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Creating skeletal complexity through an interrupted Corey–Chaykovsky reaction of activated alkynes

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We present the first interrupted Corey–Chaykovsky reaction of α,β-ynones by intercepting the zwitterionic intermediates that prevail during the addition of the Corey–Chaykovsky reagent to activated alkynes. This cascade transformation uncovers a novel mechanistic feature and leverages it to construct complex polycyclic molecular architectures featuring three new carbon–carbon bonds, four new carbo- and heterocycles and four contiguous stereocenters, two of which are quaternary carbons, all in a single-pot operation. Additionally, we demonstrate the synthetic utility of these otherwise unprecedented molecules.

Structurally complex small organic molecules with diverse molecular architectures hold significant value in medicinal chemistry.[1] Such molecules can selectively interact with biological targets and are tunable to accommodate various physicochemical properties, making them indispensable to various drug discovery programs. Consequently, developing efficient synthetic strategies for generating new and diverse sp^3-rich molecular scaffolds is crucial to advancing this field.

In this regard, sulfur ylide chemistry has become a powerful tool in synthesizing intricate molecules with step- and pot-economy.[2] Especially, the recent developments in the Corey–Chaykovsky reaction (CCR)[3] have allowed chemists to push the boundaries even further, creating various intricate structures in fewer steps with high regio- and stereo control. The reaction of activated alkenes with dimethyloxosulfonium methylide (DOSM) and a subsequent displacement of DMSO from the zwitterionic intermediate **A** generates cyclopropanes, representing the traditional CCR [path a], Scheme 1a.[4] An extended CCR, involving cyclopropanes as intermediates but not as final products, has gained popularity recently.[5] On the other hand, the interrupted CCR has redefined the landscape of the parent CCR and has become a powerful tool to achieve greater precision and versatility in complex molecule synthesis [path b].[6] This has been accomplished through the entrapment of **A** with appropriate functionalities (X = Y), enabling the formation of various carbo- and heterocycles.

Interestingly, when activated alkynes are treated with DOSM, a Corey–Chaykovsky-type reaction does not usually prevail. Rather, the zwitterionic intermediates **B** convert to vinyl sulfoxonium ylides, Scheme 1b.[7] However, to the best of our knowledge, the synthetic utility of **B** has been rarely explored, unlike **A**. Thus, we recognize a unique opportunity to engage **B**, uncover its novel reactivity patterns and establish the first interrupted CCR of activated alkynes.

Building on this background, we explored potential reaction pathways involving **B** and a hypothetical reactant X = Y, Scheme 2a. While the reactivity of **B** in the **B1** configuration (where R^1 and EWG are *cis*) suggests the possibility of a formal (3 + 2) cyclization to form 5-membered cyclic structures **C**, the *trans* orientation of R^1 and EWG in the **B2** form may hinder the cyclization due to steric constraints.

Alternatively, the initial addition of **B** to X = Y in the **B3** configuration, followed by an S_N2' (or umpolung) addition, leads to the elimination of DMSO and the formation of 3-membered cyclic structures **D**, Scheme 2b. A similar mechanistic rationale can be extended to the **B4** form, where a comparable outcome is expected.

We hypothesized that azaarenium salts would best represent X = Y and promote such cyclizations, Scheme 2b.[8] If **B** undergoes C4 addition to **E**, it generates dihydropyridines **F**, which can then facilitate the elimination of DMSO *via* an enamine-promoted S_N2' reaction to generate iminium salts **G**. The appropriately positioned *exo* olefin can trigger an Alder-ene type cyclization, resulting in the formation of N-containing bridged structures **H**. Although this model does not exclude the possibility of C2 addition of **B** to **E**, the regioselectivity (C2 *vs.* C4 addition) can be controlled by an appropriate substrate design. Thus, we evaluated the hypothesis by constraining the quinolinium ring to an α,β-ynone functionality as in **1a**.[9]

Having synthesized **1a**, we validated the hypothesis outlined in Scheme 2. Remarkably, the reaction **1a** with DOSM in DMF at room temperature yielded the bridged hexacyclic structure **2a**

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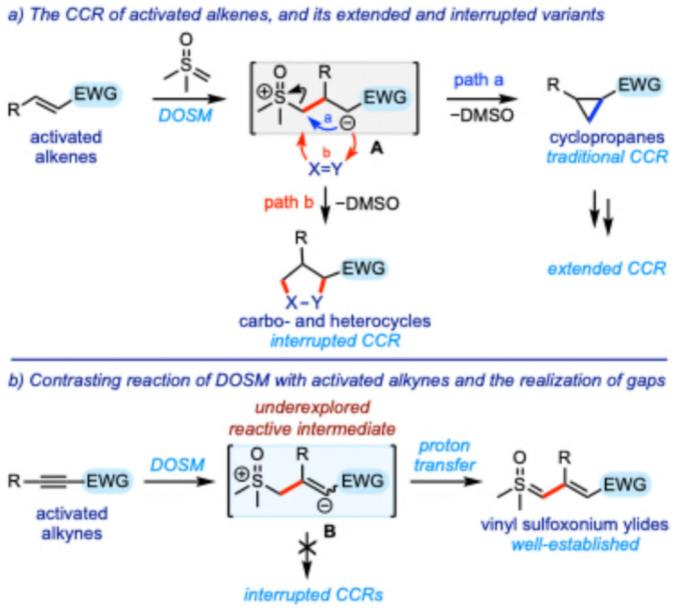
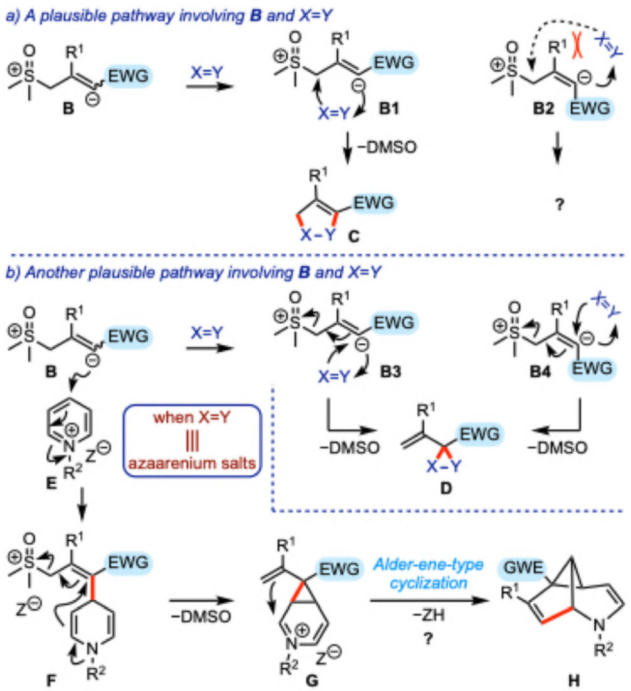


Scheme 1 (a) A representation of the CCR, and its extended and interrupted versions. (b) An extension of the concept to activated alkynes and the realization of gaps.



Scheme 2 Plausible mechanistic scenarios involving **B** and X = Y.

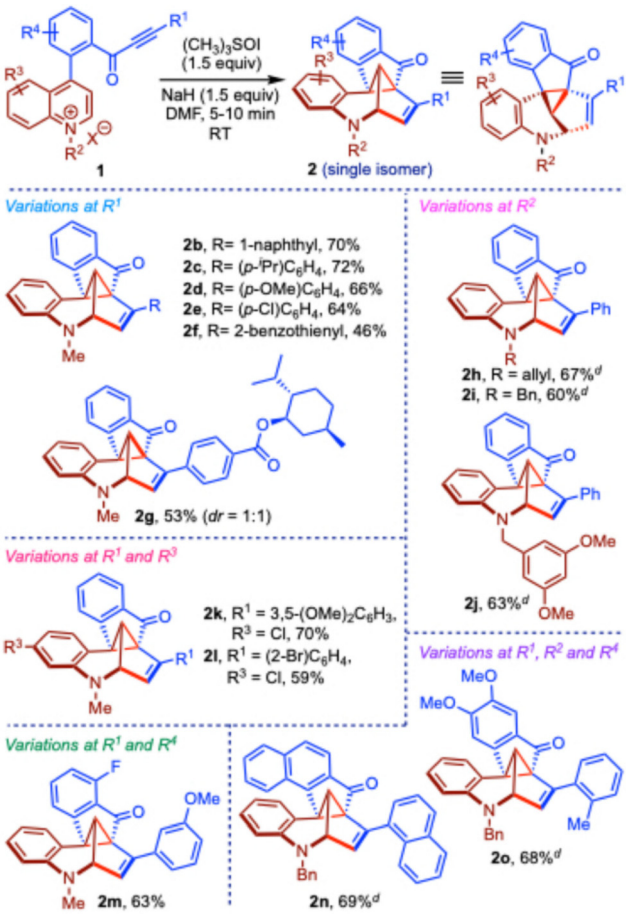
Table 1 Optimization of reaction parameters[a]

Entry	Base (equivalents)	Solvent	Yield[b] (%)
1	NaH (1)	DMF	54
2	NaH (1.2)	DMF	61
3	NaH (1.5)	DMF	72
4	NaH (2)	DMF	53
5[c]	NaH (1.5)	DMF	65
6[d]	NaH (1.5)	DMF	49
7	NaH (1.5)	DMSO	58
8	NaH (1.5)	MeCN	46
9	Cs_2CO_3 (1.5)	DMF	28
10	K_2CO_3 (1.5)	DMF	33
11	KO^{t}Bu (1.5)	DMF	43
12	DBU (1.5)	DMF	35

[a] Reaction conditions: see the SI for details. [b] Isolated yield after column chromatography. [c] At 0 °C. [d] At 50 °C.

in 54% yield within 5 min (Table 1, entry 1). The structure and relative stereochemistry of **2a** were confirmed through X-ray diffraction analysis,[10] providing compelling support for the mechanism proposed in Scheme 2b. Encouraged by this promising outcome, we optimized the reaction conditions further. From a brief screening, 1.5 equivalents of NaH was found to be optimal for achieving a better yield of the product (entries 2–4). The efficiency of the reaction did not improve at either lower or higher temperatures (entries 5 and 6). Next, we evaluated the role of solvents, but no significant improvement was observed (entries 7 and 8). A few other inorganic and organic bases were tested to enhance the yield, but no promising result was obtained (entries 9–12).

The optimized conditions were applied to a wide range of α,β-ynone-tethered quinolinium salts **1**, and the results are summarized in Scheme 3. The electronic or steric effects of various substituents were investigated, including those on the



Scheme 3 Substrate scope[a,b,c]. [a] See the SI for a detailed procedure. [b] Isolated yields after column chromatography. [c] Unless mentioned, iodide was used as the counter anion in **1**. [d] Bromide was the counter anion in the respective salts **1**.

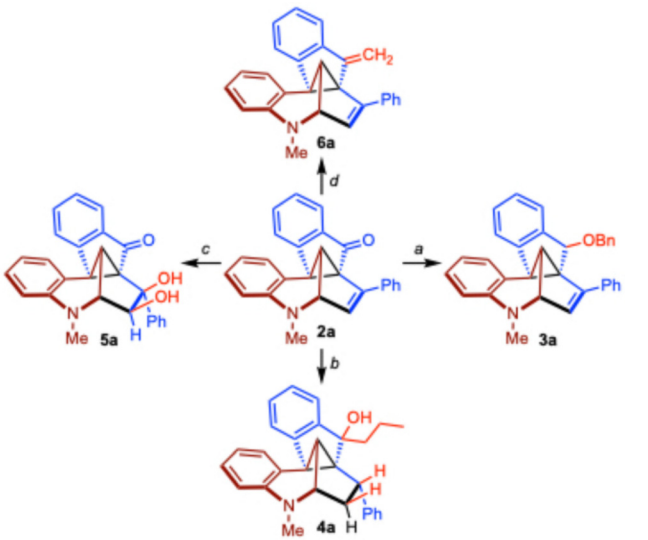
ynone moiety (R^1), *N*-substituents (R^2), quinoline backbone (R^3), and arene backbone (R^4). Encouragingly, the reaction demonstrated a broad substrate scope, yielding consistent results across various substrates evaluated. Substituents such as naphthyl groups (**2b**), electron-rich arenes (**2c–2e**), arenes with electron-withdrawing groups (**2g**), and heteroarenes (**2f**) were well-tolerated on the alkyne (R^1), leading to the formation of the corresponding products in good yields. However, substrates possessing alkyl groups at R^1 did not yield satisfactory results under the optimized conditions. Next, we examined the effect of N-substituents (R^2) on the course of the reaction. Apart from the methyl group, both linear (allyl) and branched alkyl systems (benzyl and 3,5-dimethoxybenzyl) were well-tolerated, generating the respective products **2h–2j** in good yields. Following this, we studied the influence of substituents on the quinoline (R^3) and arene backbones (R^4) in combination with variations at R^1 and R^2. In all the cases (**2k–2o**), impressive results were obtained despite electronic and steric biases. Overall, the study of the impact of R^1, R^2, R^3, and R^4 revealed that the transformation is versatile and capable of accommodating different substituents.

Next, we turned our attention to demonstrating the synthetic utility of these unprecedented molecules, Scheme 4. Accordingly, we subjected **2a** to $NaBH_4$ reduction, the alcohol which is isolable was then transformed into the corresponding benzyl ether **3a** under standard Mitsunobu conditions. To enrich the molecule with an aliphatic (sp^3) component, we treated **2a** with allyl Grignard reagent and subjected the resultant tertiary alcohol to hydrogenolysis to afford **4a**.[11] To fine-tune the lipophilic character, we subjected **2a** to osmium-promoted dihydroxylation conditions and isolated the diol **5a** in good yield.[11] To introduce an alternate functional handle in the molecule, we treated **2a** under typical Wittig conditions and obtained the *exo* methylene adduct **6a**.

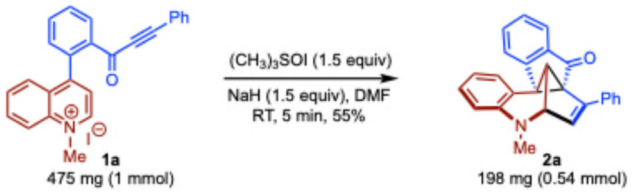
To assess the scalability of the method, we carried out the reaction of **1a** on a 1 mmol scale, Scheme 5. The corresponding product **2a** was isolated in 55% yield.

The mechanism of the transformation from **1** to **2** commences with a 1,4-addition of the sulfoxonium ylide to the α,β-ynone functionality, forming allenolates **I**, which cyclize from the C4 position of the quinolinium salts, yielding spiro indanone intermediates **J**, Scheme 6. Next, an enamine-promoted S_N2' (or umpolung) addition to the allylic sulfoxonium moiety generates iminium intermediates **K**, simultaneously installing the cyclopropane ring and eliminating DMSO. Finally, an intramolecular Alder-ene-type cyclization of **K** leads to the formation of a tertiary carbocationic species **L**, which upon proton elimination, affords the final products. The isolation of the products as single isomers suggests that all the steps leading to product formation occur in a cascade fashion.

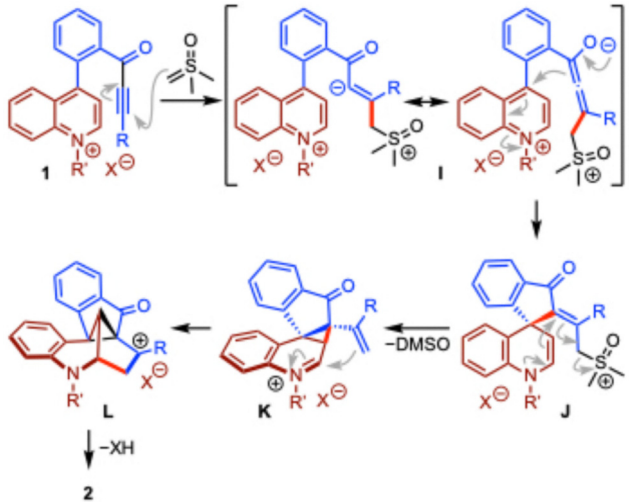
In summary, we successfully intercepted the zwitterionic intermediate **B** that prevails during the addition of sulfoxonium ylides to α,β-ynones, and developed the first interrupted CCR of activated ynones. The method proved to be general and efficient, and applicable to a wide range of substrates, which incorporate different types of privileged structures[12] including



Scheme 4 A few synthetic elaborations of **2a**. (a) (i) $NaBH_4$ (1.2 equiv.), THF-water, RT, 5 h, 95%; (ii) PPh_3 (1.5 equiv.), DIAD (1.5 equiv.), BnOH (1.5 equiv.), THF, 0 °C, 12 h, 64%. (b) (i) AllylMgBr (1.5 equiv.), THF, 0 °C, 1 h, 88%; (ii) H_2, 10% Pd/C (cat.), EtOAc, RT, 10 h, 34%. (c) OsO_4 (10 mol%), NMO (1.5 equiv.), THF : water (5 : 1), 88%. (d) CH_3PPh_3Br (1.5 equiv.), ^{n}BuLi (1.5 equiv.), THF, 0 °C, 1 h, 78%.



Scheme 5 Scaled-up reaction of **1a**.



Scheme 6 Plausible mechanism leading to the formation of **2** from **1**.

cyclopropanes,[13] indanes,[14] and tetrahydroquinolines.[15] The transformation of sp^2-rich substrates into sp^3-rich products is often regarded challenging and synthetically valuable strategy,[16] which we demonstrated in this work. Notably, this study also represents an uncommon one-pot tricarbofunctionalization of quinolinium salts,[17] enabling the installation of three new carbon–carbon bonds and four new stereocenters, two of which are quaternary carbons, across the quinolinium core under simple and practical conditions. Additionally, we showcased the synthetic utility and the scalability of the method. We believe this work lays the foundation for future developments in this field and will inspire the design of novel substrates leading to the creation of intricate molecular entities.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI. Supplementary information: Experimental details, characterisation data for new compounds. See DOI: **https://doi.org/10.1039/d5cc04277a**

CCDC 2473939 (**2a**) contain the supplementary crystallographic data for this paper.[18]

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