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Palladium-Catalyzed Decarboxylative Couplings of 2-(2-Azaaryl)acetates with Aryl Halides and Triflates

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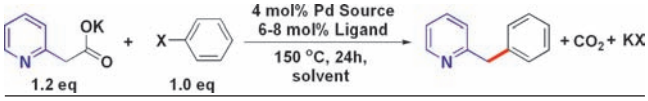
Abstract: Pd-catalyzed decarboxylative cross-couplings of 2-(2-azaaryl)acetates with aryl halides and triflates have been discovered. This reaction is potentially useful for the synthesis of some functionalized pyridines, quinolines, pyrazines, benzoxazoles, and benzothiazoles. Theoretical analysis shows that the nitrogen atom at the 2-position of the heteroaromatics directly coordinates to Pd(II) in the decarboxylation transition state.

Transition-metal-catalyzed decarboxylative cross-coupling is of great interest in synthetic chemistry because the method uses carboxylic acids as alternative reagents over organometal compounds.[1] Myers,[2] Forgione,[3] and others,[4−7] including our group,[8] found that Pd could catalyze the decarboxylative coupling of aromatic, alkenyl, and alkynyl carboxylic acids. Goossen et al. developed excellent procedures for the Pd/Cu-catalyzed decarboxylative coupling of benzoic acids and α-oxo carboxylates.[9] Our group described the Cu-catalyzed decarboxylative coupling of polyfluorobenzoic acids.[10] Related decarboxylative reactions of some aliphatic esters were reported recently by Tunge, Trost, Stoltz, and others.[11,12] Here we report a new example for breaking the C_{sp^3}−COOH bond: the Pd-catalyzed decarboxylative couplings of 2-(2-azaaryl)acetates with aryl halides and triflates. This study was inspired by the recent fascinating work of Oshima et al. on chelation-assisted activation of C_{sp^3}−C_{sp^3} bonds.[13]

Table 1. Decarboxylative Coupling under Various Conditions[a]

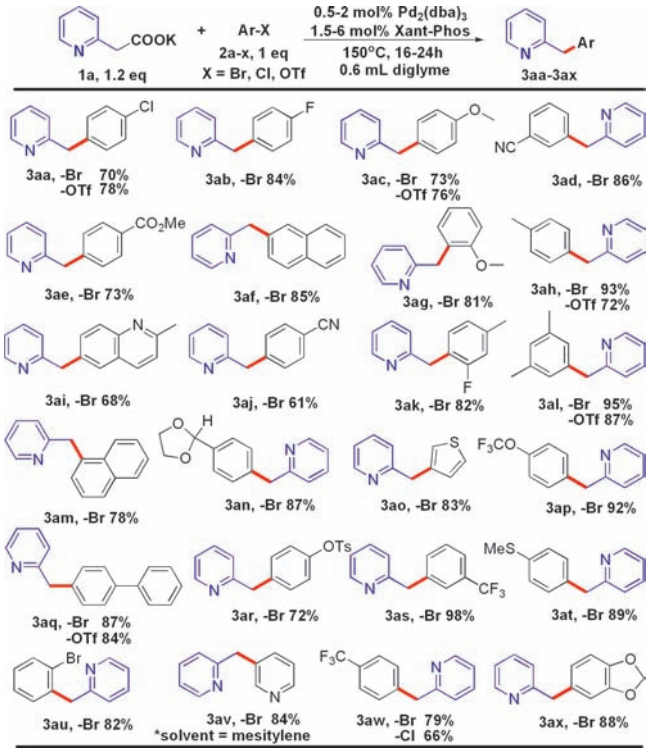


Entry	X	Pd Source	Ligand	Solvent	Yield[a] [%]
1	Br	$Pd(OAc)_2$	$P(Cy)_3$	diglyme	28
2	Br	$Pd(OAc)_2$	S-Phos	diglyme	37
3	Br	$Pd(OAc)_2$	Dave-Phos	diglyme	36
4	Br	$Pd(OAc)_2$	X-Phos	diglyme	29
5	Br	$Pd(OAc)_2$	S-BINAP	diglyme	68
6	Br	$Pd(OAc)_2$	Tol-BINAP	diglyme	65
7	Br	$Pd(OAc)_2$	DPPP	diglyme	4
8	Br	$Pd(OAc)_2$	Xant-Phos	diglyme	74
9	Br	$Pd(OAc)_2$	DPE-Phos	diglyme	72
10	Br	$Pd(OAc)_2$	DPPF	diglyme	26
11	Br	$Pd(acac)_2$	Xant-Phos	diglyme	37
12[b]	**Br**	**$Pd_2(dba)_3$**	**Xant-Phos**	**diglyme**	**96 (96**[c]**)**
13	Br	$Pd(TFA)_2$	Xant-Phos	diglyme	48
14	Br	$Pd(MeCN)_2Cl_2$	Xant-Phos	diglyme	53
15[b]	Br	$[PdCl(allyl)]_2$	Xant-Phos	diglyme	82
16[b]	Cl	$Pd_2(dba)_3$	Xant-Phos	diglyme	trace
17[b]	OTf	$Pd_2(dba)_3$	Xant-Phos	mesitylene	87 (84[c])

[a] GC yields (average of two runs) with naphthalene as internal standard. All the reactions were carried out at 0.25 mmol scale in 0.5 mL of solvent with 6 mol % bidentate ligand or 8 mol % monodentate ligand. [b] Use of 2 mol % Pd salt. [c] Isolated yields.

Our study began by testing the Pd-catalyzed decarboxylative coupling of potassium 2-(2-pyridyl)acetate with bromobenzene (Table 1). A series of Pd salts and phosphine ligands were examined. Under optimal conditions with Xant-Phos as the ligand (entry 12), the desired product was obtained in 96% yield. Chlorobenzene could not be efficiently converted under the same conditions (entry 16), whereas phenyl triflate affords the desired product with a yield of 84% (entry 17). It is interesting to note that the related potassium salts of 2-(3-pyridyl)-, 2-(4-pyridyl)-, and 2-phenyl acetic acids could not undergo this coupling reaction.[14] It is also important to point out that the intramolecular decarboxylative coupling of cinnamyl 2-(2-pyridyl)acetate esters was reported previously by Waetzig and Tunge.[11b]

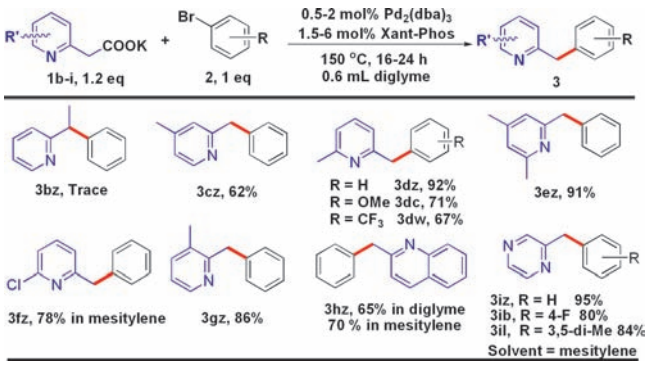
Table 2. Decarboxylative Coupling of Potassium 2-(2-Pyridyl)acetate[a]



[a] Isolated yields. All the reactions were carried out at 0.30 mmol scale in 0.6 mL of solvents. See Supporting Information for more details.

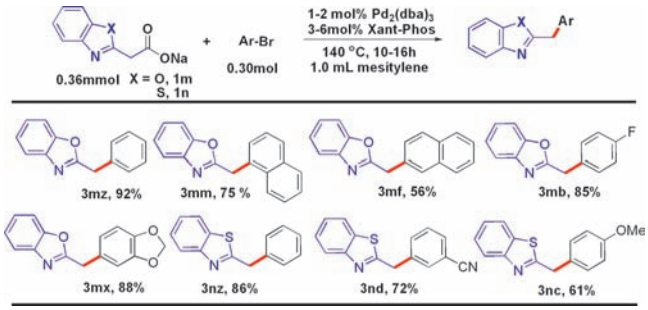
With the optimized conditions, we explored the scope of this reaction with various aryl halides and triflates (Table 2). We found that both electron-rich and electron-poor aryl bromides can be successfully converted across a range of functional groups. Aryl triflates usually give yields similar to those for aryl bromides. An

Table 3. Decarboxylative Cross-Coupling of 2-(2-Pyridyl)acetic Acid Derivatives[a]



[a] Isolated yields. All the reactions were carried out at 0.30 mmol scale in 0.6 mL solvent. See Supporting Information for more details.

Table 4. Decarboxylative Cross-Coupling of Benzooxazol-2-yl-acetate and Benzothiazol-2-yl-acetate



[a] Isolated yields. All the reactions were carried out at 0.30 mmol scale in 1.0 mL of solvents. See Supporting Information for more details.

activated aryl chloride (in the case of **3aw**) may also be used in the reaction. Moreover, many derivatives of 2-(2-pyridyl)acetate can undergo decarboxylative coupling (Tables 3−4) to produce functionalized pyridines, quinolines, pyrazines, benzoxazoles, and benzothiazoles. Recent work showed that benzylic arylation of pyridine derivatives could be accomplished through picoline *N*-oxide sp^3 arylation followed by deoxygenation.[15] The decarboxylative cross-coupling described here provides an alternative approach to synthesize related heterocyclic compounds that may be useful in medicinal chemistry.

To understand how the pyridyl group assisted the decarboxylative coupling, we conducted standard DFT calculations (Figure 1).[16] A bis-ligated Pd(0) complex is proposed to activate the aryl halide through **TS1** to produce a Pd(II) intermediate (**CP2**).[17] The energy barrier for oxidative addition is +21.2 kcal/mol. **CP2** then exchanges the anion to form **CP3** and its isomer **CP4**. From **CP4**, the decarboxylation transition state (**TS2**) was identified as a four-coordinate Pd(II) species. In **TS2**, the Pd(II) coordinates to the pyridyl nitrogen, but not to the leaving CO_2 moiety. From **CP2** to **TS2** the free energy increases by +33.9 kcal/mol, a value consistent with the temperature of the reaction (Note: a first-order reaction with a half-life of 12 h at 150 °C should have a barrier of +34.3 kcal/mol). Subsequent reductive elimination through **TS3** affords the desired product. In the catalytic cycle the decarboxylation step is rate-limiting. The coordination of nitrogen to Pd(II) is crucial to reducing the energy barrier of decarboxylation, which may be attributed to a stabilized anion effect analogous to the enolate chemistry described by Tunge and others.[11,18] Also, much higher energies were calculated for the other two possible transition states (i.e., **TS2-iso1** in which

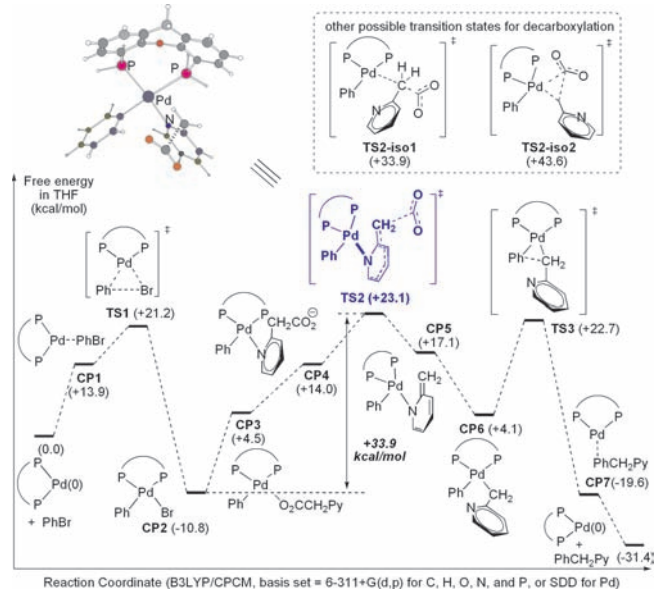


Figure 1. Proposed mechanism of decarboxylative cross-coupling. Note that four Ph groups in Xant-Phos were replaced by H to reduce the computational cost.

Pd(II) interacts with the α-carbon atom, and **TS2-iso2** in which Pd(II) interacts with both the α-carbon atom and CO_2 moiety). Furthermore, it is important to note that a transition state corresponding to decarboxylation through chelation of Pd with O and N atoms in the substrate could not be found.

In summary, Pd-catalyzed decarboxylative cross-coupling of 2-(2-azaaryl)acetates with aryl halides and triflates is discovered. This reaction is potentially useful for the synthesis of functionalized azaarenes. Theoretical analysis indicates that the nitrogen atom at the 2-position of the heteroaromatics directly coordinates to Pd(II) in the decarboxylation transition state.

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Supporting Information Available: Experimental details and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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