TRANSITION METAL-CATALYZED DECARBOXYLATIVE CARBON–CARBON BOND FORMATION

Reported by Carl Liskey October 19, 2009

INTRODUCTION

Throughout the past decade, carboxylic acids and carbonates have been employed as versatile reagents for a variety of reactions. In fact, nature uses carboxylic acids and carboxylates as precursors to carbon nucleophiles in an assortment of reactions. In many biological systems, enzyme-catalyzed decarboxylation creates a stabilized carbon nucleophile. Inspired by this idea, synthetic chemists have sought to replicate this process to perform decarboxylative carbon-carbon bond formation.

Carboxylic acids and carbonates can undergo decarboxylation in the presence of a transition metal-catalyst to generate a carbon nucleophile *in situ*. This process of generating a carbon nucleophile under mild conditions has several advantages. This decarboxylative approach has been applied to the formation of carbon-carbon bonds in aldol reactions, aryl-aryl cross-couplings, and asymmetric allylic alkylations. Herein, the development, synthetic utility, and advantages of these transformations will be discussed.

BIOSYNTHETIC DECARBOXYLATIVE REACTIONS

One of the key reactions to form carbon-carbon bonds in fatty acid and polyketide biosynthesis is a decarboxylative Claisen condensation with malonic acid half thioesters (MAHTs).[1] Fatty acids are derived from two-carbon units generated by iterative condensation reactions. The β-keto thioester formed from the condensation reaction can subsequently undergo reduction to the alcohol, dehydration, and finally another reduction to give a saturated chain extended by two methylene units. The starting acyl unit is bound to a cysteine residue in the ketosynthase (KS). The malonate unit is bound to a thiol in the acyl carrier protein (ACP), which undergoes a concerted decarboxylative Claisen reaction. This condensation step is outlined in Figure 1.[1]

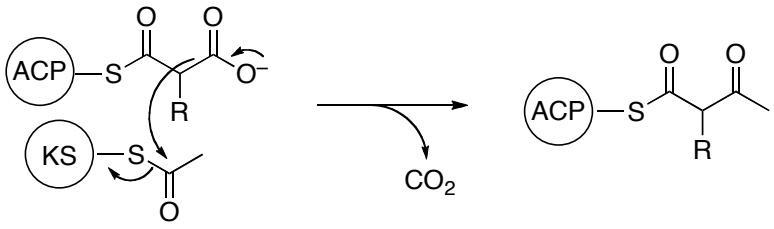


Figure 1. Claisen Condensation Step of Polyketide Biosynthesis.

Carbon nucleophiles are also formed by decarboxylation of arenes and heteroarenes in biological systems.[2] An example of this process is the decarboxylation of orotidine 5′-monophosphate (OMP). This process is essential in the biosynthesis of pyrimidine nucleotides. In the OMP decarboxylase enzyme, the carboxylate group of OMP is oriented towards an aspartate residue creating a destabilizing electrostatic interaction (Figure 2). This interaction raises the ground state energy relative to the transition state. A neighboring lysine residue protonates OMP to afforded the decarboxylated product. Synthetic reactions mimicking these processes have been applied to aldol and cross-coupling reactions.

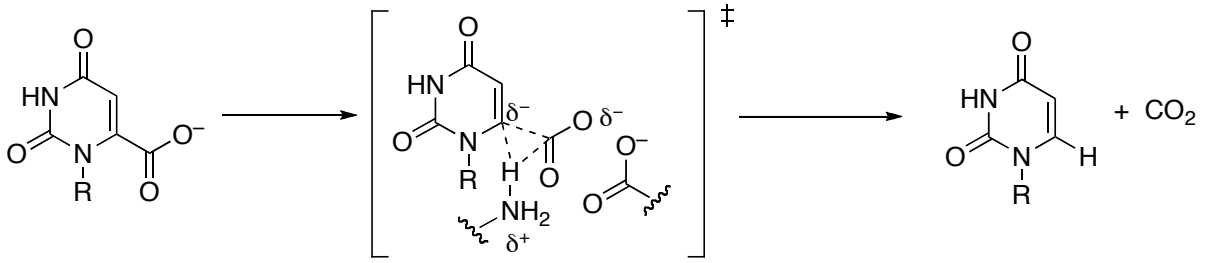


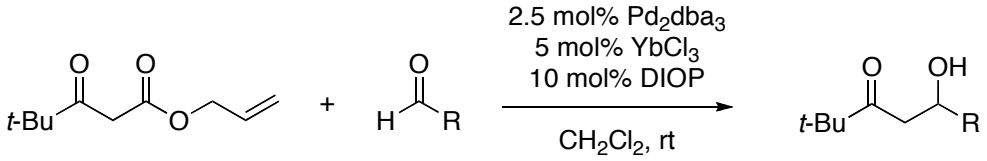
Figure 2. Proposed Mechanism for OMP Decarboxylase

ALDOL REACTIONS INVOLVING DECARBOXYLATION

Early Decarboxylative Aldol Reactions

Aldol reactions are typically sensitive to moisture, suffer from side reactions, and in many cases are incompatible with aldehydes containing α-hydrogens. Decarboxylation to generate an enolate can overcome some of these limitations. Mukaiyama and coworkers reported the first aldol reaction to proceed by decarboxylation, in which 2,2,2-trichloroethyl β-keto esters are reduced in the presence of Zn^0 and react with aldehydes to generate the aldol product following decarboxylation.[3] More than a decade later, Tsuji and coworkers reported an intramolecular aldol reaction of allyl β-keto esters that occurs in the presence of $Pd(OAc)_2$ and PPh_3.[4] More recently, Schaus and coworkers reported a decarboxylative aldol reaction of allyl β-keto esters that takes place in the presence of a heterobimetallic catalyst system.[5] The reaction of an allyl β-keto ester and a variety of aldehydes containing α-hydrogens catalyzed by a combination of Pd_2dba_3 and DIOP along with $YbCl_3$ as a co-catalyst gave the corresponding aldol product in good yields (Scheme 1). However, these reactions were not highly stereoselective and required an excess (2.5 equiv) of the allyl β-keto ester.

Scheme 1. Pd-Catalyzed Decarboxylative Aldol Reaction

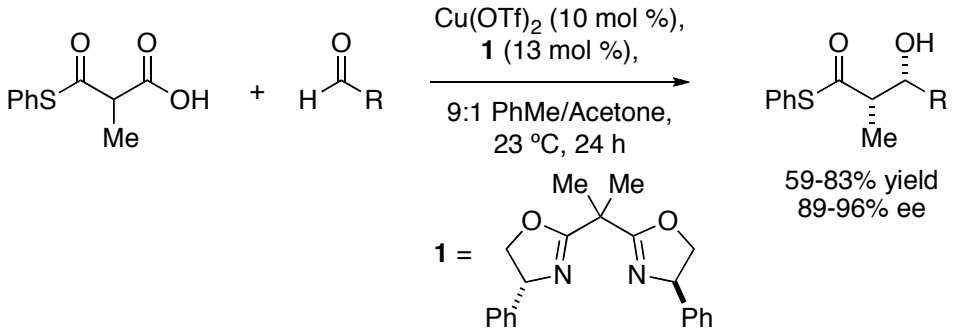


Cu-Catalyzed Aldol Reactions of MAHTs

Given the precedents of polyketide biosynthesis by the Claisen condensation reaction, Shair and coworkers developed aldol reactions with MAHTs as nucleophiles.[6] The reaction of an MAHT with an aldehyde catalyzed by Cu(2-ethylhexanoate)$_2$ and 5-methoxybenzimidazole generated the aldol product under mild conditions. Contrary to many other aldol reactions that require a strong base, these reactions can be performed at room temperature, open to the air, and in wet solvents. Aldehydes containing α-hydrogens were also compatible with these reaction conditions without generating side products. The kinetic persistence of MAHTs allows these reactions to be performed under air and in wet solvents without decomposition of the starting materials. The thermodynamic instability makes these reactions energetically favorable.

Shair and coworkers reported enantioselective aldol reactions of methyl malonic acid half thioesters (MeMAHTs) as shown in Scheme 2.[7] Reactions of *S*-phenyl MeMAHTs and an aldehydes catalyzed by a complex of Cu(OTf)$_2$ and bisoxazoline **1** formed aldol products in 59-83% yield and 89-96% ee. In general, the products were afforded in high enantioselectivity, independent of the steric or electronic properties of the aldehydes. In addition to being compatible with aldehydes containing α-hydrogens, these reactions were compatible with protic functional groups. Furthermore, these reaction conditions were compatible with acetals and ketals that are sensitive to Lewis-acids.

Scheme 2. Enantioselective Aldol Reactions with Malonic Acid Half Thioesters



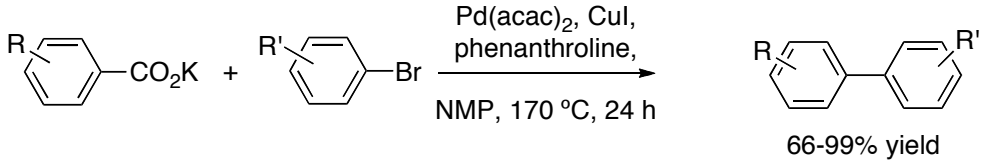
To investigate the mechanism of these reactions, labeling experiments were performed with MeMAHT-^{13}C and MeMAHT-D.[8] Complete scrambling of the deuterium label at the α-position was observed. The product was also found to be stable under the reaction conditions. This information is consistent with a mechanism that involves a deprotonation followed by a protonation after addition to the aldehyde. It was also found that no reaction occurs in the absence of the aldehyde indicating that addition to the aldehyde precedes decarboxylation. Also, a ^{13}C KIE was found to be 1.02 ± 0.002, indicating that decarboxylation is the rate-determining step. The catalyst resting state was found to be the Cu-MAHT complex ligated by **1**.

Pd-CATALYZED DECARBOXYLATIVE COUPLING OF ARENES

Synthesis of Biaryls by Decarboxylative Coupling

In addition to generation of nucleophiles through the formation of enolates, nature also generates carbon nucleophiles by decarboxylation of arenes or heteroarenes. A well-known example is OMP (*vide supra*).[2] With these enzyme-catalyzed reactions in mind, Goossen and coworkers developed the synthesis of biaryls by decarboxylative aryl-aryl coupling.[9] The reaction of a benzoic acid and an aryl bromide catalyzed by $Pd(acac)_2$, CuI, and phenathroline gave the corresponding biaryl in generally high yield (Scheme 3). However, an electron-withdrawing group, typically a nitro group, must be present at the *ortho*-position of the benzoic acid. The scope of this reaction was expanded to other substituted arenes by changing the electrophiles in these reactions to aryl triflates.[10] These reactions were still limited to substrates containing electron-withdrawing groups. However, by using carboxylic acids, stoichiometric metal waste is avoided in these reactions, which are common byproducts in cross-coupling reactions.

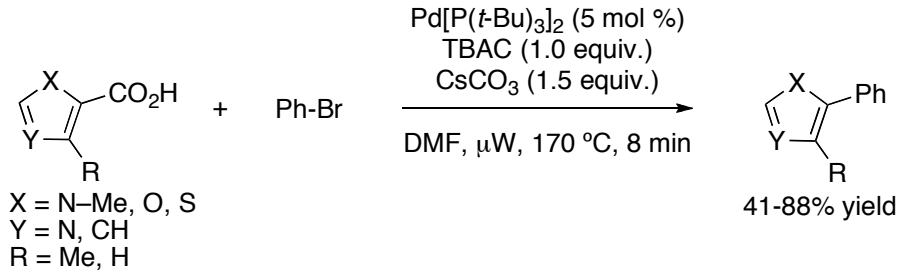
Scheme 3. Synthesis of Biaryls by Catalytic Decarboxylative Coupling



Decarboxylative Coupling of Heteroaromatic Carboxylic Acids

Heteroaromatic molecules are ubiquitous throughout the pharmaceutical industry. During their drug discovery efforts, Forgione, Bilodeau, and coworkers found herteroaromatic carboxylic acids undergo Pd-catalyzed cross-coupling with phenyl bromides.[11] The reaction of a heteroarene carboxylic acid with a phenyl bromide in the presence of Cs_2CO_3, tetrabutylammonium chloride (TBAC), and $Pd[P(t\text{-}Bu)_3]_2$ as catalyst afforded phenyl substituted heterocycles in varying yields (Scheme 4). This reaction is proposed to occur by a different mechanism than the previously mentioned reactions with benzoic acids.

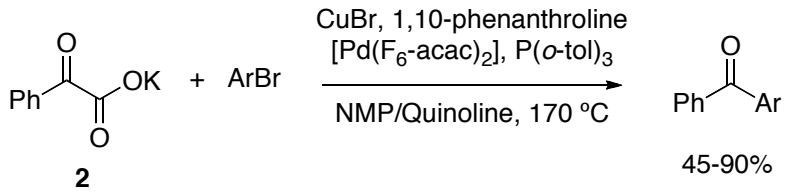
Scheme 4. Decarboxylative Coupling of Heteroaromatic Carboxylic Acids and Aryl Bromides



Synthesis of Substituted Benzophenones from α-Oxocarboxylates

Goossen and coworkers also reported the synthesis of aryl ketones by decarboxylative cross-coupling.[12] Similar to the reaction in Scheme 3, a Cu^{I} source is used to facilitate decarboxylation to generate an acyl anion equivalent, which can then undergo cross-coupling. The reaction of potassium oxophenyacetate (**2**) with an aryl bromide catalyzed by a combination of CuBr, 1,10-phenanthroline, [Pd(F_6-acac)$_2$], and P(*o*-tol)$_3$ gave the corresponding diaryl ketones in 45-90% yield (Scheme 5).

Scheme 5. Decarboxylative Coupling with α-Oxocarboxylates as Substrates



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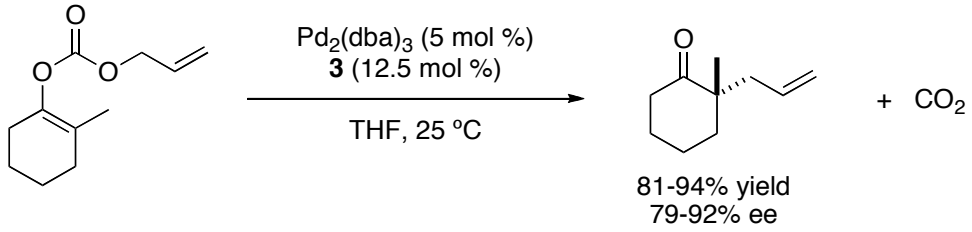
ENANTIOSELECTIVE ALKYLATIONS BY DECARBOXYLATION

Asymmetric Allylic Alkylations

Tsuji allylations form α-quaternary ketones from allyl β-keto esters in the presence of a palladium catalyst.[13] By employing various chiral ligands, this reaction now can be performed stereoselectively to form molecules containing quaternary centers. Stoltz and coworkers first reported an asymmetric Tsuji allylation of allyl enol carbonates to form α-quaternary cycloalkanones.[14] These reactions, catalyzed by $Pd_2(dba)_3$ and *(S)*-*t*-Bu-PHOX (**3**) (Figure 3), form α-quaternary cycloalkanones in 81-94% yields and 79-92% ee (Scheme 6).

Scheme 6. Enantioselective Tsuji Allylation



Shortly after this first report, Trost and coworkers reported an asymmetric decarboxylative allylic alkylation of cyclic[15] and acyclic allyl enol carbonates.[16] The reaction of both cyclic and acyclic allyl enol carbonates catalyzed by Pd_2dba_3 and **4** (Figure 3) produced the α-allylated product in good yields (64-99%) and high enantioselectivities (76-99% ee). These reactions formed not only α-quaternary ketones but also α-tertiary ketones, which were unable to be formed with the reaction conditions developed by Stoltz and coworkers.

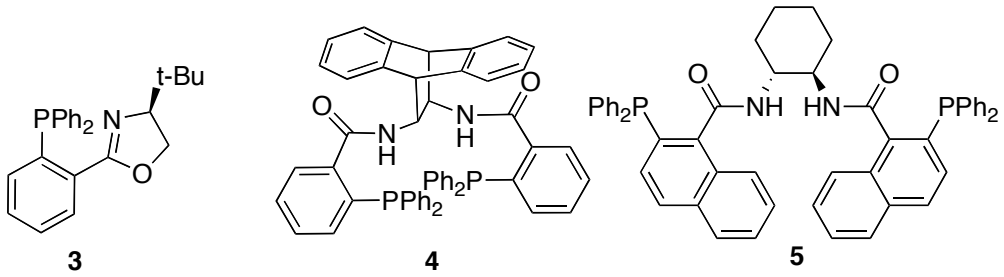
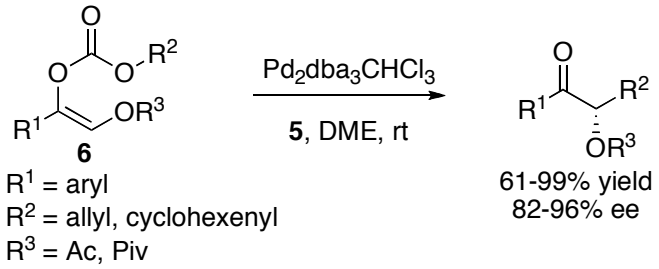


Figure 3. Chiral Ligands Employed in Pd-catalyzed Asymmetric Allylic Alkylations

Trost and coworkers further demonstrated the utility of this catalyst system by generating protected α-tertiary hydroxyaldehydes from enol allyl carbonates of α-siloxycarbonyl compounds in 76-96% yield and 64-99% ee.[17] Soon after this report, Trost and coworkers showed that protected α-hydroxyketones could be generated from substrate **6** by changing the protecting group on the alcohol from a silyl group to an acetate or a pivalate and the ligand from **4** to **5** (Figure 3).[18] Under the reaction conditions shown in Scheme 7, protected α-hydroxyketones were generated in 61-99% yield and 82-96% ee.

Scheme 7. Synthesis of Protected α-Hydroxyketones

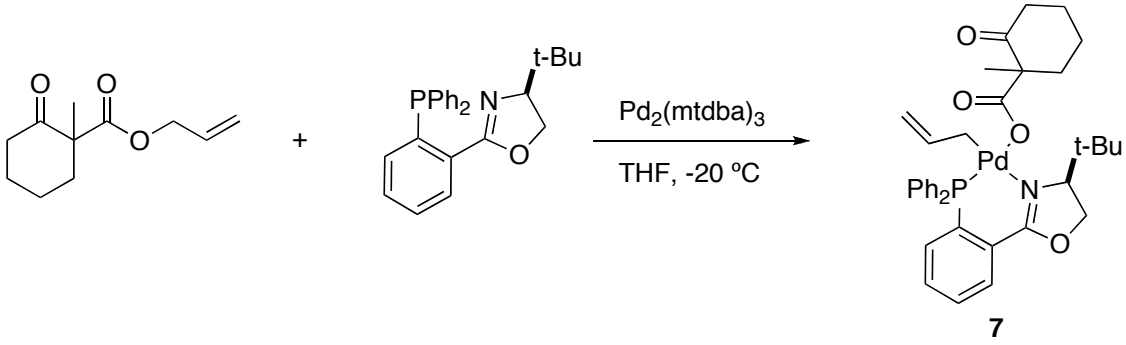


Mechanistic Studies

Various mechanistic studies have been performed to elucidate the mechanism of these reactions. Trost and coworkers reported a crossover experiment of an α-allyl enol carbonate and α-crotyl enol carbonate.[15] After submitting these two carbonates to the typical reaction conditions, a 10:1 ratio of the allyl products were produced. This is consistent with an inner-sphere mechanism that involves an (η^1-allyl)Pd(enolate) complex. In addition, a protonation experiment was reported.[16] In this experiment an acyclic allyl enol carbonate was submitted to the normal reaction conditions along with various additives of increasing acidity. This protonation experiment showed that with increasing acidity, the ability to intercept the contact ion pair to form the mono-alkylated ketone increases. Once again, this result is consistent with an inner-sphere mechanism. Recently, Stoltz and coworkers identified the resting state of the catalyst in these reactions.[19] The resting state is the product of oxidative addition of the allyl enol carbonate and *t*-Bu-PHOX-ligated palladium. This complex was prepared as shown in Scheme 8. Allowing **7** to warm to room temperature produced 2-methyl-2-allyl cyclohexanone in nearly

quantitative yield. Also, a crystal structure of **7** was obtained, which was the first reported crystal structure of a Pd(η^1-allyl)(carboxylate) complex.

Scheme 8. Synthesis of the Resting State in Pd-catalyzed Asymmetric Allylic Alkylations



Applications in Total Synthesis

The utility of asymmetric allylic α-alkylation has been demonstrated in a number of total syntheses (Figure 4).[20-22] In these syntheses, asymmetric allylic α-alkylation was used to form molecules containing α-quaternary stereocenters, as in the syntheses of cassiol and elatol. Specifically, the power of this transformation was demonstrated in the synthesis of cyanthiwigin F (Scheme 9) by performing a double asymmetric allylic α-alkylation. A 1:1 mixture of racemic and meso diastereomers of **8** was subjected to Pd(dmdba)$_2$ and *t*-Bu-PHOX to generate **7** in 99% ee and 4.4:1 mixture of the diastereomers (**7**:meso diastereomer) by a double catalytic enantioselective alkylation. Synthetic intermediate **9** was then converted into cyanthiwigin F by a ring closing metathesis and further functional group manipulations.

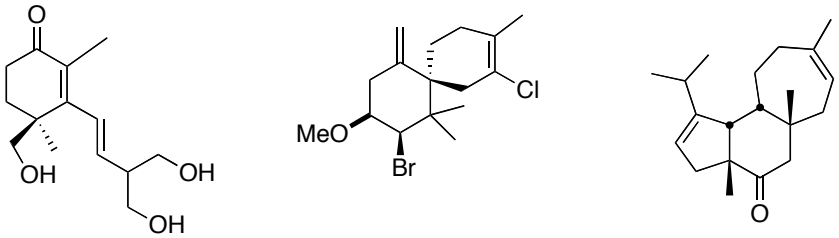
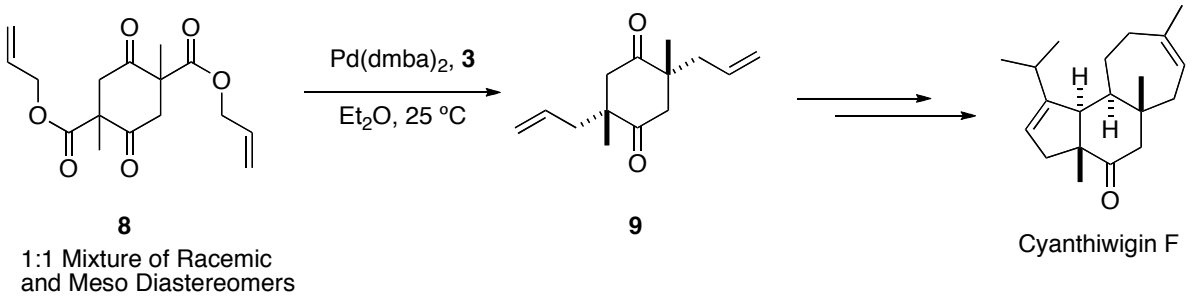


Figure 4. Total Syntheses via Asymmetric Alkylation

Scheme 9. Asymmetric Allylation in the Total Synthesis of Cyanthiwigin F



CONCLUSION

Carboxylic acids and carbonates recently have become versatile reagents for carbon-carbon bond formation. Decarboxylative aldol reactions, developed primarily by Shair and coworkers, provide a complimentary approach to traditional aldol reactions that are compatible with aldehydes containing α-hydrogens. These reactions are also air or moisture tolerant, unlike many other aldol reactions, because they do not require a strong base. Biaryl synthesis through decarboxylation offers an alternative approach to traditional cross-coupling reactions, such as Suzuki-Miyaura cross-coupling reactions. Employing carboxylic acids as nucleophillic coupling partners alleviates the need for organometallic reagents. This approach eliminates stoichiometric metal waste that is typically generated in these reactions. However, the scope of this reaction is currently limited to a electron-poor benzoic acids. Asymmetric allylic alkylations, developed independently by Stoltz and Trost provide a convenient method to form quaternary centers with good to excellent enantioselectivity. These reactions have since been employed in a number of total syntheses.

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