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Lithium Chloride-Mediated Stereoselective Synthesis of Cyclopropanecarboxamides from γ,δ-Epoxy Malonates through a Domino Cyclopropanation/Lactonization/Aminolysis Process

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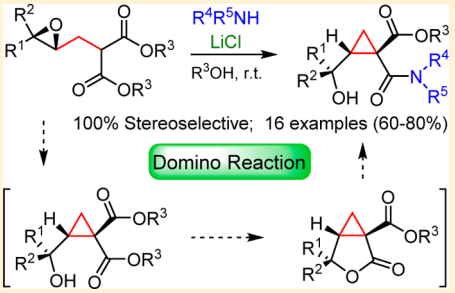
Supporting Information

ABSTRACT: The stereoselective synthesis of novel multifunctionalized cyclopropanes from γ,δ-epoxy malonates and amines mediated by LiCl under mild conditions was carried out. This domino reaction involves the initial cyclopropanation via intramolecular ring-opening of γ,δ-epoxy malonates through the cooperative catalysis of LiCl (acting as a Lewis acid) and a Brønsted base (a primary or, in selected cases, a secondary amine). The sequential events consisted of lactonization and aminolysis of the lactone ring, which ultimately furnished cyclopropanecarboxamides with different substitution patterns in good isolated yields. In all cases, a quaternary stereogenic center could be perfectly assembled, with a single diastereoisomer being obtained. This method proceeds with high atom economy, is remarkably modular and operationally simple, and tolerates a variety of functional groups. The involvement of readily available starting materials, the broad scope, and the use of a sustainable solvent (methanol or ethanol) at ambient temperature make this domino process highly effective. A reaction mechanism is proposed on the basis of the experimental observations involving the preparation and reactivity of cyclopropylidene lactones as possible intermediates of the domino process.

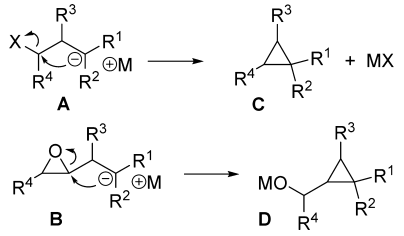


INTRODUCTION

Densely functionalized cyclopropanes are of prime importance, not only as versatile building blocks for the synthesis of various natural products[1−3] but also as biologically active substances in medicinal chemistry,[4−7] including cyclopropyl-containing amino acids and derivatives with constrained conformational flexibility.[8,9] The high strain associated with the three-membered carbocycle framework confers to this class of compounds unique reactivity toward nucleophiles, electrophiles, and radical species. Furthermore, cyclopropanes simultaneously substituted with electron-withdrawing and electron-releasing groups are known to undergo cycloaddition reactions,[10−14] leading to products with high diastereoselectivity.

Due to the interest in the chemistry of functionalized cyclopropanes, a variety of methods describing the preparation of these strained carbocycles have recently been reported in the literature.[15−19] One of the most commonly used approaches is based on intramolecular nucleophilic substitution (S_N) reactions involving the attack of a carbanion-like nucleophile on a pre-existing electrophilic site, these two reaction centers being separated by one carbon atom. While this strategy has been successfully explored with substrate **A** containing different "X" leaving groups[20−22] and also with epoxides of the **B** type[23−27] (Scheme 1), the need for the use of strong bases or sensitive organometallic reagents in an anhydrous environment is a serious restriction in terms of its wider application. Furthermore, in many circumstances the availability of the starting materials poses a challenge, the structural diversity is limited to a few examples, and the stereoselectivity related to the resulting substituted cyclopropane is only moderate.

Scheme 1. Schematic Preparation of Cyclopropanes through Intramolecular S_N-Type Reactions



Therefore, the stereocontrolled synthesis of multisubstituted cyclopropanes under mild conditions to facilitate access to this distinctive class of carbocycles is of particular significance. Herein, we describe the development of a stereoselective methodology to synthesize novel multifunctionalized cyclopropanes from (±)-γ,δ-epoxy malonates and amines mediated by LiCl (Scheme 2).

Following our interest in the nucleophilic ring-opening of epoxide acetates **1** to give β,γ-difunctionalized esters **2** en route to γ-lactams,[28] we decided to explore the reactivity of the homologous γ,δ-epoxy malonate **3a** toward primary amines in the presence of lithium chloride (to act as a mild Lewis acid)[29]

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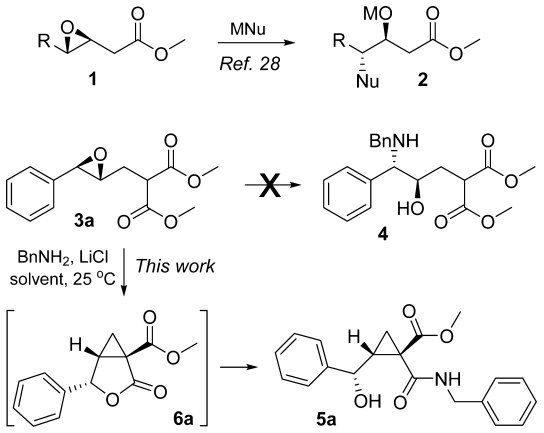
Scheme 2. Formation of the Cyclopropanecarboxamide 5a through Intramolecular Ring-Opening of the (±)-γ,δ-Epoxy Malonate 3a

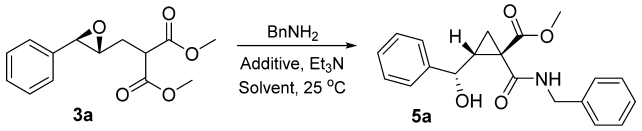


with the aim of obtaining the amino alcohol **4** as the product of a nucleophilic attack at the benzylic position (Scheme 2). However, the sole compound formed under these conditions was the cyclopropanecarboxamide **5a** (obtained through intramolecular cyclopropanation, lactonization, and aminolysis of the lactone **6a**; see below) as a single diastereoisomer containing three contiguous stereogenic centers.

RESULTS AND DISCUSSION

Racemic (±)-γ,δ-epoxy malonate **3a** and benzylamine ($BnNH_2$; 1.2 equiv) were selected as the model substrates to be investigated in a variety of reaction conditions to outline the parameters that control the domino transformation to give the cyclopropanecarboxamide **5a**. As can be seen from the data compiled in Table 1, only LiCl (entry 1) mediated the intramolecular reaction, whereas the other additives did not succeed (entries 2–6). The use of different amounts of reagents did not improve the results (data not shown). The coaddition of a small quantity (0.2 equiv) of triethylamine to act as an extra base was beneficial in relation to the reaction rate (entry 7). Hydroxylic solvents (entries 8–10) are preferred over acetonitrile, not only due to the slightly better yields but also because they provide a more sustainable process.[30]

Table 1. Optimization of the Cyclopropanation/Lactonization/Aminolysis Process Using the (±)-γ,δ-Epoxy Malonate 3a and Benzylamine[a]



entry	additive (amt, mmol)	base	solvent	time (h)	yield[b] of **5a** (%)
1	LiCl (1.0)		MeCN	16	92
2			MeCN	19	*c*
3	Li_2CO_3 (3.0)		1:1 EtOH/H_2O	2	*d*
4	LiOH (3.0)		1:1 MeCN/H_2O	2	*e*
5	NaCl (5.0)		MeCN	96	*d*
6	$Mg(ClO_4)_2$ (1.0)		MeCN	19	*c*
7	LiCl (1.0)	Et_3N	MeCN	2	85
8	LiCl (1.0)	Et_3N	EtOH	2	89[f]
9	LiCl (0.5)	Et_3N	EtOH	2	75
10	LiCl (1.0)	Et_3N	MeOH	2	90

[a]Conditions: epoxide **3a** (1.0 mmol), $BnNH_2$ (1.2 mmol), additive, Et_3N (0.2 mmol), solvent (1.0 mL). [b]Yields refer to the product obtained after aqueous workup (>95% purity; see the Experimental Section). [c]Recovered starting material. [d]Conversion below 20%. [e]Formation of a complex mixture. [f]Formation of 5% transesterification byproduct **5j**.

It should be noted that the use of ethanol as the solvent led to the formation of a small amount (ca. 5%) of a transesterification product (**5j**) which was difficult to separate from the main product **5a** (Table 1, entry 8). Consequently, methanol was selected as the solvent of choice to extend the domino transformation to a variety of amines as well as other (±)-γ,δ-epoxy malonates **3**. The use of 1.0 equiv of LiCl in combination with 0.2 equiv of Et_3N was preferred due to the higher reaction rate observed (entry 10), although reasonable conversions were obtained using lesser amounts of the lithium salt (entry 9).

This sequential cyclopropanation/lactonization/aminolysis protocol was then extended to a number of amines and (±)-γ,δ-epoxy malonates **3**, which were readily prepared by the epoxidation of the corresponding olefin **7** with Oxone in an aqueous medium (Scheme 3). Aliphatic primary amines and cyclic secondary amines were used with success, and the exclusive formation of the multifunctionalized cyclopropanecarboxamide **5** as a single diastereoisomer was observed in all events. Although the purification procedure was not optimized, the reactions consistently provided good isolated yields (60–80%) with a remarkable functional group tolerance, thus demonstrating the generality of the methodology.

However, the reaction rates are dependent upon the structure of the reactants involved. Thus, unbranched primary amines [RCH_2NH_2] are more reactive than secondary amines [RR′NH], as illustrated by the reaction of the (±)-γ,δ-epoxy malonate **3a** with 4-(aminomethyl)piperidine to give the carboxamide **5e** as the sole product and the slow formation of the carboxamide **5i** when morpholine was used. Despite being a secondary amine, pyrrolidine was an exception due to its superior reactivity among the amines tested (see the formation of **5h** and also **5n** and **5p**). On the other hand, the α-branched primary amine [RR′$CHNH_2$] tested was less reactive and led to slow formation of the carboxamide **5g**, which was isolated in reasonable yield.

As expected, the bulky *tert*-butylamine (*t*-$BuNH_2$) was unable to give the corresponding carboxamide **5** under the conditions studied, probably because of a reduced nucleophilicity caused by steric restrictions. Nevertheless, the starting (±)-γ,δ-epoxy malonate **3a** was completely consumed and gave rise to the cyclopropylidene lactone **6a** (see the discussion below). A few aromatic amines [$ArNH_2$] tested (aniline, *p*-anisidine) also furnished the bicyclic intermediate **6a** as the sole product with no trace of cyclopropanecarboxamide **5**. This is possibly associated with the low nucleophilicity of the amino group due to the delocalization of the lone pair of electrons through the aromatic ring. Therefore, the observed order of reactivity [*t*-$BuNH_2$ ≈ $ArNH_2$ ≪ RR′NH ≈ RR′$CHNH_2$ ≪ RCH_2NH_2 ≈ $(CH_2)_4NH$] is affected by stereoelectronic effects and can be related, at least in part, to the nucleophilic character[31] of each amine under study.

Other (±)-γ,δ-epoxy malonates **3b–f** with different substitution patterns were also tested in the domino transformation and behaved similarly to the model epoxide **3a**, thus furnishing good yields of the corresponding cyclopropanecar-

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Scheme 3. Preparation of Cyclopropanecarboxamides 5 from (±)-γ,δ-Epoxy Malonates 3 by Cooperative Catalysis Involving LiCl and an Amine

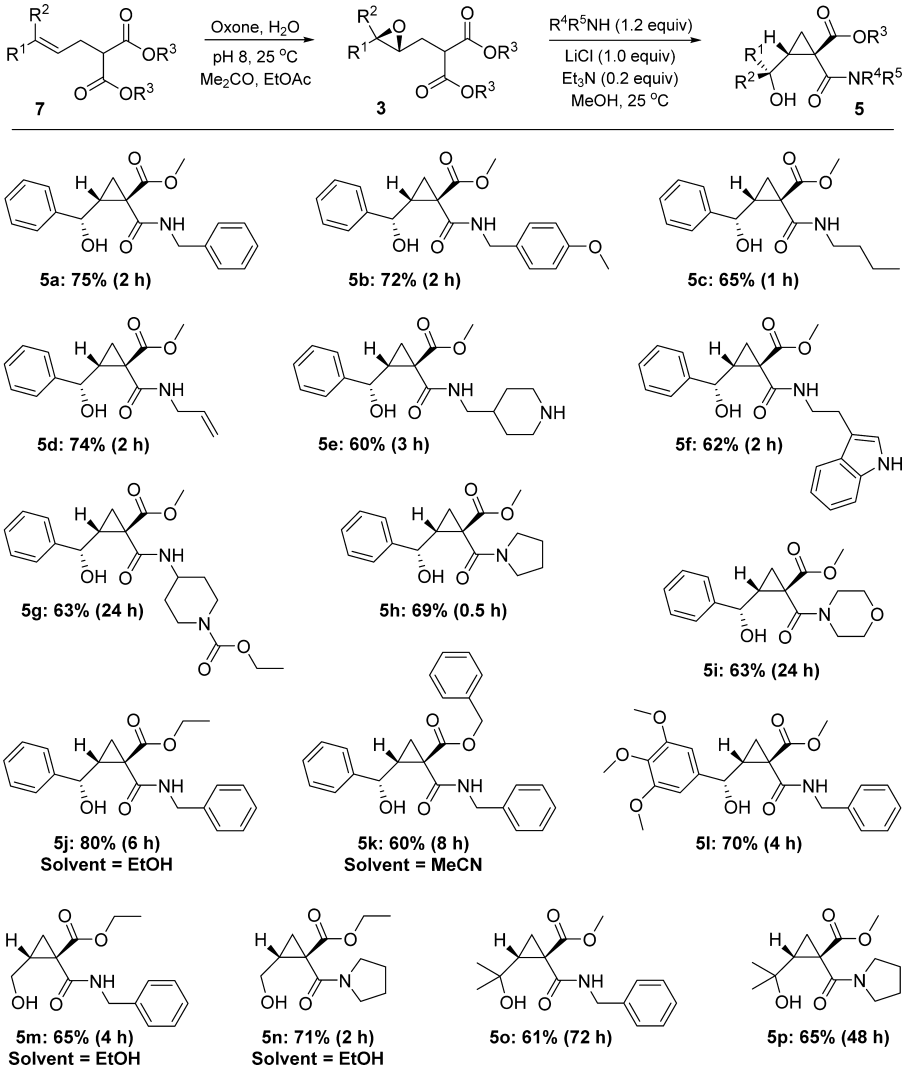
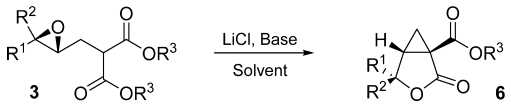


Table 2. Preparation of Cyclopropylidene Lactones 6 from (±)-γ,δ-Epoxy Malonates 3[a]



entry	3	R^1	R^2	R^3	base	solvent	T (°C)	time (h)	yield[b] of 6 (%)
1	a	C_6H_5	H	CH_3	*t*-BuNH$_2$	MeOH	25	0.5	60
2	e	H	H	C_2H_5	*t*-BuNH$_2$	EtOH	25	0.5	62
3	f	CH_3	CH_3	CH_3	*t*-BuNH$_2$	MeOH	25	8	65
4	a	C_6H_5	H	CH_3	Et_3N	EtOH	25	6	58
5	a	C_6H_5	H	CH_3	Et_3N	MeOH	60[c]	1	65
6	a	C_6H_5	H	CH_3	Et_3N	MeCN	25	6	*d*
7	a	C_6H_5	H	CH_3	DBU	MeCN	25	6	*d*

[a]Conditions: epoxide **3** (1.0 mmol), LiCl (1.0 mmol), base (1.2 mmol), solvent (1.0 mL). [b]Yields refer to the isolated product after purification by column chromatography on silica gel. [c]Maximum temperature displayed on the monomode microwave reactor (potency 2 W). [d]Incomplete reactions (conversions below 60%).

boxamides **5j–p** as the sole product (Scheme 3). The diester function originating from the malonate portion of the γ,δ-epoxy malonate **3** seems to have little influence on the formation of the products (compare **5a** with **5j** and **5k**). The observed difference in the reaction rate could be associated with the solvent used in each case to avoid the previously observed transesterification of the ester group. The substitution at the δ-position (R^1/R^2) was varied from disubstituted styrene-type epoxides (**3a–d**) to monosubstituted (**3e**) and trisubstituted (**3f**) analogues. Accordingly, each carboxamide **5** was obtained

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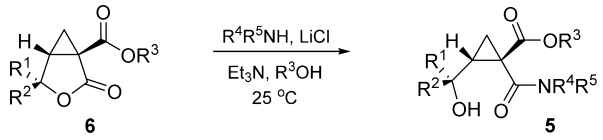
Table 3. Preparation of Cyclopropanecarboxamides 5 through Aminolysis of Cyclopropylidene Lactones 6[a]



entry	lactone/product	R^1	R^2	R^3	R^4	R^5	additive	base	time (h)	yield[b] of **5** (%)
1	**6a/5a**	C_6H_5	H	CH_3	$C_6H_5CH_2$	H			4	95
2	**6a/5a**	C_6H_5	H	CH_3	$C_6H_5CH_2$	H		Et_3N	3	95
3	**6a/5a**	C_6H_5	H	CH_3	$C_6H_5CH_2$	H	LiCl	Et_3N	1	96
4	**6a/5a**	C_6H_5	H	CH_3	$C_6H_5CH_2$	H	LiCl	$BnNH_2$	2	94
5	**6a/5h**	C_6H_5	H	CH_3	$(CH_2)_4$		LiCl	Et_3N	0.2	80
6	**6a/5i**	C_6H_5	H	CH_3	$(CH_2)_2O(CH_2)_2$		LiCl	Et_3N	24	63
7	**6b/5m**	H	H	C_2H_5	$C_6H_5CH_2$	H	LiCl	Et_3N	2[c]	84
8	**6c/5o**	CH_3	CH_3	CH_3	$C_6H_5CH_2$	H	LiCl	Et_3N	14	82

[a]Conditions: **6** (1.0 mmol), amine (1.2 mmol), LiCl (1.0 mmol), base (0.2 mmol), MeOH (1.0 mL). [b]Yields refer to the product obtained after aqueous workup (>95% purity; see the Experimental Section). [c]EtOH was used as the solvent instead of MeOH.

as one diastereoisomer in good isolated yield, although the formation of the bulkier dimethyl-substituted carboxamides **5o,p** was achieved after the reaction was conducted for 2−3 days. Therefore, the preparation of the cyclopropanecarboxamides **5a−p** from the (±)-γ,δ-epoxy malonates **3a−f** under mild conditions using readily available reagents was successfully carried out.

To provide an insight into the mechanistic aspects involved in the domino transformation mediated by the cooperative catalysis of LiCl in combination with an amine, we conducted a more detailed study. As stated above, the weakly nucleophilic amines tested (some aromatic amines as well as *t*-$BuNH_2$) did not furnish the corresponding cyclopropanecarboxamides **5**; instead, the starting (±)-γ,δ-epoxy malonates **3a,e,f** were consumed to give intermediates that could be isolated and characterized as the cyclopropylidene lactones **6a−c** (Table 2, entries 1−3). In the case of the styrene-type (**3a**) and monosubstituted (**3e**) epoxides the formation of **6a** and **6b** was completed in less than 1 h, while for the trisubstituted epoxide **3f** the reaction took longer (8 h).

The use of LiCl combined with a conventional base such as Et_3N (in place of *t*-$BuNH_2$) also led to the formation of the expected cyclopropylidene lactone **6a** in >95% conversion and good isolated yields. Surprisingly, however, the reaction required prolonged periods at 25 °C (Table 2, entry 4) or 1 h under microwave heating (entry 5). Changing the solvent to MeCN was even more unfavorable to the formation of **6** (entry 6), as was the use of a stronger base such as DBU (entry 7). Finally, it is also important to stress that in the absence of LiCl or any base no product was formed and the epoxide **3** was recovered unchanged (results not shown), thus verifying that the transformation requires the addition of both promoters (Lewis acid and Brønsted base) to the reaction medium.

The cyclopropylidene lactone **6b** and its analogues ($R^1 = R^2 = H$) have often been used as precursors for the synthesis of biologically active cyclopropanes.[8,24−26] Different procedures for the preparation of the cyclopropylidene lactone nucleus are found in the literature, and they can be divided into three distinct strategies: (i) the transition-metal-catalyzed intramolecular cyclopropanation of α-diazo esters tethered to an allylic moiety,[32,33] (ii) the reaction of malonates with epichlorohydrin derivatives in a strong basic medium,[25,26,34] and (iii) the base-catalyzed intramolecular ring-opening of γ,δ-epoxy esters.[23,24] However, the synthesis of substituted cyclopropylidene lactones (R^1 and/or $R^2 \neq H$)[24,34−37] is much less accessible through any of these methods. In this regard, the preparation of the γ-phenyl-substituted cyclopropylidene lactone **6a** and the *gem*-dimethyl derivative **6c**[36] under mild conditions and in good isolated yields is worth noting.

In all reactions studied, only one diastereoisomer was observed in the crude product. In the case of the cyclopropylidene lactone **6a**, the relative configuration of the two stereogenic centers derived from the epoxide ring was assigned from the analysis of the ^1H NMR spectra, where the contiguous methinic hydrogen nuclei showed a coupling constant (*J*) of 5.0 Hz, which is characteristic of a *cis* arrangement on the basis of the Karplus equation.[37]

To support the intermediacy of the cyclopropylidene lactones **6** in the domino process starting with the (±)-γ,δ-epoxy malonates **3** to give cyclopropanecarboxamides **5**, we investigated the reactivity of **6** under aminolysis conditions (Table 3). Although the reaction between cyclopropylidene lactone **6a** and $BnNH_2$ occurred at ambient temperature without the addition of LiCl (entries 1 and 2), the rate was significantly improved in the presence of this lithium salt (entry 3). The importance of Et_3N in accelerating this particular step was supported by the fact that the substitution of the Et_3N used (0.2 equiv) with the same amount of benzylamine (0.2 equiv plus 1.2 equiv normally used, total of 1.4 equiv) led to a decrease in the conversion to the aminolysis product **5a** (compare entries 3 and 4).

Changing the amine to the more nucleophilic pyrrolidine led to the formation of the carboxamide **5h** in only a few minutes (entry 5). On the other hand, morpholine was not able to promote high conversion of the lactone **6a** to the carboxamide **5i**, even after a prolonged reaction time, as might be expected for a weak nucleophile (entry 6). Poorer nucleophiles such as *p*-anisidine and *tert*-butylamine were unable to react with **6a** under the stated conditions (data not shown).

The aminolysis of unsubstituted (**6b**) and dimethyl-substituted (**6c**) cyclopropylidene lactones with $BnNH_2$ in the presence of LiCl and Et_3N was also undertaken and gave the corresponding cyclopropanecarboxamides **5m** and **5o** (Table 3, entries 7 and 8). As anticipated, the bulkier dimethyl-substituted cyclopropylidene lactone **6c** reacted more slowly compared with lactones **6a** and **6b**, but good conversions to **5o** were observed in less than 1 day (entry 8).

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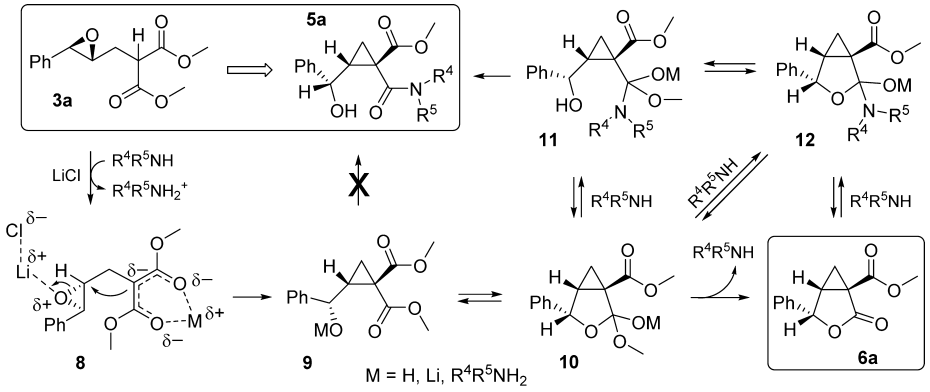
Scheme 4. Proposed Mechanism for the Domino Cyclopropanation/Lactonization/Aminolysis Process Starting with (±)-γ,δ-Epoxy Malonates



All of the observations described herein support the concept of cooperative catalysis occurring with the combination of a mild Lewis acid (LiCl) and a Brønsted base (the amine) along the pathways of the domino transformation. A proposed reaction mechanism starts with the amine-promoted formation of a stabilized enolate (**8**) through proton abstraction from the epoxide **3a**, followed by an intramolecular attack on the γ-position of the epoxide ring to build up the cyclopropane skeleton **9**, which undergoes another cyclization (lactonization) to give the cyclopropylidene lactone **6a** via the intermediate **10** (Scheme 4).

Because both LiCl and a base are essential for the formation of the cyclopropylidene lactone **6** from the (±)-γ,δ-epoxy malonates **3**, each catalyst might be involved in the activation of a reaction partner, i.e., the nucleophilic center (via the base-mediated transformation of enol to enolate) and the electrophilic epoxide moiety (which is activated by coordination with LiCl). While the role of the amine as a deprotonation agent is acceptable, other less understandable factors could take part in the formation of the cyclopropylidene lactones **6** since conventional bases such as Et_3N and DBU were less efficient than *tert*-butylamine as the catalyst (see Table 2). These results suggest that the process as a whole requires a base that does not need to be relatively strong but must possess N−H bonds. It is plausible that these bonds facilitate H-transfer from one intermediate to another and/or stabilize anionic species via hydrogen bonds.

With the information currently available, it is not possible to define the exact constitution of the intermediates involved in this multistep process, since each conceivable intermediate **8**−**12** represented in Scheme 4 possesses correlated structures where M^+ is assumed to be any cation (H^+, Li^+, $R^4R^5NH_2^+$) that can stabilize the negative charge at the oxygen atom.

Concerning the formation of the cyclopropane moiety, although the benzylic sites are usually the most reactive toward nucleophilic addition to styryl-derived epoxides (the δ-position in the case of γ,δ-epoxy malonates **3**, which might give a four-membered ring as the product), due to conformational constraints, the intramolecular attack occurred solely at the γ-position to furnish the three-membered carbocycle framework. In accordance with an S_N2-type reaction, the *anti*-attack on the epoxide ring led to inversion of the configuration at the γ-position, which is in agreement with the relative *cis*-stereochemistry of the contiguous methine protons found in the cyclopropylidene lactone **6a**, as discussed above.[37]

In the aminolysis step of the lactone ring of **6**, carried out by a nucleophilic primary/secondary amine, the absence of either LiCl or an added base is not detrimental to the reaction, but their presence clearly accelerates the process (see Table 3). Therefore, it is possible that LiCl also participates as a weak Lewis acid in the aminolysis pathway, by activating the lactone carbonyl group and facilitating the nucleophilic attack by the amine. The role of Et_3N, in turn, might be to aid the hydrogen transfer among the postulated intermediates **11** and **12**, which ultimately leads to the cyclopropanecarboxamides **5** with the regeneration of the catalysts.

Of particular importance is the finding that, in the case of the more reactive amines, the whole domino reaction from (±)-γ,δ-epoxy malonates **3** to cyclopropanecarboxamides **5** does not take more than 1−2 h at 25 °C to be completed, and equivalent periods can also be observed in the two-step methodology involving the isolation of the cyclopropylidene lactones **6** followed by the aminolysis of the lactone ring to give the carboxamides **5**, which supports the intermediacy of **6** as proposed in Scheme 4.

■ CONCLUSION

We have developed an efficient procedure for the intramolecular ring-opening of (±)-γ,δ-epoxy malonates **3** by cooperative catalysis involving LiCl and amines to give the cyclopropanecarboxamides **5** through sequential events consisting of intramolecular cyclopropanation, lactonization, and aminolysis of the lactone ring. This simple method provides a straightforward way to obtain multifunctionalized cyclopropanes in good isolated yields under mild conditions. The methodology is remarkably modular, operationally simple, and amenable to a large variety of functional groups. The whole transformation proceeds with high atom economy and generates an almost inoffensive byproduct (MeOH or EtOH, depending on the malonate used). Moreover, each sequential reaction is associated with a high thermodynamic driving force to generate a single diastereoisomer, and up to three contiguous stereogenic centers[38] can be perfectly assembled in the aryl-substituted products **5a**−**l**.

All of the advantages mentioned above, including the involvement of readily available starting materials, simple reaction conditions, and the use of a sustainable solvent (methanol or ethanol) at ambient temperature, lie at the foundation of click chemistry,[39] which describes the generation of substances quickly and reliably by joining small modular units. In fact, the ring-opening of epoxide via nucleophilic

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attack has previously been classified as click chemistry,[39] but in our study this intramolecular cyclopropanation step was followed by events (lactonization to bicyclic lactones **6** and aminolysis to **5**) that are also associated with strong driving forces, leading to the formation of the cyclopropanecarboxamides **5** with a prominent structural diversity. Further studies to develop the asymmetric version are currently under way in our laboratories and will be reported in due course.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Epoxides 3. To a stirred solution of alkene 7 (1.0 mmol), ethyl acetate (10 mL), acetone (5.0 mL), and phosphate buffer (1 M K_2HPO_4/KH_2PO_4, pH 8, 10 mL) at 25 °C was added dropwise a solution of Oxone (1.3 mmol for **7a−d,f** or 2.5 mmol for **7e**) in H_2O (5.0 mL). The reaction mixture was stirred until TLC (8:2 or 6:4 hexane/EtOAc) showed completion of the reaction (1−8 h; see below). The insoluble solid was separated by filtration under reduced pressure and washed with EtOAc. The filtrate was washed with 1 M $Na_2S_2O_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a pale yellow oil. Purification by column chromatography on silica gel (8:2 to 6:4 hexane/EtOAc) gave pure epoxides **3a−c,e,f**, except for the trimethoxyaryl-substituted epoxide **3d**, which was used in the next step without further purification.

*Methyl 4,5-Epoxy-2-(methoxycarbonyl)-5-phenylpentanoate (**3a**).* Time: 2 h. Yield: 75% (198 mg). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35−7.28 (m, 3H), 7.25−7.21 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.66 (d, J = 2.0 Hz, 1H), 3.63 (dd, J = 8.9, 5.8 Hz, 1H), 3.05 (ddd, J = 6.6, 4.8, 2.0 Hz, 1H), 2.40 (ddd, J = 14.2, 8.9, 4.8 Hz, 1H), 2.18 (app dt, J = 14.2, 6.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3 (C), 169.2 (C), 136.9 (C), 128.5 (2 × CH), 128.3 (CH), 125.6 (2 × CH), 60.0 (CH), 58.9 (CH), 52.9 (CH_3), 52.8 (CH_3), 48.5 (CH), 31.5 (CH_2). IR (ZnSe, cm^{-1}): ν = 3066, 2983, 2939, 1750, 1733, 1498, 1465, 1370, 1032, 754, 699. HRMS (positive ESI): m/z [M + Na]$^+$ calcd for $C_{14}H_{16}NaO_5$ 287.0890, found 287.0891.

*Ethyl 4,5-Epoxy-2-(ethoxycarbonyl)-5-phenylpentanoate (**3b**).* Time: 4 h. Yield: 80% (234 mg). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35−7.28 (m, 3H), 7.24−7.22 (m, 2H), 4.20 (q, J = 7.3 Hz, 4H), 3.66 (d, J = 2.0 Hz, 1H), 3.59 (dd, J = 8.9, 6.0 Hz, 1H), 3.06 (ddd, J = 6.8, 4.9, 2.0 Hz, 1H), 2.37 (ddd, J = 14.2, 8.9, 4.9 Hz, 1H), 2.19 (app dt, J = 14.2, 6.2 Hz, 1H), 1.26 (t, J = 7.3 Hz, 3H), 1.25 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9 (C), 168.8 (C), 137.0 (C), 128.5 (2 × CH), 128.3 (CH), 125.6 (2 × CH), 61.81 (CH_2), 61.77 (CH_2), 60.2 (CH), 59.0 (CH), 48.9 (CH), 31.5 (CH_2), 14.10 (CH_3), 14.09 (CH_3). IR (ZnSe, cm^{-1}): ν = 3066, 2981, 2939, 1748, 1730, 1498, 1465, 1369, 1030, 862, 698. HRMS (positive ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{20}NaO_5$ 315.1203, found 315.1205.

*Benzyl 4,5-Epoxy-2-[(benzyloxy)carbonyl]-5-phenylpentanoate (**3c**).* Time: 1 h. Yield: 72% (300 mg). Pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35−7.16 (m, 15 H), 5.18 (s, 2H) 5.17 (s, 2H), 3.73 (dd, J = 8.6, 6.0 Hz, 1H), 3.65 (d, J = 2.0 Hz, 1H), 3.05 (ddd, J = 6.5, 4.8, 2.0 Hz, 1 H), 2.44 (ddd, J = 14.1, 8.6, 4.8 Hz, 1 H), 2.24 (app dt, J = 14.1, 6.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6 (C), 168.5 (C), 136.9 (2 × C), 135.2 (C), 128.65 (2 × CH), 128.61 (CH), 128.52 (2 × CH), 128.49 (2 × CH), 128.33 (2 × CH), 128.31 (2 × CH), 128.29 (2 × CH), 125.7 (2 × CH), 67.52 (CH_2), 67.51 (CH_2), 60.0 (CH), 58.9 (CH), 48.9 (CH), 31.5 (CH_2). IR (ZnSe, cm^{-1}): ν = 3062, 3032, 1747, 1731, 1497, 1454, 1153, 882, 751, 697. HRMS (positive ESI): m/z [M + Na]$^+$ calcd for $C_{26}H_{24}NaO_5$ 439.1516, found 439.1516.

*Methyl 4,5-Epoxy-2-(methoxycarbonyl)-5-(3,4,5-trimethoxyphenyl)pentanoate (**3d**).* Time: 6 h. Yield: 90% (319 mg). Pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.45 (s, 2H), 3.83 (s, 6H), 3.80 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.62−3.58 (m, 2H), 2.99 (ddd, J = 6.8, 5.0, 2.0 Hz, 1H), 2.38 (ddd, J = 14.2, 8.6, 5.0 Hz, 1H), 2.16 (app dt, J = 14.2, 6.2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.24 (C), 169.19 (C), 153.6 (2 × C), 138.2 (C), 132.6 (C), 102.6 (2 × CH), 60.9 (CH), 60.0 (CH), 59.2 (CH_3), 56.3 (2 × CH_3), 52.9 (CH_3), 52.8 (CH_3), 48.6 (CH), 31.5 (CH_2). IR (ZnSe, cm^{-1}): ν = 3000, 2953, 2840, 1756, 1731, 1591, 1504, 1237, 1128, 1006, 833, 733. HRMS (positive ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{22}NaO_8$ 377.1207, found 377.1193.

*Ethyl 4,5-Epoxy-2-(ethoxycarbonyl)pentanoate (**3e**).* Time: 8 h. Yield: 80% (173 mg). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.22−4.13 (m, 4H), 3.49 (dd, J = 8.7, 5.8 Hz, 1H), 3.00−2.95 (m, 1H), 2.73 (t, J = 4.7 Hz, 1H), 2.48 (dd, J = 4.7, 2.6 Hz, 1H), 2.22 (ddd, J = 14.4, 8.7, 4.7 Hz, 1H), 1.96 (dt, J = 14.4, 6.4 Hz, 1H), 1.25−1.21 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9 (C), 168.8 (C), 61.69 (CH_2), 61.66 (CH_2), 49.8 (CH), 49.0 (CH), 47.3 (CH_2), 31.7 (CH_2), 14.1 (CH_3), 14.0 (CH_3). IR (ZnSe, cm^{-1}): ν = 2985, 2941, 1750, 1733, 1447, 1267, 1370, 1238, 1156, 1031, 925, 853. HRMS (positive ESI): m/z [M + Na]$^+$ calcd for $C_{10}H_{16}NaO_5$ 239.0890, found 239.0893.

*Methyl 4,5-Epoxy-2-(methoxycarbonyl)-5-methylhexanoate (**3f**).*[40] Time: 1 h. Yield: 82% (177 mg). Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.75 (s, 3H), 3.74 (s, 3H), 3.57 (dd, J = 8.8, 6.2 Hz, 1H), 2.77 (dd, J = 7.8, 4.8 Hz, 1H), 2.24 (ddd, J = 13.7, 8.8, 4.8 Hz, 1H), 1.99 (ddd, J = 13.7, 7.8, 6.2 Hz, 1H), 1.28 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.45 (C), 169.42 (C), 61.5 (CH), 59.0 (C), 52.8 (CH_3), 52.7 (CH_3), 49.2 (CH), 28.4 (CH_2), 24.7 (CH_3), 18.8 (CH_3). IR (ZnSe, cm^{-1}): ν = 2959, 1738, 1438, 1279, 1238, 1158. HRMS (positive ESI): m/z [M + Na]$^+$ calcd for $C_{10}H_{16}NaO_5$ 239.0890, found 239.0890.

Domino Synthesis of Cyclopropanecarboxamides 5 from γ,δ-Epoxy Malonates 3. To a stirred solution of (±)-γ,δ-epoxy malonate **3** (1.0 mmol) and a primary or secondary amine (1.2 mmol) in 1.0 mL of a given solvent (methanol for **3a,d,f**, ethanol for **3b,e**, acetonitrile for **3c**) at 25 °C were added Et_3N (0.20 mmol) and LiCl (1.0 mmol). The reaction mixture was stirred at 25 °C until TLC (3:2 or 1:4 hexane/EtOAc) showed completion of the reaction (see Scheme 3). Next, the mixture was quenched with 0.1 M HCl and diluted with EtOAc, then the organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude oily product. Purification by column chromatography (silica gel, 3:2 to 1:4 hexane/EtOAc) or by recrystallization with EtOAc (for **5f**) gave the desired product **5**.

*Methyl 1-(Benzylcarbamoyl)-2-(hydroxyphenylmethyl)cyclopropane-1-carboxylate (**5a**).* Yield: 75% (254 mg). White solid. Mp: 109.0−110.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.99 (br s, 1H), 7.37−7.25 (m, 10H), 4.92 (d, J = 4.4 Hz, 1H), 4.52 (dd, J = 14.9, 5.8 Hz, 1H), 4.48 (dd, J = 14.9, 5.8 Hz, 1H), 4.22 (br s, 1H), 3.61 (s, 3H), 2.38 (dd, J = 8.2, 4.2 Hz, 1H), 2.27 (ddd, J = 9.4, 8.2, 4.4 Hz, 1H), 1.93 (dd, J = 9.4, 4.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8 (C), 167.9 (C), 143.7 (C), 137.9 (C), 128.7 (2 × CH), 128.6 (2 × CH), 127.74 (2 × CH), 127.72 (CH), 127.5 (CH), 126.3 (2 × CH), 70.1 (CH), 52.6 (CH_3), 44.0 (CH_2), 40.9 (CH), 32.2 (C), 20.3 (CH_2). IR (ZnSe, cm^{-1}): ν = 3347, 3031, 2954, 2854, 1713, 1644, 1539, 1454, 1440, 1334, 1150, 700. HRMS (positive ESI): m/z [M + Na]$^+$ calcd for $C_{20}H_{21}NNaO_4$ 362.1363, found 362.1367.

*Methyl 2-(Hydroxyphenylmethyl)-1-[(4-methoxybenzyl)carbamoyl]cyclopropane-1-carboxylate (**5b**).* Yield: 72% (266 mg). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (t, J = 5.4 Hz, 1H), 7.31−7.20 (m, 5H), 7.12 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 4.85 (d, J = 5.2 Hz, 1H), 4.62 (br s, 1H), 4.39−4.30 (m, 2H), 3.72 (s, 3H), 3.54 (s, 3H), 2.30−2.20 (m, 2H), 1.84 (dd, J = 8.0, 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5 (C), 167.1 (C), 158.7 (C), 143.6 (C), 129.8 (C), 128.9 (2 × CH), 128.3 (2 × CH), 127.4 (CH), 126.0 (2 × CH), 113.8 (2 × CH), 69.9 (CH), 55.0 (CH_3), 52.3 (CH_3), 43.2 (CH_2), 40.0 (CH), 32.1 (C), 20.0 (CH_2). IR (ZnSe, cm^{-1}): ν = 3348, 3028, 2952, 2834, 1710, 1643, 1513, 1249, 1149, 1033, 701. HRMS (positive ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{24}NO_5$ 370.1649, found 370.1651.

*Methyl 1-(1-Butylcarbamoyl)-2-(hydroxyphenylmethyl)cyclopropane-1-carboxylate (**5c**).* Yield: 65% (198 mg). White solid. Mp: 58.0−59.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (br s, 1H),

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7.36−7.22 (m, 5H), 4.85 (d, J = 5.2 Hz, 1H), 4.63 (br s, 1H), 3.60 (s, 3H), 3.34−3.29 (m, 2H), 2.30 (dd, J = 8.0, 4.3 Hz, 1H), 2.21 (ddd, J = 9.4, 8.0, 5.2 Hz, 1H), 1.87 (dd, J = 9.4, 4.3 Hz, 1H), 1.47 (m, 2H), 1.33 (m, 2H), 0.91 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8 (C), 167.4 (C), 143.7 (C), 128.3 (2 × CH), 127.4 (CH), 126.1 (2 × CH), 69.9 (CH), 52.4 (CH_3), 40.5 (CH), 39.6 (CH_2), 32.0 (C), 31.2 (CH_2), 20.0 (CH_2), 19.9 (CH_2) 13.7 (CH_3). IR (ZnSe, cm^{-1}): ν = 3445, 3342, 3025, 2959, 2935, 2855, 1711, 1636, 1543, 1437, 1254, 1145, 704. HRMS (positive ESI): m/z [M + H]$^+$ calcd for $C_{17}H_{24}NO_4$ 306.1700, found 306.1700.

*Methyl 1-(Allylcarbamoyl)-2-(hydroxyphenylmethyl)cyclopropane-1-carboxylate (**5d**).* Yield: 74% (214 mg). White solid. Mp: 82.0−83.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (br s, 1H), 7.35−7.23 (m, 5H), 5.85−5.75 (m, 1H), 5.19−5.11 (m, 2H), 4.85 (d, J = 5.2 Hz, 1H), 4.48 (br s, 1H), 3.92−3.88 (m, 2H), 3.61 (s, 3H), 2.30 (dd, J = 8.0, 3.9 Hz, 1H), 2.24 (m, 1H), 1.89 (dd, J = 9.0, 3.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7 (C), 167.6 (C), 143.7 (C), 133.7 (CH), 128.4 (2 × CH), 127.6 (CH), 126.2 (2 × CH), 116.2 (CH_2), 70.0 (CH), 52.5 (CH_3), 42.2 (CH_2), 40.6 (CH), 32.1 (C), 20.2 (CH_2). IR (ZnSe, cm^{-1}): ν = 3420, 3347, 3033, 2958, 1707, 1654, 1542, 1437, 1145, 704. HRMS (positive ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{20}NO_4$ 290.1387, found 290.1387.

*Methyl 2-(hydroxyphenylmethyl)-1-[(piperidin-4-ylmethyl)-carbamoyl]cyclopropane-1-carboxylate (**5e**).* Yield: 60% (208 mg). White solid. Mp: 146.5−147.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79 (br s, 1H), 7.39−7.25 (m, 5H), 4.88 (d, J = 4.1 Hz, 1H), 3.63 (s, 3H), 3.25−3.05 (m, 4H), 2.59−2.53 (m, 2H), 2.35 (dd, J = 8.3, 4.2 Hz, 1H), 2.24 (ddd, J = 9.6, 8.3, 4.1 Hz, 1H), 1.91 (dd, J = 9.6, 4.2 Hz, 1H), 1.68−1.56 (m, 3H), 1.17−1.08 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1 (C), 167.8 (C), 143.9 (C), 128.5 (2 × CH), 127.7 (CH), 126.3 (2 × CH), 70.0 (CH), 52.6 (CH_3), 46.1 (2 × CH_2), 45.9 (CH_2), 40.8 (CH), 36.2 (CH), 32.1 (C), 30.9 (2 × CH_2), 20.0 (CH_2). IR (ZnSe, cm^{-1}): ν = 3349, 3295, 3028, 2924, 2857, 1707, 1654, 1534, 1442, 1145, 703. HRMS (positive ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{27}N_2O_4$ 347.1965, found 347.1967.

*Methyl 2-(Hydroxyphenylmethyl)-1-{[2-(1H-indol-3-yl)ethyl]-carbamoyl}cyclopropane-1-carboxylate (**5f**).* Yield: 62% (243 mg). White solid. Mp: 110.6−111.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (br s, 1H), 8.12 (br s, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.39−7.27 (m, 6H), 7.21 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.04 (s, 1H), 4.87 (d, J = 3.8 Hz, 1H), 4.40 (br s, 1H), 3.70−3.65 (m, 2H), 3.57 (s, 3H), 3.00 (t, J = 7.0 Hz, 2H), 2.35 (dd, J = 8.2, 4.5 Hz, 1H), 2.21 (ddd, J = 9.7, 8.2, 3.8 Hz, 1H), 1.89 (dd, J = 9.7, 4.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7 (C), 168.2 (C), 143.8 (C), 136.5 (C), 128.7 (2 × CH), 127.8 (CH), 127.5 (C), 126.4 (2 × CH), 122.3 (CH), 122.1 (CH), 119.5 (CH), 118.9 (CH), 113.1 (C), 111.3 (CH), 70.0 (CH), 52.6 (CH_3), 41.1 (CH), 40.4 (CH_2), 32.3 (C), 25.3 (CH_2), 19.9 (CH_2). IR (ZnSe, cm^{-1}): ν = 3412, 3328, 3058, 3032, 2950, 2850, 1713, 1650, 1536, 1454, 1150, 745. HRMS (positive ESI): m/z [M + H]$^+$ calcd for $C_{23}H_{25}N_2O_4$ 393.1809, found 393.1810.

*Methyl 1-{[1-(Ethoxycarbonyl)piperidin-4-yl]carbamoyl}-2-(hydroxyphenylmethyl)cyclopropane-1-carboxylate (**5g**).* Yield: 63% (255 mg). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (d, J = 6.8 Hz, 1H), 7.38−7.28 (m, 5H), 4.88 (d, J = 4.0 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 4.03−3.93 (m, 3H), 3.63 (s, 3H), 3.02−2.96 (m, 2H), 2.34 (dd, J = 8.2, 4.2 Hz, 1H), 2.25 (ddd, J = 9.2, 8.2, 4.0 Hz, 1H), 1.93 (dd, J = 9.2, 4.2 Hz, 1H), 1.85−1.81 (m, 2H), 1.46−1.29 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8 (C), 166.7 (C), 155.4 (C), 143.6 (C), 128.4 (2 × CH), 127.6 (CH), 126.1 (2 × CH), 70.1 (CH), 61.3 (CH_2), 52.5 (CH_3), 46.6 (CH), 42.3 (2 × CH_2) 40.3 (CH), 31.9 (C), 31.4 (2 × CH_2), 20.2 (CH_2), 14.6 (CH_3). IR (ZnSe, cm^{-1}): ν = 3414, 3338, 3029, 2980, 2950, 2858, 1708, 1692, 1533, 1440, 1273, 1238, 1143, 731. HRMS (positive ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{29}N_2O_6$ 405.2020, found 405.2019.

*Methyl 2-(Hydroxyphenylmethyl)-1-(pyrrolidin-1-ylcarbonyl)-cyclopropane-1-carboxylate (**5h**).* Yield: 69% (209 mg). White solid. Mp: 110.5−111.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39−7.28 (m, 5H), 5.03 (t, J = 4.0 Hz, 1H), 3.71 (s, 3H), 3.52−3.48 (m, 2H), 3.34−3.27 (m, 1H), 3.09 (d, J = 4.0 Hz, 1H, exchanges with D_2O), 3.07−3.01 (m, 1H), 2.24 (ddd, J = 9.5, 7.7, 4.0 Hz, 1H), 1.89−1.79 (m, 4H), 1.76 (dd, J = 7.7, 4.4 Hz, 1H), 1.55 (dd, J = 9.5, 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1 (C), 165.7 (C), 142.9 (C), 128.3 (2 × CH), 127.7 (CH), 126.5 (2 × CH), 70.6 (CH), 52.6 (CH_3), 46.6 (CH_2), 46.3 (CH_2), 34.2 (CH), 33.5 (C), 25.6 (CH_2), 23.8 (CH_2), 17.9 (CH_2). IR (ZnSe, cm^{-1}): ν = 3427, 3030, 2972, 2948, 2876, 1719, 1612, 1447, 1297, 1153, 700. HRMS (positive ESI): m/z [M + H]$^+$ calcd for $C_{17}H_{22}NO_4$ 304.1543, found 304.1545.

*Methyl 2-(Hydroxyphenylmethyl)-1-(morpholin-4-ylcarbonyl)-cyclopropane-1-carboxylate (**5i**).* Yield: 63% (201 mg). Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38−7.28 (m, 5H), 4.97 (d, J = 4.2 Hz, 1H), 3.71 (s, 3H), 3.68−3.30 (m, 7H), 3.18−3.04 (m, 1H), 2.30 (ddd, J = 9.2, 7.4, 4.2 Hz, 1H), 1.77 (dd, J = 7.4, 4.1 Hz, 1H), 1.58 (dd, J = 9.2, 4.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1 (C), 166.0 (C), 142.6 (C), 128.5 (2 × CH), 127.9 (CH), 126.5 (2 × CH), 70.6 (CH), 66.1 (CH_2), 65.6 (CH_2), 52.6 (CH_3), 46.2 (CH_2), 42.4 (CH_2), 33.6 (CH), 32.0 (C), 18.5 (CH_2). IR (ZnSe, cm^{-1}): ν = 3406, 3061, 2957, 2904, 2859, 1725, 1632, 1438, 1269, 1114, 701. HRMS (positive ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{21}NNaO_5$ 342.1312, found 342.1317.

*Ethyl 1-(Benzylcarbamoyl)-2-(hydroxyphenylmethyl)cyclopropane-1-carboxylate (**5j**).* Yield: 80% (283 mg). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.01 (br s, 1H), 7.38−7.26 (m, 10H), 4.92 (d, J = 4.8 Hz, 1H), 4.52 (dd, J = 14.8, 5.4 Hz, 1H), 4.48 (dd, J = 14.8, 5.4 Hz, 1H), 4.15−4.00 (m, 2H), 2.37 (dd, J = 8.4, 4.2 Hz, 1H), 2.27 (ddd, J = 9.4, 8.4, 4.8 Hz, 1H), 1.93 (dd, J = 9.4, 4.2 Hz, 1H), 1.19 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 (C), 167.5 (C), 143.6 (C), 137.8 (C), 128.5 (2 × CH), 128.4 (2 × CH), 127.6 (2 × CH), 127.5 (CH), 127.3 (CH), 126.1 (2 × CH), 70.0 (CH), 61.6 (CH_2), 43.8 (CH_2), 40.3 (CH), 32.1 (C), 20.2 (CH_2), 13.8 (CH_3). IR (ZnSe, cm^{-1}): ν = 3412, 3346, 3061, 3028, 2979, 2930, 2872, 1710, 1653, 1536, 1454, 1326, 1254, 1150, 1021, 699. HRMS (positive ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{24}NO_4$ 354.1700, found 354.1702.

*Benzyl 1-(Benzylcarbamoyl)-2-(hydroxyphenylmethyl)cyclopropane-1-carboxylate (**5k**).* Yield: 60% (249 mg). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.84 (t, J = 5.3 Hz, 1H), 7.32−7.19 (m, 15H), 5.07 (d, J = 12.4 Hz, 1H), 5.00 (d, J = 12.4 Hz, 1H), 4.89 (d, J = 5.6 Hz, 1H), 4.47 (dd, J = 14.7, 5.3 Hz, 1H), 4.42 (dd, J = 14.7, 5.3 Hz, 1H), 4.11 (br s, 1H), 2.37−2.27 (m, 2H), 1.94 (dd, J = 9.2, 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1 (C), 167.6 (C), 143.6 (C), 137.9 (C), 134.9 (C), 128.75 (2 × CH), 128.73 (2 × CH), 128.6 (CH), 128.5 (2 × CH), 128.1 (2 × CH), 127.8 (2 × CH), 127.7 (CH), 127.5 (CH), 126.2 (2 × CH), 70.1 (CH), 67.3 (CH_2), 44.0 (CH_2), 40.8 (CH), 32.3 (C), 20.4 (CH_2). IR (ZnSe, cm^{-1}): ν = 3347, 3088, 3063, 3031, 2927, 1707, 1644, 1538, 1454, 1328, 1256, 1148, 1134, 697. HRMS (positive ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{25}NNaO_4$ 438.1676, found 438.1675.

*Methyl 1-(Benzylcarbamoyl)-2-[hydroxy(3,4,5-trimethoxyphenyl)methyl]cyclopropane-1-carboxylate (**5l**).* Yield: 70% (301 mg). Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.12 (t, J = 5.4 Hz, 1H), 7.35−7.25 (m, 5H), 6.62 (s, 2H), 4.88 (d, J = 4.4 Hz, 1H), 4.53 (dd, J = 14.8, 5.4 Hz, 1H), 4.50 (dd, J = 14.8, 5.4 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 6H), 3.64 (s, 3H), 2.37 (dd, J = 8.4, 4.3 Hz, 1H), 2.25 (ddd, J = 9.4, 8.4, 4.4 Hz, 1H), 1.95 (dd, J = 9.4, 4.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9 (C), 168.1 (C), 153.3 (3 × C), 139.5 (C), 137.8 (C), 128.8 (2 × CH), 127.60 (CH), 127.56 (2 × CH), 103.0 (2 × CH), 69.9 (CH), 60.8 (CH_3), 56.1 (2 × CH_3), 52.7 (CH_3), 44.0 (CH_2), 41.2 (CH), 32.2 (C), 20.3 (CH_2). IR (ZnSe, cm^{-1}): ν = 3349, 3029, 2951, 2839, 1711, 1652, 1593, 1538, 1456, 1330, 1126, 701. HRMS (positive ESI): m/z [M + Na]$^+$ calcd for $C_{23}H_{27}NNaO_7$ 452.1680, found 452.1680.

*Ethyl 1-(Benzylcarbamoyl)-2-(hydroxymethyl)cyclopropane-1-carboxylate (**5m**).* Yield: 65% (180 mg). White solid. Mp: 62.4−63.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (br s, 1H), 7.36−7.28 (m, 5H), 4.57 (dd, J = 14.9, 5.5 Hz, 1H), 4.47 (dd, J = 14.9, 5.5 Hz, 1H), 4.13 (q, J = 6.9 Hz, 2H), 3.99−3.94 (m, 1H), 3.71−3.64 (m, 1H), 3.15 (t, J = 6.4 Hz, 1H, exchanges with D_2O), 2.25−2.18 (m, 1H), 1.87 (dd, J = 7.8, 4.2 Hz, 1H), 1.78 (dd, J = 9.8, 4.2 Hz, 1H), 1.24 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9 (C),

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167.7 (C), 138.0 (C), 128.5 (2 × CH), 127.4 (2 × CH), 127.2 (CH), 61.5 (CH_2), 60.3 (CH_2), 43.7 (CH_2), 33.6 (CH), 32.9 (C), 19.3 (CH_2), 13.9 (CH_3). IR (ZnSe, cm^{-1}): ν = 3420, 3346, 3087, 3063, 2985, 2877, 1724, 1624, 1540, 1272, 1167, 1024, 732. HRMS (positive ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{20}NO_4$ 278.1387, found 278.1385.

*Ethyl 2-(Hydroxymethyl)-1-(pyrrolidin-1-ylcarbonyl)cyclopropane-1-carboxylate (**5n**).* Yield: 71% (171 mg). Colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.19−3.97 (m, 2H), 3.90 (dd, J = 12.4, 4.7 Hz, 1H), 3.52−3.30 (m, 4H), 3.00 (dd, J = 12.4, 10.4 Hz, 1H), 2.09−1.91 (m, 1H), 1.88−1.78 (m, 4H), 1.53 (dd, J = 9.0, 4.4 Hz, 1H), 1.15 (t, J = 7.1 Hz, 3H), 1.01 (dd, J = 6.9, 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (C), 166.2 (C), 63.1 (CH_2), 61.4 (CH_2), 46.8 (CH_2), 46.0 (CH_2), 34.1 (C), 31.0 (CH), 25.7 (CH_2), 24.0 (CH_2), 19.0 (CH_2), 14.0 (CH_3). IR (ZnSe, cm^{-1}): ν = 3401, 3090, 2978, 2878, 1723, 1620, 1446, 1281, 1149, 1034. HRMS (positive ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{20}NO_4$ 242.1387, found 242.1388.

*Methyl 1-(Benzylcarbamoyl)-2-(2-hydroxyprop-2-yl)cyclopropane-1-carboxylate (**5o**).* Yield: 61% (178 mg). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.30 (br s, 1H), 7.36−7.27 (m, 5H), 4.56 (dd, J = 14.8, 5.6 Hz, 1H), 4.49 (dd, J = 14.8, 5.6 Hz, 1H), 3.68 (s, 3H), 2.28 (dd, J = 9.2, 4.4 Hz, 1H), 2.08 (app t, J = 9.6 Hz, 1H), 1.90 (dd, J = 10.2, 4.4 Hz, 1H), 1.34 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0 (C), 170.0 (C), 137.7 (C), 128.7 (2 × CH), 127.7 (2 × CH), 127.5 (CH), 67.8 (C), 52.6 (CH_3), 45.8 (CH), 44.0 (CH_2), 32.0 (C), 31.2 (CH_3), 29.6 (CH_3), 20.8 (CH_2). IR (ZnSe, cm^{-1}): ν = 3327, 3063, 3028, 2972, 1726, 1650, 1538, 1454, 1273, 1152, 700. HRMS (positive ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{22}NO_4$ 292.1543, found 292.1542.

*Methyl 2-(2-Hydroxyprop-2-yl)-1-(pyrrolidin-1-ylcarbonyl)cyclopropane-1-carboxylate (**5p**).* Yield: 65% (166 mg). White solid. Mp: 61.1−62.3 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.01 (s, 1H), 3.69 (s, 3H), 3.55−3.49 (m, 2H), 3.45−3.39 (m, 1H), 3.31−3.25 (m, 1H), 1.90−1.80 (m, 5H), 1.55 (dd, J = 9.8, 3.9 Hz, 1H), 1.48 (s, 3H), 1.24 (dd, J = 8.0, 3.9 Hz, 1H), 1.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8 (C), 167.7 (C), 67.9 (C), 53.0 (CH_3), 47.3 (CH_2), 46.6 (CH_2), 40.6 (CH), 33.3 (C), 30.8 (CH_3), 28.4 (CH_3), 26.1 (CH_2), 24.2 (CH_2), 17.5 (CH_2). IR (ZnSe, cm^{-1}): ν = 3367, 2974, 2880, 1730, 1619, 1448, 1267, 1154. HRMS (positive ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{21}NNaO_4$ 278.1363, found 278.1366.

Stepwise Reaction: Synthesis of Cyclopropylidene Lactones 6 from Epoxides 3. To a stirred solution of (±)-γ,δ-epoxy malonate **3** (1.0 mmol) in 1.0 mL of a given solvent (methanol for **3a,f** or ethanol for **3e**) at 25 °C were added a base (triethylamine or *tert*-butylamine, 1.2 mmol) and LiCl (1.0 mmol). The reaction mixture was stirred at 25 °C for 0.5−8 h (see Table 2). Next, the mixture was quenched with 1.0 M HCl and diluted with EtOAc, then the organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. Purification by column chromatography on silica gel (3:2 hexane/EtOAc) gave the product as a colorless oil.

*Methyl 2-Oxo-4-phenyl-3-oxabicyclo[3.1.0]hexane-1-carboxylate (**6a**).* Yield: 60% (139 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42−7.30 (m, 5H), 5.74 (d, J = 5.0 Hz, 1H), 3.83 (s, 3H), 3.07 (dt, J = 8.0, 5.0 Hz, 1H), 1.96 (dd, J = 8.0, 5.0 Hz, 1H), 1.39 (t, J = 5.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8 (C), 166.8 (C), 136.1 (C), 128.6 (2 × CH), 128.4 (CH), 125.2 (2 × CH), 77.1 (CH), 52.8 (CH_3), 32.3 (CH), 31.0 (C), 18.6 (CH_2). IR (ZnSe, cm^{-1}): ν = 3064, 3031, 2954, 1789, 1731, 1441, 1384, 1316, 1266, 1203, 1094, 1041, 974, 757. HRMS (positive ESI): m/z $[M + H]^+$ calcd for $C_{13}H_{13}O_4$ 233.0808, found 233.0810.

*Ethyl 2-Oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylate (**6b**).*[26] Yield: 62% (97 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.30 (dd, J = 9.6, 4.8 Hz, 1H), 4.21−4.14 (m, 2H), 4.12 (d, J = 9.6 Hz, 1H), 2.69 (dt, J = 8.2, 4.8 Hz, 1H), 2.05 (dd, J = 8.2, 4.8 Hz, 1H), 1.31 (t, J = 4.8 Hz, 1H), 1.23 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6 (C), 166.6 (C), 67.0 (CH_2), 61.8 (CH_2), 29.2 (C), 27.9 (CH), 20.7 (CH_2), 14.0 (CH_3). IR (ZnSe, cm^{-1}): ν = 2981, 2909, 1788, 1726, 1383, 1318, 1190, 1088, 1046. HRMS (positive ESI): m/z $[M + H]^+$ calcd for $C_8H_{11}O_4$ 171.0652, found 171.0653.

*Methyl 4,4-Dimethyl-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylate (**6c**).*[36] Yield: 65% (120 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.75 (s, 3H), 2.50 (dd, J = 8.1, 5.3 Hz, 1H), 1.91 (dd, J = 8.1, 5.3 Hz, 1H), 1.46 (s, 3H), 1.40 (t, J = 5.3 Hz, 1H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8 (C), 167.4 (C), 81.1 (C), 52.9 (CH_3), 37.7 (CH), 31.4 (C), 29.1 (CH_3), 23.8 (CH_3), 20.0 (CH_2). IR (ZnSe, cm^{-1}): ν = 3067, 2982, 2964, 1782, 1731, 1441, 1382, 1328, 1093, 1047, 927. HRMS (positive ESI): m/z $[M + H]^+$ calcd for $C_9H_{13}O_4$ 185.0808, found 185.0806.

Stepwise Reaction: Synthesis of Carboxamides 5 from Cyclopropylidene Lactones 6. To a stirred solution of cyclopropylidene lactone **6** (1.0 mmol) and a primary or secondary amine (1.2 mmol) in 1.0 mL of a given solvent (methanol for **6a,c** or ethanol for **6b**) at 25 °C were added Et_3N (0.20 mmol) and LiCl (1.0 mmol). The reaction mixture was stirred at 25 °C until TLC (3:2 or 1:4 hexane/EtOAc) showed completion of the reaction (see Table 3). Next, the mixture was quenched with 0.1 M HCl and diluted with EtOAc, then the organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the expected cyclopropanecarboxamide **5**. Characterization data matched products **5** obtained from the domino process.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra for **3a−f**, **5a−p**, and **6a−c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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