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β -*N*-Heterocyclic Cyclobutane Carboximides: Synthesis through a Tandem Base-Catalyzed Amidation/aza-Michael Addition Protocol and Facile Transformations

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A stereoselective one-pot double derivatization of cyclobutene-1-carboxylic acid via a mild organic base catalyzed amidation/aza-Michael addition of benzo[d]oxazol-2(3H)-ones has been developed. This unprecedented tandem reaction provides access to novel β -*N*-heterocyclic cyclobutane carboximide

derivatives with a *trans* geometry. The carboximide moiety reacts smoothly with nucleophiles, allowing access to diverse derivatives of *trans*- β -*N*-heterocyclic cyclobutanecarboxylic acid, including peptidomimetic structures.

Introduction

β -Aminocyclobutanecarboxylic acid derivatives (ACBCs) are valuable building blocks in organic synthesis for the preparation of multi-functionalized molecules and biologically active products.^[1] Short oligomers of ACBCs may adopt helical,^[2] ribbon,^[3] or strand architectures,^[4] or macromolecular assemblies.^[5] Other molecules incorporating ACBC units have been used as organogelators,^[6] metal catalyst ligands,^[6b] cell-penetrating agents,^[7] peptidenucleic acids,^[8] or inhibitors of protein-protein interactions.^[9] The most common synthetic approach for preparing ACBC derivatives is via a [2 + 2] cycloaddition reaction, achieved in thermal,^[10] photochemical,^[11] metal-catalyzed^[12] or multi-component^[13] modes. Other strategies include ring closure protocols^[14] or functional group transformations of other cyclobutane derivatives.^[15] Although the aza-Michael addition of lithium amides to unsaturated esters is an established method for the preparation of β -amino acids,^[16] we are aware of only one application thereof for the

preparation of an ACBC.^[17] One of the challenges in this approach lies in the controlled preparation and manipulation of esters of cyclobutene-1-carboxylic acid.^[18] We recently described the in-situ generation of a cyclobutene carboxamide intermediate (from α -sulfinyl cyclobutene-1-carboxylic amides) which underwent efficient thia-Michael addition.^[19]

On this premise, in continuation of our interest in the chemistry of aminocyclobutanes,^[20] we envisaged that a transient cyclobutene carboxamide could be generated by coupling the parent acid with a nitrogen reagent **2** then could undergo an aza-Michael addition reaction with a second equivalent of **2** to generate a β -amino cyclobutane carboxamide **3** under mild organocatalytic conditions (Scheme 1). Herein, we disclose our findings using the particular case where benzoxazolones are the reaction partners; this leads to novel ACBC derivatives featuring both an *N*-heterocyclic function and a carboxyl group activated in the form of a carboximide, which facilitates further transformations of the carboxylic center.

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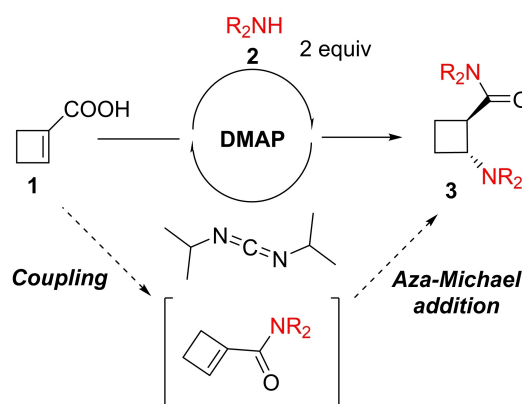
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Scheme 1. Proposed one-pot formation of β -amino cyclobutane carboximides **3**.

Results and Discussion

We began our studies by combining benzo[d]oxazol-2(3H)-one **2a** (2 equiv.) with cyclobutene-1-carboxylic acid **1** in the presence of DIC as a coupling agent and DMAP (20 mol%) as catalyst, in CH₂Cl₂ at room temperature for 24 h, as outlined in Table 1 (entry 1). To our delight, the desired β-*N*-heterocyclic cyclobutane carboximide was obtained in 64% yield as a separable mixture of *trans* and *cis* diastereomers **3a** and **3'a** (d.r. = 75/25). Compounds **3a** and **3'a** gave crystals suitable for X-ray diffraction analysis, confirming their identity (Figure 1).^[21]

Prompted by this result, we undertook an optimization of the reaction conditions by testing a range of reaction parameters (Table 1). Prolonged reaction time (40 h) increased both the yield (72%) and the diastereoselectivity (d.r. = 93/7) (entry 2). When the reaction was performed at 0 °C (entry 3) the yield was

Entry	Deviation from standard conditions	Ratio 3a : 3'a [%] ^[b]	Yield 3a / 3'a [%] ^[c]
1	none	75:25	64
2	40 h instead of 24 h	93:7 (88:12) ^[d]	72 (65) ^[d]
3	0 °C instead of R.T. and 40 h instead of 24 h	15:85	69
4	1 equiv. of 2a instead of 2 equiv.	95:5	44
5	DMF as solvent	96:4	26
6	DCC (1 equiv.) instead of DIC and 40 h instead of 24 h	83:17	74
7	EDAC (1 equiv.), Et ₃ N (1 equiv.) instead of DIC and 40 h instead of 24 h	92:8	63

[a] Conditions: **1** (0.255 mmol), **2a** (0.51 mmol), DMAP (0.051 mmol), DIC (0.255 mmol), CH₂Cl₂ (0.6 mL). [b] Determined by crude ¹H NMR. [c] Isolated yield. [d] Performed on 2 mmol scale. DIC: *N,N'*-diisopropylcarbodiimide; DCC: *N,N'*-dicyclohexylcarbodiimide; EDAC: *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride.

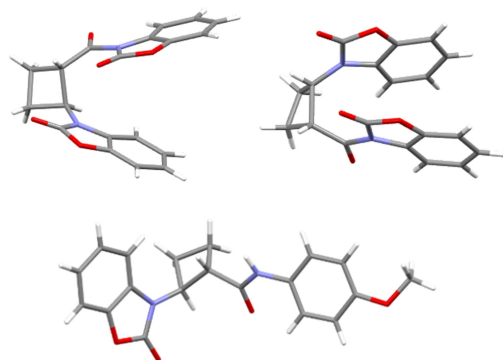
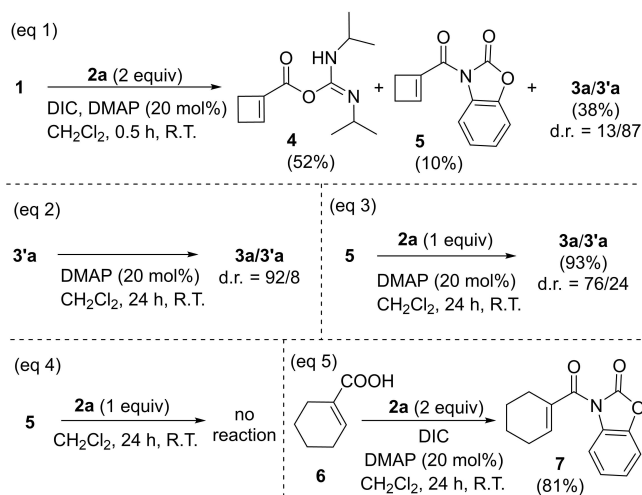


Figure 1. X-ray crystal structures of compounds **3a**, **3'a** and **11**.^[a] [a] Left panel, **3a**. Right panel, **3'a**. Lower panel, **11**.

similar (69%) while the diastereomeric ratio was inverted in favour of the *cis* isomer (**3a**/**3'a** = 15/85). The reaction conducted using 1 equiv. of **2a** (entry 4) was efficient (44% yield; theoretical yield 50%) and the high *trans* diastereoselectivity (**3a**/**3'a** = 95/5) was conserved. Upon replacement of CH₂Cl₂ with DMF (entry 5), **3a**/**3'a** was obtained with a high diastereomeric ratio (**3a**/**3'a** = 96/4) but a poor 26% yield. Other coupling reagents (DCC or EDAC; entries 6–7) brought no further advantages in terms of stereoselectivity or yield. The reaction parameters listed in entry 2 (Table 1) were considered as being optimal and retained for subsequent investigations. A reaction conducted on a larger (2 mmol) scale proceeded successfully in slightly reduced yield (65%) and diastereoselectivity (**3a**/**3'a** = 88:12).

To have a better understanding of the reaction mechanism, a series of control experiments was carried out (Scheme 2). In the first instance, in an effort to identify any intermediates, the reaction time was shortened to 0.5 h (Eq. (1)) and isourea **4** was obtained as the major product (52%); a small amount of **5** (10%) and a 13/87 mixture of **3a**/**3'a** (38%) made up the rest of the product mixture, by NMR analysis. Formation of **3'a-cis** as the major diastereomer suggested that a reversible reaction occurs. It seemed likely that **3'a-cis** was the kinetically formed product while a prolonged reaction time resulted in the formation of thermodynamically more stable **3a-trans**.

This hypothesis was supported by the observation that a diastereoisomerically pure sample of **3'a-cis** treated with 20 mol% of DMAP resulted in its epimerization into a 92/8 *trans/cis* mixture of diastereomers after 24 h at room temperature as determined by NMR (Eq. (2)). In the next experiment, cyclobutene carboximide **5** was prepared independently (see experimental section) and evaluated as a substrate in the presence of 1 equiv. of **2a** and DMAP (Eq. (3)). The reaction provided **3a**/**3'a** in high yield in a comparable diastereoisomeric ratio to that shown in the Table 1 (entry 1). Meanwhile, intermediate **5** failed to react with **2a** in the absence of DMAP, confirming the importance of the latter as catalyst also during



Scheme 2. Control experiments.

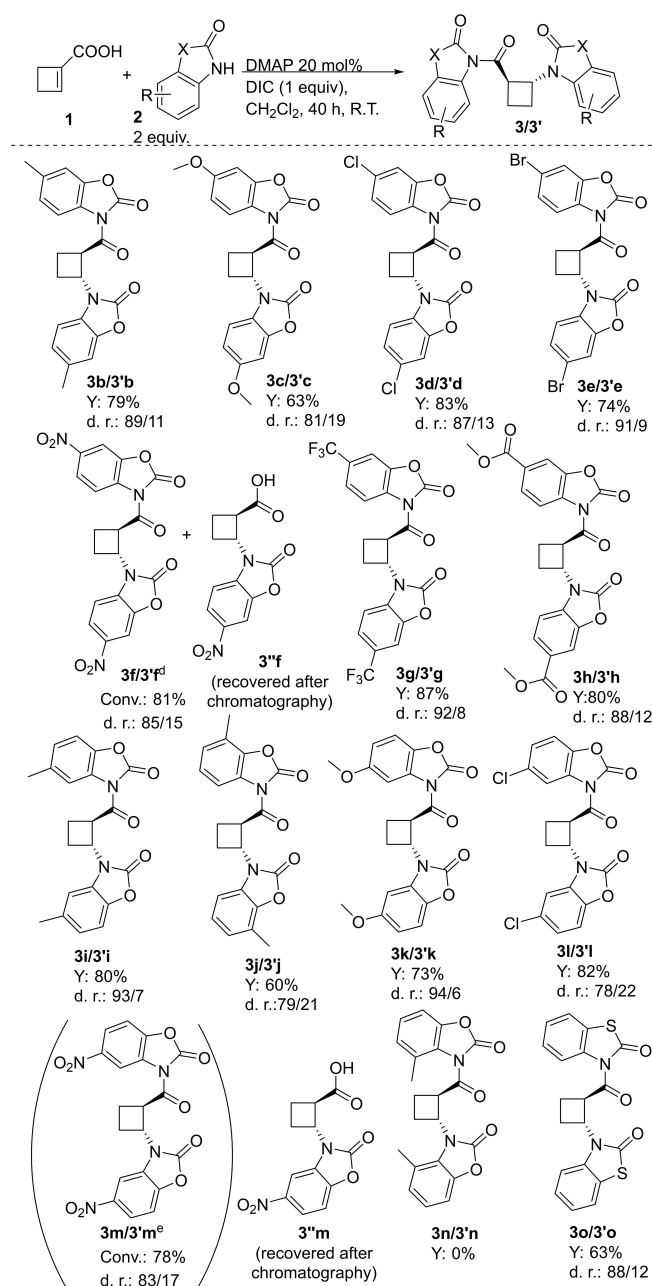
the aza-Michael addition step (Eq. (4)). Collectively, these observations supported the sequential mechanistic proposal outlined in Scheme 1. Finally, the analogous reaction carried out using cyclohexene-1-carboxylic acid **6**, lacking any ring strain, gave 3-(cyclohexene-1-carbonyl) benzo[d]oxazol-2(3H)-one **7** in high yield (81 %) as the only reaction product (Eq. (5)). On this basis, we assume that the strain release of intermediate **5** during the base catalyzed nucleophilic attack of the nitrogen heterocycle is a driving force for the process.

Using the optimal reaction conditions, various benzo[d]oxazol-2(3H)-ones **2** were examined to determine the reaction scope; results are summarized in Scheme 3. A reasonable substituent tolerance emerged, allowing access to a variety of highly functionalized *trans*- β -*N*-heterocyclic cyclobutane carboximides **3** with diverse aromatic ring-substituent patterns. Benzo[d]oxazol-2(3H)-ones bearing electron-donating groups in the 5- or 6-position furnished the corresponding carboximides **3b/3'b–3c/3'c**, **3i/3'i**, **3k/3'k** in 63–80 % yields and good to high diastereomeric ratios. Halogen (6-Cl, 6-Br, 5-Cl) substituted substrates were also well tolerated under the optimized conditions to furnish the corresponding products **3d/3'd–3e/3'e** and **3l/3'l** in good yields (74–83 %) and stereoselectivities (78/22–91/9). Similarly, reactions of benzo[d]oxazol-2(3H)-ones bearing electron withdrawing (6-NO₂, 6-CF₃, 6-COOMe, 5-NO₂) substituents were efficient, leading to the expected products **3f/3'f–3h/3'h** and **3m/3'm** in high yields (78–87 %) and diastereoselectivities (83/17–92/8). A significant observation was that carboximides **3f/3'f** and **3m/3'm** were unstable during chromatography on silica gel and underwent hydrolysis to the corresponding acids **3'f** and **3'm**. Benzo[d]oxazol-2(3H)-one bearing a methyl as the substituent in the 7-position was a good substrate, affording the corresponding product **3j/3'j** in reasonable yield (60 %) and diastereoselectivity (79/21). In contrast, benzo[d]oxazol-2(3H)-one bearing the methyl substituent in the 4-position failed to produce the corresponding carboximide **3n/3'n**. A representative benzo[d]thiazol-2(3H)-one was converted in the same reaction conditions into the corresponding carboximide **3o/3'o** with a moderate chemical yield (63 %) and high stereoselectivity (88:12).

The facile hydrolysis of carboximides **3f/3'f** and **3m/3'm** during their purification (see above) suggested that a benzo[d]oxazol-2(3H)-one was behaving as a good leaving group, effectively serving as an activation of the ACBC core for nucleophilic substitution at the carboxylic center. Following this lead, we successfully carried out a variety of transformations of the representative substrate **3a** in mild conditions (Scheme 4).

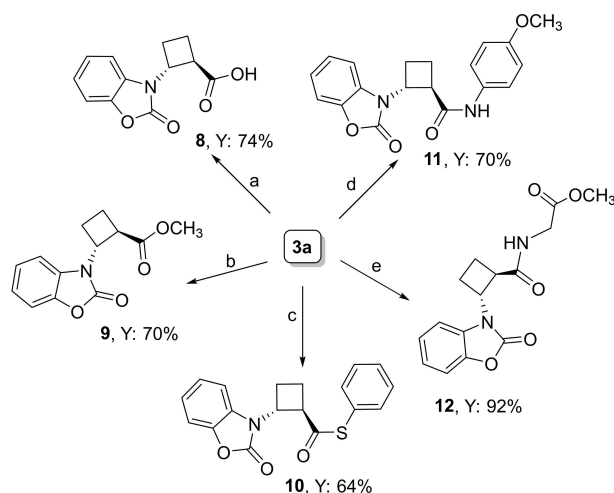
Base-mediated hydrolysis in water/dioxane provided acid **9** in good yield (74 %) whereas methanolysis gave methyl ester **8** in comparable yield (70 %). Reaction of **3a** with thiophenol gave thioester **10** in 64 % yield, while reaction with *p*-anisidine gave amide **11** in 70 % yield. We obtained a single crystal of **11** and the X-ray diffraction analysis confirmed its identity (Figure 1).^[21] Finally, reaction of **3a** with glycine methyl ester gave the peptidomimetic **12** in excellent yield (92 %).

The solution state behaviour of **11** and **12** was of interest. In low polarity solution, short peptide derivatives of *trans*-ACBC usually adopt a robust 8-membered ring hydrogen-bonded



Scheme 3. Substrate scope.^[a–f] [a] Conditions: **1** (0.255 mmol), **2** (0.51 mmol), DMAP (0.051 mmol), DIC (0.255 mmol), CH₂Cl₂ (0.6 mL), 40 h, R.T. [b] Isolated yield. [c] The diastereoisomeric ratios (d.r. = *trans/cis*) were determined by ¹H NMR analysis of the crude reaction mixture. [d] Purification by column chromatography gave an inseparable 50:50 mixture of **3f** and the corresponding acid **3'f**. [e] Only the corresponding acid **3'm** was obtained after column chromatography. [f] The major *trans* diastereoisomer is illustrated.

conformation (C8).^[5c,22] The solution state IR spectrum of **11** (5 mM, CHCl₃) showed a broad, red-shifted NH stretch absorbance in the range 3275–3375 cm⁻¹, as expected (see Supporting Information). However, the appearance of a sharper band at 3428 cm⁻¹ pointed to the presence of a second conformer with a free (non hydrogen-bonded) NH. In the IR spectrum of dipeptide **12** (0.5–10 mM range, CHCl₃) the expected broad,



Scheme 4. Transformations of product **3a**.^[a] [a] Conditions: (a) Na₂CO₃, H₂O/dioxane, R.T. 48 h; (b) Na₂CO₃, MeOH, R.T. 48 h; (c) benzenethiol, DMAP 20 mol%, CH₂Cl₂, R.T. 24 h; (d) *p*-anisidine, DMAP 20 mol%, CH₂Cl₂, R.T. 48 h; (e) methyl glycinate, CH₂Cl₂, R.T. 72 h.

red-shifted band of the C8 conformation was accompanied by two blue bands at 3425 and 3450 cm⁻¹, which can be assigned to conformers having a 5-membered ring hydrogen-bond (C5) implicating the glycine residue, and a free NH, respectively. Conformations other than C8 for *trans*-ACBC derivatives are uncommon, so support for the assignments was obtained by theoretical calculations (see Supporting Information for details). An MCM conformational analysis of the two compounds in implicit CHCl₃ was performed using MacroModel software and the OPLS 2005 force field and completed by a set of manually built conformations in order to provide a set of starting structures for quantum chemistry optimizations (DFT-D with implicit polarizable continuum). Two conformer families ap-

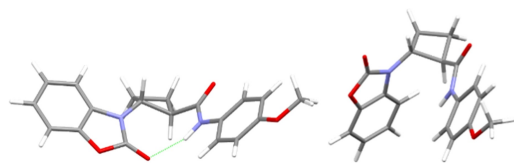


Figure 2. Solution state conformations of **11**.^[a] [a] Left panel, C8 conformation. Right panel, free NH conformation.

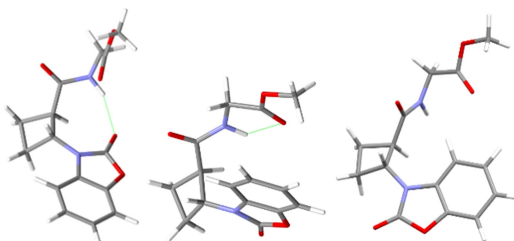


Figure 3. Solution state conformations of **12**.^[a] [a] Left panel, C8 conformation. Middle panel, C5 conformation. Right panel, free NH conformation.

peared for amide **11** and three appeared for **12**. The theoretical IR spectra of these structures were calculated, providing a good match with the experimental data. The geometry-optimized structures of the relevant conformations of **11** and **12** are illustrated in Figures 2 and 3 respectively.

Conclusion

To summarize, we have reported a diastereoselective mild base catalyzed access to *trans*-β-*N*-heterocyclic cyclobutane carboximide derivatives, via a tandem coupling/aza-Michael addition of benzo[d]oxazol-2(3H)-ones with cyclobutene-1-carboxylic acid. The reaction has good substrate scope and the products have an activated carboxylic group, facilitating the synthesis of other derivatives including peptidomimetic structures. Although the expected C8 conformations of such compounds are observed, other less common conformations are in evidence, that are not observed with other *N*-carbamate derivatives of *trans*-ACBC. These results contribute to the expansion of the inventory of multi-functional small molecules that incorporate ACBC fragments. Future work will focus on synthetic access to compounds **3** in single enantiomer form and their incorporation into small peptide sequences in order to further explore the factors that influence the conformational preferences induced by the benzo[d]oxazol-2(3H)-ones moiety in peptidomimetics.

Experimental Section

General Methods: ¹H NMR spectra were recorded on a 600 MHz spectrometer at ambient temperature with CDCl₃ or DMSO-*d*₆ as solvent. Data are reported as follows: chemical shifts (δ), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, dd=doublet of doublet, td=triplet of doublets, qd=quartet of doublets, m=multiplet, br s=broad singlet), coupling constants (Hz) and integration. ¹³C NMR spectra were recorded on the same instrument at 151 MHz with CDCl₃ or DMSO-*d*₆ as solvent. Routine infrared spectra were recorded on an FTIR spectrophotometer in ATP mode; samples were neat (for liquids) or nujol mulls (for solids). Solution state infrared spectra of **11** and **12** were recorded using 10 mM solutions in CHCl₃ held in Omni-cell Specac 1 mm path-length NaCl plates. High resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI) and a Q-TOF mass analyzer. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using columns of 230–400 mesh silica gel 60 (0.040–0.063 mm). Compound **1** was prepared following the literature procedure.^[23] Compound **6** and all other standard reagents were obtained commercially and used without further purification.

General procedure for the preparation of 3a–l, 3'f, 3'm, 3o and 4: Cyclobutene-1-carboxylic acid **1** (0.049 g, 0.255 mmol), benzoxazolone **2a–2n** (or benzo[d]thiazol-2(3H)-one **2o**) (0.51 mmol) and DMAP (0.006 g, 0.051 mmol) were dissolved in 0.6 mL of dry dichloromethane. Diisopropylcarbodiimide (0.032 g, 0.255 mmol) was added, and the resulting mixture was stirred at room temperature for 40 h. The mixture was filtered and washed through with dichloromethane. The filtrate was washed with aqueous NH₄Cl, brine, then dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography of the crude product provided the corresponding carboxamide **3**.

Procedure for the synthesis of 5: To a solution of **1** (0.05 g, 0.51 mmol) in dichloromethane (1.3 mL) was added DMF (0.0021 mL, 0.0255 mmol) followed by slow addition of thionyl chloride (0.041 mL, 0.561 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. Benzo[d]oxazol-2(3H)-one **2a** (0.069 g, 0.51 mmol) and triethylamine (0.213 mL, 1.53 mmol) were then added and the resulting mixture was stirred at room temperature overnight. The reaction was quenched with water and extracted with dichloromethane. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified by flash column chromatography (SiO₂, petroleum ether/ether=5:1→1:1) to furnish **5** (0.07 g, 64%) and **3a/3'a** (0.0052 g, 3%; d. r.=5:95). Spectral data for **5** were identical with those previously reported.^[18]

Procedure for the synthesis of 7 (control experiment Equation (5)): Cyclohexene-1-carboxylic acid **6** (0.032 g, 0.255 mmol), benzoxazolone **2a** (0.069 g, 0.51 mmol) and DMAP (0.006 g, 0.051 mmol) were dissolved in 0.6 mL of dry dichloromethane. Diisopropylcarbodiimide (0.032 g, 0.255 mmol) was added, and the resulting mixture was stirred at room temperature for 24 h. The mixture was filtered and washed through with dichloromethane. The filtrate was washed with aqueous NH₄Cl, brine, then dried over Na₂SO₄ and concentrated in vacuo. The crude product was purified by flash column chromatography (SiO₂, petroleum ether/ether=5:1→1:1).

Procedure for the synthesis of 8: The carboximide **3a** (0.070 g, 0.2 mmol) was dissolved in 2 mL of H₂O:1,4-dioxane (1:1). Sodium carbonate (0.036 g, 0.34 mmol) was added and the mixture was stirred at room temperature for 48 h. Water was then added and the mixture was extracted with ethyl acetate. The aqueous phase was acidified with 1.0 M aqueous HCl to pH 1 then extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, then evaporated in vacuo. Flash column chromatography (SiO₂, petroleum ether/ether=1:1→0:1) gave the corresponding acid **8**.

Procedure for the synthesis of 9: The carboximide **3a** (0.079 g, 0.226 mmol) was dissolved in 2.5 mL of MeOH. Sodium carbonate (0.048 g, 0.45 mmol) was added and the mixture was stirred at room temperature for 48 h. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (SiO₂, petroleum ether/ether=5:1).

Procedure for the synthesis of 10: A mixture of carboximide **3a** (0.063 g, 0.18 mmol), benzenethiol (0.022 g, 0.198 mmol) and DMAP (0.0044 g, 0.036 mmol) in 0.8 mL of dichloromethane was stirred at room temperature for 24 h. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (SiO₂, petroleum ether/ether=5:1→1:1).

Procedure for the synthesis of 11: A mixture of carboximide **3a** (0.050 g, 0.143 mmol), *p*-anisidine (0.017 g, 0.138 mmol) and DMAP (0.0034 g, 0.0276 mmol) in dichloromethane (0.6 mL) was stirred at room temperature for 48 h. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (SiO₂, petroleum ether/ether=1:1→0:1).

Procedure for the synthesis of 12: A mixture of carboximide **3a** (0.050 g, 0.143 mmol) and methyl glycinatate (0.012 g, 0.138 mmol) in dichloromethane (0.6 mL) was stirred at room temperature for 72 h. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (SiO₂, petroleum ether/ether 1:1→0:1).

Scale-up synthesis of 3a: Cyclobutene-1-carboxylic acid **1** (0.196 g, 2 mmol), benzoxazolone **2a** (0.54 g, 4 mmol) and DMAP (0.049 g, 0.4 mmol) were dissolved in 5 mL of dry dichloromethane.

Diisopropylcarbodiimide (0.252 g, 2 mmol) was added, and the resulting mixture was stirred at room temperature for 40 h. The mixture was filtered and washed through with dichloromethane. The filtrate was washed with aqueous NH₄Cl, brine, then dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (SiO₂, petroleum ether/ether=5:1→1:1) of the crude product provided the corresponding carboximide **3a** (0.455 g, 65% yield, **3a/3'a**=88:12).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: carbocycles · diastereoselectivity · heterocycles · small ring systems · synthetic methods

- [1] For selected reviews on cyclobutane preparation and reactivity, see: a) J. C. Namsylo, D. E. Kaufmann, *Chem. Rev.* **2003**, *103*, 1485–1538; b) E. Lee-Ruff, G. Mladenova, *Chem. Rev.* **2003**, *103*, 1449–1484; c) N.-Y. Fu, S.-H. Chan, *The Chemistry of Cyclobutanes*, ed. Z. Rappoport and J. F. Liebman, Wiley, Chichester **2005**, pp. 357–440; d) E. Lee-Ruff, *The Chemistry of Cyclobutanes*, ed. Z. Rappoport, J. F. Liebman, Wiley, Chichester **2005**, pp. 281–355.
- [2] a) C. M. Grison, S. Robin, D. J. Aitken, *Chem. Commun.* **2016**, *52*, 7802–7805; b) A. Altmayer-Henzi, V. Declerck, J. Farjon, D. Merlet, R. Guillot, D. J. Aitken, *Angew. Chem. Int. Ed.* **2015**, *54*, 10807–10810; *Angew. Chem.* **2015**, *127*, 10957–10960; c) C. Fernandes, S. Faure, E. Pereira, V. Théry, V. Declerck, R. Guillot, D. J. Aitken, *Org. Lett.* **2010**, *12*, 3606–3609.
- [3] C. M. Grison, S. Robin, D. J. Aitken, *Chem. Commun.* **2015**, *51*, 16233–16236.
- [4] a) A. Hassoun, C. M. Grison, R. Guillot, T. Boddaert, D. J. Aitken, *New J. Chem.* **2015**, *39*, 3270–3279; b) E. Torres, E. Gorrea, K. K. Burusco, E. Da Silva, P. Nolis, F. Rúa, S. Bousset, I. Diez-Pérez, S. Dannenberg, S. Izquierdo, E. Girault, C. Jaime, V. Branchadell, R. M. Ortuño, *Org. Biomol. Chem.* **2010**, *8*, 564–575.
- [5] a) A. Sorrenti, O. Illa, R. Pons, R. M. Ortuño, *Langmuir* **2016**, *32*, 6977–6984; b) A. Sorrenti, O. Illa, R. Pons, R. M. Ortuño, *Langmuir* **2015**, *31*, 9608–9618; c) E. Gorrea, P. Nolis, E. Torres, E. Da Silva, D. B. Amabilino, V. Branchadell, R. M. Ortuño, *Chem. Eur. J.* **2011**, *17*, 4588–4597.
- [6] a) S. Celis, P. Nolis, O. Illa, V. Branchadell, R. M. Ortuño, *Org. Biomol. Chem.* **2013**, *11*, 2839–2846; b) O. Porcar-Tost, B. Pi-Boleda, J. García-Anton, O. Illa, R. M. Ortuño, *Tetrahedron* **2018**, *74*, 7252–7260.

- [7] O. Illa, J. Ospina, J.-E. Sánchez-Aparicio, X. Pulido, M. Á. Abengozar, N. Gaztelumendi, D. Carbajo, C. Nogués, L. Rivas, J.-D. Maréchal, M. Royo, R. M. Ortuño, *Int. J. Mol. Sci.* **2021**, *22*, 5092.
- [8] a) W. Mansawat, C. Vilaivan, A. Balazs, D. J. Aitken, T. Vilaivan, *Org. Lett.* **2012**, *14*, 1440–1443; b) B. Ditmangklo, W. Sittiwong, T. Boddaert, T. Vilaivan, D. J. Aitken, *Biopolymers* **2021**, *112*, e23459.
- [9] C. M. Grison, J. A. Miles, S. Robin, A. J. Wilson, D. J. Aitken, *Angew. Chem. Int. Ed.* **2016**, *55*, 11096–11100; *Angew. Chem.* **2016**, *128*, 11262–11266.
- [10] K. C. Brannock, A. Bell, R. D. Burpitt, C. A. Kelly, *J. Org. Chem.* **1964**, *29*, 801–812.
- [11] a) Z. Chang, F. Boyaud, R. Guillot, T. Boddaert, D. J. Aitken, *J. Org. Chem.* **2018**, *83*, 527–534; b) V. Declerck, D. J. Aitken, *Amino Acids* **2011**, *41*, 587–595; c) B. Basler, O. Schuster, T. Bach, *J. Org. Chem.* **2005**, *70*, 9798–9808; d) C. Gauzy, B. Saby, E. Pereira, S. Faure, D. J. Aitken, *Synlett* **2006**, 1394–1398; e) A. Mondière, R. Peng, R. Remuson, D. J. Aitken, *Tetrahedron* **2008**, *64*, 1088–1093; f) N. Katagiri, H. Sato, C. Kaneko, *Chem. Pharm. Bull.* **1990**, *38*, 288–290; g) L. F. Tietze, A. Bergmann, K. Brüggemann, *Synthesis* **1986**, 190–192.
- [12] a) X. Zhong, Q. Tang, P. Zhou, Z. Zhong, S. Dong, X. Liu, X. Feng, *Chem. Commun.* **2018**, *54*, 10511–10514; b) F. de Nanteuil, J. Waser, *Angew. Chem. Int. Ed.* **2013**, *52*, 9009–9013; *Angew. Chem.* **2013**, *125*, 9179–9183; c) T. Mitsudo, S.-W. Zhang, N. Satake, T. Kondo, Y. Watanabe, *Tetrahedron Lett.* **1992**, *33*, 5533–5536.
- [13] a) K. Ausmees, K. Kriis, T. Pehk, F. Werner, I. Järving, M. Lopp, T. Kanger, *J. Org. Chem.* **2012**, *77*, 10680–10687; b) B. Jiang, X. Wang, H.-W. Xu, M.-S. Tu, S.-J. Tu, G. Li, *Org. Lett.* **2013**, *15*, 1540–1543; c) H. M. Sheldrake, T. W. Wallace, C. P. Wilson, *Org. Lett.* **2005**, *7*, 4233–4236.
- [14] a) X. Xin, D. Wang, F. Wu, C. Wang, H. Wang, X. Li, B. Wan, *Org. Lett.* **2013**, *15*, 4512–4515; b) T. Meiresonne, S. Mangelinckx, N. De Kimpe, *Org. Biomol. Chem.* **2011**, *9*, 7085–7091.
- [15] a) Z. Chang, R. Guillot, T. Boddaert, D. J. Aitken, *J. Org. Chem.* **2019**, *84*, 10518–10525; b) F. Hervann, G. Rasore, V. Declerck, D. J. Aitken, *Org. Biomol. Chem.* **2014**, *12*, 8212–8222; c) D. Hazeldar, A. Fadel, R. Guillot, *Tetrahedron: Asymmetry* **2008**, *19*, 2063–2067; d) C. Bolm, I. Schiffers, I. Atodiresei, C. P. R. Hackenberger, *Tetrahedron: Asymmetry* **2003**, *14*, 3455–3467; e) M. Martín-Vilà, C. Minguillón, R. M. Ortuño, *Tetrahedron: Asymmetry* **1998**, *9*, 4291–4294; f) P. Yuan, M. R. Driscoll, S. J. Raymond, D. E. Hansen, R. A. Blatchly, *Tetrahedron Lett.* **1994**, *35*, 6195–6198.
- [16] S. G. Davies, A. M. Fletcher, P. M. Roberts, J. E. Thomson, *Tetrahedron: Asymmetry* **2017**, *28*, 1842–1868, and the two previous reviews in this series.
- [17] F. Charnay-Pouget, M. Franck, J.-P. Baltazen, E. Pereira, D. J. Aitken, *Arkivoc* **2012**, *v*, 80–93.
- [18] a) Y.-J. Chen, T.-J. Hu, C.-G. Feng, G.-Q. Lin, *Chem. Commun.* **2015**, *51*, 8773–8776; b) K. Takao, K. Mori, K. Kasuga, R. Nanamiya, A. Namba, Y. Fukushima, R. Nemoto, T. Mogi, H. Yasui, A. Ogura, K. Yoshida, K. Tadano, *J. Org. Chem.* **2018**, *83*, 7060–7075; c) T. J. Saiegh, H. Chédotal, C. Meyer, J. Cossy, *Org. Lett.* **2019**, *21*, 8364–8368; d) K. Nguyen, H. A. Clement, L. Bernier, J. W. Coe, W. Farrell, C. J. Helal, M. R. Reese, N. W. Sach, J. C. Lee, D. G. Hall, *ACS Catal.* **2021**, *11*, 404–413; e) S. M. Hell, C. F. Meyer, A. Misale, J. B. I. Sap, K. E. Christensen, M. C. Willis, A. A. Trabanco, V. Gouverneur, *Angew. Chem. Int. Ed.* **2020**, *59*, 11620–11626; *Angew. Chem.* **2020**, *132*, 11717–11723; f) J.-c. Han, F. Li, C.-c. Li, *J. Am. Chem. Soc.* **2014**, *136*, 13610–13616; g) K. Takao, R. Nemoto, K. Mori, A. Namba, K. Yoshida, A. Ogura, *Chem. Eur. J.* **2017**, *23*, 3828–3831.
- [19] L. Ghisu, N. Melis, L. Serusi, A. Luridiana, F. Soddu, F. Secci, P. Caboni, R. Guillot, D. J. Aitken, A. Frongia, *Org. Biomol. Chem.* **2019**, *17*, 6143–6147.
- [20] a) D. J. Aitken, P. Caboni, H. Eijlsberg, A. Frongia, R. Guillot, J. Ollivier, P. P. Piras, F. Secci, *Adv. Synth. Catal.* **2014**, *356*, 941–945; b) L. Serusi, M. Bonnans, A. Luridiana, F. Secci, P. Caboni, T. Boddaert, D. J. Aitken, A. Frongia, *Adv. Synth. Catal.* **2019**, *361*, 1908–1912; c) L. Ghisu, N. Melis, F. Secci, P. Caboni, M. Arca, R. Guillot, T. Boddaert, D. J. Aitken, A. Frongia, *Org. Biomol. Chem.* **2017**, *15*, 9779–9784; d) L. Serusi, F. Soddu, F. Cuccu, G. Peretti, A. Luridiana, F. Secci, P. Caboni, D. J. Aitken, A. Frongia, *Adv. Synth. Catal.* **2020**, *362*, 4159–4163; e) L. Serusi, F. Cuccu, F. Secci, D. J. Aitken, A. Frongia, *Synthesis* **2021**, *53*, 673–681; f) V. Marras, P. Caboni, F. Secci, R. Guillot, D. J. Aitken, A. Frongia, *Org. Biomol. Chem.* **2021**, *19*, 8912–8916.
- [21] Deposition Numbers 2204589 (for **3a**), 2204590 (for **3'a**), 2210456 (for **11**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.
- [22] a) Z. Imani, R. Guillot, V. Declerck, D. J. Aitken, *J. Org. Chem.* **2020**, *85*, 6165–6171; b) M. Alauddin, E. Gloaguen, V. Brenner, B. Tardivel, M. Mons, A. Zehnacker-Rentien, V. Declerck, D. J. Aitken, *Chem. Eur. J.* **2015**, *21*, 16479–16493; c) E. Gorrea, G. Pohl, P. Nolis, S. Celis, K. K. Burusco, V. Branchadell, A. Perczel, R. M. Ortuño, *J. Org. Chem.* **2012**, *77*, 9795–9806; d) E. Torres, E. Gorrea, E. Da Silva, P. Nolis, V. Branchadell, R. M. Ortuño, *Org. Lett.* **2009**, *11*, 2301–2304.
- [23] M. E. Jung, G. Deng, *J. Org. Chem.* **2012**, *77*, 11002–11005.

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