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SHORT COMMUNICATION

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Palladium-Catalyzed Decarboxylative C–H Bond Arylation of Furans

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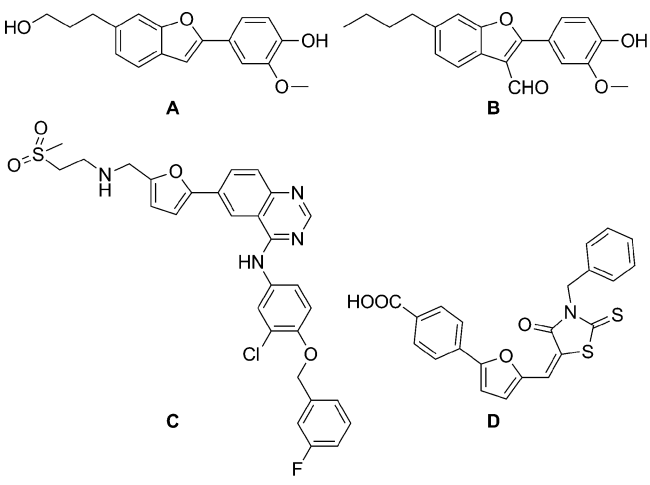
A $Pd/PCy_3/Ag_2CO_3$ (Cy = cyclohexyl) catalytic system was found to promote decarboxylative arylation through the combination of decarboxylation and C–H bond functionalization. This protocol features a good substrate scope of aromatic carboxylic acids as well as a broad range of functional groups and provides the products in high yields.

Introduction

2-Arylfuran has proven to be a useful structural motif in the development of syntheses of bioactive natural products, medicines, and functional organic materials. Four important 2-arylfuran-containing molecules are exemplified in Scheme 1.



Scheme 1. Four instances show the importance of 2-arylfurans as a significant part in compounds: adenosine receptor **A**, a drug isolated from a plant that serves as a route to intervene the biological behavior of blood platelet; adenosine antagonist **B**, which was found to be a potent antagonist of **A**; synergistic antitumor agent **C**; medicine **D**, named Leukadherin 1, which is used to increase CD11b/CD18-dependent adhesion through membrane tethers.[1]

The wide application of 2-arylfurans provides the continuous impetus for the synthetic chemist to seek simple and valid methods to construct them. As a result, traditional methods developed for the synthesis of 2-arylfurans include the transition-metal-catalyzed cross-coupling reactions of heterohalides with aryl organometallic reagents. In recent years, the rapid development of C–H bond functionalization has provided new opportunities for the construction of 2-arylfurans. In this context, the direct C–H arylation of furans with aryl halides has been achieved by using Pd, Rh, and Cu catalysts.[2] In these catalytic systems, expensive furyl organometallic reactants in traditional cross-coupling reactions were replaced by furans directly. The oxidative cross-coupling of a heterocycle and a unfunctionalized arene as an efficient method of forming 2-arylfurans has been recently achieved in the palladium-catalyzed reactions of furans.[3] Although some interesting work has been done in this area, there is still significant room to explore a new approach with high generality and functional group tolerance.

In recent years, aromatic carboxylic acids as the starting materials have been used widely in cross-coupling reactions owing to their versatile characteristics such as low cost and existing availability. Decarboxylative C–H bond functionalization has also been explored in the last few years. To achieve decarboxylative C–H bond functionalization, two procedures involving decarboxylation and direct C–H bond functionalization must be implemented. Therefore, two types of side reactions, dimerization and protonation, frequently happen in decarboxylative C–H bond functionalization, which leads to a low efficiency of this transformation.[4] How this transformation can be achieved is still a challenging goal. Herein, we develop a $Pd(tfa)_2/PCy_3/Ag_2CO_3$ (Cy = cyclohexyl, tfa = trifluoroacetate) system in which electron-rich and electron-deficient benzoic acids bearing a broad range of functional groups are tolerated to catalyze the decarboxylative C–H bond arylation of furans. Notably, in addition to furans, pyrroles and thiazoles are also suitable substrates in our reaction.

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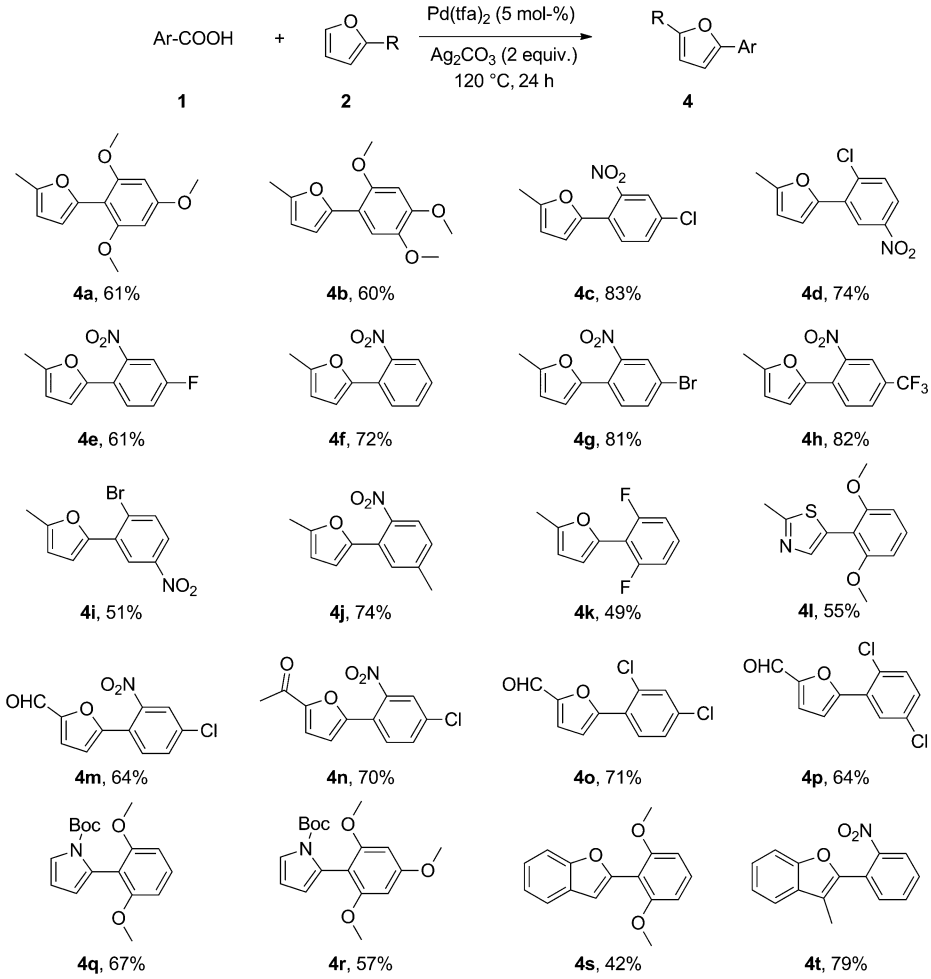
Results and Discussion

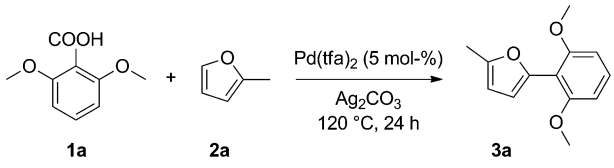
We previously reported various Pd-catalyzed decarboxylative C–H bond functionalization reactions of heterocycles.[5] On the basis of this research, we intended to apply this protocol to a broader range of heterocycles with unprecedented substrates. Consequently, we chose the reaction of 2,6-dimethoxybenzoic acid with 2-methyluran as a model reaction, and screening experiments were done to obtain better reaction conditions. Table 1 shows the yields of the isolated products obtained under different reaction conditions, and the results indicate that temperature, solvent, the phosphine ligand, and the ratio of **1a** and **2a** had more or less an effect on the transformation.[6] What satisfied us was that if a **1a**/**2a** ratio of 1:1.5 was used in the DMSO/1,2-dimethoxyethane (DME, 2:18) solvent system at 120 °C in the presence of $Pd(tfa)_2$ (5 mol-%), PCy_3 (10 mol-%), and Ag_2CO_3 (2 equiv.), the product could be isolated in 57% yield. After changing the ratio of DMSO to DME or dioxane in the mixed solvent system, we obtained different amounts of **3a** under related conditions. Finally, if a **1a**/**2a** ratio of 1.5:1 was used in DMSO/DME (3:17), we achieved high yield of the product (Table 1, entry 5). Under other conditions, no matter which factor was changed, we could not obtain a higher yield than that obtained with these aforementioned conditions.[7] We tried to use $Pd(OAc)_2$ instead of $Pd(tfa)_2$, but the result was slightly inferior. $Pd(PPh_3)_2Cl_2$ gave an even worse result. Eventually, we chose $Pd(tfa)_2$ as the catalyst for the decarboxylative C–H bond arylation of furans. Additionally, PCy_3 also played an irreplaceable role in enhancing the efficiency of the reaction.

With the optimized reaction conditions in hand, we examined the scope of the furans with different functional groups (Scheme 2). Substrate bearing ketone and aldehyde substituents provided the desired products in ideal yields, and the functional groups were preserved (see **4m**–**p**). In addition to furans, 1-Boc-pyrrole (Boc = *tert*-butoxycarbonyl) also smoothly underwent this reaction to generate the corresponding products in good yields (see **4q** and **4r**). Furthermore, 2-methylthiazole, an important type of heterocyclic compound, was also an appropriate reactant for the reaction (see **4l**). To the best of our knowledge, the use of pyrroles and thiazoles as coupling partners in decarboxylative C–H functionalization reactions is unprecedented.



Scheme 2. Scope of the aromatic carboxylic acids and furans. Reaction conditions: $Pd(tfa)_2$ (5 mol-%), PCy_3 (10–15 mol-%), Ag_2CO_3 (2 equiv.), solvent, (2 mL), 120 °C, 24 h, yields of isolated products are given.

Table 1. Selected results from the optimization studies for the decarboxylative C–H arylation of 2-methylfuran with 2,6-dimethoxybenzoic acid.[a]



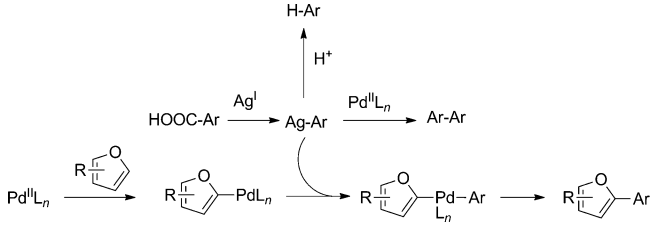
1a 2a 3a

Entry	1a/2a [mol/mol]	Ligand	Solvent (v:v)	Yield[b]
1	1:1.5	PCy_3	DMSO/DME (2:18)	57
2	1:1.5	PCy_3	DMSO/DME (3:17)	60
3	1:1.5	PCy_3	DMSO/dioxane (2:18)	48
4	1:1.5	PCy_3	DMSO/dioxane (3:17)	43
5	1.5:1	PCy_3	DMSO/DME (3:17)	69
6	1.5:1	PCy_3	DMSO/DME (4:16)	59
7	1.5:1	PCy_3	DMSO/dioxane (2:18)	43
8	1.5:1	PCy_3	DMSO/dioxane (3:17)	61
9	1.5:1	PCy_3	DMSO/dioxane (4:16)	49
10	1.5:1	PCy_3	DMSO/DMF (1:20)	10
11	2:1	PCy_3	DMSO/DME (3:17)	58
12	5:2	PCy_3	DMSO/DME (3:17)	62
13[c]	1.5:1	PCy_3	DMSO/DME (3:17)	45
14[d]	1.5:1	PCy_3	DMSO/DME (3:17)	12
15	1.5:1	XPhos[e]	DMSO/DME (3:17)	52
16	1.5:1	SPhos[f]	DMSO/DME (3:17)	47
17	1.5:1	–	DMSO/DME (3:17)	23

[a] Reaction conditions: $Pd(tfa)_2$ (5 mol-%), phosphine ligand (10 mol-%), Ag_2CO_3 (2 equiv.), solvent (2 mL), 120 °C, 24 h. [b] Yield of isolated product. [c] $Pd(OAc)_2$ was used instead of $Pd(tfa)_2$. [d] $Pd(PPh_3)_2Cl_2$ was used instead of $Pd(tfa)_2$. [e] XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. [f] SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

In the established catalytic system, a series of aromatic carboxylic acids furnished the corresponding coupling products. Unfortunately, non-*ortho*-substituted aromatic carboxylic acids did not afford the coupling products owing to their poor reactivity in the decarboxylation relative to that of *ortho*-substituted aromatic carboxylic acids.

According to related work on decarboxylative C–H bond functionalization, a proposed mechanism for the decarboxylative C–H arylation of furans is shown in Scheme 3. This reaction may involve Pd-mediated C–H cleavage of furan to form a palladium intermediate. Meanwhile, an aryl–Ag species forms through Ag-promoted decarboxylation of the aromatic carboxylic acid, and subsequently, transmetalation occurs between Ag and Pd, which is followed by reductive elimination to obtain the desired product. The Pd^0 species is then oxidized to Pd^{II} by the silver salt. A major problem preventing a successful reaction from proceeding is what we speculate to be an unstable aryl silver intermediate that can easily undergo protodecarboxylation[8] and decarboxylative homocoupling. To avoid these side reactions and facilitate the desired coupling reactions, the reaction conditions must be adjusted so that the speed of the Ag-mediated decarboxylation can be controlled, which thus makes it easier for the palladium intermediate to capture the silver intermediate. Pioneering work in our group shows that some factors including solvent, temperature, and silver salts can have some significant effects on this transformation.[9]



Scheme 3. Proposed mechanism for the decarboxylative C–H arylation of furans.

Experimental Section

Typical Procedure: In a glove box, a 25 mL tube equipped with a stir bar was charged with $Pd(tfa)_2$ (0.01 mmol), PCy_3(0.02 mmol), 2,6-dimethoxybenzoic acid (0.2 mmol), 2-methylfuran (0.3 mmol), Ag_2CO_3 (0.4 mmol), DMSO (0.3 mL), and DME (1.7 mL). The tube was fitted with a Teflon® screw cap and removed from the glove box. The reaction mixture was stirred at 120 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with diethyl ether and filtered through a silica gel pad. The filtrate was washed with water, and the organic phase was dried with Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel to provide desired product **3a** in 69% yield.

Supporting Information (see footnote on the first page of this article): All the experimental procedures, characterization data, and the copies of the ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra.

Acknowledgments

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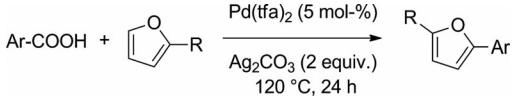
Decarboxylation



A $Pd/PCy_3/Ag_2CO_3$ catalytic system promoting decarboxylative arylation through the combination of decarboxylation and C–H bond functionalization is reported. This protocol features a good substrate scope of aromatic carboxylic acids containing a broad range of functional groups and provides the products in high yields; Cy = cyclohexyl, tfa = trifluoroacetate.

Keywords: Synthetic methods / Cross-coupling / Decarboxylation / C–H arylation / Palladium

