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Palladium-Catalyzed Heteroannulation of [60]Fullerene with Anilides via C−H Bond Activation

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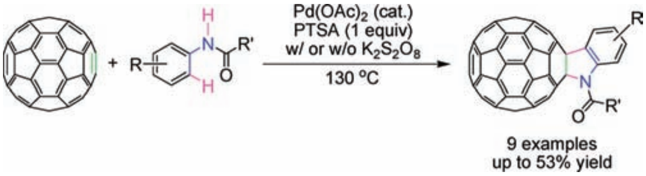
ABSTRACT



The palladium-catalyzed reaction of [60]fullerene with a variety of readily available anilides, initiated by C−H bond activation and followed by cyclization, afforded [60]fulleroindolines in a highly regioselective manner. A plausible reaction mechanism was proposed.

Fullerene chemistry has been extensively explored since the 1990s. Among the vast number of reactions discovered to functionalize fullerenes,[1] transition metal salt-mediated reactions of fullerenes are much less investigated.[2−11] Moreover, only a few of them utilized palladium complexes, in which a (sub)stoichiometric amount of palladium source was often needed.[3a−c] Recently, Itami's group reported the Pd-catalyzed hydroarylation of C_{60}[3d] as well as the Pd-catalyzed allylation and arylation of organo(hydro)fullerenes.[3e] More recently, we achieved the first synthesis of [60]fulleroindolines through Pd-catalyzed heteroannulation of C_{60} with *o*-iodoanilines.[3f] However, halide byproducts were produced, and quite a number of *o*-iodoanilines as starting materials are expensive or difficult to be prepared, thus limiting further application of this reaction. Obviously, developing a more economic and efficient method for the synthesis of fulleroindolines is highly desirable.

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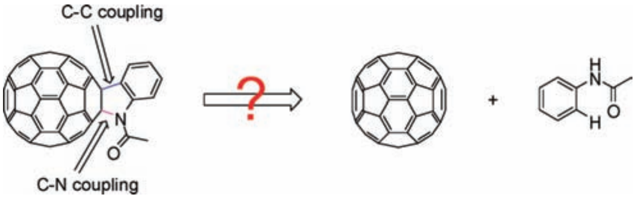
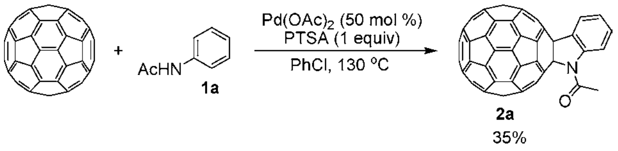
On the other hand, the C−H functionalization approach in organic synthesis has attracted great attention because of its economic and environmentally benign features.[12] Through the ortho C−H bond activation, selective oxidative couplings of anilides with alkyl halides,[13a] olefins,[13b−d] haloolefins,[13e] trialkoxyarylsilanes,[13f] arylboronic acids,[13g] aryl iodides,[13h] and simple arenes[13i] to construct C−C bonds have been reported. The C−N,[14a] C−X (X = Cl, Br),[14b] and C−O[14c] bond formations of anilides have also been demonstrated. However, to the best of our knowledge, the C−H bond activation strategy has not been applied to fullerene chemistry. We surmised that the reaction of C_{60} with readily available anilides, through C−C coupling initiated by C−H bond activation and then C−N coupling to furnish the cyclization, could be an alternative and more practical pathway for the synthesis of fulleroindolines, as shown in Scheme 1.

Scheme 1. Design of the Alternative Pathway for the Synthesis of [60]Fulleroindolines



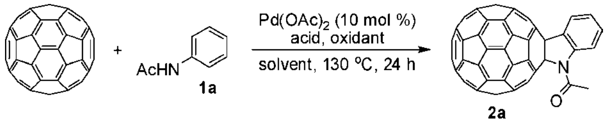
During the course of our work, a new Pd(II)-catalyzed 1,2-carboamination of electron-deficient dienes with *N*-aryl ureas, initiated by a urea-directed C−H bond activation, was reported.[15] *p*-Toluenesulfonic acid (PTSA) proves to have a large beneficial effect in the Pd-catalyzed C−H activation[13c,d,15,16] and thus was utilized in our investigation. Commercially available acetanilide **1a** was first chosen as the model substrate. At the onset, when a mixture of C_{60} (0.05 mmol) and acetanilide **1a** (5 equiv) was treated with $Pd(OAc)_2$ (50 mol %) and PTSA (1 equiv) in chlorobenzene (8 mL) at 130 °C for 30 min, much to our delight, 35% of the desired product **2a** was obtained along with 60% of recovered C_{60} (Scheme 2).

Scheme 2. Initial Result for the Synthesis of Product **2a**



The initial success encouraged us to focus on developing this reaction into a catalytic process. The loading of $Pd(OAc)_2$ was reduced to 10 mol %, and various reaction conditions including oxidants, acids, and solvent systems were screened. Due to the usage of catalytic amount of $Pd(OAc)_2$, an oxidant should be required to fulfill the catalytic cycle for the reaction of C_{60} and anilide **1a**. Therefore, the effect of oxidants on the reaction was first explored. The commonly used oxidants including $Cu(OAc)_2$,[14a,b] *p*-benzoquinone (BQ),[13c,d,16] Oxone,[17] and $K_2S_2O_8$[14c,17a] for the Pd-catalyzed C−H activations of arenes were examined. Copper salt $Cu(OAc)_2{\cdot}H_2O$ was found to afford product **2a**, yet in only 9% yield (Table 1, entry 1). *p*-Benzoquinone and Oxone gave the desired product with acceptable yields of 23% and 22% (entries 2 and 3). Nevertheless, $K_2S_2O_8$ provided a better result with a yield of 28% (entry 4). The choice of acid proved very crucial too. Without the addition of an acid, only a trace amount of product **2a** was obtained (entry 5). Other acids including

Table 1. Screening of the Reaction Conditions[a]



entry	acid	oxidant	solvent (mL)	yield (%)[b]
1	PTSA	$Cu(OAc)_2{\cdot}H_2O$	PhCl (10)/CH_3CN (0.5)	9 (82)
2	PTSA	BQ	PhCl (10)/CH_3CN (0.5)	23 (88)
3	PTSA	Oxone	PhCl (10)/CH_3CN (0.5)	22 (88)
4	PTSA	$K_2S_2O_8$	PhCl (10)/CH_3CN (0.5)	28 (85)
5	none	$K_2S_2O_8$	PhCl (10)/CH_3CN (0.5)	trace
6	CSA	$K_2S_2O_8$	PhCl (10)/CH_3CN (0.5)	15 (88)
7	PWA	$K_2S_2O_8$	PhCl (10)/CH_3CN (0.5)	<5%
8	PTSA	$K_2S_2O_8$	PhCl (10)/THF (0.5)	6 (86)
9	PTSA	$K_2S_2O_8$	PhCl (10)/DMF (0.5)	16 (70)
10	PTSA	$K_2S_2O_8$	ODCB (4)/CH_3CN (0.5)	39 (83)

[a] All the reactions were performed with 0.050 mmol of C_{60}, 0.25 mmol of **1a**, 0.050 mmol of acid, 0.25 mmol of oxidant, and 0.0050 mmol of $Pd(OAc)_2$ in the indicated solvent at 130 °C for 24 h. [b] Isolated yield. Values in parentheses were based on consumed C_{60}.

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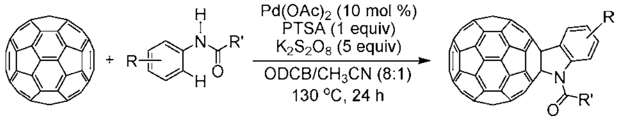
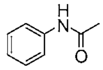
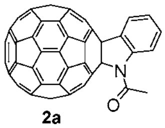
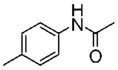
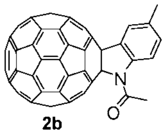
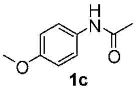
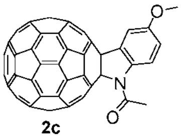
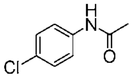
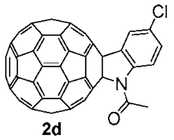
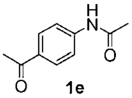
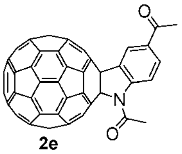
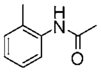
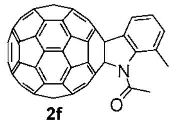
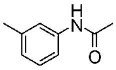
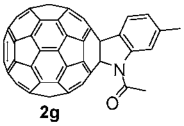
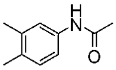
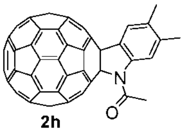
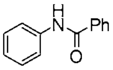
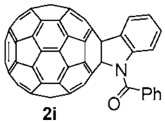
Table 2. Results for the Pd-Catalyzed Reaction of C_{60} with Anilides **1a−i**[a]



entry	substrate **1**	product **2**	yield (%)[b]	recovered C_{60} (%)
1	 **1a**	 **2a**	39 (83)	53
2	 **1b**	 **2b**	40 (78)	49
3	 **1c**	 **2c**	41 (87)	53
4	 **1d**	 **2d**	34 (85)	60
5[c]	 **1e**	 **2e**	20 (91)	78
6[d]	 **1f**	 **2f**	36 (78)	54
7	 **1g**	 **2g**	43 (77)	44
8	 **1h**	 **2h**	33 (87)	62
9	 **1i**	 **2i**	53 (69)	23

[a] Unless otherwise specified, all the reactions were performed with 0.050 mmol of C_{60}, 0.25 mmol of **1**, 0.050 mmol of PTSA, 0.25 mmol of $K_2S_2O_8$, and 0.0050 mmol of $Pd(OAc)_2$ in ODCB (4 mL)/CH_3CN (0.5 mL) at 130 °C for 24 h. [b] Isolated yield. Values in parentheses were based on consumed C_{60}. [c] The reaction was performed with 0.050 mmol of C_{60}, 0.25 mmol of **1d**, 0.025 mmol of $Pd(OAc)_2$, and 0.050 mmol of PTSA in chlorobenzene (8 mL) at 130 °C for 1.5 h. [d] The reaction was performed with 0.050 mmol of C_{60}, 0.25 mmol of **1f**, 0.025 mmol of $Pd(OAc)_2$, and 0.050 mmol of PTSA in chlorobenzene (8 mL) at 130 °C for 0.5 h.

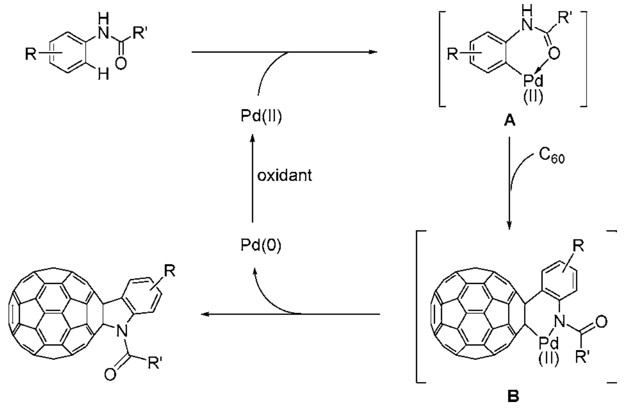
camphorsulfonic acid (CSA) and 12-phosphotungstic acid (PWA) were less effective, giving **2a** in 15% and <5% yields, respectively (entries 6 and 7). The critical role played by TsOH was believed to be the in situ formation of a more reactive mono- or bistosylate species from the $Pd(OAc)_2$ precatalyst,[15] thus promoting the current heteroannulation of C_{60}. The effect of solvents was also vital to the catalytic reaction. Notably, replacing CH_3CN with THF or DMF as the cosolvent led to an obvious decrease in the yield of product **2a** (entry 4 vs entries 8 and 9). It was reported that solvents showed drastic effects on palladium-mediated C−H functionalizations.[13a,b,14b,c] The poor results for THF and DMF relative to that of CH_3CN as the cosolvent might be due to their stronger coordination to the Pd catalyst, and hence hampering the catalytic reaction. To our satisfaction, the highest yield was achieved by decreasing the volume of the solvent to increase the reaction concentration. With a mixture of ODCB (4 mL) and CH_3CN (0.5 mL) as the solvent, product **2a** was obtained in 39% yield (entry 10). It should be noted that acetonitrile was added in the above conditions to increase the solubility of the employed inorganic salts.

With the optimal conditions in hand, the scope of this annulation was explored by using a variety of substrates as illustrated in Table 2. We were pleased to find that a wide variety of anilides could be employed and furnished the desired C_{60}-fused indoline derivatives **2a−i** in synthetically valuable yields. Substrates bearing electron-donating groups (**1b**, **1c**) and weak electron-withdrawing group (**1d**) on the para position of the phenyl ring afforded products **2b−d** in good yields comparable to that of anilide **1a** (Table 2, entries 2−4 vs entry 1). However, substrate **1e** substituted with an electron-withdrawing ketone group on the para position of the phenyl ring retarded the reaction obviously, giving the corresponding product **2e** only in 20% yield even by increasing the $Pd(OAc)_2$ loading to 50 mol % (Table 2, entry 5). It is known that ortho substitution inhibits[15] or hampers[13c,d] the Pd-catalyzed ortho C−H insertions. Therefore, it was not surprising that the *o*-methyl substitution on substrate **1f** greatly reduced the reaction yield and selectivity under standard reaction conditions. Fortunately, the corresponding product **2f** could be obtained in good yield utilizing 50 mol % of $Pd(OAc)_2$ only after 0.5 h (Table 2, entry 6). When anilides were substituted at the meta position, products resulting from the reactions at the less sterically hindered positions were regioselectively obtained in good yields (Table 2, entries 7 and 8). Interestingly, N-benzoylated aniline **1i** was found to be also an effective substrate and showed higher reactivity than acetanilide **1a** (Table 2, entry 9). Compared to our previous method[3f] for the synthesis of fulleroindolines, the present reaction allowed the synthesis of diverse fulleroindolines utilizing a wide variety of commercially available anilides as substrates and lower catalyst loading (down to 10 mol % $Pd(OAc)_2$ in most cases). In addition, functional groups such as Cl, CH_3CO, and CH_3O could be tolerated and did not alter the reaction site for the C−H bond activation.

Products **2a**[3f] and **2h**[3f] are known compounds, and their identities were confirmed by comparison of their spectral data with those reported previously by us. New compounds **2b**−**g** and **2i** were unambiguously characterized by their HRMS, ^{1}H NMR, ^{13}C NMR, FT-IR, and UV−vis spectral data. All of the MALDI or ESI FT-ICR mass spectra of these fulleroindoline products gave the correct molecular ion peaks. The ^{13}C NMR spectra of fulleroindolines **2b**−**g** and **2i** clearly exhibited less than 30 peaks with two half-intensity ones in the range of 134−153 ppm for the sp^2-carbons of the fullerene cage and two peaks at 86−87 and 70−72 ppm for the two sp^3-carbons of the fullerene skeleton, consistent with the C_s symmetry of their molecular structures. The chemical shifts for the two C_{60} sp^3-carbons of fulleroindolines **2b**−**g** and **2i** are close to those of fullerene derivatives with the nitrogen atom[1j,3f,18] and sp^2-carbon atom[3f,18] attached to the C_{60} skeleton, respectively. The typical chemical shifts at 167−172 ppm in the ^{13}C NMR spectra and the absorptions at 1661−1678 cm^{-1} in the IR spectra of **2b**−**g** and **2i** indicated the presence of an amide moiety. Their UV−vis spectra displayed a characteristic peak at 427−429 nm, which is a diagnostic absorption for the 1,2-adduct of C_{60}.[1j,3f,18]

On the basis of the above reaction results and previous acetamino-assisted Pd-catalyzed C−H bond functionalizations,[13,14] a plausible mechanism is shown in Scheme 3. The reaction is presumably initiated by an amide-directed insertion of Pd(II) complex into the aryl ortho C−H bond of anilides to afford intermediate **A**, followed by insertion of C_{60} into the arylpalladium bond to yield intermediate **B**. Subsequent reductive elimination of intermediate **B** generates fulleroindolines and Pd(0). The latter is reoxidized to Pd(II) by the oxidant to complete the catalytic cycle. The suggested ortho C−H insertion/carbopalladation/cyclization sequence for the Pd(II)-catalyzed 1,2-carboamination of dienes with *N*-aryl ureas[15] further supports our proposed reaction mechanism.

Scheme 3. Proposed Reaction Mechanism



In conclusion, we have successfully accomplished the synthesis of a wide variety of fulleroindolines in a highly regioselective manner via Pd-catalyzed annulation of C_{60} with readily available anilides instead of *o*-iodoanilines. Importantly, we have demonstrated the first example of exploiting the C−H bond activation strategy to functionalize fullerenes. A possible reaction mechanism was proposed to explain the formation of fulleroindolines.

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Supporting Information Available: Detailed experimental procedures and characterization data, as well as the ^{1}H NMR and ^{13}C NMR spectra of **2b**−**g** and **2i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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