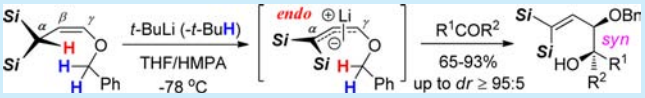
Organic Letters
Letter
pubs.acs.org/OrgLett

[1,5]-Anion Relay via Intramolecular Proton Transfer To Generate 3,3-Bis(silyl) Allyloxy Lithium: A Useful Scaffold for *Syn*-Addition to Aldehydes and Ketones

Xinglong Lin,[†] Xincui Ye,[†] Xianwei Sun,[†] Yuebao Zhang,[†] Lu Gao,[†] and Zhenlei Song*,[†,‡]

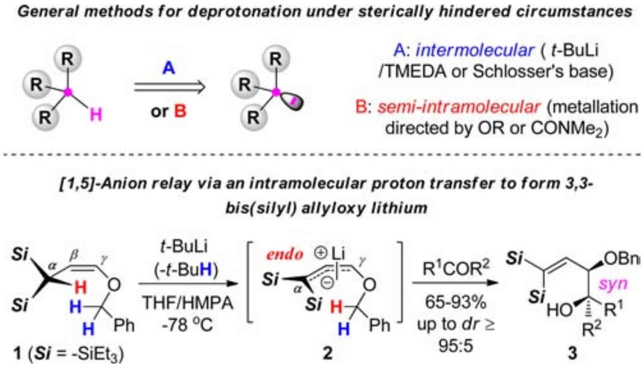
[†]Key Laboratory of Drug-Targeting of Education Ministry and Department of Medicinal Chemistry, West China School of Pharmacy, [‡]State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, P. R. China

Supporting Information



ABSTRACT: A [1,5]-anion relay has been achieved in 3,3-bis(silyl) benzyl enol ether. Deprotonation at the sterically more accessible benzyl position triggers an intramolecular proton transfer to generate the thermodynamically more stable 3,3-bis(silyl) allyloxy lithium. This *endo*-oriented allyl anion is stable at −78 °C and undergoes diastereoselective *syn*-addition at the *γ*-position with aldehydes and ketones to give monobenzyl-substituted 1,2-diols.

Deprotonation is one of the most general methods for creating carbanions.[1] Nevertheless, deprotonation can be challenging when the proton to be removed lies inside a sterically hindered microenvironment. Solutions to this problem usually involve either an intermolecular approach using extremely strong bases, such as the *t*-BuLi/TMEDA complex[2] or Schlosser's base,[3] or a semi-intramolecular approach of directed metalation[4] at a tethered alkoxy or amide group (Scheme 1, top).



Scheme 1. Deprotonation under Sterically Hindered Circumstances (top); [1,5]-Anion Relay via Intramolecular Proton Transfer (bottom)

We recently launched a series of investigations on structurally novel geminal bis(silanes).[5] In our initial attempts to generate the corresponding geminal bis(silyl) carbanion, we failed to achieve deprotonation by either intermolecular or semi-intramolecular approaches. Therefore we designed and carried out a [1,5]-anion relay[6] in 3,3-bis(silyl) allyl enol ethers involving intramolecular proton transfer.[7] However, the resulting allyl anion was unstable due to subsequent rapid [2,3]-Wittig rearrangement.[8] As a way around this problem, we describe here a [1,5]-anion relay in enol ether **1** tethered with a benzyl rather than an allyl group (Scheme 1, bottom). The deprotonation at the sterically more accessible benzyl position triggers intramolecular proton transfer to generate the thermodynamically more stable 3,3-bis(silyl) allyl anion **2**. This *endo*-oriented allyl anion is stable at −78 °C and undergoes diastereoselective *syn*-addition at the *γ*-position with aldehydes and ketones to give monobenzyl-substituted 1,2-diol **3**.

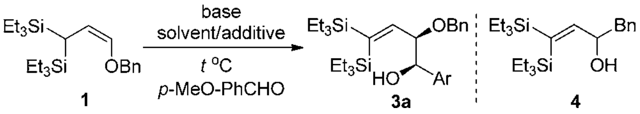
The reaction was first examined in THF and 3.0 equiv of HMPA at −78 °C using *n*-BuLi as the base. While addition with *p*-methoxybenzaldehyde gave the desired monobenzyl-substituted 1,2-diol **3a** with a *syn*/*anti* ratio of 90:10, the yield was only 26% (Table 1, entry 1). To our delight, switching *n*-BuLi to more basic *t*-BuLi gave a much higher yield of 87% with a *dr* of ≥95:5 (entry 2). Increasing the loading of HMPA to 10.0 equiv, or using DMI or DMPU as an additive, decreased both yield and diastereoselectivity (entries 3−5). No reaction occurred in the presence of TMEDA, even though it has been widely used to form a strong complex with a lithium cation and thereby enhance the basicity of the carbanion (entry 6).[9] This additive is ineffective most likely because it fails to promote the formation of a solvent-separated ion pair,[10] which is crucial for the initially formed benzyl anion to undergo intramolecular proton transfer and generate allyl anion **2**. Et_2O appeared be less effective as solvent than THF, dramatically lowering the yield (entry 7). Increasing the temperature from −78 °C, where **2** is stable, to −55 °C led to rapid [1,2]-Wittig rearrangement[11] to give alcohol **4** in 87% yield (entry 8).

To gain further mechanistic insights into this process, we performed deuterium labeling experiments (Scheme 2). Quenching allyl anion **2** with D_2O allowed complete deuterium substitution at the *γ*-position, affording *Z*-enol ether **1-D** in 82% yield. Two conclusions can be drawn from this result. First, the *α*-position, despite being more sterically hindered

Received: December 17, 2013
Published: February 5, 2014

dx.doi.org/10.1021/ol4036402 | *Org. Lett.* 2014, 16, 1084−1087

Table 1. Screening of Reaction Conditions



entry	base	solv	addit. (equiv)	t, °C	yield[b]	dr[c]
1	n-BuLi	THF	HMPA (3.0)	−78	26%	90:10
2	t-BuLi	THF	HMPA (3.0)	−78	87%	≥95:5
3[a]	t-BuLi	THF	HMPA (10.0)	−78	52%	93:7
4	t-BuLi	THF	DMI (3.0)	−78	62%	80:20
5	t-BuLi	THF	DMPU (3.0)	−78	65%	83:17
6	t-BuLi	THF	TMEDA (3.0)	−78	–	–
7	t-BuLi	Et_2O	HMPA (3.0)	−78	23%	87:13
8	t-BuLi	THF	HMPA (3.0)	−55	87%[d]	–

[a] Reaction conditions: 0.15 mmol of **1**, 0.45 mmol of HMPA, and 0.45 mmol of t-BuLi (1.3 M in pentane) in 1.2 mL of THF, −78 °C, 1.5 h; then 0.3 mmol of p-methoxybenzaldehyde, 10 min. [b] Isolated yields after purification by silica gel column chromatography. [c] Ratios were determined by ^{1}H NMR spectroscopy. The *syn*-stereochemistry was assigned based on NOE experiments with the acetonide of **12** in Scheme 5. [d] Isolated yield of **4**.

Scheme 2. Deuterium Labeling Experiments

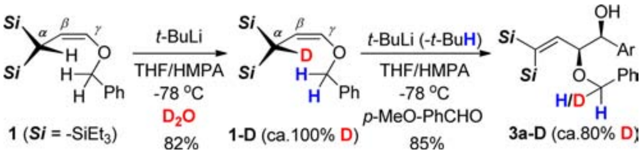
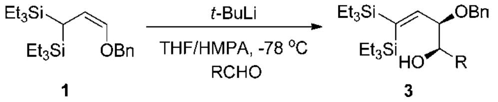
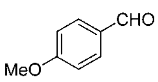
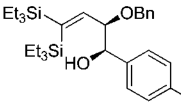
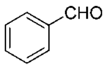
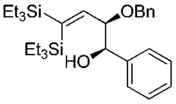
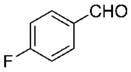
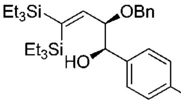
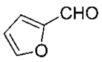
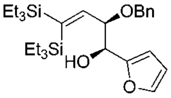
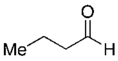
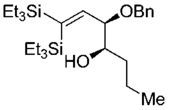
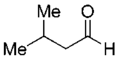
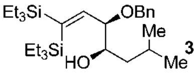
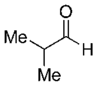
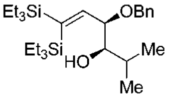
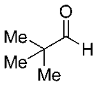
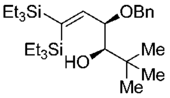
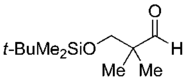
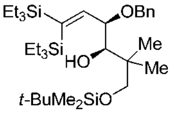
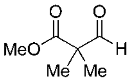
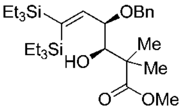


Table 2. Scope of Aldehydes



entry	RCHO	product	yield[a]	dr[b]
1		 **3a**	87%	≥95:5
2		 **3b**	78%	91:9
3		 **3c**	80%	80:20
4		 **3d**	78%	≥95:5
5		 **3e**	69%	67:33
6		 **3f**	80%	67:33
7		 **3g**	71%	≥95:5
8		 **3h**	74%	≥95:5
9		 **3i**	68%	≥95:5
10		 **3j**	65%	≥95:5

[a] Isolated yields after purification by silica gel column chromatography. [b] Ratios were determined using ^{1}H NMR spectroscopy.

than the γ-position, has higher electron density. This may reflect not only the effects of an anion-destabilizing OBn group at the γ-position but also the dual stabilizing effect of two silyl groups at the α-position, referred to as the *α-effect of silicon.*[12] Second, allyl anion **2** adopts an *endo*-orientation, probably promoted by coordination of an internal lithium ion by the OBn group.[13] Reaction of **1-D** with p-methoxybenzaldehyde under optimal conditions provided **3a-D** in 85% yield with ca. 80% D-labeled at the benzylic position.[14] This result proves that formation of **2** proceeds predominantly by [1,5]-anion relay through an intramolecular proton transfer, despite partial intermolecular deprotonation occurring probably due to the presence of excessive t-BuLi.

Next the scope of the approach was tested using various aldehydes. Electron-rich phenyl or heterocyclic aldehydes (Table 2, entries 1 and 4) reacted with higher diastereoselectivity than did phenyl or electron-deficient phenyl aldehydes (entries 2 and 3). The steric effects on the *syn*/*anti* ratio were also observed with alkyl aldehydes. While linear and β-disubstituted aldehydes gave a moderate diastereoselectivity of 67:33 (entries 5 and 6), α-di- and trisubstituted aldehydes gave a *dr* of ≥95:5 (entries 7−10). Formation of **3j** (entry 10) showed selective addition of a substituent to the aldehyde group but not to the ester group, suggesting that the γ-position in **2** features a soft nucleophilicity. Reaction of **2** with α-stereogenic aldehyde **5** gave a good *dr* of 84:8:8 with the *syn*/*syn* isomer **3k** as a predominant product (Scheme 3). The stereochemistry was confirmed by X-ray analysis of **6**,[15] which was formed by removing two silyl and benzyl groups from **3k**, followed by diesterification with 3,5-dinitrobenzoyl chloride.

This reaction also proved suitable for acyclic and cyclic ketones (Table 3). No obvious deprotonation of acetone was observed, which would have formed the corresponding lithium enolate. These results are consistent with the soft nucleophilicity and weak basicity of **2**. Reaction with acetophenone gave a *syn*/*anti* ratio of 63:37, lower than the *dr* of 91:9 obtained in the reaction with benzylaldehyde.

To interpret the *syn* selectivity that we observed during the addition, two "open" transition states **7a** and **7b** were proposed in Scheme 4. We suggest that **7a** is favored over **7b**, which suffers a gauche interaction between the bulky geminal bis(triethylsilyl) group in *endo*-**2** and the R group on the

Scheme 3. Synthesis of 3k and X-ray Structure of 6

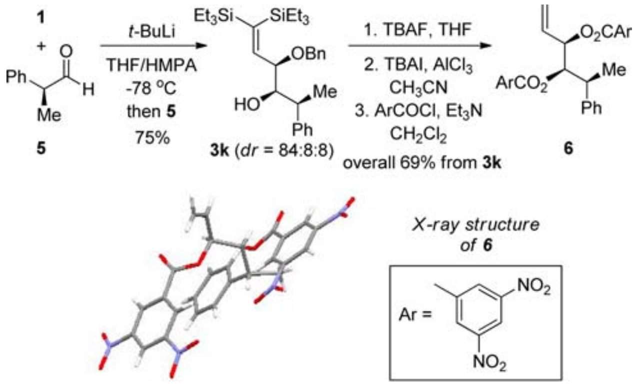
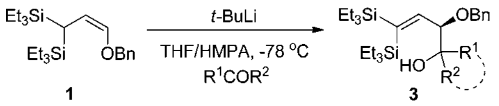
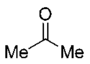
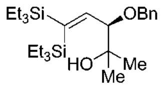
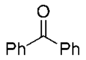
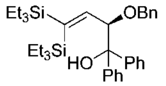
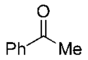
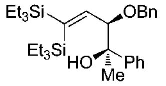
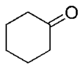
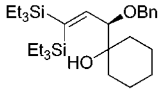
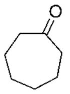
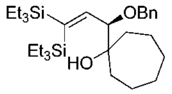


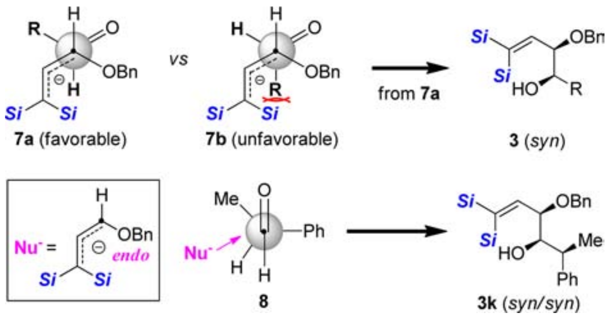
Table 3. Scope of Ketones



entry	R^1COR^2	product		yield[a]	dr
1			3l	73%	—
2			3m	85%	—
3			3n	64%	63:37[b]
4			3o	93%	—
5			3p	90%	—

[a] Isolated yields after purification by silica gel column chromatography. [b] The ratio was determined using ^1H NMR spectroscopy.

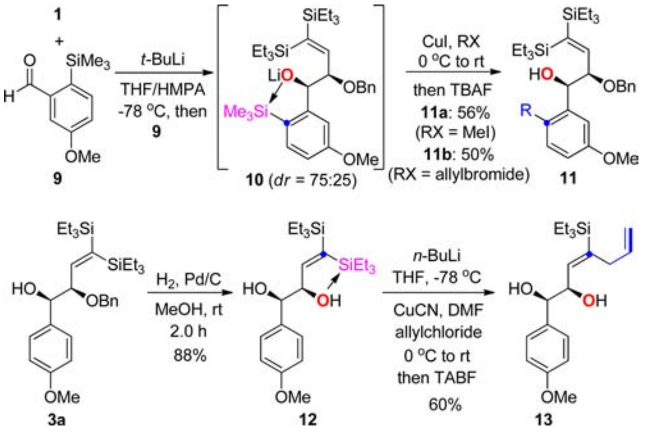
Scheme 4. Model-Based Analysis of Stereochemical Outcome



aldehyde. This preference for **7a** would explain not only the observed *syn*-selectivity but also our finding that bulkier R groups give a higher *dr* (Table 2, entries 5−10). Combining the preference for **7a** with the classical Felkin−Ahn model **8**[16] would explain the *syn*/*syn* selectivity observed during formation of **3k**.

We then demonstrated the power of this approach by achieving a sequential anion relay process, in which a negative charge is transferred in different directions (Scheme 5). The reaction of **2** with aldehyde **9** initially generated lithium alkoxide **10** with a *dr* of 75:25. Then **10** underwent CuI-promoted [1,4]-C to O-silyl migration in situ[17] to create a new phenyl anion within the electrophile structure. Subsequent alkylation with methyl iodide or allylbromide afforded, respectively, **11a** and **11b** in 56% and 50% yield. In contrast, 1,2-diol **12** underwent *n*-BuLi/CuCN-promoted [1,4]-silyl migration to generate a new vinyl anion within the nucleophile structure. Alkylation with allylchloride led to the formation of **13** in 60% yield.

Scheme 5. Sequential Anion Relay To Synthesize 11 and 13



In summary, we have described a [1,5]-anion relay in 3,3-bis(silyl) benzyl enol ether. Deprotonation at the sterically more accessible benzyl position triggers an intramolecular proton transfer to generate the thermodynamically more stable 3,3-bis(silyl) allyloxy lithium. As a demonstration of the approach, we used a sequential anion relay process to perform a multicomponent reaction. Further applications of this method are under development.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zhenleisong@scu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the NSFC (21172150, 21321061, 21290180), the NBRPC (973 Program, 2010CB833200), the NCET (12SCU-NCET-12-03), and Sichuan University 985 project.

■ REFERENCES

(1) For selected reviews, see: (a) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275. (b) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947.

(c) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414. (d) Knochel, P.; Millot, N.; Rodriguez, A.; Tucker, C. E. *Org. React.* **2001**, *58*, 417. (e) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625. (f) Xi, Z. F. *Acc. Chem. Res.* **2010**, *43*, 1342. (g) Zhang, W. X.; Zhang, S. G.; Xi, Z. F. *Acc. Chem. Res.* **2011**, *44*, 541. (h) Reich, H. J. *J. Org. Chem.* **2012**, *77*, 5471. (i) Tian, Z. X.; Kass, S. R. *Chem. Rev.* **2013**, *113*, 6986.

(2) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.

(3) (a) Schlosser, M. *Pure Appl. Chem.* **1988**, *60*, 1627. (b) Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376.

(4) For a review, see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(5) For selected advances, see: (a) Hodgson, D. M.; Barker, S. F.; Mace, L. H.; Moran, J. R. *Chem. Commun.* **2001**, 153. (b) Williams, D. R.; Morales-Ramos, Á. I.; Williams, C. M. *Org. Lett.* **2006**, *8*, 4393. (c) Li, L. J.; Ye, X. C.; Wu, Y.; Gao, L.; Song, Z. L.; Yin, Z. P.; Xu, Y. J. *Org. Lett.* **2013**, *15*, 1068. (d) Yan, L. J.; Sun, X. W.; Song, Z. L.; Li, H. Z.; Liu, Z. J. *Org. Lett.* **2013**, *15*, 1104. (e) Gao, L.; Lu, J.; Song, Z. L.; Lin, X. L.; Xu, Y. J.; Yin, Z. P. *Chem. Commun.* **2013**, *49*, 8963. (f) Groll, K.; Manolikakes, S. M.; du Jourdin, X. M.; Jaric, M.; Bredihhin, A.; Karaghiosoff, K.; Carell, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 6776. (g) Gao, L.; Zhang, Y. B.; Song, Z. L. *Synlett* **2013**, *24*, 139.

(6) For reviews of anion relay chemistry, see: (a) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065. (b) Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365. (c) Smith, A. B., III; Wuest, W. M. *Chem. Commun.* **2008**, 5883. For some leading references, see: (d) Stefano, M.; Gwerydd, G.; Stirling, C. J. M. *Chem. Commun.* **1992**, *28*, 54. (e) Talami, S.; Stirling, C. J. M. *Can. J. Chem.* **1999**, *77*, 1105. (f) Stefano, M.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 28. (g) Smith, A. B., III; Kim, W. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6787. (h) Smith, A. B., III; Tong, R. B.; Kim, W. S.; Maio, W. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8904. (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) Melillo, B.; Smith, A. B., III. *Org. Lett.* **2013**, *15*, 2282. (k) Nguyen, M. H.; Smith, A. B., III. *Org. Lett.* **2013**, *15*, 4258. (l) Nguyen, M. H.; Smith, A. B., III. *Org. Lett.* **2013**, *15*, 4872.

(7) Maercker, A.; Stoetzel, R. *Chem. Ber.* **1987**, *120*, 1695.

(8) Sun, X. W.; Lei, J.; Sun, C. Z.; Song, Z. L.; Yan, L. J. *Org. Lett.* **2012**, *14*, 1094.

(9) Haynes, R. K.; Vonwiller, S. C.; Luderer, M. R. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Eds.; J. Wiley & Sons: New York, 2006.

(10) (a) Smid, J. *Angew. Chem., Int. Ed.* **1972**, *11*, 112. (b) Ahmad, N.; Day, M. C. *J. Am. Chem. Soc.* **1977**, *99*, 941.

(11) (a) Wittig, G.; Lohmann, L. *Ann.* **1942**, *550*, 260. (b) Tomooka, K.; Yamamoto, H.; Nakai, T. *Liebigs Ann. Chem.* **1997**, 1275.

(12) For reviews, see: (a) Panek, J. S. Silicon Stabilization. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. *1*, p 579. (b) Chan, T. H.; Wang, D. *Chem. Rev.* **1995**, *95*, 1279.

(13) (a) Still, W. C.; Macdonald, T. L. *J. Am. Chem. Soc.* **1974**, *96*, 5561. (b) Hosomi, A.; Hashimoto, H.; Sakurai, H. *J. Org. Chem.* **1978**, *43*, 2551.

(14) The reaction of 3,3-bis(triethylsilyl) benzyl enol ether with two deuterium atoms at the benzylic position similarly led to ca. 80% proton transfer from Cα to benzylic carbon. These results suggest that there appears to be no obvious isotope effect in both deprotonation at the benzylic position and the subsequent [1,5]-anion relay. In contrast, methyl-substituted enol ether only underwent Cγ-deprotonation probably by the OMe-directed metalation. See Supporting Information for more details.

(15) CCDC 974844 (**6**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) (a) Felkin, H. *Tetrahedron Lett.* **1968**, *9*, 2199. (b) Ahn, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, *17*, 155.

(17) (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. (c) Smith, A. B., III; Kim, W. S.; Tong, R. B. *Org. Lett.* **2010**, *12*, 588.