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Merging Asymmetric [1,2]-Additions of Lithium Acetylides to Carbonyls with Type II Anion Relay Chemistry

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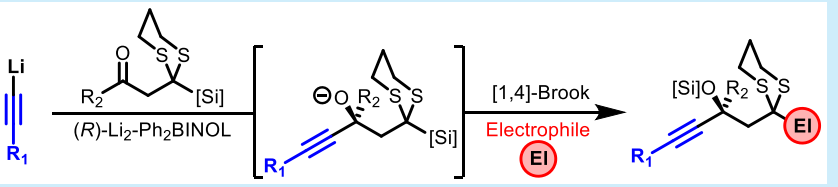
Supporting Information



ABSTRACT: An enantioselective three-component coupling reaction has been developed, enabling the union of a variety of lithium acetylides and electrophiles exploiting an achiral linchpin via an anionic reaction cascade. This Type II Anion Relay Chemistry tactic is initiated via an enantioselective [1,2]-carbonyl addition exploiting BINOL catalysis to access an enantioenriched alkoxide intermediate. Migration of charge across the linchpin via a [1,4]-Brook rearrangement with electrophile capture affords a three-component propargyl ether adduct. Herein, we report the development, scope, and limitations of this reaction sequence.

The challenge of organic synthesis is not only the ability to synthesize a target but also the efficiency with which the target is constructed. In this regard, Anion Relay Chemistry (ARC) comprises a one-pot, three-component union tactic in which a linchpin component sequentially forms a C−C bond to each of two other components via an anionic reaction cascade.[1] This tactic permits the assembly of complex polyketide fragments from simple building blocks, thereby minimizing the number of synthetic steps required to achieve the synthetic target. Accordingly, our group has exploited ARC to permit the total syntheses of several natural products, including (−)-nahuoic acid $C_{i\prime}$,[2] (−)-mandelalide A,[3] and (−)-enigmazole A.[4] The Type II ARC protocol is initiated by [1,2]-addition of an organolithium reagent to linchpin **1**, followed in turn by a [1,4]-Brook rearrangement[5] and electrophile capture to afford the three-component adduct **2** (Figure 1a). Here, diastereoselectivity arises via Felkin−Anh control with the absolute configuration set by the α-methyl stereogenic center present in **1**.[6,7]

While stereoretentive and diastereoselective processes have been successfully incorporated into the ARC protocol, an enantioselective variant has yet to be developed. We reasoned that this could be achieved via initiation of the ARC sequence with an asymmetric [1,2]-carbonyl addition. Asymmetric organometallic [1,2]-carbonyl additions commonly employ Zn acetylides,[8] although Sn, B, Li, and other metals have been employed.[9] This approach has been exploited by others, including Marek[10] and Johnson,[11] to access three-component couplings initiated by a Zn acetylide. However, these examples rely on a [1,2]-Brook rearrangement of the [1,2]-addition intermediate, whereas our envisioned strategy would comprise a [1,4]-Brook rearrangement; a protocol for the [1,4]-Brook rearrangement of Zn alkoxides remains elusive. Thus, our focus has been on lithium acetylides.

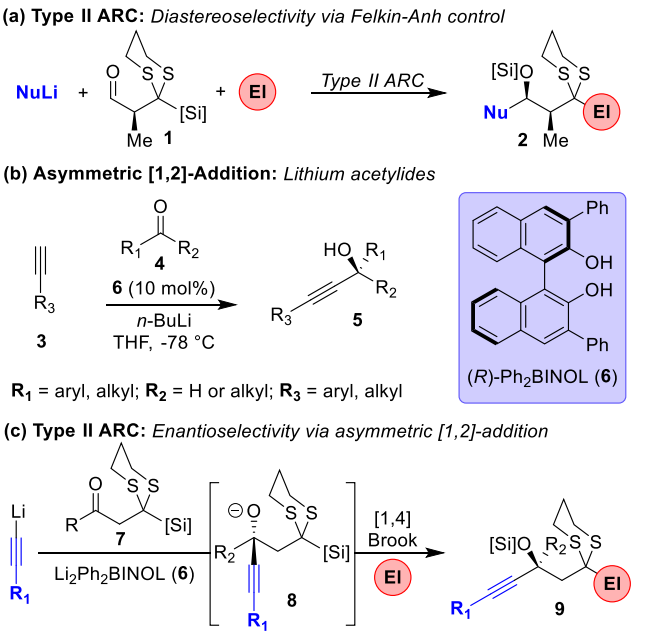


Figure 1. (a) Prior ARC Work: Diastereoselectivity; (b) Prior Asymmetric [1,2]-Addition of Lithium Acetylides to Ketones; (c) Proposed ARC Tactic

The enantioselective [1,2]-carbonyl addition of a lithium acetylide was first disclosed by Mukaiyama[12] and later

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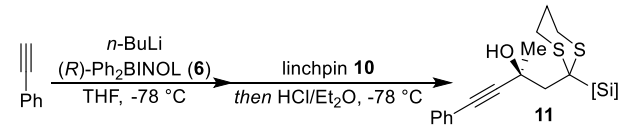
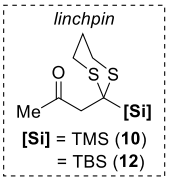
improved by the Merck[13] group in the synthesis of the HIV-1 reverse transcriptase inhibitor efavirenz. However, these early examples required several equivalents of ligand to impart high enantioselectivity. Recently, Nakajima reported a catalytic method for the asymmetric [1,2]-addition of lithium acetylides to ketones to yield enantioenriched propargyl alcohols utilizing BINOL derivative (*R*)-**6** (Figure 1b).[14] We sought to utilize (*R*)-**6** in conjunction with a lithium acetylide to access enantioenriched alkoxide **8** via an asymmetric [1,2]-addition to achiral linchpin **7** to obtain the enantioenriched three-component adduct **9** after [1,4]-Brook rearrangement and electrophile capture (Figure 1c).

Our efforts were first directed toward evaluation of the enantioselectivity of [1,2]-addition of lithium phenyl acetylide to linchpin **10** to afford propargyl alcohol **11** (Table 1). The

Table 1. Optimization of Enantioselectivity Utilizing ARC Linchpin[a]





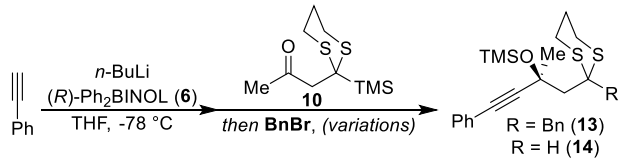
entry	ketone variation	er
1	added dropwise	90:10
2	added over 10 min	94:6[b]
3	added over 30 min	95:5
4	**12** instead of **10**	91:9[b]
5	1.0 eq Ph acetylene	97:3[b]

[a]*n*-BuLi (2.2 equiv); acetylene (2.0 equiv); (*R*)-**6** (10 mol %); **10** (1 equiv); HCl (1.5 equiv); [Si] = TMS (**11a**); TBS (**11b**). [b]**10** added over 10 min;

reaction was initiated by deprotonation of phenylacetylene in the presence of (*R*)-**6** at −78 °C, followed by the addition of linchpin **10** over a period of 10 min. The rate of ketone addition was examined first. Decreased enantioselectivity was observed with rapid dropwise addition of linchpin **10**, with no significant difference in enantioselectivity observed when linchpin **10** was added over a 30 min period. Next, the influence of silyl substitution on the linchpin was assessed by comparing TMS and TBS linchpins **10** and **12**, respectively. Greater enantioselectivity was observed for [1,2]-addition to **10** than **12**. Importantly, reduction of alkyne stoichiometry to 1 equiv afforded excellent enantioselectivity.

Having optimized the enantioselectivity of the [1,2]-addition, we turned our attention to the full ARC sequence. The temperature dependence of the [1,4]-Brook rearrangement and electrophile capture was examined first (Table 2). In these experiments, benzyl bromide (BnBr) was added to the reaction mixture after completion of the [1,2]-addition at −78 °C. Upon addition of BnBr (2.0 equiv), the mixture was warmed to a range of temperatures from −78 to +50 °C and held at the corresponding temperature for 1 h before the reaction was quenched. We anticipated the formation of products **13** and **14**, whereby [1,4]-Brook rearrangement is followed either by alkylation or protonation, respectively. The [1,4]-Brook rearrangement was observed at temperatures as low as −30 °C. The highest ratio of alkylation to protonation product (**13**/**14**) was observed with immediate transfer of the reaction vessel to a water bath at room temperature. Allowing the reaction to gradually warm to room temperature was

Table 2. Optimization of ARC Sequence[a]



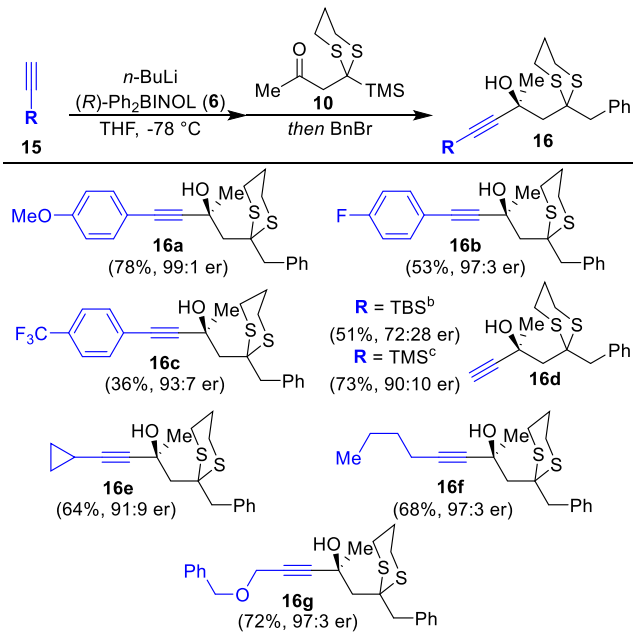
entry	variation (BnBr addition)	^{1}H NMR ratio (**13**:**14**)
1	maintained at −78 °C	*b*
2	warmed to −50 °C	*b*
3	warmed to −30 °C	54:46
4	warmed to 0 °C	59:41
5	warmed to rt	75:25
6	warmed to 50 °C	63:37
7	warmed to −30 °C, 24 h	23:77
8	gradually warmed to rt	69:31
9	HMPA added	60:40
10	1.0 equiv of BnBr	67:33

[a]*n*-BuLi (1.2 equiv); acetylene (1.0 equiv); (*R*)-**6** (10 mol %); **10** (1 equiv); BnBr (2 equiv); **10** added over 10 min. [b]Only **11** observed.

deleterious, as was either addition of HMPA, or reduction of the BnBr stoichiometry. Additionally, maintaining the temperature of the reaction at −30 °C, the lowest temperature at which [1,4]-Brook rearrangement was observed, for 24 h did not increase the formation of **13**.

With optimized conditions for the full ARC sequence in hand, the nucleophile scope was investigated. Reactions were performed with linchpin **10** and BnBr as the electrophile (Scheme 1). The influence of steric and electronic factors of the lithium acetylide on enantioselectivity was clear. Electron-rich acetylides afforded greater enantioselectivity than electron-poor acetylides. This trend is most evident in three-component adducts **16a**−**16c**, wherein enantioselectivity and yield are

Scheme 1. Nucleophile Scope[a]



[a]*n*-BuLi (1.2 equiv); **15** (1.0 equiv); (*R*)-**6** (10 mol %); **10** (1.0 equiv); BnBr (2.0 equiv); **10** added over 10 min; TBAF deprotection of crude product. [b]TBS acetylene (**15d**$_i$). [c]TMS acetylene (**15d**$_{ii}$).

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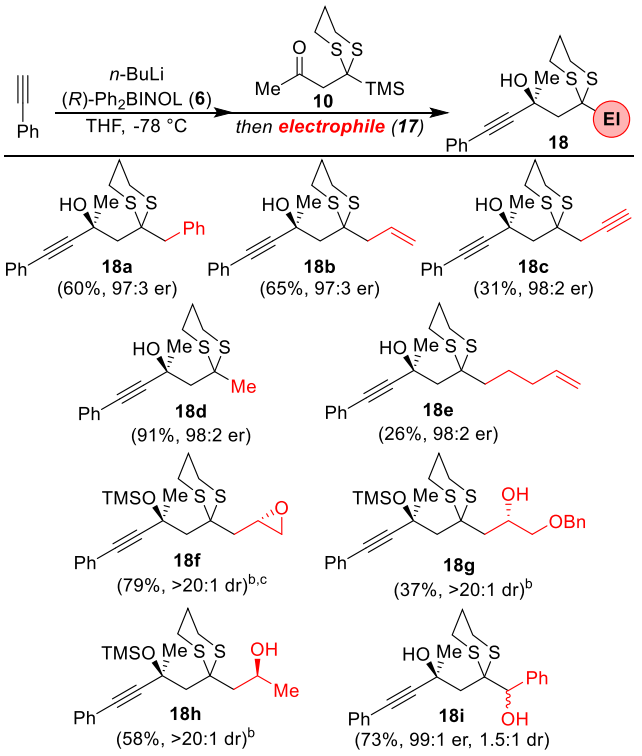
positively correlated with the electron-donating character of the para substituent.[15] Perhaps of greater significance is the influence of steric encumbrance of the nucleophile on enantioselectivity. Bulky nucleophiles such as **15d$_i$** (TBS acetylene) and **15d$_{ii}$** (TMS acetylene) afforded **16d** with modest to moderate enantiomeric ratios of 72:28 and 90:10, respectively. This steric influence was further exemplified in the comparison of cyclic and linear aliphatic lithium acetylides, wherein a greater enantiomeric ratio was observed for **16f** than **16e**. Pleasingly, the use of benzyl propargyl ether was well tolerated, providing access to diversifiable three-component adduct **16g** in good yield and excellent enantioselectivity.

Next, the scope of electrophiles was evaluated using lithium phenyl acetylide as the nucleophile and ketone linchpin **10** to afford **18** (Scheme 2). Benzyl and allyl bromide electrophiles

Scheme 2. Electrophile Scope[a]

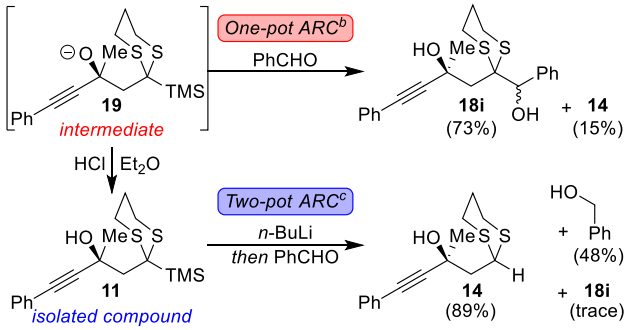


[a]*n*-BuLi (1.2 equiv); acetylene (1.0 equiv); (*R*)-**6** (10 mol %); **10** (1.0 equiv); El (2.0 equiv); **10** added over 10 min; crude TBAF deprotection. [b]No TBAF used. [c](*S*)-epichlorohydrin was used as electrophile **17f**.

provided the desired three-component adducts **18a** and **18b** in good yield. Diyne product **18c** was obtained from the corresponding silyl propargyl bromide after TBAF deprotection, albeit in modest yield. While an excellent yield of **18d** was achieved using MeI, a poor yield was observed for 5-bromo-1-pentene, likely due to the competing elimination reaction. Epoxide electrophiles were found to be viable, affording adducts **18f**–**18h** in modest to good yield, permitting inclusion of an additional stereocenter. In each case, the product was observed by ^{1}H/^{13}C NMR as a single diastereomer. Benzaldehyde was also successfully employed, proceeding with high enantioselectivity (99:1 er) to yield **18i** as an expected mixture of diastereomers (1.5:1).

An effective cascade reaction should afford the final product in greater yield than that obtained by the sequential execution of the constituent reactions. The ARC cascade was therefore divided into a two-pot sequence for comparison. The first step of the ARC sequence is [1,2]-addition of lithium phenylacetylide to linchpin **10** to arrive at alkoxide **19**. A [1,4]-Brook rearrangement of alkoxide **19** is then thermally triggered with subsequent electrophile capture terminating the standard one-pot ARC sequence (Scheme 3). Alternatively, alkoxide **19** can

Scheme 3. Comparison of One-Step and Two-Step ARC Approaches[a]



[a]TBAF deprotection of products. [b]*n*-BuLi (1.2 equiv), **10** (1.0 equiv) THF, −78 °C 2 h; PhCHO (2.0 equiv). [c]**11** (1.0 equiv), *n*-BuLi (1.2 equiv), THF, −78 °C 30 min, then PhCHO (2.0 equiv); both (*R*)-**6** and no catalyst yielded identical results.

be acidified at −78 °C to afford alcohol **11**. In the two-pot protocol, purified alcohol **11** enters the ARC sequence via deprotonation to **19**. The one-pot and two-pot methods were compared for the ARC sequence employing linchpin **10** with phenylacetylene and benzaldehyde serving as the nucleophile and electrophile, respectively, to afford three-component adduct **18i**. A drastic difference in the product distribution was observed between the one- and two-pot methods. Whereas the one-pot protocol provided **18i** in good yield (73%), the two-pot process provided only trace **18i** with most of the recovered material consisting of quenched product **14** (89%) and benzyl alcohol (48%). We suspect the reduction of benzaldehyde to benzyl alcohol occurs via a single-electron transfer (SET) process that is favored by the two-pot reaction sequence.[16] The role of the two-pot approach in favoring a SET pathway is unclear but may be a consequence of a different aggregation state that occurs via access of **19** by an alternate route. Thus, this one-pot asymmetric three-component union tactic circumvents the undesired reactivity and is more efficient than the sum of its parts.

Having demonstrated the generality of the one-pot protocol with respect to acetylides and electrophiles, we examined the viability of aldehyde linchpins **24a** and **24b** to afford secondary alcohol **25** with phenylacetylene and BnBr serving as the nucleophile and electrophile, respectively (Scheme 4). Pleasingly, good yields and moderate enantioselectivities were achieved employing aldehyde linchpins **24a** and **24b**. As opposed to ketone linchpins **10** and **12** (Table 1), the size of the silyl substituent did not affect the enantiomeric ratio of the corresponding three-component adducts **25**. Thus, either silyl ether product can be obtained at no expense of enantioselectivity, permitting convenient integration into a protecting group strategy.

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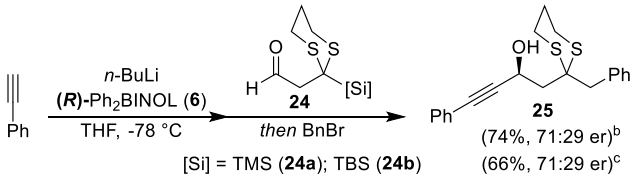
Scheme 4. Aldehyde Linchpin[a]



[a]*n*-BuLi (1.2 equiv); acetylene (1.0 equiv); (*R*)-**6** (10 mol %); **24** (1.0 equiv); BnBr (2.0 equiv); **24** added over 10 min; crude TBAF deprotection. [b]**24a**. [c]**24b**.

The greatest limitation to the generality of this tactic with respect to enantioselectivity is derived from the steric factors of the acetylene. Although many lithium acetylide substrates enabled excellent enantioselectivity with linchpin **10**, synthetically useful silyl acetylenes afforded moderate enantioselectivity for three-component adduct **16d** (Scheme 1). To overcome this limitation, the relationship between catalyst loading and enantioselectivity was investigated (Figure 2). First, we

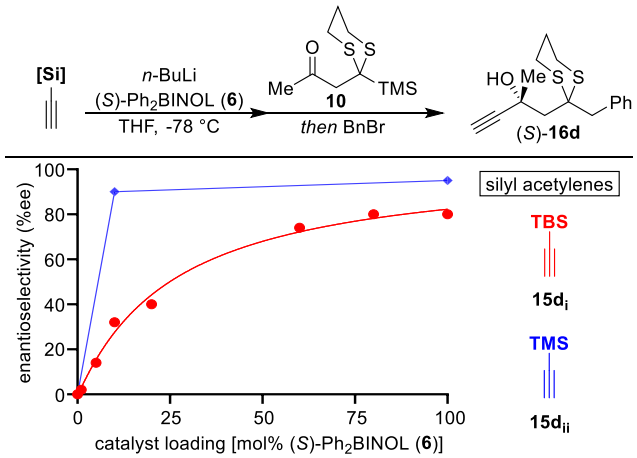


Figure 2. Catalyst loading experiments with hindered silyl acetylenes. (a) Conditions: *n*-BuLi (1.2 equiv); acetylene (1.0 equiv); **10** (1.0 equiv); electrophile (2.0 equiv); **10** added over 10 min; crude TBAF deprotection;

examined the ARC sequence with highly sterically encumbered TBS acetylene $\mathbf{15d_i}$ and linchpin **10** to afford three-component adduct **16d**. Acetylene $\mathbf{15d_i}$ was chosen because it is the least ideal nucleophile examined herein. A logarithmic relationship between enantiomeric excess (% ee) and catalyst loading (mol % (*S*)-**6**) was observed, reaching a maximum of 80%ee (90:10 er) with 80 mol % (*S*)-**6**. Alternatively, excellent enantioselectivity (97:3 er) can be achieved for the same synthon type using TMS acetylene $\mathbf{15b_{ii}}$. Generally, most carbon substituted terminal acetylenes are less sterically hindered than a TBS group and as such, this method holds the promise of excellent enantioselectivity for a broad range of terminal acetylenes. In addition, (*S*)-**6** was employed instead of (*R*)-**6** to demonstrate the interchangeable nature of the catalyst to afford the opposite enantiomer.

In summary, we disclose here a new method for the preparation of enantioenriched three-component union adducts from achiral components via an ARC tactic initiated by an organocatalytic asymmetric [1,2]-addition of a lithium acetylide. Excellent enantioselectivities were observed in the coupling of a variety of acetylenes and electrophiles with ketone linchpin **10**. Reduced enantioselectivity observed with highly sterically encumbered acetylenes can be attenuated with increased catalyst loading to permit good to excellent enantioselectivity. This tactic enables effective diversity-oriented synthesis by virtue of not only a three-component nature but also the control over absolute configuration that is exerted via the application of either (*S*)-Ph_2BINOL-**6** or (*R*)-Ph_2BINOL-**6**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02959.

General experimental procedures, optimization studies, characterization data, ^{1}H NMR/^{13}C NMR spectra, and SFC chromatographs (PDF)

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Notes

The authors declare no competing financial interest.

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