

“Click, Click, Cyclize”: A DOS Approach to Sultams Utilizing Vinyl Sulfonamide Linchpins

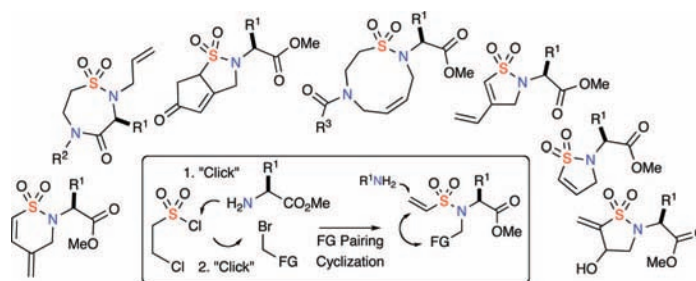
Aihua Zhou, Dinesh Rayabarapu, and Paul R. Hanson*

Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045-7582, and the NIH Center for Chemical Methodologies and Library Development at the University of Kansas (KU-CMLD), 2121 Simons Drive, Lawrence, Kansas 66047

phanson@ku.edu

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ABSTRACT



A diversity-oriented synthesis (DOS) strategy termed “Click, Click, Cyclize” is reported. This approach relies on functional group (FG) pairing between a vinyl sulfonamide and an array of functional groups to synthesize skeletally diverse sultams. Several FG pairing pathways on central tertiary vinyl sulfonamide linchpins have been developed including intramolecular Heck, aza-Michael, ring-closing enyne metathesis, Pauson–Khand, and chemoselective oxidation/Baylis–Hillman reactions.

The growing demand for quick access to small molecules with novel architectures for high throughput screening has provided challenging opportunities for synthetic chemists. Despite significant advances in this field, a lack of systematic library planning strategies has been cited as a limiting factor in the process.¹ Diversity-oriented synthesis (DOS)^{1,2} has emerged to address this deficiency as an enabling platform

for the facile production of multiple scaffolds^{1–3} displaying skeletal diversity.^{2,4} Among several features that define DOS, forward-synthetic analysis^{1,2} and functional group (FG) pairing^{5,6} have surfaced as significant tools. In particular, forward-synthetic analysis focuses on overarching strategies to generate multiple scaffolds in the fewest possible steps, while FG pairing aims to selectively pair functional groups from a central functionalized core, resulting in the quick

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production of an array of scaffolds with minimum steps. Both concepts are at the heart of the “Build/Couple/Pair (BCP)” strategy pioneered by Schreiber and co-workers.⁶ This strategy involves a “Build phase” to assemble chiral building blocks containing orthogonal sets of functionality suitable for the subsequent “Coupling and FG pairing” phases en route to an array of diverse scaffolds. In this regard, interest in the generation of skeletally diverse sultams for biological screening has provided impetus for the titled FG pairing cyclization strategy termed “Click, Click, Cyclize” enroute to five-, six-, seven-, eight-, and nine-membered ring sultams.⁷

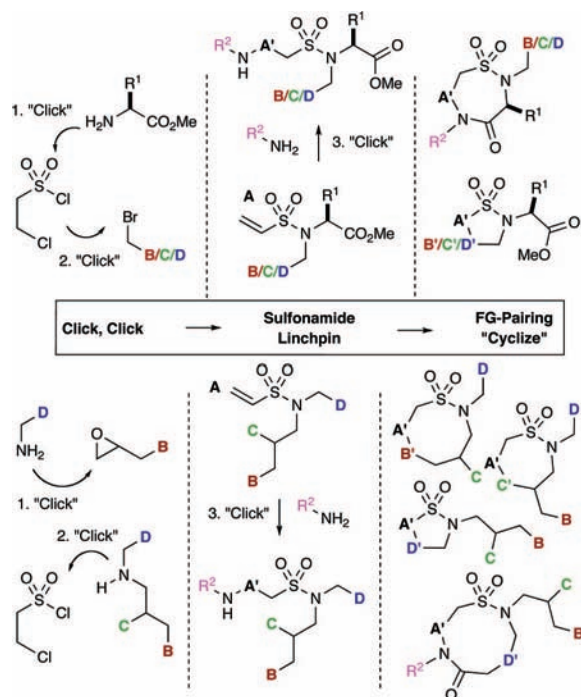
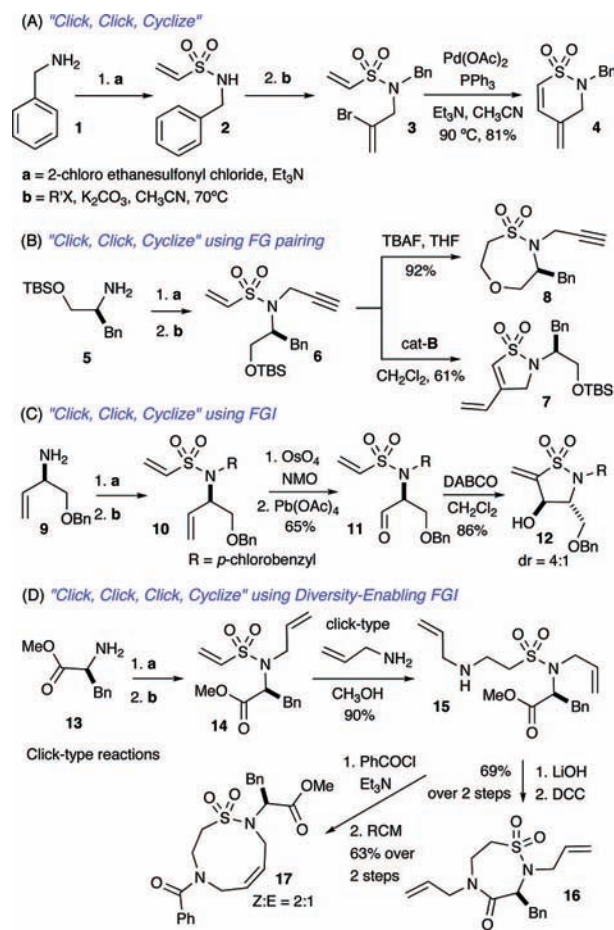


Figure 1. “Click, Click, Cyclize” or “Click, Click, Click, Cyclize” approach to skeletally diverse sultams.

Sulfonamides have long been valued for their rich biological and chemical profiles and have emerged as a promising class of compounds in drug discovery.⁸ Sultams (cyclic sulfonamides), although not found in nature, display a wide

array of potent biological activities.^{9,10} Traditionally, sultam syntheses have relied on classical cyclization protocols and a number of transition-metal-catalyzed processes that have

Scheme 1. DOS via “Click, Click, Cyclize” Reaction Manifolds



recently been reported.¹⁰ In this regard, vinyl sulfonamides represent an emerging chemotype with a wide spectrum of reaction potential to generate sultams. Literature precedence has shown their reactivity in Diels–Alder,¹¹ Heck,¹² indium-initiated radical addition,¹³ and [3 + 2] cycloadditions.¹⁴ This chemical profile is augmented by recent work using ring-closing metathesis (RCM),^{10a,15} intramolecular oxa-Michael,

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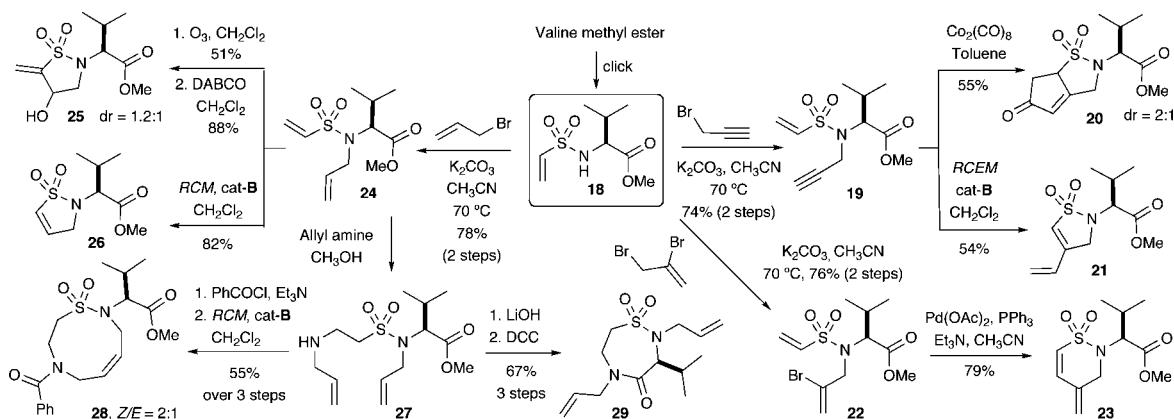
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Scheme 2. “Click, Click, Cyclize” Reaction Manifolds Utilizing FG Pairing en Route to Skeletally Diverse Sultams



and Baylis–Hillman cyclizations to generate sultams.¹⁶ Taken collectively, these methods represent opportunities for the implementation of DOS approaches to new sultams.

At the heart of the titled approach is the facile production of precursorary tertiary vinyl sulfonamides via use of two “Click” reactions⁷ (Figure 1). These two reliable reactions, include either (i) vinyl sulfonylation of amines and subsequent alkylation of the resulting secondary sulfonamides or (ii) the production of a secondary amine via an epoxide opening with an amine, followed by vinyl sulfonylation. Subsequent FG pairing in either case between the vinyl sulfonamide moiety A and FGs B, C, and D yield sultams of varying architectures.¹⁷ Alternatively, the use of a third reaction,⁷ an aza-Michael reaction, allows for broadening of FG pairing patterns and installation of an additional diversity element. Overall, these strategies rely on efficient and disparate FG pairing pathways on tertiary vinyl sulfonamides to establish reaction manifolds emanating from a single linchpin.

This study was initiated by investigating several FG pairing pathways between vinyl sulfonamides and disparate functional groups including intramolecular Heck, aza-Michael,¹⁸ ring-closing enyne metathesis (RCEM), Pauson-Khand (PK), and chemoselective oxidation/Baylis–Hillman reactions as outlined in Scheme 1. These methods set the foundation for the overall DOS approach outlined in Schemes 2 and 3, whereby multiplication of a single scaffold³ can be realized.

The first pathway investigated was commenced with a vinyl sulfonylation/allylation sequence yielding tertiary vinyl sulfonamide **3**, which undergoes a regioselective 6-*endo-trig* intramolecular Heck cyclization to afford the δ -sultam **4** in good yield (Scheme 1, pathway A). This pathway is amenable to variations in both the amine component and alkylation partner as shown in Scheme 2.

The use of a TBS-protected amino alcohol and propargyl bromide in the vinyl sulfonylation/alkylation, respectively,

produces the tertiary sulfonamide linchpin **6** (Scheme 1, pathway B). Linchpin **6** is armed for an intramolecular enyne metathesis yielding sultam **7**, whereas TBAF deprotection initiates an intramolecular oxa-Michael cyclization to afford **8** in 92% yield.

Use of FG interconversion (FGI) broadens the reaction manifold by allowing for a new FG pairing event (Scheme 1, pathway C). In this example, chemoselective oxidation of an allyl moiety in the presence of the electron-deficient vinyl sulfonamide enables FG pairing cyclization between the aldehyde and vinyl sulfonamide moieties utilizing an intramolecular Baylis–Hillman cyclization reaction. In this regard, sequential vinyl sulfonylation of amine **9** and alkylation generate vinyl sulfonamide **10** in good yield. Chemoselective oxidation with OsO₄/NMO/Pb(OAc)₄ followed by DABCO-initiated Baylis–Hillman cyclization affords the γ -sultam **12** in 86% yield (dr = 4:1).

A fourth pathway utilizes an aza-Michael reaction in a “Click, Click, Click, Cyclize” reaction sequence, which effects an umpulung FGI of an electrophilic vinyl sulfonamide into a nucleophilic amino sulfonamide (Scheme 1, pathway D). This latter concept represents a diversity-enabling step and offers a new pattern of FG pairing between the nucleophilic amine (NHR²) and remaining FGs.

Although use of an aza-Michael reaction on a vinyl sulfonamide has been previously reported,¹⁸ its use in sultam synthesis is limited.¹⁶ In this study, it was found that **14** undergoes facile aza-Michael reaction to afford sulfonamide **15** in excellent yield. Subsequent basic hydrolysis and intramolecular lactamization yields the seven-membered sultam **16**. Alternatively, reaction with benzoyl chloride, followed by RCM, produces the nine-membered sultam **17** in 63% yield (Z/E = 2:1).

Pathways A–D outlined in Scheme 1 can be integrated into DOS strategies quite readily as outlined in Schemes 2 and 3. The first DOS reaction manifold strategy we investigated began with the readily prepared vinyl sulfonamide **18** derived from vinyl sulfonylation of valine methyl ester with 2-chloro ethanesulfonyl chloride. Subsequent alkylation with propargyl bromide, 2,3-dibromopropene, or allyl bro-

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The reaction scheme illustrates the synthesis of sulfonamide 42 from an epoxide-protected allylamine derivative. The starting material is an epoxide-protected allylamine derivative with an OTf group. The synthesis proceeds through several pathways:

- Pathway 1 (Top):** Reaction with Me_2AlCl in CH_2Cl_2 yields intermediate **31** (OTBS). Subsequent reaction with NaH in THF over 2 steps yields product **32** (OTBS).
- Pathway 2 (Middle):** Reaction with Me_2AlCl in CH_2Cl_2 followed by HCl yields intermediate **33** (OH). Subsequent reaction with $\text{Pb}(\text{OAc})_4$ (1) and DABCO , CH_2Cl_2 (2) over 3 steps yields product **34** (OH) in 57% yield.
- Pathway 3 (Bottom):** Reaction with Me_2AlCl in CH_2Cl_2 followed by HCl yields intermediate **33** (OH). Subsequent reaction with RCM , cat-**B** in CH_2Cl_2 yields intermediate **35** (TBSO) in 85% yield. Subsequent reaction with OsO_4 , NMO (1) and $\text{Pb}(\text{OAc})_4$ (2) yields intermediate **36** (TBSO) in 67% yield. Subsequent reaction with DABCO in CH_2Cl_2 yields product **37** (OH) in 88% yield ($\text{dr} = 1:1$).
- Pathway 4 (Left):** Reaction with $\text{ClCH}_2\text{CH}_2\text{SO}_2\text{Cl}$ in Et_3N , CH_2Cl_2 yields product **30** in 74% yield (3 steps).
- Pathway 5 (Bottom):** Reaction with TBAF in THF yields intermediate **38** (TfO) in 90% yield. Subsequent reaction with Me_2AlCl (1) and DMP (2) yields intermediate **39** (OTBS). Subsequent reaction with DABCO over 3 steps yields product **40** (OTBS) in 67% yield.
- Pathway 6 (Bottom):** Reaction with iso-Butyl amine in CH_3OH yields intermediate **41** (OTBS). Subsequent reaction with **a** yields product **42** (OTBS) in 56% yield over 3 steps.

a: $\text{CH}_2=\text{CHCOCl}$, Et_3N , CH_2Cl_2 then RCM , cat-**B**

This latter allylation route opens three additional reaction pathways to broaden the overall DOS reaction manifold (Scheme 2). The first route employs selective oxidation by ozone to generate an aldehyde for subsequent intramolecular Baylis–Hillman cyclization affording the γ -sultam **25** in 88% yield with 1.2:1 diastereoselectivity. A second route utilizes RCM of **24** with cat-B to yield γ -sultam **26**. A third route employs the aforementioned intermolecular aza-Michael reaction of vinyl sulfonamide **24** to afford the β -amino sulfonamide **27**, which leads to yet two additional synthetic

The second DOS strategy was initiated with vinyl sulfonamide **30**, in which three functional groups are incorporated in the amine component for FG pairing. Seven synthetic routes have been developed. The first uses chemoselective deprotection of the trityl group of **30** using Me_2AlCl followed by NaH-promoted oxa-Michael addition to afford sultam **32** in 70% yield over two steps (Scheme 3). The second utilizes a global deprotection to produce diol **33**. Subsequent oxidative cleavage with $\text{Pb}(\text{OAc})_4$ and Baylis–Hillman cyclization affords sultam **34** in 57% yield over three steps. The third example involves RCM of vinyl sulfonamide **30** to yield sultam scaffold **35** in 85% yield using cat-B. Alternatively, selective oxidation of the terminal olefin in vinyl sulfonamide **30** followed by intramolecular Baylis–Hillman cyclization affords sultam **37**. A fifth example demonstrates facile oxa-Michael cyclization initiated by TBAF deprotection to produce sultam scaffold **38** in 90% yield. A sixth example involves selective trityl deprotection/Dess–Martin oxidation and intramolecular Baylis–Hillman to furnish sultam **40** in 67% yield over three steps with >20:1 diastereoselectivity. The seventh and final example utilizes an intermolecular aza-Michael reaction with allyl amine to generate β -amine sulfonamide **41**, which was reacted with acryloyl chloride and subjected to RCM with cat-B to yield the nine-membered ring sultam-lactam **42** ($Z/E = 2:1$) in 56% yield over three steps. Overall, seven unique scaffolds are produced in simple reaction sequences.

In summary, we have reported several FG pairing pathways to generate sultams based on versatile vinyl sulfonamide linchpins. Incorporation of diversity-enabling FGI expands the DOS reaction manifolds and broadens the scope of the method. These results are highly amenable to library production, and ongoing efforts are in order.

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