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Synthesis of [60]Fullerene-Fused Tetrahydrobenzooxepine and Isochroman Derivatives via Hydroxyl-Directed C−H Activation/C−O Cyclization

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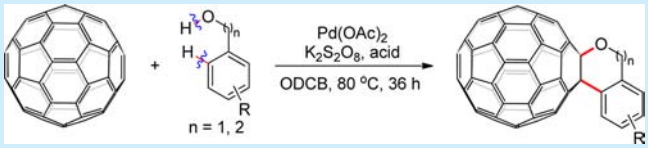
Supporting Information

ABSTRACT: The palladium-catalyzed hydroxyl-directed C−H activation/C−O cyclization reaction of [60]fullerene with 2-phenylethyl alcohols and benzyl alcohols afforded [60]-fullerene-fused tetrahydrobenzooxepine and isochroman derivatives in up to 43% yield. A plausible reaction mechanism is proposed, and the electrochemistry was also investigated.



Functionalization of fullerenes can not only maintain the unique characteristics of pristine fullerenes but also tune their properties by attaching proper organic addends.[1] Therefore, there is still demand for the development of new and useful methods for the functionalization of fullerenes. Although various reactions of [60]fullerene (C_{60}) mediated by transition metal salts[2−7] are well established, the Pd-catalyzed C−H activation strategy for the functionalization of C_{60} has still been underdeveloped.

The C−H activation/C−N cyclization strategy has been successfully applied to heteroannulations of C_{60} with various anilides,[8a] *N*-benzyl sulfonamides,[8b] *N*-substituted benzamides,[9a] and *N*-sulfonyl-2-aminobiaryls,[9b] affording C_{60}-fused indolines, tetrahydroisoquinolines, isoquinolinones, and azepines, respectively. Even though the formation of C_{60}-fused sultones via the Pd-catalyzed sulfonic acid group-directed C−H activation has been reported,[10] the challenging Pd-catalyzed hydroxyl-directed C−H activation has never been utilized to functionalize fullerenes. The Pd-catalyzed hydroxyl-directed C−H activation reactions remain scarce and difficult due to the possible oxidation, *β*-hydride elimination, and weak coordination of alcohols with Pd(II).[11] Until now, there are only three reports on the Pd-catalyzed olefination,[11a] intramolecular cyclization,[11b] and carbonylation[11c] of phenethyl alcohols. However, amino acid ligands and/or inorganic base additives are required to promote these C−H activations. It should be noted that the Pd-catalyzed C−H activation of benzyl alcohols has not been disclosed to date. In continuation of our research program on the functionalization of C_{60} via Pd-catalyzed C−H activation,[8,10] herein we report straightforward hydroxyl-directed C−H activation/C−O cyclization reactions of phenethyl alcohols and benzyl alcohols with C_{60} to acquire C_{60}-fused tetrahydrobenzooxepine and isochroman derivatives for the first time.

We commenced our study by examining the $Pd(OAc)_2$-catalyzed reaction of representative 2-phenylethanol (**1a**) with C_{60} under various reaction conditions (Table 1). At the outset, when a mixture of C_{60} (36 mg, 0.05 mmol) and 2-phenylethanol (**1a**) (2 equiv) was treated with $Pd(OAc)_2$ (10 mol %) and $K_2S_2O_8$ (2 equiv) in *o*-dichlorobenzene (ODCB) (2 mL) at 80 °C for 36 h, only a trace amount of the desired product **2a** was obtained (Table 1, entry 1). Being aware of the potential difficulty and weak coordination of alcohols with Pd(II),[11c] we set forth to investigate how to form a more reactive Pd catalyst. To our delight, when *p*-toluenesulfonic acid monohydrate (PTSA) was added, the yield was significantly improved to 40% (Table 1, entry 2). However, variation of the reaction temperature (Table 1, entries 3 and 4) or the reaction time (Table 1, entries 5 and 6) did not lead to an improvement of the yield. Nevertheless, the yield was sensitive to the molar ratio of starting materials. When the amount of substrate **1a** (Table 1, entry 7) or oxidant $K_2S_2O_8$ (Table 1, entry 9) was reduced, a significant decrease in the yield was observed. However, further increasing the amount of substrate **1a** (Table 1, entry 8) or oxidant $K_2S_2O_8$ (Table 1, entry 10) was not beneficial to improve the yield. Furthermore, the acid additives were also investigated. The use of mesitylenesulfonic acid dihydrate (MesSA) caused a slight decrease in the yield, giving **2a** in 37% yield (Table 1, entry 11). Other acids including camphorsulfonic acid (D-CSA), CH_3SO_3H, and HOAc gave **2a** in no more than 6% yield (Table 1, entries 12−14), while TFA was even totally inert to the reaction (Table 1, entry 15). Commonly used oxidants, such as NFSI, Oxone, $Cu(OAc)_2$, BQ, and $PhI(TFA)_2$, were also explored. The strongly oxidizing fluorinating reagent, NFSI, gave the desired product in 31%

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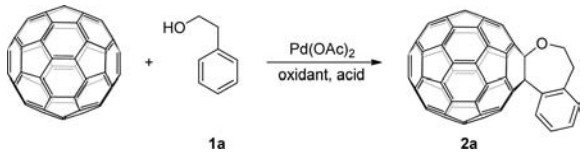
Table 1. Optimization of Reaction Conditions[a]



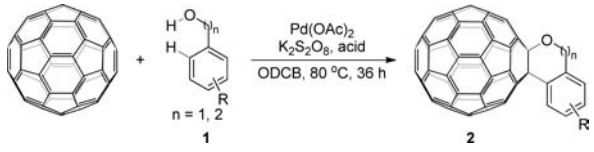
entry	molar ratio[b]	oxidant	acid	yield of **2a** (%)[c]
1	1:2:0.1:2:0	$K_2S_2O_8$	–	trace
2	1:2:0.1:2:1	$K_2S_2O_8$	PTSA	40 (53)
3[d]	1:2:0.1:2:1	$K_2S_2O_8$	PTSA	32 (53)
4[e]	1:2:0.1:2:1	$K_2S_2O_8$	PTSA	30 (48)
5[f]	1:2:0.1:2:1	$K_2S_2O_8$	PTSA	31 (53)
6[g]	1:2:0.1:2:1	$K_2S_2O_8$	PTSA	35 (42)
7	1:1:0.1:2:1	$K_2S_2O_8$	PTSA	31 (44)
8	1:3:0.1:2:1	$K_2S_2O_8$	PTSA	38 (52)
9	1:2:0.1:1:1	$K_2S_2O_8$	PTSA	30 (48)
10	1:2:0.1:3:1	$K_2S_2O_8$	PTSA	37 (44)
11	1:2:0.1:2:1	$K_2S_2O_8$	MesSA	37 (57)
12	1:2:0.1:2:1	$K_2S_2O_8$	D-CSA	6 (55)
13	1:2:0.1:2:1	$K_2S_2O_8$	CH_3SO_3H	trace
14	1:2:0.1:2:1	$K_2S_2O_8$	HOAc	trace
15	1:2:0.1:2:1	$K_2S_2O_8$	TFA	NR
16	1:2:0.1:2:1	NFSI	PTSA	31 (37)
17	1:2:0.1:2:1	Oxone	PTSA	10 (33)
18	1:2:0.1:2:1	$Cu(OAc)_2$	PTSA	5 (22)
19	1:2:0.1:2:1	BQ	PTSA	NR
20	1:2:0.1:2:1	$PhI(TFA)_2$	PTSA	—[h]

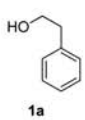
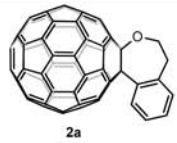
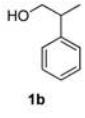
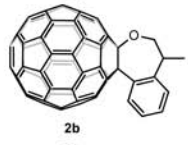
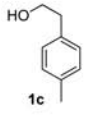
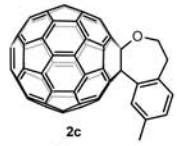
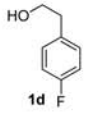
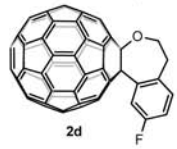
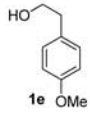
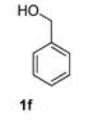
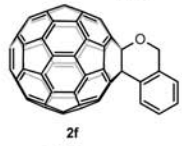
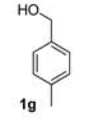
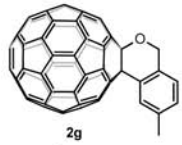
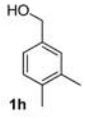
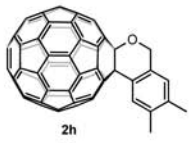
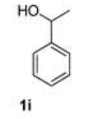
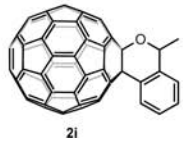
[a]Unless otherwise specified, all the reactions were performed with 0.05 mmol of C_{60}, 0.1 mmol of **1a**, 0.005 mmol of $Pd(OAc)_2$, 0.1 mmol of $K_2S_2O_8$, and 0.05 mmol of PTSA in ODCB (2 mL) at 80 °C for 36 h. [b]Molar ratio refers to C_{60}/**1a**/$Pd(OAc)_2$/oxidant/acid. [c]Values in parentheses were based on consumed C_{60}. [d]The reaction was performed at 70 °C. [e]The reaction was performed at 90 °C. [f]The reaction was performed for 24 h. [g]The reaction was performed for 48 h. [h]Complex. PTSA: *p*-toluenesulfonic acid monohydrate. MesSA: mesitylenesulfonic acid dihydrate. D-CSA: D-(+)-camphorsulfonic acid. NFSI: *N*-fluorobenzenesulfonimide.

yield (Table 1, entry 16), while Oxone and $Cu(OAc)_2$ were unfavorable to the reaction, giving only 10% and 5% yields, respectively (Table 1, entries 17 and 18). BQ and $PhI(TFA)_2$ failed to provide the desired product (Table 1, entries 19 and 20). Although polar cosolvents such as CH_3CN, DMSO, and DMF could increase the solubility of inorganic salts, they were deleterious to the weak coordination of alcohols with Pd(II), and no reaction occurred.[11]

With the optimal conditions in hand, we then examined the substrate scope. As shown in Table 2, a variety of 2-phenylethyl alcohols and benzyl alcohols could be converted to the desired products. Phenylethyl alcohol **1a** furnished the desired C_{60}-fused tetrahydrobenzooxepine **2a** in 40% yield (Table 2, entry 1). Gratifyingly, the methyl substituent at the *β*-position (**1b**) did not affect the reaction, delivering a yield of 42% (Table 2, entry 2). Substrates bearing an electron-donating group (**1c** and **1e**) or electron-withdrawing group (**1d**) on the phenyl ring could also be employed, affording the desired products in 20–31% yields (Table 2, entries 3–5). Furthermore, we found that benzyl alcohols were also compatible with this reaction protocol. When benzyl alcohol **1f** was used, it provided C_{60}-fused isochroman **2f** in 43% yield, showing the high efficiency of this C–H activation/C–O cyclization protocol (Table 2, entry 6). However, 4-methylbenzyl alcohol (**1g**) and 3,4-dimethylbenzyl alcohol (**1h**) gave inferior results as compared to nonsubstituted benzyl alcohol **1f**, furnishing the correspond-

Table 2. Results for the Pd-Catalyzed Reaction of C_{60} with 2-Phenylethyl Alcohols/Benzyl Alcohols 1a–i[a]



entry	substrate **1**	product **2**	yield (%)[b]
1			40 (53)
2			42 (61)
3			31 (72)
4[c]			20 (61)
5[c]			21 (50)
6			43 (80)
7			27 (61)
8[d]			24 (48)
9[e]			20 (45)

[a]Unless otherwise specified, all the reactions were performed with 0.05 mmol of C_{60}, 0.1 mmol of **1**, 0.005 mmol of $Pd(OAc)_2$, 0.1 mmol of $K_2S_2O_8$, and 0.05 mmol of PTSA in ODCB (2 mL) at 80 °C for 36 h. [b]Values in parentheses were based on consumed C_{60}. [c]0.05 mmol of MesSA was used instead of PTSA. [d]0.01 mmol of $Pd(OAc)_2$. [e]0.2 mmol of **1i** was used.

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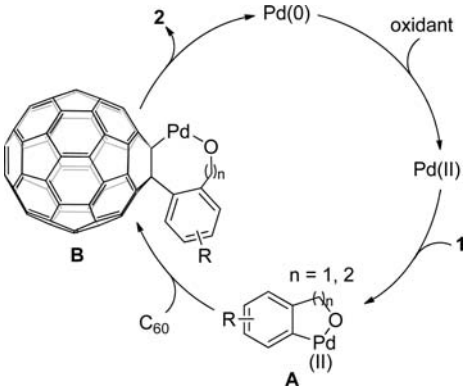
ing products **2g** and **2h** in 27% and 24% yields, respectively (Table 2, entries 7 and 8). The secondary alcohol **1i** could also be employed and gave the desired product **2i**, albeit in 20% yield even by increasing the amount of the substrate **1i** from 2 to 4 equiv (Table 2, entry 9). Unfortunately, tertiary alcohols were incompatible, probably due to the bulky steric effect. Although this protocol afforded the corresponding products in up to 43% yield, the efficiency and selectivity of the present reaction were not high because a notable amount of C_{60} was transformed to some unidentified byproducts as well as a small amount of the C_{60}-fused sultone resulted from C_{60} and PTSA.[10]

The structures of products **2a−i** were unambiguously characterized by MALDI-TOF MS, ^{1}H NMR, ^{13}C NMR, FT-IR, and UV−vis spectra. All of the mass spectra of these products gave the correct molecular ion peaks. The ^{1}H NMR spectra of **2a−i** showed all expected signals, with one less aromatic proton than the starting materials **1a−i** due to the removal of the ortho proton during the C−H activation process. In the ^{13}C NMR spectra of **2a−e** and **2i**, there were more than 44 peaks in the range 133−159 ppm with some overlapping ones for the 58 sp^2-carbons of the fullerene cage and two peaks at 91−94 and 61−71 ppm for the two sp^3-carbons of the fullerene skeleton, consistent with the C_1 symmetry of their molecular structures. The ^{13}C NMR spectra of **2f−h** displayed no more than 30 peaks with two half-intensity ones in the range 134−156 ppm for the sp^2-carbons of the fullerene cage, consistent with their C_s symmetry. It should be noted that the very low solubility of **2f** prevented us from identifying the two sp^3-carbons of the fullerene skeleton. The IR spectra of **2a−i** showed a strong absorption at about 1060 cm^{-1} due to the C−O bond. Their UV−vis spectra exhibited a peak at 430−434 nm, which is a characteristic absorption for the 1,2-adducts of C_{60}.

Based on the above reaction results and previous Pd-catalyzed hydroxyl-directed C−H activation,[11] a plausible mechanism is proposed in Scheme 1. It should be noted that

Scheme 1. Proposed Reaction Mechanism



our protocol did not require an extra base additive as well as an amino acid ligand.[11] It appears to involve the hydroxyl-directed insertion of a Pd(II) complex into the aryl *ortho* C−H bond of **1** to afford the six- or five-membered cyclic intermediate **A**, followed by insertion of C_{60} into the arylpalladium bond to yield the eight- or seven-membered-ring intermediate **B**. Subsequent reductive elimination of the intermediate **B** generates the product and Pd(0). The latter is reoxidized to a Pd(II) species by the oxidant to complete the catalytic cycle. In light of the weak coordination of Pd−OR species, PTSA is believed to *in situ* generate a more reactive mono- or bistosylate species from the $Pd(OAc)_2$ precatalyst.[8a,12] Alternatively, a Pd(II)/Pd(IV) catalytic cycle may also operate under the current strong oxidation conditions.

The half-wave reduction potentials of products **2a−i** along with C_{60} are summarized in Table 3. Both the seven- and six-membered-ring products had essentially the same CV behaviors and showed three reversible redox processes under our conditions (Supporting Information). The first reduction potentials of compounds **2a−i** were generally shifted to more negative values (Δ = 40−70 mV) when compared to that of C_{60}. Similar to the previous results, this shift can be attributed to the heteroatom attached to C_{60}.[5a,9a,13] Hashiguchi, Matsuo, and co-workers[5a] have reported that when fullerenyl esters (E_1 = −1.1 ev) with lower LUMO levels than that of PCBM were used as acceptors and PBDTTT instead of P3HT was used as the donor material to fabricate organic photovoltaic (OPV) devices, a power conversion efficiency of up to 1.3% could be obtained. Similarly, our synthesized C_{60}-fused tetrahydrobenzooxepine and isochroman derivatives with comparable LUMO levels may have potential application in OPVs by utilizing appropriate donor material.[5a]

Table 3. Half-Wave Reduction Potentials of 2a−i and C_{60}[a]

compd	E_1	E_2	E_3
C_{60}	−1.08	−1.47	−1.93
2a	−1.14	−1.53	−2.07
2b	−1.15	−1.53	−2.07
2c	−1.14	−1.52	−2.05
2d	−1.12	−1.51	−2.04
2e	−1.14	−1.52	2.05
2f[b]	−1.13	−1.51	−2.03
2g	−1.14	−1.51	−2.03
2h	−1.14	−1.53	−2.06
2i	−1.14	−1.53	−2.06

[a]Potential in V versus a ferrocene/ferrocenium couple. Experimental conditions: 0.1 mM of **2a−i**/C_{60} and 0.1 M of *n*-Bu_4NClO_4 in anhydrous ODCB; reference electrode, SCE; working electrode, Pt; auxiliary electrode, Pt wire; scanning rate, 20 mV s^{-1}. [b]Saturated solution.

In summary, we have successfully utilized the Pd-catalyzed hydroxyl-directed C−H activation/C−O cyclization strategy to functionalize C_{60} with both 2-phenylethyl alcohols and benzyl alcohols. The Pd-catalyzed C−H activation of benzyl alcohols has no precedent. Unlike the previous Pd-catalyzed hydroxyl-directed C−H activations,[11] our protocol does not require extra base additives as well as amino acid ligands, and both C_{60}-fused tetrahydrobenzooxepine and isochroman derivatives can be obtained for the first time.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data, the ^{1}H and ^{13}C NMR spectra, CVs, and DPVs of **2a−i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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