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Palladium-Catalyzed Decarbonylative Sonogashira Coupling of Terminal Alkynes with Carboxylic Acids

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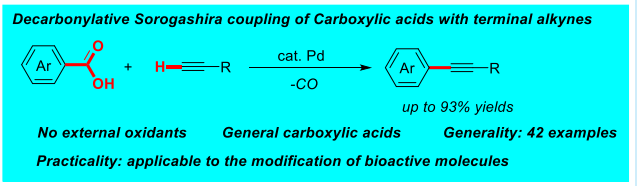
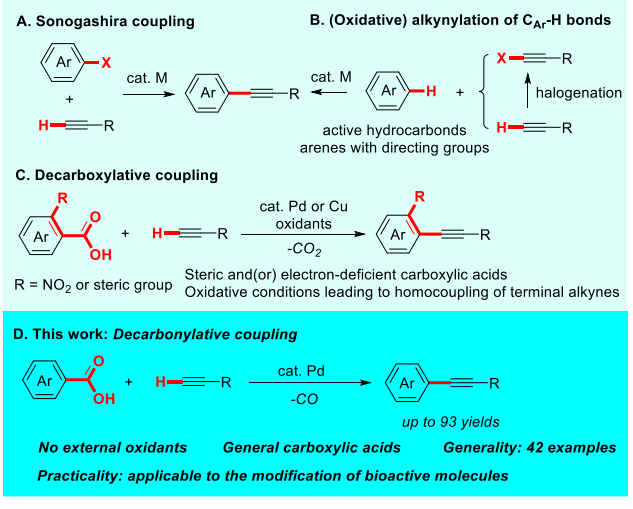
ABSTRACT: A direct decarbonylative Sonogashira coupling of terminal alkynes with carboxylic acids was achieved through palladium catalysis. This reaction did not use overstoichiometric oxidants, thus overcoming the homocoupling issue of terminal alkynes. Under the reaction conditions, a wide range of carboxylic acids including those bioactive ones could couple readily with various terminal alkynes, thus providing a relative general method for preparing internal alkynes.



Carbon−carbon triple bonds (alkynes) are important structural unit of many natural products, pharmaceuticals, and material functional molecules.[1] They are also important building blocks in organic synthesis due to the diverse reactivity.[2] Therefore, their efficient synthesis always is the key point of chemists' attention.[3−5] Among the established synthetic methods, Sonogashira coupling can efficiently produce alkynes (Scheme 1A).[4] The C−H alkynylation of active hydrocarbons or those bearing directing groups with the preactivated alkynylating reagents such as alkynyl halides or hypervalent iodine reagents is also extensively used for the synthesis of alkynes (Scheme 1B).[5] Despite the high efficiency, those reactions highly depend on the transformation of organohalides/pseudohalides. The requirement for presynthesizing those starting materials also greatly decreases the step efficiency and the total atom utilization. Recently, the oxidative C−H alkynylation with terminal alkynes emerges as an alternative method (Scheme 1B).[6] However, besides the relatively narrow substrate scope, the oxidative conditions usually lead to the severe homocoupling issues of terminal alkynes.

Scheme 1. Transition Metal Catalyzed Cross Couplings Forming Internal Alkynes



Carboxylic acids are naturally abundant. They are also readily available in the synthetic world. Direct utilization of carboxylic acids for constructing functional molecules in organic synthesis attracts much attention from chemists.[7] During the past decades, great progress has been made. As for the synthesis of internal alkynes, decarboxylative coupling has been achieved by Su,[8] Tan,[9] and Jana[10] dependently (Scheme 1C); however, the three reactions were conducted under the oxidative conditions with the use of NBS, dioxygen and Ag_2CO_3/CuI as the oxidant, which also lead to the production of byproduct 1,3-diynes through homocoupling of terminal alkynes. In addition, steric and (or) electron-deficient carboxylic acids were required in order to facilitate the decarboxylation. Herein, we reported a redox-neutral reaction of carboxylic acids with terminal alkynes through decarbonylative coupling.[11] This reaction overcame those issues such as the use of overstoichiometric oxidants, homocouplings of terminal alkynes, and the narrow substrate scope of carboxylic acids encountered in the oxidative decarboxylative cou-

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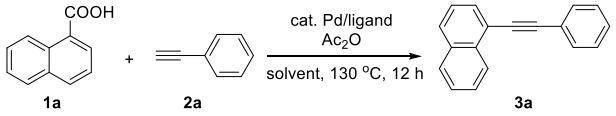
plings.[8−10] High tolerance of functional groups was also demonstrated, i.e., alkyl, MeO, CF_3O, TMS, F, Cl, CF_3, CN, carbonyl, sulfonamide, and heterocycles all survived well under the reaction conditions. These advantages are also the embodiment of sustainable chemical principles.[12]

A mixture of 1-naphthyl acid **1a** and phenyl acetylene **2a** dissolved in DME was allowed to react at 130 °C for 12 h in the presence of 2.5 mol % $Pd_2(dba)_3$, 10 mol % Xantphos (bis(diphenylphosphino)-9,9-dimethylxanthene), and 1.5 equiv of Ac_2O, producing decarbonylative coupling product **3a** in 85% yield (Table 1, entry 1). The palladium catalyst was essential to this reaction; no reaction was observed in its absence (Table 1, entry 2). $Pd(dba)_2$, $Pd(OAc)_2$, $Pd(TFA)_2$, and $PdCl_2$ could also efficiently mediate the reaction, though the yields decreased to some extent (Table 1, entries 3−6). The phosphine ligand was also pivotal.[13] Without any phosphine ligand, no **3a** was detected (Table 1, entry 7).

Table 1. Palladium-Catalyzed Decarbonylative Coupling of 1-Naphthyl Acids with Phenyl Acetylene[a]



1a 2a 3a

entry	cat. Pd	P ligand	solvent	yields (%)[b]
1	$Pd_2(dba)_3$	Xantphos	DME	85
2		Xantphos	DME	N.D.
3	$Pd(dba)_2$	Xantphos	DME	78
4	$Pd(OAc)_2$	Xantphos	DME	66
5	$Pd(TFA)_2$	Xantphos	DME	65
6	$PdCl_2$	Xantphos	DME	30
7	$Pd_2(dba)_3$		DME	N.D.
8	$Pd_2(dba)_3$	dppm	DME	trace
9	$Pd_2(dba)_3$	dppe	DME	16
10	$Pd_2(dba)_3$	dppp	DME	60
11	$Pd_2(dba)_3$	dppb	DME	46
12	$Pd_2(dba)_3$	dpph	DME	16
13	$Pd_2(dba)_3$	DPE-phos	DME	34
14	$Pd_2(dba)_3$	PPh_3	DME	trace
15	$Pd_2(dba)_3$	TFP	DME	trace
16	$Pd_2(dba)_3$	PPh_2Cy	DME	trace
17	$Pd_2(dba)_3$	PCy_3	DME	trace
18	$Pd_2(dba)_3$	Xantphos	dioxane	63
19	$Pd_2(dba)_3$	Xantphos	ECS	61
20	$Pd_2(dba)_3$	Xantphos	PhOMe	55
21	$Pd_2(dba)_3$	Xantphos	cyclohexane	77
22	$Pd_2(dba)_3$	Xantphos	toluene	64
23	$Pd_2(dba)_3$	Xantphos	NMP	44
24	$Pd_2(dba)_3$	Xantphos	DMF	29
25[c]	$Pd_2(dba)_3$	Xantphos	DME	N.D.
26[d]	$Pd_2(dba)_3$	Xantphos	DME	54
27[e]	$Pd_2(dba)_3$	Xantphos	DME	60
28[f]	$Pd_2(dba)_3$	Xantphos	DME	44
29[g]	$Pd_2(dba)_3$	Xantphos	DME	89
30[h]	$Pd_2(dba)_3$	Xantphos	DME	76

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv), Pd catalysts (5 mol % Pd), phosphine ligand (Pd/P = 1:4), anhydride (1.5 equiv), solvent (2 mL), 130 °C, 12 h, N_2 atmosphere. DME: 1,2-dimethoxyethane. ECS: ethylene glycol diethyl ether. [b]GC yields using tridecane as an internal standard. [c]Without Ac_2O. [d]Using Piv_2O instead of Ac_2O. [e]Using Boc_2O instead of Ac_2O. [f]At 120 °C. [g]At 140 °C. [h]Using 2 mol % Pd.

When dppm (bis(diphenylphosphino)methane), dppe (1,2-bis(diphenylphosph-ino)ethane), dpph (1,6-bis-(diphenylphosphino)hexane), and monodentate phosphine ligands such as PPh_3, TFP (tri(2-furyl)phosphine), PPh_2Cy, and PCy_3 were used, the reaction progressed sluggishly; the yield was also low with dppp (1,3-bis(diphenylphosphino)-propane), dppb (1,4-bis(diphenylphosphino)butane), and DPE-phos ((oxidi-2,1-phenylene)bis(diphenylphosphine)) (Table 1, entries 8−17). As for the solvents, the reaction also proceeded in cyclohexane, toluene, dioxane, ECS, PhOMe, NMP, and DMF (Table 1, entries 18−24). In the absence of Ac_2O, the reaction did not take place (Table 1, entry 25). Piv_2O and Boc_2O could also act as the in situ activator for carboxylic acids, furnishing **3a** in 54 and 60% yield, respectively (Table 1, entries 26 and 27). Finally, the reaction temperature was investigated. When the reaction was conducted at 120 °C, the yield of **3a** decreased quickly, while the reaction efficiency was almost not enhanced by further elevating the reaction temperature to 140 °C (Table 1, entries 28 and 29). Finally, reducing the loading of palladium catalyst to 2 mol % (1 mol % $Pd_2(dba)_3$) led to a slight decrease of the yield (Table 1, entry 30).

With the optimized reaction conditions at hand, the substrate scope was subsequently investigated. This palladium-catalyzed decarbonylative coupling is a rather general reaction. A variety of internal alkynes including those with functional groups were produced in good to high yields under the reaction conditions. Thus, derivatives of phenyl acetylenes bearing 2-methyl, 3-methyl, 4-methyl, 4-*tertiary*-butyl, 4-methoxy, and 4-phenyl groups produced the coupling products in high yields (Table 2, **3a**−**3g**). Fluoride and chloride survived well in the current catalytic system (Table 2, **3h**−**3k**). Substrates with electron-withdrawing groups such as CF_3 and CN also gave the expected alkynes in good yields (Table 2, **3l** and **3m**). Exemplified by 3-ethynylpridine, 3-ethynylthiophene, and 2-ethynylthiophene, heterocyclic aromatic alkynes also worked, furnishing the corresponding internal alkynes **3n**, **3o**, and **3p** in 44, 89, and 54% yields, respectively. In addition to aromatic terminal alkynes, conjugated enyne and aliphatic alkynes were also decarbonylatively arylated with the strategy (Table 2, **3q**−**3s**). Notably, by slightly tuning the reaction conditions, silyl terminal alkynes were also applicable to this reaction, giving the expected products in moderate yields (Table 2, **3t** and **3u**). Also worth noting is that those silyl alkynes could be easily transformed into other internal alkynes via protodesilylation and subsequent Sonogashira couplings or sila-Sonogashira couplings.[4b,14] However, when buta-1,3-diynylbenzene was used, only a trace amount of coupling product was detected under the reaction conditions (Table 2, **3v**).

Notably, compared with the oxidative decarboxylative alkynylation,[8−10] the scope of carboxylic acids was also rather general. Both electron-rich and electron-deficient benzoic acids underwent decarbonylative coupling with terminal alkynes under the similar reaction conditions. Thus, 2-naphthyl acid coupled with 4-methoxyphenyl acetylene readily to produce **3w** in 72% yield. Benzoic acid and its derivatives with valuable functional groups such as methyl, acetoxy, trifuloromethoxy, phenyl, fluoride, chloride, benzoyl, acetyl, and nitrile groups also proved to be the right substrate and coupled smoothly with terminal alkynes to give the decarbonylatively coupling products in moderate to high yields (Table 2, **3x**−**3ai**). Heteroaromatic carboxylic acids and cinnamic acid also

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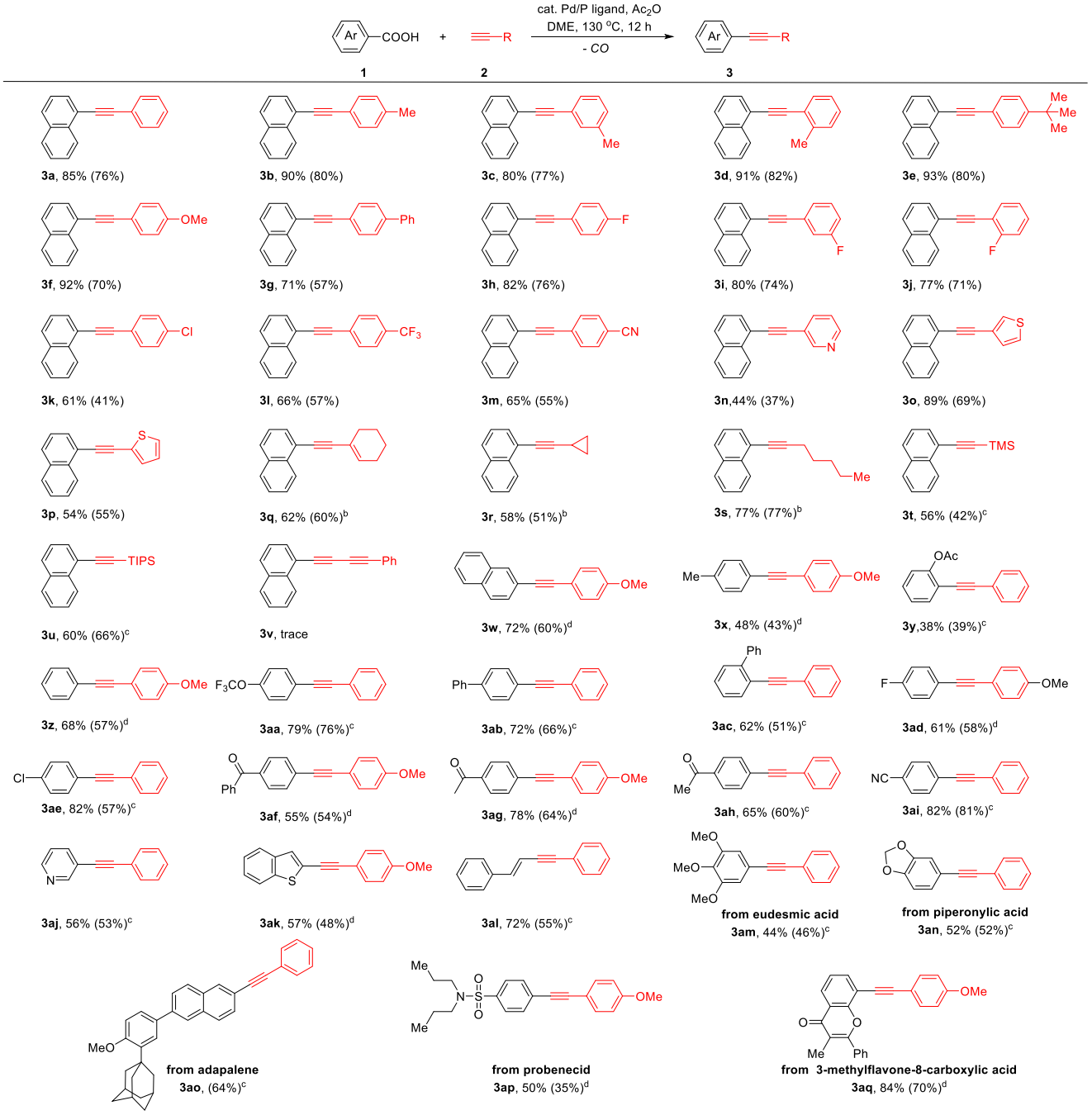
Table 2. Palladium-Catalyzed Decarbonylative Coupling of Aryl Acids with Terminal Alkynes[a]



[a]Reaction conditions: carboxylic acid **1** (0.2 mmol), alkyne **2** (1.5 equiv), $Pd_2(dba)_3$ (2.5 mol %), Xantphos (10 mol %), Ac_2O (1.5 equiv), DME (2 mL), 130 °C, 12 h, N_2 atmosphere. GC yields were reported using tridecane as the internal standard. The data in parentheses are the isolated yields. [b]Alkyne **2** (2 equiv), $Pd(dba)_2$ (5 mol %), Piv_2O (1.5 equiv), dioxane, 150 °C. [c]$Pd(dppp)Cl_2$ (5 mol %), dppb (10 mol %), CuI (10 mol %), Et_3N (1 equiv), Boc_2O (1.5 equiv), dioxane: Cy = 3:1, 120 °C. [d]Acid **1** (0.15 mmol), alkyne **2** (2 equiv), $PdCl_2$ (5 mol %), dppp (10 mol %), Piv_2O (1.5 equiv), dioxane, 150 °C, 16 h.

worked well in the current catalytic system, and the expected coupling products were obtained in moderate yields (Table 2, **3aj**−**3al**).

Practically, this reaction was applicable to the modification of bioactive carboxylic acids. For example, eudesmic acid and piperonylic acid were transformed into the expected internal alkynes by the strategy (Table 2, **3am** and **3an**). Adapalene, a clinic drug for the skin treatment of acne vulgaris with acne, papule, and pustule, was decarbonylatively alkylated readily in the current catalytic system (Table 2, **3ao**). Probenecid shows positive effect for chronic gout in clinic. It also coupled with phenyl acetylene readily to produce the corresponding internal alkynes (Table 2, **3ap**). 3-Methylflavone-8-carboxylic acid also served well to produce the coupling product in 84% yield under the present reaction conditions (Table 2, **3aq**).

The reaction mechanism is not fully understood at present. We proposed that this palladium-catalyzed decarbonylative coupling might take place as shown in Scheme 2.[11] Carboxylic

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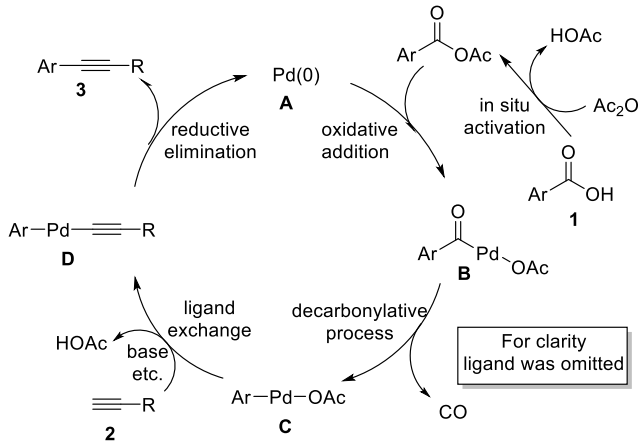
Scheme 2. Proposed Mechanism for the Palladium-Catalyzed Decarbonylative Coupling



acid was first activated in situ by acetic anhydride to produce an asymmetric anhydride,[15] followed by oxidative addition with Pd(0) complex and decarbonylation to generate species **C**. The resulting complex, **C**, underwent further ligand exchange with terminal alkynes to give intermediate **D**. Finally, reductive elimination of **C** afforded coupling product **3** and regenerated the active Pd(0) catalyst.[16]

In conclusion, we have disclosed an efficient palladium-catalyzed decarbonylative Sonogashira coupling. This is a redox neutral reaction, thus avoided the production of byproduct 1,3-diynes encountered under the oxidative reaction conditions.[6,8−10] The substrate scope was also general, i.e., a variety of carboxylic acids and terminal alkynes can be used in this reaction. We believe this reaction is a new relatively general method for preparing internal alkynes from the readily available and environment friendly chemicals. Along this line, works including scope, limitations, and mechanistic studies are underway in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00768.

General information, experimental procedures, characterized data, copies of ^{1}H and ^{13}C NMR spectroscopies (PDF)

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Notes

The authors declare no competing financial interest.

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