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Palladium-Catalyzed Decarbonylative Cross-Coupling of Azinecarboxylates with Arylboronic Acids

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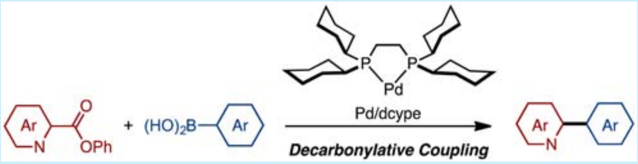
Supporting Information

ABSTRACT: The first palladium-catalyzed decarbonylative coupling of phenyl 2-azinecarboxylates and arylboronic acids is presented. The key for the development of this decarbonylative coupling is the use of Pd/dcype as a catalyst. A wide range of 2-azinecarboxylates can undergo the present coupling reaction to afford 2-arylazines. By combination with previously reported nickel-catalyzed decarbonylative coupling, we achieved a chemoselective sequential decarbonylative coupling of pyridine dicarboxylate to synthesize 2,4-diarylpyridine.



Nitrogen-containing heterobiaryls such as arylpyridines, arylpyrazines, and arylquinolines are important frameworks and are widely used as pharmaceuticals as well as ligands in metal catalysts.[1] Therefore, the development of efficient synthetic methods allowing facile access to such heterobiaryls is of significant importance in the field of synthetic chemistry. To synthesize these frameworks, a metal-catalyzed cross-coupling of (hetero)aryl halides and (hetero)aryl metals is regarded as one of the most reliable synthetic methods (Figure 1).[2] However, the use of haloazines as aryl electrophiles inevitably generates caustic halogen waste after the coupling reaction, and some haloazines are expensive.

Recently, arenecarboxylates and arenecarboxylic acids have gained significant interest as new aryl-coupling partners in biaryl synthesis since arenecarboxylates are inexpensive and readily available both synthetically and commercially.[3] Moreover, employing carboxylates in cross-coupling can avoid production of halogen waste. Therefore, the use of heteroarenecarboxylates instead of the corresponding heteroaryl halides is advantageous from both synthetic and environmental points of view. In 2006, the Goßen group reported that aryl carboxylic acids can be coupled with aryl halides using a Pd/Cu bimetallic catalyst.[4] Since this pioneering study, various decarboxylative[5] and decarbonylative[6] biaryl cross-couplings have been reported. Our group also contributed to this area by developing the first nickel-catalyzed decarbonylative biaryl coupling of aromatic esters and arylboronic acids.[7] In this reaction, arenecarboxylates work as alternative aryl electrophiles to haloarenes. This method allowed for the synthesis of a variety of (hetero)biaryls; however, the reaction was not applicable to 2-azinecarboxylates. Herein, we report a new protocol to realize the decarbonylative coupling of 2-azinecarboxylates and arylboronic acids by a palladium catalyst.

We began our study to develop the decarbonylative coupling of 2-azinecarboxylate by investigating the reaction conditions of phenyl picolinate (**1A**) and *p*-anisylboronic acid (**2a**) (Table 1). Attempts using nickel catalysts with several phosphine ligands such as P(n-Bu)$_3$ resulted in less than 20% yield of desired coupling product **3Aa** (Table 1, entry 1). Ni/dcype (dcype: 1,2-bis(dicyclohexylphosphino)ethane), which was previously reported to be effective for decarbonylative coupling also gave a poor result (Table 1, entry 2).[8] Next, we turned our attention to use palladium catalysts. As a result, the combination of Pd(OAc)$_2$ and P(n-Bu)$_3$ improved the reaction yield to 38% yield (Table 1, entry 3). Fortunately, the use of a palladium catalyst led to lowering the reaction temperature to 130 °C (Table 1, entry 4). Through careful ligand screening, we found that dcype is the most effective ligand, producing 2-

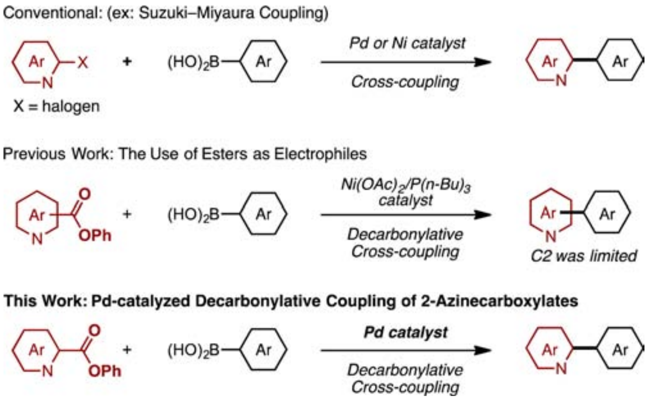


Figure 1. Cross-coupling to construct 2-arylazines.

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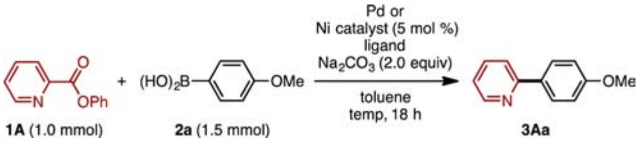
Table 1. Effect of Parameters



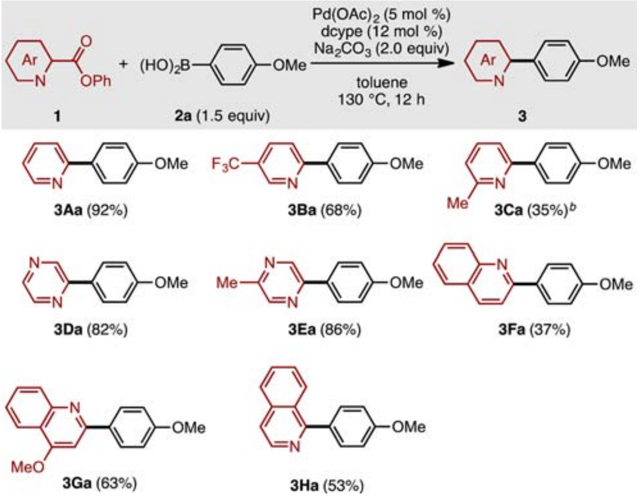
entry	catalyst	ligand	temp	**3Aa**, yield (%)[b]
1	$Ni(OAc)_2$	P(*n*-Bu)$_3$	150	12
2	$Ni(OAc)_2$	dcype	150	12
3	$Pd(OAc)_2$	P(*n*-Bu)$_3$	150	38
4	$Pd(OAc)_2$	P(*n*-Bu)$_3$	130	48
5	$Pd(OAc)_2$	PCy_3	130	7
6	$Pd(OAc)_2$	PPh_3	130	13
7	$Pd(OAc)_2$	dcype	130	97
8	$Pd(OAc)_2$	dcypt	130	<2
9	$Pd(OAc)_2$	dppe	130	11

[a] Unless otherwise noted, the reaction conditions were as follows: **1A** (1.0 mmol), **2a** (1.5 equiv), $Ni(OAc)_2$ or $Pd(OAc)_2$ (5 mol %), ligand (monodentate: 20 mol %, bidentate: 12 mol %), Na_2CO_3 (2.0 equiv), toluene (4.0 mL), 130 or 150 °C, 18 h. [b] Yields were determined by ^1H NMR analysis using CH_2Br_2 as an internal standard.

arylpyridine **3Aa** in almost quantitative yield (Table 1, entry 7). Structurally similar ligands, dcypt (3,4-bis(dicyclohexylphosphino)thiophene)[9] and dppe (1,2-bis(diphenylphosphino)ethane), did not work well for the reaction (Table 1, entries 8 and 9). Finally, we identified optimal conditions using the $Pd(OAc)_2$/dcype catalyst and Na_2CO_3 as the base in toluene at 130 °C.

With the optimized conditions in hand, substrate generality of the reaction was examined regarding azine carboxylates (Scheme 1). The reaction is applicable to picolinates bearing both electron-donating and electron-withdrawing substituents, whereas the reaction yield of an electron-rich substrate was relatively low. Quinoline-, isoquinoline-, and pyrazinecarboxylates can also be coupled with **2a** to afford 2-arylazines. It is worth mentioning that these azinecarboxylates are readily available and less expensive than their halogen congeners. For example, pyrazine carboxylic acid is approximately 100 times cheaper than bromopyrazine, representing the benefit of using azinecarboxylates as alternative coupling agents to conventional halogen-based agents.

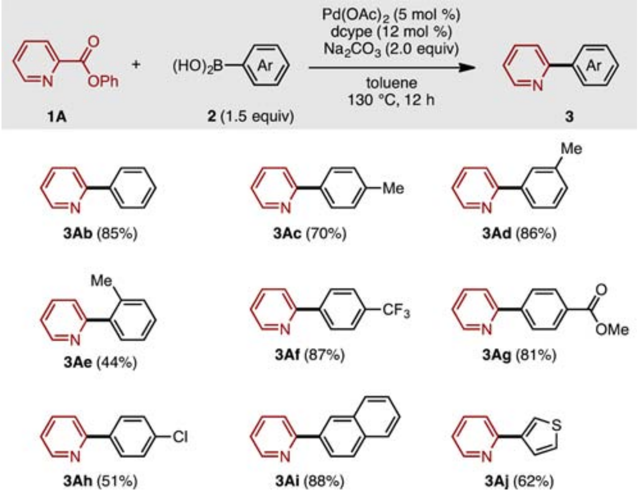
Scheme 1. Substrate Scope of 2-Azinecarboxylates



[a] Reaction conditions: **1** (1.0 mmol), **2a** (1.5 equiv), $Pd(OAc)_2$ (5 mol %), dcype (12 mol %), Na_2CO_3 (2.0 equiv), toluene (4.0 mL), 130 °C, 12 h. [b] 41% of 2-azinecarboxylate **1C** was recovered.

A variety of arylboronic acids can undergo the decarbonylative coupling under the present catalytic conditions (Scheme 2). *p*-, and *m*-tolylboronic acid can participate in the present coupling reaction, but *o*-tolyl product **3Ae** was only obtained in moderate yield owing to its steric bulk. As for the electronic influence of arylboronic acids, azinecarboxylates possessing both electron-donating and -withdrawing groups can cross-couple with arylboronic acid. C−Cl bonds are compatible and remained unscathed on coupling product **3Ah**. π-Extended aryl and heteroarylboronic acids are also applicable to the decarbonylative coupling. Similar to our previous nickel-catalyzed decarbonylative coupling, this palladium catalytic system selectively reacted with phenyl esters, as methyl esters were completely unreactive.

Scheme 2. Substrate Scope of Arylboronic Acids



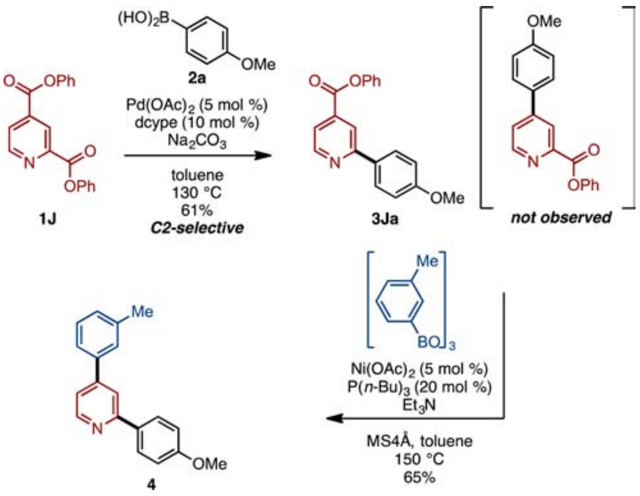
[a] Reaction conditions: **1A** (1.0 mmol), **2** (1.5 equiv), $Pd(OAc)_2$ (5 mol %), dcype (12 mol %), Na_2CO_3 (2.0 equiv), toluene (4.0 mL), 130 °C, 12 h.

We further evaluated whether the present catalytic reaction can be applied for nicotinate **1I** (Scheme 3). In the case of **1I**, $Pd(OAc)_2$/dcype catalyst was not effective, but we found that the use of P(*n*-Bu)$_3$ ligand instead of dcype could realize the decarbonylative coupling of **1I** to afford 3-arylpyridine **3Ib** in 55% yield.

Scheme 3. Ligand Effect for Decarbonylative Coupling of 1I

Guided by the fact that $Pd(OAc)_2$/dcype can selectively work for 2-azinecarboxylates, we envisioned that it would be possible to conduct a sequential decarbonylative biaryl coupling

Scheme 4. Diarylpyridine Synthesis by Sequential Decarbonylative Coupling



of diphenyl 2,4-pyridine dicarboxylate (**1J**) (Scheme 4). The first palladium-catalyzed coupling reaction at the C2 position of the pyridine smoothly provided 2-arylpyridine **3Ja** in 61% yield. In this reaction, 4-arylpyridine was not detected at all as judged by ^{1}H NMR analysis. Transformation of the remaining ester functionality was accomplished by nickel-catalyzed decarbonylative coupling at the C4 position of the pyridine to provide 2,4-diarylpyridine **4** in 65% yield.[11] Thus, the developed ester-based coupling reactions would be potentially useful for the selective synthesis of highly arylated pyridines.

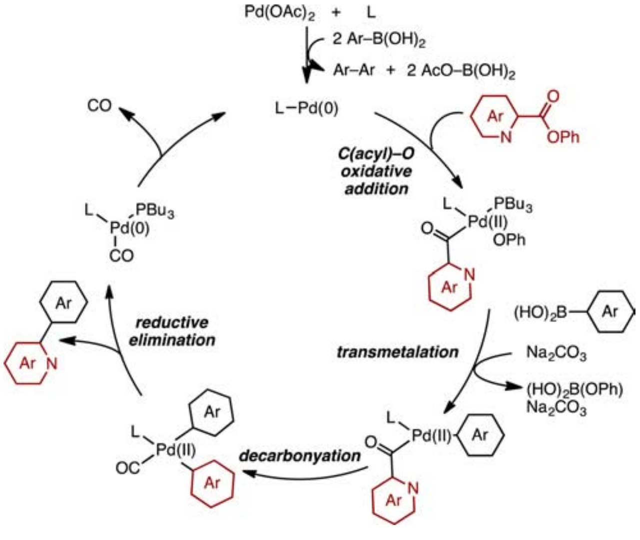


Figure 2. Plausible reaction mechanism.

A plausible mechanism of the present coupling reaction, which is based on our previous nickel catalysis, is shown in Figure 2.[7,10] First, an active Pd(0) species would be generated by dimerization of arylboronic acids.[12] To this Pd(0) species, the C(acyl)−O bond of the ester undergoes oxidative addition to give an acyl−Pd(II) species. Then, diarylpalladium would be generated by transmetalation of arylboronic acids using base, followed by CO migration. Finally, reductive elimination affords the desired biaryl product and Pd(0)−CO, which can then decarbonylate to regenerate the active Pd(0) species.

In summary, we have developed a palladium-catalyzed decarbonylative biaryl coupling of phenyl 2-azinecarboxylates and arylboronic acids. Various 2-azinecarboxylates can undergo decarbonylative coupling to furnish 2-arylpyridines. Further development and application of this decarbonylative reaction methodology will be reported in due course.[13]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02556.

> Detailed experimental procedures and spectral data for all compounds, including scanned image of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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