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Benzyl and Phenylthiomethyl Silanes: A New Class of Bifunctional Linchpins for Type II Anion Relay Chemistry (ARC)

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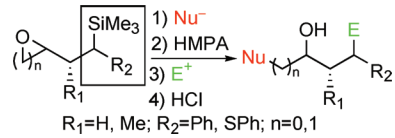
ABSTRACT



A new class of bifunctional linchpins bearing electrophilic sites β or γ to a silyl group have been designed, synthesized, and demonstrated to be competent in tricomponent unions exploiting Type II Anion Relay Chemistry (ARC). High diastereoselectivities were observed when a phenyl moiety (R_2) served as an anion-stabilizing group (ASG) adjacent to a methyl susbtituent (R_1), while diastereomeric mixtures were obtained when a phenylthiol moiety served as the ASG, irrespective of α-substitution.

Efficient union of architecturally complex fragments constitutes a critical prerequisite in natural product total syntheses. One such tactic, Anion Relay Chemistry (ARC), a one-pot tricomponent union tactic, has proven highly effective in our laboratory.[1] First exploited in 1997,[2] two structurally different epoxides were united in a single flask to furnish advanced fragments for the total syntheses of (+)-spongistatins 1 and 2.[3] This tactic was subsequently employed in conjuction with a formal total synthesis of (+)-mycoticin[4] and more recently in the synthesis of the aglycon skeleton of (+)-rimocidin.[5] Now termed Type I ARC (Scheme 1A),[1] this strategy was based on the union of two epoxides as introduced by Matsuda[6a] and Tietze.[6b] Hale and co-workers subsequently took advantage of this protocol, employing the Tietze homocoupling version in their formal total synthesis of (+)-bryostatin 1.[7]

In 2004, we extended the Type I process to permit anion migration along the linchpin chain to generate a new reactive anion at a distal site (Scheme 1B).[8] Termed Type II ARC,[1,9] initial nucleophilic attack at the electrophilic site of the linchpin (cf. aldehyde or epoxide) leads to an alkoxide, which upon a silyl C(sp^3)→O Brook rearrangement,[8,9] triggered by addition of a polar solvent (HMPA) or by temperature increase, produces a new carbon anion. For silyl migration to occur, the newly generated anionic site must possess a viable anion stabilizing group (ASG). Capture of the derived anion is then possible with a variety of electrophiles to generate, in a single flask, diverse three-component adducts. The synthetic utility of the Type II ARC protocol was demonstrated in the construction of an advanced intermediate

(1) 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. (c) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065 Also see ref 3.

(2) Smith, A. B., III; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 69.

(3) (a) Smith, A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 191. (b) Smith, A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 196. Also see: Smith, A. B., III. et al. *Tetrahedron* **2009**, *65*, 6470; 6488.

(4) Smith, A. B., III; Pitram, S. M. *Org. Lett.* **1999**, *1*, 2001.

(5) Smith, A. B., III; Foley, M. A.; Dong, S.; Orbin, A. *J. Org. Chem.* **2009**, *74*, 5987.

(6) (a) Matsuda, I.; Murata, S.; Ishii, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 26. (b) Tietze, L. F.; Geissler, H.; Gewert, J. A.; Jakobi, U. *Synlett* **1994**, 511. (c) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron* **1996**, *52*, 503. (d) Takaku, K.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1998**, *39*, 2575.

(7) Hale, K. J.; Hummersone, M. C.; Bhatia, G. S. *Org. Lett.* **2000**, *2*, 2189.

(8) Smith, A. B., III; Duffey, M. O. *Synlett* **2004**, *8*, 1363.

(9) (a) Smith, A. B., III; Xian, M.; Kim, W.-S.; Kim, D.-S. *J. Am. Chem. Soc.* **2006**, *128*, 12368. (b) Smith, A. B., III; Xian, M. *J. Am. Chem. Soc.* **2006**, *128*, 66.

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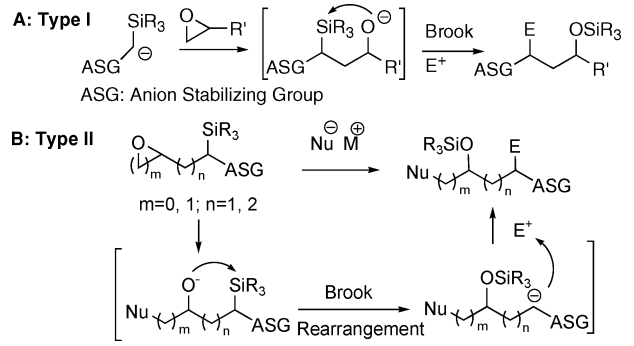
in our prospective syntheses of (+)-spirastrellolides A and B, architecturally complex sponge metabolites.[10]

Scheme 1. Type I and II Anion Relay Chemistry (ARC)



Early in the development of the ARC technique, the dithiane moiety played the role of a highly effective ASG, furnishing after Brook rearrangement, a powerful nucleophile for reaction with a variety of electrophiles. One drawback, however, of the dithiane moeity as an ASG is the lack of reactivity of α-substituted linchpins such as **3** (Figure 1; R = CH_3).[10b] We now recognize this lack of reactivity to be due to a preferred linchpin conformation that buries the terminus of the electrophilic epoxide in the dithiane ring. We therefore turned, in 2007, to possible alternative ASGs; preliminary studies with linchpins **4** and **5**, bearing cyano or allyl groups, proved promising.[11] A general search for other viable ASGs that would extend the scope and general utility of the ARC tactic was therefore initiated. Central to this venture was an ASG that would prove to be competent with α-substituted linchpins in order to access a variety of polyketide natural products and/or natural product-like analogues for diversity-oriented synthesis (DOS).[12] In this paper, we report on one aspect of this program, the design, synthesis, and evaluation of a new class of bifunctional Type II ARC linchpins that employ the phenyl or phenylthio[13] group as the ASGs (Figure 1).

Unlike earlier linchpins employing a disubstituted ASG (cf. dithiane), use of a monosubstituent ASG, such as phenyl or phenylthio moiety, leads to introduction of an asymmetric center at the silyl-bearing carbon. The question thus arises as to the stereochemical outcome (i.e., retention, inversion or racemization) resulting from capture of the Brook derived anion. In the case of the 1,2-Brook rearrangement of α-silyl alcohols bearing a phenyl ASG, elegant studies by Brook[14b] and Mosher[14c] revealed that inversion occurs at carbon and retention at silicon.[14] We therefore designed a series of enantiomerically pure linchpins (Figure 1, **6**−**10**) possessing phenyl or phenylthio moieties as ASGs to explore both the viability of the Type II ARC process and the stereochemical outcome at carbon upon Brook rearrangement and anion capture.

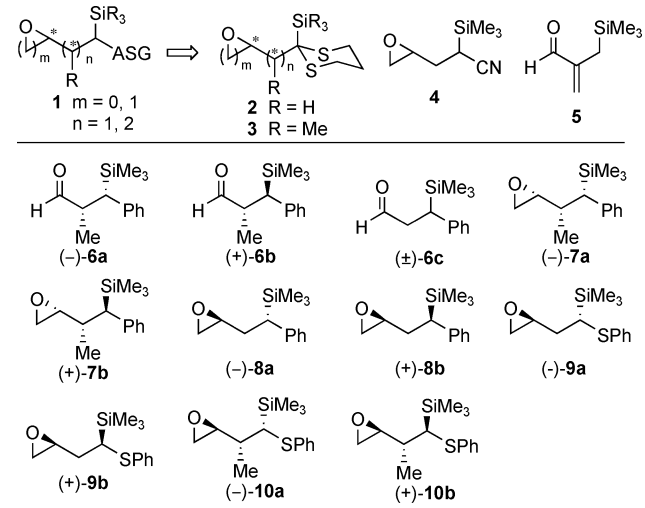


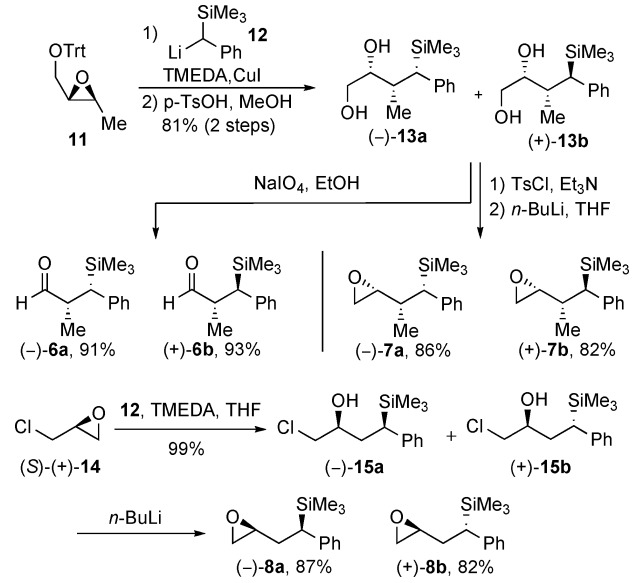
Figure 1. New Bifunctional Linchpins for Type II ARC

Access to linchpins **6**−**10** called upon the protocol developed by Sato and co-workers[15] that entails regioselective opening of disubstituted epoxide **11**.[15a] Reaction of **12** with **11** furnished (−)-**13a** and (+)-**13b** as a diastereomeric mixture (ca. 1:1). Removal of the trityl group with *p*-TsOH pleasingly furnished diastereomers (−)-**13a** and (+)-**13b** that could be separated by flash chromatography. X-ray diffraction of the primary 4-bromobenzoate of diol (+)-**13b**, permitted assignment of the relative and absolute configurations.[16] Oxidative cleavage of the diols led to aldehyde linchpins (−)-**6a** and (+)-**6b** in excellent yields (Scheme 2). Epoxide linchpins (−)-**7a** and (+)-**7b** were prepared from (−)-**13a** and (+)-**13b** by monotosylation of the hydroxyl, followed by treatment with *n*-BuLi. Preparation of the non-α-substituted linchpins, (−)-**8a** and (+)-**8b**, entailed a two-step sequence employing the readily separable chloro alcohols (−)-**15a** and (+)-**15b**, derived from (*S*)-(+)-epichlorohydrin. The relative and absolute configurations of (+)-**15b** were established by X-ray analysis of the corresponding 3,5-dinitrobenzoate.[16]

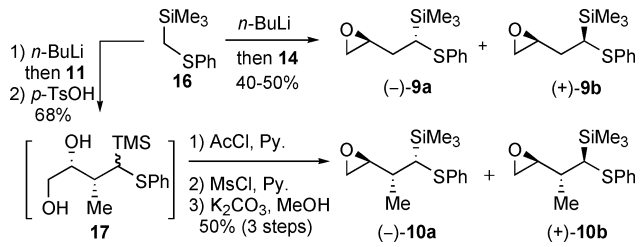
Construction of the phenylthio linchpins (−)-**9a**, (+)-**9b**, (−)-**10a**, and (+)-**10b** proceeded in similar fashion (Scheme 3). For (−)-**10a** and (+)-**10b**, a three-step sequence: (1) acetylation, (2) mesylation, and (3) epoxide formation upon deacetylation was employed. The relative and absolute configurations of (−)-**9a** and (−)-**10a** were again assigned by X-ray analysis.[16]

(10) (a) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2007**, *9*, 3311. (b) Unpublished results: Atasoylu, O. University of Pennsylvania.
(11) Smith, A. B., III; Kim, D.-S.; Xian, M. *Org. Lett.* **2007**, *9*, 3307.
(12) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.
(13) (a) Fleming, I.; Floyd, C. O. *J. Chem. Soc., Perkin Trans. 1* **1981**, 969. (b) Takeda, K.; Ubayama, H.; Sano, A.; Yoshi, E.; Koizumi, T. *Tetrahedron Lett.* **1998**, *39*, 5243.
(14) (a) Brook, A. G. *J. Am. Chem. Soc.* **1958**, *80*, 1886. (b) Biernbaum, M. S.; Mosher, H. S. *J. Am. Chem. Soc.* **1971**, *93*, 6221. (c) Brook, A. G.; Pascoe, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 6224. Review: Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77.
(15) (a) Kobayashi, Y.; Kitano, Y.; Sato, F. *Chem. Commun.* **1984**, 1329. (b) Sato, F.; Kusakabe, M.; Kobayashi, Y. *Chem. Commun.* **1984**, 1130.
(16) See the Supporting Information for details.

Scheme 2. Synthesis of Linchpins **6a**, **6b**, **7a**, and **7b**



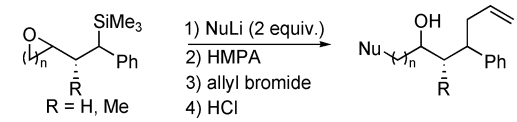
Scheme 3. Synthesis of Linchpins of **9a**, **9b**, **10a**, and **10b**

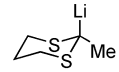
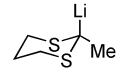
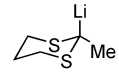
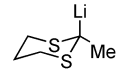
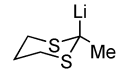
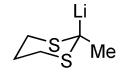


With linchpins **6a**−**10b** in hand, we evaluated both their viability as linchpins for the Type II ARC tactic and the stereochemical outcome at carbon upon Brook rearrangement followed by alkylation. Polar aprotic additives (cf. HMPA) were employed to trigger the Brook rearrangement[9] of the initially generated lithium alkoxides. As illustrated in the Tables 1 and 2, the phenyl and phenylthio moieties proved viable as ASGs for the ARC process. Initiating nucleophiles included *n*-BuLi, lithiated 2-methyl-1,3-dithiane, and lithium di-*n*-butyl cuprate. Yields ranged from 50 to 81%. Of particular note is the stereochemical outcome. Addition of *n*-BuLi to linchpin (−)-**6a** furnished a diastereomeric mixture (95:5) with the *all-syn*-product (−)-**18** predominating (Table 1, entry 1). The relative stereochemistry of (−)-**18** was established by 2D NOESY analysis of the δ-lactone derived from (−)-**18** upon oxidative cleavage and lactonization.[16] The stereochemical outcome at the carbinol of (−)-**18** was predicted via the Felkin−Anh model as observed by Sato upon addition of ethyl Grignard to vinylsilyl aldehydes;[15] the stereochemical outcome of alkylation after Brook rearrangement only had potential precedent (i.e., inversion at carbon) based on the Brook[14b] and Mosher[14c] observations.

Interestingly, in the case of linchpin (+)-**6b**, addition of *n*-BuLi led to the same product [(−)-**18**] with the same

Table 1. Anion Relay Chemistry of Linchpins **6a**−**8b**

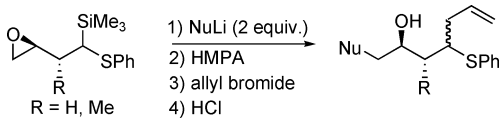


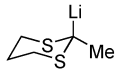
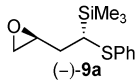
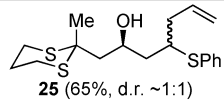
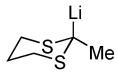
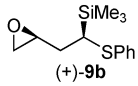
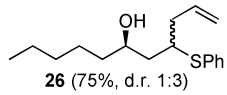
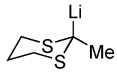
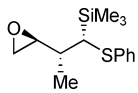
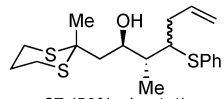
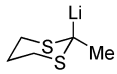
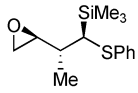
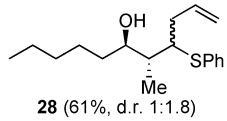
entry	NuLi	linchpin	products (yield%)[a]
1	*n*-BuLi	(–)-**6a**	(–)-**18** (65%, d.r. >95:5)
2	*n*-BuLi	(+)-**6b**	(–)-**18** (60%, d.r. >95:5)
3		(–)-**6a**	(–)-**19** (64%, d.r. >95:5)
4		(+)-**6b**	(–)-**19** (62%, d.r. >95:5)
5		(–)-**7a**	(–)-**20** (68%, d.r. >98:2)
6		(+)-**7b**	(–)-**20** (64%, d.r. >98:2)
7	(*n*-Bu)$_2$CuLi	(–)-**7a**	(–)-**21** (65%, d.r. >90:10)
8	(*n*-Bu)$_2$CuLi	(+)-**7b**	(–)-**21** (72%, d.r. >90:10)
9	*n*-BuLi	(±)-**6C**	**22** (59%, d.r. 1:1.3)
10		(–)-**8a**	**23** (81%, d.r. 2.3:1)
11		(+)-**8b**	**23** (76%, d.r. 1.8:1)
12	(*n*-Bu)$_2$CuLi	(–)-**8a**	**24** (77%, d.r. 1:1)
13	(*n*-Bu)$_2$CuLi	(+)-**8b**	**24** (73%, d.r. 1.1:1)

[a] Isolated yields based on linchpins; diastereomer ratio was determined by ^{1}H NMR.

diastereoselectivity as observed with (−)-**6a** (entry 2). When employing lithiated 2-methyl-1,3-dithiane as the nucleophile both linchpins (−)-**6a** and (+)-**6b** again furnished the same product (−)-**19**, with similar high selectivities (Table 1, entries 3 and 4). Linchpins (−)-**7a** and (+)-**7b** also proved viable substrates for the ARC process; again single products (−)-**20** or (−)-**21** predominated when lithiated 2-methyl-1,3-dithiane or lithium di-*n*-butyl cuprate served as nucleophiles (entries 5−8).[16] In contrast, poor diastereoselectivities were obtained when linchpin (±)-**6c**[17] or linchpins (−)-**8a** and (+)-**8b**, lacking the methyl subtituent were employed (Table

Table 2. Anion Relay Chemistry of Linchpins **9a**−**10b**



entry	NuLi	linchpin	products (yield%)[a]
1		 (−)-**9a**	 **25** (65%, d.r. ~1:1)
2		 (+)-**9b**	**25** (65%, d.r. ~1:1)
3	(*n*-Bu)$_2$CuLi	(−)-**9a**	 **26** (75%, d.r. 1:3)
4	(*n*-Bu)$_2$CuLi	(+)-**9b**	**26** (72%, d.r. 1:4)
5		 (−)-**10a**	 **27** (58%, d.r. 1:1)
6		 (+)-**10b**	**27** (55%, d.r. 1:1)
7	(*n*-Bu)$_2$CuLi	(−)-**10a**	 **28** (61%, d.r. 1:1.8)
8	(*n*-Bu)$_2$CuLi	(+)-**10b**	**28** (60%, d.r. 1:1.9)

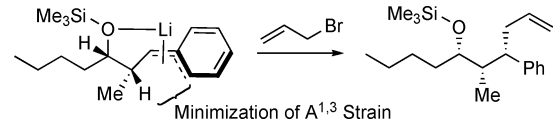
[a] Isolated yields based on linchpins; diastereomer ratio was determined by ^{1}H NMR.

1, entries 9−13). Although there are few reports[18] on diastereoselective alkylation of carbon anions generated via Brook rearrangement, our results are consistent with alkylation of configurationally labile benzyl anions.[19]

The stereochemical outcome employing linchpins **9a**−**10b** bearing phenylthio moieties as the ASG proved different (Table 2). Although the ARC process proceeded in good yield (Table 2, entries 1−8), diastereomeric mixtures resulted in all cases. That is, an α-chiral center adjacent to the reactive anion generated via Brook rearrangement [linchpins (−)-**10a** and (+)-**10b**] imposed little or no stereochemical bias toward the alkylation process (Table 2, entries **5**−**8**). This stereochemical outcome is not totally unexpected,[20] given that α-thio carbanions are known to be configurationally labile,[21] even at −78 °C.

The divergence in stereochemical outcome observed with linchpins possessing the phenyl and phenylthio ASG with adjacent α-substituent can be understood in terms of A^{1,3} strain interactions available only to the linchpins possessing the phenyl ASG (Scheme 4). A similar divergence was observed by Beak and co-workers in their pioneering work on directed amide alkylations.[22]

Scheme 4. *A*^{1,3} Strain in Diastereoselective Alkylation



In summary, we have designed, synthesized, and evaluated ten chiral nonracemic linchpins (**6**−**10**) for use in Anion Relay Chemistry (ARC). Both the phenyl and phenylthio moieties proved competent as anion stabilizing groups (ASG) for the ARC proccess. High diastereoselectivities were observed with linchpins possessing a methyl substituent α to the silyl group, when a phenyl moiety serves as the ASG, while poor diastereoselectivity is observed when a phenylthio moiety is employed as the ASG, irrespective of the presence of an α substituent. Studies directed toward both the design and synthesis of related linchpins, as well as analysis of the scope and limitations of Anion Relay Chemistry continue in our laboratory.

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

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