Synthetic Methods

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# Anion Relay Chemistry: Access to the Type II ARC Reaction Manifold through a Fundamentally Different Reaction Pathway Exploiting 1-Oxa-2-silacyclopentanes and Related Congeners**

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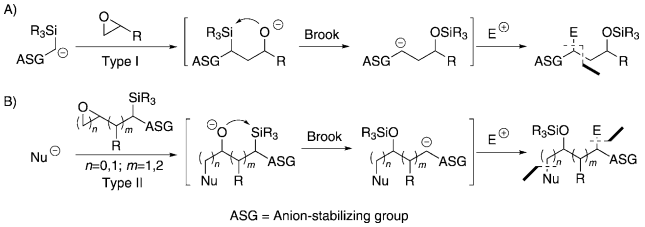
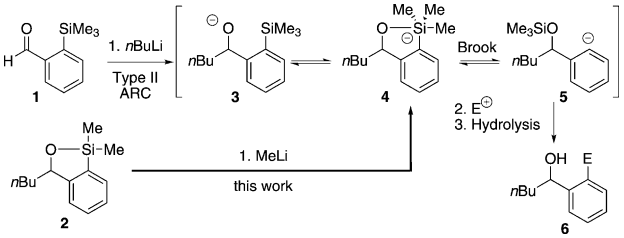
Type I and II anion relay chemistry (ARC)[1] exploiting [1,*n*]-Brook rearrangements[2] (Scheme 1 A and B, respectively), comprise an effective set of synthetic tactics that unite multiple components, in a single reaction flask, that permits rapid access to architecturally diverse polyketide and alkaloid molecular arrays.[2]




***Scheme 1.*** Type I and II anion relay chemistry (ARC).

To extend the ARC concept, we recently designed, synthesized and evaluated a number of new bifunctional linchpins for the type II process,[3] and then demonstrated their utility both in natural product[4] and diversity oriented synthesis (DOS).[5] During the development of the type II multicomponent process, we became intrigued with the possibility of accessing the type II ARC reaction manifold through a fundamentally different pathway employing 1-oxa-2-silacyclopentanes and related congeners (cf. **2**, Scheme 2).

Based on the structural resemblance of 1-oxa-2-silacyclopentene **2** to the proposed ARC silicon ate intermediate **4**, we envisioned that addition of a nucleophile (MeLi) might provide access to the type II reaction products. We were of course cognizant of the elegant observation of Mosher and Brook,[6] that in the [1,2]-Brook rearrangement, charge transfer from the initially derived oxyanion to carbon proceeds through a silicon ate intermediate.[7] However to achieve success with the type II ARC protocol, we learned early on that a change in temperature, solvent polarity, and/or




***Scheme 2.*** Type I and II anion relay chemistry (ARC).

metal ion additive was required to trigger the [1,4]-Brook rearrangement after initial addition of a nucleophile. The presumed silicon ate intermediate[7] then furnishes the reactive anion **5**, capable of alkylation,[3d] or in the presence of a palladium catalyst, cross-coupling.[3d,f,8] By arriving at the silicon ate intermediate through a different pathway (cf. **2**→**4**), we anticipated that the use of such "triggers" might not be required to arrive at **5**. That is, access to the pentacoordinate silicon ate species **4**, followed by conversion and capture of the resultant anion **5** might only require addition of methyllithium in a compatible solvent (Scheme 2).

The synthetic utility of 1-oxa-2-silacyclopentanes and related congeners has been widely recognized by other laboratories. Ito[9] and Woerpel[10] exploited the Tamao–Fleming oxidation to furnish 1,3-diols; Hiyama,[11a] Tamao,[11b] and Denmark[11c,d] achieved Hiyama-type palladium-catalyzed cross-coupling reactions induced by fluoride; and both Roush[12] and Schreiber[13] employed 1-oxa-2-silacyclopentanes as templates for intramolecular Diels–Alder reactions. More recently, Trost[14] and Lee[15] exploited 1-oxa-2-silacyclopentanes respectively both to access aldol-type products and to achieve anionic desilylation followed by C-alkylation, the latter induced by fluoride ion.

We began our study with the recognition that *o*-trimethylsilylbenzaldehyde **1** is a competent linchpin in a variety of type II ARC processes.[3d] For example, addition of a nucleophile (i.e., *n*BuLi) to **1** (Scheme 2), followed by a solvent/metal-mediated [1,4]-Brook rearrangement, employing HMPA (hexamethylphosphoramide) and CuI as the triggering conditions, leads to charge migration "across space" from oxygen to carbon with subsequent anion capture. Based on the structural resemblance of the pentacoordinate silicon ate complex envisioned to arise during validated ARC type II protocols,[3f,g] 1-oxa-2-silacyclopentenes **2** and **10**, and the saturated congener 1-oxa-2-silacyclopentane **12**, a diastereomeric mixture (4:1, *syn: anti*),[16] were synthesized (Scheme 3) and evaluated as progenitors of the respective silyl ate complexes (see Supporting Information).

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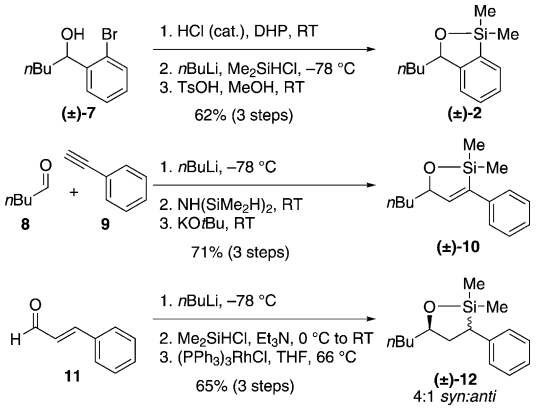
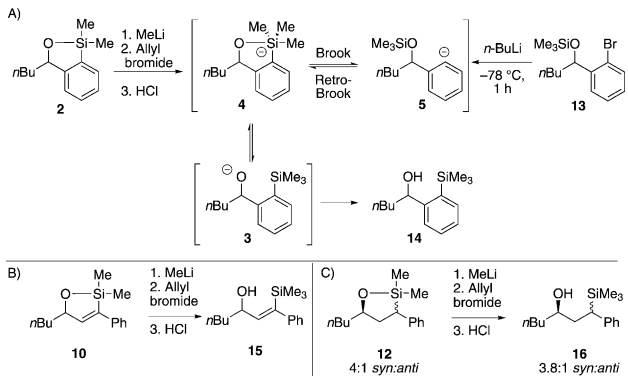


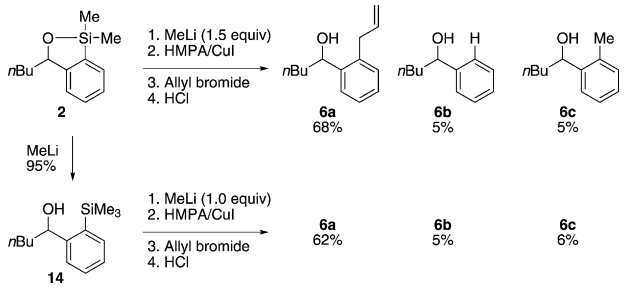

***Scheme 3.*** Synthesis of 1-oxa-2-silacyclopentanes and -pentenes. TsOH = *p*-toluenesulfonic acid.

With **2**, **10** and **12** in hand, we quickly recognized that addition of methyllithium to **2** led only to rupture of the silicon–oxygen bond to produce trimethylsilyl alcohol **14** (Scheme 4 A).[17] Even in the presence of excess allyl bromide, no C-alkylation or protodesilylation could be detected. Similar results were observed for **10** and **12**. Thus, our initial hypothesis that direct access to the pentacoordinate silicon ate intermediate through addition of a nucleophile that would lead directly to **5** through the silicon ate intermediate without additives was not correct. We also discovered that treatment of aryl bromide **13** with *n*BuLi at −78 °C led only to trimethylsilyl alcohol **14** through a retro-Brook rearrangement process.[18] From these experiments we conclude that the oxyanion **3**, and the corresponding oxyanions derived from **10** and **12** (Scheme 4 A and C), comprise the more stable intermediate resulting from anion equilibrium (cf. **3**⇌**5**), presumably through intermediacy of the pentacoordinate silicon ate species.

We next attempted to shift the equilibrium (**3**⇌**5**) to be in favor of anion **5**, exploiting the previously documented triggering conditions of HMPA and CuI addition required in the type II ARC protocol for conversion of **1** to **5**. Pleasingly, treatment of **2** with MeLi, followed by addition of a mixture of HMPA/CuI, and in turn allyl bromide, furnished alcohol **6a** (68 %), the tricomponent type II ARC adduct (Scheme 5). Also of interest was isolation of proto-



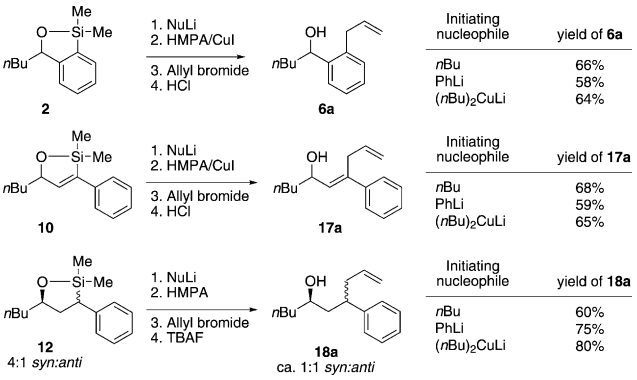

***Scheme 4.*** MeLi addition to 1-oxa-2-silacyclopentanes and -pentenes.




***Scheme 5.*** MeLi addition to 1-oxa-2-silacyclopentanes and -pentenes. HMPA = hexamethylphosphoramide.

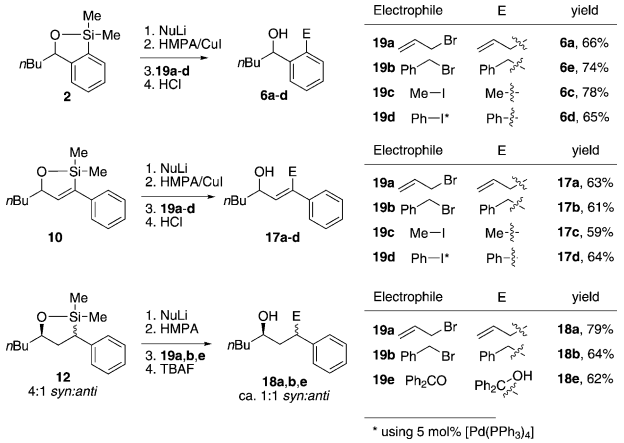
desilylated alcohol **6b** and *o*-methylbenzyl alcohol **6c**. At first, we envisioned that the unexpected *o*-methylbenzyl alcohol was the result of the excess methyllithium (1.5 equiv) employed for complete consumption of the starting 1-oxa-2-silacyclopentane. However, when alcohol **14** was treated with only one equivalent of *n*BuLi, we again observed a minor amount of product **6c**. Similar products were observed employing 1-oxa-2-silacyclopentene **10** (ca. 2–8 %), although not with the saturated oxasilane congener **12**, where, as in the type II ARC protocol, CuI is not required.[3g] While protodesilylation events (e.g., **6b**) are known to occur in polar aprotic solvents,[19] the mechanism for the formation of **6c** remains unclear.

To demonstrate that addition of nucleophiles to 1-oxa-2-silacyclopentenes **2** and **10** and to the saturated congener **12** can in general serve as surrogates to access the corresponding ARC type II three-component adducts, we explored *n*BuLi, PhLi, and the cuprate $(n\text{Bu})_2\text{CuLi}$, exploiting the conditions optimized for methyllithium-mediated formation of **6a**, employing allyl bromide as the electrophile (Scheme 6). Yields of the allylation products were comparable, if not better than those obtained employing MeLi. To the best of our knowledge, this is the first documented example of a cuprate leading to cleavage of a silicon–oxygen bond. The ability to exploit different carbon nucleophiles to access ate intermediates holds the promise of orchestrating the steric and electronic features at silicon, that once generated, would furnish a variety of silyl protected alcohols (i.e., TMS, TBS ethers, etc).




***Scheme 6.*** Scope of nucleophile initiation for 1-oxa-2-silacyclopentanes and -pentenes. Conditions: THF, NuLi (1.5 equiv), CuI (1.2 equiv for **2** and **10**), allyl bromide (3 equiv). TBAF = tetra-*n*-butylammonium fluoride.



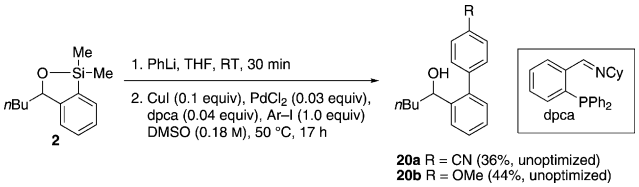

***Scheme 7.*** Scope of electrophile termination for 1-oxa-2-silacyclopentanes and -pentenes. Conditions: THF, MeLi (1.5 equiv), CuI (1.2 equiv for **2** and **10**), electrophile (3.0 equiv). For cross-coupling: $[Pd(PPh_3)_4]$ (0.05 equiv), Ar-I (2.0 equiv).

We also explored the use of different reactive electrophiles (Scheme 7). With 1-oxa-2-silacyclopentenes **2** and **10**, both C-alkylation and palladium-catalyzed cross-coupling reactions were achieved, the latter when a catalytic amount of $[Pd(PPh_3)_4]$ was employed with iodobenzene in THF. Pleasingly, the cross-coupling reactions proceed at room temperature. Although the literature provides many examples of 1-oxa-2-silacyclopentanes reacting to yield products of protodesilylation,[19] oxidative desilylation[9,10] and cross-coupling,[11] few reports of C-alkylation have been described.[15]

The saturated oxasilane congener **12** also furnished alkylation products analogous to the type II ARC counterpart with electrophiles **19a**, **b**, and **e**; however in these examples, as with the corresponding type II ARC reaction, CuI was not required. Here, use of the diastereomeric mixture of **12** (4:1) led to **18a** and **b**, wherein the diastereomeric ratio degraded to 1:1. This result is in accord with our observations employing β-TMS-hydrocinnamaldehyde as an ARC linchpin.[3g] We attribute the lack of stereoretention to anion equilibration via resonance stabilization with the π-system of the aromatic ring.[3g,20]

Having achieved room temperature cross-coupling protocols upon addition of MeLi to **2** and **10** employing stoichiometric copper iodide, HMPA and a catalytic amount of $[Pd(PPh_3)_4]$ (Scheme 7, **6d** and **17d**), we initiated a search for a version of this process that would also prove catalytic in CuI. After considerable experimentation, we found that cross-coupling adducts **20a** and **b** could be obtained in unoptimized yields of 36% and 44%, respectively (Scheme 8), when 10 mol% CuI and 3 mol% $PdCl_2$ were employed in the presence of 4 mol% of the iminophosphine ligand dpca.[21] Although preliminary, these results suggest that a version of the type II ARC cross-coupling tactic catatlytic in both palladium and copper is viable in a "single flask." Studies to explore this and other aspects of the type II ARC reaction manifold continue in our laboratory.

In summary, 1-oxa-2-silacyclopentane and -pentenes (**2**, **10**, and **12**) have been synthesized, screened and demonstrated to provide access to the type II anion relay chemistry




***Scheme 8.*** Catalytic CuI-promoted Brook rearrangement/cross-coupling.

(ARC) reaction manifold through a fundamentally different pathway. By exploring the scope of this transformation with a number of nucleophiles and electrophiles, these studies offer insight into the mechanistic details of the [1,4]-Brook rearrangement, namely that charge migration from oxygen to carbon is not the immediate result of direct access to the pentacoordinate silicon ate species. Even when the silicon ate intermediate is accessed through a distinctly different route, a change of solvent polarity and/or the use of metal additives is required to complete either the observed alkylation or cross-coupling reactions.

## *Experimental Section*

General procedure for the alkylation of **2** and **10**: To a solution of 1-oxa-2-silacyclopentene (0.2 mmol) in dry THF (1 mL) was added MeLi (1.6 M in $Et_2O$, 0.14 mL, 0.22 mmol) at −78 °C. After stirring for 30 min, the solution was transferred through cannula to a pre-mixed homogeneous solution of HMPA (0.5 mL) and copper iodide (45.6 mg, 0.24 mmol) at room temperature. The resulting black solution was stirred for 30 min at room temperature and the electrophile (0.4 mmol) was added. The resulting solution was stirred at room temperature overnight (ca. 16 h), then diluted with $Et_2O$ (2 mL) and quenched by addition of aqueous HCl (1N, 2 mL), and was vigorously stirred for 20 min. The organic layer was collected and the aqueous layer was extracted with $Et_2O$ (3 × 2 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (1:10, EtOAc/Hexane) to afford the desired alkylated products with yields indicated in Scheme 6 and 7.

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**Keywords:** alkylating desilylation · anion relay chemistry · Brook rearrangement · cross coupling · siloxanes

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