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Synthesis of Homoallylic Amines via the Palladium-Catalyzed Decarboxylative Coupling of Amino Acid Derivatives

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Due in part to their application in the synthesis of a variety of heterocycles that are commonly found in biologically active compounds, the synthesis of homoallylic amines has received much attention.[1] Traditional approaches for the synthesis of homoallylic amines have focused on the addition of nucleophilic metal allyls to electrophilic aldimines.[2] Herein we report a complementary route for the synthesis of protected homoallylic amines, which instead couples an electrophilic allyl moiety with an α-amino anion derived from an amino acid precursor.[3]

In nature, the generation of α-imino anions from α-amino acids is achieved by pyridoxal 5′-phosphate (PLP)-dependent decarboxylases.[4] The transformation involves condensation of PLP with an amino acid to form an iminium carboxylate intermediate (Scheme 1). Decarboxylation produces the resonance-stabilized α-imino anion, which is ultimately protonated. We postulated that decarboxylation could also be facilitated by stabilization of the incipient charge with a transition metal rather than a proton, giving rise to α-imino organometallic intermediates that may be useful in C−C bond-forming reactions.

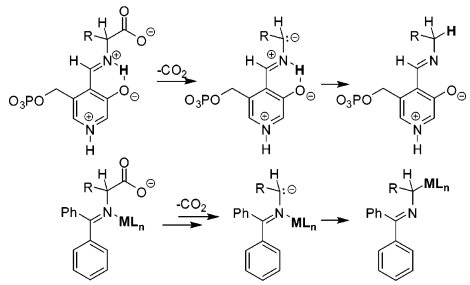
Our lab has recently demonstrated the effectiveness of palladium in promoting the decarboxylation of allylic esters in which the anionic intermediate is stabilized by a ketone, a nitrogen-containing heterocycle, or an alkyne.[5,6] In an extension of this chemistry, we now report that decarboxylation also readily occurs from allylic esters of amino acids in which the amine is protected as a diphenyl ketimine.

To begin, the allylic ester of phenylglycine was protected as a ketimine via reaction with benzophenone imine to produce **1a**.[7] Decarboxylative coupling was facile at 25 °C when **1a** was subjected to the catalytic system of 5 mol % Pd_2dba_3 and 10 mol % dppf [1,1′-bis(diphenylphosphino)ferrocene]. The major side product (**3a**) observed by ^1H and ^{13}C NMR in this reaction arises from nucleophilic attack of the α′ carbon into the Pd π-allyl, suggesting the accessibility of a 2-aza-allyl intermediate akin to **B** (Scheme 2). Reaction through ion pairs is also possibile. The ratio of **2a**/**3a** was found to have a moderate solvent dependence. When the reaction was run in toluene at room temperature, a 2.5:1 ratio of products was obtained, while in THF, the selectivity improved to 5:1. Protonation of the putative intermediate α-imino anion was also found to lead to a minor side product with certain substrates;[8] in these cases, the use of dppb [1,1′-bis(diphenylphosphino)butane] as the ligand minimized the amount of protonation.

Modification of the allyl group was also found to impact the regioselectivity of allylation. When the 2-methallyl ester was utilized, the reaction rate decreased, however, the regioselectivity and isolated yields of desired products were greatly improved (Table 1). For example, decarboxylation of **1d** resulted in a 5:1 mixture of **2d**/**3d**, while **1e** reacted with an improved regioselectivity of 13:1.

The decarboxylation of substrates derived from phenylalanine (R^1═CH_2Ph) proved to be more difficult, requiring temperatures

Scheme 1



Scheme 2

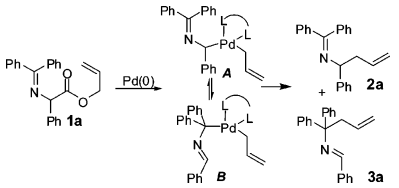
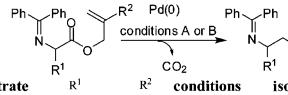


Table 1. Substrate Scope for Protected Homoallylic Amine[a]



substrate	R^1	R^2	conditions	isolated yield
1a		H	A, 25°C	67%
1b		CH_3	A, 40 °C	81%
1c		Ph	A, 40 °C	75%
1d		H	B, 25°C	66%
1e		CH_3	B, 40°C	93%
1f		CH_3	B, 40°C	85%
1g		CH_3	A, 110°C	63%
1h		Ph	A, 110°C	46%
1i		H	B, 102°C	67%
1j		CH_3	A, 110°C	26%

[a] Conditions: A = 5 mol % Pd_2dba_3 and 10 mol % dppf; B = 5 mol % Pd_2dba_3 and 10 mol % dppb. Substrates **1a**−**f** in 0.1 M THF, **1g**, **h**, and **j** in 0.1 M toluene, and **1i** in 0.1 M dioxane.

at or above 100 °C. Presumably, this reflects the higher activation energy required to form an α-imino anion that is no longer benzylic. Nevertheless, decarboxylative coupling of phenylalanine-derived substrates **1g**−**i** occurred smoothly at elevated temperatures (Table 1). The valine-derived substrate **1j** also underwent decarboxylative coupling, albeit in low yield.

Surprisingly, attempted coupling of the phenylalanine-derived ketimine **1k** bearing an *unsubstituted* allyl ester led to the predominant formation of *N*-allyl aziridine **4k** (Table 2). *N*-allyl aziridines proved to be the major products arising from the

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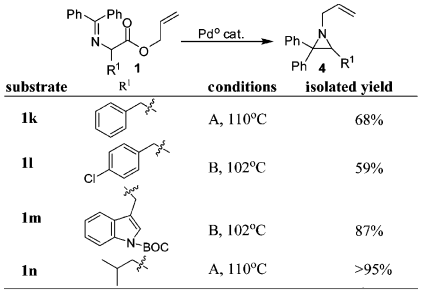
Table 2. Substrate Scope for Aziridine Formation[a]



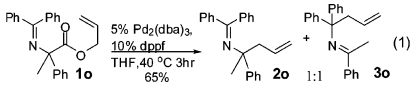
substrate	R¹	conditions	isolated yield
1k		A, 110°C	68%
1l	Cl	B, 102°C	59%
1m	N-BOC	B, 102°C	87%
1n		A, 110°C	>95%

[a] Conditions: A = 5 mol % Pd_2dba_3 and 10 mol % dppf; B = 5 mol % Pd_2dba_3 and 10 mol % dppb. Substrates **1k** and **1n** in 0.1 M toluene and **1l** and **1m** in 0.1 M dioxane.

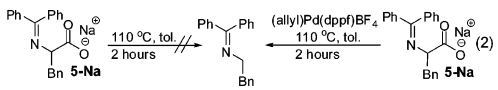
decarboxylation of substrates **1k**−**n** in which an unsubstituted Pd π-allyl intermediate coupled with an alkyl-substituted amino acid (Table 2).[9]

Next, preliminary experiments were performed with the goal of investigating the mechanism of the decarboxylative C−C coupling reaction. First, the stereochemical course of the reaction was probed by treatment of allyl ester **1b** derived from (*R*)-phenylglycine (83% ee) under standard reaction conditions. The resulting product (**2b**) was racemic. Importantly, the reactant **1b** was still optically active at 75% conversion (82% ee). Thus, an intermediate is formed that is achiral or rapidly racemizes under the reaction conditions but is not in equilibrium with an α-imino ester. This implies that the stereochemical determining step is after decarboxylation and that appropriate chiral ligands may promote enantioselective coupling. Indeed, treatment of **1g** with 5 mol % Pd_2dba_3 and (*R*)-BINAP provided optically active **2g**, however, the enantioselectivity is not high (30% ee).[8]

Further mechanistic insight was obtained from the reaction of α-disubstituted substrate **1o**. Decarboxylative coupling of **1o** occurred under mild conditions to give a 1:1 mixture of α and α′ allylated products (eq 1). Because **1o** lacks an α-hydrogen, coupling can only take place if decarboxylation precedes allylation.

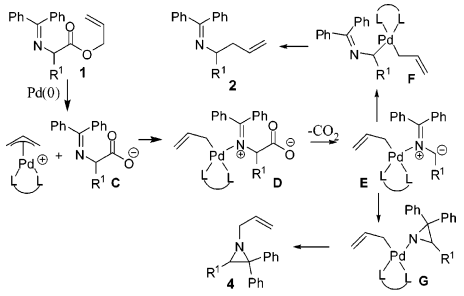


To probe the role of palladium in the decarboxylation process, sodium carboxylate **5-Na** was heated in the absence of palladium for 12 h at 110 °C in toluene (eq 2). It was found that, in contrast to the analogous carboxylic acid **5-H**, no decarboxylation took place. Similar treatment of the sodium carboxylate in the presence of (allyl)Pd(dppf)BF_4 resulted in quantitative decarboxylation, however, the major product resulted from decarboxylative protonation.[10] Nonetheless, these experiments suggest that palladium plays a role in activating the substrate for decarboxylation and may facilitate decarboxylation by a mechanism similar to that for thermal decarboxylation in the presence of protons. Proton-induced decarboxylation of amino acid imines is known to proceed by formation of stabilized azomethine ylide intermediates.[11] Thus, it is possible that the analogous palladium-stabilized azomethine ylides are intermediates in the decarboxylative coupling of amino acids.



As illustrated in Scheme 3, imine and aziridine formation both are likely to begin with the oxidative addition of substrate to Pd^0,

Scheme 3



leading to intermediate **C**. Similar to proton-catalyzed decarboxylation, coordination of nitrogen is expected to facilitate decarboxylation to produce intermediate **E**. Here the reaction can follow one of two pathways. A 1,2 shift of palladium gives **F**, which can form **2** upon reductive elimination. Alternatively, in analogy to related azomethine ylides,[12] **E** can undergo electrocyclization to yield aziridine **G**.[13] Reductive elimination would liberate *N*-allyl aziridine **4**.

In conclusion, we have demonstrated a bioinspired method for the synthesis of protected homoallylic amines. The key step in the reaction involves formation of nucleophilic α-imino anion equivalents via decarboxylative metalation of α-amino acid derivatives. Subsequent addition to electrophilic π-allyl palladium intermediates allows C−C bond-forming reactions. We have also identified a unique decarboxylative cyclization that leads to *N*-allyl aziridine products and provides interesting mechanistic insights.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) See Supporting Information for more details.
(9) For reasons that are not clear, substrate **1i** proved to be an exception.
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