Uniting Anion Relay Chemistry with Pd-Mediated Cross Coupling: Design, Synthesis and Evaluation of Bifunctional Aryl and Vinyl Silane Linchpins
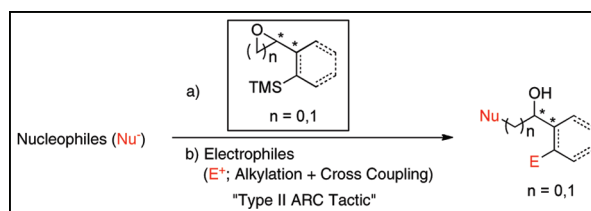
Amos B. Smith III,* Won-Suk Kim, and Rongbiao Tong

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

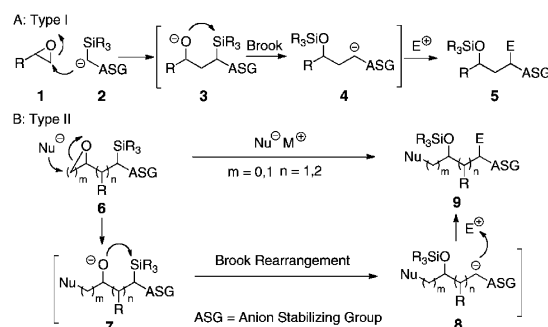*smithab@sas.upenn.edu*

ABSTRACT

Union of type II Anion Relay Chemistry (ARC) with Pd-induced Cross Coupling Reactions (CCR) has been achieved, in conjunction with the design, synthesis, and evaluation of a new class of bifunctional linchpins, comprising a series of vinyl silanes bearing β- or γ-electrophilic sites. The synthetic tactic permits both alkylation and Pd-mediated CCR of the anions derived via 1,4-silyl $C(sp^2) \rightarrow O$ Brook Rearrangements.

Type I and II Anion Relay Chemistry (ARC),[1] exploiting Brook Rearrangements (Scheme 1A and B),[2] comprises a powerful linchpin tactic for the rapid assembly of high levels of molecular complexity, as demanded by natural product total synthesis. Extension of the Type II ARC process (Scheme 1B) to include transition metal promoted Cross-Coupling Reactions (CCR), as the culminating event in the Type II ARC process (cf. **8→9**), would, if general, greatly extend the scope of this evolving synthetic tactic. Recently, we recorded a single example (Table 1, Entry 1) employing *ortho*-TMS benzaldehyde **10** as linchpin that demonstrated the feasibility of uniting ARC with Pd-mediated cross coupling.[3] Convinced that this "one-flask" multicomponent protocol would hold considerable potential, if general, we initiated a program to unite ARC with the cross coupling

tactic. We quickly recognized, as reported by Takeda et al.[4] for *ortho*-TMS benzyl alcohol, that the use of CuI,

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

and in our case a mixture of HMPA and THF (1:1), is required to trigger the 1,4-Brook rearrangement. Toward this

(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.

(2) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77.

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

end, addition of *n*-BuLi to **10**, followed by CuI/HMPA:THF induced silyl migration. Subsequent addition of diverse vinyl and aryl halides in the presence of 3 mol % Pd(PPh₃)₄ in THF at room temperature led to a series of cross coupled adducts (**10a−10h**) with yields ranging from 50−67% (Table 1).

Table 1. Pd-Mediated Cross-Coupling Reactions via Type II ARC[a]

entry	electrophile	R	entry	electrophile	R
1	Br⌇	**10a:** (67%)	5	I⌇CN	**10e:** (60%)
2	Br⌇	**10b:** (55%)	6	I⌇NO₂	**10f:** (58%)
3	Br⌇	**10c:** (65%)	7	I⌇	**10g:** (58%)
4	Br⌇	**10d:** (57%)	8	I⌇	**10h:** (50%)

[a] Conditions: 1.2 equiv *n*-BuLi, 1.2 equiv CuI.

Having established the initial scope of the combined ARC-II/Pd-mediated CCR protocol, we turned to the design, synthesis, and evaluation of a new class of bifunctional vinyl silanes, with electrophilic sites β or γ to the silane (Figure 1), first to explore
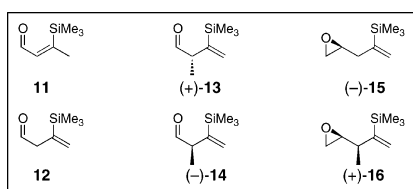
Figure 1. Vinyl silane bifunctional linchpins.

their utility as linchpins for the Type II ARC tactic and then as linchpins in the combined ARC-II/Pd-mediated CCR process.

Linchpin **11** was readily available via oxidation of known alcohol **17**,[5] whereas **12** was prepared from epoxide **18**[6] and commercial vinyl bromide **19** (Scheme 2).

Scheme 2. Preparation of Linchpins **11** and **12**
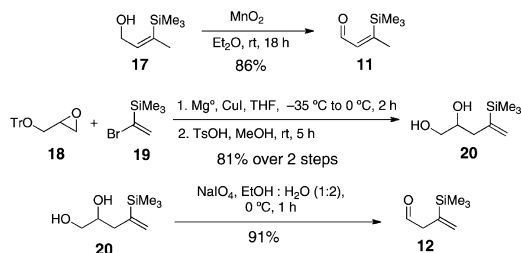
To explore the ARC tactic with **11**, we selected conditions that proved effective with **10**.[3] As illustrated in Table 2,

Table 2. Three-Component Coupling of Linchpin **11** with Various Electrophiles[a]

entry	electrophile	R	entry	electrophile	R
1	Br⌇	**21a:** (65%)	5	Br⌇	**21e:** (53%)[a]
2	Br⌇	**21b:** (66%)	6	I⌇NO₂	**21f:** (52%)[a]
3	PhS-SPh	**21c:** (68%)	7	I⌇	**21g:** (54%)[a]
4	Bu₃SnCl	**21d:** (63%)	8	I⌇	**21h:** (61%)[a]

[a] Conditions: 1.2 equiv *n*-BuLi, 1.2 equiv CuI. (a) 3 mol % Pd(PPh₃)₄, THF, rt, 6 h.

addition of *n*-BuLi in Et₂O, followed by CuI (1.2 equiv) in a mixture of HMPA/THF (1:1), and then a variety of carbon- and heteroatom-based electrophiles furnished adducts **21a−21d** in 63−68% yield. Under these conditions, the 1,4-silyl migration proceeded rapidly (ca. 30 min). Equally important, palladium-mediated cross coupling reactions, initiated via the ARC Type II process, proved feasible. For example, addition of 3 mol % Pd(PPh₃)₄ and a series of vinyl and aryl halides after the HMPA/THF induced Brook rearrangement furnished cross coupled adducts **21e−22h** in 52−61% yield. Other common nucleophiles proved effective as initiators of both the Type II ARC and the combined ARC-II/Pd-mediated CCR tactics (Table 3). Use of TBAF to remove the TMS group proved critical to avoid partial allylic rearrangements of **22a−22f**; use of 1 N HCl led to facile allylic rearrangement (cf. **22h−22j**). Neither allylic rearrangement nor cross-coupling was observed upon use of anion derived from methyl dithiane, the latter due to catalyst poisoning by the dithiane.[7]

Encouraged by the viability of the Type II ARC process employing **11**, we turned next to **12** as the bifunctional linchpin (Table 4). Initially, silyl migration proved problematic, furnishing only trace amounts of the desired product when employing the conditions which proved effective at triggering silyl migration with **11**. However, when two equivalents of both *n*-BuLi as the nucleophile and CuI were employed in a mixture of HMPA and THF (1:1), complete 1,4-silyl C(sp²)→O migration occurred albeit more slowly over the course of 2 h. Addition of a

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(5) Han, S.; Kass, R. S. *Tetrahderon Lett.* **1997**, *38*, 7503.
(6) Kamal, A.; Ramesh, G. B. K.; Krishnaji, T.; Ramu, R. *Tetrahderon: Asymmetry* **2006**, *17*, 1281.

Table 3. Three-Component Coupling of Linchpin **11** with Various Nucleophiles and CCR with Phenyl Iodide[a]
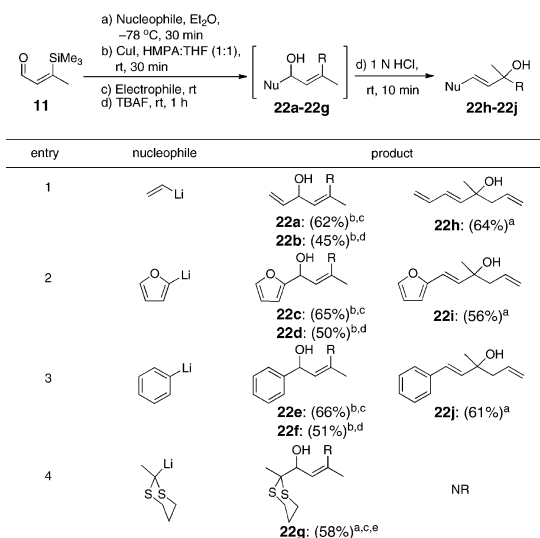
a Conditions: (a) 1 N HCl, rt, 10 min (b) TBAF, rt, 1 h. (c) R = Allyl, Allyl bromide, rt, 2 h. (d) R = Ph, 3 mol % Pd(PPh$_3$)$_4$, Phenyl iodide THF, rt, 6 h. (e) No cross-coupling product was obtained due to catalyst poisoning by dithiane.

series of electrophiles (2.0 equiv) furnished alkylation adducts **23a**−**23d** (Table 4, Entries 1−4) in ca. 50% yield, while modest yields of cross-coupling products **23e**−**23f** were obtained upon addition of 3 mol % Pd(PPh$_3$)$_4$ followed by aryl iodides (Entries 5−6).

**Table 4.** Three-Component Coupling of Linchpin **12** with Various Electrophiles[a]
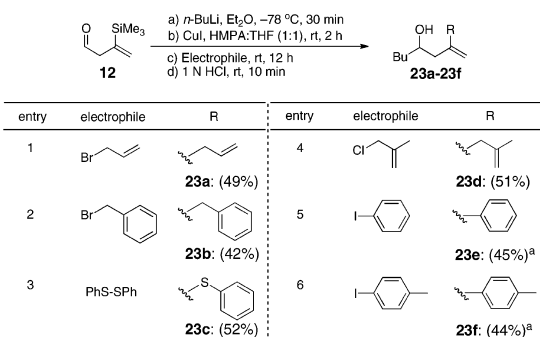
a Conditions: 2.0 equiv *n*-BuLi, 2.0 equiv CuI. (a) 3 mol % Pd(PPh$_3$)$_4$, THF, rt, 12 h.

The variable time course between **11** and **12** for 1,4-silyl group migration is understandable in terms of the mechanism of the Brook rearrangement.[8] In the case of linchpin **12**, the 1,4-silyl C(sp^2)→O migration is slow, due to a combination of the distance between the silicon and oxygen atoms and the multiple bond rotations required to arrive at the cyclic transition state.[9]

From the perspective of complex molecule synthesis, a drawback of employing non-α-substituted linchpin aldehydes **11** and **12** entails the lack of stereochemical control upon initial nucleophilic addition and the lack of the ubiquitous methyl substituents found in polyketides. We therefore turned to α-methyl-substituted linchpins (+)-**13** and (−)-**14**.[10] We reasoned that addition of alkyllithiums to (+)-**13** and (−)-**14** would produce, with good diastereoselectivity, the corresponding *syn* alkoxides. Confirmation of this scenario would further increase the utility of both the Type II ARC and ARC-II/Pd-induced CCR tactics, not only for natural product total synthesis but also for polyketide diversity synthesis.[11]

Pleasingly, addition of *n*-BuLi to either (+)-**13** or (−)-**14** (Table 5), followed in turn by silyl migration induced

Table 5. Three-Component Coupling of Linchpin (+)-**13** or (−)-**14** with Various Electrophiles[a]
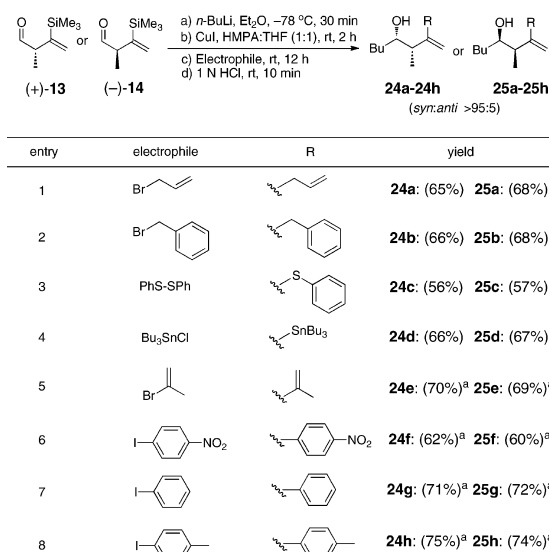
a Conditions: 2.0 equiv *n*-BuLi, 2.0 equiv CuI. (a) 3 mol % Pd(PPh$_3$)$_4$, THF, rt, 12 h.

by CuI in a mixture of HMPA and THF (1:1) and reaction with a series of electrophiles furnished multicomponent adducts **24a**−**25h** in yields ranging from 56 to 75% (Table 5).[12] Effective cross coupling unions also occurred after 1,4-Brook rearrangement, upon addition of 3 mol % Pd(PPh$_3$)$_4$, followed by vinyl or aryl halides. Importantly, no epimerization of the α-methyl substituent was observed during this process.

As with linchpin **11**, other nucleophiles derived from furan, phenyl bromide and 2-methyl-1,3-dithiane prove to be

(7) Main, C. A.; Petersson, H. M.; Rahman, S. S.; Hartley, R. C. *Tetrahderon* **2008**, *64*, 901.

(8) (a) Jiang, X.; Bailey, W. F. *Organometallics* **1995**, *14*, 5704. (b) Kawashima, T.; Naganuma, K.; Okazaki, R. *Organometallics* **1998**, *17*, 367. (c) Naganuma, K.; Kawashima, T.; Okazaki, R. *Chem. Lett.* **1999**, 1139.

(9) The results on silyl migration are in accord with Takeda and coworkers. Tsubouchi, A.; Itoh, M.; Onishi, K.; Takeda, T. *Synthesis* **2004**, *9*, 1504.

effective at initiating the Type II ARC tactic to furnish, in a single flask, both three-component alkylation and cross-coupled adducts **26a**−**27e** (Table 6).

Table 6. Three-Component Coupling of Linchpin (+)-**13** or (−)-**14** with Various Nucleophiles and CCR with Phenyl Iodide[a]

[a] Conditions: (a) R = Allyl, Allyl bromide, rt, 12 h. (b) R = Ph, 3 mol % Pd(PPh₃)₄, Phenyl iodide, THF, rt, 12 h.

We next explored the possibility of extending the Type II ARC and ARC-II/Pd-induced CCR tactics to epoxide-based linchpins possessing an electrophilic site γ to the vinyl silane. This design led to linchpins (−)-**15** and (+)-**16**, constructed as illustrated in Scheme 3.[13,14]

Scheme 3. Preparation of Linchpins (−)-**15** and (+)-**16**
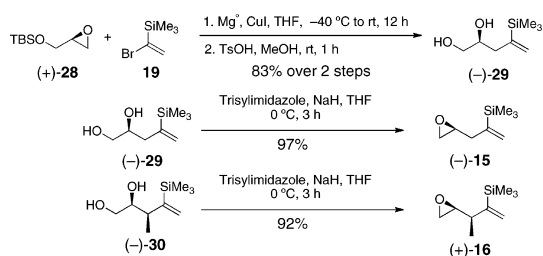
With the four-carbon bifunctional linchpins in hand, we employed lithium dibutylcuprate **31**, known both to add to epoxides[15] and to initiate 1,4-silyl C(sp³)→O migration in Anion Relay Chemistry.[1b] Capture of allyl bromide after Brook rearrangement led respectively to adducts (+)-**32** and (+)-**34** (Scheme 4). Cross coupling reactions also proceeded upon addition of 3 mol % Pd(PPh₃)₄, followed

Scheme 4. Three-Component Coupling of Linchpins (−)-**15** or (+)-**16** with Various Electrophiles[a]
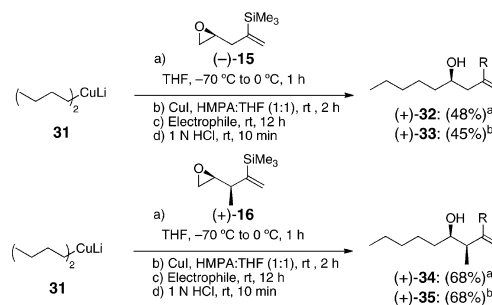
[a] Conditions: 1.2 equiv dibutylcuprate, 1.2 equiv CuI. (a) R = Allyl, Allyl bromide, rt, 12 h. (b) R = Ph, 3 mol % Pd(PPh₃)₄, Phenyl iodide, THF, rt, 12 h.

by reaction with phenyl iodide to furnish (+)-**33** and (+)-**35**, respectively.

In summary, the union of Type II Anion Relay Chemistry with Pd-mediated Cross Coupling has been achieved, thereby greatly expanding the scope of this multicomponent "one-flask" linchpin protocol. Equally important, a new class of three and four carbon, bifunctional linchpins comprising aryl and vinyl silanes bearing β- or γ-electrophilic sites, have been designed, synthesized and demonstrated to be competent in both Type II ARC and combined ARC-II/Pd-induced CCR processes. Studies to improve the efficiency of this tactic continue in our laboratory.

Supporting Information Available: Procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Sato and co-workers demonstrated (+)-**13** and (−)-**14** underwent Grignard reactions with high syn diastereoselectivity, the result of a Cram product-like transition state.[10b,e] (a) Sato, F.; Kusakabe, M.; Kobayashi, Y. *J. Chem. Soc., Chem. Commun* **1984**, 1130. (b) Sato, F.; Takeda, Y.; Uchiyama, H.; Kobayashi, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1132. (c) Kobayashi, Y.; Kitano, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1984**, 1329. (d) Sato, F.; Kusakabe, M.; Kato, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1331. (e) Samaddar, A. K.; Chiba, T.; Kobayashi, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1985**, 329.
(11) Schreiber, S. L. *Science* **2000**, *287*, 1964.
(12) Absolute configuration was confirmed by Mosher ester analysis.
(13) (a) Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203. (b) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 8122.
(14) Kobayashi, Y.; Kitano, Y.; Takeda, Y.; Sato, F. *Tetrahedron* **1986**, *42*, 2937.
(15) Herr, R. W.; Wieland, D. M.; Johnson, C. R. *J. Am. Chem. Soc.* **1970**, *92*, 3813.