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Stereospecific Syntheses of Enaminonitriles and *β*-Enaminoesters via Domino Ring-Opening Cyclization (DROC) of Activated Cyclopropanes with Pronucleophilic Malononitriles

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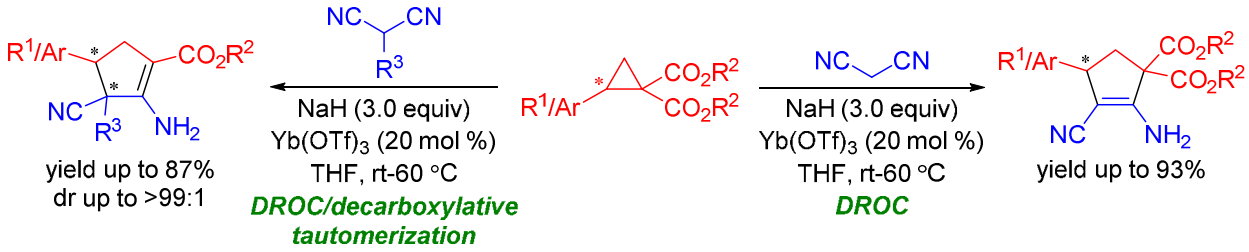


Two novel synthetic protocols for the syntheses of highly functionalized five-membered carbocyclic enaminonitriles and *β*-enaminoesters have been developed via domino ring-opening cyclization (DROC) and DROC/decarboxylative tautomerization of activated cyclopropanes with malononitrile pronucleophiles, respectively. Both of the efficient strategies (yield up to 93%) have been generalized with various donor-acceptor and acceptor cyclopropanes as well as with malononitrile derivatives. The stereospecific variants of the two S_N2-type DROC strategies have also been developed by employing enantiopure donor-acceptor (DA) cyclopropanes to synthesize

the corresponding nonracemic products with excellent stereoselectivities (dr up to >99:1, ee up to >99%).

Introduction

Five-membered carbocyclic enaminonitriles and *β*-enaminoesters, as shown in Figure 1, are ubiquitous structural motifs in natural products and other synthetic compounds with a wide spectrum of biological activities. **I** having a five-membered enaminonitrile framework exhibits antiviral activity against HSV-1 and HIV-1[1] and **II**, also possessing the same structural core, exhibits a limited antimicrobial activity.[2] On the other hand, five-membered *β*-enaminoester motif-bearing compounds **III** and **IV** exhibit lifespan-altering properties in eukaryotic organisms.[3]

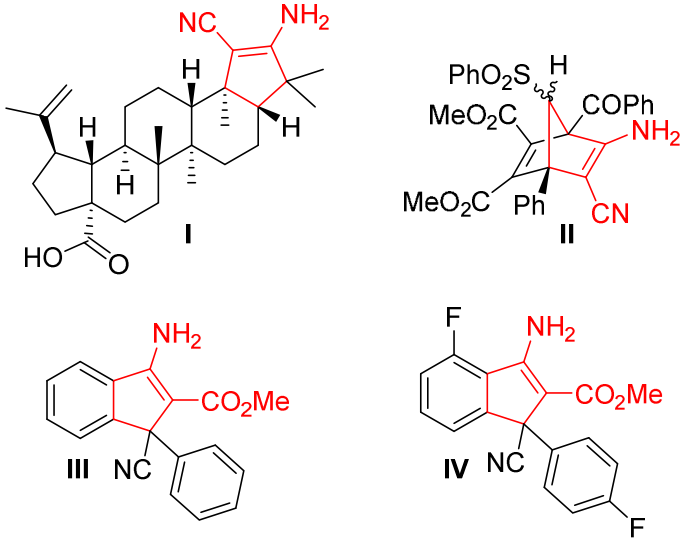


Figure 1. Biologically Active Five-Membered Carbocyclic Enaminonitriles and *β*-Enaminoesters

Owing to the presence of the aforementioned enaminonitrile scaffold in beneficial bioactive compounds, a number of reports exists in the literature for the synthesis of five-membered

carbocyclic enaminonitriles.[4] A few strategies engage cyclopropanes as the substrates for this purpose such as radical cyclization of dicyanocyclopropanes,[5] Fe-catalyzed allylic substitution of vinyl cyclopropane with malononitrile,[6] and the ring-expansion reaction of cyclopropanedicarboximides with malononitrile.[7] There are also a few reports available for the synthesis of five-membered carbocyclic *β*-enaminoesters that describe trapping of Blaise reaction intermediates with alkynes,[8] amination of cyclic *β*-ketoesters,[9] superacid-catalyzed intramolecular cyclization reactions of arylcyanopropionates,[10] cyclization of cyano-substituted unsaturated esters[11] etc. Ren and co-workers have also observed the formation of the carbocyclic *β*-enaminoesters from the reaction of cyclopropanedicarboximides with ethyl cyanoacetate.[7] However, the existing reports could only provide a few varieties of enaminonitriles and enaminoesters. As the highly functionalizable appendages (nitrile, amino or ester groups) confer biological activities to these classes of five-membered carbocyclic compounds,[4] it is challenging and highly desirable to develop new protocols for the construction of these frameworks with the required architectural and stereogenic complexity.

In recent years, donor-acceptor (DA) cyclopropanes have become one of the important classes of building blocks and the related chemistry has made significant contributions to organic synthesis.[12] Synthetic exploration of DA cyclopropanes by utilizing their inherent proclivity to undergo a wide range of ring-opening transformations with functionalized nucleophiles has led to the development of interesting routes to various carbo-[13] and heterocyclic[14] compounds. For over a decade and a half we have been exploring and utilizing a wide variety of S_N2-type ring-opening transformations of activated small ring aza-hetero- and carbacycles[15] to conveniently access a number of heterocyclic[16] and carbocyclic compounds,[4e,17] respectively, of contemporary interest. We are keenly interested in designing convenient and economical synthetic plans for

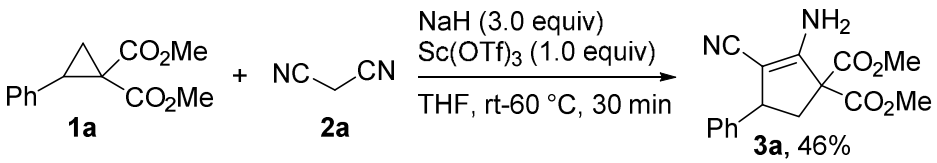
various carbocyclic frameworks via state-of-the-art domino ring-opening cyclization (DROC) strategies employing a wide range of donor-acceptor (DA) cyclopropanes and functionalized amphiphilic species bearing both nucleophilic and electrophilic termini.[4e,15b,17] We earlier communicated the preparative procedures for carbocyclic enaminonitriles[4e] and *β*-enaminoesters[17c] via S_N2-type DROC and DROC/decarboxylative tautomerization of DA cyclopropanes with malononitrile and substituted malononitrile pronucleophiles, respectively. Owing to the sustained and ever-increasing pharmaceutical significance and synthetic potentials of the aforementioned product classes, we have explored further for generalization and enhanced flexibility of the two protocols in terms of reactivity and functionalizability of the cyclopropane and malononitrile substrates. We have also aimed to develop a highly desirable extension to their enantiospecific variants. Herein, we wish to record the comprehensive results of our endeavours as an article.

Results And Discussion

Based on our report for the synthesis of 4,5-dihydropyrroles containing enaminonitrile moiety via DROC of *N*-sulfonylaziridines with malononitrile,[18] we envisaged that carbocyclic enaminonitriles could easily be synthesized via DROC of DA cyclopropanes with malononitrile nucleophile under appropriate reaction conditions. To realize our idea, we studied the reaction of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**1a**) with malononitrile (**2a**) in THF at rt–60 °C. Stoichiometric amount of $Sc(OTf)_3$ was used as the Lewis acid (LA) to further activate **1a** and 3.0 equiv of NaH was used as the base to generate the active nucleophile from **2a**. To our pleasure, the reaction completed in 30 min and the desired carbocyclic enaminonitrile derivative

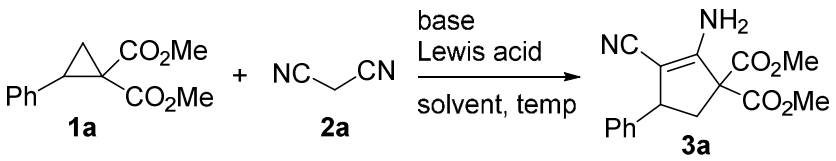
3a was produced in 46% yield (Scheme 1). The compound **3a** was characterized by spectral data and its structure was unambiguously confirmed by single crystal X-ray analysis.[4e]

Scheme 1. Synthesis of Carbocyclic Enaminonitrile 3a via Lewis Acid Mediated DROC of DA Cyclopropane 1a and Malononitrile (2a)



To optimize the reaction condition for obtaining enhanced yield of the product **3a**, we screened several Lewis acids such as Ti(^{i}PrO)$_4$, Zn(OTf)$_2$, Cu(OTf)$_2$, BF_3·OEt_2, and Yb(OTf)$_3$. Yb(OTf)$_3$ was found to be the most effective LA and **3a** was produced in 87% yield within 10 min (entry 6, Table 1). Altering the solvent from THF to toluene drastically reduced the yield of **3a** (39%, entry 7, Table 1). The use of catalytic amount of Yb(OTf)$_3$ (20 mol %) in THF at rt–60 °C was found to be the best condition (88% yield, entry 8, Table 1). Further reduction in the catalyst loading (entry 9), or dropping the temperature (entry 10), or using ^{t}BuOK instead of NaH (entry 11) were found to have adverse effect on the efficiency of the transformation. Notably, the reaction did not proceed at all in the absence of any Lewis acid (entry 12). All the results are summarized in Table 1.

Table 1. Optimization Studies for the Synthesis of Carbocyclic Enaminonitrile 3a via Lewis Acid Catalyzed DROC of DA Cyclopropane 1a and Malononitrile (2a)



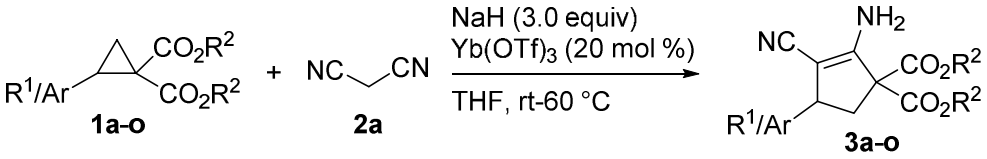
entry	Lewis acid (mol %)	base[a]	solvent	temp (°C)	time	yield (%)
1	$Sc(OTf)_3$ (100)	NaH	THF	rt–60	30 min	46
2	$Ti(O^iPr)_4$ (100)	NaH	THF	rt–60	10 min	21
3	$Zn(OTf)_2$ (100)	NaH	THF	rt–60	1 h	70
4	$Cu(OTf)_2$ (100)	NaH	THF	rt–60	30 min	5
5	$BF_3{\cdot}OEt_2$ (100)	NaH	THF	rt–60	5 min	11
6	$Yb(OTf)_3$ (100)	NaH	THF	rt–60	10 min	87
7	$Yb(OTf)_3$ (100)	NaH	toluene	rt–60	45 min	39
8	**$Yb(OTf)_3$ (20)**	**NaH**	**THF**	**rt–60**	**15 min**	**88**
9	$Yb(OTf)_3$ (10)	NaH	THF	rt–60	20 min	70
10	$Yb(OTf)_3$ (20)	NaH	THF	Rt	9 h	86
11	$Yb(OTf)_3$ (20)	^{t}BuOK	THF	rt–60	15 min	80
12	-	NaH	THF	rt–60	12 h	-

[a]3.0 equiv of base was used in all of the reactions.

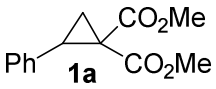
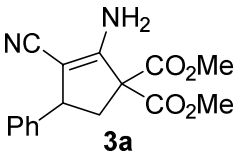
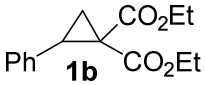
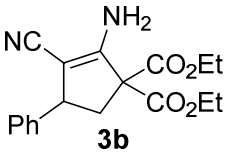
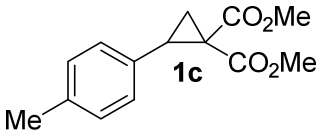
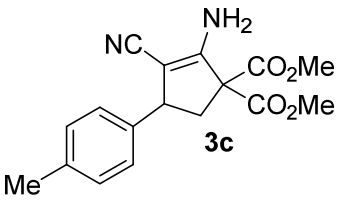
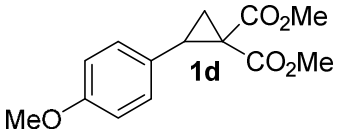
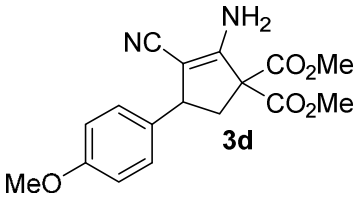
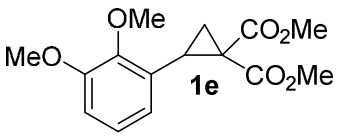
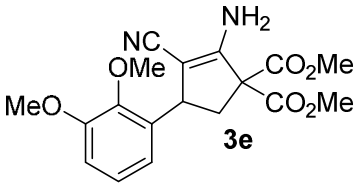
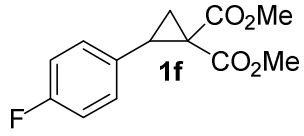
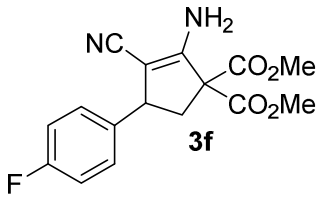
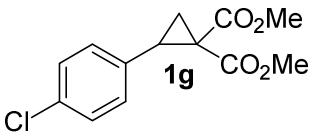
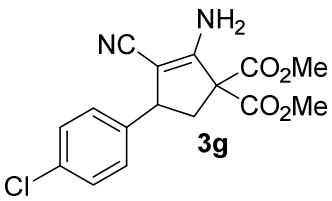
Under the optimized reaction conditions, we next generalized our approach employing a wide range of DA cyclopropanes possessing different substituents of varying electronic and steric properties with malononitrile and the results are described in Table 2. The reaction proceeded well with diethyl 2-phenylcyclopropane-1,1-dicarboxylate (**1b**) giving rise to the corresponding product **3b** in 83% yield (entry 2). With electron-donating groups such as 4-Me, 4-OMe, and 2,3-$(OMe)_2$ on the 2-aryl groups of the DA cyclopropanes (**1c**–**e**), the corresponding products **3c**–**e** were obtained in high yields (up to 90%, entries 3–5). The reactions of halogen-substituted DA cyclopropanes (**1f**–**j**) with malononitrile were successful and the corresponding carbocyclic enaminonitriles **3f**–**j** were obtained in excellent yields (up to 92%, entries 6–10). Naphthyl-

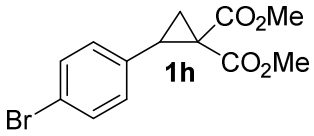
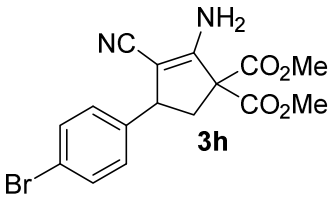
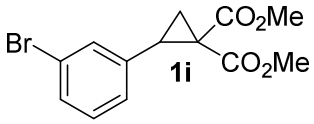
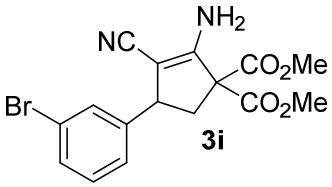
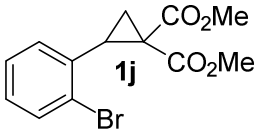
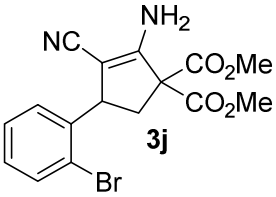
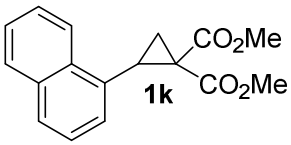
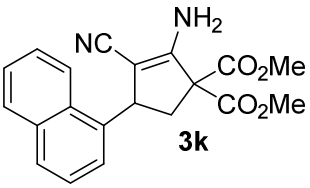
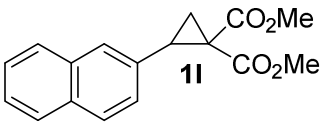
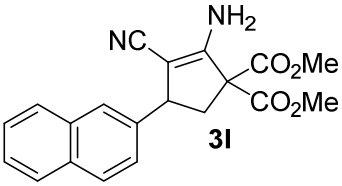
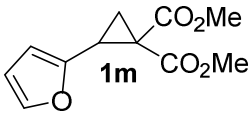
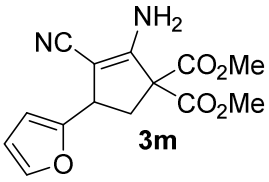
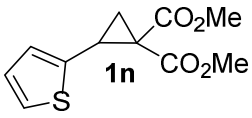
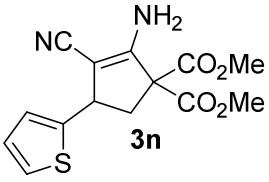
substituted carbocyclic enaminonitriles **3k–l** were also obtained in high yields (up to 82%) when the corresponding DA cyclopropanes **1k–l** were reacted with malononitrile under the optimized conditions (entries 11–12). The lower yield and longer reaction time required for the formation of **3k** was presumably due to the steric crowding exerted by the 1-naphthyl group, rendering the corresponding DA cyclopropane **1k** less reactive towards nucleophilic attack. To extend the scope of our strategy for the synthesis of heteroaryl-substituted carbocyclic enaminonitriles, we performed reactions of the 2-furyl and 2-thienyl-substituted cyclopropanes **1m** and **1n**, respectively, with **2a**. To our delight, the corresponding products **3m** and **3n** were obtained in excellent yields (91% and 93%, entries 13 and 14). The DA cyclopropane with a styryl substituent at its 2-position (**1o**) provided the corresponding product **3o** in excellent yield (93%, entry 15). It is pertinent here to note that the presence of highly functionalizable synthetic units in the 2-aryl groups of the cyclopropanes such as halogens in **1f–j** and olefin in **1o** could allow further structural elaboration, thereby adding further values to the protocol.

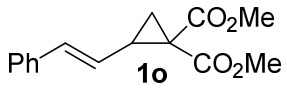
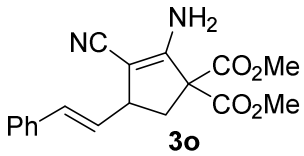
Table 2. Generalization and Substrate Scope for the Synthesis of Carbocyclic Enaminonitriles via Lewis Acid Catalyzed DROC of DA Cyclopropanes with Malononitrile



entry	DA cyclopropane (**1**)	*β*-enaminonitrile (**3**)	time (min)	yield (%)

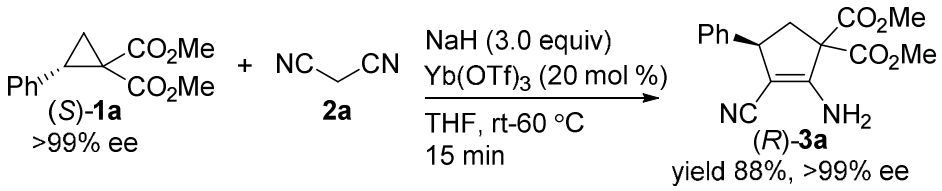
1	 **1a**	 **3a**	15	88
2	 **1b**	 **3b**	20	83
3	 **1c**	 **3c**	15	85
4	 **1d**	 **3d**	15	90
5	 **1e**	 **3e**	15	90
6	 **1f**	 **3f**	30	80
7	 **1g**	 **3g**	25	84

8			30	92
9			45	80
10			60	78
11			120	65
12			45	82
13			25	91
14			30	93

15	 **1o**	 **3o**	30	93

Inspired by these results, we extended the scope of the strategy for the synthesis of enantioenriched carbocyclic enaminonitrile derivatives employing optically pure dimethyl (*S*)-2-phenylcyclopropane-1,1-dicarboxylate (*S*)-**1a** as the substrate.[19] When (*S*)-**1a** (>99% ee) was treated with 3.0 equiv of malononitrile (**2a**) in the presence of 20 mol % $Yb(OTf)_3$ and 3.0 equiv of sodium hydride in anhydrous tetrahydrofuran at rt–60 °C,[4e] to our delight, the desired nonracemic carbocyclic enaminonitrile derivative (*R*)-**3a** was obtained within 15 min in 88% yield with excellent enantiopurity (>99% ee, Scheme 2).

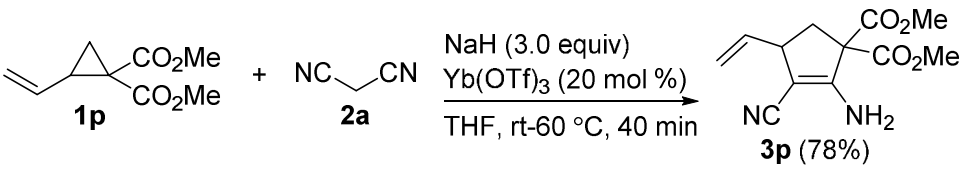
Scheme 2. Synthesis of Enantioenriched Carbocyclic Enaminonitrile (*R*)-3a via Domino Ring-Opening Cyclization of DA Cyclopropane (*S*)-1a with Malononitrile (2a)



To accommodate additional functionalities in the products as well as to generalize the methodology with comparatively less reactive DA cyclopropanes, we employed dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**1p**)[12l] as the substrate that could easily be functionalized but was expected to be less reactive due to weaker π-electron-donating ability of the vinyl group compared to its aryl analogues. When **1p** along with malononitrile (**2a**, 3.0 equiv) were exposed to the optimized DROC conditions in the presence of 20 mol % $Yb(OTf)_3$ and 3.0 equiv of NaH

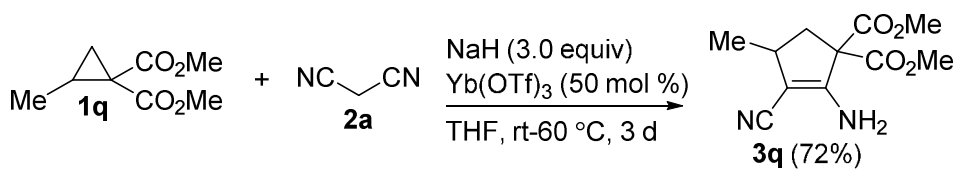
in THF, the corresponding carbocyclic enaminonitrile derivative **3p** was obtained within 40 min in high yield (78%, Scheme 3).

Scheme 3. Synthesis of Highly Functionalizable Carbocyclic Enaminonitrile 3p via DROC of 2-Vinyl Substituted DA Cyclopropane 1p with Malononitrile (2a)



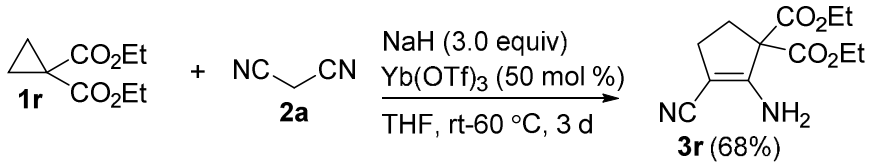
We generalized our methodology further by employing even less reactive DA cyclopropanes possessing weaker donor groups such as alkyl groups at the 2-position that could stabilize the incipient electrophilic center probably through hyperconjugation. To achieve this, dimethyl 2-methylcyclopropane-1,1-dicarboxylate (**1q**)[20] was reacted with malononitrile (**2a**, 3.0 equiv) in the presence of 50 mol % $Yb(OTf)_3$ and 3.0 equiv of NaH in THF at rt–60 °C. Although the conversion was found to be sluggish, the expected carbocyclic enaminonitrile derivative **3q** was obtained in considerably good yield after 3 d (72%, Scheme 4). It is worth noting that the relatively low propensity of the 2-methyl DA cyclopropane to undergo nucleophilic ring-opening transformations compared to their 2-aryl or 2-vinyl analogues necessitated the use of the additional amount (50 mol %) of Lewis acid.

Scheme 4. Synthesis of Methyl Substituted Carbocyclic Enaminonitrile via DROC of 2-Methyl Substituted DA Cyclopropane 1q with Malononitrile (2a)



Our success in generalizing the methodology incited us to evaluate the effectiveness of the cyclopropanes bearing no electron-donating groups at the vicinal position of the two electron-accepting ester groups for the syntheses of carbocyclic enaminonitriles. Therefore, diethyl cyclopropane-1,1-dicarboxylate (**1r**), synthesized following a literature report,[20] was subjected to the DROC protocol with malononitrile (**2a**) in the presence of 50 mol % $Yb(OTf)_3$ and 3.0 equiv of NaH in THF at rt–60 °C. In this case also the reaction was found to be sluggish and the corresponding carbocyclic enaminonitrile derivative **3r** was obtained in good yield after 3 days (68%, Scheme 5).

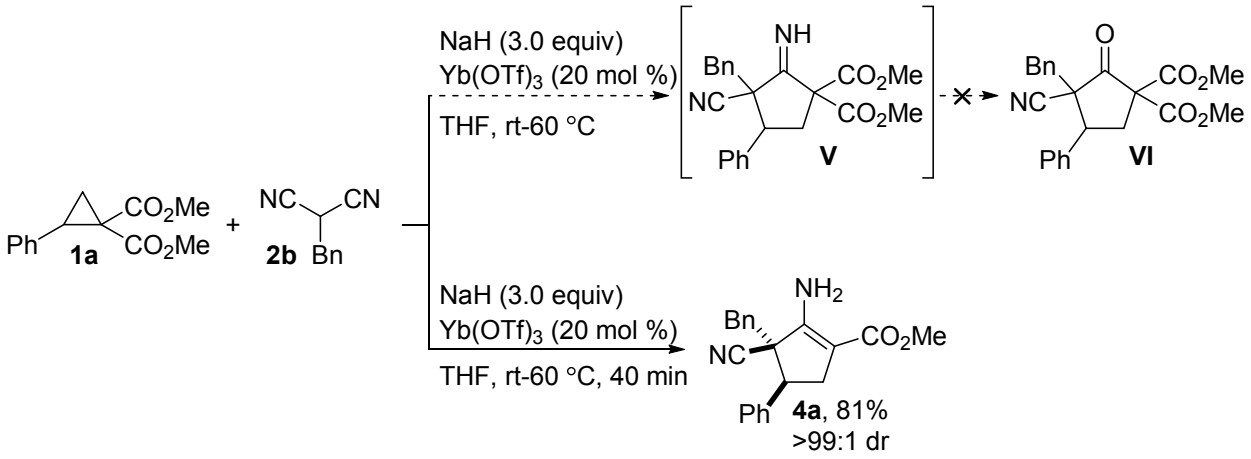
Scheme 5. Synthesis of Carbocyclic Enaminonitrile via DROC of Acceptor Cyclopropane with Malononitrile



After successfully generalizing the methodology for the synthesis of a wide range of substituted and functionalized carbocyclic enaminonitriles in their racemic and nonracemic forms via DROC of the corresponding activated cyclopropanes with malononitrile, we intended to further explore the scope of the above-described DROC transformation of activated cyclopropanes with 2-substituted malononitriles. We expected the reaction to give rise to a new class of ketonic compound **VI** as shown in Scheme 6. For this purpose, as a preliminary experiment, when **1a** was reacted with 2-benzylmalononitrile (**2b**) in the presence of 20 mol % $Yb(OTf)_3$ as the Lewis acid and 3.0 equiv of NaH as the base to generate the active nucleophile in THF at rt–60 °C, to our great surprise the carbocyclic β-enaminoester derivative **4a** bearing an all-carbon quaternary

stereocenter was obtained as a single diastereomer presumably via a sequence of one-pot DROC followed by an *in situ* decarboxylation and tautomerization in very high yield (81%, Scheme 6). The formation of the ketonic compound **VI** was not observed at all. The structure of **4a** was unambiguously determined by spectroscopic analysis.[21]

Scheme 6. Diastereoselective Synthesis of Carbocyclic *β*-Enaminoester 4a via DROC/Decarboxylative Tautomerization of 1a with 2-Benzylmalononitrile (2b)



In order to optimize the reaction conditions, several other Lewis acids such as $Cu(OTf)_2$, $Zn(OTf)_2$, and $Sc(OTf)_3$ were screened. However, the best result was obtained with 20 mol % $Yb(OTf)_3$ and 3.0 equiv of NaH in THF at rt–60 °C. Reduced loading of $Yb(OTf)_3$ resulted in incompletion of the reaction. When the reaction was performed at room temperature, **1a** remained unreacted and **2b** was found to be converted into a polymeric material in the reaction mixture. Hence, elevated temperature was required for successful completion of the reaction.

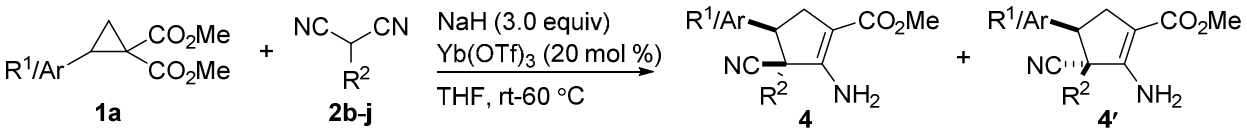
Cognizant of the biological relevance of the substituted carbocyclic *β*-enaminoesters, subsequent studies were focused towards the generalization of the developed methodology by employing a wide range of 2-aryl, 2-heteroaryl and 2-styryl-substituted DA cyclopropanes of different

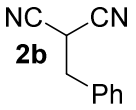
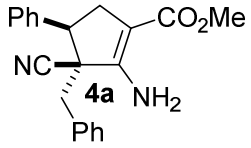
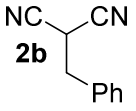
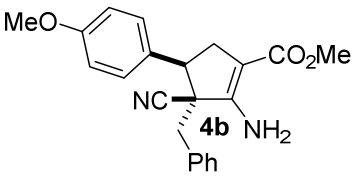
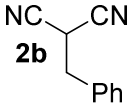
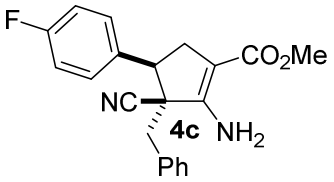
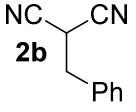
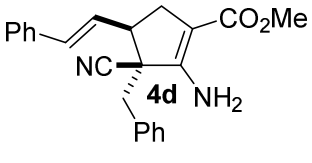
stereoelectronic nature with various 2-alkyl, 2-allyl, and 2-cycloalkyl-substituted malononitriles. All the results are summarized in Table 3. When an electron-rich substrate, dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1d**) was reacted with 2-benzylmalononitrile (**2b**) under the optimized reaction conditions, the reaction completed in 30 min and the corresponding carbocyclic *β*-enaminoester derivative **4b** was obtained in 85% yield as a single diastereomer (entry 2, Table 3). Subsequently, **2b** was employed as the pronucleophile for relatively electron-deficient 4-fluorophenyl-substituted DA cyclopropane **1f** and 2-styryl-substituted DA cyclopropane **1o** and in both of the cases, we gratifyingly observed the formations of the corresponding products **4c** and **4d**, respectively, in very high yields (85%, entry 3 and 87%, entry 4, Table 3). Interestingly, it was discovered that malononitriles with benzyl or heteroaryl groups attached to their 2-position could impart excellent diastereocontrol to the transformation. Accordingly, when 2-(4-methylbenzyl)malononitrile (**2c**) and 2-(furan-2-ylmethyl)malononitrile (**2d**) were employed as the pronucleophiles in the DROC/decarboxylative tautomerization protocol with DA-cyclopropane **1a** under the optimized reaction conditions, the corresponding carbocyclic *β*-enaminoesters **4e** and **4f**, respectively, formed in excellent yields (up to 84%) as single diastereomers (dr >99:1, entries 5 and 6, Table 3). Interestingly, when **1a** and **1f** were reacted with 2-methylmalononitrile (**2e**), the diastereoselectivity of the reaction was notably reduced and the corresponding carbocyclic *β*-enaminoesters **4g** and **4i** were obtained in very high yields as a mixture of separable diastereomers (entries 7 and 9, Table 3). However, electron-rich **1d** upon reacting with **2e** afforded the desired product **4h** in 80% yield as a single diastereomer (entry 8, Table 3). When relatively more sterically encumbered malononitrile derivative **2f** with a 3-pentyl group at its 2-position was used as the pronucleophile, the corresponding carbocyclic *β*-enaminoester **4j** was

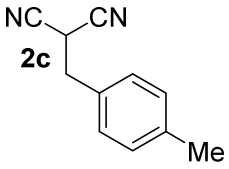
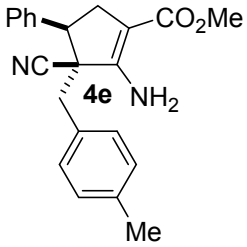
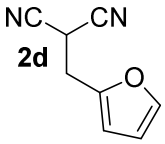
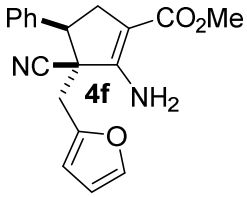
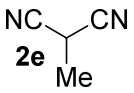
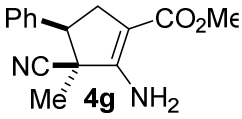
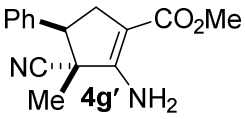
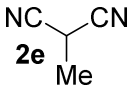
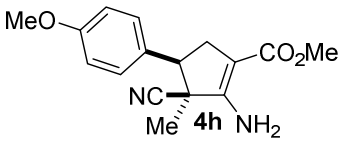
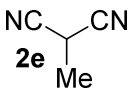
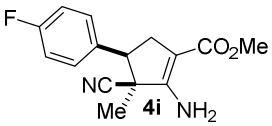
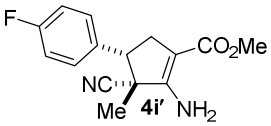
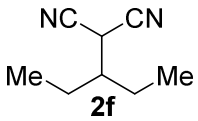
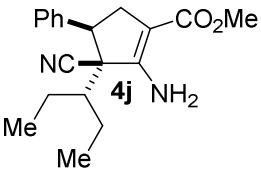
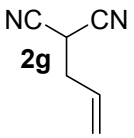
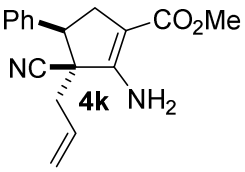
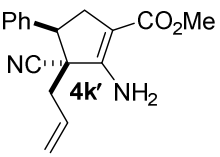
obtained in excellent yield (81%, entry 10, Table 3) as a single diastereomer. When DA cyclopropane **1a** reacted with 2-allylmalononitrile (**2g**) under the optimized DROC/decarboxylative tautomerization conditions, the corresponding *β*-enaminoesters **4k** and **4k′** were obtained in excellent yields as a mixture of separable diastereomers with moderate diastereoselectivity (dr 1.32:1, entry 11, Table 3). The relative stereochemistry of the major and the minor diastereomers were determined to be *syn* and *anti*, respectively, by single crystal X-ray analysis.[21] When highly electron-rich DA cyclopropanes such as **1d** and **1e** and relatively electron-deficient DA cyclopropanes such as **1g** and **1h** were reacted with 2-allylmalononitrile (**2g**) under the identical conditions, the corresponding five-membered carbocyclic β-enaminoesters **4l**–**o** formed in excellent yields as single diastereomers (dr >99:1, up to 86% yield, entries 12–15, Table 3). Similar observations were recorded when 1-naphthyl substituted DA cyclopropane **1k** and 2-thienyl substituted DA cyclopropane **1n** were reacted with **2g** under the optimized reaction conditions, the desired products **4p** and **4q** were obtained in excellent yields as single diastereomers (entries 16 and 17, Table 3). However, when 2-styryl substituted DA cyclopropane **1o** was reacted with **2g**, the corresponding carbocyclic *β*-enaminoesters **4r** and **4r′** were obtained with 7:1 diastereomeric ratio (entry 18, Table 3). When cyclopentyl-substituted malononitrile derivative **2h** along with **1a** was exposed to the optimized conditions, the corresponding carbocyclic *β*-enaminoesters **4s** and **4s′** were obtained in good yields with moderate diastereoselectivity (dr 1:0.43, entry 19, Table 3). Notable enhancement in the diastereoselectivity was observed (dr 9:1) when cyclohexyl-substituted malononitrile **2i** was employed and the major diastereomer of the corresponding product **4t** was isolated (76%, entry 20, Table 3). Lastly, **1a** was reacted with 2-phenylmalononitrile (**2j**) under the optimized reaction conditions. However, no advancement of the reaction was observed (entry 21, Table 3)

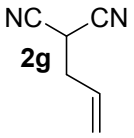
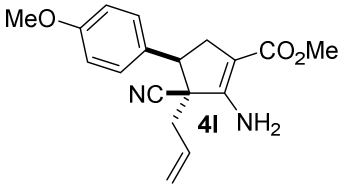
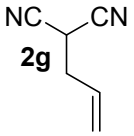
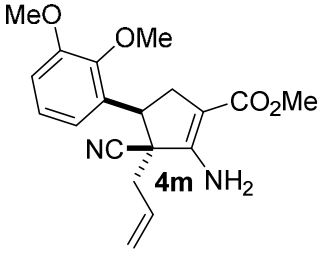
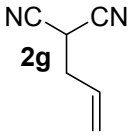
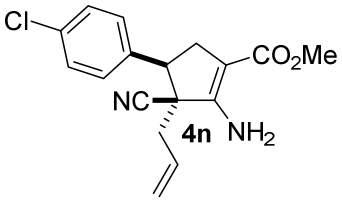
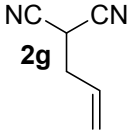
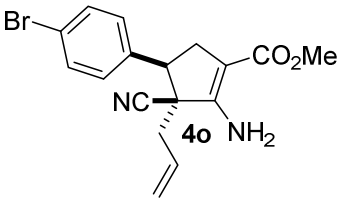
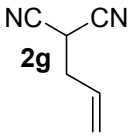
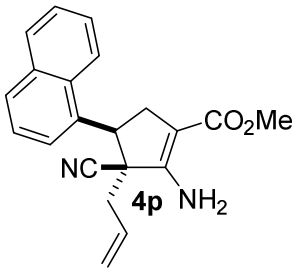
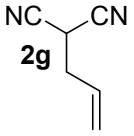
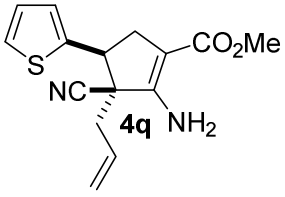
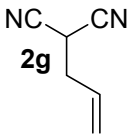
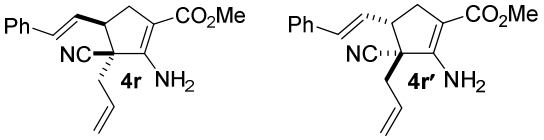
presumably due to the increased steric hindrance and high degree of stabilization of the incipient carbanion generated *in situ* by the phenyl group rendering it less nucleophilic towards the cyclopropane.

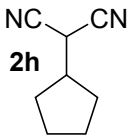
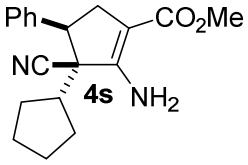
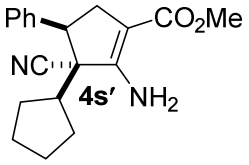
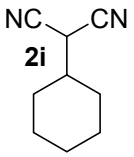
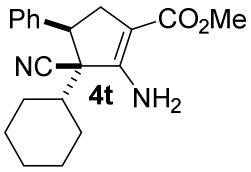
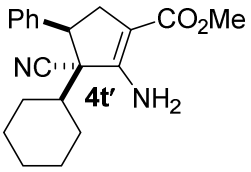
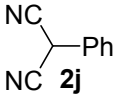
Table 3. Synthesis of Densely Substituted Carbocyclic *β*-Enaminoesters via Domino Ring-Opening Cyclization/Decarboxylative Tautomerization of DA Cyclopropanes with 2-Substituted Malononitriles



entry	**1**	**2**	major (**4**)	minor (**4′**)	time (min)	yld (%)	dr[a]
1	**1a**			-	40	81	>99:1
2	**1d**			-	30	85	>99:1
3	**1f**			-	35	85	>99:1
4	**1o**			-	15	87	>99:1

5	**1a**			-	40	82	>99:1
6	**1a**			-	35	84	>99:1
7	**1a**				35	85	1:0.86
8	**1d**			-	30	80	>99:1
9	**1f**				45	75	3:1
10	**1a**			-	45	81	>99:1
11	**1a**				40	86	1.32:1

12	**1d**			-	30	86	>99:1
13	**1e**			-	25	86	>99:1
14	**1g**			-	40	80	>99:1
15	**1h**			-	40	82	>99:1
16	**1k**			-	60	80	>99:1
17	**1n**			-	15	82	>99:1
18	**1o**				15	87	7:1

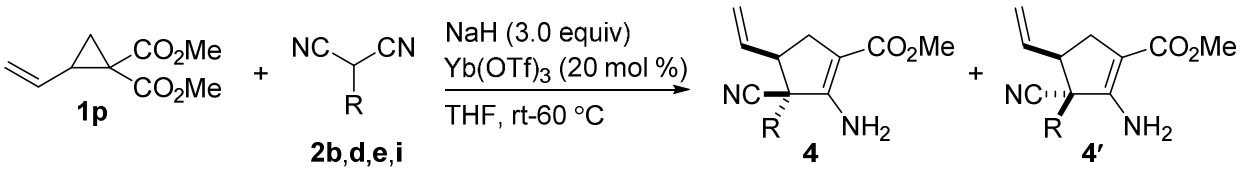
19	**1a**	 **2h**	 **4s**	 **4s′**	60	74	1:0.43
20[b]	**1a**	 **2i**	 **4t**	 **4t′**	60	76	9:1
21	**1a**	 **2j**	NR	NR	120	-	-

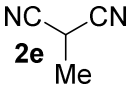
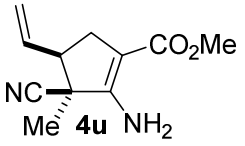
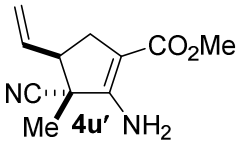
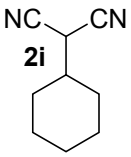
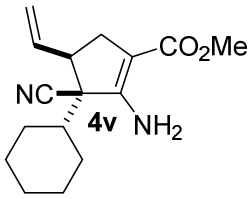
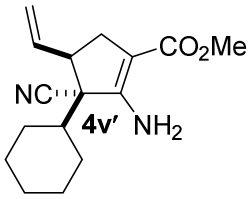
[a]The diastereomeric ratio have been determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Only the major diastereomer could be isolated.

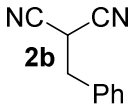
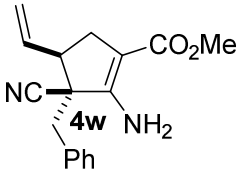
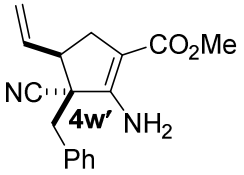
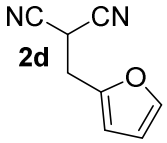
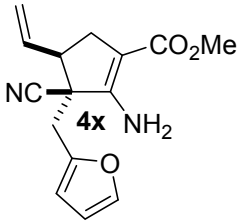
In order to obtain highly functionalizable carbocyclic *β*-enaminoesters utilizing our strategy, reactions of 2-vinyl substituted DA cyclopropane with substituted malononitriles were explored. A wide range of 2-substituted malononitriles containing various alkyl, cycloalkyl, aryl, and heteroaryl groups were deployed for this purpose and the results are detailed in Table 4. When **1p** was reacted with 2-methylmalononitrile (**2e**, 3.0 equiv) in the presence of 20 mol % $Yb(OTf)_3$ and 3.0 equiv of NaH in THF, the corresponding vinyl-substituted carbocyclic *β*-enaminoesters **4u** and **4u′** were obtained in good yields with good diastereoselectivity (dr 3.41:1, entry 1, Table 4). The relative stereochemistry at the 3 and 4-positions of the products were confirmed by single crystal X-ray analysis of both of these diastereomers.[21] Next, when cyclohexyl-substituted malononitrile derivative **2i** was reacted with **1p** under the optimized reaction conditions, the corresponding carbocyclic *β*-enaminoesters **4v** and **4v′** formed in good yields with moderate diastereomeric ratio (1.83:1, entry 2, Table 4). Based on our previous studies (Table 3) we attempted to improve the diastereoselectivity of the products by introducing a benzyl-substituted

malononitrile derivative as the pronucleophile. When **2b** together with **1p** were exposed to the optimized reaction conditions, the corresponding products **4w** and **4w′** were obtained in good yields with significantly increased diastereomeric ratio (6.18:1, entry 3, Table 4). Finally, excellent diastereoselectivity was observed when 2-furyl-substituted malononitrile derivative (**2d**) was reacted with **1p** and the corresponding carbocyclic *β*-enaminoester **4x** was obtained exclusively in good yield (dr >99:1, entry 4, Table 4).

Table 4. Synthesis of Highly Functionalizable Carbocyclic *β*-Enaminoesters via DROC/Decarboxylative Tautomerization of 2-Vinyl Substituted DA Cyclopropanes with Substituted Malononitriles



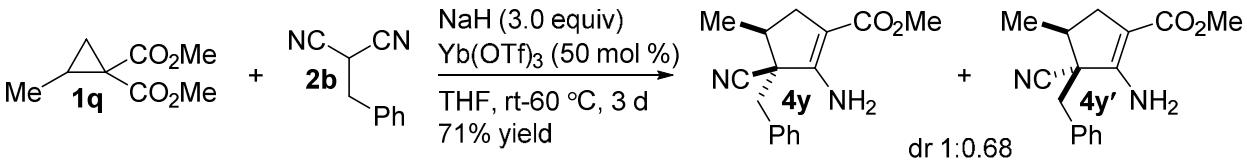
entry	malononitrile (**2**)	*β*-enaminoester (**4**)	*β*-enaminoester (**4′**)	time (min)	yield (%)	dr[a]
1				50	75	3.41:1
2[b]				75	72	1.83:1

3[b]				60	73	6.18:1
4			-	55	70	>99:1

[a]The diastereomeric ratio have been determined by analyzing the ^{1}H NMR spectra of the crude reaction mixture. [b]Only the major diastereomer could be isolated.

Next, we endeavored to synthesize highly substituted carbocyclic *β*-enaminoester via DROC/decarboxylative tautomerization of 2-methyl substituted DA cyclopropane **1q** with 2-benzyl malononitrile (**2b**, 3.0 equiv) in the presence of 50 mol % $Yb(OTf)_3$ and 3.0 equiv of NaH in THF at 60 °C. The reaction completed in 3 d and the corresponding products **4y** and **4y′** formed as a mixture of diastereomers in good combined yields (71%) with moderate diastereoselectivity (dr 1:0.68, Scheme 7).

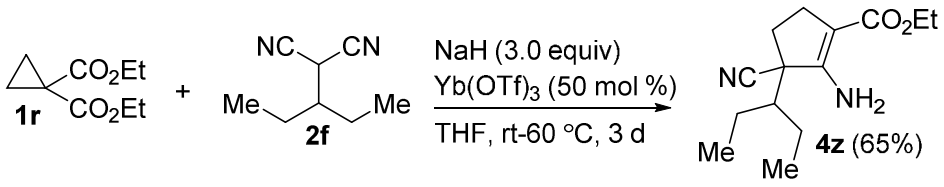
Scheme 7. Synthesis of Highly Substituted Carbocyclic *β*-Enaminoesters via DROC/Decarboxylative Tautomerization of 2-Methyl Substituted DA Cyclopropane with Substituted Malononitrile



Inspired by our result for the synthesis of enaminonitriles from acceptor cyclopropane, we subsequently studied the reaction of acceptor cyclopropane with 2-substituted malononitrile to

synthesize substituted carbocyclic *β*-enaminoester. When **1r** was reacted with 2-(pentan-3-yl)malononitrile (**2f**, 3.0 equiv) in the presence of 50 mol % $Yb(OTf)_3$ and 3.0 equiv of NaH in THF at 60 °C, the corresponding carbocyclic *β*-enaminoester **4z** was obtained after 3 d in relatively reduced yield (65%, Scheme 8).

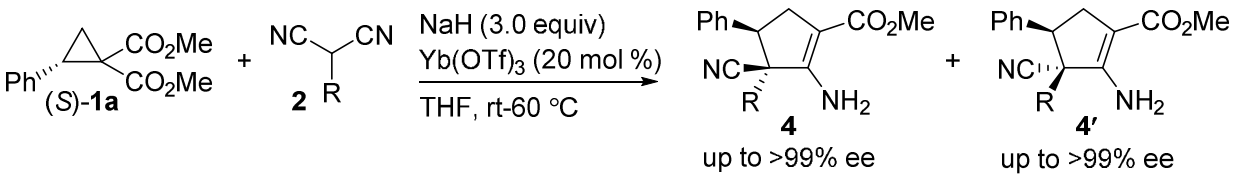
Scheme 8. Synthesis of Carbocyclic *β*-Enaminoester via DROC/Decarboxylative Tautomerization of Acceptor Cyclopropane with Substituted Malononitrile

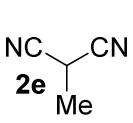
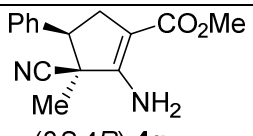
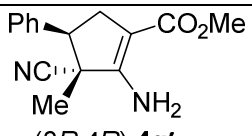


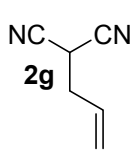
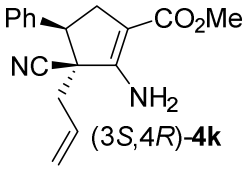
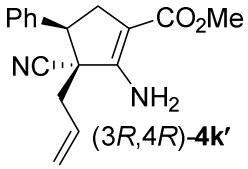
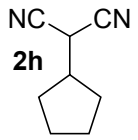
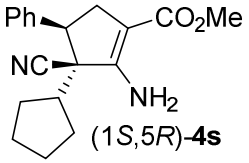
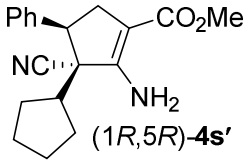
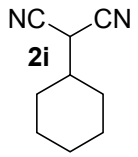
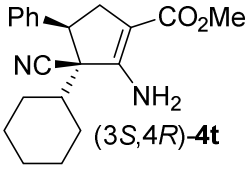
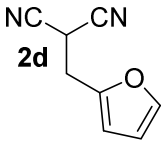
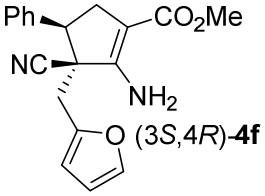
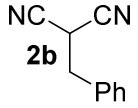
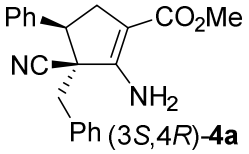
Finally, the synthetic significance of our strategy was demonstrated by developing the enantiospecific variant of the DROC/decarboxylative tautomerization protocol to obtain the carbocyclic *β*-enaminoesters in enantioenriched forms. When the enantiopure 2-phenyl DA-cyclopropane (*S*)-**1a** (>99% ee) was reacted with substituted malononitriles (**2**) under the optimized reaction conditions, the corresponding highly substituted carbocyclic *β*-enaminoesters **4** and **4′** were obtained with excellent ee. The results are summarized in Table 5 (*cf.* Table 3). When (*S*)-**1a** was reacted with 2-methylmalononitrile (**2e**, 3.0 equiv) in the presence of 20 mol % $Yb(OTf)_3$ and 3.0 equiv of NaH in THF at 60 °C, the corresponding products were obtained as a mixture of separable diastereomers (dr 1:0.86, see entry 1, Table 3). Both of the diastereomers, (3*S*,4*R*)-**4g** and (3*R*,4*R*)-**4g′**, were found to possess excellent enantiomeric excess (98% and >99% ee, respectively, entry 1, Table 5).[21] A marginal decrease in enantiopurity was observed in case of 2-allylmalononitrile (**2g**) wherein both of the diastereomers of the corresponding carbocyclic *β*-enaminoesters, (3*S*,4*R*)-**4k** and (3*R*,4*R*)-**4k′**, formed with 92% enantiomeric excess

(enantiospecificity 97%, entry 2, Table 5). When cyclopentyl-substituted malononitrile derivative **2h** was employed as the pronucleophile with (*S*)-**1a**, the corresponding products (1*S*,5*R*)-**4s** and (1*R*,5*R*)-**4s′** formed with 95% and 94% ee, respectively (enantiospecificities >99% and 99%, entry 3, Table 5). When (*S*)-**1a** was exposed to the optimized DROC/decarboxylative tautomerization conditions with 2-cyclohexylmalononitrile (**2i**), the corresponding major diastereomer of the carbocyclic *β*-enaminoester (3*S*,4*R*)-**4t** was obtained with 96% ee (enantiospecificity 98%, entry 4, Table 5). DROC/decarboxylative tautomerization of (*S*)-**1a** could be accomplished with malononitriles bearing either a 2-furyl group (**2d**) or a benzyl group (**2b**) at their 2-positions and the corresponding products (3*S*,4*R*)-**4f** and (3*S*,4*R*)-**4a**, respectively, formed as single diastereomers with >99% ee (entries 5 and 6, Table 5).

Table 5. Stereospecific Synthesis of Enantioenriched *β*-Enaminoesters via DROC/Decarboxylative Tautomerization of Enantiopure DA Cyclopropane with Substituted Malononitriles



entry	malononitrile (**2**)	*β*-enaminoester (**4**)	ee (%)[a]	es (%)[b]	*β*-enaminoester (**4′**)	ee (%)[a]	es (%)[b]	dr[c]
1	 **2e**	 (3*S*,4*R*)-**4g**	98	98	 (3*R*,4*R*)-**4g′**	>99	>99	1:0.86

2[d]	 **2g**	 (3*S*,4*R*)-**4k**	92	97	 (3*R*,4*R*)-**4k′**	92	97	1.32:1
3[d]	 **2h**	 (1*S*,5*R*)-**4s**	95	>99	 (1*R*,5*R*)-**4s′**	94	99	1:0.43
4[e]	 **2i**	 (3*S*,4*R*)-**4t**	96	98	-	-	-	9:1
5	 **2d**	 (3*S*,4*R*)-**4f**	>99	>99	-	-	-	>99:1
6	 **2b**	 (3*S*,4*R*)-**4a**	>99	>99	-	-	-	>99:1

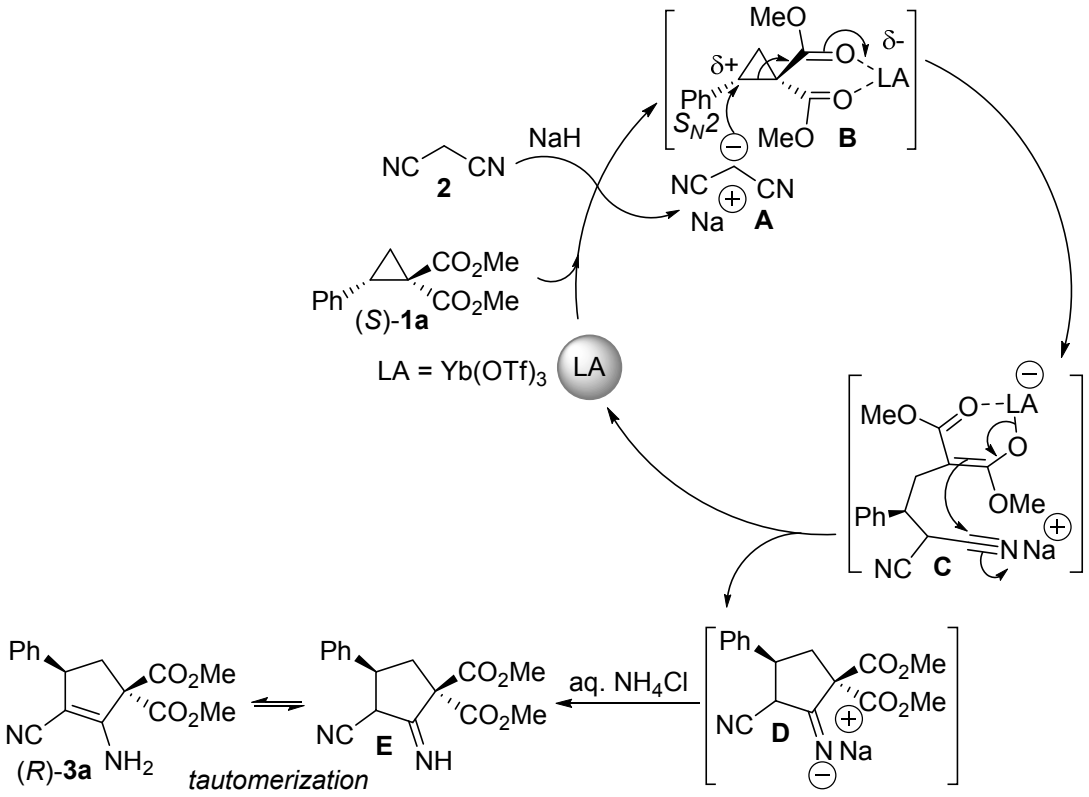
[a]Enantiomeric excesses have been determined by chiral HPLC analysis. [b]Enantiospecificity (es) = [ee of product / ee of starting material] × 100%. [c]The diastereomeric ratio have been determined by ^{1}H NMR analysis of the crude reaction mixture. [d]The enantiomeric excess of the starting material was 95%. [e]The enantiomeric excess of the starting material was 98%.

Mechanism

Based on our experimental observations and previous reports,[4e,17c] we have proposed two mechanistic pathways for the formation of the nonracemic carbocyclic enaminonitriles and *β*-enaminoesters. Scheme 9 depicts the mechanism of the enantiospecific formation of the

carbocyclic enaminonitriles from enantiopure DA cyclopropanes. At first, (*S*)-**1a** gets activated by the chelation of the Lewis acid, $Yb(OTf)_3$, with the two carbonyl oxygen atoms of the two ester (acceptor) groups (**B**). NaH abstracts a proton from the malononitrile to generate the naked anionic nucleophile **A** which subsequently attacks the benzylic position of the DA cyclopropane in an S_N2 fashion to generate the ring-opening intermediate **C**. Concomitant intramolecular cyclization and ring-closure in a *5-exo-dig* fashion in intermediate **C** generates another cyclic intermediate **D** which upon protonation and tautomerization furnishes the carbocyclic enaminonitrile (*R*)-**3a** as the final product in good yield.

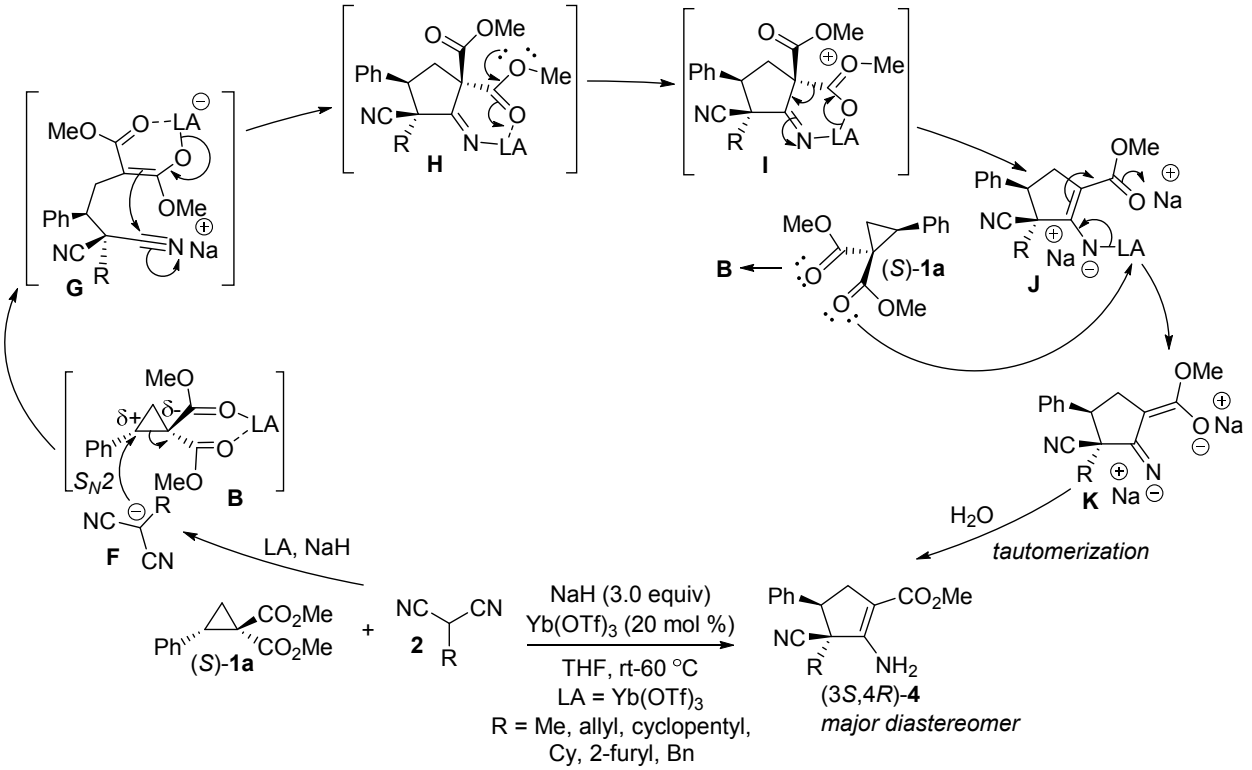
Scheme 9. Mechanistic Pathway for the Formation of Enantioenriched Carbocyclic Enaminonitrile via S_N2-Type DROC of Enantiopure DA Cyclopropane with Malononitrile



On the other hand, the formation of enantioenriched carbocyclic *β*-enaminoesters from enantiopure DA cyclopropanes follows a different and comparatively complex mechanistic

pathway as shown in Scheme 10.[17c] It is worth noting that a Lewis acid-catalyzed decarboxylation process takes place from the complex **H** which forms after the initial S_N2-type ring opening of the activated cyclopropane species (**B**) with the substituted malononitrile nucleophile (**F**) and concomitant ring-closure in a *5-exo-dig* fashion. Subsequently, the final product, five-membered carbocyclic *β*-enaminoester (3*S*,4*R*)-**4** is generated following a sequence of decarboxylation, protonation, and tautomerization of the corresponding synthetic intermediates.

Scheme 10. Mechanistic Pathway for the Formation of Enantioenriched Carbocyclic *β*-Enaminoesters via DROC/Decarboxylative Tautomerization of Enantiopure DA Cyclopropane with Substituted Malononitriles



Conclusion

We have developed simple synthetic strategies for the syntheses of carbocyclic enaminonitriles

and *β*-enaminoesters via domino ring-opening cyclization and domino ring-opening cyclization/decarboxylative tautomerization of donor-acceptor cyclopropanes, respectively, with malononitrile(s). We have generalized our approach employing a number of donor-acceptor cyclopropanes with different electron-donating groups or without any donor groups at the 2-position of DA cyclopropanes. We have successfully developed the enantiospecific variants of the aforementioned protocols to furnish the enaminonitriles and *β*-enaminoesters with excellent ee from enantiopure DA-cyclopropanes. We strongly believe that the synthetic strategies will find wide applications in synthetic organic and medicinal chemistry for accessing such valuable and functionalizable carbocyclic frameworks.

Experimental Section

General Procedures. Analytical thin layer chromatography (TLC) was carried out using silica gel 60 F_{254} precoated plates. Visualization was accomplished with UV lamp or I_2 strain. Silica gel 230-400 mesh size was used for flash chromatography using the combination of ethyl acetate and petroleum ether as eluent. Unless noted otherwise, all of the reactions were carried out in oven-dried glassware under an atmosphere of nitrogen/argon using anhydrous solvents. Where appropriate, all of the reagents were purified prior to use following the guidelines of Armarego and Chai.[22] Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate,[23] dimethyl (*S*)-2-phenylcyclopropane-1,1-dicarboxylate,[19] dimethyl 2-vinylcyclopropane-1,1-dicarboxylate,[14a] dimethyl 2-methylcyclopropane-1,1-dicarboxylate[20] and diethyl cyclopropane-1,1-dicarboxylate[20] were prepared using literature procedure. 2-Substituted malononitriles were synthesized using literature method.[17c,24] All of the other commercial reagents were used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 or 500

MHz. The chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), triplet (t), AB quartet (ABq), multiplet (m). Proton-decoupled carbon nuclear magnetic resonance (^{13}C{^{1}H} NMR) were recorded at 100 or 125 MHz. High resolution mass spectra (HRMS) were obtained using an ESI mass spectrometers (TOF). KBr plates were used for IR spectra of solid compounds, whereas liquid compounds were recorded neat. The melting point measurements were made using a hot-stage apparatus and are reported as uncorrected. The enantiomeric excess (ee) was determined by chiral HPLC using a Chiralcel OD-H or cellulose-2 column (detection at 254 nm). Optical rotations were measured using a 6.0 mL cell with 1.0 dm path length and are reported as $[\alpha]^{25}_{D}$ (*c* in g per 100 mL of solvent) at 25 °C. Diastereomeric ratio (dr) were determined by analysis of ^{1}H NMR spectra of the crude reaction mixtures.

General Experimental Procedure for the DROC and DROC/Decarboxylative Tautomerization of DA Cyclopropanes with Malononitrile and Substituted Malononitriles. *Method A*.[4e,17c] To a suspension of NaH (25.6 mg, 0.640 mmol, 3.0 equiv) in 0.5 mL THF, a THF solution (0.5 mL) of malononitrile derivative (for Scheme 2, 36 μL, 0.640 mmol, 3.0 equiv) was added and the reaction mixture was stirred at room temperature under argon atmosphere until the evolution of H_2 gas ceased. Then, appropriate racemic or enantiopure dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (for (*S*)-**1a**, Scheme 2, 50.0 mg, 0.213 mmol, 1.0 equiv) or dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (1.0 equiv) and $Yb(OTf)_3$ (26.5 mg, 0.043 mmol, 0.2 equiv) dissolved in THF (0.5 mL) were added sequentially to the reaction mixture at the same temperature and it was stirred at 60 °C until the reaction was complete. After complete consumption of the starting material (monitored by TLC) the reaction mixture was quenched by

saturated aqueous NH_4Cl solution. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with brine solution and dried over anhydrous sodium sulphate. After removal of the organic solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230–400 mesh) using 10–20% ethyl acetate in petroleum ether as the eluent to give the diastereomers in pure form.

Method B. To a suspension of NaH (34.8 mg, 0.871 mmol, 3.0 equiv) in 0.5 mL THF, a THF solution (0.5 mL) of malononitrile derivative (for Scheme 4, 48 μL, 0.871 mmol, 3.0 equiv) was added and the reaction mixture was stirred at room temperature under argon atmosphere until the evolution of H_2 gas ceased. Then, dimethyl 2-methylcyclopropane-1,1-dicarboxylate (for Scheme 4, 50.0 mg, 0.290 mmol, 1.0 equiv) or diethyl cyclopropane-1,1-dicarboxylate (1.0 equiv) and $Yb(OTf)_3$ (36.0 mg, 0.058 mmol, 0.5 equiv) dissolved in THF (0.5 mL) were added sequentially to the reaction mixture at the same temperature and it was stirred at 60 °C until the reaction was complete. After complete consumption of the starting material (monitored by TLC) the reaction mixture was quenched by saturated aqueous NH_4Cl solution. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with brine solution and dried over anhydrous sodium sulphate. After removal of the organic solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230–400 mesh) using 10–20% ethyl acetate in petroleum ether as the eluent to give the diastereomers in pure forms, wherever applicable.

The general method A described above was followed to prepare the enaminonitrile derivatives **3b**–**3o** and their data were provided in our previous report.[4e] The general method A described

above was also followed to prepare the enaminoester derivatives **4b**–**4d**, **4h**–**4i′** and **4l**–**4r′** and their data were provided in another of our previous report.[17c]

(R)-Dimethyl 2-amino-3-cyano-4-phenylcyclopent-2-ene-1,1-dicarboxylate ((R)-3a).[4e] The general method A described above was followed when (*S*)-**1a** (>99% ee, 50 mg, 0.213 mmol) was added to the mixture of **2a** (36 μL, 0.640 mmol) and NaH (25.6 mg, 0.640 mmol) followed by the addition of $Yb(OTf)_3$ (26.5 mg, 0.043mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 15 min to afford (*R*)-**3a** (45.5 mg, 0.188 mmol) in 88% yield as a white solid. mp 127–129 °C; $[\alpha]^{25}_{D}$ −58.7 (*c* 0.221 in CH_2Cl_2) for a >99% ee sample. Optical purity was determined by chiral HPLC analysis (Cellulose-2 column), hexane–2-propanol, 95:5; flow rate = 1.0 mL/min; t_R 1: 56.68 min (major): R_f 0.35 (ethyl acetate/petroleum ether, 2:3); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3459, 3360, 3275, 3232, 3028, 2956, 2923, 2851, 2196, 1737, 1647, 1603, 1495, 1454, 1435, 1393, 1354, 1279, 1212, 1078, 1066, 1030; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, J = 7.3 Hz, 2H), 7.26–7.22 (m, 3H), 5.16 (s, 2H), 4.12 (t, J = 7.8 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.01 (dd, J = 13.8, 7.7 Hz, 1H), 2.27 (dd, J = 13.7, 7.9 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.0, 168.5, 156.7, 141.9, 128.9, 127.5, 127.4, 117.0, 84.1, 64.9, 53.8, 53.5, 46.8, 41.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{16}N_2O_4$ 301.1188; Found 301.1180.

Dimethyl 2-amino-3-cyano-4-vinylcyclopent-2-ene-1,1-dicarboxylate (3p).[6] The general method A described above was followed when **1p** (50 mg, 0.271 mmol) was added to the mixture of **2a** (45 μL, 0.814 mmol) and NaH (32.6 mg, 0.814 mmol) followed by the addition of $Yb(OTf)_3$ (33.7 mg, 0.054 mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 40 min to afford **3p** (53.0 mg, 0.212 mmol) in 78% yield as a white solid. mp 65–67 °C; R_f 0.44 (ethyl acetate/petroleum ether, 1:1); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3460, 3360, 2956, 2925, 2854, 2196, 1739, 1650, 1461, 1378, 1278, 1211; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73–5.61 (m, 1H), 5.22–

5.08 (m, 2H), 5.02 (br s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.48 (dd, J = 15.1, 7.8 Hz, 1H), 2.75 (dd, J = 13.7, 7.3 Hz, 1H), 2.17 (dd, J = 13.7, 6.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.0, 168.6, 155.9, 138.6, 117.0, 116.8, 83.4, 64.9, 53.7, 53.5, 45.2, 38.1; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{15}N_2O_4$ 251.1026; Found 251.1030.

Dimethyl 2-amino-3-cyano-4-methylcyclopent-2-ene-1,1-dicarboxylate (3q). The general method B described above was followed when **1q** (50 mg, 0.290 mmol) was added to the mixture of **2a** (48 μL, 0.871 mmol) and NaH (34.8 mg, 0.871 mmol) followed by the addition of $Yb(OTf)_3$ (36.0 mg, 0.058 mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 3 d to afford **3q** (49.8 mg, 0.209 mmol) in 72% yield as a white solid. mp. 44–46 °C. R_f 0.47 (ethyl acetate/petroleum ether, 1:1); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3462, 3364, 3279, 3236, 2958, 2925, 2872, 2853, 2192, 1738, 1646, 1619, 1453, 1436, 1272, 1217, 1111, 1075; ^1H NMR (500 MHz, $CDCl_3$) δ 4.91 (br s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 2.97 (dd, J = 13.8, 6.9 Hz, 1H), 2.73 (dd, J = 13.8, 7.5 Hz, 1H), 1.96 (dd, J = 13.2, 7.5 Hz, 1H), 1.16 (d, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.2, 168.6, 155.0, 117.0, 86.0, 65.1, 53.5, 53.3, 35.6, 20.1, 19.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{15}N_2O_4$ 239.1026; Found 239.1034.

Diethyl 2-amino-3-cyanocyclopent-2-ene-1,1-dicarboxylate (3r). The general method B described above was followed when **1r** (50 mg, 0.269 mmol) was added to the mixture of **2a** (45 μL, 0.806 mmol) and NaH (32.2 mg, 0.806 mmol) followed by the addition of $Yb(OTf)_3$ (83.3 mg, 0.134 mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 3 d to afford **3r** (46.1 mg, 0.183 mmol) in 68% yield as a white solid. mp. 58–60 °C; R_f 0.30 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3357, 2982, 2193, 1731, 1644, 1268, 1218, 1160, 1066, 1012; ^1H NMR (400 MHz, $CDCl_3$) δ 4.97 (br s, 2H), 4.28–4.19 (m, 4H), 2.57–2.51 (m, 2H), 2.49–2.43 (m, 2H), 1.27 (t, J = 6.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.5,

156.3, 117.7, 79.4, 65.4, 62.6, 31.3, 28.3, 14.1; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{17}N_2O_4$ 253.1183; Found 253.1188.

Methyl (3S,4R)-2-amino-3-benzyl-3-cyano-4-phenylcyclopent-1-ene-1-carboxylate ((3S,4R)-4a).[17c] The general method A described above was followed when (*S*)-**1a** (>99% ee, 50 mg, 0.213 mmol) was added to the mixture of **2b** (100 mg, 0.640 mmol) and NaH (25.6 mg, 0.640 mmol) followed by the addition of $Yb(OTf)_3$ (26.5 mg, 0.043mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 40 min to afford (3*S*,4*R*)-**4a** (57.5 mg, 0.173 mmol) in 81% yield with >99:1 diastereomeric ratio. $[\alpha]^{25}_D$ −94.8 (*c* 0.067 in $CHCl_3$) for a >99% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane–2-propanol, 95:5; flow rate = 1.0 mL/min; t_R 1: 22.00 min (major): mp 157–159 °C; R_f 0.40 (ethyl acetate/petroleum ether, 2:3); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3435, 3405, 3325, 3252, 3192, 3087, 3061, 3030, 3004, 2948, 2863, 2234, 1676, 1647, 1632, 1575, 1496, 1442, 1329, 1284, 1251, 1185, 1121, 1082, 1031; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.33 (m, 5H), 7.31–7.26 (m, 2H); 7.16–7.14 (m, 2H), 5.64 (s, 2H), 3.75 (s, 3H), 3.37 (dd, J = 7.6, 3.4 Hz, 1H), 3.21 (d, J = 13.8 Hz, 1H), 3.18 (d, J = 13.7 Hz, 1H), 2.90–2.86 (m, 1H), 2.81–2.77 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.6, 156.0, 140.9, 134.3, 130.5, 128.8, 128.1, 128.0, 127.8, 118.8, 96.2, 57.7, 51.0, 49.2, 43.7, 34.5; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{20}NaN_2O_2$ 355.1422; Found 355.1422.

Methyl 2-amino-3-cyano-3-(4-methylbenzyl)-4-phenylcyclopent-1-ene-1-carboxylate (4e). The general method A described above was followed when **1a** (50 mg, 0.213 mmol) was added to the mixture of **2c** (109 mg, 0.640 mmol) and NaH (25.6 mg, 0.640 mmol) followed by the addition of $Yb(OTf)_3$ (26.5 mg, 0.043 mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 40 min to afford **4e** (60.6 mg, 0.175 mmol) in 82% yield with >99:1 diastereomeric

ratio. mp 174–176 °C; R_f 0.45 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3436, 3339, 3027, 2924, 2856, 1680, 1637, 1562, 1442, 1288, 1247, 1187, 1108; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5H), 7.19–7.10 (m, 4H), 5.62 (br s, 2H), 3.75 (s, 3H), 3.37 (dd, J = 7.5, 3.4 Hz, 1H), 3.15 (s, 2H), 2.90 (dd, J = 14.9, 8.0 Hz, 1H), 2.80 (dd, J = 14.9, 3.4 Hz, 1H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.6, 156.1, 140.9, 137.8, 131.2, 130.3, 129.5, 128.8, 127.95, 127.89, 118.8, 96.1, 57.7, 51.0, 49.3, 43.3, 34.5, 21.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{23}N_2O_2$ 347.1754; Found 347.1751.

Methyl (3S,4R)-2-amino-3-cyano-3-(furan-2-ylmethyl)-4-phenylcyclopent-1-ene-1-carboxylate ((3S,4R)-4f). The general method A described above was followed when (*S*)-**1a** (>99% ee, 50 mg, 0.213 mmol) was added to the mixture of **2d** (93.6 mg, 0.640 mmol) and NaH (25.6 mg, 0.640 mmol) followed by the addition of $Yb(OTf)_3$ (26.5 mg, 0.043 mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 35 min to afford (3*S*,4*R*)-**4f** (57.8 mg, 0.179 mmol) in 84% yield with >99:1 diastereomeric ratio. White solid; mp 142–144 °C; $[\alpha]^{25}_D$ −45.3 (*c* 0.212 in $CHCl_3$) for a >99% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane–2-propanol, 95:5; flow rate = 1.0 mL/min; t_R 1: 9.57 min (minor), t_R 2: 10.21 min (major): R_f 0.37 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3439, 3342, 3030, 2950, 2866, 2235, 1681, 1638, 1566, 1498, 1443, 1285, 1246, 1189, 1113, 1081; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 1.8 Hz, 1H), 7.36–7.22 (m, 5H), 6.41–6.28 (m, 2H), 5.78 (br s, 2H), 3.74 (s, 3H), 3.43–3.39 (m, 1H), 3.22 (ABq, J = 23.1, 15.0 Hz, 2H), 2.88 (ABq, J = 24.0, 15.0 Hz, 1H), 2.87 (ABq, J = 14.5, 10.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.6, 155.2, 148.7, 142.7, 139.7, 128.8, 128.2, 128.1, 118.4, 111.0, 110.0, 96.9, 56.4, 51.0, 49.5, 35.0, 34.1; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ Calcd for $C_{19}H_{18}N_2NaO_3$ 345.1210; Found 345.1214.

Methyl 2-amino-3-cyano-3-methyl-4-phenylcyclopent-1-ene-1-carboxylate (4g and 4g'). The general method A described above was followed when (*S*)-**1a** (>99% ee, 50 mg, 0.213 mmol) was added to the mixture of **2e** (51.3 mg, 0.640 mmol) and NaH (25.6 mg, 0.640 mmol) followed by the addition of $Yb(OTf)_3$ (26.5 mg, 0.043 mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 35 min to afford (3*S*,4*R*)-**4g** and (3*R*,4*R*)-**4g′** in 85% yield (46.5 mg, 0.181 mmol) with 1:0.86 diastereomeric ratio. The diastereomers were separated by flash column chromatography using 15% ethyl acetate in petroleum ether as the eluent. ***Major diastereomer ((3S,4R)-4g).*** White solid; mp 144–146 °C; $[\alpha]^{25}_{D}$ −69.8 (*c* 0.186 in CH_2Cl_2) for a 98% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane–2-propanol, 95:5; flow rate = 1.0 mL/min; t_R 1: 18.75 min (minor), t_R 2: 29.82 min (major): R_f 0.34 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3440, 3342, 3030, 2985, 2950, 2967, 2235, 1681, 1634, 1564, 1443, 1285, 1248, 1189, 1094; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (m, 5H), 5.71 (br s, 2H), 3.74 (s, 3H), 3.18 (t, J = 7.3 Hz, 1H), 2.97–2.88 (m, 2H), 1.60 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.7, 156.2, 138.7, 128.8, 128.5, 128.2, 119.5, 96.3, 53.3, 51.0, 50.9, 33.7, 22.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{17}N_2O_2$ 257.1285; Found 257.1270. ***Minor diastereomer ((3R,4R)-4g').*** White solid; mp 148–150 °C; $[\alpha]^{25}_{D}$ −40.0 (*c* 0.150 in CH_2Cl_2) for a >99% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane–2-propanol, 95:5; flow rate = 1.0 mL/min; t_R 1: 14.59 min (major), t_R 2: 16.02 min (minor): R_f 0.44 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3422, 3327, 3253, 3197, 2980, 2951, 2924, 2865, 2242, 1675, 1634, 1580, 1443, 1289, 1249, 1190, 1103; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.30 (m, 5H), 5.74 (br s, 2H), 3.83 (dd, J = 10.0, 7.9 Hz, 1H), 3.75 (s, 3H), 2.93 (dd, J = 14.2, 10.2 Hz, 1H), 2.84 (dd, J = 14.3, 8.0 Hz, 1H), 1.13 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.7, 157.8, 136.2, 128.7, 128.4,

127.9, 121.6, 94.6, 50.9, 50.8, 48.4, 30.2, 19.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{17}N_2O_2$ 257.1285; Found 257.1291.

Methyl 2-amino-3-cyano-3-(pentan-3-yl)-4-phenylcyclopent-1-ene-1-carboxylate (4j). The general method A described above was followed when **1a** (50 mg, 0.213 mmol) was added to the mixture of **2f** (87.2 mg, 0.640 mmol) and NaH (25.6 mg, 0.640 mmol) followed by the addition of $Yb(OTf)_3$ (26.5 mg, 0.043 mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 45 min to afford **4j** (54.0 mg, 0.173 mmol) in 81% yield with >99:1 diastereomeric ratio. White solid; mp 104–106 °C; R_f 0.50 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3438, 3340, 3029, 2960, 2926, 2874, 2235, 1738, 1682, 1637, 1564, 1496, 1442, 1288, 1246, 1188, 1099; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.18 (m, 5H), 5.78 (br s, 2H), 3.75 (s, 3H), 3.36 (dd, J = 8.2, 3.2 Hz, 1H), 2.98 (dd, J = 15.1, 8.2 Hz, 1H), 2.77 (dd, J = 15.1, 3.2 Hz, 1H), 1.80–1.48 (m, 4H), 1.48–1.34 (m, 1H), 1.11–0.97 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.5, 155.8, 142.5, 128.8, 127.84, 127.80, 119.5, 97.3, 62.1, 51.0, 48.9, 46.4, 36.7, 24.8, 23.6, 13.7, 13.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{25}N_2O_2$ 313.1911; found 313.1911.

Methyl 3-allyl-2-amino-3-cyano-4-phenylcyclopent-1-ene-1-carboxylate (4k and 4k'). The general method A described above was followed when (*S*)-**1a** (95% ee, 50 mg, 0.213 mmol) was added to the mixture of **2g** (68.0 mg, 0.640 mmol) and NaH (25.6 mg, 0.640 mmol) followed by the addition of $Yb(OTf)_3$ (26.5 mg, 0.043 mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 40 min to afford (3*S*,4*R*)-**4k** and (3*R*,4*R*)-**4k′** in 86% yield (51.8 mg, 0.184 mmol) with 1.32:1 diastereomeric ratio. The diastereomers were separated by flash column chromatography using 10–20% ethyl acetate in petroleum ether as the eluent. ***Major diastereomer ((3S,4R)-4k).*** White solid; mp 94–96 °C; $[\alpha]^{25}_D$ −38.1 (*c* 0.341 in CH_2Cl_2) for a

92% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane–2-propanol, 95:5; flow rate = 1.0 mL/min; t_R 1: 13.07 min (minor), t_R 2: 17.85 min (major): R_f 0.40 (ethyl acetate/petroleum ether, 3:7). IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3438, 3340, 3029, 2948, 2862, 2236, 1680, 1637, 1561, 1496, 1443, 1285, 1243, 1188, 1106; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H), 5.98–5.85 (m, 1H), 5.78 (br s, 2H), 5.40–5.32 (m, 2H), 3.74 (s, 3H), 3.33 (dd, J = 7.3, 5.5 Hz, 1H), 2.94 (dd, J = 15.1, 7.8 Hz, 1H), 2.86 (dd, J = 15.1, 6.0 Hz, 1H), 2.68–2.59 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.6, 155.5, 139.7, 131.5, 128.9, 128.3, 128.1, 121.7, 118.5, 96.6, 55.4, 51.0, 49.5, 40.9, 34.2; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{18}N_2NaO_2$ 305.1260; Found 305.1266. ***Minor diastereomer ((3R,4R)-4k').*** White solid; mp 112–114 °C; $[\alpha]^{25}_D$ −103.2 (*c* 0.116 in CH_2Cl_2) for a 92% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane–2-propanol, 95:5; flow rate = 1.0 mL/min; t_R 1: 12.55 min (major), t_R 2: 16.69 min (minor): R_f 0.44 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3437, 3340, 2948, 2866, 2237, 1679, 1637, 1560, 1443, 1302, 1247, 1188, 1107; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.28 (m, 5H), 6.05–5.36 (m, 3H), 5.18–5.03 (m, 2H), 3.91 (dd, J = 10.1, 7.8 Hz, 1H), 3.74 (s, 3H), 2.97 (dd, J = 14.2, 10.1 Hz, 1H), 2.81 (dd, J = 14.2, 7.8 Hz, 1H), 2.15 (dd, J = 13.7, 7.8 Hz, 1H), 1.97 (dd, J = 13.7, 6.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.9, 157.1, 136.1, 131.2, 128.8, 128.6, 128.1, 121.2, 120.4, 94.8, 52.9, 51.7, 51.0, 37.1, 30.2; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{18}N_2NaO_2$ 305.1260; Found 305.1261.

Methyl 2-amino-1-cyano-5-phenyl-[1,1'-bi(cyclopentan)]-2-ene-3-carboxylate (4s and 4s'). The general method A described above was followed when (*S*)-**1a** (95% ee, 50 mg, 0.213 mmol) was added to the mixture of **2h** (85.9 mg, 0.640 mmol) and NaH (25.6 mg, 0.640 mmol) followed by the addition of $Yb(OTf)_3$ (26.5 mg, 0.043mmol) in 2 mL THF at rt and then the

reaction mixture was stirred at 60 °C for 1 h to afford (1*S*,5*R*)-**4s** and (1*R*,5*R*)-**4s′** in 74% yield (49.0 mg, 0.158 mmol) with 1:0.43 diastereomeric ratio. The diastereomers were separated by flash column chromatography using 10–20% ethyl acetate in petroleum ether as the eluent. ***Major diastereomer ((1S,5R)-4s).*** White solid; mp 108–110 °C; $[\alpha]^{25}_{D}$ −31.53 (*c* 0.159 in CH_2Cl_2) for a 95% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane–2-propanol, 95:5; flow rate = 1.0 mL/min; t_R 1: 10.73 min (minor), t_R 2: 13.41 min (major): R_f 0.47 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3438, 3340, 3063, 3029, 2958, 2870, 2238, 1737, 1680, 1634, 1557, 1496, 1443, 1288, 1261, 1244, 1190, 1106, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.21 (m, 5H), 5.81 (br s, 2H), 3.74 (s, 3H), 3.39–3.35 (m, 1H), 3.03 (dd, *J* = 15.1, 7.8 Hz, 1H), 2.76 (dd, *J* = 15.1, 1.8 Hz, 1H), 2.38–2.29 (m, 1H), 2.01–1.90 (m, 2H), 1.78–1.51 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.8, 156.8, 142.4, 128.9, 127.9, 127.5, 118.3, 95.6, 61.1, 51.0, 48.8, 47.6, 35.3, 29.5, 29.3, 25.5, 24.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{23}N_2O_2$ 311.1754; Found 311.1751. ***Minor diastereomer ((1R,5R)-4s').*** White solid; mp 126–128 °C; $[\alpha]^{25}_{D}$ −22.95 (*c* 0.087 in CH_2Cl_2) for a 94% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane–2-propanol, 95:5; flow rate = 1.0 mL/min; t_R 1: 10.63 min (major), t_R 2: 16.40 min (minor): R_f 0.51 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3436, 3337, 3030, 2953, 2925, 2871, 2856, 2236, 1735, 1681, 1634, 1557, 1499, 1444, 1286, 1247, 1189, 1105; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.40 (m, 2H), 7.39–7.28 (m, 3H), 5.88 (br s, 2H), 3.91 (dd, *J* = 10.5, 7.8 Hz, 1H), 3.74 (s, 3H), 2.98 (dd, *J* = 14.2, 10.5 Hz, 1H), 2.74 (dd, *J* = 14.2, 7.8 Hz, 1H), 1.91–1.80 (m, 1H), 1.75–1.56 (m, 2H), 1.49–1.38 (m, 1H), 1.37–1.21 (m, 3H), 1.20–1.07 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.9, 157.1, 137.0, 128.8, 128.5, 128.0, 120.9, 95.7,

56.6, 52.5, 50.9, 42.0, 30.4, 29.8, 29.1, 24.8, 24.2, HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{23}N_2O_2$ 311.1754; Found 311.1759.

Methyl (3S,4R)-2-amino-3-cyano-3-cyclohexyl-4-phenylcyclopent-1-ene-1-carboxylate ((3S,4R)-4t). The general method A described above was followed when (*S*)-**1a** (98% ee, 50 mg, 0.213 mmol) was added to the mixture of **2i** (94.9 mg, 0.640 mmol) and NaH (25.6 mg, 0.640 mmol) followed by the addition of $Yb(OTf)_3$ (26.5 mg, 0.043 mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 1 h to afford (3*S*,4*R*)-**4t** and (3*R*,4*R*)-**4t′** in 76% yield (52.6 mg, 0.162 mmol) with 9:1 diastereomeric ratio. The major diastereomer was isolated by flash column chromatography using 10–20% ethyl acetate in petroleum ether as the eluent. White solid; mp 138–140 °C; $[\alpha]^{25}_D$ −54.5 (*c* 0.349 in CH_2Cl_2) for a 96% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane–2-propanol, 95:5; flow rate = 1.0 mL/min; t_R 1: 8.95 min (minor), t_R 2: 11.95 min (major): R_f 0.49 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3436, 3339, 3028, 2928, 2856, 2235, 1735, 1681, 1635, 1564, 1496, 1443, 1290, 1242, 1190, 1114; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.18 (m, 5H), 5.77 (br s, 2H), 3.75 (s, 3H), 3.41 (dd, *J* = 8.2, 2.3 Hz, 1H), 2.98 (dd, *J* = 15.1, 8.2 Hz, 1H), 2.76 (dd, *J* = 15.1, 2.3 Hz, 1H), 2.06–1.68 (m, 6H), 1.40–1.12 (m, 5H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.5, 155.2, 142.8, 128.8, 127.8, 127.6, 118.8, 96.8, 62.4, 51.0, 46.1, 45.6, 36.6, 28.8, 27.9, 26.3, 26.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{25}N_2O_2$ 325.1911; Found 325.1915.

Methyl 2-amino-3-cyano-3-methyl-4-vinylcyclopent-1-ene-1-carboxylate (4u and 4u'). The general method A described above was followed when **1p** (50 mg, 0.271 mmol) was added to the mixture of **2e** (65.2 mg, 0.814 mmol) and NaH (32.6 mg, 0.814 mmol) followed by the addition of $Yb(OTf)_3$ (33.7 mg, 0.054 mmol) in 2 mL THF at rt and then the reaction mixture was stirred

at 60 °C for 50 min to afford **4u** and **4u′** in 75% yield (42.0 mg, 0.204 mmol) with 3.41:1 diastereomeric ratio. The diastereomers were separated by flash column chromatography using 10–20% ethyl acetate in petroleum ether as the eluent. ***Major diastereomer (4u).*** White solid; mp 128–130 °C; R_f 0.35 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3453, 3332, 3241, 3080, 2954, 2925, 2854, 2230, 1678, 1648, 1566, 1463, 1445, 1423, 1284, 1254, 1215, 1189, 1153, 1080; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02–5.92 (m, 1H), 5.63 (br s, 2H), 5.27–5.21 (m, 2H), 3.72 (s, 3H), 2.71 (dd, J = 13.8, 6.9 Hz, 1H), 2.58 (dd, J = 15.5, 7.5 Hz, 1H), 2.51 (dd, J = 13.8, 7.5 Hz, 1H), 1.52 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 167.7, 156.2, 135.9, 119.3, 119.1, 96.3, 52.1, 50.9, 48.9, 33.0, 21.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{15}N_2O_2$ 207.1128; Found 207.1137. ***Minor diastereomer (4u').*** White solid; mp 126–128 °C. R_f 0.46 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3412, 3325, 3249, 3188, 3079, 2924, 2851, 2251, 1682, 1651, 1575, 1460, 1441, 1285, 1249, 1195, 1092; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90–5.78 (m, 1H), 5.67 (br s, 2H), 5.36–5.22 (m, 2H), 3.71 (s, 3H), 3.14 (dd, J = 17.2, 8.0 Hz, 1H), 2.69 (dd, J = 14.3, 8.0 Hz, 1H), 2.41 (dd, J = 13.8, 9.2 Hz, 1H), 1.37 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 167.7, 158.2, 133.7, 121.2, 119.6, 94.7, 50.9, 49.8, 47.9, 31.4, 18.8; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{11}H_{15}N_2O_2$ 207.1128; Found 207.1133.

Methyl 2-amino-3-cyano-3-cyclohexyl-4-vinylcyclopent-1-ene-1-carboxylate (4v). The general method A described above was followed when **1p** (50 mg, 0.271 mmol) was added to the mixture of **2i** (120.7 mg, 0.814 mmol) and NaH (32.6 mg, 0.814 mmol) followed by the addition of $Yb(OTf)_3$ (33.7 mg, 0.054 mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 75 min to afford **4v** and **4v′** (53.6 mg, 0.195 mmol) in 72% yield as a white solid with 1.83:1 diastereomeric ratio. The major diastereomer was isolated by flash column chromatography using 10–20% ethyl acetate in petroleum ether as the eluent. mp. 88–90 °C; R_f

0.53 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3439, 3339, 3188, 3081, 2931, 2856, 2672, 2234, 1681, 1633, 1565, 1443, 1288, 1254, 1189, 1117; ^1H NMR (500 MHz, $CDCl_3$) δ 5.98–5.82 (m, 1H), 5.68 (br s, 2H), 5.19–5.07 (m, 2H), 3.71 (s, 3H), 2.93–2.83 (m, 1H), 2.78–2.67 (m, 1H), 2.40 (dd, J = 14.9, 4.0 Hz, 1H), 2.06–1.62 (m, 6H), 1.42–1.05 (m, 5H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.7, 155.0, 138.6, 118.9, 117.1, 96.4, 59.3, 50.9, 44.7, 44.2, 34.5, 28.6, 27.8, 26.4, 26.3, 26.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{23}N_2O_2$ 275.1754; Found 275.1752.

Methyl 2-amino-3-benzyl-3-cyano-4-vinylcyclopent-1-ene-1-carboxylate (4w). The general method A described above was followed when **1p** (50 mg, 0.271 mmol) was added to the mixture of **2b** (127.2 mg, 0.814 mmol) and NaH (32.6 mg, 0.814 mmol) followed by the addition of $Yb(OTf)_3$ (33.7 mg, 0.054 mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 60 min to afford **4w** and **4w′** in 73% yield (56.0 mg, 0.198 mmol) with 6.18:1 diastereomeric ratio. The major diastereomer was isolated by flash column chromatography using 10–20% ethyl acetate in petroleum ether as the eluent. White solid; mp. 112–114 °C; R_f 0.46 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3437, 3339, 3064, 3030, 2949, 2856, 2233, 1679, 1637, 1562, 1443, 1288, 1252, 1189, 1116, 1085; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (m, 5H), 5.90–5.81 (m, 1H), 5.56 (br s, 2H), 5.17–5.07 (m, 2H), 3.70 (s, 3H), 3.09 (ABq, J = 21.1, 14.2 Hz, 2H), 2.80–2.75 (m, 1H), 2.65 (dd, J = 14.7, 7.3 Hz, 1H), 2.43 (dd, J = 14.2, 4.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.8, 155.7, 136.7, 134.1, 130.4, 128.8, 128.1, 118.8, 118.3, 95.9, 55.0, 50.9, 48.6, 42.0, 33.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{19}N_2O_2$ 283.1441; Found 283.1440.

Methyl 2-amino-3-cyano-3-(furan-2-ylmethyl)-4-vinylcyclopent-1-ene-1-carboxylate (4x). The general method A described above was followed when **1p** (50 mg, 0.271 mmol) was added to the

mixture of **2d** (119.0 mg, 0.814 mmol) and NaH (32.6 mg, 0.814 mmol) followed by the addition of $Yb(OTf)_3$ (33.7 mg, 0.054 mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 55 min to afford **4x** (51.7 mg, 0.190 mmol) in 70% yield as a white solid with >99:1 diastereomeric ratio. mp. 96–98 °C; R_f 0.40 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3441, 3341, 2950, 2854, 2236, 1680, 1635, 1564, 1444, 1290, 1252, 1189, 1115, 1010; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.37 (m, 1H), 6.36–6.34 (m, 1H), 6.32–6.29 (m, 1H), 5.91 (ddd, J = 16.9, 10.1, 8.7 Hz, 1H), 5.79 (br s, 2H), 5.24–5.15 (m, 2H), 3.70 (s, 3H), 3.13 (s, 2H), 2.77 (dd, J = 16.0, 7.3 Hz, 1H), 2.67 (dd, J = 14.2, 7.3 Hz, 1H), 2.48 (dd, J = 14.7, 6.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.7, 155.3, 148.6, 142.7, 136.0, 119.1, 118.1, 111.0, 110.0, 96.6, 53.8, 51.0, 49.2, 33.6, 32.9; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{16}N_2NaO_3$ 295.1053; Found 295.1060.

Methyl 2-amino-3-benzyl-3-cyano-4-methylcyclopent-1-ene-1-carboxylate (4y and 4y'). The general method B described above was followed when **1q** (50 mg, 0.290 mmol) was added to the mixture of **2b** (136 mg, 0.871 mmol) and NaH (34.8 mg, 0.871 mmol) followed by the addition of $Yb(OTf)_3$ (36.0 mg, 0.058 mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 3 d to afford **4y** and **4y′** in 71% yield (55.7 mg, 0.206 mmol) with 1:0.68 diastereomeric ratio. The diastereomers were separated by flash column chromatography using 10–20% ethyl acetate in petroleum ether as the eluent. ***Major diastereomer (4y).*** White solid; mp. 86–88 °C; R_f 0.43 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3433, 3338, 3087, 3063, 3029, 2965, 2949, 2871, 2835, 2234, 1676, 1636, 1564, 1443, 1296, 1253, 1188, 1105, 1083; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 5.53 (br s, 2H), 3.70 (s, 3H), 3.04 (dd, J = 32.5, 13.7 Hz, 2H), 2.64 (dd, J = 14.2, 6.9 Hz, 1H), 2.35–2.24 (m, 1H), 2.18 (dd, J = 14.2, 3.7 Hz, 1H), 1.10 (d, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.1, 156.1,

134.4, 130.3, 128.7, 127.9, 119.0, 95.5, 55.7, 50.9, 42.6, 38.2, 34.8, 18.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O_2$ 271.1441; Found 271.1440. ***Minor diastereomer (4y').*** White solid; mp 130–132 °C; R_f 0.46 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3480, 3344, 2950, 2846, 2236, 1678, 1631, 1554, 1443, 1303, 1261, 1231, 1188, 1139, 1119, 1100, 1065; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5H), 5.08 (br s, 2H), 3.70 (s, 3H), 3.01 (d, J = 13.3 Hz, 1H), 2.74 (d, J = 13.3 Hz, 1H), 2.84–2.62 (m, 2H), 2.28 (dd, J = 13.7, 10.1 Hz, 1H), 1.28 (d, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.9, 158.3, 134.6, 130.4, 128.7, 127.9, 120.6, 94.8, 53.2, 50.8, 43.3, 37.2, 34.0, 13.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O_2$ 271.1441; Found 271.1451.

Ethyl 2-amino-3-cyano-3-(pentan-3-yl)cyclopent-1-ene-1-carboxylate (4z). The general method B described above was followed when **1r** (50 mg, 0.269 mmol) was added to the mixture of **2f** (109.7 mg, 0.806 mmol) and NaH (32.2 mg, 0.806 mmol) followed by the addition of $Yb(OTf)_3$ (83.3 mg, 0.134 mmol) in 2 mL THF at rt and then the reaction mixture was stirred at 60 °C for 3 d to afford **4z** (43.7 mg, 0.175 mmol) in 65% yield as a white solid. mp 92–94 °C; R_f 0.45 (ethyl acetate/petroleum ether, 3:7); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3442, 3340, 2964, 2927, 2875, 2233, 1743, 1680, 1634, 1564, 1466, 1299, 1274, 1232, 1099; ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 (br s, 2H), 4.21–4.13 (m, 2H), 2.64–2.57 (m, 1H), 2.52–2.45 (m, 1H), 2.22–2.15 (m, 1H), 2.07–1.99 (m, 1H), 1.80–1.70 (m, 1H), 1.61–1.46 (m, 2H), 1.42–1.32 (m, 1H), 1.32–1.16 (m, 1H), 1.27 (t, J = 7.3 Hz, 3H), 1.05 (t, J = 7.8 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.5, 155.8, 122.1, 98.7, 59.5, 54.0, 46.3, 29.6, 27.4, 24.7, 22.4, 14.6, 13.6, 12.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{23}N_2O_2$ 251.1754; Found 251.1761.

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Supporting Information

Copies of NMR spectra for all the compounds, HPLC chromatograms for ee determination and X-ray crystallographic data (CIF) of **4k** (CCDC 1567533), **4k′** (CCDC 1567532), **4u** (CCDC 1568659) and **4u′** (CCDC 1567531). This material is available free of charge via the internet at http://pubs.acs.org.

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