Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

Pd-Catalyzed Decarboxylative Sonogashira Reaction via Decarboxylative Bromination

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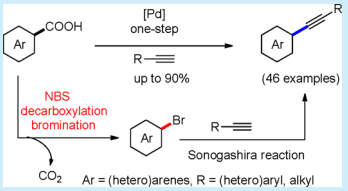
Supporting Information

ABSTRACT: The decarboxylative alkynylation of (hetero)aryl carboxylic acids with terminal alkynes has been achieved by using a $Pd(PPh_3)_4/PCy_3$ catalyst. This Pd-catalyzed method exhibits good functional group tolerance for both coupling partners and enables chemical modification of complex molecules. The establishment of this decarboxylative alkynylation reaction is attributed to the discovery of a highly selective decarboxylative bromination of (hetero)aryl carboxylic acids with NBS (*N*-bromosuccinimide).



(Hetero)aryl carboxylic acids are readily available in large structural diversity from nature and synthetic sources. Efforts to exploit the applications of (hetero)aryl carboxylic acids in organic syntheses have led to the discovery of a wealth of decarboxylative cross-coupling reactions.[1] In this context, aryl carboxylic acids are able to cross-couple with aryl halides,[2] organoboron reagents,[3] olefins,[4] and even aryl carboxylic acids[5] and functionalize the C−H bond of (hetero)arenes[6] through metal-promoted decarboxylation to form an aryl-metal intermediate. (Hetero)aryl carboxylic acids also participate in various metal-catalyzed carboxyl-directed *ortho*-C−H functionalization reactions,[7] of which products can be further elaborated via decarboxylative cross-coupling[8] or protodecarboxylation.[9] These decarboxylative cross-coupling reactions complement conventional cross-coupling reactions such as Suzuki−Miyaura coupling and provide a set of new possibilities for construction of the targeted compounds, especially in the cases where aryl halide starting materials are not easy to access. Despite this substantial progress, the decarboxylative cross-coupling of (hetero)aryl carboxylic acids with terminal alkynes to generate alkynylated (hetero)arenes has remained untouched to date.

In fact, alkynylated (hetero)arenes represent a class of attractive structural motifs due to their prevalence in natural products, pharmaceuticals, and organic materials[10] and their ability to function as versatile synthetic intermediates in useful chemical transformations.[11] The most popular and reliable method for the installation of alkyne moieties to aromatic rings is the Sonogashira reaction.[12] Recently, a series of metal-catalyzed C−H alkynylation reactions have emerged as a viable alternative to the Sonogashira reaction.[13−17] Generally, these C−H alkynylation reactions use the preactivated alkynylating reagents, such as alkynyl halides[13] and benziodoxolone-based hypervalent iodine reagents,[14] instead of terminal alkynes to avoid formation of a 1,3-diyne side product, with the exception of polyfluoroarenes, azoles,[15] thiophenes, indoles,[16] and arenes bearing bidentate directing groups.[17]

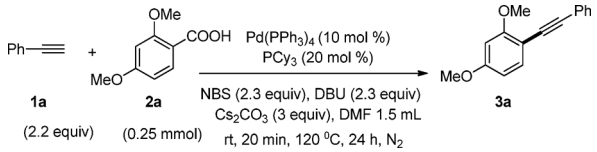
Successful strategies to achieve the C−H alkynylation reactions led us to consider whether the decarboxylative Sonogashira reaction of an aryl carboxylic acid with a terminal alkyne could be realized via in situ generation of an alkynyl bromide from a terminal alkyne or conversion of an aryl carboxylic acid to a more active reaction intermediate. The implementation of such a cascade reaction for decarboxylative Sonogashira reaction represents a great challenge due to the following reasons: (1) compatibility beween the formation reaction intermediate process and subsequent cross-coupling process; (2) lack of methods for conversion of relatively inert benzoic acids to an active intermediate. In this regard, Gooßen et al. reported pioneering work on the decarbonylative Heck reaction of aryl esters,[18] and very recently, Larrosa and co-workers established the oxidative cross-coupling reactions of benzoic acids via decarboxylative iodination of benzoic acids.[19] These seminal studies encouraged us to develop a tandem sequence for a decarboxylative Sonogashira reaction.

Herein, we provide a solution to this long-standing challenge and present a palladium-catalyzed method for synthesis of alkynylated (hetero)arenes via a decarboxylative cross-coupling of (hetero)aryl carboxylic acids with terminal alkynes. Initially, we chose the reaction of phenylacetylene **1a** with 2,4-dimethoxybenzoic acid **2a** as a model system to examine the possibility of our proposed decarboxylative Sonogashira reaction (Table 1). After screening palladium precursors, ligands, solvents, oxidants, and additives, we found that the use of $Pd(PPh_3)_4$ as the precatalyst, tricyclohexylphosphine (PCy_3) as the ligand, Cs_2CO_3 as the base, NBS (*N*-bromosuccinimide) as the oxidant, and DBU (1,8-diazabicyclo-[5.4.0]-7-undecene) as the additive in DMF was optimal to generate the desired product. With the optimized conditions, the desired decarboxylative alkynylation product **3a** could be isolated in 75% yield from the reaction system that was stirred

Received: March 7, 2018

DOI: 10.1021/acs.orglett.8b00772
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Selected Reaction Development



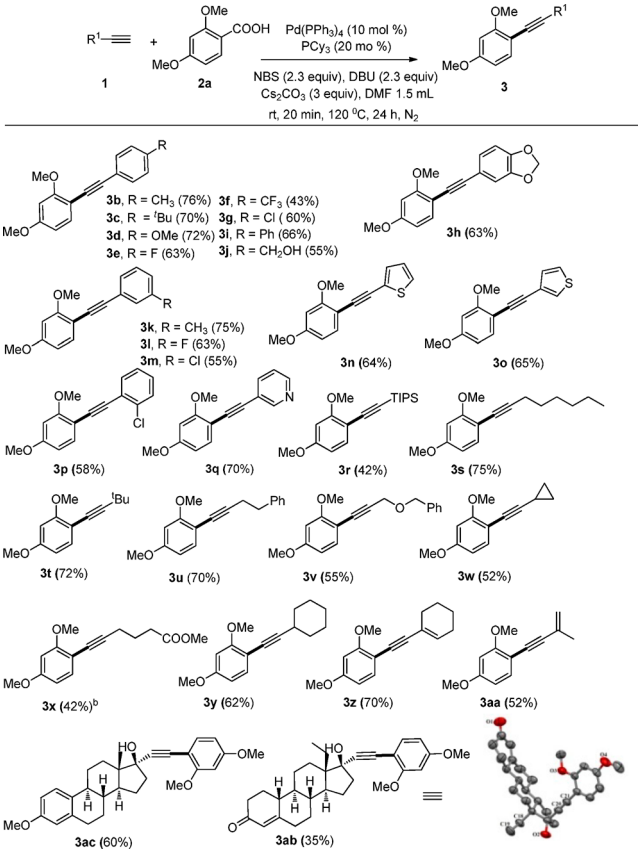
entry	variations from standard conditions	isolated yield (%)
1	none	75
2	w/o 20 min stirring at rt	48
3	w/o $Pd(PPh_3)_4$	0
4	w/o NBS	0
5	w/o DBU	25

for 20 min at room temperature and then heated at 120 °C for 24 h (Table 1, entry 1). Omitting the 20 min of stirring at room temperature led to a decrease in yield (Table 1, entry 2). Control experiments revealed that no product was formed in the absence of $Pd(PPh_3)_4$ or NBS, implying the vital roles of these two reaction components (Table 1, entries 3 and 4). Removing DBU from the reaction system significantly reduced the yield to 25% (Table 1, entry 5). Although DBU was present as a base in the reaction system, Cs_2CO_3 is essential for the desired reaction; a 53% yield was obtained in the absence of the PCy_3 ligand, indicating that an additional ligand exerted a beneficial effect on this reaction. Surprisingly, the choice of palladium source is important for this reaction. The use of $Pd(OAc)_2$ and $Pd_2(dba)_3$ gave no product. Analogues of NBS, namely, NIS and NCS, did not work for this reaction.

With this established reaction system in hand, we evaluated the substrate scope with respect to alkynes (Scheme 1). As illustrated, the phenylacetylenes contains electron-donating groups such as methyl, *tert*-butyl, or methoxy at the para or meta positions of the aryl rings were efficiently coupled with the benzoic acid, producing the desired products with good yields (**3b**, **3c**, **3d**, **3k**). Electron-rich disubstituted phenylacetylene also furnished high yield product (**3h**). Notably, the hydroxymethyl group, which is rarely tolerated by the Pd-catalyzed oxidative cross-coupling reaction, remained intact in this decarboxylative alkynylation reaction with a 55% yield obtained (**3j**). Phenylacetylenes bearing electron-withdrawing groups such as chloro, fluoro groups at the para or meta positions also smoothly underwent reaction to furnish the corresponding products in good yields (**3e**, **3g**, **3l**, **3m**). 1-Ethynyl-4-(trifluoromethyl)benzene, which is a weak nucleophile because of its strong electron-withdrawing trifluoromethyl group, could be used as an alkynylating reagent, albeit in slightly diminished yield (**3f**). The heteroaryl-substituted alkynes also served as suitable coupling partners to offer high-to-good yields, as exemplified by **3n**, **3o**, and **3q**.

Further, we expanded the scope of alkynes beyond (hetero)aryl acetylenes. The silyl-protected (triisopropylsilyl)-acetylene produced an alkynylated arene in synthetically useful yield (**3r**). A broad range of aliphatic alkynes proved to be efficient alkynylating reagents (**3s**–**3y**) and cyclohexenyl-substituted alkynes also smoothly participated in the reaction (**3z**), fully exhibiting the generality of this decarboxylative alkynylation reaction. It is noteworthy that the decarboxylative cross-coupling product from methyl hex-5-ynoate (**3x**), which is a useful synthetic intermediate,[20] could be prepared on gram scale in 42% yield by virtue of this decarboxylative alkynylation reaction. To further investigate the flexibility of this protocol in the synthesis of natural product analogues or the decoration of

Scheme 1. Substrate Scope of Alkynes in Pd-Catalyzed Decarboxylative Sonogashira Reaction[a]



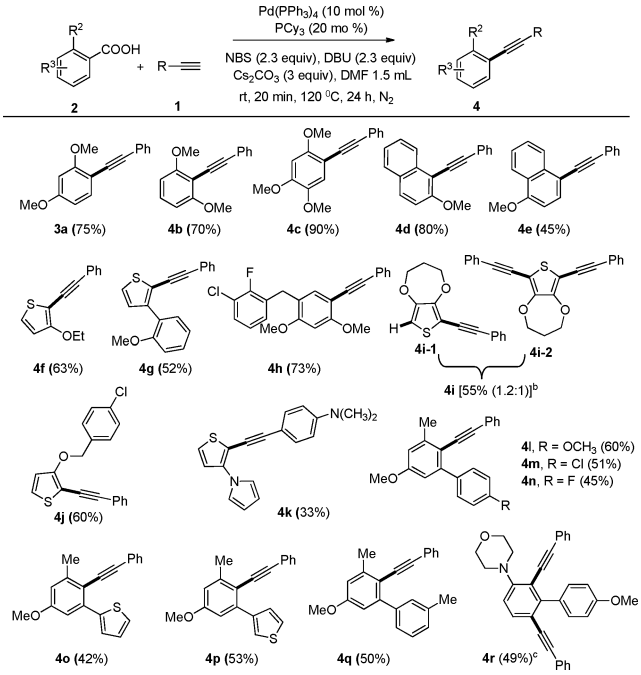
[a]Reaction conditions: **2a** (0.25 mmol), **1** (2.2 equiv), $Pd(PPh_3)_4$ (10 mol %), PCy_3 (20 mol %), Cs_2CO_3 (3 equiv), NBS (2.3 equiv), DBU (2.3 equiv), DMF (1.5 mL). After being stirred for 20 min at room temperature, the reaction system is heated with stirring at 120 °C for 24 h, under a N_2 atmosphere. All yields are isolated ones. [b]5 mmol scale, yield of isolated product: 0.55 g.

the pharmaceuticals, our protocol was applied to the synthesis of **3aa** that was the analogue of Antrocamphin A, which is a potentially useful chemical compound for anti-inflammatory activities.[21] As demonstrated in the cases of **3ab** and **3ac**, our protocol also enabled decoration of complex pharmaceutical molecules containing a terminal alkyne moiety, that is, Levonorgestrel and Mestranol.[22]

Subsequently, we investigated the substrate scope of this decarboxylative Sonogashira reaction with regard to the benzoic acids (Scheme 2). Electron-rich aryl carboxylic acids underwent decarboxylative cross-coupling with phenylacetylene to give the corresponding products in good-to-excellent yields (**3a**, **4b**, **4c**). Naphthoic acids also participated in this transformation to obtain satisfying yields (**4d**, **4e**). Aryl carboxylic acids containing chloro and fluoro groups worked very well in 73% yield (**4h**). Heteroaryl carboxylic acids were also suitable substrates in this decarboxylative Sonogashira reaction (**4f**, **4g**, **4i**–**4k**). Thiophene containing dicarboxyl groups were observed to produce a mixture of mono- and dialkynylated products **4i**. Pyrrol-substituted thiophene-2-carboxylic acid, which was very reluctant to undergo decarboxylation, participated in the decarboxylative alkynylation to give the corresponding product in synthetically useful yield (**4k**). Currently, 2-arylbenzoic acids are readily accessible through

DOI: 10.1021/acs.orglett.8b00772
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 2. Substrate Scope of (Hetero)aryl Carboxylic Acids in Pd-Catalyzed Decarboxylative Sonogashira Reaction[a]

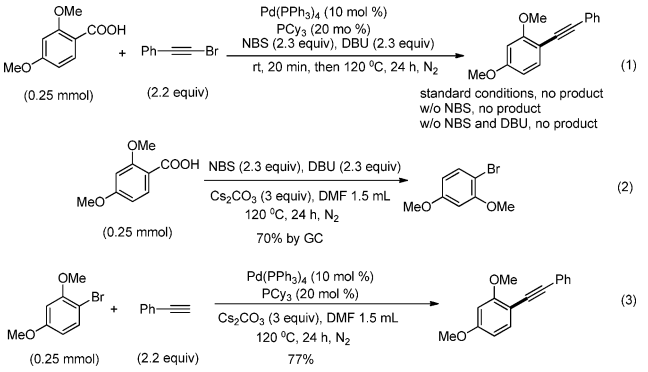


[a]Reaction conditions: **2** (0.25 mmol), **1** (2.2 equiv), $Pd(PPh_3)_4$(10 mol %), PCy_3 (20 mol %), Cs_2CO_3 (3 equiv), NBS (2.3 equiv), DBU (2.3 equiv), DMF (1.5 mL). After being stirred for 20 min at room temperature, reaction system is heated with stirring at 120 °C for 24 h, under a N_2 atmosphere. All yields are isolated ones. [b]**1a** (4 equiv), Cs_2CO_3 (4 equiv), NBS (4.2 equiv), DBU (3 equiv). [c]**1a** (4 equiv), NBS (4 equiv), and 4′-methoxy-3-morpholino-[1,1′-biphenyl]-2-carboxylic acid used as a substrate.

carboxyl-directed C−H arylation.[7a,c,e] A series of 2-arylbenzoic acids were synthesized and verified to undergo the decarboxylative alkynylation reaction (**4l**−**4r**) to furnish *ortho*-alkynylated biphenyls that are useful precursors to organic materials and bioactive molecules.[23] 2-Arylbenzoic acid containing an amino substituent afforded dialkynylated product **4r**.

Mechanistic investigations were performed to understand the decarboxylative alkynylation of (hetero)aryl carboxylic acids with terminal alkynes. (Bromoethynyl)benzene was used in place of phenylacetylene to react with 2.4-dimethoxybenzoic acid under the standard conditions, which did not give any of the decarboxylative alkynylation product (Scheme 3, eq 1). Moreover, after removal of NBS or both NBS and DBU from the reaction system, the reaction of (bromoethynyl)benzene with 2.4-dimethoxybenzoic acid under otherwise identical conditions did not give any alkynylation product either. These observations ruled out the possibility that the decarboxylative alkynylation reaction occurs via in situ generation of alkynyl bromide from the reaction of a terminal alkyne, NBS, and DBU.[24] However, we found that the reaction of 2.4-dimethoxybenzoic acid (0.25 mmol) with 2.3 equiv of NBS in the presence of Cs_2CO_3 (3 equiv) and DBU (2.3 equiv) at 120 °C for 24 h produced 1-bromo-2,4-dimethoxybenzene in 70% GC yield (Scheme 3, eq 2). Notably, the newly found decarboxylative bromination reaction of aryl carboxylic acids with NBS has an advantage of high selectivity for monobrominated arenes over the previously reported methods,[25] exhibiting great potential to simplify the synthesis of valuable

Scheme 3. Mechanism Study in Pd-Catalyzed Decarboxylative Sonogashira Reaction



aryl bromides with good selectivity starting from abundant aryl carboxylic acids.

Furthermore, we observed the aryl bromide species in the reaction mixture when the reaction was carried out for 2 h. The cross-coupling of aryl bromide with a terminal alkyne could take place in 77% isolated yield (Scheme 3, eq 3). These findings suggested that our Pd-catalyzed decarboxylative Sonogashira reaction likely proceeded via decarboxylative bromination of aryl carboxylic acid with NBS to generate aryl bromide and a subsequent Sonogashira reaction of aryl bromide with terminal alkyne. In the absence of NBS and an alkyne, the decarboxylative protonation of aryl carboxylic acids did not occur under otherwise identical conditions, which excluded the possibility that the decarboxylative alkynylation reaction proceeded through decarboxylative protonation and the subsequent bromination of the resultant arene with NBS.

In conclusion, we have developed the first example of the Pd-catalyzed decarboxylative alkynylation reaction of aryl carboxylic acids with terminal alkynes. This method exhibited a broad substrate scope with respect to both coupling partners and enabled the late-stage elaboration of complex pharmaceutical molecules and the preparative synthesis of useful compounds. The mechanistic investigations disclosed that this decarboxylative cross-coupling reaction proceeded via decarboxylative bromination of (hetero)aryl carboxylic acid with NBS and Sonogashira reaction of the in situ generated aryl bromide. The decarboxylative bromination discovered by us, in combination with the cross-coupling of aryl bromides, would allow for the development of a variety of decarboxylative cross-coupling reactions since aryl bromides are versatile building blocks in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00772.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1815934 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge

DOI: 10.1021/acs.orglett.8b00772
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the NSFC (21431008, 21332001, u1505242, and 21602221), the CAS/SAFEA International Partnership Program for Creative Research Teams, the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB20000000), and the Key Research Program of Frontier Sciences, CAS (QYZDJ-SSW-SLH024).

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DOI: 10.1021/acs.orglett.8b00772
Org. Lett. XXXX, XXX, XXX−XXX