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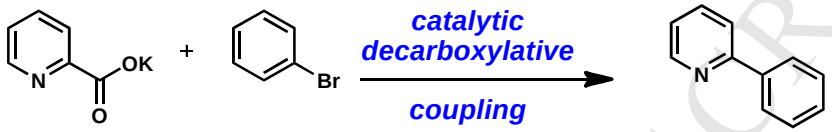

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ABSTRACT

A catalytic method for the decarboxylative coupling of 2-(azaaryl)carboxylates with aryl halides is described. The decarboxylative cross-coupling presented is mediated by a system catalytic in both palladium and copper without requiring stoichiometric amounts of organometallic reagents or organoboronic acids. This method circumvents additional synthetic steps required to prepare 2-azaaryl organometallics and organoborates as nucleophilic coupling partners, which are prone to protodemetallation and protodeborylation and produce potentially toxic byproducts.

Dedicated to Professor Melanie Sanford on receipt of the Tetrahedron Young Investigator Award

1. Introduction

The 2-substituted pyridine motif (Figure 1), is present in a number of important small molecules,[1] however 2-azaaryl nucleophiles typically used in cross-coupling reactions, such as organozincs, Grignards, organolithiums, organostannanes, and boronic acids, are notoriously unstable and difficult to prepare.[2] While some modifications have been made to improve their synthetic viability, especially within the realm of boronic acid derivatives, these approaches are often inconvenient or produce toxic waste.[3] The development of a decarboxylative method of generating these organometallic species (e.g., **2**) in situ from (2-azaaryl)carboxylates (**1**) represents a desirable alternative to traditional aryl nucleophiles for the synthesis of 2-aryl pyridine structures (**3**). 2-(azaaryl)carboxylates are generally inexpensive, are stable to both air and water, and represent a more ecologically friendly alternative to their organometallic counterparts.

Myers and co-workers reported the first practical decarboxylative cross-coupling in 2002,[4] a palladium-catalyzed decarboxylative Heck-type olefination (Figure 2). This work demonstrated that olefinated arenes are accessible from benzoic acids and olefins in the presence of catalytic palladium(II) triflate and silver carbonate. This represented an important advance as it provided an alternative to aryl halides and aryl pseudo-halides usually used in Heck reactions. A critical development within the field of decarboxylative cross-coupling was reported in 2006; Goossen and co-workers disclosed a catalytic decarboxylative cross-coupling reaction, utilizing a dual-catalyst system of copper and palladium. Mechanistically, this dual catalyst approach likely proceeds through a decarboxylative cupration of the arylcarboxylate partner. The resulting aryl copper species subsequently undergoes transmetallation onto the palladium, which furnishes the coupled product through reductive elimination (Figure 2).[5] Unlike typical cross-couplings, which require stoichiometric aryl organometallic nucleophiles, decarboxylative couplings proceed through an in situ generation of the nucleophilic coupling partner. A variety of non-aryl carboxylates have proven to act as efficient coupling partners in decarboxylative cross-coupling reactions,[6] including alkynes,[7] α-keto acids,[8] and 2-(2-azaaryl)acetates.[9] While these represent great advances within the field, the robust coupling of a key class of molecules, namely 2-(azaaryl)carboxylates, has been elusive. Recently, during the course of our own work on this topic, Wu and co-workers reported on the palladium-catalyzed decarboxylative cross-coupling reactions of 2-picolinic acid (Figure 2).[10] In light this work, we sought to supplement their studies with our own findings.

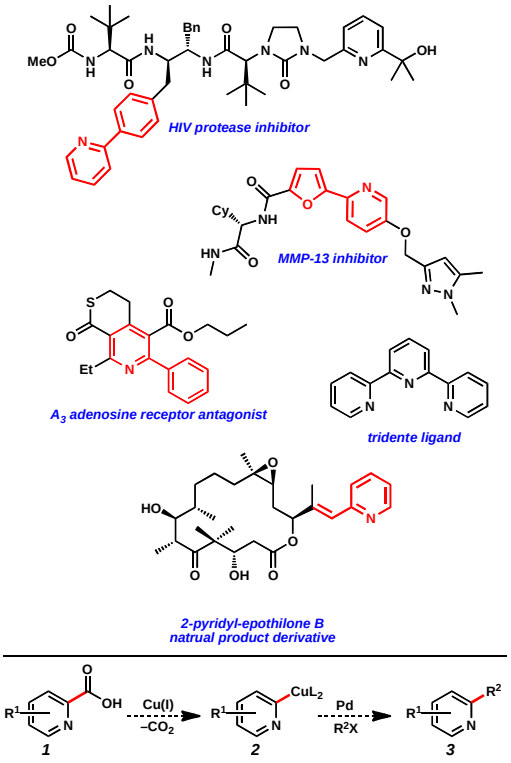


Fig. 1. The importance of 2-substituted pyridines.

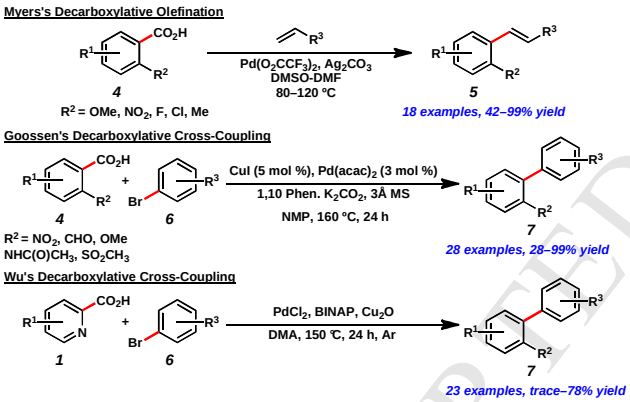


Fig. 2. The decarboxylative olefination and cross-coupling of aryl carboxylates .

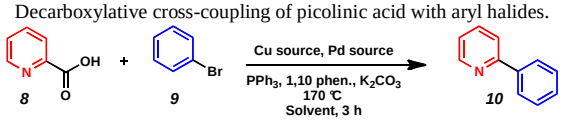
2. Results and discussion.

2.1 Optimization of a decarboxylative cross-coupling of picolinic acid with bromobenzene

To develop a general cross-coupling methodology, we selected simple substrates for optimization studies, namely picolinic acid (**8**) and bromobenzene (**9**, Table 1). We began our investigations by applying conditions similar to those reported by Goossen with disappointing results. (Table 1, entry 1). Using the same catalyst system we examined microwave irradiation and observed an increase in yield over heating in an oil bath (Table 1, entry 2). Similar results were disclosed by Goossen and Crabtree who independently reported enhanced yields using microwave irradiation.[11]

Table 1.

Decarboxylative cross-coupling of picolinic acid with aryl halides.



Entry	Cu Source	Pd Source	Solvent	Heat Source	% Yield[a]
1	Cu_2O	PdI_2	NMP	oil bath	6
2	Cu_2O	PdI_2	NMP	μwave	36
3[b]	Cu_2O	PdI_2	NMP	μwave	0
4	Cu_2O	$PdCl_2$	NMP	μwave	9
5	Cu_2O	$PdBr_2$	NMP	μwave	12
6	Cu_2O	$Pd(OAc)_2$	NMP	μwave	6
7	Cu_2O	$Pd(acac)_2$	NMP	μwave	8
8	Cu_2O	$Pd(TFA)_2$	NMP	μwave	14
9	Cu_2O	$Pd(F_6\text{-acac})_2$	NMP	μwave	6
10	Cu_2O	$Pd(PPh_3)_4$	NMP	μwave	13
11	Cu_2O	$Pd_2(dba)_2$	NMP	μwave	14
12	CuCl	PdI_2	NMP	μwave	7
13	CuBr	PdI_2	NMP	μwave	16
14	CuI	PdI_2	NMP	μwave	31
15	CuOTf	PdI_2	NMP	μwave	20
16[c]	Cu_2O(1.0eq)	PdI_2	NMP	μwave	7
17	Cu_2O	PdI_2	DMSO	μwave	12
18	Cu_2O	PdI_2	DMF	μwave	4
19	Cu_2O	PdI_2	NMP:Quin(1:1)	μwave	18
20	Cu_2O	PdI_2	Toluene	μwave	2

Conditions: 0.464 mmol **8**, 1.39 mmol **9**, Cu (10 mol %), Pd (5 mol %), PPh_3 (15 mol %), 1,10 phen. (15 mol %) 0.5 mL Solvent
[a] Yields determined by LCMS analysis with 4,4' di-*tert*-butyl biphenyl as internal standard.
[b] Performed at 120 °C.
[c] Utilized 1 equiv of Cu_2O.

With these initial results in hand we set about screening palladium and copper sources. Both palladium(II) and palladium(0) sources were examined, with palladium(II) iodide providing 2-phenyl pyridine (**10**) in 36% yield (Table 1, entry 2). Ultimately, cuprous oxide (Cu_2O), the copper source reported by Goossen and co-workers, gave consistently higher yields than copper (I) halides (Table 1, entries 12–16). Importantly, for both copper and palladium sources, weakly coordinating counterions were favored. While these results were encouraging, we sought to further improve the system. Concurrent with these studies, we examined several other solvents, however were limited to high boiling solvents as a consequence of the temperatures required for the copper-catalyzed decarboxylation of picolinic acid (Table 1, entries 17–20).

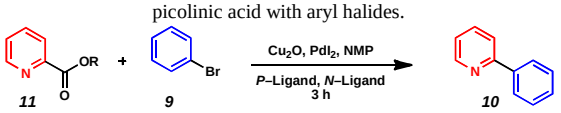
With these copper and palladium sources, we next examined several phosphine ligands. None showed improvement over the triphenylphosphine used in our initial studies. During the course of our studies we discovered that preheating the mixture at 50 ºC for 10 minutes prior to heating to 190 ºC was advantageous. Gratifyingly, we discovered that changing from the bidentate ligand 1,10 phenanthroline to the monodentate ligand pyridine caused a substantial increase in yield (Table 2, entry 6).

The implementation of a pre-formed potassium picolinate salt lead to a 10% increase in yield over its in situ generated counterpart (Table 2, entry 7). In examining the stereoelectronics of the *N*-ligand we discovered sterically encumbered nitrogen-contain ligands proved detrimental to the yield (Table 2, entries 8 and 13), while both electron-rich and deficient ligands also did not improve yields. Interestingly, as observed with 1,10 phenanthroline, other bidentate ligands such as TMEDA lead to lower yields (Table 2, entry 15). We hypothesize the formation of a stable 18 electron copper complex (**12**) is detrimental to decarboxylation (Figure 3). As seen, by LCMS analysis, much of our reduced yield could be accounted for by the persistence of

picolinic acid, indicating the initial decarboxylation is challenging.

Table 2.

Investigation of *P*- and *N*- ligands for the decarboxylative cross-coupling of picolinic acid with aryl halides.



Entry	R	Phosphine Ligand	Nitrogen Ligand	Temperature (°C)	Heat Source	Base	% Yield[a]
1	H	dppm	1,10 Phen	170	μwave	K_2CO_3	7
2	H	dppb	1,10 Phen	170	μwave	K_2CO_3	16
3	H	dppe	1,10 Phen	170	μwave	K_2CO_3	31
4	H	BINAP	1,10 Phen	170	μwave	K_2CO_3	6
5	H	PPh_3/KF	1,10 Phen	170	μwave	K_2CO_3	2
6	H	PPh_3	pyridine	50→190	μwave	K_2CO_3	52
7	K	PPh_3	pyridine	50→190	μwave	-	62
8	K	PPh_3	2,6 lutidene	50→190	μwave	-	46
9	K	PPh_3	ethyl Isonicotinate	50→190	μwave	-	49
10	K	PPh_3	DMAP	50→190	μwave	-	56
11	K	PPh_3	4-MeO Pyridine	50→190	μwave	-	43
12	K	PPh_3	DABCO	50→190	μwave	-	43
13	K	PPh_3	Et_3N	50→190	μwave	-	38
14	K	PPh_3	Hunig's Base	50→190	μwave	-	60
15	K	PPh_3	TMEDA	50→190	μwave	-	27
16	K	PPh_3	$(iPr)_2NH$	50→190	μwave	-	51
17	K	PPh_3	quinuclidine	50→190	μwave	-	62

Conditions: 0.464 mmol **11**, 1.39 mmol **9**, Cu (10 mol %), Pd (5 mol %), *P*-ligand (15 mol %), *N*-ligand (30 mol %) 0.5 mL NMP

[a] Yields determined by LCMS analysis with 4,4' di-*tert*-butyl biphenyl as internal standard.

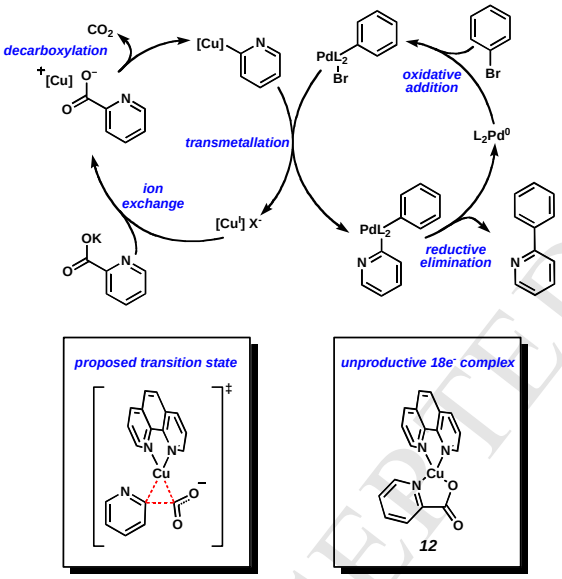


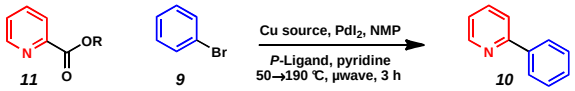
Fig. 3.

Proposed mechanism of the decarboxylative cross-coupling of picolinic acid with aryl halides.

With a suitable *N*-ligand in hand we hoped to gain better insight into the influence of the *P*-ligands on our catalytic system; like their nitrogen counter parts, bidentate phosphorous ligands performed poorly under the reaction conditions (Table 3, entries 8 and 13). We also reexamined copper sources, this time including copper(II) salts (Table 3, entries 16–20). All of these were inferior to copper(I) oxide. We investigated other counter ions of the picolinate salts such as cesium and sodium (Table 3, entries 14 and 15). None of these fared as well as potassium; confirming a trend was also observed in Goossen's studies.

Table 3.

Investigation of *P*-ligands and copper sources for the decarboxylative cross-coupling of picolinic acid with aryl halides.



Entry	R	Cu Source	*P*-Ligand	% Yield*
1	K	Cu_2O	$P(o\text{-}Tolyl)_3$	26
2	K	Cu_2O	$P(Cy)_3$	42
3	K	Cu_2O	$P(t\text{-}Bu)_3$	21
4	K	Cu_2O	$P(2\text{-}Furyl)_3$	42
5	K	Cu_2O	$P((CF_3)_2Ph)_3$	36
6	K	Cu_2O	$P(4\text{-}MeO\text{-}Ph)_3$	45
7	K	Cu_2O	$P(EtO)_3$	31
8	K	Cu_2O	dppe	46
9	K	Cu_2O	Ph_2PO	49
10	K	Cu_2O	$(PhO)_2POH$	20
11	K	Cu_2O	JohnPhos	44
12	K	Cu_2O	$AsPh_3$	48
13	K	Cu_2O	BINAP	38
14	Na	Cu_2O	PPh_3	4
15	Cs	Cu_2O	PPh_3	1
16	K	Cu(OAc)	PPh_3	34
17	K	$Cu_2(CO_3)(OH)_2$	PPh_3	29
18	K	$Cu(SO_4)$	PPh_3	47
19	K	CuO	PPh_3	27
20	K	$Cu(OTf)_2$	PPh_3	31
21	K	$Cu(OTf)_2$	PPh_3	62

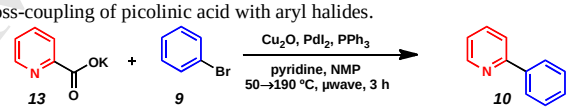
Conditions: 0.464 mmol **11**, 1.39 mmol **9**, Cu (10 mol %), PdI_2 (5 mol %), *P*-ligand (15 mol %), pyridine (30 mol %), 0.5 mL NMP

[a] Yields determined by LCMS analysis with 4,4' di-*tert*-butyl biphenyl as internal standard.

One of the unproductive side-reactions of our decarboxylative cross-coupling is the formation of biphenyl through an Ullmann-type dimerization of bromobenzene. By modulating the stoichiometry of bromobenzene (**9**) we attempted to suppress the unproductive dimerization and increase cross-coupling (Table 4). Ultimately, reducing the equivalents of bromobenzene from 3.0 to 2.0 was slightly beneficial to our yield (Table 4, entry 5).

Table 4.

Examination of the equivalents of bromobenzene in the decarboxylative cross-coupling of picolinic acid with aryl halides.



Entry	Bromobenzene (equiv)	% Yield[a]
1	3.0	62
2	2.0	65
3	1.0	55
4	0.75	57

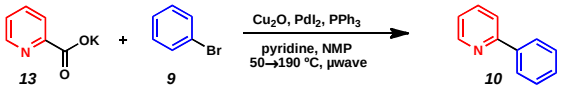
Conditions: 0.464 mmol **13**, Cu_2O (10 mol %), PdI_2 (5 mol %), PPh_3 (15 mol %), pyridine (30 mol %), 0.5 mL NMP

[a] Yields determined by LCMS analysis with 4,4' di-*tert*-butyl biphenyl as internal standard.

Concurrent to these studies, we examined the impact of reaction times on the yield of our cross-coupling. Though a reaction time of 8 hours provided the highest yield of 2-phenylpyridine at 72%, it represented only a marginal improvement over shorter times (Table 5).

Table 5.

Examination of reaction time in the decarboxylative cross-coupling of picolinic acid with aryl halides.

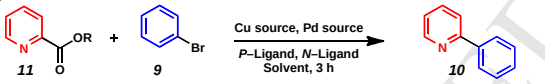


Entry	Time (h)	% Yield[a]
1	0.5	15
2	1.0	38
3	2.5	64
4	4.0	62
5	5.0	69
6	8.0	72

Conditions: 0.464 mmol **13**, 0.928 mmol **9**, CuO_2 (5 mol %), PdI_2 (5 mol %), PPh_3 (15 mol %), pyridine (30 mol %), 0.5 mL NMP
[a] Yields determined by LCMS analysis with 4,4' di-*tert*-butyl biphenyl as internal standard.

In order to better understand the reaction mechanism, we performed a series of control experiments in which we omitted each of the reagents. We discovered pyridine was not able to facilitate the necessary deprotonation of picolinic acid in situ (Table 6, entry 1). Omission of triphenylphosphine substantially decreased the yield of 2-phenyl pyridine (**10**) (Table 6, entry 2). Both copper and palladium proved crucial for our reaction; removal of either metal lead to little or no reactivity (Table 6, entries 3 and 4). Ultimately, pyridine was not necessary to facilitate the reaction (Table 6, entry 5). However this is most likely due to an unproductive protodecarboxylative side reaction that produces pyridine from picolinic acid.[12] 2-Phenyl pyridine is a common substrate for functional group directed C–H activation and can serve as a ligand for copper or palladium.[13] Consequently, we explored the possibility of product inhibition. However, yields were not effected by addition of 2-phenyl pyridine to the reaction (Table 6, entry 6), ruling out this inhibitory interaction.

Table 6.
Control experiments for the decarboxylative cross-coupling of picolinic acid with aryl halides.



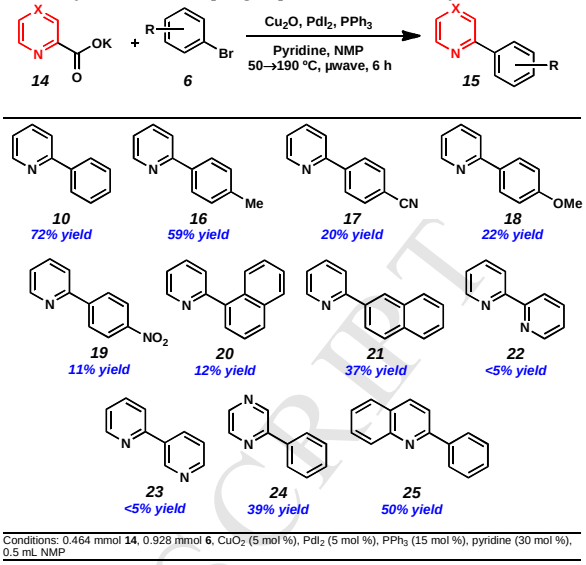
Entry	R	Cu Source	Pd Source	Solvent	Phosphine Ligand	Nitrogen Ligand	Addltive	% Yield[a]
1	H	Cu_2O	PdI_2	NMP	PPh_3	pyridine	pyridine	5
2	K	Cu_2O	PdI_2	NMP	-	pyridine	-	22
3	K	-	PdI_2	NMP	PPh_3	pyridine	-	9
4	K	Cu_2O	-	NMP	PPh_3	pyridine	-	0
5	K	Cu_2O	PdI_2	NMP	PPh_3	-	-	62
6[b]	K	Cu_2O	PdI_2	NMP	PPh_3	pyridine	2-phenyl pyridine	65

Conditions: 0.464 mmol **11**, 0.928 mmol **9**, Cu_2O (5 mol %), PdI_2 (5 mol %), PPh_3 (15 mol %), pyridine (30 mol %), 0.5 mL NMP, 50→190 °C, μwave
[a] Yields determined by LCMS analysis with 4,4' di-*tert*-butyl biphenyl as internal standard.
[b] 0.464 mmol of 2-phenyl pyridine was added to the reaction mixture.

2.2 The cross-coupling of (2-azaaryl)carboxylates with aryl halides

With our best conditions to date identified, we turned our attention to examination of the substrate scope of the decarboxylative cross-coupling (Figure 4). Electronically neutral aryl halides (**10** and **16**) performed well under the reaction conditions. Both electron rich and electron deficient aryl halides fared modestly (**17** and **18**). One of the major byproducts of reactions using electron deficient aryl bromides was an Ullmann-type coupled product. Heteroaromatic halides produced coupled products in disappointingly low yields (**22** and **23**). Other (2-azaaryl)carboxylates performed well under the reaction conditions (**24** and **25**), representing an expansion of the substrate scope detailed in Wu's report.

Fig. 4.
The decarboxylative cross-coupling of picolinic acid with aryl halides.



Conditions: 0.464 mmol **14**, 0.928 mmol **6**, CuO_2 (5 mol %), PdI_2 (5 mol %), PPh_3 (15 mol %), pyridine (30 mol %), 0.5 mL NMP

2.1 Conclusion

Decarboxylative coupling is an attractive alternative to traditional cross-coupling reactions. The starting materials are stable and inexpensive while the byproducts of these reactions are less toxic and easier to dispose of than traditional organometallic reagents and boronic acids. 2-metallated heteroarenes are particularly unstable, difficult to prepare and expensive. Herein we have reported an approach to circumvent the need to use these undesirable reagents. We have shown that 2-(azaaryl)carboxylates can be effectively used in decarboxylative cross-coupling reactions with aryl halides to furnish 2-(azaaryl)arenes, a motif present in a wide variety of important small molecules.

4. Selected experimental

Spectral data for compounds **10**, **16**, **17**, **18**, **19**, **20**, **21**, **22**, **23**, **24**, **25** were consistent with previously reported data.[10,14, 15]

A representive procedure for the decarboxylative cross-coupling of (2-azaaryl)carboxylates with aryl halides:

2-phenylpyridine (10) 74.9 mg (0.464 mmol) **13**, 18.3 mg (0.0697 mmol) PPh_3, 8.36 mg (0.0464 mmol) PdI_2, and 6.6 mg (0.046 mmol) Cu_2O were added to a flame-dried 2.0 mL microwave vial equipped with a spin vane. The vial was sealed, evacuated and back-filled with argon (3 times). 0.5 mL NMP (degassed with Ar, >10 min.) and 97.6 μl (0.929 mmol) bromobenzene were added sequentially via syringe. The mixture was stirred at room temperature for 10 min. The mixture was then irradiated in the microwave, with a 90 s prestirring period followed by 10 min at 50 °C and increase in temperature to 190 °C. The reaction was heated at this temperature for 6 h. The crude mixture was purified on a silica column.

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