Small Ring Systems

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Silylative Cyclopropanation of Allyl Phosphates with Silylboronates**

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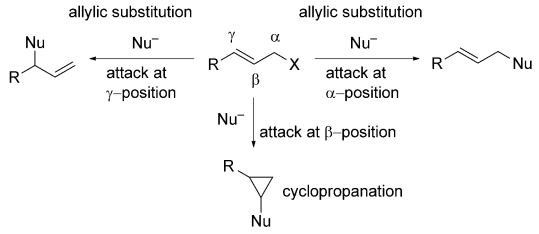
Abstract: *A potassium-bis(trimethylsilyl)amide-mediated cyclopropanation of allyl phosphates with silylboronates has been developed. Unlike the reported copper-catalyzed allylic substitution reactions, the nucleophile selectively attacks at the β-position of the allylic substrates under the present reaction conditions. The mechanism of this process has also been investigated, thus indicating the involvement of a silylpotassium species as the active nucleophilic component.*

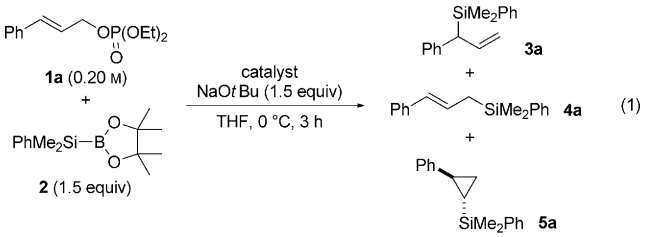
Changing the existing reaction patterns to unusual ones by adding catalysts or reagents represents a powerful approach to the development of new synthetic methods in organic chemistry. In this regard, the nucleophilic attack on an allylic electrophile at its β-position, rather than at the usual α- or γ-position, could lead to cyclopropanes instead of the allylic substitution products (Scheme 1). Except for the use of



Scheme 1. Allylic substitution versus cyclopropanation in the nucleophilic attack to an allylic electrophile.

Michael acceptors (R = electron-withdrawing group in Scheme 1),[1,2] which electronically facilitate the selective attack of a nucleophile at the β-position, a limited number of methods have been developed to date for cyclopropanation of less electronically biased allylic electrophiles (e.g., R = aryl, alkyl, H, etc.). For example, palladium-mediated[3] or palladium-catalyzed[4] cyclopropanation through π-allylpalladium intermediates have been reported by using enolate-based carbon nucleophiles for intermolecular reactions, as well as nitrogen[5] and oxygen[6] nucleophiles for intramolecular cyclization reactions, but the use of other heteroatom nucleophiles has been scarcely explored. In fact, a copper-catalyzed intermolecular borylative cyclopropanation[7] and an intramolecular silylative cyclopropanation using elaborate (allyloxy)silyllithiums generated in situ[8] have only been reported as far as we are aware. In this context, we herein describe the development of a potassium-bis(trimethylsilyl)-amide-mediated carbon–silicon bond-forming cyclopropanation of allyl phosphates with silylboronates, in the absence of any transition-metal catalysts, to provide straightforward access to silicon-containing cyclopropanes with high selectivity.

The reaction of allyl phosphates with silylboronates is known to be promoted by copper catalysts in the presence of a metal alkoxide or hydroxide base to give allylsilanes as the product through an allylic substitution pathway.[9,10] During the course of our study on the effect of a base on this copper catalysis, we unexpectedly found that a silylative cyclopropanation through nucleophilic attack at the β-position could take place when no copper catalysts were employed. Thus, a reaction of cinnamyl diethyl phosphate (**1a**) with 1.5 equivalents of the silylboronate **2**[11,12] in the presence of 5 mol% of CuI and 1.5 equivalents of NaO*t*Bu in THF at 0 °C gave only allylic substitution products as a mixture of the γ-substitution product **3a** (34% yield) and α-substitution product **4a** (51% yield) as shown in Equation (1) (THF = tetrahydrofuran).



(1)

catalyst = CuI (5 mol%): **3a** 34%, **4a** 51%, **5a** 0%
catalyst = none: **3a** 0%, **4a** 17%, **5a** 51%

In contrast, when this reaction was conducted in the absence of a copper catalyst under otherwise identical conditions, the cyclopropane *trans*-**5a** was obtained as the major product (51% yield) along with **4a** (17% yield).[13] Subsequently, we found that the use of KO*t*Bu[14] instead of NaO*t*Bu improved the selectivity towards **5a** (Table 1, entry 1 versus entry 2), and high selectivity of **5a** was realized by employing $KN(SiMe_3)_2$[15] (**5a**/**4a** = 99:1; entry 3). In comparison, the use of the related $NaN(SiMe_3)_2$ or $LiN(SiMe_3)_2$ resulted in somewhat lower selectivity of **5a** (entries 4 and 5). In addition, the use of a phosphate as the leaving group

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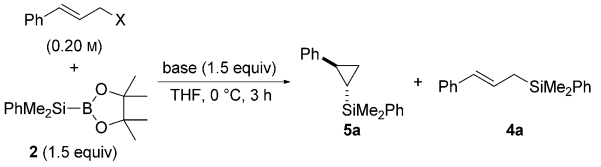
Table 1: Silylative cyclopropanation versus allylic substitution: Effect of bases and leaving groups.

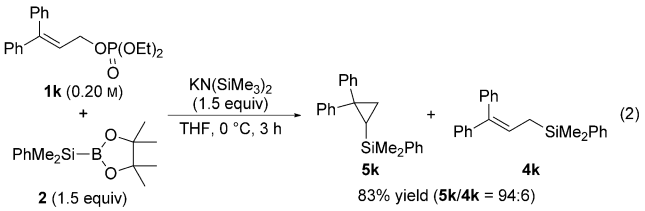


Entry	Substrate	Base	Yield [%][a] 5a + 4a	5a/4a[a]
1	**1a** (X=OP(O)(OEt)$_2$)	NaO*t*Bu	68	75:25
2	**1a**	KO*t*Bu	54	85:15
3	**1a**	KN(SiMe$_3$)$_2$	77	99:1
4	**1a**	NaN(SiMe$_3$)$_2$	83	77:23
5	**1a**	LiN(SiMe$_3$)$_2$	57	78:22
6	**6** (X=Cl)	KN(SiMe$_3$)$_2$	22	<1:99
7	**7** (X=OCO$_2$Et)	KN(SiMe$_3$)$_2$	0	–

[a] Determined by ^{1}H NMR spectroscopy.

was essential for the present silylative cyclopropanation. For example, cinnamyl chloride (**6**) gave only **4a** in 22% yield (entry 6) and cinnamyl ethyl carbonate (**7**) did not give any substitution or cyclopropanation products because of the decomposition of **7** under these reaction conditions (entry 7).

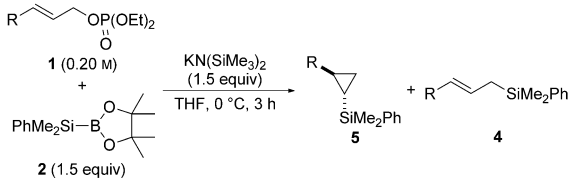
Under the reaction conditions described in Table 1, entry 3, several substituted phenyl groups are tolerated at the γ-position of allyl phosphates **1** for the reaction with **2** to give the corresponding cyclopropanes **5** as the major product, although the use of the electron-rich substrate **1e** results in somewhat lower selectivity (Table 2, entries 2–5). Substrates with naphthyl, thienyl, pyridyl, or alkenyl groups can also be employed with high selectivity toward the cyclopropanes **5**, albeit in a low yield for the pyridyl cyclopropane **5i** because of the partial decomposition of **1i** during the reaction (**5**/**4** ≥ 92:8; entries 6–10).[16] In addition to these γ-monosubstituted allyl phosphates, the γ,γ-disubstituted allyl phosphate **1k** is a suitable substrate and provides the cyclopropane **5k** selectively over the allylsilane **4k** in 83% combined yield as shown in Equation (2).



(2)

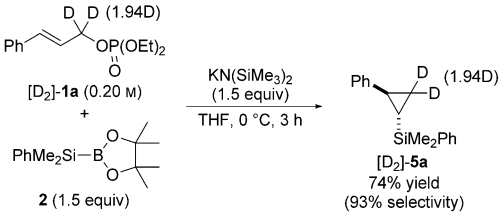
Having established the potassium bis(trimethylsilyl)-amide-mediated silylative cyclopropanation of allyl phosphates with a silylboronate, we turned our attention to understanding how this reaction takes place. At first, we confirmed that the silylation does occur at the β-position of allyl phosphates by employing the α,α-bis(deuterated) substrate [D$_2$]-**1a** as illustrated in Equation (3). To gain insights into the nature of the active nucleophilic component, we

Table 2: Silylative cyclopropanation of the allyl phosphates **1** with silylboronate **2**: Scope.



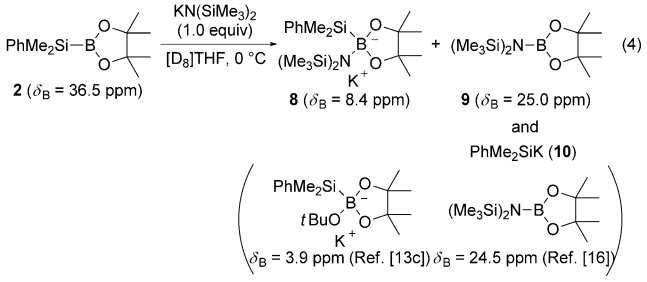
Entry	R	5[a]	Yield [%][b] 5 + 4	5/4[c]
1	(**1a**)	**5a**	71	99:1
2	Ph (**1b**)	**5b**	75	99:1
3	Cl (**1c**)	**5c**	68[d]	>99:1
4	OMe (**1d**)	**5d**	75	99:1
5	(**1e**)	**5e**	79	77:23
6	(**1f**)	**5f**	73	96:4
7	(**1g**)	**5g**	84	96:4
8	(**1h**)	**5h**	63	99:1
9[e]	(**1i**)	**5i**	38[f]	92:8
10[g]	Ph, Ph (**1j**)	**5j**[h]	71	93:7

[a] Obtained as a *trans* isomer unless otherwise noted. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Calculated yield of **5c** after silica gel chromatography (contained inseparable PhMe$_2$SiSiMe$_2$Ph; 10% based on **2**). [e] The reaction was conducted at −20 °C for 4.5 h. [f] Yield of **5i** + **4i** as determined by ^{1}H NMR analysis after silica gel chromatography. [g] The reaction was conducted at −20 °C for 6 h. [h] **5j** was obtained as a mixture of *trans*/*cis* = 94:6.

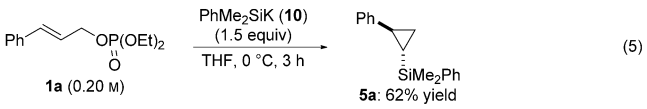


(3)

monitored a [D$_8$]THF solution of a 1:1 mixture of silylboronate **2** and potassium bis(trimethylsilyl)amide by ^{11}B NMR spectroscopy at 0 °C [Eq. (4)]. As a result, two broad peaks at $\delta = 8.4$ and 25.0 ppm were observed with the area ratio of 1:1.4. Based on the relevant literature precedents,[13b,c,17] these peaks could be assigned as tetracoordinated anionic boron species **8** and the desilylated three-coordinate boron species **9**,

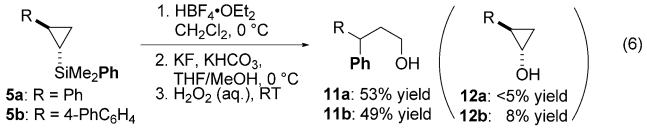


respectively. The formation of **9** indicates the generation of dimethylphenylsilylpotassium (**10**) as the byproduct,[18] which could be the active nucleophile in the present cyclopropanation. To probe its possibility, we separately prepared **10** by the known procedure from the corresponding disilane and metallic potassium[19] and reacted it with **1a** [Eq. (5)].



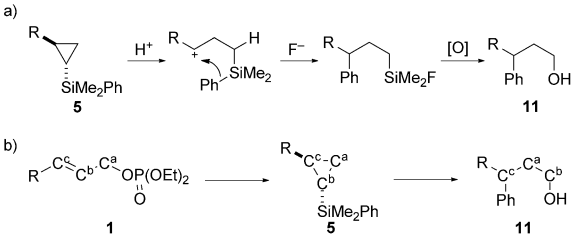
Under these reaction conditions, **5a** was obtained in 62% yield with no formation of **4a**. These results suggest that **10** is at least partially responsible as the active nucleophile in the present cyclopropanation using **2** and potassium bis(trimethylsilyl)amide.[20]

With regard to the derivatization of these cyclopropanes, we have found an unusual oxidation reactions using the Tamao–Fleming conditions.[21–23] Thus, in our preliminary experiment, the reaction of **5a** under the reaction conditions shown in Equation (6) preferentially produced the ring-



opened alcohol **11a** with concomitant migration of the phenyl group from silicon to carbon,[24,25] and almost no direct oxidation product (**12a**) was obtained. Similarly, the reaction of **5b** gave **11b** in 49% yield along with a minor amount of the cyclopropanol **12b**. These reactions presumably go through a pathway illustrated in Scheme 2a, and the overall two-step sequence from the allyl phosphate **1** to alcohol **11** through the cyclopropane **5** results in the skeletal rearrangement of the carbon framework as summarized in Scheme 2b.[26]

In summary, we have developed a potassium bis(trimethylsilyl)amide-mediated cyclopropanation of allyl phosphates with a silylboronate. Unlike the previously reported copper-catalyzed allylic substitution reactions, the nucleophile selectively attacks at the β-position of the allylic substrates under the present reaction conditions. We have also investigated the mechanistic aspect of this process and found that a silylpotassium species could be the active nucleophilic component.



Scheme 2. a) Proposed reaction pathway from **5** to **11** in Equation (6). b) Overall skeletal rearrangement of C^a-C^b-C^c from **1** to **11**.

Experimental Section

General procedure for reaction shown in Table 2: The silylboronate **2** (123 μL, 0.451 mmol) and THF (0.20 mL) were added to a solution of $KN(SiMe_3)_2$ (89.8 mg, 0.450 mmol) in THF (1.00 mL) at 0 °C. The compound **1** (0.300 mmol) was then added to the reaction mixture with additional THF (0.30 mL), and the resulting mixture was stirred for 3 h at 0 °C. After dilution with Et_2O, the reaction mixture was passed through a pad of silica gel with EtOAc, and the solvent was removed under vacuum. The residue was purified by silica gel preparative TLC with *n*-hexane/EtOAc to afford compound **5**/**4**.

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[1] For reviews, see: a) H. Pellissier, *Tetrahedron* **2008**, *64*, 7041; b) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977.

[2] For selected examples, see: a) S. Torii, H. Tanaka, Y. Nagai, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2825; b) R. Verhé, N. De Kimpe, L. De Buyck, D. Courtheyn, L. Van Caenegem, N. Schamp, *Bull. Soc. Chim. Belg.* **1983**, *92*, 371; c) M. P. Cooke, Jr., J. Y. Jaw, *J. Org. Chem.* **1986**, *51*, 758; d) E. Vilsmaier, R. Adam, C. Tetzlaff, R. Cronauer, *Tetrahedron* **1989**, *45*, 3683; e) S. Nakamura, Y. Watanabe, T. Toru, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3403; f) H.-S. Jeon, S. Koo, *Tetrahedron Lett.* **2004**, *45*, 7023; g) T. den Hartog, A. Rudolph, B. Marciá, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2010**, *132*, 14349.

[3] a) L. S. Hegedus, W. H. Darlington, C. E. Russell, *J. Org. Chem.* **1980**, *45*, 5193; b) H. M. R. Hoffmann, A. R. Otte, A. Wilde, *Angew. Chem.* **1992**, *104*, 224; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 234; c) A. Wilde, A. R. Otte, H. M. R. Hoffmann, *J. Chem. Soc. Chem. Commun.* **1993**, 615; d) A. R. Otte, A. Wilde, H. M. R. Hoffmann, *Angew. Chem.* **1994**, *106*, 1352; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1280; e) H. M. R. Hoffmann, A. R. Otte, A. Wilde, S. Menzer, D. J. Williams, *Angew. Chem.* **1995**, *107*, 73; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 100.

[4] a) M. Formica, A. Musco, R. Pontellini, K. Linn, C. Mealli, *J. Organomet. Chem.* **1993**, *448*, C6; b) A. Satake, T. Nakata, *J. Am. Chem. Soc.* **1998**, *120*, 10391; c) A. Satake, H. Koshino, T. Nakata, *Chem. Lett.* **1999**, 49; d) A. Satake, H. Kadohama, H. Koshino, T. Nakata, *Tetrahedron Lett.* **1999**, *40*, 3597; e) W. Liu,

D. Chen, X.-Z. Zhu, X.-L. Wan, X.-L. Hou, *J. Am. Chem. Soc.* **2009**, *131*, 8734.
[5] a) R. Grigg, M. Kordes, *Eur. J. Org. Chem.* **2001**, 707; b) R. Shintani, S. Park, F. Shirozu, M. Murakami, T. Hayashi, *J. Am. Chem. Soc.* **2008**, *130*, 16174; c) R. Shintani, T. Tsuji, S. Park, T. Hayashi, *J. Am. Chem. Soc.* **2010**, *132*, 7508; d) R. Shintani, K. Moriya, T. Hayashi, *Chem. Commun.* **2011**, *47*, 3057; e) R. Shintani, T. Ito, M. Nagamoto, H. Otomo, T. Hayashi, *Chem. Commun.* **2012**, *48*, 9936.
[6] R. Shintani, T. Ito, T. Hayashi, *Org. Lett.* **2012**, *14*, 2410.
[7] C. Zhong, S. Kunii, Y. Kosaka, M. Sawamura, H. Ito, *J. Am. Chem. Soc.* **2010**, *132*, 11440.
[8] A. Kawachi, H. Maeda, H. Nakamura, N. Doi, K. Tamao, *J. Am. Chem. Soc.* **2001**, *123*, 3143.
[9] a) L. B. Delvos, D. J. Vyas, M. Oestreich, *Angew. Chem.* **2013**, *125*, 4748; *Angew. Chem. Int. Ed.* **2013**, *52*, 4650; b) M. Takeda, R. Shintani, T. Hayashi, *J. Org. Chem.* **2013**, *78*, 5007.
[10] For recent reviews on Si–B compounds, see: a) M. Oestreich, E. Hartmann, M. Mewald, *Chem. Rev.* **2013**, *113*, 402; b) T. Ohmura, M. Suginome, *Bull. Chem. Soc. Jpn.* **2009**, *82*, 29.
[11] For pioneering work on the preparation and use of this silylboronate, see: a) M. Suginome, H. Nakamura, Y. Ito, *Chem. Commun.* **1996**, 2777; b) M. Suginome, T. Matsuda, Y. Ito, *Organometallics* **2000**, *19*, 4647.
[12] For selected recent examples for the transition-metal-catalyzed reactions using silylboronates, see: a) T. Ohmura, K. Masuda, M. Suginome, *J. Am. Chem. Soc.* **2008**, *130*, 1526; b) C. Walter, M. Oestreich, *Angew. Chem.* **2008**, *120*, 3878; *Angew. Chem. Int. Ed.* **2008**, *47*, 3818; c) K. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 2898; d) T. Ohmura, K. Oshima, H. Taniguchi, M. Suginome, *J. Am. Chem. Soc.* **2010**, *132*, 12194; e) E. Hartmann, M. Oestreich, *Angew. Chem.* **2010**, *122*, 6331; *Angew. Chem. Int. Ed.* **2010**, *49*, 6195; f) D. J. Vyas, M. Oestreich, *Angew. Chem.* **2010**, *122*, 8692; *Angew. Chem. Int. Ed.* **2010**, *49*, 8513; g) P. Wang, X.-L. Yeo, T.-P. Loh, *J. Am. Chem. Soc.* **2011**, *133*, 1254; h) K. Oshima, T. Ohmura, M. Suginome, *J. Am. Chem. Soc.* **2011**, *133*, 7324; i) C. Kleeberg, M. S. Cheung, Z. Lin, T. B. Marder, *J. Am. Chem. Soc.* **2011**, *133*, 19060; j) N. Saito, A. Kobayashi, Y. Sato, *Angew. Chem.* **2012**, *124*, 1254; *Angew. Chem. Int. Ed.* **2012**, *51*, 1228; k) T. Fujihara, Y. Tani, K. Semba, J. Terao, Y. Tsuji, *Angew. Chem.* **2012**, *124*, 11655; *Angew. Chem. Int. Ed.* **2012**, *51*, 11487; l) V. Cirriez, C. Rasson, T. Hermant, J. Petrignet, J. Díaz Álvarez, K. Robeyns, O. Riant, *Angew. Chem.* **2013**, *125*, 1829; *Angew. Chem. Int. Ed.* **2013**, *52*, 1785; m) C. Zarate, R. Martin, *J. Am. Chem. Soc.* **2014**, *136*, 2236.
[13] For examples of the usage of silylboronates in the absence of transition-metal catalysts, see: a) A. Kawachi, T. Minamimoto, K. Tamao, *Chem. Lett.* **2001**, 1216; b) J. M. O'Brien, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133*, 7712; c) H. Ito, Y. Horita, E. Yamamoto, *Chem. Commun.* **2012**, *48*, 8006; d) E. Yamamoto, K. Izumi, Y. Horita, H. Ito, *J. Am. Chem. Soc.* **2012**, *134*, 19997.
[14] Addition of silylboronates to styrenes catalyzed by KO*t*Bu has been reported in Ref. [13c].
[15] ICP-AES analysis of $KN(SiMe_3)_2$ (Aldrich, 95%) showed that detectable trace metals were Na (480 ppm), Mg (2.7 ppm), Ca (5.6 ppm), Fe (0.7 ppm), and Zr (0.2 ppm) where $1\ ppm = 1 \times 10^{-6}$ mg per 1 mg of $KN(SiMe_3)_2$.
[16] Notes: a) The substrates **1** bearing a heteroaryl group such as R = 2-furyl or 1-methyl-6-indolyl could not be employed because of their thermal instability. b) The substrates **1** bearing an alkyl group such as R = *n*-pentyl were not applicable to the present cyclopropanation, resulting in the exclusive formation of the allylic substitution products **4**.
[17] Y. Cui, W. Li, T. Sato, Y. Yamashita, S. Kobayashi, *Adv. Synth. Catal.* **2013**, *355*, 1193.
[18] Generation and spectroscopic confirmation of a silyllithium by the reaction of a silylboronate with MeLi or *n*BuLi have been reported in Ref. [13a]. Similarly, generation of a silylpotassium from a silylboronate and excess KO*t*Bu and a silylmagnesium bromide from a silylboronate and excess MeMgBr have also been suggested (with no spectroscopic evidence) in this paper.
[19] E. Buncel, T. K. Venkatachalam, B. Eliasson, U. Edlund, *J. Am. Chem. Soc.* **1985**, *107*, 303.
[20] We currently do not have a good explanation for the origin of the selective nucleophilic attack at the β-position. For relevant examples using silicon nucleophiles, see Refs. [8] and [13c].
[21] For a review, see: G. R. Jones, Y. Landais, *Tetrahedron* **1996**, *52*, 7599.
[22] a) K. Tamao, N. Ishida, T. Tanaka, M. Kumada, *Organometallics* **1983**, *2*, 1694; b) K. Tamao, N. Ishida, *J. Organomet. Chem.* **1984**, *269*, C37; c) K. Tamao, E. Nakajo, Y. Ito, *J. Org. Chem.* **1987**, *52*, 4412; d) K. Tamao in *Organosilicon and Bioorganosilicon Chemistry* (Ed.: H. Sakurai), Ellis Horwood, Chichester, **1985**, p. 231.
[23] a) I. Fleming, R. Henning, H. Plaut, *J. Chem. Soc. Chem. Commun.* **1984**, 29; b) I. Fleming, P. E. J. Sanderson, *Tetrahedron Lett.* **1987**, *28*, 4229.
[24] For a related example of the migration of a phenyl group from silicon to carbon, see Ref. [23a].
[25] For a review on the cleavage of aryl–silicon bonds, see: C. Eaborn, *J. Organomet. Chem.* **1975**, *100*, 43.
[26] This was confirmed by using [D_2]-**5a** (obtained from [D_2]-**1a**) for the ring-opening oxidation reaction. See the Supporting Information for details.

