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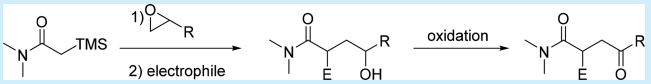
α-Silyl Amides: Effective Bifunctional Lynchpins for Type I Anion Relay Chemistry

Thomas D. Montgomery and Amos B. Smith, III*

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

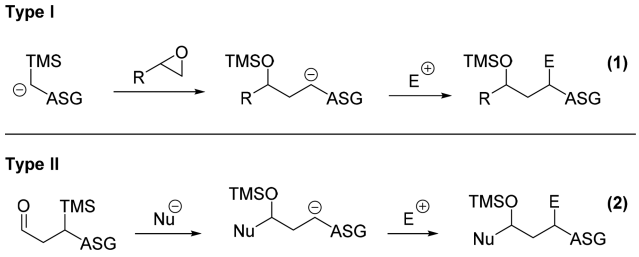
Supporting Information

ABSTRACT: Lynchpins comprising α-silyl amides have been validated for type I anion relay chemistry (ARC) to permit ready access to γ-ketoamides. Importantly, the ARC protocol can be run at ambient temperature without the need of additional reagents to trigger the [1,4] Brook rearrangement.



The rapid and efficient construction of complex molecular architecture has been a longstanding hallmark for the total synthesis of natural products. A protocol developed in our laboratory, termed anion relay chemistry (ARC), has proven highly effective toward this end via the construction of polyketide natural products. The ARC tactic can be categorized into through-bond[1] and through-space[2] negative charge migration, the later further divided into type I and type II.[3] Type I ARC involves the generation of an anion adjacent to an anion stabilizing group (ASG); following addition to a reactive electrophile, a [1,*n*]-Brook rearrangement[4] returns the derived anion to the originating site, which can then be captured with a second suitable electrophile to yield a three-component product in a single flask. We first reported the use of type I ARC in 1997,[5] employing dithianes as the anion-stabilizing groups as a strategic step in our total synthesis of spongistatins 1 and 2 (Scheme 1, entry 1).[6]

Scheme 1. Anion Relay Chemistry

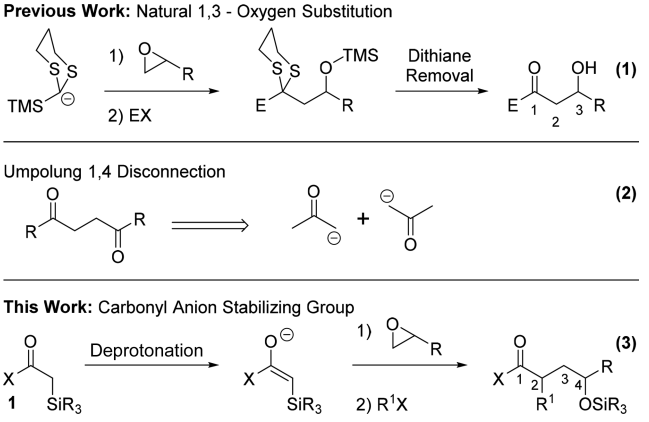


In 2004, we extended the ARC tactic via the use of bifunctional lynchpins. In this case, the first step involves addition of a nucleophile to a suitable oxygen-containing electrophile which can lead by migration of the derived anion via a Brook rearrangement to a new carbon center bearing an anion-stabilizing group. The reaction can then be terminated by reaction of the new anion with a suitable electrophile. This tactic was termed type II ARC and has subsequently been employed to great advantage in a number of total syntheses, including our recent synthesis of mandelalide A (Scheme 1, entry 2).[7]

While we and others have employed type I ARC, the available lynchpins remain limited, with dithiane-based lynchpins by far the most common.[3] Other effective ASGs for type I lynchpins include bischloro,[8] cyano,[9] and allyl.[10] Use of dithianes as anion-stabilizing groups followed by the Brook rearrangement is, however, limited to oxidative or reductive removal, resulting in a ketone or methylene moiety. In an effort to expand the scope of the ARC tactic to different connectivity patterns, we reasoned that a carbonyl-based ASG would permit access to 1,4 oxygenation patterns. This tactic becomes even more appealing due to the comparative difficulty in preparing such compounds given incompatibility with the typical aldol[11] or Michael reactions (Scheme 2).[12] Significant work has been done relating to the synthesis of 1,4-dicarbonyls involving metal-catalyzed couplings[13] and Stetter reactions[14] and through the use of umpolung synthons.[15]

With this constraint in mind, we turned to amide-based lynchpins as a potential carbonyl bifunctional lynchpin.[16] Importantly, Rathke and co-workers early on had demonstrated that C-silylated amides can be prepared and reacted at the α-

Scheme 2. Typical 1,3-Oxygen Spacing



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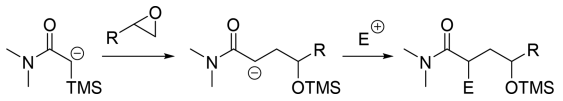
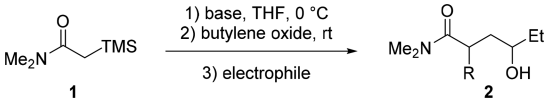
carbon with both aldehydes[17] and epoxides.[18] We therefore postulated that after amide deprotonation of **1** the enolate would open the epoxide at ambient temperature. A spontaneous Brook rearrangement of the resultant alkoxide could then ensue, migrating the negative charge to be captured with an appropriate electrophile (Scheme 3).

Scheme 3. Amide-Based Lynchpin



Gratifyingly, exposure of the anion derived from lynchpin **1** to butylene oxide at ambient temperature led both to ring opening of the epoxide and subsequent [1,4] thermal Brook rearrangement to furnish **2** (R = H) (Table 1, entry 1).

Table 1. Initial Results and Optimization[a]



entry	solvent	electrophile	base	NMR yield[b] (%)
1	THF	H_3O^+	LDA	80[c]
2	Et_2O	H_3O^+	LDA	0
3	toluene	H_3O^+	LDA	69
4	DCM	H_3O^+	LDA	72
5	THF	allyl bromide	LDA	45[c]
6	THF	allyl bromide	*n*-BuLi	60
7	THF	allyl bromide	*s*-BuLi	89[c]
8	THF	allyl bromide	LiHMDS	56
9	THF	allyl bromide	NaH	0

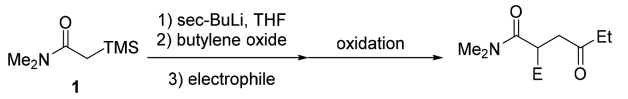
[a]Amide (1.00 equiv), base (1.10 equiv), butylene oxide (1.05 equiv), electrophile (1.60 equiv), solvent (0.2 M). [b]^{1}H NMR yield determined by reference to internal standard. [c]Isolated yield.

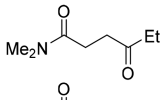
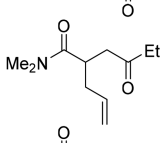
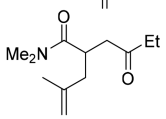
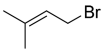
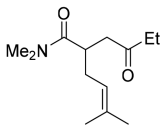
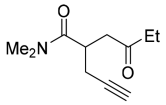
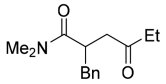
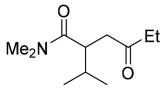
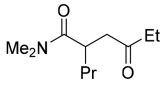
Following this initial success, we screened a series of commonly used solvents (entries 2−4) with THF providing the best yield, although both toluene and DCM were tolerated. We subsequently performed the reaction with allyl bromide as the terminal electrophile for the ARC protocol to capture the generated amide stabilized anion. Pleasingly, following aqueous workup, we were able to isolate alcohol **2** (R = allyl) in modest yield (entry 5). Capitalizing on this result, we next examined several bases to affect the deprotonation of **1**; *s*-BuLi gave the cleanest reaction, providing the product in 89% yield (entry 7).

With optimized reaction conditions in hand, we turned to explore the scope of this type I ARC tactic employing butylene oxide (Table 2). While the yields were generally good to excellent, the diastereoselectivities of the intermediate amide enolates proved only modest. Efforts to improve this selectivity though increased steric bulk at the nitrogen or via the employment of chiral auxiliaries led to limited success.[19]

To demonstrate more fully the synthetic utility of this method, we oxidized the derived alcohols to the γ-ketoamides (**3**−**10**).[20] Along with the unsubstituted compound (entry 1), various allyl bromides were well tolerated producing **4**−**6** after oxidation. Similarly, both propargyl and benzyl bromides were also tolerated (entries 5 and 6), in the ARC tactic, with both subsequently oxidized in high yields to furnish **7** and **8**. Finally, alkylation with either a secondary or primary alkyl halide

Table 2. Substrate Scope for Electrophile Component[a]



entry	electrophile	yield alcohol[b] (%, dr)	product		yield ketone (%)
1	H^+	85		**3**	91[c]
2		83 (3:2)		**4**	89[c]
3		81 (2:1)		**5**	93[d]
4		83 (2:1)		**6**	94[e]
5		92 (3:2)		**7**	95[e]
6		70 (3:2)		**8**	93[d]
7		83 (2:1)		**9**	92[e]
8		93 (7:3)		**10**	96[e]

[a]Amide (1.00 equiv), sec-BuLi (1.10 equiv), butylene oxide (1.05 equiv), electrophile (1.60 equiv), THF (0.2 M). [b]Diastereomeric ratio determined from crude ^{1}H NMR. [c]PCC oxidation. [d]Dess−Martin periodinane oxidation. [e]Swern oxidation.

proceeded in good to excellent yield (entries 7 and 8); similar oxidation led to γ-ketoamides **9** and **10**.

At this point, we examined which epoxide structures would be compatible with the bifunctional amide lynchpin (Table 3). Styrene oxide proved to be an excellent substrate; the allyl, benzyl, and propargyl targets were also available in good to excellent yield (entries 1−3). Subsequent oxidation provided the phenyl derivatives **11**−**13**. We next examined the impact of a heteroatom substituent and were delighted to find the compatibility of both benzyl and TBS protected glycidol ethers (entries 4−7). This group of adducts could be similarly oxidized to the corresponding γ-ketoamides, and in the case of compounds **16** and **17**, selective cleavage of the TMS group preceded oxidation. Finally, an aryl sulfide could be incorporated to yield **18** in moderate yield following oxidation.

With the scope of this type I ARC tactic secure, we next examined the inherent reactivity of the derived products. One such reaction comprises the direct cyclization of the γ-hydroxyamides to furnish γ-lactones (Scheme 4).[21] To this end, lynchpin **1** was combined with (*R*)-(−)-benzyl glycidol ether **19** to furnish **20** in good yield with modest levels of diastereoselectivity. Following exposure to triflic anhydride, the known lactone **21**[22] was isolated in 80% yield.

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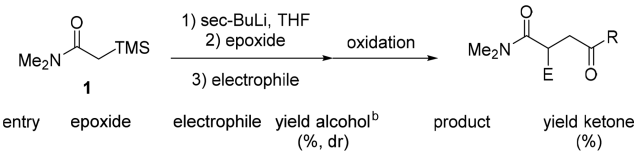
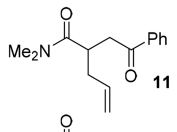
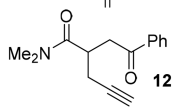
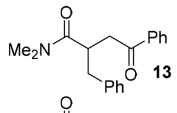
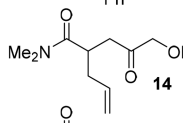
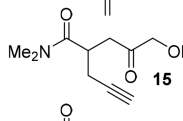
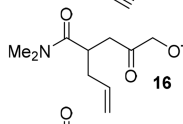
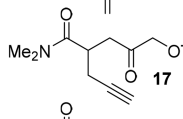
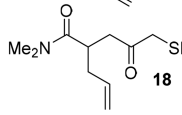
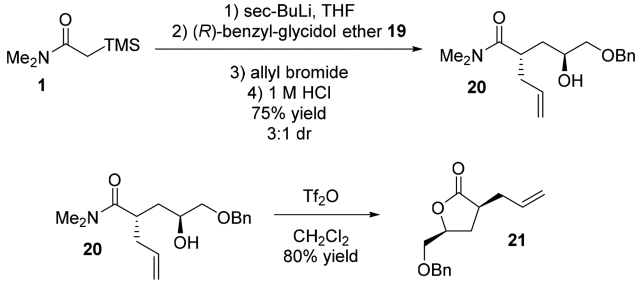
Table 3. Substrate Scope for Epoxide Component[a]



entry	epoxide	electrophile	yield alcohol[b] (%, dr)	product	yield ketone (%)
1			98 (2:1)	 **11**	96[d]
2			78 (3:2)	 **12**	98[d]
3			71 (2:1)	 **13**	90[c]
4			75 (3:1)	 **14**	90[c]
5			83 (2:1)	 **15**	95[c]
6			92 (2:1)	 **16**	96[c]
7			50 (5:2)	 **17**	91[c]
8			66 (2:1)	 **18**	97[d]

[a]Amide (1.00 equiv), secBuLi (1.10 equiv), butylene oxide (1.05 equiv), electrophile (1.60 equiv), THF (0.2 M). [b]Diastereomeric ratio determined from crude ^{1}H NMR. [c]Dess–Martin periodinane oxidation. [d]Swern oxidation.

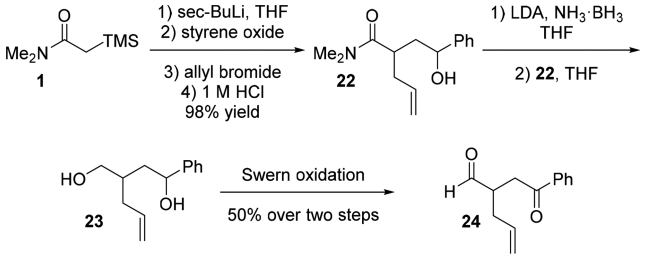
Scheme 4. Lactone Formation and Relative Stereochemistry



We next turned to methods to further elaborate and functionalize the amide moiety in the three-component adducts (Scheme 5). First, amide **22** was reduced to alcohol **23** using BH_3NH_3 and LDA. The resultant free diol was then oxidized to aldehyde **23** in 50% yield over the two steps.

In summary, we have successfully developed a new type 1 ARC lynchpin utilizing the ability of amides to open epoxides and stabilize the resulting anion. This tactic represents an expansion of the current ARC tactic, given the fact that the bifunctional amide lynchpin permits the exploration of new chemical space but also does not require HMPA or other toxic compounds to trigger the Brook rearrangement.[3,4] Further studies into this and related lynchpins are ongoing in our laboratory.

Scheme 5. Functionalization of Amide Portion



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03142.

Experimental procedures and spectral data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: absmith@sas.upenn.edu.

ORCID

Thomas D. Montgomery: 0000-0002-6526-8564
Amos B. Smith III: 0000-0002-1712-8567

Notes

The authors declare no competing financial interest.

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