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A Route to Highly Functionalized β-Enaminoesters via a Domino Ring-Opening Cyclization/Decarboxylative Tautomerization Sequence of Donor−Acceptor Cyclopropanes with Substituted Malononitriles

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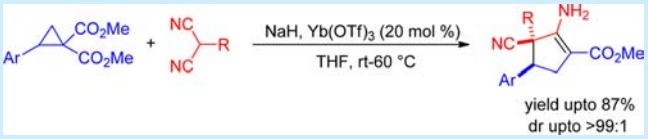
Supporting Information

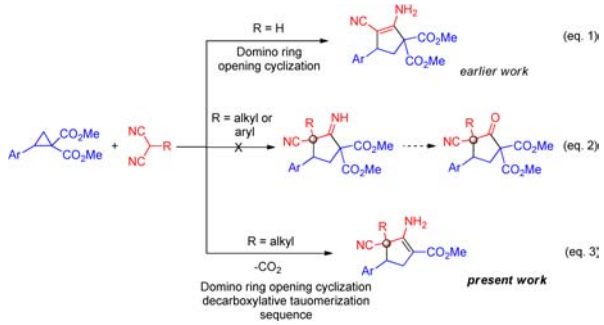
ABSTRACT: An unprecedented and domino synthetic strategy for the synthesis of highly functionalized carbocyclic β-enaminoesters bearing an all-carbon quaternary center via $Yb(OTf)_3$-catalyzed ring-opening cyclization/decarboxylative tautomerization of donor−acceptor cyclopropanes with 2-alkyl malononitriles in excellent yields is described. The products are obtained as a single diastereomer in most cases where the nitrile and aryl groups are aligning in a *cis* orientation across the ring.



Donor−acceptor (DA) cyclopropanes have recently been recognized as one of the most versatile building blocks in modern organic synthesis, and the realm of their synthetic utility is exponentially expanding.[1−4] Synergistic "push−pull" character imparted to the ring by the donor and acceptor functionalities enables them to undergo a variety of synthetic transformations.[1] Based on the special reactivity patterns (possessing both nucleophilic and electrophilic terminals) of DA cyclopropanes, several strategies have evolved for the synthesis of various acyclic and cyclic compounds.[2] At the same instant, a number of complex molecular architectures have been brought forth exploiting the same concept. DA cyclopropanes are reported to be one of the most acclaimed building blocks for their ability to undergo various cycloaddition reactions, such as [3 + 2], [3 + 3], [4 + 3], [8 + 3], etc., and intramolecular ring-opening cyclization reactions.[2,3] Meanwhile, several domino synthetic strategies have also been developed for the synthesis of various cyclic compounds via ring-opening cyclization of DA cyclopropanes with several reagents bearing both nucleophilic and electrophilic moieties.[4]

In recent years, we have become interested in developing domino synthetic protocols for the synthesis of functionalized carbo- and heterocyclic compounds exploiting chemistry of small-ring aza- and carbocycles. We have successfully developed a novel domino ring-opening cyclization (DROC) strategy for this purpose.[5] Recently, we have reported an elegant DROC approach for the synthesis of carbocyclic β-enaminonitriles via the reaction of DA cyclopropanes with malononitrile (eq 1, Scheme 1).[5d] We envisioned that DROC of DA cyclopropanes with 2-substituted malononitriles could generate the corresponding imine derivatives (eq 2, Scheme 1), which could further be converted into various substituted five-membered carbocyclic compounds including functionalized cyclopentanones which are present in several bioactive natural products like prezawlskin B and the picrotoxanes.[6]

Scheme 1. Reactivity of DA Cyclopropanes with Substituted Malononitriles



When DA cyclopropanes were reacted with 2-alkyl malononitriles, carbocyclic β-enaminoesters bearing an all-carbon stereocenter were generated via a DROC/decarboxylative tautomerization sequence (eq 3, Scheme 1). It is important to mention that β-enaminoesters are privileged building blocks extensively used for the synthesis of various nitrogen-containing organic compounds.[7] They have served as key substrates for the synthesis of various natural products[8] such as taxol, pukelimide, 11-deoxy-8-azaprostaglandin E1, etc., and several pharmaceutical agents.[9] In the literature, β-enaminoesters have been mostly synthesized via Gewald reaction,[10] alkyne hydroamination,[11] and amination of β-ketoesters.[12] Most of these synthetic strategies suffer from limited substrate scope, harsh reaction conditions, and costly starting compounds. Therefore, development of new

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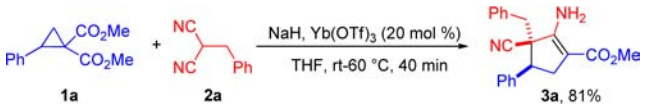
and efficient synthetic routes for the synthesis of β-enaminoesters is highly desirable.

Herein, we report a new and efficient protocol for the synthesis of substituted carbocyclic β-enaminoesters via DROC/decarboxylative tautomerization sequence of DA cyclopropanes with substituted malononitriles. We carried out our preliminary reactions utilizing DA cyclopropane **1a** as the substrate and 2-benzyl malononitrile (**2a**) as the nucleophile employing $Yb(OTf)_3$ (20 mol %) as the Lewis acid (LA) catalyst and NaH as the base in THF at 60 °C (Scheme 2).[5d] To our surprise,

Scheme 2. Diastereoselective Synthesis of Enaminoesters via Reaction of DA Cyclopropanes with Substituted Malononitriles

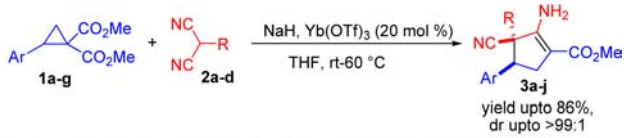


the carbocyclic β-enaminoester **3a** was obtained in 81% yield in diastereomerically pure form after in situ decarboxylation. The presence of a single ester group was confirmed by ^{1}H NMR and other spectroscopic techniques.

To optimize the reaction conditions further, several LA catalysts such as $Cu(OTf)_2$, $Zn(OTf)_2$, and $Sc(OTf)_3$ were screened. However, $Yb(OTf)_3$ was found to be the best LA catalyst. Further reduction in the amount of the LA catalyst resulted in incomplete reaction. When the reaction was performed at room temperature, substrate **1a** remained unreacted and only polymerization nucleophile **2a** was observed. It appears that elevated temperature is necessary for the reaction to proceed.

To evaluate the scope of our protocol for the synthesis of a large variety of carbocyclic β-enaminoesters, various substituted DA cyclopropanes bearing electron-rich and electron-deficient aryl groups were studied (Scheme 3).

Scheme 3. Substrate Screening for the Synthesis of β-Enaminoesters

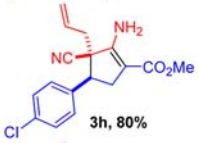


1a: Ar = C_6H_5, **1b**: Ar = 4-OMe-C_6H_4, **1c**: Ar = 2,3-$(OMe)_2$-C_6H_3, **1d**: Ar = 4F-C_6H_4, **1e**: Ar = 4Cl-C_6H_4, **1f**: Ar = 4-Br-C_6H_4, **1g**: Ar = 1-naphthyl
2a: R = -$CH_2C_6H_5$, **2b**: R = -CH_3, **2c**: R = -$CH_2CH{=}CH_2$, **2d**: R = -C_6H_5

A clean reaction was encountered in all cases where DA cyclopropanes with electron-rich aryl groups were employed as the substrates. For instance, **1b** having with a 4-methoxy phenyl group as the donor site on the ring, the cyclopropane underwent reaction with several 2-alkyl malononitriles **2a−c** to generate the corresponding β-enaminoesters (**3b−d**) in excellent yields (Table 1). Highly electron-rich 2,3-dimethoxycyclopropane **1c** generated the β-enaminoester **3e** in 86% yield upon reaction with **2c**.

DA cyclopropanes with electron-deficient aryl substituents, such as **1d** (bearing a 4-fluorophenyl group), reacted with 2-alkyl malononitriles **2a**,**b** to produce the β-enaminoesters **3f−g** in excellent yields (Table 1). Other halo-substituted DA cyclopropanes (**1e**,**f**) reacted similarly to generate the corresponding β-enaminoesters (**3h**,**i**) in excellent yields and diastereoselectivity. Naphthyl-substituted **1g** behaved in a similar way to the electron-rich substrates, producing **3j** in 80% yield.

Table 1. Substrate Screening for the Synthesis of β-Enaminoesters

1	2	β-enaminoester **3**, yield[a]	1	2	β-enaminoester **3**, yield[a]
1a	**2a**	 **3a, 81%**	**1d**	**2a**	 **3f, 85%**
1b	**2a**	 **3b, 85%**	**1d**	**2b**	 **3g, 75%[b]**
1b	**2b**	 **3c, 80%**	**1e**	**2c**	 **3h, 80%**
1b	**2c**	 **3d, 86%**	**1f**	**2c**	 **3i, 82%**
1c	**2c**	 **3e, 86%**	**1g**	**2c**	 **3j, 80%**
1a	**2d**	No reaction			

[a]Isolated yields. [b]Compound was obtained as a mixture of diastereomers (dr 3:1).

Products **3a−j** were characterized by spectroscopic techniques, and the structure of **3g** was determined by X-ray crystallographic analysis (see Supporting Information). In the major diastereomer, the 4-fluorophenyl and nitrile groups were found to have *cis* orientation.

The strategy was further extended for the synthesis of heteroaryl-substituted β-enaminoesters (Scheme 4). When thiophene-substituted cyclopropane **1h** was reacted with **2c** under our reaction conditions, enaminoester **3k** was obtained in 82% yield in diastereomerically pure form. Our methodology could also provide enaminoesters bearing synthetically explorable functionalities. When styryl cyclopropane **1i** was reacted with substituted **2b**,**c**, the corresponding products **3l**,**m** were obtained in excellent yields (Scheme 4). Unfortunately, **3m** was generated as mixture of diastereomers with high diastereoselectivity (7:1). β-Enaminoesters **3l**,**m** have potential to be converted into several substituted heterocycles upon routine synthetic transformations of the two olefinic bonds.[13−16]

The reaction follows an S_N2-type pathway where the nucleophile attacks the benzylic carbon of the cyclopropane ring to generate intermediate **A** (Scheme 5). In order to align itself in the proper position for cyclization, **A** can adopt two different conformations: **B** and **C**. Conformer **B** suffers from severe eclipsing interaction of the aryl group with the tetrahedral alkyl group, whereas the conformer **C** experiences lesser eclipsing

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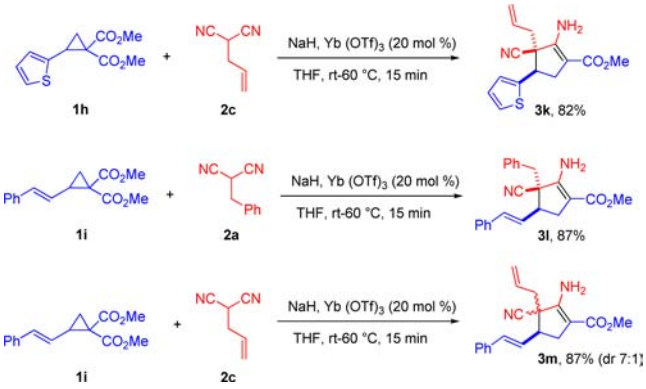
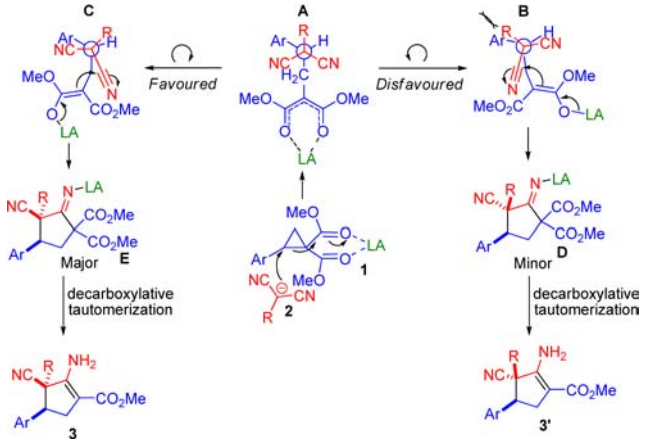
Scheme 4. Synthesis of Heteroaryl- and Styryl-Substituted Carbocyclic Enaminoesters via Domino Ring-Opening Cyclization/Decarboxylative Tautomerization Sequence



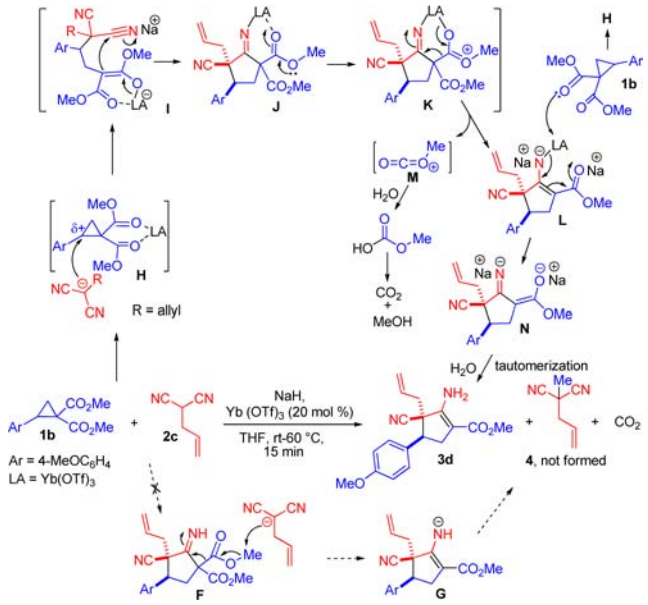
Scheme 5. Origin of Diastereoselectivity



interaction from its aryl and the cylindrical nitrile groups. The more stable **C** is preferred over **B**, and it undergoes cyclization with nitrile functionalities, generating intermediate **E**. Finally, **E** after going through a decarboxylative tautomerization sequence produces carbocyclic β-enaminoesters **3**.

We next investigated the mechanism of the unexpected decarboxylative tautomerization step. Initially, we proposed that the decarboxylation was following a Krapcho-type pattern[17] where a nucleophile (halide in Krapcho decarboxylation) attacks the ester moiety, leaving an alkyl halide as the side product. To confirm our proposal, we performed reaction of **1b** with **2c** under our reaction condition, and the reaction mixture was scanned for all of its components. Absence of **4** which could be generated via attack of malononitrile anion generated from **2c** on the ester Me group of intermediate **F** (Scheme 6) from the crude reaction mixture (^{1}H NMR spectrum of the crude reaction mixture indicated complete absence of **4**) ruled out the possibility of a Krapcho-type decarboxylation process.[18] Eventually, we proposed a LA-catalyzed decarboxylation process where a LA-chelated complex **J**, which is generated after ring-opening cyclization of LA, activated DA cyclopropane **H** with substituted malononitrile. In **J**, the LA weakens the C═O bond by binding to the carbonyl oxygen, which apparently weakens the *O*-methyl bond and helps in the decarboxylation process.[19] Intermediate **J** converts into **K** which expels a cationic species **M**, leaving another intermediate **L**.[20] **L**, upon releasing LA (which is captured by the DA cyclopropane to regenerate the LA-activated complex **H**), generates disodium intermediate **N**. In the presence

Scheme 6. Mechanism of Decarboxylative Tautomerization



of water (at the time of quenching), **N** provides the corresponding β-enaminoester **3d** (after protonation followed by tautomerization), whereas **M** is converted into methyl hydrogen carbonate which is eventually hydrolyzed to carbon dioxide and methanol (Scheme 6).

In summary, we have developed an unprecedented domino synthetic route for the synthesis of substituted carbocyclic β-enaminoesters via the reaction of a large variety of substituted DA cyclopropanes with 2-alkyl malononitriles. Our method utilizes both electron-rich and electron-deficient aryl groups on the cyclopropane rings. The reaction proceeds through an unprecedented decarboxylative tautomerization to provide the enaminoesters bearing an all-carbon quaternary stereocenter in diastereomerically pure form.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedure and characterization data. 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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(18) If Krapcho-type decarboxylation is occurring, the alkyl malononitrile carbanion is the only available nucleophile which can attack the ester moiety. The triflate anion, released from the catalyst having much less nucleophilicity, cannot participate in the reaction.

(19) Probably the Lewis acid weakens the O−Me bond, and conversion of imine to a more stable enaminoester (also exocyclic double bond becomes endocyclic) serves as the driving force for the decarboxylation process.

(20) We did not observe even traces of enamine carbamate, which could possibly be generated via reaction of **L** and **M**. Perhaps **L** and **M** converted into their respective products, immediately after their formation (Scheme 6), before reacting with each other to generate enamine carbamate.