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Asymmetric Organocatalytic Cyclopropanation – Highly Stereocontrolled Synthesis of Chiral Cyclopropanes with Quaternary Stereocenters

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A convenient and novel domino reaction for the synthesis of highly functionalized cyclopropanes is reported. The addition of 2-bromoketo esters to a variety of α,β-unsaturated aldehydes catalyzed by secondary amines leads to chiral cyclopropanes with three stereogenic carbon atoms, including one quaternary stereocenter, in a highly stereocontrolled fashion.

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Introduction

The discovery of new reactions that allow us to build complex molecular scaffolds in an efficient way from readily available starting materials remains a challenging goal in chemical synthesis. Cascade or tandem reactions,[1] in which several bond-forming steps take place in a single operation, have received much attention in this regard, because they address one of the fundamental issues related to synthetic efficiency.

The stereocontrolled construction of quaternary stereocenters is one of the most difficult challenges for synthetic chemists nowadays. Consequently, asymmetric processes that are able to build quaternary carbon atoms have been the subject of intense research in recent years.[2] However, a limited number of catalytic enantioselective cascade reactions, which enable the facile construction of chiral quaternary carbon atoms, have been developed thus far.

The cyclopropane motif has long been an interesting target for organic chemists. The cyclopropane ring is present in more than 4000 natural isolated[3] and 100 biologically active agents. In addition to serving as drug and agrochemical targets, the rigid cyclopropane scaffolds are important as intermediates in complex molecule synthesis,[4] as synthetic building blocks,[5] and as templates for the construction of conformationally restricted amino acids and peptides.[6] Moreover, cyclopropanes can undergo a variety of ring-opening reactions to generate new molecular skeletons.[7]

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Because of these important properties, there is abundance in the literature on the asymmetric synthesis of this important group of compounds.[8] Notably, in the last few years high levels of asymmetric induction have been achieved involving metal-catalyzed intermolecular cyclopropanations between diazoesters and electron-rich olefins,[9] as well as with asymmetric versions of the Simmons–Smith reaction.[10]

In the realm of organocatalysis, cyclopropane construction has been accomplished by using catalyst-bonded ylides,[11] with cinchona alkaloids as organocatalysts for the addition of halomalonates to nitroalkenes[12] and cinchonidin-catalyzed reactions between chloro methyl ketones and β-substituted methylidenemalononitriles.[13] Recently, Gaunt and Ley reported an efficient catalytic intramolecular cyclopropanation using modified cinchona alkaloids as organocatalysts.[14] MacMillan and co-workers reported a highly enantioselective cyclopropanation of α,β unsaturated aldehydes by using stabilized ylides with dihydroindole as a catalyst, achieving high levels of enantio- and diastereoselectivities.[15] In 2007, Córdova[16] and co-workers reported a very elegant cyclopropanation, using 2-bromomalonates and α,β-unsaturated aldehydes. Soon after, Wang reported a similar reaction.[17] In 2008, Córdova also reported a synthesis of cyclopropanes from bromonitromethane and α,β-unsaturated aldehydes with high enantioselectivity but moderate diastereoselectivity.[18]

Results and Discussion

With this information on mind, we envisioned an easy entry to chiral cyclopropanes bearing three stereogenic centers, one of them quaternary, by using 2-bromo-3-keto esters instead of 2-bromomalonates. (Scheme 1).

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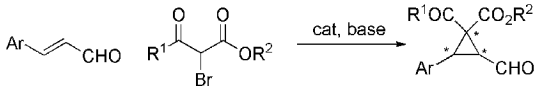
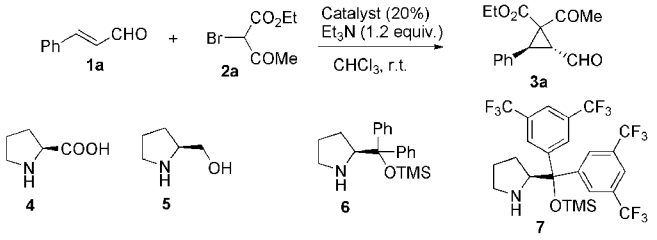


Scheme 1. Cyclopropanation reaction with 2-bromo-3-keto esters.

In initial experiments, we screened different chiral amines for the reaction between cinnamic aldehyde (**1a**) and 2-bromoacetoacetate (**2a**)[19] with Et_3N as a proton scavenger in $CHCl_3$ (Table 1). As described by Córdova[16] and Wang,[17] the reaction between 2-bromomalonates and cinnamaldehyde derivatives gives total *trans* diastereoselectivity between the aldehyde and aryl groups. For this reason, we assumed that the diastereoselectivity observed in our reaction is determined by the stereochemistry of the new quaternary center created. To our delight, (*S*)-proline (**4**) catalyzed the asymmetric formation of the corresponding cyclopropane **3a** in high yield but low enantio- and diastereoselectivity (entry 1, Table 1). The use of (*S*)-prolinol (**5**) (entry 2) led to even lower enantioselectivity. Increasing the bulk of the chiral moiety to TMS-protected arylmethanol, as in catalyst **6**[19] or **7**, gave the corresponding cyclopropane **3a** in high yields and excellent enantioselectivity but moderate diastereoselectivity (entries 3 and 4, Table 1).

Table 1. Catalyst screening.[a]

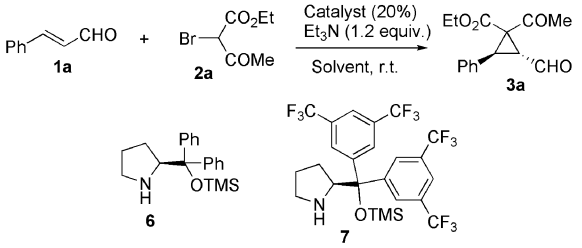


Entry	Catalyst	Solvent	Time	Yield (%)[b]	*dr*[c]	*ee* (%)[d]
1	**4**	$CHCl_3$	3 h	93	2.7:1	31
2	**5**	$CHCl_3$	3 h	93	2.4:1	8
3	**6**	$CHCl_3$	3 h	82	3:1	94
4	**7**	$CHCl_3$	3 h	85	3.7:1	96

[a] Experimental conditions: A mixture of **1a** (0.25 mmol), catalyst (20%), **2a** (0.30 mmol), and Et_3N (0.30 mmol) in $CHCl_3$ (1 mL) was stirred at room temperature for 3 h. Crude product **3a** was purified by column chromatography. [b] Isolated yield. [c] Determined by NMR spectroscopic analysis of the crude reaction. [d] Determined by chiral HPLC analysis of the major diastereomer.

Next, we decided to perform a solvent screening by using chiral amines **6** and **7** as catalysts (Table 2), in order to increase the diastereoselectivity of the process. Catalyst **6** was able to catalyze the formation of **3a** with excellent yield and enantioselectivity in toluene and chloroform (entries 1 and 2, Table 2); fortunately, when the reaction was carried out in toluene we obtained the cyclopropane **3a** with higher diastereoselectivity (entry 2, Table 2) without losing either yield or enantioselectivity. DMF and methanol (entries 3 and 4) were not suitable solvents for cyclopropanation. In AcOEt (entry 5, Table 2), **3a** was isolated in good diastereoselectivity and excellent enantiomeric excess, but the yield was quite low (43%). Surprisingly enough, catalyst **7** did not catalyze the reaction in toluene (entry 6, Table 2).

Table 2. Solvent screening.[a]



Entry	Catalyst	Solvent	Time	Yield (%)[b]	*dr*[c]	*ee* (%)[d]
1	**6**	$CHCl_3$	3 h	81	3:1	94
2	**6**	Toluene	14 h	88	5.5:1	93
3	**6**	DMF	14 h	0	–	–
4	**6**	MeOH	14 h	traces	–	–
5	**6**	AcOEt	14 h	43	5:1	93
6	**7**	Toluene	14 h	<10	n.d.	n.d.

[a] Experimental conditions: A mixture of **1a** (0.25 mmol), catalyst (20%), **2a** (0.30 mmol), and Et_3N (0.30 mmol) in $CHCl_3$ (1 mL) was stirred at room temperature for 3 h. Crude product **3a** was purified by column chromatography. [b] Isolated yield. [c] Determined by NMR spectroscopic analysis of the crude reaction. [d] Determined by chiral HPLC analysis of the major diastereomer.

Then, we optimized the base used in the reaction (Table 3). Excellent enantioselectivities and good yields were achieved for all bases investigated except DBU (entry 1); when DBU was used, only decomposition was observed. However, Et_3N (entry 2) shows slightly better diastereoselectivities and enantioselectivities than lutidine (entry 3) or $NaHCO_3$ (entry 4).

In order to achieve higher levels of diastereoselectivity, we ran the reaction at different temperatures and solvents (Table 4). Gratifyingly, when the reaction was run at 4 °C in toluene with catalyst **6**, the diastereoselectivity rose to 9.5:1 and enantioselectivity was 94% (entry 4, Table 4). Catalyst **7**, which gives the best results in $CHCl_3$ at room temperature, becomes inert in toluene or at 4 °C.

Once we optimized the reaction conditions for the cyclopropanation of cinnamic aldehyde (catalyst **6** in toluene at 4 °C), we studied the scope of the reaction with different α,β-unsaturated aldehydes (Table 5).

To our delight, in all the entries we achieved high levels of diastereo- and enantioselectivity. The reaction works fine with aldehydes bearing electron-withdrawing groups such as nitro, nitrile or halides such as Br in the aromatic ring, leading to the corresponding cyclopropanes in excellent yields (89–93%), diastereoselectivities (>7.5:1 *dr*), and

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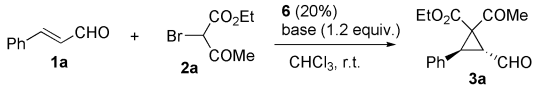
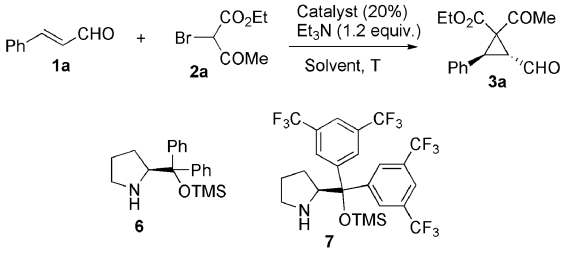
Table 3. Base screening.[a]



Entry	Base	Time	Yield (%)[b]	*dr*[c]	*ee* (%)[d]
1	DBU	14 h	–	2.7:1	31
2	Et_3N	14 h	82	3:1	94
3	Lutidine	14 h	81	2.9:1	92
4	$NaHCO_3$	14 h	57	2.6:1	90

[a] Experimental conditions: A mixture of **1a** (0.25 mmol), catalyst (20%), **2a** (0.30 mmol), and Et_3N (0.30 mmol) in $CHCl_3$ (1 mL) was stirred at room temperature for 3 h. Crude product **3a** was purified by column chromatography. [b] Isolated yield. [c] Determined by NMR spectroscopic analysis of the crude reaction. [d] Determined by chiral HPLC analysis of the major diastereomer.

Table 4. Temperature screening.[a]

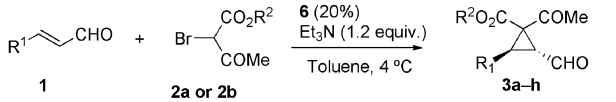


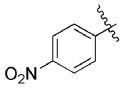
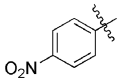
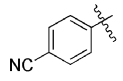
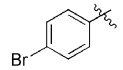
Entry	Catalyst	Solvent	Temp.	Yield (%)[b]	*dr*[c]	*ee* (%)[d]
1	**6**	$CHCl_3$	r.t.	82	3:1	94
2	**6**	$CHCl_3$	4 °C	85	3.6:1	95
3	**6**	Toluene	r.t.	88	5.5:1	93
4	**6**	Toluene	4 °C	90	9.5:1	94
5	**7**	Toluene	r.t.	<10	n.d.	n.d.
6	**7**	Toluene	4 °C	traces	n.d.	n.d.
7	**7**	$CHCl_3$	r.t.	85	3.7:1	93
8	**7**	$CHCl_3$	4 °C	<10	n.d.	n.d.

[a] Experimental conditions: A mixture of **1a** (0.25 mmol), catalyst (20%), **2a** (0.30 mmol), and Et_3N (0.30 mmol) in $CHCl_3$ (1 mL) was stirred at room temperature for 3 h. Crude product **3a** was purified by column chromatography. [b] Isolated yield. [c] Determined by NMR spectroscopic analysis of the crude reaction. [d] Determined by chiral HPLC analysis of the major diastereomer.

enantioselectivities (94–99% *ee*). When aliphatic aldehydes are used, the diastereoselectivity decreases to 2.4:1, probably because of the weaker steric hindrance of the alkyl moiety. However, the enantioselectivity of aliphatic adducts is only little bit less than that of aromatics, and the yields are

Table 5. Aldehyde scope.[a]



Entry	Product	R^2	R^1	Time	Yield (%)[b]	*dr*[c]	*ee* (%)[d]
1	**3a**	Et		14 h	90	9.5:1	94
2	**3b**	Me		14 h	90	7.5:1	99
3	**3c**	Et		14 h	88	12:1	96
4	**3d**	Me		14 h	88	9:1	96
5	**3e**	Me		14 h	93	10:1	98
6	**3f**	Me		14 h	92	14:1	96
7	**3g**	Et	*n*Bu	14 h	95	2.4:1	90
8	**3h**	Et	Et	14 h	91	3:1	85

[a] Experimental conditions: A mixture of **1a** (0.25 mmol), catalyst (20%), **2a** (0.30 mmol), and Et_3N (0.30 mmol) in $CHCl_3$ (1 mL) was stirred at room temperature for 3 h. Crude product **3a**–**h** was purified by column chromatography. [b] Isolated yield. [c] Determined by NMR spectroscopic analysis of the crude reaction. [d] Determined by chiral HPLC analysis of the major diastereomer.

excellent. This shows the broad range of applicability of this methodology. (entries 7 and 8; Table 5). Exhaustive analysis of the NMR spectrum of minor diastereomers showed that the relative configuration is *trans* between formyl and aryl, with the only difference of the quaternary carbon. This is in accordance with the high diastereoselectivity observed in the cyclopropanation of the same compounds with bromomalonates.[16,17]

Next, we studied the scope of the reaction by using different 2-bromo-3-keto esters, evaluating the effects of the steric bulk in the ester and of the ketone moieties in the outcome of the process (Table 6). Surprisingly, when *tert*-butyl-2-bromoacetoacetate (**2c**) was used, the diastereoselectivity decreased to 2.5:1 and the enantioselectivity was 63%; the reaction was also very slow and was carried out in $CHCl_3$ at room temperature for this reason (entry 3). On the other hand, when ethyl 2-bromo-4-*tert*-butyl-3-oxobutanoate (**2d**) was used, we obtained high levels of enantio- and diastereoselectivity (96% *ee* and >25:1 *dr*, entry 4, Table 6).

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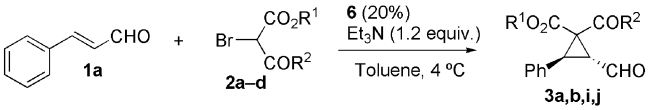
Table 6. Bromo keto ester scope.[a]



Entry	Product	R^1	R^2	Time	Yield (%)[b]	*dr*[c]	*ee* (%)[d]
1	**3a**	Et	Me	14 h	90	9.5:1	94
2	**3b**	Me	Me	14 h	90	7:5	99
3[e]	**3i**	*t*Bu	Me	72 h	68	2.5:1	63
4	**3j**	Et	*t*Bu	72 h	76	>25:1	96

[a] Experimental conditions: A mixture of **1a** (0.25 mmol), catalyst (20%), **2a** (0.30 mmol), and Et_3N (0.30 mmol) in $CHCl_3$ (1 mL) was stirred at room temperature for 3 h. Crude product **3a**–**j** was purified by column chromatography. [b] Isolated yield. [c] Determined by NMR spectroscopic analysis of the crude reaction. [d] Determined by chiral HPLC analysis of the major diastereomer.

Then, we examined the absolute configuration of cyclopropanes **3**. The relative stereochemistry of the major diastereomers was determined as depicted in Figure 1 through analysis of 2D NOESY experiments.[20,21] The nOe observed in each compound are consistent with a *cis* relationship between keto group and aryl moiety and a *trans* relationship between aryl moiety and aldehyde. The 2D NOESY experiments were acquired with a 400 MHz spectrometer at 25 °C with 400 ms as mixing time and 1 s as relaxation delay.

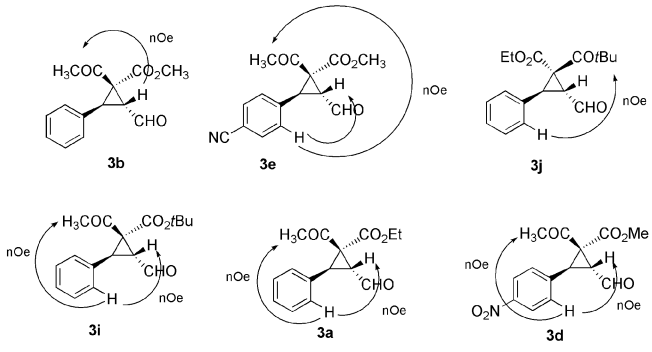
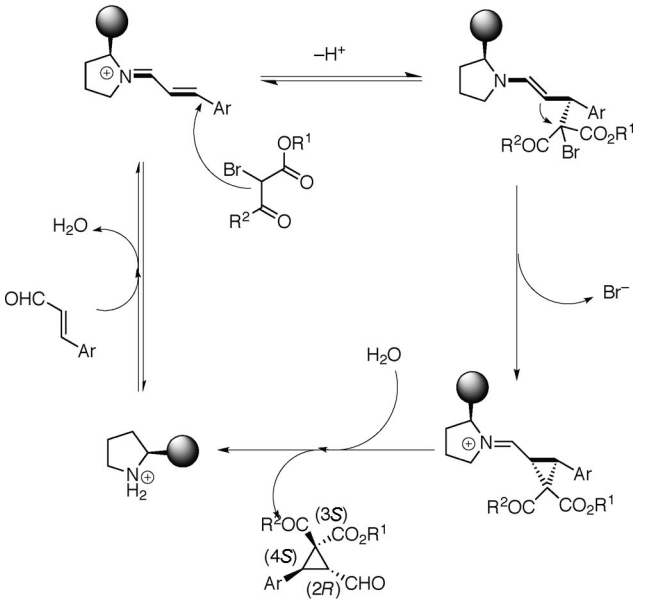


Figure 1. Major diastereomers studied by NOESY experiments and their absolute configuration.

Those results indicate that electronic interactions between 2-bromoketo ester and enal are more important than stereochemical interactions. This leads to an enhanced utility of the present reaction, because we can control and predict the stereochemical outcome of the reaction for any substituent in the ketone and/or ester.

For the absolute configuration, the mechanism of addition of 2-bromomalonates to enals has been well established by Córdova[16] and Wang.[17] In the reaction of 2-bromo keto esters, the mechanism and transition states have to be similar, and we have assigned the absolute configuration as follows: the reactions with catalyst **6** give access to (2*R*, 3*S*, 4*S*)-2-formylcyclopropanes **3**. Thus, efficient shielding of the *Si*-face of the chiral iminium intermediate by the bulky aryl groups of chiral pyrrolidine **6** leads to stereoselective *Re*-facial nucleophilic conjugate addition by 2-bromo-3-keto esters. Then, the generated chiral enamine intermediate undergoes an intramolecular 3-*exo*-*tet* nucleophilic attack to form the cyclopropane ring. Intramolecular ring closure pushes the equilibrium forward and makes this step irreversible (Scheme 2).



Scheme 2. Mechanism of cyclopropanation.

Conclusions

We report a highly chemo-, diastereo-, and enantioselective cyclopropanation of α,β-unsaturated aldehydes with 2-bromo-3-keto esters, giving highly functionalized cyclopropanes with three stereogenic carbon atoms including one quaternary stereocenter. The reaction is efficiently catalyzed by commercially available chiral pyrrolidine derivatives and affords the corresponding cyclopropanes in high yields and up to >25:1 diastereomer ratio and up to 99% enantiomeric excess. Moreover, this reaction allows us to build stereogenic quaternary centers with an excellent control of the stereoselectivity. Mechanistic studies, synthetic applications of this new methodology, and the discovery of new reactions based on this concept are ongoing in our laboratory.

Experimental Section

General Procedure for the Cyclopropanation Reaction: In a round-bottomed flask, unsaturated aldehyde (0.25 mmol, 1 equiv.), 2-

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bromo-3-keto ester (0.3 mmol, 1.2 equiv.), catalyst (0.05 mmol, 20 mol-%), and triethylamine (0.3 mmol, 1.2 equiv.) were added sequentially in toluene (1 mL). The reaction was stirred at 4 °C overnight. Then, the crude product was purified by column chromatography to furnish cyclopropane adducts **3**.

(1*S*,2*R*,3*S*)-Ethyl 1-Acetyl-2-formyl-3-phenylcyclopropanecarboxylate (3a): 58 mg (90% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMSint): δ = 9.50 (d, J = 4.8 Hz, 1 H), 7.35–715 (m, 5 H), 4.38–4.26 (m, 2 H), 3.89 (d, J = 7.6 Hz, 1 H), 3.49 (dd, J = 4.8, 7.6 Hz, 1 H), 1.98 (s, 3 H), 1.33 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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. HRMS: calcd. for $C_{15}H_{16}NaO_4$ $[M + Na]^+$ 283.0941; found 283.0950. $[a]_D$ = –66.8 (c = 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC with a Chiralcel® ODH column: (*n*-hexane/*i*PrOH = 90:10, λ = 240 nm), 1 mL/min; t_R = major enantiomer 10.8 min, minor enantiomer 17.3 min.

(1*S*,2*R*,3*S*)-Methyl 1-Acetyl-2-formyl-3-phenylcyclopropanecarboxylate (3b): 55 mg (90% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMSint): δ = 9.57 (d, J = 4.5 Hz, 1 H), 7.35–7.20 (m, 5 H), 3.93 (d, J = 7.6 Hz, 1 H), 3.91 (s, 3 H), 3.49 (dd, J = 7.6, J' = 4.5 Hz, 1 H), 2.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.4, 196.0, 168.9, 131.6, 128.9, 128.5, 128.4, 64.0, 53.5, 51.7, 37.5, 37.2, 29.4 ppm. HRMS: calcd. for $C_{14}H_{14}NaO_4$ $[M + Na]^+$ 283.0891; found 283.0791. $[a]_D$ = –56.2 (c = 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC with a Chiralpak® IC column: (*n*-hexane/*i*PrOH = 95:5, λ = 254 nm), 1 mL/min; t_R = major enantiomer 26.2 min, minor enantiomer 28.0 min.

(1*S*,2*R*,3*S*)-Ethyl 1-Acetyl-2-formyl-3-(4-nitrophenyl)cyclopropanecarboxylate (3c): 67 mg (88% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$ TMSint): δ = 9.58 (d, J = 3.8 Hz, 1 H), 8.17 (d, J = 8.9 Hz, 2 H), 7.36 (d, J = 8.9 Hz, 2 H), 4.40–4.30 (m, 2 H), 3.92 (d, J = 7.6 Hz, 1 H), 3.92 (d, J = 7.6, J' = 3.8 Hz, 1 H), 2.05 (s, 3 H), 1.35 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ TMSint): δ = 199.1, 195.4, 166.7, 147.8, 139.4, 129.7, 124.0, 63.2, 52.2, 37.6, 36.5, 29.5, 14.29 ppm. $[a]_D$ = –75.4 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{15}H_{15}NNaO_6$ $[M + Na]^+$ 328.0792; found 328.0788. The enantiomeric excess was determined by HPLC with a Chiralcel® ODH column: (*n*-hexane/*i*PrOH = 90:10, λ = 240 nm), 1 mL/min; t_R = major enantiomer 10.8 min, minor enantiomer 17.3 min.

(1*S*,2*R*,3*S*)-Methyl 1-Acetyl-2-formyl-3-(4-nitrophenyl)cyclopropanecarboxylate (3d): 64 mg (88% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$ TMSint): δ = 9.60 (d, J = 3.6 Hz, 1 H), 8.17 (d, J = 8.8 Hz, 2 H), 7.36 (d, J = 8.9 Hz, 2 H),3.89 (s, 3 H), 3.87 (d, J = 7.6 Hz, 1 H), 3.60 (d, J = 7.6, J' = 3.6 Hz, 1 H), 2.06 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.3, 195.4, 166.5, 148.8, 139.2, 129.7, 124.0, 53.8, 52.0, 37.6, 36.7, 29.5 ppm. $[a]_D$ = –59.2 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{14}H_{14}NO_6$ $[M + H]^+$ 292.0816; found 292.0806. The enantiomeric excess was determined by HPLC with a Chiralpak® IC column: (*n*-hexane/*i*PrOH = 95:5, λ = 254 nm), 1 mL/min; t_R = major enantiomer 62.9 min, minor enantiomer 70.8 min.

(1*S*,2*R*,3*S*)-Methyl 1-Acetyl-2-formyl-3-(4-cyanophenyl)cyclopropanecarboxylate (3e): 63 mg (93% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$ TMSint): δ = 9.57 (d, J = 3.6 Hz, 1 H), 7.60 (d, J = 8.4 Hz, 2 H), 7.29 (d, J = 8.4 Hz, 2 H), 3.88 (s, 3 H), 3.87 (d, J = 7.6 Hz, 1 H), 3.55 (d, J = 8.0, J' = 3.6 Hz, 1 H), 2.04 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.4, 195.5, 167.3, 137.2, 132.5.8, 129.5, 118.4, 112.3, 53.8, 51.9, 37.4, 36.9, 29.5 ppm. $[a]_D$ = –62.2 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{15}H_{13}NO_4$ $[M + H]^+$ 272.0917; found 272.0906. The enantiomeric excess was determined by HPLC with a Chiralpak® IC column: (*n*-hexane/*i*PrOH = 80:20, λ = 220 nm), 1 mL/min; t_R = major enantiomer 12.3 min, minor enantiomer 17.6 min.

(1*S*,2*R*,3*S*)-Methyl 1-Acetyl-2-formyl-3-(4-bromophenyl)cyclopropanecarboxylate (3f): 75 mg (92% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$ TMSint): δ = 9.73 (d, J = 4.3 Hz, 1 H), 7.63 (d, J = 8.5 Hz, 2 H), 7.24 (d, J = 8.5 Hz, 2 H), 4.05 (s, 3 H), 4.01 (d, J = 7.7 Hz, 1 H), 3.92 (d, J = 7.7, J' = 4.3 Hz, 1 H), 2.21 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 195.4, 167.6, 139.2, 129.6, 129.5, 122.5, 53.8, 52.0, 37.6, 36.7, 29.3 ppm. $[a]_D$ = –51.4 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{14}H_{12}BrO_3$ $[M + H – H_2O]^+$ 306.9964; found 306.9963. The enantiomeric excess was determined by HPLC with a Chiralpak® IC column: (*n*-hexane/*i*PrOH = 90:10, λ = 220 nm), 1 mL/min; t_R = major enantiomer 11.0 min, minor enantiomer 11.5 min.

(1*S*,2*R*,3*R*)-Ethyl 1-Acetyl-2-butyl-3-formylcyclopropanecarboxylate (3g): 57 mg (95% yield). Colorless oil. ^{1}H NMR (300 MHz. CDCl3, TMSint): δ = 9.28 (d, J = 5.0 Hz, 1 H), 4.34–4.20 (m, 2 H), 2.82–2.76 (m, 1 H), 2.61–2.52 (m, 1 H), 1.36–1.26 (m,10 H), 0.92–0.84 (m, 5 H) ppm. ^{13}C NMR (100 MHz. $CDCl_3$): δ = 198.8, 196.9, 167.7, 62.3, 52.3, 49.5, 40.0, 34.2, 31.1, 25.4, 22.1, 14.0, 13.9 ppm. HRMS: calcd. for $[C_{13}H_{20}NaO_4]^+$ 263.1254; found 263.1255. The enantiomeric excess was determined by Chiral GC analysis: alpha-DEX, 120, 30 m, 0.25 mm, Supelco, initial temperature 50 °C, 10 °C/min rate 50–200 °C, hold time 1 min, 2 °C/min rate 200–240 °C, hold time 10 min. Linear velocity 25.4 cm/s. t_R = major enantiomer 26.7 min, minor enantiomer 29.2 min.

(1*S*,2*R*,3*R*)-Ethyl 1-Acetyl-2-ethyl-3-formylcyclopropanecarboxylate (3h): 48 mg (91% yield). Colorless oil. ^{1}H NMR (300 MHz. CDCl3, TMSint): δ = 9.41 (d, J = 4.8 Hz, 1 H), 4.45–4.30 (m, 2 H), 2.91 (dd, J = 7.1, J' = 5.0 Hz, 1 H), 2.70–2.65 (m, 1 H), 2.46 (s, 3 H), 1.60–1.40 (m, 5 H), 1.10 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz. $CDCl_3$): δ = 198.7, 197.6, 168.4, 63.0, 50.3, 40.6, 36.5, 30.2, 20.0, 14.7, 14.0 ppm. HRMS: calcd. for $[C_9H_{11}NaO_4]^+$ 235.0941; found 235.0943. The enantiomeric excess was determined by Chiral GC analysis: alpha-DEX, 120, 30 m, 0.25 mm, Supelco, initial temperature 50 °C, 10 °C/min rate 50–200 °C, hold time 1 min, 2 °C/min rate 200–240 °C, hold time 10 min. Linear velocity 25.4 cm/s. t_R = major enantiomer 22.3 min, minor enantiomer 22.1 min.

(1*S*,2*R*,3*S*)-*tert*-Butyl 1-Acetyl-2-formyl-3-phenylcyclopropanecarboxylate (3i): 49 mg (68% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$ TMSint): δ = 9.70 (d, J = 4.8 Hz, 1 H), 7.35–7.25 (m, 5 H), 4.06 (d, J = 7.6 Hz, 1 H), 3.66 (d, J = 7.6, J' = 4.8 Hz, 1 H), 2.22 (s, 3 H), 1.75 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.4, 196.6, 166.1, 131.9, 128.8, 128.5, 128.2, 84.2, 53.0, 49.9, 37.4, 36.6, 28.1 ppm. $[a]_D$ = –5.2 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{17}H_{20}NaO_4$ $[M + Na]^+$ 311.1254; found 311.1253. The enantiomeric excess was determined by HPLC with a Chiralpak® IC column: (*n*-hexane/*i*PrOH = 90:10, λ = 254 nm), 1 mL/min; t_R = major enantiomer 31.5 min, minor enantiomer 38.5 min.

(1*S*,2*R*,3*S*)-Ethyl 2-Formyl-3-phenyl-1-pivaloylcyclopropanecarboxylate (3j): 57 mg (76% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$ TMSint): δ = 9.41 (d, J = 5.1 Hz, 1 H), 7.40–7.25 (m, 5 H), 4.40–4.30 (m, 2 H), 3.97 (d, J = 7.5 Hz, 1 H), 3.54 (d, J = 7.5, J' = 5.1 Hz, 1 H), 1.25 (t, J = 7.2 Hz, 3 H), 0.92 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.6, 196.6, 167.0, 128.8, 128.4, 128.4, 62.8, 52.2, 36.9, 35.6, 29.5, 14.2 ppm. $[a]_D$ = –51.1 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{18}H_{22}NaO_4$ $[M + Na]^+$ 325.1410; found 325.1415. The enantiomeric excess was determined by HPLC with a Chiralpak® IC column: (*n*-hexane/*i*PrOH = 90:10,

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λ = 220 nm), 1 mL/min; t_R = major enantiomer 6.5 min, minor enantiomer 7.8 min.

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