ANION RELAY CHEMISTRY: DEVELOPMENT AND APPLICATIONS IN TOTAL SYNTHESIS

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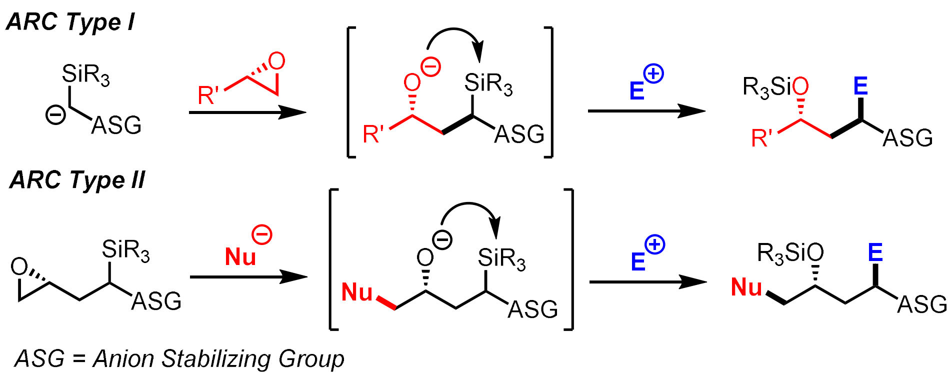
BACKGROUND

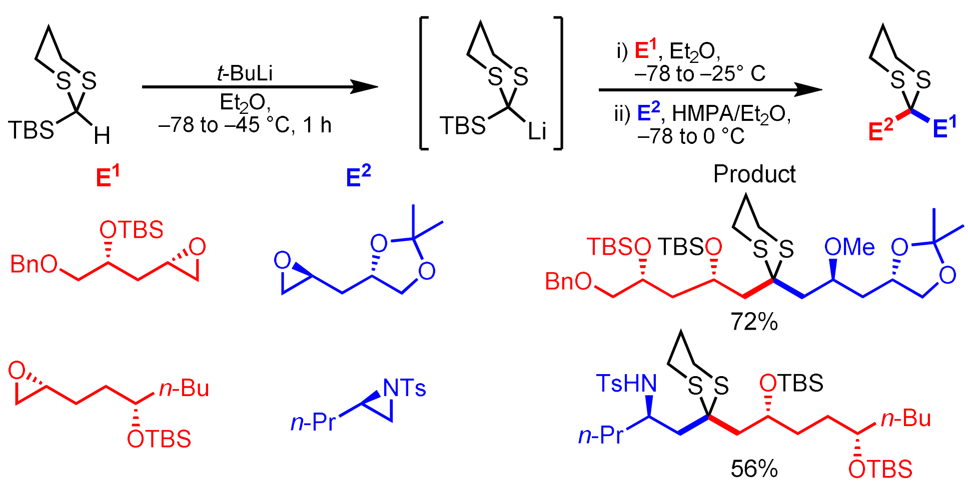
Anion relay chemistry (ARC) is a one-pot, multi-component union protocol which rapidly generates structurally complex scaffolds from simple building blocks. This procedure exploits an intramolecular [1,4]-Brook rearrangement to "relay" an anion from one locus of the intermediate to another, allowing for serial bond forming events. These structurally diverse adducts can be rapidly elaborated to numerous synthetically useful motifs including indolizidines, 1,3-polyols, spiroketals, and polyterpenes.



Scheme 1: Anion relay chemistry (ARC) of type I and II.

Type I Anion Relay Chemistry

Since the late 1970's, various gr oups have disclosed tandem [1,4]-Brook rearrangements resulting from nucleophilic epoxide openings.[1] Initially, researchers could not trap the putative carbanions with a second electrophile to obtain heterocoupled products. In 1994, Oshima demonstrated the first synthetically useful three component coupling by modulating the solvent mixture to control the [1,4]-Brook rearrangement.[2] Initial alkylation in Et_2O prevented the [1,4]-Brook rearrangement and gave the monoalkylated product. However, subsequent addition of HMPA, with a second electrophile triggered the silyl transfer and selectively delivered a heterocoupled product. Inspired by Oshima's work, Smith and coworkers demonstrated a series of type I ARC couplings between 2-trialyklsilyl-1,3-dithianes, and simple epoxides.[3] Furthermore, Smith and



Scheme 2: Type I ARC and selected applications

coworkers demonstrated a five component coupling could be achieved with epichlorohydrin. Since 1997, Smith has accessed a variety of complex structures with ARC type I tactics, including the AB and CD spiroketal rings of the spongistatins, the indolizidine cores of several alkaloids, and Schreiber's *tris*-acetonide fragment of mycoticin (Scheme 2).[4,5]

Type II Anion Relay Chemistry

Early examples of Type II ARC suffered from poor functional group tolerance and harsh reaction conditions. In 2004, Smith began a program to rationally develop novel type II linchpins. In order to effect a Brook rearrangement, the new linchpin must have an appropriately stabilized carbanion as well as an appropriate length between the oxyanion and silyl group. Mechanistic investigations revealed the [1,4]-Brook rearrangement to be more feasible than the [1,5] or the [1,6] variants.[6] Utilizing this tether length and various anion stabilizing groups, Smith devised a library of novel type II linchpins and demonstrated their utility in a series of type II ARC couplings. Most notably, the total synthesis of a Gorgonian sesquiterpene was achieved in 5 steps utilizing a three component Type II ARC coupling with a novel 2-((trimethylsilyl)methyl)acrylaldehyde linchpin. [7]

Conclusion

ARC represents a powerful multicomponent synthetic protocol to efficiently access highly functionalized motifs. The applicability of this strategy has been demonstrated several times in synthesis of complex natural products, including (+)-spirastrellolide A, secu'amamine A, and (−)-mandelalide A.[8]

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