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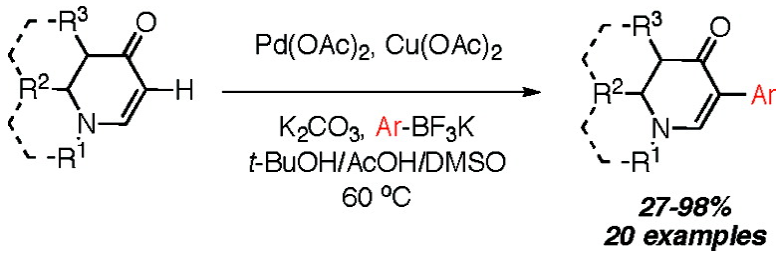

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Palladium(II)-Catalyzed Direct Arylation of Enaminones Using Organotrifluoroborates

Haibo Ge,[†] Micah J. Niphakis,[‡] and Gunda I. Georg*,[§]

Department of Medicinal Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045, Center for Chemical Methodologies and Library Development, University of Kansas, 1501 Wakarusa Drive, Lawrence, Kansas 66047, and Department of Medicinal Chemistry and the Institute for Therapeutics Discovery and Development, University of Minnesota, 717 Delaware Street SE, Minneapolis, Minnesota 55414

Received November 11, 2007; E-mail: georg239@umn.edu

The direct conversion of C−H to C−C bonds is an exceedingly valuable process in contemporary organic synthesis. Recent developments in this field have allowed concise and economical routes to useful materials and synthetic intermediates.[1] The current rise of palladium-catalyzed methods,[2,3] in particular, is evidence of this transformation's versatility. The well-known liabilities of C−H functionalization, namely overfunctionalization and regioselectivity,[2c] have limited its applicability. Indeed, the need for a broader pool of viable C−H donors as well as reagent choices is clear.

In light of the advances in this area, our interest in the synthesis of biologically active natural products and lead discovery libraries inspired us to explore the 3-arylpiperidine system. Many compounds which feature this scaffold are known to have high affinity for an array of validated targets (Figure 1).[4] Expanding upon our recently developed method for the enantiospecific construction of cyclic enaminones[5] we sought a general method for C-3 arylation. This transformation has been achieved via a two-step sequence involving halogenation and subsequent coupling using Pd(0).[6] We envisaged a more direct protocol, which allowed us to avoid preactivation of the enaminone. We hoped to take advantage of the innate nucleophilic character of the enaminone and reasoned that the same putative transition-metal species as in the two-step process could be accessed in a catalytic, one-step fashion. Furthermore, we planned to intercept this intermediate with a suitable coupling partner. We describe here the realization of this proposal as well as a unique use of organotrifluoroborates[7] as coupling partners in palladium-catalyzed C−H functionalization.

To our delight, initial attempts to couple enaminone **1a** and trifluoroborate **2** using $Pd(OAc)_2$ were successful despite the observation of the biphenyl homocoupled product (Table 1, entry 1). 4-Methoxyboronic acid, used in place of the trifluoroborate **2**, gave poor yields of enaminone **3a** (Table 1, entry 2). It should be noted that the use of an acidic cosolvent, thought to promote palladation by increasing the electrophilicity of the Pd(II) center,[8] consequently limits the potential of basic or nucleophile-promoted organometallic coupling partners (i.e., boronic acids, organozinc reagents, silanes, etc.). Additionally, Molander et al. have found organotrifluoroborates to be robust equivalents of organoboronic acids[7a] and therefore were deemed to be apposite reagents for further optimization studies.

We first identified $Cu(OAc)_2$ as being an economic and efficacious reoxidant (Table 1, entries 3−7). Furthermore, $Pd(OAc)_2$ was found to be a superior catalyst compared with $PdCl_2$ and $Pd(OTFA)_2$ (Table 1, entries 8 and 9). Considering the limited stability of our substrate, a higher Pd(II)-catalyst loading was used to circumvent long reaction times and high temperatures which were otherwise required to drive the reaction to completion. The addition of trifluoroacetate salts (Table 1, entries 10−12) also reduced the reaction time but resulted in lower yields. The slow addition of the trifluoroborate was found to give the desired product in excellent yield and was most effective for suppressing homocoupling (Table 1, entry 13).

With optimized conditions in hand, we embarked on an investigation of the reaction scope. Electron-rich trifluoroborates undergo rapid (2−6 h) and high-yielding cross-coupling as compared to their electron-deficient counterparts (Table 2). Sterically encumbered trifluoroborates (Table 2, entries 3 and 4) require longer reaction times (24 h) and proceed in moderate yields. Furthermore, aryl halides (Table 2, entries 7 and 8) are tolerant under these conditions demonstrating a unique feature of this reaction compared

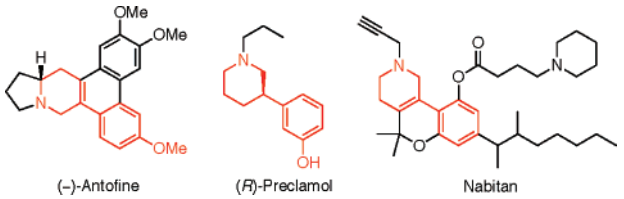
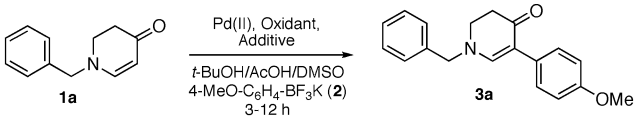


Figure 1. Examples of 3-arylpiperidine medicinal agents.

Table 1. Reaction Optimization for C−H Functionalization of Enaminones



entry[a]	oxidant	Pd(II)	additive (eq)	yield (%)[b]
1	$Cu(OAc)_2$	$Pd(OAc)_2$	None	63[c]
2[d]	$Cu(OAc)_2$	$Pd(OAc)_2$	K_2CO_3 (3.0)	20
3	$Cu(OAc)_2$	$Pd(OAc)_2$	K_2CO_3 (3.0)	82
4	benzoquinone	$Pd(OAc)_2$	K_2CO_3 (3.0)	14
5	$CuCl_2$	$Pd(OAc)_2$	K_2CO_3 (3.0)	66
6	$Cu(OTFA)_2$	$Pd(OAc)_2$	K_2CO_3 (3.0)	82
7	$Cu(OAc)_2$[e] + O_2	$Pd(OAc)_2$	K_2CO_3 (3.0)	40
8	$Cu(OAc)_2$	$PdCl_2$	K_2CO_3 (3.0)	61
9	$Cu(OAc)_2$	$Pd(OTFA)_2$	K_2CO_3 (3.0)	60
10	$Cu(OAc)_2$	$Pd(OAc)_2$	AgOTFA (3.0)	41
11	$Cu(OAc)_2$	$Pd(OAc)_2$	KOTFA (1.0)	49
12[f]	$Cu(OAc)_2$	$Pd(OAc)_2$	KOTFA (3.0)	70
13[g]	$Cu(OAc)_2$	$Pd(OAc)_2$	K_2CO_3 (2.0)	93

[a] Reaction conditions unless otherwise specified: enaminone **1a** (0.1 M), trifluoroborate **2** (2−3 equiv), Pd(II) (0.3 equiv), oxidant (3 equiv) at 60 °C. [b] Isolated yield. [c] 2:3 **3a**/homodimer ratio. [d] 4-Methoxyphenylboronic acid (3 equiv) was used in the place of trifluoroborate **2.** [e] 1.0 equiv. [f] Complete in 3 h at 30 °C. [g] Trifluoroborate (2−3 equiv) was added slowly (see the Supporting Information for details).

[†] Department of Medicinal Chemistry, University of Kansas.
[‡] Center for Chemical Methodologies and Library Development, University of Kansas.
[§] University of Minnesota.

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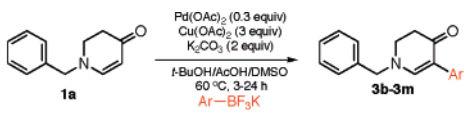
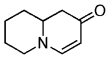
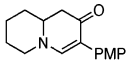
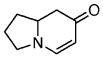
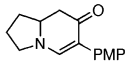
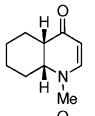
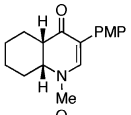
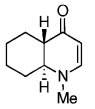
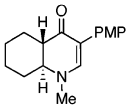
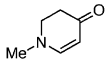
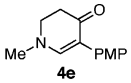
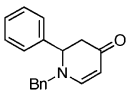
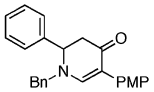
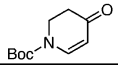
Table 2. Scope of Aryltrifluoroborates in C−H Functionalization



entry[a]	Ar (Product)	yield (%)[b]	entry[a]	Ar (Product)	yield (%)[b]
1	Ph (**3b**)	72	7	4-Br-C_6H_4 (**3h**)	73
2	4-Me-C_6H_4 (**3c**)	86	8	4-Cl-C_6H_4 (**3i**)	71
3	2-Me-C_6H_4 (**3d**)	40	9	2-Naphthyl (**3j**)	96
4	2-MeO-C_6H_4 (**3e**)	27	10	3,4,5-$(MeO)_3$-C_6H_2 (**3k**)	83
5	4-CF_3-C_6H_4 (**3f**)	44	11	3-HO-C_6H_4 (**3l**)	97
6	4-Ac-C_6H_4 (**3g**)	42	12	4-CbzNH-C_6H_4 (**3m**)	80

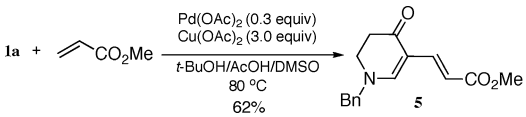
[a] Reaction conditions: enaminone **1a** (0.1 M), R-BF_3K (2−3 equiv), $Pd(OAc)_2$ (0.3 equiv), $Cu(OAc)_2$ (3 equiv), K_2CO_3 (2 equiv) in *t*-BuOH/AcOH/DMSO (20:5:1) at 60 °C. [b] Isolated yield.

Table 3. Scope of Enaminones in C−H Functionalization

entry[a]	enaminone	product		time (h)	yield (%)[b]
1			**4a**	3	98
2			**4b**	8	70
3			**4c**	7	86
4			**4d**	7	77
5		 **4e**	**4e**	6	80
6			**4f**	7	79
7		Not Observed		24	0[c]

[a] Reaction conditions: enaminone (0.1 M), trifluoroborate **2** (2−3 equiv), $Pd(OAc)_2$ (0.3 equiv), $Cu(OAc)_2$ (3 equiv), K_2CO_3 (2 equiv) in *t*-BuOH/AcOH/DMSO (20:5:1) at 60 °C. [b] Isolated yield. [c] Starting material was recovered. PMP = 4-methoxyphenyl.

to classical Suzuki-Miyaura protocols. We have also had success in the oxidative Heck coupling of enaminones with alkenes (eq 1) and will disclose our results in due time.[9]



(1)

An initial investigation of enaminone compatibility revealed that monocyclic and bicyclic, unattenuated enaminones were viable substrates in this reaction. These mildly acidic conditions are suitable for diastereomeric enaminones (Table 3, entries 3 and 4), which react with no observable epimerization. *N*-Boc-protected enaminones, however, were found to be unreactive under our optimized conditions, which we suggest is due to their decreased nucleophilicity (Table 3, entry 7).

We believe that the mechanism for palladation of enaminones resembles that of indoles,[1e] initiated by an electrophilic attack of palladium on the enaminone (**6**, Figure 2) and subsequent deprotonation. In the presence of an appropriate organometallic substrate, transmetalation and reductive elimination would provide the desired coupled product. Finally, in situ oxidation of Pd(0) to Pd(II) by $Cu(OAc)_2$ completes the catalytic cycle. Alternatively, transmetalation may precede enaminone palladation providing an intermediate that could favor homocoupling.

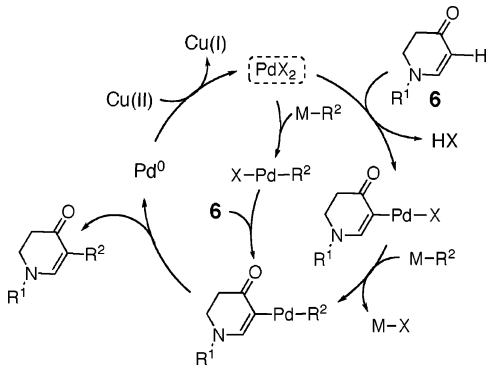


Figure 2. Proposed catalytic cycle for direct arylation of enaminones.

In summary, this methodology provides a direct method for the construction of 3-arylpiperidine scaffolds, a privileged structure and prevalent motif in many natural products. This method is a significant advance over the existing two-step method. This reaction also represents an unprecedented example of C−H functionalization on enaminones (a *nonaromatic* enamine system).

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Supporting Information Available: Representative experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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