Decarbonylative Sonogashira Cross-Coupling of Carboxylic Acids

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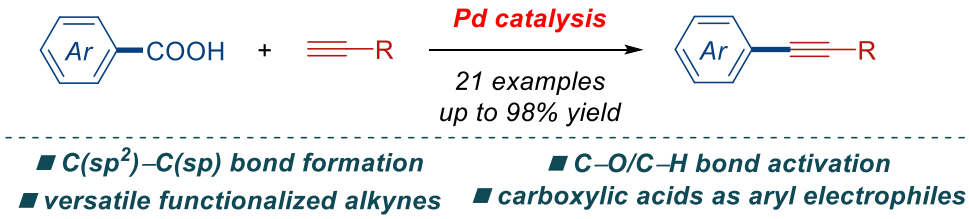
Supporting Information



ABSTRACT: Decarbonylative Sonogashira cross-coupling of carboxylic acids by palladium catalysis is presented. The carboxylic acid is activated in situ by the formation of a mixed anhydride, further decarbonylates using $Pd(OAc)_2$/Xantphos system to provide aryl–Pd intermediate, which is intercepted by alkynes to access the traditional Pd(0)/(II) cycle using carboxylic acids as ubiquitous and orthogonal electrophilic cross-coupling partners. The methodology efficiently constructs new $C(sp^2)$–C(sp) bonds and can be applied to the derivatization of pharmaceuticals. Mechanistic studies give support to decarbonylation preceding transmetallation in this process.

Sonogashira cross-coupling represents a powerful and one of the most widely utilized strategies for incorporating alkynes into organic molecules.[1] Recent surveys place Sonogashira cross-coupling as the third most commonly used cross-coupling method in industrial settings.[2] In particular, the capacity of alkynes to function as an important functional group on their own as well as participate in an array of reactions as synthetic intermediates[3] has resulted in a broad interest to establish new protocols to incorporate alkyne motifs by the Sonogashira cross-coupling.[1,2]

Typical electrophilic substrates for Sonogashira cross-coupling include aryl halides and pseudohalides, such as sulfonates,[1,2] while more recent attention has focused on iodonium salts, diazonium salts, phosphonium salts, and sulfonium salts among other electrophiles by C–X, C–O, C–N, C–P and C–S cleavage.[4] In this context, it is important to note that while many exciting achievements have been made using Pd/Cu-co-catalyzed variant, including cross-coupling of alkyl electrophiles,[5] the Pd-catalyzed/Cu-free variant has received increased attention.[6a–c] Recently, C–H alkynylation methods, in particular transforms enabled by directing groups have also been developed.[7]

In this context, our laboratory has developed new methods for decarbonylative cross-coupling of carboxylic acids.[8,9] In this reaction manifold, carboxylic acid is activated in situ to form a mixed anhydride,[8a–e] followed by selective oxidative addition of the C(O)–OR bond to a low valent metal and decarbonylation to furnish the traditional Ar–metal intermediate using ubiquitous carboxylic acids as cross-coupling partners.[10] The particular value of this approach is that carboxylic acids represent pervasive substrates in organic synthesis[11] and are derived from an orthogonal pool of precursors to aryl halides and pseudohalides.[11] The inherent presence of carboxylic acids in pharmaceuticals, natural products and functional materials renders the growing cross-coupling repertoire of carboxylic acids attractive for organic synthesis.[12]

In the continuation of our studies on decarbonylative borylation,[8a] arylation,[8b] reduction,[8c] phosphorylation[8d] and heteroarylation[8e] of carboxylic acids,[9] we became interested in the development of decarbonylative Sonogashira cross-coupling of carboxylic acids (Figure 1). Herein, we present the development of this method, including derivatization of pharmaceuticals and mechanistic studies that give support to decarbonylation preceding transmetallation in this process. The identified catalyst system involves $Pd(OAc)_2$ (5 mol%)/Xantphos (10 mol%) with piv_2O (1.5 equiv) and DMAP (1.5 equiv), dioxane (0.25 M), 160 °C, 15 h, as activators. Very recently, Chen and coworkers reported the first study of the decarbonylative cross-coupling of carboxylic acids with alkynes.[13] The conditions reported use $Pd_2(dba)_3$ (2.5 mol%), Xantphos (10 mol%), Ac_2O (1.5 equiv), DME (0.10 M), 130 °C, 12 h.[13] In our experience[8a–e] piv_2O with or without Lewis base is superior to Ac_2O in promoting selective decarbonylative coupling of carboxylic acids.[8,10,11] In light of this development and our own studies, we considered it appropriate to report our findings. The two catalytic systems should be considered

complementary,[14] while our study excludes the direct decarbonylation of ynones as intermediates in this process.

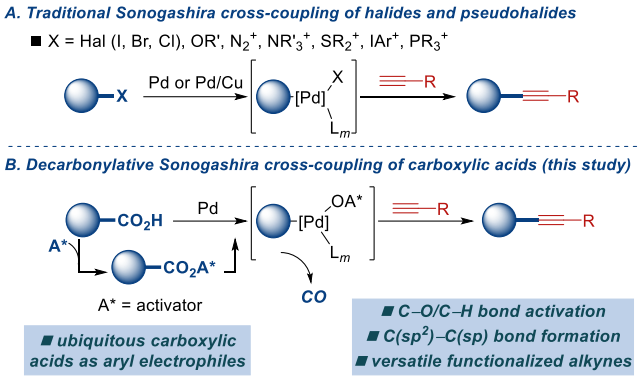


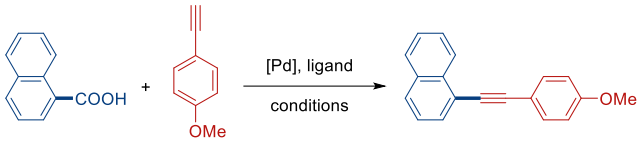
Figure 1. (a) Sonogashira cross-coupling. (b) This work: Sonogashira cross-coupling of carboxylic acids by decarbonylation.

Selected optimization results are presented in Table 1. After extensive optimization, we identified the combined use of $Pd(OAc)_2$ and Xantphos in dioxane at 160 °C as effective catalytic promoters for the process (entries 1-19). Interestingly, several phosphine ligands can be used, including dppb, dppp, dppent, dppf; however, Xantphos proved most effective, while monodentate phosphines were ineffective (entries 10-19). Out of several activators tested, such as Ac_2O, Boc_2O and piv_2O, the latter was identified as giving the best reactivity (entries 20-22), in agreement with our previous studies.[8,14] It is important to note that Cu is not required for this process (entries 24-31), resulting in a Cu-free Sonogashira variant. Finally, we demonstrated that the reaction proceeds at temperatures as low as 120 °C, demonstrating efficient decarbonylation under these conditions (entry 33). Furthermore, the use of $Pd(OAc)_2$ at 1 mol% resulted in promising 45% yield for future reaction development (entry 35). Overall, the catalytic system is complementary to the one developed by Chen and co-workers.[13] The use of large bite angle phosphines, such as Xantphos (108°), promotes decarbonylation in the process.[8a–e]

Having identified optimal reaction conditions for the coupling, we investigated the scope of this decarbonylative process for the synthesis of alkynes (Scheme 1). As shown in Scheme 1A, this method is successful with an array of aryl carboxylic acids. Naphthyl-carboxylic acids (**3a-3c**) as well as electronically-differentiated benzoic acids (**3d-3f**) are well-tolerated. Importantly, halides, such as chlorides, are compatible with this process (**3g**), enabling derivatization by standard cross-coupling technologies and showing complementarity of our catalytic system. As shown previously by us,[8a–e] the reactivity of carboxylic acids is comparable to Ar–Br in this manifold. Furthermore, steric ortho-substitution, such as Me (**3h**), CF_3 (**3i**), and even sterically-hindered Ph (**3j**) is also possible. As expected, meta-substitution is well-tolerated (**3k-3l**). This method can also be used to cross-couple heterocyclic carboxylic acids, such as thienyl-carboxylic acids (**3m-3n**).

Finally, the potential of the method in derivatization of pharmaceuticals has been demonstrated in the direct

Table 1. Optimization of the Cross-Coupling[a]



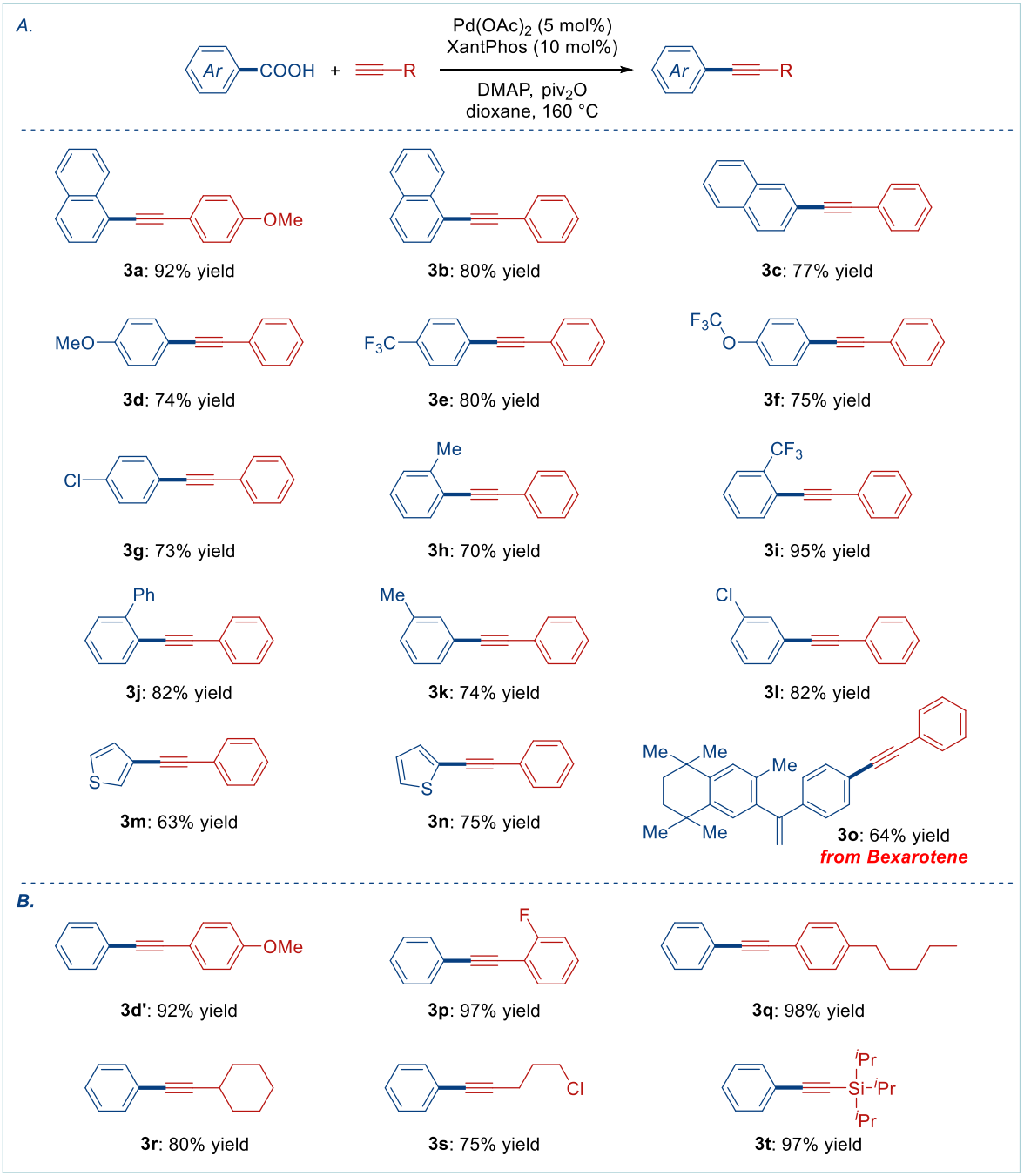
entry	[Pd]	ligand	base	additive	yield (%)
1	-	-	DMAP	piv_2O	<2
2[b]	-	-	DMAP	piv_2O	<2
3	$Pd(OAc)_2$	dppb	DMAP	piv_2O	68
4	$Pd(OAc)_2$	dppb	-	piv_2O	7
5	$Pd(OAc)_2$	dppb	DMAP	-	<2
6	$Pd(OAc)_2$	dppb	Et_3N	piv_2O	18
7	$Pd(OAc)_2$	dppb	py	piv_2O	<2
8	$Pd_2(dba)_3$	dppb	Na_2CO_3	piv_2O	<2
9	$Pd(OAc)_2$	dppb	K_2CO_3	piv_2O	33
10	$Pd(OAc)_2$	dppp	DMAP	piv_2O	45
11	$Pd(OAc)_2$	dppent	DMAP	piv_2O	35
12	$Pd(OAc)_2$	dppf	DMAP	piv_2O	31
13	$Pd(OAc)_2$	XantPhos	DMAP	piv_2O	92
14	$Pd(OAc)_2$	DPEPhos	DMAP	piv_2O	7
15	$Pd(OAc)_2$	BINAP	DMAP	piv_2O	<2
16	$Pd(OAc)_2$	PCy_3	DMAP	piv_2O	<2
17	$Pd(OAc)_2$	PCy_2Ph	DMAP	piv_2O	<2
18	$Pd(OAc)_2$	PPh_3	DMAP	piv_2O	<2
19	$Pd(OAc)_2$	DavePhos	DMAP	piv_2O	<2
20	$Pd(OAc)_2$	XantPhos	DMAP	Ac_2O	47
21	$Pd(OAc)_2$	XantPhos	DMAP	Boc_2O	58
22[c]	$Pd(OAc)_2$	XantPhos	DMAP	piv_2O	74
23[d]	$Pd(OAc)_2$	XantPhos	DMAP	piv_2O	80
24[e]	$Pd(OAc)_2$	XantPhos	DMAP	piv_2O	13
25[f]	$Pd(OAc)_2$	XantPhos	DMAP	piv_2O	77
26[g]	$Pd(OAc)_2$	XantPhos	DMAP	piv_2O	87
27[h]	$Pd(OAc)_2$	XantPhos	DMAP	piv_2O	30
28[i]	$Pd(OAc)_2$	XantPhos	DMAP	piv_2O	42
29[j]	$Pd(OAc)_2$	XantPhos	DMAP	piv_2O	37
30[k]	$Pd(OAc)_2$	XantPhos	DMAP	piv_2O	24
31[l]	$Pd(OAc)_2$	XantPhos	DMAP	piv_2O	3
32[m]	$Pd(OAc)_2$	XantPhos	DMAP	piv_2O	84
33[n]	$Pd(OAc)_2$	XantPhos	DMAP	piv_2O	69
34[o]	$Pd(OAc)_2$	XantPhos	DMAP	piv_2O	73
35[p]	$Pd(OAc)_2$	XantPhos	DMAP	piv_2O	45

[a]Conditions: 1-Np-CO_2H (1.0 equiv), alkyne (4.0 equiv), $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), DMAP (1.5 equiv), piv_2O (1.5 equiv), dioxane (0.25 M), 160 °C, 15 h. [b]CuI (10 mol%). [c]alkyne (3.0 equiv). [d]alkyne (5.0 equiv). [e]CuCl (10 mol%). [f]CuBr (10 mol%). [g]CuI (10 mol%). [h]CuCN (10 mol%). [i]CuF_2 (10 mol%). [j]$CuSO_4$ (10 mol%). [k]$Cu(OAc)_2$ (10 mol%). [l]$Cu(OTf)_2$ (10 mol%). [m]140 °C. [n]120 °C. [o]toluene. [p]$Pd(OAc)_2$ (1 mol%), Xantphos (2 mol%). See SI for details.

Sonogashira cross-coupling of *Bexarotene*, an antineoplastic agent (**30**). It is important to note that in contrast to oxidative methods for cross-coupling of carboxylic acids,[10,11] this redox-neutral manifold by decarbonylation does not require steric- or electronic bias to facilitate decarboxylation, resulting in a general method.

Next, the scope of the alkyne component was briefly investigated (Scheme 1B). As shown, the reaction is

Scheme 1. Decarbonylative Sonogashira Cross-Coupling of Carboxylic Acids[a,b]



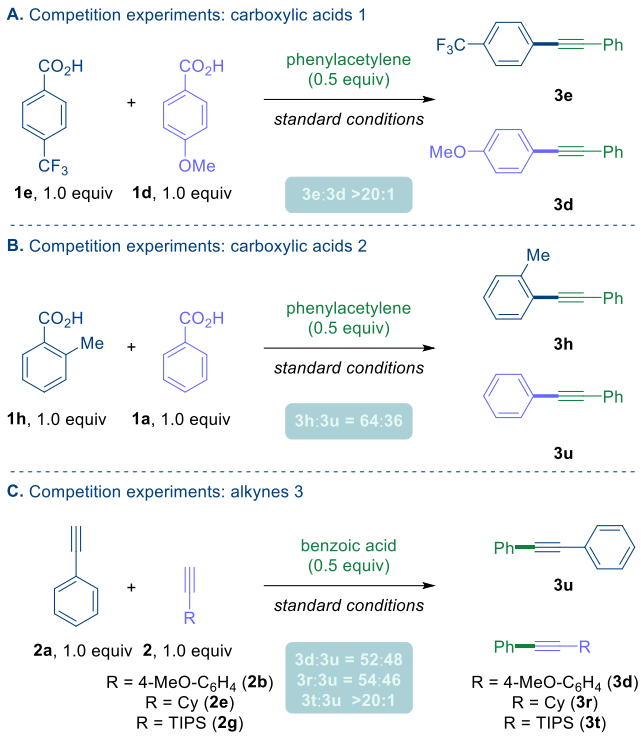
[a]Conditions: carboxylic acid (1.0 equiv), alkyne (4.0 equiv), $Pd(OAc)_2$ (5 mol%), XantPhos (10 mol%), DMAP (1.5 equiv), piv_2O (1.5 equiv), dioxane (0.20 M), 160 °C, 15 h. [b]Isolated yields. See SI for details.

compatible with electronically-differentiated phenylacetylenes (**3d'**, **3p-3q**). Furthermore, alkylacetylenes, such as cyclohexylacetylene, couple in high yields (**3r**). Sensitive alkyl electrophiles that can be utilized in further functionalization, such as halides, are also tolerated (**3s**). Finally, silyl-acetylenes, such as (triisopropylsilyl)acetylene can be used (**3t**), providing access to terminal alkynes after deprotection. At the present stage, heterocyclic acids, such as thienyl are tolerated. 3-Pyridyl carboxylic acid gave lower but promising yield (20%). Carbonyl groups, such as ketones, are tolerated in decarbonylative coupling.[8–12]

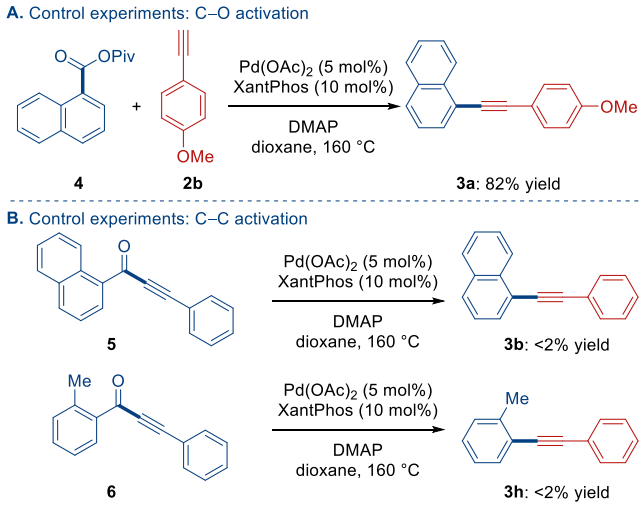
Mechanistic studies were conducted to gain insight into this process (Scheme 2). Thus, intermolecular competition experiments between differently substituted acid electrophiles revealed that electron-deficient carboxylic acids are

inherently more reactive (Scheme 2A). Furthermore, sterically-hindered acid electrophiles are more reactive than unsubstituted benzoic acids (Scheme 2B), which is consistent with decarbonylation favored by steric-demand of acyl–Pd complexes.[10] In contrast, intermolecular competition experiments using differently substituted acetylenes revealed that electron-rich acetylenes are more reactive (Scheme 2C). Next, we prepared the mixed acyl anhydride **4** and subjected this compound to the reaction conditions, resulting in the formation of the decarbonylative cross-coupling product in 82% yield (Scheme 3A). Furthermore, to test the potential of the direct decarbonylation of ynones,[10] compounds **5** and **6** were tested as potential substrates, resulting in no conversion to the desired products (Scheme 3B). We also note that subjecting phenylacetylene to the reaction conditions results in 29% of diphenylacetylene by alkyne dimerization as a minor reaction pathway. Overall, these studies are consistent with decarbonylation preceding transmetallation in the process.

Scheme 2. Mechanistic Studies



Scheme 3. Control Experiments



In summary, we have developed palladium-catalyzed decarbonylative Sonogashira cross-coupling of carboxylic acids. The reaction is promoted by $Pd(OAc)_2$/Xantphos catalytic system and proceeds by a selective oxidative addition of a mixed anhydride and decarbonylation. The reaction is compatible with various carboxylic acids and alkynes, leading to the facile formation of $C(sp^2)$–C(sp) bonds from ubiquitous carboxylic acids. The potential of this method in pharmaceutical derivatization has been demonstrated. Mechanistic studies support the pathway by direct decarbonylation/transmetallation vs. acyl cross-coupling/ynone decarbonylation. The method expands the portfolio of decarbonylative transformations of carboxylic acids as effective aryl electrophiles in organic synthesis. Further studies on decarbonylative cross-coupling of carboxylic acids are ongoing and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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