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Synthesis of [60]Fullerene-Fused Sultones via Sulfonic Acid Group-Directed C−H Bond Activation

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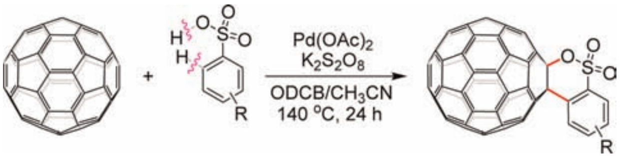
ABSTRACT



Functionalization with the sulfonic acid group as the directing group in a C−H activation reaction has been revealed for the first time. [60]Fullerene has been employed in the unprecedented palladium-catalyzed C−H activation reaction of arylsulfonic acids to afford [60]fullerene-fused sultones.

Transition-metal-mediated or -catalyzed reactions of fullerenes have provided useful methods for the preparation of a wide range of functionalized fullerene derivatives.[1] Our previous work in this direction has been focused on the free-radical reactions of [60]fullerene (C_{60}), which was mainly promoted by $Mn(OAc)_3$[2] and $Fe(ClO_4)_3$.[3] Recently, we have developed the Pd-catalyzed reactions of C_{60} and obtained novel C_{60}-fused indoline and isoquinolinone derivatives in a highly regioselective manner.[4]

On the other hand, C−H bond activation has emerged as one of the most important methodologies to construct C−C and C−X (X = heteroatom) bonds in organic synthesis.[5] A directing group is usually required to achieve high regioselectivity. A diverse range of directing groups, such as amides, anilides, pyridines, oxime ethers, quinolines, oxazolines, and amines, have been reported for C−H activation reactions.[5] However, only one type of acids, that is, carboxylic acid, has been exploited to direct C−H bond activations, and C−H halogenation, arylation, alkylation, olefination, hydroxylation, and carboxylation reactions

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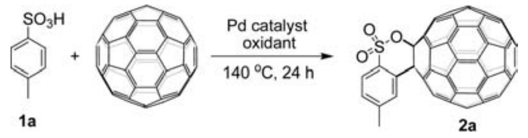
have been successfully realized.[6] Our interest in C−H activation reactions[4b,c,7] prompted us to explore another type of organic acids for directing C−H functionalization. *p*-Toluenesulfonic acid (TsOH) has been added frequently to promote Pd-catalyzed C−H activation reactions by increasing the electrophilicity of the Pd(II) center.[4b,8] Pd(OTs)$_2$ has also been employed as the palladium source in a few C−H activation reactions.[8b,9] Just like carboxylic acids, it is possible that arylsulfonic acids can be functionalized via sulfonic acid group-directed C−H activation. However, such TsOH derivatives have not been reported in all the aforementioned cases.[4b,8,9] The electron-deficient aryl ring of arylsulfonic acids is less prone to the C−H activation step compared to that of aryl carboxylic acids. We have addressed this challenge, and herein report the synthesis of sultones by Pd-catalyzed reaction of arylsulfonic acids with C$_{60}$ via unprecedented sulfonic acid group-directed C−H bond activation.

The readily available TsOH (**1a**) was chosen as a model substrate. Our initial attempts to olefinate TsOH failed with both acrylate esters and styrene under conditions previously employed for aromatic carboxylic acids[10] or other combinations of Pd(OAc)$_2$, oxidants, and solvents. Gratifyingly, when C$_{60}$ was utilized, TsOH could be functionalized to give C$_{60}$-fused sultone derivative **2a**. This sultone construction via Pd-catalyzed sp^2 C−H activation of arylsulfonic acids has no precedent in the literature.

This reaction of C$_{60}$ (36.0 mg, 0.05 mmol) with TsOH (3 equiv) was screened in the presence of different palladium catalysts (10 mol %), oxidants (3 equiv), and solvents. The results are summarized in Table 1. Because of the poor solubility of TsOH in ODCB, a mixture of ODCB (4 mL) and CH$_3$CN (0.5 mL) was first used as the solvent to afford product **2a** in 30% yield (73% based on consumed C$_{60}$) when the reaction was catalyzed with Pd(OAc)$_2$ (Table 1, entry 1). However, the absence of CH$_3$CN as the cosolvent lowered the yield to 11% (Table 1, entry 2). Replacing CH$_3$CN with DMSO and DMF generated only a trace amount of the desired product (Table 1, entries 3 and 4). Further examination of other oxidants, including Cu(OAc)$_2$, Cu(OTf)$_2$, AgOAc, Ag$_2$O, Ag$_2$CO$_3$, oxone, BQ, and PhI(OAc)$_2$, proved that K$_2$S$_2$O$_8$ was the best for this reaction with Pd(OAc)$_2$ as the catalyst and provided the highest product yield (Table 1, entry 1 vs entries 5−12). Similar superior performance of CH$_3$CN and K$_2$S$_2$O$_8$ was also observed previously for the Pd-catalyzed reaction of C$_{60}$ with anilides via C−H bond activation.[4b] The exact reason is unknown now, although the inefficiency of DMSO and DMF compared to CH$_3$CN might be due to their stronger coordination to the palladium species and thus inhibiting the catalytic reaction.[4b] With K$_2$S$_2$O$_8$ as the oxidant, various Pd catalysts were screened (Table 1, entries 13−16). It was found that Pd(TFA)$_2$ gave comparable yield to that of Pd(OAc)$_2$ (Table 1, entry 13 vs entry 1), while PdCl$_2$, Pd(PPh$_3$)$_2$Cl$_2$, and Pd(PPh$_3$)$_4$ exhibited slightly lower yields (Table 1, entries 14−16 vs entry 1). A control experiment showed that the absence of a palladium catalyst under otherwise identical conditions did not produce any **2a** (Table 1, entry 17). With economic considerations, the optimized reaction conditions were thus chosen as follows: Pd(OAc)$_2$ and K$_2$S$_2$O$_8$ as the catalyst and oxidant, respectively, in ODCB/CH$_3$CN = 8:1 at 140 °C for 24 h.

Table 1. Screening the Reaction Conditions for the Pd-Catalyzed Reaction of C$_{60}$ with **1a**[a]



entry	catalyst	oxidant	solvent (mL)	yield of **2a** (%)[b]
1	Pd(OAc)$_2$	K$_2$S$_2$O$_8$	ODCB/CH$_3$CN (4:0.5)	30 (73)
2	Pd(OAc)$_2$	K$_2$S$_2$O$_8$	ODCB (4)	11 (61)
3	Pd(OAc)$_2$	K$_2$S$_2$O$_8$	ODCB/DMF (4:0.5)	trace
4	Pd(OAc)$_2$	K$_2$S$_2$O$_8$	ODCB/DMSO (4:0.5)	trace
5	Pd(OAc)$_2$	Cu(OAc)$_2$	ODCB/CH$_3$CN (4:0.5)	6 (33)
6	Pd(OAc)$_2$	Cu(OTf)$_2$	ODCB/CH$_3$CN (4:0.5)	5 (25)
7	Pd(OAc)$_2$	AgOAc	ODCB/CH$_3$CN (4:0.5)	11 (31)
8	Pd(OAc)$_2$	Ag$_2$O	ODCB/CH$_3$CN (4:0.5)	trace
9	Pd(OAc)$_2$	Ag$_2$CO$_3$	ODCB/CH$_3$CN (4:0.5)	trace
10	Pd(OAc)$_2$	oxone	ODCB/CH$_3$CN (4:0.5)	10 (27)
11	Pd(OAc)$_2$	BQ	ODCB/CH$_3$CN (4:0.5)	trace
12	Pd(OAc)$_2$	PhI(OAc)$_2$	ODCB/CH$_3$CN (4:0.5)	18 (41)
13	Pd(TFA)$_2$	K$_2$S$_2$O$_8$	ODCB/CH$_3$CN (4:0.5)	31 (72)
14	PdCl$_2$	K$_2$S$_2$O$_8$	ODCB/CH$_3$CN (4:0.5)	24 (80)
15	PdCl$_2$(PPh$_3$)$_2$	K$_2$S$_2$O$_8$	ODCB/CH$_3$CN (4:0.5)	27 (77)
16	Pd(PPh$_3$)$_4$	K$_2$S$_2$O$_8$	ODCB/CH$_3$CN (4:0.5)	26 (79)
17		K$_2$S$_2$O$_8$	ODCB/CH$_3$CN (4:0.5)	0 (0)

[a] All reactions were carried out with C$_{60}$ (36.0 mg, 0.05 mmol), catalyst (0.005 mmol), TsOH (28.5 mg, 0.15 mmol), and oxidant (0.15 mmol) in the indicated solvent at 140 °C for 24 h in air. [b] Isolated yield. Values in parentheses were based on consumed C$_{60}$.

The scope of this annulation reaction was investigated next by exploring different arylsulfonic acids. As shown in Table 2, a variety of arylsulfonic acids reacted efficiently to afford the desired C$_{60}$-fused sultones in synthetically valuable yields. Arylsulfonic acids with both electron-donating (Table 2, entries 1, 3, and 5) and electron-withdrawing (Table 2, entry 4) substituents on the phenyl ring could be smoothly transformed into the desired products in 18−30% yields (60−81% based on consumed C$_{60}$). β-Naphthylsulfonic acid (**1f**) could also be employed and furnished sultone **2f** in 22% yield (69% based on consumed C$_{60}$). In principle, two isomers could

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(8) For selected examples, see: (a) Boele, M. D. K.; van Strijdonck, G. P. F; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (b) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066. (c) Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 686.

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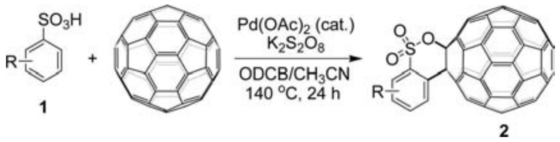
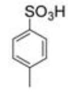
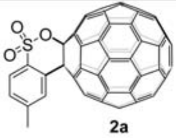
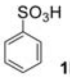
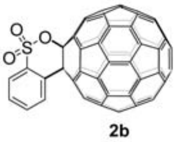
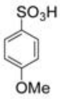
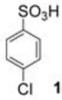
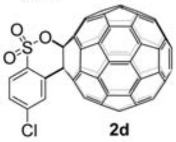
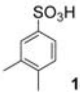
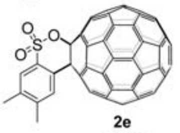
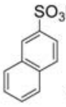
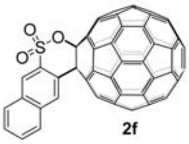
Table 2. Results for the Pd-Catalyzed Reaction of C_{60} with Arylsulfonic Acids **1a**−**f**[a]



entry	arylsulfonic acid **1**	product **2**	yield of **2** (%)[b]
1	 **1a**	 **2a**	30 (73)
2	 **1b**	 **2b**	24 (77)
3[c]	 **1c**	 **2c**	18 (60)
4	 **1d**	 **2d**	26 (74)
5	 **1e**	 **2e**	22 (81)
6	 **1f**	 **2f**	22 (69)

[a] Unless otherwise specified, all reactions were performed with C_{60} (36.0 mg, 0.05 mmol), **1** (0.15 mmol), $K_2S_2O_8$ (40.5 mg, 0.15 mmol), and $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) in ODCB (4 mL)/CH_3CN (0.5 mL) at 140 °C for 24 h. [b] Isolated yield by column chromatography. Values in parentheses were based on consumed C_{60}. [c] Substrate **1c** (30.9 mg, 0.15 mmol) was first dissolved in acetonitrile (0.5 mL) and then added to the ODCB (4 mL) solution of C_{60} (36.0 mg, 0.05 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), and $K_2S_2O_8$ (40.5 mg, 0.15 mmol).

be produced for the reaction with both **1e** and **1f**. The regioselective formation of **2e** and **2f** may be governed by steric factors.[4,7] It should be pointed out that the 18−30% yields (60−81% based on consumed C_{60}) of **2a**−**f** are comparable with the reported yields for most other monoadducts[2−4,11] in fullerene chemistry, as C_{60} has 30 reactive C═C bonds and tended to give a mixture of regioisomers from bisadducts and multiadducts when overreacted.

The structures of C_{60}-fused sultones **2a**−**f** were fully characterized by HRMS, ^1H NMR, ^{13}C NMR, FT-IR, and UV−vis spectroscopy. The high-resolution mass spectra of **2a**−**f** displayed the correct molecular ion peaks. The ^1H NMR spectra of **2a**−**f** showed all expected signals, with one less aromatic proton than the starting material **1a**−**f** due to the removal of one proton during the C−H activation process. In the ^{13}C NMR spectra of **2a**−**f**, there were 29−30 peaks including two half-intensity ones in the 134.60−153.19 ppm region for the 58 sp^2-carbons of the C_{60} moiety, consistent with their C_s symmetry. The two sp^3-carbons of the C_{60} skeleton were located at 97.56−98.25 ppm and 59.91−60.38 ppm, close to those of the previously reported C_{60}-fused lactone derivatives.[11] It should be pointed out that the very low solubility of **2c** prevented us from obtaining its ^{13}C NMR spectrum with good signal/noise ratio. The IR spectra of **2a**−**f** showed two strong absorptions at 1370−1377 and 1190−1200 cm^{-1} due to the sultone group. Their UV−vis spectra exhibited a peak at 421−422 nm, which is a characteristic absorption for the 1,2-adducts of C_{60}.[2−4,11]

Sultones exhibit biological activities[12] and are synthetically valuable heterocycles that can react with a variety of compounds to afford other useful products.[13] It is expected that our C_{60}-fused sultones can be further elaborated to produce functionalized fullerenes. Indeed, we successfully achieved the ring-opening of C_{60}-fused sultone **2a** by treating with excess $BF_3 \cdot OEt_2$ in ODCB at 150 °C and obtained arylsulfonic ester-substituted hydrofullerene **3** in 86% yield (Scheme 1). To the best of our knowledge, the unusual ring-opening of a sultone by $BF_3 \cdot OEt_2$ is also unprecedented. Hydrofullerene **3** was likely formed via the BF_3-mediated cleavage of diethyl ether followed by hydride transfer (see the Supporitng Information).[14] The acidic hydrogen attached to the fullerene skeleton in hydrofullerene **3** could be easily deprotonated with KO^tBu in THF at room temperature.[15] The color of the solution changed immediately from brown to dark green, indicating the formation of a monoanion $C_{60}R^-$. Further nucleophilic substitution reaction of the in situ generated $C_{60}R^-$ with CH_3I gave 1,4-bisadduct **4** in 82% yield (Scheme 1).[16] When the monoanion $C_{60}R^-$ was treated with I_2, the singly bonded dimer **5** existed as a mixture of *racemic* and *meso* isomers and was formed in 91% yield by coupling of the monomer radicals $C_{60}R^\bullet$,[17] which were produced by one-electron oxidation of $C_{60}R^-$ with I_2 (Scheme 1).[16]

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(11) For C_{60}-fused lactones, see: (a) Bernstein, R.; Foote, C. S. *Tetrahedron Lett.* **1998**, *39*, 7051. (b) Wang, G.-W.; Li, F.-B.; Zhang, T.-H. *Org. Lett.* **2006**, *8*, 1355. (c) Wang, G.-W.; Zhu, B. *Chem. Commun.* **2009**, 1769. (d) Li, F.-B.; Liu, T.-X.; Huang, Y.-S.; Wang, G.-W. *J. Org. Chem.* **2009**, *74*, 7743. (e) Li, F.-B.; Zhu, S.-E; Wang, G.-W. *Chin. Sci. Bull.* **2010**, *55*, 2909. (f) Li, F.-B.; You, X.; Wang, G.-W. *Org. Lett.* **2010**, *12*, 4896.

(12) (a) Meschkat, E.; Barratt, M. D.; Lepoittevin, J.-P. *Chem. Res. Toxicol.* **2001**, *14*, 110. (b) Pérez-Pérez, M.-J.; Balzarini, J.; Hosoya, M.; Clercq, E. D.; Camarasa, M. J. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 647.

(13) For a review on sultone chemistry, see: Metz, P. *J. Prakt. Chem.* **1998**, *340*, 1.

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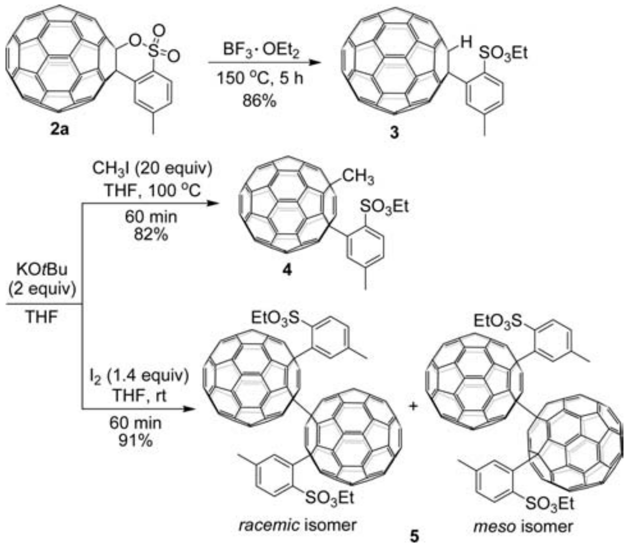
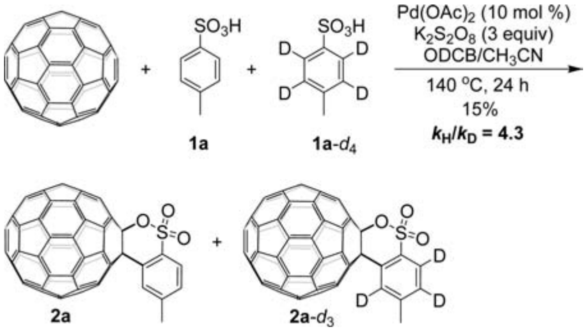
Scheme 1. Ring-Opening and Further Functionalization of Sultone **2a**



To gain insight into the reaction mechanism for the formation of sultones **2**, we performed a kinetic isotope effect (KIE) study. Experiments revealed that the Pd-catalyzed reaction of C_{60} with 1.5 equiv of **1a** and 1.5 equiv of **1a**-d_4 exhibited a primary kinetic isotope effect $k_H/k_D = 4.3$ (Scheme 2).

During our work, Bedford et al. reported the Pd-catalyzed *ortho*-selective halogenation of anilides in the presence of TsOH, and identified that the orthopalladated species of TsOH was actually the catalyst.[18] Nevertheless, the palladacyclic complex was fragile and underwent rapid loss of TsOH.[18] Therefore, the C−H functionalization of arylsulfonic acids is viewed to be extremely difficult. Although the exact reaction mechanism for the formation of **2** is currently unknown, the reaction is believed to proceed through the sulfonic acid group-directed *ortho* sp^2 C−H bond activation to afford the same palladacycles,[18] which undergo subsequent cyclization with C_{60} to eventually afford sultones **2**.

Scheme 2. Kinetic Isotope Effect Study for the Formation of Sultone **2a**



In summary, we have addressed the challenge of using the sulfonic acid group for directing C−H activation reactions for the first time. C_{60} could be successfully utilized in the Pd-catalyzed C−H activation of arylsulfonic acids leading to C_{60}-fused sultones, albeit the attempts to olefinate TsOH with acrylates and styrenes failed. The present reaction involves the cleavage of C−H and O−H bonds as well as the formation of C−C and C−O bonds. The unprecedented ring-opening of C_{60}-fused sultones was achieved by heating with $BF_3 \cdot OEt_2$, and could be further functionalized to 1,4-adduct and singly bonded fullerene dimer.

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Supporting Information Available. Experimental procedures, characterization data, and the ^1H NMR and ^{13}C NMR spectra of products **2a**−**f**, **3**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.