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Special Issue

# Beyond the Corey–Chaykovsky Reaction: Synthesis of Unusual Cyclopropanoids via Desymmetrization and Thereof

Kaushalendra Patel[+], Uttam K. Mishra[+], Dipto Mukhopadhyay, and S. S. V. Ramasastry*[a]

**Abstract:** Desymmetrization-based protocols for the synthesis of highly functionalized indeno-spirocyclopropanes and cyclopropa-fused indanes have been established through unexpected reactions triggered by the Corey–Chaykovsky reagent. These structures were further elaborated in one step to privileged scaffolds such as fluorenones, indenones, and naphthaphenones. For instance, an acid-catalyzed transformation of indeno-spirocyclopropanes provided fluorenones via a homo-Nazarov-type cyclization, and naphthaphenones were obtained via an acid-catalyzed cyclopropane ring-opening/retro-Michael sequence.

Cyclopropanes are important structural units present in several bioactive natural products and pharmaceutically relevant compounds including a few marketed drugs (Figure 1).[1] Medicinal chemists take advantage of the enhanced metabolic stability and conformational rigidity offered by cyclopropanes during drug design and development.[2] In addition, the strained three-membered carbocycles can undergo a broad spectrum of ring transformations to generate new molecular architectures.[3] These impressive features promoted synthetic chemists to develop newer synthetic routes for the synthesis of cyclopropanes.[4]

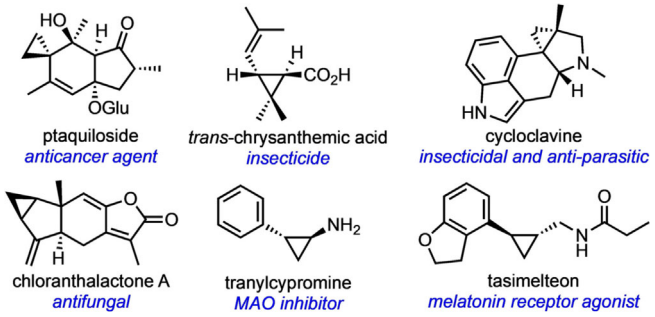


**Figure 1.** Representative cyclopropane-containing bioactive natural products and medicinally important compounds.

Some of the prominent methods for the preparation of cyclopropanes include: (i) the halomethyl-metal-mediated reactions (for example, the Simmons-Smith reaction), (ii) metal-catalyzed decomposition of diazo compounds, (iii) the nucleophilic addition-ring closure sequence (for example, the Kulinkovich cyclopropanation, reactions mediated by ylides, etc.).[4] Among them, the Corey-Chaykovsky reaction is a metal-free cyclopropanation strategy facilitated by sulfur ylides and it is applicable to a wide-range of electron-deficient olefins.[5] This reaction can also be employed for the synthesis of epoxides and aziridines from carbonyls and imines, respectively. The nucleophilic character of the Corey-Chaykovsky reagent [dimethyloxosulfonium methylide (DOSM)] is also known to trigger unexpected rearrangements which often provide access to otherwise difficult-to-access cyclopropanoids.[6]

While sulfur ylides have widespread applications in organic synthesis, to our knowledge, these species are yet to be employed in a desymmetrization process. Desymmetrization is a powerful means of achieving architectural complexity.[7] This strategy often allows the incorporation of multiple stereogenic centers in a single step. Here, we demonstrate an efficient and straightforward desymmetrization strategy facilitated by the DOSM for the formation of cyclopropanoids possessing up to three contiguous stereogenic centers (Scheme 1). The reaction also involves the formation of three new carbon-carbon bonds.

To establish a desymmetrizing event facilitated by the DOSM, we have chosen **1a** as the model substrate, Scheme 2.[8] It is anticipated that the reaction of **1a** with DOSM can involve an initial Michael addition followed by either an aldol-type reaction (path-a) or a Michael reaction (path-b) leading to the formation of zwitterionic species **A** or **B**, respectively.[9] A subsequent 1,3-proton shift provides enolates **C** or **D**, which can form indanone **2a** or fused-cycloheptanedione **3a**, respectively, via the nucleophilic displacement of the dimethylsulfoxonium group. On the other hand, the formation of the epoxide **4a** and the cyclopropane **5a** can also be expected under the reaction conditions. However, under the standard conditions, only the indanone **2a** was obtained in 90% yield in 2.5:1 diastereomeric ratio.

Encouraged by the unusual and straightforward transformation leading to the formation of highly functionalized indanone incorporated with three contiguous stereogenic centers, one of them being a spiro carbon, and others being a tetra-

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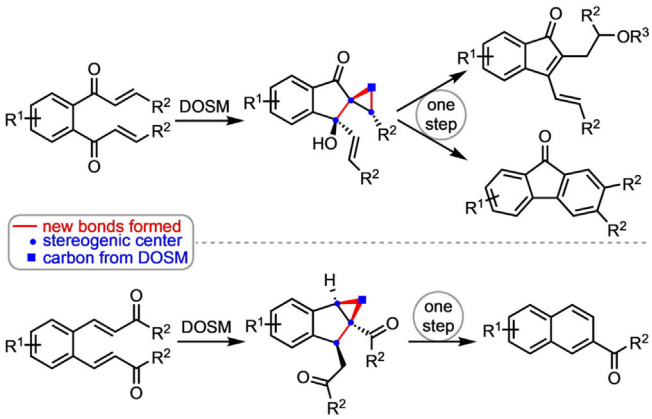
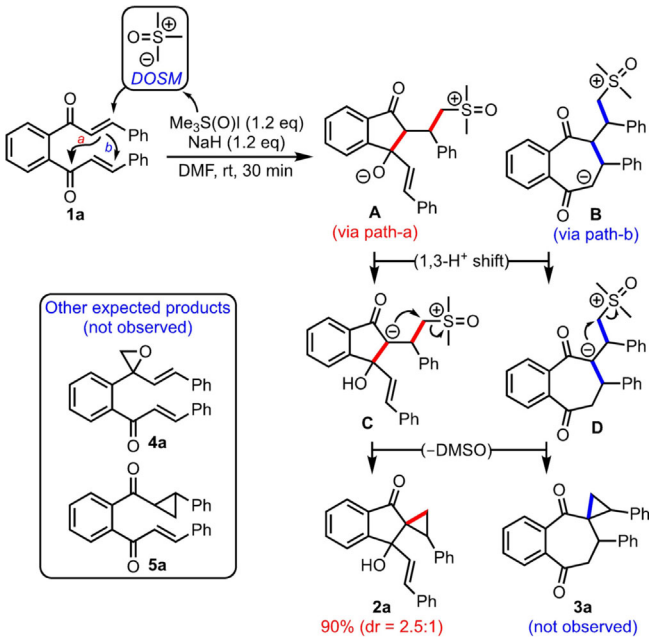



**Scheme 1.** This work: Unexpected desymmetrizing events triggered by DOSM, and elaboration to certain privileged structures.

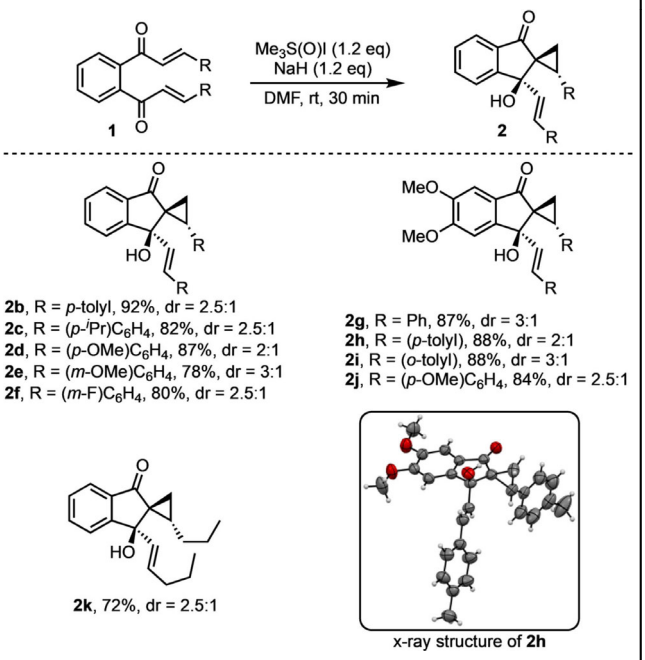



**Scheme 2.** Highly selective formation of indeno-spirocyclopropane **2a** among several other possibilities.

substituted carbon and a tertiary carbon, we proceeded to investigate the scope and generality of the reaction, Table 1.

A diverse set of otherwise difficult-to-access indeno-spirocyclopropanes (**2b**–**2k**) were conveniently synthesized in a one-step process, Table 1. The structures including the relative stereochemistry of major isomers were assigned based on the *x*-ray diffraction analysis of **2h**.[10] The diastereoselectivity in each case was determined by the analysis of the $^1$H-NMR of the crude reaction mixture. It is interesting to note that the presence of strong electron-donating groups on the aromatic backbone as well as on the enone, which in general are undesired for nucleophile-induced reactions, display no noticeable impact, indeed the reactions are complete within 30 min (for example, **2b**–**2e** and **2g**–**2j**). The reaction is also found to be general with aliphatic substituents on the enone moiety (**2k**).

**Table 1.** Scope for indeno-spirocyclopropanes **2**.[a,b]




[a] Isolated yield after column chromatography. [b] The diastereomeric ratio (d.r.) was obtained from the $^1$H NMR of the crude reaction mixture.

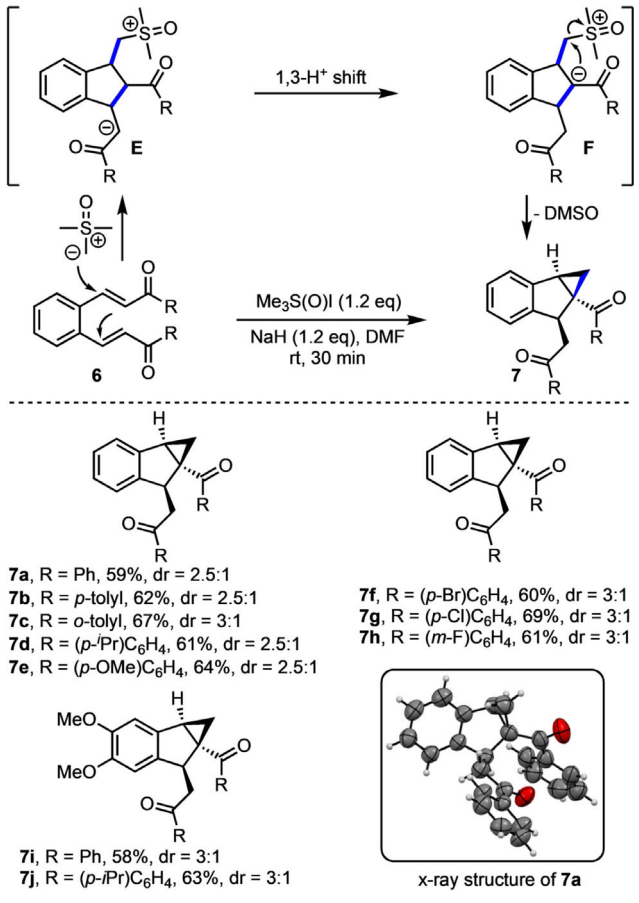
A narrow yield range (72–92%) indicates the generality and reliability of the method.

With the encouraging results obtained for enone-enones **1**, the reaction of enone-enone **6a** under the prototypical conditions was considered, Table 2.[11] To our surprise, the cyclopropa-fused indane **7a** was isolated in 59% yield in 2.5:1 diastereoselectivity. The structure and the relative stereochemistry of the major diastereomer was assigned based on the *x*-ray crystal structure obtained for **7a**.[10] The formation of **7a** can be rationalized by considering a Michael/Michael sequence on **6a**, initiated by the DOSM. The so formed zwitterion **E** then undergoes a 1,3-proton shift and the resultant enolate **F** facilitates the formation of **7a** by eliminating DMSO. In this manner, a variety of cyclopropa-fused indanes (**7b**–**7j**) were synthesized.[12] Some of the salient features of this reaction are: (i) aryl ketones possessing both electron-donating as well as electron-withdrawing groups were well-tolerated (**7b**–**7h**), (ii) consistent results were obtained despite the presence of strong electron-donating groups on the aryl backbone (**7i** and **7j**), (iii) three contiguous stereogenic centers, one of them being a quaternary carbon, and three new C–C bonds formed in a single synthetic operation.

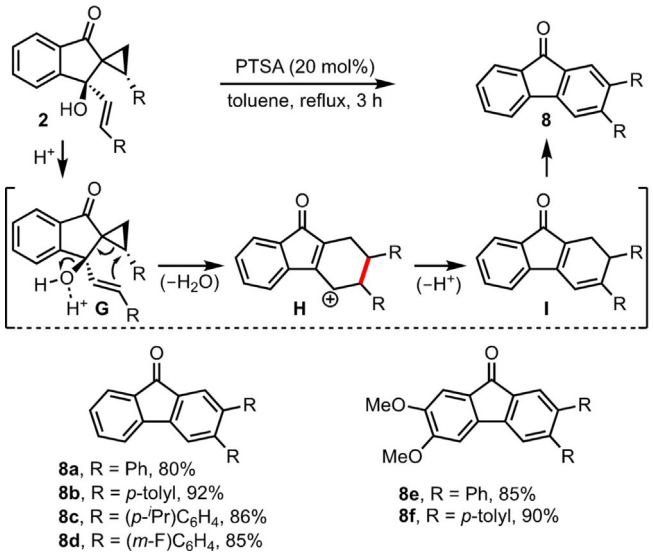
Having successfully established efficient methods for the synthesis of new classes of cyclopropanoids such as **2** and **7**, we turned our attention to demonstrate the synthetic utility of these compounds by considering a few elaborations.

With the presence of allylic-benzylic tertiary alcohol moiety in **2**, it was envisioned that its reaction under acidic conditions could trigger cationic cyclizations. Accordingly, when **2a** was treated with a catalytic amount of PTSA at an elevated temper-

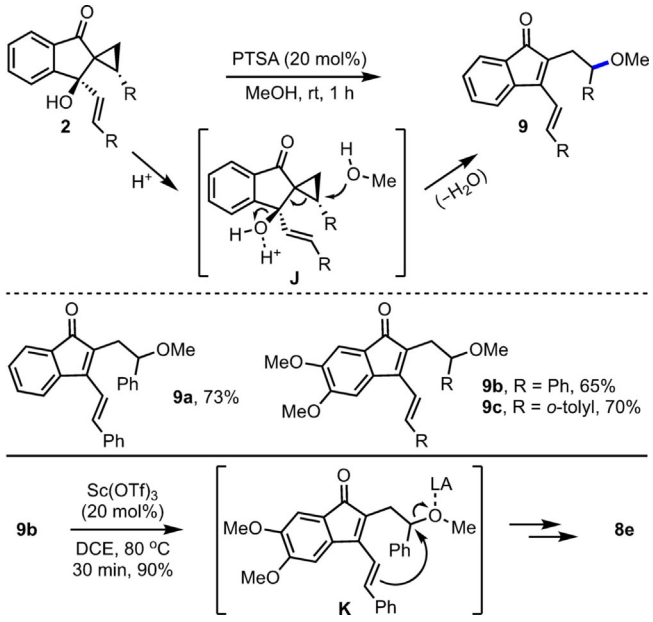
**Table 2.** Scope for cyclopropa-fused indanes **7**.[a]




[a] Isolated yield after column chromatography. [b] The diastereomeric ratio (d.r.) was obtained from the $^1$H NMR of the crude reaction mixture.




**Scheme 3.** Unexpected formation of fluorenones **8** from indeno-spirocyclopropanes **2**.



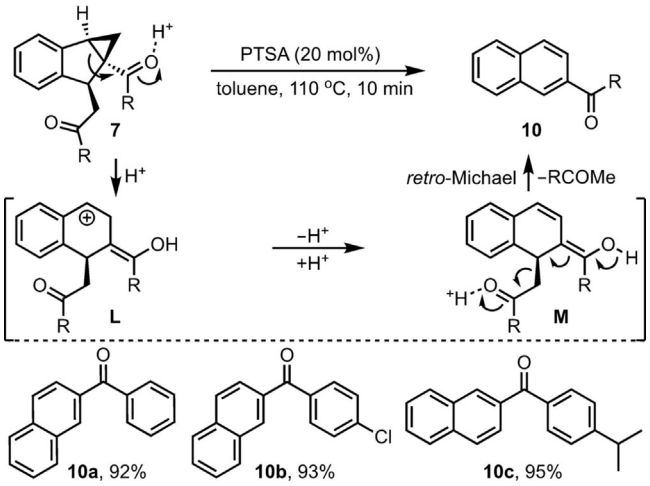

**Scheme 4.** Acid-catalyzed ring-opening of spirocyclopropanes **2** to indenones **9**, and the conversion of indenones **9** to fluorenones **8**.

ature, an exclusive formation of the fluorenone **8a** was realized, Scheme 3. As indicated in **G**, a formal homo-Nazarov-type cyclization of vinyl-cyclopropyl cationic system[13] generates tetrahydrofluorenyl cation **H**, which undergoes deprotonation followed by aromatization to provide the fluorenone **8a**. Intrigued by the unexpected outcome and having realized the significance of fluorenones,[9,14] we verified the generality of the reaction in few other cases (**8b**–**8f**). All the reactions were found to be extremely efficient and provided fluorenones in excellent yields.

During the optimization of the reaction described in Scheme 3 (conversion of **2** to **8**), we made an interesting observation. When the reaction of **2a** was performed in methanol, the β-styryl indenone **9a** was obtained in 73% yield, Scheme 4. In this manner, few other indenones (**9b** and **9c**) were prepared. The mechanism of formation of **9** from **2** can be conveniently explained as depicted in **J**.

Further, when **9b** was treated with a Lewis acid such as $Sc(OTf)_3$, the fluorenone **8e** was obtained in excellent yield, Scheme 4. This transformation indicates that the PTSA-promoted reaction of **2** in methanol could also have delivered fluorenones **8** in the presence of PTSA, but the reversibility that prevails due to the strong nucleophilic solvent (methanol) has resulted in the formation of only **9**. It could indeed be the reason why indenone **9b** could be readily converted to fluorenone **8e** in a non-alcoholic solvent under mild (Lewis) acidic conditions.

Next, a synthetic elaboration of cyclopropa-fused indanes **7** was also considered, Scheme 5. It was hypothesized that the activation of cyclopropyl keto moiety in **7** might involve the cleavage of the C–C bond that experiences the most overlapping with the carbonyl group and trigger further bond reorganizations. As per the plan, when **7a** was treated with a catalytic amount of PTSA at elevated temperature, interestingly, 2-




**Scheme 5.** Acid-catalyzed ring-opening/aromatization sequence of cyclopropa-fused indanes **7** to 2-naphthaphenones **10**.

naphthaphenone **10a** was isolated in 92% yield. The other naphthaphenones (**10b** and **10c**) were obtained analogously in excellent yields. As of the mechanism of the formation of **10**, activation of the carbonyl group by the acid and a subsequent ring-opening of the cyclopropane leads to the formation of the benzylic cation **L**, which converts to the dihydronaphthalene **M**. Aromaticity is achieved by the acid-catalyzed retro-Michael reaction of **M**.

In conclusion, we presented serendipitous transformations triggered by DOSM for the synthesis of otherwise difficult-to-access cyclopropanoids. Furthermore, one-step synthetic elaborations were established to access privileged structures such as fluorenones, indenones, and naphthaphenones with unusual substitution patterns. The methods described herein are operationally straightforward one-pot synthetic transformations, which are mechanistically intriguing. Efforts to extend these methods to new substrate classes are in progress and the details will be communicated in due course.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** Corey-Chaykovsky reagent · cyclopropanes · desymmetrization · rearrangements · sulphur ylides

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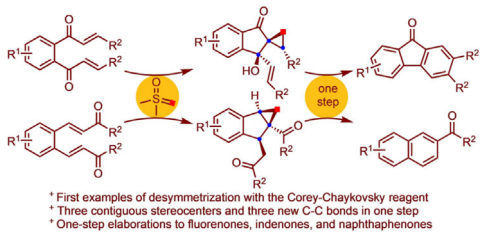
# COMMUNICATION




**Above and beyond**: A set of desymmetrization events triggered by the Corey–Chaykovsky reagent are reported. Thereby, efficient and straightforward synthetic routes for indeno-spirocyclopropanes and cyclopropa-fused indanes have been established. These structures were transformed in one step to privileged structures such as fluorenones, indenones, and naphthaphenones. The methods described herein can have implications in medicinal chemistry as well as materials science.

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