Type II Anion Relay Chemistry: Exploiting Bifunctional Weinreb Amide Linchpins for the One-Pot Synthesis of Differentiated 1,3-Diketones, Pyrans, and Spiroketals

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Abstract: *The design, synthesis, and validation of new highly effective bifunctional linchpins for type II anion relay chemistry (ARC) has been achieved. The mechanistically novel negative-charge migration that comprises the Brook rearrangement is now initiated by a stabilized tetrahedral intermediate, which is generated by nucleophilic addition to a Weinreb amide, rather than by a simple oxyanion that is generated from an epoxide. As a result, the linchpin preserves the carbonyl functionality in the ARC adducts, thus permitting access to functionally complex systems in a single flask without the need for further chemical manipulations. This tactic was validated with the one-pot preparation of monoprotected 1,3-diketones as well as pyran and spiroketal scaffolds, depending on the choice of nucleophile, electrophile, and work-up conditions.*
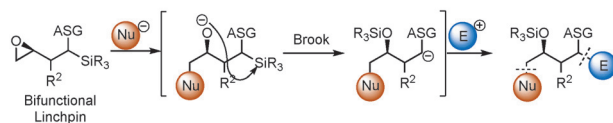
*I*n an attempt to mimic Nature's elegant synthesis of complex molecules, the concept of anion relay chemistry (ARC) has been developed and validated as a versatile synthetic platform for the union of complex fragments to furnish multicomponent adducts in an effective and stereocontrolled fashion.[1] ARC methods can be categorized based on the nature of the negative-charge migration: "Through-bond" ARC (e.g., conjugate addition) has been widely exploited in organic chemistry, whereas "through-space" ARC has come to fruition only over the past two decades. Our interests in this area focus on the development and implementation of "through-space" ARC, which can be subdivided into type I and type II tactics. Type I ARC was developed based on the precedent set by the groups of Matsuda and Tietze,[2] wherein linchpins react with 2 equivalents of an epoxide to furnish symmetric tricomponent adducts. Later, by controlling the timing of the Brook rearrangement through a change in solvent polarity, counterion, or temperature, the formation of unsymmetric tricomponent adducts was achieved, thus increasing the utility of the tactic for complex-molecule synthesis (Scheme 1a).[3] Subsequently, we designed and validated the type II ARC tactic, which involves charge migration across a bifunctional linchpin, again through a controlled Brook rearrangement, resulting in a distinct class of tricomponent adducts (Scheme 1b).[4]

Whereas both the type I and II ARC tactics have been exploited in a number of total synthetic ventures in our
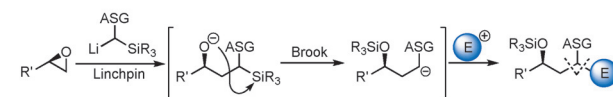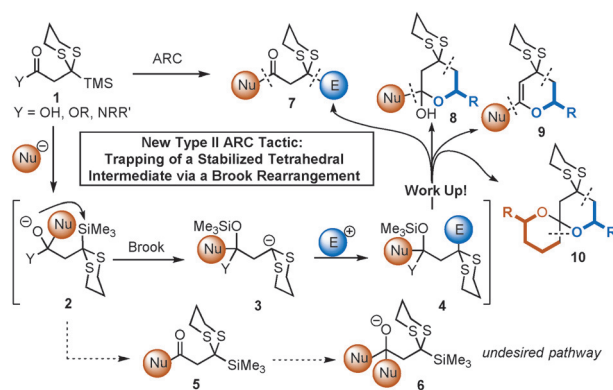

Scheme 1. a) Type I and b) type II anion relay chemistry. ASG = anion-stabilizing group.

laboratory,[5] we have continued to design and validate new ARC linchpins. To this end, we envisioned a new class of type II linchpins that would permit access to multicomponent adducts bearing monoprotected 1,3-dicarbonyl functional groups by means of a mechanistically new ARC tactic. Specifically, we turned to the introduction of a carboxylic acid derivative at the electrophilic terminus of the linchpin (**1**; Scheme 2), reasoning that the relative stability of the derived tetrahedral intermediate resulting from nucleophilic addition (see **2**; Scheme 2) would permit the desired Brook rearrange-

**Scheme 2.** Type II anion relay chemistry linchpin: a new concept.

ment to outcompete premature collapse to the ketone (**5**), thereby preventing over-addition of the initiating nucleophile. If effective, the Brook rearrangement would reveal a nucleophilic carbanion, which in turn could add to an electrophile and thereby construct a multicomponent adduct (Scheme 2). Although precedent can be found for the capture of a tetrahedral intermediate by N-to-O and S-to-O silyl

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migrations,[6] the potential for premature collapse of the tetrahedral intermediate in the polar medium typically required to trigger the Brook rearrangement (i.e., C-to-O silyl group migration) would have to be overcome to realize our goal.

To explore the envisioned new ARC tactic, we first constructed the prospective linchpins **12–15** (Scheme 3). Carboxylic acid **12** and ethyl ester **13** were prepared in analogous fashion, namely by nucleophilic addition of TMS-
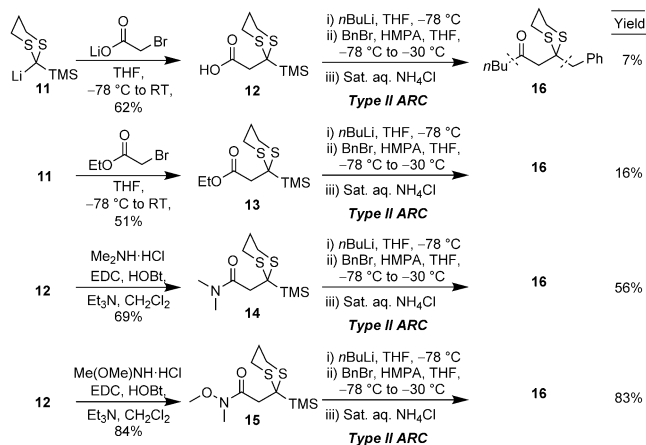
Scheme 3. Linchpin synthesis and preliminary studies.

dithiane to lithium bromoacetate and ethyl bromoacetate, respectively.[7] In turn, amide coupling of **12** with the HCl salts of *N,N*-dimethylamine and *N,O*-dimethylhydroxylamine provided amide linchpins **14** and **15**; the latter compound is a Weinreb amide (Scheme 3).[8] With the first linchpins **12** and **13** in hand, the feasibility of the proposed ARC tactic was explored in THF at −78 °C, using *n*-butyl lithium (*n*BuLi) as the nucleophile and benzyl bromide (BnBr) as the electrophile; hexamethylphosphoramide (HMPA) was employed to trigger the Brook rearrangement. Unfortunately, the reaction sequence resulted in the formation of complex mixtures, with only minor amounts of the desired product **16** (<16%). Pleasingly, however, when **14** and **15** were subjected to the aforementioned reaction conditions, the desired product **16** could be isolated in good to excellent yield after protic workup and flash chromatography. The superiority of the Weinreb amide linchpin **15**, relative to congener **14**, suggests that the stabilization of the tetrahedral intermediate imparted by the *N*-methoxy moiety, presumably by chelation of lithium, prevents premature Brook rearrangement and is pivotal to the success of this ARC tactic.[8]

Excited by the initial results, we proceeded to analyze the scope and utility of this new ARC tactic with linchpin **15** and diverse electrophiles and nucleophiles (Tables 1 and 2). Pleasingly, the ARC reactions proceeded smoothly in good yield with methyl iodide and allyl bromide (entries 1 and 2, Table 1), whereas the yields achieved with homoallylic, alkynyl, and alkyl bromides were somewhat lower than with the corresponding iodide congeners (entries 3–5). The reaction with chlorotriethylsilane also proceeded effectively to

Table 1: Electrophile scope with linchpin **15**.[a]

Entry	E+	Product	Yield
1	MeI	**17**	78%
2	Br⌒ (allyl bromide)	**18**	75%
3	X⌒⌒ a) X = Br b) X = I	**19**	a) 59% b) 74%
4	X⌒⌒⌒ a) X = Br b) X = I	**20**	a) 52% b) 67%
5	X⌒⌒≡Me a) X = Br b) X = I	**21**	a) 55% b) 69%
6	Et₃SiCl	**22**	71%
7	(R)-epichlorohydrin	(R)-**23**	60%

[a] Reaction conditions: i) **15**, THF, −78 °C, then slow addition of *n*BuLi; ii) electrophile, HMPA, THF, −78 °C to −30 °C; iii) sat. aq. NH₄Cl.

provide adduct **22** in 71% yield. Finally, when epichlorohydrin was employed as the terminating electrophile, epoxide **23** was obtained in good yield, resulting as expected from nucleophilic attack at the terminal epoxide carbon atom rather than direct displacement of the chloride.[9]

Next, we explored the nature of the nucleophilic component of the ARC reaction, employing benzyl bromide as the electrophilic species (Table 2). Again, the ARC reactions proceeded in good yield with alkyl, alkenyl, alkynyl, allyl, and aryl lithium nucleophiles (entries 1–7). The addition of softer nucleophiles was also explored (entries 8–10). To achieve these transformations, greater control over the timing of the Brook rearrangement was required: Key to success was the addition of a solution of benzyl bromide in THF to the tetrahedral intermediate, followed by the slow addition of a precooled HMPA/THF solution. With this procedure, the reactions furnished the desired tricomponent adducts in generally good yields.

To demonstrate the utility of the monoprotected 1,3-diketone motif that is now readily accessible by this ARC tactic, we studied the one-pot construction of substituted pyran and spiroketal scaffolds from structurally simple components (Scheme 4).[10] Initial attempts at the single-flask ARC cyclization method entailed use of *n*BuLi as the initiating nucleophile with ethylene oxide as the terminating electrophile; **41** was isolated in good yield after protic workup and chromatography (entry 1, Table 3). Use of (R)-benzyl

Table 2: Nucleophile scope with linchpin **15**.[a]

Entry	NuLi	Product	Yield
1	MeLi	**24**	78%
2	PhLi	**25**	71%
3	vinylLi	**26**	53%
4	allylLi	**27**	66%
5	phenylacetylide Li	**28**	74%
6	2-pyridylLi	**29**	71%
7	2-thienylLi	**30**	59%
8	(EtO)$_2$P(O)CH=CH OLi	**31**	68%[b]
9	tBuO(OLi)C=CH$_2$	**32**	63%[b]
10	tBuO(ONa)C=CH-CH=CH OLi	**33**	64%[b]

[a] Reaction conditions: i) **15**, THF, −78 °C, then slow addition of NuLi; ii) BnBr, HMPA, THF, −78 °C to −30 °C; iii) sat. aq. NH$_4$Cl. [b] i) **15**, THF, −78 °C, then slow addition of NuLi; ii) BnBr, THF, then slow addition of HMPA/THF solution, −78 °C to −30 °C; iii) sat. aq. NH$_4$Cl.

Scheme 4. Proposed preparation of cyclic compounds.

Table 3: Preparation of cyclic systems utilizing **15**.[a]

Entry	NuLi	E+	Quench	Product	Yield
1	nBuLi	epoxide	A	**41**	68%
2	nBuLi	glycidyl OBn	A	**42**	65%
3	nBuLi	glycidyl OBn	B	**43**	72%
4	TBSO...Li **44**	BnBr	B	**45**	60%
5	TBSO...Li **44**	ethylene oxide	B	**46** (Y,Y = S(CH$_2$)$_3$S) → **49** (Y = H) Ra-Ni 85%	64%
6	BnO...OTBS...Li **47**	glycidyl OBn	B	**48** (Y,Y = S(CH$_2$)$_3$S; R = Bn) → **50** (Y = H; R = H) Ra-Ni 98%	67%

[a] Reaction conditions: i) **15**, Et$_2$O, −78 °C, then slow addition of NuLi; ii) BnBr, HMPA, Et$_2$O, −78 °C to −30 °C; iii) quench A with sat. aq. NH$_4$Cl or quench B with 48% aq. HF, then NaHCO$_3$.

glycidyl ether as the terminating electrophile led to lactol **42** also in good yield, whereas simply altering the workup procedure (i.e., more acidic conditions; quench B, Table 3) led to dihydropyran **43**. Next, an alkyl lithium reagent bearing a terminal TBS ether, which was envisioned to undergo in situ deprotection, was employed as the initiating nucleophile with benzyl bromide as the terminating electrophile. Upon reaction completion (determined by TLC), addition of aqueous HF furnished **45** in 60% yield. Similarly, the use of ethylene oxide resulted in the formation of spiroketal **46**. Turning to nucleophile **47** and (R)-benzyl glycidyl ether as the electrophile, followed by silyl group removal, led to spiroketal **48** in 67% yield. Treatment of **46** and **48** with Raney nickel under a hydrogen atmosphere furnished (±)-olean (**49**) and SPIKET-P (**50**) respectively.[11,12]

Finally, we have also achieved the construction of complex aldehydes in a similar manner to that presented for the preparation of tricomponent ketones and ketals. Treatment of **15** with a nucleophilic hydride (LiAlH$_4$) and subsequent addition of BnBr in a HMPA/THF solution did not result in the formation of the envisioned adduct (Scheme 5, **52**). Whereas this was not the desired outcome, we envisioned that the addition of lithium N,O-dimethylhydroxylamine **54** to
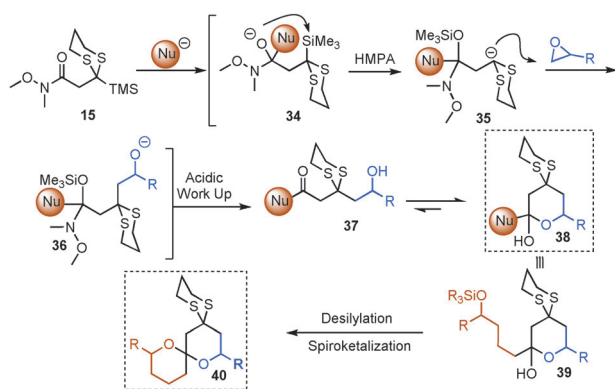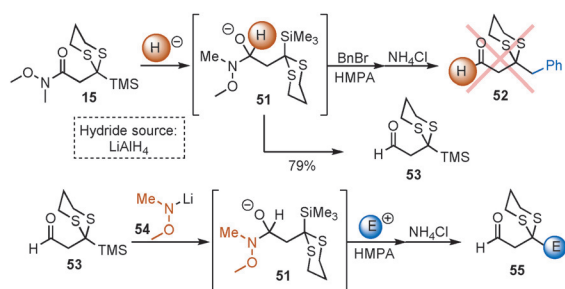
Scheme 5. Preparation of aldehyde-containing adducts.

53 would permit formation of intermediate **51**;[13] subsequent Brook rearrangement, electrophile addition, and protic work up would then yield adduct **55**. Gratifyingly, addition of **54** to **53** followed by a solution of benzyl bromide in HMPA/Et$_2$O and protic workup provided aldehyde **56** in 78% yield (Table 4, entry 1). In similar fashion, use of ethylene oxide and (*R*)-benzyl glycidyl ether as the terminating electrophiles permitted the preparation of **57** and **58** in good yields (entries 2 and 3).

Table 4: Application of aldehyde linchpin **51**.[a]

Entry	E$^+$	Product	Yield
1	BnBr	**56**	78%
2	(ethylene oxide)	**57**	65%
3	(glycidyl ether OBn)	**58**	68%

[a] Reaction conditions: i) **51**, Et$_2$O, −78 °C, then slow addition of NuLi; ii) BnBr, HMPA, Et$_2$O, −78 °C to −30 °C; iii) sat. aq. NH$_4$Cl.

In summary, we have designed, synthesized, and validated Weinreb amide **15** as a new type II ARC linchpin for the efficient preparation of architecturally complex scaffolds. This linchpin showcases a novel ARC tactic that permits the ready construction of differentiated 1,3-diketones and derivatives while circumventing the requirement for protecting-group and oxidation-state manipulations. In turn, we have illustrated the utility of this new ARC linchpin, most notably in the preparation of di- and tetrahydropyrans as well as spiroketals in one-pot processes.

[1] A. B. Smith III, W. M. Wuest, *Chem. Commun.* **2008**, 5883–5895.
[2] a) I. Matsuda, S. Murata, Y. Ishii, *J. Chem. Soc. Perkin Trans. 1* **1979**, 26–30; b) L. F. Tietze, H. Geissler, J. A. Gewert, U. Jakobi, *Synlett* **1994**, 511–512.
[3] a) H. Shinokubo, K. Miura, K. Oshima, K. Utimoto, *Tetrahedron* **1996**, *52*, 503–514; b) H. Shinokubo, K. Miura, K. Oshima, K. Utimoto, *Tetrahedron Lett.* **1993**, *34*, 1951–1954; c) A. B. Smith III, A. M. Boldi, *J. Am. Chem. Soc.* **1997**, *119*, 6925–6926.
[4] A. B. Smith III, M. Xian, *J. Am. Chem. Soc.* **2006**, *128*, 66–67.
[5] a) A. B. Smith III, T. Tomioka, C. A. Risatti, J. B. Sperry, C. Sfouggatakis, *Org. Lett.* **2008**, *10*, 4359–4362; b) A. B. Smith III, D.-S. Kim, *J. Org. Chem.* **2006**, *71*, 2547–2557; c) A. B. Smith III, D.-S. Kim, *Org. Lett.* **2005**, *7*, 3247–3250; d) B. Melillo, A. B. Smith III, *Org. Lett.* **2013**, *15*, 2282–2285; e) H. Han, A. B. Smith III, *Org. Lett.* **2015**, *17*, 4232–4235.
[6] a) J. L. Adams, T. M. Chen, B. W. Metcalf, *J. Org. Chem.* **1985**, *50*, 2730–2736; X. Sun, Z. Song, H. Li, C. Sun, *Chem. Eur. J.* **2013**, *19*, 17589–17594.
[7] V. Cerè, S. De Angelis, S. Pollicino, A. Ricci, C. K. Reddy, P. Knochel, G. Cahiez, *Synthesis* **1997**, 1174–1178.
[8] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
[9] D. E. McClure, B. H. Arison, J. J. Baldwin, *J. Am. Chem. Soc.* **1979**, *101*, 3666–3668.
[10] Such scaffolds are ubiquitous in bioactive natural products; see: a) A. Zampella, M. V. D'Auria, L. Minale, C. Debitus, C. Roussakis, *J. Am. Chem. Soc.* **1996**, *118*, 11085–11088; b) G. R. Pettit, F. Gao, P. M. Blumberg, C. L. Herald, J. C. Coll, Y. Kamano, N. E. Lewin, J. M. Schmidt, J.-C. Chapuis, *J. Nat. Prod.* **1996**, *59*, 286–289; c) H. C. Kwon, C. A. Kauffman, P. R. Jensen, W. Fenical, *J. Org. Chem.* **2009**, *74*, 675–684.
[11] R. Baker, R. H. Herbert, *J. Chem. Soc. Perkin Trans. 1* **1987**, 1123–1127.
[12] H. Huang, C. Mao, S.-T. Jan, F. M. Uckun, *Tetrahedron Lett.* **2000**, *41*, 1699–1702.
[13] D. L. Comins, J. D. Brown, *Tetrahedron Lett.* **1981**, *22*, 4213–4216.