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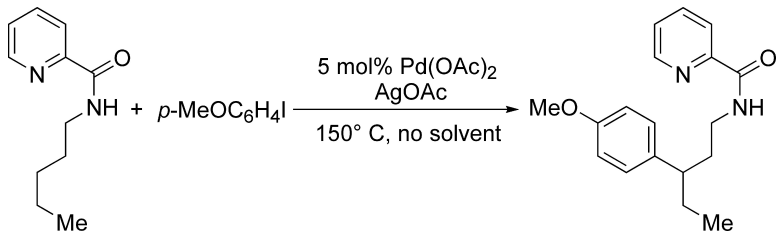

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Highly Regioselective Arylation of sp³ C−H Bonds Catalyzed by Palladium Acetate

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Development of transition metal complexes capable of selective, catalytic functionalization of C−H bonds is a challenge of intense current interest.[1] Several distinct strategies for addressing this problem have appeared in the literature. First, the most important industrially, is the selective oxidation of methane and other small hydrocarbons.[2] Second is the use of the C−H bond as a functional group that can be transformed to other useful functionalities. This strategy allows shorter reaction sequences resulting in environmental advantages, unique regioselectivities, and use of easily accessible starting materials. Currently, most of the examples involving alkyl sp³ C−H bond functionalization result in the formation of C−heteroatom bonds. In many cases, the products from these transformations are intended to be used to achieve carbon−carbon bond formation.[3] As a consequence, development of efficient methods leading directly to C−C bond formation is of particular value. Most of such reactions fall under four main categories. First, various heterocycles may be arylated α to the heteroatom by aryl halides, usually under Pd(0) or Rh(I) catalysis.[4] Second, compounds possessing an ortho-directing group may be arylated, usually by using Pd(0), Rh(I), or Ru(II) catalysts.[5] Examples mechanistically relevant to this work have been published by Tremont, Liebeskind, and Sanford.[5c,e,f] Third, the C−H activation/C−C coupling sequence may be initiated by oxidative addition of Pd(0) to Ar−Hal bonds.[6] Fourth, alkenes and alkynes may be arylated under transition metal catalysis.[7] Catalytic carbon−carbon bond formation by using an unactivated alkyl C−H bond as one of the reaction partners is rare. Two recent examples have been reported by Sames and Buchwald.[8]

We have recently reported the palladium-catalyzed arylation of acetanilide derivatives.[9a] This method is also applicable to the arylation of pyridines.[9b] In the latter case, not only sp² but also unactivated sp³ C−H bonds may be arylated. Incorporation of a detachable, pyridine-containing auxiliary in the molecule to be activated (Scheme 1) could result in selective arylation of a variety of classes of organic compounds. Furthermore, this chelating pyridine functionality should facilitate both the C−H activation[10] and the oxidative addition step,[11] assuming that the mechanism involves a Pd(II)−Pd(IV) couple.[5c,e,f] This reasoning has worked remarkably well, and we report here a unique and unprecedented catalytic method for highly regioselective arylation of unactivated sp³ C−H bonds.

Initially, the 2-aminomethylpyridine moiety was chosen as an auxiliary for arylation of carboxylic acids. Unfortunately, it is susceptible to destruction under the reaction conditions, presumably by C−H activation of the benzylic methylene group. The conversions even in the best cases were not acceptable, and multiple side products were observed in reaction mixtures.[12] As a consequence, 8-aminoquinoline was chosen as an auxiliary that does not contain activated benzylic C−H bonds. The results exceeded our expectations, and a mild, highly regioselective catalytic *β*-arylation of carboxylic amides possessing a directing aminoquinoline group was developed (Table 1).

Scheme 1. Pyridine as a Directing Group

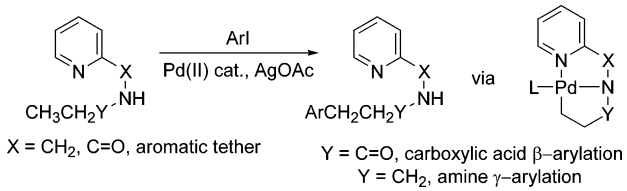
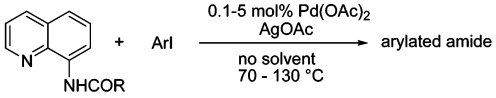
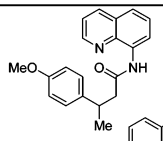
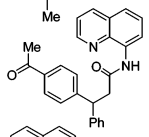
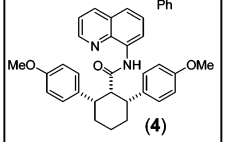
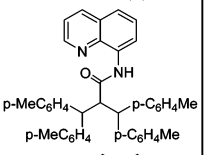
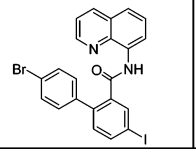


Table 1. Catalytic Arylation of 8-Aminoquinoline Amides[a]



Entry	Amide, ArI	Time Temp	Arylated Amide	Yield
1	R = n-Pr (**1**) Ar = 4-MeOC$_6$H$_4$	5 min 110 °C		92%
2	R = (CH$_2$)$_2$Ph (**2**) Ar = 4-AcC$_6$H$_4$	20 min 120 °C		60%[b]
3	R= Cyclohexyl (**3**) Ar = 4-MeOC$_6$H$_4$	5 h 70 °C	 (**4**)	61%[c]
4	R = i-Pr (**5**) Ar = 4-MeC$_6$H$_4$	30 min 120 °C		60%
5[d]	R = 3-IC$_6$H$_4$ (**6**) Ar = 4-BrC$_6$H$_4$	16 h 130 °C		65%

[a] Amide (1 equiv), ArI (4−6 equiv), AgOAc (1.1−4.1 equiv), Pd(OAc)$_2$ (0.1−5 mol %). Yields are isolated yields. See the Supporting Information for details. [b] 4-Phenyl-1,2,3,4-tetrahydro-1,10-phenanthroline-2-one (30%) obtained as a side product. [c] Monoarylation (9%) and *trans*-diarylation (8%) products also isolated. Relative configuration of the major product determined by X-ray crystallography. [d] With 0.1 mol % of Pd(OAc)$_2$.

An extremely fast reaction was observed in the *p*-methoxyphenylation of propionamide **1**—arylation was complete in less than 5 min at 110 °C. The arylation of a benzylic methylene group was also successful (entry 2). Even cyclohexanecarboxylic acid derivative **3** was diarylated, producing mostly the all-*cis* product **4** (entry 3). Interestingly, secondary C−H bonds react faster than primary ones, allowing the tetraarylation of isobutyric amide **5** (entry 4). As expected, aromatic C−H bonds can also be arylated (entry 5).

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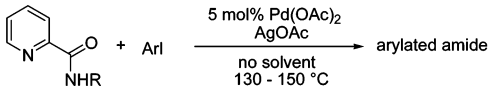
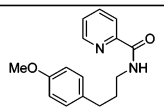
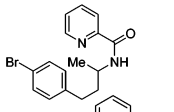
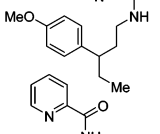
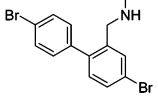
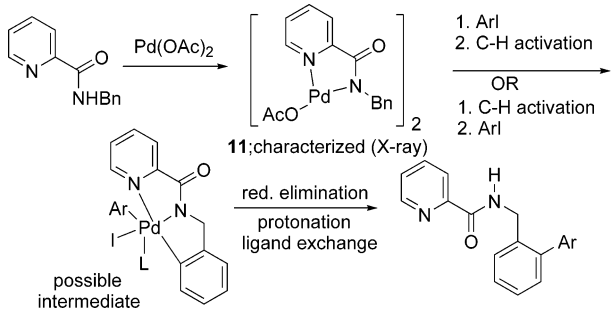
Table 2. Catalytic Arylation of Picolinamides[a]



Entry	Amide, ArI	Time Temp	Arylated Amide	Yield
1	R = n-Pr (**7**) Ar = 4-$MeOC_6H_4$	6 h 130 °C		76%
2	R = s-Bu (**8**) Ar = 4-BrC_6H_4	1 h 150 °C		72%
3	R = n-Amyl (**9**) Ar = 4-$MeOC_6H_4$	12 h 150 °C		54%
4	R = 3-Bromobenzyl (**10**) Ar = 4-BrC_6H_4	5 h 150 °C		81%

[a] Amide (1 equiv), ArI (4 equiv), AgOAc (1.1 equiv), $Pd(OAc)_2$ (5 mol %). Yields are isolated yields. See the Supporting Information for details.

Scheme 2. Mechanistic Considerations



This reaction was carried out with 0.1 mol % palladium loading, resulting in 650 turnovers. Remarkably, iodide on the benzamide is compatible with the reaction conditions. This reaction is a synthetic equivalent of conjugate addition of an arylmetal to α,β-unsaturated acids.

A similar approach may be applied for arylation of amine derivatives (Table 2). In this case, the inverted position of carbonyl requires 2-picolinic acid as an auxiliary, and the result is an unprecedented reaction—γ-arylation of amine derivatives. Again, palladation forming a five-membered ring is preferred. The reactions are somewhat slower than in the case of aminoquinoline amides. Primary C−H bonds react faster than the secondary C−H bonds, allowing for the selective monoarylation of methyl groups, which is not possible for aminoquinoline amides. The method is compatible with bromo substituents on arene (entries 2 and 4). Aromatic C−H bonds of benzylamine derivatives also may be arylated (entry 4).

Only a somewhat speculative discussion about mechanism of these transformations is possible at this point (Scheme 2). If benzyl picolinamide is heated with $Pd(OAc)_2$ in $CHCl_3$ or acetic acid, palladium amide **11** is cleanly formed. Since the arylation reactions require a free NH,[13] one can assume that Pd amides are involved in the catalytic cycle. Canty and co-workers have shown that diaryliodonium triflates can transfer Ph^+ to nitrogen-ligated Pd(II), leading to the formation of unstable Pd(IV) species that decompose via reductive elimination pathways.[11] This finding may be relevant to the mechanism of this arylation procedure. The timing of C−H activation process versus the oxidative addition of ArI to Pd(II) is unclear at this point, and mechanistic investigations are in progress.

In conclusion, we have developed a new arylation process based on C−H activation. This method allows for the β-arylation of carboxylic acid derivatives and γ-arylation of amine derivatives. Efforts are underway to extend this methodology to arylation of esters and alkenylation of amides and esters.

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Supporting Information Available: Detailed experimental procedures, characterization data for new compounds, and X-ray crystallography data for **4** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Attempted arylation of hydrocinnamic acid 2-pyridinemethylamide resulted in production of *N*-hydrocinnamoyl picolinamide and hydrocinnamamide.

(13) The corresponding *N*-methyl-substituted amides are unreactive.

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