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Organocatalyzed Cyclopropanation of α-Substituted α,β-Unsaturated Aldehydes: Enantioselective Synthesis of Cyclopropanes Bearing a Chiral Quaternary Center

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Abstract: An enantioselective cyclopropanation of α-substituted α,β-unsaturated aldehydes with bromomalonate has been successfully developed through a domino Michael/α-alkylation strategy. The method allows the efficient formation of cyclopropanes bearing a quaternary carbon stereocenter at the α-position of the aldehydes by using iminium/enamine catalysis and gives a nice extension on the organocatalytic cyclopropanation of bromomalonate and α,β-unsaturated aldehydes previously reported by other groups. Very good yields (up to 81%) and enantioselectivities (up to 97% *ee*) have been obtained. The optically active cyclopropane derivatives are of high synthetic interest as useful targets for further elaboration into more complex structures.

Keywords: aldehydes · cyclopropanes · domino reactions · organocatalysis · quaternary stereocenters

Introduction

Amongst the most relevant transformations for carbon–carbon bond-formation, asymmetric construction of quaternary stereocenters represents a real challenging and exciting area for which new procedures are particularly demanding.[1,2] As part of our ongoing work on total synthesis of complex natural products and organocatalysis, we were looking to combine organocatalysis with α-substituted α,β-unsaturated aldehydes for the synthesis of cyclopropanes bearing a carbon center with four different carbon substituents. Over the years, cyclopropanes have gained many synthetic groups' interest and inspired new asymmetric routes allowing to their stereocontrolled construction.[3] Nevertheless, in the field of organocatalysis,[4,5] none of such studies have yet been able to establish the synthesis of cyclopropanes in which the stereogenic carbon at the α-position of the aldehydes involves a chiral quaternary center.[6] Although syntheses of these unique strained rings which are useful targets for further elaboration into more complex structures are well documented,[7] the α,β-difunctionalization of α-substituted α,β-unsaturated enals by chiral aminocatalysis is still unexplored. Indeed, in this special case, very sluggish enamine activation rates or even inert capacities are generally observed for secondary aminocatalysts which usually results in a complete absence of enantiocontrol at the α-position.[8] Breakthrough findings on this goal were recently reported by Melchiorre and co-workers in which primary amines derived from cinchona alkaloids were employed as catalysts for the organocascade intermolecular aryl-amination and thio-amination of α-substituted α,β-unsaturated aldehydes.[9]

In this paper, we report the potential of commercially available Jørgensen–Hayashi catalyst **I**[10] to guide enantioselective cyclopropanations with α-substituted α,β-unsaturated aldehydes and bromomalonate **2** that has an ambiphilic function (Scheme 1). Before starting our studies, we speculated whether the ability of **I** to generate iminium/enamine intermediates could control first, a Michael-type conjugated

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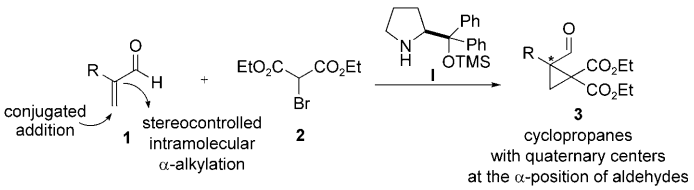
addition of bromomalonate **2** to the β-position of the unsaturated aldehyde (iminium catalysis) and then, an intramolecular enamine-based α-alkylation reaction in an enantiocontrolled way to construct the quaternary carbon.

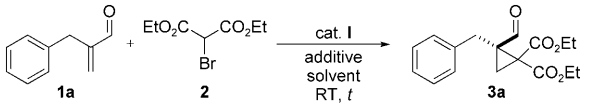


Scheme 1. Targeted chiral cyclopropanes from α-substituted α,β-unsaturated enals.

Results and Discussion

Based on these assumptions, our investigations started by using aldehyde **1a** as a model compound in order to explore the viability of an enantioselective cyclopropanation. In a first experiment, the reaction of aldehyde **1a** with bromomalonate **2**, in the presence of 10 mol% of organocatalyst **I** in ethanol,[11] lead to the desired cyclopropane **3a** in a gratifying 67% *ee*, albeit in low yield (<20%) (Table 1, entry 1). It is noteworthy that longer reaction times block the catalytic cycle due to the alkylation of the organocatalyst.[12] Moving to the Et_3N/**I** catalytic system, previously reported for the cyclopropanation of α,β-unsaturated aldehydes, proved to be poorly effective in our case.[5] This combination dramatically decreases the enantioselection of the reaction even under slow addition techniques (syringe pump) (Table 1, entries 2–3). These observations prompted us to surmise that, under the presence of this base, the cyclopropanation might occur via another mechanism which is not driven by the organocatalyst (Scheme 2). Indeed, in the absence of organocatalyst **I**, Et_3N is able to promote a racemic cyclopropanation (Table 1, entry 4).

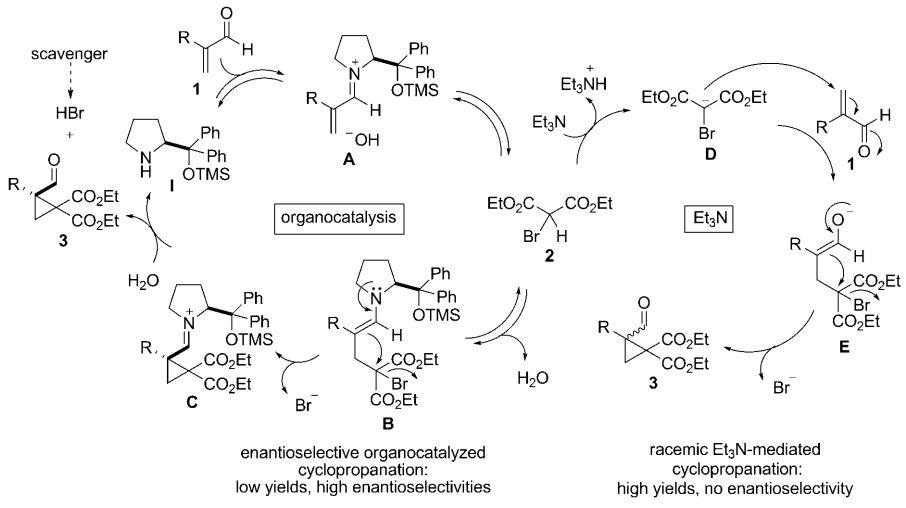
Table 1. Optimization of the reaction conditions for the cyclopropanation of aldehyde **1a** with bromomalonate **2**.[a]



Entry	Cat. **I** [mol%]	Additive [equiv]	Solvent	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	10	–	EtOH	21	<20	67
2	10	Et_3N (1)	$CHCl_3$	15	65	*rac*
3[d]	10	Et_3N (1)	EtOH	12	75	22
4	–	Et_3N (1)	EtOH	7	78	*rac*
5	10	propylene oxide (5)	EtOH	48	50	79
6	10	2,6-lutidine (5)	EtOH	36	38[e]	94
7	10	*N*-Me-imidazole (5)	EtOH	5	55	91
8	10	2,6-lutidine (3)	EtOH	120	60	91
9	10	2,6-lutidine (1)	EtOH	120	24[e]	70
10[f]	20	pyridine (5)	EtOH	48	45	91
11	10	2,6-lutidine (5)	CH_2Cl_2	72	n.r.	–
12	10	2,6-lutidine (5)	THF	48	<20	–
13	10	2,6-lutidine (5)	CH_3CN	48	15	92
14	20	2,6-lutidine (3)	EtOH	144	72	92
15	20	*N*-Me-imidazole (5)	EtOH	3	75	91

[a] Experimental conditions: To a solution of aldehyde **1a** (0.68 mmol) and cat. **I** (0.07 mmol or 0.14 mmol) in solvent (2.5 mL) at room temperature were added bromomalonate **2** (0.57 mmol) and additive. The mixture was stirred over the time (*t*) and the cyclopropane **3a** was purified via column chromatography. [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] Syringe pump addition over 8 h of a pre-mixed mixture of **2** and Et_3N. [e] Low conversion of starting materials. [f] Pyridine in CH_2Cl_2 or THF allows to unidentified side products.

Based on these preliminary results, we hypothesized whether a base is crucial or only an acid scavenger could allow the transformation without loss in enantioselectivity. To validate this proposal, the potential of simple or sterically hindered mild bases was investigated. Moreover, such additives might prevent alkylation of the catalyst and thus allow our cyclopropanation in an enantioselective manner. Propylene oxide proved to be a good additive promoter and cyclopropane **3a** was isolated in 50% yield and 79% *ee* (Table 1, entry 5).[13] Moving to 2,6-lutidine or *N*-methyl imidazole, we were delighted to observe that high levels of enantioselection (up to 94% *ee*) could be reached in satisfactory yields (Table 1, entries 6–7). Reducing lutidine's loading resulted in a deleterious effect on the enantioselectivity and reaction rate (Table 1, entries 8–9). We have also evaluated the capacity of pyridine to participate to the transformation. With this latter as additive, compound **3a**



Scheme 2. Rational about the mechanism of the cyclopropanation via organocatalysis and via Et_3N.

was isolated in an excellent 91% *ee*, nevertheless, the yield was modest and unidentified side products were also formed (Table 1, entry 10). At this point, a brief examination of the solvent has been undertaken. CH_2Cl_2, THF or CH_3CN gave no reaction or only traces of the desired cyclopropanes, however, high enantioselectivity could be observed in CH_3CN (Table 1, entries 11–13).

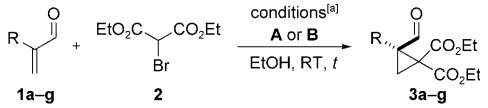
Upon these observations, we have established that in our enantioselective cyclopropanation the best compromise between enantioselectivity and yield was reached with 20 mol% **I**[14] in ethanol[11] at room temperature. Either with 2,6-lutidine or *N*-methyl imidazole, cyclopropane **3a** was isolated in 72% yield, 92% *ee* and 75% yield, 91% *ee*, respectively (Table 1, entries 14 and 15).[15] It should be emphasized that the rate acceleration for the cyclopropanation observed with *N*-methyl imidazole was impressive (144 vs. 3 h, Table 1, entries 14 and 15).

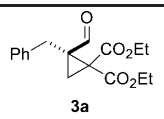
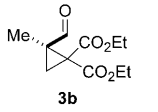
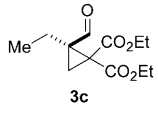
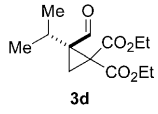
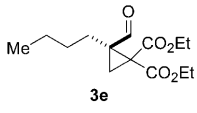
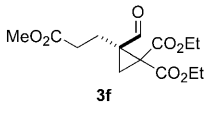
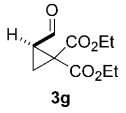
The experiments that explored the scope of this organocatalytic cyclopropanation are summarized in Table 2. Aldehydes **1** were synthesized by using the Pihko methylenation.[16] In general, all reactions were very clean, especially when 2,6-lutidine has been used as additive, and the cyclopropanes were obtained in high yields and enantioselectivities (up to 97% *ee*) under the previously optimized conditions.[17] Different alkyl groups at the α-position of the aldehyde (R = Me, Et, Bu, Bn and *i*Pr) were well tolerated (Table 2, entries 1–5).[18,19] The more sterically encumbered *i*Pr substituent allowed to a slight decrease in the *ee* (Table 2, entry 4). An ester-substituted side chain at the α-position can also participate to the transformation with an excellent 97% *ee* and 66% yield (Table 2, entry 6). The same was observed when the alkyl side chain was replaced by a hydrogen (Table 2, entry 7).

Conclusion

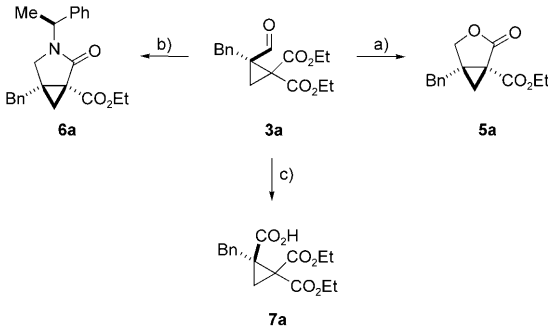
In summary, we have developed an efficient diphenylprolinol trimethylsilyl ether **I** mediated enantioselective cyclopropanation of α-substituted α,β-unsaturated aldehydes, which involves easily prepared aldehydes **1a–g** and commercially available bromomalonate **2**. To the best of our knowledge, in the field of secondary-amine organocatalysts, this is the first example in which a quaternary stereocenter in the α-position of the aldehyde moiety is created in an enantiocontrolled pathway affording cyclopropanes. The lower enamine activation or even inert capacity which is commonly observed with α,β-disubstituted α,β-unsaturated aldehydes is a longstanding problem related to secondary amino catalysts.[9] Nevertheless, by iminium/enamine catalysis with **I**, the rapid access of cyclopropanes has been attained via a domino Michael/α-alkylation reaction in high yields and enantioselectivities (up to 97% *ee*). At the present stage, the success of the protocol relies on the use of α-substituted α,β-unsaturated aldehydes in which the α-substituents are an alkyl or hydrogen group.[19] As illustrated in Scheme 3, synthetically attractive applications can arise from products

Table 2. Substrate scope of organocatalytic cyclopropanation.



Entry	Product	Conditions[a]	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	 3a	**A**	144	72	92
		B	3	75	91
2	 3b	**A**	144	78	>95
		B	3	72	96[e]
3	 3c	**A**	144	77	82
		B	4	72	91
4	 3d	**A**	144	35[d]	79
		B	7	43	86
5	 3e	**A**	144	65	94
		B	6	58	97
6	 3f	**A**	144	66	97
		B	7	52	91[e]
7	 3g	**A**	144	81	85[e]

[a] Experimental conditions: **A**: 2,6-Lutidine (3 equiv) and catalyst **I** (20 mol%); **B**: *N*-Methylimidazole (5 equiv) and catalyst **I** (20 mol%). [b] Isolated yields after column chromatography. [c] Determined by chiral HPLC. [d] By NMR, only 40% conversion of starting material was detected. [e] The *ee* value could be determined after conversion of **3b**, **3f** and **3g** to the corresponding α,β-unsaturated ester (see Supporting Information).



Scheme 3. a) $NaBH_3CN$, AcOH, THF, 0 °C→RT, overnight, 99%; b) (*S*)-1-phenylethanamine, $NaBH_3CN$, AcOH, THF, 0 °C→RT, overnight, 85%; c) $NaClO_2$, NaH_2PO_4, *t*BuOH/H_2O, 2-methyl-2-butene; RT, overnight, 96%.

3. In order to determine the stereochemical outcome of the domino cyclopropanation, single crystals were obtained from lactone **5a**, and the absolute configuration was determined by X-ray analysis to be 2*S*,3*R*, thus confirming the *R* stereochemistry for compounds **3** (Figure 1).[20] Future work within the group is aimed at expanding this concept to other asymmetric reactions (e.g., α,β-disubstituted unsaturated aldehydes) as well as to use the isolated cyclopropanes in order to prepare more elaborated scaffolds.

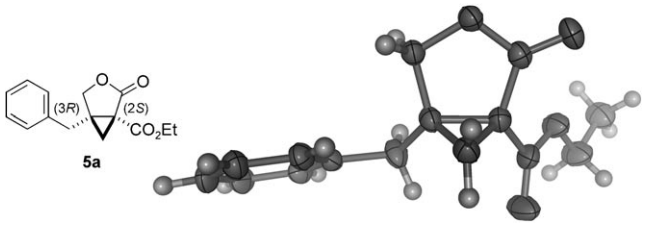


Figure 1. X-ray crystal structure of lactone **5a**.[20]

Experimental Section

General methods: Commercial reagents were used without purification. Reactions were carried out in round-bottom flasks equipped with a magnetic stirring bar. TLC analysis of all reactions was performed on silica gel 60 F254 TLC plates (using 2,4-dinitrophenylhydrazine stain for aldehydes and phosphomolybdic acid for the other compounds). Flash chromatography was carried out on silica gel 60 A (35–70 μm). Melting points were determined with a Büchi Melting Point B-540 unit. FT-IR spectra were recorded with a Perkin–Elmer Spectrum 1000. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Ultra shield 400 plus. ^{1}H chemical shifts are reported in delta (δ) units in parts per million (ppm) relative to the singlet at 7.26 ppm for $CDCl_3$ (residual $CHCl_3$). ^{13}C chemical shifts are reported in ppm relative to the central line of the triplet at 77.0 ppm for $CDCl_3$. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; h, heptet; m, multiplet; and br, broad and combinations thereof. Optical rotations were measured with a Perkin–Elmer 341 polarometer. Low resolutions mass spectra were recorded on a Waters QTof-I spectrometer using electrospray ionization. High resolution mass spectra were obtained using the mass spectrometers operated by the Laboratoire de Mesure Physique of University Montpellier 2.

General procedure for the organocatalyzed asymmetric cyclopropanation: The α-methylene aldehydes (**1a–f**) were prepared according to the procedure described by Pihko.[16] To a solution of the α-substituted α,β-unsaturated aldehydes (**1a–g**; 0.684 mmol, 1.2 equiv) and organocatalyst (**I**; 37.0 mg, 0.114 mmol, 20 mol%) in EtOH (2.5 mL) were successively added the additive (2,6-lutidine: 199 μL, 1.71 mmol, 3.0 equiv or *N*-methylimidazole: 227 μL, 2.85 mmol, 5.0 equiv) and diethyl bromomalonate (**2**; 97.0 μL, 0.57 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for the indicated time (see Table 2) and the solvent was removed. The residue was purified by flash chromatography on silica gel (pentane/Et_2O) to afford the desired cyclopropane **3a–g**.

Cyclopropane 3a: 2,6-Lutidine: 72% yield, *N*-methylimidazole: 75% yield; colorless oil; $R_f = 0.25$ (pentane/Et_2O 9:1); $[\alpha]_D^{25} = +21.6$ ($c = 1.205$, $CHCl_3$); HPLC (CHIRALCEL OD-H (250×4.6 mm ID) *n*-hexane/*i*PrOH 99:1; flow rate: 1.0 mL min^{-1}, 25 °C, $\lambda = 254$ nm, $t_{major} = 10.92$, $t_{minor} = 13.85$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.26$ (s, 1H), 7.29–7.16 (m, 5H), 4.25–4.06 (m, 4H), 3.44 (d, $J = 15.4$ Hz, 1H), 3.01 (d, $J = 15.4$ Hz, 1H), 2.09 (d, $J = 5.4$ Hz, 1H), 2.05 (d, $J = 5.4$ Hz, 1H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.19 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 197.6$, 166.7, 166.4, 137.7, 128.7 (2C), 128.4 (2C), 126.4, 62.3, 62.2, 42.8, 42.4, 31.5, 23.5, 13.9, 13.8 ppm; IR (film): $\tilde{\nu} = 3030$, 2983, 2938, 1731, 1497, 1454, 1370, 1252, 1183, 1108, 1017, 863, 699 cm^{-1}; MS (ESI): *m/z* (%): 306 (20), 305 (100) $[M+H]^+$; HRMS: *m/z*: calcd for $C_{17}H_{21}O_5$: 305.1389; found: 305.1377 $[M+H]^+$.

Cyclopropane 3b: 2,6-Lutidine: 78% yield, *N*-methylimidazole: 72% yield; colorless oil; $R_f = 0.20$ (pentane/Et_2O 9:1); $[\alpha]_D^{25} = -9.7$ ($c = 1.13$, $CHCl_3$); HPLC (after derivatization to **8b** (see Supporting Information): CHIRALCEL OD-H (250×4.6 mm ID) *n*-hexane/*i*PrOH 99:1; flow rate: 1.0 mL min^{-1}, 25 °C, $\lambda = 254$ nm, $t_{major} = 8.81$, $t_{minor} = 12.17$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.26$ (s, 1H), 4.29–4.19 (m, 4H), 2.09 (d, $J = 5.6$ Hz, 1H), 1.89 (d, $J = 5.6$ Hz, 1H), 1.35 (s, 3H), 1.29 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.2$, 167.2, 166.2, 62.2, 62.1, 42.2, 38.2, 24.2, 14.0, 13.9, 12.5 ppm; IR (film): $\tilde{\nu} = 2983$, 2940, 1731, 1448, 1370, 1333, 1231, 1110, 1020, 960, 862 cm^{-1}; MS (ESI): *m/z* (%): 301 (40), 275 (10), 230 (15), 229 (100) $[M+H]^+$; HRMS: *m/z*: calcd for $C_{11}H_{17}O_5$: 229.1076; found: 229.1075 $[M+H]^+$.

Cyclopropane 3c: 2,6-Lutidine: 77% yield, *N*-methylimidazole: 72% yield; colorless oil; $R_f = 0.30$ (pentane/Et_2O 9:1); $[\alpha]_D^{25} = -5.4$ ($c = 1.115$, $CHCl_3$); HPLC (CHIRALCEL OJ (250×4.6 mm ID) *n*-hexane/*i*PrOH 99.5:0.5; flow rate: 1.0 mL min^{-1}, 25 °C, $\lambda = 200$ nm, $t_{major} = 10.26$, $t_{minor} = 12.65$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.18$ (s, 1H), 4.24–4.13 (m, 4H), 1.96 (m, 2H), 1.81 (d, $J = 5.6$ Hz, 1H), 1.56 (m, 1H), 1.24 (m, 6H), 0.92 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 197.9$, 167.0, 166.6, 62.2, 62.1, 43.7, 42.3, 23.0, 19.9, 14.0, 13.9, 11.5 ppm; IR (film): $\tilde{\nu} = 2981$, 2870, 1793, 1730, 1469, 1369, 1277, 1251, 1218, 1111, 1026 cm^{-1}; MS (ESI): *m/z* (%): 470 (10), 244 (15), 243 (100) $[M+H]^+$, 197 (10); HRMS: *m/z*: calcd for $C_{12}H_{19}O_5$: 243.1232; found: 243.1228 $[M+H]^+$.

Cyclopropane 3d: 2,6-lutidine: 35% yield (conversion of the starting material: 40%), *N*-methyl imidazole: 43% yield; colorless oil; $R_f = 0.35$ (pentane/Et_2O 9:1); $[\alpha]_D^{25} = -25.6$ ($c = 0.975$, $CHCl_3$); HPLC (CHIRALCEL OJ (250×4.6 mm ID) *n*-hexane/*i*PrOH 99.5:0.5; flow rate: 1.0 mL min^{-1}, 25 °C, $\lambda = 200$ nm, $t_{major} = 8.11$, $t_{minor} = 9.15$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.54$ (s, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 4.12 (q, $J = 7.2$ Hz, 2H), 1.94 (d, $J = 5.2$ Hz, 1H), 1.77 (h, $J = 7.0$ Hz, 1H), 1.66 (d, $J = 5.2$ Hz, 1H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.22–1.18 (m, 6H), 1.08 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 167.0, 166.8, 62.2, 61.9, 46.5, 43.2, 28.2, 23.2, 19.7, 19.1, 14.0, 13.9 ppm; IR (film): $\tilde{\nu} = 2979$, 2877, 1793, 1731, 1466, 1370, 1310, 1223, 1130, 1106, 1021, 926, 859 cm^{-1}; MS (ESI): *m/z* (%): 625 (20), 624 (40), 403 (20), 402 (100), 257 (40) $[M+H]^+$; HRMS: *m/z*: calcd for $C_{13}H_{21}O_5$: 257.1389; found: 257.1382 $[M+H]^+$.

Cyclopropane 3e: 2,6-Lutidine: 65% yield, *N*-methylimidazole: 58% yield; colorless oil; $R_f = 0.40$ (pentane/Et_2O 9:1); $[\alpha]_D^{25} = +6.5$ ($c = 1.075$, $CHCl_3$); HPLC (CHIRALCEL OJ (250×4.6 mm ID) *n*-hexane/*i*PrOH 99.5:0.5; flow rate: 1.0 mL min^{-1}, 25 °C, $\lambda = 200$ nm, $t_{major} = 7.24$, $t_{minor} = 8.87$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.23$ (s, 1H), 4.25–4.16 (m, 4H), 1.94–2.01 (m, 2H), 1.84 (d, $J = 5.6$ Hz, 1H), 1.56–1.49 (m, 1H), 1.41–1.23 (m, 10H), 0.87 ppm (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.1$, 167.0, 166.6, 62.1, 62.0, 42.8, 42.3, 29.3, 26.3, 23.1, 22.7, 14.0, 13.9, 13.8 ppm; IR (film): $\tilde{\nu} = 2961$, 2873, 1731, 1466, 1370, 1301, 1240, 1201, 1107, 1020, 908, 862 cm^{-1}; MS (ESI): *m/z* (%): 640 (20), 639 (50), 272 (15), 271 (100) $[M+H]^+$; HRMS: *m/z*: calcd for $C_{14}H_{23}O_5$: 271.1545; found: 271.1537 $[M+H]^+$.

Cyclopropane 3f: 2,6-Lutidine: 66% yield, *N*-methylimidazole: 52% yield; colorless oil; $R_f = 0.20$ (pentane/Et_2O 4:1); $[\alpha]_D^{25} = +16.6$ ($c = 1.205$, $CHCl_3$); HPLC (after derivatization to **8f** (see Supporting Information): CHIRALCEL OJ (250×4.6 mm ID) *n*-hexane/*i*PrOH 99.5:0.5; flow rate: 1.0 mL min^{-1}, 25 °C, $\lambda = 200$ nm, $t_{minor} = 33.39$, $t_{major} = 62.76$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.11$ (s, 1H), 4.27–4.16 (m, 4H), 3.64 (s, 3H), 2.53–2.45 (m, 1H), 2.38–2.30 (m, 1H), 2.27–2.19 (m, 1H), 2.03 (d, $J = 5.6$ Hz, 1H), 1.97–1.89 (m, 2H), 1.26 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 197.2$, 172.8, 166.7, 166.1, 62.4, 62.3, 51.6, 42.1, 41.7, 31.3, 23.0, 22.0, 13.9, 13.8 ppm; IR (film): $\tilde{\nu} = 2985$, 1731, 1440, 1370, 1235, 1108, 1019, 913, 861, 838 cm^{-1}; MS (ESI): *m/z* (%): 302 (20), 301 (100) $[M+H]^+$; HRMS: *m/z*: calcd for $C_{14}H_{21}O_7$: 301.1287; found: 301.1284 $[M+H]^+$.

Cyclopropane 3g: 2,6-Lutidine: 81% yield; colorless oil; $R_f = 0.30$ (pentane/Et_2O 4:1); $[\alpha]_D^{25} = -83.3$ ($c = 1.14$, $CHCl_3$); HPLC (after derivatization to **8g** (see Supporting Information): CHIRALCEL OD-H (250×

4.6 mm ID) *n*-hexane/*i*PrOH 99:1; flow rate: 1.0 mL min^{-1}, 25 °C, λ = 254 nm, t_{major} = 8.68, t_{minor} = 10.12 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.30 (d, J = 4.4 Hz, 1H), 4.27–4.16 (m, 4H), 2.73 (ddd, J = 4.4, 6.9, 8.8 Hz, 1H), 2.06 (dd, J = 5.0, 6.9 Hz, 1H), 1.80 ppm (dd, J = 5.0, 8.8 Hz, 1H), 1.27 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.3, 167.8, 165.8, 62.4, 62.1, 37.7, 34.7, 19.2, 13.9 ppm (2C); IR (film): $\tilde{\nu}$ = 2984, 1731, 1447, 1371, 1316, 1267, 1202, 1134, 1065, 1023, 862 cm^{-1}; MS (ESI): *m*/*z* (%): 301 (10), 215 (100) $[M+H]^+$; HRMS: *m*/*z*: calcd for $C_{10}H_{15}O_5$: 215.0919; found: 215.0919 $[M+H]^+$. Data are in accordance with previously reported analysis.[12a]

Procedure for the sequential reduction/lactonization

Synthesis of lactone 5a: To a solution of the cyclopropane **3a** (100 mg, 0.329 mmol, 1.0 equiv) in THF (2.0 mL) at 0 °C were added AcOH (0.4 mL) and $NaBH_3CN$ (37.0 mg, 0.494 mmol, 1.5 equiv). The mixture was slowly warmed to room temperature and stirred overnight. The reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with Et_2O (3×10 mL) and the organic layers were combined, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel (pentane/EtOAc 4:1) to afford the desired lactone **5a** (85 mg, 0.327 mmol, 99%). White solid; R_f = 0.50 (pentane/EtOAc 4:1); m.p. 50–52 °C; $[\alpha]_D^{25} = -120.4$ (c = 1.37, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 3H), 7.19–7.16 (m, 2H), 4.37–4.29 (m, 2H), 4.17 (d, J = 9.2 Hz, 1H), 4.05 (d, J = 9.2 Hz, 1H), 3.08 (d, J_{AB} = 15.0 Hz, 1H), 3.03 (d, J_{AB} = 15.0 Hz, 1H), 2.24 (d, J = 4.8 Hz, 1H), 1.51 (d, J = 4.8 Hz, 1H), 1.35 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 166.0, 136.4, 128.9 (2C), 128.5 (2C), 127.2, 70.4, 62.2, 39.9, 34.7, 34.1, 24.7, 14.2 ppm; IR (KBr): $\tilde{\nu}$ = 2980, 1782, 1713, 1451, 1402, 1376, 1343, 1293, 1271, 1208, 1199, 1096, 1023, 712 cm^{-1}; MS (ESI): *m*/*z* (%): 522 (10), 521 (25) $[2M+H]^+$, 320 (10), 262 (20), 261 (100) $[M+H]^+$; HRMS: *m*/*z*: calcd for $C_{15}H_{17}O_4$: 261.1127; found: 261.1120 $[M+H]^+$.

Procedure for the sequential reductive amination/lactamization

Synthesis of lactame 6a: To a solution of the cyclopropane **3a** (100 mg, 0.329 mmol, 1.0 equiv) in THF (2.0 mL) at room temperature were added (*S*)-(α)-methylbenzylamine (64.0 μL, 60.0 mg, 0.494 mmol, 1.5 equiv) and AcOH (28.0 μL, 30.0 mg, 0.494 mmol, 1.5 equiv). The mixture was stirred for 15 min, then cooled to 0 °C and $NaBH_3CN$ (27.0 mg, 0.428 mmol, 1.3 equiv) was added. The solution was slowly warmed to room temperature and stirred overnight. The reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with Et_2O (3×10 mL) and the organic layers were combined, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel (pentane/EtOAc 4:1) to afford the desired lactame **6a** (102 mg, 0.281 mmol, 85%). Colorless oil; R_f = 0.20 (pentane/EtOAc 4:1); $[\alpha]_D^{25} = -99.1$ (c = 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.19 (m, 6H), 7.16–7.13 (m, 4H), 5.46 (q, J = 7.2 Hz, 1H), 4.31 (dq, J = 1.3 and 7.0 Hz, 2H), 3.32 (d, J = 10.4 Hz, 1H), 2.97 (d, J_{AB} = 14.8 Hz, 1H), 2.91 (d, J_{AB} = 14.8 Hz, 1H), 2.77 (d, J = 10.4 Hz, 1H), 1.96 (d, J = 4.8 Hz, 1H), 1.48 (d, J = 7.2 Hz, 3H), 1.33 (t, J = 7.0 Hz, 3H), 0.97 ppm (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 167.6, 140.2, 137.5, 128.7 (2C), 128.5 (2C), 128.4 (2C), 127.5, 126.8 (3C), 61.6, 48.4, 46.5, 36.8, 35.8, 33.7, 23.8, 15.6, 14.3 ppm; IR (film): $\tilde{\nu}$ = 2976, 2931, 2873, 1682, 1603, 1495, 1453, 1417, 1377, 1350, 1271, 1223, 1177, 1099, 1049, 1024, 699 cm^{-1}; MS (ESI): *m*/*z* (%): 728 (10), 727 (30) $[2M+H]^+$, 365 (30), 364 (100) $[M+H]^+$; HRMS: *m*/*z*: calcd for $C_{23}H_{26}NO_3$: 364.1913; found: 364.1909 $[M+H]^+$.

Procedure for the Pinnick oxidation[21] of the aldehyde 3a: To a solution of the aldehyde **3a** (100 mg, 0.329 mmol) in *t*BuOH (6.0 mL) and 2-methyl-2-butene (1.6 mL) at room temperature was added dropwise a solution of sodium chlorite (275 mg, 3.04 mmol) and sodium dihydrogenphosphate (275 mg, 2.29 mmol) in water (2.75 mL). The reaction mixture was stirred overnight, and then volatile solvents were evaporated. The residue was dissolved in water (10 mL) and the aqueous phase was extracted with pentane (2×10 mL). The aqueous solution was acidified to pH 1 with concentrated HCl and extracted with Et_2O (3×20 mL). The organic layers were combined, washed with a saturated aqueous NaCl solution (5 mL), dried ($MgSO_4$), and evaporated to afford the desired acid **7a** (101 mg, 0.316 mmol, 96%) as a white solid. R_f = 0.35 (pentane/EtOAc 1:1); m.p. 70–72 °C; $[\alpha]_D^{25} = +5.8$ (c = 0.685, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.12 (br s, 1H), 7.28–7.25 (m, 4H), 7.24–7.18 (m, 1H), 4.23–4.08 (m, 4H), 3.41 (d, J = 15.2 Hz, 1H), 2.94 (d, J = 15.2 Hz, 1H), 2.18 (d, J = 5.2 Hz, 1H), 1.92 (d, J = 5.2 Hz, 1H), 1.25–1.18 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 166.8, 166.7, 137.9, 128.6 (2C), 128.3 (2C), 126.4, 62.4, 61.9, 41.8, 37.6, 33.2, 23.7, 13.9, 13.7 ppm; IR (KBr): $\tilde{\nu}$ = 3227, 1721, 1499, 1434, 1397, 1371, 1263, 1233, 1132, 1015, 856, 734, 699 cm^{-1}; MS (ESI): *m*/*z* (%): 640 (50), 639 (100) $[2M-H]^-$, 433 (20), 320 (30), 319 (95) $[M-H]^-$; HRMS: *m*/*z*: calcd for $C_{17}H_{19}O_6$: 319.1182; found: 319.1186 $[M-H]^-$.

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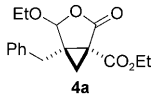

4a

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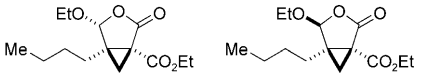
[18] In the case of R = Bu, we have observed, after 18 h of reaction with *N*-methyl imidazole, the transformation of cyclopropane **3e** into products **4e** as two diastereoisomers (see Supporting Information). These compounds are easily separated by column chromatography and, surprisingly, are relatively stable for few days at −18 °C.



4e

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[20] CCDC-758189 (**5a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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