Communication

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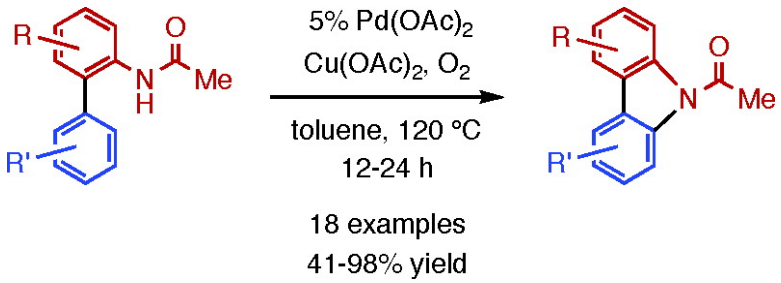

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Combined C−H Functionalization/C−N Bond Formation Route to Carbazoles

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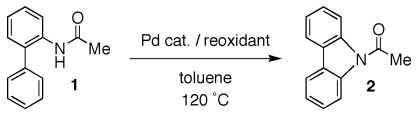
The prevalence of heterocycles in medicinally important compounds continues to drive the need for new methods for their preparation.[1,2] The majority of nitrogen heterocycles are prepared by processes in which a carbonyl is condensed with a nitrogen nucleophile. An attractive alternative to this protocol is to construct the heterocyclic ring and the C−N bond simultaneously by the combination of a nitrogen-containing functional group and an arene, alkene, or alkane. In this communication, we disclose a new method in which the combination of an amide and an unactivated arene, under palladium catalysis, can be used to efficiently produce a series of carbazoles, the derivatives of which have important photophysical and biological properties.[3] The key feature of this method is the combination of C−H functionalization and C−N bond-forming processes.

Our group has a long-standing interest in the formation of aromatic carbon−nitrogen bonds via both Pd- and Cu-catalyzed combination of aryl halides and sulfonates with amines and related nucleophiles.[4] We wondered whether it would be possible to affect a similar catalytic C−N bond formation in which a C−H bond was directly "substituted". In recent years, significant progress has been made in combining selective C−H functionalization and C−C bond-forming processes with the aid of a directing functional group.[5,6] Additionally, Stahl has described the synthetic equivalent of replacing a C−H bond with a C−N bond in the combination of phthalimide and aryl sulfonamide nucleophiles to both activated and unactivated olefins.[7,8] The directed *ortho*-functionalization of acetanilides, pioneered by Tremont[9] and elegantly employed in recent years,[10] provided a conceptual basis for our approach.

We began by studying the conversion of 2-acetaminobiphenyl (**1**) to *N*-acetyl carbazole (**2**) using a combination of a palladium precatalyst and a reoxidant (Table 1). Preliminary results suggested that the use of a combination of 5% $Pd(OAc)_2$ and a stoichiometric amount of $Cu(OAc)_2$ at 120 °C under an atmosphere of air or oxygen provided a near quantitative yield of **2** in toluene (Table 1, entries 5 and 6). We later found that a catalytic amount of $Cu(OAc)_2$ (10%, Table 1, entry 12) was sufficient to mediate the reoxidation process in the presence of oxygen and deliver **2** in comparable yields.

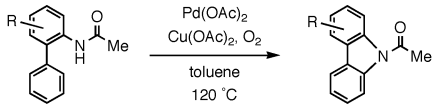
Table 1. Screen of Reaction Conditions for Carbazole Synthesis

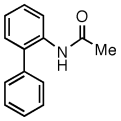
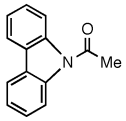
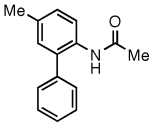
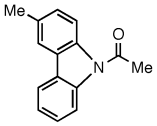
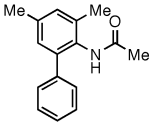
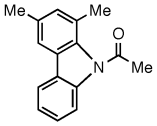
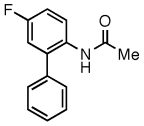
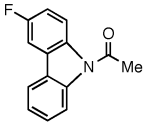
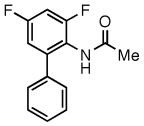
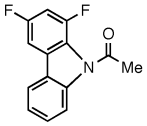
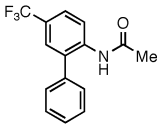
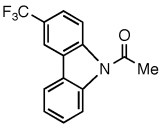


Entry	Pd catalyst	Reoxidant	Gas atm	Time (h)	Conv. (%)	Yield (%)[a]
1	25% $Pd(OAc)_2$	1 $Cu(OAc)_2$	air	24	93	76
2	25% $Pd(OAc)_2$		air	24	26	19
3		1 $Cu(OAc)_2$	air	24	<3	0
4	25% $Pd(OAc)_2$	1 benzoquinone	Ar	24	16	10
5	5% $Pd(OAc)_2$	1 $Cu(OAc)_2$	air	24	97	93[b]
6	5% $Pd(OAc)_2$	1 $Cu(OAc)_2$	O_2	18	>99	92
7	5% $Pd(O_2CCF_3)_2$	1 $Cu(OAc)_2$	O_2	24	82	70
8	5% $PdCl_2$	1 $Cu(OAc)_2$	O_2	24	31	21
9	5% $PdCl_2(CH_3CN)_2$	1 $Cu(OAc)_2$	O_2	24	38	27
10	5% $Pd(OAc)_2$	50% $Cu(OAc)_2$	O_2	24	>99	93
11	5% $Pd(OAc)_2$	25% $Cu(OAc)_2$	O_2	24	>99	93
12	5% $Pd(OAc)_2$	10% $Cu(OAc)_2$	O_2	24	>99	95

[a] GC yield versus internal standard. [b] Average of two runs, isolated yield: 94%.

Table 2. Cyclization of 2-Phenylacetanilides



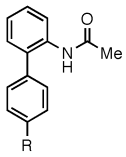
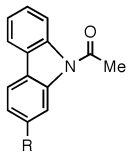
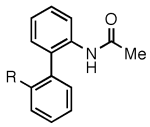
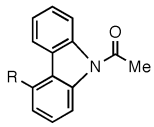
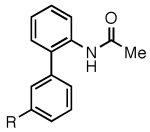
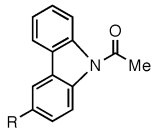
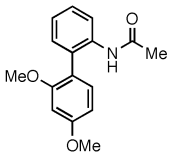
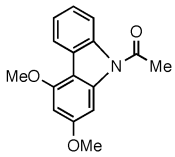
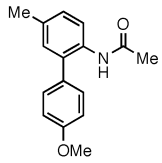
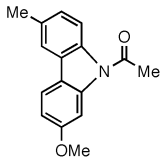
Entry	Substrate	Product	Yield (%)[a,b]
1			94
2			92
3			93
4			94
5			90
6			88

[a] Conditions: 5 mol % $Pd(OAc)_2$, 1 equiv $Cu(OAc)_2$, 1 atm O_2, 12−24 h. [b] Isolated yield after silica gel chromatography, average of two runs.

With these results in hand, we sought to examine the scope and generality of the method. Following a procedure for the Suzuki−Miyaura coupling reaction recently developed in our laboratory,[11] a series of substituted analogues of **1** were prepared by using 2-haloacetamides and the appropriate aryl boronic acid. As can be seen from the results in Table 2, the method tolerates substitution

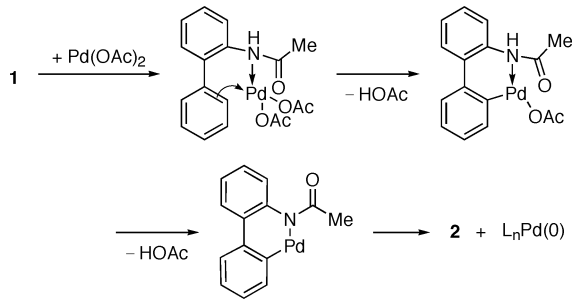
10.1021/ja055353i CCC: $30.25

Table 3. Cyclization of Substituted 2-Arylacetanilides

Entry	Substrate	Product	R	Yield (%)[a,b]
1			Me	98
2			*t*-Bu	96
3			OMe	97
4			CF_3	94
5			F	87
6			OMe	81
7			CF_3	81
8			F	78
9[c]			OMe	41[d]
10[c]			Me	82[e]
11				85
12				88

[a] For conditions, see Table 2. [b] Isolated yield after silica gel chromatography, average of two runs. [c] Only the major regioisomeric product is shown; yield corresponds to the major regioisomer. [d] Selectivity = 16:1 (GC). [e] Selectivity = 18:1 (GC).

Scheme 1. Possible Reaction Pathway for Conversion of **1** to **2**



on the "upper" aromatic group. In particular, the presence of a substituent adjacent to the acetamide moiety was inconsequential.

More in question was whether the method would tolerate the presence of substituents on the ring undergoing substitution. As the results shown in Table 3 attest, this process is compatible with a variety of electron-withdrawing and electron-donating groups.

In cases where two regioisomeric products could be obtained (Table 3, entries 9 and 10), the major carbazole product, as shown in the table, was formed with excellent selectivity (16:1 and 18:1). These results suggest that the ring-forming reaction may be controlled by steric factors.

On the basis of previous mechanistic studies in *ortho*-metalation reactions,[6] we propose a plausible reaction pathway, as shown in Scheme 1. Pre-association of the amide moiety of **1** to $Pd(OAc)_2$ facilitates the *ortho*-palladation process with concomitant release of an acetic acid. The formation of the six-membered palladacycle and subsequent reductive elimination leads to product **2** and Pd(0) compounds. The Pd(0) species are reoxidized to Pd(II) by $Cu(OAc)_2$, thus completing the catalytic cycle. Similar to the Wacker process,[12] the reduced Cu species are reoxidized to Cu(II) in the presence of oxygen and the acetic acid released from the palladation reactions.

In summary, we describe the tandem directed C−H functionalization and amide arylation for the efficient construction of substituted carbazoles. The products can be assembled in a simple two-step protocol from readily available reagents. Future investigations will focus on further expanding the scope of the reaction and gaining a mechanistic understanding of the process.

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

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