ORGANIC LETTERS

2013
Vol. 15, No. 18
4758–4761

Direct Arylation of Primary and Secondary sp^3 C−H Bonds with Diarylhyperiodonium Salts via Pd Catalysis

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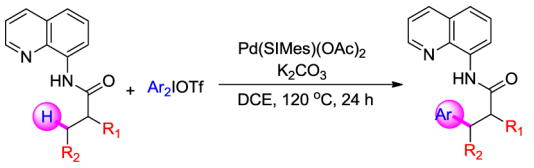
Received July 26, 2013

ABSTRACT



Palladium-catalyzed primary and secondary sp^3 C−H bond arylation is reported. The method using diarylhyperiodonium salts as arylation reagents shows good functional group tolerance and proceeds under mild reaction conditions. The KIE experiments show that the C−H bond activation is the rate-determining step.

Transition-metal-catalyzed direct C−H arylation has emerged as an attractive alternative to traditional synthetic methods.[1] In comparison, most achievements in this field to carry out the formation of C−C bonds or C−N bonds are being focused on the activation of sp^2 C−H bonds of (hetero)arenes.[2] The unreactive sp^3 C−H activation remains challenging, facing problems that approach both efficiency and selectivity.[3] Some achievements have been made to functionalize the relatively active benzylic and allylic C−H bonds directly.[4] More recently, many efforts have also been made to perform direct functionalization of the "unreactive" sp^3 C−H bonds via Pd catalysis. For example, work to achieve Pd-catalzyed "unreactive" sp^3 C−H arylation was accomplished by using the N- or S-contained directing groups with either aryl halides or organometallic reagents as arylation reagents.[5] Daugulis

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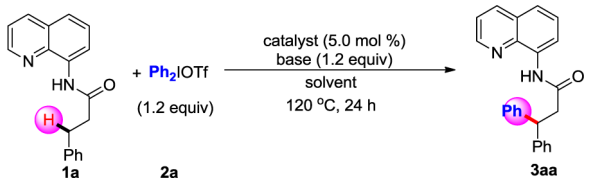
10.1021/ol402116a
Published on Web 09/04/2013

reported the first example of β-arylation of carboxylic derivatives and γ-arylation of amine derivatives by using 8-aminoquinolinyl or picolinyl directing groups with aryl iodides.[6] Corey has achieved arylation of sp^3 C−H bonds in amino acid derivatives with a similar strategy.[7] Chen, Chatani, and other groups made significant contributions to achieve a number of "unreactive" sp^3 C−H functionalizations, including arylation/alkenylation/alkynylation/alkylation with the corresponding organic halides.[8]

As mentioned above, aryl halides have been broadly and successfully used as electrophiles to achieve sp^3 C−H arylation. However, arylhyperiodonium salts, which generally showed higher reactivity, have never been used to approach direct arylation of "unreactive" sp^3 C−H bonds although they exhibited great stability, availability, electrophilicity, and lower toxicity, as well as the application of sp^2 C−H arylation.[9,10] Because of its highly electron-deficient nature and hyperleaving group ability, this reagent might provide the convenient and efficient arylation of sp^3 C−H bonds, especially for the more challenging secondary C−H bonds. Herein, we demonstrate the first successful example to approach direct arylation of primary and secondary sp^3 C−H bonds using diarylhyperiodonium salts as arylation reagents.

According to previous reports in the field of C−H activation via Pd catalysis,[5−8,11] we first tested direct arylation of a steric hindered benzylic sp^3 C−H bond of *N*-3-phenylpropoyl-8-aminoquinoline with diarylhyperiodonium salts in the presence of Pd catalysts (Table 1). Among

Table 1. Optimization Studies for Pd-Catalyzed sp^3 C−H Bond Arylation[a]



entry	catalyst	base	solvent	yield[b] (%)
1	$Pd(OAc)_2$	K_2CO_3	$ClCH_2CH_2Cl$	72
2	$Pd(OAc)_2$	K_2CO_3	toluene	16
3	$Pd(OAc)_2$	K_2CO_3	DMF	<10
4	$Pd(OAc)_2$	K_2CO_3	THF	<10
5	$Pd(OAc)_2$	K_2CO_3	dioxane	14
6	$Pd(OAc)_2$	Cs_2CO_3	$ClCH_2CH_2Cl$	68
7	$Pd(OAc)_2$	K_3PO_4	$ClCH_2CH_2Cl$	75
8	$Pd(OAc)_2$		$ClCH_2CH_2Cl$	17
9	$Pd(OAc)_2$	Na_2CO_3	$ClCH_2CH_2Cl$	65
10	$Pd(OAc)_2$	$Cu(OAc)_2$	$ClCH_2CH_2Cl$	52
11	$Pd(OAc)_2$	KO^tBu	$ClCH_2CH_2Cl$	<10
12	$Pd(IPr)Cl_2$	K_2CO_3	$ClCH_2CH_2Cl$	19
13	$Pd_2(dba)_3$	K_2CO_3	$C1CH_2CH_2C1$	18
14	$Pd(TFA)_2$	K_2CO_3	$ClCH_2CH_2Cl$	16
15	$Pd(dba)_2$	K_2CO_3	$ClCH_2CH_2Cl$	<10
16	$Pd(SIMes)(OAc)_2$	K_2CO_3	$ClCH_2CH_2Cl$	86 (82)[c]
17	$PdCl_2(d_{ppp})$	K_2CO_3	$ClCH_2CH_2Cl$	<10
18	$Pd(MeCN)_4(BF_4)_2$	K_2CO_3	$ClCH_2CH_2Cl$	11
19	$PdCl_2$	K_2CO_3	$ClCH_2CH_2Cl$	<10

[a] The reactions were conducted with 0.10 mmol of **1a**, 0.12 mmol of **2a**, 0.005 mmol of catalyst, 0.12 mmol of base, and 1.0 mL of solvent and stirred for 24 h unless otherwise noted. [b] Determined by crude ^1H NMR spectroscopy. [c] Yield of isolated product.

various solvents, $ClCH_2CH_2Cl$ exhibited the best efficacy, and the desired product **3aa** was observed in a good yield only in the presence of K_2CO_3 as the base with $Pd(OAc)_2$ as the catalyst (entries 1−5). After screening the different bases, we found that the carbonates could sharply promote this transformation (entries 6−11).[12] In the absence of bases, the efficacy of arylation was obviously reduced (entry 8). Phosphates and acetates could accelerate the reaction, although they were not comparable with carbonates (entries 7 and 9). Notably, such an arylation is not sensitive to both moisture and air; thus, they can be conveniently carried out with commercially available solvents. Notably, the starting material **1a** was not completely consumed in the presence of $Pd(OAc)_2$, and the efficiency could not be enhanced by simply lengthening the reaction time and/or raising the temperature. Considering the possible deactivation of the catalysts, we tested the catalysts with the support of a different ligand set (entries 12−19). To our delight, $Pd(SIMes)(OAc)_2$ (SIMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidane) resulted in a significant promotion, and the desired product **3aa** was obtained in 82% isolated yield (Table 1, entry 16).[12] Under

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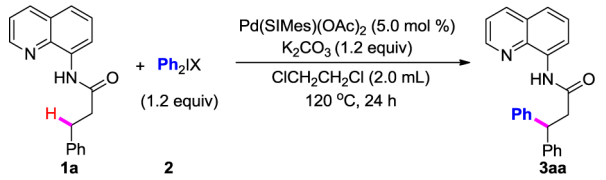
such arylation conditions, arylation on either the aromatic ring or biarylated products was not observed.

Table 2. Effects of Counteranions.[a]



entry	X	yield[b] (%)
1	OTf	86
2	BF_4	31
3	PF_6	30
4	OTs	12
5	Br	13
6	[c]	37

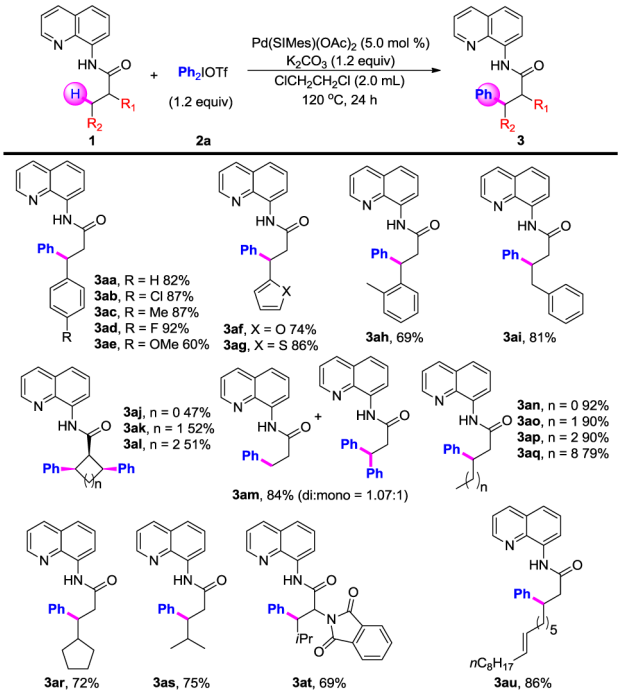
[a] The reactions were conducted with 0.10 mmol of **1a**, 0.12 mmol of **2a**, 0.005 mmol of catalyst, 0.12 mmol of base, and 1.0 mL of solvent and stirred for 24 h unless otherwise noted. [b] Determined by crude ^{1}H NMR spectroscopy. [c] Using iodobenzene as arylation reagent.

Subsequently, we examined the effects of the counteranion of diarylhyperiodonium salts (Table 2). We found that tetrafluoroborates (BF_4^-), hexafluorophosphates (PF_6^-), *p*-toluenesulfonates (OTs^-), or bromides (Br^-) could be applied as counterions, and **3aa** was obtained with lower efficacy (comparing entry 1 to entries 2−5). The low yields can be explained by the solubility of each salt in $ClCH_2CH_2Cl$. Alternatively, the anion may be participate in the rate-limiting proton-abstraction step. To determine the reactivity of the corresponding ArI from Ar_2IOTf, we also tested PhI as an electrophile. The reaction indeed took place but the efficiency was much lower. This result indicated that the reactivity of diarylhyperiodonium triflates is much higher than that of ArI under the same conditions (entry 6).

With the optimized conditions in hand, we investigated the scope of amide derivatives (Scheme 1). We found that (1) various substituents with different electronic features at the *para*- position of phenyl showed good to excellent reactivity (**3aa**−**ae**), (2) the steric effect weakly affected this transformation (**3ah**), and (3) Other 3-heteroaryl substituted amides, such as thiophenyl and furanyl, could also be tolerated and the desired arylation products were obtained in good to excellent yields (**3af** and **3ag**). Thus, starting from different amides and diarylhyperiodonium triflates, there are two alternative routes to approach the same products, which might be the complementary methods for each other.

Since common sp^3 C−H bonds, especially secondary C−H bonds other than the benzylic position, exhibit poor reactivity, we turned to explore the potential reactivity with aliphatic carboxylic amides (Scheme 1). We first tested the cyclic substrates and found that 3-membered, 4-membered, and 5-membered ring substrates are arylated

Scheme 1. Pd-Catalyzed Direct Arylation of sp^3 C−H Bonds with Different 8-Aminoquinoline Amides[a]



[a] The reactions were conducted with 0.20 mmol of **1a**, 0.24 mmol of **2a**, 0.01 mmol of Pd(SIMes)(OAc)$_2$, 0.24 mmol of K_2CO_3, and 2.0 mL of $ClCH_2CH_2C1$ and stirred for 24 h at 120 °C unless otherwise noted.

smoothly. However, only the double arylations at both *ortho* positions were observed (**3aj**−**al**). The primary sp^3 C−H bonds of propionyl derivatives also performed well, while only mono- and diarylated products were isolated as a mixture at a nearly 1:1 ratio (**3am**). To extend the application of this arylation further, different aliphatic carboxylic acid derivatives were tested. We found that, in general, the length of the chain did not affect the efficacy (**3an**−**aq**), unless a very long chain was involved. The benzyl and sterically hindered cyclopentyl and isopropyl groups were compatible, which extended the substrate scope (**3ai**, **3ar**, and **3as**). We further tested the derivatives of protected amino acids. To our delight, direct arylation took place, and **3at** was isolated in a 69% yield. The natural oleic acid derivative was also arylated in good yield, leaving the double bond and allylic C−H bonds untouched under these oxidative conditions (**3au**).[13]

Considering that different substituents with distinct electronic and steric features may influence the reactivity of the diarylhyperiodonium salts, we then surveyed different functional groups of diarylhyperiodonium triflates (Scheme 2). Gratifyingly, a variety of symmetrical or unsymmetrical diarylhyperiodonium triflates successfully coupled with **1n**. Different functional groups on the aryl group of diarylhyperiodonium triflates, no matter whether

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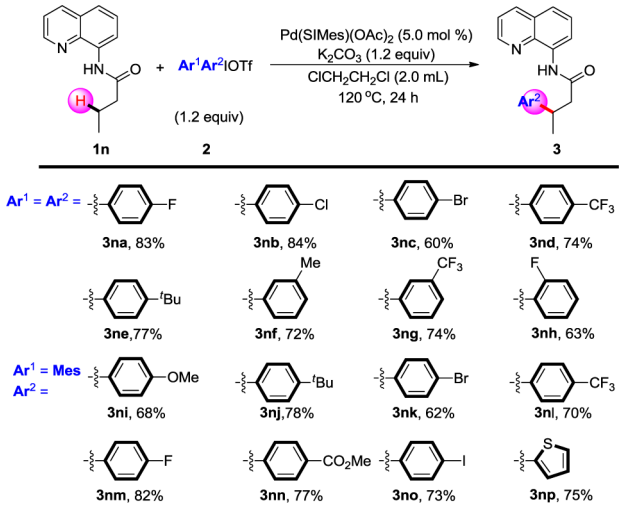
Scheme 2. Pd-Catalyzed Direct Arylation of sp^3 C−H Bonds with Different Diarylhyperiodonium Salts[a]



[a] The reactions were conducted with 0.20 mmol of **1a**, 0.24 mmol of **2a**, 0.01 mmol of $Pd(SIMes)(OAc)_2$, 0.24 mmol of K_2CO_3, and 2.0 mL of $ClCH_2CH_2Cl$ and stirred for 24 h at 120 °C unless otherwise noted.

electron-withdrawing or electron-donating groups, were compatible with this arylation. However, the electron-poor aryl groups performed better (**3na** vs **3ne**, **3ni** vs **3nm**). Notably, the reaction exhibited excellent tolerance of functional group. For example, fluoro (**3na, 3nh**, **3nm**), chloro (**3nb**), bromo (**3nc**, **3nk**), iodo (**3no**), trifluoromethyl (**3nd**, **3nl**), and ester (**3nn**) groups are tolerated, and the desired products were obtained in moderate to good yields.[14] The *ortho*-substituted diarylhyperiodonium triflates (**3nh**) were also suitable with a little decrease of reactivity, which indicated that the considerable effect of steric hindrance. It is important to note that the electron-rich heterocyclic group (**3np**) could be also transferred in a good yield, which highly expanded the substrate scope.

To understand the pathway of this arylation better, we performed KIE experiments. Both intermolecular KIE (3.8) and intramolecular KIE (3.9) indicated the involvement of C−H bond cleavage into the rate determining step (see the Supporting Information, eqs 2 and 3). Most importantly, the H/D exchange was examined by simply heating the substrate **1b** in the presence of the catalyst in the mixed solvent of $AcOD/ClCH_2CH_2Cl$. After 24 h at 120 °C, 46% of deuterium incorporation was observed at β position, thus implying the C−H cleavage in the absence of diarylhyperiodonium triflates

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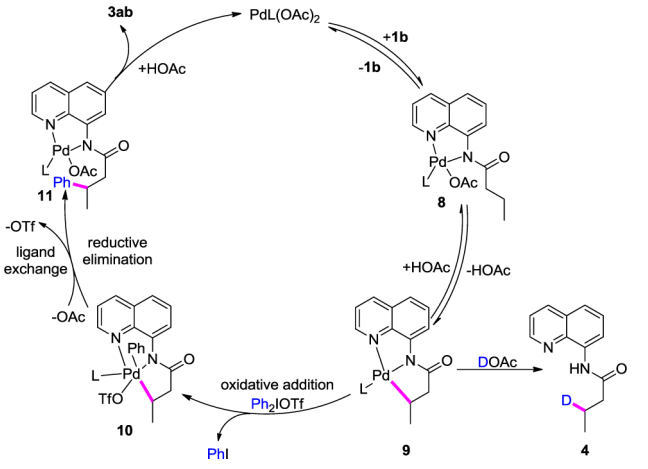
Scheme 3. Proposed Mechanism (L = SIMes)



(see the Supporting Information, eq 1). On the basis of these preliminary results, a proposed mechanism is shown in Scheme 3. The coordination of the amide **1b** with palladium catalyst formed complex **8**, which further underwent the C−H activation to produce **9**. Diarylhyperiodonium salts oxidized the complex **9** to form Pd(IV) complex **10**. Following by the reductive elimination, the desired product **3ab** was generated, releasing the Pd(II) catalyst to fulfill the catalytic cycle.[15]

In summary, we reported a successful example of Pd-catalyzed primary and secondary sp^3 C−H arylation by first using diarylhyperiodonium salts as arylation reagents. Various acid derivatives and different diarylhyperiodonium reagents were compatible with this arylation. This method could be applied to direct arylation of naturally important structural units, such as the derivatives of amino acids and oleic acid. Preliminary mechanistic studies indicated the possible Pd(II)/Pd(IV) catalytic cycle of this transformation. These studies provided a new method for an efficient functionalization of "unreactive" sp^3 C−H bonds and an alternative way to process direct arylation of primary and secondary sp^3 C−H bonds under mild conditions. Further efforts to extend the applications of this method are underway.

Acknowledgment. We acknowledge financial support from the National Basic Research Program of China (973 Program, 2009CB825300) and the national NSF of China (nos. 20925207 and 21002001).

Supporting Information Available. Experimental procedures and NMR spectra analysis of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.