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Transformation of Carbonates into Sulfones at the Benzylic Position via Palladium-Catalyzed Benzylic Substitution

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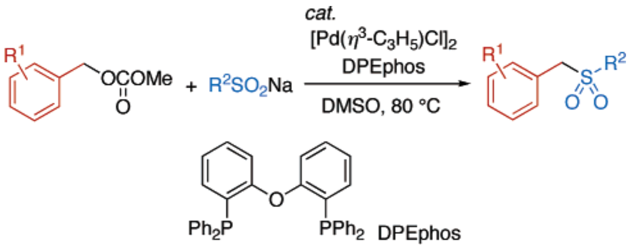
ABSTRACT



The nucleophilic substitution of benzylic carbonates with sodium arenesulfinates was catalyzed by the palladium complex generated in situ from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and DPEphos [bis(2-diphenylphosphinophenyl)ether]. The catalytic reaction proceeded in DMSO at 80 °C and gave a variety of benzylic sulfones in high yields.

The sulfonyl group is a strong electron-withdrawing group and stabilizes its α-carbanion.[1] The α-carbanion is readily generated by reaction with a base and reacts with various electrophiles such as alkyl halides and aldehydes.[2] The sulfonyl group is readily removed under mild reductive conditions. Reductive elimination of α-acetoxysulfones, which are obtainable through the aldol-type reaction of sulfones, yields olefins with high (*E*)-selectivity as compared to Wittig olefination.[3] Therefore, aryl alkyl sulfones are frequently used as key synthetic intermediates for various natural products.[4]

Aryl alkyl sulfones are typically prepared either by oxidation of thioether or by nucleophilic substitution of alkyl halide with sodium arenesulfinate. In the latter case, benzyl sulfones are prepared from benzylic halides. However, benzylic halides are sometimes lachrymatory and not always stable and easy to handle. A new synthetic pathway that does not use benzylic halides will expand the utility of benzylic sulfones in organic synthesis.

Allylic sulfones can be prepared from allylic acetates by means of homogeneous palladium catalysis, which involves the activation of an allylic C−O bond by palladium(0) and the nucleophilic attack of alkali metal arenesulfinate on (η^3-allyl)palladium.[5] This reaction has been utilized to prepare optically active allylic sulfones by means of asymmetric catalysis.[6]

Recently, we reported the palladium-catalyzed alkylation of stabilized carbanions or amines with benzylic carbonates.[7,8] The catalytic benzylation may involve an (η^3-benzyl)palladium intermediate. Herein, we describe a palladium-

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(1) (a) Bordwell, F. G.; Van der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1883−1885. (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.

(2) Reviews: Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019−2045.

(3) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833−4836. (b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563−2585.

(4) Recent examples: (a) Adams, C. M.; Ghosh, I.; Kishi, Y. *Org. Lett.* **2004**, *6*, 4723−4726. (b) Trost, B. M.; Shen, H. C.; Surivet, J.-P. *J. Am. Chem. Soc.* **2004**, *126*, 12565−12579. (c) Wang, Q.; Sasaki, N. A. *J. Org. Chem.* **2004**, *69*, 4767−4773.

(5) Representative examples: (a) Julia, M.; Nel, M.; Saussine, L. *J. Organomet. Chem.* **1979**, *181*, C17−C20. (b) Tamura, R.; Hayashi, K.; Kakihana, M.; Tsuji, M.; Oda, D. *Tetrahedron Lett.* **1985**, *26*, 851−854.

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catalyzed nucleophilic substitution of benzylic carbonates with sodium arenesulfinates. The catalytic reaction provides a new pathway for synthesizing benzylic sulfones from the corresponding alcohols, because benzylic carbonates are readily obtained from the esterification of benzylic alcohols with methyl chloroformate.

In our previous studies on palladium-catalyzed benzylation,[7] the yields of the benzylation products were strongly affected by the bite angle of the bidentate bisphosphine ligand on the palladium catalyst. The ligands DPPF[9] and DPEphos[10] were preferred for the benzylation of stabilized carbanions and amines, respectively. We evaluated the role of DPPF− and DPEphos−palladium catalysts in the reaction of benzyl methyl carbonate (**1a**) with sodium benzenesulfinate (**2a**) in THF at a catalyst loading of 5% palladium. Both the palladium catalysts efficiently promoted the sulfonylation of **1a**, thus producing the desired benzyl phenyl sulfone (**3a**) in 60−70% yields after 3 h. No benzyl benzenesulfinate resulting from O-attack of **2a** was detected by GC analysis of the reaction mixture. Use of DMSO as a solvent brought about significant enhancement of the reaction rate. The yield of **3a** by DPEphos was slightly higher than that of DPPF. The reaction of **1a** with **2a** was completed within 1 h at 80 °C in the presence of 1% DPEphos−0.5[Pd(η^3-C_3H_5)Cl]$_2$, and **3a** was isolated in 95% yield (Scheme 1).

Scheme 1. Reaction of Benzyl Methyl Carbonate (**1a**) with Sodium Benzenesulfinate (**2a**)

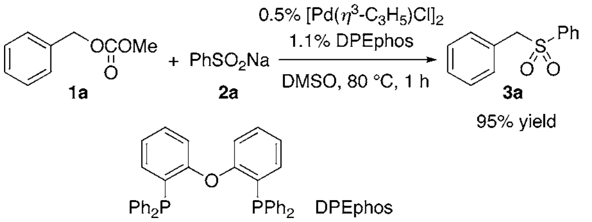
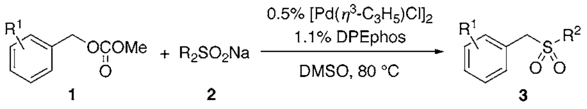
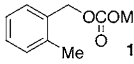
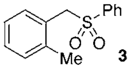
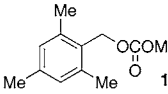
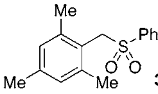
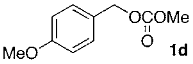
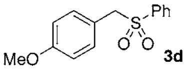
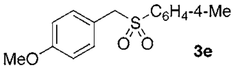
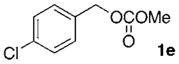
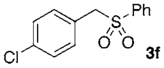
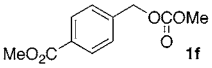
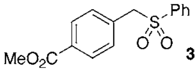
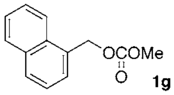
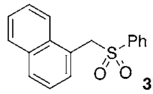
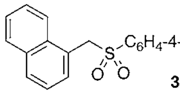
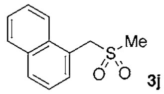
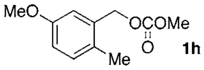
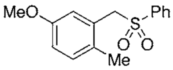
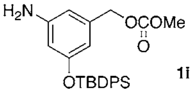
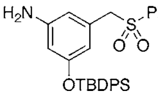


Table 1. Sulfonylation of Benzylic Carbonates (**1**)[a]



2a: R^2 = Ph, **2b**: R^2 = 4-MeC_6H_4
2c: R^2 = 4-ClC_6H_4, **2d**: R^2 = Me

entry	1	2	time, h	product (3)	yield, %[b]
1	 **1b**	**2a**	3	 **3b**	95
2	 **1c**	**2a**	48	 **3c**	89
3	 **1d**	**2a**	3	 **3d**	89
4	**1d**	**2b**	1	 **3e**	95
5	 **1e**	**2a**	24	 **3f**	90
6	 **1f**	**2a**	1	 **3g**	92
7	 **1g**	**2a**	1	 **3h**	95
8	**1g**	**2c**	1	 **3i**	80
9	**1g**	**2d**	1	 **3j**	99
10[c]	 **1h**	**2a**	24	 **3k**	77
11[d]	 **1i**	**2a**	4	 **3l**	72

[a] Reactions were conducted in DMSO (1.0 mL) at 80 °C. The ratio of **1** (1.0 mmol):**2**:[Pd(η^3-C_3H_5)Cl]$_2$:DPEphos was 100:110:0.5:1.1. [b] Isolated yield. [c] Reaction was conducted with 2 mol % palladium. [d] Reaction was conducted with 5 mol % palladium.

As seen in Table 1, a variety of benzylic sulfones were synthesized from benzylic carbonates by DPEphos−palladium catalysis. The ortho-substituted **1b** was converted into sulfone **3b** in 95% yield after 3 h (entry 1). However, the reaction of **1c** bearing two *ortho*-methyl groups proceeded sluggishly and afforded **3c** in 89% yield after 48 h (entry 2). Both electron-rich **1d** and electron-poor **1f** reacted rapidly with **2a** to yield **3d** and **3g**, respectively (entries 3 and 6). The sulfonylation of **1e** proceeded slowly compared to the above reactions (entry 5). The benzylation of sodium *p*-toluenesulfinate (**2b**) with **1d** proceeded well, and **3e** was produced efficiently (entry 4). However, the use of *p*-chlorobenzenesulfinate **2c** brought about a remarkable decrease in the catalytic efficiency and produced the corresponding sulfone in only 15% yield after 72 h. Methanesulfinate **2d** failed to react with **1d**, and no sulfone was obtained. In contrast, naphthylmethyl carbonate **1g** reacted with **2c** and **2d** as well as **2a**, and the sulfonylation products were obtained in high yields in all cases (entries 7−9). The palladium-catalyzed benzylic sulfonylation was effective in the preparation of **3k** and **3l**[11] (entries 10 and 11). The former

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(6) Representative examples: (a) Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662−9670. (b) Trost, B. M.; Crawley, M. L.; Lee, C. B. *J. Am. Chem. Soc.* **2000**, *122*, 6120−6121. (c) Eichelmann, H.; Gais, H.-J. *Tetrahedron: Asymmetry* **1995**, *6*, 643−646. (d) Gais, H.-J.; Eichelmann, H.; Spalthoff, N.; Gerhards, F.; Frank, M.; Raabe, G. *Tetrahedron: Asymmetry* **1998**, *9*, 235−248.

(7) (a) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104−12105. (b) Kuwano, R.; Kondo, Y. *Org. Lett.* **2004**, *6*, 3545−3547.

(8) Palladium-catalyzed substitution of (α-naphthyl)methyl acetate with malonate carbanion had been reported by Legros and Fiaud; see: (a) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1992**, *33*, 2509−2510. (b) Legros, J.-Y.; Toffano, M.; Fiaud, J.-C. *Tetrahedron* **1995**, *51*, 3235−3246.

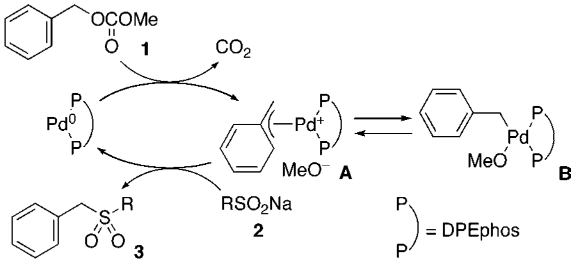
(9) DPPF = 1,1′-bis(diphenylphosphino)ferrocene: Sishop, J. J.; Davison, A.; Katcher, M. L.; Lichtenberg, D. W.; Merrill, R. E.; Smart, J. C. *J. Organomet. Chem.* **1971**, *27*, 241−249.

(10) DPEphos = bis(2-diphenylphosphinophenyl)ether: Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081−3089.

sulfone was a building block of (−)-calicopherol B,[12] and the latter was employed in the total synthesis of (+)-trienomycins A and F.[13]

A plausible mechanism of the catalytic sulfonylation is shown in Scheme 2. The benzylic C−O bond of **1** is cleaved by palladium(0) through a reaction pathway similar to the formation of (η^3-allyl)palladium from allylic esters.[14] The resulting (η^3-benzyl)palladium **A** reacted with nucleophile **2** to produce sulfone **3**. The intermediate **A** may isomerize to (η^1-benzyl)palladium **B** in the presence of methoxide.[15] However, **B** can revert to **A** when **A** is consumed during the nucleophilic attack of **2**. This mechanistic insight is consistent with the remarkable difference between the reactivities of **1b** and **1c** (Table 1, entry 1 vs entry 2). The two ortho substituents of **1c** sterically hinder the formation of **A**, while **1b** can afford (η^3-benzyl)palladium at the ortho position with no methyl group.

Scheme 2. Plausible Mechanism of Catalytic Sulfonylation



To confirm whether the nucleophilic attack of **2** on **A** is irreversible, the mixture of **3a** and **2b** was heated at 80 °C in DMSO in the presence of 5% DPEphos−palladium. No benzyl *p*-tolyl sulfone was detected in the GC analysis, and **3a** was recovered quantitatively. During the catalytic sulfonylation, the C−S bond of product **3** was never cleaved by palladium(0), contrary to the case of allylic sulfones.[16]

In summary, we have realized the palladium-catalyzed sulfonylation of benzylic carbonates. To the best of our knowledge, the present sulfonylation is the first catalytic reaction involving the attack of an S-nucleophile on the (η^3-benzyl)palladium complex. This novel catalytic reaction will offer a new pathway for synthesizing sulfones from benzylic alcohols and is useful for the preparation of benzylic sulfone building blocks.

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Supporting Information Available: 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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[11] No benzylation of the unprotected amino group in **1i** was observed.

[12] Taber, D. F.; Jiang, Q.; Chen, B.; Zhang, W.; Campbell, C. L. *J. Org. Chem.* **2002**, *67*, 4821−4827.

[13] Smith, A. B., III; Barbosa, J.; Wong, W.; Wood, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 8316−8328.

[14] MO study on oxidative addition of allylic ester to palladium(0): Suzuki, T.; Fujimoto, H. *Inorg. Chem.* **1999**, *38*, 370−382.

[15] Nagayama, K.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 799−803.

[16] Allylic sulfones are usable as substrates in palladium-catalyzed allylic substitutions; see: Trost, B. M.; Schmuff, N. R.; Miller, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 5979−5981.