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Catalytic Decarboxylative sp−sp³ Coupling

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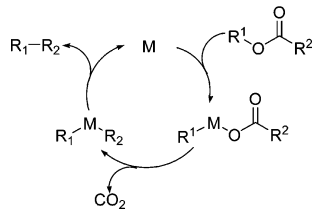
The majority of C−C bond forming cross-coupling reactions (i.e., Negishi, Stille, Suzuki−Miyaura, Sonogashira, Kumada) involve three basic transformations: oxidative addition, transmetalation, and reductive elimination.[1] The transmetalation steps in many of these reactions involve the use of toxic (Stille) or highly basic (Kumada) reagents. In addition, the reagents required for transmetalation necessarily produce stoichiometric quantities of unwanted byproducts. We envisioned that the transmetalation step could be circumvented by decarboxylative metalation of carboxylic acid derivatives (Scheme 1), where the only byproduct would be CO_2. Since carboxylic acid derivatives are ubiquitous synthetic building blocks, the ability to access reactive organometallic species via decarboxylation offers clear practical advantages.[2]

Scheme 1



Recent notable examples of the synthetic utilization of organometallics generated by decarboxylation include a decarboxylative Heck coupling,[3] aldol additions,[4,5] and asymmetric decarboxylative enolate alkylations.[6,7] Herein we report that propiolic acid derivatives readily decarboxylate under the influence of a palladium catalyst, and the resulting metal acetylides can be coupled with palladium π-allyl electrophiles to afford 1,4-enynes.

To demonstrate the principle of decarboxylative coupling, the sp−sp³ coupling of metal acetylides with allyl electrophiles was explored.[8] Previous palladium-catalyzed sp−sp³ couplings to give 1,4-enynes have focused on the formation of palladium acetylides by transmetalation from alkynyl tin reagents.[8a,b] On the basis of the model proposed above, it was expected that treatment of allylic alkynoate **1a** under conditions favorable for oxidative addition to form π-allyl palladium intermediates would allow access to palladium−allyl−acetylides through decarboxylation (Scheme 2). Specifically, substrate **1a** was treated with 10 mol % of $Pd(PPh_3)_4$ in toluene. Heating this solution for 2 h at 75 °C resulted in formation of 1,4-enyne **2a** in 80% yield.

Scheme 2

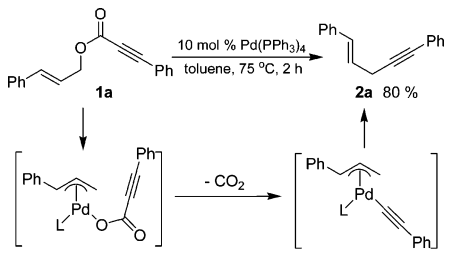
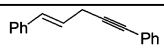
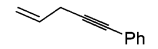
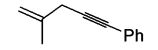
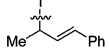
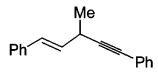
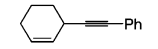
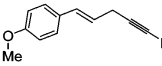
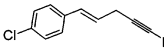
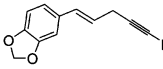
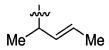
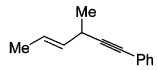
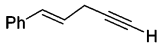
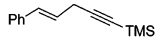
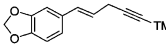


Table 1. Palladium-Catalyzed Decarboxylative Coupling of Allyl−CO_2−Acetylide[a]

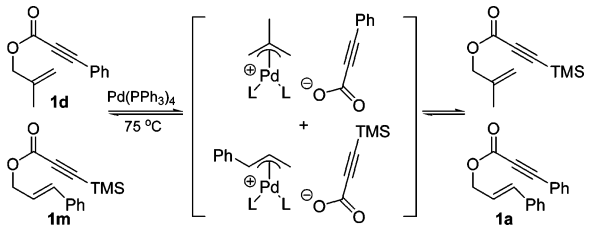
entry	allyl	acetylide	product	yield %
1b				77
1c				64
1d				88
1e				73
1f				43
1g				82
1h				84
1i				91
1j				70
1k				<5
1m				81
1n				81
1o				76
1p				42[b]
1q				69

[a] A quantity of 0.5 mmol of **1** was treated with 0.05 mmol of $Pd(PPh_3)_4$ in toluene at 75 °C. [b] The mass balance was dimeric product akin to **3r**.

Next, we briefly examined the scope of the decarboxylative allyl−acetylide coupling. A variety of aliphatic allyl fragments are compatible with the decarboxylative coupling and provide 1,4-enynes in good to high yield (Table 1). Interestingly, substrates that are expected to give rise to 1,3-unsubstituted π-allyl palladium intermediates require longer reaction times. For instance, cinnamyl phenylpropiolate (**1a**) requires only 2 h for reaction completion, while allyl phenylpropiolate (**1c**) requires 40 h to reach complete conversion; 1,3-disubstituted allyl substrates, such as **1e**, react over a period of 8 h. Thus, the order of reactivity with respect to allyl substitution is: monosubstituted aromatic > disubstituted > terminally unsubstituted. This order is somewhat unusual and suggests that the rate-limiting step of this reaction is something

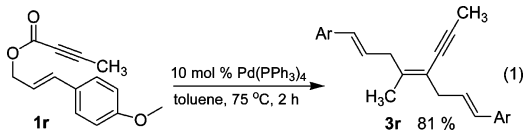
10.1021/ja0542688 CCC: $30.25

Scheme 3

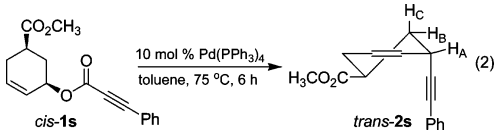


other than π-allyl formation.[9] In support of this hypothesis, complete crossover is observed between **1d** and **1m** prior to decarboxylation (ca. 30 min); the exchange presumably proceeds through π-allyl palladium intermediates (Scheme 3).

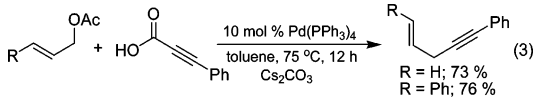
A variety of acetylide reaction partners were investigated, as well. While aromatic propiolates react smoothly, providing *E*-1,4-enynes in high yield, the unsubstituted propiolate **1k** produces an inseparable mixture of products that does not contain **2k**. Furthermore, propiolates substituted with small aliphatic groups, such as **1r**, give the dimeric products **3** exclusively (eq 1).[10] However, the allyl−acetylide coupling is not limited to aryl acetylides, as is shown by the formation of 1,4-enynes with 1-cyclohexenyl (**2p**) and TMS substituents (**2m**−**o**). Additionally, the benzyl-protected propargylic alcohol derivative **1q** provided a good yield of coupling product.



To gain a better understanding of the mechanism of 1,4-enyne formation, the stereochemistry of acetylide addition to palladium π-allyl complexes was determined. While substitution of allylic acetates with "soft" nucleophiles is known to occur with overall retention, substitution with "hard" nucleophiles occurs with inversion of stereochemistry.[11] To examine the stereochemistry of acetylide addition, we performed the decarboxylative acetylide−allyl coupling on a standard probe substrate (**1s**).[12] Treatment of *cis*-**1s** under standard conditions produced **2s** in 39% yield; the mass balance was made up of elimination products (eq 2).[13] The stereochemistry of the product is assigned as *trans* based on ^{1}H NMR spectroscopy. In particular, the absence of a large axial−axial coupling constant for H_A (dd, $J = 3.2$, 5.2 Hz) indicates that H_A is in a pseudoequatorial position. This assignment is consistent with the preference of cyclohexenes to place a 3-substituent rather than a 5-substituent in an axial position.[14] Furthermore, this is the conformation that would be predicted based on the smaller *A* value of an alkyne as compared to that of the carbomethoxy substituent. Thus, the overall transformation occurs with inversion of configuration, confirming that the acetylide is bound to palladium prior to reductive elimination.[15]



Finally, the intermolecular coupling of allylic acetates with propiolic acids was investigated since the above results suggested that we could readily access metal acetylide intermediates through catalytic decarboxylation of propiolic acids. Indeed, treatment of allyl acetates with phenyl propiolic acid and 10 mol % of $Pd(PPh_3)_4$ produced 1,4-enynes in yields similar to those obtained through the decarboxylative coupling of allylic propiolates **1** (eq 3). However, this approach required the addition of a stoichiometric amount of base to avoid palladium-catalyzed decarboxylation of the propiolic acid to the corresponding alkyne.[16]



In conclusion, we have demonstrated that palladium acetylides are readily accessible through decarboxylation of propiolic acid derivatives. Thus, decarboxylative metalation was established as an alternative to the common practice of transmetalation. The synthetic utility of decarboxylative metalation was demonstrated by the development of a convenient sp−sp^3 coupling of acetylides with allyl electrophiles to form 1,4-enynes.

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Supporting Information Available: Spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Palladium-induced ionization of allylic acetates occurs mainly with inversion of stereochemistry. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc*. **1980**, *102*, 4730−4743.
(16) $Pd(OAc)_2$ (5 mol %) catalyzes the decarboxylation of $PhCCCO_2H$ to PhCCH in 10 min at room temperature.

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