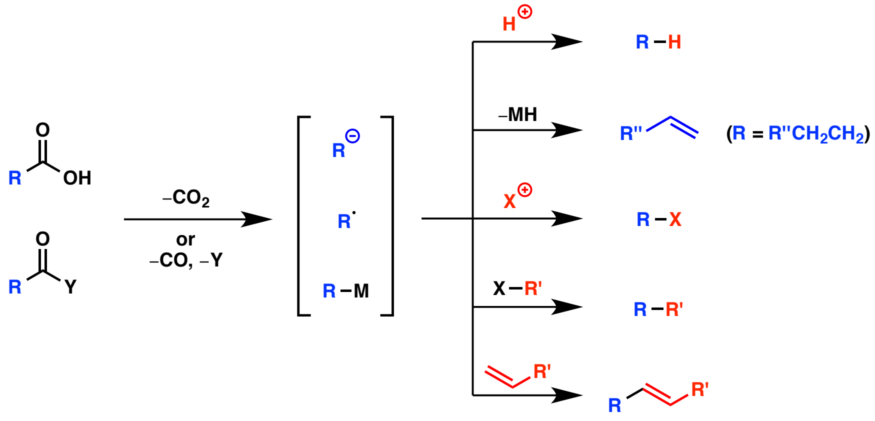
CHAPTER 1

Palladium-Catalyzed Decarboxylative and Decarbonylative Transformations: Past, Present, and Future

1.1 Introduction

Decarboxylation and decarbonylation are important transformations in synthetic organic chemistry. Loss of carbon dioxide or carbon monoxide from a carboxylic acid (R–COOH) or its derivatives (R–COY) generates a reactive intermediate (formally a carbocation, carbanion, radical, or organometallic species) of the R fragment, which may participate in a variety of subsequent transformations, including protonation, elimination, electrophilic halogenation, cross-coupling, and Heck-type reactions (Scheme 1.1). Since many carboxylic acids and their derivatives are readily available and inexpensive, using these compounds as starting materials in organic synthesis is an attractive option.

Scheme 1.1 Decarboxylation/decarbonylation and subsequent transformations

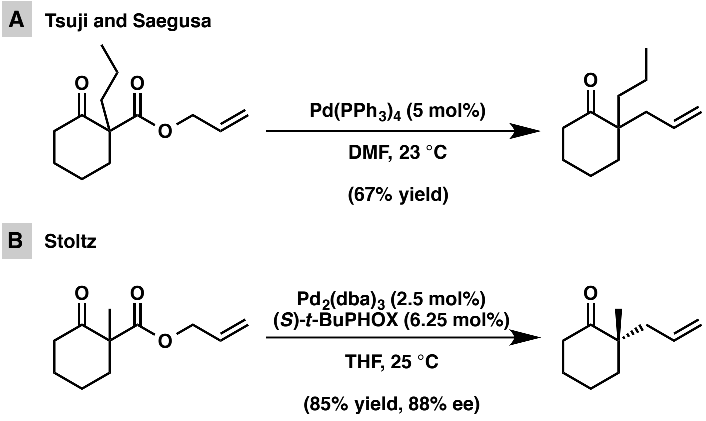


Since the 1980s, palladium-catalyzed decarboxylative and decarbonylative reactions have received significant attention from the synthetic community. Due to the excellent catalytic activity of palladium, a large number of synthetically useful decarboxylative and decarbonylative transformations using palladium catalysis have been developed. In this chapter, we will review past literature, then discuss our own adventure in this exciting field, and finally point out future directions for decarboxylative and decarbonylative chemistry.

1.2 Palladium-Catalyzed Decarboxylative Reactions

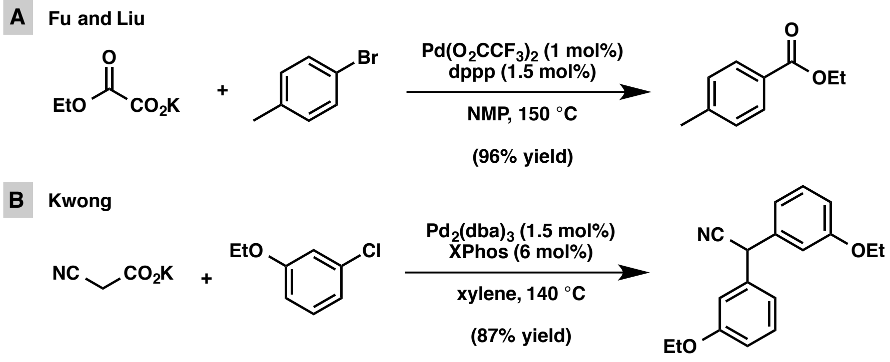
The earliest accounts of palladium-catalyzed decarboxylative reactions focused on carboxylates that readily undergo decarboxylation, e.g. β-keto carboxylates. Saegusa[1] and Tsuji[2] independently reported palladium-catalyzed decarboxylative allylic alkylation of β-keto esters in the early 1980s (Scheme 1.2A). Presumably, the Pd-carboxylate is generated upon deallylation of the ester. Two decades later, the Stoltz group developed enantioselective variants of this reaction (Scheme 1.2B).[3]

Scheme 1.2 Palladium-catalyzed decarboxylative allylic alkylation reactions



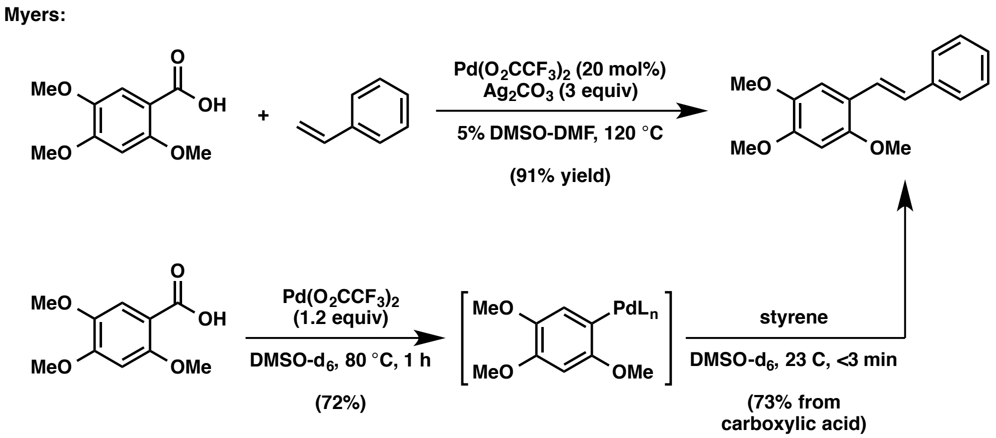
Besides β-keto carboxylates, other α- or β-activated carboxylic acids and derivatives have also been utilized in palladium-catalyzed reactions. For example, Fu and Liu jointly reported the decarboxylative coupling of potassium oxalate monoesters with aryl bromides and chlorides (Scheme 1.3A).[4] Kwong and co-workers developed a palladium-catalyzed decarboxylative arylation of potassium cyanoacetate (Scheme 1.3B).[5]

Scheme 1.3 Decarboxylative reactions of other activated carboxylic acids



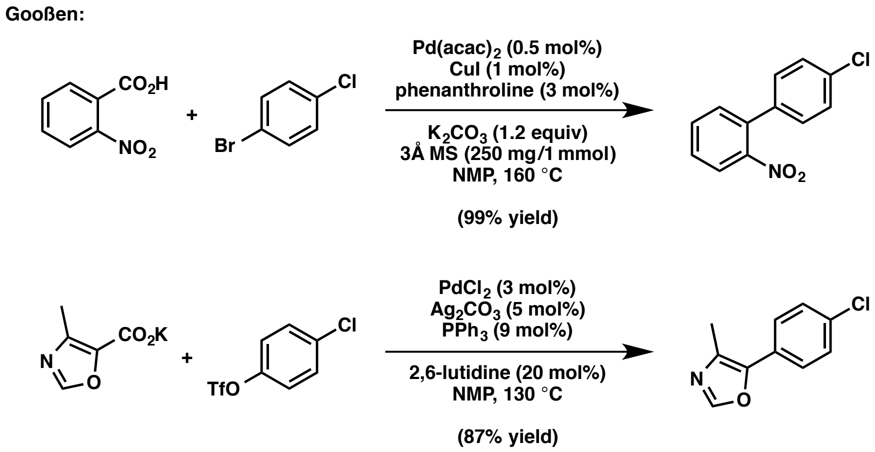
Another broad class of substrates for decarboxylation is aromatic carboxylic acids. A seminal publication from the Myers group describes the decarboxylative Heck-type olefination of aromatic carboxylic acids (Scheme 1.4).[6] The reaction requires Ag_2CO_3 for catalyst turnover; however, decarboxylation is thought to be promoted by palladium alone as evidenced by the results of control experiments using 1.2 equiv $Pd(O_2CCF_3)_2$ in the absence of Ag_2CO_3 (Scheme 1.4).

Scheme 1.4 Decarboxylative Heck-type olefination of aromatic carboxylic acids

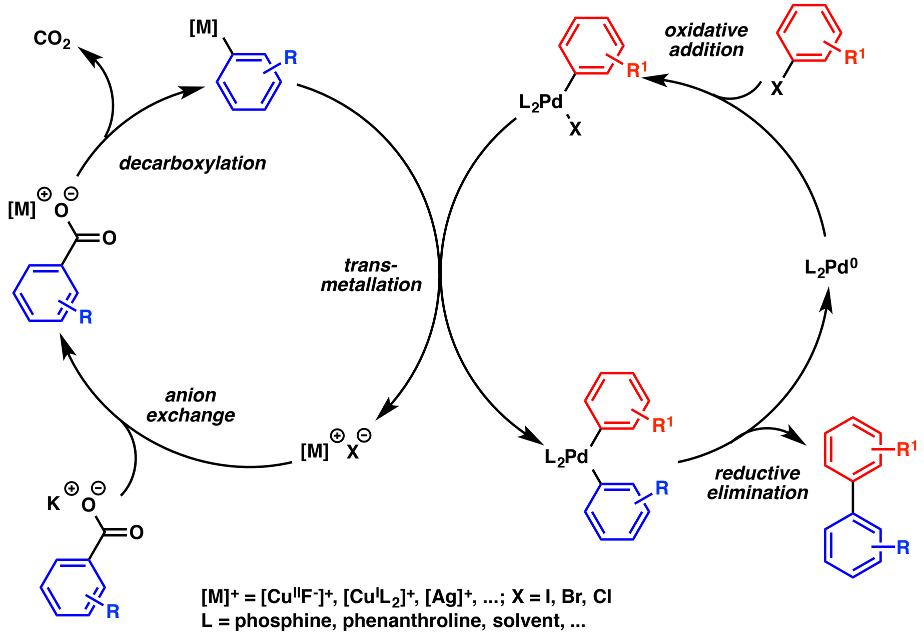


In the past decade, decarboxylative cross-coupling reactions have experienced a tremendous growth, in part because aromatic carboxylic acids can serve as the carbanion equivalent through decarboxylation and replace conventional but more expensive organometallic reagents (e.g. arylboronic acids).[7] These reactions often involve another transition metal (catalytic or stoichiometric) such as copper or silver that facilitates decarboxylation.[8] The Gooßen group has pioneered this field (Scheme 1.5).[9] A proposed reaction mechanism is outlined in Scheme 1.6.[7] In addition to aromatic carboxylic acids, alkenyl carboxylic acids such as cinnamic acid have also been employed in palladium-catalyzed decarboxylative cross coupling reactions under similar conditions.[10]

Scheme 1.5 Palladium-catalyzed decarboxylative cross-coupling reactions

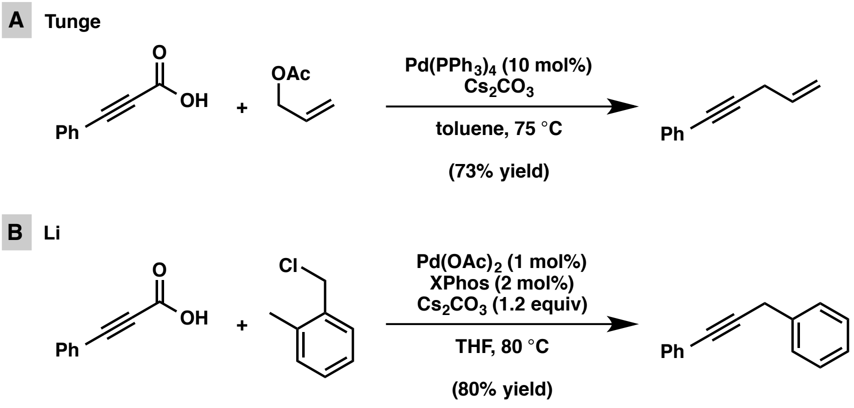


Scheme 1.6 Proposed reaction mechanism for decarboxylative cross-coupling



A third class of substrates are alkynyl carboxylic acids, which decarboxylate upon heating to produce an alkynylpalladium species that may be coupled with allylic or benzylic electrophiles (Scheme 1.7).[11]

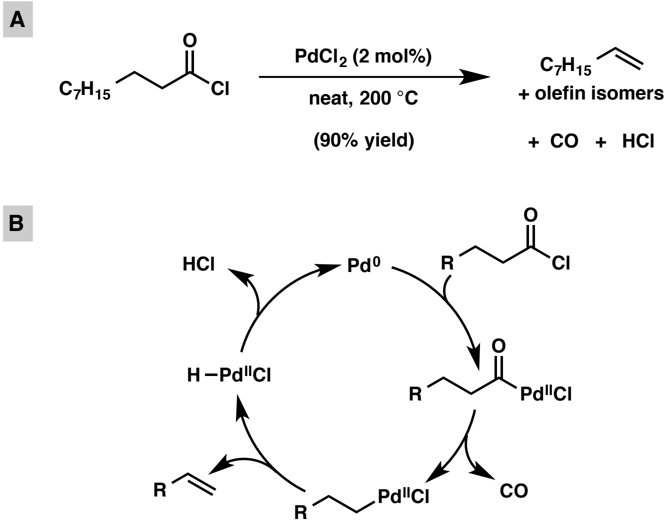
Scheme 1.7 Palladium-catalyzed decarboxylative allylic alkylation and benzylation of alkynyl carboxylic acids



1.3 Palladium-Catalyzed Decarbonylative Reactions

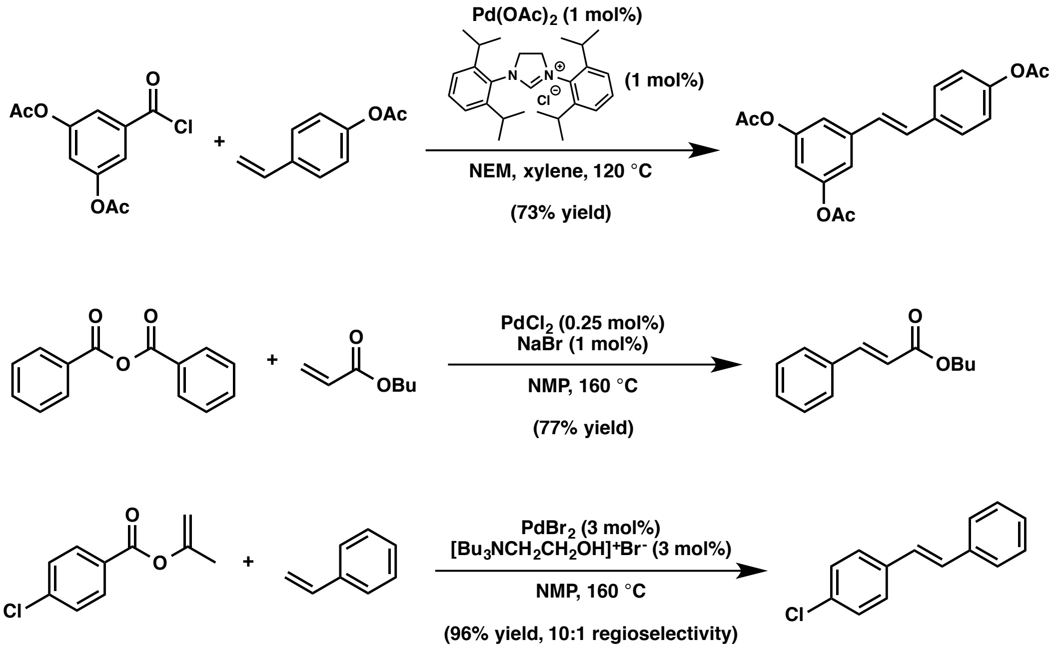
As an alternative to decarboxylation, decarbonylation represents another approach to cleaving the carbonyl group in a carboxylic acid derivative and generating an activated species for the remaining fragment. In 1965, Tsuji and co-workers reported the first example of palladium-catalyzed decarbonylation of aliphatic acyl chlorides to form alkenes along with CO and HCl (Scheme 1.8A). The reaction is thought to proceed via oxidative addition of the acyl chloride to Pd(0), forming an acylpalladium(II) species, which loses carbon monoxide to generate an alkylpalladium(II) species that undergoes β-hydride elimination to deliver the olefin product and regenerate the active Pd(0) catalyst (Scheme 1.8B). However, this reaction requires high temperature (200 °C) and the product is a mixture of double bond positional isomers.

Scheme 1.8 Palladium-catalyzed decarbonylation of aliphatic acyl chlorides



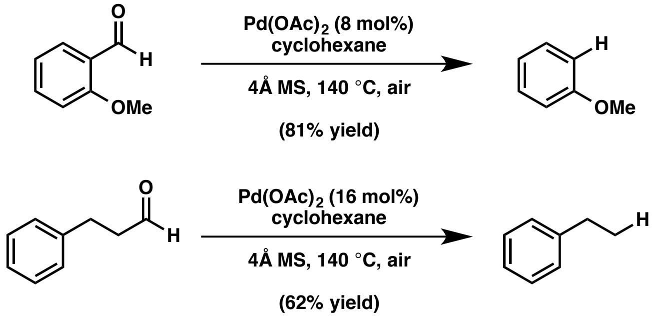
On the other hand, aromatic/alkenyl carboxylic acid derivatives have been extensively studied in the context of palladium-catalyzed decarbonylation. Since the corresponding aryl- or alkenylpalladium(II) species cannot undergo β-hydride elimination, they could be employed in further transformations, especially Heck-type olefination (Scheme 1.9). The starting material can be aroyl chlorides,[12] anhydrides,[13] or activated esters.[14] These decarbonylative Heck reactions are particularly interesting because they avoid the use of base and thus the generation of stoichiometric salt byproducts.[13,14]

Scheme 1.9 Palladium-catalyzed decarbonylative Heck olefinations



In addition to carboxylic acid derivatives, aldehydes have also been employed in decarbonylation reactions. Maiti and co-workers developed a decarbonylation process for converting aromatic and aliphatic aldehydes to arenes and alkanes, respectively (Scheme 1.10).

Scheme 1.10 Palladium-catalyzed decarbonylation of aldehydes

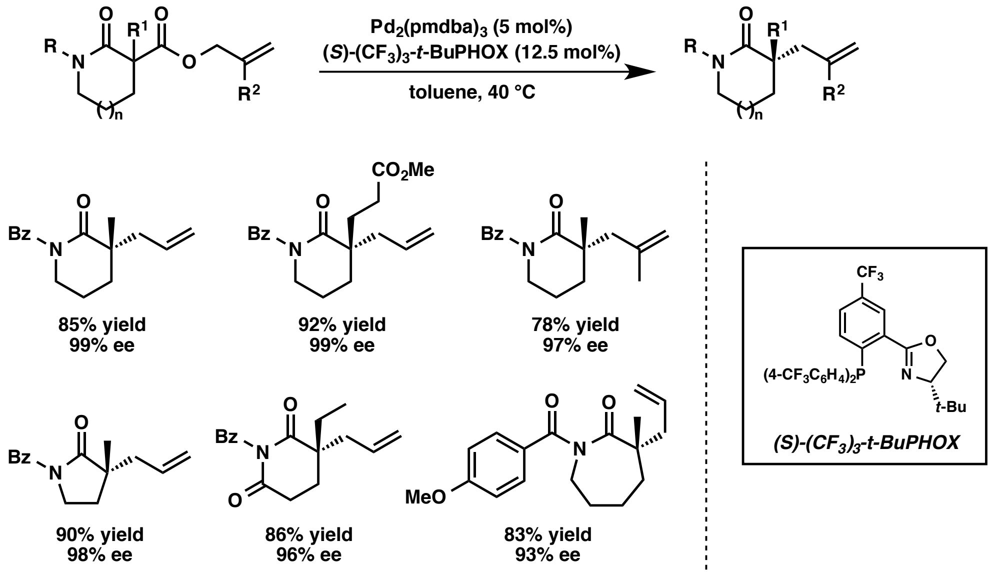


1.4 Our Explorations in the Field of Palladium-Catalyzed Decarboxylative and Decarbonylative Reactions

1.4.1 Palladium-Catalyzed Enantioselective Decarboxylative Allylic Alkylation of Lactams

At the outset of this study, our group had developed a palladium-catalyzed decarboxylative asymmetric allylic alkylation reaction that delivers α-quaternary ketones in high yield and enantioselectivity.[3] Considering the ubiquity and medicinal importance of *N*-heterocycles, as well as the lack of direct, catalytic enantioselective methods for the synthesis of α-quaternary lactams, we became interested in extending our allylic alkylation methodology to this important class of substrates. A combinatorial screen of ligand, solvent, and lactam *N*-protecting group allowed us to identify a set of optimal reaction parameters. A wide range of α-quaternary lactams bearing various substituents, functional groups, and scaffolds were synthesized using our decarboxylative allylic alkylation reaction in high yield and exceptionally high enantioselectivity (Scheme 1.11, see Chapter 2 for details).[15]

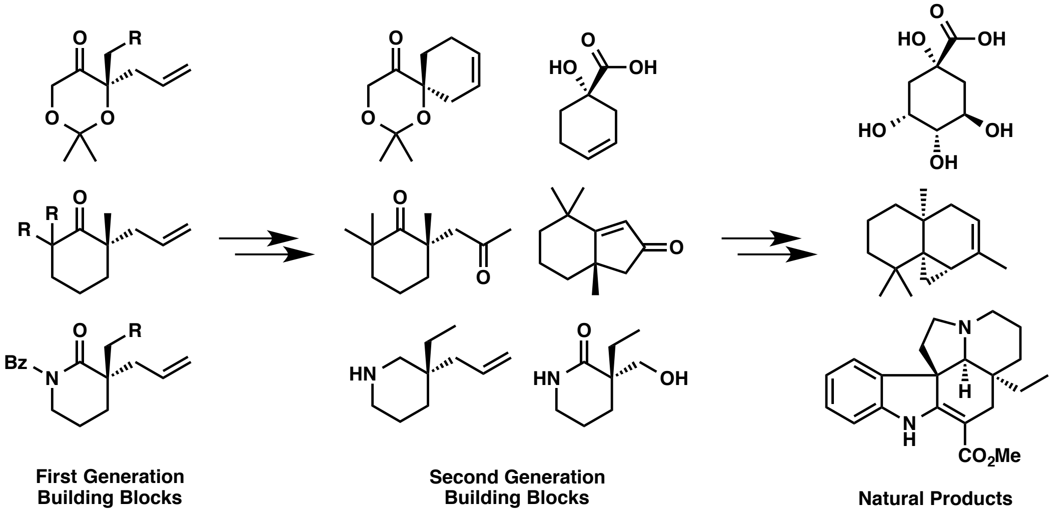
Scheme 1.11 Palladium-catalyzed enantioselective decarboxylative allylic alkylation of lactams



1.4.2 Formal Syntheses of Classical Natural Product Target Molecules via Palladium-Catalyzed Enantioselective Alkylation

Following the development of decarboxylative allylic alkylation chemistry of lactams, we became interested in the potential application of this chemistry in natural product synthesis. From a broader perspective, chiral α-quaternary carbonyl compounds represent an important class of building blocks that can be further elaborated into complex bioactive molecules. A brief literature survey reveals that many such building blocks are used as racemic compounds or require chiral auxiliaries for obtaining enantioenriched compounds en route to the target natural product. We envisioned that our palladium-catalyzed enantioselective alkylation chemistry presented a good opportunity to access these building blocks in enantioenriched form. In addition to the alkylation products (α-quaternary carbonyl compounds), which are the first generation of building blocks, we carried out chemical derivatization to produce a second generation of building blocks that enable the catalytic asymmetric formal total synthesis of numerous classical natural products (Scheme 1.12, see Chapter 3 for details).[16]

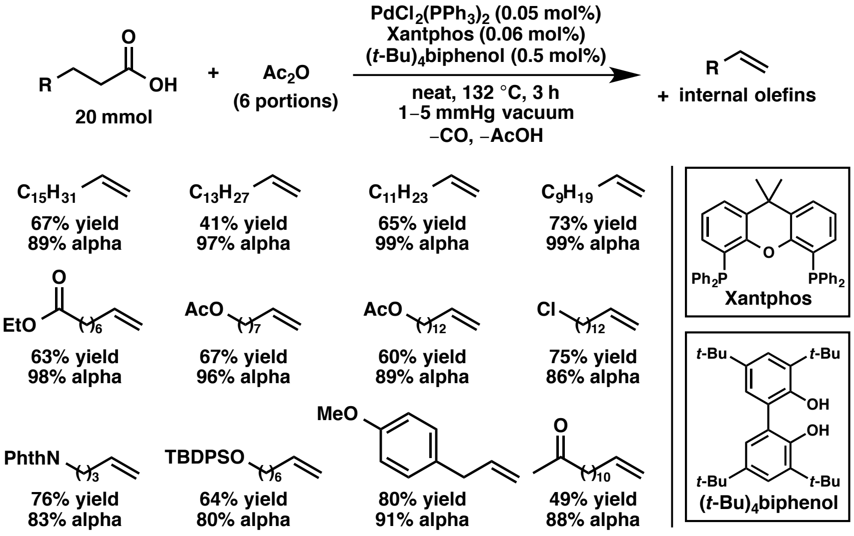
Scheme 1.12 Formal synthesis of classical natural products via palladium-catalyzed enantioselective alkylation chemistry



1.4.3 Palladium-Catalyzed Decarbonylative Dehydration of Fatty Acids for the Synthesis of Linear Alpha Olefins

The aforementioned projects focus primarily on fine chemical synthesis, i.e. natural products and pharmaceutical building blocks. As a synthetic organic chemistry group, we are also interested in commodity (bulk) chemical synthesis, especially in the context of green chemistry and sustainability. Linear alpha olefins represent an important class of commodity chemicals with a wide range of industrial applications. Currently, these olefins are mainly produced by oligomerization of ethylene derived from petroleum, a nonrenewable source. We envisioned that alpha olefins could also be obtained via either oxidative decarboxylation or decarbonylative dehydration of long chain fatty acids, which are abundant, renewable, and inexpensive. However, existing methods for converting fatty acids to alpha olefins require either very high temperature or high loading of precious metal catalysts. To address these issues, we developed a new decarbonylative dehydration process that uses low catalyst loading and proceeds under relatively mild conditions. Alpha olefins of various chain lengths and bearing different functional groups are prepared, and the reaction can be easily scaled up (Scheme 1.13, see Chapter 4 for details).[17]

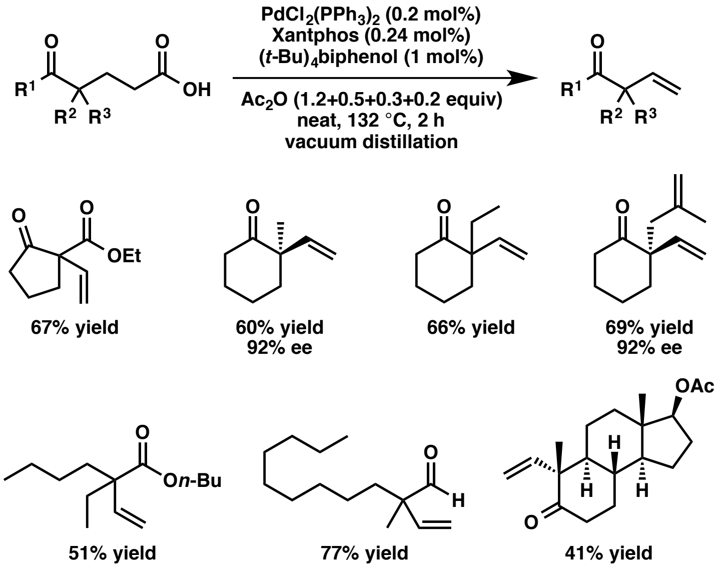
Scheme 1.13 Palladium-catalyzed decarbonylative dehydration of fatty acids for the synthesis of linear alpha olefins



1.4.4 Palladium-Catalyzed Decarbonylative Dehydration for the Synthesis of α-Vinyl Carbonyl Compounds and Total Synthesis of (–)-Aspewentin B

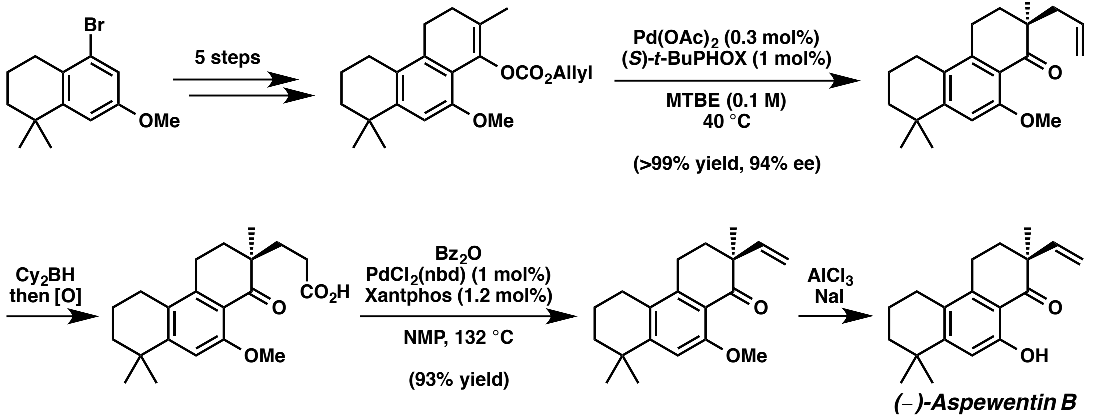
Having established our decarbonylative dehydration process for commodity alpha olefin synthesis, we became interested in the application of this chemistry to the synthesis of fine chemicals containing a terminal olefin moiety. An all-carbon quaternary center bearing an ethylene substituent is a common structural motif in many natural products. An important approach to the construction of this unit is the α-vinylation of carbonyl compounds. However, direct enolate vinylation is particularly challenging due to the unreactive nature of vinyl electrophiles. Current methods for installing a vinyl group α to a carbonyl often rely on an indirect alkylation-elimination strategy and are generally limited in substrate scope. Asymmetric vinylation reactions are rare and severely limited in scope. At the outset of our investigation, even the simple 2-methyl-2-vinylcyclohexanone was not known as a single enantiomer in the literature. We hypothesized that our decarbonylative dehydration chemistry would be a good method for obtaining enantioenriched α-vinyl carbonyl compounds since the quaternary stereocenter in the substrate carboxylic acid can be constructed in an asymmetric fashion using well-established chemistry. To test this hypothesis, we prepared a variety of γ-quaternary-δ-oxocarboxylic acids, subjected them to slightly modified decarbonylative dehydration conditions, and were pleased to obtain the corresponding α-vinyl carbonyl compounds in good yields (Scheme 1.14, see Chapter 5 for details).

Scheme 1.14 Palladium-catalyzed decarbonylative dehydration for the synthesis of α-vinyl carbonyl compounds



To further demonstrate the utility of this chemistry, we embarked on the total synthesis of (–)-aspewentin B. The quaternary carbon was built by palladium-catalyzed enantioselective allylic alkylation chemistry, and the vinyl substituent was revealed by palladium-catalyzed decarbonylative dehydration (Scheme 1.15, see Chapter 5 for details). This total synthesis represents a perfect union of the allylic alkylation and decarbonylative dehydration chemistries developed in our group.

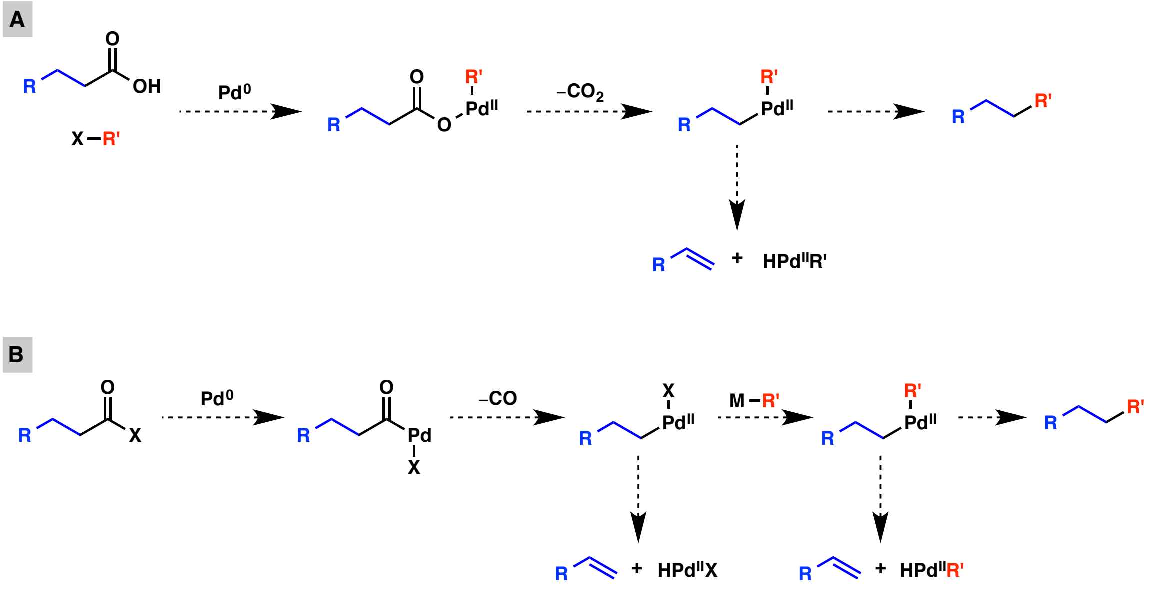
Scheme 1.15 Total synthesis of (–)-aspewentin B: union of palladium-catalyzed allylic alkylation and decarbonylative dehydration reactions



1.5 Future Directions

While we have made remarkable progress in palladium-catalyzed decarboxylative and decarbonylative transformations, there are several enduring challenges that have yet to be addressed. For example, palladium-catalyzed decarboxylative reactions have so far focused on carboxylic acids bearing *sp*^{2}-, *sp*-, or activated *sp*^{3}-hybridized substituents. Decarboxylative reactions of unactivated *sp*^{3}-hybridized (aliphatic) carboxylic acids via palladium catalysis remains elusive (Scheme 1.16A). This reaction could potentially allow us to use fatty acids as alkyl Grignard equivalents in cross-coupling reactions. The challenge is twofold: first, decarboxylation of alkyl carboxylic acids has a high energy barrier; and second, the resulting alkylpalladium(II) species are prone to β-hydride elimination. The second issue is also present in palladium-catalyzed decarbonylation reactions, in which β-hydride elimination is currently the only pathway for the alkylpalladium(II) species. If this reaction pathway could be inhibited, we may be able to explore other chemistry such as cross coupling with a nucleophile (Scheme 1.16B).

Scheme 1.16 Challenges and opportunities in palladium-catalyzed decarboxylative and decarbonylative reactions



1.6 Concluding Remarks

Palladium-catalyzed decarboxylative and decarbonylative transformations are of great utility in organic synthesis. Research in the past three decades has led to a variety of synthetic methods. We contributed to this field through the development of a palladium-catalyzed enantioselective decarboxylative allylic alkylation reaction of lactams and a palladium-catalyzed decarbonylative dehydration reaction of carboxylic acids. These reactions address challenges in both commodity and fine chemical synthesis, and should find application in the context of both academic and industrial research.

1.7 Notes and References

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