initial screen of metal catalysts for this reaction revealed that $\text{Cu}(\text{OAc})_2$ combined with imidazole was an active catalyst system for the decarboxylative addition of malonic acid half thioesters to aldehydes; optimization led to the use of $\text{Cu}(\text{2-ethylhexanoate})_2$ and 5-methoxybenzimidazole base. Thus, stoichiometric aldehyde and malonic acid thioester were combined in THF with 20 mol% of Cu and 22 mol% benzimidazole to provide aldol adducts in 65–97% yield. While most aliphatic aldehydes provided product within 4 h at room temp, less reactive benzaldehydes reacted more slowly. For example, benzaldehyde provided only 22% aldol product after 24 h. However, typically sensitive aldehydes like 4-pentynal react smoothly under the above conditions.

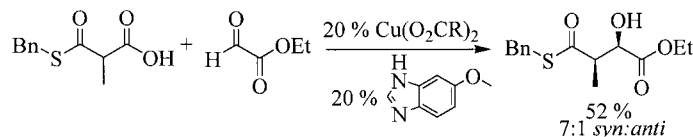
Perhaps the most attractive feature of the Cu-catalyzed decarboxylative aldol reaction is its insensitivity to water and oxygen; wet THF and crude acetone were adequate solvents for the aldol chemistry.

While little is known about the mechanism, decarboxylation of the malonic acid half thioester is not observed in the absence of aldehyde. This observation suggests that decarboxylation occurs after aldol adduct formation, which in turn implicates enolization of the malonic thioester as a key step in the reaction.

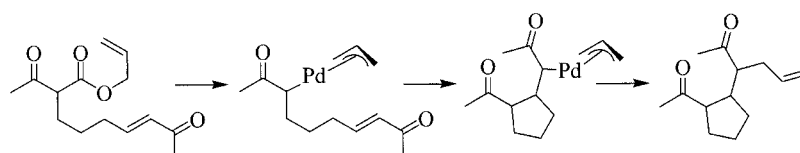
Decarboxylative Michael Additions

Using a strategy similar to that outlined for intramolecular decarboxylative aldol chemistry, Tsuji and Nokami investigated the decarboxylative Michael reaction.^[41] The approach is particularly clever because the product of the Michael addition is also an enolate and thus should allow tandem-Michael addition–allylation as outlined in Scheme 32.

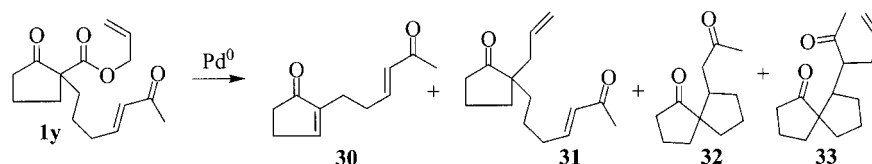
With this goal in mind, α,β -unsaturated methyl ketones were tethered to the allyl β -keto carboxylate by taking advantage of the ease and selectivity of α -alkylation of β -keto esters. The standard substrate **1y** was then treated under a variety of conditions, many of which led to complex mixtures of products (Scheme 33). Deallylcarboxylation to provide the palladium enolate followed by elimination or allylation (*vide supra*) accounts for products **30** and **31**. Prod-



Scheme 31.



Scheme 32.

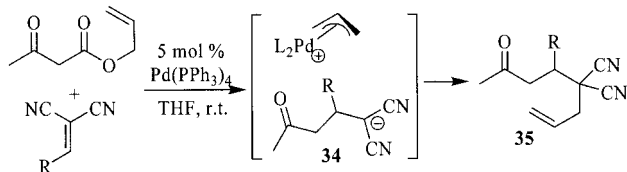


Scheme 33.

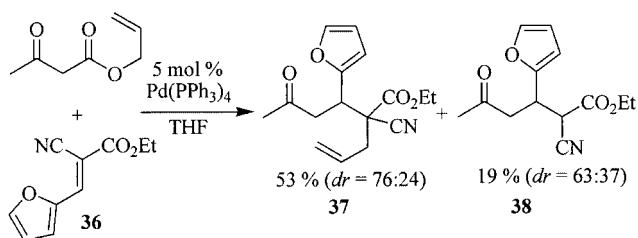
ucts **32** and **33** result from trapping the palladium enolate by the Michael acceptor followed by protonation or allylation respectively.

Acetonitrile solvent favored the formation of Michael adduct **32** and under optimized conditions treatment of **1y** with $[\text{Pd}(\text{PPh}_3)_4]$ at room temperature for 1 h led to **32** in 84% yield with no evidence of sideproducts. In an attempt to favor tandem Michael-allylation, THF was explored as a potential solvent. While room temperature reactions in THF produced a 1.9:1 mix of **33** and **32** in a combined 47% yield, refluxing **1y** in THF for 15–30 min provided the tandem-Michael allylation product **33** in 48% yield, but also leads to substantial formation (22%) of the Carroll product **31** and 18% of the simple Michael adduct **32**.

In an extension of this chemistry, Yamamoto reported the intermolecular tandem Michael addition-allylation.^[42] By utilizing benzylidene- and (furylmethylidene)malonitrile derivatives as Michael acceptors, the product anionic Michael adduct **34** resembles stabilized enolates that are known to effectively undergo Tsuji–Trost allylation (Scheme 34).^[43] Using 5 mol% $[\text{Pd}(\text{PPh}_3)_4]$, the tandem products **35** were obtained in good yield after < 5 h at room temperature. Aromatic 2-cyanoacrylates **36** were also compatible substrates, however, the reactions required longer time (15–24 h) and simple Michael adducts **38** were significant sideproducts (Scheme 35).



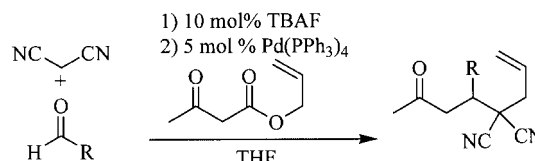
Scheme 34.



Scheme 35.

The preceding chemistry was limited to (arylmethyl)malonitriles because the related alkyl derivatives could not be isolated in acceptable yields. This prompted the investigation of in situ generation of (alkylmethylidene)malonitriles. Using a one-pot procedure, alkyl-substituted adducts were

obtained in moderate yield (Scheme 36), with secondary R groups (cyclohexyl) providing higher yields (74%) than primary straight chain aldehydes (pentanal, 48%). The authors surmised that the straight chain (alkylmethylidene) malonitriles partially decomposed over the timescale of the Michael addition.



Scheme 36.

Summary

Decarboxylation is a convenient route for the regioselective generation of transition metal enolates under neutral conditions. Strategically, this approach offers the opportunity to exploit both the selectivity of alkylation of β -diketo derivatives and the higher reactivity of nonstabilized ketone enolates. Recent examples of highly enantioselective and regioselective decarboxylative allylation highlight the potential power of these methods. However, the utility of decarboxylative additions is currently somewhat limited by low diastereoselectivities. A greater understanding of the geometry and nature of coordination of enolates generated (*O*-bound vs. *C*-bound vs. oxo- π -allyl) will likely allow rational design of catalysts that overcome the low diastereoselectivities for enolate alkylation.

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