Organic LETTERS

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# A Novel Intramolecular Homoenolate Annulation Leading to the Formation of Cyclopentene-Fused Macrocycles[‖]

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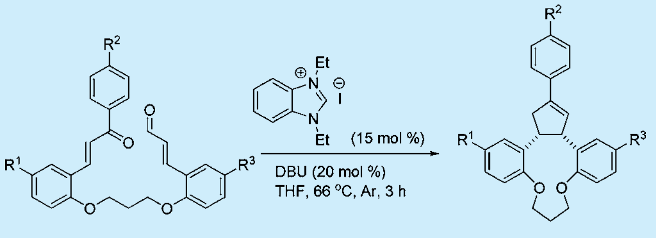
*Supporting Information*

**ABSTRACT:** A nucleophilic heterocyclic carbene-mediated intramolecular homoenolate reaction strategy for the efficient synthesis of cyclopentene-fused macrocycles is reported.

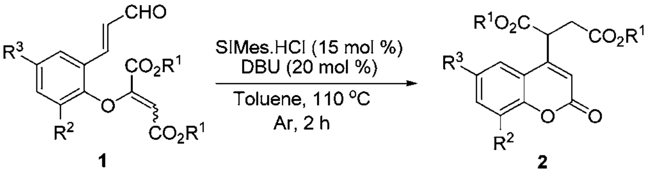


In the general context of organocatalysis,[1] reactions catalyzed by N-heterocyclic carbenes (NHCs)[2] are in vogue. During the past decade, a variety of NHC-catalyzed reactions leading to a wide range of products have been reported from different laboratories. Of special interest to us have been the NHC-catalyzed reactions of enals with aldehydes via the intermediacy of homoenolate pioneered by Glorius[3] and Bode.[4] Inter alia, homoenolate reactions have been successfully employed in the synthesis of cyclopentenes,[5,6] lactams,[7] γ-butyrolactones,[3,4,8] cyclopentanols,[9] pyrazolidinones,[10] γ-spirolactones,[11] and pyranones.[12]

Interestingly, however, despite the plethora of reactions uncovered in this area, very little is known about intramolecular participation of homoenolate.[13] Recently, we reported an intramolecular reaction in which cinnamaldehyde-appended 2-*O*-alkenoate on treatment with NHC underwent a cascading process leading to the formation of a coumarin derivative (Scheme 1).[14]

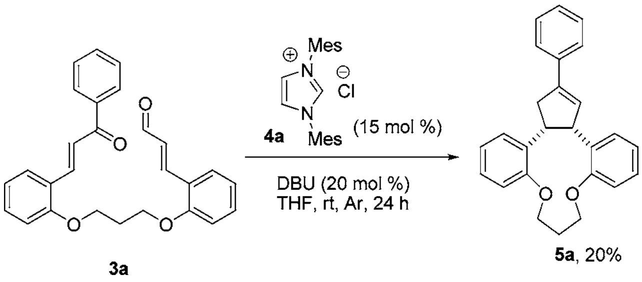
The success of the above reaction prompted us to explore other intramolecular homoenolate reactions. In this context, we speculated that a cinnamaldehyde tethered to a chalcone may be prone to undergo homoenolate reactions under the influence of NHC to deliver a cyclopentene derivative or a γ-lactone.

**Scheme 1. Previous Work**



In a prototype experiment, the chalcone-appended enal **3a** was exposed to imidazolium precatalyst **4a** and DBU in dry THF under argon atmosphere. After 24 h of stirring, the solvent was removed and crude product on column chromatography afforded the product **5a** as white solid in 20% yield (Scheme 2).

**Scheme 2. NHC-Catalyzed Annulation of Chalcone-Appended Enal**



The structure of compound **5a** was assigned by usual spectroscopic analysis. In the $^1H$ NMR spectrum, the peak corresponding to olefinic proton was discernible as a singlet at δ 6.34. All other signals were in good agreement with the assigned structure. Conclusive evidence for the structure and relative stereochemistry of **5a** was ascertained from the single-crystal X-ray data (Figure 1).

In view of the pleasing result, it was decided to carry out optimization studies in detail. For this, commonly available NHC precursors **4a–h** were used for screening (Table 1).

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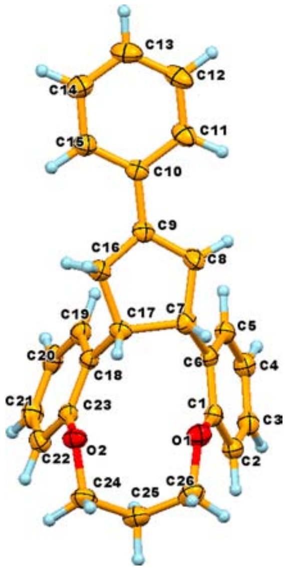
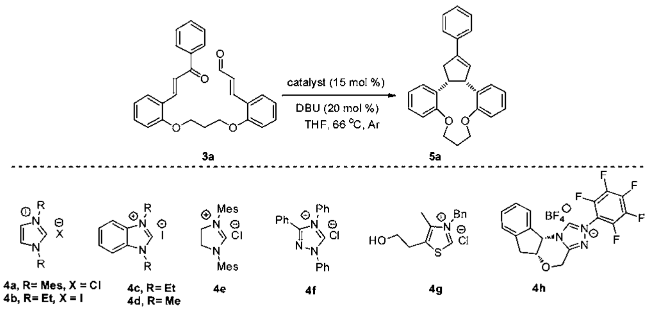


**Figure 1.** ORTEP diagram of **5a**.

### Table 1. Catalyst Screening



| entry | catalyst | time (h) | yield (%) |
|---|---|---|---|
| 1 | **4a** | 24 | 20[a] |
| 2 | **4a** | 1 | 26 |
| 3 | **4b** | 24 | 29 |
| 4 | **4c** | 3 | 62 |
| 5 | **4d** | 24 | 25 |
| 6 | **4e** | 24 | 27 |
| 7 | **4f** | 24 | |
| 8 | **4g** | 24 | |
| 9 | **4h** | 24 | |

[a] At room temperature.

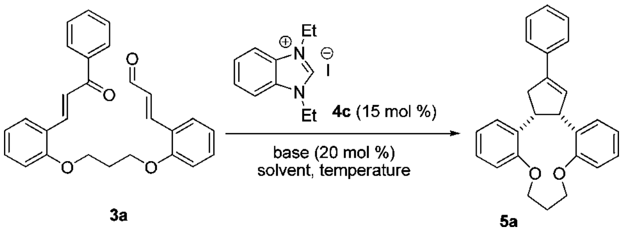
The poor results obtained with **4a** and **4b** may be attributed to steric factors. However, no conclusion can be drawn for the efficiency of **4c** vis-à-vis **4d**. Further, we examined other factors like solvent, base, and temperature on the reaction, and the results are summarized in Table 2.

In order to examine the generality of the reaction, various enal substrates have been used, and the results are summarized in Table 3.

The above results prompted us to extend the reaction to substrates with varying chain lengths. To our delight, in these cases also the reaction afforded the cyclopentene-fused macrocycles (Figure 2).

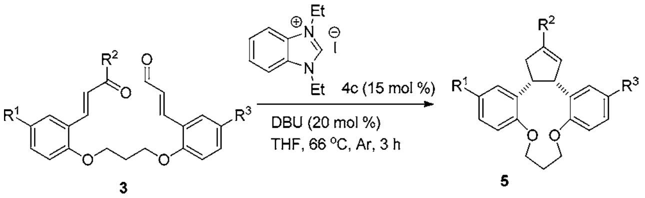
The plausible mechanism for the formation of cyclopentenes may be outlined as follows. The homoenolate **I** formed by the reaction of NHC with enal undergoes conjugate addition to the chalcone moiety and subsequent to a proton transfer generates the enolate **II**, which then participates in the intramolecular aldol reaction to afford the cyclopentane carbinolate **III**. The latter undergoes lactone formation accompanied by the ejection of NHC. The *β*-lactone **V** thus formed is unstable, and it undergoes a retro [2 + 2] process to yield the cyclopentene **5a**, with the loss of carbon dioxide (Scheme 3). It may be mentioned that the sequence of events presented here is

### Table 2. Condition Optimization



| entry | base | solvent | temp (°C) | time (h) | yield (%) |
|---|---|---|---|---|---|
| 1 | DBU | DCM | rt | 24 | 40 |
| 2 | DBU | THF | rt | 24 | 10 |
| 3 | DBU | DCM | 40 | 24 | 49 |
| 4 | DBU | THF | 66 | 3 | 62 |
| 5 | DBU | $CH_3CN$ | 82 | 24 | 19 |
| 6 | DBU | toluene | 110 | 24 | 17 |
| 7 | DBU | MeOH | 65 | 24 | |
| 8 | DMAP | THF | 66 | 24 | |
| 9 | $K_2CO_3$ | THF | 66 | 24 | |

### Table 3. Scope of the Reaction[a]



| entry | $R^1$ | $R^2$ | $R^3$ | product | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | H | Ph | H | **5a** | 62 |
| 2 | Br | 4-OMe$C_6H_4$ | H | **5b** | 76 |
| 3 | Cl | Ph | H | **5c** | 72 |
| 4 | Br | 4-Br$C_6H_4$ | Br | **5d** | 69 |
| 5 | Br | 4-Br$C_6H_4$ | H | **5e** | 68 |
| 6 | Cl | 4-Br$C_6H_4$ | H | **5f** | 65 |
| 7 | H | Ph | $CH_3$ | **5g** | 67 |
| 8 | Cl | 4-OMe$C_6H_4$ | H | **5h** | 62 |
| 9 | Br | Ph | H | **5i** | 58 |
| 10 | Br | thienyl | H | **5j** | 67 |
| 11 | Br | furyl | H | **5k** | 61 |
| 12 | Br | pyridyl | H | **5l** | 62 |
| 13 | H | 4-Br$C_6H_4$ | H | **5m** | 57 (68)[c] |
| 14 | H | Ph | Br | **5n** | 55 |
| 15 | Br | thienyl | $CH_3$ | **5o** | 48 (55)[c] |
| 16 | H | 4-Me$C_6H_4$ | Br | **5p** | 63 |

[a] Reactions were carried out with chalcone-appended enal **3** (0.2 mmol), carbene precursor **4c** (15 mol %), and DBU (20 mol %) in 3 mL of dry THF (refluxed for 3 h). [b] Yields of isolated pure compounds. [c] Yields based on recovered starting material in parentheses. It is surmised that the relatively lower yield of products in these reactions vis a vis other homoenolate reactions may be attributed to polymerization via intermolecular reactions as indicated by the presence of small amounts polymeric materials in the reaction mixture.

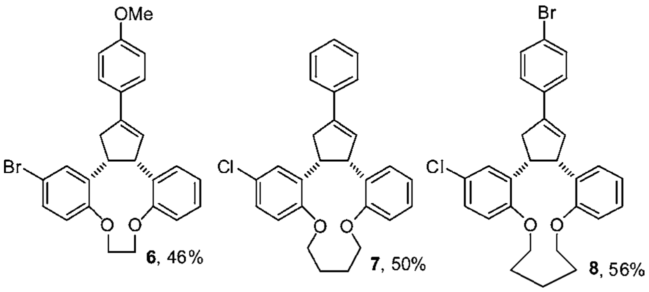
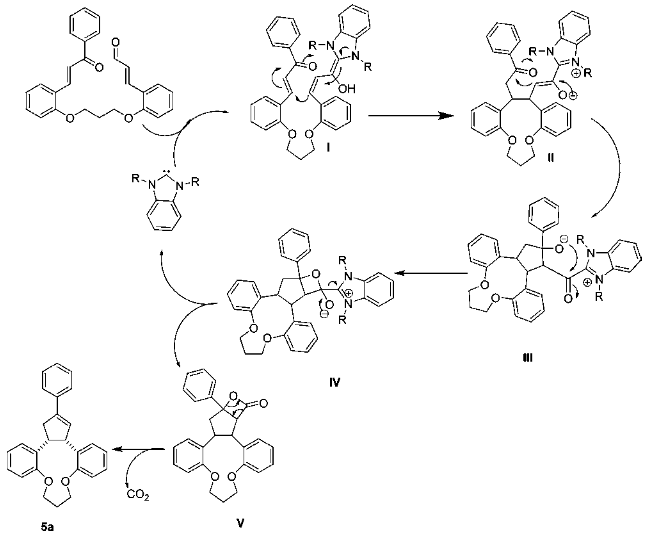


**Figure 2.** Cyclopentenes fused to different macrocycles.

**Scheme 3. Proposed Mechanism**

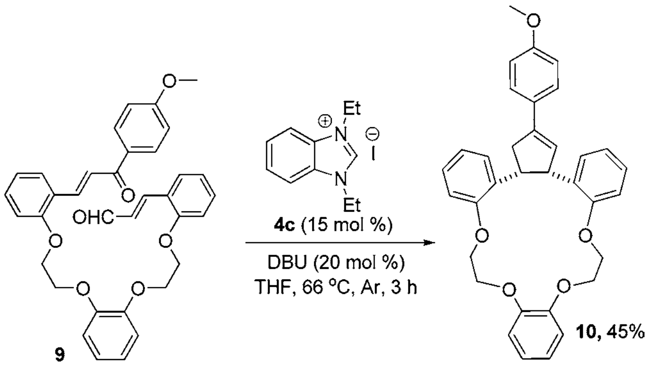


analogous to the one that was established experimentally[5a] and theoretically[15] for the 1,3,4-triarylcyclopentene synthesis reported previously.

Encouraged by the above results, we decided to study the reaction of chalcone-appended enal **9** having the alkyl chains linked through a catechol moiety under the same reaction conditions. The catechol-linked tether was interesting since it offered the potential for the synthesis of novel "semicrown" molecules. To our delight, cyclopentene **10** was obtained albeit in lower yield (Scheme 4).

In conclusion, we have uncovered a new intramolecular homoenolate annulation leading to the formation of cyclopentene-bearing macrocycles. It is conceivable that this protocol may be useful for the construction of semicrown ethers and related compounds.[16]

**Scheme 4**



## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and spectral data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## ■ DEDICATION

[‖]Dedicated with best wishes to Professor Gilbert Stork.

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