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Long-Range Anion Relay Chemistry (LR-ARC): A Validated ARC Tactic

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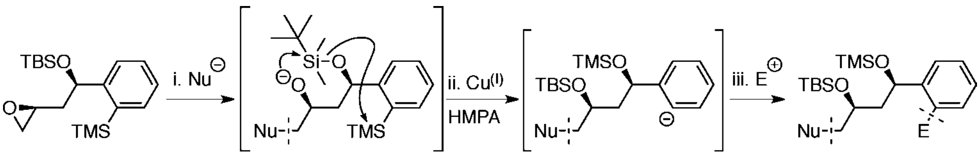
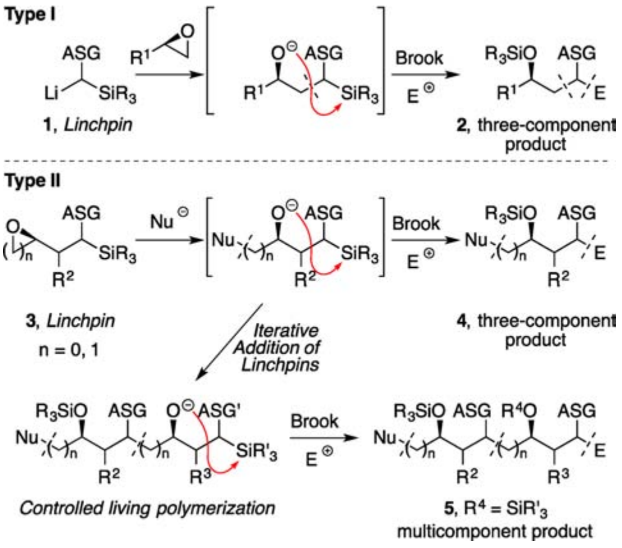
ABSTRACT



The design, synthesis, and validation of linchpins for Anion Relay Chemistry (ARC) capable of iterative silyl group migrations have been achieved. This tactic permits "long-range" relocation of negative charge across space, to generate reactive distal nucleophilic centers for both alkylation and palladium-catalyzed coupling reactions.

Scheme 1. Type I and Type II Anion Relay Chemistry[a]



[a] ASG = anion stabilizing group.

Anion Relay Chemistry (ARC Types I and II)[1] comprises an effective strategy to construct architecturally complex structures[2] via the union of diverse building blocks (Scheme 1).[3] The Type II version of the ARC protocol, in particular, holds considerable promise for the rapid assembly of the diverse scaffolds[4] often found in natural products, many of which display significant bioregulatory properties. The Type II ARC protocol entails three components: (a) an initiating nucleophile; (b) 1,4- and/or 1,5-bifunctional linchpins deployed in a single or iterative fashion that undergo facile intramolecular Brook rearrangements triggered either by a change in solvent polarity, temperature, and/or gegenion;[5] and (c) a terminating electrophile. The controlled iterative union of such building blocks, a process not dissimilar to "living polymerization",[6] is feasible due to the latent nucleophilicity of the various ARC linchpins, generated upon carefully timed Brook rearrangements. Of further significance, the ARC tactic yields terminal anions amenable to either alkylation or Pd-catalyzed cross-coupling reactions (CCR).[7] Having demonstrated the synthetic utility of 1,4- and 1,5-Brook[5] rearrangements in Anion Relay Chemistry (ARC), we recently integrated the

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(1) Smith, A. B., III; Wuest, W. M. *Chem. Commun.* **2008**, 5883.

(2) (a) Smith, A. B., III; Tomioka, T.; Risatti, C. A.; Sperry, J. B.; Sfouggatakis, C. *Org. Lett.* **2008**, *10*, 4359. (b) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2007**, *9*, 3311.

(3) For reviews on multicomponent reactions, see: (a) Zhu, J.; Bienaymé, H. *Multicomponent reactions*; Wiley-VCH: Weinheim, 2005. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(4) (a) Smith, A. B., III; Kim, W.-S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6787. (b) Smith, A. B., III; Han, H.; Kim, W.-S. *Org. Lett.* **2011**, *13*, 3328.

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

(6) Hirao, A.; Nakahama, S. *Acta Polym.* **1998**, *49*, 133.

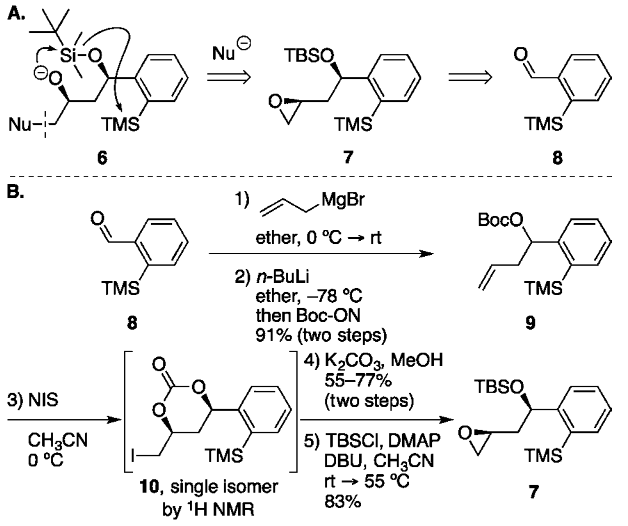
(7) Smith, A. B., III; Kim, W. S.; Tong, R. B. A. *Org. Lett.* **2010**, *12*, 588.

10.1021/ol303080h

ARC reaction manifold with Takeda and Hiyama cross-coupling reactions,[8] which in turn led to the identification of an effective recoverable silicon-based transfer agent for cross-coupling reactions.[9] Higher order 1,*n*-Brook rearrangements ($n = 6$ or higher) are not particularly effective in the ARC protocol, presumably due to the larger ring transition states required for intramolecular silyl group migration. Thus, these results set 1,4- and 1,5-charge relocation as the current *optimal* migration distance for the Type II ARC process.

Well aware that oxygen-bound silyl groups are known to migrate under anionic conditions,[10] especially when an alkoxy anion is within 1,4- or 1,5-proximity,[11] we reasoned that an appropriately placed[12] silyl ether might provide a vehicle to augment charge relocation and thereby overcome the current distance constraints of Brook rearrangements. For example, transfer of a silyl group (i.e., TBS), present on the benzylic oxygen in intermediate **6** (Scheme 2A), could be envisioned to occur upon nucleophile-initiated epoxide ring opening of **7**; a 1,4-Brook rearrangement could then generate a reactive ion, in a manner equivalent to an elongated or *long-range* version of our validated Type II ARC protocol with linchpin **8**.[13]

Scheme 2. (A) Design of LR-ARC Linchpin **7** Based on Validated Linchpin **8**; (B) Preparation of **7**



To explore this scenario, we constructed the prospective linchpin **7** from *o*-TMS-benzaldehyde **8** (Scheme 2B). Namely, addition of allylmagnesium bromide to **8**, followed by Boc protection, furnished **9**, which in turn was subjected to an *N*-iodosuccinimide (NIS)-promoted stereoselective iodocyclization/methanolysis sequence.[14] The resulting *syn*-epoxyalcohol, obtained as a single diastereomer, was then protected with TBS chloride to provide the prospective linchpin **7** in good overall yield.

As envisioned, **7** performed effectively as a *long-range* Type II ARC linchpin employing allyl bromide as the electrophile (Scheme 3). A series of experiments were carried out to track the formation of each intermediate during the three-step LR-ARC sequence.[15] Importantly, the overall efficiency of this process could be adjusted by modulating both the equivalents of CuI and concentration of the reaction mixture during the silyl group migration steps. Optimization afforded the three-component adduct **16** in 69% isolated yield. Monoprotected diols **14** and **15** (protonated forms of **11** and **12**) could be isolated as the main components after steps i and ii respectively; each was characterized to define the structures of the epoxide opening and migration intermediates. These studies verify that the 1,5-O→O silyl migration takes place only after application of the conditions required to trigger the 1,4-C→O Brook rearrangement (step ii: Cu(I) salt, THF/HMPA). Moreover, Ley oxidation[16] of **14**, **15**, and **16** provided ketone **17** and benzophenones **18** and **19**, respectively, confirming the location of the migrating TBS group during the course of the LR-ARC transformation.

Having established that the silyl group migrations occurred as predicted, the nature of the ARC anionic species **12** was evaluated in a series of alkylation experiments (Table 1). With reactive electrophiles, three-component ARC adducts were produced in good yields as the free benzylic alcohols (**16**, **20a**–**c**) upon aqueous workup. Isolation of TMS-ether adducts (**13** and **21**) was also feasible by carefully maintaining the amount of nucleophile to near 1.0 equiv (entries 4 and 13), indicating possible involvement of the excess cuprate in TMS removal. Interestingly, use of propargyl bromide as an electrophile (entries 8–10) furnished exclusively the S_N2' allene product **20b**, which suggests that, upon 1,5-O→O silyl migration and subsequent 1,4-Brook rearrangement, the resultant aryl anion undergoes conversion to a heterocuprate species [ArCu(X)M].[17] Of special note, use of CuBr·SMe$_2$ in place of CuI in some cases led to equal or superior results (entries 2, 6, and 9); however, the use of this Cu(I) source often resulted in

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(8) (a) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845. (b) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471. (c) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58. (d) Nakao, Y.; Imanaka, H.; Sahoo, A. K.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 6952. (e) Chen, J.; Tanaka, M.; Sahoo, A. K.; Takeda, M.; Yada, A.; Nakao, Y.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 554. (f) Nakao, Y.; Takeda, M.; Matsumoto, T.; Hiyama, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 4447.

(9) Smith, A. B., III; Hoye, A. T.; Martinez-Solorio, D.; Kim, W.-S.; Tong, R. *J. Am. Chem. Soc.* **2012**, *134*, 4533.

(10) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley-Interscience: Hoboken, NJ, 2007; pp 166–169.

(11) (a) For a report on 1,4 O→O migrations of TBDPS groups in polyols under basic conditions, see: Mulzer, J.; Schöllhorn, B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 431. (b) For an interesting 1,11-O→O silyl group migration, see: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

(12) For examples of silyl group migrations followed by a subsequent reaction, see: (a) Hillier, M. C.; Meyers, A. I. *Tetrahedron Lett.* **2001**, *42*, 5145. (b) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 1049.

(13) Smith, A. B., III; Kim, W.-S.; Wuest, W. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7082.

(14) Stereochemical assignments of **7**, **26**, and **28** are based on previously reported iodocyclizations; see: (a) Taylor, R. E.; Jin, M. *Org. Lett.* **2003**, *5*, 4959. (b) Duan, J. J. W.; Smith, A. B., III. *J. Org. Chem.* **1993**, *58*, 3703.

(15) See Supporting Information for details.

(16) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(17) Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2011**, *112*, 2339.

Scheme 3. Analysis of the Reactive Species at Each Stage of the Long-Range ARC Protocol

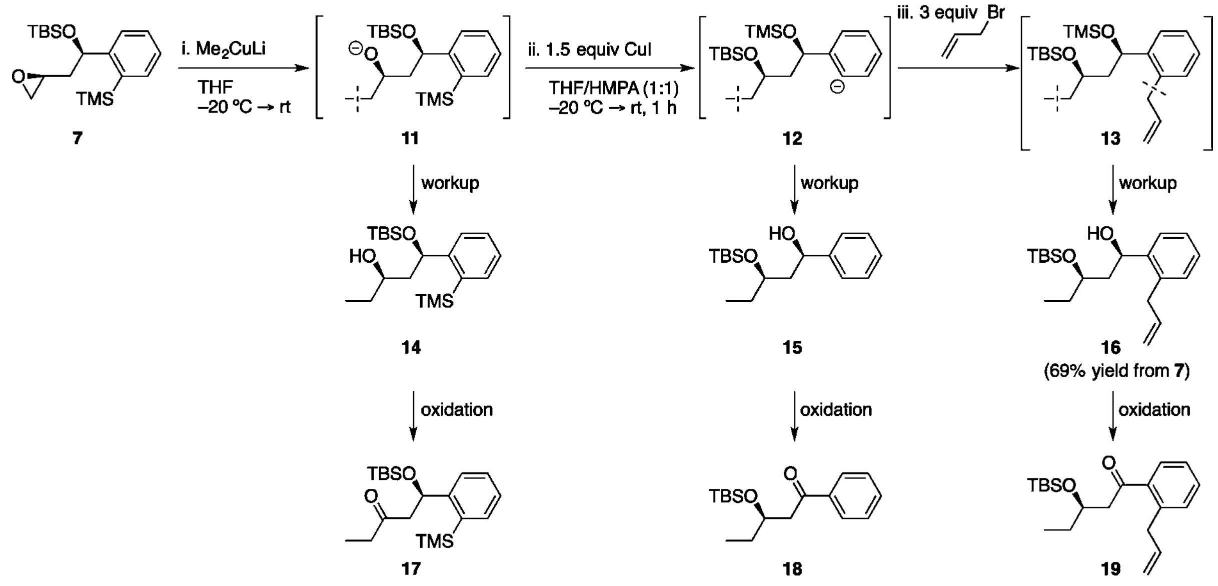
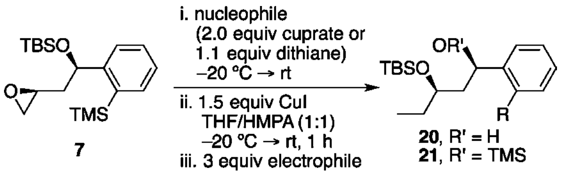
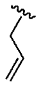
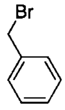
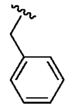
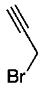
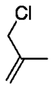
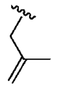
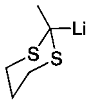
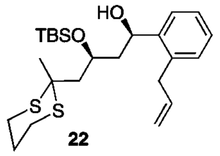


Table 1. Three-Component ARC Union of Cuprate or Dithiane Nucleophiles, Linchpin **7**, and a Series of Electrophiles



entry	nucleophile	electrophile	product	R	% yield
1	Me_2CuLi		**16**		69%
2					78%[a]
3					67%[b,c]
4			**13**		82%[b,d]
5	"		**20a**		67%
6					63%[a]
7					79%[e,f]
8	"		**20b**		58%
9					71%[a]
10					70%[b,c]
11	"		**20c**		53%
12					71%[e,f]
13			**21**		83%[b,e,d]
14			 **22**		70%[b,c]

[a] $CuBr\cdot SMe_2$ was used as additive instead of CuI in step ii. [b] 1.05 equiv of Me_2CuLi was used in step i. [c] A K_2CO_3/MeOH TMS-deprotection step was used. [d] A pH 7 aqueous workup was used. [e] The reaction mixture was concentrated prior to the alkylation step. [f] A pH 4 aqueous workup was used.

variable outcomes that appeared to be $CuBr\cdot SMe_2$ batch-dependent.[18] Importantly, overall yields could be notably improved by concentrating the reaction mixture prior to the alkylation step (compare entries 5 and 7, also 11 and 12). Operationally, concentration was achieved by evaporating the volatiles using a nitrogen gas stream or *in vacuo*.[15] When the bulky dithiane anion was employed as a nucleophile for epoxide opening in place of methylcuprate, the LR-ARC Type-II protocol proved equally effective furnishing product **22** in 70% yield (entry 14).

We next turned to exploring the viability of exploiting the derived LR-ARC anions in cross-coupling reactions (Table 2). After some experimentation, effective conditions were found using $Pd(OAc)_2$ (5 mol %) and dppf ligand (10 mol %) to furnish cross-coupled products **23a**–**b** and **24a**–**b** in good yields. Both higher concentration and temperature were required during the cross-coupling step, and use of more complex aryl halides as coupling partners resulted in low conversions. Currently we are evaluating conditions that may overcome the presumed steric hindrance that appears to play a role.

Given the viability of the sequential 1,4- and 1,5-silyl group migrations (Scheme 3), we were intrigued by the potential use of the LR-ARC concept in the design of building blocks containing oxygenated centers in moieties other than *syn*-1,3-diols. We thus constructed and tested linchpin **26**, the *anti*-congener of **7** (Scheme 4).[14] Effective LR-ARC formation of the three-component alkylation adduct **27** was again achieved.

The observation that the intermediate after 1,5-O→O silyl group migration pre-(1,4-O→Si) Brook was not observed in significant, if any, quantity in reactions with either linchpin **7** or **26** suggests that formation of the critical aryl heterocuprate, upon Brook rearrangement, provides a strong driving force for the consecutive silyl group

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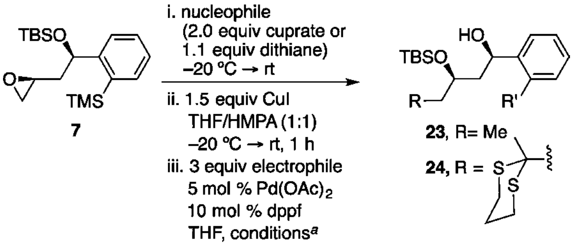
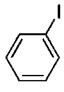
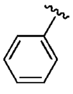
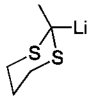
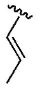
(18) Lipshutz, B. H.; Whitney, S.; Kozlowski, J. A.; Breneman, C. M. *Tetrahedron Lett.* **1986**, *27*, 4273.

Table 2. Three-Component ARC Union of Nucleophiles, Linchpin **7**, and Electrophiles under Coupling Conditions



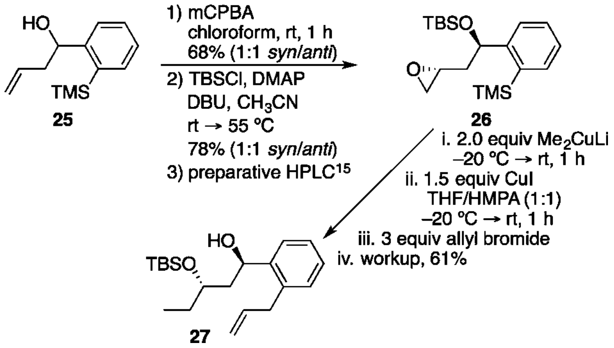
entry	nucleophile	electrophile	product	R'	% yield
1	Me$_2$CuLi		**23a**		68%
2	"		**23b**		42%
3			**24a**		72%
4	"		**24b**		69%

[a] Entries 1,3: 55 °C, 2 h. Entry 2: 85 °C, 6 h. Entry 4: 55 °C, 6 h.

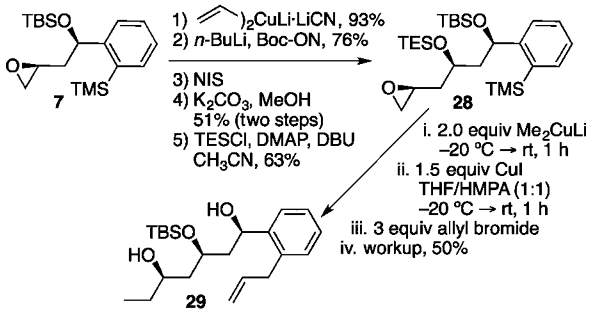
migrations. With this in mind, we explored the possibility of further charge migration (i.e., a *longer-range* ARC process).

To this end, we constructed **28** (Scheme 5) following a sequence similar to that employed for the preparation of **7**.[14,15] Gratifyingly, under the same LR-ARC conditions, linchpin **28** furnished the corresponding three-component alkylation adduct **29** in 50% yield. The structure of the final product was again confirmed by derivatization,[15] thereby validating that the silyl group migrations occur in sequential fashion to transfer the negative charge to a position now eight atoms removed from the origin!

Scheme 4. Preparation of Linchpin **26**, the *anti* Isomer of Linchpin **7**, and Validation of the LR-ARC Protocol



Scheme 5. Synthesis of Extended Linchpin **28** and Validation of the LR-ARC Protocol



In summary, long-range relocation of negative charges to sites positioned six and eight atoms distal to their origin, well beyond the known distance limitation of classic Brook rearrangements,[5] can be achieved under carefully controlled conditions by the combination of 1,4-Brook rearrangements with 1,5-O→O silyl group migrations. Importantly, the multiple transfer of the silyl group, orchestrated by 1,5-O→O and 1,4-C→O migrations, proceeds in a sequential manner to furnish nucleophiles capable of both alkylations and, in several cases, cross-coupling reactions. To the best of our knowledge, there are no previous reports of controlled, consecutive silyl group migrations. Taken together, the successful design, validation, and application of long-range Anion Relay Chemistry (LR-ARC) hold the promise for even greater structural diversity and synthetic efficiency to emanate from Type II Anion Relay Chemistry.

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

The authors declare no competing financial interest.