C–H Functionalization

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Benzofurans Prepared by C–H Bond Functionalization with Acylsilanes**

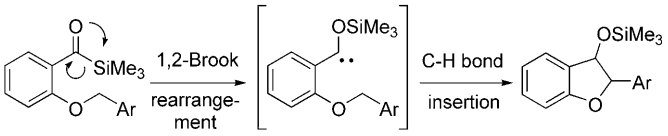
*Zengming Shen and Vy M. Dong**

Dedicated to Professor Adrian Brook on the occasion of his 85th birthday

The functionalization of inert carbon–hydrogen bonds has emerged as an exciting strategy in organic synthesis as it enables unconventional and remarkable bond-forming reactions.[1] Within the broad field of C–H bond functionalization, the insertion of carbenes into C–H bonds is arguably the best approach for directly elaborating a C–H bond into a C–C bond.[2] However, this strategy remains limited by the methods and precursors available for generating carbene intermediates. While many creative carbene insertions have been accomplished, the vast majority of these processes have focused on diazocarbonyl compounds as the carbene precursors.[2] Herein, we report a novel and operationally simple strategy for functionalizing benzylic sp^3-hybridized C–H bonds. This method features the use of siloxycarbenes generated directly from acylsilanes by a microwave-assisted Brook rearrangement.

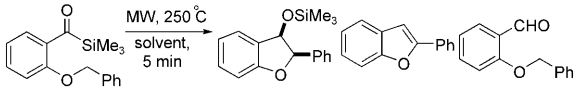
Our strategy for C–H bond functionalization is inspired by Adrian Brook's discovery of the unique ability of acylsilanes to undergo thermal and photochemically induced 1,2 silicon-to-oxygen migration.[3] The Brook rearrangement of acylsilanes has been featured in a range of umpolung processes with the acylsilanes acting as a carbonyl anion equivalent.[4] However, the synthetic utility of acylsilanes as siloxycarbene precursors has remained virtually unexplored since these seminal reports.[3] Inspired by these accounts, we envisioned that a thermally induced Brook rearrangement would generate a transient siloxycarbene that would undergo rapid insertion to a neighboring C–H bond (Scheme 1). Notably, this Brook rearrangement/insertion cascade would allow rapid access to important heterocyclic motifs[5] including dihydrobenzofurans. Few methods for making 2-phenyl-3-hydroxydihydrobenzofurans exist.[5a,6] Furthermore, methods such as the photoinduced cyclization of *o*-benzyloxybenzaldehyde[6] are plagued by competing radical pathways.

Our studies began with acylsilane **1a** derived from readily available methyl salicylate. Based on its demonstrated effectiveness for promoting a range of chemical processes in both academic and industrial settings,[7] we chose microwave irradiation to induce the desired thermal Brook rearrangement. A variety of high-boiling solvents were examined (Table 1). In accordance with our mechanistic design, irradiation of **1a** at 250 °C in *o*-dichlorobenzene for 5 min resulted in formation of the expected 3-silyloxy-2,3-dihydrobenzofuran **2a** in excellent yield (92 %) and good stereoselectivity (*cis*/*trans* 72:28; Table 1, entry 1). The major isomer was identified to be the *cis* diastereomer **2a** by single-crystal X-ray analysis.[8] Microwave heating of **1a** in nitrobenzene provided **2a** in quantitative yield, albeit with lower diastereoselectivity (*cis*/*trans* 67:33) (Table 1, entry 2).[9] A significant solvent effect was observed: when the reaction was conducted in ethyl benzoate (Table 1, entry 3) or DMSO (entry 4), the benzofuran product **3a** was obtained as the major product (72 % and 80 % yield, respectively). Formation of the benzofuran presumably occurs by loss of silanol from **2a**. The use of *N*-methylpyrrolidinone (NMP) and diethylene glycol diethyl



Scheme 1. Proposed mechanism for intramolecular C–H bond functionalization of acylsilanes.

Table 1: Solvent effects on the microwave-assisted Brook rearrangement.[a]



1a **2a** **3a** **4a**

Entry 1[a]	Solvent	**2a** [%][b] *cis*/*trans*[c]	**3a** [%][b]	**4a** [%][b]
1	*o*-dichlorobenzene	92 (72:28)	–	4
2	nitrobenzene	>99 (67:33)	–	–
3	ethyl benzoate	–	72	27
4	DMSO	–	80	20
5	NMP	–	–	50
6	diethylene glycol diethyl ether	–	–	22

[a] Reaction conditions: substrate **1a** (0.05 M), 250 °C, 5 min under microwave irradiation. [b] Yield was determined from the ^{1}H NMR spectrum yield with 1,3,5-trimethoxybenzene as the internal standard. [c] Determined by ^{1}H NMR spectroscopy.

[*] Dr. Z. Shen, Prof. V. M. Dong
Department of Chemistry, University of Toronto
80 St. George Street, Toronto, ON, M5S 3H6 (Canada)
E-mail: vdong@chem.utoronto.ca
Homepage: http://www.chem.utoronto.ca/staff/vdong

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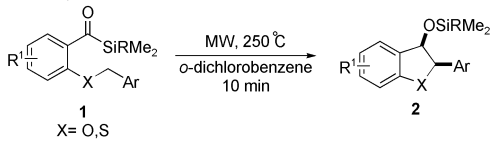
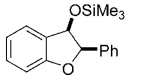
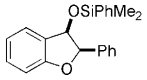
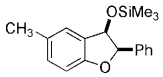
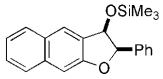
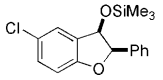
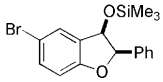
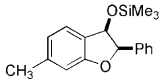
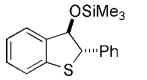
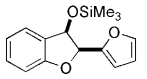
ether resulted in protodesilylation to form aldehyde **4a** as the major product (Table 1, entries 5 and 6).

We next examined the scope of acylsilane substrates by varying the substituents on the aromatic ring and the alkoxy chain (Table 2). The desired 2,3-dihydrobenzofuran **2a** could

Table 2: Microwave-assisted Brook rearrangement/C–H bond insertion yielding 2,3-dihydrobenzofurans.[a]



Entry	Product		Yield [%][b]	*cis*/*trans*[c]
1		**2a**	87	72:28
2		**2b**	72	67:33
3		**2c**	89	70:30
4		**2d**	74	69:31
5		**2e**	91	74:26
6		**2f**	82	74:26
7		**2g**	81	76:24
8		**2h**	53	25:75
9		**2i**	31	76:24

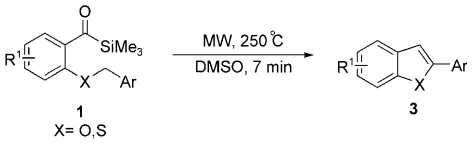
[a] Reaction conditions: substrate (0.2 mmol), *o*-dichlorobenzene (2 mL), 250 °C, 10 min, under microwave irradiation. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy.

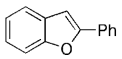
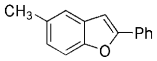
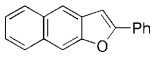
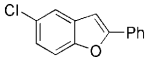
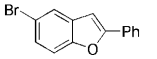
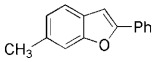
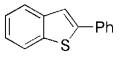
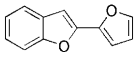
be isolated in good yield (87 %; Table 2, entry 1).[10] The sterically bulkier dimethylphenylsilyl substituent could also be tolerated in this process to provide the corresponding dihydrobenzofuran **2b** (72 % yield, *cis*/*trans* 67:33; Table 2, entry 2). A number of substrates investigated (including those with Me-, Cl-, and Br-substituted aromatic rings) underwent tandem Brook rearrangement and C–H bond insertion to provide the corresponding 2,3-dihydrobenzofurans in good to excellent yields (81–92 %; Table 2, entries 3 and 5–7) with moderate diastereocontrol (*cis*/*trans* 70:30 to 76:24). Notably, these products were generated efficiently after microwave irradiation for less than 10 minutes.

The 2-furylmethoxy substituent was not well tolerated in this process, and product **2i** was obtained in 31 % yield (*cis*/*trans* 74:26; Table 2, entry 9). The sulfur-containing 2,3-dihydrobenzothiophene could also be synthesized (53 % yield, *cis*/*trans* 25:75; Table 2, entry 8). However, under these reaction conditions, alkoxy-substituted derivatives **1j** and **1k** do not undergo the corresponding aliphatic C–H bond insertion.[11]

Remarkably, by simply using DMSO as the solvent, we could access benzofuran derivatives efficiently; this cascade sequence requires three distinct steps (Brook rearrangement, C–H bond insertion, and loss of silanol) (Table 3). The

Table 3: Cascade route to benzofurans consisting of Brook rearrangement, C–H bond insertion, and desiloxylation.[a]



Entry	Product		Yield [%][b]
1		**3a**	64
2		**3c**	65
3		**3d**	67
4		**3e**	61
5		**3f**	64
6		**3g**	50
7		**3h**	74
8		**3i**	38

[a] Reaction conditions: substrate (0.2 mmol), *o*-dichlorobenzene (2 mL), 250 °C, 10 min, under microwave irradiation. [b] Yield of isolated product.

competing byproduct formed is the aldehyde that results from protodesilylation of the acylsilane precursor. Additives such as 4 Å molecular sieves, CaH_2 (1 equiv), and trimethylsilyl chloride (1 equiv) were ineffective at inhibiting this decomposition. Different substituents (e.g., CH_3, Cl, and Br) were tolerated on the aromatic ring and the corresponding benzofurans (**3c**, **3e**–**3g**) were obtained in 50 to 65 % yield (Table 3, entries 2 and 4–6). The naphthyl-based acylsilane was transformed into product **3d** in 67 % yield (Table 3, entry 3). Notably, the sulfur-containing heterocycle **3h** could be obtained in 74 % yield (Table 3, entry 7). The 2-furyl substituent was tolerated to some extent as **3i** was isolated in 38 % yield (Table 3, entry 8).

In summary, we have designed and executed a new approach to forming 2,3-dihydrobenzofuran and benzofuran derivatives under microwave irradiation. This C–H bond-functionalization strategy involves a thermally induced Brook rearrangement to form a putative siloxycarbene intermediate. Solvents play a critical role in product selectivity. We are currently focused on identifying catalysts to promote this new

transformation and further exploring the use of acylsilanes as carbene precursors.

Experimental Section

Representative procedure for microwave-assisted siloxycarbene C–H bond insertion in *o*-dichlorobenzene: A solution of **1a** (0.20 mmol, 56.8 mg) in anhydrous *o*-dichlorobenzene (2.0 mL) was heated to 250 °C under microwave irradiation in a sealed 5 mL vial (Biotage) for 10 min. The reaction mixture was then passed through a column of silica gel (eluted with 100 % pentanes until all the *o*-dichlorobenzene was removed, followed by elution with 10 % EtOAc/pentanes) to afford the diastereomers **2a** in 87 % yield. (*cis*/*trans* = 72:28). See the Supporting Information for details.

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Keywords: acylsilanes · Brook rearrangement · C–H insertion · carbenes

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[7] See: a) *Microwaves in Organic and Medicinal Chemistry* (Eds.: C. O. Kappe, A. Stadler), Wiley-VCH, Weinheim **2005**; b) M. Nüchter, B. Ondruschka, W. Bonrath, A. Gum, *Green Chem.* **2004**, *6*, 128 – 141.

[8] Removal of the silicon group from **2a** results in *cis*-2,3-dihydro-2-phenylbenzofuran-3-ol (**5a**), a derivative whose structure was determined by single-crystal X-ray analysis. See the Supporting Information for details.

[9] When a solution of **1a** in toluene was heated in an oil bath at 150 °C for 4 days, 2,3-dihydrobenzofuran **2a** was obtained in 84 % yield (determined by ^{1}H NMR spectroscopy) and 75:25 *cis*/*trans* selectivity.

[10] Reactions in freshly distilled *o*-dichlorobenzene afford higher yields presumably because trace water can promote the decomposition of the acylsilane to the aldehyde; see a) A. G. Brook, T. J. D. Vandersar, W. Limburg, *Can. J. Chem.* **1978**, *56*, 2758; b) A. G. Brook, N. V. Schwartz, *J. Org. Chem.* **1962**, *27*, 2311 – 2315.

[11] See the Supporting Information for structures and spectroscopic data of **1j** and **1k**.

