ORGANIC LETTERS

2009
Vol. 11, No. 3
511−513

Si-Based Benzylic 1,4-Rearrangement/ Cyclization Reaction

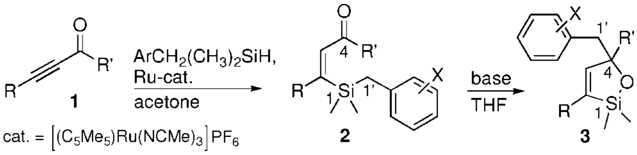
Barry M. Trost* and Andreas Bertogg

Department of Chemistry, Stanford University, Stanford, California 94305-5080

bmtrost@stanford.edu

Received October 2, 2008

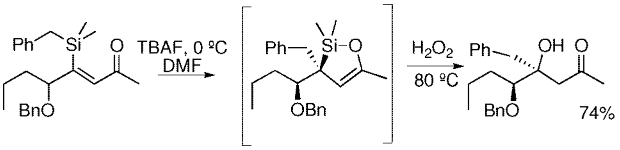
ABSTRACT



The trans-selective hydrosilylation of ynones (1) yields *β*-silylated enones (2) that undergo a benzylic 1,4-rearrangement/cyclization reaction in the presence of base, yielding 2,5-dihydro-1,2-oxasiloles (3).

Use of silicon compounds for the formation of C−C bonds has largely revolved around electrophilic substitutions involving allyl, vinyl, or aryl systems.[1] More recently, their use as nucleophilic partners in cross-coupling reactions has shown great promise.[2] In conjunction with our studies directed at a trans hydrosilylation,[3] we investigated a geminal alkylation−hydroxylation of alkynyl carbonyl compounds as shown in Scheme 1.[3b]

Scheme 1. Si-Based Benzylic 1,2-Shift



In conjunction with our studies of exploiting this process in complex natural product chemistry, we discovered a totally different and, to the best of our knowledge, unprecedented 1,4-shift in such substrates (**2**→**3**) in the presence of nonfluoride base to give 2,5-dihydro-1,2-oxasiloles (see abstract).[4]

The initial observation evolved from our efforts to examine a Peterson-style olefination as shown in Figure 1, path A.

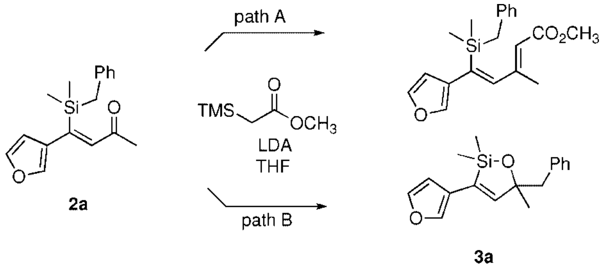


Figure 1. Discovery of the benzylic 1,4-shift.

---

[1] (a) Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*; John Wiley & Sons: Toronto, 2000; pp 569−595. Strained silacycles have also been used to transfer allyl and crotyl fragments with a high degree of enantioselectivity. (b) Burns, N. Z.; Hackman, B. M.; Ng, P. Y.; Powelson, I. A.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3811–3813. (c) Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 2796–2797. (d) Wang, X.; Meng, Q.; Perl, N. R.; Xu, Y.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12806–12807.

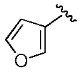
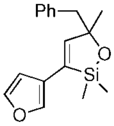
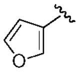
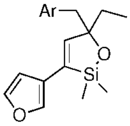
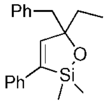
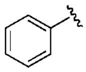
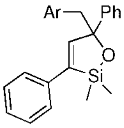
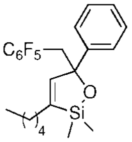
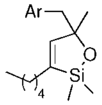
[2] (a) Hiyama, T.; Shirakawa, E. In *Cross-Coupling Reactions: A Practical Guide*; Miyaura, N., Ed.; Topics in Current Chemistry; Springer-Verlag: Berlin, Heidelberg, 2002, Vol. *219*. (b) Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P., Eds.; Wiley-VCH: Weinheim, 1998. (c) Hatanaka, Y.; Fukushima, S.; Hiyama, T. *Heterocycles* **1990**, *30*, 303–306. (d) Denmark, S.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835. (e) Denmark, S. E.; Tymonko, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 8004–8005.

[3] (a) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726–12727. (b) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2004**, *126*, 13942–13944. (c) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644–17655.

10.1021/ol802289f CCC: $40.75

Surprisingly, none of the expected enoate was observed. The mass spectrum and elemental analysis indicated a molecular formula of $C_{17}H_{20}O_2Si$. The infrared spectrum showed no carbonyl peaks. Combined with the ^1H and ^{13}C NMR spectra, the only structure that can be assigned is depicted as **3a** (see Table 1) which was further confirmed by subsequent transformations (vide infra).[5] Since the olefinating agent was clearly not involved, the reaction was repeated just with LDA and an even more hindered amide base, lithium *t*-butyltritylamide (LiTTA). Adding the base at −78° and allowing the reaction to warm to 0° before quenching gave the same product **3a**, which in the case of LiTTA as base was isolated in 86% yield (98% based on recovered starting material). A nonamide base, trityllithium, also promoted the reaction. In this case, keeping the reaction at −78° and quenching at that temperature gave a 66% conversion after 5.5 h.

Table 1. Novel 1,4-Rearrangement/Cyclization Reaction[a,b]

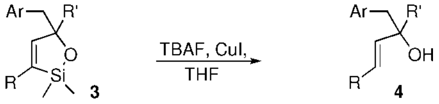
entry	R	R'	Ar	silacycle **3**		base	yield
a		CH_3	Ph	**3a**		LiTTA[c]	86%
b		C_2H_5	Ph	**3b**		LiTTA[c]	71%
c			C_6F_5	**3c**		$LiCPh_3$	95%
d			p-$CF_3C_6H_4$	**3d**		$LiCPh_3$	87%
e	Ph	C_2H_5	Ph	**3e**		LDA	76%[d]
f		Ph	Ph	**3f**		$LiCPh_3$[e]	86%
g			C_6F_5	**3g**		LDA	88%
h			p-$CF_3C_6H_4$	**3h**		LDA	90%
i	*n*-C_5H_{11}	Ph	C_6F_5	**3i**		LDA	60%
j	*n*-C_5H_{11}	CH_3	C_6F_5	**3j**		LDA	56%
k			p-$CF_3C_6H_4$	**3k**		$LiCPh_3$	43%

[a] A solution of the enone was treated with 1.00−1.25 equiv of the base indicated at −78 °C. The solution was either stirred and quenched at −78 °C (entries 3, 4, 7, 8, 9, 10, 11) or quenched after warming to 0 °C (entry 1), to 4 °C (entry 6) or rt (entries 2, 5). [b] Protocol of a typical rearrangement/cyclization reaction (**2h** → **3h**): A solution of (*Z*)-3-(dimethyl(4-(trifluoromethyl)benzyl)silyl)-1,3-diphenylprop-2-en-1-one (**2h**; 160 mg, 377 μmol, 1.00 equiv) in 0.8 mL of THF was treated with Li-diisopropylamide (798 mM solution in THF/hexanes; 590 μL, 471 μmol, 1.25 equiv) at −78 °C. After stirring for 1 h 40 min, the reaction was quenched by addition of phosphate buffer (pH = 7), extracted with diethyl ether, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography yielded 2,2-dimethyl-3,5-diphenyl-5-(4-(trifluoromethyl)benzyl)-2,5-dihydro-1,2-oxasilole (**3h**; 144 mg, 338 μmol, 90%) as a colorless solid. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.00$ (s, 3 H, $SiCH_3$), 0.40 (s, 3 H, $SiCH_3$), 3.29 (d, $J = 13.2$ Hz, 1 H, CH_2), 3.38 (d, $J = 13.2$ Hz, 1 H, CH_2), 7.23−7.36 (m, 9 H, 9 CH), 7.38−7.42 (m, 2 H, 2 CH), 7.49 (d, $J = 7.6$ Hz, 2 H, 2 CH), 7.53−7.56 (m, 2 H, 2 CH). $^{13}C\{^1H,^{19}F\}$ NMR ($CDCl_3$, 100 MHz): $\delta = 0.65$ ($SiCH_3$), 1.48 ($SiCH_3$), 49.7 (CH_2), 89.1 (C_{quat}), 124.6, 124.7, 125.1, 127.0, 127.1, 127.7, 128.7, 128.9, 129.0, 131.7, 137.3, 141.0, 141.4, 146.0, 147.1. $^{19}F\{^1H\}$ NMR ($CDCl_3$, 376.3 MHz): $\delta = -62.6$. IR (neat): ν (cm^{-1}) 3058, 3026, 2954, 1618, 1491, 1446, 1418, 1326, 1254, 1164, 1122, 1067, 1020, 955, 922, 881, 849, 824, 789, 756, 697, 635, 609. HRMS (EI): $(MNa)^+$ calcd for $C_{25}H_{23}OF_3SiNa$ 447.1368, found 447.1360. $C_{25}H_{23}F_3OSi$ (424.53): calcd C 70.73, H 5.46; meas. C 70.52, H 5.62. mp = 90.0 °C. [c] LiTTA is lithium *tert*-butyl(trityl)amide. [d] This reaction was performed on a 1.52 g (4.92 mmol) scale. [e] 2.00 equiv of base was employed.

To explore the generality of the process, a series of ynones were hydrosilylated using the Ru-catalyzed trans hydrosilylation protocol[3b] using the appropriately functionalized benzyldimethylsilane as summarized in Table 1. It is interesting to note that in the 1,4-rearrangement/cyclization reaction electron-deficient benzyl silanes work as well as benzylsilane itself. While LDA or trityllithium was generally used, LiTTA gave the cleanest reactions with the furyl substrates **2a**−**2d**. Given the basic nature of the reaction conditions, the effect of the presence of enolizable hydrogens in both R and R′ were explored. Interestingly, aryl−aryl, aryl−alkyl, alkyl−aryl, and alkyl−alkyl (for R and R′, respectively) all work with the alkyl−alkyl enones being the slowest. Regarding the migrating benzyl group, the more electron-deficient ones migrate the fastest.

To provide further proof of the structures of the 2,5-dihydro-1,2-oxasiloles **3**, we performed degradation reactions on several silacycles. Applying protodesilylation conditions to the silyl ethers provided *trans*-allylic alcohols (Table 2), thus proving both the correctness of our structural assignment and the unusual nature of the benzylic 1,4-shift. The transformation **3** → **4** represents a method for accessing stereodefined allylic alcohols from ynones that is comple-

Table 2. *Trans*-Allylic Alcohols: Proof of Structure



entry	substituent R	substituent R′	aryl substituent Ar	yield
1	C_6H_5	CH_2CH_3	C_6H_5	90%
2	3-furyl	CH_3	C_6H_5	81%
3	3-furyl	CH_2CH_3	C_6H_5	87%
4	3-furyl	CH_2CH_3	4-$(F_3C)C_6H_4$	88%

---

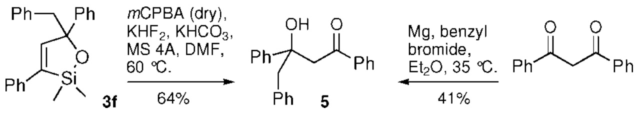
(4) A 1,4-shift of allyl or crotyl substituents from Si to carbonyl C under thermal conditions was reported recently. See: Bashiardes, G.; Chaussebourg, V.; Laverdan, G.; Pornet, J. *Chem. Commun.* **2004**, 122–123. An interesting allylic 1,4-rearrangement as part of a two-step process including a Rh-catalyzed silylformylation (notably, in this transformation no silacycle is isolated) was described. See: O'Malley, S. J.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 2915–1917. Applying thermal conditions (such as described by Bashiardes et al.) to the γ-silylated enones used in this study did not result in a rearrangement.

(5) The structural assignment for the 2,5-dihydro-1,2-oxasilole products by NMR experiments was verified based on two-dimensional NMR measurements for **3b**.

mentary to known protocols with respect to reaction conditions and reagents.

Furthermore, we subjected silacycle **3f** to Tamao−Fleming oxidation conditions (Scheme 2), leading to the isolation of the aldol **5**. The independent synthesis of this aldol structure by the addition of a benzyl Grignard reagent to 1,3-diphenyl-1,3-propanedione provided another proof for the structure of the silacycles **3**.

Scheme 2. Further Proof for Structure: Use of the Rearrangement As an Alternative Access to the Aldol Structural Motif



Earlier, we reported[3b] a benzylic 1,2-rearrangement which had been applied to substrates that are similar to the enones **2** used for the benzylic 1,4-rearrangement/cyclization reaction presented here. To verify that the two rearrangement reactions are independent processes, we subjected a *β*-silylated enone used herein to the reported reaction conditions (Figure 2). The experiment showed that the nature of the rearrangement (1,2- vs 1,4-shift) is determined by the reaction conditions, not by the structure of the substrate, and thus proved that the two processes under comparison are complementary. Mechanistically, initiation of the transformation by deprotonation appears unlikely given that nonenolizable substrates react the fastest. The lack of deuterium incorporation in the benzylic position upon quenching the reaction with D_2O at partial conversion also rules out any deprotonation there.

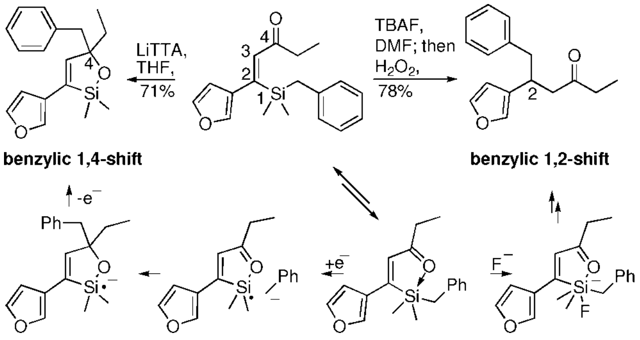


Figure 2. Benzylic 1,4-shift vs 1,2-shift: a mechanistic proposal.

The attractive interaction between carbonyl functions and silyl substituents in respective *cis*-olefins[6] increases the electrophilicity of the Si nucleus. The coordination of a relatively small fluoride anion to Si[3b] presumably puts the benzyl substituent in a pseudoaxial position thus facilitating a benzylic 1,2-shift. Since the use of sterically demanding bases as reagents excludes a coordination to Si, a single-electron transfer mechanism seems most likely, leading to a benzylic 1,4-shift. Following the reduction of the substrate to a radical anion, the benzyl substituent migrates as an anion. This view is supported by the fact that electron-withdrawing substituents at the benzyl substituents increase the rate of the reaction.

In summary, we have discovered a benzylic 1,4-rearrangement/cyclization reaction. Our current efforts focus on deepening our mechanistic understanding of this transformation.

Acknowledgment. We thank the NSF and the General Medical Sciences Institute of NIH (GM13598) for their support of our programs. We also thank the Swiss National Science Foundation and the Roche Research Foundation for fellowship support. Johnson-Matthey is greatly acknowledged for their generous gift of Ru salts.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802289F

---

(6) Shindo, M.; Matsumoto, K.; Shishido, K. *Angew. Chem., Int. Ed.* **2004**, 104–106.