ORGANIC LETTERS

2013
Vol. 15, No. 5
1104–1107

Geminal Bis(silyl) Enal: A Versatile Scaffold for Stereoselective Synthesizing C^3,O^1-Disilylated Allylic Alcohols Based upon Anion Relay Chemistry

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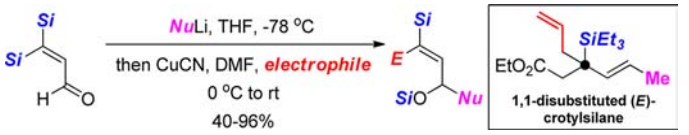
Received January 17, 2013

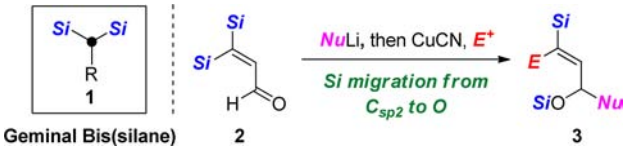
ABSTRACT



Geminal bis(silyl) enal 2a is shown to be a useful scaffold for anion relay chemistry (ARC) aimed at the stereoselective synthesis of C^3,O^1-disilylated allylic alcohols. The ARC reaction is initiated by the addition of an alkyllithium to the aldehyde and features a CuCN-promoted C^{sp2}-to-O 1,4-silyl migration to generate a vinylcuprate that reacts with activated electrophiles.

Geminal bis(silanes) **1** are a special type of organosilane in which two silyl groups are attached to one carbon center.[1] Although these molecules show potential as synthons in various contexts, so far they have been used primarily because of their bulkiness to prepare sterically demanding ligands for transition metal complexes.[2] To explore potential new reactivities and applications of this valuable species, we recently launched a series of investigations on geminal bis(silanes).[3] Our results so far show that these compounds exhibit attractive bifunctional reactivity, suggesting that they can contribute to a much broader range of reactions than previously thought.

Scheme 1. General Structure of Geminal Bis(silane) (left); CuCN-Promoted Anion Relay Chemistry of Geminal Bis(silyl) Enal (right)



Brook rearrangement,[4] which is the intramolecular migration of a silyl group from a carbon to an oxygen atom,

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(1) For selected studies on geminal bis(silanes), see: (a) Fleming, I.; Floyd, C. D. *J. Chem. Soc., Perkin Trans. 1* **1981**, 969. (b) Brook, A. G.; Chrusciel, J. J. *Organometallics* **1984**, *3*, 1317. (c) Klumpp, G. W.; Mierop, A. J. C.; Vrielink, J. J.; Brugman, A.; Schakel, M. *J. Am. Chem. Soc.* **1985**, *107*, 6740. (d) Bellasoued, M.; Majidi, A. *J. Org. Chem.* **1993**, *58*, 2517. (e) Lautens, M.; Delanghe, P. H. M.; Goh, J. B.; Zhang, C. H. *J. Org. Chem.* **1995**, *60*, 4213. (f) Princet, B.; Gariglio, H. G.; Pornet, J. *J. Organomet. Chem.* **2000**, *604*, 186. (g) Hodgson, D. M.; Barker, S. F.; Mace, L. H.; Moran, J. R. *Chem. Commun.* **2001**, 153. (h) Inoue, A.; Kondo, J.; Shinokubo, H.; Oshima, K. *Chem.—Eur. J.* **2002**, *8*, 1370. (i) Williams, D. R.; Morales-Ramos, A. I.; Williams, C. M. *Org. Lett.* **2006**, *8*, 4393.

(2) For the most recent examples, see: (a) Althaus, H.; Breunig, H. J.; Rösler, R.; Lork, E. *Organometallics* **1999**, *18*, 328. (b) Saito, M.; Tokitoh, N.; Okazaki, R. *J. Am. Chem. Soc.* **2004**, *126*, 15572. (c) Agou, T.; Sugiyama, Y.; Sasamori, T.; Sakai, H.; Furukawa, Y.; Takagi, N.; Guo, J. D.; Nagase, S.; Hashizume, D.; Tokitoh, N. *J. Am. Chem. Soc.* **2012**, *134*, 4120.

(3) (a) Song, Z. L.; Lei, Z.; Gao, L.; Wu, X.; Li, L. J. *Org. Lett.* **2010**, *12*, 5298. (b) Gao, L.; Lin, X. L.; Lei, J.; Song, Z. L.; Lin, Z. *Org. Lett.* **2012**, *14*, 158. (c) Sun, X. W.; Lei, J.; Sun, C. Z.; Song, Z. L.; Yan, L. J. *Org. Lett.* **2012**, *14*, 1094. (d) Gan, Z. B.; Wu, Y.; Gao, L.; Sun, X. W.; Lei, J.; Song, Z. L.; Li, L. J. *Tetrahedron* **2012**, *68*, 6928. (e) Lu, J.; Song, Z. L.; Zhang, Y. B.; Gan, Z. B.; Li, H. Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 5367. (f) Gao, L.; Zhang, Y. B.; Song, Z. L. *Synlett* **2013**, *24*, 139–144.

10.1021/ol400145z
Published on Web 02/15/2013

could potentially offer a very powerful method for the functionalization of organosilanes, if initiated by a nearby lithium alkoxide, which generated an organolithium or cuprate, to set up a subsequent trapping with an electrophile. Recent work with this reaction has led to many significant achievements in both areas of synthetic methodology and natural product synthesis.[5] For example, the group of Smith has developed a series of elegant reactions involving anion relay chemistry (ARC) over the past decade. In this approach, diverse organosilanes serve as linchpins in rapid multicomponent couplings that give complex molecules in a single step.[6] Herein we describe geminal bis(silyl) enal **2a** as a new type of scaffold that can undergo ARC via CuCN-promoted C^{sp2}-to-O 1,4-silyl migration[7] (Scheme 1). This approach provides an efficient starting point for the stereoselective synthesis of trisubstituted vinylsilanes, which can be further transformed into 1,1-disubstituted (*E*)-crotylsilanes. Crotylsilanes, in turn, can serve as useful synthons in the Sakurai reaction with acetals.

The required geminal bis(silyl) enals were synthesized by two different methods, routes A and B (Scheme 2). In route A, 3,3-bis(triethylsilyl) benzyl enol ether **4**[3a,d] underwent deprotonation and regioselective thiolation to give **5**,[8] which was transformed via *m*-CPBA oxidation[9] into geminal bis(triethylsilyl) enal **2a** in 54% overall yield. In route B, the known 3-iodide-substituted 3-trimethylsilyl allyloxysilane **6** first underwent a retro-Brook rearrangement to generate geminal bis(trimethylsilyl) allylic alcohol **7**,[10] which was then oxidized by IBX to provide enal **2b** in 75% overall yield.

Scheme 2. Synthesis of Geminal Bis(silyl) Enals **2a** and **2b**

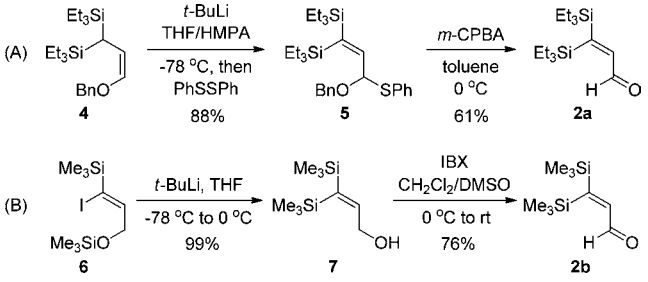


Table 1. Screening of Reaction Conditions

entry	sub.	*n*-BuLi (equiv)	add. (equiv)	Cu(I) (equiv)	**3**(%[c])	**8**(%[c])	**9**(%[c])
1	**2a**	2.0	HMPA (4.0)	---	**3a**: 0	**8a**: 46	**9a**: 0
2	**2a**	2.0	HMPA (4.0)	CuI (1.0)	**3a**: 0	**8a**: 42	**9a**: 0
3	**2a**	2.0	HMPA (4.0)	CuCN (1.0)	**3a**: 34	**8a**: 17	**9a**: 0
4	**2a**	2.0	THF/HMPA=1:3	CuCN (1.0)	**3a**: 15	**8a**: 22	**9a**: 28
5	**2a**	2.0	THF/DMF=1:3	CuCN (1.0)	**3a**: 57	**8a**: 9	**9a**: 0
6[a]	**2a**	2.0	THF/DMF=1:3	CuCN (2.0)	**3a**: 85	**8a**: 0	**9a**: 0
7	**2a**	1.2	THF/DMF=1:3	CuCN (2.0)	**3a**: 25	**8a**: 0	**9a**: 26
8	**2b**	2.0	THF/DMF=1:3	CuCN (2.0)	**3b**: 36	**8b**: 0	**9b**: 0

[a] Reaction conditions: **2a** (0.14 mmol) and *n*-BuLi (0.28 mmol) in THF (0.6 mL) at −78 °C for 30 min, followed by CuCN (0.28 mmol) in DMF (1.8 mL) at 0 °C for 30 min, and finally allyl chloride (0.42 mmol) at rt for 2 h. [b] The *E*-configuration was assigned based on NOE experiments on the corresponding allylic alcohol of **3c**. [c] Isolated yields after purification by silica gel column chromatography.

Using geminal bis(triethylsilyl) enal **2a** as a scaffold, we examined an ARC reaction involving 2.0 equiv of *n*-BuLi as the nucleophile and allyl chloride as the electrophile (Table 1). While 4.0 equiv of HMPA promoted silyl migration of the initially formed lithium alkoxide of **9a**, no further allylation occurred in the absence of any Cu(I) or in the presence of 1.0 equiv of CuI. Only protonated product **8a** was formed in ~40% yield (entries 1 and 2). Replacing CuI with CuCN led to the desired allylated product **3a**, but the yield was only 34% and **8a** was generated in parallel in 17% yield (entry 3). Interestingly, using a large excess of HMPA appeared to suppress silyl migration to a certain extent, giving **9a** in 28% yield (entry 4). Incorporating DMF as a cosolvent remarkably improved both the selectivity and yield of the reaction (entry 5).

(4) For reviews, see: (a) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77. (b) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065.

(5) For the selected advances, see: (a) Boyce, G. R.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8930. (b) Song, Z. L; Kui, L. Z; Sun, X. W.; Li, L. J. *Org. Lett.* **2011**, *13*, 1440. (c) Hayashi, M.; Nakamura, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 2249. (d) Li, H.; Liu, L. T.; Wang, Z. T; Zhao, F.; Zhang, S. G; Zhang, W. X; Xi, Z. F. *Chem.—Eur. J.* **2011**, *17*, 7399. (e) Sasaki, M.; Kondo, Y.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 6375. (f) Martin, D. B. C.; Vanderwal, C. D. *Chem. Sci.* **2011**, *2*, 649. (g) Matsuya, Y.; Koiwai, A.; Minato, D.; Sugimoto, K.; Toyooka, N. *Tetrahedron Lett.* **2012**, *53*, 5955. (h) He, Y. P.; Hu, H. T.; Xie, X. G.; She, X. G. *Tetrahedron Lett.* **2013**, *69*, 559.

(6) For reviews, see: (a) Smith, A. B., III.; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365. (b) Smith, A. B., III.; Wuest, W. M. *Chem. Commun.* **2008**, 5883. For the latest advances from this research group, see: (c) Smith, A. B., III.; Kim, W. S.; Tong, R. B. *Org. Lett.* **2010**, *12*, 588. (d) Smith, A. B., III.; Tong, R. B. *Org. Lett.* **2010**, *12*, 1260. (e) Smith, A. B., III.; Kim, W. S. *Proc. Nat. Acad. Sci.* **2011**, *108*, 6787. (f) Smith, A. B., III.; Tong, R. B.; Kim, W. S.; Maio, W. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8904. (g) Smith, A. B., III.; Han, H.; Kim, W. S. *Org. Lett.* **2011**, *13*, 3328. (i) Smith, A. B., III.; Hoye, A. T.; Martinez-Solorio, D.; Kim, W.-S.; Tong, R. B. *J. Am. Chem. Soc.* **2012**, *134*, 4533. (j) Sokolsky, A.; Smith, A. B., III. *Org. Lett.* **2012**, *14*, 4470. (k) Sanchez, L.; Smith, A. B., III. *Org. Lett.* **2012**, *14*, 6314.

(7) (a) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2001**, *3*, 3811. (b) Tsubouchi, A.; Enatsu, S.; Kanno, R.; Takeda, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7089.

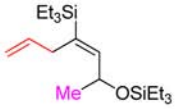
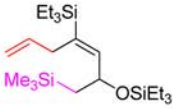
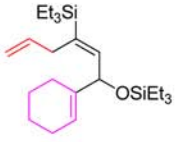
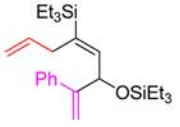
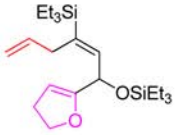
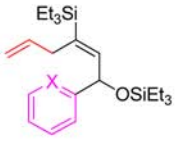
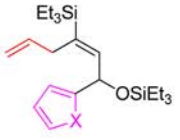
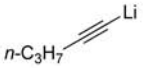
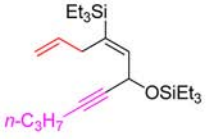
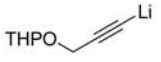
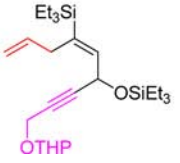
(8) Pelter, A.; Al-Bayati, R. I. H.; Ayoub, M. T.; Lewis, W.; Pardasani, P.; Hansel, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 717.

(9) Mandai, T.; Hara, K.; Nakajima, T.; Kawada, M.; Otera, J. *Tetrahedron Lett.* **1983**, *24*, 4993.

(10) Kim, K. D.; Wagtiotis, P. A. *Tetrahedron Lett.* **1990**, *131*, 6137.

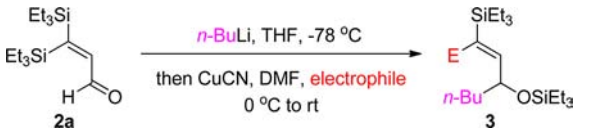
(11) In both reactions of entries 5 and 6, excess *n*-BuLi should competitively consume a certain amount of CuCN to form *n*-Bu(CuCN)Li. Therefore, compared to 1.0 equiv of CuCN, 2.0 equiv would lead to the desired transformation of ROLi into ROCu more completely, which would further result in a higher yield of **3c**.

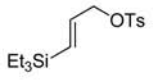
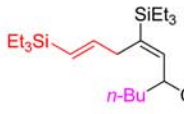
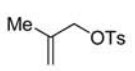
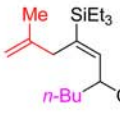
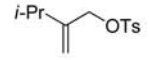
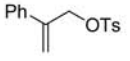
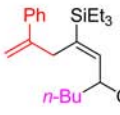
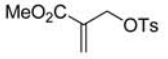
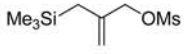
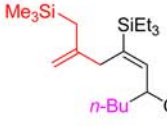
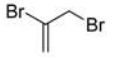
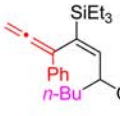
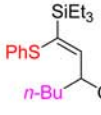
Table 2. Scope of Nucleophiles[a]

entry	NuLi	product		yield[b]
1	MeLi		**3c**	63%
2	Me_3SiCH_2Li		**3d**	70%
3			**3e**	57%
4			**3f**	60%
5			**3g**	85%
6			**3h** (X=CH)	85%
7			**3i** (X=N)	96%
8			**3j** (X=O)	95%
9			**3k** (X=S)	87%
10			**3l**	63%
11			**3m**	66%

[a] Reaction conditions: **2a** (0.14 mmol) and NuLi (0.28 mmol) in THF (0.6 mL) at −78 °C for 30 min, followed by CuCN (0.28 mmol) in DMF (1.8 mL) at 0 °C for 30 min, and finally allyl chloride (0.42 mmol) at rt for 2 h. [b] Isolated yields after purification by silica gel column chromatography.

Table 3. Scope of Electrophiles[a]



entry	electrophile	product		yield[b]
1			**3n**	87%
2			**3o**	57%
3			**3p**	53%
4			**3q**	82%
5			**3r**	70%
6			**3s**	72%
7			**3t**	67%
8			**3u**	94%
9			**3v**	72%
10	PhSSPh		**3w**	40%

[a] Reaction conditions: **2a** (0.14 mmol) and *n*-BuLi (0.28 mmol) in THF (0.6 mL) at −78 °C for 30 min, followed by CuCN (0.28 mmol) in DMF (1.8 mL) at 0 °C for 30 min, and finally allyl chloride (0.42 mmol) at rt for 2 h. [b] Isolated yields after purification by silica gel column chromatography.

Moreover, increasing the loading of CuCN from 1.0 to 2.0 equiv led to **3a** in an even higher yield of 85%, with no byproducts **8a** and **9a** detected (entry 6).[11] Decreasing the loading of *n*-BuLi to 1.2 equiv still gave complete addition

but only partial subsequent silyl migration (entry 7).[12] In addition, the silyl group in enal **2** dramatically affected the reaction efficiency: using trimethylsilyl-substituted **2b** gave **3b** in only 36% yield (entry 8).

The scope of this ARC approach was further evaluated using **2a** and allyl chloride (Table 2). The reaction could be applied to a wide variety of organolithiums, including ones that were alkyl (entries 1 and 2), vinyl (entries 3−5), aryl and heterocyclic (entries 6−9), and alkynyl (entries 10 and 11). Interestingly, the reaction generating **3d** in 70% yield (entry 2) showed selectivity for 1,4-triethylsilyl migration over 1,3-trimethylsilyl migration. This selectivity is surprising given that 1,3-silyl migration is thought to be much faster than the corresponding 1,4-migration,[13] and the $SiMe_3$ group migrates more easily than does the $SiEt_3$ group.[14] A possible explanation for the observed selectivity is that 1,4-triethylsilyl migration generates a silicon-stabilized[15] vinyl carbon anion, which has greater anionic stability than the primary anion generated in the competing 1,3-trimethylsilyl migration.

The ARC reaction also proved suitable for coupling a wide range of 2- or 3-substituted allyl electrophiles in good to excellent yields (Table 3, entries 1−7). Moreover, the leaving group was not limited to halides. Sulfonated electrophiles, which are easier to synthesize and isolate than halides, gave similarly good results. Using propargyl electrophiles altered the regioselectivity of the reaction (entries 8 and 9). While the reaction involving $SiEt_3$-substituted propargyl tosylate led to normal α-propargylation to produce **3u** in 94% yield (entry 8), using phenyl-substituted propargyl tosylate led to a reaction in which γ-allenylation dominated, affording **3v** in 72% yield (entry 9). In addition, phenyl disulfide also proved to be a good coupling partner, generating **3w** in 40% yield (entry 10).

(12) Detailed studies are underway to explore the mechanism by which excess *n*-BuLi promotes silyl migration.

(13) (a) Eisch, J. J.; Tsai, M.-R. *J. Organomet. Chem.* **1982**, *225*, 5. (b) Lautens, M.; Delanghe, P. H. M.; Goh, J. B.; Zhang, C. H. *J. Org. Chem.* **1992**, *57*, 3270.

(14) Evans, D. A.; Takacs, J. M.; Hurst, K. M. *J. Am. Chem. Soc.* **1979**, *101*, 371.

(15) (a) Brinkman, E. A.; Berger, S.; Brauman, J. I. *J. Am. Chem. Soc.* **1994**, *116*, 8304. (b) Chan, T. H.; Wang, D. *Chem. Rev.* **1995**, *95*, 1279.

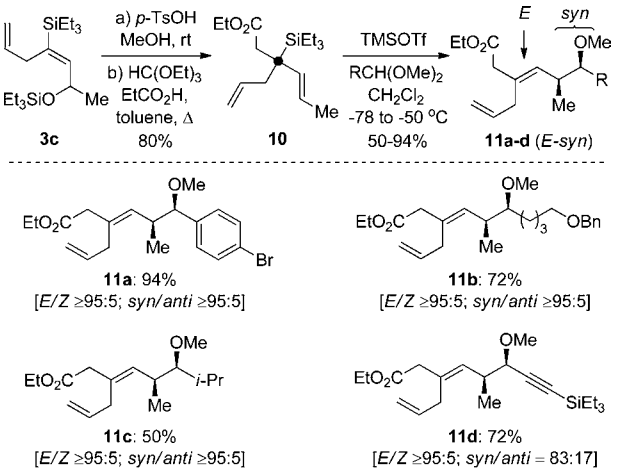
(16) (a) Zhang, Y.; Panek, J. S. *Org. Lett.* **2007**, *9*, 3141. (b) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554.

(17) For a selected review, see: Fleming, I. Allylsilanes, allylstannanes and related systems. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 563−593.

(18) The *E*-configuration was assigned based on NOE experiments on **11a**. See Supporting Information for details. The *syn*-stereochemistry was assigned based on Panek's elegant studies on the Sakurai reaction of various 1-mono- or 1,1-disubstituted crotylsilanes with acetals. In those reactions similar to ours, reliable *syn*-stereochemical control is generally predominant. For selected references, see: (a) Panek, J. S.; Masse, C. E. *Chem. Rev.* **1995**, *95*, 1293. (b) Panek, J. S.; Zhu, B. *J. Am. Chem. Soc.* **1997**, *119*, 12022. (c) Hu, T.; Panek, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 12022. (d) Huang, H. B.; Panek, J. S. *Org. Lett.* **2004**, *6*, 4383. (e) Kesavan, S.; Panek, J. S.; Porco, J. A., Jr. *Org. Lett.* **2007**, *9*, 5203. (f) Qin, H. L.; Panek, J. S. *Org. Lett.* **2008**, *10*, 2477. (g) Wu, J.; Chen, Y.; Panek, J. S. *Org. Lett.* **2010**, *12*, 2112. (h) Wu, J.; Panek, J. S. *J. Org. Chem.* **2011**, *76*, 9900.

In order to demonstrate the bifunctionality of geminal bis(silane), the resulting vinylsilane **3c** was further transformed by selective desilylation on the oxygen and subsequent Johnson−Claisen rearrangement (Scheme 3). The resulting 1,1-disubstituted (*E*)-crotylsilane **10**[16] was produced in 80% overall yield. Crotylsilane **10** is a valuable synthon in Sakurai reactions[17] involving diverse acetals. The reaction gave rise to a range of highly functionalized homoallylic methyl ethers **11** in good yield and with high *E*-*syn*-selectivity.[18]

Scheme 3. Transformation of **3c** to 1,1-Disubstituted (*E*)-Crotylsilane **10**, followed by Sakurai-Type Allylation of **10** with Acetals



In summary, we have demostrated that geminal bis(silyl) enal **2a** is a new and useful scaffold for ARC that allows the stereoselective synthesis of trisubstituted vinylsilanes. The reaction features a CuCN-promoted C^{sp2}-to-O 1,4-silyl migration and can be implemented with a wide range of nucleophiles and electrophiles. The resulting vinylsilanes can be converted into 1,1-disubstituted (*E*)-crotylsilanes, which are valuable synthons for the Sakurai reaction with diverse acetals. More extensive studies on other applications of this reaction are underway.

Acknowledgment. We are grateful for financial support from the National Natural Science Foundation of China (21172150, 21021001, 21290180), the National Basic Research Program of China (973 Program, 2010CB833200), and the 985 Project of Sichuan University.

Supporting Information Available. Experimental procedures and spectra data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.