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# One-Pot Organocatalytic Domino Michael/α-Alkylation Reactions: Direct Catalytic Enantioselective Cyclopropanation and Cyclopentanation Reactions

**Ismail Ibrahem,[a, b] Gui-Ling Zhao,[a, b] Ramon Rios,[a] Jan Vesely,[a, b] Henrik Sundén,[a] Pawel Dziedzic,[a, b] and Armando Córdova*[a, b]**

**Abstract:** The development of one-pot organocatalytic domino Michael/α-alkylation reactions between bromomalonates or bromoacetoacetate esters and α,β-unsaturated aldehydes is presented. The chiral-amine-catalyzed reactions with bromomalonates as substrates give access to the corresponding 2-formylcyclopropane derivatives in high yields with excellent diastereoselectivity and up to 99% *ee*. The catalytic domino Michael/α-alkylation reactions between 4-bromo-acetoacetate and enals provide a route for the synthesis of functionalized cyclopentanones in good to high yields with 93–99% *ee*. The products from the organocatalytic reactions were also reduced with high diastereoselectivity to the corresponding cyclopropanols and cyclopentanols, respectively. Moreover, one-pot combinations of amine and heterocyclic carbene catalysis (AHCC) enabled the highly enantioselective synthesis of β-malonate esters (91–97% *ee*) from the reaction between bromomalonates and enals. The tandem catalysis included the catalytic domino reaction followed by catalytic in situ chemoselective ring-opening of the 2-formylcyclopropane intermediates.

**Keywords:** Unsaturated aldehydes · asymmetric catalysis · cyclopentanes · cyclopropanes · domino reactions · organocatalysis

## Introduction

Carbon–carbon bond-forming reactions are of immense importance in organic synthesis. Domino, tandem, or cascade reactions, which involve the formation of multiple C–C bonds and stereocenters in one pot, are a rapidly growing research field within the synthesis of small molecules with complex molecular scaffolds.[1] The undeniable benefits of domino reactions include "green chemistry" factors such as atom economy,[2] reduction of synthetic steps, and minimization of solvents and waste.[3] Thus, significant efforts have been made in the development of asymmetric domino and tandem reactions by using chiral precursors for stereocontrol. However, it is more challenging to develop catalytic asymmetric domino reactions. Therefore, there are still only a limited number of catalytic enantioselective domino reactions. In this context, the development of organocatalytic enantio- and diastereoselective one-pot domino reactions is a rapidly growing research area.[4–5]

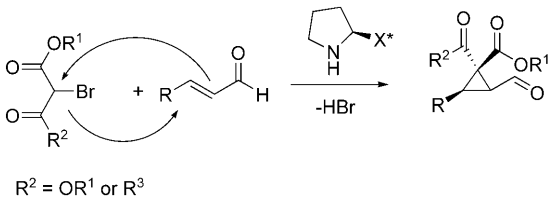
The cyclopropane motif has long been an exciting target for organic chemists and is an important molecular architecture in a large number of naturally occurring and medicinally relevant substances (>4000 isolated; 100 biological active).[6] Moreover, cyclopropyl derivatives are attractive as intermediates in complex molecule synthesis,[7] synthetic building blocks,[8] and as templates for the construction of conformationally restricted amino acids and peptides.[9] In addition, the strained cyclopropane derivatives can undergo a variety of ring-opening reactions leading to the synthesis of a variety of complex molecules.[10] Thus, it is not surprising that an intense research effort has been focused on finding new catalytic methods for the preparation of cyclopropane derivatives. High levels of asymmetric induction have been achieved in metal-catalyzed intermolecular cyclopropa-

[a] Dr. I. Ibrahem, Dr. G.-L. Zhao, Dr. R. Rios, Dr. J. Vesely, Dr. H. Sundén, P. Dziedzic, Prof. Dr. A. Córdova
Department of Organic Chemistry, The Arrhenius Laboratory
Stockholm University, 106 91 Stockholm (Sweden)
Fax: (+46) 8-154-908
E-mail: acordova@organ.su.se
acordova1a@netscape.net

[b] Dr. I. Ibrahem, Dr. G.-L. Zhao, Dr. J. Vesely, P. Dziedzic, Prof. Dr. A. Córdova
Berzelii Center EXSELENT on Porous Materials
Arrhenius Laboratory, Stockholm University
106 91 Stockholm (Sweden)

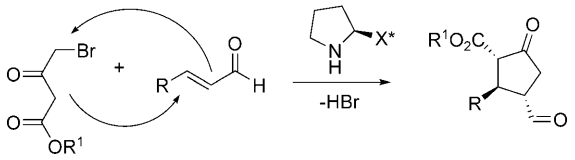
  

nations of electron-rich olefins involving Simmons–Smith and metal-carbenoid methodologies.[11] Aggarwal,[12] Gaunt,[13] and MacMillan[14] and their co-workers have pioneered the development of enantioselective cyclopropanations of α,β-unsaturated ketones, amides, esters, nitriles, sulfones, and aldehydes by using either preformed or in situ generated ylides.[12–14] Connon and co-workers have also reported the employment of Cinchona alkaloid derivatives as catalysts for the asymmetric cyclopropanation of nitroalkenes.[15] Inspired by these investigations and our previous experience in organocatalytic cascade catalysis,[16] we envisioned a simple asymmetric entry to 2-formyl cyclopropanes by chiral-amine-mediated domino reactions between halomalonates or 2-halo-β-ketoesters and α,β-unsaturated aldehydes (Scheme 1).




Scheme 1. Asymmetric synthesis of 2-formyl cyclopropanes.

Moreover, based on the importance of the cyclopentanone molecular architecture in natural products (e.g. prostaglandins),[17,18] we became intrigued as to whether we could expand the scope of chiral-amine-catalyzed domino Michael/intramolecular α-alkylation reactions to the assembly of highly substituted cyclopentanones in an asymmetric fashion (Scheme 2).[19–20]Notably, during our initial studies Ley



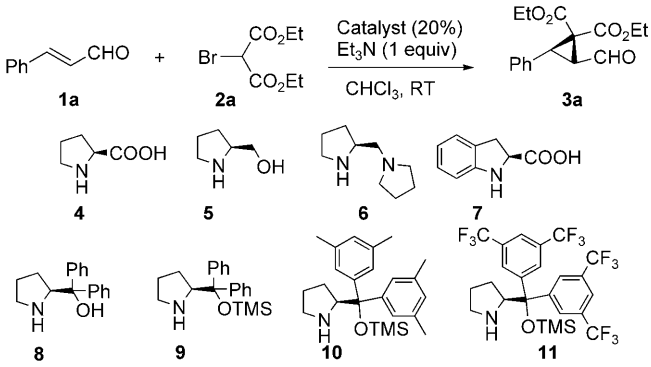

Scheme 2. Organocatalytic synthesis of highly substituted cyclopentanones.

and co-workers disclosed an elegant organocatalytic nitrocyclopropanation of cyclohexanone.[21] Our group has recently reported the organocatalytic asymmetric domino Michael/α-alkylation between bromomalonates and enals.[22] We also employed this catalytic strategy for the synthesis of cyclopentanones by using enals as substrates.[23] Wang and co-workers later reported very elegant similar results.[24] Herein, we describe our findings, including the scope, the combination with heterocyclic carbene catalysis, synthetic applications, and mechanisms of chiral-amine-catalyzed domino-asymmetric conjugate addition/α-alkylation reactions.

## Results and Discussion

**Catalyst screen for the cyclopropanation reaction**: In initial experiments, we screened chiral amines **4**–**11** (20 mol%) for the reaction between cinnamic aldehyde **1a** (0.3 mmol) and bromomalonate **2a** (0.25 mmol) with $NEt_3$ (0.25 mmol) as a proton sponge in $CHCl_3$ (1 mL) (Table 1). To our delight,

Table 1. Catalyst screen.[a]




| Entry | Catalyst | *t* [h] | Yield [%][b] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|
| 1 | **4** | 14 | 80 | >25:1 | 30 |
| 2 | **5** | 14 | 62 | >25:1 | 9 |
| 3 | **6** | 14 | 55 | >25:1 | 71 |
| 4 | **7** | 14 | 72 | >25:1 | −63 |
| 5 | **8** | 24 | Traces | >25:1 | nd[e] |
| 6 | **9** | 3 | 91 | >25:1 | 96 |
| 7 | **10** | 14 | 87 | >25:1 | 99 |
| 8 | **11** | 14 | traces | nd[e] | nd[e] |

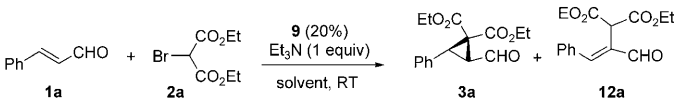
[a] Experimental conditions: A mixture of **2a** (0.25 mmol), aldehyde **1a** (0.3 mmol), $NEt_3$ (0.25 mmol) and catalyst (20 mol%) in 1.0 mL $CHCl_3$ was stirred at the temperature and conditions displayed in the Table. [b] Yield of isolated product. [c] Determined by NMR analyses of the crude reaction mixture. [d] Determined by chiral-phase HPLC analysis. [e] Not determined.

(*S*)-proline catalyzed the asymmetric formation of the corresponding 2-formylcyclopropane **3a** with excellent diastereoselectivity (>25:1 d.r. (*trans*/*cis*)) but low enantioselectivity (30% *ee*). Decreasing the bulk of the chiral pyrrolidine to an alcohol moiety as in catalyst **5** did not affect the diastereoselectivity but decreased the enantioselectivity of the transformation (Table 1, entry 2). Increasing the bulk of the chiral moiety to pyrrolidine as in catalyst **6** gave the corresponding cyclopropane **3a** in moderate yield with excellent diastereoselectivity (>25:1 d.r.) and good enantioselectivity (71% *ee*) (Table 1, entry 3).

The use of 2-carboxylic acid dihydroindole **7**, which has been successfully employed in the cyclopropanation of enals with dimethylphenylacyl sulfonium ylide, allowed the formation of *ent*-**3a** in 72% yield with >25:1 d.r. and 63% *ee* (Table 1, entry 4). Furthermore, the bulky prolinol **8** catalyzed the cyclopropanation reaction with very low conversion (Table 1, entry 5). Notably, chiral amines **9**[25] and **10** were the most efficient catalysts under our reaction conditions and catalyzed the formation of **3a** with excellent dia-

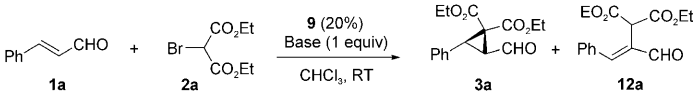
Table 2. Solvent screen.[a]




| Entry | Solvent | t [h] | Yield [%][b] | d.r.[c] | *ee* [%][d] | **3a**/**12a**[c] |
|---|---|---|---|---|---|---|
| 1 | $CHCl_3$ | 3 | 91 | >25:1 | 96 | >25:1 |
| 2 | MeOH | 3 | 23 | >25:1 | 89 | >25:1 |
| 3 | DMF | 24 | 24 | >25:1 | 87 | 2:1 |
| 4 | Toluene | 3 | 76 | >25:1 | 92 | >25:1 |
| 5 | $CH_2Cl_2$ | 6 | 50 | >25:1 | 97 | 2:1 |
| 6 | $CH_3CN$ | 6 | 50 | >25:1 | 91 | 3:1 |
| 7 | $Et_2O$ | 14 | 45 | >25:1 | 99 | 1:1 |
| 8 | EtOH | 14 | 55 | >25:1 | 88 | 2:1 |

[a] Experimental conditions: A mixture of **2a** (0.25 mmol), aldehyde **1a** (0.3 mmol), $NEt_3$ (0.25 mmol) and catalyst **9** (20 mol%) in 1.0 mL solvent was stirred at the temperature and conditions displayed in the Table. [b] Yield of isolated product. [c] Determined by NMR analyses of the crude reaction mixture. [d] Determined by chiral-phase HPLC analyses.

Table 3. The direct asymmetric α-aminomethylation of aldehydes **2** catalyzed by chiral diphenyl prolinol **9**.[a]




| Entry | Base | *t* [h] | Yield [%][b] | d.r.[c] | *ee* [%][d] | **3a**/**12a**[c] |
|---|---|---|---|---|---|---|
| 1 | $NEt_3$ | 3 | 91 | >25:1 | 96 | >25:1 |
| 2 | NaOAc | 14 | 68 | >25:1 | 98 | 9:1 |
| 3 | KOH | 14 | 59 | >25:1 | 90 | 7:1 |
| 4 | $K_2CO_3$ | 14 | 44 | >25:1 | 89 | >25:1 |
| 5 | DABCO[e] | 14 | 48 | >25:1 | 93 | >25:1 |
| 6 | DBU[f] | 14 | 68 | >25:1 | 96 | 14:1 |

[a] Experimental conditions: A mixture of **2a** (0.25 mmol), aldehyde **1a** (0.3 mmol), base (1 equiv) and catalyst **9** (20 mol%) in 1.0 mL $CHCl_3$ was stirred at the temperature and conditions displayed in the Table. [b] Isolated yield. [c] Determined by NMR analyses of the crude reaction mixture. [d] Determined by chiral-phase HPLC analyses. [e] DABCO = 1,4-diazabicyclo[2.2.2]octane. [f] DBU = 1,5-Diazabicyclo[5.4.0]undec-5-ene.

stereo- (>25:1) and enantioselectivity (96 and 99% *ee*, respectively; Table 1, entries 6 and 7).

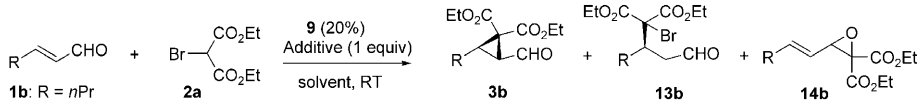
**Solvent and base screen**: We next decided to perform a solvent screen by using chiral amine **9** as the catalyst (Table 2).

The chiral amine **9** was able to catalyze the formation of **3a** with excellent diastereoselectivity (>25:1) and high enantioselectivity (87–99% *ee*) in all solvents investigated. We also found that the optically active cyclopropane **3a** could rearrange under our reaction conditions to the achiral enal **12a** in DMF, $CH_2Cl_2$, $CH_3CN$, $Et_2O$, and EtOH. The ratio of **3a**/**12a** ranged from 1:1 to >25:1. The highest yield and *ee* of **3a** were obtained in $CHCl_3$ where **12a** was not detected (Table 2, entry 1). The enantioselectivity of the reaction slightly decreased in DMF, $CH_3CN$, and EtOH (Table 2, entries 3, 6, and 8). In diethyl ether, **3a** was isolated with excellent enantiomeric excess (99% *ee*) but significant amounts of **12a** (**3a**/**12a** = 1:1) were also formed (Table 2, entry 7). We also screened the influence of the base additive on the chiral-amine-**9**-catalyzed reactions in $CHCl_3$ (Table 3).

Excellent diastereoselectivity (>25:1) and high enantioselectivity (89–98% *ee*) were achieved for all bases investigated and the side product **12a** was formed in low amounts (0–13%). The reactions with organic amine-base additives were efficient and gave the corresponding formylcyclopropyl derivative **3a** in high yield. Of the organic bases investigated, the addition of $NEt_3$ gave the best results with respect to the efficiency of the reaction (Table 3, entry 1). However, the inorganic base additives KOH and $K_2CO_3$ slightly decreased the enantioselectivity (Table 3, entries 3 and 4). The catalytic cyclopropanation reaction between the aliphatic enal **1b** and **2a** was also investigated (Table 4).

Interestingly, in this case cyclopropane **3b**, Michael adduct **13b,** and epoxide **14b** were formed depending upon the solvent. The aliphatic rearrangement product **12b** was not detected. For example, the reaction in $CHCl_3$ without the addition of $NEt_3$ gave the corresponding cyclopropane derivative **3b** in 20% (99% *ee*) conversion together with Michael adduct **13b** in 20% conversion after 3 h (Table 4, entry 1). Prolonging the reaction time did not increase the conversion of enal **1b** (Table 4, entry 2). The addition of $NEt_3$ as a proton sponge significantly improved the efficiency and diastereoselectivity of the reaction (15:1 d.r.) while the excellent enantioselectivity (99% *ee*) of the transformation was maintained. Hence, the in situ formation of HBr in the α-alkylation step inhibits the product formation. Performing the reaction in methanol without addition of $NEt_3$

Table 4. The asymmetric cyclopropanation of enal **1b** catalyzed by the chiral diphenyl prolinol **9**.[a]

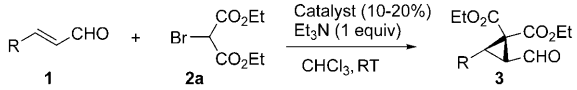


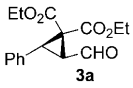
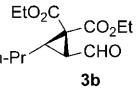
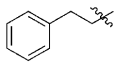
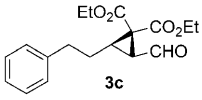
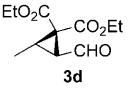
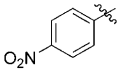
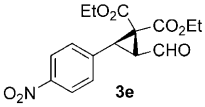
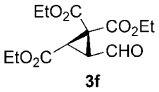
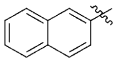
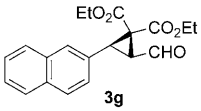
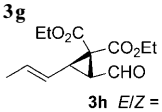
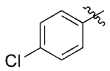
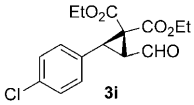
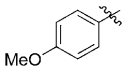
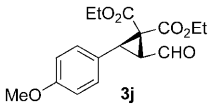
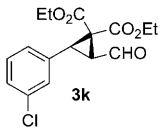
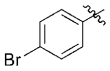
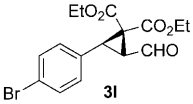

| Entry | Solvent | Additive | *t* [h] | Conv. [%][b] | **3b** [%][c] | d.r.[b] | *ee* [%][d] | **13b** [%][c] | **14b** [%][c] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $CHCl_3$ | None | 3 | 41 | 20 | 5:1 | 99 | 20 | <1 |
| 2 | $CHCl_3$ | None | 16 | 41 | 20 | 5:1 | 99 | 20 | <1 |
| 3 | $CHCl_3$ | $NEt_3$ | 1 | 50 | 50 | 15:1 | 99 | <1 | 0 |
| 4 | $CHCl_3$ | $NEt_3$ | 3 | 95 | 95 | 15:1 | 99 | <1 | 0 |
| 5 | MeOH | None | 3 | 40 | 0 | – | – | 0 | 40 |
| 6 | MeOH | None | 16 | 65 | 5 | nd[e] | nd[e] | 0 | 60 |
| 7 | $CH_3CN$ | None | 3 | 20 | 20 | >25:1 | 99 | 0 | 0 |
| 8 | $CH_3CN$ | None | 16 | 20 | 20 | >25:1 | 99 | 0 | 0 |

[a] Experimental conditions: A mixture of **2a** (0.25 mmol), aldehyde **1b** (0.3 mmol) and catalyst **9** (20 mol%) in 1.0 mL solvent was stirred at the temperature and conditions displayed in the Table. [b] Determined by NMR analyses of the crude reaction mixture. [c] Percent formed product as determined by NMR analyses. [d] Determined by chiral-phase GC analyses. [e] Not determined (nd).

Table 5. Scope of the organocatalytic asymmetric cyclopropanation reaction.[a]




| Entry | R | Catalyst | Product | Time [h] | Yield [%][b] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|---|
| 1 | Ph | **10** |  **3a** | 14 | 87 | >25:1 | 99 |
| 2 | Ph | **9** | | 3 | 83 | >25:1 | 94[e] |
| 3 | *n*-Pr | **9** |  **3b** | 3 | 80 | 15:1 | 99 |
| 4 |  | **9** |  **3c** | 3 | 74 | 25:1 | 94 |
| 5 | Me | **9** |  **3d** | 5 | 88 | 9:1 | 94 |
| 6 |  | **10** |  **3e** | 14 | 81 | >25:1 | 98 |
| 7 | $CO_2Et$ | **9** |  **3f** | 14 | 50 | >25:1 | 93[f] |
| 8 |  | **9** |  **3g** | 14 | 83 | >25:1 | 96[g] |
| 9 | | **10** | **3g** | 14 | 80 | >25:1 | 93 |
| 10 |  *E*/*Z* = 3:1 | **9** |  **3h** *E*/*Z* = 14:1 | 3 | 76 | 14:1 | 99 |
| 11 |  | **9** |  **3i** | 4 | 60 | >25:1 | 96 |
| 12 |  | **9** |  **3j** | 14 | 72 | >25:1 | 90 |
| 13 |  | **9** |  **3k** | 4 | 79 | >25:1 | 94 |
| 14 |  | **9** |  **3l** | 3 | 61 | >25:1 | 98 |

[a] Experimental conditions: A mixture of **2** (0.25 mmol), aldehyde **1** (0.30 mmol), triethylamine (0.25 mmol) and catalyst **9** or **10** (10 or 20 mol%) in $CHCl_3$ (1.0 mL) was stirred at room temperature. The crude product **3** was purified by column chromatography. [b] Isolated yield of pure product **3** after silica-gel column chromatography. [c] Determined by NMR analysis. [d] Determined by chiral-phase HPLC or GC analyses. [e] 10 mol% catalyst. [f] Reaction performed at −20°C. [g] Reaction performed at 4°C.

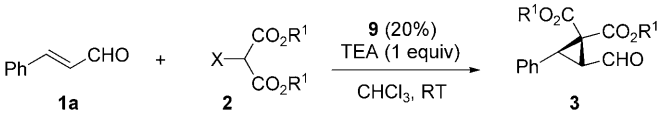
completely switched the chemoselectivity of the transformation and the corresponding Darzens epoxidation compound **14b** was exclusively furnished.

**Substrate scope**: Based on the results from the catalyst-, solvent-, and base-screens, we decided to investigate the scope of the reaction by using chiral amines **9** or **10** as the catalysts, $NEt_3$ as the base and $CHCl_3$ as the solvent (Table 5).

The reactions had a broad substrate scope and catalyst **9** was the most efficient. The corresponding products **3a–3l** were isolated in good to high yields with up to >25:1 d.r. and 90–99% *ee*. Moreover, the substrates did not rearrange to compounds **12** under these reaction conditions. α,β-Unsaturated aldehydes with an aryl substituent were isolated in high yields with excellent diastereomeric ratios (>25:1) and high *ee* values (90–99%). Enals with aliphatic substituents were rapidly converted to their corresponding 2-formyl cyclopropane derivatives and formed with high diastereoselectivity (9:1–25:1 d.r.) and 94–99% *ee* (Table 5, entries 3–5). Notably, the reaction was regiospecific when 2,4-hexadienal was used as the substrate (Table 5, entry 10). In this case, the *E*/*Z* ratio of the starting dienal **1h** was 3:1, while the diastereomeric ratio of the corresponding *trans* product **3h** was 14:1. The reaction also gave similar results when the catalyst loading was decreased to 10 mol% (Table 5, entry 2). We also investigated the effect of the ester moiety of the 2-halomalonates **2** (Table 6).

Table 6. Enantioselective cyclopropanation with different halomalonates **2** catalyzed by the chiral diphenyl prolinol **9**.[a]

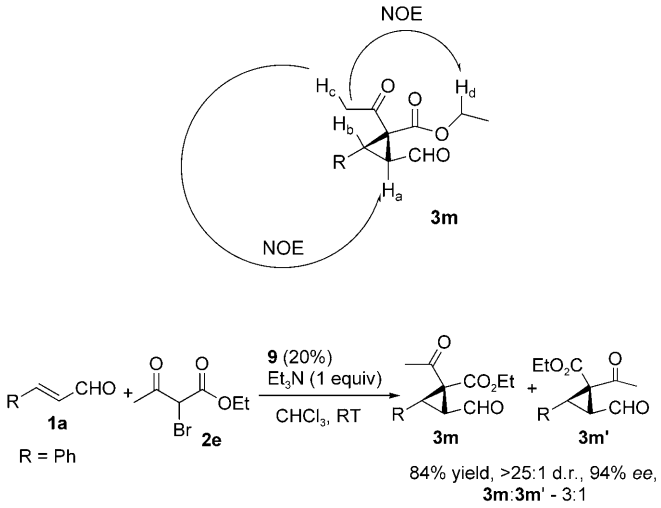



| Entry | $R^1$ | X | Prod. | *t* [h] | Yield [%][b] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|---|
| 1 | Et | Br | **3a** | 3 | 91 | >25:1 | 96 |
| 2 | Bn | Br | **3ab** | 14 | 42 | >25:1 | 99 |
| 3 | Me | Br | **3ac** | 14 | 78 | >25:1 | 96 |
| 4 | Et | Cl | **3a** | 14 | 73 | >25:1 | 97 |

[a] Experimental conditions: A mixture of **2** (0.25 mmol), aldehyde **1a** (0.30 mmol), triethylamine (0.25 mmol) and catalyst **9** (20 mol%) in $CHCl_3$ (1.0 mL) was stirred at room temperature. The crude product **3** was purified by column chromatography. [b] Isolated yield of pure product **3** after silica-gel column chromatography. [c] Determined by NMR analysis. [d] Determined by chiral-phase HPLC analyses.

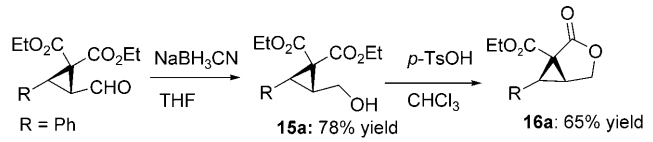
We found that the efficiency of the reaction decreased with increased size of the ester groups of halomalonates **2a–2d**. However, the enantioselectivity increased. For example, the reaction between enal **1a** and dibenzyl bromomalonate ester **2b** gave the corresponding cyclopropane derivative **3ab** in 42% yield and 99% *ee* (Table 6, entry 2). Moreover, changing the halogen substituent from bromo to chloro did not affect the reaction. We also investigated the enantioselective organocatalytic cyclopropanation reaction between 2-bromoketoesters and enals. For example, the reaction between enal **1a** and ethyl-2-bromo-3-oxobutanoate **2e** was highly diastereo- and enantioselective (>25:1 d.r., 94% *ee*) and gave the corresponding cyclopropane products **3m** and **3m′** in a 3:1 ratio (Scheme 3).

The relative configuration of cyclopropane **3m** was established by NOE experiments. Hence, NOEs were measured between $H_a$ and $H_c$, and $H_b$ and $H_d$, respectively. The protected diarylprolinol catalysts could also catalyze highly enantioselective nitrocyclopropanation reactions between



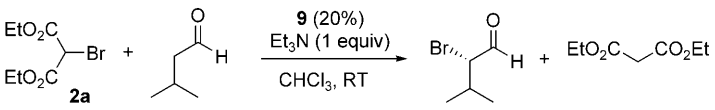

Scheme 3. Chiral amine-**9**-catalyzed domino reaction between **2e** and enal **1a**.

bromonitromethane and enals **1**. For example, chiral amine **9** catalyzed the domino reaction between cinnamic aldehyde **1a** and bromonitromethane and the corresponding 2-formylcyclopropane derivative was isolated in 67% yield with 1:1 d.r. and 95% *ee*.[26] The 2-formyl cyclopropanes **3** from the catalytic reaction are valuable chiral precursors to 3–5 bicyclic frameworks with a quarternary carbon stereocenter. Accordingly, cyclopropane **3a** was treated with $NaBH_3CN$ in THF, to afford the corresponding alcohol **15a**, which upon intramolecular cyclization gave the corresponding lactone **16a** by treatment with *p*-TsOH in $CHCl_3$ (Scheme 4).




Scheme 4. Two-step asymmetric synthesis of chiral lactone **16**.

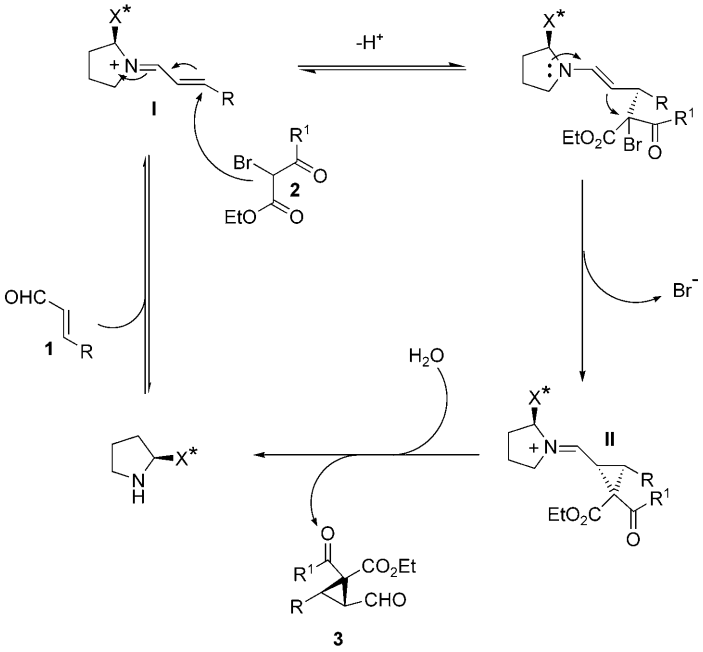
Notably, we also investigated whether bromomalonates **2** could be used as electrophiles in intermolecular α-alkylation reactions of aldehydes by using chiral amine **9** as the catalyst (Scheme 5). However, only the α-brominated aldehyde product was formed.




Scheme 5. Synthesis of α-bromoaldehydes.

The mechanism of the chiral-amine-catalyzed cyclopropanation is depicted in Scheme 6. Accordingly, efficient shielding of the *Si*-face (*Re* when R = Aryl) of the chiral iminium intermediate **I** by the bulky aryl groups of chiral pyrrroli-

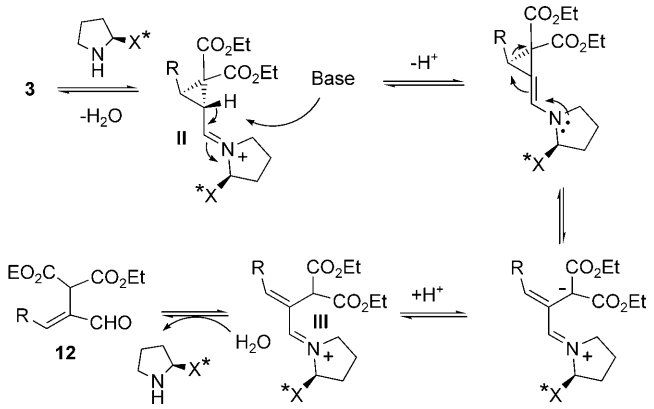
  



Scheme 6. Catalytic tandem asymmetric cyclopropanation/esterification of enals.

dines **9** and **10** leads to stereoselective *Re*-facial nucleophilic conjugate addition by the 2-bromo substituted malonates and β-ketoesters **2** (Scheme 6). Next, the generated chiral enamine intermediate performs an intramolecular 3-*exo-tet* nucleophilic attack to form the cyclopropane ring. The intramolecular ring-closure pushes the equilibrium forward and makes this step irreversible. This is the same type of mechanism that is present in the organocatalytic asymmetric epoxidation of enals[5h,k] and asymmetric aziridination of enals.[16d] Hydrolysis of iminium intermediate **II** releases the catalyst and gives the corresponding 2-formyl cyclopropane **3**. In the case of (*S*)-2-carboxylic acid dihydroindole **7** catalysis, the bromomalonate **2** approached the opposite face of the iminium intermediate to give cyclopropanes *ent*-**3**.

The proposed mechanism for the formation of side-product **12** is depicted in Scheme 7. Thus, iminium intermediate

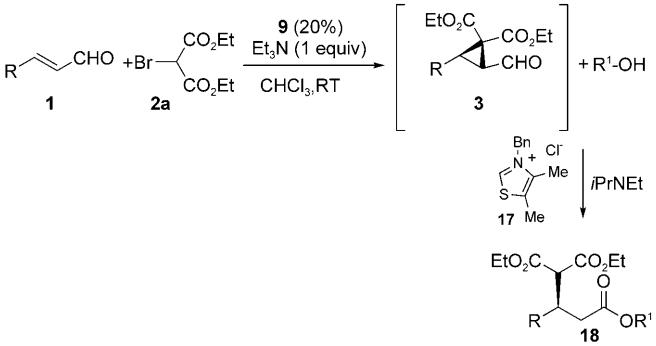


Scheme 7. Catalytic formation of side-product **12**.

**II**, which is formed either from the cyclopropanation reaction (Scheme 7) or by in situ condensation between the chiral-amine catalyst and the cyclopropyl derivative **3**, undergoes base promoted enamine formation followed by subsequent ring-opening. Hydrolysis of iminium intermediate **III** liberates the chiral-amine catalysts and gives the enal **12**.

The mechanism was further supported by the ability of chiral amine **9** to catalytically rearrange cyclopropyl derivative **3a** to enal **12a** in the presence of $NEt_3$ in $CH_2Cl_2$.[24] Performing the reaction without catalyst did not give the corresponding enal **12a**.

**One-pot combination of catalytic domino Michael/α-alkylation reactions and heterocyclic carbene catalysis**: Selective ring-openings of cyclopropane derivatives are important in organic synthesis.[10] In this context, Bode has recently shown that 2-cyclopropyl aldehydes can be converted into the corresponding acyclic esters under mild conditions.[27] Intrigued by this and the benefits of developing asymmetric one-pot multicomponent reactions, we decided to investigate the possibility of combining amine and heterocyclic carbene catalysis (AHCC) for the direct conversions of enals **1** to valuable β-malonate esters (Scheme 8).[28]



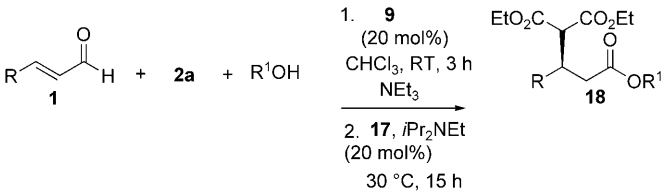
Scheme 8. Catalytic tandem asymmetric cyclopropanation/esterification of enals.

To achieve this, we envisioned that enal **1** first would react according to our organocatalytic cyclopropanation reaction with bromomalonate **2a** to form the corresponding 2-formylcyclopropane **3**. Next, organocatalytic in situ C–C bond-cleavage/ring-opening followed by concomitant oxidation of the aldehyde and subsequent esterification would give the corresponding optically active β-malonate ester **18**. In Table 7, the results from our combined AHCC experiments are shown.

The organocatalytic one-pot tandem reactions gave the corresponding β-malonate esters **18** in good to high yields with 94–97% *ee*. For example, β-malonate ester **18b** was isolated in 74% overall yield with 94% *ee* (Table 7, entry 3). The enantioselectivity achieved in the catalytic cyclopropanation step was not affected by the ring-opening step. Moreover, the alcohol used in the ring-opening step can be readily changed and β-malonate esters are valuable chiral syn-

Table 7. Catalytic tandem asymmetric cyclopropanation/esterification of enals.




| Entry | R | $R^1$ | Product | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|
| 1 | Ph | Et | **18a** | 69 | 97 |
| 2 | Ph | Me | **18b** | 56 | 97 |
| 3 | Ph | Me | **18b** | 74[c] | 94[c] |
| 4 | 4-$NO_2C_6H_4$ | Me | **18c** | 74[d] | 95 |
| 5 | 2-Naph | Me | **18d** | 74[e] | 96 |

[a] Isolated yield of the pure product **18** after silica-gel chromatography. [b] Determined by chiral-phase HPLC analyses. [c] 30 mol% **17**. [d] Reaction first run for 1.5 h at room temperature followed by addition of **17**. [e] Reaction first run for 6 h at 4°C followed by addition of **17**. DIPEA = Diisopropylethyl amine.

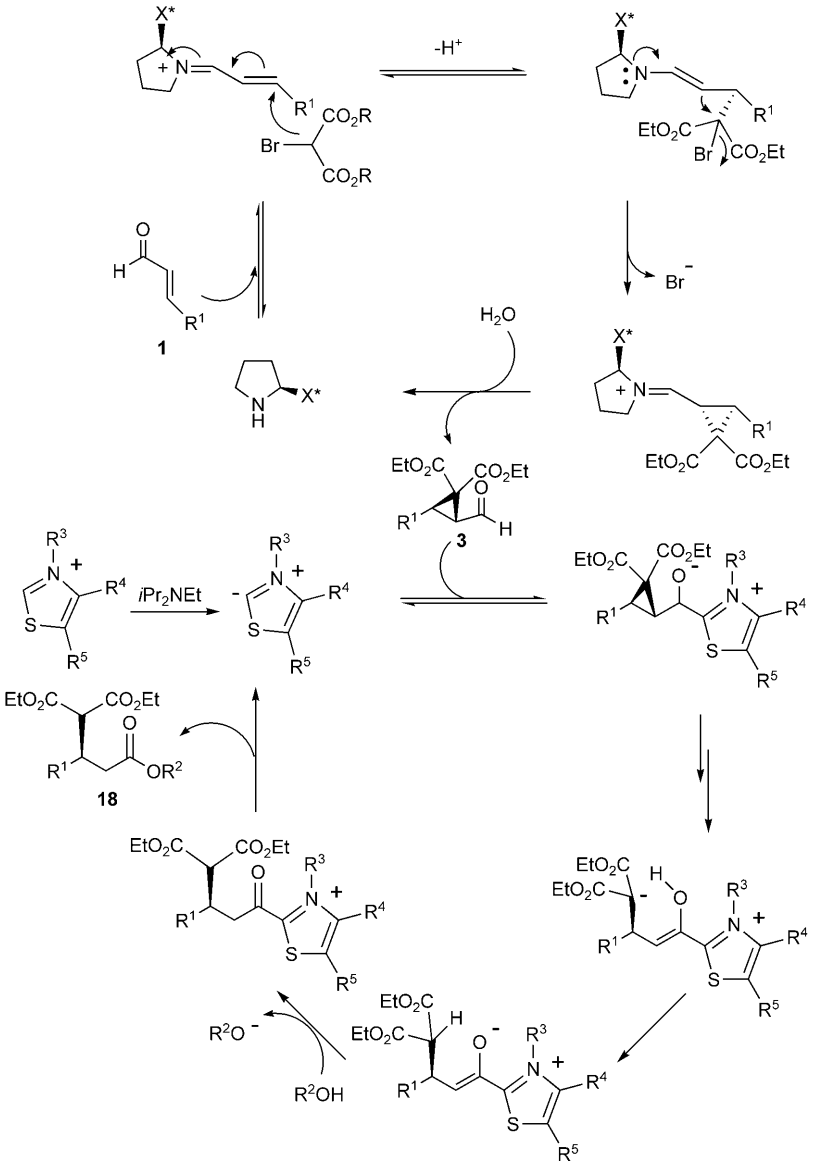
thons for further transformations. Comparison with the literature revealed that the absolute configuration of compound **18b** at C3 was *R* ($[\alpha]_D^{25} = -33.2$ ($c = 1.0$, $CHCl_3$), Lit. ((*R*)-**18b**, $[\alpha]_D^{25} = -29$ ($c = 1.0$, $CHCl_3$)[29]). Hence, the reactions with catalysts (*S*)-**9** and (*S*)-**10** give access to (2*R*,3*R*)-2-formyl-cyclopropanes **3**.

The mechanism of the one-pot conversion of enals **1** to β-malonate esters **18** by tandem AHCC catalysis starts with the diastereo- and enantioselective domino-iminium/enamine-activation mechanism (Scheme 9). Next, the base-generated heterocyclic carbene catalyst catalyzes the C–C bond-cleavage/ring-opening, which is followed by concomitant oxidation of the aldehyde and subsequent esterification.

**Amine-catalyzed domino Michael/α-alkylation reactions between enals and 4-bromo-acetoacetate**: As described below, we became intrigued as to whether highly substituted cyclopentanones could be assembled in an asymmetric fashion by our organocatalytic domino Michael/intramolecular α-alkylation reaction strategy by using enals **1** and 4-bromo-acetoacetate **2** as substrates (Scheme 2). This was not straightforward, since Jørgensen and co-workers recently showed that the reaction between 4-choloro-acetoacetate and enals **1** only gave the corresponding Michael adduct.[30] Nevertheless, in an initial experiment, we performed the reaction between heptenal **1j** and 4-bromo-acetoacetate **2f** under our optimized cyclopropanation conditions (Scheme 10). To our dismay, the reaction did not give the desired cyclopentane product **19a**.

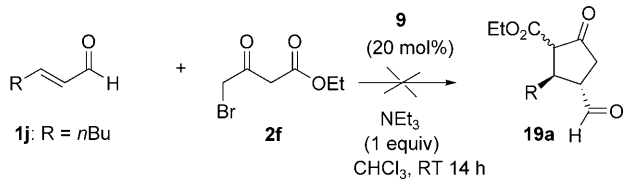
However, a catalyst and solvent screen for the organocatalytic reaction between heptenal **1j** and 4-bromo-acetoacetate **2f** was performed (Table 8).

Several chiral amines were screened and it was found that (*S*)-proline catalyzed the formation of *ent*-**19a** in high yield with moderate enantioselectivity (55% *ee*) when AcONa was used as the proton sponge (Table 8, entry 1). Out of the four possible diastereoisomers only two (**19a** and **19a′**) were



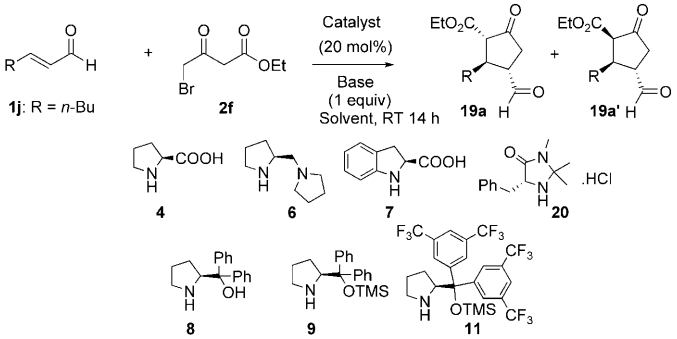

Scheme 9. One-pot combination of AHCC catalysis.




Scheme 10. Attempted synthesis of cyclopentanone **19a**.

Table 8. Catalytic domino reactions between enal **1j** and bromoacetoacetate **2f**.[a]

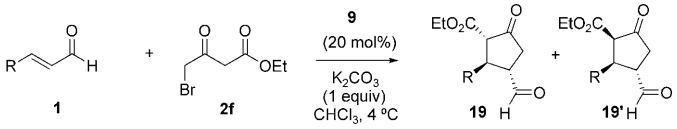


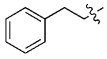

| Entry | Catalyst | Solvent | Base | Yield [%][b] | d.r.[c] | *ee*[d] |
|---|---|---|---|---|---|---|
| 1 | **4** | $CHCl_3$ | AcONa | 74 | 8:1 | −53 |
| 2 | **6** | $CHCl_3$ | AcONa | 0 | – | – |
| 3 | **7** | $CHCl_3$ | AcONa | 0 | – | – |
| 4 | **20** | $CHCl_3$ | AcONa | 0 | – | – |
| 5 | **8** | $CHCl_3$ | AcONa | 0 | – | – |
| 6 | **9** | $CHCl_3$ | AcONa | 67 | 8:1 | 97 |
| 7 | **10** | $CHCl_3$ | AcONa | 0 | – | – |
| 8 | **9** | $CHCl_3$ | $NEt_3$ | 0 | – | – |
| 9 | **9** | $CHCl_3$ | $K_2CO_3$ | 88 | 8:1 | 98 |
| 10 | **9** | $CHCl_3$ | KOH | 55 | 8:1 | 96 |
| 11 | **9** | $CH_3CN$ | AcONa | 77 | 8:1 | 91 |
| 12 | **9** | toluene | AcONa | 62 | 8:1 | 96 |
| 13 | **9** | THF | AcONa | 55 | 8:1 | 96 |
| 14 | **9** | MeOH | AcONa | 80 | 8:1 | 88 |
| 15 | **9**[e] | $CHCl_3$ | AcONa | 72 | 10:1 | 99 |

[a] Experimental conditions: To a stirred solution of catalyst (20 mol%) in solvent (1.0 mL) was added α,β-unsaturated aldehyde **1j** (0.30 mmol), base (0.25 mmol) and ethyl 4-bromo-3-oxobutanoate **2f** (0.25 mmol). The reaction was vigorously stirred for 14 h at room temperature. The crude product was purified by silica-gel column chromatography (pentane/EtOAc mixtures) to give cyclopentanone **19a**. [b] Isolated yield of pure compound **19a**. [c] The ratio of **19a**/**19a′** as determined by $^1$H NMR. [d] Determined by chiral-phase GC analysis. [e] Reaction run at 4 °C.

formed in a ratio of 8:1. To our delight, chiral amine **9** catalyzed the formation of cyclopentanone **19a** with three contiguous stereocenters with high diastereo- (8:1 d.r.) and enantioselectivity (97% *ee*, Table 8, entry 6). Hence, one predominant enantiomer was formed under these reaction conditions. In contrast to the cyclopropanation reactions, the use of an inorganic base additive was essential for product formation. The chiral amine **9** catalyzed highly stereoselective assembly of cyclopentane **19a** in an asymmetric fashion in several solvents. Notably, cyclopentanone **19a** was isolated in 88% yield with 8:1 d.r. and 98% *ee* when $K_2CO_3$ was used as the base (Table 8, entry 9). The diastereo- and enantioselectivity of the domino reaction could be further improved if the reaction temperature was decreased. For example, running the reaction at 4 °C with $K_2CO_3$ as the proton sponge allowed for the isolation of **19e** in 72% yield with 10:1 d.r. and 99% *ee* (Table 8, entry 15). With these results in hand we decided to investigate the catalytic domino reaction between 4-bromo-β-ketoester **2f** and different enals **1** with (*S*)-chiral amine **9** as the organocatalyst and $K_2CO_3$ as the inorganic base (Table 9).

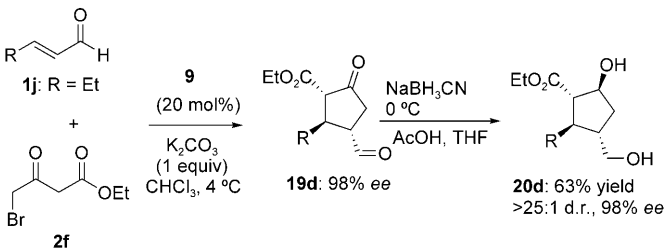
Table 9. Direct organocatalytic asymmetric domino reactions between 4-bromo β-ketoester **2f** and enals **1**.[a]




| Entry | R | Prod. | *T* [°C] | *t* [h] | Yield[b] | d.r.[c] | *ee*[d] |
|---|---|---|---|---|---|---|---|
| 1 | *n*-Bu | **19a** | 4 | 14 | 72 | 10:1 | 99 |
| 2 | *n*-Bu | **19a** | RT | 14 | 88 | 8:1 | 98 |
| 3 | *n*-Pr | **19b** | 4 | 14 | 83 | 10:1 | >99 |
| 4 |  | **19c** | RT | 3 | 58 | 12:1 | 99 |
| 5 | Et | **19d** | 4 | 14 | 70 | 9:1 | 98 |
| 6 | Me | **19e** | 4 | 14 | 76 | 6:1 | 93 |

[a] Experimental conditions: α,β-Unsaturated aldehyde **1** (0.30 mmol), $K_2CO_3$ (0.25 mmol) and ethyl 4-bromo-3-oxobutanoate **2f** (0.25 mmol) were added to a stirred solution of catalyst (20 mol%) in solvent (1.0 mL). The reaction was vigorously stirred for the time shown in the Table at 4 °C or room temperature. Next, the crude product was purified by silica-gel column chromatography (pentane/EtOAc-mixtures) to give the corresponding cyclopentanones **19**. [b] Isolated yield of pure compound **19**. [c] The ratio of **19**:**19′** as determined by $^1$H NMR analysis. [d] Determined by chiral-phase GC analysis.

The organocatalytic domino process allowed for the formation of chiral cyclopentanones **19a–e** possessing three new stereocenters in good to high yields with 6:1–12:1 d.r. and 93–>99% *ee* from simple starting materials. For example, cyclopentanone **19c** was isolated in 58% yield with 12:1 d.r. and 99% *ee* (Table 9, entry 4). In this case, the best results were achieved at room temperature. Highly diastereoselective reduction of chiral cyclopentanones **19** with $NaBH_3CN$ gave access to the corresponding diols **20** containing four stereocenters without affecting the enantiomeric excess. For example, diol **20d** was isolated in 63% yield as the predominant diastereomer with 98% *ee* (Scheme 11).

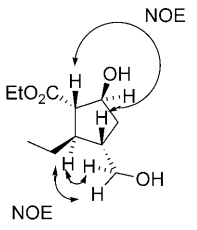


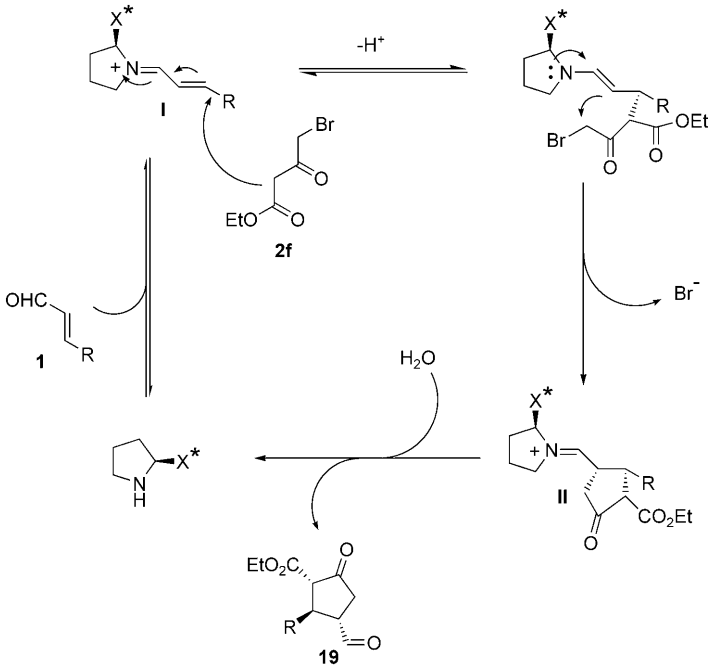

Scheme 11. Synthesis of cyclopentanediol **20d**.

Thus, highly functionalized cyclopentanes containing primary and secondary alcohol groups can be synthesized by the organocatalytic domino reaction.

The relative stereochemistry of the alcohol **20d** was established by NOE experiments and from the coupling constants of the ring protons. The experiments revealed that all the substituents of **20d** were *trans*. The proposed mechanism for the organocatalytic domino Michael/α-alkylation reaction between enals **1** and 4-bromo-acetoacetate **2f** is similar to that of the cyclopropanation reaction (Scheme 12). Thus, efficient shielding of the *Si*-face of the




Scheme 12. The proposed mechanism for the chiral-amine-catalyzed enantioselective domino Michael/α-alkylation reaction between enals **1** and **2f**.

chiral iminium intermediate **I** by the bulky aryl groups of chiral pyrrrolidine **9** leads to stereoselective *Re*-facial nucleophilic conjugate addition by the 4-bromoacetoacetate **2f**. Next, the in situ generated chiral enamine undergoes an intramolecular 5-*exo-tet* cyclization from the same face as the incoming **2f**, followed by hydrolysis of the resulting iminium intermediate **II** to give the cyclopentanone product **19**. In the case of (*S*)-proline **5** catalysis, the β-ketoester approached the opposite face of the iminium intermediate to give cyclopentanones *ent*-**19**.

## Conclusion

We report the scope, applications, and mechanism of organocatalytic asymmetric domino Michael/α-alkylation reactions between α,β-unsaturated aldehydes and bromomalonates or bromoacetoacetate esters. The protected chiral diarylprolinol-catalyzed reactions were highly diasetereo- and enantioselective and provide direct routes to functionalized cyclopropanes and cyclopentanes with 90–99% *ee*. The chiral-amine-catalyzed domino reactions were also combined in a one-pot tandem process with heterocyclic carbene catalysis for the conversion of enals to valuable optically active products such as β-malonate esters (94–97% *ee*). Thus, amine and heterocyclic carbene catalysis (AHCC) can be combined. Further, expansion of organocatalytic asymmetric domino Michael/α-alkylation reactions such as nitrocyclopropanations and application in functional carbocycle synthesis are ongoing.

## Experimental Section

**General procedures**: Chemicals and solvents were either purchased puriss p. A. from commercial suppliers or purified by standard techniques. Catalysts **9** and **10** were synthesized according to literature procedures.[5h,k,25] For thin-layer chromatography (TLC), silica-gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2{\cdot}H_2O$ (10 g), conc. $H_2SO_4$ (60 mL), and $H_2O$ (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. $H_2SO_4$ (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed with silica-gel Merck 60 (particle size 0.040–0.063 mm), $^1H$ and $^{13}C$ NMR spectra were recorded on a Varian AS 400 spectrometer. Chemical shifts are given in $\delta$ relative to tetramethylsilane (TMS), the coupling constants $J$ are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature, TMS served as internal standard ($\delta=0$ ppm) for $^1H$ NMR spectroscopy, and $CDCl_3$ was used as internal standard ($\delta=77.0$ ppm) for $^{13}C$ NMR spectroscopy. HPLC was carried out with a Waters 2690 Millennium instrument with a photodiode array detector. Optical rotations were recorded on a Perkin–Elemer 241 Polarimeter ($\lambda=589$ nm, 1 dm cell). HRMS were recorded on a Bruker MicrOTOF spectrometer.

**Typical experimental procedure for the organocatalytic cyclopropanation reactions**: α,β-Unsaturated aldehyde **1** (0.3 mmol, 1.2 equiv), triethylamine (0.25 mmol, 1.0 equiv), and diethyl bromomalonate **2a** (0.25 mmol, 1.0 equiv) were added to a stirred solution of catalyst (20 mol%) in $CHCl_3$ (1.0 mL). The reaction was vigorously stirred for the time described in the Tables. Next, the crude product was purified by silica-gel chromatography (pentane (toluene)/EtOAc-mixtures) to give the corresponding cyclopropane derivatives **3**.

**Cyclopropane 3a:** Colorless oil; $[\alpha]_D^{25}=-20.8$ ($c=1.0$ in $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta=9.45$ (d, $J=4.4$ Hz, 1H), 7.35–7.20 (m, 5H), 4.35–4.25 (m, 2H), 3.92 (qd, $J=7.2$ Hz, $J'=2.0$ Hz, 2H), 3.82 (d, $J=7.2$ Hz, 1H), 3.37 (dd, $J=7.2$ Hz, $J'=4.4$ Hz, 1H), 1.30 (t, $J=7.2$ Hz, 3H), 0.93 ppm (t, $J=7.2$ Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta=196.1$, 166.0, 164.6, 132.2, 128.5, 128.4, 128.0, 62.5, 62.0, 44.7, 38.1, 35.3, 14.0, 13.7 ppm; IR (KBr): $\tilde{\nu}=2983$, 2938, 2872, 1732, 1448, 1369, 1295, 1288, 1247 1217, 1182, 1145, 1028 $cm^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{16}H_{18}O_5Na$: 313.1046 [$M$+Na$^+$]; found: 313.1049; HPLC (ODH column, *n*-hexane/*i*PrOH 95:5, $\lambda=210$ nm, 0.5 mL $min^{-1}$): $t_R$ (major enantiomer) = 19.0, $t_R$ (minor enantiomer) = 25.6 min.

**Cyclopropane 3b:** Colorless oil; $[\alpha]_D^{25}=-43.4$ ($c=1.0$ in $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta=9.23$ (d, $J=5.2$ Hz, 1H), 4.32–4.14 (m,

4H), 2.65 (dd, $J=7.2$ Hz, $J'=5$–2 Hz, 1H), 2.49 (m, 1H), 1.52–1.40 (m, 4H), 1.30–1.20 (m, 6H), 0.92 ppm (t, $J=6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): 196.7, 166.5, 166.0, 62.1, 62.1, 42.9, 40.3, 32.0, 28.5, 21.8, 14.1, 13.9, 13.5 ppm; IR (KBr): $\tilde{\nu}=2964$, 2936, 2874, 1731, 1466, 1447, 1369, 1295, 1223, 1201, 1146 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{13}H_{20}O_5+Na^+$: 279.1203 $[M+Na]^+$; found: 279.1195; GC (chrompak CP-Chirasil-Dex CB-column; Temperature program: 5 min,70 °C//2 °C min$^{-1}$//110 °C, 10 min//10 °C min$^{-1}$//200,10 min): $t_R$ (major enantiomer) = 40.3, $t_R$ (minor enantiomer) = 40.4 min.

**Cyclopropane 3c**: Colorless oil; $[\alpha]_D^{25}=-12.8$ ($c=1$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta=9.18$ (d, $J=4.8$ Hz, 1H), 7.40–7.10 (m, 5H), 4.35–4.10 (m, 4H), 2.71 (td, $J=7.8$ Hz, $J'=2.1$ Hz, 2H), 2.61 (dd, $J=7.2$ Hz, $J'=5.1$ Hz, 1H), 2.48 (m, 1H), 1.96–1.82 (m, 1H), 1.82–1.68 (m, 1H), 1.30–1.22 ppm (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): 196.5, 166.3, 166.0, 140.4, 128.5, 128.5, 126.3, 62.2, 62.2, 42.8, 40.2, 34.8, 31.7, 28.5, 14.1, 14.0 ppm; IR (KBr): $\tilde{\nu}=2983$, 1733, 1466, 1288, 1217, 697 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{18}H_{22}O_5+Na^+$: 341.1359 $[M+Na]^+$; found: 341.1371; the enantiomeric excess was determined after in situ reduction with $NaBH_4$ of the aldehyde to the corresponding alcohol: HPLC (OD-H column, *n*-hexane/*i*PrOH 90:10, $\lambda=250$ nm, 0.5 mL min$^{-1}$): $t_R$ (major enantiomer) = 16.9, $t_R$ (minor enantiomer) = 19.6 min.

**Cyclopropane 3d**: Colorless oil; $[\alpha]_D^{25}=-62.2$ ($c=1$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta=$ 9.21 (d, $J=5.3$ Hz, 1H) 4.11–4.28 (m, 4H), 2.59 (dd, $J=$ 7.4, 5.2 Hz, 1H), 2.52 (m, 1H), 1.24 (q, $J=7.3$, 15.1 Hz, 6H), 1.20 ppm (d, $J=6.2$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=$ 196.8, 166.5, 165.8, 62.2, 62.1, 43.2, 41.1, 26.6, 14.1, 14.0, 11.8 ppm; HRMS (ESI): $m/z$: calcd for $C_{11}H_{16}O_5+Na^+$: 251.0890 $[M+Na]^+$; found: 251.0895; GC (chrompak CP-Chirasil-Dex CB-column; temperature program: 5 min,70 °C//2 °C min$^{-1}$//110 °C, 10 min//10 °C min$^{-1}$//200,10 min.): $t_R$ (major enantiomer) = 36.7, $t_R$ (minor enantiomer) = 38.2 min.

**Cyclopropane 3e**: Colorless oil; $[\alpha]_D^{25}=-58.2$ ($c=1$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta=$ 9.54 (d, $J=4.1$ Hz, 1H) , 8.17 (d, $J=8.6$ Hz, 2H), 7.44 (d, $J=8.62$ Hz, 2H) , 4.23–4.38 (m, 2H), 3.91–4.05 (m, 2H), 3.85 (d, $J=7.6$ Hz,1H), 3.44 (dd, $J=7.6$,4.1 Hz, 1H) , 1.31 (t, $J=7.0$ Hz, 3H), 1.01 ppm (t, $J=7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=$ 195.0, 165.3, 165.3, 147.6, 139.8, 129.6, 123.6, 62.8, 62.5, 45.0, 38.0, 34.6, 14.0, 13.8 ppm; HRMS $m/z$ calcd for $C_{16}H_{17}NO_7+Na^+$: 358.0897 $[M+Na]^+$; found: 358.0897; the enantiomeric excess was determined after in situ reduction with $NaBH_4$ of the aldehyde to the corresponding alcohol; HPLC (AD column, *n*-hexane/*i*PrOH 90:10, $\lambda=250$ nm, 1 mL min$^{-1}$): $t_R$ (major enantiomer) = 22.2, $t_R$ (minor enantiomer) = 30.7 min.

**Cyclopropane 3f**: Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta=9.40$ (d, $J=4.6$ Hz, 1H), 4.33–4.14 (m, 6H), 3.27 (d, $J=6.7$ Hz, 1H), 3.12 (dd, $J=$ 4.5, 6.9 Hz, 1H), 1.27 ppm (m, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=$ 194.3, 166.9, 165.0, 164.0, 63.0, 62.5, 62.1, 43.1, 38.3, 32.2, 14.0, 13.9 13.9 ppm; HRMS $m/z$: calcd for $C_{13}H_{18}O_7+Na^+$: 309.0945 $[M+Na]^+$; found: 309.0954; $[\alpha]_D^{25}=-42.2$ ($c=1$ in $CHCl_3$). The enantiomeric excess was determined after in situ reduction with $NaBH_4$ of the aldehyde to the corresponding alcohol. GC (chrompak CP-Chirasil-Dex CB-column, temperature program: 130 °C isocratic): $t_R$ (minor enantiomer) = 14.3, $t_R$ (major enantiomer) = 14.5 min.

**Cyclopropane 3g**: Pale yellow oil; $[\alpha]_D^{25}=-55.7$ ($c=1.0$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta=9.52$ (d, $J=4.8$ Hz, 1H), 7.82–7.75 (m, 3H), 7.69 (s, 1H), 7.50–7.30 (m, 3H) 4.40–4.20 (m, 2H), 3.98 (d, $J=$ 7.6 Hz, 1H), 3.90–3.80 (m, 2H), 3.51 (dd, $J=7.6$ Hz, $J'=4.8$ Hz, 1H), 1.32 (t, $J=7.6$ Hz, 3H), 0.86 ppm (t, J=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=196.1$, 166.0, 164.6, 132.9, 132.8, 129.6, 128.2, 127.7, 127.6, 127.5, 126.4, 126.3, 126.3, 62.5, 62.0, 44.8, 38.3, 35.5, 14.0, 13.7 ppm; IR (KBr): $\tilde{\nu}=$ 3054, 2982, 2929, 2850, 1731, 1715, 1369, 1287, 1213, 1020, cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{20}H_{20}O_5+Na^+$: 363.1203 $[M+Na]^+$; found: 363.1215; HPLC (ODH column, *n*-hexane/*i*PrOH = 90:10, $\lambda=250$ nm, 1 mL min$^{-1}$): $t_R$ (major enantiomer) = 10.7, $t_R$ (minor enantiomer) = 29.6 min.

**Cyclopropane 3h**: Colorless oil; $[\alpha]_D^{25}=-31.4$ (c=1.0 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta=9.30$ (d, $J=4.8$ Hz, 1H), 5.86 (ddq, $J=$ 14.4 Hz, $J'=6.8$ Hz, $J''=0.8$ Hz, 1H), 5.15 (ddq, $J=14.4$ Hz, $J'=7.6$ Hz, $J''=1.6$ Hz, 1H), 4.30–4.10 (m, 4H), 3.09 (dd, $J=7.2$ Hz, $J'=7.2$ Hz, 1H), 2.89 (dd, $J=7.2$ Hz, $J'=4.8$ Hz, 1H), 1.68 (dd, $J=6.8$ Hz, $J'=1.6$ Hz, 3H), 1.30–1.23 ppm (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=196.0$, 166.0, 166.5, 132.2, 122.5, 62.2, 62.2, 43.4, 39.9, 34.3, 18.0, 14.0, 13.9 ppm; IR (KBr): $\tilde{\nu}=2983$, 2856, 1731, 1465, 1369, 1294, 1280, 1224, 1199, 1019 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{13}H_{18}O_5+Na^+$: 277.1046 $[M+Na]^+$, found 277.1057; GC (chrompak CP-Chirasil-Dex CB-column. Temperature program: 5 min,70 °C//2 °C min$^{-1}$//110 °C, 10 min//10 °C min$^{-1}$//200,10 min): $t_R$ (major enantiomer) = 15.2, $t_R$ (minor enantiomer) = 15.4 min.

**Cyclopropane 3i**: Colorless oil; $[\alpha]_D^{25}=-31.6$ ($c=0.6$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta=9.46$ (d, $J=4.7$ Hz, 1H), 8.27 (d, $J=8.4$ Hz, 2H), 7.17 (d, $J=8.4$ Hz, 2H), 4.20–4.35 (m, 2H), 3.89–4.02 (m, 2H), 3.76 (d, $J=7.4$ Hz, 1H), 3.33 (dd, $J=4.7$, 7.6 Hz, 1H), 1.29 (t, $J=7.2$ Hz, 3H), 0.99 ppm (t, $J=7.4$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=$ 195.7, 165.8, 164.4, 134.0, 130.8, 129.9, 128.6, 62.5, 62.2, 44.7, 38.1, 34.5, 14.0, 13.8 ppm; HRMS (ESI) $m/z$: calcd for $C_{16}H_{17}ClO_5+Na^+$: 347.0657 $[M+Na^+]$; found 347.0656; the enantiomeric excess was determined after in situ reduction with $NaBH_4$ of the aldehyde to the corresponding alcohol: HPLC (AD column, *n*-hexane/*i*PrOH 95:5, $\lambda=254$ nm, 1 mL min$^{-1}$): $t_R$ (major enantiomer) = 24.6, $t_R$ (minor enantiomer) = 29.3 min.

**Cyclopropane 3j**: Colorless oil. $[\alpha]_D=-32.9$ ($c=1.0$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta=9.43$ (d, $J=4.7$ Hz, 1H), 7.15 (d, $J=8.9$ Hz, 2H), 6.81 (d, $J=8.8$ Hz, 2H), 4.34–4.21 (m, 2H), 4.00–3.90 (m, 2H), 3.85 (d, $J=1.0$ Hz 1H), 3.77 (s, 3H), 3.31 (d,d, $J=3.8$–7.5 Hz, 1H), 1.30 (t, $J=$ 7.1–14.3 Hz, 3H), 0.98 ppm (t, $J=7.1$–14.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=196.5$, 166.4, 165.0, 159.6, 129.9, 124.3, 114.1, 62.6, 62.2, 55.5, 38.7, 35.1, 14.2, 14.0 ppm; IR (KBr): $\tilde{\nu}=2982$, 2938, 2873, 1732, 1465, 1445, 1369, 1287, 1254, 1245, 1218, 1177, 1145, 1030 cm$^{-1}$; HRMS (ESI) $m/z$: calcd for $[C_{17}H_{20}O_6+Na]^+$: 343.1152$[M+Na]^+$; found: 343.1165; HPLC (ODH column, *n*-hexane/*i*PrOH 97:3, 0.5 mL min$^{-1}$): $t_R$ (major enantiomer) = 37.2, $t_R$ (minor enantiomer) = 46.9 min.

**Cyclopropane 3k**: Colorless oil; $[\alpha]_D=-28.1$ ($c=1.0$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta=9.47$ (d, $J=4.5$ Hz, 1H), 7.30–7.22 (m, 4H), 4.34–4.23 (m, 2H), 4.01–3.94 (m, 2H), 3.77 (d, $J=7.56$ Hz 1H), 3.35 (d,d, $J=4.3$–7.4 Hz, 1H), 1.30 (t, $J=7.2$–14.2 Hz, 3H), 0.99 ppm (t, $J=$ 7.1–14.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=195.8$, 166.0, 164.7, 134.6, 134.5, 130.0, 129.1, 128.5, 127.0, 62.8, 62.4, 38.2, 35.0, 14.2, 14.0 ppm; IR (KBr): $\tilde{\nu}=2984$, 2939, 2873, 1732, 1466, 1445, 1369, 1291, 1278, 1245, 1218, 1186, 1145, 1021 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{16}H_{17}ClO_5+Na^+$: 347.0657 $[M+Na]^+$, found: 347.0673; the enantiomeric excess was determined after in situ reduction of the aldehyde to the corresponding alcohol with $NaBH_4$: HPLC (AD column, n-hexane/*i*PrOH 97:3, 1.0 mL min$^{-1}$): $t_R$ (major enantiomer) = 37.7, $t_R$ (minor enantiomer) = 66.8 min.

**Cyclopropane 3l**: Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta=9.46$ (d, $J=4.6$ Hz, 1H), 7.42 (d, $J=8.4$ Hz, 2H), 7.11 (d, $J=8.4$ Hz, 2H), 4.35–4.21 (m, 2H), 4.03–3.90 (m, 2H), 3.74 (d, $J=7.6$ Hz 1H), 3.33 (dd, $J=$ 4.5,7.5 Hz, 1H), 1.30 (t, $J=7.1$ Hz, 3H), 0.99 ppm (t, $J=7.0$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=195.9$, 166.0, 165.0, 131.8, 131.6, 130.5, 122.3, 62.8, 62.4, 38.2, 35.0, 14.2, 14.0 ppm; IR (KBr): $\tilde{\nu}=2982$, 2937, 2873, 1735, 1466, 1445, 1369, 1288, 1278, 1245, 1218, 1181, 1145, 1011 cm$^{-1}$; $[\alpha]_D=-31.0$ ($c=1.0$ in $CHCl_3$); HRMS (ESI): $m/z$: calcd for $C_{16}H_{17}BrO_5+Na^+$: 391.0152 $[M+Na]^+$; found: 391.0145; The enantiomeric excess was determined after in situ reduction of the aldehyde to the corresponding alcohol with $NaBH_4$: HPLC (ODH column, *n*-hexane/*i*PrOH 97:3, 1.0 mL min$^{-1}$): $t_R$ (major enantiomer) = 41.5, $t_R$ (minor enantiomer) = 43.8 min.

**Cyclopropane 3ab**: Colorless oil; $[\alpha]_D=-56.5$ ($c=1.0$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta=9.40$ (d, $J=4.6$ Hz, 1H), 7.36–7.19 (m, 13H), 6.98–6.94 (m, 2H), 5.23 (q, $J=12.4$–38.1 Hz, 2H), 4.84 (q, $J=12.1$–26.7 Hz, 2H), 3.86 (d, $J=7.6$ Hz, 1H), 3.41 ppm (dd, $J=4.6$–7.7 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=196.1$, 166.1, 165.0, 135.1, 134.8, 132.2, 129.6, 129.3, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 68.4, 68.1, 38.6, 36.0 ppm; IR (KBr): $\tilde{\nu}=2955$, 2924, 2850, 1728, 1498, 1455, 1378, 1286, 1278, 1215, 1217, 1179, 1142, 1029 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{26}H_{22}O_5+Na^+$: 437.1359 $[M+Na]^+$; found 437.1351; HPLC (ODH column, *n*-hexane/*i*PrOH 97:3, 1.0 mL min$^{-1}$): $t_R$ (major enantiomer) = 37.8, $t_R$ (minor enantiomer) = 53.1 min.

**Cyclopropane 3ac**: Colorless oil; $[\alpha]_D = -51.1$ (c = 1.0 in $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 9.49$ (d, $J = 4.5$ Hz, 1H), 7.30–7.22 (m, 5H), 3.83–3.82 (m, 1H), 3.81 (s, 3H), 3.46 (s, 3H), 3.39 ppm (dd, $J = 7.5$, 4.5 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 196.2$, 166.7, 165.3, 132.4, 128.7, 128.6, 128.3, 53.6, 53.1, 38.5, 36.0 ppm; IR (KBr): $\tilde{\nu} = 2956$, 2936, 2849, 1731, 1499, 1437, 1392, 1291, 1278, 1251, 1217, 1195, 1144, 1028 $cm^{-1}$; HRMS (ESI): *m/z*: calcd for $C_{14}H_{14}O_5+Na^+$: 285.0733 $[M+Na]^+$; found 285.0743; HPLC (ODH column, *n*-hexane/*i*PrOH 97:3, 0.5 mL $min^{-1}$): $t_R$ (major enantiomer) = 39.0, $t_R$ (minor enantiomer) = 54.8 min.

**Cyclopropane 3m**: Colorless oil; $[\alpha]_D^{25} = -66.8$ (c = 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 9.50$ (d, $J = 4.8$ Hz, 1H), 7.35–715 (m, 5H), 4.38–4.26 (m, 2H), 3.89 (d, $J = 7.6$ Hz, 1H), 3.49 (dd, $J = 4.8$, 7.6 Hz, 1H), 1.98 (s, 3H), 1.33 ppm (t, $J = 7.2$ Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): 196.4, 196.0, 167.1, 131.3, 128.6, 128.2, 128.2, 62.6, 51.6, 37.2, 36.8, 29.2, 14.0 ppm; IR (KBr): $\tilde{\nu} = 2983$, 2855, 1708, 1358, 1279, 1176, 698 $cm^{-1}$; HRMS *m/z*: calcd for $C_{15}H_{16}O_4+Na^+$: 283.0941 ($[M+Na]^+$); found 283.0950; HPLC (ODH column, *n*-hexane/*i*PrOH 90:10, $\lambda = 240$ nm, 1 mL $min^{-1}$): $t_R$ (major enantiomer) = 10.8, $t_R$ (minor enantiomer) = 17.3 min.

**Synthesis of alcohol 15a:** Concentrated AcOH (0.18 mL) and $NaCNBH_3$ (0.225 mmol, 1.5 equiv) were added to a solution of cyclopropane **3a** (0.15 mmol, 1 equiv) in THF (1 mL)at 0°C. The reaction mixture was warmed up to RT overnight. Next, brine (1 mL) was added and pH was adjusted to 7 with saturated $NaHCO_3$ solution. The aqueous layer was extracted with $Et_2O$ (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvents under vacuum the crude product was purified by column chromatography to afford the corresponding alcohol **15a**.

**Alcohol 15a**: Colorless oil; $[\alpha]_D^{25} = -91.3$ ($c = 1.0$ in $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.30$–7.10 (m, 5H), 4.35–4.25 (m, 2H), 4.02 (dd, $J = 12.0$, 5.6 Hz, 1H), 3.91–3.82 (m, 2H), 3.62 (dd, $J = 12.0$, 8.4 Hz, 1H), 3.17 (d, $J = 8.0$ Hz, 1H), 2.87–2.80 (m, 1H), 1.31 (t, 7.2 Hz, 3H), 0.89 ppm (t, 7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 168.3$, 166.8, 134.3, 128.8, 128.3, 127.5, 62.2, 61.5, 61.0, 42.2, 35.0, 32.3, 14.2, 13.8 ppm; IR (KBr): $\tilde{\nu} = 3430$, 2981, 2933, 1723, 1370, 1298, 1029 $cm^{-1}$; HRMS (ESI): *m/z*: calcd for $C_{16}H_{20}O_5+Na^+$: 315.1203 $[M+Na]^+$; found: 315.1203;.

**Synthesis of lactone 16a**: *p*-Toluenesulfonic acid (0.01 mmol, 0.1 equiv) was added to a solution of compound **15a** (0.1 mmol, 1 equiv) in $CHCl_3$ (10 mL). The reaction was stirred overnight at 45°C. Next, the reaction mixture was treated with sat. aq. $NaHCO_3$ and extracted with $CHCl_3$ (2 × 5 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc mixtures) to afford the cyclic compound **16a**.

**Compound 16a**: Colorless oil; $[\alpha]_D^{25} = -21.7$ ($c = 1.0$, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.35$–7.20 (m, 5H), 4.51 (dd, $J = 9.2$, 4.8 Hz, 1H), 4.37 (d, $J = 9.2$ Hz, 1H), 4.04–3.88 (m, 2H), 3.31 (t, $J = 5.2$ Hz, 1H), 2.91 (d, $J = 5.6$ Hz, 1H), 0.91 ppm (t, 7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 170.2$, 163.6, 131.9, 128.8, 128.5, 67.4, 61.9, 37.9, 37.5, 27.5, 13.9 ppm; IR (KBr): $\tilde{\nu}$2980, 2918, 1779, 1726, 1374, 1351, 1058 $cm^{-1}$; HRMS *m/z*: calcd for $C_{14}H_{14}O_4+Na^+$: 269.0784 [M+Na]$^+$; found: 269.0796.

**Synthesis of thiazolium catalyst 17**: Benzyl chloride (1.27 g, 10 mmol, 1.0 equiv) was added dropwise over 10 min To 2,3-dimethylthiazole (1.074 mL, 10 mmol, 1.0 equiv) in $CH_3CN$ (5 mL). The solution was heated to reflux for 24 h. Following cooling to room temperature and gentle scraping with a spatula, a white precipitate formed, which was collected by filtration and washed with cold $CH_3CN$. Vacuum drying gave **17** (2.13 g, 72%) as a white solid.

**17**:[31] $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta = 12.1$ (s, 1H), 7.38–7.34 (m, 5H), 6.15 (s, 2H), 2.47 (s, 3H), 2.38 ppm (s, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta = 158.4$, 141.9, 133.2, 132.2, 129.6, 129.5, 128.4, 57.5 ppm.

**One-pot reaction procedure for the synthesis of tri-carboxylate esters 18a and 18b from enal 1a:** To a stirred solution of (*S*)-**9** (16 mg, 20 mol%) in $CHCl_3$ (1 mL), was added *trans*-cinnamic aldehyde **1a** (0.3 mmol), $BrCH(CO_2Et)_2$ **2a** (0.25 mmol), $NEt_3$ (0.25 mmol) and EtOH or MeOH (3.0 equiv). The reaction mixture was vigorously stirred at RT for 3 h. To this mixture was added DIPEA (40 mol%) and thiazolium precatalyst **17** (20 mol%). The resulting solution was warmed to 30°C and stirred for 15 h. Next, the reaction mixture was treated with sat. aq. $NH_4Cl$ (1 mL) and extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 6:1) to afford the corresponding esters **18a** and **18b**, respectively.

**(*R*)-1,1-diethyl 3-ethyl 2-phenylpropane-1,1,3-tricarboxylate 18a**:[32] $[\alpha]_D^{25} = -8.4$ ($c = 0.5$ in $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta = 7.26$–7.21 (m, 5H), 4.21 (q, $J = 7.2$ Hz, 2H), 3.90–4.00 (m, 5H), 3.72 (d, $J = 10.4$ Hz, 1H), 2.84 (dd, $J = 15.6$, 5.2 Hz, 1H), 2.72 (dd „$J = 15.6$, 10.0 Hz, 1H), 1.26 (t, $J = 7.2$ Hz, 3H), 1.07 (t, $J = 7.2$ Hz, 3H), 0.98 ppm (t, $J = 7.2$ Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta = 171.3$, 168.2, 167.7, 140.0, 128.5, 128.4, 127.4, 61.8, 61.5, 60.6, 57.5, 41.7, 38.9, 14.19, 14.15, 13.9 ppm; HRMS(ESI) *m/z*: calcd for $C_{18}H_{24}O_6+Na^+$: 359.1465 $[M+Na]^+$; found 359.1476; HPLC (Chiralpak AD column, hexane/2-propanol 95:5, 0.5 mL $min^{-1}$, 210 nm): $t_R$ (major) = 24.714, $t_R$ (minor) = 38.629 min.

**(*R*)-1,1-diethyl 3-methyl 2-phenylpropane-1,1,3-tricarboxylate 18b**:[29] $[\alpha]_D^{25} = -33.2$ (c = 1 in $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta = 7.29$–7.19 (m, 5H), 4.20 (q, $J = 7.2$ Hz, 2H), 3.92 (q, $J = 7.2$ Hz, 2H), 3.92–3.87 (m, 1H), 3.74 (d, $J = 7.2$ Hz, 1H), 3.52 (s, 3H), 2.86 (dd, $J = 4.5$, 15.6 Hz, 1H), 2.74 (dd „$J = 6.9$, 15.6 Hz, 1H), 1.26 (t, $J = 7.2$ Hz, 3H), 0.98 ppm (t, $J = 7.2$ Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta = 171.7$, 168.1, 167.6, 140.0, 128.5, 128.2, 127.4, 61.8, 61.5, 57.4, 51.7, 41.6, 38.7, 14.2, 13.8 ppm; HRMS(ESI): *m/z*: calcd for $C_{17}H_{22}O_6+Na^+$: 345.1309 $[M+Na]^+$; found: 345.1306; HPLC (Chiralpak ODH column, hexane/2-propanol 97:3, 1.0 mL/min, 210 nm): $t_R$ (minor enantiomer) = 15.513, $t_R$ (major enantiomer) = 18.297 min.

**One-pot reaction procedure for the synthesis of tri-carboxylate ester 18c:** To a stirred solution of (*S*)-**9** (16 mg, 20 mol%) in $CHCl_3$ (1 mL), was added *trans*-4-nitro-cinnamic aldehyde (0.3 mmol), $BrCH(CO_2Et)_2$ **2a** (0.25 mmol), $NEt_3$ (0.25 mmol) and MeOH (30 μL, 3.0 equiv). The reaction was vigorously stirred at room temperature for 1.5 h. To this mixture was added diisopropylethylamine (40 mol%) and thiazolium precatalyst **17** (20 mol%). The resulting solution was warmed to 30°C and stirred for 15 h. Next the reaction mixture was treated with sat. aq. $NH_4Cl$ (1 mL) and extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 6:1) to afford the corresponding ester **18c**.

**(*R*)-1,1-Diethyl 3-methyl 2-(4-nitrophenyl)propane-1,1,3-tricarboxylate 18c**: $[\alpha]_D^{25} = -20.4$ ($c = 1$ in $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta = 8.15$ (d, $J = 8.8$ Hz, 2H), 7.45 (d, $J = 8.8$ Hz, 2H), 4.22 (dq, $J = 1.2$, 7.2 Hz, 2H), 4.07–4.03 (m, 1H), 3.97 (dq, $J = 2.4$, 7.2 Hz, 2H), 3.76 (d, $J = 10.0$ Hz, 1H), 3.54 (s, 3H), 2.91 (dd, $J = 4.8$, 16.4 Hz, 1H), 2.78 (dd „$J = 10.0$, 16.4 Hz, 1H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.04 ppm (t, $J = 7.2$ Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta = 171.1$, 167.6, 167.2, 147.9, 147.3, 129.4, 123.8, 62.2, 61.9, 56.7, 52.0, 41.1, 38.1, 14.2, 14.0 ppm; HRMS (ESI): *m/z*: calcd for $C_{17}H_{21}O_8N+Na^+$: 390.1159 $[M+Na]^+$; found 390.1150; HPLC (Chiralpak ODH column, *n*-hexane/2-propanol 90:10, 0.5 mL $min^{-1}$, 210 nm): $t_R$ (major enantiomer) = 26.499, $t_R$ (minor enantiomer) = 32.644 min.

**One-pot reaction procedure for the synthesis of tri-carboxylate esters 18d:**

To a stirred solution of (*S*)-**11** (16 mg, 20 mol%) in $CHCl_3$ (1 mL) at 4°C, was added aldehyde **1h** (0.3 mmol), $BrCH(CO_2Et)_2$ **2a** (0.25 mmol), $NEt_3$ (0.25 mmol) and MeOH (30 μL, 3.0 equiv). The reaction was vigorously stirred at 4°C for 6 h. To this mixture was added DIPEA (40 mol%) and thiazolium precatalyst **17** (20 mol%). The resulting solution was warmed to 30°C and stirred for 15 h. Next the reaction mixture was treated with sat. aq. $NH_4Cl$ (1 mL) and extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 6:1) to afford the corresponding ester **18d**.

**(*R*)-1,1-diethyl 3-methyl 2-(naphthalen-2-yl)propane-1,1,3-tricarboxylate 18d**: $[\alpha]_D^{25} = -17.3$ ($c = 1$ in $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta =$ 7.79–7.76 (m, 3H), 7.70 (d, $J = 1.2$ Hz, 1H), 7.46–7.43 (m, 2H), 7.39 (dd, $J = 1.2$, 8.8 Hz, 1H), 4.23 (q, $J = 7.2$ Hz, 2H), 4.11 (ddd, $J = 4.8$, 10.0, 10.0 Hz, 1H), 3.92–3.85 (m, 3H), 3.50 (s, 3H), 2.95 (dd, $J = 4.8$, 15.6 Hz, 1H), 2.87 (dd $J = 10.0$, 15.6 Hz, 1H), 1.27 (t, $J = 7.2$ Hz, 3H), 0.92 ppm (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta = 171.7$, 168.1, 167.6, 137.6, 133.4, 132.8, 128.3, 128.0, 127.7, 127.2, 126.22, 126.16, 125.9, 61.9, 61.5, 57.4, 51.7, 41.6, 38.6, 14.2, 13.8 ppm; HRMS (ESI): *m/z*: $C_{21}H_{24}O_6 + Na^+$ requires 395.1465 $[M+Na]^+$; found: 395.1459; HPLC (Chiralpak AD column, *n*-hexane/2-propanol = 80:20, 0.5 mL min$^{-1}$, 210 nm): $t_R$ (major enantiomer) = 18.178, $t_R$ (minor enantiomer) = 28.392 min.

**Typical experimental procedure for the organocatalytic domino reactions with 4-bromoacetoacetate 2f**: α,β-Unsaturated aldehyde **1** (0.30 mmol, 1.2 equiv), $K_2CO_3$ (0.25 mmol, 1.0 equiv) and ethyl 4-bromo-3-oxobutanoate **2f** (0.25 mmol, 1.0 equiv) were added to a stirred solution of catalyst **9** (0.05 mmol, 20 mol%) in $CHCl_3$ (1.0 mL). The reaction was vigorously stirred for the time and the temperature listed in Table 2. Next, the crude product was purified by silica-gel chromatography (pentane/EtOAc mixtures) to give the corresponding cyclopentanone **19**.

**Cyclopentanone 19a:** Colorless oil; $[\alpha]_D = -65.5$ ($c = 1.0$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 9.73$ (d, $J = 2.8$ Hz, 1H), 4.21 (q, $J =$ 7.2 Hz, 2H), 3.05–2.45 (m, 4H), 1.76–1.60 (m, 2H), 1.60–1.43 (m, 2H), 1.40–1.20 (m, 6H), 0.88 ppm (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 207.7$, 200.1, 168.6, 61.8, 61.2, 52.3, 41.6, 38.6, 34.0, 29.5, 22.6, 14.1, 13.8 ppm; HRMS (ESI): *m/z*: calcd for $C_{13}H_{20}O_4 + Na^+$: 263.1254 $[M+Na]^+$; found 263.1253; GC (chrompak CP- Chirasil-Dex CB-column, temperature program: 5 min,70 °C//2 °C min$^{-1}$//110 °C, 10 min//10 °C min$^{-1}$//200,10 min): $t_R$ (major enantiomer) = 11.3, $t_R$ (minor enantiomer) = 11.6 min.

**Cyclopentanone 19b:** Colorless oil; $[\alpha]_D = -78.4$ ($c = 1.0$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 9.73$ (d, $J = 2.8$ Hz, 1H), 4.25–4.18 (m, 2H), 3.05–2.40 (m, 4H), 1.70–1.25 (m, 8H), 1.00–0.90 ppm (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 207.6$, 200.1, 168.6, 61.8, 61.2, 52.3, 41.4, 38.6, 35.5, 20.6, 14.1, 14.0 ppm; IR (KBr): $\tilde{\nu} = 2964$, 2936, 2874, 1731, 1466, 1447, 1369, 1295, 1223, 1201, 1146 cm$^{-1}$; HRMS (ESI): *m/z*: calcd. for $C_{12}H_{18}O_4 + Na^+$ 249.1097 $[M+Na]^+$; found 249.1100; GC (chrompak CP- Chirasil-Dex CB-column, temperature program: 130 °C 10 min, 130 °C//3 °C min$^{-1}$//160 °C, 160 °C 2 min, 130 °C//80 °C min$^{-1}$//200 °C min$^{-1}$//5 min): $t_R$ (major enantiomer) = 12.8, $t_R$ (minor enantiomer) = 13.2 min.

**Cyclopentanone 19c:** Colorless oil; $[\alpha]_D = -34.2$ ($c = 1.0$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 9.71$ (d, $J = 2.8$ Hz, 1H), 7.30–7.10 (m, 5H), 4.22 (q, $J = 7.2$ Hz, 2H), 3.10–2.55 (m, 4H), 2.08–1.98 (m, 1H), 1.92–1.80 (m, 1H), 1.30–1.20 ppm (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 207.2$, 199.8, 168.4, 140.6, 128.6, 128.5, 128.1, 126.3, 61.9, 61.1, 52.4, 41.1, 38.5, 36.1, 33.5, 14.1 ppm; IR (KBr): $\tilde{\nu} = 2962$, 2937, 2877, 1751, 1730, 1459, 1443, 1374, 1301, 1265, 1194, 1106, 1054, 1027 cm$^{-1}$; HRMS (ESI): *m/z*: calcd for $C_{13}H_{20}O_4 + Na^+$: 263.1254 $[M+Na]^+$; found 263.1253; HPLC(ODH column, *n*-hexane: *i*PrOH = 95:5, $\lambda = 305$ nm), 0.5 mL min$^{-1}$): $t_R$ (major enantiomer) = 26.3, $t_R$ (minor enantiomer) = 35.6 min.

**Cyclopentanone 19d**: Colorless oil; $[\alpha]_D = +103.8$ ($c = 1.0$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 9.74$ (d, $J = 2.4$ Hz, 1H), 4.21 (q, $J =$ 7.2 Hz, 2H), 3.02–2.66 (m, 4H), 2.60–2.53 (m, 1H), 1.78–1.69 (m, 1H), 1.64–1.54 (m, 1H), 1.32–1.26 (m, 3H), 0.96 ppm (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 207.7$, 200.2, 168.7, 62.0, 60.9, 52.0, 43.2, 38.8, 27.1, 14.3 ppm, 11.8 ppm; IR (KBr): $\tilde{\nu} = 2968$, 2937, 2880, 1755, 1728, 1464, 1447, 1372, 1262, 1174, 1096, 1030, 854 cm$^{-1}$; HRMS (ESI): *m/z*: calcd for $C_{11}H_{16}O_4 + Na^+$ 235.0941 $[M+Na]^+$; found 235.0939; GC (chrompak CP- Chirasil-Dex CB-column, temperature program: 120 °C 10 min, 120 °C//3 °C min$^{-1}$//160 °C//80 °C min$^{-1}$//200 °C min$^{-1}$//5 min.): $t_R$ (major enantiomer) = 8.8 min, $t_R$ (minor enantiomer) = 9.2 min.

**Cyclopentanone 19e**: Colorless oil. $[\alpha]_{D=}^{25} = +53.4$ ($c = 0.5$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 9.75$ (d, $J = 2.4$ Hz, 1H), 4.23 (q, $J =$ 7.2 Hz, 2H), 2.96 (dd, $J = 0.8$, 7.2 Hz, 1H), 2.85–2.84 (m, 1H), 2.73–2.61 (m, 3H), 1.30 (s, 3H), 1.30 ppm (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 207.1$. 199.9, 168.0, 62.8, 62.0, 53.7, 38.9, 37.0, 18.5, 14.3 ppm; IR (KBr): $\tilde{\nu} = 3584$, 2967, 2922, 2882, 1724, 1463, 1372, 1259, 1147, 1030 cm$^{-1}$; HRMS(ESI): *m/z*: calcd for $C_{10}H_{14}O_4 + Na^+$: 221.0784 $[M+Na]^+$; found: 221.0789; GC(IVADEX-1 chiral column (25 m, 0.25 mm, 0.15 μm), temperature program: 105 °C 45 min, 105 °C//0.5 °C min$^{-1}$//110 °C, 110 °C//80 °C min$^{-1}$//200 °C 5 min): $t_R$ (major enantiomer) = 43.8, $t_R$ (minor enantiomer) = 45.3 min.

**Diasteroselective synthesis of cyclopentanediol 20d**: Acetic acid (225 μL) and $NaBH_3CN$ (29 mg, 0.45 mmol) were added to a stirred solution of cyclopentanone **19d** (42 mg, 0.20 mmol) in THF (1.0 mL), at 0 °C. The reaction was stirred at this temperature for 1 h and then at RT overnight. The crude product was purified by silica-gel chromatography (pentane/EtOAc mixtures) to give the corresponding cyclopentanol **20d** (27 mg, 63% yield).

**Cyclopentanol 20d**: Colourless oil; $[\alpha]_D = -9.7$ ($c = 1.0$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 4.37$ (dd, $J = 7.6$ Hz, 13.6 Hz, 1H; C*H*OH), 4.17 (q, $J = 7.2$ Hz, 2H; $COOCH_2CH_3$), 3.64 (dd, $J = 4.4$ Hz, 10.4 Hz, 1H; $CH_2OH$), 3.51 (dd, $J = 7.6$ Hz, 10.4 Hz, 1H; $CH_2OH$), 2.43 (dd, $J = 7.6$ Hz, 8.8 Hz, 1H; $CHCOOCH_2CH_3$), 2.10–2.01 (m, 1H; $CHCH_2CH_3$), 1.99–1.78 (m, 3H; $CH_2$, $CHCH_2OH$), 1.64–1.52 (m, 2H; $CH_2CH_3$), 1.27 (t, $J = 7.2$ Hz, 3H; $CH_2CH_3$), 0.92 ppm (t, $J = 7.2$ Hz, 3H; $COOCH_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 175.0$, 75.6, 66.2, 60.9, 58.7, 44.9, 44.0, 37.1, 27.8, 14.4, 11.8 ppm. IR (KBr): $\tilde{\nu} = 3353$, 2960, 2932, 2877, 1727, 1463, 1378, 1261, 1162, 1095, 1037, 914 cm$^{-1}$; HRMS (ESI): *m/z*: calcd for $C_{11}H_{20}O_4 + Na^+$: 239.1254 $[M+Na]^+$; found: 239.1262.

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